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(54) Title: HETEROCYCLIC COMPOUNDS AS 5HT2A BIASED AGONISTS

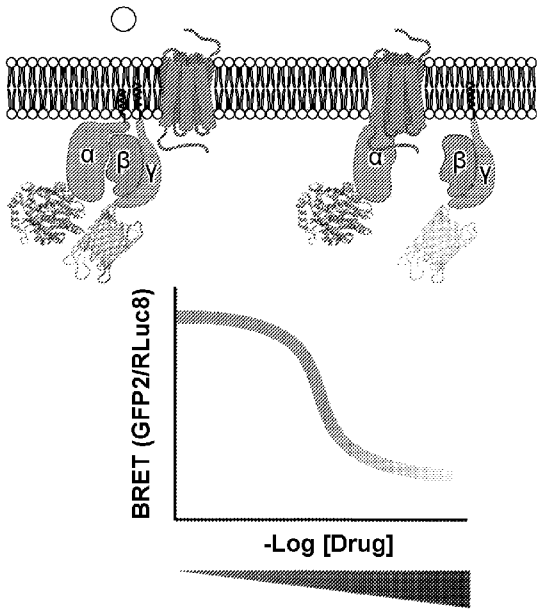

FIG. 1A

(57) Abstract: Disclosed are compounds that are 5HT2A Gq-biased agonists and methods for use of such compounds in 5HT2A mediated diseases.

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[Continued on next page]

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HETEROCYCLIC COMPOUNDS AS 5HT2A BIASED AGONISTS

STATEMENT REGARDING GOVERNMENT FUNDING

This invention was made with government support under HR00112020029 awarded by the Defense Advanced Research Projects Agency. The government has certain rights in the invention.

TECHNICAL FIELD

This disclosure relates to small-molecule heterocyclic compounds, which are Gq-biased agonists of the G protein-coupled receptor 5HT2A. This disclosure also pertains to methods of use thereof for the treatment of diseases in a subject in need thereof.

BACKGROUND

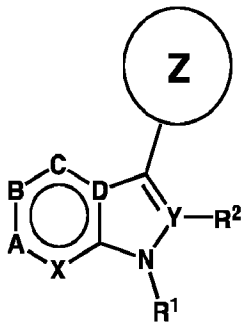
Depression, anxiety and substance abuse represent major unsolved medical problems, as safe, effective and rapid treatments are currently unavailable. Commonly prescribed antidepressant medications frequently take weeks-months for full efficacy and many patients do not achieve symptom relief and remain disabled. Therefore, new treatments are needed.

The 5HT2A receptor, a G protein-coupled receptor, is a target of much interest, owing to its role in psychiatric disorders including psychosis, depression, dyskinesias, and hallucination (Slocum et al., 2021). Progress towards therapeutic leads against this target, has been slowed by the need for selectivity versus related off-targets, such as 5HT2B receptor (Hutcheson et al., 2011; McCorvy and Roth, 2015; Roth, 2007), versus other receptors such as the serotonin transporter SERT, and for functional selectivity in signaling (i.e., for G protein vs. β-arrestin recruitment)(Kim et al., 2020; Slocum *et al.*, 2021); these features make 5HT2A a therapeutically worthy yet challenging target. Gq-biased 5HT2A agonists, which selectively activate 5HT2A-mediated Gq signaling over β-arrestin recruitment, are highly sought-after therapeutics. To date, Gq-biased 5HT2A agonists that are selective for 5HT2A over 5HT2B and SERT are unprecedented.

SUMMARY

Disclosed are heterocyclic small-molecules heterocyclic compounds, which are Gq-biased agonists of 5HT2A and are selective for 5HT2A over 5HT2B and 5HT2C. These compounds are effective therapeutics for the treatment of psychiatric disorders such as depression, anxiety and substance abuse.

In some embodiments, provided herein are compounds having the structure of FORMULA 1, or a pharmaceutically acceptable salt or solvate thereof:



FORMULA 1

A is selected from N, CH or CR^6;

B is selected from N, CH or CR^5;

C is selected from N, CH or CR^4;

D is selected from N or C;

X is selected from N, CH or CR^7;

Y is selected from N or C;

R^1 and R^2 at each occurrence, are independently selected from null, hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, $C(O)R^{21}$, $C(O)OR^{21}$, $C(O)NR^{21}R^{22}$, $S(O)R^{21}$, $S(O)_2R^{21}$, $S(O)_2NR^{21}R^{22}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

R^{21} and R^{22} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{21} and R^{22}, together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring;

R^4, R^5, R^6 and R^7 at each occurrence, are independently selected from hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, CN, NO_2, OR^{23}, SR^{23}, $NR^{23}R^{24}$, $C(O)R^{23}$, $C(O)OR^{23}$, $C(O)NR^{23}R^{24}$, $S(O)R^{23}$, $S(O)_2R^{23}$, $S(O)_2NR^{23}R^{24}$, $NR^{25}C(O)OR^{23}$, $NR^{25}C(O)R^{23}$, $NR^{25}C(O)NR^{23}R^{24}$, $NR^{25}S(O)R^{23}$, $NR^{25}S(O)_2R^{23}$, $NR^{25}S(O)_2NR^{23}R^{24}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

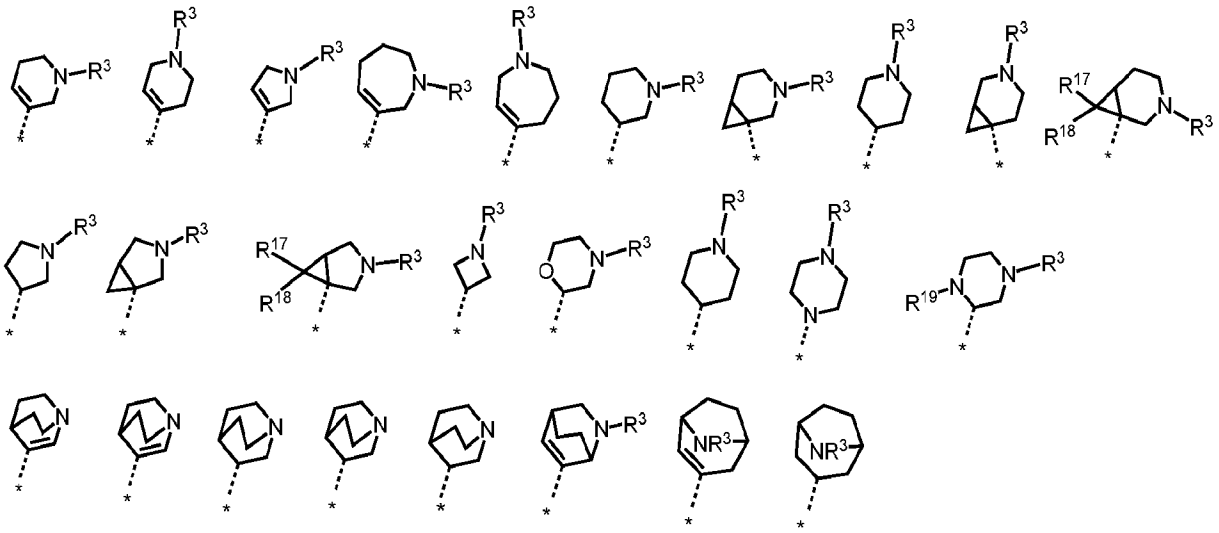
wherein

R^{23}, R^{24}, and R^{25} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{23} and R^{24}, R^{23} and R^{25}, R^{24} and R^{25} together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring; and

is at each occurrence independently selected from an optionally substituted 3-10 membered carbocyclyl, optionally substituted 3-10 membered heterocyclyl, optionally substituted 4-13 membered fused carbocyclyl, optionally substituted 4-13 membered fused heterocyclyl, optionally substituted 4-13 membered bridged carbocyclyl, optionally substituted 4-13 membered bridged heterocyclyl, optionally substituted 4-13 membered spiro carbocyclyl, optionally substituted 4-13 membered spiro heterocyclyl, optionally substituted aryl, optionally substituted bicyclic fused aryl, optionally substituted tricyclic fused aryl, and optionally substituted heteroaryl, optionally substituted bicyclic fused heteroaryl, and optionally substituted tricyclic fused heteroaryl.

In an embodiment,  at each occurrence can be selected from the following groups, or their optionally substituted analogs, wherein * denotes the attachment:



wherein,

R^3 at each occurrence, are independently selected from hydrogen, methyl, ethyl, n-propyl, C_1-C_8 alkyl, CD_3, Ph, $C(O)R^{26}$, $C(O)OR^{26}$, $C(O)NR^{26}R^{27}$, $S(O)R^{26}$, $S(O)_2R^{26}$, $S(O)_2NR^{26}R^{27}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

R^{26} and R^{27} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{26} and R^{27}, together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring;

R^{17} and R^{18} at each occurrence, are independently selected from hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, CN, NO_2, OR^{28}, SR^{28}, $NR^{28}R^{29}$, $C(O)R^{28}$, $C(O)OR^{29}$, $C(O)NR^{28}R^{29}$, $S(O)R^{28}$, $S(O)_2R^{28}$,

$S(O)_2NR^{28}R^{29}$, $NR^{30}C(O)OR^{28}$, $NR^{30}C(O)R^{28}$, $NR^{30}C(O)NR^{28}R^{29}$, $NR^{30}S(O)R^{28}$, $NR^{30}S(O)_2R^{28}$, $NR^{30}S(O)_2NR^{28}R^{29}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C3-C8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

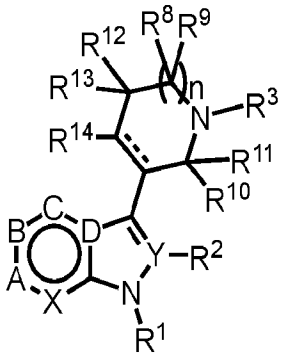
wherein;

R^{28}, R^{29}, and R^{30} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{28} and R^{29}, R^{28} and R^{30}, R^{29} and R^{30} together with the atom to which they are connected form an optionally substituted 3-20 membered cycloalkyl or heterocyclyl ring;

and pharmaceutically acceptable salts thereof.

In another embodiment, the 5HT2A agonist is a compound of FORMULA 2:



FORMULA 2

wherein;

definitions of A, B, C, D, X, Y, R^1, R^2 and R^3 are the same as for FORMULA 1

n is selected from 0, 1 or 2;

R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14}, at each occurrence, are independently selected from hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, CN, NO_2, OR^{31}, SR^{31}, $NR^{31}R^{32}$, $C(O)R^{31}$, $C(O)OR^{31}$, $C(O)NR^{31}R^{32}$,

$S(O)R^{31}$, $S(O)_2R^{31}$, $S(O)_2NR^{31}R^{32}$, $NR^{33}C(O)OR^{31}$, $NR^{33}C(O)R^{31}$, $NR^{33}C(O)NR^{31}R^{32}$, $NR^{33}S(O)R^{31}$, $NR^{33}S(O)_2R^{31}$, $NR^{33}S(O)_2NR^{31}R^{32}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

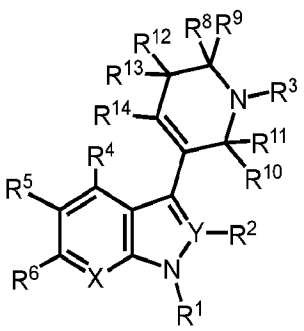
wherein

R^{31}, R^{32}, and R^{33} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

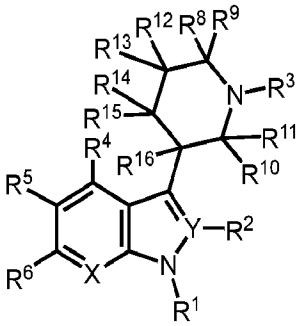
R^{31} and R^{32}, R^{31} and R^{33}, R^{32} and R^{33} together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring;

and pharmaceutically acceptable salts thereof.

In another embodiment, the 5HT2A agonist is a compound of FORMULAE 2A or 2B:



FORMULA 2A



FORMULA 2B

wherein;

X is selected from N, CH or CR^7;

Y is selected from N or C;

the definitions of R^1, R^2, R^3, R^4, R^5, R^6, R^7 are the same as for FORMULA 1;

and definitions of R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are the same as for FORMULA 2;

R^{15} and R^{16}, at each occurrence, are independently selected from hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, CN, NO_2, OR^{34}, SR^{34}, $NR^{34}R^{35}$, $C(O)R^{34}$, $C(O)OR^{34}$, $C(O)NR^{34}R^{35}$, $S(O)R^{34}$, $S(O)_2R^{34}$, $S(O)_2NR^{34}R^{35}$, $NR^{36}C(O)OR^{34}$, $NR^{36}C(O)R^{34}$, $NR^{36}C(O)NR^{34}R^{35}$, $NR^{36}S(O)R^{34}$, $NR^{36}S(O)_2R^{34}$, $NR^{36}S(O)_2NR^{34}R^{35}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

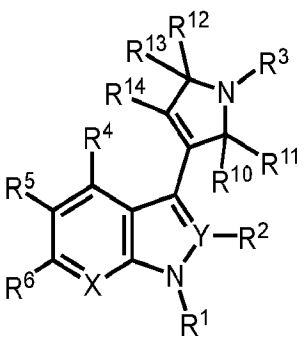
R^{34}, R^{35}, and R^{36} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{34} and R^{35}, R^{34} and R^{36}, R^{35} and R^{36} together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring; and

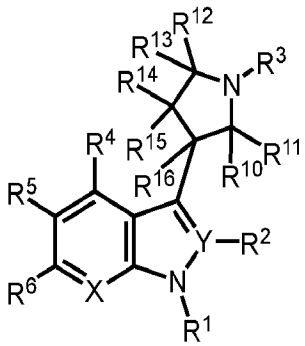
optionally, R^{15} and R^{16} together with the atom to which they are connected form an optionally substituted 3-20 membered cycloalkyl or heterocyclyl ring; and

pharmaceutically acceptable salts thereof.

In another embodiment, the 5HT2A agonist is a compound of FORMULAE 2C or 2D:



FORMULA 2C



FORMULA 2D

wherein,

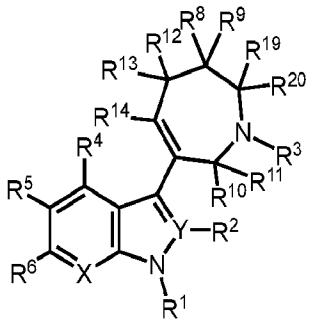
X is selected from N, CH or CR^7;

Y is selected from N or C;

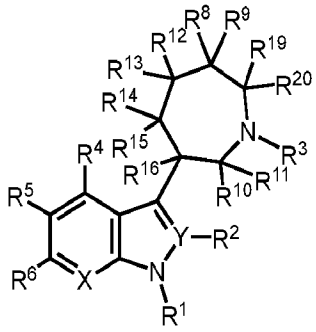
The definitions of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} an R^{16} are the same as for FORMULAE 2A and 2B;

and pharmaceutically acceptable salts thereof.

In another embodiment, the 5HT2A agonist is a compound of FORMULAE 2E or 2F:



FORMULA 2E



FORMULA 2F

wherein,

X is selected from N, CH or CR^7;

Y is selected from N or C;

The definitions of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are the same as for FORMULAE 2A and 2B;

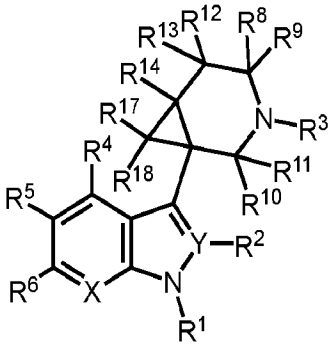
R^{19} and R^{20}, at each occurrence, are independently selected from hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, CN, NO_2, OR^{37}, SR^{37}, $NR^{37}R^{38}$, $C(O)R^{37}$, $C(O)OR^{38}$, $C(O)NR^{37}R^{38}$, $S(O)R^{37}$, $S(O)_2R^{37}$, $S(O)_2NR^{37}R^{38}$, $NR^{39}C(O)OR^{37}$, $NR^{39}C(O)R^{37}$, $NR^{39}C(O)NR^{37}R^{38}$, $NR^{39}S(O)R^{37}$, $NR^{39}S(O)_2R^{37}$, $NR^{36}S(O)_2NR^{37}R^{38}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

R^{37}, R^{38}, and R^{39} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{37} and R^{38}, R^{37} and R^{39}, $R^{38}$and R^{39} together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring; and pharmaceutically acceptable salts thereof.

In another embodiment, the 5HT2A agonist is a compound of FORMULA 3:



FORMULA 3

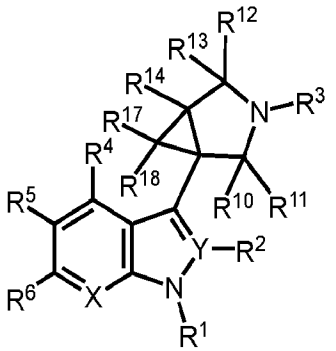
wherein;

X is selected from N, CH or CR^7;

Y is selected from N or C;

The definitions of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{17} and R^{18} are the same as for FORMULA 1; and definitions of R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are the same as for FORMULA 2A; and pharmaceutically acceptable salts thereof.

In another embodiment, the 5HT2A agonist is a compound of FORMULA 4:



FORMULA 4

wherein;

X is selected from N, CH or CR^7;

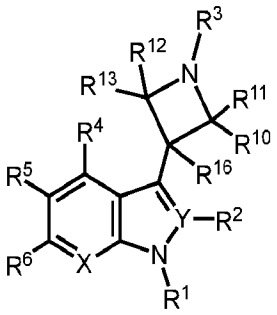
Y is selected from N or C;

The definitions of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{17} and R^{18} are the same as for FORMULA 1;

And definitions of R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are the same as for FORMULA 2A;

and pharmaceutically acceptable salts thereof.

In another embodiment, the 5HT2A agonist is a compound of FORMULA 5:



FORMULA 5

wherein;

X is selected from N, CH or CR^7;

Y is selected from N or C;

the definitions of R^1, R^2, R^3, R^4, R^5, R^6, R^7 are the same as for FORMULA 1;

and definitions of R^{10}, R^{11}, R^{12}, R^{13} and R^{16} are the same as for FORMULA 2A; and pharmaceutically acceptable salts thereof.

In some aspects, the compound is selected from the following: NS131-179, NS131-178, NS131-177, NS136-006, NS131-169, NS131-168, NS131-167, NS131-173, NS131-180, RS134-52, RS134-48, NS131-185, NS131-170, RS134-45, RS134-40, NS131-184, RS134-49, RS134-53, RS134-41, RS134-46, NS131-172, RS134-38, RS134-65, RS134-62, RS134-70, NS136-081, RS134-73, RS134-72, NS136-092, NS136-091, NS136-096, NS136-095, NS136-102, NS136-101, NS136-115, NS136-116, NS136-117, NS136-118, NS136-119, NS136-120, NS136-109, NS136-110, NS136-111, NS136-112, RS134-37, RS134-56, NS136-002, NS136-004, RS130-132, YX129-177C, YX129-180C, YX143-19, YX143-20, YX143-2, YX143-21, NS144-042, NS144-043, NS144-044, YS135-44, YS135-45, YS135-34, YS135-32, YS135-38, YS135-41, YS135-39, YX143-14A-2, NS144-019, NS144-021, YX143-15, YX143-16, YX143-17C, YX143-18C, NS144-047, NS144-048, NS144-049, NS136-128, NS136-129, NS136-130, NS136-131, NS136-150, NS136-151, NS136-152, NS136-166, NS144-011, NS136-158, NS136-167, NS136-159, NS136-135, NS136-136, NS136-137, NS144-046, NS144-045, NS136-140, NS136-141, NS136-142, NS136-143, NS136-153, NS136-154, NS136-155, NS136-175, NS144-016, NS136-160, NS136-176, NS136-161, NS136-144, NS136-145, NS136-146, NS144-051, NS144-

050, YX143-41C, YX143-42C, YX143-43D, NS144-059-2, NS144-054-2, NS144-067, NS144-085, NS144-093, NS144-094, NS144-095, NS144-096, XQ148-012, XQ148-023, ZX147-015, ZX147-016, ZX147-017, ZX147-019, NS144-097, NS144-098, NS144-102, NS144-101, NS144-107, NS144-108, NS144-109, NS144-110, YS135-52, YS135-53, YS135-54, YS135-80, YS135-81, YS135-82, YS135-96, YS135-98, YS135-99, YS135-100, ZX147-026-01, ZX147-026-02, ZX147-027, ZX147-028, ZX147-029, ZX147-031, ZX147-054, ZX147-055, ZX147-056, ZX147-092, ZX147-093, ZX147-094, ZX147-095, ZX147-096, ZX147-097, ZX147-098, ZX147-099, ZX147-100, ZX147-128, ZX147-129, ZX147-130, ZX147-131, ZX147-137, ZX147-183, ZX156-011, ZX156-012, ZX156-014-1, ZX156-014-2, ZX156-019, ZX156-059, ZX156-069, ZX156-070, ZX156-071, ZX156-089, ZX156-090, ZX162-100, ZX162-031, ZX162-104, ZX162-105, ZX162-110, ZX162-111, ZX162-112, ZX162-113, ZX162-124, ZX162-126, ZX162-127, ZX162-128, ZX162-129, ZX162-138, ZX162-139, ZX162-140, ZX162-141, ZX162-147, ZX162-148, ZX162-151, ZX162-173, ZX162-174, ZX162-175, ZX162-176, YX143-103B, YX143-103C, YX143-105C, YX143-108, YX143-110B, YX143-112B, YX143-129, YX143-134C, YX143-138C, YX143-182C-1, YX143-183A, YX143-184B-1, YX143-184B-2, YX143-185B, YX143-186B, YX157-19A, YX157-20A, YX157-29B, YX157-42B, YX157-51B, YX157-51C, YX157-55A, XS159-153, XS159-155, XS159-160, XS159-163, XS159-180, XS159-186, XS165-3, XS165-5, XS165-8, XQ148-93, XQ158-012, XQ158-055, XQ158-056, XQ158-078, XQ158-093A, XQ158-082, XQ158-115, XQ158-164, XQ158-167, XQ158-168, ZD160-34, ZD160-140, ZD160-141, ZD160-149, ZD160-11, ZD160-133, ZD160-130, ZD160-131, QC166-005, QC166-008, QC-166-032, XQ148-86, QC166-096, QC166-097, QC179-001, QC179-002, QC179-025, QC-179-032, QC-179-033, QC179-038, QC179-039, QC179-040, ZX167-072, ZX167-077, ZX167-074, ZX167-090, ZX167-091, ZX162-100-1 (Enantiomer 1 of ZX162-100), ZX162-100-2 (Enantiomer 2 of ZX162-100), ZX162-031-1 (Enantiomer 1 of ZX162-031), ZX162-031-2 (Enantiomer 2 of ZX162-031), ZX167-074-1 (Enantiomer 1 of ZX167-074), ZX167-074-2 (Enantiomer 2 of ZX167-074), ZX177-057, ZX177-058, ZX177-058BY, ZX177-059, ZX177-060 and analogs thereof.

In some aspects, the compound is selected from the following: NS131-179, NS131-178, NS131-177, NS136-006, NS131-169, NS131-168, NS131-167, NS131-173, NS131-180, RS134-52, RS134-48, NS131-185, NS131-170, RS134-45, RS134-40, NS131-184, RS134-49, RS134-53, RS134-41, RS134-46, NS131-172, RS134-38, RS134-65, RS134-62, RS134-70, NS136-081, RS134-73, RS134-72, NS136-092, NS136-091, NS136-096, NS136-095, NS136-102, NS136-

101, NS136-115, NS136-116, NS136-117, NS136-118, NS136-119, NS136-120, RS134-37, RS134-56, NS136-002, NS136-004, YS135-34, YS135-32, YS135-38, YS135-41, YS135-39, YX143-14A-2, NS144-019, NS144-021, YX143-15, YX143-16, YX143-17C, YX143-18C, NS144-047, NS144-048, NS144-049, NS136-128, NS136-129, NS136-130, NS136-131, NS136-150, NS136-151, NS136-152, NS136-166, NS144-011, NS136-158, NS136-167, NS136-159, NS136-140, NS136-141, NS136-142, NS136-143, NS136-153, NS136-154, NS136-155, NS136-175, NS144-016, NS136-160, NS136-176, NS136-161, NS144-093, NS144-094, NS144-095, NS144-096, YS135-80, YS135-81, YS135-82, YS135-96, YS135-98, ZX156-069, and analogs thereof.

In some aspects, the compound is selected from the following: RS130-132, YX129-177C, YX129-180C, YX143-19, YX143-20, YX143-2, YX143-21, NS144-042, NS144-043, NS144-044, YS135-44, YS135-45, NS136-135, NS136-136, NS136-137, NS144-046, NS144-045, NS136-144, NS136-145, NS136-146, NS144-051, NS144-050, YX143-41C, YX143-42C, YX143-43D, NS144-059-2, NS144-054-2, NS144-067, NS144-085, XQ148-012, XQ148-023, ZX147-015, ZX147-016, ZX147-017, ZX147-019, NS144-097, NS144-098, NS144-102, NS144-101, NS144-107, NS144-108, NS144-109, NS144-110, YS135-52, YS135-53, YS135-54, YS135-99, YS135-100, ZX147-026-01, ZX147-026-02, ZX147-027, ZX147-028, ZX147-029, ZX147-054, ZX147-055, ZX147-056, ZX147-092, ZX147-093, ZX147-094, ZX147-095, ZX147-096, ZX147-097, ZX147-098, ZX147-099, ZX147-100, ZX147-128, ZX147-129, ZX147-130, ZX147-137, ZX147-183, ZX156-019, ZX156-059, ZX156-070, ZX156-071, ZX156-089, ZX156-090, XQ148-93, XQ158-012, XQ158-055, XQ158-056, XQ148-86, and analogs thereof.

In some aspects, the compound is selected from the following: YX143-103B, YX143-103C, YX143-105C, YX143-108, YX143-110B, YX143-112B, YX143-129, YX143-134C, YX143-138C, YX143-182C-1, YX143-183A, YX143-184B-1, YX143-184B-2, YX143-185B, YX143-186B, YX157-19A, YX157-20A, YX157-29B, YX157-42B, YX157-51B, YX157-51C, YX157-55A, and analogs thereof.

In some aspects, the compound is selected from the following: XS159-180, XS159-186, XS165-3, XS165-5, XS165-8, XQ158-078, XQ158-093A, XQ158-082, XQ158-115, XQ158-164, XQ158-167, XQ158-168, ZD160-34, ZD160-140, ZD160-141, ZD160-149, ZD160-11, ZD160-133, ZD160-130, ZD160-131, and analogs thereof.

In some aspects, the compound is selected from the following: QC166-005, QC166-008, QC-166-032, QC166-096, QC166-097, QC179-001, QC179-002, QC179-025, QC-179-032, QC-179-033, QC179-038, QC179-039, QC179-040, and analogs thereof.

In some aspects, the compound is selected from the following: ZX162-100, ZX162-031, ZX162-104, ZX162-105, ZX162-110, ZX162-111, ZX162-112, ZX162-113, ZX162-124, ZX162-126, ZX162-127, ZX162-128, ZX162-129, ZX162-138, ZX162-139, ZX162-140, ZX162-141, ZX162-147, ZX162-148, ZX162-151, ZX162-173, ZX162-174, ZX162-175, ZX162-176, XS159-153, XS159-155, XS159-160, XS159-163, ZX167-072, ZX167-077, ZX167-074, ZX167-090, ZX167-091, ZX162-100-1 (Enantiomer 1 of ZX162-100), ZX162-100-2 (Enantiomer 2 of ZX162-100), ZX162-031-1 (Enantiomer 1 of ZX162-031), ZX162-031-2 (Enantiomer 2 of ZX162-031), ZX167-074-1 (Enantiomer 1 of ZX167-074), ZX167-074-2 (Enantiomer 2 of ZX167-074), ZX177-057, ZX177-058, ZX177-058BY, ZX177-059, ZX177-060 and analogs thereof.

In some aspects, the compound is selected from the following: NS136-109, NS136-110, NS136-111, NS136-112, NS136-145, RS134-40, RS134-45, RS134-48, RS134-46, YX143-19 and analogs thereof.

In some aspects, the compound is selected from the following: YX143-108, YX143-129, YX143-134C, ZX147-031, ZX147-131, ZX162-031, ZX162-031-1, ZX162-100, ZX162-100-2, ZX162-105, ZX167-074, ZX167-091, QC166-008, QC166-096, QC166-097, and analogs thereof.

In some aspects, the compound is selected from the following: ZX162-031, ZX162-031-1, ZX162-100, ZX162-100-2, ZX162-105, ZX167-074, ZX167-091, QC166-008, QC166-096, QC166-097, and analogs thereof.

In some aspects, the compound is selected from the following:

3-(3-azabicyclo[4.1.0]heptan-1-yl)-7-chloro-1*H*-indazole (ZX162-031);

3-(3-azabicyclo[3.1.0]hexan-1-yl)-7-chloro-1H-indazole (ZX162-100);

3-(3-azabicyclo[3.1.0]hexan-1-yl)-7-chloro-1H-indole (ZX167-074); and

3-(3-azabicyclo[3.1.0]hexan-1-yl)-7-methyl-1H-indole (ZX167-091), including its pure enantiomers, mixtures of enantiomers, and pharmaceutically acceptable salts, solvent complexes, morphological forms, or deuterated and fluorinated derivatives thereof.

In some aspects, the compound is selected from the following:

3-(azetidin-3-yl)-7-chloro-1H-indole (QC166-008);
3-(azetidin-3-yl)-7-methyl-1*H*-indole (QC166-096); and
3-(azetidin-3-yl)-7-fluoro-1*H*-indole (QC166-097),
and pharmaceutically acceptable salts, solvent complexes, morphological forms, or deuterated and fluorinated derivatives thereof.

In an embodiment, the disclosure includes a pharmaceutical composition, including a 5HT2A agonist as disclosed above, and pharmaceutically acceptable carrier.

In an embodiment, the pharmaceutical composition is formulated to be administered orally, parenterally, intradermally, subcutaneously, topically, and/or rectally.

In an embodiment, disclosed is a method of treating a psychiatric disorder, including administering to a subject in need thereof, a 5HT2A agonist as disclosed above.

In an embodiment, the psychiatric disorder is depression, anxiety, psychosis, dyskinesias, hallucination or substance abuse.

The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

Other features and advantages of the invention will be apparent from the following detailed description and figures, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A- 1C. Bioluminescence Resonance Energy Transfer Assays. A) The BRET2-based TRUPATH platform is used to measure the dissociation of the Gαq subunit from its cognate Gβγ dimer. The RLuc and GFP2 components provide a BRET signal (GFP2/RLuc) that is highest when the heterotrimer is intact in the absence of drug or receptor-mediated dissociation, and decreases upon dissociation in a concentration-dependent manner. B) The BRET1-based beta-arrestin2 recruitment is used to measure the recruitment of beta-arrestin2 to 5HT2A receptor C-terminally tagged with RLuc. Here, the RLuc and mVenys provide a BRET signal (mVenus/RLuc) that is lowest in the absence of drug or recruitment, and increases upon recruitment to the receptor in a concentration-dependent manner. C) Plotting of the data in a semi-logarithmic fashion allows determination of the efficacy (Emax) and potency (EC50).

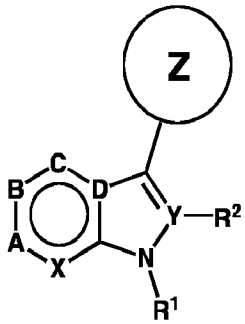
Figure 2A – 2C. BRET Data from Select Compounds**.** 5HT2A receptor displaying biased signaling towards Gαq (blue) versus beta-arrestin2 (red) signaling in response to novel compounds as measured in the BRET assays. Biased signaling is represented by either preferential efficacy, potency, or both through the G protein over beta-arrestin2 pathway.

Figure 3. Calcium Mobilization Assays**.** The calcium flux assays depend upon conical Gαq-mediated signaling, in which the Gαq subunit activates phospholipase C, which hydrolyzes phosphatidylinositol 4,5-bisphosphate into diacyclygerol (not shown) and inositol 1,4,5-triphosphate (IP3). IP3 activates IP3-gated channels on the endoplasmic reticulum, gating the release of intracellular calcium. This calcium then binds to the Fluo-4 dye to produce a signal, with the extent of calcium release – and thus signal produced – increasing in a concentration-dependent manner.

Figure 4A – 4C. Calcium Mobilization Data from Select Compounds**.** Comparison of compound-induced calcium flux at 5HT2A, 5HT2B, and 5HT2C, with a subset of compounds displaying selective activation 5HT2A alone.

DETAILED DESCRIPTION

In an embodiment, 5HT2A agonist is a compound of FORMULA 1:



FORMULA 1

A is selected from N, CH or CR^6;

B is selected from N, CH or CR^5;

C is selected from N, CH or CR^4;

D is selected from N or C;

X is selected from N, CH or CR^7;

Y is selected from N or C;

R^1, R^2 at each occurrence, are independently selected from hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, $C(O)R^{21}$, $C(O)OR^{21}$, $C(O)NR^{21}R^{22}$, $S(O)R^{21}$, $S(O)_2R^{21}$, $S(O)_2NR^{21}R^{22}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

R^{21} and R^{22} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{21} and R^{22}, together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring;

R^4, R^5, R^6 and R^7 at each occurrence, are independently selected from hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, CN, NO_2, OR^{23}, SR^{23}, $NR^{23}R^{24}$, $C(O)R^{23}$, $C(O)OR^{23}$, $C(O)NR^{23}R^{24}$, $S(O)R^{23}$, $S(O)_2R^{23}$, $S(O)_2NR^{23}R^{24}$, $NR^{25}C(O)OR^{23}$, $NR^{25}C(O)R^{23}$, $NR^{25}C(O)NR^{23}R^{24}$, $NR^{25}S(O)R^{23}$,

$NR^{25}S(O)_2R^{23}$, $NR^{25}S(O)_2NR^{23}R^{24}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

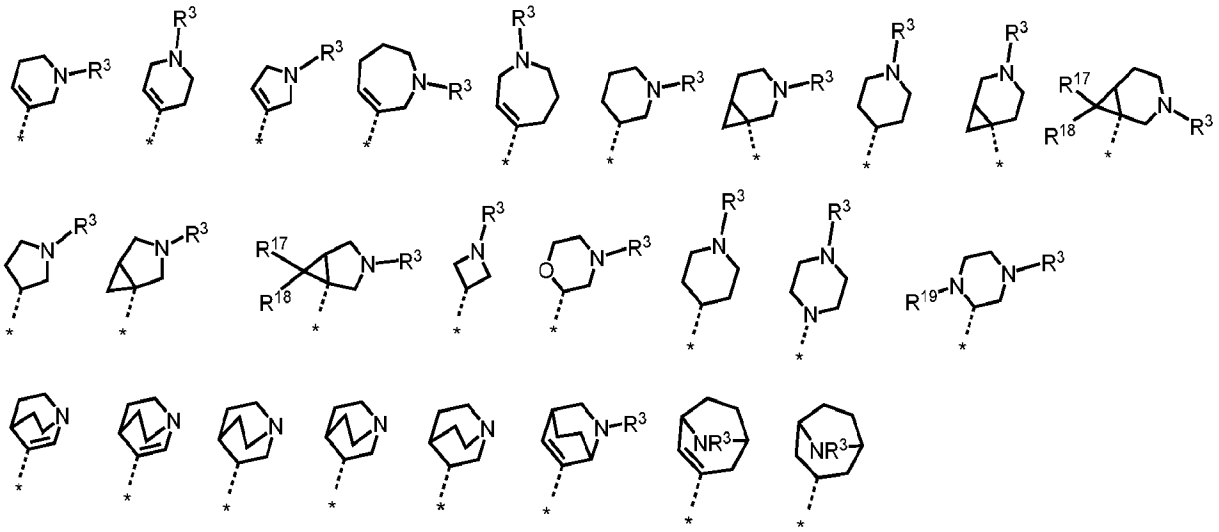
wherein

R^{23}, R^{24}, and R^{25} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{23} and R^{24}, R^{23} and R^{25}, R^{24} and R^{25} together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring; and

is at each occurrence independently selected from an optionally substituted 3-10 membered carbocyclyl, optionally substituted 3-10 membered heterocyclyl, optionally substituted 4-13 membered fused carbocyclyl, optionally substituted 4-13 membered fused heterocyclyl, optionally substituted 4-13 membered bridged carbocyclyl, optionally substituted 4-13 membered bridged heterocyclyl, optionally substituted 4-13 membered spiro carbocyclyl, optionally substituted 4-13 membered spiro heterocyclyl, optionally substituted aryl, optionally substituted bicyclic fused aryl, optionally substituted tricyclic fused aryl, and optionally substituted heteroaryl, optionally substituted bicyclic fused heteroaryl, and optionally substituted tricyclic fused heteroaryl.

In an embodiment,  at each occurrence can be selected from the following groups, or their optionally substituted analogs, wherein * denotes the attachment:



wherein,

R^3 at each occurrence, are independently selected from hydrogen, methyl, ethyl, n-propyl, C_1-C_8 alkyl, CD_3, Ph, $C(O)R^{26}$, $C(O)OR^{26}$, $C(O)NR^{26}R^{27}$, $S(O)R^{26}$, $S(O)_2R^{26}$, $S(O)_2NR^{26}R^{27}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

R^{26} and R^{27} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{26} and R^{27}, together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring;

R^{17} and R^{18} at each occurrence, are independently selected from hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, CN, NO_2, OR^{28}, SR^{28}, $NR^{28}R^{29}$, $C(O)R^{28}$, $C(O)OR^{29}$, $C(O)NR^{28}R^{29}$, $S(O)R^{28}$, $S(O)_2R^{28}$, $S(O)_2NR^{28}R^{29}$, $NR^{30}C(O)OR^{28}$, $NR^{30}C(O)R^{28}$, $NR^{30}C(O)NR^{28}R^{29}$, $NR^{30}S(O)R^{28}$, $NR^{30}S(O)_2R^{28}$, $NR^{30}S(O)_2NR^{28}R^{29}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted

C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C3-C8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

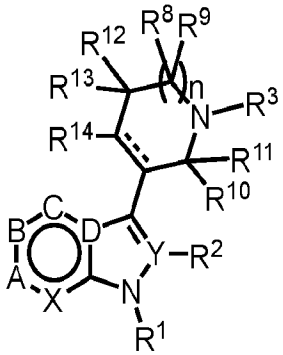
wherein;

R^{28}, R^{29}, and R^{30} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{28} and R^{29}, R^{28} and R^{30}, R^{29} and R^{30} together with the atom to which they are connected form an optionally substituted 3-20 membered cycloalkyl or heterocyclyl ring;

and pharmaceutically acceptable salts thereof.

In another embodiment, the 5HT2A agonist is a compound of FORMULA 2:



FORMULA 2

wherein;

definitions of A, B, C, D, X, Y, R^1, R^2 and R^3 are the same as for FORMULA 1

n is selected from 0, 1 or 2;

R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14}, at each occurrence, are independently selected from hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, CN, NO_2, OR^{31}, SR^{31}, $NR^{31}R^{32}$, $C(O)R^{31}$, $C(O)OR^{31}$, $C(O)NR^{31}R^{32}$, $S(O)R^{31}$, $S(O)_2R^{31}$, $S(O)_2NR^{31}R^{32}$, $NR^{33}C(O)OR^{31}$, $NR^{33}C(O)R^{31}$, $NR^{33}C(O)NR^{31}R^{32}$, $NR^{33}S(O)R^{31}$, $NR^{33}S(O)_2R^{31}$, $NR^{33}S(O)_2NR^{31}R^{32}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8

alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

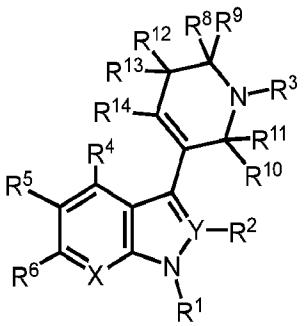
wherein

R^{31}, R^{32}, and R^{33} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

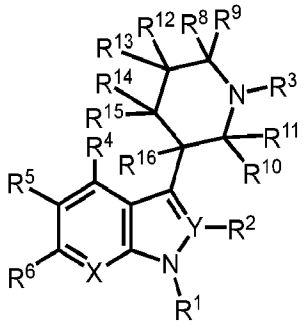
R^{31} and R^{32}, R^{31} and R^{33}, R^{32} and R^{33} together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring;

and pharmaceutically acceptable salts thereof.

In another embodiment, the 5HT2A agonist is a compound of FORMULAE 2A or 2B:



FORMULA 2A



FORMULA 2B

wherein;

X is selected from N, CH or CR^7;

Y is selected from N or C;

the definitions of R^1, R^2, R^3, R^4, R^5, R^6, R^7 are the same as for FORMULA 1;

and definitions of R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are the same as for FORMULA 2;

R^{15} and R^{16}, at each occurrence, are independently selected from hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, CN, NO_2, OR^{34}, SR^{34}, $NR^{34}R^{35}$, $C(O)R^{34}$, $C(O)OR^{34}$, $C(O)NR^{34}R^{35}$, $S(O)R^{34}$, $S(O)_2R^{34}$, $S(O)_2NR^{34}R^{35}$, $NR^{36}C(O)OR^{34}$, $NR^{36}C(O)R^{34}$, $NR^{36}C(O)NR^{34}R^{35}$, $NR^{36}S(O)R^{34}$, $NR^{36}S(O)_2R^{34}$, $NR^{36}S(O)_2NR^{34}R^{35}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl,

optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

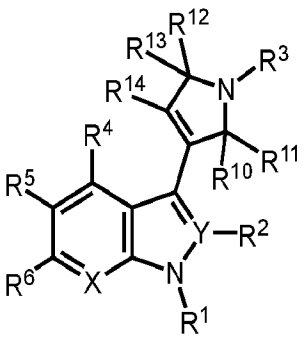
R^{34}, R^{35}, and R^{36} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{34} and R^{35}, R^{34} and R^{36}, R^{35} and R^{36} together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring; and

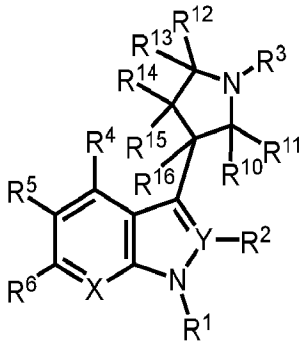
optionally, R^{15} and R^{16} together with the atom to which they are connected form an optionally substituted 3-20 membered cycloalkyl or heterocyclyl ring; and

pharmaceutically acceptable salts thereof.

In another embodiment, the 5HT2A agonist is a compound of FORMULAE 2C or 2D:



FORMULA 2C



FORMULA 2D

wherein,

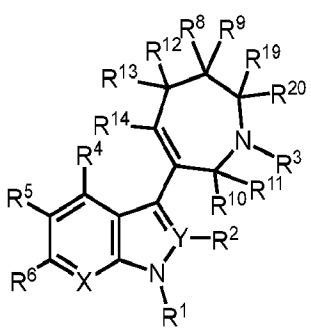
X is selected from N, CH or CR^7;

Y is selected from N or C;

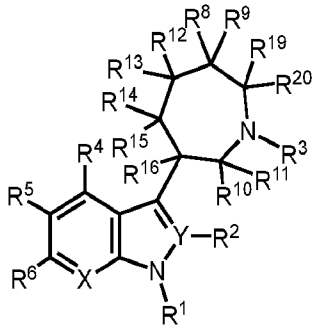
The definitions of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} an R^{16} are the same as for FORMULAE 2A and 2B;

and pharmaceutically acceptable salts thereof.

In another embodiment, the 5HT2A agonist is a compound of FORMULAE 2E or 2F:



FORMULA 2E



FORMULA 2F

wherein,

X is selected from N, CH or CR^7;

Y is selected from N or C;

The definitions of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are the same as for FORMULAE 2A and 2B;

R^{19} and R^{20}, at each occurrence, are independently selected from hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, CN, NO_2, OR^{37}, SR^{37}, $NR^{37}R^{38}$, $C(O)R^{37}$, $C(O)OR^{38}$, $C(O)NR^{37}R^{38}$, $S(O)R^{37}$, $S(O)_2R^{37}$, $S(O)_2NR^{37}R^{38}$, $NR^{39}C(O)OR^{37}$, $NR^{39}C(O)R^{37}$, $NR^{39}C(O)NR^{37}R^{38}$, $NR^{39}S(O)R^{37}$, $NR^{39}S(O)_2R^{37}$, $NR^{36}S(O)_2NR^{37}R^{38}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

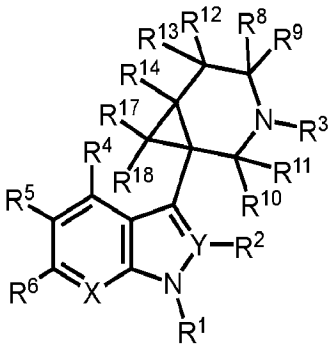
wherein

R^{37}, R^{38}, and R^{39} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{37} and R^{38}, R^{37} and R^{39}, $R^{38}$and R^{39} together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring; and

pharmaceutically acceptable salts thereof.

In another embodiment, the 5HT2A agonist is a compound of FORMULA 3:



FORMULA 3

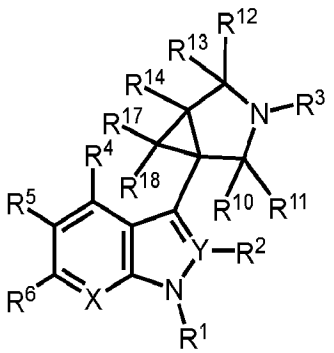
wherein;

X is selected from N, CH or CR^7;

Y is selected from N or C;

The definitions of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{17} and R^{18} are the same as for FORMULA 1; and definitions of R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are the same as for FORMULA 2A; and pharmaceutically acceptable salts thereof.

In another embodiment, the 5HT2A agonist is a compound of FORMULA 4:



FORMULA 4

wherein;

X is selected from N, CH or CR^7;

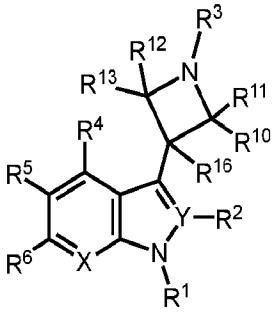
Y is selected from N or C;

The definitions of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{17} and R^{18} are the same as for FORMULA 1;

And definitions of R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are the same as for FORMULA 2A;

and pharmaceutically acceptable salts thereof.

In another embodiment, the 5HT2A agonist is a compound of FORMULA 5:



FORMULA 5

wherein;

X is selected from N, CH or CR^7;

Y is selected from N or C;

the definitions of R^1, R^2, R^3, R^4, R^5, R^6, R^7 are the same as for FORMULA 1;

and definitions of R^{10}, R^{11}, R^{12}, R^{13} and R^{16} are the same as for FORMULA 2A; and pharmaceutically acceptable salts thereof.

In some aspects, compound is a compound selected from those synthesized in the Examples below: NS131-179, NS131-178, NS131-177, NS136-006, NS131-169, NS131-168, NS131-167, NS131-173, NS131-180, RS134-52, RS134-48, NS131-185, NS131-170, RS134-45, RS134-40, NS131-184, RS134-49, RS134-53, RS134-41, RS134-46, NS131-172, RS134-38, RS134-65, RS134-62, RS134-70, NS136-081, RS134-73, RS134-72, NS136-092, NS136-091, NS136-096, NS136-095, NS136-102, NS136-101, NS136-115, NS136-116, NS136-117, NS136-118, NS136-119, NS136-120, NS136-109, NS136-110, NS136-111, NS136-112, RS134-37, RS134-56, NS136-002, NS136-004, RS130-132, YX129-177C, YX129-180C, YX143-19, YX143-20, YX143-2, YX143-21, NS144-042, NS144-043, NS144-044, YS135-44, YS135-45, YS135-34, YS135-32, YS135-38, YS135-41, YS135-39, YX143-14A-2, NS144-019, NS144-021, YX143-15, YX143-16, YX143-17C, YX143-18C, NS144-047, NS144-048, NS144-049, NS136-128, NS136-129, NS136-130, NS136-131, NS136-150, NS136-151, NS136-152, NS136-166, NS144-011, NS136-158, NS136-167, NS136-159, NS136-135, NS136-136, NS136-137, NS144-046, NS144-045, NS136-140, NS136-141, NS136-142, NS136-143, NS136-153, NS136-154, NS136-155, NS136-175, NS144-016, NS136-160, NS136-176, NS136-161, NS136-144, NS136-145, NS136-146, NS144-051, NS144-050, YX143-41C, YX143-42C, YX143-43D, NS144-059-2, NS144-054-2, NS144-067, NS144-085, NS144-093, NS144-094, NS144-095, NS144-096, XQ148-012, XQ148-023, ZX147-015, ZX147-016, ZX147-017, ZX147-019, NS144-097, NS144-098, NS144-102, NS144-101, NS144-107, NS144-108, NS144-109, NS144-110, YS135-

52, YS135-53, YS135-54, YS135-80, YS135-81, YS135-82, YS135-96, YS135-98, YS135-99, YS135-100, ZX147-026-01, ZX147-026-02, ZX147-027, ZX147-028, ZX147-029, ZX147-031, ZX147-054, ZX147-055, ZX147-056, ZX147-092, ZX147-093, ZX147-094, ZX147-095, ZX147-096, ZX147-097, ZX147-098, ZX147-099, ZX147-100, ZX147-128, ZX147-129, ZX147-130, ZX147-131, ZX147-137, ZX147-183, ZX156-011, ZX156-012, ZX156-014-1, ZX156-014-2, ZX156-019, ZX156-059, ZX156-069, ZX156-070, ZX156-071, ZX156-089, ZX156-090, ZX162-100, ZX162-031, ZX162-104, ZX162-105, ZX162-110, ZX162-111, ZX162-112, ZX162-113, ZX162-124, ZX162-126, ZX162-127, ZX162-128, ZX162-129, ZX162-138, ZX162-139, ZX162-140, ZX162-141, ZX162-147, ZX162-148, ZX162-151, ZX162-173, ZX162-174, ZX162-175, ZX162-176, YX143-103B, YX143-103C, YX143-105C, YX143-108, YX143-110B, YX143-112B, YX143-129, YX143-134C, YX143-138C, YX143-182C-1, YX143-183A, YX143-184B-1, YX143-184B-2, YX143-185B, YX143-186B, YX157-19A, YX157-20A, YX157-29B, YX157-42B, YX157-51B, YX157-51C, YX157-55A, XS159-153, XS159-155, XS159-160, XS159-163, XS159-180, XS159-186, XS165-3, XS165-5, XS165-8, XQ148-93, XQ158-012, XQ158-055, XQ158-056, XQ158-078, XQ158-093A, XQ158-082, XQ158-115, XQ158-164, XQ158-167, XQ158-168, ZD160-34, ZD160-140, ZD160-141, ZD160-149, ZD160-11, ZD160-133, ZD160-130, ZD160-131, QC166-005, QC166-008, QC-166-032, XQ148-86, QC166-096, QC166-097, QC179-001, QC179-002, QC179-025, QC-179-032, QC-179-033, QC179-038, QC179-039, QC179-040, ZX167-072, ZX167-077, ZX167-074, ZX167-090, ZX167-091, ZX162-100-1 (Enantiomer 1 of ZX162-100), ZX162-100-2 (Enantiomer 2 of ZX162-100), ZX162-031-1 (Enantiomer 1 of ZX162-031), ZX162-031-2 (Enantiomer 2 of ZX162-031), ZX167-074-1 (Enantiomer 1 of ZX167-074), ZX167-074-2 (Enantiomer 2 of ZX167-074), ZX177-057, ZX177-058, ZX177-058BY, ZX177-059, ZX177-060 and analogs thereof.

In some aspects, compound is a compound selected from those synthesized in the Examples below, incuding, but not limited to: NS131-179, NS131-178, NS131-177, NS136-006, NS131-169, NS131-168, NS131-167, NS131-173, NS131-180, RS134-52, RS134-48, NS131-185, NS131-170, RS134-45, RS134-40, NS131-184, RS134-49, RS134-53, RS134-41, RS134-46, NS131-172, RS134-38, RS134-65, RS134-62, RS134-70, NS136-081, RS134-73, RS134-72, NS136-092, NS136-091, NS136-096, NS136-095, NS136-102, NS136-101, NS136-115, NS136-116, NS136-117, NS136-118, NS136-119, NS136-120, RS134-37, RS134-56, NS136-002, NS136-004, YS135-34, YS135-32, YS135-38, YS135-41, YS135-39, YX143-14A-2, NS144-019, NS144-021, YX143-15, YX143-16, YX143-17C, YX143-18C, NS144-047, NS144-048, NS144-

049, NS136-128, NS136-129, NS136-130, NS136-131, NS136-150, NS136-151, NS136-152, NS136-166, NS144-011, NS136-158, NS136-167, NS136-159, NS136-140, NS136-141, NS136-142, NS136-143, NS136-153, NS136-154, NS136-155, NS136-175, NS144-016, NS136-160, NS136-176, NS136-161, NS144-093, NS144-094, NS144-095, NS144-096, YS135-80, YS135-81, YS135-82, YS135-96, YS135-98, ZX156-069, and analogs thereof.

In some aspects, compound is a compound selected from those synthesized in the Examples below, incuding, but not limited to: RS130-132, YX129-177C, YX129-180C, YX143-19, YX143-20, YX143-2, YX143-21, NS144-042, NS144-043, NS144-044, YS135-44, YS135-45, NS136-135, NS136-136, NS136-137, NS144-046, NS144-045, NS136-144, NS136-145, NS136-146, NS144-051, NS144-050, YX143-41C, YX143-42C, YX143-43D, NS144-059-2, NS144-054-2, NS144-067, NS144-085, XQ148-012, XQ148-023, ZX147-015, ZX147-016, ZX147-017, ZX147-019, NS144-097, NS144-098, NS144-102, NS144-101, NS144-107, NS144-108, NS144-109, NS144-110, YS135-52, YS135-53, YS135-54, YS135-99, YS135-100, ZX147-026-01, ZX147-026-02, ZX147-027, ZX147-028, ZX147-029, ZX147-054, ZX147-055, ZX147-056, ZX147-092, ZX147-093, ZX147-094, ZX147-095, ZX147-096, ZX147-097, ZX147-098, ZX147-099, ZX147-100, ZX147-128, ZX147-129, ZX147-130, ZX147-137, ZX147-183, ZX156-019, ZX156-059, ZX156-070, ZX156-071, ZX156-089, ZX156-090, XQ148-93, XQ158-012, XQ158-055, XQ158-056, XQ148-86, and analogs thereof.

In some aspects, compound is a compound selected from those synthesized in the Examples below, incuding, but not limited to: YX143-103B, YX143-103C, YX143-105C, YX143-108, YX143-110B, YX143-112B, YX143-129, YX143-134C, YX143-138C, YX143-182C-1, YX143-183A, YX143-184B-1, YX143-184B-2, YX143-185B, YX143-186B, YX157-19A, YX157-20A, YX157-29B, YX157-42B, YX157-51B, YX157-51C, YX157-55A, and analogs thereof.

In some aspects, compound is a compound selected from those synthesized in the Examples below, incuding, but not limited to: XS159-180, XS159-186, XS165-3, XS165-5, XS165-8, XQ158-078, XQ158-093A, XQ158-082, XQ158-115, XQ158-164, XQ158-167, XQ158-168, ZD160-34, ZD160-140, ZD160-141, ZD160-149, ZD160-11, ZD160-133, ZD160-130, ZD160-131, and analogs thereof.

In some aspects, compound is a compound selected from those synthesized in the Examples below, incuding, but not limited to: QC166-005, QC166-008, QC-166-032, QC166-096, QC166-097, QC179-001, QC179-002, QC179-025, QC-179-032, QC-179-033, QC179-038, QC179-039, QC179-040, and analogs thereof.

In some aspects, compound is a compound selected from those synthesized in the Examples below, incuding, but not limited to: ZX162-100, ZX162-031, ZX162-104, ZX162-105, ZX162-110, ZX162-111, ZX162-112, ZX162-113, ZX162-124, ZX162-126, ZX162-127, ZX162-128, ZX162-129, ZX162-138, ZX162-139, ZX162-140, ZX162-141, ZX162-147, ZX162-148, ZX162-151, ZX162-173, ZX162-174, ZX162-175, ZX162-176, XS159-153, XS159-155, XS159-160, XS159-163, ZX167-072, ZX167-077, ZX167-074, ZX167-090, ZX167-091, ZX162-100-1 (Enantiomer 1 of ZX162-100), ZX162-100-2 (Enantiomer 2 of ZX162-100), ZX162-031-1 (Enantiomer 1 of ZX162-031), ZX162-031-2 (Enantiomer 2 of ZX162-031), ZX167-074-1 (Enantiomer 1 of ZX167-074), ZX167-074-2 (Enantiomer 2 of ZX167-074), ZX177-057, ZX177-058, ZX177-058BY, ZX177-059, ZX177-060 and analogs thereof.

In some aspects, compound is a compound selected from those synthesized in the Examples below, incuding, but not limited to: NS136-109, NS136-110, NS136-111, NS136-112, NS136-145, RS134-40, RS134-45, RS134-48, RS134-46, YX143-19 and analogs thereof.

In some aspects, compound is a compound selected from those synthesized in the Examples below, incuding, but not limited to: YX143-108, YX143-129, YX143-134C, ZX147-031, ZX147-131, ZX162-031, ZX162-031-1, ZX162-100, ZX162-100-2, ZX162-105, ZX167-074, ZX167-091, QC166-008, QC166-096, QC166-097, and analogs thereof.

In some aspects, compound is a compound selected from those synthesized in the Examples below, incuding, but not limited to: ZX162-031, ZX162-031-1, ZX162-100, ZX162-100-2, ZX162-105, ZX167-074, ZX167-091, QC166-008, QC166-096, QC166-097, and analogs thereof.

In some aspects, compound is a compound selected from those synthesized in the Examples below, incuding, but not limited to:

a) 3-(3-azabicyclo[4.1.0]heptan-1-yl)-7-chloro-1*H*-indazole (ZX162-031) including its pure enantiomers, mixtures of enantiomers, and pharmaceutically acceptable salts, solvent complexes, morphological forms, or deuterated and fluorinated derivatives thereof.

b) 3-(3-azabicyclo[3.1.0]hexan-1-yl)-7-chloro-1H-indazole (ZX162-100) including its pure enantiomers, mixtures of enantiomers, and pharmaceutically acceptable salts, solvent complexes, morphological forms, or deuterated and fluorinated derivatives thereof.

c) 3-(3-azabicyclo[3.1.0]hexan-1-yl)-7-chloro-1H-indole (ZX167-074) including its pure enantiomers, mixtures of enantiomers, and pharmaceutically acceptable salts, solvent complexes, morphological forms, or deuterated and fluorinated derivative thereof.

d) 3-(3-azabicyclo[3.1.0]hexan-1-yl)-7-methyl-1H-indole (ZX167-091) including its pure enantiomers, mixtures of enantiomers, and pharmaceutically acceptable salts, solvent complexes, morphological forms, or deuterated and fluorinated derivatives thereof.

In some aspects, compound is a compound selected from those synthesized in the Examples below, incuding, but not limited to:

a. 3-(azetidin-3-yl)-7-chloro-1H-indole (QC166-008), and pharmaceutically acceptable salts, solvent complexes, morphological forms, or deuterated and fluorinated derivatives thereof.

b. 3-(azetidin-3-yl)-7-methyl-1*H*-indole (QC166-096), and pharmaceutically acceptable salts, solvent complexes, morphological forms, or deuterated and fluorinated derivatives thereof.

c. 3-(azetidin-3-yl)-7-fluoro-1*H*-indole (QC166-097), and pharmaceutically acceptable salts, solvent complexes, morphological forms, or deuterated and fluorinated derivatives thereof.

In some aspects of the disclosed methods, the compounds can be administered by any of several routes of administration including, *e.g.*, orally, parenterally, intradermally, subcutaneously, topically, and/or rectally.

Any of the above-described methods can further include treating the subject with one or more additional therapeutic regimens for treatment.

As used herein, the terms "about" and "approximately" are defined as being within plus or minus 10% of a given value or state, preferably within plus or minus 5% of said value or state. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Methods and materials are described herein for use in the present invention; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

Other features and advantages of the invention will be apparent from the following detailed description and figures, and from the claims.

Synthesis and Testing of the Compounds

Pharmaceutically acceptable isotopic variations of the compounds disclosed herein are contemplated and can be synthesized using conventional methods known in the art or methods corresponding to those described in the Examples (substituting appropriate reagents with appropriate isotopic variations of those reagents). Specifically, an isotopic variation is a compound in which at least one atom is replaced by an atom having the same atomic number, but an atomic mass different from the atomic mass usually found in nature. Useful isotopes are known in the art and include, for example, isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, and chlorine. Exemplary isotopes thus include, *e.g.*, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl.

Isotopic variations (*e.g.*, isotopic variations containing ^{2}H) can provide therapeutic advantages resulting from greater metabolic stability, *e.g.*, increased *in vivo* half-life or reduced dosage requirements. In addition, certain isotopic variations (particularly those containing a radioactive isotope) can be used in drug or substrate tissue distribution studies. The radioactive isotopes tritium (^{3}H) and carbon-14 (^{14}C) are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Pharmaceutically acceptable solvates of the compounds disclosed herein are contemplated. A solvate can be generated, *e.g.*, by substituting a solvent used to crystallize a compound disclosed herein with an isotopic variation (*e.g.*, D_2O in place of H_2O, d_6-acetone in place of acetone, or d_6-DMSO in place of DMSO).

Pharmaceutically acceptable fluorinated variations of the compounds disclosed herein are contemplated and can be synthesized using conventional methods known in the art or methods corresponding to those described in the Examples (substituting appropriate reagents with appropriate fluorinated variations of those reagents). Specifically, a fluorinated variation is a compound in which at least one hydrogen atom is replaced by a fluoro atom. Fluorinated variations can provide therapeutic advantages resulting from greater metabolic stability, *e.g.*, increased *in vivo* half-life or reduced dosage requirements.

Definition of Terms

As used herein, the terms "comprising" and "including" are used in their open, non-limiting sense.

"Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation. An alkyl may comprise one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, or sixteen carbon atoms. In certain embodiments, an alkyl comprises one to fifteen carbon atoms (*e.g.*, C_1-C_{15} alkyl). In certain embodiments, an alkyl comprises one to thirteen carbon atoms (*e.g.*, C_1-C_{13} alkyl). In certain embodiments, an alkyl comprises one to eight carbon atoms (*e.g.*, C_1-C_8 alkyl). In other embodiments, an alkyl comprises five to fifteen carbon atoms (*e.g.*, C_5-C_{15} alkyl). In other embodiments, an alkyl comprises five to eight carbon atoms (*e.g.*, C_5-C_8 alkyl). The alkyl is attached to the rest of the molecule by a single bond, for example, methyl (Me), ethyl (Et), *n*-propyl, 1-methylethyl (*iso*-propyl), *n*-butyl, *n*-pentyl, 1,1-dimethylethyl (*t*-butyl), pentyl, 3-methylhexyl, 2-methylhexyl, and the like.

"Alkenyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one double bond. An alkenyl may comprise two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, or sixteen carbon atoms. In certain embodiments, an alkenyl comprises two to twelve carbon atoms (*e.g.*, C_2-C_{12} alkenyl). In certain embodiments, an alkenyl comprises two to eight carbon atoms (*e.g.*, C_2-C_8 alkenyl). In certain embodiments, an alkenyl comprises two to six carbon atoms

(*e.g.*, C_2-C_6 alkenyl). In other embodiments, an alkenyl comprises two to four carbon atoms (*e.g.*, C_2-C_4 alkenyl). The alkenyl is attached to the rest of the molecule by a single bond, for example, ethenyl (*i.e.*, vinyl), prop-1-enyl (*i.e.*, allyl), but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like.

The term "allyl," as used herein, means a $-CH_2CH=CH_2$ group.

As used herein, the term "alkynyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one triple bond. An alkynyl may comprise two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, or sixteen carbon atoms. In certain embodiments, an alkynyl comprises two to twelve carbon atoms (*e.g.*, C_2-C_{12} alkynyl). In certain embodiments, an alkynyl comprises two to eight carbon atoms (*e.g.*, C_2-C_8 alkynyl). In other embodiments, an alkynyl has two to six carbon atoms (*e.g.*, C_2-C_6 alkynyl). In other embodiments, an alkynyl has two to four carbon atoms (*e.g.*, C_2-C_4 alkynyl). The alkynyl is attached to the rest of the molecule by a single bond. Examples of such groups include, but are not limited to, ethynyl, propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 2-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, and the like.

The term " alkoxy", as used herein, means an alkyl group as defined herein witch is attached to the rest of the molecule via an oxygen atom. Examples of such groups include, but are not limited to, methoxy, ethoxy, n-propyloxy, iso-propyloxy, n-butoxy, iso-butoxy, tert-butoxy, pentyloxy, hexyloxy, and the like.

The term "aryl", as used herein, " refers to a radical derived from an aromatic monocyclic or multicyclic hydrocarbon ring system by removing a hydrogen atom from a ring carbon atom. The aromatic monocyclic or multicyclic hydrocarbon ring system contains only hydrogen and carbon atoms. An aryl may comprise from six to eighteen carbon atoms, where at least one of the rings in the ring system is fully unsaturated, *i.e.*, it contains a cyclic, delocalized (4n+2) π–electron system in accordance with the Hückel theory. In certain embodiments, an aryl comprises six to fourteen carbon atoms (C_6-C_{14} aryl). In certain embodiments, an aryl comprises six to ten carbon atoms (C_6-C_{10} aryl). Examples of such groups include, but are not limited to, phenyl, fluorenyl and naphthyl. The terms "Ph" and "phenyl," as used herein, mean a $-C_6H_5$ group.

The term "heteroaryl", refers to a radical derived from a 3- to 18-membered aromatic ring radical that comprises two to seventeen carbon atoms and from one to six heteroatoms selected from nitrogen, oxygen and sulfur. As used herein, the heteroaryl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, wherein at least one of the rings in the ring system is fully unsaturated, *i.e.*, it contains a cyclic, delocalized (4n+2) π–electron system in accordance with the Hückel theory. Heteroaryl includes fused or bridged ring systems. The heteroatom(s) in

the heteroaryl radical is optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heteroaryl is attached to the rest of the molecule through any atom of the ring(s). Examples of such groups include, but not limited to, pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl,pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, furopyridinyl, and the like. In certain embodiments, an heteroaryl is attached to the rest of the molecule via a ring carbon atom. In certain embodiments, an heteroaryl is attached to the rest of the molecule via a nitrogen atom (N-attached) or a carbon atom (C-attached). For instance, a group derived from pyrrole may be pyrrol-1-yl (N-attached) or pyrrol-3-yl (C-attached). Further, a group derived from imidazole may be imidazol-1-yl (N-attached) or imidazol-3-yl (C-attached).

The term "heterocyclyl", as used herein, means a non-aromatic, monocyclic, bicyclic, tricyclic, or tetracyclic radical having a total of from 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 atoms in its ring system, and containing from 3 to 12 carbon atoms and from 1 to 4 heteroatoms each independently selected from O, S and N, and with the proviso that the ring of said group does not contain two adjacent O atoms or two adjacent S atoms. A heterocyclyl group may include fused, bridged or spirocyclic ring systems. In certain embodiments, a hetercyclyl group comprises 3 to 10 ring atoms (3-10 membered heterocyclyl). In certain embodiments, a hetercyclyl group comprises 3 to 8 ring atoms (3-8 membered heterocyclyl). In certain embodiments, a hetercyclyl group comprises 4 to 8 ring atoms (4-8 membered heterocyclyl). In certain embodiments, a hetercyclyl group comprises 3 to 6 ring atoms (3-6 membered heterocyclyl). A heterocyclyl group may contain an oxo substituent at any available atom that will result in a stable compound. For example, such a group may contain an oxo atom at an available carbon or nitrogen atom. Such a group may contain more than one oxo substituent if chemically feasible. In addition, it is to be understood that when such a heterocyclyl group contains a sulfur atom, said sulfur atom may be oxidized with one or two oxygen atoms to afford either a sulfoxide or sulfone. An example of a 4 membered heterocyclyl group is azetidinyl (derived from azetidine). An example of a 5 membered cycloheteroalkyl group is pyrrolidinyl. An example of a 6 membered cycloheteroalkyl group is piperidinyl. An example of a 9 membered cycloheteroalkyl group is indolinyl. An example of a 10 membered cycloheteroalkyl group is 4H-quinolizinyl. Further examples of such heterocyclyl groups include, but are not limited to, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl,

tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4*H*-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3*H*-indolyl, quinolizinyl, 3-oxopiperazinyl, 4-methylpiperazinyl, 4-ethylpiperazinyl, and 1-oxo-2,8,diazaspiro[4.5]dec-8-yl. A heteroaryl group may be attached to the rest of molecular via a carbon atom (C-attached) or a nitrogen atom (N-attached). For instance, a group derived from piperazine may be piperazin-1-yl (N-attached) or piperazin-2-yl (C-attached).

The term " cycloalkyl" means a saturated, monocyclic, bicyclic, tricyclic, or tetracyclic radical having a total of from 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 carbon atoms in its ring system. A cycloalkyl may be fused, bridged or spirocyclic. In certain embodiments, a cycloalkyl comprises 3 to 8 carbon ring atoms (C_3-C_8 cycloalkyl). In certain embodiments, a cycloalkyl comprises 3 to 6 carbon ring atoms (C_3-C_6 cycloalkyl). Examples of such groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptyl, adamantyl, and the like.

The term “cycloalkylene” is a bidentate radical obtained by removing a hydrogen atom from a cycloalkyl ring as defined above. Examples of such groups include, but are not limited to, cyclopropylene, cyclobutylene, cyclopentylene, cyclopentenylene, cyclohexylene, cycloheptylene, and the like.

The term "spirocyclic" as used herein has its conventional meaning, that is, any ring system containing two or more rings wherein two of the rings have one ring carbon in common. Each ring of the spirocyclic ring system, as herein defined, independently comprises 3 to 20 ring atoms. Preferably, they have 3 to 10 ring atoms. Non-limiting examples of a spirocyclic system include spiro[3.3]heptane, spiro[3.4]octane, and spiro[4.5]decane.

The term cyano" refers to a -C≡N group.

An "aldehyde" group refers to a –C(O)H group.

An "alkoxy" group refers to both an –O-alkyl, as defined herein.

An "alkoxycarbonyl" refers to a -C(O)-alkoxy, as defined herein.

An "alkylaminoalkyl" group refers to an -alkyl-NR-alkyl group, as defined herein.

An "alkylsulfonyl" group refer to a -SO_2alkyl, as defined herein.

An "amino" group refers to an optionally substituted -NH_2.

An "aminoalkyl" group refers to an –alky-amino group, as defined herein.

An "aminocarbonyl" refers to a -C(O)-amino, as defined herein.

An "arylalkyl" group refers to -alkylaryl, where alkyl and aryl are defined herein.

An "aryloxy" group refers to both an –O-aryl and an –O-heteroaryl group, as defined herein.

An "aryloxycarbonyl" refers to -C(O)-aryloxy, as defined herein.

An "arylsulfonyl" group refers to a -SO_2aryl, as defined herein.

A "carbonyl" group refers to a -C(O)- group, as defined herein.

A "carboxylic acid" group refers to a –C(O)OH group.

A “cycloalkoxy” refers to a –O-cycloalkyl group, as defined herein.

A "halo" or "halogen" group refers to fluorine, chlorine, bromine or iodine.

A "haloalkyl" group refers to an alkyl group substituted with one or more halogen atoms.

A "hydroxy" group refers to an -OH group.

A "nitro" group refers to a -NO_2 group.

An “oxo” group refers to the =O substituent.

A "trihalomethyl" group refers to a methyl substituted with three halogen atoms.

The term “substituted,” means that the specified group or moiety bears one or more substituents independently selected from C_1-C_4 alkyl, aryl, heteroaryl, aryl-C_1-C_4 alkyl-, heteroaryl-C_1-C_4 alkyl-, C_1-C_4 haloalkyl, -OC_1-C_4 alkyl, -OC_1-C_4 alkylphenyl, -C_1-C_4 alkyl-OH, -OC_1-C_4 haloalkyl, halo, -OH, -NH_2, -C_1-C_4 alkyl-NH_2, -N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_4 alkylphenyl), -NH(C_1-C_4 alkylphenyl), cyano, nitro, oxo, -CO_2H, -C(O)OC_1-C_4 alkyl, -CON(C_1-C_4 alkyl)(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -$CONH_2$, -NHC(O)(C_1-C_4 alkyl), -NHC(O)(phenyl), -N(C_1-C_4 alkyl)C(O)(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)C(O)(phenyl), -C(O)C_1-C_4 alkyl, -C(O)C_1-C_4 alkylphenyl, -C(O)C_1-C_4 haloalkyl, -OC(O)C_1-C_4 alkyl, -SO_2(C_1-C_4 alkyl), -SO_2(phenyl), -SO_2(C_1-C_4 haloalkyl), -SO_2NH_2, -SO_2NH(C_1-C_4 alkyl), -SO_2NH(phenyl), -NHSO_2(C_1-C_4 alkyl), -NHSO_2(phenyl), and -NHSO_2(C_1-C_4 haloalkyl).

The term “optionally substituted” means that the specified group may be either unsubstituted or substituted by one or more substituents as defined herein. It is to be understood that in the compounds of the present invention when a group is said to be “unsubstituted,” or is “substituted” with fewer groups than would fill the valencies of all the atoms in the compound, the remaining valencies on such a group are filled by hydrogen. For example, if a C_6 aryl group, also called “phenyl” herein, is substituted with one additional substituent, one of ordinary skill in the

art would understand that such a group has 4 open positions left on carbon atoms of the C_6 aryl ring (6 initial positions, minus one at which the remainder of the compound of the present invention is attached to and an additional substituent, remaining 4 positions open). In such cases, the remaining 4 carbon atoms are each bound to one hydrogen atom to fill their valencies. Similarly, if a C_6 aryl group in the present compounds is said to be "disubstituted," one of ordinary skill in the art would understand it to mean that the C_6 aryl has 3 carbon atoms remaining that are unsubstituted. Those three unsubstituted carbon atoms are each bound to one hydrogen atom to fill their valencies.

"Pharmaceutically acceptable salt" includes both acid and base addition salts. A pharmaceutically acceptable salt of any one of the compounds described herein is intended to encompass any and all pharmaceutically suitable salt forms. Preferred pharmaceutically acceptable salts of the compounds described herein are pharmaceutically acceptable acid addition salts and pharmaceutically acceptable base addition salts.

"Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, hydroiodic acid, hydrofluoric acid, phosphorous acid, and the like. Also included are salts that are formed with organic acids such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and. aromatic sulfonic acids, etc. and include, for example, acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Exemplary salts thus include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, nitrates, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, trifluoroacetates, propionates, caprylates, isobutyrates, oxalates, malonates, succinate suberates, sebacates, fumarates, maleates, mandelates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, phthalates, benzenesulfonates, toluenesulfonates, phenylacetates, citrates, lactates, malates, tartrates, methanesulfonates, and the like. Also contemplated are salts of amino acids, such as arginates, gluconates, and galacturonates (see, for example, Berge S.M. et al., "Pharmaceutical Salts," *Journal of Pharmaceutical Science*, 66:1-19 (1997), which is hereby incorporated by reference in its entirety). Acid addition salts of basic

compounds may be prepared by contacting the free base forms with a sufficient amount of the desired acid to produce the salt according to methods and techniques with which a skilled artisan is familiar.

"Pharmaceutically acceptable base addition salt" refers to those salts that retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Pharmaceutically acceptable base addition salts may be formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Salts derived from inorganic bases include, but are not limited to, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, for example, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, diethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, *N,N*-dibenzylethylenediamine, chloroprocaine, hydrabamine, choline, betaine, ethylenediamine, ethylenedianiline, *N*-methylglucamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, *N*-ethylpiperidine, polyamine resins and the like. See Berge et al., *supra*.

Pharmaceutical Compositions

In some aspects, the compositions and methods described herein include the manufacture and use of pharmaceutical compositions and medicaments that include one or more compounds as disclosed herein. Also included are the pharmaceutical compositions themselves.

In some aspects, the compositions disclosed herein can include other compounds, drugs, or agents used for the treatment. For example, in some instances, pharmaceutical compositions disclosed herein can be combined with one or more (*e.g.*, one, two, three, four, five, or less than ten) compounds.

In some aspects, the pH of the compositions disclosed herein can be adjusted with pharmaceutically acceptable acids, bases, or buffers to enhance the stability of the compounds or its delivery form.

Pharmaceutical compositions typically include a pharmaceutically acceptable carrier, adjuvant, or vehicle. As used herein, the phrase "pharmaceutically acceptable" refers to molecular entities and compositions that are generally believed to be physiologically tolerable and do not typically produce an allergic or similar untoward reaction, such as gastric upset, dizziness and the

like, when administered to a human. A pharmaceutically acceptable carrier, adjuvant, or vehicle is a composition that can be administered to a patient, together with a compound of the invention, and which does not destroy the pharmacological activity thereof and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the compound. Exemplary conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles include saline, solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration.

In particular, pharmaceutically acceptable carriers, adjuvants, and vehicles that can be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as d-α-tocopherol polyethylene glycol 1000 succinate, surfactants used in pharmaceutical dosage forms such as Tweens or other similar polymeric delivery matrices, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat. Cyclodextrins such as α-, β-, and γ-cyclodextrin, may also be advantageously used to enhance delivery of compounds of the formulae described herein.

As used herein, the compounds disclosed herein are defined to include pharmaceutically acceptable derivatives or prodrugs thereof. A "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, solvate, or prodrug, *e.g.*, carbamate, ester, phosphate ester, salt of an ester, or other derivative of a compound or agent disclosed herein, which upon administration to a recipient is capable of providing (directly or indirectly) a compound described herein, or an active metabolite or residue thereof. Particularly favored derivatives and prodrugs are those that increase the bioavailability of the compounds disclosed herein when such compounds are administered to a mammal (*e.g.*, by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to a biological compartment (*e.g.*, the brain or lymphatic system) relative to the parent species. Preferred prodrugs include derivatives where a group that enhances aqueous solubility or active transport through the gut membrane is appended to the structure of formulae described herein. Such derivatives are recognizable to those skilled in the art without undue experimentation. Nevertheless, reference is

made to the teaching of Burger's Medicinal Chemistry and Drug Discovery, 5th Edition, Vol. 1: Principles and Practice, which is incorporated herein by reference to the extent of teaching such derivatives.

The compounds disclosed herein include pure enantiomers, mixtures of enantiomers, pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixtures of diastereoisomeric racemates and the meso-form and pharmaceutically acceptable salts, solvent complexes, morphological forms, or deuterated derivative thereof.

In particular, pharmaceutically acceptable salts of the compounds disclosed herein include, *e.g.*, those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acid salts include acetate, adipate, benzoate, benzenesulfonate, butyrate, citrate, digluconate, dodecylsulfate, formate, fumarate, glycolate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, lactate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, palmoate, phosphate, picrate, pivalate, propionate, salicylate, succinate, sulfate, tartrate, tosylate, trifluoromethylsulfonate, and undecanoate. Salts derived from appropriate bases include, *e.g.*, alkali metal (*e.g.*, sodium), alkaline earth metal (*e.g.*, magnesium), ammonium salts. The invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersible products can be obtained by such quaternization.

In some aspects, the pharmaceutical compositions disclosed herein can include an effective amount of one or more compounds. The terms "effective amount" and "effective to treat," as used herein, refer to an amount or a concentration of one or more compounds or a pharmaceutical composition described herein utilized for a period of time (including acute or chronic administration and periodic or continuous administration) that is effective within the context of its administration for causing an intended effect or physiological outcome. In some aspects, pharmaceutical compositions can further include one or more additional compounds, drugs, or agents used for the treatment in amounts effective for causing an intended effect or physiological outcome.

In some aspects, the pharmaceutical compositions disclosed herein can be formulated for sale in the United States, import into the United States, or export from the United States.

Administration of Pharmaceutical Compositions

The pharmaceutical compositions disclosed herein can be formulated or adapted for administration to a subject via any route, *e.g.*, any route approved by the Food and Drug

Administration (FDA). Exemplary methods are described in the FDA Data Standards Manual (DSM) (available at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/DataStandardsManualmonographs). In particular, the pharmaceutical compositions can be formulated for and administered via oral, parenteral, or transdermal delivery. The term "parenteral" as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraperitoneal, intra-articular, intra-arterial, intrasynovial, intrasternal, intrathecal, intralesional, and intracranial injection or infusion techniques.

For example, the pharmaceutical compositions disclosed herein can be administered, *e.g.*, topically, rectally, nasally (*e.g.*, by inhalation spray or nebulizer), buccally, vaginally, subdermally (*e.g.*, by injection or via an implanted reservoir), or ophthalmically.

For example, pharmaceutical compositions of this invention can be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, emulsions and aqueous suspensions, dispersions and solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions or emulsions are administered orally, the active ingredient may be suspended or dissolved in an oily phase is combined with emulsifying or suspending agents. If desired, certain sweetening, flavoring, or coloring agents can be added.

For example, the pharmaceutical compositions of this invention can be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax, and polyethylene glycols.

For example, the pharmaceutical compositions of this invention can be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and can be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, or other solubilizing or dispersing agents known in the art.

For example, the pharmaceutical compositions of this invention can be administered by injection (*e.g.*, as a solution or powder). Such compositions can be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example,

Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, *e.g.*, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil can be employed, including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, *e.g.*, olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions can also contain a long-chain alcohol diluent or dispersant, or carboxymethyl cellulose or similar dispersing agents which are commonly used in the formulation of pharmaceutically acceptable dosage forms such as emulsions and or suspensions. Other commonly used surfactants such as Tweens, Spans, or other similar emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms can also be used for the purposes of formulation.

In some aspects, an effective dose of a pharmaceutical composition of this invention can include, but is not limited to, *e.g.*, about 0.00001, 0.0001, 0.001, 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.15, 0.2, 0.25, 0.3, 0.35, 0.4, 0.45, 0.5, 0.55, 0.6, 0.65, 0.7, 0.75, 0.8, 0.85, 0.9, 0.95, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 2500, 5000, or 10000 mg/kg/day, or according to the requirements of the particular pharmaceutical composition.

When the pharmaceutical compositions disclosed herein include a combination of a compound of the formulae described herein and one or more additional compounds (*e.g.*, one or more additional compounds, drugs, or agents used for the treatment of Alzeimers Disease (AD) or any other age related condition or disease, including conditions or diseases known to be associated with or caused by AD), both the compound and the additional compound should be present at dosage levels of between about 1 to 100%, and more preferably between about 5 to 95% of the dosage normally administered in a monotherapy regimen. The additional agents can be administered separately, as part of a multiple dose regimen, from the compounds of this invention. Alternatively, those agents can be part of a single dosage form, mixed together with the compounds of this invention in a single composition.

In some aspects, the pharmaceutical compositions disclosed herein can be included in a container, pack, or dispenser together with instructions for administration.

Methods of Treatment

The methods disclosed herein contemplate administration of an effective amount of a compound or composition to achieve the desired or stated effect. Typically, the compounds or compositions of the invention will be administered from about 1 to about 6 times per day or, alternately or in addition, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that can be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Alternatively, such preparations can contain from about 20% to about 80% active compound.

In some aspects, the present disclosure provides methods for using a composition comprising a compound, including pharmaceutical compositions (indicated below as 'X') disclosed herein in the following methods:

Substance X for use as a medicament in the treatment of one or more diseases or conditions disclosed herein. Use of substance X for the manufacture of a medicament for the treatment of Y; and substance X for use in the treatment of Y.

In some aspects, the methods disclosed include the administration of a therapeutically effective amount of one or more of the compounds or compositions described herein to a subject (*e.g.*, a mammalian subject, *e.g.*, a human subject) who is in need of, or who has been determined to be in need of, such treatment. In some aspects, the methods disclosed include selecting a subject and administering to the subject an effective amount of one or more of the compounds or compositions described herein, and optionally repeating administration as required for the prevention or treatment of AD or age related diseases.

In some aspects, subject selection can include obtaining a sample from a subject (*e.g.*, a candidate subject) and testing the sample for an indication that the subject is suitable for selection. In some aspects, the subject can be confirmed or identified, *e.g.* by a health care professional, as having had or having a condition or disease. In some aspects, suitable subjects include, for example, subjects who have or had a condition or disease but that resolved the disease or an aspect thereof, present reduced symptoms of disease (*e.g.*, relative to other subjects (*e.g.*, the majority of subjects) with the same condition or disease), or that survive for extended periods of time with the condition or disease (*e.g.*, relative to other subjects (*e.g.*, the majority of subjects) with the same condition or disease), *e.g.*, in an asymptomatic state (*e.g.*, relative to other subjects (*e.g.*, the majority of subjects) with the same condition or disease). In some aspects, exhibition of a positive

immune response towards a condition or disease can be made from patient records, family history, or detecting an indication of a positive immune response. In some aspects, multiple parties can be included in subject selection. For example, a first party can obtain a sample from a candidate subject and a second party can test the sample. In some aspects, subjects can be selected or referred by a medical practitioner (*e.g.*, a general practitioner). In some aspects, subject selection can include obtaining a sample from a selected subject and storing the sample or using the in the methods disclosed herein. Samples can include, *e.g.*, cells or populations of cells.

In some aspects, methods of treatment can include a single administration, multiple administrations, and repeating administration of one or more compounds disclosed herein as required for the prevention or treatment of the disease or condition from which the subject is suffering. In some aspects, methods of treatment can include assessing a level of disease in the subject prior to treatment, during treatment, or after treatment. In some aspects, treatment can continue until a decrease in the level of disease in the subject is detected.

The term "subject," as used herein, refers to any animal. In some instances, the subject is a mammal. In some instances, the term "subject," as used herein, refers to a human (*e.g.*, a man, a woman, or a child).

The terms "administer," "administering," or "administration," as used herein, refer to implanting, ingesting, injecting, inhaling, or otherwise absorbing a compound or composition, regardless of form. For example, the methods disclosed herein include administration of an effective amount of a compound or composition to achieve the desired or stated effect.

The terms "treat", "treating," or "treatment," as used herein, refer to partially or completely alleviating, inhibiting, ameliorating, or relieving the disease or condition from which the subject is suffering. This means any manner in which one or more of the symptoms of a disease or disorder are ameliorated or otherwise beneficially altered. As used herein, amelioration of the symptoms of a particular disorder refers to any lessening, whether permanent or temporary, lasting or transient that can be attributed to or associated with treatment by the compositions and methods of the present invention.

The terms "prevent," "preventing," and "prevention," as used herein, shall refer to a decrease in the occurrence of a disease or decrease in the risk of acquiring a disease or its associated symptoms in a subject. The prevention may be complete, *e.g.*, the total absence of disease or pathological cells in a subject. The prevention may also be partial, such that the occurrence of the disease or pathological cells in a subject is less than, occurs later than, or develops more slowly than that which would have occurred without the present invention.

As used herein, the term "preventing a disease" in a subject means for example, to stop the development of one or more symptoms of a disease in a subject before they occur or are detectable, *e.g.*, by the patient or the patient's doctor. Preferably, the disease does not develop at all, i.e., no symptoms of the disease are detectable. However, it can also mean delaying or slowing of the development of one or more symptoms of the disease. Alternatively, or in addition, it can mean decreasing the severity of one or more subsequently developed symptoms.

Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the disease, condition or symptoms, the patient's disposition to the disease, condition or symptoms, and the judgment of the treating physician.

An effective amount can be administered in one or more administrations, applications or dosages. A therapeutically effective amount of a therapeutic compound (i.e., an effective dosage) depends on the therapeutic compounds selected. Moreover, treatment of a subject with a therapeutically effective amount of the compounds or compositions described herein can include a single treatment or a series of treatments. For example, effective amounts can be administered at least once. The compositions can be administered one from one or more times per day to one or more times per week; including once every other day. The skilled artisan will appreciate that certain factors can influence the dosage and timing required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health or age of the subject, and other diseases present.

Following administration, the subject can be evaluated to detect, assess, or determine their level of disease. In some instances, treatment can continue until a change (*e.g.*, reduction) in the level of disease in the subject is detected. Upon improvement of a patient's condition (*e.g.*, a change (*e.g.*, decrease) in the level of disease in the subject), a maintenance dose of a compound, or composition disclosed herein can be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, can be reduced, *e.g.*, as a function of the symptoms, to a level at which the improved condition is retained. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

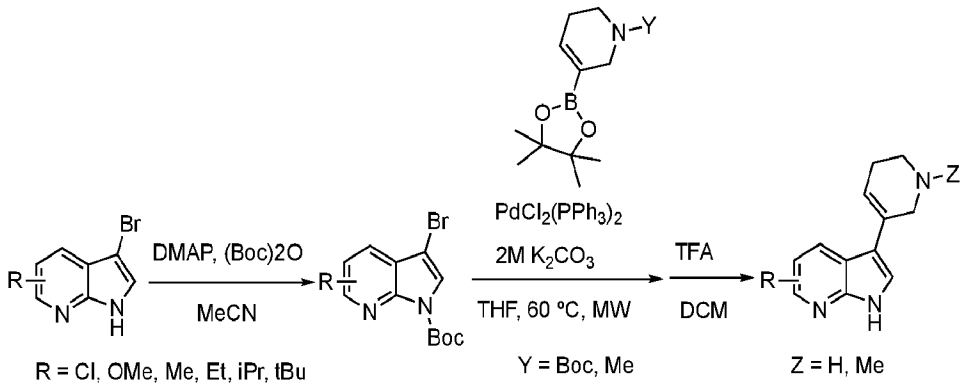
EXAMPLES

The following Examples describe the synthesis of exemplary 5HT2A agonist compounds according to the present invention.

Synthetic procedures and characterization data

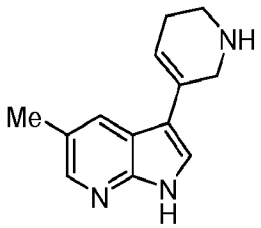
Prep-HPLC was used in the final product purifications unless otherwise noted.

Method A:



Example 1

Synthesis of NS131-179



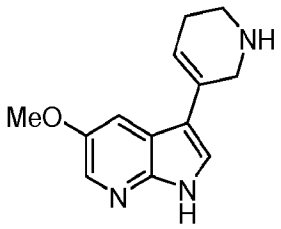
5-methyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine (NS131-179).

NS131-179 was synthesized following the method A. To a solution of 3-bromo-5-methyl-1H-pyrrolo[2,3-b]pyridine (211 mg, 1 mmol, 1 equiv) in MeCN (4 mL) were added DMAP (147 mg, 1.2 mmol, 1.2 equiv), $(Boc)_2O$ (240 mg, 1.1 mmol, 1.1 equiv). After being stirred for 2 h at room temperature, the resulting mixture was purified by silica gel (10% ethyl acetate in hexane) to afford tert-butyl 3-bromo-5-methyl-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (295 mg, 95%, yellow solid) as an intermediate, then to a solution of the intermediate (31.1 mg, 0.1 mmol, 1 equiv) in THF (1 mL) were added tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (31 mg, 0.1 mmol, 1 equiv), 2M K_2CO_3 solution (0.15 mL, 0.3 mmol, 3 equiv), $Pd(PPh_3)_2Cl_2$ (7.0 mg, 0.01 mmol, 0.1 equiv), and the atmosphere evacuated and backfilled with nitrogen three times. After being stirred for 1 h at 60 °C by microwave, the resulting mixture was purified by preparative HPLC (10%-100% acetonitrile / 0.1% TFA in H_2O) to get the crude compound, then added 0.5 mL DCM and 0.5 mL TFA, stirred for 2 h at rt, evaporated and the resulting mixture was purified by preparative HPLC (10%-100% acetonitrile / 0.1% TFA in

H_2O) to give NS131-179 as a white solid (24 mg, 55%). ^1H NMR (600 MHz, Methanol-d_4) δ 8.54 – 8.50 (m, 1H), 8.26 – 8.22 (m, 1H), 7.65 (s, 1H), 6.53-6.48 (m, 1H), 4.09 (q, J = 2.1 Hz, 2H), 3.43 (t, J = 6.2 Hz, 2H), 2.69-2.63 (m, 2H), 2.55 (s, 3H). LRMS (ESI) m/z: calcd for $C_{13}H_{16}N_3^+$ [M + H]$^+$, 214.13; found, 214.21.

Example 2

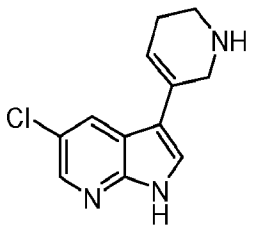
Synthesis of NS131-178



5-methoxy-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine (NS131-178). NS131-178 was synthesized following the standard procedure for preparing NS131-179 from 3-bromo-5-methoxy-1H-pyrrolo[2,3-b]pyridine and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 23.4 mg, 51%) ^1H NMR (600 MHz, Methanol-d_4) δ 8.07 (s, 1H), 7.94 (d, J = 2.5 Hz, 1H), 7.54 (s, 1H), 6.40 (tt, J = 4.1, 1.8 Hz, 1H), 4.08 (q, J = 2.1 Hz, 2H), 3.93 (s, 3H), 3.42 (t, J = 6.2 Hz, 2H), 2.69-2.63 (m, 2H). LRMS (ESI) m/z: calcd for $C_{13}H_{16}N_3O^-$ [M + H]$^+$, 230.13; found, 230.11.

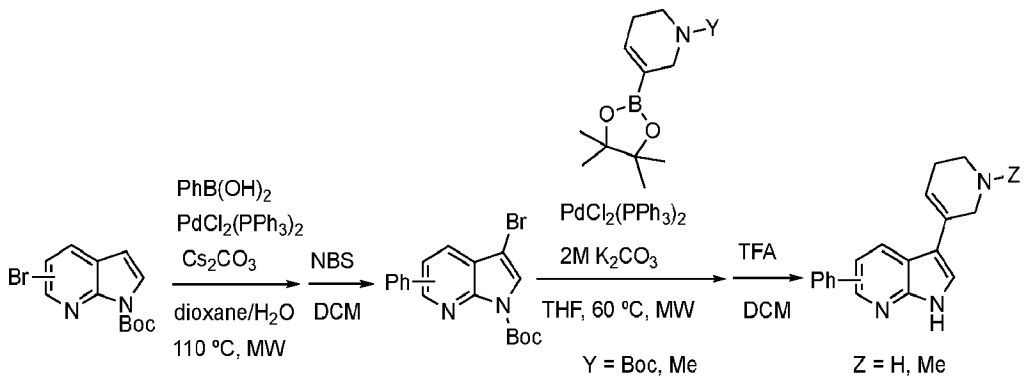
Example 3

Synthesis of NS131-177



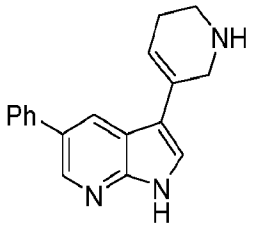
5-chloro-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine (NS131-177). NS131-177 was synthesized following the standard procedure for preparing NS131-179 from 3-bromo-5-chloro-1H-pyrrolo[2,3-b]pyridine and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 9.0 mg, 49%) ^1H NMR (600 MHz, Methanol-d_4) δ 8.26 (d, J = 2.2 Hz, 1H), 8.23 (d, J = 2.2 Hz, 1H), 7.57 (s, 1H), 6.40 (tt, J = 4.1, 1.8 Hz, 1H), 4.07 (q, J = 2.1 Hz, 2H), 3.42 (t, J = 6.2 Hz, 2H), 2.67-2.64 (m, 2H). LRMS (ESI) m/z: calcd for $C_{12}H_{13}N_3Cl^+$ [M + H]$^+$, 234.08; found, 234.19.

Method B:



Example 4

Synthesis of NS136-006

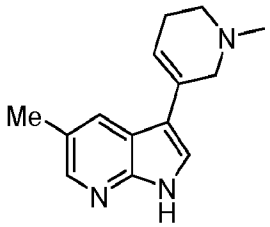


5-phenyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine (NS136-006). NS136-006 was synthesized following the method B. To a solution of tert-butyl 5-bromo-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (297 mg, 1 mmol, 1 equiv) in dioxane (5 mL) and water (0.5 mL) were added $PhB(OH)_2$ (146 mg, 1.2 mmol, 1.2 equiv), $Pd(PPh_3)_2Cl_2$ (7 mg, 0.01 mmol, 0.01 equiv), Cs_2CO_3 (651.6 mg, 2 mmol, 2 equiv). After being stirred for 2 h at 110 °C by microwave, the resulting mixture was purified by silica gel (10% to 20% ethyl acetate in hexane) to afford tert-butyl 5-phenyl-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (230 mg, 78%, yellow solid). Then to a solution of tert-butyl 5-phenyl-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (58.8 mg, 0.2 mmol, 1 equiv) in DCM (2 mL) was added NBS (28 mg, 0.22 mmol, 1.1 equiv), after being stirred for 2 h at rt, the resulting mixture was purified by silica gel (20% ethyl acetate in hexane) to afford the bromo-substituted compound (71.7 mg, 96%) as an intermediate, then follow the same procedure with NS131-179, to a solution of the last step intermediate (37.3 mg, 0.1 mmol, 1 equiv) in THF (1 mL) were added tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (31 mg, 0.1 mmol, 1 equiv), 2M K_2CO_3 solution (0.15 mL, 0.3 mmol, 3 equiv), $Pd(PPh_3)_2Cl_2$ (7.0 mg, 0.01 mmol, 0.1 equiv), and the atmosphere evacuated and backfilled with nitrogen three times. After being stirred for 1 h at 60 °C by microwave, the resulting

mixture was purified by preparative HPLC (10%-100% acetonitrile / 0.1% TFA in H_2O) to get the crude compound, then added 0.5 mL DCM and 0.5 mL TFA, stirred for 2 h at rt, evaporated and the resulting mixture was purified by preparative HPLC (10%-100% acetonitrile / 0.1% TFA in H_2O) to give NS136-006 as a white solid (9.3 mg, 18%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.52 (s, 1H), 8.46 (s, 1H), 7.68 (d, J = 7.6 Hz, 2H), 7.57 (s, 1H), 7.50 (t, J = 7.6 Hz, 2H), 7.41 – 7.36 (m, 1H), 6.51 (s, 1H), 4.12 (d, J = 2.4 Hz, 2H), 3.43 (t, J = 6.2 Hz, 2H), 2.73 – 2.64 (m, 2H). LRMS (ESI) m/z: calcd for $C_{18}H_{18}N_3^-$ $[M + H]^+$, 276.15; found, 276.27.

Example 5

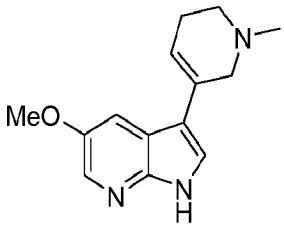
Synthesis of NS131-169



5-methyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine (NS131-169). NS131-169 was synthesized following the standard procedure for preparing NS131-179 from 3-bromo-5-methyl-1H-pyrrolo[2,3-b]pyridine and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine. (white solid, 14 mg, 34%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.38 (t, J = 1.4 Hz, 1H), 8.20 (s, 1H), 7.59 (s, 1H), 6.47 (dt, J = 4.2, 2.1 Hz, 1H), 4.35 (d, J = 15.8 Hz, 1H), 4.02 (d, J = 15.8 Hz, 1H), 3.67 (s, 1H), 3.07 (s, 3H), 2.78 (s, 1H), 2.72-2.67 (m, 1H), 2.52 (s, 3H). LRMS (ESI) m/z: calcd for $C_{14}H_{18}N_3^+$ $[M + H]^+$, 228.15; found, 228.04.

Example 6

Synthesis of NS131-168

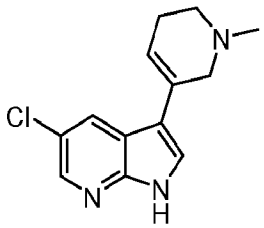


5-methoxy-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine (NS131-168). NS131-168 was synthesized following the standard procedure for preparing NS131-179 from 3-bromo-5-methoxy-1H-pyrrolo[2,3-b]pyridine and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine. (white solid, 17.4 mg, 41%) ^{1}H NMR (600 MHz,

Methanol-d_4) δ 8.03 (d, J = 2.6 Hz, 1H), 7.82 (d, J = 2.6 Hz, 1H), 7.50 (s, 1H), 6.40 – 6.37 (m, 1H), 4.34 (d, J = 15.7 Hz, 1H), 4.00 (d, J = 15.9 Hz, 1H), 3.92 (s, 3H), 3.66 (dd, J = 12.3, 6.1 Hz, 1H), 3.34 (s, 1H), 3.07 (s, 3H), 2.78 (d, J = 8.7 Hz, 1H), 2.69 (d, J = 19.2 Hz, 1H). LRMS (ESI) m/z: calcd for $C_{14}H_{18}N_3O^+$ [M + H]$^+$, 244.14; found, 244.15.

Example 7

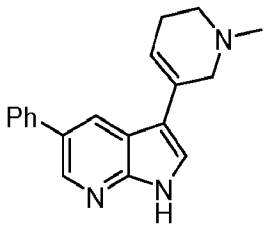
Synthesis of NS131-167



5-chloro-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine (NS131-167). NS131-167 was synthesized following the standard procedure for preparing NS131-179 from 3-bromo-5-chloro-1H-pyrrolo[2,3-b]pyridine and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine. (white solid, 16.3 mg, 38%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.27 (d, J = 2.2 Hz, 1H), 8.23 (d, J = 2.3 Hz, 1H), 7.58 (s, 1H), 6.38 (dq, J = 4.2, 1.8 Hz, 1H), 4.34 (d, J = 15.7 Hz, 1H), 4.03 – 3.97 (m, 1H), 3.66 (dd, J = 12.1, 5.9 Hz, 1H), 3.30 – 3.27 (m, 1H), 3.07 (s, 3H), 2.82 – 2.74 (m, 1H), 2.68 (d, J = 19.1 Hz, 1H). LRMS (ESI) m/z: calcd for $C_{13}H_{15}N_3Cl^+$ [M + H]$^+$, 248.09; found, 248.19.

Example 8

Synthesis of NS131-173

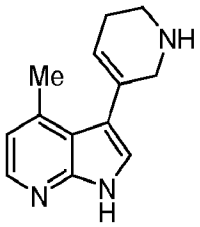


3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-5-phenyl-1H-pyrrolo[2,3-b]pyridine (NS131-173). NS131-173 was synthesized following the standard procedure for preparing NS136-006 from tert-butyl 5-bromo-1H-pyrrolo[2,3-b]pyridine-1-carboxylate and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine. (white solid, 20.3 mg, 39%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.55 – 8.52 (m, 1H), 8.50 (d, J = 2.0 Hz, 1H), 7.71 – 7.67 (m, 2H), 7.61 (s, 1H), 7.50 (t, J = 7.8 Hz, 2H), 7.42 – 7.38 (m, 1H), 6.51 (dt, J = 4.2, 2.0 Hz, 1H), 4.39

(d, J = 15.8 Hz, 1H), 4.05 (d, J = 15.8 Hz, 1H), 3.70-3.65 (m, 1H), 3.36 – 3.33 (m, 1H), 3.08 (s, 3H), 2.79 (d, J = 7.0 Hz, 1H), 2.71 (d, J = 19.0 Hz, 1H). LRMS (ESI) m/z: calcd for $C_{19}H_{20}N_3^+$ [M + H]$^+$, 290.17; found, 290.24.

Example 9

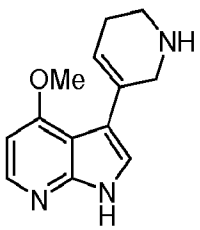
Synthesis of NS131-180



4-methyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine (NS131-180). NS131-180 was synthesized following the standard procedure for preparing NS131-179 from 3-bromo-4-methyl-1H-pyrrolo[2,3-b]pyridine and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 12.8 mg, 29%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.30 (s, 1H), 7.62 (s, 1H), 7.37 (d, J = 5.9 Hz, 1H), 6.12 (tt, J = 3.9, 1.9 Hz, 1H), 3.97 (q, J = 2.3 Hz, 2H), 3.44 (t, J = 6.2 Hz, 2H), 2.83 (s, 3H), 2.66-2.62 (m, 2H). LRMS (ESI) m/z: calcd for $C_{13}H_{16}N_3^-$ [M + H]$^+$, 214.13; found, 214.25.

Example 10

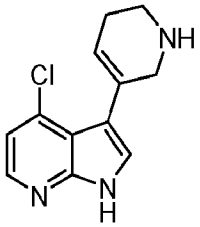
Synthesis of RS134-52



4-methoxy-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine (RS134-52). **RS134-52** was synthesized following the standard procedure for preparing NS131-179 from 3-bromo-4-methoxy-1H-pyrrolo[2,3-b]pyridine and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 16.5 mg, 36%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.36 (d, J = 6.8 Hz, 1H), 7.47 (s, 1H), 7.17 (d, J = 6.8 Hz, 1H), 6.18 (tt, J = 3.9, 1.8 Hz, 1H), 4.24 (s, 3H), 4.06 (q, J = 2.2 Hz, 2H), 3.41 (t, J = 6.3 Hz, 2H), 2.62-2.59 (m, 2H). LRMS (ESI) m/z: calcd for $C_{13}H_{16}N_3O^+$ [M + H]$^+$, 230.13; found, 230.32.

Example 11

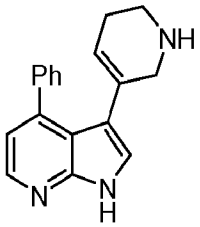
Synthesis of RS134-48



4-chloro-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine (RS134-48). RS134-48 was synthesized following the standard procedure for preparing NS131-179 from 3-bromo-4-chloro-1H-pyrrolo[2,3-b]pyridine and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 10.2 mg, 22%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.17 (dd, J = 5.4, 2.8 Hz, 1H), 7.46 (d, J = 4.5 Hz, 1H), 7.21 (t, J = 5.3 Hz, 1H), 6.07 (tt, J = 3.9, 1.9 Hz, 1H), 4.02 (q, J = 2.2 Hz, 2H), 3.41 (t, J = 6.2 Hz, 2H), 2.62-2.58 (m, 2H). LRMS (ESI) m/z: calcd for $C_{12}H_{13}N_3Cl^+$ [M + H]$^+$, 234.08; found, 234.35.

Example 12

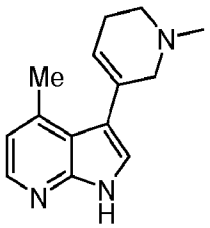
Synthesis of NS131-185



4-phenyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine (NS131-185). NS131-185 was synthesized following the standard procedure for preparing NS136-006 from tert-butyl 4-bromo-1H-pyrrolo[2,3-b]pyridine-1-carboxylate and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 11.6 mg, 23%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.47 – 8.42 (m, 1H), 7.68 (s, 1H), 7.58 (dt, J = 5.1, 2.2 Hz, 3H), 7.56 – 7.52 (m, 2H), 7.41 (d, J = 5.6 Hz, 1H), 5.48 (tt, J = 4.0, 1.9 Hz, 1H), 3.38 (q, J = 2.3 Hz, 2H), 3.04 (t, J = 6.2 Hz, 2H), 2.19-2.15 (m, 2H). LRMS (ESI) m/z: calcd for $C_{18}H_{18}N_3^+$ [M + H]$^+$, 276.15; found, 276.29.

Example 13

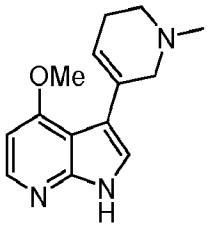
Synthesis of NS131-170



4-methyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine (NS131-170). NS131-170 was synthesized following the standard procedure for preparing NS131-179 from 3-bromo-4-methyl-1H-pyrrolo[2,3-b]pyridine and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine. (white solid, 10.3 mg, 25%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.21 (d, J = 5.5 Hz, 1H), 7.51 (s, 1H), 7.19 (d, J = 5.5 Hz, 1H), 6.09 (dq, J = 4.0, 2.0 Hz, 1H), 4.17 (d, J = 16.3 Hz, 1H), 3.94 (d, J = 16.4 Hz, 1H), 3.67 (s, 1H), 3.06 (s, 3H), 2.74 (s, 4H), 2.65 (d, J = 22.0 Hz, 1H). LRMS (ESI) m/z: calcd for $C_{14}H_{18}N_3^+$ $[M+H]^+$, 228.15; found, 228.08.

Example 14

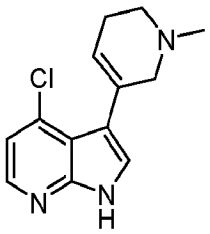
Synthesis of RS134-45



4-methoxy-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine (RS134-45). RS134-45 was synthesized following the standard procedure for preparing NS131-179 from 3-bromo-4-methoxy-1H-pyrrolo[2,3-b]pyridine and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine. (white solid, 14.6 mg, 31%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.37 (d, J = 6.9 Hz, 1H), 7.49 (s, 1H), 7.19 (d, J = 6.8 Hz, 1H), 6.20 (tt, J = 3.8, 1.8 Hz, 1H), 4.31 – 4.26 (m, 1H), 4.25 (s, 3H), 4.00 – 3.93 (m, 1H), 3.65 (t, J = 9.8 Hz, 1H), 3.33 (d, J = 11.4 Hz, 1H), 3.06 (s, 3H), 2.79 – 2.70 (m, 1H), 2.63 (d, J = 19.3 Hz, 1H). LRMS (ESI) m/z: calcd for $C_{14}H_{18}N_3O^+$ $[M+H]^+$, 244.14; found, 244.22.

Example 15

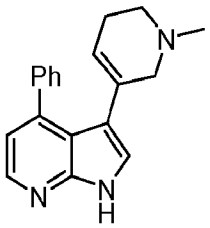
Synthesis of RS134-40



4-chloro-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine (RS134-40). RS134-40 was synthesized following the standard procedure for preparing NS131-179 from 3-bromo-4-chloro-1H-pyrrolo[2,3-b]pyridine and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine. (white solid, 12.4 mg, 26%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.21 (d, J = 5.4 Hz, 1H), 7.52 (d, J = 2.0 Hz, 1H), 7.26 (dd, J = 5.5, 2.3 Hz, 1H), 6.07 (tt, J = 3.8, 1.9 Hz, 1H), 4.23 (d, J = 16.2 Hz, 1H), 3.95 (dq, J = 16.2, 2.6 Hz, 1H), 3.69 – 3.62 (m, 1H), 3.35 – 3.31 (m, 1H), 3.05 (s, 3H), 2.78-2.71 (m, 1H), 2.67 – 2.58 (m, 1H). LRMS (ESI) m/z: calcd for $C_{13}H_{15}N_3Cl^+$ $[M + H]^+$, 248.09; found, 248.22.

Example 16

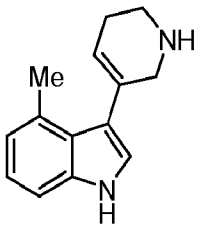
Synthesis of NS131-184



3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-4-phenyl-1H-pyrrolo[2,3-b]pyridine (NS131-184). NS131-184 was synthesized following the standard procedure for preparing NS136-006 from tert-butyl 4-bromo-1H-pyrrolo[2,3-b]pyridine-1-carboxylate and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine. (white solid, 12.5 mg, 24%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.44 (d, J = 5.6 Hz, 1H), 7.70 (s, 1H), 7.58 (dq, J = 4.6, 2.8, 2.2 Hz, 3H), 7.53 (dt, J = 6.8, 2.2 Hz, 2H), 7.40 (d, J = 5.6 Hz, 1H), 5.37 (tt, J = 3.9, 1.9 Hz, 1H), 3.86 (d, J = 16.2 Hz, 1H), 3.39 (s, 1H), 3.21 (d, J = 16.0 Hz, 1H), 2.86 (t, J = 5.6 Hz, 1H), 2.81 (s, 3H), 2.36 (d, J = 11.8 Hz, 1H), 2.09 – 1.99 (m, 1H). LRMS (ESI) m/z: calcd for $C_{19}H_{20}N_3^+$ $[M + H]^+$, 290.17; found, 290.29.

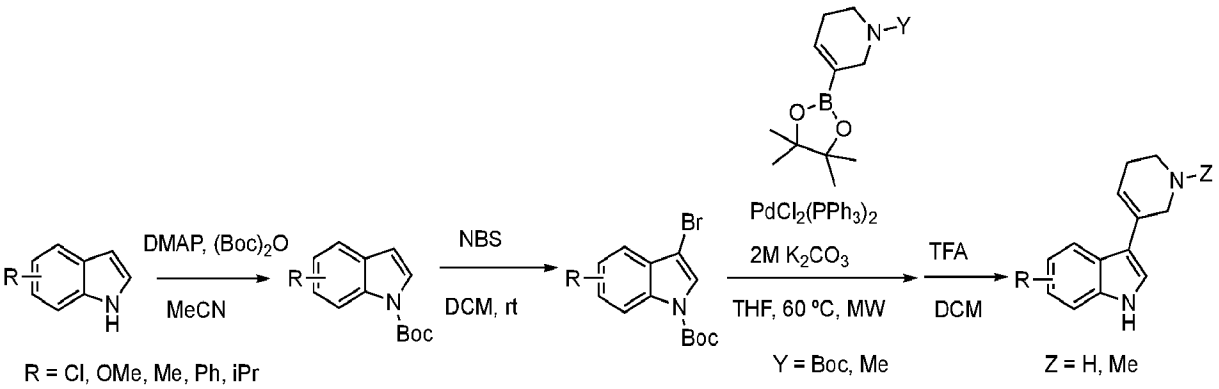
Example 17

Synthesis of RS134-49



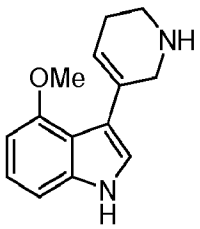
4-methyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (RS134-49). RS134-49 was synthesized following the standard procedure for preparing NS131-179 from tert-butyl 3-bromo-4-methyl-1H-indole-1-carboxylate and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 6.9 mg, 21%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.21 (d, J = 8.2 Hz, 1H), 7.15 (s, 1H), 7.01 (dd, J = 8.2, 7.1 Hz, 1H), 6.80 (dt, J = 7.1, 0.9 Hz, 1H), 5.93 (tt, J = 3.7, 1.8 Hz, 1H), 3.91 (q, J = 2.2 Hz, 2H), 3.39 (t, J = 6.2 Hz, 2H), 2.61 – 2.53 (m, 5H). LRMS (ESI) m/z: calcd for $C_{14}H_{17}N_2^+$ $[M + H]^+$, 213.14; found, 213.43.

METHOD C:



Example 18

Synthesis of RS134-53

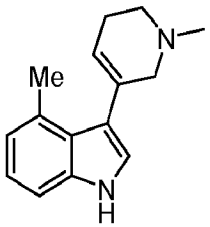


4-methoxy-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (RS134-53). RS134-53 was synthesized following the method C. To a solution of 4-methoxy-1H-indole (147 mg, 1 mmol, 1 equiv) in MeCN (4 mL) were added DMAP (147 mg, 1.2 mmol, 1.2 equiv), $(Boc)_2O$ (240 mg, 1.1 mmol, 1.1 equiv). After being stirred for 2 h at room temperature, the resulting mixture was purified by silica gel (10% ethyl acetate in hexane) to afford tert-butyl 4-methoxy-1H-indole-1-

carboxylate (240 mg, 97%, yellow solid). Then to a solution of tert-butyl 5-phenyl-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (240 mg, 1 mmol, 1 equiv) in DCM (3 mL) was added NBS (195.8 mg, 1.1 mmol, 1.1 equiv), after being stirred for 1 h at rt, the resulting mixture was purified by silica gel (10% ethyl acetate in hexane) to afford the bromo-substituted compound (163 mg, 50%) as an intermediate, then follow the same procedure with NS131-179, to a solution of the last step intermediate (32.6 mg, 0.1 mmol, 1 equiv) in THF (1 mL) were added tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (31 mg, 0.1 mmol, 1 equiv), 2M K_2CO_3 solution (0.15 mL, 0.3 mmol, 3 equiv), $Pd(PPh_3)_2Cl_2$ (7.0 mg, 0.01 mmol, 0.1 equiv), and the atmosphere evacuated and backfilled with nitrogen three times. After being stirred for 1 h at 60 °C by microwave, the resulting mixture was purified by preparative HPLC (10%-100% acetonitrile / 0.1% TFA in H_2O) to get the crude compound, then added 0.5 mL DCM and 0.5 mL TFA, stirred for 2 h at rt, evaporated and the resulting mixture was purified by preparative HPLC (10%-100% acetonitrile / 0.1% TFA in H_2O) to give **RS134-53** as a white solid (12 mg, 35%). ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.11 (s, 1H), 7.06 (t, J = 7.9 Hz, 1H), 7.00 (dd, J = 8.1, 0.7 Hz, 1H), 6.55 (d, J = 7.7 Hz, 1H), 5.98 (tt, J = 3.9, 1.8 Hz, 1H), 4.12 (q, J = 2.1 Hz, 2H), 3.93 (s, 3H), 3.37 (t, J = 6.3 Hz, 2H), 2.58-2.55 (m, 2H). LRMS (ESI) m/z: calcd for $C_{14}H_{17}N_2O^+$ $[M + H]^+$, 229.13; found, 229.32.

Example 19

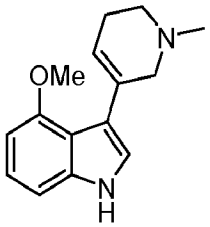
Synthesis of RS134-41



4-methyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (RS134-41). RS134-41 was synthesized following the standard procedure for preparing NS131-179 from tert-butyl 3-bromo-4-methyl-1H-indole-1-carboxylate and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine. (white solid, 13.3 mg, 39%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.21 (d, J = 8.2 Hz, 1H), 7.17 (s, 1H), 7.02 (t, J = 7.7 Hz, 1H), 6.80 (d, J = 7.1 Hz, 1H), 5.93 (tt, J = 4.1, 1.9 Hz, 1H), 4.12 (d, J = 16.4 Hz, 1H), 3.92 – 3.84 (m, 1H), 3.63 (dd, J = 12.4, 6.1 Hz, 1H), 3.28 (dd, J = 11.7, 5.2 Hz, 1H), 3.03 (s, 3H), 2.76 – 2.69 (m, 1H), 2.60 (d, J = 19.5 Hz, 1H), 2.56 (s, 3H). LRMS (ESI) m/z: calcd for $C_{15}H_{19}N_2^+$ $[M + H]^+$, 227.15; found, 227.38.

Example 20

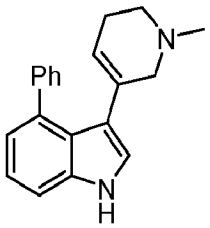
Synthesis of RS134-46



4-methoxy-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (RS134-46). RS134-46 was synthesized following the standard procedure for preparing **RS134-53** from 4-methoxy-1H-indole and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine. (white solid, 11.1 mg, 31%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.13 (s, 1H), 7.07 (t, J = 8.0 Hz, 1H), 7.00 (d, J = 8.2 Hz, 1H), 6.56 (d, J = 7.8 Hz, 1H), 5.98 (q, J = 2.9, 1.8 Hz, 1H), 4.40 (d, J = 15.8 Hz, 1H), 4.00 – 3.95 (m, 1H), 3.93 (s, 3H), 3.63 – 3.57 (m, 1H), 3.30 – 3.26 (m, 1H), 3.04 (s, 3H), 2.72-2.66 (m, 1H), 2.63 – 2.55 (m, 1H). LRMS (ESI) m/z: calcd for $C_{15}H_{19}N_2O^+$ [M + H]$^+$, 243.15; found, 243.37.

Example 21

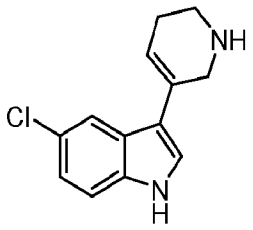
Synthesis of NS131-172



3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-4-phenyl-1H-indole (NS131-172). NS131-172 was synthesized following the standard procedure for preparing **RS134-53** from 4-phenyl-1H-indole and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine. (white solid, 10.1 mg, 25%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.49 – 7.43 (m, 3H), 7.43 – 7.39 (m, 3H), 7.31 (d, J = 2.2 Hz, 1H), 7.23 (dd, J = 8.2, 7.2 Hz, 1H), 7.01 (dd, J = 7.2, 1.0 Hz, 1H), 5.44 (dq, J = 3.9, 1.9 Hz, 1H), 3.62 (d, J = 16.1 Hz, 1H), 3.34 (s, 1H), 2.93 (d, J = 16.1 Hz, 1H), 2.71 (s, 4H), 2.37 (s, 1H), 2.09 (d, J = 18.9 Hz, 1H). LRMS (ESI) m/z: calcd for $C_{20}H_{21}N_2^+$ [M + H]$^+$, 289.17; found, 289.29.

Example 22

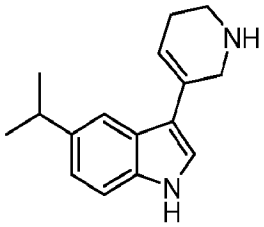
Synthesis of RS134-38



5-chloro-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (RS134-38). RS134-38 was synthesized following the standard procedure for preparing NS131-179 from tert-butyl 3-bromo-5-chloro-1H-indole-1-carboxylate and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 8.3 mg, 24%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.78 (d, J = 2.0 Hz, 1H), 7.40 (s, 1H), 7.37 (d, J = 8.6 Hz, 1H), 7.14 (dd, J = 8.6, 2.0 Hz, 1H), 6.37 – 6.31 (m, 1H), 4.05 (q, J = 2.1 Hz, 2H), 3.41 (t, J = 6.2 Hz, 2H), 2.68 – 2.61 (m, 2H). LRMS (ESI) m/z: calcd for $C_{13}H_{14}ClN_2^+$ $[M + H]^+$, 233.08; found, 233.22.

Example 23

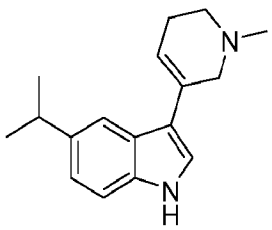
Synthesis of RS134-65



5-isopropyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (RS134-65). RS134-65 was synthesized following the standard procedure for preparing **RS134-53** from 5-isopropyl-1H-indole and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 11.4 mg, 32%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.64 – 7.60 (m, 1H), 7.32 (d, J = 8.4 Hz, 1H), 7.29 (s, 1H), 7.08 (dd, J = 8.4, 1.6 Hz, 1H), 6.36 (tt, J = 4.1, 1.8 Hz, 1H), 4.06 (q, J = 2.1 Hz, 2H), 3.40 (t, J = 6.2 Hz, 2H), 3.03-2.96 (m, 1H), 2.67-2.63 (m, 2H), 1.30 (d, J = 6.9 Hz, 6H). LRMS (ESI) m/z: calcd for $C_{16}H_{21}N_2^+$ $[M + H]^+$, 241.17; found, 241.40.

Example 24

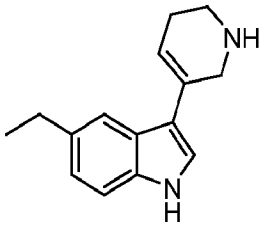
Synthesis of RS134-62



5-isopropyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (RS134-62). RS134-62 was synthesized following the standard procedure for preparing **RS134-53** from 5-isopropyl-1H-indole and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine. (white solid, 12.1 mg, 33%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.62 (s, 1H), 7.32 (dd, J = 8.2, 3.6 Hz, 2H), 7.09 (d, J = 7.6 Hz, 1H), 6.37 (s, 1H), 4.32 (d, J = 15.9 Hz, 1H), 4.00 (d, J = 14.6 Hz, 1H), 3.65 (s, 1H), 3.36-3.33 (m, 1H), 3.06 (q, J = 5.2, 4.3 Hz, 3H), 3.03 – 2.96 (m, 1H), 2.78 (s, 1H), 2.68 (d, J = 29.9 Hz, 1H), 1.30 (d, J = 7.4 Hz, 6H). LRMS (ESI) m/z: calcd for $C_{17}H_{23}N_2^+$ [M + H]$^+$, 255.19; found, 255.33.

Example 25

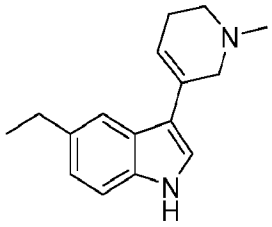
Synthesis of RS134-70



5-ethyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (RS134-70). RS134-70 was synthesized following the standard procedure for preparing **RS134-53** from 5-ethyl-1H-indole and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 11.9 mg, 35%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.60 (s, 1H), 7.31 (d, J = 8.3 Hz, 1H), 7.29 (s, 1H), 7.04 (dd, J = 8.3, 1.6 Hz, 1H), 6.38 (tt, J = 4.0, 1.7 Hz, 1H), 4.06 (q, J = 2.1 Hz, 2H), 3.41 (t, J = 6.2 Hz, 2H), 2.74 (q, J = 7.5 Hz, 2H), 2.67-2.64 (m, 2H), 1.27 (t, J = 7.6 Hz, 3H). LRMS (ESI) m/z: calcd for $C_{15}H_{19}N_2^+$ [M + H]$^+$, 227.15; found, 227.38.

Example 26

Synthesis of NS136-081

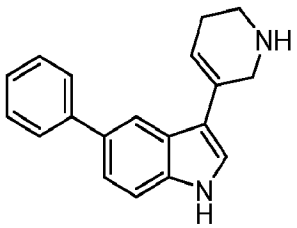


5-ethyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (NS136-081). NS136-081 was synthesized following the standard procedure for preparing **RS134-53** from 5-ethyl-1H-indole and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine. (white

solid, 5.3 mg, 15%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.62 – 7.59 (m, 1H), 7.31 (t, J = 4.2 Hz, 2H), 7.04 (dd, J = 8.3, 1.6 Hz, 1H), 6.37 (dt, J = 4.1, 1.9 Hz, 1H), 4.32 (d, J = 15.6 Hz, 1H), 4.00 (d, J = 15.7 Hz, 1H), 3.65 (dd, J = 12.2, 5.9 Hz, 1H), 3.33 (s, 1H), 3.06 (s, 3H), 2.74 (q, J = 7.6 Hz, 4H), 1.27 (t, J = 7.6 Hz, 3H). LRMS (ESI) m/z: calcd for $C_{16}H_{21}N_2^+$ $[M + H]^+$, 241.17; found, 241.28.

Example 27

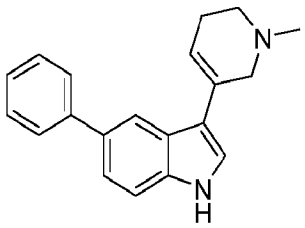
Synthesis of RS134-73



5-phenyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (RS134-73). RS134-73 was synthesized following the standard procedure for preparing **RS134-53** from 5-phenyl-1H-indole and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 7.4 mg, 19%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.99 (d, J = 2.0 Hz, 1H), 7.65 – 7.60 (m, 2H), 7.48 (d, J = 8.4 Hz, 1H), 7.45 – 7.40 (m, 3H), 7.38 (d, J = 2.0 Hz, 1H), 7.28 (dd, J = 8.3, 6.5 Hz, 1H), 6.45-6.43 (m, 1H), 4.09 (dd, J = 3.9, 2.0 Hz, 2H), 3.41 (t, J = 6.1 Hz, 2H), 2.68-2.64 (m, 2H). LRMS (ESI) m/z: calcd for $C_{19}H_{19}N_2^+$ $[M + H]^+$, 275.15; found, 275.31.

Example 28

Synthesis of RS134-72

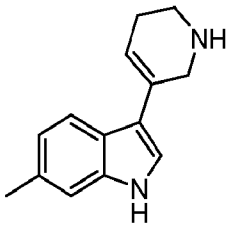


3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-5-phenyl-1H-indole (RS134-72). RS134-72 was synthesized following the standard procedure for preparing **RS134-53** from 5-phenyl-1H-indole and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine. (white solid, 8.5 mg, 21%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.01 – 7.98 (m, 1H), 7.63 (dd, J = 7.9, 1.4 Hz, 2H), 7.50 – 7.45 (m, 2H), 7.45 – 7.39 (m, 3H), 7.29 (t, J = 7.3 Hz, 1H), 6.44 (q, J = 4.3,

3.0 Hz, 1H), 4.35 (d, J = 15.7 Hz, 1H), 4.03 (d, J = 15.6 Hz, 1H), 3.66 (dd, J = 12.2, 6.2 Hz, 1H), 3.34 (d, J = 5.0 Hz, 1H), 3.07 (s, 3H), 2.79 (t, J = 8.2 Hz, 1H), 2.70 (d, J = 19.3 Hz, 1H). LRMS (ESI) m/z: calcd for $C_{20}H_{21}N_2^-$ $[M + H]^+$, 289.17; found, 289.25.

Example 29

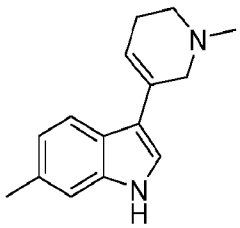
Synthesis of NS136-092



6-methyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (NS136-092). NS136-092 was synthesized following the standard procedure for preparing **RS134-53** from 6-methyl-1H-indole and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 6.2 mg, 21%) ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.39 – 7.33 (m, 1H), 7.13 (s, 1H), 6.84 (d, J = 8.1 Hz, 1H), 6.40 (dd, J = 7.8, 4.8 Hz, 2H), 4.11 (s, 2H), 3.40 (p, J = 4.7 Hz, 2H), 2.64 (dd, J = 8.3, 4.0 Hz, 2H), 2.41 (t, J = 2.4 Hz, 3H). LRMS (ESI) m/z: calcd for $C_{19}H_{19}N_2^+$ $[M + H]^+$, 213.14; found, 213.28.

Example 30

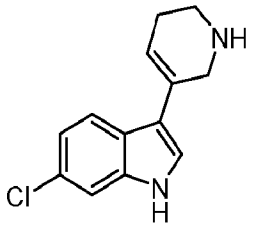
Synthesis of NS136-091



6-methyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (NS136-091). NS136-091 was synthesized following the standard procedure for preparing **RS134-53** from 6-methyl-1H-indole and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine. (white solid, 7.1 mg, 23%) ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.37 (d, J = 8.1 Hz, 1H), 7.13 (s, 1H), 6.87 – 6.82 (m, 1H), 6.41 (d, J = 6.5 Hz, 2H), 4.40 (d, J = 15.8 Hz, 1H), 4.02 (d, J = 15.8 Hz, 1H), 3.65 (d, J = 9.8 Hz, 1H), 2.70 (t, J = 19.6 Hz, 2H), 2.41 (d, J = 3.4 Hz, 3H). LRMS (ESI) m/z: calcd for $C_{15}H_{19}N_2^+$ $[M + H]^+$, 227.15; found, 227.12.

Example 31

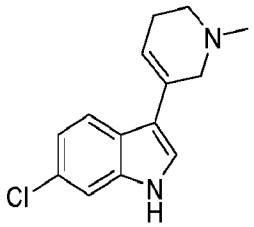
Synthesis of NS136-096



6-chloro-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (NS136-096). NS136-096 was synthesized following the standard procedure for preparing **RS134-53** from 6-chloro-1H-indole and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 6.0 mg, 19%) ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.77 (d, J = 8.4 Hz, 1H), 7.43 – 7.34 (m, 2H), 7.08 (d, J = 8.6 Hz, 1H), 6.38 (s, 1H), 4.06 (s, 2H), 3.41 (p, J = 4.9 Hz, 2H), 2.64 (s, 2H). LRMS (ESI) m/z: calcd for $C_{13}H_{14}ClN_2^+$ $[M + H]^+$, 233.08; found, 233.23.

Example 32

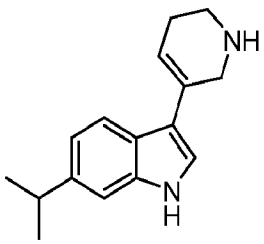
Synthesis of NS136-095



6-chloro-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (NS136-095). NS136-095 was synthesized following the standard procedure for preparing **RS134-53** from 6-chloro-1H-indole and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine. (white solid, 6.9 mg, 21%) ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.77 (d, J = 8.4 Hz, 1H), 7.43 – 7.34 (m, 2H), 7.08 (d, J = 8.6 Hz, 1H), 6.38 (s, 1H), 4.06 (s, 2H), 3.41 (p, J = 4.9 Hz, 2H), 2.64 (s, 2H). LRMS (ESI) m/z: calcd for $C_{14}H_{16}ClN_2^+$ $[M + H]^+$, 247.10; found, 247.25.

Example 33

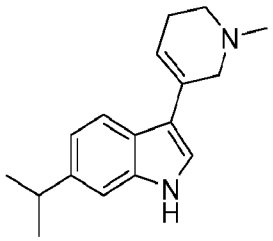
Synthesis of NS136-102



6-isopropyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (NS136-102). NS136-102 was synthesized following the standard procedure for preparing **RS134-53** from 6-isopropyl-1H-indole and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 7.8 mg, 22%) ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.43 – 7.37 (m, 1H), 7.19 (s, 1H), 6.95 – 6.88 (m, 1H), 6.41 (t, J = 6.6 Hz, 2H), 4.12 (s, 2H), 3.41 (q, J = 5.3 Hz, 2H), 3.01 – 2.92 (m, 1H), 2.63 (d, J = 8.2 Hz, 2H), 1.31 – 1.27 (m, 6H). LRMS (ESI) m/z: calcd for $C_{16}H_{21}N_2^+$ $[M + H]^+$, 241.17; found, 241.32.

Example 34

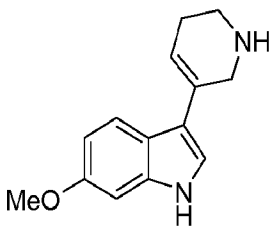
Synthesis of NS136-101



6-isopropyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (NS136-101). NS136-101 was synthesized following the standard procedure for preparing **RS134-53** from 6-isopropyl-1H-indole and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine. (white solid, 4.1 mg, 11%) ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.45 – 7.37 (m, 1H), 7.19 (s, 1H), 6.96 – 6.89 (m, 1H), 6.43 (s, 2H), 4.41 (d, J = 15.7 Hz, 1H), 4.03 (d, J = 15.7 Hz, 1H), 3.65 (s, 1H), 3.08 (d, J = 2.7 Hz, 3H), 2.96 (d, J = 9.3 Hz, 1H), 2.85 – 2.64 (m, 2H), 1.29 (dt, J = 6.2, 2.8 Hz, 6H). LRMS (ESI) m/z: calcd for $C_{17}H_{23}N_2^+$ $[M + H]^+$, 255.19; found, 255.28.

Example 35

Synthesis of NS136-115

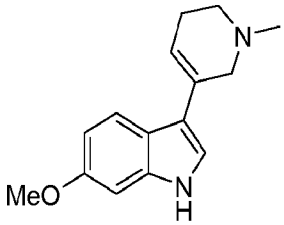


6-methoxy-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (NS136-115). NS136-115 was synthesized following the standard procedure for preparing **RS134-53** from 6-methoxy-1H-indole and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 4.1 mg, 12%) ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.67 (t, J = 5.6 Hz,

1H), 7.21 (t, J = 3.4 Hz, 1H), 6.92 (s, 1H), 6.76 (dd, J = 8.7, 4.5 Hz, 1H), 6.37 (s, 1H), 4.05 (s, 2H), 3.83 (d, J = 3.9 Hz, 3H), 3.40 (d, J = 5.9 Hz, 2H), 2.63 (d, J = 8.1 Hz, 2H). LRMS (ESI) m/z: calcd for $C_{14}H_{17}N_2O^+$ $[M + H]^+$, 229.13; found, 229.25.

Example 36

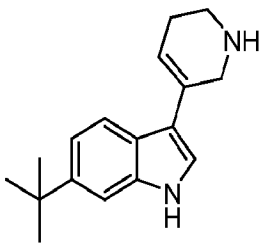
Synthesis of NS136-116



6-methoxy-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (NS136-116). NS136-116 was synthesized following the standard procedure for preparing **RS134-53** from 6-methoxy-1H-indole and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine. (white solid, 5.0 mg, 14%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.67 (d, J = 8.8 Hz, 1H), 7.23 (s, 1H), 6.92 (d, J = 2.3 Hz, 1H), 6.76 (dd, J = 8.9, 2.4 Hz, 1H), 6.36 (s, 1H), 4.31 (d, J = 15.7 Hz, 1H), 3.98 (d, J = 15.8 Hz, 1H), 3.82 (s, 3H), 3.69 – 3.62 (m, 1H), 3.06 (s, 3H), 2.80 – 2.73 (m, 1H), 2.66 (d, J = 19.1 Hz, 2H).LRMS (ESI) m/z: calcd for $C_{15}H_{19}N_2O^+$ $[M + H]^+$, 243.15; found, 243.19.

Example 37

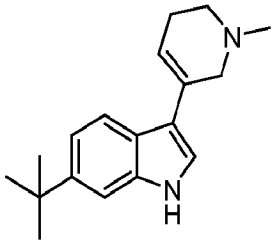
Synthesis of NS136-117



6-(tert-butyl)-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (NS136-117). NS136-117 was synthesized following the standard procedure for preparing **RS134-53** from 6-(tert-butyl)-1H-indole and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 4.8 mg, 13%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.72 (d, J = 8.5 Hz, 1H), 7.40 (s, 1H), 7.28 (s, 1H), 7.21 (d, J = 8.6 Hz, 1H), 6.40 (s, 1H), 4.07 (s, 2H), 3.41 (t, J = 6.3 Hz, 2H), 2.69 – 2.59 (m, 2H), 1.52 – 1.34 (m, 9H). LRMS (ESI) m/z: calcd for $C_{17}H_{23}N_2^+$ $[M + H]^+$, 255.19; found, 255.26.

Example 38

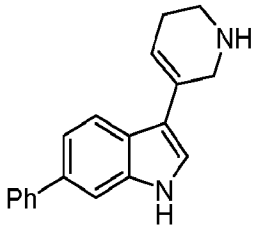
Synthesis of NS136-118



6-(tert-butyl)-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (NS136-118). NS136-118 was synthesized following the standard procedure for preparing **RS134-53** from 6-(tert-butyl)-1H-indole and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine. (white solid, 4.2 mg, 11%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.73 (d, J = 8.5 Hz, 1H), 7.45 – 7.39 (m, 1H), 7.30 (s, 1H), 7.25 – 7.19 (m, 1H), 6.39 (s, 1H), 4.33 (d, J = 15.7 Hz, 1H), 4.00 (d, J = 16.1 Hz, 1H), 3.65 (s, 1H), 3.06 (s, 3H), 2.78 (s, 1H), 2.69 (s, 1H), 1.37 (d, J = 2.6 Hz, 9H). LRMS (ESI) m/z: calcd for $C_{18}H_{25}N_2^+$ $[M + H]^+$, 269.20; found, 269.34.

Example 39

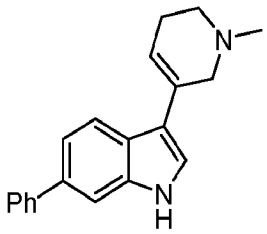
Synthesis of NS136-119



6-phenyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (NS136-119). NS136-119 was synthesized following the standard procedure for preparing **RS134-53** from 6-phenyl-1H-indole and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 4.3 mg, 11%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.88 (dd, J = 8.4, 2.4 Hz, 1H), 7.69 – 7.62 (m, 3H), 7.47 – 7.37 (m, 4H), 7.33 – 7.29 (m, 1H), 6.45 (tt, J = 3.9, 1.8 Hz, 1H), 4.16 – 4.09 (m, 2H), 3.43 (t, J = 6.1 Hz, 2H), 2.69-2.65 (m, 2H). LRMS (ESI) m/z: calcd for $C_{19}H_{19}N_2^+$ $[M + H]^+$, 275.15; found, 275.32.

Example 40

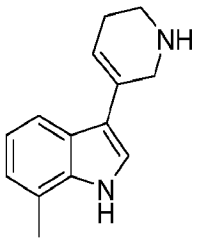
Synthesis of NS136-120



3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-6-phenyl-1H-indole (NS136-120). NS136-120 was synthesized following the standard procedure for preparing **RS134-53** from 6-phenyl-1H-indole and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine. (white solid, 4.0 mg, 10%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.92 – 7.85 (m, 1H), 7.65 (d, J = 9.2 Hz, 3H), 7.50 – 7.37 (m, 4H), 7.30 (t, J = 7.4 Hz, 1H), 6.44 (s, 1H), 4.36 (d, J = 15.7 Hz, 1H), 4.03 (d, J = 15.7 Hz, 1H), 3.66 (d, J = 9.8 Hz, 1H), 3.42 (s, 1H), 3.12 (s, 3H), 2.81 (d, J = 18.4 Hz, 1H), 2.70 (d, J = 19.7 Hz, 1H). LRMS (ESI) m/z: calcd for $C_{20}H_{21}N_2^+$ [M + H]$^+$, 289.17; found, 289.25.

Example 41

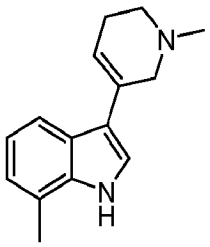
Synthesis of NS136-109



7-methyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (NS136-109). NS136-109 was synthesized following the standard procedure for preparing **RS134-53** from 7-methyl-1H-indole and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 3.9 mg, 12%)^{1}H NMR (600 MHz, Methanol-d_4) δ 7.33 (dd, J = 6.9, 2.0 Hz, 1H), 6.93 – 6.89 (m, 2H), 6.64 – 6.61 (m, 1H), 6.47 (s, 1H), 4.13 (q, J = 2.0 Hz, 2H), 3.41 (d, J = 6.2 Hz, 2H), 2.68 – 2.64 (m, 2H), 2.51 (s, 3H). LRMS (ESI) m/z: calcd for $C_{19}H_{19}N_2^+$ [M + H]$^+$, 213.14; found, 213.23.

Example 42

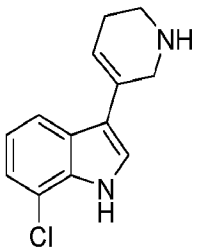
Synthesis of NS136-111



7-methyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (NS136-111). NS136-111 was synthesized following the standard procedure for preparing **RS134-53** from 7-methyl-1H-indole and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine. (white solid, 5.1 mg, 15%)^{1}H NMR (600 MHz, Methanol-d_4) δ 7.64 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 1.9 Hz, 1H), 7.01 (t, J = 7.5 Hz, 1H), 6.97 (d, J = 7.0 Hz, 1H), 6.38 (td, J = 4.3, 3.9, 1.8 Hz, 1H), 4.34 (d, J = 15.7 Hz, 1H), 4.01 (d, J = 15.7 Hz, 1H), 3.65 (dd, J = 12.3, 6.1 Hz, 1H), 3.06 (s, 3H), 2.67 (d, J = 18.8 Hz, 1H), 2.49 (s, 3H). LRMS (ESI) m/z: calcd for $C_{15}H_{19}N_2^+$ [M + H]$^+$, 227.15; found, 227.19.

Example 43

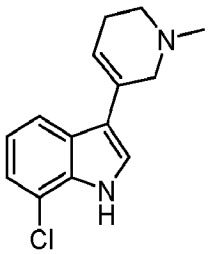
Synthesis of NS136-110



7-chloro-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (NS136-110). NS136-110 was synthesized following the standard procedure for preparing **RS134-53** from 7-chloro-1H-indole and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 4.0 mg, 11%)^{1}H NMR (600 MHz, Methanol-d_4) δ 7.76 (d, J = 8.2 Hz, 1H), 7.42 (s, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.08 (d, J = 8.1 Hz, 1H), 4.08 (s, 2H), 2.65 (s, 2H), 2.04 (d, J = 2.4 Hz, 2H).LRMS (ESI) m/z: calcd for $C_{13}H_{14}ClN_2^+$ [M + H]$^+$, 233.08; found, 233.27.

Example 44

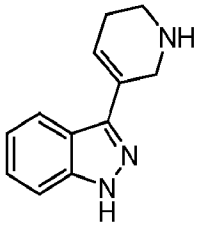
Synthesis of NS136-112



7-chloro-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (NS136-112). NS136-112 was synthesized following the standard procedure for preparing **RS134-53** from 7-chloro-1H-indole and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine. (white solid, 4.0 mg, 11%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.76 (d, J = 8.0 Hz, 1H), 7.44 (s, 1H), 7.20 (d, J = 7.9 Hz, 1H), 7.12 – 7.06 (m, 1H), 6.40 (s, 1H), 4.34 (d, J = 15.8 Hz, 1H), 4.01 (d, J = 16.0 Hz, 1H), 3.67 (d, J = 10.6 Hz, 1H), 3.40 – 3.34 (m, 1H), 3.13 – 3.04 (m, 3H), 2.78 (d, J = 19.8 Hz, 1H), 2.68 (d, J = 19.2 Hz, 1H). LRMS (ESI) m/z: calcd for $C_{14}H_{16}ClN_2^+$ [M + H]$^+$, 247.10; found, 247.23.

Example 45

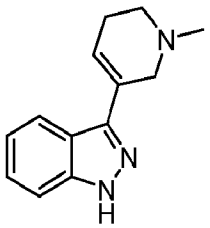
Synthesis of RS134-37



3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole (RS134-37). RS134-37 was synthesized following the standard procedure for preparing NS131-179 from 3-bromo-1H-indazole and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 19.2 mg, 61%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.98 (d, J = 8.3 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.40 (ddd, J = 8.2, 6.8, 1.0 Hz, 1H), 7.21 (ddd, J = 8.1, 6.8, 0.9 Hz, 1H), 6.83 (tt, J = 4.1, 1.8 Hz, 1H), 4.27 (q, J = 2.2 Hz, 2H), 3.45 (t, J = 6.2 Hz, 2H), 2.73-2.69 (m, 2H). LRMS (ESI) m/z: calcd for $C_{12}H_{14}N_3^-$ [M + H]$^+$, 200.12; found, 200.34.

Example 46

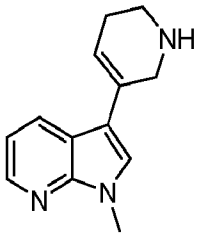
Synthesis of RS134-56



3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole (RS134-56). RS134-56 was synthesized following the standard procedure for preparing NS131-179 from 3-bromo-1H-indazole and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine. (white solid, 22.3 mg, 68%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.98 (dd, J = 8.2, 1.1 Hz, 1H), 7.54 (dd, J = 8.4, 1.0 Hz, 1H), 7.41 (ddd, J = 8.2, 6.9, 1.0 Hz, 1H), 7.21 (ddd, J = 8.0, 6.9, 0.9 Hz, 1H), 6.83 (tt, J = 3.6, 1.7 Hz, 1H), 4.67 – 4.60 (m, 1H), 4.12-4.08 (m, 1H), 3.73 – 3.66 (m, 1H), 3.39 – 3.32 (m, 1H), 3.09 (s, 3H), 2.87-2.81 (m, 1H), 2.79 – 2.70 (m, 1H). LRMS (ESI) m/z: calcd for $C_{13}H_{16}N_3^-$ $[M + H]^+$, 214.13; found, 214.33.

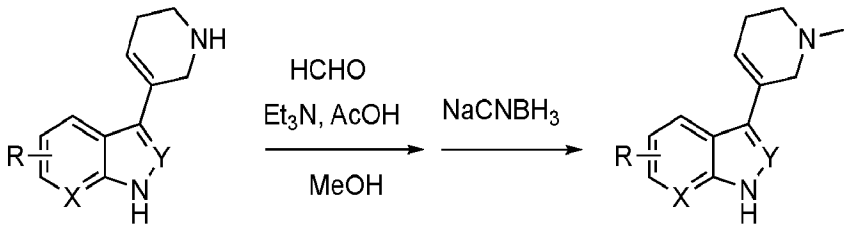
Example 47

Synthesis of NS136-002



1-methyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine (NS136-002). NS136-002 was synthesized following the standard procedure for preparing NS131-179 from 3-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridine and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 9.7 mg, 22%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.41 (dd, J = 8.0, 1.4 Hz, 1H), 8.35 (dd, J = 5.0, 1.4 Hz, 1H), 7.56 (s, 1H), 7.29 (dd, J = 8.0, 5.0 Hz, 1H), 6.46 (tt, J = 4.1, 1.8 Hz, 1H), 4.08 (q, J = 2.1 Hz, 2H), 3.90 (s, 3H), 3.42 (t, J = 6.2 Hz, 2H), 2.69-2.65 (m, 2H).LRMS (ESI) m/z: calcd for $C_{13}H_{16}N_3^+$ $[M + H]^+$, 214.13; found, 214.26.

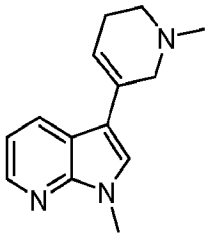
METHOD D:



X = N, CH; Y = N, CH

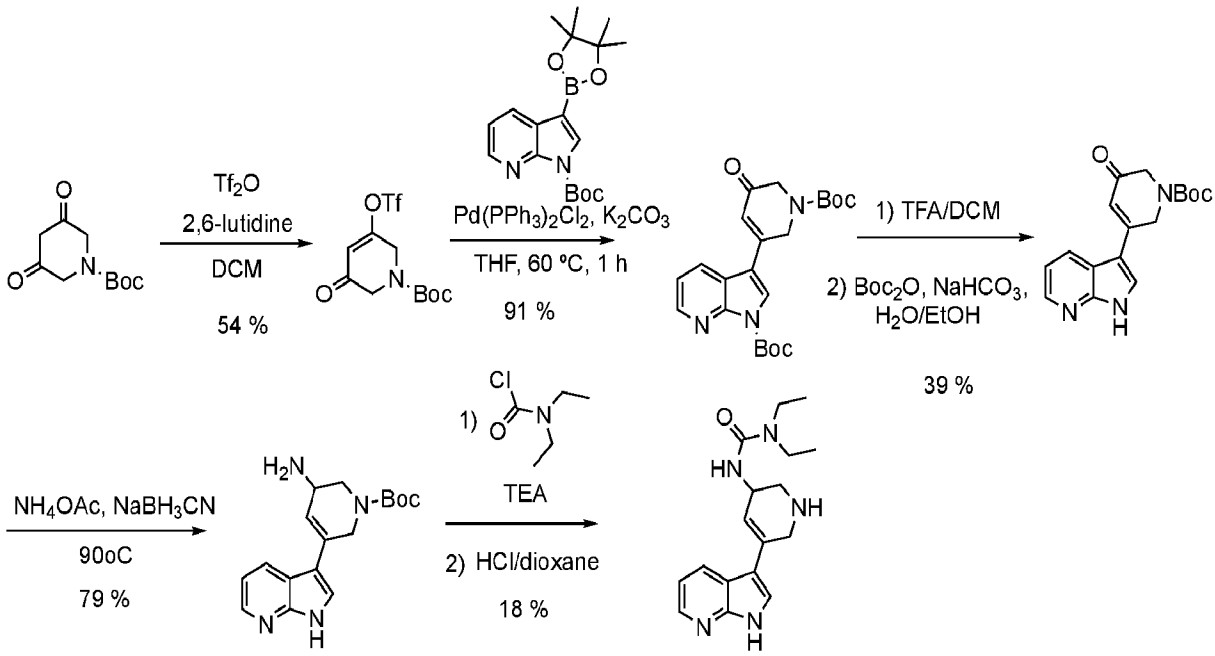
Example 48

Synthesis of NS136-004



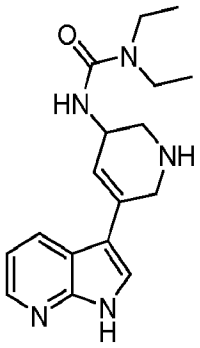
1-methyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine (NS136-004). NS136-004 was synthesized following the method D. To a solution of 1-methyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine (8.8 mg, 0.02 mmol, 1 equiv) in MeOH (1 mL) were added Et_3N (3 drops), AcOH (5 drops), HCHO (10 mg). After being stirred for 1 h at room temperature, the resulting mixture was added $NaCNBH_3$ (3.8 mg, 0.06 mmol, 3 equiv), stirred for 1 h at rt, the resulting mixture was purified by preparative HPLC (10%-100% acetonitrile / 0.1% TFA in H_2O) to give NS136-004 as a white solid (7.6 mg, 83%). ^1H NMR (600 MHz, Methanol-d_4) δ 8.33 (d, J = 6.5 Hz, 2H), 7.53 (s, 1H), 7.26 – 7.21 (m, 1H), 6.46 – 6.42 (m, 1H), 4.33 (d, J = 15.7 Hz, 1H), 4.01 (d, J = 16.2 Hz, 1H), 3.88 (d, J = 1.1 Hz, 3H), 3.67 (dd, J = 12.0, 6.4 Hz, 1H), 3.34 (s, 1H), 3.08 (s, 3H), 2.84 – 2.74 (m, 1H), 2.70 (s, 1H). LRMS (ESI) m/z: calcd for $C_{14}H_{18}N_3^+$ $[M + H]^+$, 228.15; found, 228.32.

METHOD E:



Example 49

Synthesis of RS130-132

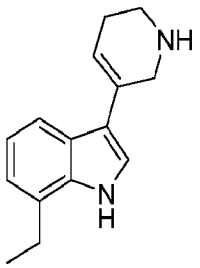


3-(5-(1H-pyrrolo[2,3-b]pyridin-3-yl)-1,2,3,6-tetrahydropyridin-3-yl)-1,1-diethylurea (RS130-132). RS130-132 was synthesized following method E. To a solution of tert-butyl 3,5-dioxopiperidine-1-carboxylate (2 g, 9.4 mmol, 1 equiv) and 2,6-lutidine (2 g, 18.8 mmol, 2 equiv) in DCM (40 mL) was added Tf_2O (1.2 mL, 7 mmol, 0.75 equiv), then stirred for 30 min at 0 °C, the resulting mixture was stirred at rt for 1h. The mixture was washed with 1N HCl, extracted by DCM, dried by Na_2SO_4, purified by silica gel (0% to 50% ethyl acetate in hexane) to afford tert-butyl 3-oxo-5-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (1.76 g, 73%, yellow oil). Then to a solution of tert-butyl 3-oxo-5-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (3.4 g, 9.85 mmol, 1 equiv) in THF (2 mL) were added tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (4.07g, 1.2 equiv), 2M K_2CO_3 solution (14.8 mL, 3 equiv), $Pd(PPh_3)_2Cl_2$ (691 mg, 0.1 equiv), and the atmosphere evacuated and backfilled with nitrogen three times. After being stirred for 1 h at

60 °C, the resulting mixture was purified by silica gel (0 to 30% ethyl acetate in hexane) to afford tert-butyl 3-(1-(tert-butoxycarbonyl)-5-oxo-1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (red oil, 3.7 g, 91%) as an intermediate. To a solution of the last step intermediate (769 mg, 1.86 mmol, 1 equiv) in 3 mL DCM, was added 3 mL TFA, stirred for 1 h at rt, evaporated, then to a solution of the crude compound (1.86 mmol, 1equiv) in EtOH (2 mL) and water (2 mL) were added $(Boc)_2O$ (400 mg, 1.86 mmol, 1 equiv), $NaHCO_3$ (156 mg, 1.86 mmol, 1 equiv), after being stirred for 1 h at rt, the resulting mixture was filtered and washed with water and methanol, then the filter cake was dried by vacuum to afford tert-butyl 3-oxo-5-(1H-pyrrolo[2,3-b]pyridin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate as a light yellow solid (350 mg, 60%). A mixture of tert-butyl 3-oxo-5-(1H-pyrrolo[2,3-b]pyridin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate (300 mg, 0.96 mmol, 1 equiv), NH_4OAc (738 mg, 9.6 mmol, 10 equiv) and $NaBH_3CN$ (72.3 mg, 1.2 equiv) in methanol was stirred at 90 °C for 3 h, then the mixture was purified by preparative HPLC (10%-100% acetonitrile / 0.1% TFA in H_2O) to get the compound tert-butyl 3-amino-5-(1H-pyrrolo[2,3-b]pyridin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate as a yellow solid (240 mg, 79%). To a solution of tert-butyl 3-amino-5-(1H-pyrrolo[2,3-b]pyridin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate (265 mg, 0.84 mmol, 1 equiv) in DCM (2 mL) were added TEA (0.234 mL, 2 equiv) and diethylcarbamic chloride (0.106 mL, 0.84 mmol, 1 equiv) at 0 °C, then the mixture was stirred for 3 h at rt, evaporated and the resulting mixture was purified by C18 column (10%-100% acetonitrile / 0.1% TFA in H_2O) to give the intermediate as a yellow oil, then add 2 mL 4N HCl in dioxane, stirred at rt for 1h, purified by preparative HPLC (10%-100% acetonitrile / 0.1% TFA in H_2O) to give the final compound RS130-132 as a yellow solid (47.4 mg, 18%). ^1H NMR (600 MHz, Methanol-d_4) δ 8.65 (dd, J = 16.1, 8.0, 1.3 Hz, 1H), 8.41 (dd, J = 4.9, 3.4 Hz, 1H), 7.64 (s, 1H), 7.60 (d, J = 6.0 Hz, 1H), 7.53-7.48 (m, 1H), 4.24-4.17 (m, 1H), 3.58-3.55 (m, 1H), 3.39 – 3.34 (m, 1H), 3.31 – 3.28 (m, 4H), 3.21 (t, J = 12.0 Hz, 1H), 3.11 (t, J = 12.1 Hz, 1H), 1.19 – 1.10 (m, 6H). LRMS (ESI) m/z: calcd for $C_{14}H_{18}N_3^+$ $[M + H]^+$, 314.20; found, 314.60.

Example 50

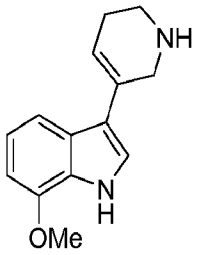
Synthesis of YX129-177C



7-ethyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (YX129-177C). YX129-177C was synthesized following the standard procedure for preparing **RS134-53** from 7-ethyl-1H-indole and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (2 mg, 10%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.66 (t, J = 7.3 Hz, 1H), 7.34 (d, J = 6.9 Hz, 1H), 7.07 (q, J = 7.2 Hz, 1H), 7.02 (t, J = 6.8 Hz, 1H), 6.41 (s, 1H), 4.10 (s, 2H), 3.43 (q, J = 6.3 Hz, 2H), 2.95 – 2.86 (m, 2H), 2.72 – 2.62 (m, 2H), 1.34 (q, J = 7.4 Hz, 3H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{19}N_2$, 227.1543; found: 227.1560.

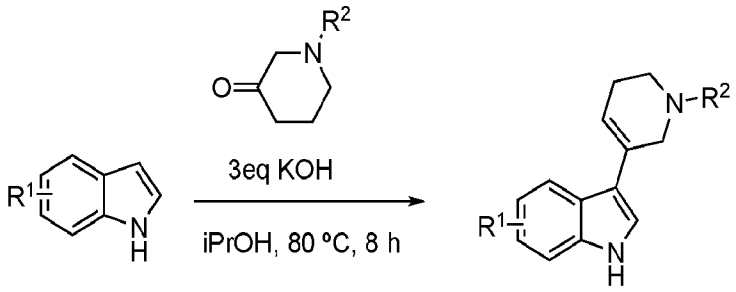
Example 51

Synthesis of YX129-180C



7-methoxy-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (YX129-180C). YX129-180C was synthesized following the standard procedure for preparing **RS134-53** from 7-methoxy-1H-indole and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (3 mg, 11%). ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.26 (d, J = 3.1 Hz, 1H), 6.89 (d, J = 7.9 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 6.58 (d, J = 3.1 Hz, 1H), 6.28 (s, 1H), 4.13 – 4.06 (m, 2H), 3.98 (s, 3H), 3.45 (t, J = 6.3 Hz, 2H), 2.69 – 2.61 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{17}N_2O$, 229.1335; found: 229.1321.

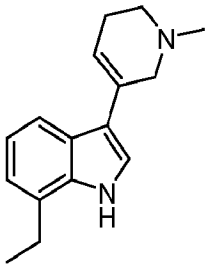
METHOD F:



R^2 = Me or Bn

Example 52

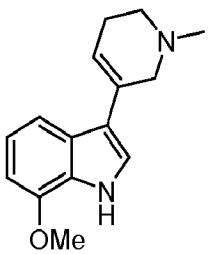
Synthesis of YX143-19



7-ethyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (YX143-19). YX143-19 was synthesized following the method F. To a solution of 7-ethyl-1H-indole (29 mg, 0.2 mmol, 1 equiv) in ^{i}PrOH (2 mL) were added KOH (56 mg, 5 equiv) and 1-methylpiperidin-3-one HCl salt (89.4 mg, 0.6 mmol, 3 equiv) at rt, then the mixture was stirred for 8 h at 80 °C, evaporated and the resulting mixture was purified by C18 column (10%-100% acetonitrile / 0.1% TFA in H_2O) to give the product as a yellow oil (18 mg, 60%). ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.66 (d, J = 8.0 Hz, 1H), 7.36 (s, 1H), 7.10 – 7.04 (m, 1H), 7.02 (d, J = 7.0 Hz, 1H), 6.41 – 6.34 (m, 1H), 4.40 – 4.29 (m, 1H), 4.04 – 3.95 (m, 1H), 3.69 – 3.60 (m, 1H), 3.31 – 3.24 (m, 1H), 3.06 (s, 3H), 2.91 (q, J = 7.6 Hz, 2H), 2.84 – 2.74 (m, 1H), 2.71 – 2.61 (m, 1H), 1.34 (t, J = 7.6 Hz, 3H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{21}N_2$, 241.1699; found: 241.1693.

Example 53

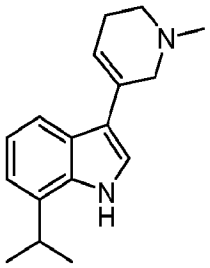
Synthesis of YX143-20



7-methoxy-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (YX143-20). YX143-20 was synthesized following the standard procedure for preparing **YX143-19** from 7-methoxy-1H-indole and 1-methylpiperidin-3-one. (20 mg, 58%). ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.40 (d, J = 8.1 Hz, 1H), 7.31 (s, 1H), 7.05 (t, J = 7.9 Hz, 1H), 6.72 (d, J = 7.7 Hz, 1H), 6.40 – 6.33 (m, 1H), 4.32 (d, J = 15.7 Hz, 1H), 4.01 – 3.92 (m, 4H), 3.68 – 3.60 (m, 1H), 3.32 – 3.23 (m, 1H), 3.05 (s, 3H), 2.84 – 2.73 (m, 1H), 2.70 – 2.59 (m, 1H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{19}N_2O$, 243.1492; found: 243.1488.

Example 54

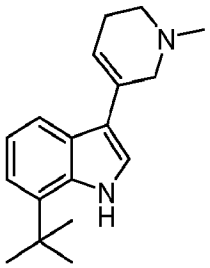
Synthesis of YX143-2



7-isopropyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (YX143-2). YX143-2 was synthesized following the standard procedure for preparing **YX143-19** from 7-methoxy-1H-indole and 1-methylpiperidin-3-one. (3 mg, 20%). ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.66 (dd, J = 6.6, 2.5 Hz, 1H), 7.36 (d, J = 1.9 Hz, 1H), 7.12 – 7.06 (m, 2H), 6.41 – 6.37 (m, 1H), 4.40 – 4.28 (m, 1H), 4.08 – 3.96 (m, 1H), 3.72 – 3.62 (m, 1H), 3.40 – 3.35 (m, 2H), 3.08 (s, 3H), 2.85 – 2.65 (m, 2H), 1.37 (d, J = 6.9 Hz, 6H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{23}N_2$, 255.1856; found: 255.1833.

Example 55

Synthesis of YX143-21

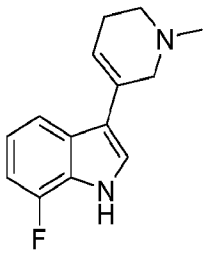


7-(tert-butyl)-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (YX143-21). YX143-21 was synthesized following the standard procedure for preparing **YX143-19** from 7-methoxy-1H-indole and 1-methylpiperidin-3-one. (21 mg, 62%). ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.69 (dd,

J = 8.0, 1.0 Hz, 1H), 7.35 (s, 1H), 7.15 – 7.10 (m, 1H), 7.06 (t, J = 7.7 Hz, 1H), 6.37 – 6.29 (m, 1H), 4.33 (d, J = 15.7 Hz, 1H), 4.04 – 3.94 (m, 1H), 3.69 – 3.63 (m, 1H), 3.31 – 3.26 (m, 1H), 3.06 (s, 3H), 2.83 – 2.73 (m, 1H), 2.71 – 2.59 (m, 1H), 1.50 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{25}N_2$, 269.1012; found: 269.1001.

Example 56

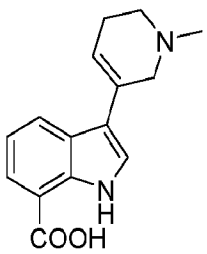
Synthesis of NS144-042



7-fluoro-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (NS144-042). NS144-042 was synthesized following the standard procedure for preparing **YX143-19** from 7-fluoro-1H-indole and 1-methylpiperidin-3-one. (yellow oil, 7.2 mg, 10%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.60 (d, J = 8.1 Hz, 1H), 7.41 (s, 1H), 7.05 (m, 1H), 6.91 (dd, J = 11.3, 7.8 Hz, 1H), 6.40 (d, J = 4.4 Hz, 1H), 4.33 (d, J = 15.7 Hz, 1H), 4.01 (d, J = 15.8 Hz, 1H), 3.66 (dd, J = 12.5, 6.1 Hz, 1H), 3.33 (d, J = 5.1 Hz, 1H), 3.06 (s, 3H), 2.78 (d, J = 9.7 Hz, 1H), 2.67 (d, J = 19.1 Hz, 1H). LRMS (ESI) m/z: calcd for $C_{14}H_{16}FN_2^+$ $[M + H]^+$, 231.13; found, 231.27.

Example 57

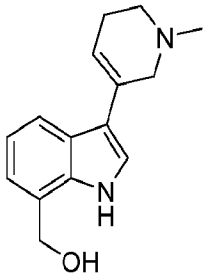
Synthesis of NS144-043



3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole-7-carboxylic acid (NS144-043). NS144-043 was synthesized following the standard procedure for preparing **YX143-19** from 1H-indole-7-carbonitrile and 1-methylpiperidin-3-one. (yellow oil, 6.8 mg, 9%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.04 (dd, J = 7.9, 2.1 Hz, 1H), 7.75 – 7.68 (m, 1H), 7.49 – 7.44 (m, 1H), 7.19 (td, J = 7.7, 2.2 Hz, 1H), 6.43 – 6.36 (m, 1H), 4.34 (d, J = 15.6 Hz, 1H), 4.01 (d, J = 15.9 Hz, 1H), 3.69 – 3.62 (m, 1H), 3.39 (s, 1H), 3.07 (s, 3H), 2.79 (s, 1H), 2.70 (d, J = 7.5 Hz, 1H). LRMS (ESI) m/z: calcd for $C_{15}H_{17}N_2O_2^+$ $[M + H]^+$, 257.13; found, 257.41.

Example 58

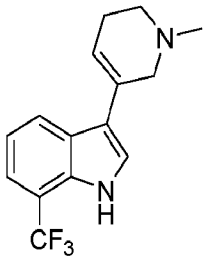
Synthesis of NS144-044



(3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indol-7-yl)methanol (NS144-044). NS144-044 was synthesized following the standard procedure for preparing **YX143-19** from (1H-indol-7-yl)methanol and 1-methylpiperidin-3-one. (yellow oil, 7.9 mg, 11%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.76 (d, J = 8.1 Hz, 1H), 7.38 (d, J = 2.7 Hz, 1H), 7.16 (d, J = 7.0 Hz, 1H), 7.12 – 7.07 (m, 1H), 6.39 (d, J = 4.3 Hz, 1H), 4.91 (s, 2H), 4.34 (d, J = 15.5 Hz, 1H), 4.01 (d, J = 15.4 Hz, 1H), 3.69 – 3.62 (m, 1H), 3.07 (d, J = 3.0 Hz, 3H), 2.79 (d, J = 20.7 Hz, 1H), 2.68 (d, J = 19.4 Hz, 1H). LRMS (ESI) m/z: calcd for $C_{15}H_{19}N_2O^+$ $[M + H]^+$, 243.15; found, 243.42.

Example 59

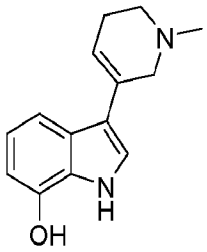
Synthesis of YS135-44



3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-7-(trifluoromethyl)-1H-indole (YS135-44). YS135-44 was synthesized following the standard procedure for preparing **YX143-19** from 7-(trifluoromethyl)-1H-indole and 1-methylpiperidin-3-one. (15 mg, 30%)^{1}H NMR (600 MHz, Methanol-d_4) δ 7.98 (d, J = 8.1 Hz, 1H), 7.45 – 7.30 (m, 2H), 7.15 (t, J = 7.8 Hz, 1H), 6.39 – 6.25 (m, 1H), 4.32 – 4.16 (m, 1H), 4.03 – 3.87 (m, 1H), 3.64 – 3.50 (m, 1H), 3.28 – 3.21 (m, 1H), 2.97 (s, 3H), 2.77 – 2.55 (m, 2H). LR-MS (ESI) m/z 281.3$[M + H]^+$.

Example 60

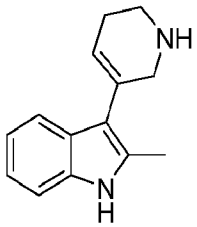
Synthesis of YS135-45



3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indol-7-ol (YS135-45). YS135-45 was synthesized following the standard procedure for preparing **YX143-19** from 1H-indol-7-ol and 1-methylpiperidin-3-one. (11mg, 23%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.34 – 7.13 (m, 2H), 6.90 (t, J = 7.9 Hz, 1H), 6.57 (d, J = 7.6 Hz, 1H), 6.39 – 6.29 (m, 1H), 4.31 (d, J = 15.8 Hz, 1H), 4.03 – 3.91 (m, 1H), 3.69 – 3.60 (m, 1H), 3.34 – 3.29 (m, 1H), 3.05 (d, J = 1.7 Hz, 3H), 2.81 – 2.58 (m, 2H). MS (ESI) m/z 229.1[M + H]$^+$.

Example 61

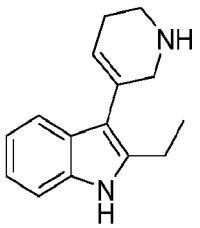
Synthesis of YS135-34



2-methyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (YS135-34). YS135-34 was synthesized following the standard procedure for preparing **RS134-53** from 2-methyl-1H-indole and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (5 mg, yield 9%). ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.63 (t, J = 8.2 Hz, 1H), 7.44 (d, J = 7.9 Hz, 1H), 7.32 – 7.20 (m, 1H), 7.08 – 6.89 (m, 1H), 6.01 – 5.84 (m, 1H), 4.03 – 3.77 (m, 2H), 3.47 – 3.38 (m, 2H), 2.61 (d, J = 8.8, 3.0 Hz, 1H), 2.49 – 2.31 (m, 4H). MS (ESI) m/z 213.2[M + H]$^+$.

Example 62

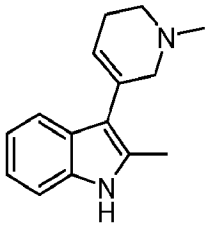
Synthesis of YS135-32



2-ethyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (YS135-32). YS135-32 was synthesized following the standard procedure for preparing **RS134-53** from 2-ethyl-1H-indole and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (10 mg, yield 15%). ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.77 – 7.56 (m, 1H), 7.28 (s, 1H), 7.07 – 6.86 (m, 2H), 6.01 – 5.72 (m, 1H), 3.98 – 3.87 (m, 1H), 3.50 – 3.45 (m, 1H), 3.42 (d, J = 6.3 Hz, 1H), 3.36 – 3.31 (m, 1H), 2.84 – 2.68 (m, 3H), 2.62 – 2.60 (m, 1H), 1.30 (dt, J = 12.0, 7.6 Hz, 3H). MS (ESI) m/z 227.1[M + H]$^+$.

Example 63

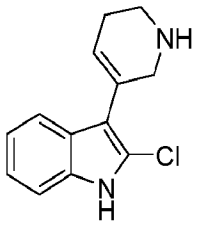
Synthesis of YS135-38



2-methyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (YS135-38). YS135-38 was synthesized following the standard procedure for preparing **RS134-53** from 2-methyl-1H-indole and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine. (7 mg, yield 20%). ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.55 – 7.41 (m, 1H), 7.34 – 7.19 (m, 1H), 7.16 – 6.93 (m, 2H), 5.96 (dd, J = 4.9, 2.6 Hz, 1H), 4.17 (d, J = 16.2 Hz, 1H), 4.05 – 3.93 (m, 1H), 3.69 (dd, J = 12.3, 6.3 Hz, 1H), 3.42 – 3.32 (m, 1H), 3.06 (s, 3H), 2.82 – 2.76 (m, 1H), 2.68 (d, J = 5.2 Hz, 1H), 2.45 (s, 3H). MS (ESI) m/z 227.2 [M + H]$^+$.

Example 64

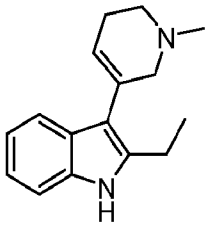
Synthesis of YS135-41



2-chloro-3-(1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indole (YS135-41). YS135-41 was synthesized following the standard procedure for preparing **RS134-53** from 2-chloro-1H-indole and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (3 mg, 5%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.45 (d, J = 8.0 Hz, 1H), 7.21 (d, J = 8.1 Hz, 1H), 7.12 – 7.02 (m, 1H), 6.99 (dd, J = 8.0, 6.9 Hz, 1H), 6.10 (dq, J = 3.9, 2.1 Hz, 1H), 3.97 (q, J = 2.3 Hz, 2H), 3.35 (t, J = 6.3 Hz, 2H), 2.68 – 2.48 (m, 2H). MS (ESI) m/z 233.1 $[M + H]^+$.

Example 65

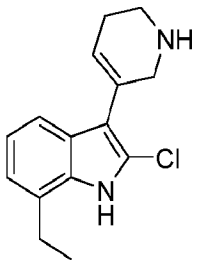
Synthesis of YS135-39



2-ethyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (YS135-39). YS135-39 was synthesized following the standard procedure for preparing **RS134-53** from 2-ethyl-1H-indole and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine. (8 mg, yield 17%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.36 (d, J = 7.9 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 7.04 – 6.92 (m, 1H), 6.89 (t, J = 7.5 Hz, 1H), 5.82 (dp, J = 3.9, 1.9 Hz, 1H), 4.02 (d, J = 16.1 Hz, 1H), 3.90 – 3.75 (m, 1H), 3.56 (dd, J = 12.5, 6.3 Hz, 1H), 3.31 – 3.23 (m, 1H), 2.93 (s, 3H), 2.76 – 2.60 (m, 3H), 2.52 (d, J = 19.1 Hz, 1H), 1.22 (t, J = 7.6 Hz, 3H). MS (ESI) m/z 241.2 $[M + H]^+$.

Example 66

Synthesis of YX143-14A-2

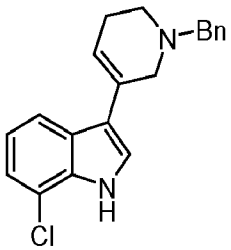


2-chloro-7-ethyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (YX143-14A-2). YX143-14A-2 was synthesized following the standard procedure for preparing **RS134-53** from 2-chloro-7-ethyl-1H-indole and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (2 mg, 13%). ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.35 (dd, J = 7.1, 2.0 Hz, 1H), 7.11 – 7.04 (m, 2H), 6.65 – 6.60 (m, 1H), 4.35 – 4.29 (m, 2H), 3.45 (t, J = 6.2 Hz, 2H), 2.93

(q, J = 7.6 Hz, 3H), 2.73 – 2.64 (m, 2H), 1.34 (t, J = 7.6 Hz, 3H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{18}ClN_2$, 261.1153; found: 261.1158.

Example 67

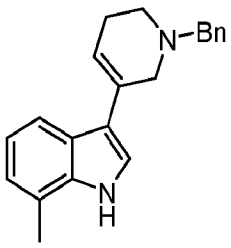
Synthesis of NS144-019



3-(1-benzyl-1,2,5,6-tetrahydropyridin-3-yl)-7-chloro-1H-indole (NS144-019). NS144-019 was synthesized following the standard procedure for preparing **YX143-19** from 7-chloro-1H-indole and 1-benzylpiperidin-3-one. (yellow oil, 48 mg, 11%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.72 (d, J = 8.1 Hz, 1H), 7.58 (dd, J = 6.7, 3.0 Hz, 2H), 7.53 (q, J = 3.6 Hz, 3H), 7.35 (d, J = 2.2 Hz, 1H), 7.19 (d, J = 7.6 Hz, 1H), 7.07 (t, J = 7.8 Hz, 1H), 6.40 – 6.36 (m, 1H), 4.51 (d, J = 48.7 Hz, 2H), 4.15 (d, J = 62.9 Hz, 2H), 3.65 (s, 1H), 2.69 (d, J = 6.6 Hz, 2H). LRMS (ESI) m/z: calcd for $C_{20}H_{20}N_2Cl^+$ $[M + H]^+$, 323.13; found, 323.34.

Example 68

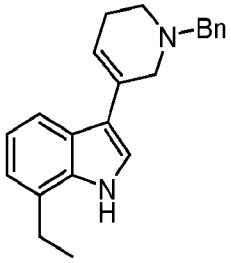
Synthesis of NS144-021



3-(1-benzyl-1,2,5,6-tetrahydropyridin-3-yl)-7-methyl-1H-indole (NS144-021). NS144-021 was synthesized following the standard procedure for preparing **YX143-19** from 7-methyl-1H-indole and 1-benzylpiperidin-3-one. (yellow oil, 50 mg, 12%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.71 – 7.48 (m, 7H), 7.27 (s, 1H), 7.01-6.95 (m, 2H), 6.42 – 6.36 (m, 1H), 4.61 – 4.44 (m, 2H), 4.25 – 4.08 (m, 2H), 3.66 (s, 1H), 2.70 (s, 2H), 2.49 (d, J = 4.9 Hz, 3H). LRMS (ESI) m/z: calcd for $C_{21}H_{23}N_2^+$ $[M + H]^+$, 303.19; found, 303.35.

Example 69

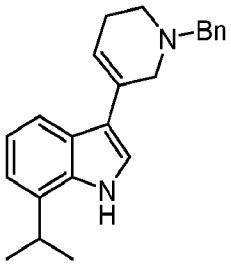
Synthesis of YX143-15



3-(1-benzyl-1,2,5,6-tetrahydropyridin-3-yl)-7-ethyl-1H-indole (YX143-15). YX143-15 was synthesized following the standard procedure for preparing **YX143-19** from 7-ethyl-1H-indole and 1-benzylpiperidin-3-one. (12 mg, 50%).^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.08 (s, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 7.1 Hz, 2H), 7.37 (q, *J* = 7.5 Hz, 2H), 7.34 – 7.24 (m, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.10 – 7.04 (m, 2H), 6.30 – 6.24 (m, 1H), 3.74 (s, 2H), 3.45 – 3.39 (m, 2H), 2.86 (q, *J* = 7.6 Hz, 3H), 2.71 (t, *J* = 5.8 Hz, 2H), 2.47 – 2.40 (m, 2H), 1.38 (t, *J* = 7.6 Hz, 3H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{22}H_{25}N_2$, 317.2012; found: 317.2001.

Example 70

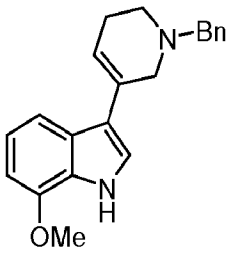
Synthesis of YX143-16



3-(1-benzyl-1,2,5,6-tetrahydropyridin-3-yl)-7-(propan-2-yl)-1H-indole (YX143-16). YX143-16 was synthesized following the standard procedure for preparing **YX143-19** from 7-isopropyl-1H-indole and 1-benzylpiperidin-3-one. (15 mg, 61%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.13 (s, 1H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.47 – 7.42 (m, 2H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.32 – 7.29 (m, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.12 – 7.08 (m, 2H), 6.32 – 6.13 (m, 1H), 3.75 (s, 2H), 3.45 – 3.37 (m, 2H), 3.27 – 3.14 (m, 1H), 2.72 (t, *J* = 5.8 Hz, 2H), 2.47 – 2.41 (m, 2H), 1.40 (d, *J* = 6.9 Hz, 6H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{23}H_{27}N_2$, 331.2169; found: 331.2155.

Example 71

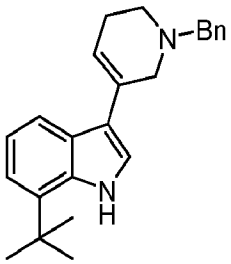
Synthesis of YX143-17C



3-(1-benzyl-1,2,5,6-tetrahydropyridin-3-yl)-7-methoxy-1H-indole (YX143-17C). YX143-17C was synthesized following the standard procedure for preparing **YX143-19** from 7-methoxy-1H-indole and 1-benzylpiperidin-3-one. (15 mg, 55%). ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.63 – 7.57 (m, 2H), 7.57 – 7.53 (m, 3H), 7.36 (d, J = 8.1 Hz, 1H), 7.22 (s, 1H), 7.04 (t, J = 7.9 Hz, 1H), 6.72 (d, J = 7.7 Hz, 1H), 6.40 – 6.34 (m, 1H), 4.59 – 4.50 (m, 1H), 4.50 – 4.38 (m, 1H), 4.29 – 4.15 (m, 1H), 4.12 – 4.00 (m, 1H), 3.97 (s, 3H), 3.71 – 3.58 (m, 1H), 3.31 – 3.20 (m, 1H), 2.75 – 2.62 (m, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{23}N_2O$, 319.1805; found: 319.1830.

Example 72

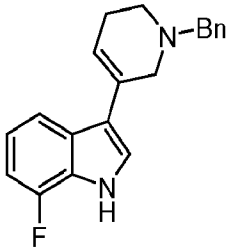
Synthesis of YX143-18C



3-(1-benzyl-1,2,5,6-tetrahydropyridin-3-yl)-7-tert-butyl-1H-indole (YX143-18C). YX143-18C was synthesized following the standard procedure for preparing **YX143-19** from 7-(tert-butyl)-1H-indole and 1-benzylpiperidin-3-one. (18 mg, 60%). ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.65 (d, J = 8.0 Hz, 1H), 7.62 – 7.57 (m, 2H), 7.58 – 7.53 (m, 3H), 7.26 (s, 1H), 7.12 (d, J = 7.4 Hz, 1H), 7.05 (t, J = 7.7 Hz, 1H), 6.39 – 6.34 (m, 1H), 4.61 – 4.53 (m, 1H), 4.53 – 4.43 (m, 1H), 4.28 – 4.16 (m, 1H), 4.16 – 4.03 (m, 1H), 3.72 – 3.63 (m, 1H), 3.33 (s, 1H), 3.31 (s, 0H), 2.76 – 2.63 (m, 2H), 1.50 (s, 9H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{29}N_2$, 345.2325; found: 345.2338.

Example 73

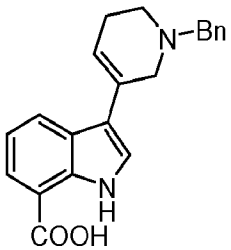
Synthesis of NS144-047



3-(1-benzyl-1,2,5,6-tetrahydropyridin-3-yl)-7-fluoro-1H-indole (NS144-047). NS144-047 was synthesized following the standard procedure for preparing **YX143-19** from 7-fluoro-1H-indole and 1-benzylpiperidin-3-one. (yellow oil, 17.7 mg, 21%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.62 – 7.52 (m, 6H), 7.32 (s, 1H), 7.04 (dt, J = 8.1, 4.2 Hz, 1H), 6.90 (dd, J = 11.2, 7.8 Hz, 1H), 6.43 – 6.36 (m, 1H), 4.62 – 4.42 (m, 2H), 4.27 – 4.08 (m, 2H), 3.66 (s, 1H), 3.40 (s, 1H), 2.70 (s, 2H). LRMS (ESI) m/z: calcd for $C_{20}H_{20}FN_2^+$ $[M + H]^+$, 307.16; found, 307.20.

Example 74

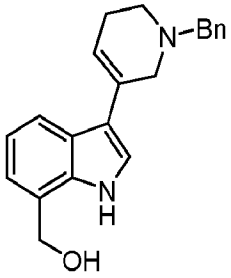
Synthesis of NS144-048



3-(1-benzyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole-7-carboxylic acid (NS144-048). NS144-048 was synthesized following the standard procedure for preparing **YX143-19** from 1H-indole-7-carbonitrile and 1-benzylpiperidin-3-one. (yellow oil, 13.5 mg, 15%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.01 (d, J = 7.9 Hz, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.63 – 7.46 (m, 5H), 7.38 (s, 1H), 7.18 (t, J = 7.7 Hz, 1H), 6.41 (s, 1H), 4.59 – 4.48 (m, 2H), 4.17 (d, J = 46.4 Hz, 2H), 3.68 (s, 1H), 3.42 (s, 1H), 2.72 (s, 2H). LRMS (ESI) m/z: calcd for $C_{21}H_{21}N_2O_2^+$ $[M + H]^+$, 333.16; found, 333.29.

Example 75

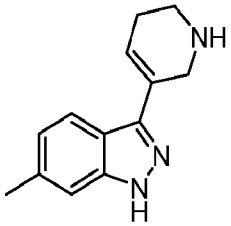
Synthesis of NS144-049



(3-(1-benzyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indol-7-yl)methanol (NS144-049). NS144-049 was synthesized following the standard procedure for preparing **YX143-19** from (1H-indol-7-yl)methanol and 1-benzylpiperidin-3-one. (yellow oil, 11.3 mg, 13%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.72 (d, J = 8.0 Hz, 1H), 7.59 (dd, J = 6.7, 3.0 Hz, 2H), 7.56 – 7.52 (m, 3H), 7.29 (s, 1H), 7.15 (d, J = 7.1 Hz, 1H), 7.08 (t, J = 7.6 Hz, 1H), 6.39 (t, J = 2.0 Hz, 1H), 4.90 (s, 2H), 4.59 – 4.54 (m, 1H), 4.46 (d, J = 12.9 Hz, 1H), 4.22 (d, J = 15.6 Hz, 1H), 4.10 (d, J = 16.0 Hz, 1H), 3.65 (s, 1H), 2.70 (d, J = 6.6 Hz, 2H). LRMS (ESI) m/z: calcd for $C_{21}H_{23}N_2O^+$ $[M + H]^+$, 319.18; found, 319.25.

Example 76

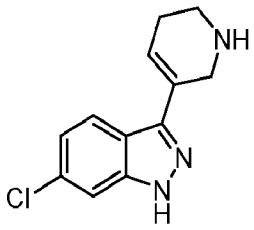
Synthesis of NS136-128



6-methyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole (NS136-128). NS136-128 was synthesized following the standard procedure for preparing NS131-179 from 3-bromo-6-methyl-1H-indazole and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 22 mg, 67%) ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.87 – 7.80 (m, 1H), 7.30 (d, J = 4.5 Hz, 1H), 7.05 (t, J = 6.5 Hz, 1H), 6.80 (s, 1H), 4.25 (s, 2H), 3.44 (q, J = 6.1 Hz, 2H), 2.69 (d, J = 7.7 Hz, 2H), 2.47 (t, J = 3.7 Hz, 3H). LRMS (ESI) m/z: calcd for $C_{13}H_{16}N_3^+$ $[M + H]^+$, 214.13 found, 214.38.

Example 77

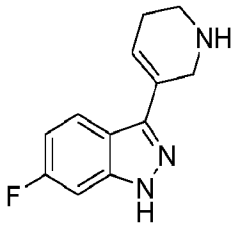
Synthesis of NS136-129



6-chloro-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole (NS136-129). NS136-129 was synthesized following the standard procedure for preparing NS131-179 from 3-bromo-6-chloro-1H-indazole and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 22.2 mg, 64%) ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.98 – 7.91 (m, 1H), 7.55 (d, J = 4.4 Hz, 1H), 7.18 (t, J = 6.6 Hz, 1H), 6.81 (s, 1H), 4.25 (s, 2H), 3.44 (q, J = 6.1 Hz, 2H), 2.70 (d, J = 7.9 Hz, 2H). LRMS (ESI) m/z: calcd for $C_{12}H_{13}ClN_3^+$ $[M + H]^+$, 234.08 found, 234.22.

Example 78

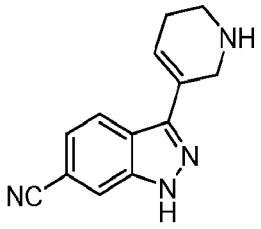
Synthesis of NS136-130



6-fluoro-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole (NS136-130). NS136-130 was synthesized following the standard procedure for preparing NS131-179 from 3-bromo-6-fluoro-1H-indazole and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 13.6 mg, 41%) ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.98 (dt, J = 7.8, 3.9 Hz, 1H), 7.24 – 7.16 (m, 1H), 7.04-6.98 (m, 4.8 Hz, 1H), 6.82 (s, 1H), 4.25 (s, 2H), 3.45 (q, J = 6.0 Hz, 2H), 2.71 (t, J = 5.8 Hz, 2H). LRMS (ESI) m/z: calcd for $C_{12}H_{13}FN_3^+$ $[M + H]^+$, 218.11 found, 218.23.

Example 79

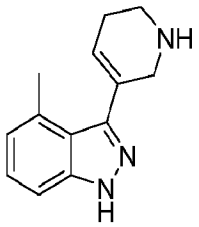
Synthesis of NS136-131



3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole-6-carbonitrile (NS136-131). NS136-131 was synthesized following the standard procedure for preparing NS131-179 from 3-bromo-1H-indazole-6-carbonitrile and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 19.6 mg, 58%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.24 – 8.11 (m, 1H), 8.01 (s, 1H), 7.46 (d, J = 8.6 Hz, 1H), 6.93 – 6.81 (m, 1H), 4.36 – 4.19 (m, 2H), 3.55 – 3.41 (m, 2H), 2.79 – 2.67 (m, 2H). LRMS (ESI) m/z: calcd for $C_{13}H_{13}N_4^+$ [M + H]$^+$, 225.11 found, 225.38.

Example 80

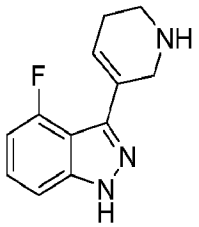
Synthesis of NS136-150



4-methyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole (NS136-150). NS136-150 was synthesized following the standard procedure for preparing NS131-179 from 3-bromo-4-methyl-1H-indazole and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 20.6 mg, 63%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.35 (d, J = 8.4 Hz, 1H), 7.27 (dd, J = 8.5, 6.9 Hz, 1H), 6.93 (d, J = 6.9 Hz, 1H), 6.25 (dq, J = 4.1, 2.0 Hz, 1H), 4.10 (q, J = 2.3 Hz, 2H), 3.45 (t, J = 6.2 Hz, 2H), 2.69-2.61 (m, 2H), 2.61 (s, 3H). LRMS (ESI) m/z: calcd for $C_{13}H_{16}N_3^+$ [M + H]$^+$, 214.13 found, 214.43.

Example 81

Synthesis of NS136-151

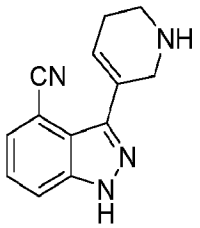


4-fluoro-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole (NS136-151). NS136-151 was synthesized following the standard procedure for preparing NS131-179 from 3-bromo-4-fluoro-1H-indazole and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 17.9 mg, 54%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.46 – 7.26

(m, 2H), 6.99 – 6.81 (m, 2H), 4.38 – 4.25 (m, 2H), 3.44 (q, J = 6.4 Hz, 2H), 2.78 – 2.63 (m, 2H). LRMS (ESI) m/z: calcd for $C_{12}H_{13}FN_3^+$ $[M + H]^+$, 218.11 found, 218.28.

Example 82

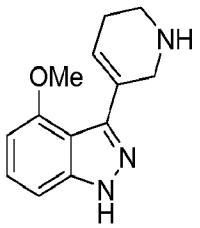
Synthesis of NS136-152



3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole-4-carbonitrile (NS136-152). NS136-152 was synthesized following the standard procedure for preparing NS131-179 from 3-bromo-1H-indazole-4-carbonitrile and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 20 mg, 59%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.90 (d, J = 8.5 Hz, 1H), 7.69 (d, J = 7.1 Hz, 1H), 7.54 (t, J = 8.1 Hz, 1H), 6.69 – 6.57 (m, 1H), 4.34 – 4.15 (m, 2H), 3.47 (t, J = 6.4 Hz, 2H), 2.83 – 2.64 (m, 2H). LRMS (ESI) m/z: calcd for $C_{13}H_{13}N_4^+$ $[M + H]^+$, 225.11 found, 225.28.

Example 83

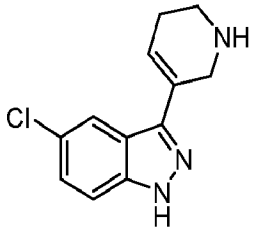
Synthesis of NS136-166



4-methoxy-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole (NS136-166). NS136-166 was synthesized following the standard procedure for preparing NS131-179 from 3-bromo-4-methoxy-1H-indazole and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 21 mg, 61%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.32 (t, J = 8.0 Hz, 1H), 7.08 (d, J = 8.3 Hz, 1H), 6.84 (td, J = 4.1, 2.0 Hz, 1H), 6.60 (d, J = 7.7 Hz, 1H), 4.23 (q, J = 2.2 Hz, 2H), 3.96 (s, 3H), 3.42 (t, J = 6.3 Hz, 2H), 2.69-2.64 (m, 2H). LRMS (ESI) m/z: calcd for $C_{13}H_{16}N_3O^+$ $[M + H]^+$, 230.13 found, 230.32.

Example 84

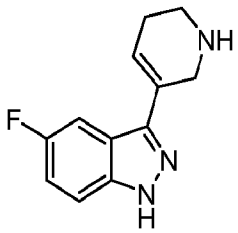
Synthesis of NS144-011



5-chloro-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole (NS144-011). NS144-011 was synthesized following the standard procedure for preparing NS131-179 from 3-bromo-5-chloro-1H-indazole and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 23.6 mg, 68%) ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.98 (t, J = 4.7 Hz, 1H), 7.52 (t, J = 6.9 Hz, 1H), 7.38 (d, J = 7.9 Hz, 1H), 6.76 (s, 1H), 4.25 (d, J = 6.2 Hz, 2H), 3.44 (p, J = 5.9 Hz, 2H), 2.70 (d, J = 7.8 Hz, 2H). LRMS (ESI) m/z: calcd for $C_{12}H_{13}ClN_3^+$ $[M + H]^+$, 234.08 found, 234.22.

Example 85

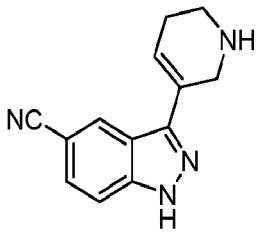
Synthesis of NS136-158



5-fluoro-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole (NS136-158). NS136-158 was synthesized following the standard procedure for preparing NS131-179 from 3-bromo-5-fluoro-1H-indazole and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 29.2 mg, 88%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.67 (dd, J = 9.5, 2.4 Hz, 1H), 7.54 (dd, J = 9.1, 4.3 Hz, 1H), 7.23 (td, J = 9.0, 2.4 Hz, 1H), 6.76 – 6.69 (m, 1H), 4.26 (q, J = 2.2 Hz, 2H), 3.45 (t, J = 6.2 Hz, 2H), 2.75 – 2.66 (m, 2H). LRMS (ESI) m/z: calcd for $C_{12}H_{13}FN_3^+$ $[M + H]^+$, 218.11 found, 218.33.

Example 86

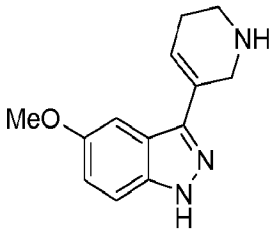
Synthesis of NS136-167



3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole-5-carbonitrile (NS136-167). NS136-167 was synthesized following the standard procedure for preparing NS131-179 from 3-bromo-1H-indazole-5-carbonitrile and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 20 mg, 59%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.52 (d, J = 10.3 Hz, 1H), 7.78 – 7.60 (m, 2H), 7.00 – 6.84 (m, 1H), 4.43 – 4.20 (m, 2H), 3.55 – 3.38 (m, 2H), 2.85 – 2.65 (m, 2H). LRMS (ESI) m/z: calcd for $C_{13}H_{13}N_4^+$ $[M + H]^+$, 225.11 found, 225.28.

Example 87

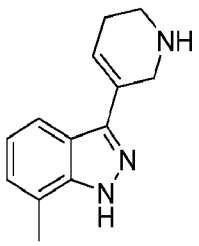
Synthesis of NS136-159



5-methoxy-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole (NS136-159). NS136-159 was synthesized following the standard procedure for preparing NS131-179 from 3-bromo-5-methoxy-1H-indazole and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 11 mg, 32%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.44 (dd, J = 9.0, 2.5 Hz, 1H), 7.30 (s, 1H), 7.12 – 7.07 (m, 1H), 6.76 (s, 1H), 4.25 (s, 2H), 3.87 (d, J = 2.3 Hz, 3H), 3.49 – 3.42 (m, 2H), 2.76 – 2.67 (m, 2H). LRMS (ESI) m/z: calcd for $C_{13}H_{16}N_3O^+$ $[M + H]^+$, 230.13 found, 230.37.

Example 88

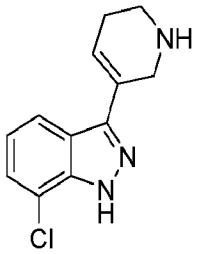
Synthesis of NS136-135



7-methyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole (NS136-135). NS136-135 was synthesized following the standard procedure for preparing NS131-179 from 3-bromo-7-methyl-1H-indazole and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 17.4 mg, 53%) ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.79 (t, J = 6.7 Hz, 1H), 7.15 (dt, J = 22.7, 6.8 Hz, 2H), 6.81 (s, 1H), 4.28 (s, 2H), 3.45 (q, J = 6.2 Hz, 2H), 2.70 (d, J = 6.3 Hz, 2H), 2.55 (t, J = 4.0 Hz, 3H). LRMS (ESI) m/z: calcd for $C_{13}H_{16}N_3^+$ $[M + H]^+$, 214.13 found, 214.18.

Example 89

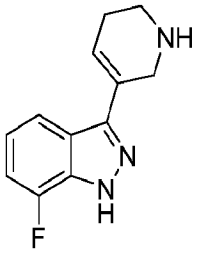
Synthesis of NS136-136



7-chloro-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole (NS136-136). NS136-136 was synthesized following the standard procedure for preparing NS131-179 from 3-bromo-7-chloro-1H-indazole and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 13.9 mg, 40%) ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.94 (t, J = 6.9 Hz, 1H), 7.44 (d, J = 7.2 Hz, 1H), 7.20 (dd, J = 8.9, 4.9 Hz, 1H), 6.85 (s, 1H), 4.28 (s, 2H), 3.46 (q, J = 6.1 Hz, 2H), 2.72 (d, J = 5.9 Hz, 2H). LRMS (ESI) m/z: calcd for $C_{12}H_{13}ClN_3^+$ $[M + H]^+$, 234.08 found, 234.27.

Example 90

Synthesis of NS136-137

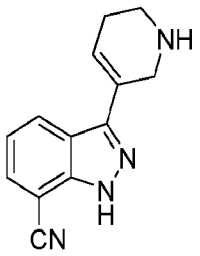


7-fluoro-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole (NS136-137). NS136-137 was synthesized following the standard procedure for preparing NS131-179 from 3-bromo-7-fluoro-1H-indazole and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-

1(2H)-carboxylate. (white solid, 17.6 mg, 53%) ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.79 (t, J = 6.5 Hz, 1H), 7.15 (p, J = 6.7, 5.4 Hz, 2H), 6.85 (s, 1H), 4.28 (d, J = 4.9 Hz, 2H), 3.45 (d, J = 6.5 Hz, 2H), 2.77 – 2.64 (m, 2H). LRMS (ESI) m/z: calcd for $C_{12}H_{13}FN_3^+$ $[M + H]^+$, 218.11 found, 218.23.

Example 91

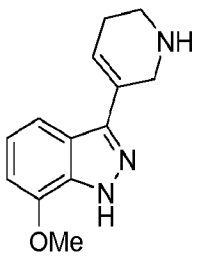
Synthesis of NS144-046



3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole-7-carbonitrile (NS144-046). NS144-046 was synthesized following the standard procedure for preparing NS131-179 from 3-bromo-1H-indazole-7-carbonitrile and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 16.6 mg, 49%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.35 (dd, J = 8.5, 2.8 Hz, 1H), 7.86 (dd, J = 7.5, 2.8 Hz, 1H), 7.36 (dd, J = 9.1, 6.4 Hz, 1H), 6.90 (td, J = 4.1, 2.0 Hz, 1H), 4.34 – 4.26 (m, 2H), 3.46 (t, J = 6.1 Hz, 2H), 2.73 (tt, J = 4.3, 2.2 Hz, 2H). LRMS (ESI) m/z: calcd for $C_{13}H_{13}N_4^+$ $[M + H]^+$, 225.11 found, 225.33.

Example 92

Synthesis of NS144-045

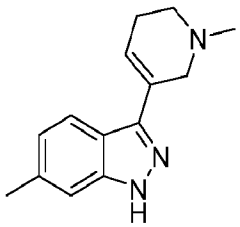


7-methoxy-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole (NS144-045). NS144-045 was synthesized following the standard procedure for preparing NS131-179 from 3-bromo-7-methoxy-1H-indazole and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 15.5 mg, 45%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.16 (d, J = 5.1 Hz, 1H), 7.01 (d, J = 7.8 Hz, 1H), 6.82 (d, J = 7.8 Hz, 1H), 6.40 (d, J = 4.6 Hz, 1H), 4.18 –

4.12 (m, 2H), 4.02 (d, J = 14.0 Hz, 3H), 3.45 (d, J = 6.2 Hz, 2H), 2.75 – 2.61 (m, 2H). LRMS (ESI) m/z: calcd for $C_{13}H_{16}N_3O^-$ $[M + H]^+$, 230.13 found, 230.32.

Example 93

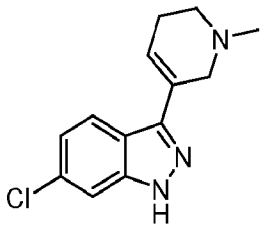
Synthesis of NS136-140



6-methyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole (NS136-140). NS136-140 was synthesized following the method D which the standard procedure for preparing NS136-004. (white solid, 8.3 mg, 81%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.95 – 7.75 (m, 1H), 7.31 (s, 1H), 7.13 – 6.99 (m, 1H), 6.80 (s, 1H), 4.60 (d, J = 15.9 Hz, 1H), 4.09 (d, J = 16.1 Hz, 1H), 3.68 (s, 1H), 3.38 (s, 1H), 3.09 (q, J = 10.2 Hz, 3H), 2.90 – 2.69 (m, 2H), 2.47 (d, J = 6.5 Hz, 3H). LRMS (ESI) m/z: calcd for $C_{14}H_{18}N_3^-$ $[M + H]^+$, 228.15 found, 228.27.

Example 94

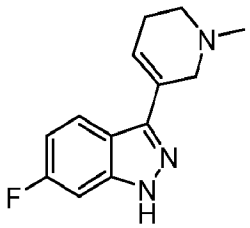
Synthesis of NS136-141



6-chloro-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole (NS136-141). NS136-141 was synthesized following the method D which the standard procedure for preparing NS136-004. (white solid, 6.6 mg, 61%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.95 – 7.75 (m, 1H), 7.31 (s, 1H), 7.13 – 6.99 (m, 1H), 6.80 (s, 1H), 4.60 (d, J = 15.9 Hz, 1H), 4.09 (d, J = 16.1 Hz, 1H), 3.68 (s, 1H), 3.38 (s, 1H), 3.09 (q, J = 10.2 Hz, 3H), 2.90 – 2.69 (m, 2H), 2.47 (d, J = 6.5 Hz, 3H). LRMS (ESI) m/z: calcd for $C_{13}H_{15}ClN_3^+$ $[M + H]^+$, 248.09 found, 248.27.

Example 95

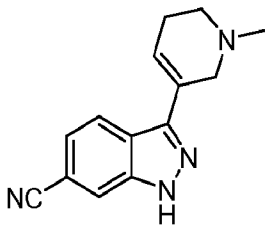
Synthesis of NS136-142



6-fluoro-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole (NS136-142). NS136-142 was synthesized following the method D which the standard procedure for preparing NS136-004. (white solid, 7.5 mg, 72%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.05 – 7.94 (m, 1H), 7.22 (dt, J = 9.2, 2.6 Hz, 1H), 7.05-7.01 (m, 1H), 6.91 – 6.78 (m, 1H), 4.61 (d, J = 16.3 Hz, 1H), 4.09 (d, J = 16.4 Hz, 1H), 3.69 (s, 1H), 3.42 – 3.34 (m, 1H), 3.09 (d, J = 2.2 Hz, 3H), 2.79 (d, J = 33.6 Hz, 2H). LRMS (ESI) m/z: calcd for $C_{13}H_{15}FN_3^+$ $[M + H]^+$, 232.12 found, 232.37.

Example 96

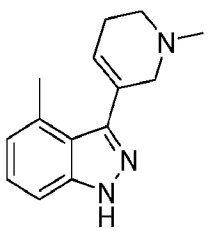
Synthesis of NS136-143



3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole-6-carbonitrile (NS136-143). NS136-143 was synthesized following the method D which the standard procedure for preparing NS136-004. (white solid, 7.2 mg, 68%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.24 – 8.12 (m, 1H), 8.01 (s, 1H), 7.52 – 7.40 (m, 1H), 6.95 – 6.81 (m, 1H), 4.65 (d, J = 16.2 Hz, 1H), 4.13 (d, J = 16.2 Hz, 1H), 3.80 – 3.66 (m, 1H), 3.45 – 3.35 (m, 1H), 3.16 – 3.07 (m, 3H), 2.89 – 2.72 (m, 2H). LRMS (ESI) m/z: calcd for $C_{14}H_{15}N_4^+$ $[M + H]^+$, 239.13 found, 239.32.

Example 97

Synthesis of NS136-153

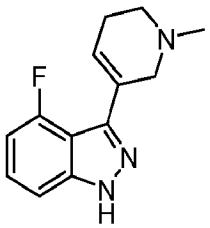


4-methyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole (NS136-153). NS136-153 was synthesized following the method D which the standard procedure for preparing NS136-004.

(white solid, 8.3 mg, 81%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.35 (d, J = 8.4 Hz, 1H), 7.28 (dd, J = 8.4, 6.9 Hz, 1H), 6.94 (d, J = 6.9 Hz, 1H), 6.26 (dd, J = 4.1, 2.1 Hz, 1H), 4.37 (d, J = 16.4 Hz, 1H), 4.03 (d, J = 16.4 Hz, 1H), 3.69 (s, 1H), 3.37 (s, 1H), 3.08 (s, 3H), 2.75 (d, J = 26.5 Hz, 2H), 2.61 (s, 3H). LRMS (ESI) m/z: calcd for $C_{14}H_{18}N_3^+$ [M + H]$^+$, 228.15 found, 228.32.

Example 98

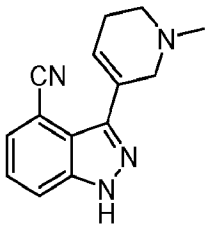
Synthesis of NS136-154



4-fluoro-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole (NS136-154). NS136-154 was synthesized following the method D which the standard procedure for preparing NS136-004. (white solid, 7.1 mg, 68%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.43 – 7.27 (m, 2H), 6.87 (td, J = 7.8, 2.5 Hz, 2H), 4.62 (s, 1H), 4.13 (s, 1H), 3.68 (s, 1H), 3.09 (s, 3H), 2.77 (d, J = 30.9 Hz, 2H). LRMS (ESI) m/z: calcd for $C_{13}H_{15}FN_3^+$ [M + H]$^+$, 232.12 found, 232.32.

Example 99

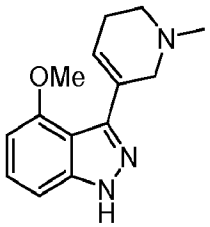
Synthesis of NS136-155



3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole-4-carbonitrile (NS136-155). NS136-155 was synthesized following the method D which the standard procedure for preparing NS136-004. (white solid, 7.5 mg, 71%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.91 (d, J = 8.5 Hz, 1H), 7.70 (d, J = 7.1 Hz, 1H), 7.55 (dd, J = 8.5, 7.1 Hz, 1H), 6.65 (dq, J = 4.0, 2.0 Hz, 1H), 4.53 (d, J = 16.2 Hz, 1H), 4.09 (d, J = 16.0 Hz, 1H), 3.71 (s, 1H), 3.39 (d, J = 13.7 Hz, 1H), 3.09 (s, 3H), 2.80 (q, J = 19.3, 14.5 Hz, 2H). LRMS (ESI) m/z: calcd for $C_{14}H_{15}N_4^+$ [M + H]$^+$, 239.13 found, 239.22.

Example 100

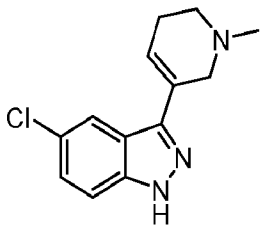
Synthesis of NS136-175



4-methoxy-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole (NS136-175). NS136-175 was synthesized following the method D which the standard procedure for preparing NS136-004. (white solid, 7.2 mg, 81%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.32 (dd, J = 9.6, 7.0 Hz, 1H), 7.09 (dd, J = 8.0, 2.6 Hz, 1H), 6.87 (s, 1H), 6.61 (dd, J = 7.9, 2.6 Hz, 1H), 4.55 (d, J = 16.0 Hz, 1H), 4.08 (d, J = 16.1 Hz, 1H), 3.97 (d, J = 2.5 Hz, 3H), 3.70 – 3.61 (m, 1H), 3.35 (s, 1H), 3.13 – 2.99 (m, 3H), 2.85 – 2.67 (m, 2H). LRMS (ESI) m/z: calcd for $C_{14}H_{18}N_3O^+$ [M + H]$^+$, 244.14 found, 244.27.

Example 101

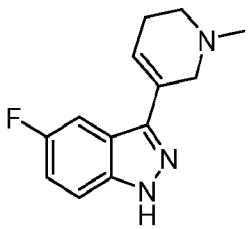
Synthesis of NS144-016



5-chloro-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole (NS144-016). NS144-016 was synthesized following the method D which the standard procedure for preparing NS136-004. (white solid, 9.4 mg, 87%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.00 (s, 1H), 7.60 – 7.46 (m, 1H), 7.39 (d, J = 8.8 Hz, 1H), 6.78 (s, 1H), 4.62 (d, J = 16.2 Hz, 1H), 4.09 (d, J = 16.2 Hz, 1H), 3.79 – 3.64 (m, 1H), 3.35 (s, 1H), 3.09 (d, J = 3.4 Hz, 3H), 2.92 – 2.71 (m, 2H). LRMS (ESI) m/z: calcd for $C_{13}H_{15}ClN_3^+$ [M + H]$^+$, 248.09 found, 248.27.

Example 102

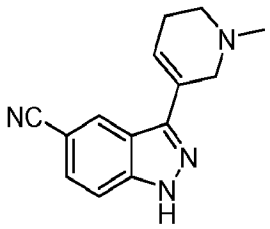
Synthesis of NS136-160



5-fluoro-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole (NS136-160). NS136-160 was synthesized following the method D which the standard procedure for preparing NS136-004. (white solid, 8.7 mg, 84%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.68 (dd, J = 9.4, 2.3 Hz, 1H), 7.54 (dd, J = 9.1, 4.3 Hz, 1H), 7.24 (td, J = 9.0, 2.3 Hz, 1H), 6.75 (tt, J = 3.9, 1.8 Hz, 1H), 4.62 (d, J = 16.1 Hz, 1H), 4.10 (d, J = 16.1 Hz, 1H), 3.71-3.68 (m, 1H), 3.36-3.33 (m, 1H), 3.09 (s, 3H), 2.85 – 2.69 (m, 2H). LRMS (ESI) m/z: calcd for $C_{13}H_{15}FN_3^+$ $[M + H]^+$, 232.12 found, 232.27.

Example 103

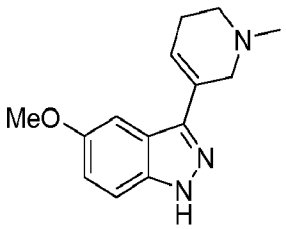
Synthesis of NS136-176



3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole-5-carbonitrile (NS136-176). NS136-176 was synthesized following the method D which the standard procedure for preparing NS136-004. (white solid, 6.8 mg, 64%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.53 (s, 1H), 7.79 – 7.61 (m, 2H), 6.96 – 6.83 (m, 1H), 4.64 (d, J = 16.2 Hz, 1H), 4.12 (d, J = 16.3 Hz, 1H), 3.71 (s, 1H), 3.37 (s, 1H), 3.18 – 3.05 (m, 3H), 2.81 (d, J = 28.5 Hz, 2H). LRMS (ESI) m/z: calcd for $C_{14}H_{15}N_4^+$ $[M + H]^+$, 239.13 found, 239.37.

Example 104

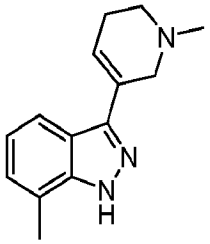
Synthesis of NS136-161



5-methoxy-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole (NS136-161). NS136-161 was synthesized following the method D which the standard procedure for preparing NS136-004. (white solid, 4.7 mg, 52%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.44 (d, J = 8.9 Hz, 1H), 7.30 (d, J = 2.3 Hz, 1H), 7.09 (dd, J = 9.2, 2.4 Hz, 1H), 6.81 – 6.73 (m, 1H), 4.62 (d, J = 15.9 Hz, 1H), 4.09 (d, J = 16.6 Hz, 1H), 3.96 – 3.85 (m, 3H), 3.69 (d, J = 13.1 Hz, 1H), 3.09 (s, 3H), 2.81 (d, J = 32.1 Hz, 2H). LRMS (ESI) m/z: calcd for $C_{14}H_{18}N_3O^+$ $[M + H]^+$, 244.14 found, 244.27.

Example 105

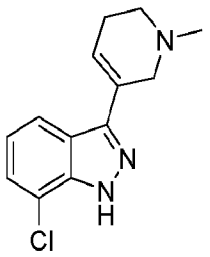
Synthesis of NS136-144



7-methyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole (NS136-144). NS136-144 was synthesized following the method D which the standard procedure for preparing NS136-004. (white solid, 7.4 mg, 72%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.79 (d, J = 8.2 Hz, 1H), 7.18 (dt, J = 6.9, 1.1 Hz, 1H), 7.12 (dd, J = 8.2, 6.9 Hz, 1H), 6.81 (dt, J = 4.2, 2.1 Hz, 1H), 4.64 (d, J = 16.1 Hz, 1H), 4.11 (d, J = 16.2 Hz, 1H), 3.69 (s, 1H), 3.35 (s, 1H), 3.09 (s, 3H), 2.79 (d, J = 40.7 Hz, 2H), 2.55 (s, 3H). LRMS (ESI) m/z: calcd for $C_{14}H_{18}N_3^+$ [M + H]$^+$, 228.15 found, 228.37.

Example 106

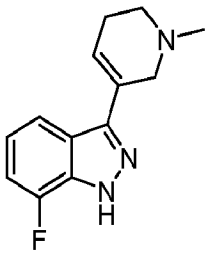
Synthesis of NS136-145



7-chloro-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole (NS136-145). NS136-145 was synthesized following the method D which the standard procedure for preparing NS136-004. (white solid, 7.0 mg, 64%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.97 – 7.92 (m, 1H), 7.44 (dd, J = 7.5, 0.7 Hz, 1H), 7.20 (dd, J = 8.2, 7.5 Hz, 1H), 6.89 – 6.83 (m, 1H), 4.65 (d, J = 16.1 Hz, 1H), 4.13 (d, J = 16.3 Hz, 1H), 3.70 (d, J = 6.2 Hz, 1H), 3.38 (d, J = 11.2 Hz, 1H), 3.10 (s, 3H), 2.80 (d, J = 30.4 Hz, 2H). LRMS (ESI) m/z: calcd for $C_{13}H_{15}ClN_3^+$ [M + H]$^+$, 248.09 found, 248.32.

Example 107

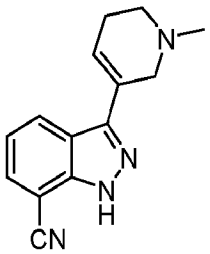
Synthesis of NS136-146



7-fluoro-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole (NS136-146). NS136-146 was synthesized following the method D which the standard procedure for preparing NS136-004. (white solid, 7.5 mg, 72%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.81 – 7.77 (m, 1H), 7.20 – 7.12 (m, 2H), 6.85 (dt, J = 4.2, 1.9 Hz, 1H), 4.64 (d, J = 16.1 Hz, 1H), 4.16 – 4.09 (m, 1H), 3.70 (dd, J = 12.1, 6.1 Hz, 1H), 3.36 (td, J = 11.4, 5.3 Hz, 1H), 3.09 (s, 3H), 2.85-2.81 (m, 1H), 2.79 – 2.72 (m, 1H). LRMS (ESI) m/z: calcd for $C_{13}H_{15}FN_3^+$ $[M + H]^+$, 232.12 found, 232.57.

Example 108

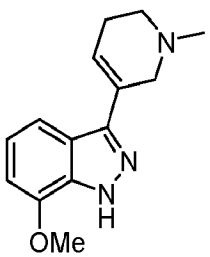
Synthesis of NS144-051



3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole-7-carbonitrile (NS144-051). NS144-051 was synthesized following the method D which the standard procedure for preparing NS136-004. (white solid, 6.7 mg, 63%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.36 (t, J = 6.5 Hz, 1H), 7.94 – 7.84 (m, 1H), 7.45 – 7.30 (m, 1H), 6.90 (s, 1H), 4.66 (d, J = 16.2 Hz, 1H), 4.15 (s, 1H), 3.71 (d, J = 11.1 Hz, 1H), 3.48 (s, 1H), 3.18 – 3.05 (m, 3H), 2.81 (d, J = 30.7 Hz, 2H). LRMS (ESI) m/z: calcd for $C_{14}H_{15}N_4^-$ $[M + H]^+$, 239.13 found, 239.33.

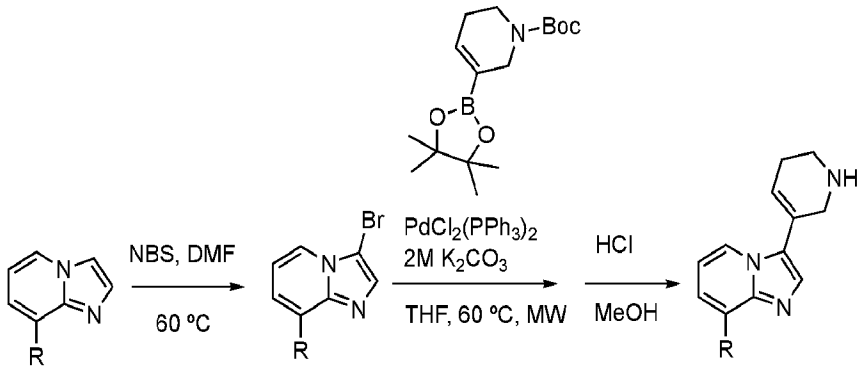
Example 109

Synthesis of NS144-050



7-methoxy-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole (NS144-050). NS144-050 was synthesized following the method D which the standard procedure for preparing NS136-004. (white solid, 7.6 mg, 71%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.17 (s, 1H), 7.02 (d, J = 7.8 Hz, 1H), 6.82 (d, J = 7.8 Hz, 1H), 6.44 – 6.35 (m, 1H), 4.34 (d, J = 15.7 Hz, 1H), 4.15 – 4.07 (m, 1H), 4.01 (s, 3H), 3.68 (dd, J = 12.3, 6.2 Hz, 1H), 3.35 (dd, J = 11.3, 5.4 Hz, 1H), 3.07 (s, 3H), 2.85 – 2.65 (m, 2H). LRMS (ESI) m/z: calcd for $C_{14}H_{18}N_3O^+$ [M + H]$^+$, 244.14 found, 244.25.

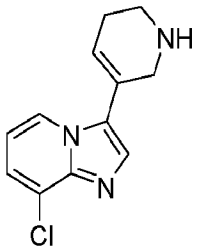
METHOD G:



R = Cl, F, Me

Example 110

Synthesis of YX143-41C

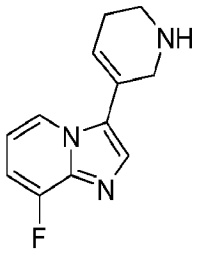


8-chloro-3-(1,2,5,6-tetrahydropyridin-3-yl)imidazo[1,2-a]pyridine (YX143-41C). YX143-41C was synthesized following the method G. Intermediate 8-chloroimidazo[1,2-a]pyridine (60 mg, 0.4 mmol), NBS (80 mg, 0.45 mmol) were dissolved in DMF (2 mL). The solution was heated at 60°C. After 2 h, the solution was cooled to room temperature, poured into water, and extracted with ethyl ether (3 × 5 mL). The organic layer was collected. After dried with Na_2SO_4, the solvent was removed, the residue was purified by ISCO to yield intermediate 3-bromo-8-chloroimidazo[1,2-a]pyridine (46 mg, 50%) as white solid. Intermediate 3-bromo-8-chloroimidazo[1,2-a]pyridine (23 mg, 0.1 mmol), boronic acid ester (44 mg, 0.15 mmol), $PdCl_2(PPh_3)_2$ (7mg, 0.01 mmol) and K_2CO_3 (0.15 mL, 2M in water, 0.3 mmol) were mixed together with THF (1 mL). The mixture was heated under microwave irritation at 60°C for 1 h.

after cooling down to room temperature, the mixture was filtered and the filtrate was collected and purified by prep-HPLC to get oil. The oil was treated with HCl in dioxane (1 mL, 4M, 4 mmol) for 0.5 h. Then the solvent was removed to yield the titled the compound as yellow solid. (24 mg, 80%).^{1}H NMR (600 MHz, Methanol-d_4) δ 9.04 (s, 1H), 8.34 (s, 1H), 8.19 (s, 1H), 7.59 (s, 1H), 6.71 (s, 1H), 4.13 (s, 2H), 3.81 – 3.59 (m, 2H), 3.56 (s, 2H), 2.83 (s, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{13}N_3Cl$, 234.0793; found: 234.0790.

Example 111

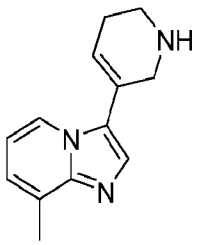
Synthesis of YX143-42C



8-fluoro-3-(1,2,5,6-tetrahydropyridin-3-yl)imidazo[1,2-a]pyridine (YX143-42C). YX143-42C was synthesized following the standard procedure for preparing **YX143-41C** from 8-fluoroimidazo[1,2-a]pyridine and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (18 mg, 77%).^{1}H NMR (600 MHz, Methanol-d_4) δ 8.91 (s, 1H), 8.32 (s, 1H), 7.92 (s, 1H), 7.57 (s, 1H), 6.71 (s, 1H), 4.12 (s, 2H), 3.78 – 3.61 (m, 2H), 3.56 (s, 2H), 2.82 (s, 2H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{13}N_3F$, 218.1088; found: 218.1201.

Example 112

Synthesis of YX143-43D

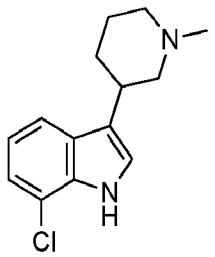


8-methyl-3-(1,2,5,6-tetrahydropyridin-3-yl)imidazo[1,2-a]pyridine (YX143-43D). YX143-43D was synthesized following the standard procedure for preparing **YX143-41C** from 8-methylimidazo[1,2-a]pyridine and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (15 mg, 81%).^{1}H NMR (600 MHz, Methanol-d_4) δ 8.88 (s, 1H), 8.23 (s, 1H), 7.86 (s, 1H), 7.50 (s, 1H), 6.67 (s, 1H), 4.12 (s, 2H), 3.80 – 3.49 (m, 4H), 2.82

(s, 2H), 2.72 (s, 3H). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{15}N_3$, 214.1399; found: 214.1387.

Example 113

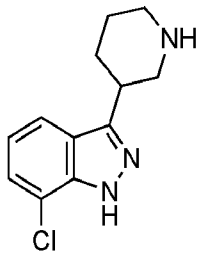
Synthesis of NS144-059-2



7-chloro-3-(1-methylpiperidin-3-yl)-1H-indole (NS144-059-2). NS144-059-2 was synthesized following the method H. To a solution of 7-chloro-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (8.5 mg, 0.03 mmol, 1 equiv) in MeOH (1 mL) were added Pd/C (20 mg) and filled with H_2 at rt, then the mixture was stirred for 20 min at rt, evaporated and the resulting mixture was purified by C18 column (10%-100% acetonitrile / 0.1% TFA in H_2O) to give the product as the second peak (white solid, 4.0 mg, 40%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.58 (dd, J = 8.0, 0.9 Hz, 1H), 7.25 (s, 1H), 7.16 (d, J = 7.6 Hz, 1H), 7.04 (t, J = 7.8 Hz, 1H), 3.73-3.68 (m, 1H), 3.63-3.57 (m, 1H), 3.36 – 3.32 (m, 1H), 3.12 – 3.02 (m, 2H), 2.92 (s, 3H), 2.23 – 2.17 (m, 1H), 2.16-2.12 (m, 1H), 2.02 – 1.93 (m, 1H), 1.87 – 1.81 (m, 1H). LRMS (ESI) m/z: calcd for $C_{14}H_{18}ClN_2^+$ $[M + H]^+$, 249.12 found, 249.22.

Example 114

Synthesis of NS144-054-2

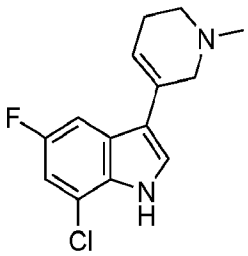


7-chloro-3-(piperidin-3-yl)-1H-indazole (NS144-054-2). NS144-054-2 was synthesized following the method H which the standard procedure for preparing NS144-059-2. (white solid, 3.8 mg, 47%) ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.75 (d, J = 8.1 Hz, 1H), 7.42 (d, J = 7.4 Hz, 1H), 7.15 (t, J = 7.8 Hz, 1H), 3.64-3.58 (m, 2H), 3.51 (dd, J = 12.9, 10.3 Hz, 1H), 3.42-3.33 (m, 1H), 3.22 – 3.15 (m, 1H), 2.28 (d, J = 9.9 Hz, 1H), 2.05 – 1.89 (m, 3H). LRMS (ESI) m/z: calcd

for $C_{12}H_{15}ClN_3^+$ $[M + H]^+$, 236.09 found, 236.05.

Example 115

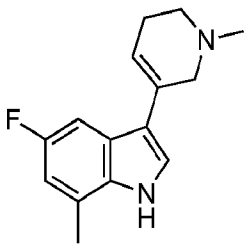
Synthesis of NS144-067



7-chloro-5-fluoro-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (NS144-067). **NS144-067** was synthesized following the standard procedure for preparing **YX143-19** from 7-chloro-5-fluoro-1H-indole and 1-methylpiperidin-3-one. (white solid, 13.3 mg, 35%) ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.53 – 7.47 (m, 2H), 7.09 (dd, J = 9.0, 2.2 Hz, 1H), 6.35 – 6.31 (m, 1H), 4.32 (d, J = 15.8 Hz, 1H), 4.00 (d, J = 15.9 Hz, 1H), 3.65 (s, 1H), 3.24 (s, 1H), 3.06 (s, 3H), 2.72 (d, J = 19.4 Hz, 2H). LRMS (ESI) m/z: calcd for $C_{14}H_{15}ClFN_2^+$ $[M + H]^+$, 265.09 found, 265.13.

Example 116

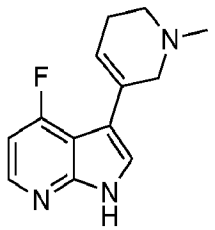
Synthesis of NS144-085



5-fluoro-7-methyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (NS144-085). **NS144-085** was synthesized following the standard procedure for preparing **YX143-19** from 7-methyl-5-fluoro-1H-indole and 1-methylpiperidin-3-one. (white solid, 21 mg, 12%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.41 (s, 1H), 7.31 (dd, J = 10.2, 2.4 Hz, 1H), 6.81 – 6.76 (m, 1H), 6.30 (t, J = 3.9 Hz, 1H), 4.32 (d, J = 15.7 Hz, 1H), 4.01 – 3.96 (m, 1H), 3.65 (dd, J = 12.5, 6.1 Hz, 1H), 3.29 (d, J = 12.2 Hz, 1H), 3.06 (s, 3H), 2.75 (d, J = 9.3 Hz, 1H), 2.67 (d, J = 19.0 Hz, 1H), 2.49 (s, 3H). LRMS (ESI) m/z: calcd for $C_{15}H_{18}FN_2^+$ $[M + H]^+$, 245.14 found, 245.18.

Example 117

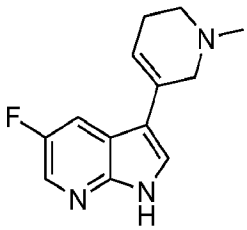
Synthesis of NS144-093



4-fluoro-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine (NS144-093). NS144-093 was synthesized following the standard procedure for preparing NS131-179 from 3-bromo-4-fluoro-1H-pyrrolo[2,3-b]pyridine and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine. (white solid, 14.3 mg, 62%) ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.27 (dd, J = 7.4, 5.6 Hz, 1H), 7.54 (s, 1H), 6.99 (dd, J = 11.2, 5.6 Hz, 1H), 6.37 – 6.32 (m, 1H), 4.31 (d, J = 15.9 Hz, 1H), 4.05 – 3.96 (m, 1H), 3.69 – 3.60 (m, 1H), 3.31 – 3.25 (m, 1H), 3.06 (s, 3H), 2.78 – 2.70 (m, 1H), 2.64 (d, J = 19.2 Hz, 1H).LRMS (ESI) m/z: calcd for $C_{13}H_{15}FN_3^+$ $[M + H]^+$, 232.12 found, 232.18.

Example 118

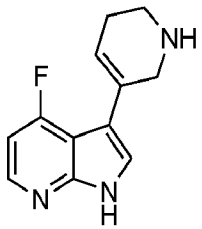
Synthesis of NS144-094



5-fluoro-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine (NS144-094). NS144-094 was synthesized following the standard procedure for preparing NS131-179 from 3-bromo-5-fluoro-1H-pyrrolo[2,3-b]pyridine and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine. (white solid, 11 mg, 48%) ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.18 (t, J = 2.2 Hz, 1H), 8.04 (dd, J = 9.5, 2.7 Hz, 1H), 7.60 (s, 1H), 6.39-6.33 (m, 1H), 4.34 (d, J = 15.8 Hz, 1H), 4.04-4.95 (m, 1H), 3.68 – 3.60 (m, 1H), 3.28 (d, J = 5.4 Hz, 1H), 3.07 (s, 3H), 2.84 – 2.72 (m, 1H), 2.67 (d, J = 19.5 Hz, 1H). LRMS (ESI) m/z: calcd for $C_{13}H_{15}FN_3^+$ $[M + H]^+$, 232.12 found, 232.16.

Example 119

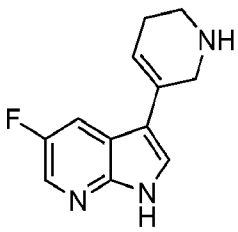
Synthesis of NS144-095



4-fluoro-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine (NS144-095). NS144-095 was synthesized following the standard procedure for preparing NS131-179 from 3-bromo-4-fluoro-1H-pyrrolo[2,3-b]pyridine and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 11.6 mg, 52%) ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.27 (dd, J = 7.3, 5.7 Hz, 1H), 7.53 (s, 1H), 7.00 (dd, J = 11.1, 5.7 Hz, 1H), 6.36-6.32 (m, 1H), 4.07 (q, J = 2.2 Hz, 2H), 3.40 (t, J = 6.2 Hz, 2H), 2.63-2.58 (m, 2H). LRMS (ESI) m/z: calcd for $C_{12}H_{13}FN_3^+$ $[M + H]^+$, 218.11 found, 218.15.

Example 120

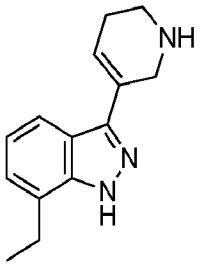
Synthesis of NS144-096



5-fluoro-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine (NS144-096). NS144-096 was synthesized following the standard procedure for preparing NS131-179 from 3-bromo-5-fluoro-1H-pyrrolo[2,3-b]pyridine and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 11.1 mg, 49%) ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.17 (t, J = 2.2 Hz, 1H), 8.03 (dd, J = 9.6, 2.6 Hz, 1H), 7.58 (s, 1H), 6.37 (tt, J = 4.0, 1.8 Hz, 1H), 4.07 (q, J = 2.2 Hz, 2H), 3.41 (t, J = 6.2 Hz, 2H), 2.67-2.63 (m, 2H). LRMS (ESI) m/z: calcd for $C_{12}H_{13}FN_3^+$ $[M + H]^+$, 218.11 found, 218.15.

Example 121

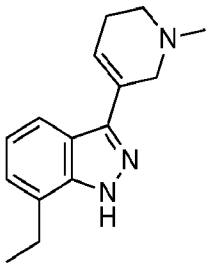
Synthesis of XQ148-012



7-ethyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole (XQ148-012). XQ148-012 was synthesized following the standard procedure for preparing NS131-179 from 3-bromo-7-ethyl-1H-indazole and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 10 mg, 6%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.82 (d, J = 8.2 Hz, 1H), 7.23 (d, J = 7.0 Hz, 1H), 7.17 (t, J = 7.6 Hz, 1H), 6.84 (s, 1H), 4.30 (s, 2H), 3.47 (t, J = 6.2 Hz, 2H), 2.96 (q, J = 7.6 Hz, 2H), 2.75 – 2.71 (m, 2H), 1.36 (t, J = 7.6 Hz, 3H). LRMS (ESI) m/z: calcd for $C_{14}H_{18}N_3^+$ $[M + H]^+$, 228.15 found, 228.22.

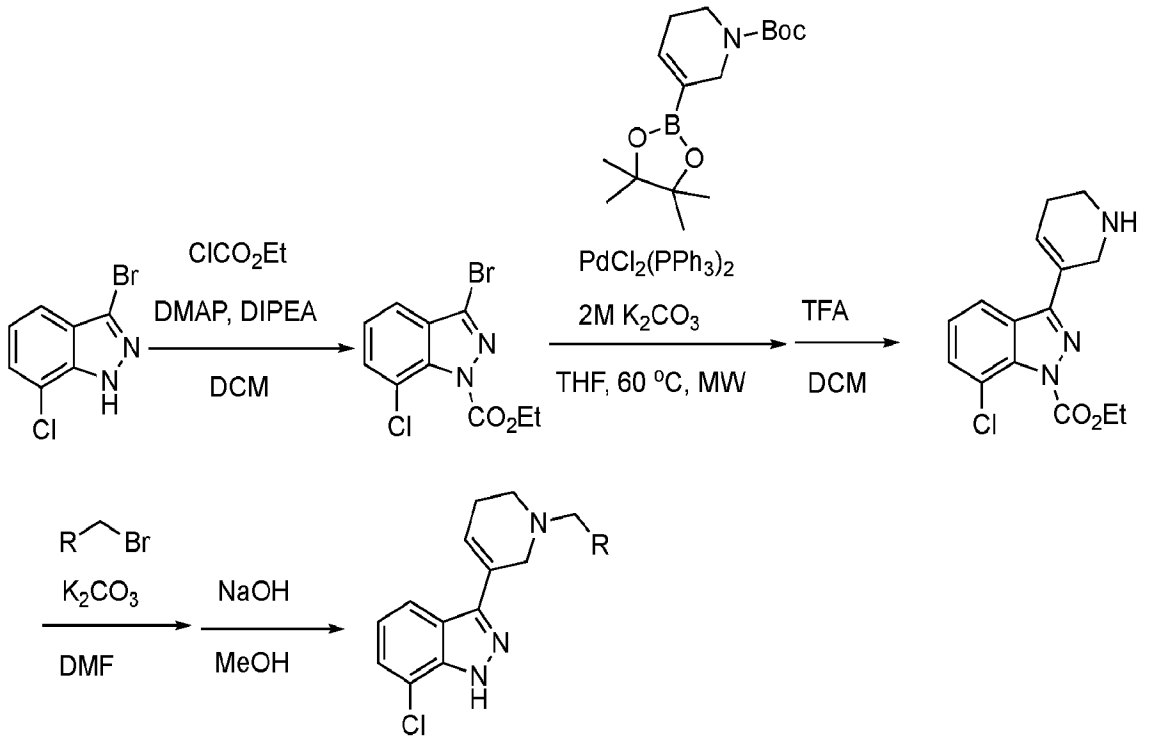
Example 122

Synthesis of XQ148-023



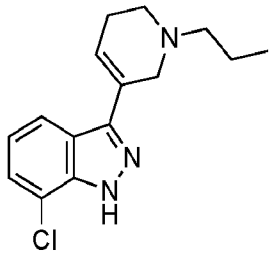
7-ethyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole (XQ148-023). XQ148-023 was synthesized following the method D which the standard procedure for preparing NS136-004. (white solid, 5.4 mg, 64%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.82 (d, J = 8.2 Hz, 1H), 7.23 (d, J = 7.0 Hz, 1H), 7.17 (t, J = 7.6 Hz, 1H), 6.84 (s, 1H), 4.30 (s, 2H), 3.47 (t, J = 6.2 Hz, 2H), 2.96 (q, J = 7.6 Hz, 2H), 2.75 – 2.71 (m, 2H), 1.36 (t, J = 7.6 Hz, 3H). LRMS (ESI) m/z: calcd for $C_{15}H_{20}N_3^+$ $[M + H]^+$, 242.17 found, 242.27.

Method I



Example 123

Synthesis of ZX147-015

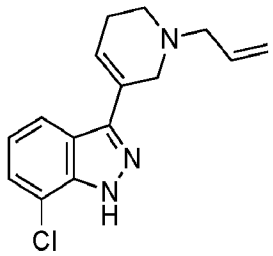


7-chloro-3-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole (ZX147-015). ZX147-015 was synthesized following the method I. 3-bromo-7-chloro-1H-indazole (100 mg, 0.43 mmol) was dissolved into 5 mL DCM, and DMAP (79 mg, 0.65 mmol) and DIEA (0.37 mL, 2.15 mmol) were added. Ethyl chloroformate (0.21 mL, 2.15 mmol) was added by drop and the mixture was reacted overnight. The mixture was quenched with $NaHCO_3$ (aq.), separated and the aqueous phase was extracted with DCM for 2 times. The organic phases were combined and concentrated. The residue was purified by flash chromatography (silica gel, PE/EA = 5/1) to afford compound ethyl 3-bromo-7-chloro-1H-indazole-1-carboxylate (70mg, 53%). $[M+H]^+$, 305.05. Then the similar coupling reaction was used according to the preparing NS131-179 from tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (69% yield). The compound was

dissolved into 3 mL DCM and 1 mL trifluoroacetate was added. The reaction mixture was stirred for 1 h, and all the organic solution and acid were removed under reduced pressure to yield the compound ethyl 7-chloro-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole-1-carboxylate as crude product and used directly into the next step. Ethyl 7-chloro-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole-1-carboxylate (22 mg, 0.055mmol), 1-bromopropane (1.5 equiv) and K_2CO_3 (2.0 equiv) were dissolved into 1 mL DMF and stirred for 5 h. The reaction mixture was quenched with water and extracted with DCM for 3 times. The organic phases were combined and concentrated under reduced pressure. The residue was dissolved into 2 mL methanol and further hydrolyzed by 1 M NaOH (aq.) (2.0 equiv). After the reaction was completed, and the mixture was purified by prepared HPLC to give the product (white solid, 8.3 mg, 39%) ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.85 (d, J = 8.3 Hz, 1H), 7.35 (d, J = 7.4 Hz, 1H), 7.11 (t, J = 7.9 Hz, 1H), 6.76 (p, J = 2.1 Hz, 1H), 4.59 – 4.49 (m, 1H), 4.03 (d, J = 15.8 Hz, 1H), 3.64 (s, 1H), 3.29 – 3.15 (m, 3H), 2.82 – 2.59 (m, 2H), 1.81 (dt, J = 9.4, 7.3 Hz, 2H), 0.99 (t, J = 7.4 Hz, 3H). LRMS (ESI) m/z: calcd for $C_{15}H_{19}ClN_3^+$ $[M + H]^+$, 276.1262, found, 276.1282.

Example 124

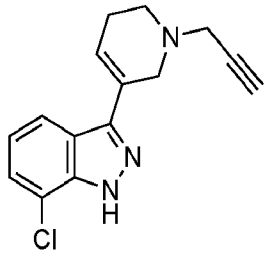
Synthesis of ZX147-016



3-(1-allyl-1,2,5,6-tetrahydropyridin-3-yl)-7-chloro-1H-indazole (ZX147-016). ZX147-016 was synthesized following the method I which the standard procedure for preparing **ZX147-015**. (white solid, 7.8 mg, 37%) ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.85 (d, J = 8.1 Hz, 1H), 7.35 (d, J = 7.4 Hz, 1H), 7.11 (t, J = 7.9 Hz, 1H), 6.76 (p, J = 2.3 Hz, 1H), 5.98 (ddt, J = 17.3, 10.1, 7.2 Hz, 1H), 5.66 – 5.53 (m, 2H), 4.49 (s, 1H), 4.05 (s, 1H), 3.89 (d, J = 7.3 Hz, 2H), 3.63 (s, 1H), 3.25 (s, 1H), 2.70 (s, 2H). LRMS (ESI) m/z: calcd for $C_{15}H_{17}ClN_3^+$ $[M + H]^+$, 274.1106, found, 274.1120.

Example 125

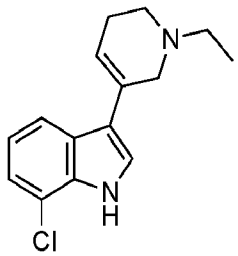
Synthesis of ZX147-017



7-chloro-3-(1-(prop-2-yn-1-yl)-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole (ZX147-017). ZX147-017 was synthesized following the method I which the standard procedure for preparing **ZX147-015**. (white solid, 5.9 mg, 28%) ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.85 (d, J = 8.3 Hz, 1H), 7.35 (d, J = 7.4 Hz, 1H), 7.11 (t, J = 7.9 Hz, 1H), 6.77 (dt, J = 4.1, 2.2 Hz, 1H), 4.39 (s, 2H), 4.22 (d, J = 2.5 Hz, 2H), 3.54 (t, J = 6.3 Hz, 2H), 3.32 (t, J = 2.6 Hz, 1H), 2.73 (dtt, J = 6.3, 4.0, 2.2 Hz, 2H). LRMS (ESI) m/z: calcd for $C_{15}H_{15}ClN_3^+$ $[M+H]^-$, 272.0949, found, 272.0955.

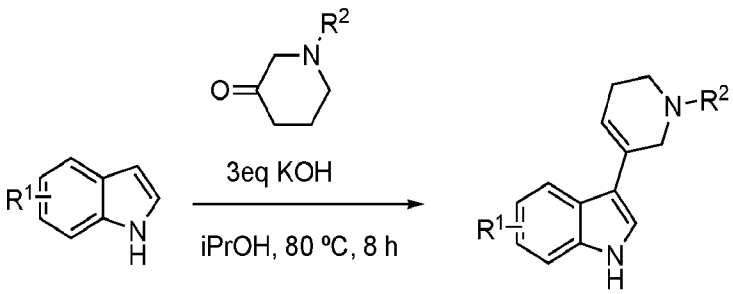
Example 126

Synthesis of ZX147-019



7-chloro-3-(1-ethyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (ZX147-019). ZX147-019 was synthesized following the standard procedure for preparing **YX143-19** from 7-chloro-1H-indole and 1-ethylpiperidin-3-one. (white solid, 40 mg, 32%) ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.67 (d, J = 8.0 Hz, 1H), 7.38 (s, 1H), 7.10 (d, J = 7.6 Hz, 1H), 6.99 (t, J = 7.9 Hz, 1H), 6.31 (t, J = 4.3 Hz, 1H), 4.21 (d, J = 15.8 Hz, 1H), 3.91 (d, J = 15.6 Hz, 1H), 3.61 (t, J = 6.6 Hz, 1H), 3.28 (qd, J = 7.4, 4.5 Hz, 2H), 3.19 – 3.07 (m, 1H), 2.61 (t, J = 20.1 Hz, 2H), 1.37 (t, J = 7.4 Hz, 3H). LRMS (ESI) m/z: calcd for $C_{15}H_{18}ClN_2^+$ $[M+H]^+$, 261.1153, found, 261.1094.

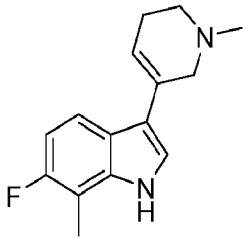
METHOD K:



R^2 = Me or Bn

Example 127

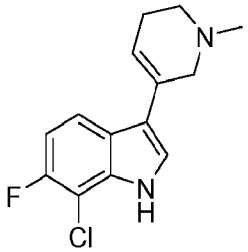
Synthesis of NS144-097



6-fluoro-7-methyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (NS144-097). NS144-097 was synthesized following the Method K. To a solution of 6-fluoro-7-methyl-1*H*-indole (30 mg, 0.2 mmol, 1 equiv) in ^{i}PrOH (2 mL) were added KOH (56 mg, 1.0 mmol, 5 equiv) and 1-methylpiperidin-3-one HCl salt (89.4 mg, 0.6 mmol, 3 equiv) at rt, then the mixture was stirred for 8 h at 80 °C, evaporated and the resulting mixture was purified by prep-HPLC to give the product (white solid, 36 mg, 20%) ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.59 (dd, J = 8.8, 4.9 Hz, 1H), 7.36 (s, 1H), 6.86 (dd, J = 10.2, 8.8 Hz, 1H), 6.35 (dt, J = 4.4, 1.9 Hz, 1H), 4.32 (d, J = 15.8 Hz, 1H), 3.97 (dd, J = 15.9, 2.8 Hz, 1H), 3.64 (dd, J = 12.4, 6.0 Hz, 1H), 3.30 – 3.24 (m, 1H), 3.05 (s, 3H), 2.81 – 2.71 (m, 1H), 2.65 (d, J = 18.9 Hz, 1H), 2.39 (d, J = 1.6 Hz, 3H). MS (ESI) m/z: calcd for $C_{15}H_{18}FN_2^+$ $[M + H]^+$, 245.1; found, 245.2.

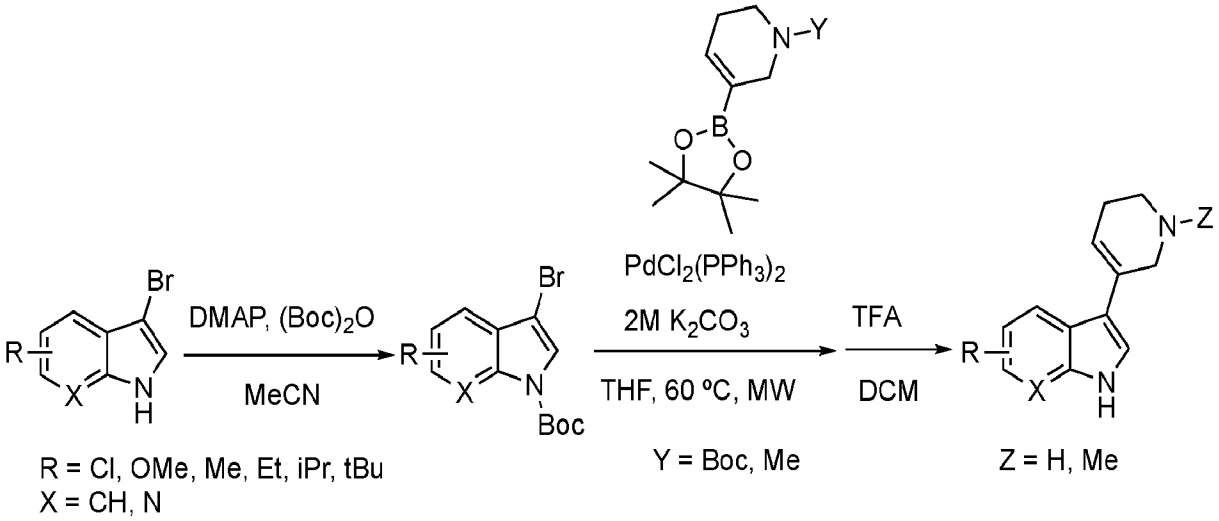
Example 128

Synthesis of NS144-098



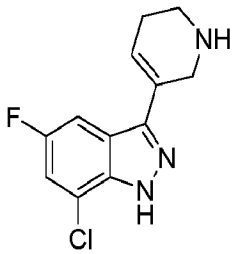
7-chloro-6-fluoro-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (NS144-098). NS144-098 was synthesized following the standard procedure for preparing NS144-097 from 7-chloro-6-fluoro-1H-indole and 1-methylpiperidin-3-one. (white solid, 20 mg, 13%) ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.73 (dd, J = 8.8, 4.5 Hz, 1H), 7.44 (s, 1H), 7.02 (dd, J = 9.9, 8.8 Hz, 1H), 6.38 (dt, J = 4.2, 2.0 Hz, 1H), 4.32 (d, J = 15.8 Hz, 1H), 4.02 – 3.94 (m, 1H), 3.69 – 3.60 (m, 1H), 3.29 (d, J = 8.2 Hz, 1H), 3.06 (s, 3H), 2.83 – 2.63 (m, 2H). MS (ESI) m/z: calcd for $C_{14}H_{15}ClFN_2^+$ $[M + H]^+$, 265.1; found, 265.1.

Method L:



Example 129

Synthesis of NS144-102

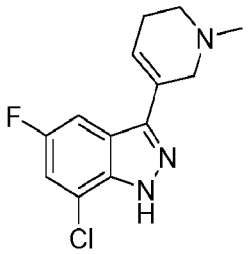


7-chloro-5-fluoro-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole (NS144-102). NS144-102 was synthesized following the Method L. To a solution of 3-bromo-7-chloro-5-fluoro-1H-indazole (1 mmol, 1 equiv) in MeCN (4 mL) were added DMAP (147 mg, 1.2 mmol, 1.2 equiv), $(Boc)_2O$ (240 mg, 1.1 mmol, 1.1 equiv). After being stirred for 2 h at room temperature, the resulting mixture was purified by silica gel (10% ethyl acetate in hexane) to afford tert-butyl 3-bromo-7-chloro-5-fluoro-1H-pyrrolo[2,3-b]pyridine-1-carboxylate as an intermediate. To a solution of the intermediate (0.1 mmol, 1 equiv) in THF (1 mL) were added tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (31 mg, 0.1 mmol, 1 equiv), 2M K_2CO_3 solution (0.15 mL, 0.3 mmol, 3 equiv), $Pd(PPh_3)_2Cl_2$ (7.0 mg, 0.01 mmol, 0.1 equiv), under nitrogen atmosphere. After being stirred for 1 h at 60 °C under microwave irradiation, the crude product was added DCM/TFA (1 mL, 1:1), and stirred for 2 h at rt, followed by purified by prep-HPLC to yield NS144-102 (white solid, 22.3 mg, 61%) ^1H NMR (400 MHz, Methanol-d_4) δ 8.09 (d, J = 6.9 Hz, 1H), 7.38 (d, J = 9.1 Hz, 1H), 6.77 (dq, J = 4.0, 2.0 Hz, 1H), 4.24 (q, J = 2.2 Hz,

2H), 3.44 (t, J = 6.2 Hz, 2H), 2.73-2.68 (m, 2H). MS (ESI) m/z: calcd for $C_{12}H_{12}ClFN_3^+$ $[M + H]^+$, 252.1; found, 252.1.

Example 130

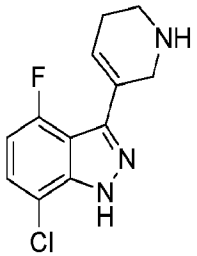
Synthesis of NS144-101



7-chloro-5-fluoro-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole (NS144-101). NS144-101 was synthesized following the standard procedure for preparing NS144-102 from 3-bromo-7-chloro-5-fluoro-1H-indazole and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine. (white solid, 20.5 mg, 54%) ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.09 (d, J = 6.9 Hz, 1H), 7.38 (d, J = 9.1 Hz, 1H), 6.77 (dt, J = 4.2, 2.0 Hz, 1H), 4.60 (d, J = 16.2 Hz, 1H), 4.12 – 4.02 (m, 1H), 3.75 – 3.63 (m, 1H), 3.35 (dd, J = 11.1, 5.7 Hz, 1H), 3.08 (s, 3H), 2.89 – 2.67 (m, 2H). MS (ESI) m/z: calcd for $C_{13}H_{14}ClFN_3^+$ $[M + H]^+$, 266.1; found, 266.2.

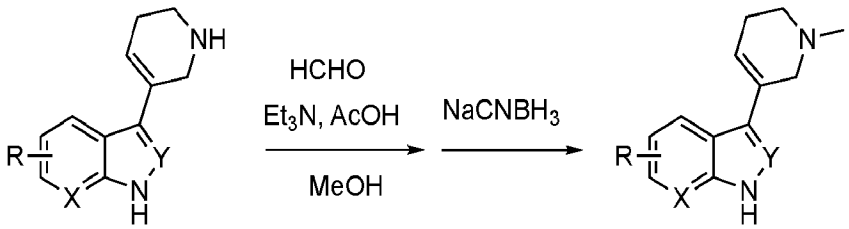
Example 131

Synthesis of NS144-107



7-chloro-4-fluoro-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole (NS144-107). NS144-107 was synthesized following the standard procedure for preparing NS144-102 from 3-bromo-7-chloro-4-fluoro-1H-indazole and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 25.3 mg, 69%) ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.43 – 7.38 (m, 1H), 6.92 – 6.85 (m, 2H), 4.28 (t, J = 2.2 Hz, 2H), 3.44 (t, J = 6.2 Hz, 2H), 2.71-2.65 (m, 2H). MS (ESI) m/z: calcd for $C_{12}H_{12}ClFN_3^+$ $[M + H]^+$, 252.1; found, 252.1.

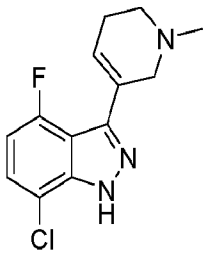
METHOD M:



X = N, CH; Y = N, CH

Example 132

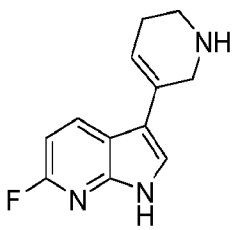
Synthesis of NS144-108



7-chloro-4-fluoro-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole (NS144-108). NS144-108 was synthesized following the Method M. To a solution of NS144-107 (0.02 mmol, 1 equiv) in MeOH (1 mL) were added Et_3N (3 drops), AcOH (5 drops), paraformaldehyde (10 mg). After being stirred for 1 h at room temperature, the resulting mixture was added $NaCNBH_3$ (3.8 mg, 0.06 mmol, 3 equiv), stirred for 1 h at rt, the resulting mixture was purified by prep-HPLC to give **NS144-108** (white solid, 9.7 mg, 85%) ^1H NMR (400 MHz, Methanol-d_4) δ 7.41 (ddd, J = 8.3, 3.9, 0.9 Hz, 1H), 6.94 – 6.85 (m, 2H), 4.63 (d, J = 16.2 Hz, 1H), 4.13 (d, J = 16.1 Hz, 1H), 3.68 (t, J = 7.6 Hz, 1H), 3.36 (dd, J = 11.1, 5.7 Hz, 1H), 3.09 (d, J = 0.9 Hz, 3H), 2.86 – 2.68 (m, 2H). MS (ESI) m/z: calcd for $C_{13}H_{14}ClFN_3^+$ $[M + H]^+$, 266.1; found, 266.2.

Example 133

Synthesis of NS144-109

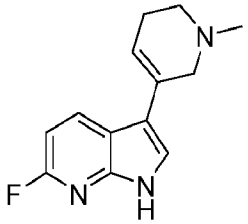


6-fluoro-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine (NS144-109). NS144-109 was synthesized following the standard procedure for preparing NS144-102 from 3-bromo-6-

fluoro-1H-pyrrolo[2,3-b]pyridine and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 24.5 mg, 55%) ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.27 (t, J = 6.5 Hz, 1H), 7.53 (s, 1H), 7.00 (dd, J = 11.2, 5.6 Hz, 1H), 6.35 (td, J = 4.3, 2.3 Hz, 1H), 4.07 (d, J = 2.9 Hz, 2H), 3.40 (t, J = 6.2 Hz, 2H), 2.66-2.61 (m, 2H). MS (ESI) m/z: calcd for $C_{12}H_{13}FN_3^+$ $[M + H]^+$, 218.1; found, 218.2.

Example 134

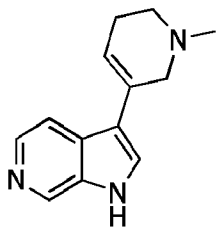
Synthesis of NS144-110



6-fluoro-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine (NS144-110). NS144-110 was synthesized following the Method M from NS144-109. (white solid, 5.5 mg, 60%) ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.25 (t, J = 6.5 Hz, 1H), 7.52 (s, 1H), 6.96 (dd, J = 11.3, 5.5 Hz, 1H), 6.35 (d, J = 4.4 Hz, 1H), 4.31 (d, J = 15.8 Hz, 1H), 4.01 (d, J = 16.0 Hz, 1H), 3.65 (t, J = 9.0 Hz, 1H), 3.28 (d, J = 5.3 Hz, 1H), 3.06 (s, 3H), 2.78 – 2.59 (m, 2H).MS (ESI) m/z: calcd for $C_{13}H_{15}FN_3^+$ $[M + H]^+$, 232.1; found, 232.1.

Example 135

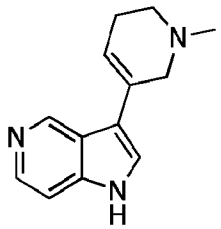
Synthesis of YS135-52



3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-pyrrolo[2,3-*c*]pyridine (YS135-52). YS135-52 was synthesized following the Method L which the standard procedure for preparing NS144-102. ^{1}H NMR (400 MHz, MeOD) δ 9.13 (d, J = 2.5 Hz, 1H), 8.45 – 8.17 (m, 3H), 6.80 – 6.43 (m, 1H), 4.54 – 4.00 (m, 2H), 3.83 – 3.64 (m, 1H), 3.52 – 3.34 (m, 1H), 3.11 (s, 3H), 2.89 – 2.59 (m, 2H). MS (ESI) m/z: 214.2 $[M+H]^+$.

Example 136

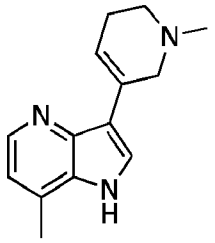
Synthesis of YS135-53



3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-pyrrolo[3,2-*c*]pyridine (YS135-53). YS135-53 was synthesized following the Method L. ^{1}H NMR (400 MHz, MeOD) δ 9.40 (s, 1H), 8.42 (d, J = 6.1 Hz, 1H), 8.11 – 7.90 (m, 2H), 6.81 – 6.39 (m, 1H), 4.50 – 3.93 (m, 2H), 3.79 – 3.44 (m, 2H), 3.11 (s, 3H), 2.88 – 2.64 (m, 2H). MS (ESI) m/z: $[M+H]^+$ 214.3.

Example 137

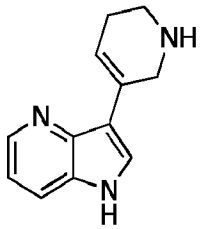
Synthesis of YS135-54



7-methyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-pyrrolo[3,2-*b*]pyridine (YS135-54). YS135-54 was synthesized following the Method L. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.22 (m, 1H), 7.22 – 6.73 (m, 2H), 6.22 (t, J = 9.0 Hz, 1H), 5.07 – 4.82 (m, 4H), 3.62 (s, 3H), 2.26 – 1.76 (m, 5H). MS (ESI) m/z: $[M+H]^+$ 228.1.

Example 138

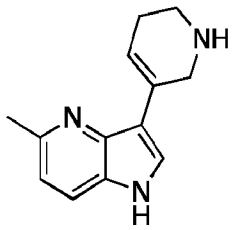
Synthesis of YS135-80



3-(1,2,5,6-tetrahydropyridin-3-yl)-1*H*-pyrrolo[3,2-*b*]pyridine (YS135-80). YS135-80 was synthesized following the Method L. ^{1}H NMR (400 MHz, MeOD) δ 8.51 (dd, J = 9.8, 7.0 Hz, 2H), 8.12 (s, 1H), 7.65 (dd, J = 8.2, 5.9 Hz, 1H), 6.45 (s, 1H), 3.79 – 3.57 (m, 2H), 3.36 (t, J = 6.2 Hz, 2H), 2.76 – 2.50 (m, 2H). MS (ESI) m/z: $[M+H]^+$ 200.1.

Example 139

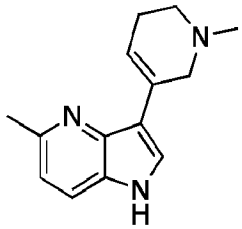
Synthesis of YS135-81



5-methyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1*H*-pyrrolo[3,2-*b*]pyridine (YS135-81). YS135-81 was synthesized following the Method L. ^{1}H NMR (400 MHz, MeOD) δ 8.48 (dd, J = 8.5, 2.1 Hz, 1H), 8.10 (s, 1H), 7.57 (d, J = 8.2 Hz, 1H), 6.56 – 6.34 (m, 1H), 4.11 – 4.05 (m, 1H), 3.71 (d, J = 2.6 Hz, 1H), 3.47 (t, J = 6.2 Hz, 1H), 3.37 – 3.25 (m, 1H), 2.91 (s, 3H), 2.78 – 2.57 (m, 1H), 2.57 – 2.39 (m, 1H). MS (ESI) m/z: $[M+H]^+$ 214.2.

Example 140

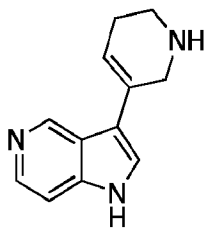
Synthesis of YS135-82



5-methyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-pyrrolo[3,2-*b*]pyridine (YS135-82). YS135-82 was synthesized following the Method L. ^{1}H NMR (400 MHz, MeOD) δ 8.36 (d, J = 8.4 Hz, 1H), 7.98 (s, 1H), 7.46 (d, J = 8.5 Hz, 1H), 6.58 – 6.12 (m, 1H), 4.24 (d, J = 16.1 Hz, 1H), 3.88 (d, J = 16.0 Hz, 1H), 3.69 – 3.46 (m, 1H), 3.31 – 3.23 (m, 1H), 2.97 (s, 3H), 2.80 (s, 3H), 2.76 – 2.40 (m, 2H). MS (ESI) m/z: $[M+H]^+$ 228.1.

Example 141

Synthesis of YS135-96

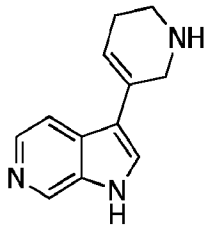


3-(1,2,5,6-tetrahydropyridin-3-yl)-1*H*-pyrrolo[3,2-*c*]pyridine (YS135-96). YS135-96 was synthesized following the Method L. ^{1}H NMR (400 MHz, MeOD) δ 9.38 (d, J = 1.1 Hz, 1H), 8.41

(d, J = 6.8 Hz, 1H), 8.14 – 7.58 (m, 2H), 6.82 – 6.33 (m, 1H), 4.16 (q, J = 2.0 Hz, 2H), 3.47 (t, J = 6.2 Hz, 2H), 2.95 – 2.48 (m, 5H). MS (ESI) m/z: $[M+H]^+$ 200.1.

Example 142

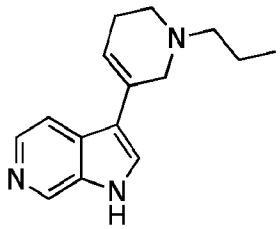
Synthesis of YS135-98



3-(1,2,5,6-tetrahydropyridin-3-yl)-1*H*-pyrrolo[2,3-*c*]pyridine (YS135-98). YS135-98 was synthesized following the Method L. ^{1}H NMR (400 MHz, MeOD) δ 9.12 (d, J = 1.0 Hz, 1H), 8.62 – 8.17 (m, 3H), 6.94 – 6.35 (m, 1H), 4.17 (d, J = 2.3 Hz, 2H), 3.47 (t, J = 6.2 Hz, 2H), 2.91 – 2.62 (m, 2H). MS (ESI) m/z: $[M+H]^+$ 200.2.

Example 143

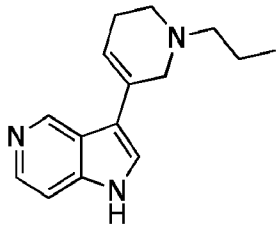
Synthesis of YS135-99



3-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-pyrrolo[2,3-*c*]pyridine (YS135-99). YS135-99 was synthesized following the Method M using propionaldehyde instead of formaldehyde. ^{1}H NMR (400 MHz, MeOD) δ 9.13 (d, J = 2.0 Hz, 1H), 8.52 – 8.14 (m, 3H), 6.55 (tt, J = 3.8, 2.0 Hz, 1H), 4.41 (d, J = 16.0 Hz, 1H), 4.12 (d, J = 16.0 Hz, 1H), 3.76 (d, J = 8.1 Hz, 1H), 3.39 – 3.24 (m, 3H), 2.97 – 2.60 (m, 2H), 1.95 – 1.82 (m, 2H), 1.37 – 0.86 (m, 3H). MS (ESI) m/z: $[M+H]^+$ 242.3.

Example 144

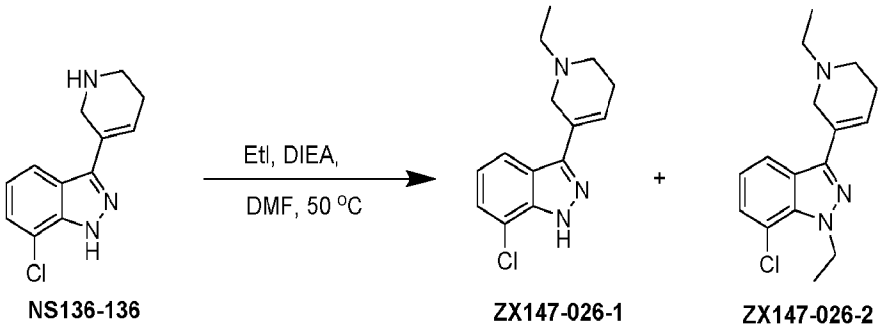
Synthesis of YS135-100



3-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-pyrrolo[3,2-*c*]pyridine (YS135-100). YS135-100 was synthesized following the Method M using propionaldehyde instead of formaldehyde. ^{1}H NMR (400 MHz, MeOD) δ 9.39 (s, 1H), 8.42 (d, J = 6.6 Hz, 1H), 8.01 (d, J = 7.1 Hz, 2H), 6.87 – 6.35 (m, 1H), 4.66 – 4.20 (m, 1H), 4.20 – 3.96 (m, 1H), 3.90 – 3.72 (m, 1H), 3.51 – 3.15 (m, 3H), 3.05 – 2.47 (m, 2H), 1.99 – 1.69 (m, 2H), 1.11 (t, J = 1.6 Hz, 3H). MS (ESI) m/z: $[M+H]^+$ 242.2.

Examples 145 and 146

Synthesis of compounds ZX147-026-1 and ZX147-026-2:



NS136-136 ZX147-026-1 ZX147-026-2

7-chloro-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole (NS136-136). NS136-136 was synthesized following Method L from 3-bromo-7-chloro-1H-indazole and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 13.9 mg, 40%) ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.94 (t, J = 6.9 Hz, 1H), 7.44 (d, J = 7.2 Hz, 1H), 7.20 (dd, J = 8.9, 4.9 Hz, 1H), 6.85 (s, 1H), 4.28 (s, 2H), 3.46 (q, J = 6.1 Hz, 2H), 2.72 (d, J = 5.9 Hz, 2H). MS (ESI) m/z: calcd for $C_{12}H_{13}ClN_3^+$ $[M + H]^+$, 234.1 found, 234.3.

The mixture of NS136-136 (25 mg, 0.075 mmol, 1 equiv.), EtI (23 mg, 2.0 equiv.) and DIEA (49mg, 5.0 equiv.) in DMF (1 mL) was stirred at 50°C in a sealed tube overnight. The reaction mixture was purified by preparative HPLC to yield ZX147-026-1 (white solid, 10 mg, 37% yield) and ZX147-026-2 (white solid, 8 mg, 26% yield).

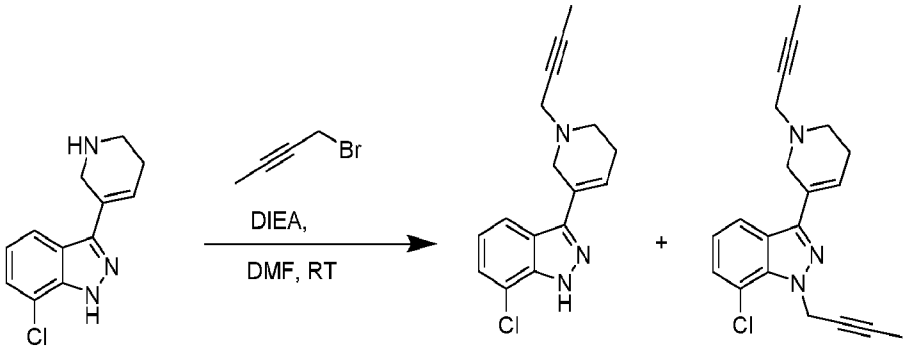
7-chloro-3-(1-ethyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole (ZX147-026-1). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.95 (d, J = 8.3 Hz, 1H), 7.45 (d, J = 7.4 Hz, 1H), 7.21 (t, J = 7.9 Hz, 1H), 6.86 (dt, J = 4.1, 2.1 Hz, 1H), 4.64 (d, J = 15.2 Hz, 1H), 4.11 (d, J = 12.6 Hz, 1H), 3.81 –

3.69 (m, 1H), 3.41 (q, J = 7.3 Hz, 2H), 3.35 - 3.25 (m, 1H), 2.85 - 2.75 (m, 2H), 1.47 (t, J = 7.3 Hz, 3H). MS (ESI) m/z: $[M + H]^+$ 262.2.

7-chloro-1-ethyl-3-(1-ethyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole (ZX147-026-2). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.96 (d, J = 8.1 Hz, 1H), 7.45 (d, J = 7.4 Hz, 1H), 7.22 (t, J = 7.9 Hz, 1H), 6.87 (dp, J = 4.0, 1.8 Hz, 1H), 4.52 (q, J = 2.2 Hz, 2H), 3.66 (t, J = 6.3 Hz, 2H), 3.55 (dh, J = 21.0, 7.2 Hz, 4H), 2.82 (tq, J = 6.4, 4.0, 3.2 Hz, 2H), 1.44 (t, J = 7.3 Hz, 6H). MS (ESI) m/z: $[M + H]^+$ 290.1.

Examples 147 and 148

Synthesis of compounds ZX147-027 and ZX147-029:



NS136-136 ZX147-029 ZX147-027

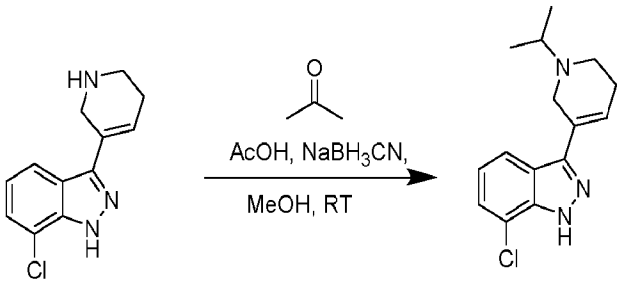
ZX147-027 and ZX147-029 were synthesized following similar procedure for preparing ZX147-026-1 and ZX147-026-2.

1-(but-2-yn-1-yl)-3-(1-(but-2-yn-1-yl)-1,2,5,6-tetrahydropyridin-3-yl)-7-chloro-1*H*-indazole (ZX147-029). Yield: 37%. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.94 (d, J = 8.1 Hz, 1H), 7.44 (d, J = 7.5 Hz, 1H), 7.20 (t, J = 7.9 Hz, 1H), 6.85 (dp, J = 4.1, 1.9 Hz, 1H), 4.71 (br, 2H), 4.21 (q, J = 2.6 Hz, 2H), 3.60 (br, 2H), 2.82 (s, 2H), 1.96 (t, J = 2.5 Hz, 3H). MS(ESI) $[M + H]^+$: 286.4.

7-chloro-3-(1-isopropyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole (ZX147-027). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.95 (d, J = 8.3 Hz, 1H), 7.44 (d, J = 7.4 Hz, 1H), 7.21 (t, J = 7.9 Hz, 1H), 6.87 (dt, J = 4.1, 2.1 Hz, 1H), 4.66 (d, J = 2.3 Hz, 2H), 4.46 (q, J = 2.5 Hz, 4H), 3.82 (t, J = 6.3 Hz, 2H), 2.86 (tq, J = 6.4, 4.0, 3.2 Hz, 2H), 1.99 (t, J = 2.5 Hz, 6H). MS(ESI) m/z: $[M + H]^+$ 337.9.

Example 149

Synthesis of compound ZX147-028:



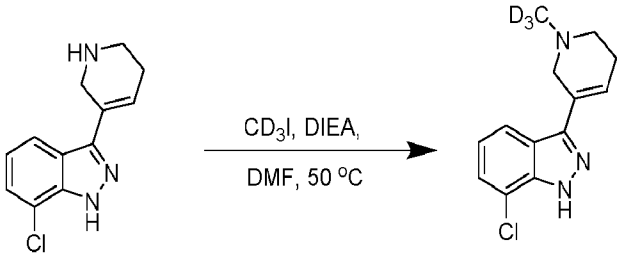
NS136-136 ZX147-028

3-(1-(but-2-yn-1-yl)-1,2,5,6-tetrahydropyridin-3-yl)-7-chloro-1*H*-indazole (ZX147-028).

ZX147-028 was synthesized following Method M using acetone instead of paraformaldehyde (white solid, 65% yield) ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.85 (d, J = 8.3 Hz, 1H), 7.34 (d, J = 7.5 Hz, 1H), 7.10 (t, J = 7.9 Hz, 1H), 6.75 (tt, J = 3.9, 1.9 Hz, 1H), 4.41 (d, J = 15.5 Hz, 1H), 4.10 (d, J = 15.3 Hz, 1H), 3.70 - 3.55 (m, 2H), 3.29 – 3.16 (m, 1H), 2.86 – 2.60 (m, 2H), 1.39 (d, J = 6.6 Hz, 6H). MS(ESI) m/z: $[M + H]^+$ 276.3.

Example 150

Synthesis of ZX147-031:



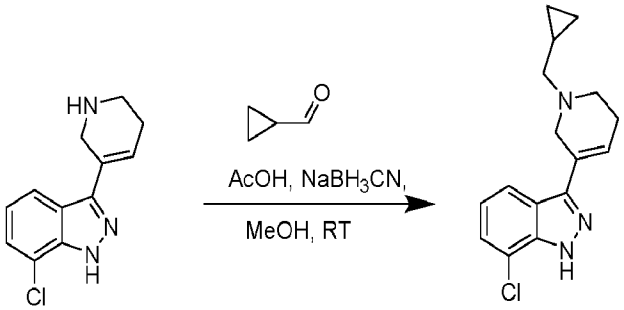
NS136-136 ZX147-031

7-chloro-3-(1-(methyl-d_3)-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole (ZX147-031).

The mixture of NS136-136 (25 mg, 0.075 mmol, 1.0 equiv.), CD_3I (16.5 mg, 0.11 mmol, 1.5 equiv.) and DIEA (65 uL, 0.38 mmol, 5.0 equiv.) in DMF (2 mL) was stirred at 50 °C in a sealed tube overnight. The reaction mixture was diluted by DCM (10 mL), washed with brine, dried over Na_2SO_4 and concentrated, followed by purified by silica gel chromatography (DCM – DCM/MeOH = 5/1), further purified by prep-HPLC. (white solid, 20%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.97 (d, J = 8.3 Hz, 1H), 7.46 (d, J = 7.5 Hz, 1H), 7.22 (t, J = 7.9 Hz, 1H), 6.87 (tt, J = 3.9, 1.9 Hz, 1H), 4.67 (d, J = 15.9 Hz, 1H), 4.14 (d, J = 16.3 Hz, 1H), 3.77 – 3.67 (m, 1H), 3.43 – 3.35 (m, 1H), 2.92 – 2.73 (m, 2H). HRMS (ESI-TOF) m/z: calcd for $C_{13}H_{12}D_3ClN_3^+$ $[M + H]^+$ 251.1137; found 251.1144.

Example 151

Synthesis of ZX147-054:

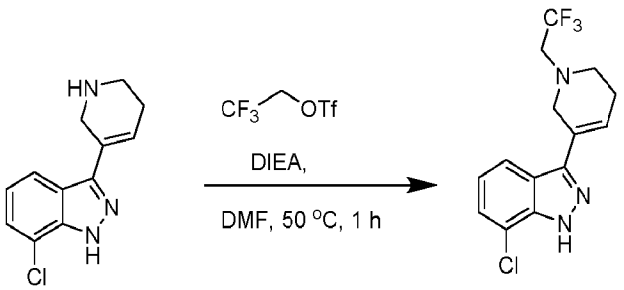


NS136-136 ZX147-054

7-chloro-3-(1-(cyclopropylmethyl)-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole (ZX147-054). ZX147-054 was prepared according to the same procedure for ZX147-028 but using cyclopropanecarbaldehyde instead of acetone. Yield: 45%. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.96 (d, J = 8.3 Hz, 1H), 7.46 (d, J = 7.5 Hz, 1H), 7.29 – 7.16 (m, 1H), 6.87 (td, J = 4.3, 1.9 Hz, 1H), 4.73 (s, 1H), 4.21 (s, 1H), 3.82 (s, 1H), 3.44 (s, 1H), 3.27 (d, J = 7.4 Hz, 2H), 2.82 (s, 2H), 1.35 – 1.23 (m, 1H), 0.85 (d, J = 8.1 Hz, 2H), 0.54 (d, J = 4.9 Hz, 2H). MS (ESI) m/z: $[M + H]^+$ 288.3.

Example 152

Synthesis of ZX147-055:

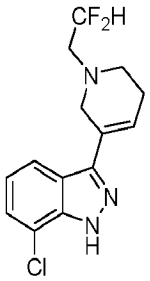


NS136-136 ZX147-055

7-chloro-3-(1-(2,2,2-trifluoroethyl)-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole (ZX147-055). ZX147-055 was synthesized following similar procedure for preparing ZX147-031 (27% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.81 (d, J = 8.3 Hz, 1H), 7.31 (d, J = 7.4 Hz, 1H), 7.06 (t, J = 7.9 Hz, 1H), 6.61 (dq, J = 4.3, 2.1 Hz, 1H), 3.95 – 3.88 (m, 2H), 3.52 (q, J = 9.6 Hz, 2H), 3.06 (t, J = 5.9 Hz, 2H), 2.50 (dt, J = 6.4, 2.9 Hz, 2H). MS (ESI) m/z: $[M + H]^+$ 316.4.

Example 153

Synthesis of ZX147-056:

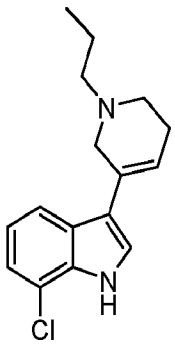


7-chloro-3-(1-(2,2-difluoroethyl)-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole(ZX147-056)

ZX147-056 was prepared according to the similar procedure for ZX147-055 but using 2,2-difluoroethyl trifluoromethanesulfonate instead of 2,2,2-trifluoroethyl trifluoromethanesulfonate (36% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.85 (d, J = 8.4 Hz, 1H), 7.34 (d, J = 7.6 Hz, 1H), 7.11 (t, J = 8.0 Hz, 1H), 6.76 (s, 1H), 6.42 (tq, J = 53.5, 3.3 Hz, 1H), 4.39 (s, 2H), 3.78 (tt, J = 15.1, 3.2 Hz, 2H), 3.54 (t, J = 6.3 Hz, 2H), 2.77 – 2.68 (m, 2H). MS (ESI) m/z: $[M + H]^+$ 298.1.

Example 154

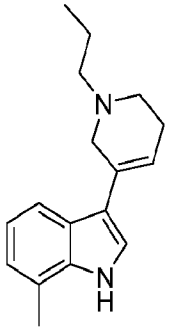
Synthesis of ZX147-092:



7-chloro-3-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indole (ZX147-092). ZX147-092 was synthesized following the standard procedure for preparing NS144-097 from 7-chloro-1H-indole and 1-propylpiperidin-3-one. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.76 (d, J = 8.1 Hz, 1H), 7.47 (s, 1H), 7.20 (d, J = 7.7 Hz, 1H), 7.08 (t, J = 8.1 Hz, 1H), 6.40 (s, 1H), 4.31 (d, J = 14.9 Hz, 1H), 4.02 (d, J = 15.5 Hz, 1H), 3.76 – 3.67 (m, 1H), 3.29 – 3.23 (m, 3H), 2.72 (d, J = 21.5 Hz, 2H), 1.90 (q, J = 8.9, 8.0 Hz, 2H), 1.08 (t, J = 8.3 Hz, 3H). MS (ESI) m/z: $[M + H]^+$ 275.2.

Example 155

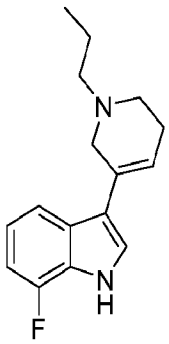
Synthesis of ZX147-093:



7-methyl-3-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indole (ZX147-093). ZX147-093 was synthesized following the standard procedure for preparing NS144-097 from 7-methyl-1H-indole and 1-propylpiperidin-3-one. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.64 (d, J = 7.9 Hz, 1H), 7.38 (s, 1H), 7.04 – 6.94 (m, 2H), 6.38 (s, 1H), 4.31 (d, J = 16.4 Hz, 1H), 4.01 (d, J = 14.9 Hz, 1H), 3.73 - 3.68 (m, 1H), 3.30 - 3.20 (m, 3H), 2.84 – 2.60 (m, 2H), 2.49 (s, 3H), 1.89 (q, J = 7.0 Hz, 2H), 1.08 (t, J = 6.9 Hz, 3H). MS (ESI) m/z: $[M + H]^+$ 255.4.

Example 156

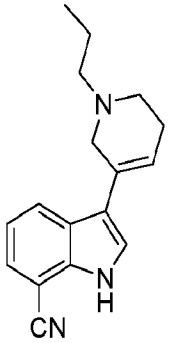
Synthesis of ZX147-094:



7-fluoro-3-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indole (ZX147-094). ZX147-094 was synthesized following the standard procedure for preparing NS144-097 from 7-fluoro-1H-indole and 1-propylpiperidin-3-one. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.60 (d, J = 10.1 Hz, 1H), 7.44 (s, 1H), 7.09 - 7.01 (m, 1H), 6.93 - 6.89 (m, 1H), 6.40 (s, 1H), 4.29 (s, 1H), 4.02 (d, J = 15.8 Hz, 1H), 3.78 – 3.64 (m, 1H), 3.30 - 3.22 (m, 3H), 2.86 – 2.61 (m, 2H), 1.89 (q, J = 7.2 Hz, 2H), 1.08 (t, J = 7.5 Hz, 3H). MS(ESI) m/z: $[M + H]^+$ 259.4.

Example 157

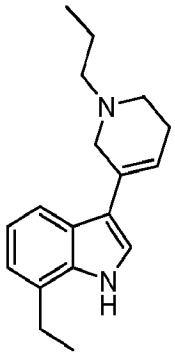
Synthesis of ZX147-095:



3-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indole-7-carbonitrile (ZX147-095). ZX147-095 was synthesized following the standard procedure for preparing NS144-097 from 1*H*-indole-7-carbonitrile and 1-propylpiperidin-3-one. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.14 (d, J = 8.2 Hz, 1H), 7.60 - 7.55 (m, 2H), 7.23 (t, J = 7.8 Hz, 1H), 6.42 (s, 1H), 4.32 (d, J = 15.5 Hz, 1H), 4.03 (d, J = 16.0 Hz, 1H), 3.79 – 3.68 (m, 1H), 3.30 - 3.24 (m, 3H), 2.85 – 2.63 (m, 2H), 1.90 (h, J = 9.1 Hz, 2H), 1.08 (t, J = 7.4 Hz, 3H). MS (ESI) m/z: $[M + H]^+$ 265.4.

Example 158

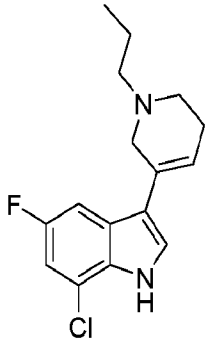
Synthesis of ZX147-096:



7-ethyl-3-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indole (ZX147-096). ZX147-096 was synthesized following the standard procedure for preparing NS144-097 from 7-ethyl-1H-indole and 1-propylpiperidin-3-one. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.64 (d, J = 8.0 Hz, 1H), 7.37 (s, 1H), 7.04 (t, J = 7.6 Hz, 1H), 7.00 (d, J = 7.2 Hz, 1H), 6.37 (s, 1H), 4.31 (d, J = 16.3 Hz, 1H), 3.99 (d, J = 13.7 Hz, 1H), 3.74 – 3.64 (m, 1H), 3.28 - 3.20 (m, 3H), 2.89 (q, J = 7.6 Hz, 2H), 2.83 – 2.57 (m, 2H), 1.88 (q, J = 8.9, 7.9 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H), 1.07 (t, J = 7.4 Hz, 3H). MS (ESI) m/z: $[M + H]^+$ 269.5.

Example 159

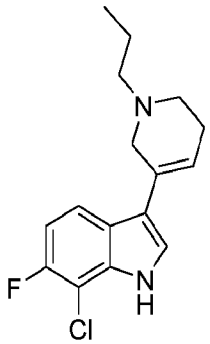
Synthesis of ZX147-097:



7-ethyl-3-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indole (ZX147-097). ZX147-097 was synthesized following the standard procedure for preparing NS144-097 from 7-chloro-5-fluoro-1*H*-indole and 1-propylpiperidin-3-one. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.53 (s, 1H), 7.47 (d, J = 9.9 Hz, 1H), 7.06 (d, J = 9.0 Hz, 1H), 6.31 (s, 1H), 4.36 – 4.22 (m, 1H), 4.01 (s, 1H), 3.70 (s, 1H), 3.30 - 3.20 (m, 3H), 2.81 – 2.59 (m, 2H), 1.89 (h, J = 7.3 Hz, 2H), 1.07 (t, J = 7.5 Hz, 3H). MS (ESI) m/z: $[M + H]^+$ 293.2.

Example 160

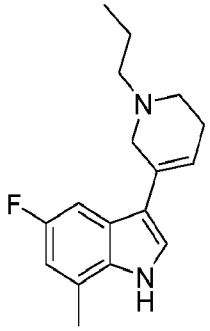
Synthesis of ZX147-098:



7-ethyl-3-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indole (ZX147-098). ZX147-098 was synthesized following the standard procedure for preparing NS144-097 from 7-chloro-6-fluoro-1*H*-indole and 1-propylpiperidin-3-one. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.72 (dd, J = 7.6, 4.6 Hz, 1H), 7.47 (s, 1H), 7.00 (t, J = 9.0 Hz, 1H), 6.37 (s, 1H), 4.29 (d, J = 15.9 Hz, 1H), 3.99 (d, J = 15.9 Hz, 1H), 3.73 - 3.67 (m, 1H), 3.30 - 3.20 (m, 3H), 2.78 - 2.65 (m, 2H), 1.89 (h, J = 7.6 Hz, 2H), 1.07 (t, J = 6.9 Hz, 3H). MS (ESI) m/z: $[M + H]^+$ 293.2.

Example 161

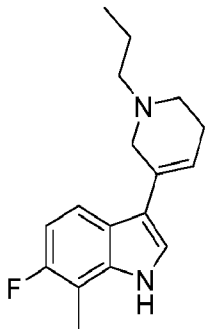
Synthesis of ZX147-099:



5-fluoro-7-methyl-3-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indole (ZX147-099). ZX147-099 was synthesized following the standard procedure for preparing NS144-097 from 5-fluoro-7-methyl-1*H*-indole and 1-propylpiperidin-3-one. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.44 (s, 1H), 7.31 (d, J = 10.2 Hz, 1H), 6.78 (d, J = 9.8 Hz, 1H), 6.30 (s, 1H), 4.29 (d, J = 15.4 Hz, 1H), 3.99 (d, J = 17.0 Hz, 1H), 3.76 – 3.66 (m, 1H), 3.29 - 3.21 (m, 3H), 2.80 - 2.62 (m, 2H), 2.49 (s, 3H), 1.89 (h, J = 7.5 Hz, 2H), 1.07 (t, J = 7.4 Hz, 3H). MS (ESI) m/z: $[M + H]^+$ 273.2.

Example 162

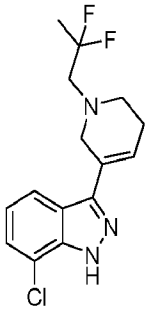
Synthesis of ZX147-100:



6-fluoro-7-methyl-3-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indole (ZX147-100). ZX147-100 was synthesized following the standard procedure for preparing NS144-097 from 6-fluoro-7-methyl-1*H*-indole and 1-propylpiperidin-3-one. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.59 (dd, J = 8.4, 5.2 Hz, 1H), 7.39 (s, 1H), 6.90 – 6.83 (m, 1H), 6.37 (s, 1H), 4.29 (d, J = 15.4 Hz, 1H), 4.00 (d, J = 15.8 Hz, 1H), 3.76 – 3.66 (m, 1H), 3.29 – 3.21 (m, 3H), 2.83 – 2.61 (m, 2H), 2.39 (s, 3H), 1.90 (p, J = 7.2 Hz, 2H), 1.08 (t, J = 6.6 Hz, 3H). MS (ESI) m/z: $[M + H]^+$ 273.4.

Example 163

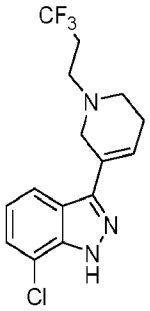
Synthesis of ZX147-128:



7-chloro-3-(1-(2,2-difluoropropyl)-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole (ZX147-128). ZX147-128 was synthesized following the standard procedure for preparing ZX147-055 from NS136-136 and 2,2-difluoropropyl trifluoromethanesulfonate. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.96 (d, J = 8.3 Hz, 1H), 7.44 (d, J = 7.5 Hz, 1H), 7.20 (t, J = 7.8 Hz, 1H), 6.87 (dt, J = 4.1, 2.3 Hz, 1H), 4.01 (t, J = 15.2 Hz, 2H), 3.68 (t, J = 6.1 Hz, 2H), 2.88 – 2.77 (m, 2H), 1.84 (t, J = 19.3 Hz, 3H). MS (ESI) m/z: $[M + H]^+$ 312.2.

Example 164

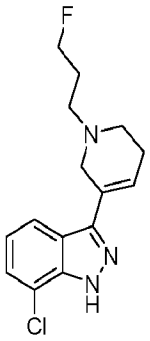
Synthesis of ZX147-129:



7-chloro-3-(1-(3,3,3-trifluoropropyl)-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole (ZX147-129). ZX147-129 was synthesized following the standard procedure for preparing ZX147-055 from NS136-136 and 3,3,3-trifluoropropyl trifluoromethanesulfonate. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.96 (d, J = 8.3 Hz, 1H), 7.45 (d, J = 7.5 Hz, 1H), 7.21 (t, J = 7.8 Hz, 1H), 6.88 (hept, J = 1.8 Hz, 1H), 4.47 (s, 2H), 3.71 – 3.51 (m, 4H), 3.05 – 2.88 (m, 2H), 2.86 – 2.76 (m, 2H). MS (ESI) m/z: $[M + H]^+$ 330.3.

Example 165

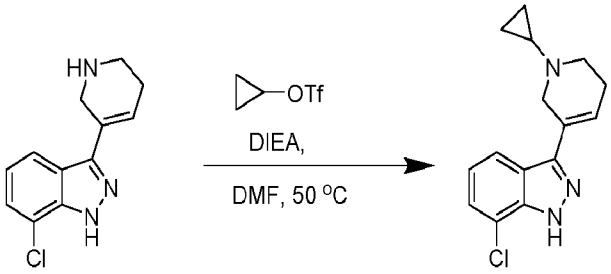
Synthesis of ZX147-130:



7-chloro-3-(1-(3-fluoropropyl)-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole (ZX147-129). ZX147-129 was synthesized following the standard procedure for preparing ZX147-055 from NS136-136 and 3-fluoropropyl trifluoromethanesulfonate. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.96 (d, J = 8.3 Hz, 1H), 7.47 – 7.41 (m, 1H), 7.21 (t, J = 7.9 Hz, 1H), 6.87 (p, J = 2.1 Hz, 1H), 4.69 (t, J = 5.5 Hz, 2H), 4.58 (t, J = 5.5 Hz, 1H), 4.20 (s, 1H), 3.79 (s, 1H), 3.52 (dd, J = 9.9, 6.2 Hz, 2H), 3.39 (s, 1H), 2.80 (s, 2H), 2.40 – 2.21 (m, 2H). MS (ESI) m/z: $[M + H]^+$ 294.4.

Example 166

Synthesis of ZX147-131

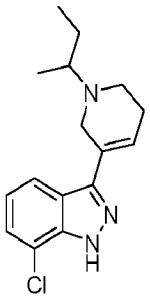


NS136-136 ZX147-131

7-chloro-3-(1-cyclopropyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole (ZX147-131). ZX147-131 was prepared according to the same procedure for ZX147-031 using cyclopropyl trifluoromethanesulfonate instead of CD_3I and the reaction mixture was purified by preparative HPLC. (white solid, 24%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.95 (dd, J = 8.3, 0.8 Hz, 1H), 7.44 (dd, J = 7.5, 0.8 Hz, 1H), 7.20 (t, J = 7.9 Hz, 1H), 6.86 (p, J = 2.1 Hz, 1H), 6.08 (ddt, J = 17.3, 10.1, 7.3 Hz, 1H), 5.76 – 5.63 (m, 2H), 4.61 (s, 1H), 4.15 (s, 1H), 3.99 (d, J = 7.3 Hz, 2H), 3.74 (s, 1H), 2.79 (s, 2H). MS (ESI) m/z: calcd for $C_{15}H_{17}ClN_3^+$ $[M + H]^+$ 274.1; found 274.3.

Example 167

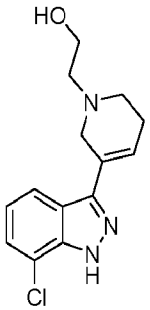
Synthesis of ZX147-137



3-(1-(*sec*-butyl)-1,2,5,6-tetrahydropyridin-3-yl)-7-chloro-1*H*-indazole (ZX147-137). ZX147-137 was prepared according to the same procedure for ZX147-028 but using butan-2-one instead of acetone. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.84 (d, J = 8.1 Hz, 1H), 7.33 (d, J = 7.5 Hz, 1H), 7.09 (t, J = 7.9 Hz, 1H), 6.74 (s, 1H), 4.40 (t, J = 14.6 Hz, 1H), 4.23 – 4.08 (m, 1H), 3.56 (dd, J = 12.4, 6.1 Hz, 1H), 3.49 – 3.35 (m, 1H), 3.34 – 3.19 (m, 1H), 2.85 – 2.58 (m, 2H), 1.99 – 1.82 (m, 1H), 1.64 (td, J = 15.8, 6.5 Hz, 1H), 1.36 (d, J = 6.6 Hz, 3H), 0.99 (t, J = 7.4 Hz, 3H). MS (ESI) m/z: $[M + H]^+$ 290.3.

Example 168

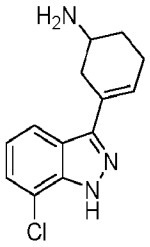
Synthesis of ZX147-183:



2-(5-(7-chloro-1*H*-indazol-3-yl)-3,6-dihydropyridin-1(2*H*)-yl)ethan-1-ol (ZX147-183). ZX147-183 was prepared according to the same procedure for ZX147-031 but using 2-bromoethan-1-ol instead of CD_3I. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.95 (d, J = 8.3 Hz, 1H), 7.45 (d, J = 7.5 Hz, 1H), 7.20 (t, J = 7.4 Hz, 1H), 6.86 (s, 1H), 4.67 (d, J = 16.5 Hz, 1H), 4.23 (d, J = 16.3 Hz, 1H), 3.99 (t, J = 6.4 Hz, 2H), 3.80 (s, 1H), 3.49 – 3.44 (m, 2H), 3.44 - 3.33 (m, 1H), 2.92 – 2.69 (m, 2H). MS (ESI) m/z: $[M + H]^+$ 278.4.

Example 169

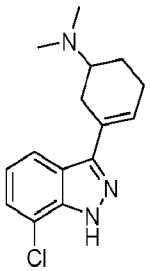
Synthesis of ZX156-011:



3-(7-chloro-1*H*-indazol-3-yl)cyclohex-3-en-1-amine (ZX156-011). ZX156-011was synthesized following the standard procedure for preparing NS144-102 from 3-bromo-7-chloro -1H-indazole and *tert*-butyl (3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-en-1-yl)carbamate. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.87 (d, J = 8.2 Hz, 1H), 7.38 (d, J = 7.4 Hz, 1H), 7.13 (t, J = 7.9 Hz, 1H), 6.63 (s, 1H), 3.58 (t, J = 13.2 Hz, 1H), 3.21 (d, J = 17.2 Hz, 1H), 2.70 – 2.59 (m, 1H), 2.58 - 2.44 (m, 2H), 2.20 - 2.12 (m, 1H), 1.84 (q, J = 10.4, 9.0 Hz, 1H). MS (ESI) m/z: $[M + H]^+$ 248.2.

Example 170

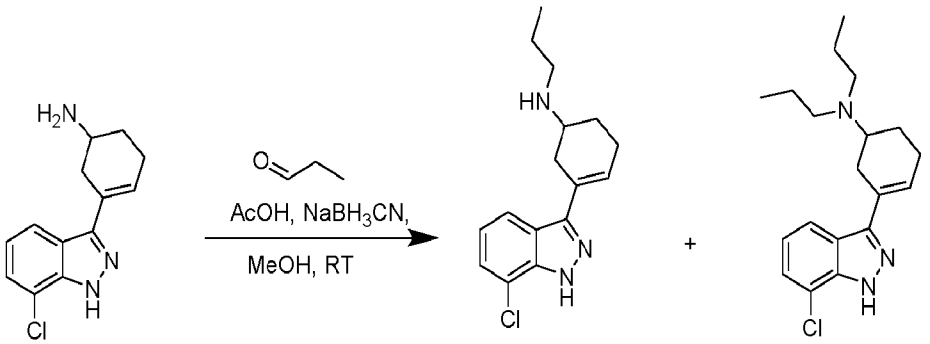
Synthesis of ZX156-012:



3-(7-chloro-1*H*-indazol-3-yl)-*N*,*N*-dimethylcyclohex-3-en-1-amine (ZX156-012). ZX156-012 was prepared according to the same procedure for ZX147-028 from ZX156-011 and paraformaldehyde. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.90 (d, J = 8.4 Hz, 1H), 7.41 (d, J = 7.5 Hz, 1H), 7.15 (t, J = 7.9 Hz, 1H), 6.65 (s, 1H), 3.72 – 3.62 (m, 1H), 3.27 (d, J = 12.1 Hz, 1H), 2.98 (s, 6H), 2.85 – 2.74 (m, 1H), 2.71 – 2.60 (m, 1H), 2.60 – 2.47 (m, 1H), 2.30 - 2.24 (m, 1H), 1.94 – 1.81 (m, 1H). MS (ESI) m/z: $[M + H]^+$ 276.3.

Example 171 and 172

Synthesis of ZX156-014-1 and 156-014-2:

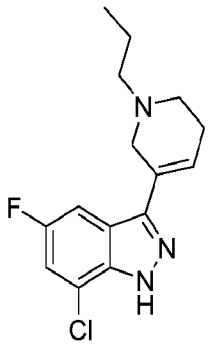


3-(7-chloro-1*H*-indazol-3-yl)-*N*-propylcyclohex-3-en-1-amine (ZX156-014-1). ZX156-014-1 was prepared according to the same procedure as ZX147-028 from ZX156-011 and propionaldehyde. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.90 (d, J = 8.5 Hz, 1H), 7.41 (d, J = 5.6 Hz, 1H), 7.15 (t, J = 7.9 Hz, 1H), 6.67 (s, 1H), 3.54 (d, J = 12.2 Hz, 1H), 3.38 – 3.26 (m, 1H), 3.13 (t, J = 7.6 Hz, 2H), 2.71 – 2.45 (m, 3H), 2.31 – 2.23 (m, 1H), 1.87 – 1.72 (m, 3H), 1.08 (t, J = 7.5 Hz, 3H). MS (ESI) m/z: $[M + H]^+$ 290.3.

3-(7-chloro-1*H*-indazol-3-yl)-*N*,*N*-dipropylcyclohex-3-en-1-amine (ZX156-014-2). MS (ESI) m/z: $[M + H]^+$ 332.2.

Example 173

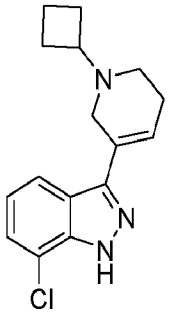
Synthesis of ZX156-019.



7-chloro-5-fluoro-3-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole (ZX156-019). ZX156-019 was prepared according to the same procedure for ZX147-028 from NS144-102 and propionaldehyde. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.13 (d, J = 6.9 Hz, 1H), 7.40 (d, J = 9.2 Hz, 1H), 6.81 (s, 1H), 4.60 (d, J = 15.5 Hz, 1H), 4.09 (d, J = 14.8 Hz, 1H), 3.73 (s, 1H), 3.38 - 3.24 (m, 2H), 2.78 (s, 2H), 1.90 (h, J = 7.8 Hz, 2H), 1.08 (t, J = 7.5 Hz, 3H). MS (ESI) m/z: $[M + H]^+$ 294.3.

Example 174

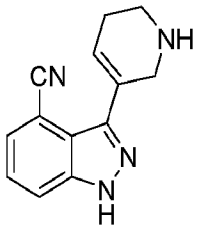
Synthesis of ZX156-059.



7-chloro-3-(1-cyclobutyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole (ZX156-059). ZX156-059 was prepared according to the same procedure for ZX147-028 from NS136-136 and cyclobutanone. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.93 (d, J = 8.4 Hz, 1H), 7.43 (d, J = 7.5 Hz, 1H), 7.22 – 7.16 (m, 1H), 6.85 (s, 1H), 4.52 (s, 1H), 3.91 (p, J = 9.3, 8.4 Hz, 2H), 3.63 (s, 1H), 3.17 (s, 1H), 2.77 (s, 2H), 2.51 - 2.42 (m, 2H), 2.42 – 2.28 (m, 2H), 1.94 (h, J = 10.3, 9.9 Hz, 2H). MS (ESI) m/z: $[M + H]^+$ 288.2.

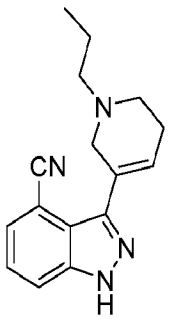
Example 175

Step 1: Synthesis of NS136-152



3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole-4-carbonitrile (NS136-152). NS136-152 was synthesized following the standard procedure for preparing NS144-102 from 3-bromo-1H-indazole-4-carbonitrile and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 20 mg, 59%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.90 (d, J = 8.5 Hz, 1H), 7.69 (d, J = 7.1 Hz, 1H), 7.54 (t, J = 8.1 Hz, 1H), 6.69 – 6.57 (m, 1H), 4.34 – 4.15 (m, 2H), 3.47 (t, J = 6.4 Hz, 2H), 2.83 – 2.64 (m, 2H). MS (ESI) m/z: calcd for $C_{13}H_{13}N_4^+$ $[M + H]^+$, 225.1 found, 225.3.

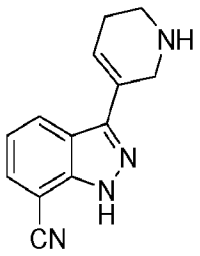
Step 2: Synthesis of ZX156-069.



3-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole-4-carbonitrile (ZX156-069). ZX156-069 was prepared according to the same procedure for ZX147-028 from NS136-152 and propionaldehyde. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.91 (d, J = 8.8 Hz, 1H), 7.70 (d, J = 7.3 Hz, 1H), 7.56 (t, J = 7.1 Hz, 1H), 6.65 (s, 1H), 4.54 (d, J = 16.0 Hz, 1H), 4.10 (d, J = 13.7 Hz, 1H), 3.76 (s, 1H), 3.36 (s, 1H), 2.79 (s, 2H), 1.89 (q, J = 7.7 Hz, 2H), 1.08 (t, J = 6.8 Hz, 3H). MS (ESI) m/z: $[M + H]^+$ 266.7.

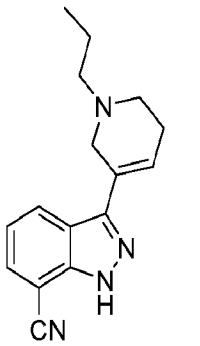
Example 176

Step 1: Synthesis of NS144-046



3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole-7-carbonitrile (NS144-046). NS144-046 was synthesized following the standard procedure for preparing NS144-102 from 3-bromo-1H-indazole-7-carbonitrile and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. (white solid, 16.6 mg, 49%) ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.35 (dd, J = 8.5, 2.8 Hz, 1H), 7.86 (dd, J = 7.5, 2.8 Hz, 1H), 7.36 (dd, J = 9.1, 6.4 Hz, 1H), 6.90 (td, J = 4.1, 2.0 Hz, 1H), 4.34 – 4.26 (m, 2H), 3.46 (t, J = 6.1 Hz, 2H), 2.73 (tt, J = 4.3, 2.2 Hz, 2H). MS (ESI) m/z: calcd for $C_{13}H_{13}N_4^+$ $[M + H]^+$, 225.1 found, 225.3.

Step 2: Synthesis of ZX156-070

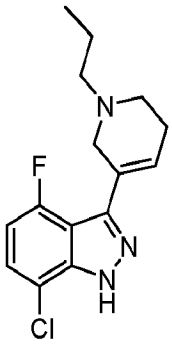


3-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole-7-carbonitrile (ZX156-070). ZX156-070 was prepared according to the same procedure as ZX147-028 from NS144-046 and propionaldehyde. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.35 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 7.3 Hz, 1H), 7.36 (t, J = 7.8 Hz, 1H), 6.90 (s, 1H), 4.65 (d, J = 16.1 Hz, 1H), 4.14 (d, J = 15.9 Hz,

1H), 3.75 (s, 1H), 3.38 (s, 1H), 2.80 (s, 2H), 1.90 (h, J = 6.8, 6.3 Hz, 2H), 1.09 (t, J = 6.9 Hz, 3H). MS (ESI) m/z: $[M + H]^+$ 267.0.

Example 177

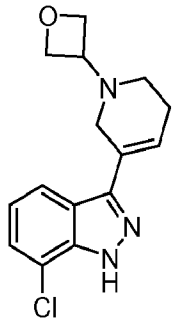
Synthesis of ZX156-071



7-chloro-4-fluoro-3-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole (ZX156-071). ZX156-071 was prepared according to the same procedure as ZX147-028 from NS144-107 and propionaldehyde. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.43 - 7.40 (m, 1H), 6.93 – 6.89 (m, 1H), 6.87 (s, 1H), 4.63 (d, J = 15.4 Hz, 1H), 4.14 (d, J = 14.3 Hz, 1H), 3.73 (s, 1H), 3.29 (s, 1H), 2.75 (s, 2H), 1.90 (h, J = 7.2 Hz, 2H), 1.09 (t, J = 7.4 Hz, 3H). MS (ESI) m/z: $[M + H]^+$ 294.8.

Example 178

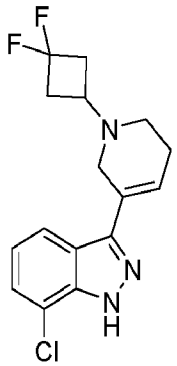
Synthesis of ZX156-089



7-chloro-3-(1-(oxetan-3-yl)-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole (ZX156-089). ZX156-089 was prepared according to the same procedure as ZX147-028 from NS136-136 and oxetan-3-one. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.94 (d, J = 8.2 Hz, 1H), 7.44 (d, J = 7.5 Hz, 1H), 7.20 (t, J = 7.9 Hz, 1H), 6.88 (s, 1H), 4.98 (d, J = 8.1 Hz, 2H), 4.96 – 4.91 (m, 2H), 4.64 (p, J = 6.8, 6.2 Hz, 1H), 4.32 (s, 2H), 3.46 (s, 2H), 2.82 (s, 2H). MS (ESI) m/z: $[M + H]^+$ 290.0.

Example 179

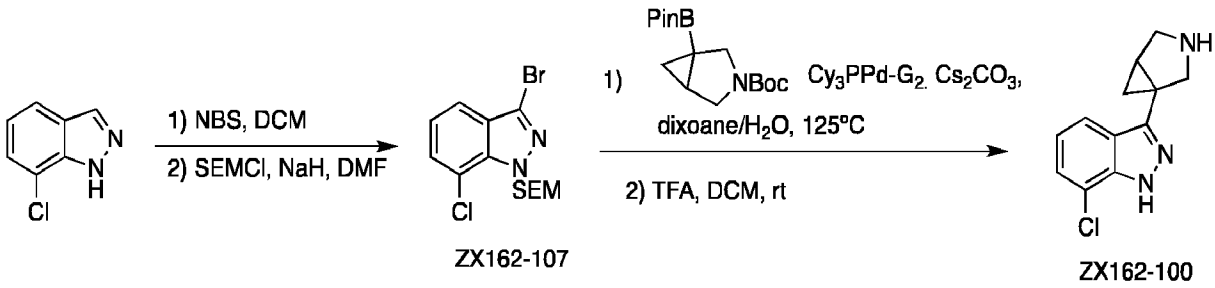
Synthesis of ZX156-090



7-chloro-3-(1-(3,3-difluorocyclobutyl)-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole (ZX156-090). ZX156-090 was prepared according to the same procedure as ZX147-028 from NS136-136 and 3,3-difluorocyclobutan-1-one. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.95 (d, J = 8.3 Hz, 1H), 7.45 (d, J = 7.5 Hz, 1H), 7.20 (t, J = 7.9 Hz, 1H), 6.87 (s, 1H), 4.34 (s, 2H), 3.94 (h, J = 7.4 Hz, 1H), 3.48 (s, 2H), 3.25 – 3.12 (m, 2H), 3.11 – 2.98 (m, 2H), 2.81 (s, 2H). MS (ESI) m/z: $[M + H]^+$ 324.3.

Example 180

Synthesis of compound ZX162-100

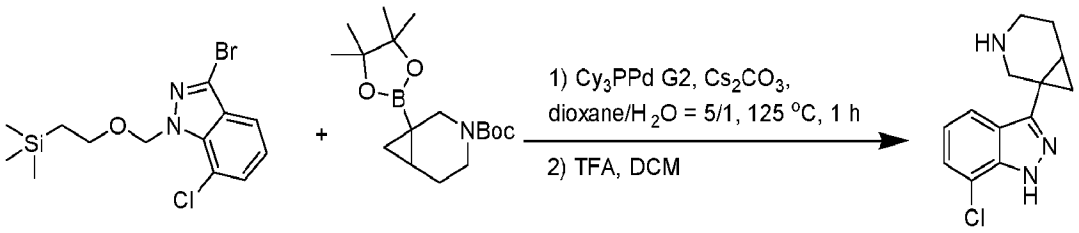


3-(3-azabicyclo[3.1.0]hexan-1-yl)-7-chloro-1*H*-indazole (ZX162-100). Indazole (2.0 g, 13.1 mmol, 1.0 equiv.), NBS (2.8 g, 15.7 mmol, 1.2 equiv.) and DCM (20 mL) were stirred at room temperature overnight followed by quenched with Sat. Na_2SO_3 aqueous solution (20 mL). The organic layer was separated, dried over Na_2SO_4, concentrated. The resulted residue was dissolved in DMF (50 mL) at 0 °C, NaH (1.05 g, 26.2 mmol, 2.0 equiv.) was added to the solution and stirred for 10 min followed by SEMCl (3.5 mL, 19.7 mmol, 1.5 equiv.). After stirred for another 4 h, the mixture was quenched with sat. $NaHCO_3$ aqueous solution (20 mL), the organic phase was separated, concentrated, and purified by silica gel chromatography(PE – PE/EA = 5/1) to yield ZX162-107 (colorless oil, 3.9 g, 82% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.55 (d, J = 8.1 Hz, 1H), 7.47 (d, J = 7.5 Hz, 1H), 7.18 (t, J = 8.2 Hz, 1H), 5.99 (s, 2H), 3.60 (t, J = 7.5 Hz, 2H), 0.93 – 0.83 (m, 2H), -0.07 (s, 9H).

To a solution of ZX162-107 (250 mg, 0.71 mmol, 1.0 equiv.) in dioxane/water (8 mL, 5:1) was added Cy_3P Pd G2 (42 mg, 0.071 mmol, 0.1 equiv.), Cs_2CO_3 (463 mg, 1.42 mmol, 2.0 equiv.) and *tert*-butyl 1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (219 mg, 0.71 mmol, 1.0 equiv.). The mixture was heated at 125 °C under microwave irradidation condition at nitrogen atmosphere for 1 h, followed by diluted with DCM (20 mL) and washed with brine (20 mL). After dried over Na_2SO_4 and concentrated, the residue was dissolved into DCM/TFA (5 mL, 2:1) and stirred at room temperature for 1 h followed by purified by prep-HPLC to yield title compound (white solid, 99 mg, 40% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.67 (d, J = 8.3 Hz, 1H), 7.42 (d, J = 7.5 Hz, 1H), 7.14 (t, J = 7.8 Hz, 1H), 3.90 (s, 2H), 3.75 (dd, J = 11.6, 4.0 Hz, 1H), 3.60 (d, J = 11.6 Hz, 1H), 2.52 (dt, J = 8.7, 4.3 Hz, 1H), 1.64 (t, J = 7.6 Hz, 1H), 1.26 (t, J = 5.7 Hz, 1H). MS (ESI) m/z: $[M + H]^+$ 234.3.

Example 181

Synthesis of compound ZX162-031

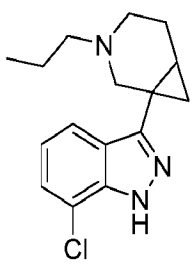


ZX162-107 ZX162-031

3-(3-azabicyclo[4.1.0]heptan-1-yl)-7-chloro-1*H*-indazole (ZX162-031). ZX162-031 was prepared according to the procedure similar to ZX162-100. Yield: 30%. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.71 (d, J = 8.1 Hz, 1H), 7.40 (d, J = 7.5 Hz, 1H), 7.18 – 7.08 (m, 1H), 4.12 (d, J = 13.5 Hz, 1H), 3.60 (d, J = 13.5 Hz, 1H), 3.23 (dt, J = 12.5, 5.9 Hz, 1H), 3.07 – 2.95 (m, 1H), 2.48 (ddt, J = 15.1, 9.4, 6.2 Hz, 1H), 2.21 – 2.08 (m, 1H), 2.01 (dtd, J = 8.6, 6.5, 2.0 Hz, 1H), 1.63 (dd, J = 9.4, 5.8 Hz, 1H), 1.25 (t, J = 6.1 Hz, 1H). MS (ESI) m/z: $[M + H]^+$ 248.3.

Example 182

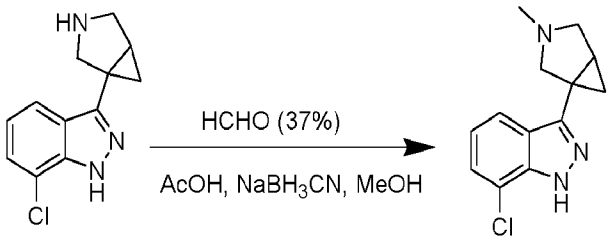
Synthesis of compound ZX162-104



7-chloro-3-(3-propyl-3-azabicyclo[4.1.0]heptan-1-yl)-1*H*-indazole (ZX162-104). ZX162-104 was prepared according to the same procedure as ZX147-028 from ZX162-031 and propionaldehyde. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.65 (d, J = 8.2 Hz, 1H), 7.35 (d, J = 7.5 Hz, 1H), 7.07 (t, J = 7.9 Hz, 1H), 4.19 (s, 1H), 3.45 (d, J = 12.3 Hz, 1H), 2.98 (t, J = 7.0 Hz, 2H), 2.89 (s, 1H), 2.54 – 2.42 (m, 1H), 2.15 (d, J = 14.9 Hz, 1H), 1.99 (q, J = 7.6, 7.0 Hz, 1H), 1.71 (h, J = 7.4 Hz, 2H), 1.57 (dd, J = 9.7, 5.6 Hz, 1H), 0.96 (t, J = 7.4 Hz, 3H). MS (ESI) m/z: $[M + H]^+$ 290.0.

Example 183

Synthesis of compound ZX162-105

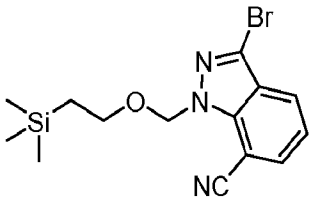


ZX162-100 ZX162-105

7-chloro-3-(3-methyl-3-azabicyclo[3.1.0]hexan-1-yl)-1*H*-indazole (ZX162-105). ZX162-100 was dissolved into methanol, and AcOH (5 equiv.), HCHO (aqueous solution) (10 equiv.), $NaBH_3CN$ (3.0 equiv.) were added and stirred at room temperature for 1 h. Purified by preparative HPLC. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.68 (d, J = 8.2 Hz, 1H), 7.41 (d, J = 7.4 Hz, 1H), 7.13 (t, J = 7.9 Hz, 1H), 4.02 (d, J = 11.0 Hz, 1H), 3.74 (t, J = 11.3 Hz, 2H), 3.56 (dd, J = 11.3, 4.0 Hz, 1H), 2.95 (s, 3H), 2.50 (dt, J = 8.9, 4.4 Hz, 1H), 1.59 (t, J = 7.5 Hz, 1H), 1.41 (t, J = 5.7 Hz, 1H). MS (ESI) m/z: $[M + H]^+$ 248.3.

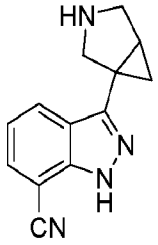
Example 184

Step 1: Synthesis of compound ZX162-102



ZX162-102 was prepared according to the procedure similar to ZX162-107. White solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.90 (d, J = 8.2 Hz, 1H), 7.85 (d, J = 7.4 Hz, 1H), 7.34 (t, J = 8.4 Hz, 1H), 5.97 (s, 2H), 3.64 (t, J = 7.7 Hz, 2H), 0.92 (t, J = 7.7 Hz, 2H), -0.05 (s, 9H).

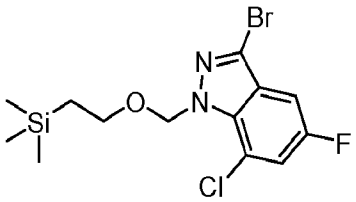
Step 2: Synthesis of compound ZX162-110



3-(3-azabicyclo[3.1.0]hexan-1-yl)-1*H*-indazole-7-carbonitrile (ZX162-110). ZX162-110 was prepared according to the procedure similar to ZX162-100 from ZX162-102 and *tert*-butyl 1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.06 (d, J = 8.3 Hz, 1H), 7.82 (d, J = 7.3 Hz, 1H), 7.29 (t, J = 7.8 Hz, 1H), 3.92 (s, 2H), 3.75 (dd, J = 11.8, 4.0 Hz, 1H), 3.61 (d, J = 11.7 Hz, 1H), 2.55 (dt, J = 9.0, 4.6 Hz, 1H), 1.66 (t, J = 7.7 Hz, 1H), 1.30 (t, J = 5.8 Hz, 1H). MS (ESI) m/z: $[M + H]^+$ 225.4.

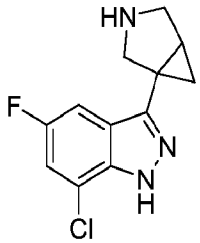
Example 185

Step 1: Synthesis of compound ZX162-101



ZX162-101 was prepared according to the procedure similar to ZX162-107. White solid, yield: 77%. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.68 (d, J = 6.5 Hz, 1H), 7.34 (d, J = 8.6 Hz, 1H), 5.63 (s, 2H), 3.55 (t, J = 9.2 Hz, 2H), 0.88 (t, J = 9.2 Hz, 2H), -0.05 (s, 9H).

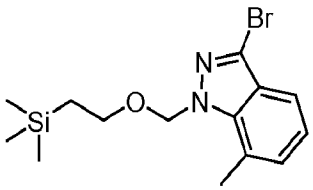
Step 2: Synthesis of compound ZX162-111



3-(3-azabicyclo[3.1.0]hexan-1-yl)-7-chloro-5-fluoro-1*H*-indazole (ZX162-111). ZX162-111 was prepared according to the procedure similar to ZX162-100 from ZX162-101 and *tert*-butyl 1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.87 (d, J = 7.0 Hz, 1H), 7.37 (d, J = 9.1 Hz, 1H), 3.86 (s, 2H), 3.75 (dd, J = 11.6, 4.0 Hz, 1H), 3.60 (d, J = 11.6 Hz, 1H), 2.47 (dt, J = 8.7, 4.5 Hz, 1H), 1.59 (t, J = 7.6 Hz, 1H), 1.26 (t, J = 5.7 Hz, 1H). MS (ESI) m/z: $[M + H]^+$ 252.3.

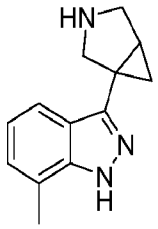
Example 186

Step 1: Synthesis of compound ZX162-108



ZX162-108 was prepared according to the procedure similar to ZX162-107. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.46 (d, *J* = 8.1 Hz, 1H), 7.22 (d, *J* = 7.1 Hz, 1H), 7.14 (t, *J* = 7.7 Hz, 1H), 5.79 (s, 2H), 3.55 (t, *J* = 7.4 Hz, 2H), 2.75 (s, 3H), 0.86 (t, *J* = 6.9 Hz, 2H), -0.07 (s, 9H).

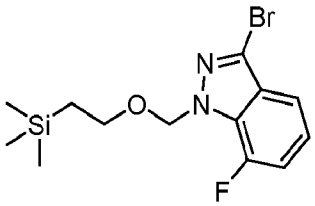
Step 2: Synthesis of compound ZX162-112



3-(3-azabicyclo[3.1.0]hexan-1-yl)-7-methyl-1*H*-indazole (ZX162-112). ZX162-112 was prepared according to the procedure similar to ZX162-100 from ZX162-108 and *tert*-butyl 1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.53 (d, *J* = 8.2 Hz, 1H), 7.16 (d, *J* = 6.9 Hz, 1H), 7.06 (t, *J* = 7.6 Hz, 1H), 3.87 (s, 2H), 3.75 (dd, *J* = 11.6, 3.9 Hz, 1H), 3.61 (d, *J* = 11.5 Hz, 1H), 2.53 (s, 3H), 2.46 (dt, *J* = 8.7, 4.5 Hz, 1H), 1.61 (t, *J* = 7.6 Hz, 1H), 1.25 (t, *J* = 5.7 Hz, 1H). MS (ESI) m/z: $[M + H]^+$ 214.4.

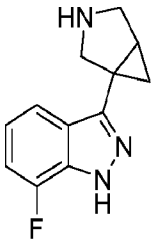
Example 187

Step 1: Synthesis of compound ZX162-109



ZX162-109 was prepared according to the procedure similar to ZX162-107. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 (dt, *J* = 6.8, 2.4 Hz, 1H), 7.20 – 7.13 (m, 2H), 5.78 (s, 2H), 3.60 (t, *J* = 8.1 Hz, 2H), 0.89 (t, *J* = 8.2 Hz, 2H), -0.07 (s, 9H).

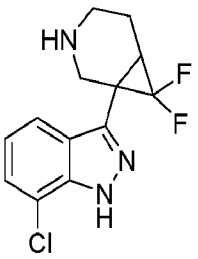
Step 2: Synthesis of compound ZX162-113



3-(3-azabicyclo[3.1.0]hexan-1-yl)-7-fluoro-1*H*-indazole (ZX162-113). ZX162-113 was prepared according to the procedure similar to ZX162-100 from ZX162-109 and *tert*-butyl 1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.54 - 7.48 (m, 1H), 7.15 – 7.07 (m, 2H), 3.89 (s, 2H), 3.75 (dd, J = 11.8, 4.0 Hz, 1H), 3.61 (d, J = 11.6 Hz, 1H), 2.55 – 2.45 (m, 1H), 1.63 (t, J = 7.5 Hz, 1H), 1.27 (t, J = 5.7 Hz, 1H). MS (ESI) m/z: $[M + H]^+$ 218.3.

Example 188

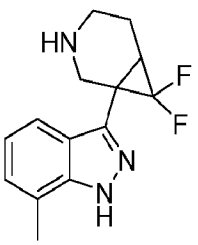
Synthesis of compound ZX162-124



7-chloro-3-(7,7-difluoro-3-azabicyclo[4.1.0]heptan-1-yl)-1*H*-indazole (ZX162-124). ZX162-124 was prepared according to the procedure similar to ZX162-100 from ZX162-107 and potassium 3-(*tert*-butoxycarbonyl)-7,7-difluoro-3-azabicyclo[4.1.0]heptan-1-yl)trifluoroborate. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.71 (d, J = 8.1 Hz, 1H), 7.45 (d, J = 7.4 Hz, 1H), 7.19 (t, J = 7.9 Hz, 1H), 3.97 – 3.83 (m, 2H), 3.35 - 3.24 (m, 1H), 3.08 – 2.99 (m, 1H), 2.99 – 2.90 (m, 1H), 2.50 (h, J = 8.2 Hz, 1H), 2.33 – 2.23 (m, 1H). MS (ESI) m/z: $[M + H]^+$ 284.3.

Example 189

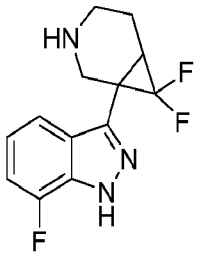
Synthesis of compound ZX162-126



3-(7,7-difluoro-3-azabicyclo[4.1.0]heptan-1-yl)-7-methyl-1*H*-indazole (ZX162-126). ZX162-126 was prepared according to the procedure similar to ZX162-100 from ZX162-108 and potassium 3-(*tert*-butoxycarbonyl)-7,7-difluoro-3-azabicyclo[4.1.0]heptan-1-yl)trifluoroborate. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.56 (d, J = 8.2 Hz, 1H), 7.20 (d, J = 6.9 Hz, 1H), 7.12 (t, J = 7.6 Hz, 1H), 3.87 (s, 2H), 3.27 (t, J = 6.1 Hz, 1H), 3.09 – 3.00 (m, 1H), 2.95 – 2.85 (m, 1H), 2.55 (s, 3H), 2.47 (d, J = 8.3 Hz, 1H), 2.33 – 2.22 (m, 1H). MS (ESI) m/z: $[M + H]^+$ 264.4.

Example 190

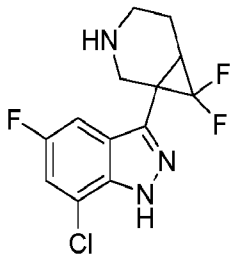
Synthesis of compound ZX162-127



3-(7,7-difluoro-3-azabicyclo[4.1.0]heptan-1-yl)-7-fluoro-1*H*-indazole (ZX162-127). ZX162-127 was prepared according to the procedure similar to ZX162-100 from ZX162-109 and potassium 3-(*tert*-butoxycarbonyl)-7,7-difluoro-3-azabicyclo[4.1.0]heptan-1-yl)trifluoroborate. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.58 – 7.53 (m, 1H), 7.21 – 7.13 (m, 2H), 3.90 (q, J = 14.6, 14.0 Hz, 2H), 3.28 (t, J = 6.0 Hz, 1H), 3.09 – 3.00 (m, 1H), 2.99 – 2.91 (m, 1H), 2.51 (dt, J = 15.9, 7.9 Hz, 1H), 2.29 (dd, J = 14.8, 7.0 Hz, 1H). MS (ESI) m/z: $[M + H]^+$ 268.3.

Example 191

Synthesis of compound ZX162-128

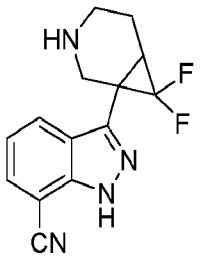


7-chloro-3-(7,7-difluoro-3-azabicyclo[4.1.0]heptan-1-yl)-5-fluoro-1*H*-indazole (ZX162-128). ZX162-128 was prepared according to the procedure similar to ZX162-100 from ZX162-101 and potassium 3-(*tert*-butoxycarbonyl)-7,7-difluoro-3-azabicyclo[4.1.0]heptan-1-yl)trifluoroborate. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.83 (d, J = 6.9 Hz, 1H), 7.33 (d, J = 9.2 Hz, 1H), 3.88 – 3.70

(m, 2H), 3.17 (t, J = 6.0 Hz, 1H), 2.98 – 2.87 (m, 1H), 2.80 (tt, J = 8.3, 4.3 Hz, 1H), 2.39 (h, J = 8.5 Hz, 1H), 2.20 -2.13 (m, 1H). MS (ESI) m/z: $[M + H]^+$ 302.5.

Example 192

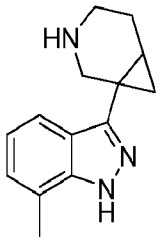
Synthesis of compound ZX162-129



3-(7,7-difluoro-3-azabicyclo[4.1.0]heptan-1-yl)-1*H*-indazole-7-carbonitrile (ZX162-129). ZX162-129 was prepared according to the procedure similar to ZX162-100 from ZX162-102 and potassium 3-(*tert*-butoxycarbonyl)-7,7-difluoro-3-azabicyclo[4.1.0]heptan-1-yl)trifluoroborate. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.12 (d, J = 8.2 Hz, 1H), 7.88 (d, J = 7.2 Hz, 1H), 7.39 – 7.33 (m, 1H), 3.98 (d, J = 16.0 Hz, 1H), 3.87 (d, J = 14.0 Hz, 1H), 3.35 - 3.27 (m, 1H), 3.09 – 2.94 (m, 2H), 2.51 (dq, J = 15.9, 7.8 Hz, 1H), 2.33 – 2.23 (m, 1H). MS (ESI) m/z: $[M + H]^+$ 275.5.

Example 193

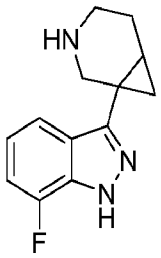
Synthesis of compound ZX162-138



3-(3-azabicyclo[4.1.0]heptan-1-yl)-7-methyl-1*H*-indazole (ZX162-129). ZX162-129 was prepared according to the procedure similar to ZX162-100 from ZX162-108 and *tert*-butyl 1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-azabicyclo[4.1.0]heptane-3-carboxylate. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.58 (d, J = 8.1 Hz, 1H), 7.14 (d, J = 6.9 Hz, 1H), 7.05 (t, J = 7.6 Hz, 1H), 4.02 (d, J = 13.4 Hz, 1H), 3.62 (d, J = 13.6 Hz, 1H), 3.22 (dt, J = 12.3, 5.9 Hz, 1H), 3.06 - 2.97 (m, 1H), 2.51 (s, 3H), 2.47 (dd, J = 14.7, 6.9 Hz, 1H), 2.12 (dt, J = 15.0, 5.6 Hz, 1H), 1.94 (q, J = 7.9, 6.8 Hz, 1H), 1.57 (dd, J = 9.5, 5.6 Hz, 1H), 1.24 – 1.18 (m, 1H). MS (ESI) m/z: $[M + H]^+$ 228.5.

Example 194

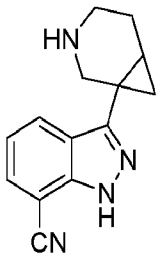
Synthesis of compound ZX162-139



3-(3-azabicyclo[4.1.0]heptan-1-yl)-7-fluoro-1*H*-indazole (ZX162-139). ZX162-139 was prepared according to the procedure similar to ZX162-100 from ZX162-109 and *tert*-butyl 1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-azabicyclo[4.1.0]heptane-3-carboxylate. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.58 - 7.53 (m, 1H), 7.14 – 7.05 (m, 2H), 4.10 (d, J = 13.5 Hz, 1H), 3.61 (d, J = 13.5 Hz, 1H), 3.22 (dt, J = 12.4, 5.9 Hz, 1H), 3.02 (ddd, J = 13.6, 9.1, 4.9 Hz, 1H), 2.48 (td, J = 15.5, 5.9 Hz, 1H), 2.13 (dt, J = 15.1, 5.6 Hz, 1H), 2.05 – 1.96 (m, 1H), 1.61 (dd, J = 9.7, 5.4 Hz, 1H), 1.27 – 1.21 (m, 1H). MS (ESI) m/z: $[M + H]^+$ 232.4.

Example 195

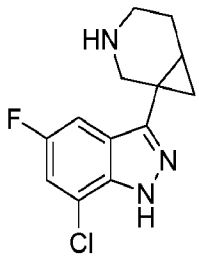
Synthesis of compound ZX162-140



3-(3-azabicyclo[4.1.0]heptan-1-yl)-1*H*-indazole-7-carbonitrile (ZX162-140). ZX162-140 was prepared according to the procedure similar to ZX162-100 from ZX162-102 and *tert*-butyl 1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-azabicyclo[4.1.0]heptane-3-carboxylate. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.11 (d, J = 8.3 Hz, 1H), 7.81 (d, J = 7.3 Hz, 1H), 7.28 (t, J = 7.8 Hz, 1H), 4.16 (d, J = 13.6 Hz, 1H), 3.61 (d, J = 13.6 Hz, 1H), 3.24 (dt, J = 12.2, 5.8 Hz, 1H), 3.02 (ddd, J = 13.8, 9.2, 4.9 Hz, 1H), 2.49 (td, J = 15.6, 5.9 Hz, 1H), 2.14 (dt, J = 15.1, 5.4 Hz, 1H), 2.08 – 1.99 (m, 1H), 1.64 (dd, J = 9.5, 5.8 Hz, 1H), 1.29 (t, J = 6.2 Hz, 1H). MS (ESI) m/z: $[M + H]^+$ 239.5.

Example 196

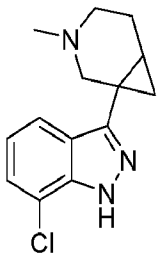
Synthesis of compound ZX162-141



3-(3-azabicyclo[4.1.0]heptan-1-yl)-7-chloro-5-fluoro-1*H*-indazole(ZX162-141). ZX162-141 was prepared according to the procedure similar to ZX162-100 from ZX162-101 and *tert*-butyl 1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-azabicyclo[4.1.0]heptane-3-carboxylate. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.92 (d, J = 6.9 Hz, 1H), 7.36 (d, J = 9.2 Hz, 1H), 4.04 (d, J = 13.5 Hz, 1H), 3.60 (d, J = 13.6 Hz, 1H), 3.23 (dt, J = 12.5, 5.9 Hz, 1H), 2.99 (ddd, J = 14.1, 9.1, 4.9 Hz, 1H), 2.49 (dt, J = 15.5, 7.7 Hz, 1H), 2.13 (dt, J = 15.0, 5.3 Hz, 1H), 1.99 – 1.91 (m, 1H), 1.58 (dd, J = 9.5, 5.7 Hz, 1H), 1.24 (t, J = 5.4 Hz, 1H). MS (ESI) m/z: $[M + H]^+$ 266.5.

Example 197

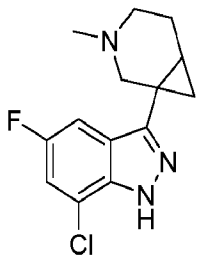
Synthesis of compound ZX162-147



7-chloro-3-(3-methyl-3-azabicyclo[4.1.0]heptan-1-yl)-1*H*-indazole (ZX162-147). ZX162-147 was prepared according to the procedure similar to ZX162-105 from ZX162-031 and formaldehyde. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.71 (d, J = 8.1 Hz, 1H), 7.40 (d, J = 7.5 Hz, 1H), 7.13 (t, J = 7.8 Hz, 1H), 4.46 (d, J = 13.2 Hz, 1H), 4.06 – 3.76 (m, 1H), 3.45 (d, J = 10.9 Hz, 1H), 2.95 (s, 1H), 2.87 (s, 3H), 2.64 - 2.50 (m, 1H), 2.29 (d, J = 14.9 Hz, 1H), 2.16 - 1.95 (m, 1H), 1.62 (dd, J = 9.7, 5.4 Hz, 1H), 1.34 (t, J = 6.6 Hz, 1H). MS (ESI) m/z: $[M + H]^+$ 262.5.

Example 198

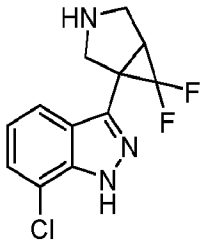
Synthesis of compound ZX162-148



7-chloro-5-fluoro-3-(3-methyl-3-azabicyclo[4.1.0]heptan-1-yl)-1*H*-indazole (ZX162-148). ZX162-148 was prepared according to the procedure similar to ZX162-105 from ZX162-141 and formaldehyde. ^{1}HNMR (400 MHz, Methanol-d_4) δ 7.81 (d, J = 6.9 Hz, 1H), 7.26 (d, J = 9.1 Hz, 1H), 4.28 (d, J = 13.6 Hz, 1H), 3.77 (dd, J = 80.2, 14.1 Hz, 1H), 3.35 (d, J = 14.2 Hz, 1H), 2.85 (s, 1H), 2.76 (s, 3H), 2.59 – 2.37 (m, 1H), 2.19 (d, J = 14.3 Hz, 1H), 1.94 - 1.87 (m, 1H), 1.47 (dd, J = 9.6, 5.8 Hz, 1H), 1.22 (t, J = 7.1 Hz, 1H). MS (ESI) m/z: $[M + H]^+$ 280.6.

Example 199

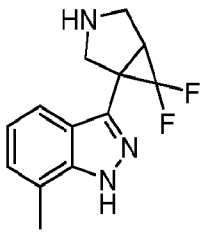
Synthesis of compound ZX162-151



7-chloro-3-(6,6-difluoro-3-azabicyclo[3.1.0]hexan-1-yl)-1*H*-indazole (ZX162-151). ZX162-151 was prepared according to the procedure similar to ZX162-100 from ZX162-107 and potassium (3-(*tert*-butoxycarbonyl)-6,6-difluoro-3-azabicyclo[3.1.0]hexan-1-yl)trifluoroborate. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.72 (d, J = 8.2 Hz, 1H), 7.46 (d, J = 9.2 Hz, 1H), 7.20 (t, J = 7.9 Hz, 1H), 4.28 (d, J = 12.3 Hz, 1H), 4.11 – 4.01 (m, 2H), 3.90 (d, J = 12.5 Hz, 1H), 3.47 (dd, J = 11.4, 5.5 Hz, 1H). MS (ESI) m/z: $[M + H]^+$ 270.4.

Example 200

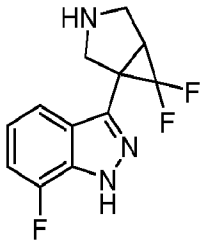
Synthesis of compound ZX162-173



3-(6,6-difluoro-3-azabicyclo[3.1.0]hexan-1-yl)-7-fluoro-1*H*-indazole (ZX162-173). ZX162-173 was prepared according to the procedure similar to ZX162-100 from ZX162-108 and potassium (3-(*tert*-butoxycarbonyl)-6,6-difluoro-3-azabicyclo[3.1.0]hexan-1-yl)trifluoroborate. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.57 (d, J = 8.1 Hz, 1H), 7.21 (d, J = 6.9 Hz, 1H), 7.12 (t, J = 7.6 Hz, 1H), 4.27 (d, J = 12.4 Hz, 1H), 4.09 (dd, J = 11.8, 6.0 Hz, 1H), 3.99 (dd, J = 12.4, 3.8 Hz, 1H), 3.90 (d, J = 12.4 Hz, 1H), 3.41 (dd, J = 11.2, 5.5 Hz, 1H). MS (ESI) m/z: $[M + H]^+$ 250.4.

Example 201

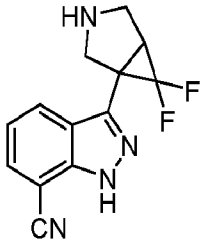
Synthesis of compound ZX162-174



3-(6,6-difluoro-3-azabicyclo[3.1.0]hexan-1-yl)-7-fluoro-1*H*-indazole (ZX162-174). ZX162-174 was prepared according to the procedure similar to ZX162-100 from ZX162-109 and potassium (3-(*tert*-butoxycarbonyl)-6,6-difluoro-3-azabicyclo[3.1.0]hexan-1-yl)trifluoroborate. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.56 (d, J = 7.6 Hz, 1H), 7.20 – 7.14 (m, 2H), 4.28 (d, J = 12.3 Hz, 1H), 4.12 – 4.01 (m, 2H), 3.90 (d, J = 12.5 Hz, 1H), 3.46 (dd, J = 11.4, 5.6 Hz, 1H). MS (ESI) m/z: $[M + H]^+$: 254.4.

Example 202

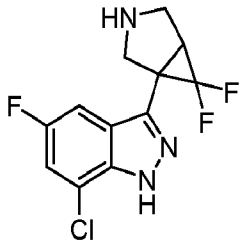
Synthesis of compound ZX162-175



3-(6,6-difluoro-3-azabicyclo[3.1.0]hexan-1-yl)-1*H*-indazole-7-carbonitrile (ZX162-175). ZX162-175 was prepared according to the procedure similar to ZX162-100 from ZX162-102 and potassium (3-(*tert*-butoxycarbonyl)-6,6-difluoro-3-azabicyclo[3.1.0]hexan-1-yl)trifluoroborate. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.12 (d, J = 8.3 Hz, 1H), 7.89 (d, J = 7.3 Hz, 1H), 7.36 (t, J = 7.8 Hz, 1H), 4.31 (d, J = 12.4 Hz, 1H), 4.13 - 4.05(m, 2H), 3.91 (d, J = 12.5 Hz, 1H), 3.52 (dd, J = 11.5, 5.5 Hz, 1H). MS (ESI) m/z: $[M + H]^+$ 261.4.

Example 203

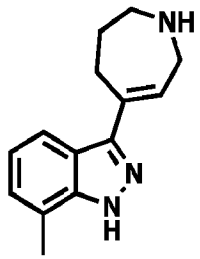
Synthesis of compound ZX162-176



7-chloro-3-(6,6-difluoro-3-azabicyclo[3.1.0]hexan-1-yl)-5-fluoro-1*H*-indazole (ZX162-176). **ZX162-176** was prepared according to the procedure similar to **ZX162-100** from **ZX162-101** and potassium (3-(*tert*-butoxycarbonyl)-6,6-difluoro-3-azabicyclo[3.1.0]hexan-1-yl)trifluoroborate. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.93 (d, J = 6.9 Hz, 1H), 7.44 (d, J = 9.3 Hz, 1H), 4.28 (d, J = 12.4 Hz, 1H), 4.12 – 4.00 (m, 2H), 3.89 (d, J = 12.6 Hz, 1H), 3.46 (dd, J = 11.4, 5.6 Hz, 1H). MS (ESI) m/z: $[M + H]^+$ 288.3.

Example 204

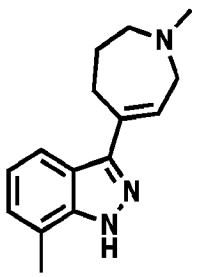
Synthesis of YX143-103B



7-methyl-3-(2,5,6,7-tetrahydro-1*H*-azepin-4-yl)-1*H*-indazole (YX143-103B) YX143-103B was synthesized following the standard procedure for preparing NS131-179 from *tert*-butyl 3-bromo-7-methyl-1*H*-indazole-1-carboxylate and commercial available *tert*-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3,4,7-tetrahydro-1*H*-azepine-1-carboxylate. (white solid, 5 mg, 23% yield). MS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{18}N_3$ 228.1; found 228.4.

Example 205

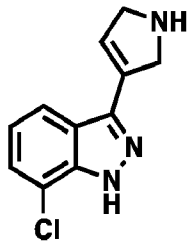
Synthesis of YX143-103C



7-methyl-3-(1-methyl-2,5,6,7-tetrahydro-1*H*-azepin-4-yl)-1*H*-indazole (YX143-103C) YX143-103C was synthesized following the Method M from YX143-103B, (white solid, 6 mg, 80% yield). MS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{20}N_3$ 242.2; found 242.4.

Example 206

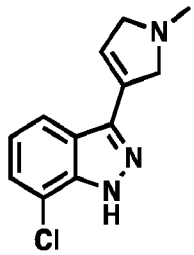
Synthesis of YX143-105C



7-chloro-3-(2,5-dihydro-1*H*-pyrrol-3-yl)-1*H*-indazole (YX143-105C) YX143-105C was synthesized following the standard procedure for preparing NS131-179 from *tert*-butyl 3-bromo-7-methyl-1*H*-indazole-1-carboxylate and *tert*-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (brown solid, 17 mg, 25% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.85 (d, J = 8.3 Hz, 1H), 7.36 (d, J = 7.6 Hz, 1H), 7.13 (t, J = 7.8 Hz, 1H), 6.54 (p, J = 2.2 Hz, 1H), 4.53 (q, J = 2.3 Hz, 2H), 4.28 (q, J = 2.4 Hz, 2H). MS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{11}ClN_3$ 220.1; found 220.2.

Example 207

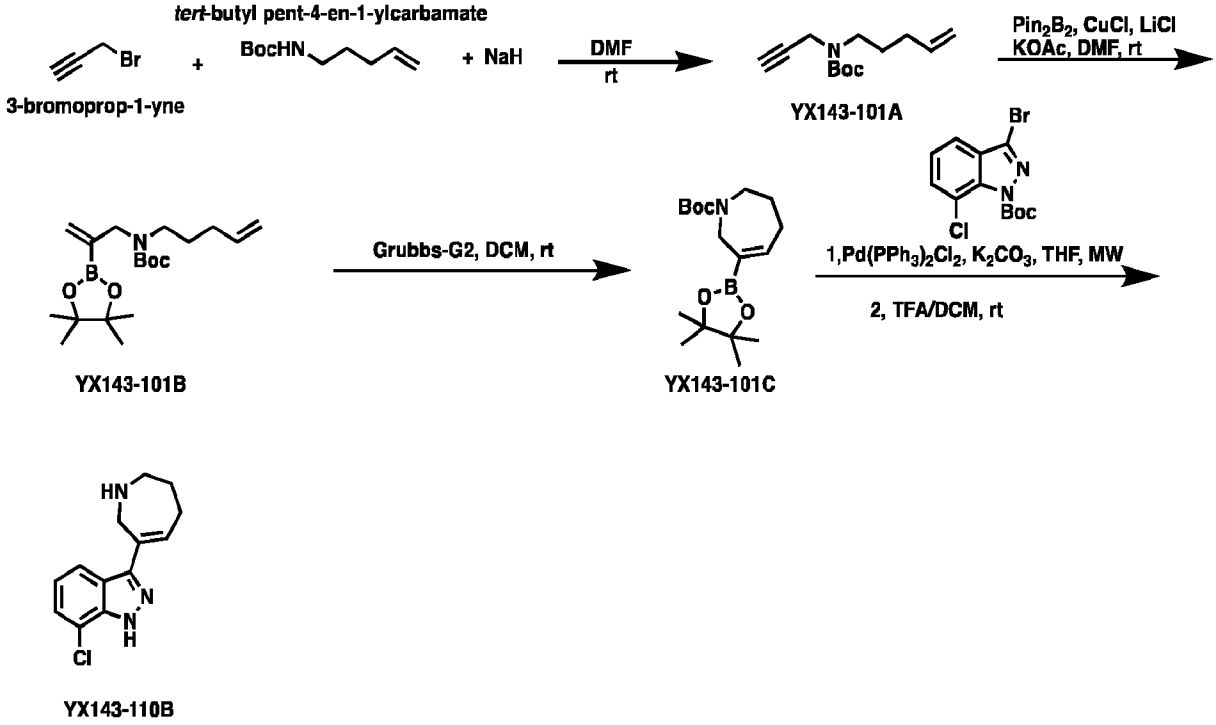
Synthesis of YX143-108



7-chloro-3-(1-methyl-2,5-dihydro-1*H*-pyrrol-3-yl)-1*H*-indazole (YX143-108). YX143-105C was synthesized following the Method M from YX143-105C (white solid, 8 mg, 80% yield) ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.98 (d, J = 8.2 Hz, 1H), 7.50 (d, J = 7.5 Hz, 1H), 7.27 (t, J = 7.8 Hz, 1H), 6.65 (s, 1H), 4.98 (d, J = 14.6 Hz, 1H), 4.70 (d, J = 15.7 Hz, 1H), 4.53 (d, J = 14.5 Hz, 1H), 4.27 (d, J = 15.7 Hz, 1H), 3.18 (s, 3H). MS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{13}ClN_3$ 234.1; found 234.3.

Example 208

Synthesis of YX143-110B



7-chloro-3-(2,5,6,7-tetrahydro-1*H*-azepin-3-yl)-1*H*-indazole (YX143-110B) To a solution of *tert*-butyl pent-4-en-1-ylcarbamate (1 g, 5.4 mmmol) in DMF (10 mL), was added NaH (0.5 g, 12.5 mmol) and continued stirred at room temperature. After 30 min, Propargyl bromide (1 mL, 89% in Tol, 6.7 mmol) was added, the mixture was continued stirred at room temperature. After 24 hours, sat. NH_4Cl solution (10 mL) was added to quenched the reaction followed by extracted with Et_2O (3 × 10 mL). The organic layer was collected and concentrated, resulted residue was purified by ISCO to yield intermediate YX143-101A as brown oil (370 mg, 31% yield). ^1H NMR (400 MHz, Chloroform-*d*) δ 5.86 – 5.65 (m, 1H), 5.06 – 4.83 (m, 2H), 4.11 – 3.83 (m, 2H), 3.25 (t, *J* = 7.5 Hz, 2H), 2.12 (t, *J* = 2.5 Hz, 1H), 1.99 (q, *J* = 7.5 Hz, 2H), 1.60 (p, *J* = 7.5 Hz, 2H), 1.40 (s, 9H).

Intermediate YX143-101A (370 mg, 1.7 mmol), Pin2B2 (518 mg, 5.0 mmol), CuCl (207 mg, 2.1 mmol) LiCl (46 mg, 1.1 mmol) and KOAc (206 mg, 2.1 mmol was mixed in DMF (10 mL). The mixture was stirred at room temperature for 12 hours followed by quenched with water (5 mL) and extracted with Et_2O (3 × 5 mL). The organic layer was collected and concentrated, resulted residue was purified by ISCO to yield intermediate YX143-101B as brown oil (380 mg, 65% yield). ^1H NMR (400 MHz, Chloroform-*d*) δ 6.51 – 6.35 (m, 0.5H), 5.86 – 5.65 (m, 1.5H), 5.59 –

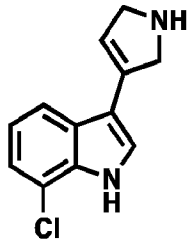
5.36 (m, 1H), 5.03 – 4.80 (m, 2H), 3.98 – 3.71 (m, 2H), 3.19 – 2.94 (m, 2H), 2.07 – 1.89 (m, 2H), 1.62 – 1.50 (m, 2H), 1.44 – 1.31 (m, 9H), 1.25 – 1.13 (m, 12H).

Intermediate YX143-101B (380 mg, 1.1 mmol) was dissolved in DCM (50 mL) followed by Grubbs 2nd generation catalyst (45 mg, 0.055 mmol). The mixture was stirred at room temperature for 2 hour, then concentrated and purified by ISCO to yield the intermediate YX143-101C as brown oil (24 mg, 7% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.65 – 6.47 (m, 1H), 4.07 – 3.84 (m, 2H), 3.56 – 3.33 (m, 2H), 2.35 – 2.12 (m, 2H), 1.84 – 1.61 (m, 2H), 1.37 (s, 9H), 1.19 (s, 12H).

YX143-110B was synthesized following the standard procedure for preparing NS131-179 from *tert*-butyl 3-bromo-7-chloro-1*H*-indazole-1-carboxylate and intermediate YX143-101C (brown solid, 3 mg, 15% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.82 (d, J = 8.3 Hz, 1H), 7.33 (d, J = 7.7 Hz, 1H), 7.09 (p, J = 6.3 Hz, 1H), 7.01 (t, J = 6.5 Hz, 1H), 4.46 (s, 2H), 3.52 – 3.37 (m, 2H), 2.69 – 2.56 (m, 2H), 1.99 – 1.78 (m, 2H). MS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{15}ClN_3$ 248.1; found 248.3.

Example 209

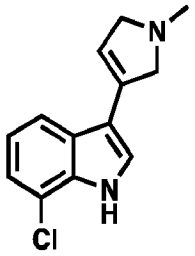
Synthesis of YX143-112B



7-chloro-3-(2,5-dihydro-1*H*-pyrrol-3-yl)-1*H*-indole (YX143-112B) YX143-112B was synthesized following the standard procedure for preparing NS131-179 from *tert*-butyl 3-bromo-7-chloro-1*H*-indole-1-carboxylate and *tert*-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (brown solid, 10mg, 15% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.67 (d, J = 8.0 Hz, 1H), 7.13 (d, J = 7.8 Hz, 1H), 7.03 (t, J = 7.8 Hz, 1H), 6.10 (p, J = 2.1 Hz, 1H), 4.37 (q, J = 2.3 Hz, 2H), 4.20 (q, J = 2.3 Hz, 2H). MS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{12}ClN_2$ 219.1; found 219.2.

Example 210

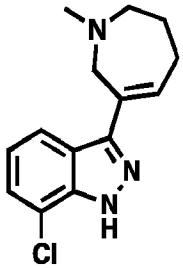
Synthesis of YX143-129



7-chloro-3-(1-methyl-2,5-dihydro-1*H*-pyrrol-3-yl)-1*H*-indole (YX143-129) YX143-129 was synthesized following the Method M from YX143-112B brown solid (7 mg, 90% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.80 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 2.2 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.16 (t, J = 7.8 Hz, 1H), 6.23 – 6.16 (m, 1H), 4.79 (d, J = 14.1 Hz, 1H), 4.61 (d, J = 14.9 Hz, 1H), 4.38 (d, J = 14.0 Hz, 1H), 4.18 (d, J = 14.8 Hz, 1H), 3.15 (s, 3H). MS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{14}ClN_2$ 233.1; found 233.3.

Example 211

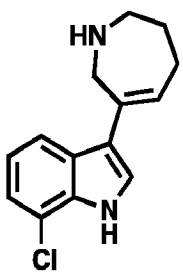
Synthesis of YX143-134C



7-chloro-3-(1-methyl-2,5,6,7-tetrahydro-1*H*-azepin-3-yl)-1*H*-indazole (YX143-134C) YX143-134C was synthesized following Method M from YX143-110B brown solid (4 mg, 85% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.83 (d, J = 8.3 Hz, 1H), 7.34 (d, J = 7.5 Hz, 1H), 7.14 – 7.04 (m, 2H), 4.65 (d, J = 14.5 Hz, 1H), 4.52 (d, J = 14.4 Hz, 1H), 3.73 – 3.54 (m, 1H), 3.54 – 3.34 (m, 1H), 2.92 (s, 3H), 2.72 – 2.53 (m, 2H), 2.14 – 1.79 (m, 2H). MS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{17}ClN_3$ 262.1; found 262.2.

Example 212

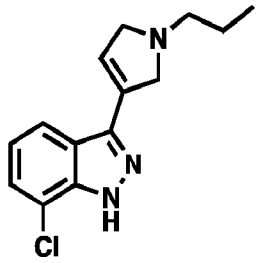
Synthesis of YX143-138C



7-chloro-3-(2,5,6,7-tetrahydro-1*H*-azepin-3-yl)-1*H*-indole (YX143-138C) YX143-138C was synthesized following the standard procedure for preparing NS131-179 from *tert*-butyl 3-bromo-7-chloro-1*H*-indole-1-carboxylate and intermediate YX143-101C brown solid (2 mg, 10% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.71 (d, J = 8.0 Hz, 1H), 7.45 (s, 1H), 7.21 (d, J = 7.6 Hz, 1H), 7.09 (t, J = 7.9 Hz, 1H), 6.63 (t, J = 6.5 Hz, 1H), 4.26 (s, 2H), 3.61 – 3.47 (m, 2H), 2.66 (t, J = 6.1 Hz, 2H), 2.04 (s, 2H). MS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{16}ClN_2$ 247.1; found 247.2.

Example 213

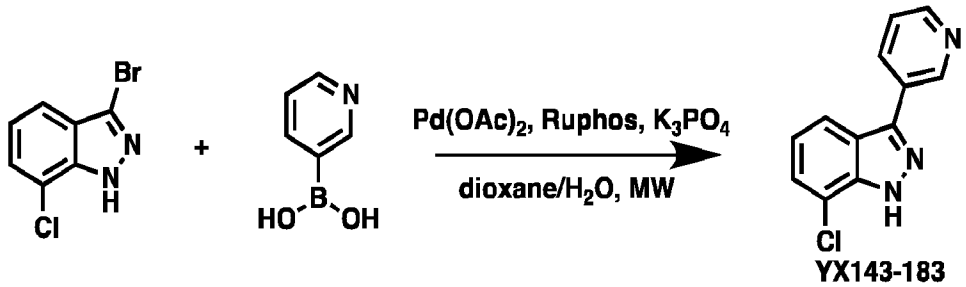
Synthesis of YX143-182C-1



7-chloro-3-(1-propyl-2,5-dihydro-1*H*-pyrrol-3-yl)-1*H*-indazole (YX143-182C-1) YX143-182C-1 was synthesized following the Method M from YX143-105C brown solid (8 mg, 80% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.97 (d, J = 8.3 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.26 (t, J = 7.8 Hz, 1H), 6.76 – 6.61 (m, 1H), 4.77 – 4.14 (m, 4H), 3.43 (d, J = 9.2 Hz, 2H), 2.00 – 1.77 (m, 2H), 1.11 (t, J = 7.8 Hz, 3H). MS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{17}ClN_3$ 262.1; found 262.3.

Example 214

Synthesis of YX143-183A

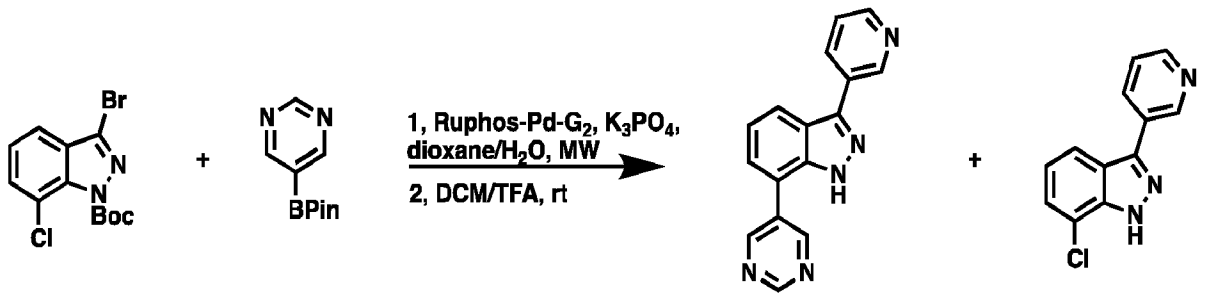


7-chloro-3-(pyridin-3-yl)-1*H*-indazole (YX143-183A) 3-bromo-7-chloro-1*H*-indazole (32 mg, 0.14 mmol), pyridin-3-ylboronic acid (24 mg, 0.20 mmol), $Pd(OAc)_2$ (25 mg, 0.11 mmol), Ruphos (24 mg, 0.051 mmol) and K_3PO_4 (127 mg, 0.60 mmol) were mixed in dioxane/H_2O (4:1, 1.5 mL). The mixture was irradiated under microwave condition at 140°C for 30 min. after cooling down to room temperature, the mixture was filtered and purified by prep-HPLC to yield title compound as brown oil (2 mg, 6% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.36 (s, 1H), 8.92 (d, J = 8.2

Hz, 1H), 8.77 (s, 1H), 8.09 (d, J = 8.2 Hz, 1H), 8.05 – 7.92 (m, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.33 (t, J = 7.9 Hz, 1H). MS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{12}H_9ClN_3$ 230.0; found 230.2.

Examples 215 and 216

Synthesis of YX143-184B-1 and YX143-184B-2



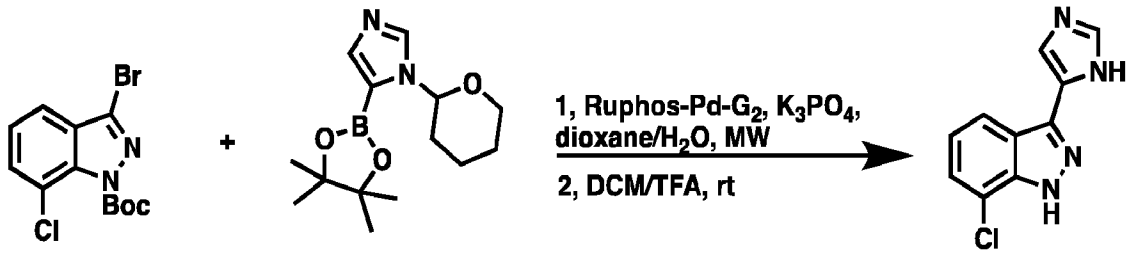
YX143-184B-1 YX143-184B-2

3,7-di(pyrimidin-5-yl)-1*H*-indazole (YX143-184B-1) *tert*-butyl 3-bromo-7-chloro-1*H*-indazole-1-carboxylate (33 mg, 0.10 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (26 mg, 0.13 mmol), Ruphos-Pd-G2 (15 mg, 0.019 mmol) and K_3PO_4 (35 mg, 0.17 mmol) were mixed in dioxane/H_2O (9:1, 2 mL). The mixture was irradiated under microwave condition at 150°C for 30 min. After cooling down to room temperature, the mixture was concentrated and re-dissovled in DCM/TFA (2:1, 1 mL). The solution was stirred at room temperature for 30 min followed by purification by prep-HPLC to yield the title compounds. YX143-184B-1, brown oil (5 mg, 13% yield), ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.46 (t, J = 2.3 Hz, 2H), 9.29 (s, 1H), 9.24 (s, 1H), 9.21 – 9.14 (m, 2H), 8.24 (d, J = 8.3 Hz, 1H), 7.64 (d, J = 7.0 Hz, 1H), 7.51 (t, J = 7.6 Hz, 1H). MS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{15}H_1N_6$ 275.1; found 275.3.

7-chloro-3-(pyrimidin-5-yl)-1*H*-indazole (YX143-184B-2), brown oil (4 mg, 12% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.42 (s, 2H), 9.22 (s, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 7.5 Hz, 1H), 7.31 (d, J = 7.8 Hz, 1H). MS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{11}H_8ClN_4$ 230.0; found 230.2.

Example 217

Synthesis of YX143-185B

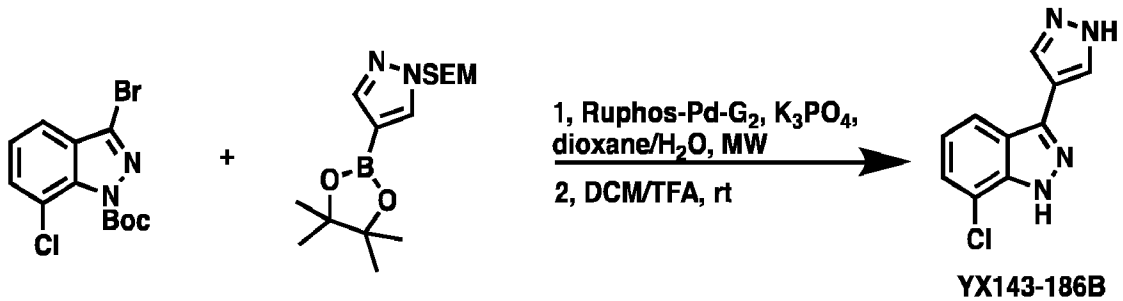


YX143-185B

7-chloro-3-(1*H*-imidazol-5-yl)-1*H*-indazole (YX143-185B) YX143-185B was synthesized following the same procedure for preparing YX143-184B-1 brown solid (7 mg, 22% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.04 (s, 1H), 8.22 (s, 1H), 8.00 (d, J = 8.2 Hz, 1H), 7.54 (d, J = 7.4 Hz, 1H), 7.31 (t, J = 8.3 Hz, 1H). MS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{10}H_8ClN_4$ 219.0; found 219.2.

Example 218

Synthesis of YX143-186B

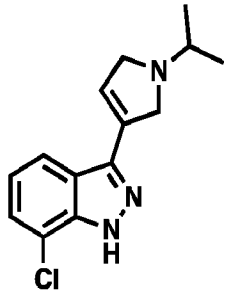


YX143-186B

7-chloro-3-(1*H*-pyrazol-4-yl)-1*H*-indazole (YX143-186B) YX143-186B was synthesized following the same procedure for preparingYX143-184B-1 brown solid (4 mg, 18% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.25 (s, 2H), 7.96 (d, J = 8.3 Hz, 1H), 7.46 (d, J = 7.4 Hz, 1H), 7.21 (t, J = 7.3 Hz, 1H). MS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{10}H_8ClN_4$ 219.0; found 219.2.

Example 219

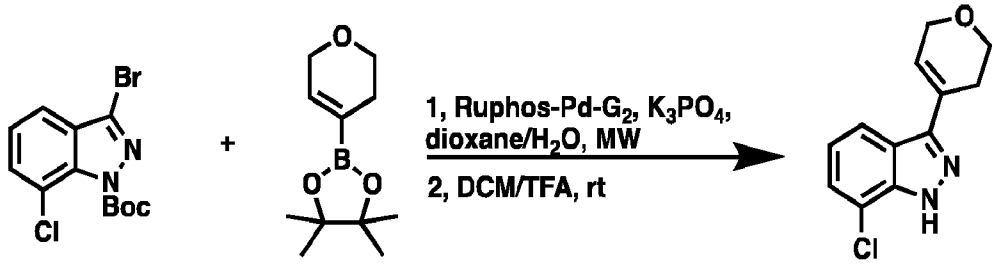
Synthesis of YX157-19A



7-chloro-3-(1-isopropyl-2,5-dihydro-1*H*-pyrrol-3-yl)-1*H*-indazole (YX157-19A) YX157-19A was synthesized following Method M from YX143-105C, brown solid (5 mg, 79% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.96 (d, J = 8.4 Hz, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.26 (t, J = 8.0 Hz, 1H), 6.74 – 6.59 (m, 1H), 4.86 – 4.77 (m, 1H), 4.71 – 4.51 (m, 2H), 4.47 – 4.30 (m, 1H), 3.87 – 3.67 (m, 1H), 1.49 (s, 6H). MS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{17}ClN_3$ 262.1; found 262.1.

Example 220

Synthesis of YX157-20A

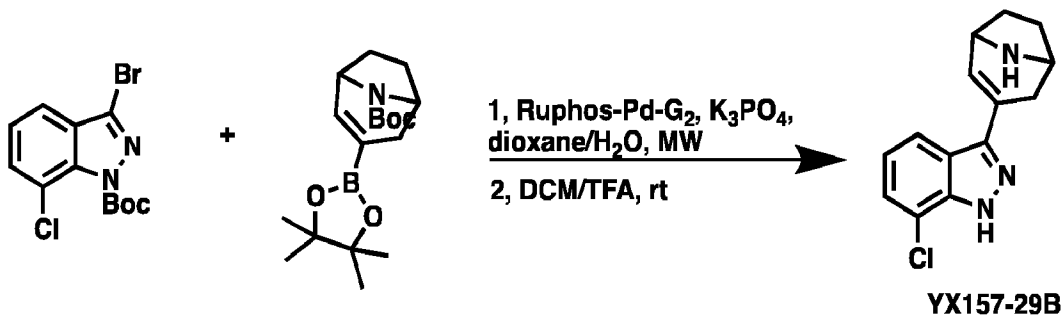


YX157-20A

7-chloro-3-(3,6-dihydro-2*H*-pyran-4-yl)-1*H*-indazole (YX157-20A) YX157-20A was synthesized following the same procedure for preparingYX143-184B-1 brown solid (2 mg, 180% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.93 (d, J = 8.6 Hz, 1H), 7.42 (d, J = 7.8 Hz, 1H), 7.16 (t, J = 8.2 Hz, 1H), 6.59 (s, 1H), 4.48 – 4.33 (m, 2H), 4.10 – 3.90 (m, 2H), 2.86 – 2.69 (m, 2H). MS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{12}ClN_2O$ 235.1; found 235.2.

Example 221

Synthesis of YX157-29B



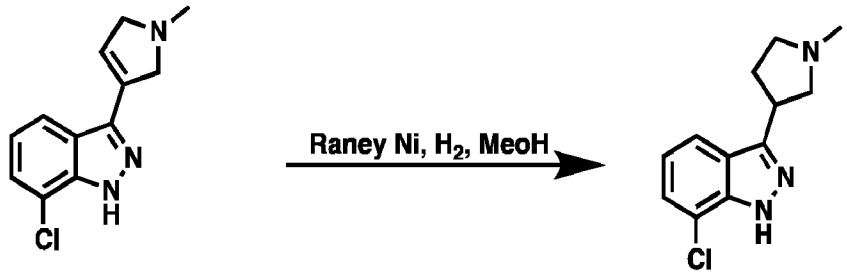
YX157-29B

3-(8-azabicyclo[3.2.1]oct-2-en-3-yl)-7-chloro-1*H*-indazole (YX157-29B) YX157-29B was synthesized following the same procedure for YX143-184B-1, brown oil (10 mg, 40% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.85 (t, J = 6.4 Hz, 1H), 7.46 – 7.28 (m, 1H), 7.20 – 7.00 (m, 1H), 6.82 – 6.62 (m, 1H), 4.50 – 4.34 (m, 1H), 4.34 – 4.21 (m, 1H), 3.69 – 3.47 (m, 1H), 3.02 –

2.82 (m, 1H), 2.46 – 2.11 (m, 3H), 2.04 – 1.83 (m, 1H). MS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{15}ClN_3$ 260.1; found 260.3.

Example 222

Synthesis of YX157-42B

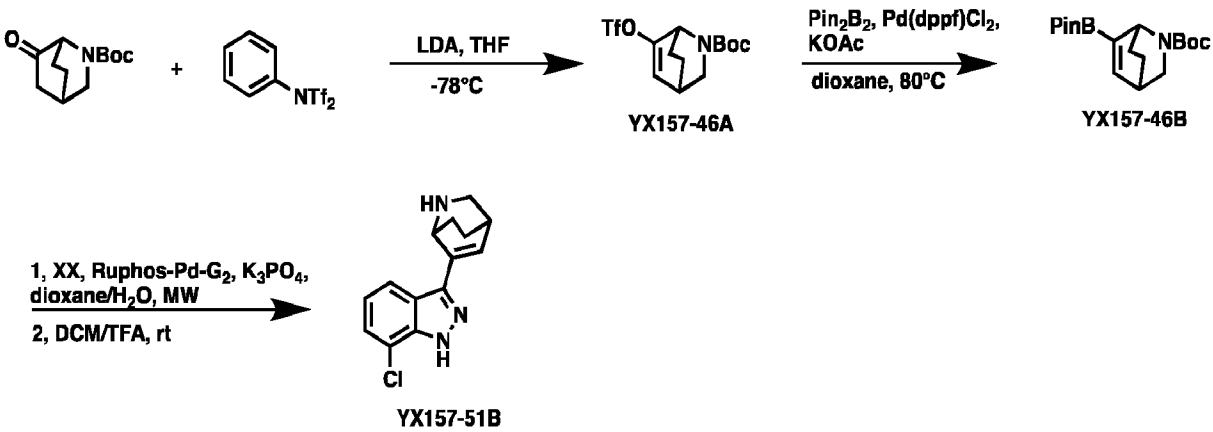


YX143-108 **YX157-42B**

7-chloro-3-(1-methylpyrrolidin-3-yl)-1*H*-indazole (YX157-42B) To a solution of YX143-108 (10 mg, 0.029 mmol) in MeOH (2 mL) was added Raney Ni. The resulted mixture was stirred at room temperature under H_2 atmosphere for 2 hour followed by filtered. The filtrate was collected, concentrated and purified by prep-HPLC to yield YX157-42B, brown solid (8 mg, 80% yield). ^1H NMR (400 MHz, Methanol-d_4) δ 7.76 (d, J = 8.1 Hz, 1H), 7.44 (d, J = 7.4 Hz, 1H), 7.17 (t, J = 8.1 Hz, 1H), 4.36 – 4.06 (m, 2H), 3.98 – 3.77 (m, 1H), 3.70 – 3.54 (m, 1H), 3.21 – 3.01 (m, 3H), 2.86 – 2.58 (m, 1H), 2.54 – 2.29 (m, 1H). MS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{15}ClN_3$ 236.1; found 236.4.

Example 223

Synthesis of YX157-51B



YX157-46A **YX157-46B** **YX157-51B**

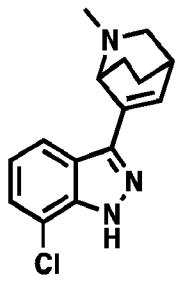
6-(7-chloro-1*H*-indazol-3-yl)-2-azabicyclo[2.2.2]oct-5-ene (YX157-51B) To *tert*-butyl 6-oxo-2-azabicyclo[2.2.2]octane-2-carboxylate (250 mg, 1.1 mmmol) in THF (3 mL) in -78°C, 1,1,1-trifluoro-*N*-phenyl-*N*-((trifluoromethyl)sulfonyl)methanesulfonamide (548 mg, 1.5 mmol) was added. The solution was warmed up overnight, and quenched with sat. NH_4Cl solution (2 mL), and extracted with EA (3 × 5 mL). the organic layer was collected and concentration followed by purified by ISCO to yield intermediate YX157-46A, brown oil (237 mg, 0.66 mmol). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.08 (dd, *J* = 7.5, 2.5 Hz, 1H), 4.91 – 4.52 (m, 1H), 3.16 (d, *J* = 10.6 Hz, 1H), 3.02 – 2.81 (m, 2H), 2.04 – 1.87 (m, 2H), 1.72 – 1.50 (m, 2H), 1.38 (s, 9H).

Under Nitrogen atmosphere, intermediate YX157-46A (237 mg, 0.66 mmol), Pin_2B_2 (287 mg, 1.16 mmol), $Pd(dppf)Cl_2$ (154 mg, 0.19 mmol) and KOAc (215 mg, 2.19 mmol) were mixed with dioxane/H_2O (10 mL, 9:1), followed by heated at 80°C overnight. After cooled down, the mixture was filtered, the filtrated was concentrated and purified by prep-HPLC to yield intermediate YX157-46B as brown oil (85 mg, 38% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.12 (s, 1H), 4.95 – 4.70 (m, 1H), 3.37 – 3.05 (m, 1H), 3.07 – 2.85 (m, 1H), 2.85 – 2.61 (m, 1H), 2.07 – 1.81 (m, 1H), 1.69 – 1.54 (m, 1H), 1.44 (s, 9H), 1.38 – 1.11 (m, 14H).

YX157-51B was synthesized following the same procedure for preparing YX143-184B-1 from *tert*-butyl 3-bromo-7-chloro-1*H*-indazole-1-carboxylate and YX157-46B, white solid (5 mg, 23% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.99 (d, *J* = 8.2 Hz, 1H), 7.47 (d, *J* = 7.4 Hz, 1H), 7.40 (dd, *J* = 7.1, 1.6 Hz, 1H), 7.23 (t, *J* = 7.8 Hz, 1H), 5.27 (s, 1H), 3.25 – 3.16 (m, 1H), 2.95 (dt, *J* = 11.2, 2.9 Hz, 1H), 2.68 (s, 1H), 2.34 – 2.20 (m, 1H), 2.02 – 1.92 (m, 1H), 1.83 – 1.62 (m, 2H). MS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{15}ClN_3$ 260.1; found 260.3.

Example 224

Synthesis of YX157-51C

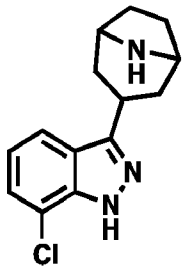


6-(7-chloro-1*H*-indazol-3-yl)-2-methyl-2-azabicyclo[2.2.2]oct-5-ene (YX157-51C) YX157-51C was synthesized following Method M from YX157-51B, white solid (4 mg, 73% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.05 – 7.98 (m, 1H), 7.53 – 7.46 (m, 1H), 7.46 – 7.35 (m, 1H),

7.30 – 7.21 (m, 1H), 5.34 – 5.07 (m, 1H), 3.79 – 3.60 (m, 1H), 3.26 – 3.16 (m, 1H), 3.12 – 2.99 (m, 1H), 2.77 (s, 3H), 2.37 – 2.22 (m, 1H), 1.95 – 1.75 (m, 2H), 1.75 – 1.60 (m, 1H). MS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{17}ClN_3$ 274.1; found 274.3.

Example 225

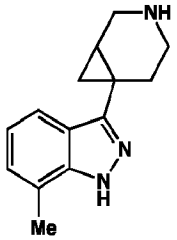
Synthesis of YX157-55A



3-(8-azabicyclo[3.2.1]octan-3-yl)-7-chloro-1*H*-indazole (YX157-55A) YX157-55A was synthesized following the same procedure for preparing YX157-42B from YX157-29B, white solid (4 mg, 60% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.71 (d, J = 8.1 Hz, 1H), 7.41 (d, J = 7.4 Hz, 1H), 7.14 (t, J = 7.8 Hz, 1H), 4.18 – 4.02 (m, 2H), 3.73 (t, J = 8.1 Hz, 1H), 2.88 – 2.77 (m, 2H), 2.66 – 2.50 (m, 2H), 2.18 – 2.03 (m, 2H), 1.98 – 1.85 (m, 2H). MS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{17}ClN_3$ 262.1; found 262.3.

Example 226

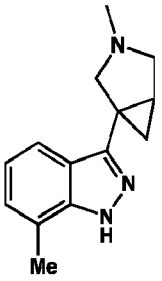
Synthesis of XS159-153



3-(3-azabicyclo[4.1.0]heptan-6-yl)-7-methyl-1*H*-indazole (XS159-153) XS159-153 was synthesized following the same procedure for preparing ZX162-100. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.65 (d, J = 8.2 Hz, 1H), 7.16 (d, J = 7.0 Hz, 1H), 7.11 – 7.01 (m, 1H), 3.84 (dd, J = 13.5, 7.6 Hz, 1H), 3.35-3.29 (m, 1H), 3.26 (t, J = 7.0 Hz, 1H), 3.06-2.99 (m, 1H), 2.65-2.58 (m, 1H), 2.53-2.46 (m, 4H), 1.94-1.87 (m, 1H), 1.51-1.48 (m, 1H), 1.21 (t, J = 8.0 Hz, 1H). MS (ESI) m/z: $[M+H]^+$ 228.47.

Example 227

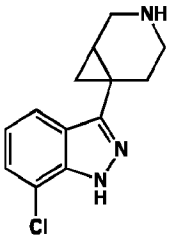
Synthesis of XS159-155



7-methyl-3-(3-methyl-3-azabicyclo[3.1.0]hexan-1-yl)-1*H*-indazole (XS159-155) XS159-155 was synthesized following the same procedure for preparing ZX162-105. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.55 (d, J = 8.2 Hz, 1H), 7.17 (d, J = 7.0 Hz, 1H), 7.11 – 7.02 (m, 1H), 4.18 (d, J = 11.4 Hz, 1H), 3.91-3.82 (m, 2H), 3.71-3.67 (m, 1H), 3.05 (s, 3H), 2.54-2.51 (m, 4H), 1.61 (t, J = 7.7 Hz, 1H), 1.37 (t, J = 5.9 Hz, 1H). MS (ESI) m/z: $[M+H]^+$ 228.4.

Example 228

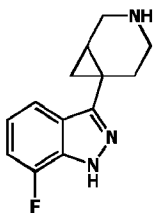
Synthesis of XS159-160



3-(3-azabicyclo[4.1.0]heptan-6-yl)-7-chloro-1*H*-indazole (XS159-160). XS159-160 was synthesized following the same procedure for preparing ZX162-100. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.80 (d, J = 8.2 Hz, 1H), 7.42 (d, J = 7.4 Hz, 1H), 7.14 (t, J = 7.8 Hz, 1H), 3.87-3.82 (m, 1H), 3.35-3.27 (m, 2H), 3.07 – 3.00 (m, 1H), 2.69-2.62 (m, 1H), 2.55-2.49 (m, 1H), 1.99-1.93 (m, 1H), 1.54-1.51 (m, 1H), 1.25 (t, J = 5.7 Hz, 1H). MS (ESI) m/z: $[M+H]^+$ 248.2.

Example 229

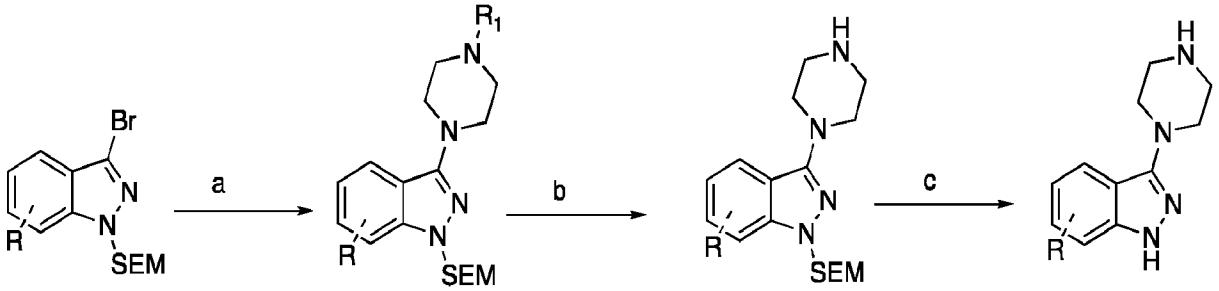
Synthesis of XS159-163



3-(3-azabicyclo[4.1.0]heptan-6-yl)-7-fluoro-1*H*-indazole (XS165-163). XS165-163 was synthesized following the same procedure for preparing ZX162-100. ^{1}H NMR (400 MHz,

Methanol-d_4) δ 7.65-7.63(m, 1H), 7.14 – 7.10 (m, 2H), 3.84 (dd, J = 13.5, 7.6 Hz, 1H), 3.35-3.26 (m, 2H), 3.07-3.00 (m, 1H), 2.69-2.62 (m, 1H), 2.54-2.48 (m, 1H), 1.99-1.92 (m, 1H), 1.54-1.50 (m, 1H), 1.26– 1.23 (m, 1H). MS (ESI) m/z: $[M+H]^+$ 232.3.

METHOD N;



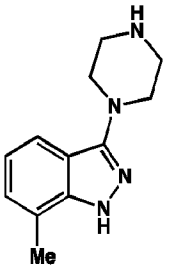
Step a. To a mixture of 3-bromoindazole derivatives (0.1 mmol, 1.0 eq), 1-Cbz-piperazine (0.2 mmol, 2.0 eq), $Pd(OAc)_2$ (0.01 mmol, 0.1 eq), XantPhos(0.012 mmol, 0.12 eq), and Cs_2CO_3(0.28 mmol, 2.8 eq) was added 1,4-dioxane (1 mL). The mixture was heated 115 °C under nitrogen atmosphere overnight followed by filtered through a short column of silica gel. The filtrate was collected and concentrated to yield crude product used for next step directly without further purification.

Step b. The obtain crude product from last step was mixed with Pd/C (5%, 1 eq) in MeOH and stirred at room temperature for 6 h under hydrogen atmosphere. The reaction solution was filtered through a short column of silica gel, and the solvent was removed to yield crude product used for next step directly without further purification.

Step c. The obtain crude product from last step was dissolved in DCM followed by TFA (10 eq). After stirred at room temperature for 2 h, the solvent was removed, resulted residue was purified by prep-HPLC to yield desired compound.

Example 230

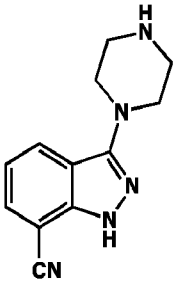
Synthesis of XS159-180



7-methyl-3-(piperazin-1-yl)-1*H*-indazole (XS159-180). XS159-180 was synthesized following Method N. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.57 (d, J = 8.2 Hz, 1H), 7.14 (d, J = 6.9 Hz, 1H), 7.03 – 6.95 (m, 1H), 3.65 – 3.62 (m, 4H), 3.46-3.43 (m, 4H), 2.50 (s, 3H). MS (ESI) m/z: $[M+H]^+$ 217.4.

Example 231

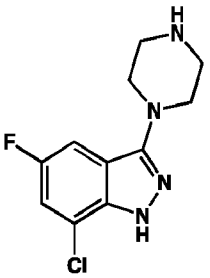
Synthesis of XS159-186



3-(piperazin-1-yl)-1*H*-indazole-7-carbonitrile (XS159-186). XS159-186 was synthesized following Method N. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.13 (d, J = 8.2 Hz, 1H), 7.79 (d, J = 7.3 Hz, 1H), 7.24 – 7.16 (m, 1H), 3.69-3.66 (m, 4H), 3.47-3.44 (m, 4H). MS (ESI) m/z: $[M+H]^+$ 228.5.

Example 232

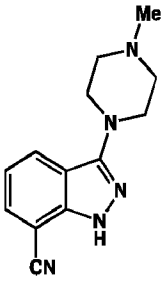
Synthesis of XS165-3



7-chloro-5-fluoro-3-(piperazin-1-yl)-1*H*-indazole (XS165-3) XS165-3 was synthesized following Method N. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.95 (d, J = 6.9 Hz, 1H), 7.27 (d, J = 9.4 Hz, 1H), 3.64 – 3.57 (m, 4H), 3.45-3.43 (m, 4H). MS (ESI) m/z: $[M+H]^+$ 255.4.

Example 233

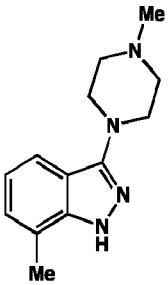
Synthesis of XS165-5



3-(4-methylpiperazin-1-yl)-1*H*-indazole-7-carbonitrile (XS165-5). XS165-5 was synthesized following Method N. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.14 (d, J = 8.2 Hz, 1H), 7.81 (d, J = 7.3 Hz, 1H), 7.26 – 7.18 (m, 1H), 4.21-4.10 (m, 2H), 3.66-3.62 (m, 3H), 3.49 – 3.33 (m, 3H), 3.01 (s, 3H). MS (ESI) m/z: $[M+H]^+$ 242.3.

Example 234

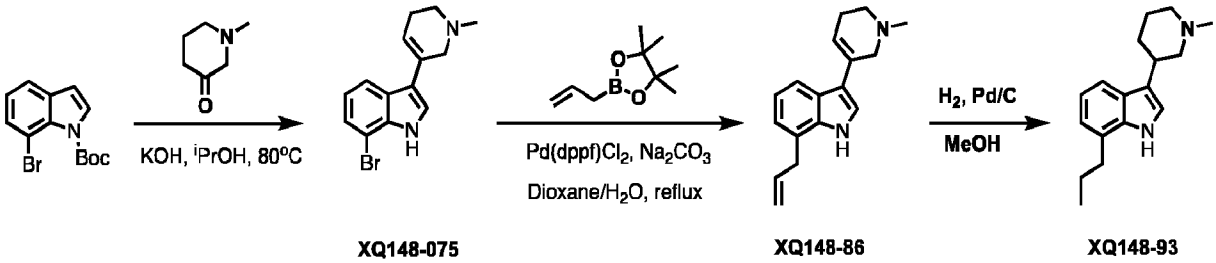
Synthesis of XS165-8



7-methyl-3-(4-methylpiperazin-1-yl)-1*H*-indazole (XS165-8). XS165-8 was synthesized following Method N.^{1}H NMR (400 MHz, Methanol-d_4) δ 7.56 (d, J = 8.2 Hz, 1H), 7.14 (d, J = 7.0 Hz, 1H), 6.99 (t, J = 7.6 Hz, 1H), 4.06 (d, J = 13.6 Hz, 2H), 3.63 (d, J = 12.8 Hz, 2H), 3.40 (t, J = 12.3 Hz, 2H), 3.26 (d, J = 12.8 Hz, 2H), 3.00 (s, 3H), 2.49 (s, 3H). MS (ESI) m/z: $[M+H]^+$ 231.6.

Example 235

Synthesis of XQ148-93



3-(1-methylpiperidin-3-yl)-7-propyl-1H-indole (XQ148-93)

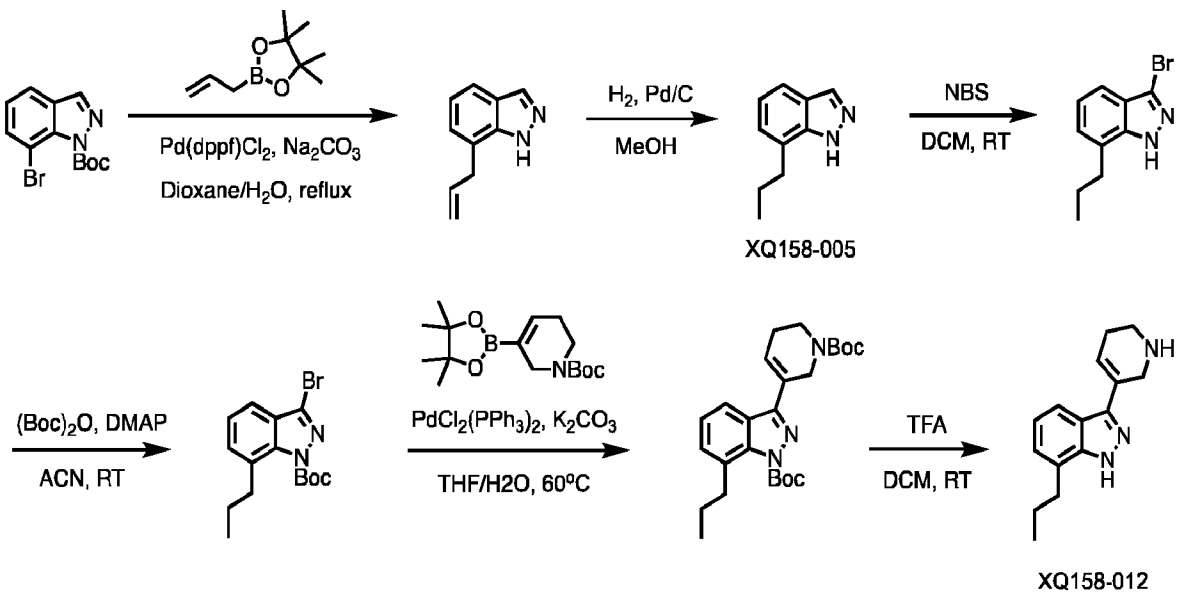
Step 1: To a solution of *tert*-butyl 7-bromo-1H-indole-1-carboxylate (180 mg, 0.6 mmol, 1 equiv) in ^{i}PrOH (4 mL) were added KOH (337 mg, 10 equiv) and 1-methylpiperidin-3-one HCl salt (359 mg, 1.8 mmol, 3 equiv) at rt, then the mixture was stirred for 8 h at 80 °C, evaporated and the resulting mixture was purified by C18 column (10%-100% acetonitrile / 0.1% TFA in H_2O) to give the product as a yellow solid (18 mg, 60%).

Step 2: to a solution of XQ148-075 (87.4 mg, 0.3 mmol, 1 equiv) in Dioxane (2 mL) were added 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (100.8 mg, 0.6 mmol, 2 equiv), 2M Na_2CO_3 solution (0.3 mL, 0.6 mmol, 2 equiv), $Pd(dppf)Cl_2$ (22.0 mg, 0.03 mmol, 0.1 equiv), and the atmosphere evacuated and backfilled with nitrogen three times. After being stirred at 110 °C overnight, the resulting mixture was purified by C18 column (10%-100% acetonitrile / 0.1% TFA in H_2O) to get compound XQ148-86 as a light yellow solid (23 mg, 30%).

Step 3: to a solution of XQ148-86 (10 mg) in Methanol (2 mL) were added palladium on carbon (catalytic amount), evacuated and recharged with hydrogen for 3 times, then stirred at rt for 3 hours. After filter and concentration, the resulting mixture was purified by prep-HPLC to get compound XQ148-93 as a light yellow solid (10 mg, 100%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.40 (dd, J = 7.7, 1.3 Hz, 1H), 7.08 (s, 1H), 6.98 – 6.86 (m, 2H), 3.61 (d, J = 12.2 Hz, 1H), 3.49 (d, J = 12.4 Hz, 1H), 3.04 – 2.92 (m, 2H), 2.84 (s, 2H), 2.82 – 2.74 (m, 2H), 2.19 – 2.03 (m, 2H), 1.97 – 1.86 (m, 1H), 1.85 – 1.77 (m, 1H), 1.68 (q, J = 7.5 Hz, 2H), 1.56 (d, J = 7.5 Hz, 1H), 1.29 (s, 1H), 0.93 (t, J = 7.3 Hz, 3H). MS (ESI) m/z: calcd for $C_{17}H_{25}N_2^+$ $[M + H]^+$, 257.2 found, 257.4.

Example 236

Synthesis of XQ158-012



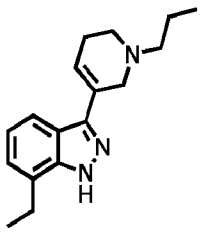
3-(piperidin-3-yl)-7-propyl-1H-indazole (XQ158-012)

Step 1 and 2: to a solution of tert-butyl 7-bromo-1H-indazole-1-carboxylate (178.2 mg, 0.6 mmol) in Dioxane (4 mL) were added 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (201.6 mg, 1.2 mmol), 2M Na_2CO_3 solution (0.6 mL, 1.2 mmol), $Pd(dppf)Cl_2$ (44.0 mg, 0.06 mmol), and the atmosphere evacuated and backfilled with nitrogen three times. After being stirred at 110 °C overnight, the mixture was purified by silica gel (10% to 20% ethyl acetate in hexane), the resulting intermediate was dissolved in Methanol (2 mL), added palladium on carbon (catalytic amount), evacuated and recharged with hydrogen for 3 times, then stirred at rt for 3 hours. After filter and concentration, the resulting mixture was purified by silica gel (10% to 20% ethyl acetate in hexane) to get compound XQ158-005 as a yellow oil (43 mg, 45%).

Step 3: XQ158-012 was synthesized following the standard procedure for preparing NS144-102 from XQ158-005 and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (yellow solid, 2 mg, 3%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.82 (d, J = 8.1 Hz, 1H), 7.21 (d, J = 6.9 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 6.84 (s, 1H), 4.30 (s, 2H), 3.47 (t, J = 6.2 Hz, 2H), 2.92 (t, J = 7.6 Hz, 2H), 2.73 (s, 2H), 1.78 (h, J = 7.1 Hz, 2H), 1.02 (t, J = 7.3 Hz, 3H). MS (ESI) m/z: calcd for $C_{15}H_{20}N_3^+$ $[M + H]^+$, 242.2 found, 242.3.

Example 237

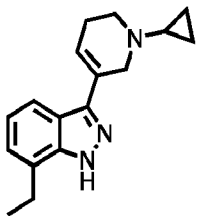
Synthesis of XQ158-055



7-ethyl-3-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole (XQ158-055). XQ158-055 was synthesized following the standard procedure for preparing XQ158-115 from compound XQ148-012 (light yellow solid, 6 mg, 22%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.83 (d, J = 8.1 Hz, 1H), 7.24 (d, J = 7.1 Hz, 1H), 7.18 (t, J = 7.8 Hz, 1H), 6.85 (s, 1H), 4.67 (d, J = 16.2 Hz, 2H), 4.15 (d, J = 16.3 Hz, 2H), 3.76 (s, 2H), 2.97 (q, J = 7.2 Hz, 2H), 2.86 – 2.70 (m, 2H), 2.00 – 1.86 (m, 2H), 1.37 (t, J = 7.5 Hz, 3H), 1.12 (t, J = 7.4 Hz, 3H). MS (ESI) m/z: calcd for $C_{17}H_{24}N_3^+$ $[M + H]^+$, 270.2 found, 270.3.

Example 238

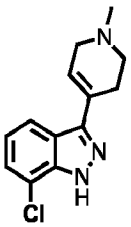
Synthesis of XQ158-056



3-(1-cyclopropyl-1,2,5,6-tetrahydropyridin-3-yl)-7-ethyl-1H-indazole (**XQ158-056**). XQ158-056 was synthesized following the standard procedure for preparing XQ158-115 from compound 148-012 using bromocyclopropane (yellow solid, 14 mg, 52%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.82 (d, J = 8.1 Hz, 1H), 7.24 (d, J = 7.0 Hz, 1H), 7.18 (t, J = 8.0 Hz, 1H), 6.85 (s, 1H), 6.18 – 6.04 (m, 1H), 5.79 – 5.66 (m, 2H), 4.65 (d, J = 15.9 Hz, 1H), 4.15 (d, J = 16.7 Hz, 1H), 4.01 (d, J = 7.2 Hz, 2H), 3.76 (s, 1H), 2.97 (q, J = 7.3 Hz, 2H), 2.81 (s, 2H), 1.37 (t, J = 7.5 Hz, 4H). MS (ESI) m/z: calcd for $C_{17}H_{22}N_3^-$ $[M + H]^+$, 268.2 found, 268.4.

Example 239

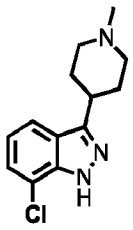
Synthesis of XQ158-078



7-chloro-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indazole (**XQ158-078**). XQ158-078 was synthesized following the standard procedure for preparing NS144-102 from 3-bromo-7-chloro-1*H*-indazole and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine (yellow solid, 55 mg, 74%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.96 (dd, J = 8.3, 1.9 Hz, 1H), 7.46 (dd, J = 7.5, 1.9 Hz, 1H), 7.26 – 7.18 (m, 1H), 6.60 (dd, J = 4.2, 2.1 Hz, 1H), 4.19 (d, J = 16.9 Hz, 1H), 3.94 (d, J = 17.1 Hz, 1H), 3.84 – 3.74 (m, 1H), 3.47 (d, J = 14.4 Hz, 1H), 3.24 (d, J = 19.8 Hz, 1H), 3.17 – 3.03 (m, 4H). MS (ESI) m/z: calcd for $C_{13}H_{15}ClN_3^+$ $[M + H]^+$, 248.1 found, 248.2.

Example 240

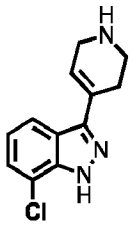
Synthesis of XQ158-093A



7-chloro-3-(1-methylpiperidin-4-yl)-1H-indazole (XQ158-093A). XQ158-093A was synthesized following the standard procedure for preparing YX157-27A-2 from XQ158-078 (yellow solid, 8 mg, 32%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.78 (d, J = 8.3 Hz, 1H), 7.43 (d, J = 7.3 Hz, 1H), 7.18 – 7.12 (M, 1H), 3.74 – 3.64 (m, 2H), 3.59 – 3.45 (m, 1H), 3.26 (t, J = 12.7 Hz, 2H), 2.98 (d, J = 2.0 Hz, 3H), 2.37 (d, J = 15.2 Hz, 2H), 2.29 – 2.17 (m, 2H). MS (ESI) m/z: calcd for $C_{13}H_{17}ClN_3^+$ $[M + H]^+$, 250.1 found, 250.1.

Example 241

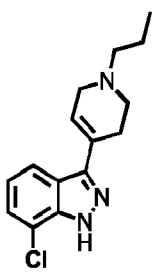
Synthesis of XQ158-082



7-chloro-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indazole (XQ158-082). XQ158-082 was synthesized following the standard procedure for preparing NS144-102 from 3-bromo-7-chloro-1*H*-indazole and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (light yellow solid, 48 mg, 69%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.96 (dd, J = 8.3, 1.9 Hz, 1H), 7.46 (dd, J = 7.4, 1.9 Hz, 1H), 7.25 – 7.18 (m, 1H), 6.63 (dd, J = 3.5, 1.9 Hz, 1H), 3.99 (t, J = 2.9 Hz, 2H), 3.58 – 3.52 (m, 2H), 3.09 (d, J = 7.0 Hz, 2H). MS (ESI) m/z: calcd for $C_{12}H_{13}ClN_3^+$ $[M + H]^+$, 234.1 found, 234.2.

Example 242

Synthesis of XQ158-115

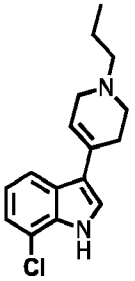


7-chloro-3-(1-propyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indazole (XQ158-115). XQ158-115

was synthesized following similar procedure for preparing NS144-108 (yellow solid, 12 mg, 46%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.96 (dd, J = 8.3, 2.0 Hz, 1H), 7.46 (dd, J = 7.5, 1.9 Hz, 1H), 7.22 (t, J = 8.1 Hz, 1H), 6.65 – 6.56 (m, 1H), 4.22 (d, J = 17.1 Hz, 1H), 4.00 – 3.76 (m, 2H), 3.42 (s, 1H), 3.31 – 3.19 (m, 3H), 3.11 (s, 1H), 1.97 – 1.82 (m, 2H), 1.11 (td, J = 7.5, 1.6 Hz, 3H). MS (ESI) m/z: calcd for $C_{15}H_{19}ClN_3^+$ $[M + H]^+$, 276.1 found, 276.4.

Example 243

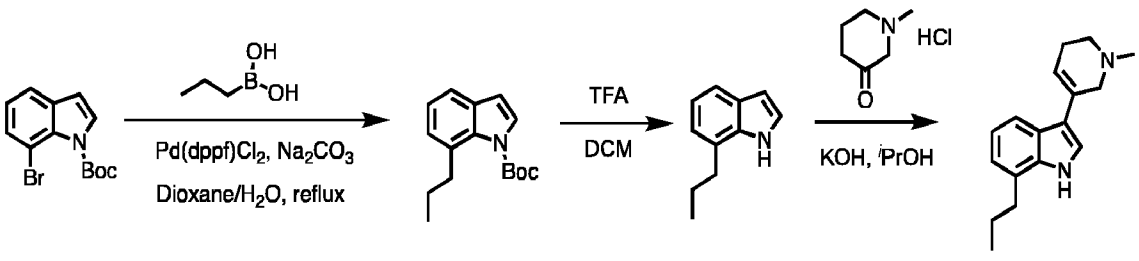
Synthesis of XQ158-164



7-chloro-3-(1-propyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole (XQ158-164). XQ158-164 was synthesized following the standard procedure for preparing XQ158-115 (yellow solid, 6 mg, 38%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.69 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 1.5 Hz, 1H), 7.10 (d, J = 7.6 Hz, 1H), 6.99 (t, J = 7.9 Hz, 1H), 6.10 (s, 1H), 4.01 (s, 1H), 3.72 (d, J = 38.8 Hz, 2H), 3.29 (s, 1H), 3.17 – 3.07 (m, 2H), 2.85 (s, 2H), 1.83 – 1.68 (m, 2H), 0.97 (t, J = 6.6 Hz, 3H). MS (ESI) m/z: calcd for $C_{16}H_{20}ClN_2^+$ $[M + H]^+$, 275.1 found, 275.3.

Example 244

Synthesis of XQ158-167



3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-7-propyl-1H-indole (XQ158-167)

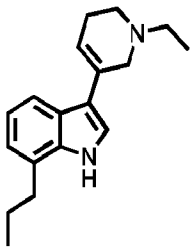
Step 1 and 2: to a solution of *tert*-butyl 7-bromo-1H-indole-1-carboxylate (296.2 mg, 1 mmol, 1 equiv) in Dioxane (5 mL) were added propylboronic acid (175.8 mg, 2 mmol, 2 equiv), 2M Na_2CO_3 solution (1 mL, 2 mmol, 2 equiv), $Pd(dppf)Cl_2$ (36.6 mg, 0.05 mmol, 0.05 equiv), and the atmosphere evacuated and backfilled with nitrogen three times. After refluxed overnight, the

resulting mixture was filtered and concentrated. Then treated with TFA (3 mL) in DCM (1 mL) for 1 h. purified by silica gel (10% to 20% ethyl acetate in hexane) to get compound XQ148-166 as a yellow oil (86 mg, 54%).

Step 3: To a solution of XQ158-166 (31.8 mg, 0.2 mmol) in ^{i}PrOH (2 mL) were added KOH (112.2 mg, 2 mmol) and 1-methylpiperidin-3-one HCl salt (89.8 mg, 0.6 mmol) at, then the mixture was stirred for 12 h at 80 °C, evaporated and the resulting mixture was purified by prep-HPLC to give the final product as a yellow solid (4 mg, 8%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.67 (d, J = 7.9 Hz, 1H), 7.37 (d, J = 1.8 Hz, 1H), 7.06 (t, J = 7.1 Hz, 1H), 7.01 (d, J = 6.8 Hz, 1H), 6.40 (s, 1H), 3.51 (s, 1H), 3.16 (s, 1H), 3.08 (s, 1H), 2.90 – 2.83 (m, 1H), 2.73 (s, 1H), 1.76 (q, J = 7.6 Hz, 2H), 1.42 – 1.29 (m, 4H), 1.04 – 0.97 (m, 2H), 0.94 (s, 3H). MS (ESI) m/z: calcd for $C_{17}H_{23}N_2^+$ $[M + H]^+$, 255.2 found, 255.3.

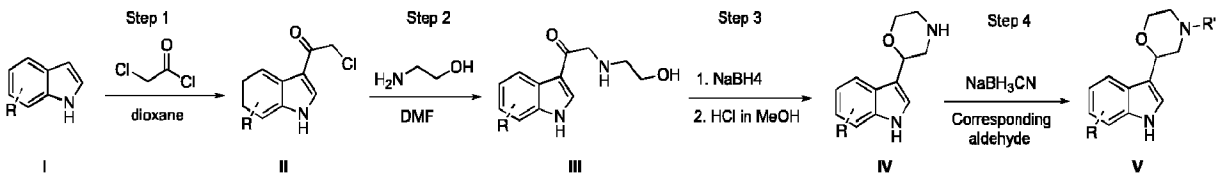
Example 245

Synthesis of XQ158-168



3-(1-ethyl-1,2,5,6-tetrahydropyridin-3-yl)-7-propyl-1H-indole (XQ158-168). XQ158-168 was synthesized following the standard procedure for preparing XQ158-167 from 1-ethylpiperidin-3-one HCl salt (yellow solid, 3 mg, 6%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.66 (d, J = 7.9 Hz, 1H), 7.35 (s, 1H), 7.06 (t, J = 7.6 Hz, 1H), 7.00 (d, J = 7.2 Hz, 1H), 6.38 (s, 1H), 4.11 (s, 2H), 3.52 – 3.49 (m, 1H), 3.16 (s, 1H), 3.03 (s, 1H), 2.86 (t, J = 7.8 Hz, 1H), 2.72 (s, 1H), 1.76 (q, J = 7.5 Hz, 1H), 1.31 (s, 2H), 1.01 (t, J = 7.2 Hz, 2H), 0.92 (s, 6H). MS (ESI) m/z: calcd for $C_{18}H_{25}N_2^+$ $[M + H]^+$, 269.2 found, 269.4.

METHOD O;



Step1: A mixture of substrate **I** (1.0 eq) and 2-chloroacetyl chloride (1.0 eq) in dioxane (0.4 M) was reflux for 1~16 h. After the substrate disappears, the mixture was allowed to cool to rt and

then poured to water followed by extracted with ethyl acetate and purified by column chromatography on silica to get compound **II.**

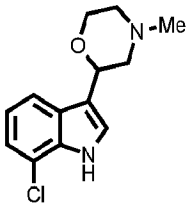
Step 2: A mixture of compound **II** (1.0 eq) and ethanolamine (2.5 eq) in DMF (0.2 M) was stirred at rt. for 5h. After concentration, the residue was purified by column chromatography on silica (eluting with gradient formed from DCM/Methanol/NH_3 aq) to get compound **III.**

Step 3: A mixture of compound **III (**1.0 eq) and sodium borohydride (17 eq) in Methanol (0.01 M) was stirred at rt. for 20 h. After concentration, the residue was treated with THF, ethyl acetate and Na_2CO_3 aq.(10%), the aqueous phase extracted with THF/Ethyl acetate. Evaporated to dryness and the residue was taken up in methanol (0.1 M) and treated at 0 °C with 1.25 N HCl in methanol for 45 min. The mixture was evaporated to dryness and purified by column chromatography on silica with a gradient formed from DCM/Methanol/NH3 aq to get compound **IV.**

Step 4: To a solution of compound **IV (**1.0 eq) in methanol was added corresponding aldehyde (10.0 eq) and $NaBH_3CN$ (2.0 eq). The mixture was stirred at rt for 2 h followed by purified by prep-HPLC to get compound **V**.

Example 246

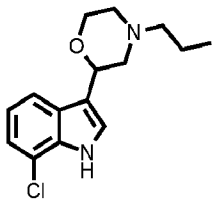
Synthesis of ZD160-34



2-(7-chloro-1*H*-indol-3-yl)-4-methylmorpholine (ZD160-34). ZD160-34 was synthesized following Method O from 7-chloro-1*H*-indole. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.67 (dd, J = 8.0, 1.8 Hz, 1H), 7.44 (d, J = 1.8 Hz, 1H), 7.20 (dd, J = 7.6, 1.8 Hz, 1H), 7.08 (td, J = 7.8, 1.8 Hz, 1H), 5.08 (d, J = 11.1 Hz, 1H), 4.29 (d, J = 13.4 Hz, 1H), 4.05 (t, J = 12.7 Hz, 1H), 3.72 (d, J = 12.4 Hz, 1H), 3.57 (d, J = 12.6 Hz, 1H), 3.43 (t, J = 11.9 Hz, 1H), 3.30 (d, J = 9.6 Hz, 0H), 3.01 (s, 3H). MS(ESI) m/z: $[M+H]^+$ 251.7.

Example 247

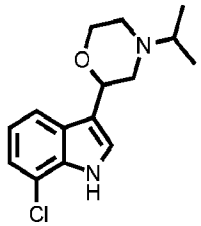
Synthesis of ZD160-140



2-(7-chloro-1*H*-indol-3-yl)-4-propylmorpholine (ZD160-140). ZD160-140 was synthesized following Method O from 7-chloro-1*H*-indole.^{1}H NMR (400 MHz, Methanol-d_4) δ 7.57 – 7.53 (m, 1H), 7.32 (d, J = 2.0 Hz, 1H), 7.09 (dd, J = 7.6, 2.0 Hz, 1H), 6.96 (td, J = 7.8, 2.1 Hz, 1H), 4.97 (d, J = 11.1 Hz, 1H), 4.18 (d, J = 13.3 Hz, 1H), 3.93 (t, J = 12.7 Hz, 1H), 3.62 (d, J = 12.5 Hz, 1H), 3.51 (d, J = 12.8 Hz, 1H), 3.29 (t, J = 11.9 Hz, 1H), 3.18 – 3.03 (m, 3H), 1.79 – 1.66 (m, 2H), 0.95 (td, J = 7.4, 2.1 Hz, 3H). MS(ESI) m/z: $[M+H]^+$ 279.5.

Example 248

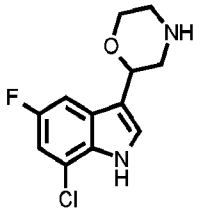
Synthesis of ZD160-141



2-(7-chloro-1*H*-indol-3-yl)-4-isopropylmorpholine (ZD160-141). ZD160-141 was synthesized following Method O from 7-chloro-1*H*-indole. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.44 (s, 1H), 7.67 (d, J = 7.9 Hz, 1H), 7.31 (d, J = 2.3 Hz, 1H), 7.24 (d, J = 8.3 Hz, 1H), 7.11 (t, J = 7.8 Hz, 1H), 5.35 (d, J = 10.7 Hz, 1H), 4.32 (t, J = 12.3 Hz, 1H), 4.23 (dd, J = 13.5, 3.9 Hz, 1H), 3.63 (d, J = 11.8 Hz, 1H), 3.58 – 3.42 (m, 2H), 3.01 (q, J = 14.1, 11.7 Hz, 2H), 1.39 (dd, J = 6.5, 2.8 Hz, 6H). MS(ESI) m/z: $[M+H]^+$ 279.6.

Example 249

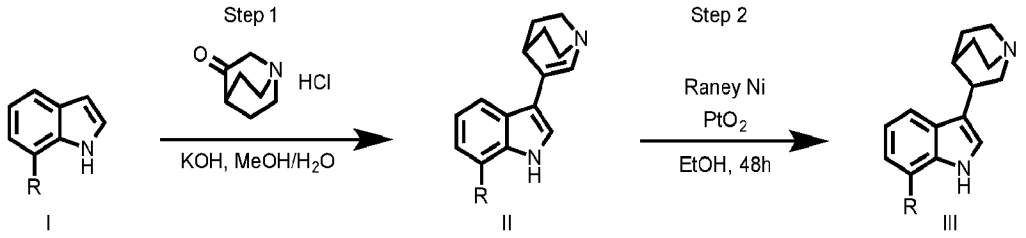
Synthesis of ZD160-149



2-(7-chloro-5-fluoro-1*H*-indol-3-yl)morpholine (ZD160-149). ZD160-149 was synthesized following Method O from 7-chloro-5-fluoro-1*H*-indole. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.49 (d, J = 1.8 Hz, 1H), 7.40 (dt, J = 9.3, 2.4 Hz, 1H), 7.08 (dd, J = 9.1, 2.4 Hz, 1H), 5.05 (dt, J = 11.1,

2.4 Hz, 1H), 4.33 – 4.19 (m, 1H), 4.06 (ddt, *J* = 13.1, 9.2, 3.1 Hz, 1H), 3.57 – 3.51 (m, 1H), 3.44 (ddd, *J* = 12.9, 10.4, 1.8 Hz, 1H), 3.38 (d, *J* = 3.3 Hz, 2H). MS(ESI) m/z: $[M+H]^+$ 255.4.

METHOD P;

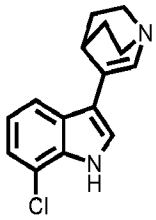


Step 1: A solution of substrate **I** (1.0 eq) in MeOH/H_2O (1:1, 0.3M) was treated with KOH (5.0 eq), followed by 3-quinoclidine hydrochloride (2.0 eq) at rt. After heated at refluxed for 36 h, the reaction was brought to rt, filtered and washed with MeOH/H_2O (1:1), followed by methanol. The solid was collected and dried under vacumn to obtain the compound **II**.

Step 2: A solution of compound **II** (1.0 eq) in EtOH was added Raney Ni (0.1 eq) and PtO_2 (0.1 eq) under H_2, the mixture was stirred at rt for 48h. Then filted through diatomaceous earth and the residue was purified by prep-HPLC to get compound **III**.

Example 250

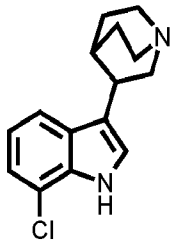
Synthesis of ZD160-11



3-(7-chloro-1*H*-indol-3-yl)-1-azabicyclo[2.2.2]oct-2-ene (ZD160-11). ZD160-11 was synthesized following Method P from 7-chloro-1*H*-indole. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.69 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.48 (s, 1H), 7.19 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.08 (t, *J* = 7.8 Hz, 1H), 6.81 (d, *J* = 1.5 Hz, 1H), 3.18 (dt, *J* = 4.5, 2.3 Hz, 1H), 3.15 – 3.06 (m, 2H), 2.73 (tdd, *J* = 13.3, 4.9, 2.4 Hz, 2H), 1.89 (dddd, *J* = 11.7, 9.0, 4.7, 2.6 Hz, 2H), 1.71 (tdd, *J* = 13.0, 6.5, 3.9 Hz, 2H). MS(ESI) m/z: $[M+H]^+$ 259.3.

Example 251

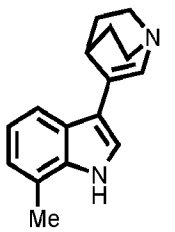
Synthesis of ZD160-133



3-(7-chloro-1*H*-indol-3-yl)quinuclidine (ZD160-133). ZD160-133 was synthesized following Method P from 7-chloro-1*H*-indole. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.40 (dd, J = 7.9, 2.0 Hz, 1H), 7.32 (s, 1H), 7.07 (dd, J = 7.6, 2.0 Hz, 1H), 6.93 (td, J = 8.0, 1.8 Hz, 1H), 3.71 (m, J = 23.6, 15.1, 10.3 Hz, 2H), 3.47 – 3.32 (m, 5H), 2.23 (s, 1H), 2.20 – 2.13 (m, 1H), 2.04 (dt, J = 13.2, 9.5 Hz, 1H), 1.97 – 1.86 (m, 1H), 1.69 (t, J = 12.4 Hz, 1H). MS(ESI) m/z: $[M+H]^+$ 261.4.

Example 252

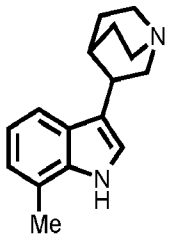
Synthesis of ZD160-130



3-(7-methyl-1*H*-indol-3-yl)-1-azabicyclo[2.2.2]oct-2-ene (ZD160-130). ZD160-130 was synthesized following Method P from 7-methyl-1*H*-indole. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.45 (d, J = 7.8 Hz, 1H), 7.28 (d, J = 2.0 Hz, 1H), 6.89 (td, J = 7.4, 2.0 Hz, 1H), 6.84 (d, J = 7.2 Hz, 1H), 6.67 (s, 1H), 3.06 (s, 1H), 3.01 – 2.93 (m, 2H), 2.67 – 2.56 (m, 2H), 1.81 – 1.71 (m, 2H), 1.63 – 1.53 (m, 2H). MS(ESI) m/z: $[M+H]^+$ 239.4.

Example 253

Synthesis of ZD160-131

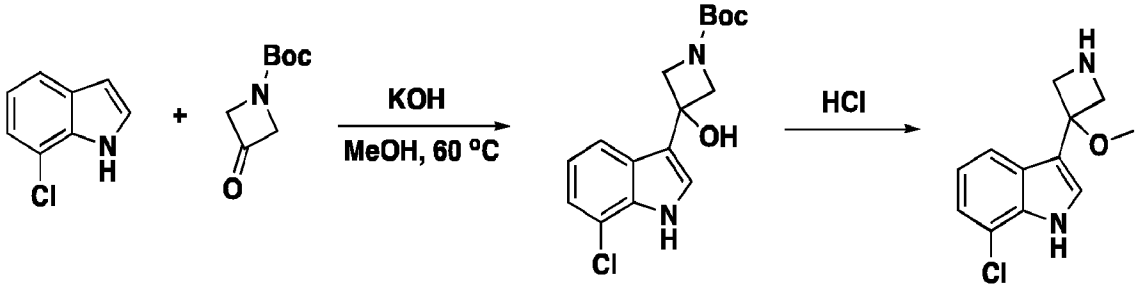


3-(7-methyl-1*H*-indol-3-yl)-1-azabicyclo[2.2.2]oct-2-ene (ZD160-131). ZD160-131 was synthesized following Method P from 7-methyl-1*H*-indole. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.39 (dd, J = 6.7, 2.5 Hz, 1H), 7.34 (d, J = 2.0 Hz, 1H), 7.01 – 6.94 (m, 2H), 3.90 – 3.75 (m, 2H), 3.60 – 3.44 (m, 4H), 3.29 (s, 1H), 2.38 (d, J = 3.7 Hz, 1H), 2.29 (d, J = 8.1 Hz, 1H), 2.21 – 2.13

(m, 1H), 2.07 (m, J = 13.2, 10.3, 7.4, 2.2 Hz, 1H), 1.80 (t, J = 12.4 Hz, 1H). MS(ESI) m/z: $[M+H]^+$ 241.5.

Example 254

Synthesis of QC166-005



QC166-005

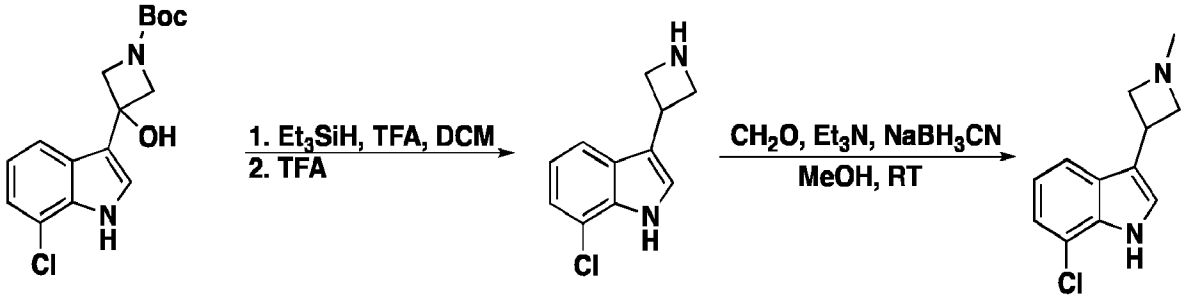
7-chloro-3-(3-methoxyazetidin-3-yl)-1*H*-indole (QC166-005)

Step 1:7-chloro-1*H*-indole (300 mg, 2.0 mmol, 1.0 eq) and *tert*-butyl 3-oxoazetidine-1-carboxylate (380 mg, 2.2 mmol, 1.1 eq) were dissolved in MeOH (6 mL). Then KOH (123 mg, 2.2 mmol, 1.1 eq) was added. The mixture was stirred at 60 °C for 12 h. After removal of the solvents, the residue was purified by silica gel (Hexane : Ethyl Acetate = 1:1) and obtained *tert*-butyl 3-(7-chloro-1*H*-indol-3-yl)-3-hydroxyazetidine-1-carboxylate as a white solid (112 mg, 16% yield). ^{1}H NMR (400 MHz, MeOD) δ 7.44 (d, J = 7.8 Hz, 1H), 7.26 (s, 1H), 7.06 (d, J = 7.8 Hz, 1H), 6.91 (t, J = 7.8 Hz, 1H), 4.26 (d, J = 9.0 Hz, 2H), 4.08 (d, J = 9.0 Hz, 2H), 1.37 (s, 9H).

Step 2:*tert*-butyl 3-(7-chloro-1*H*-indol-3-yl)-3-hydroxyazetidine-1-carboxylate (15 mg) was dissolved in MeOH (0.5 mL), then HCl in dixoane (4M, 1.0 mL, 4 mmol) was added. The mixture was stirred at room temperature for 2 h. After removal of the solvents, the residue was purified by prep-HPLC to yield title compound (white solid, 6 mg, 58% yield). ^{1}H NMR (400 MHz, MeOD) δ 7.60 (s, 1H), 7.50 (d, J = 8.0, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.07 (t, J = 8.0 Hz, 1H), 4.50 – 4.36 (m, 4H), 3.06 (s, 3H). MS (ESI) m/z: $[M+H]^+$ 237.3.

Examples 255 and 256

Synthesis of QC166-008 and QC166-032



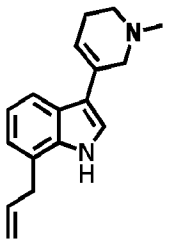
QC166-005 QC166-008 QC166-032

Step 1:**3-(azetidin-3-yl)-7-chloro-1*H*-indole (QC166-008)**. *tert*-butyl 3-(7-chloro-1*H*-indol-3-yl)-3-hydroxyazetidine-1-carboxylate (25 mg, 0.08 mmol, 1.0 eq) and Et_3SiH (90 mg, 0.78 mmol, 10 eq) were dissolved in DCM (2 mL). After stirred at 0 °C for 10 min, TFA (45 mg, 0.4 mmol, 5.0 eq) was added dropwise. The mixture was stirred at 0 °C for 20 min. Then TFA (1 mL) was added. The mixture was stirred at room temperature for another 1 h and removed all the solvents. The residue was purified by prepared HPLC to yield light yellow oil (3.5 mg, 22% yield). ^{1}H NMR (400 MHz, MeOD) δ 7.52 (d, J = 8.0 Hz, 1H), 7.42 (s, 1H), 7.16 (d, J = 8.0 Hz, 1H), 7.03 (t, J = 8.0 Hz, 1H), 4.48 – 4.40 (m, 3H), 4.36 – 4.27 (m, 2H). MS (ESI) m/z: $[M+H]^+$ 207.3.

Step 2:**7-chloro-3-(1-methylazetidin-3-yl)-1H-indole (QC166-032).** 3-(azetidin-3-yl)-7-chloro-1*H*-indole (20 mg, 0.1 mmol, 1.0 eq), Et_3N (25 mg, 0.3 mmol, 2.5 eq), CH_2O (37% wt in H_2O, 0.1 ml), $NaBH_3CN$ (10 mg, 0.15 mmol, 1.5 eq), were dissolved in 2 mL MeOH. The mixture was stirred at room temperature overnight. After removal all the volatiles, the residue was purified with prepared HPLC to yield colorless oil (4 mg, 17%). ^{1}H NMR (400 MHz, MeOD) δ 7.41- 7.35 (m, 2H), 7.12 - 7.05 (m, 1H), 6.95 (t, J = 7.8 Hz, 1H), 4.63 – 4.55 (m, 1H), 4.46 – 4.22 (m, 3H), 4.13 (t, J = 9.6 Hz, 1H), 2.94 (d, J = 29.4, 3H). MS (ESI) m/z: $[M+H]^+$ 221.0.

Example 257

Synthesis of XQ148-86

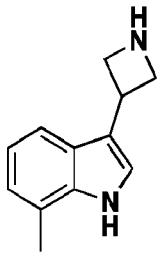


7-allyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (XQ148-86). XQ148-086 was synthesized following the standard procedure for preparing XQ148-093, light yellow solid (23 mg, 30%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.59 (d, J = 8.0 Hz, 1H), 7.18 (s, 1H), 6.95 (t, J = 7.6 Hz, 1H), 6.88 (d, J = 7.1 Hz, 1H), 6.23 – 6.14 (m, 1H), 6.06 – 5.92 (m, 1H), 5.06 – 4.94 (m, 2H),

3.57 – 3.47 (m, 4H), 2.84 (t, J = 6.0 Hz, 2H), 2.56 (s, 3H), 2.50 – 2.42 (m, 2H). MS (ESI) m/z: calcd for $C_{17}H_{21}N_2^+$ $[M + H]^+$, 253.4 found, 253.2.

Example 258

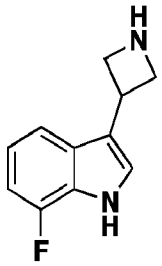
Synthesis of compound QC166-096



3-(azetidin-3-yl)-7-methyl-1*H*-indole (QC166-096), was synthesized following the standard procedure for preparing QC166-008. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.41 (d, J = 6.6 Hz, 1H), 7.32 (s, 1H), 7.02 – 6.91 (m, 2H), 4.49 – 4.38 (m, 3H), 4.37 – 4.27 (m, 2H), 2.48 (s, 3H). MS (ESI) m/z: $[M + H]^+$ 187.0.

Example 259

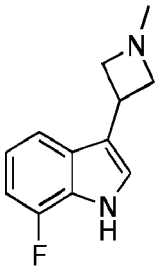
Synthesis of compound QC166-097



3-(azetidin-3-yl)-7-fluoro-1*H*-indole (QC166-097), was synthesized following the standard procedure for preparing QC166-008. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.42 - 7.37 (m, 1.6 Hz, 2H), 7.06 – 6.98 (m, 1H), 6.93 – 6.86 (m, 1H), 4..50 - 4.42 (m, 3H), 4.39 - 4.28 (m, 2H). MS (ESI) m/z: $[M + H]^+$ 191.2.

Example 260

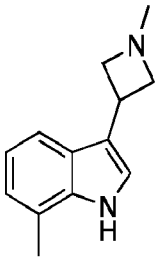
Synthesis of compound QC179-001



7-fluoro-3-(1-methylazetidin-3-yl)-1*H*-indole (QC179-001), was synthesized following the standard procedure for preparing QC166-032. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.46 (s, 1H), 7.39 – 7.31 (m, 1H), 7.08 - 7.00 (m, 1H), 6.96 - 6.88 (m, 1H), 4.71 (t, J = 8.8 Hz, 1H), 4.59 - 4.34 (m, 3H), 4.24 (d, J = 9.4 Hz, 1H), 3.07 (d, J = 28.8 Hz, 3H). MS (ESI) m/z: $[M + H]^+$ 205.3.

Example 261

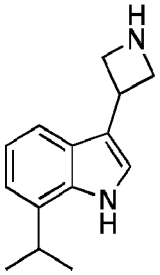
Synthesis of compound QC179-002



7-methyl-3-(1-methylazetidin-3-yl)-1*H*-indole (QC179-002), was synthesized following the standard procedure for preparing QC166-032. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.43 – 7.32 (m, 1H), 7.07 – 6.90 (m, 1H), 4.70 (t, J = 8.7 Hz, 1H), 4.59 - 4.33 (m, 1H), 4.24 (t, J = 9.4 Hz, 1H), 3.06 (d, J = 28.5 Hz, 1H), 2.51 (s, 1H). MS (ESI) m/z: $[M + H]^+$ 201.0.

Example 262

Synthesis of compound QC179-025

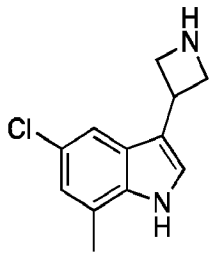


3-(azetidin-3-yl)-7-isopropyl-1*H*-indole (QC179-025), was synthesized following the standard procedure for preparing QC166-008. ^{1}H NMR (400 MHz, MeOD) δ 7.45 – 7.41 (m, 1H), 7.34 (s,

1H), 7.09 – 7.03 (m, 2H), 4.52 – 4.41 (m, 3H), 4.40 – 4.32 (m, 2H), 3.42 – 3.34 (m, 1H), 1.37 (d, J = 6.9 Hz, 6H). MS (ESI) m/z: $[M + H]^+$ 215.4.

Example 263

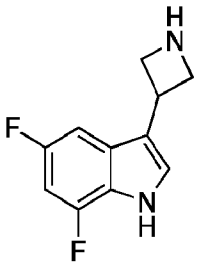
Synthesis of compound QC179-032



3-(azetidin-3-yl)-5-chloro-7-methyl-1*H*-indole (QC179-032), was synthesized following the standard procedure for preparing QC166-008. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.46 (s, 1H), 7.42 (s, 1H), 6.97 (s, 1H), 4.39 - 4.50 (m, 3H), 4.38 – 4.28 (m, 2H), 2.50 (s, 3H). MS (ESI) m/z: $[M + H]^+$ 221.3.

Example 264

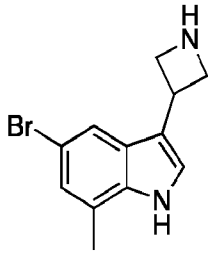
Synthesis of compound QC179-033



3-(azetidin-3-yl)-5,7-difluoro-1*H*-indole (QC179-033), was synthesized following the standard procedure for preparing QC166-008. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.50 (s, 1H), 7.18 (d, J = 9.1 Hz, 1H), 6.82 (t, J = 10.3 Hz, 1H), 4.51 - 4.39 (m, 3H), 4.38 – 4.27 (m, 2H). MS (ESI) m/z: $[M + H]^+$ 209.3.

Example 265

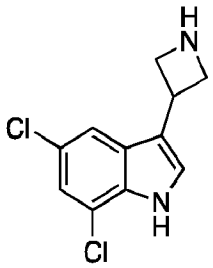
Synthesis of compound QC179-038



3-(azetidin-3-yl)-5-bromo-7-methyl-1*H*-indole (QC179-038), was synthesized following the standard procedure for preparing QC166-008. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.61 (s, 1H), 7.41 (s, 1H), 7.09 (s, 1H), 4.51 – 4.39 (m, 3H), 4.36 – 4.23 (m, 2H), 2.49 (s, 3H). MS (ESI) m/z: $[M + H]^+$ 265.3.

Example 266

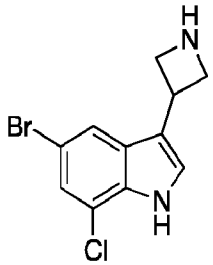
Synthesis of compound QC179-039



3-(azetidin-3-yl)-5,7-dichloro-1*H*-indole (QC179-039), was synthesized following the standard procedure for preparing QC166-008. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.60 (s, 1H), 7.53 (s, 1H), 7.21 (s, 1H), 4.52 – 4.40 (m, 3H), 4.38 – 4.26 (m, 2H). MS (ESI) m/z: $[M + H]^+$ 241.3.

Example 267

Synthesis of compound QC179-040

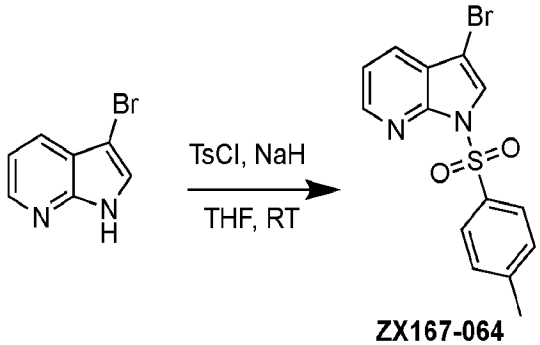


3-(azetidin-3-yl)-5-bromo-7-chloro-1*H*-indole (QC179-040), was synthesized following the standard procedure for preparing QC166-008. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.74 (s, 1H), 7.52 (s, 1H), 7.32 (s, 1H), 4.51 – 4.39 (m, 3H), 4.38 – 4.24 (m, 2H). MS (ESI) m/z: $[M + H]^+$ 284.7.

Example 268

Synthesis of ZX167-072

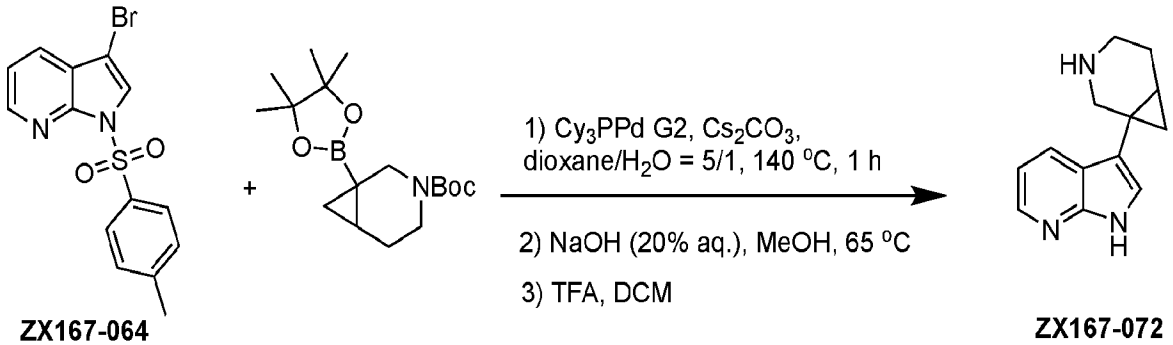
Synthesis of intermediate ZX167-064



ZX167-064

3-bromo-1-tosyl-1H-pyrrolo[2,3-b]pyridine (ZX167-064). 3-Bromo-1H-pyrrolo[2,3-b]pyridine (200 mg, 1.01 mmol, 1.0 equiv) was dissolved into 10 mL THF and cooled to 0 °C, NaH (60% in mineral oil) (61 mg, 1.52 mmol, 1.5 equiv) was added to the solution, stirred for 15 min and 4-toluolsulfonyl chloride (212 mg, 1.11 mmol, 1.1 equiv) was added and the reaction mixture was warmed to room temperature and stirred for another 2 h. The reaction mixture was quenched with 20 mL $NaHCO_3$ aqueous solution and extracted with 20 mL EA twice. The organic phase was combined and washed with brine. Dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography (PE – PE/EA = 5/1) to yield ZX167-064 (white solid, 0.26 g, 73% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.47 (d, *J* = 4.6 Hz, 1H), 8.08 (d, *J* = 7.3 Hz, 2H), 7.81 (d, *J* = 7.9 Hz, 1H), 7.79 (s, 1H), 7.29 (d, *J* = 7.6 Hz, 2H), 7.25 (d, *J* = 4.0 Hz, 1H), 2.38 (s, 3H). MS (ESI) m/z: $[M + H]^+$ 351.1.

Synthesis of compound ZX167-072



ZX167-064 **ZX167-072**

3-(3-azabicyclo[4.1.0]heptan-1-yl)-1H-pyrrolo[2,3-b]pyridine (ZX167-072).

Step 1: To a solution of ZX162-064 (35 mg, 0.1 mmol, 1.0 equiv.) in dioxane/water (2 mL, 5:1) was added Cy_3P Pd G2 (11.8 mg, 0.02 mmol, 0.2 equiv.), Cs_2CO_3 (65 mg, 0.2 mmol, 2.0 equiv.) and *tert*-butyl 1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-azabicyclo[4.1.0]hexane-3-carboxylate (39 mg, 0.12 mmol, 1.2 equiv.). The mixture was heated at 140 °C under microwave

irradiation condition at nitrogen atmosphere for 1 h, followed by diluted with EA (20 mL) and washed with brine (20 mL). After dried over Na_2SO_4 and concentrated, the residue was purified by pre-HPLC. MS (ESI) m/z: $[M + H]^+$ 468.4.

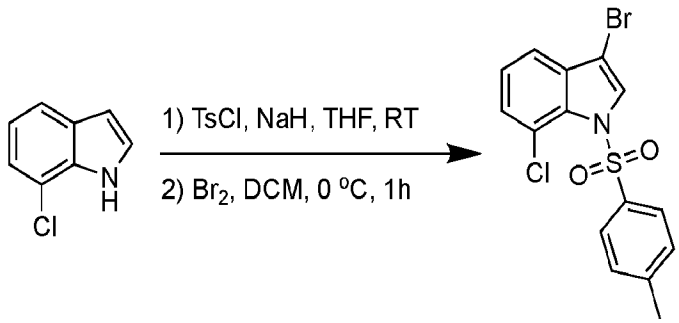
Step 2: The above product was dissolved into 1 mL MeOH and 0.2 mL 20% NaOH aqueous solution was added. The reaction mixture was stirred at 65 °C for 1 h and cooled to room temperature. The solution was extracted with 10 mL DCM twice, the organic phase was combined and washed with brine. Dried over anhydrous Na_2SO_4 and concentrated.

Step 3: The residue was dissolved into DCM/TFA (5 mL, 2:1) and stirred at room temperature for 1 h followed by purified by prep-HPLC to yield title compound. (17 mg, white solid, 38% yield). ^1H NMR (400 MHz, Methanol-d_4) δ 8.60 (d, J = 7.9 Hz, 1H), 8.38 (s, 1H), 7.56 (s, 1H), 7.47 – 7.42 (m, 1H), 3.71 – 3.58 (m, 2H), 3.23 (dt, J = 11.3, 5.5 Hz, 1H), 3.07 – 2.96 (m, 1H), 2.53 (dt, J = 14.9, 7.5 Hz, 1H), 2.12 (dt, J = 15.0, 6.3 Hz, 1H), 1.68 (q, J = 6.8 Hz, 1H), 1.28 (t, J = 6.6 Hz, 1H), 1.13 (t, J = 5.1 Hz, 1H). MS (ESI) m/z: $[M + H]^+$ 214.1.

Example 269

Synthesis of compound ZX167-077

Synthesis of intermediate ZX167-067



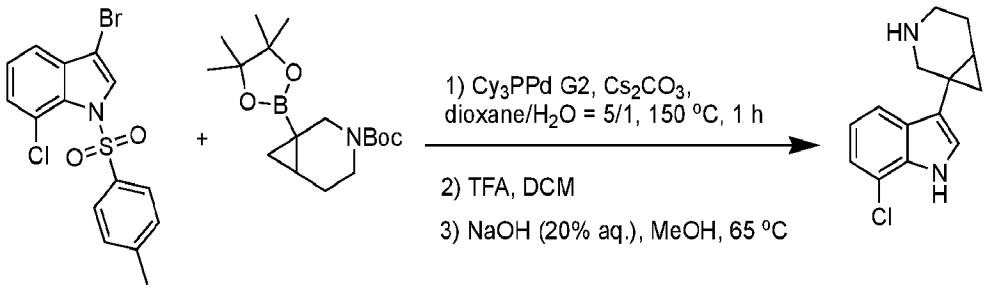
ZX167-067

3-bromo-7-chloro-1-tosyl-1H-indole (ZX167-067).

Step 1: 7-chloro-1H-indole (0.5 g, 3.3 mmol, 1.0 equiv.) was dissolved into 20 mL THF and cooled to 0 °C, NaH (60% in mineral oil) (198 mg, 4.9 mmol, 1.5 equiv.) was added to the solution, stirred for 15 min and 4-Toluolsulfonyl chloride (692 mg, 3.6 mmol, 1.1 equiv) was added and the reaction mixture was warmed to room temperature and stirred for another 2 h. The reaction mixture was quenched with 20 mL $NaHCO_3$ aqueous solution and extracted with 20 mL EA twice. The organic phase was combined and washed with brine. Dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography (PE – PE/EA = 5/1) (colorless oil, 0.76 g, 75% yield).

Step 2: The above product (250 mg, 0.82 mmol, 1.0 equiv.) was dissolved into 5 mL DCM and cooled to 0 °C. To the reaction mixture was added Br_2 (50 μL, 0.98 mmol, 1.2 equiv.). The reaction mixture was stirred at 0 °C for 2 h and quenched with 2 mL Na_2SO_3 aqueous solution. 5 mL $NaHCO_3$ aqueous solution was added, and the solution was extracted with 5 mL DCM twice. The organic phase was combined and washed with brine. Dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography (PE – PE/EA = 5/1) to yield ZX167-067 (white solid, 0.30 g, 94% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.90 (s, 1H), 7.65 (d, *J* = 6.2 Hz, 2H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.24 - 7.18 (m, 3H), 7.14 (td, *J* = 7.8, 2.2 Hz, 1H), 2.34 (s, 3H).

Synthesis of compound ZX167-077

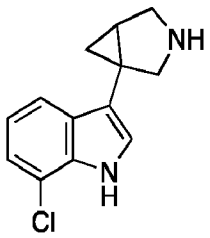


ZX167-067 ZX167-077

3-(3-azabicyclo[4.1.0]heptan-1-yl)-7-chloro-1H-indole (ZX167-077). ZX167-077 was synthesized following the similar procedure for ZX167-072 except for the temperature was 150 °C in the step 1 and the sequence of step 2 and step 3 was reversed. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.62 (d, *J* = 6.9 Hz, 1H), 7.25 (s, 1H), 7.16 (d, *J* = 6.5 Hz, 1H), 7.05 (t, *J* = 7.7 Hz, 1H), 3.63 (d, *J* = 13.4 Hz, 1H), 3.57 (d, *J* = 11.8 Hz, 1H), 3.19 (q, *J* = 6.1, 5.4 Hz, 1H), 3.07 – 2.97 (m, 1H), 2.50 (h, *J* = 7.9 Hz, 1H), 2.11 (dt, *J* = 13.8, 5.5 Hz, 1H), 1.62 (q, *J* = 7.4 Hz, 1H), 1.27 – 1.20 (m, 1H), 1.04 (t, *J* = 6.7 Hz, 1H). MS (ESI) m/z: $[M + H]^+$ 247.2.

Example 270

Synthesis of ZX167-074



3-(3-azabicyclo[3.1.0]hexan-1-yl)-7-chloro-1H-indole (ZX167-074). ZX167-074 was synthesized following the same procedure for ZX167-077 from ZX167-067 and *tert*-butyl 1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate at 140 °C.

White solid (16 mg, 46% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.56 (d, J = 8.3 Hz, 1H), 7.31 (s, 1H), 7.16 (d, J = 8.1 Hz, 1H), 7.04 (t, J = 7.8 Hz, 1H), 3.80 (d, J = 11.5 Hz, 1H), 3.71 (d, J = 11.4 Hz, 1H), 3.59 (s, 1H), 3.56 (s, 1H), 2.07 (h, J = 4.0 Hz, 1H), 1.30 (t, J = 7.4 Hz, 1H), 1.10 (t, J = 5.8 Hz, 1H). MS (ESI) m/z: $[M + H]^+$ 233.3.

Example 271

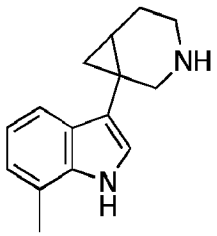
Synthesis of ZX167-090

Synthesis of intermediate ZX167-087

ZX167-087

3-bromo-7-methyl-1-tosyl-1H-indole (ZX167-087). ZX167-087 was prepared following the similar procedure for ZX167-067 using DMF instead of THF in the first step. White solid, yield 31% (2 steps). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.88 (s, 1H), 7.60 (d, J = 6.7 Hz, 2H), 7.41 (d, J = 7.8 Hz, 1H), 7.29 (d, J = 4.0 Hz, 2H), 7.22 (d, J = 7.6 Hz, 1H), 7.12 (d, J = 7.5 Hz, 1H), 2.58 (s, 3H), 2.41 (s, 3H).

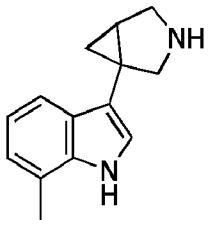
Synthesis of compound ZX167-090



3-(3-azabicyclo[4.1.0]heptan-1-yl)-7-methyl-1H-indole (ZX167-090). ZX167-090 was prepared following the similar procedure for ZX167-077, except for the last step, the reaction mixture was stirred at 80 °C for 12 h. white solid, yield 24%. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.49 (d, J = 7.8 Hz, 1H), 7.15 (s, 1H), 7.01 – 6.95 (m, 1H), 6.93 (d, J = 7.2 Hz, 1H), 3.60 (s, 2H), 3.17 (q, J = 7.4 Hz, 1H), 3.02 (dt, J = 12.0, 5.5 Hz, 1H), 2.55 – 2.48 (m, 1H), 2.46 (s, 3H), 2.16 – 2.06 (m, 1H), 1.59 (q, J = 7.0 Hz, 1H), 1.25 – 1.20 (m, 1H), 1.01 (t, J = 6.1 Hz, 1H). MS (ESI) m/z: $[M + H]^+$ 227.1.

Example 272

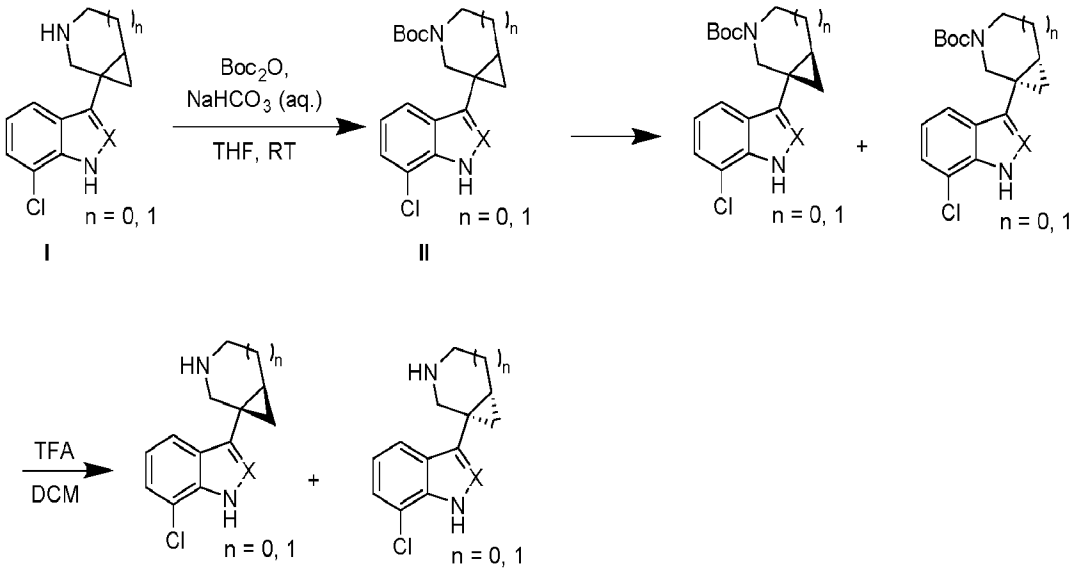
Synthesis of compound ZX167-091



3-(3-azabicyclo[3.1.0]hexan-1-yl)-7-methyl-1H-indole (ZX167-091). ZX167-091 was prepared following the similar procedure for ZX167-077, except for the last step, the reaction mixture was stirred at 80 °C for 12 h. white solid, yield 67%. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.42 (d, J = 7.7 Hz, 1H), 7.21 (s, 1H), 6.97 (t, J = 7.2 Hz, 1H), 6.92 (d, J = 7.1 Hz, 1H), 3.78 (d, J = 11.5 Hz, 1H), 3.68 (d, J = 11.4 Hz, 1H), 3.57 (t, J = 10.3 Hz, 2H), 2.47 (s, 3H), 2.02 (h, J = 4.1 Hz, 1H), 1.28 (t, J = 7.5 Hz, 1H), 1.09 – 1.04 (m, 1H). MS (ESI) m/z: $[M + H]^+$ 213.1.

Examples 273, 274, 275, 276, 277 & 278

General procedure for chiral separation of ZX162-031, ZX162-100 and ZX167-074 enantiomers to generate **Example 274**: ZX162-100-1 (former peak) and **Example 275**: ZX162-100-2 (latter peak), **Example 276:** ZX162-031-1 (former peak) and **Example 277**: ZX162-031-2 (latter peak), **Example 278**: ZX167-074-1 (former peak) and **Example 279**: ZX167-074-2 (latter peak).



Step 1: compound I (0.13 mmol, 1.0 equiv) was dissolved into 2 mL THF, and Boc_2O (1.5 equiv) and 1mL $NaHCO_3$ saturated aqueous solution was added to the solution. The reaction mixture was stirred at room temperature for 2 h until the compound I was consumed. Separated and the aqueous

phase was extracted with 5 mL DCM twice. The organic phase was combined and washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to yield compound II.

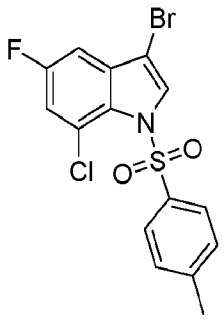
Step 2: Compound II was chiral separated by Lux ^{R} 5 μM i-Amylose-3 column (solvent: CH_3CN/H_2O (0.1% TFA): 10% - 100%).

Step 3: Chiral Compound II was dissolved into DCM/TFA (2 mL, 2 : 1), and stirred at room temperature for 1 h, concentrated and purified by pre-HPLC.

Example 279

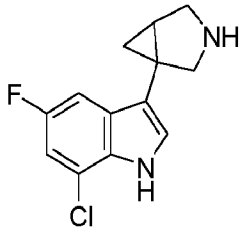
Synthesis of ZX177-057

Synthesis of compound ZX177-039



3-bromo-7-chloro-5-fluoro-1-tosyl-1H-indole (ZX177-039). ZX177-039 was prepared following the similar procedure for ZX167-067 using DMF instead of THF in the first step. White solid, yield 80% (2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.93 (s, 1H), 7.63 (d, *J* = 7.4 Hz, 2H), 7.22 (d, *J* = 7.7 Hz, 2H), 7.07 (d, *J* = 7.8 Hz, 1H), 6.99 (d, *J* = 9.4 Hz, 1H), 2.33 (s, 3H).

Synthesis of compound ZX177-057

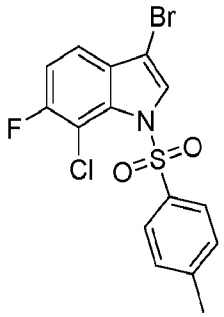


3-(3-azabicyclo[3.1.0]hexan-1-yl)-7-chloro-5-fluoro-1H-indole (ZX177-057) was synthesized following the same procedure for ZX167-077 from ZX177-039 and *tert*-butyl 1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate at 125 °C. White solid, yield 73%. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.39 (s, 1H), 7.29 (d, *J* = 9.2 Hz, 1H), 7.01 (d, *J* = 9.2 Hz, 1H), 3.80 (d, *J* = 11.4 Hz, 1H), 3.70 (d, *J* = 11.6 Hz, 1H), 3.54 (t, *J* = 11.8 Hz, 2H), 2.10 – 1.99 (m, 1H), 1.26 (t, *J* = 8.9 Hz, 1H), 1.13 – 1.06 (m, 1H). MS (ESI) m/z: $[M+H]^+$ 251.2.

Examples 280 and 281

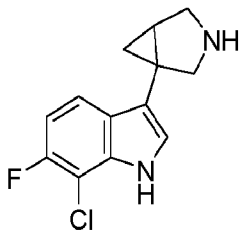
Synthesis of ZX177-058 and ZX177-058BY

Synthesis of compound ZX177-040

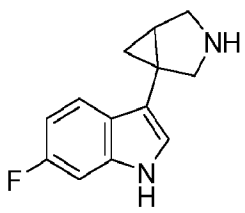


3-bromo-7-chloro-6-fluoro-1-tosyl-1H-indole (ZX177-040). ZX177-040 was prepared following the similar procedure for ZX167-067 using DMF instead of THF in the first step. White solid, yield 68% (2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.88 (s, 1H), 7.66 (d, *J* = 7.1 Hz, 2H), 7.38 – 7.30 (m, 1H), 7.23 (d, *J* = 5.7 Hz, 2H), 7.08 (t, *J* = 9.4 Hz, 1H), 2.35 (s, 3H).

Synthesis of compound ZX177-058 and ZX177-058BY



3-(3-azabicyclo[3.1.0]hexan-1-yl)-7-chloro-6-fluoro-1H-indole (ZX177-058) was synthesized following the same procedure for ZX167-077 from ZX177-040 and *tert*-butyl 1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate at 125 °C. White solid, yield 53%. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.52 (dt, *J* = 8.8, 4.6 Hz, 1H), 7.32 (s, 1H), 7.01 – 6.93 (m, 1H), 3.79 (d, *J* = 11.7 Hz, 1H), 3.71 (d, *J* = 11.3 Hz, 1H), 3.61 – 3.52 (m, 2H), 2.07 (dd, *J* = 8.5, 4.3 Hz, 1H), 1.28 (t, *J* = 7.8 Hz, 1H), 1.14 – 1.07 (m, 1H). MS (ESI) m/z: [M + H]$^+$ 251.5.

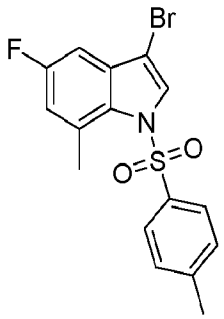


3-(3-azabicyclo[3.1.0]hexan-1-yl)-6-fluoro-1H-indole (ZX177-058BY) was separated as a byproduct. White solid, yield 16%. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.60 – 7.53 (m, 1H), 7.22 (s, 1H), 7.08 (d, J = 9.7 Hz, 1H), 6.89 – 6.80 (m, 1H), 3.79 (d, J = 11.3 Hz, 1H), 3.70 (d, J = 11.4 Hz, 1H), 3.56 (d, J = 11.5 Hz, 2H), 2.06 (h, J = 4.4 Hz, 1H), 1.29 (t, J = 8.8 Hz, 1H), 1.09 – 1.04 (m, 1H). MS (ESI) m/z: $[M + H]^+$ 217.1.

Example 282

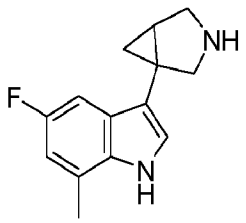
Synthesis of ZX177-059

Synthesis of intermediate ZX177-041



3-bromo-7-chloro-6-fluoro-1-tosyl-1H-indole (ZX177-041). ZX177-041 was prepared following the similar procedure for ZX167-067 using DMF instead of THF in the first step. White solid, yield 48% (2 steps). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.79 (s, 1H), 7.47 (d, J = 7.8 Hz, 2H), 7.18 (d, J = 7.9 Hz, 2H), 6.95 (d, J = 9.6 Hz, 1H), 6.75 (d, J = 9.5 Hz, 1H), 2.47 (s, 3H), 2.31 (s, 3H).

Synthesis of compound ZX177-059

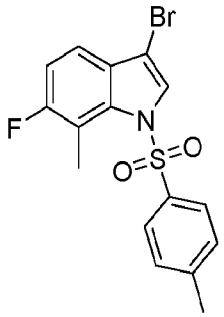


3-(3-azabicyclo[3.1.0]hexan-1-yl)-7-chloro-6-fluoro-1H-indole (ZX177-059) was synthesized following the same procedure for ZX167-077 from ZX177-040 and *tert*-butyl 1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate at 125 °C. White solid, yield 43%. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.28 (s, 1H), 7.10 (d, J = 9.4 Hz, 1H), 6.73 (d, J = 10.0 Hz, 1H), 3.79 (d, J = 11.3 Hz, 1H), 3.67 (d, J = 11.4 Hz, 1H), 3.58 – 3.51 (m, 2H), 2.46 (s, 3H), 2.02 (h, J = 4.4 Hz, 1H), 1.26 (t, J = 8.8 Hz, 1H), 1.09 – 1.03 (m, 1H). MS (ESI) m/z: $[M + H]^+$ 231.2.

Example 283

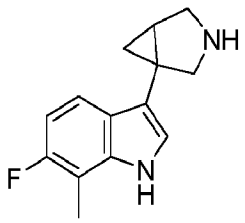
Synthesis of ZX177-060

Synthesis of intermediate ZX177-042



3-bromo-7-chloro-6-fluoro-1-tosyl-1H-indole (ZX177-042). ZX177-042 was prepared following the similar procedure for ZX167-067 using DMF instead of THF in the first step. White solid, yield 47% (2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.74 (s, 1H), 7.49 (d, *J* = 8.8 Hz, 2H), 7.26 – 7.13 (m, 3H), 7.04 – 6.93 (m, 1H), 2.38 (s, 3H), 2.32 (s, 3H).

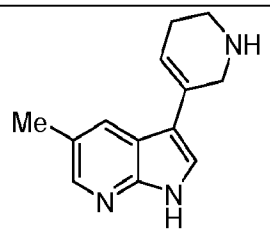
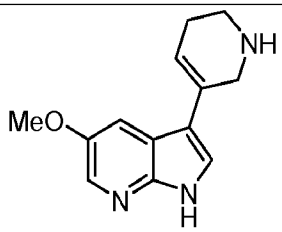
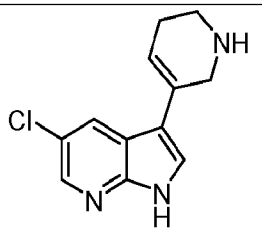
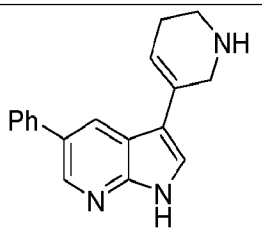
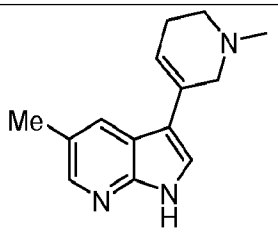
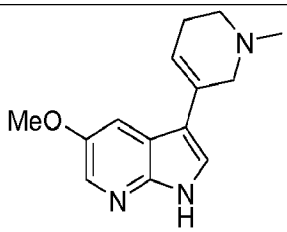
Synthesis of compound ZX177-060

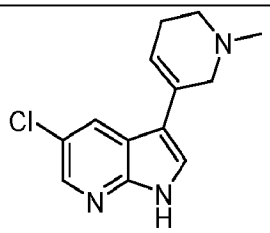
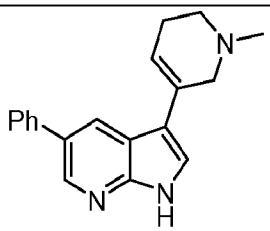
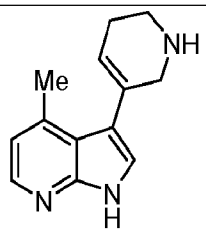
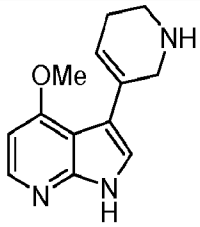
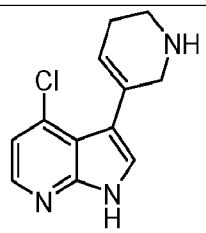
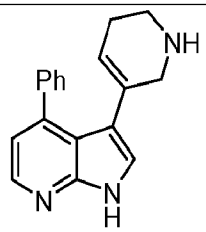
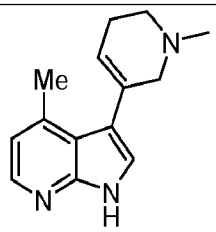


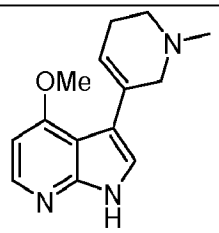
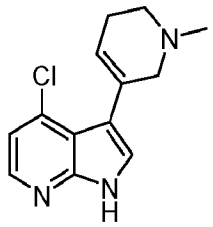
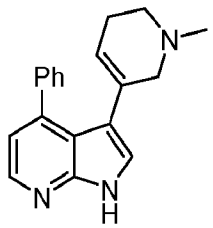
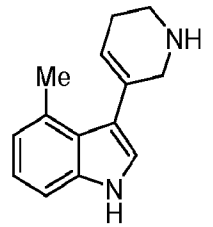
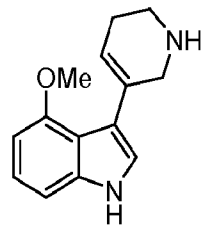
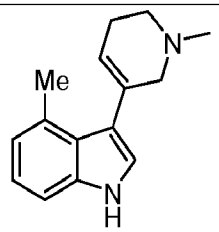
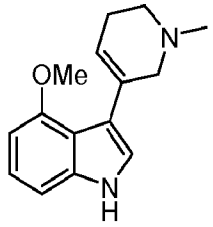
3-(3-azabicyclo[3.1.0]hexan-1-yl)-7-chloro-6-fluoro-1H-indole (ZX177-060) was synthesized following the same procedure for ZX167-077 from ZX177-040 and *tert*-butyl 1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate at 125 °C. White solid, yield 45%. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.38 (p, *J* = 4.8 Hz, 1H), 7.22 (s, 1H), 6.82 (t, *J* = 9.1 Hz, 1H), 3.78 (d, *J* = 11.5 Hz, 1H), 3.69 (d, *J* = 11.3 Hz, 1H), 3.56 (d, *J* = 11.4 Hz, 2H), 2.38 (s, 3H), 2.03 (h, *J* = 4.4 Hz, 1H), 1.27 (t, *J* = 8.9 Hz, 1H), 1.10 – 1.04 (m, 1H). MS (ESI) m/z: $[M + H]^+$ 231.2.

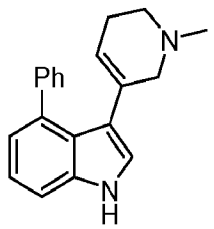
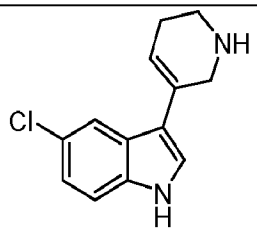
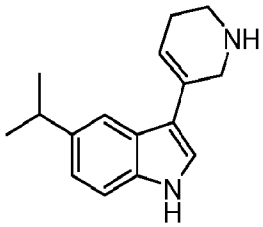
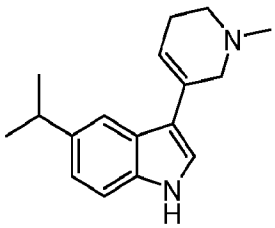
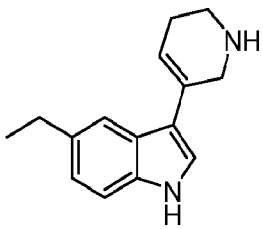
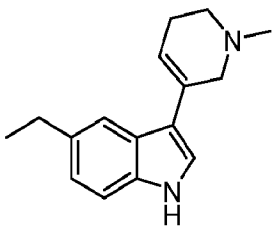
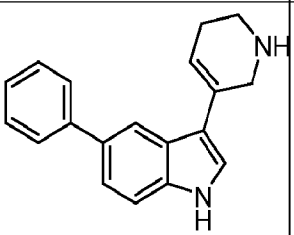
Example compounds are set forth in Table 1 & 2 below

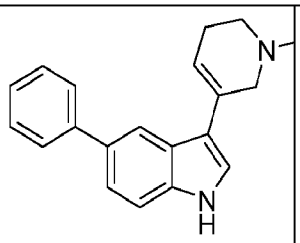
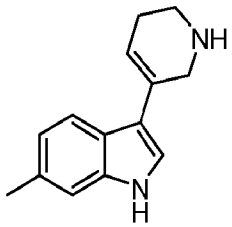
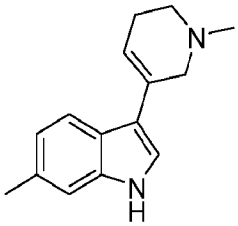
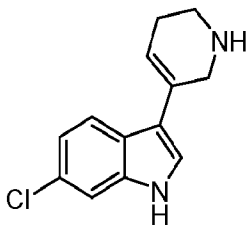
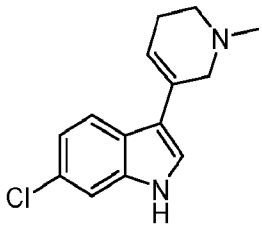
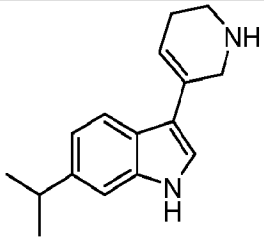
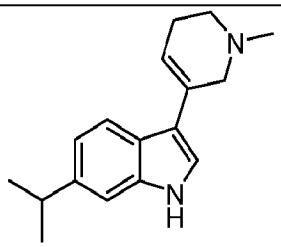
Table 1.

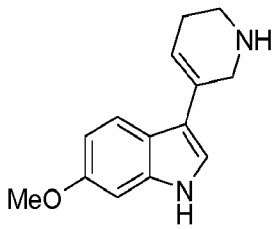
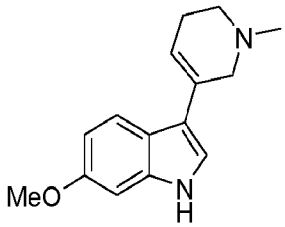
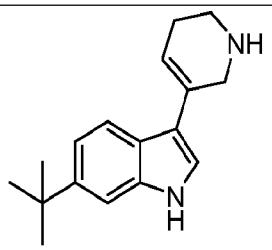
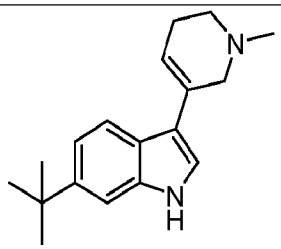
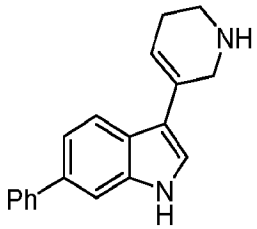
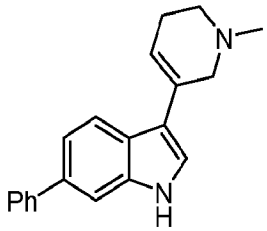
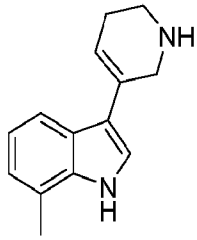
Examples	Compound code	Structure	Chemical Name
1	NS131-179		5-methyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine
2	NS131-178		5-methoxy-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine
3	NS131-177		5-chloro-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine
4	NS136-006		5-phenyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine
5	NS131-169		5-methyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine
6	NS131-168		5-methoxy-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine

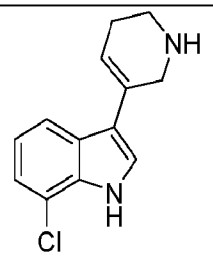
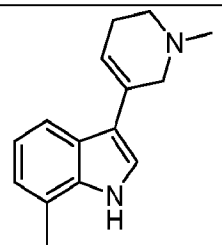
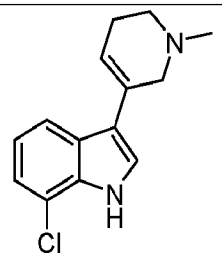
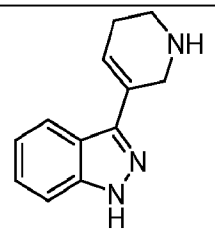
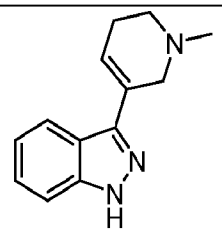
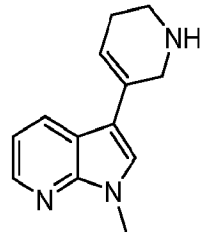
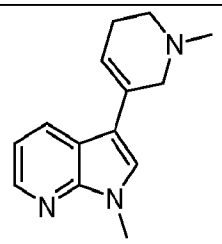
7	NS131-167		5-chloro-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine
8	NS131-173		3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-5-phenyl-1H-pyrrolo[2,3-b]pyridine
9	NS131-180		4-methyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine
10	RS134-52		4-methoxy-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine
11	RS134-48		4-chloro-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine
12	NS131-185		4-phenyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine
13	NS131-170		4-methyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine

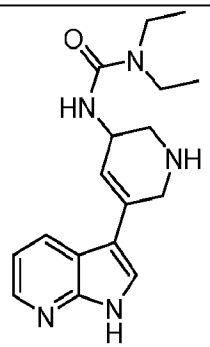
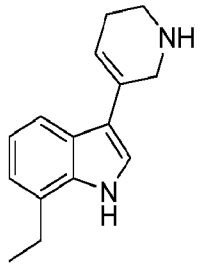
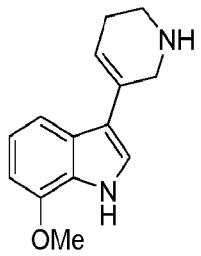
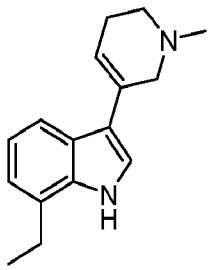
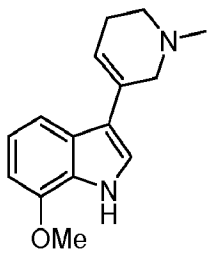
14	RS134-45		4-methoxy-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine
15	RS134-40		4-chloro-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine
16	NS131-184		3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-4-phenyl-1H-pyrrolo[2,3-b]pyridine
17	RS134-49		4-methyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indole
18	RS134-53		4-methoxy-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indole
19	RS134-41		4-methyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole
20	RS134-46		4-methoxy-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole

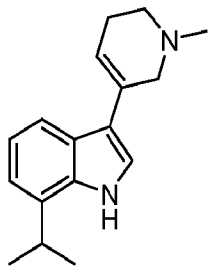
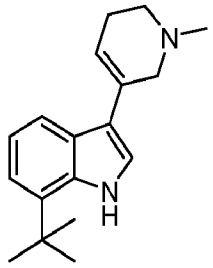
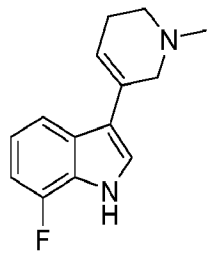
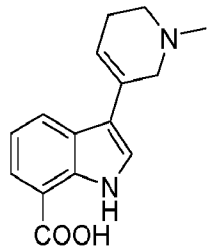
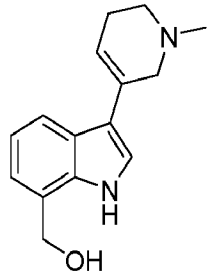
21	NS131-172		3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-4-phenyl-1H-indole
22	RS134-38		5-chloro-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indole
23	RS134-65		5-isopropyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indole
24	RS134-62		5-isopropyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole
25	RS134-70		5-ethyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indole
26	NS136-081		5-ethyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole
27	RS134-73		5-phenyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indole

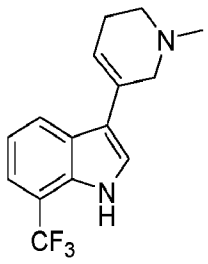
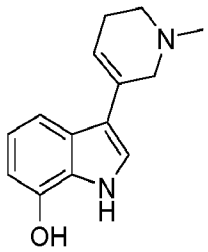
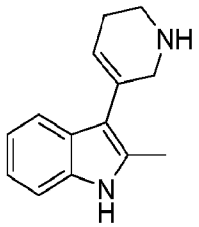
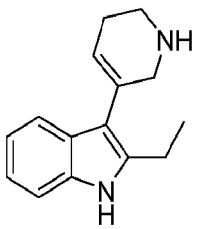
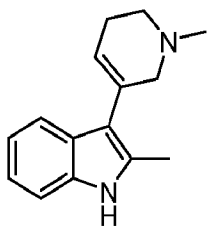
28	RS134-72		3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-5-phenyl-1H-indole
29	NS136-092		6-methyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indole
30	NS136-091		6-methyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole
31	NS136-096		6-chloro-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indole
32	NS136-095		6-chloro-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole
33	NS136-102		6-isopropyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indole
34	NS136-101		6-isopropyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole

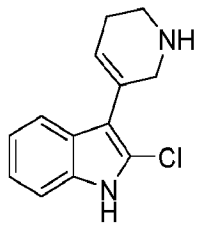
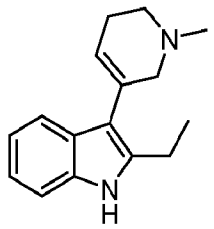
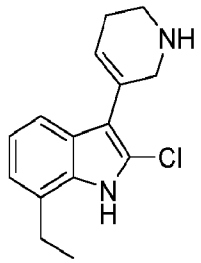
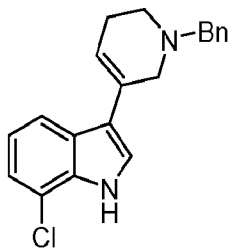
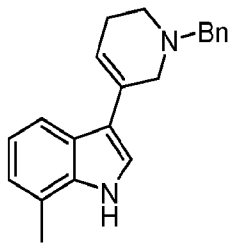
35	NS136-115		6-methoxy-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indole
36	NS136-116		6-methoxy-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole
37	NS136-117		6-(tert-butyl)-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indole
38	NS136-118		6-(tert-butyl)-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole
39	NS136-119		6-phenyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indole
40	NS136-120		3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-6-phenyl-1H-indole
41	NS136-109		7-methyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indole

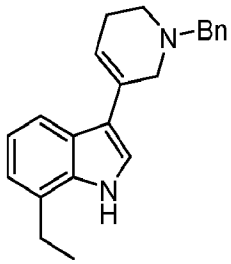
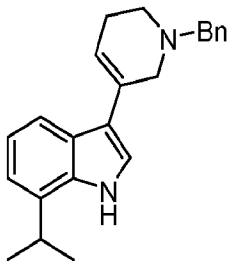
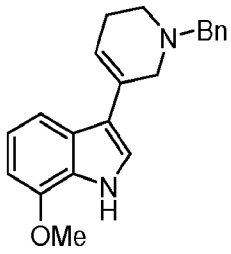
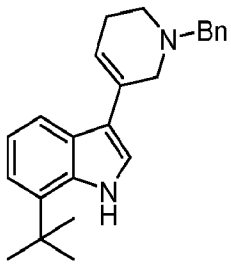
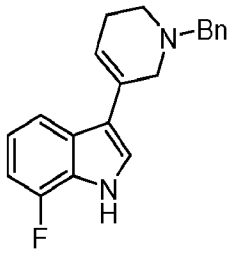
42	NS136-110		7-chloro-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indole
43	NS136-111		7-methyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole
44	NS136-112		7-chloro-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole
45	RS134-37		3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole
46	RS134-56		3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole
47	NS136-002		1-methyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine
48	NS136-004		1-methyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine

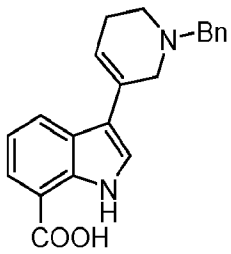
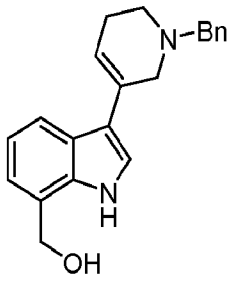
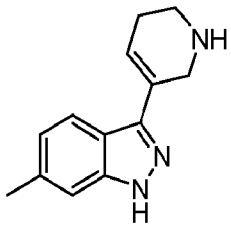
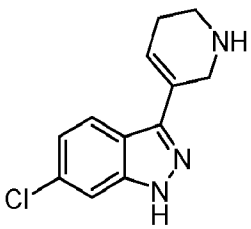
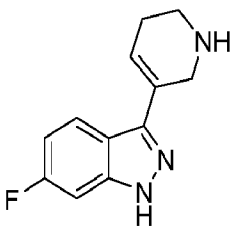
49	RS130-132		3-(5-(1H-pyrrolo[2,3-b]pyridin-3-yl)-1,2,3,6-tetrahydropyridin-3-yl)-1,1-diethylurea
50	YX129-177C		7-ethyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indole
51	YX129-180C		7-methoxy-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indole
52	YX143-19		7-ethyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole
53	YX143-20		7-methoxy-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole

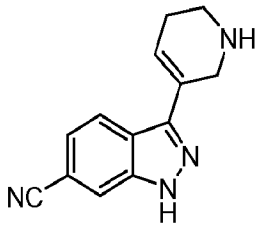
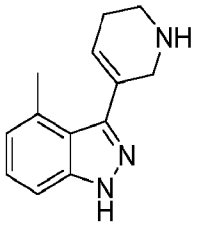
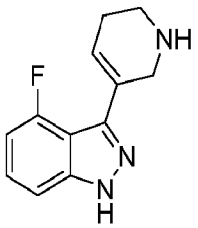
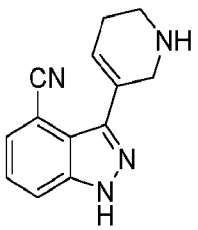
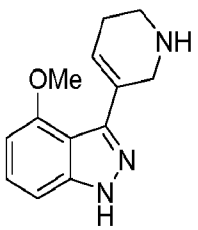
54	YX143-2		7-isopropyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole
55	YX143-21		7-(tert-butyl)-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole
56	NS144-042		7-fluoro-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole
57	NS144-043		3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole-7-carboxylic acid
58	NS144-044		(3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indol-7-yl)methanol

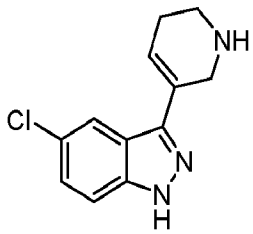
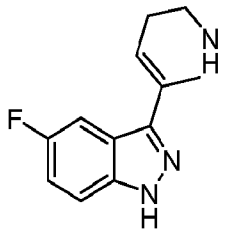
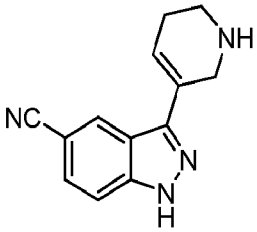
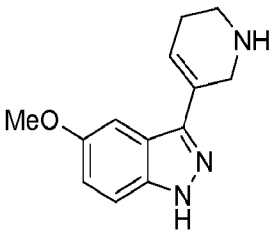
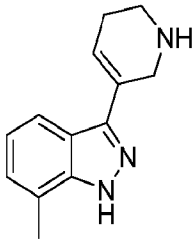
59	YS135-44		3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-7-(trifluoromethyl)-1H-indole
60	YS135-45		3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indol-7-ol
61	YS135-34		2-methyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indole
62	YS135-32		2-ethyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indole
63	YS135-38		2-methyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole

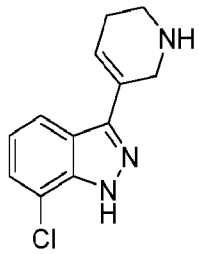
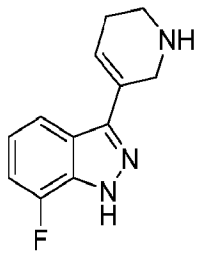
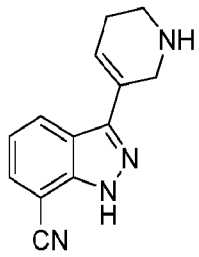
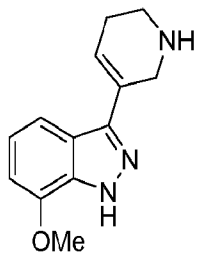
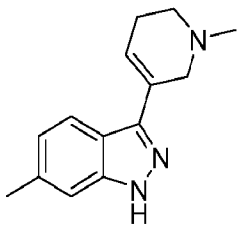
64	YS135-41		2-chloro-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indole
65	YS135-39		2-ethyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole
66	YX143-14A-2		2-chloro-7-ethyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indole
67	NS144-019		3-(1-benzyl-1,2,5,6-tetrahydropyridin-3-yl)-7-chloro-1H-indole
68	NS144-021		3-(1-benzyl-1,2,5,6-tetrahydropyridin-3-yl)-7-methyl-1H-indole

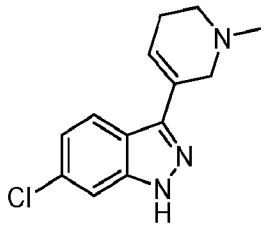
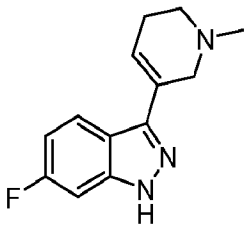
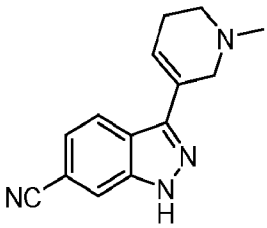
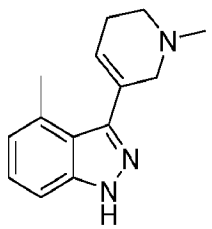
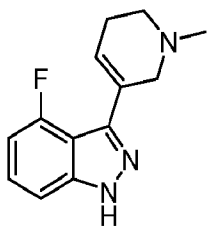
69	YX143-15		3-(1-benzyl-1,2,5,6-tetrahydropyridin-3-yl)-7-ethyl-1H-indole
70	YX143-16		3-(1-benzyl-1,2,5,6-tetrahydropyridin-3-yl)-7-isopropyl-1H-indole
71	YX143-17C		3-(1-benzyl-1,2,5,6-tetrahydropyridin-3-yl)-7-methoxy-1H-indole
72	YX143-18C		3-(1-benzyl-1,2,5,6-tetrahydropyridin-3-yl)-7-(tert-butyl)-1H-indole
73	NS144-047		3-(1-benzyl-1,2,5,6-tetrahydropyridin-3-yl)-7-fluoro-1H-indole

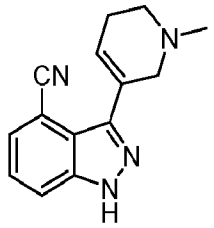
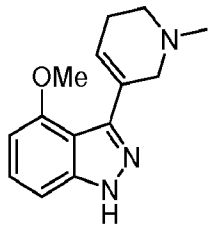
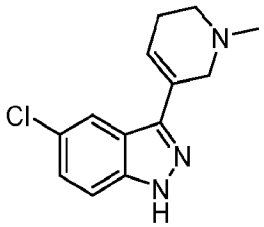
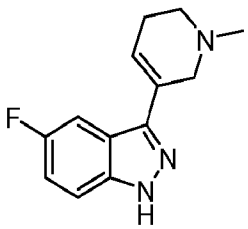
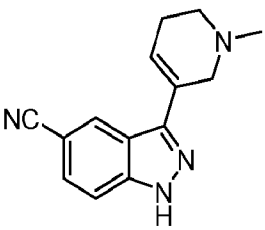
74	NS144-048		3-(1-benzyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole-7-carboxylic acid
75	NS144-049		(3-(1-benzyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indol-7-yl)methanol
76	NS136-128		6-methyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole
77	NS136-129		6-chloro-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole
78	NS136-130		6-fluoro-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole

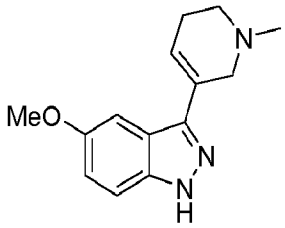
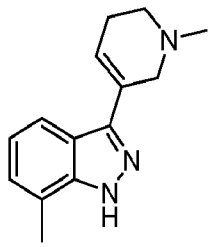
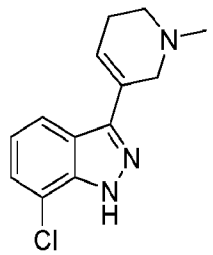
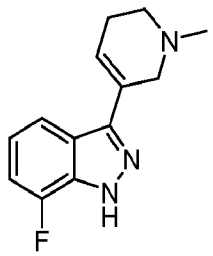
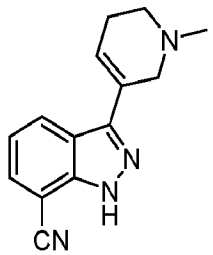
79	NS136-131		3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole-6-carbonitrile
80	NS136-150		4-methyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole
81	NS136-151		4-fluoro-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole
82	NS136-152		3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole-4-carbonitrile
83	NS136-166		4-methoxy-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole

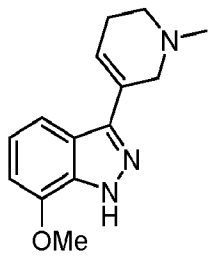
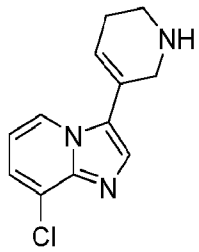
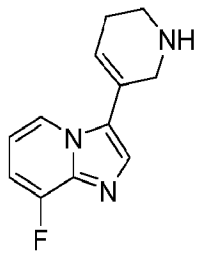
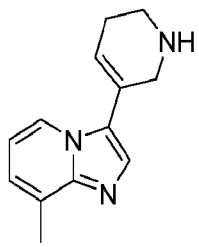
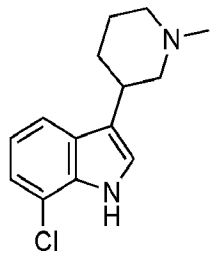
84	NS144-011		5-chloro-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole
85	NS136-158		5-fluoro-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole
86	NS136-167		3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole-5-carbonitrile
87	NS136-159		5-methoxy-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole
88	NS136-135		7-methyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole

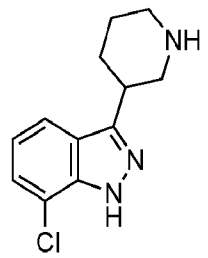
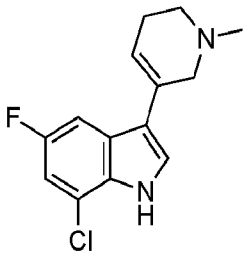
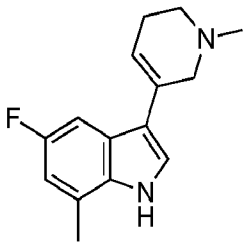
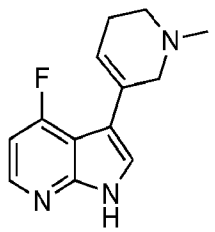
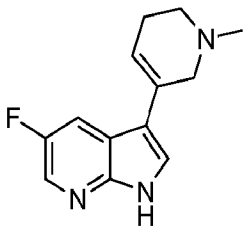
89	NS136-136		7-chloro-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole
90	NS136-137		7-fluoro-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole
91	NS144-046		3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole-7-carbonitrile
92	NS144-045		7-methoxy-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole
93	NS136-140		6-methyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole

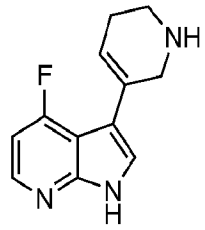
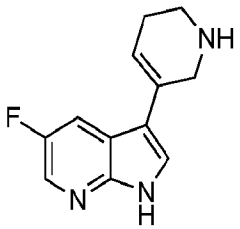
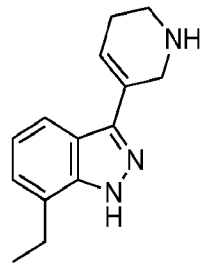
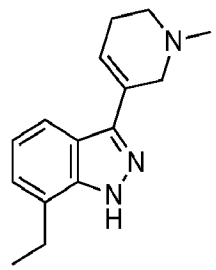
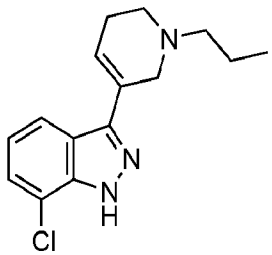
94	NS136-141		6-chloro-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole
95	NS136-142		6-fluoro-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole
96	NS136-143		3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole-6-carbonitrile
97	NS136-153		4-methyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole
98	NS136-154		4-fluoro-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole

99	NS136-155		3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole-4-carbonitrile
100	NS136-175		4-methoxy-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole
101	NS144-016		5-chloro-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole
102	NS136-160		5-fluoro-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole
103	NS136-176		3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole-5-carbonitrile

104	NS136-161		5-methoxy-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole
105	NS136-144		7-methyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole
106	NS136-145		7-chloro-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole
107	NS136-146		7-fluoro-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole
108	NS144-051		3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole-7-carbonitrile

109	NS144-050		7-methoxy-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole
110	YX143-41C		8-chloro-3-(1,2,5,6-tetrahydropyridin-3-yl)imidazo[1,2-a]pyridine
111	YX143-42C		8-fluoro-3-(1,2,5,6-tetrahydropyridin-3-yl)imidazo[1,2-a]pyridine
112	YX143-43D		8-methyl-3-(1,2,5,6-tetrahydropyridin-3-yl)imidazo[1,2-a]pyridine
113	NS144-059-2		7-chloro-3-(1-methylpiperidin-3-yl)-1H-indole

114	NS144-054-2		7-chloro-3-(piperidin-3-yl)-1H-indazole
115	NS144-067		7-chloro-5-fluoro-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole
116	NS144-085		5-fluoro-7-methyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole
117	NS144-093		4-fluoro-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine
118	NS144-094		5-fluoro-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine

119	NS144-095		4-fluoro-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine
120	NS144-096		5-fluoro-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine
121	XQ148-012		7-ethyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole
122	XQ148-023		7-ethyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole
123	ZX147-015		7-chloro-3-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole

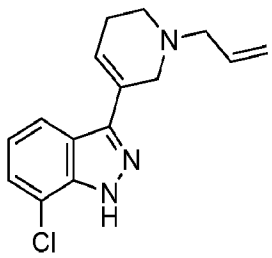
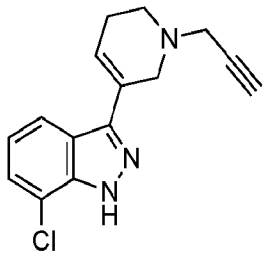
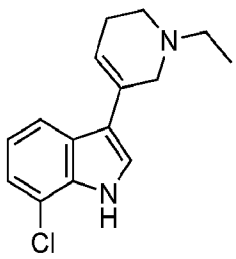
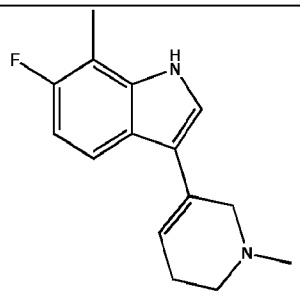
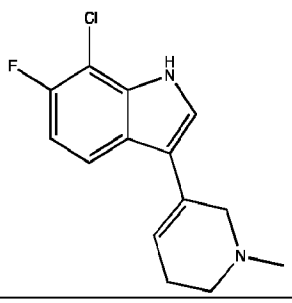
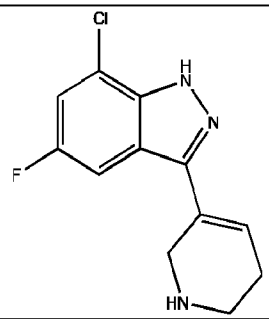
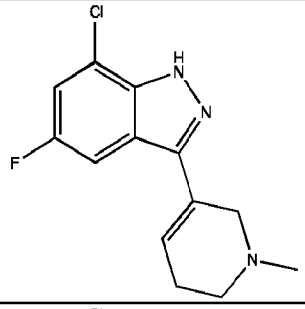
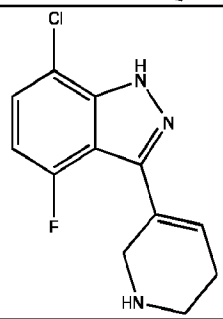
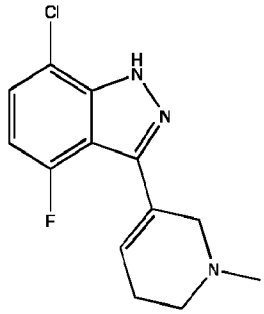
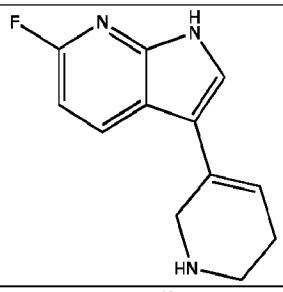
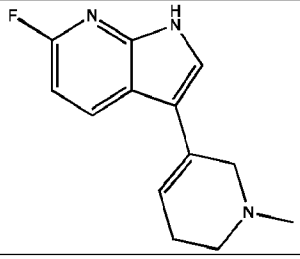
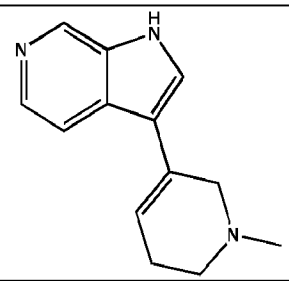
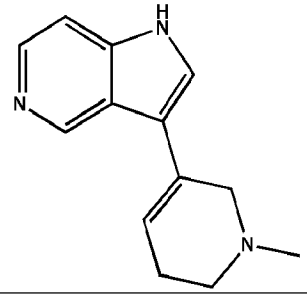
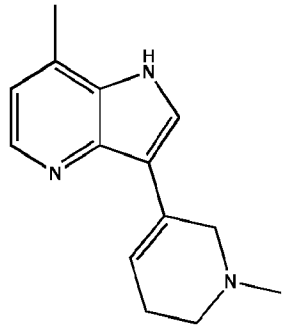
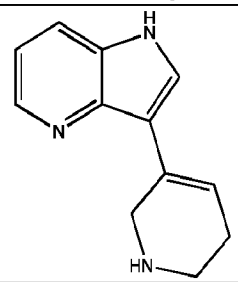
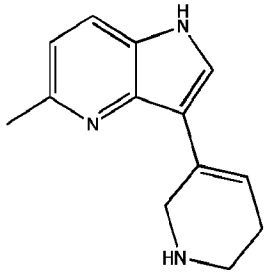
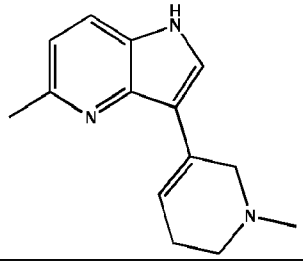
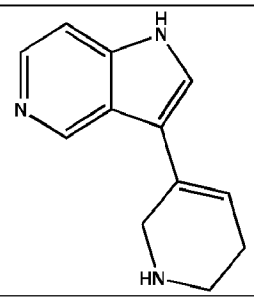
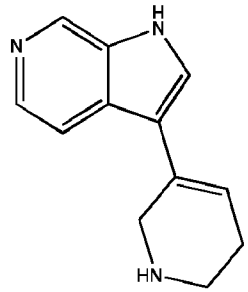
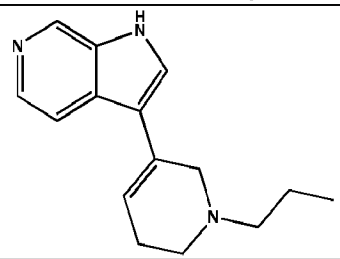
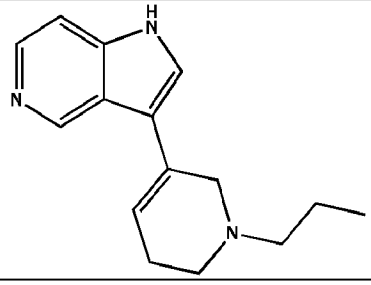
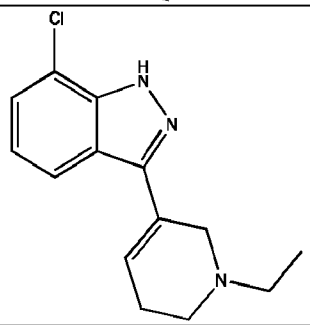
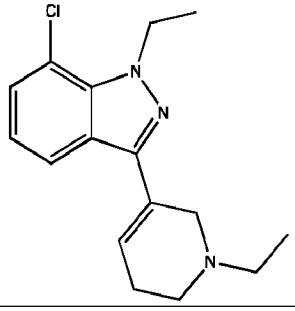
124	ZX147-016		3-(1-allyl-1,2,5,6-tetrahydropyridin-3-yl)-7-chloro-1H-indazole
125	ZX147-017		7-chloro-3-(1-(prop-2-yn-1-yl)-1,2,5,6-tetrahydropyridin-3-yl)-1H-indazole
126	ZX147-019		7-chloro-3-(1-ethyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole

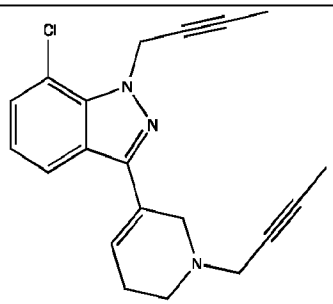
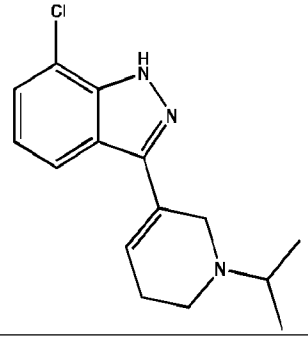
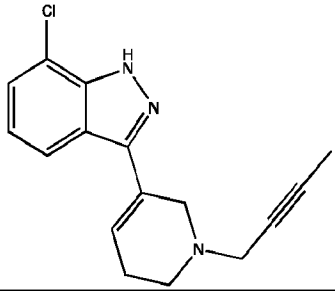
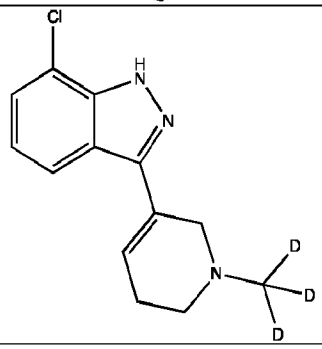
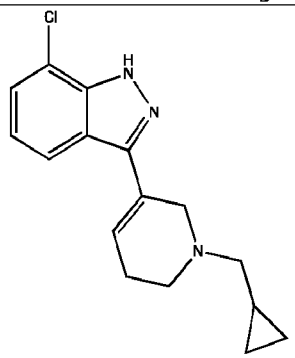
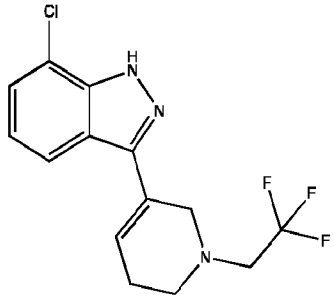
Table 2.

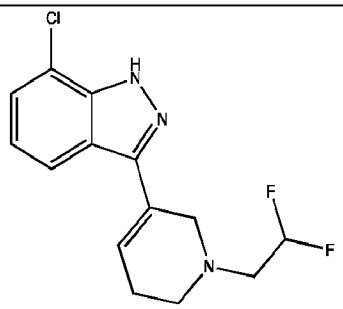
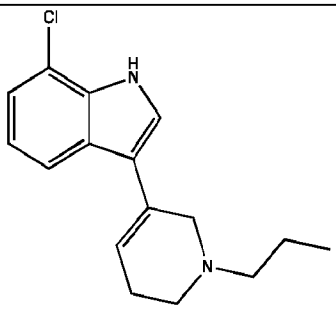
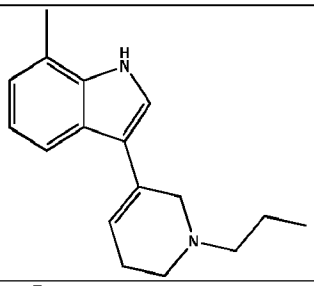
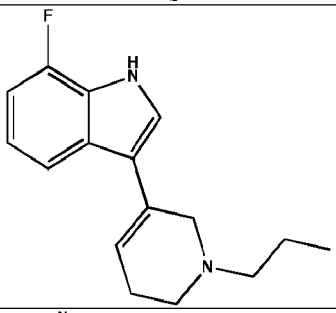
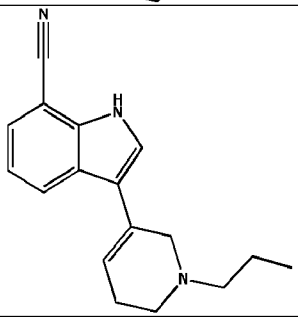
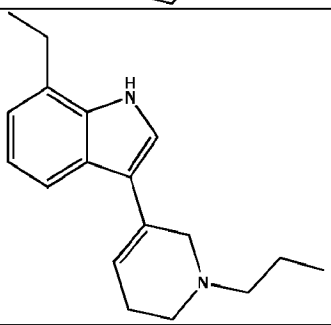
Examples	Compound code	Structure	Chemical Name
127	NS144-097		6-fluoro-7-methyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indole
128	NS144-098		7-chloro-6-fluoro-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indole

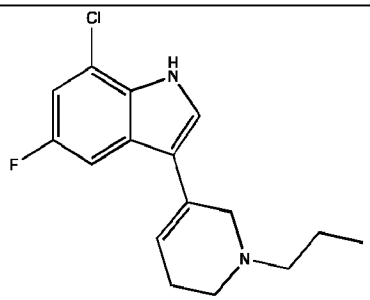
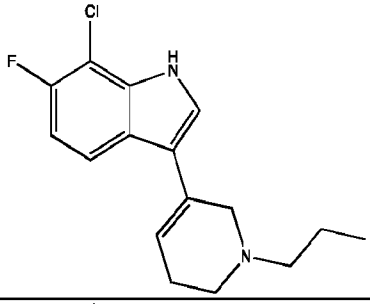
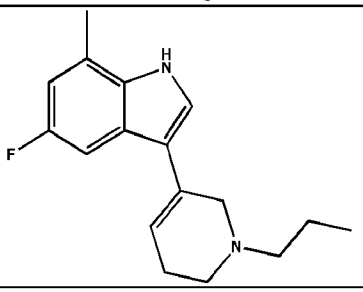
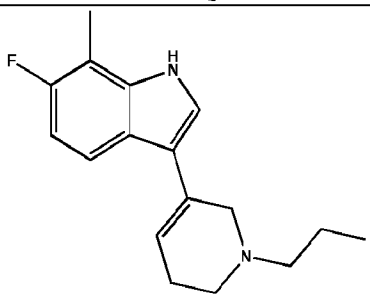
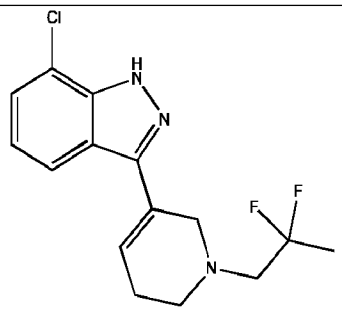
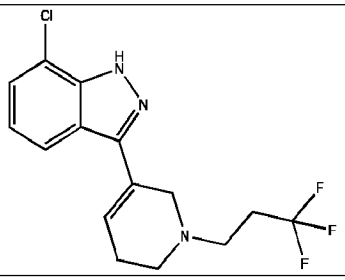
129	NS144-102		7-chloro-5-fluoro-3-(1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole
130	NS144-101		7-chloro-5-fluoro-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole
131	NS144-107		7-chloro-4-fluoro-3-(1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole
132	NS144-108		7-chloro-4-fluoro-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole
133	NS144-109		6-fluoro-3-(1,2,5,6-tetrahydropyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridine
134	NS144-110		6-fluoro-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridine

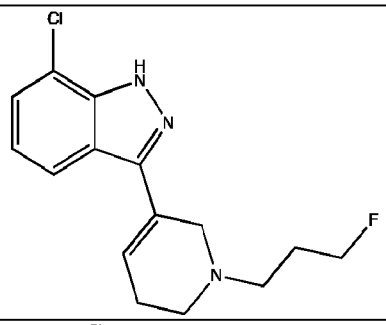
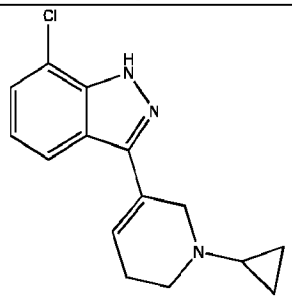
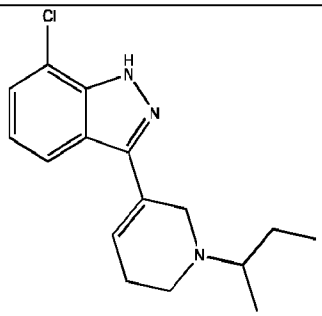
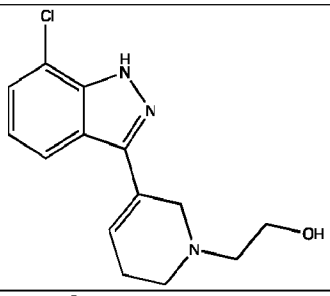
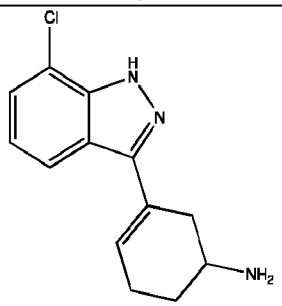
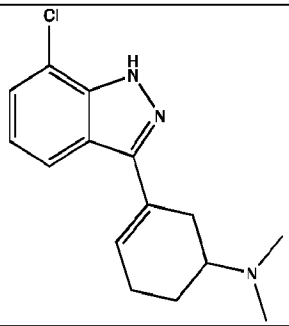
135	YS135-52		3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-pyrrolo[2,3-*c*]pyridine
136	YS135-53		3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-pyrrolo[3,2-*c*]pyridine
137	YS135-54		7-methyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-pyrrolo[3,2-*b*]pyridine
138	YS135-80		3-(1,2,5,6-tetrahydropyridin-3-yl)-1*H*-pyrrolo[3,2-*b*]pyridine
139	YS135-81		5-methyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1*H*-pyrrolo[3,2-*b*]pyridine
140	YS135-82		5-methyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-pyrrolo[3,2-*b*]pyridine

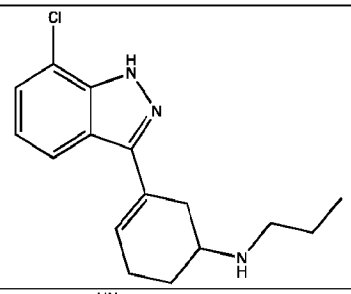
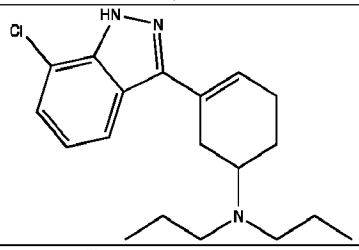
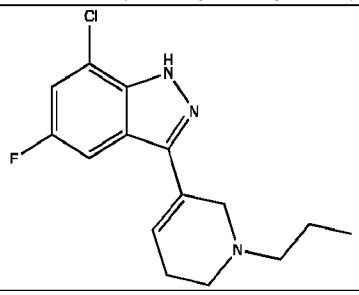
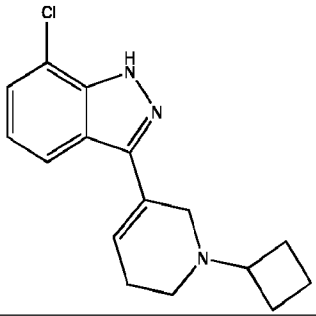
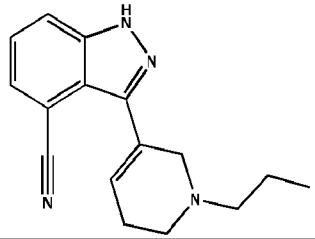
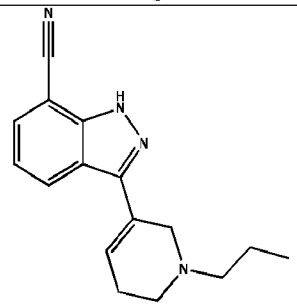
141	YS135-96		3-(1,2,5,6-tetrahydropyridin-3-yl)-1*H*-pyrrolo[3,2-*c*]pyridine
142	YS135-98		3-(1,2,5,6-tetrahydropyridin-3-yl)-1*H*-pyrrolo[2,3-*c*]pyridine
143	YS135-99		3-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-pyrrolo[2,3-*c*]pyridine
144	YS135-100		3-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-pyrrolo[3,2-*c*]pyridine
145	ZX147-026-01		7-chloro-3-(1-ethyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole
146	ZX147-026-02		7-chloro-1-ethyl-3-(1-ethyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole

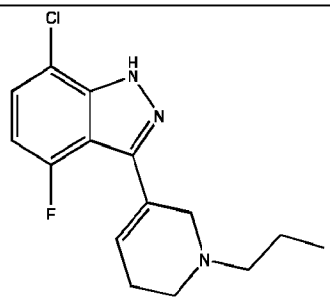
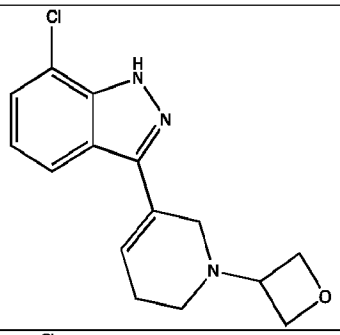
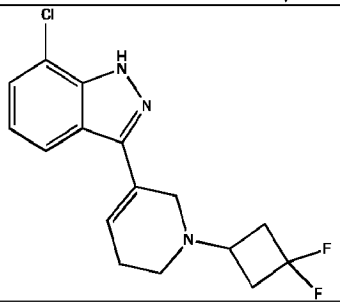
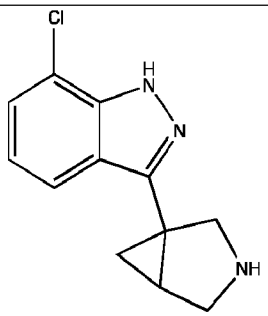
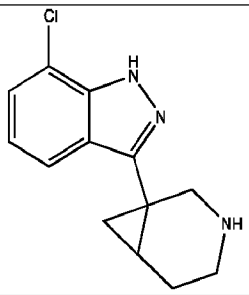
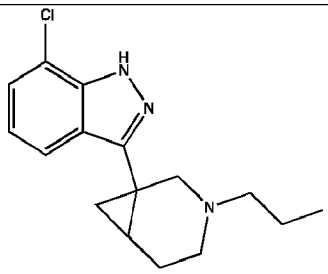
147	ZX147-027		1-(but-2-yn-1-yl)-3-(1-(but-2-yn-1-yl)-1,2,5,6-tetrahydropyridin-3-yl)-7-chloro-1*H*-indazole
148	ZX147-028		7-chloro-3-(1-isopropyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole
149	ZX147-029		3-(1-(but-2-yn-1-yl)-1,2,5,6-tetrahydropyridin-3-yl)-7-chloro-1*H*-indazole
150	ZX147-031		7-chloro-3-(1-(methyl-d_3)-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole
151	ZX147-054		7-chloro-3-(1-(cyclopropylmethyl)-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole
152	ZX147-055		7-chloro-3-(1-(2,2,2-trifluoroethyl)-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole

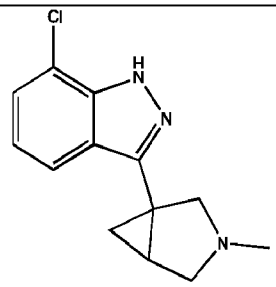
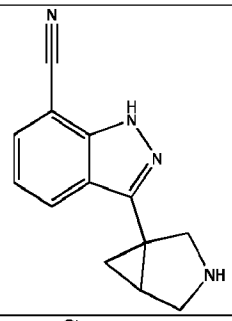
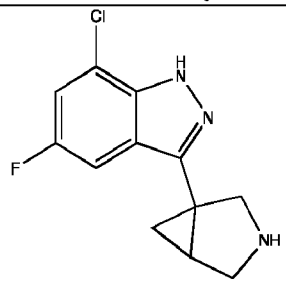
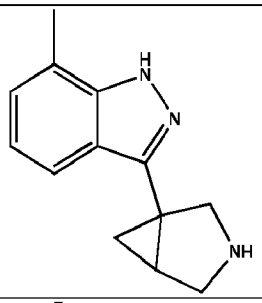
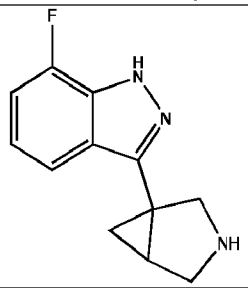
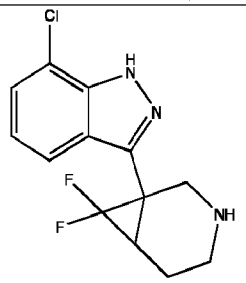
153	ZX147-056		7-chloro-3-(1-(2,2-difluoroethyl)-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole
154	ZX147-092		7-chloro-3-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indole
155	ZX147-093		7-methyl-3-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indole
156	ZX147-094		7-fluoro-3-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indole
157	ZX147-095		3-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indole-7-carbonitrile
158	ZX147-096		7-ethyl-3-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indole

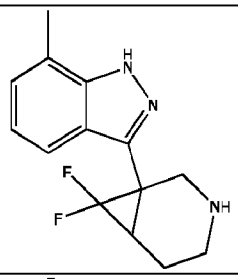
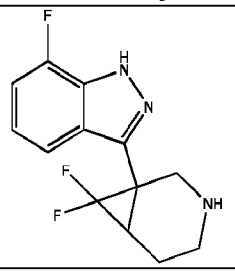
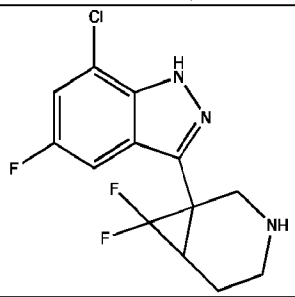
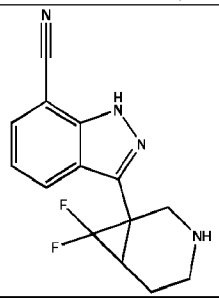
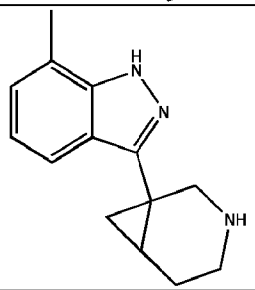
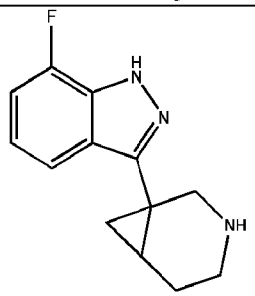
159	ZX147-097		7-chloro-5-fluoro-3-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indole
160	ZX147-098		7-chloro-6-fluoro-3-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indole
161	ZX147-099		5-fluoro-7-methyl-3-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indole
162	ZX147-100		6-fluoro-7-methyl-3-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indole
163	ZX147-128		7-chloro-3-(1-(2,2-difluoropropyl)-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole
164	ZX147-129		7-chloro-3-(1-(3,3,3-trifluoropropyl)-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole

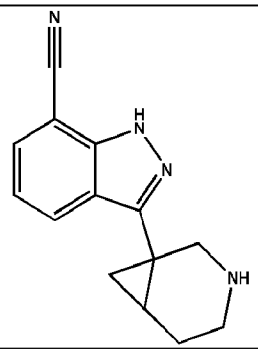
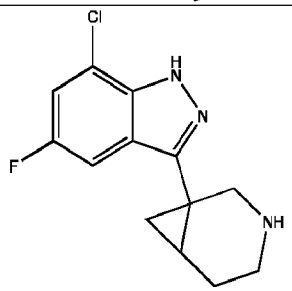
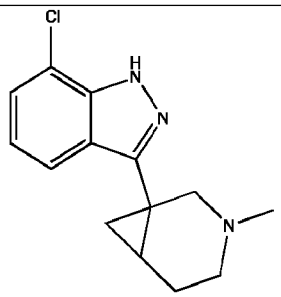
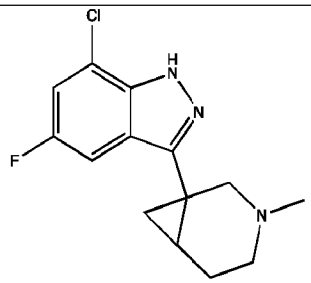
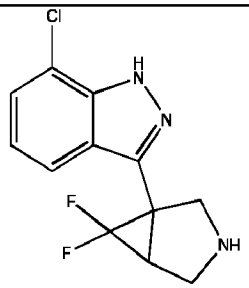
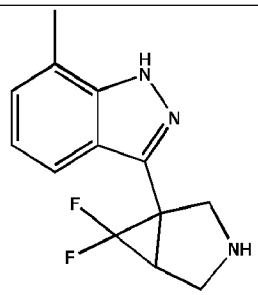
165	ZX147-130		7-chloro-3-(1-(3-fluoropropyl)-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole
166	ZX147-131		7-chloro-3-(1-cyclopropyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole
167	ZX147-137		3-(1-(*sec*-butyl)-1,2,5,6-tetrahydropyridin-3-yl)-7-chloro-1*H*-indazole
168	ZX147-183		2-(5-(7-chloro-1*H*-indazol-3-yl)-3,6-dihydropyridin-1(2*H*)-yl)ethan-1-ol
169	ZX156-011		3-(7-chloro-1*H*-indazol-3-yl)cyclohex-3-en-1-amine
170	ZX156-012		3-(7-chloro-1*H*-indazol-3-yl)-*N*,*N*-dimethylcyclohex-3-en-1-amine

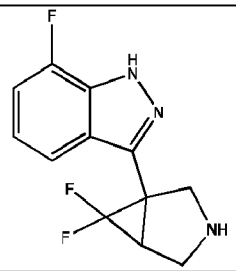
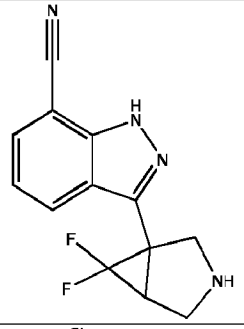
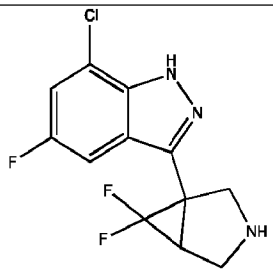
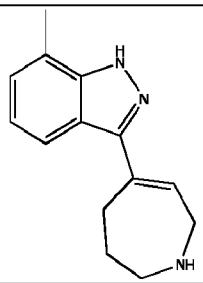
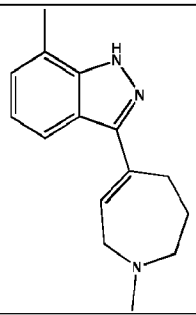
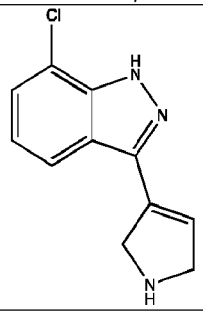
171	ZX156-014-1		3-(7-chloro-1*H*-indazol-3-yl)-*N*-propylcyclohex-3-en-1-amine
172	ZX156-014-2		3-(7-chloro-1*H*-indazol-3-yl)-*N*,*N*-dipropylcyclohex-3-en-1-amine
173	ZX156-019		7-chloro-5-fluoro-3-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole
174	ZX156-059		7-chloro-3-(1-cyclobutyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole
175	ZX156-069		3-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole-4-carbonitrile
176	ZX156-070		3-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole-7-carbonitrile

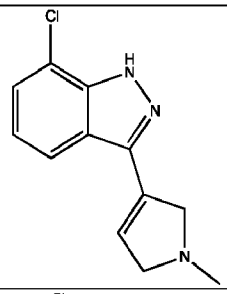
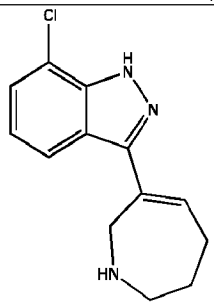
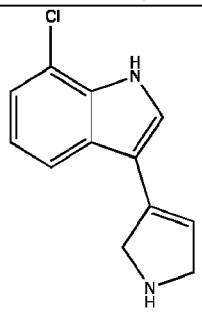
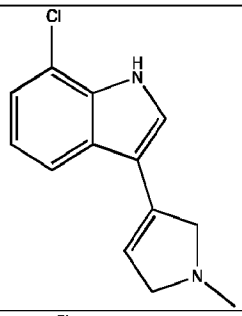
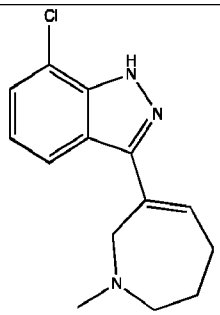
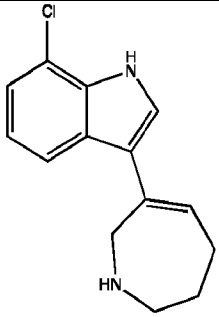
177	ZX156-071		7-chloro-4-fluoro-3-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole
178	ZX156-089		7-chloro-3-(1-(oxetan-3-yl)-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole
179	ZX156-090		7-chloro-3-(1-(3,3-difluorocyclobutyl)-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole
180	ZX162-100		3-(3-azabicyclo[3.1.0]hexan-1-yl)-7-chloro-1*H*-indazole
181	ZX162-031		3-(3-azabicyclo[4.1.0]heptan-1-yl)-7-chloro-1*H*-indazole
182	ZX162-104		7-chloro-3-(3-propyl-3-azabicyclo[4.1.0]heptan-1-yl)-1*H*-indazole

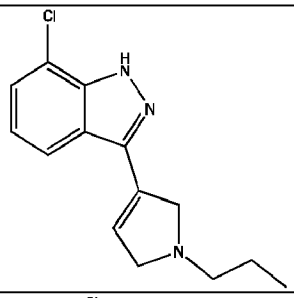
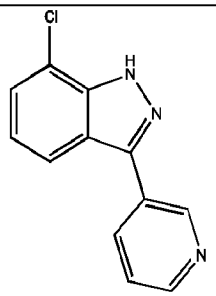
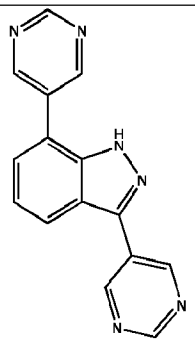
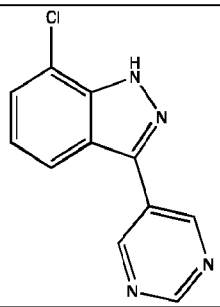
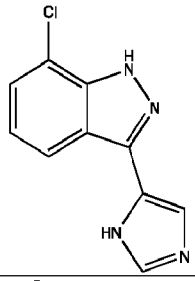
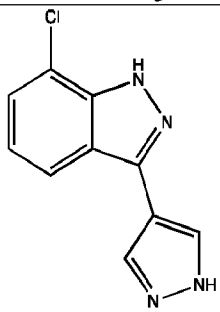
183	ZX162-105		7-chloro-3-(3-methyl-3-azabicyclo[3.1.0]hexan-1-yl)-1*H*-indazole
184	ZX162-110		3-(3-azabicyclo[3.1.0]hexan-1-yl)-1*H*-indazole-7-carbonitrile
185	ZX162-111		3-(3-azabicyclo[3.1.0]hexan-1-yl)-7-chloro-5-fluoro-1*H*-indazole
186	ZX162-112		3-(3-azabicyclo[3.1.0]hexan-1-yl)-7-methyl-1*H*-indazole
187	ZX162-113		3-(3-azabicyclo[3.1.0]hexan-1-yl)-7-fluoro-1*H*-indazole
188	ZX162-124		7-chloro-3-(7,7-difluoro-3-azabicyclo[4.1.0]heptan-1-yl)-1*H*-indazole

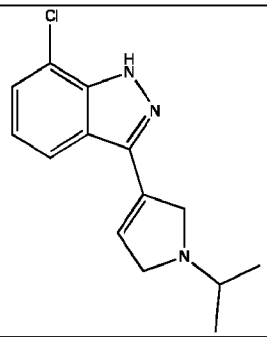
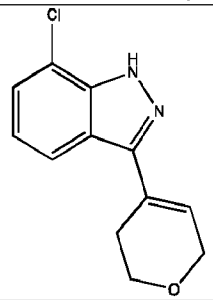
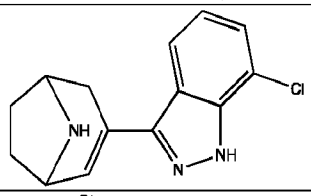
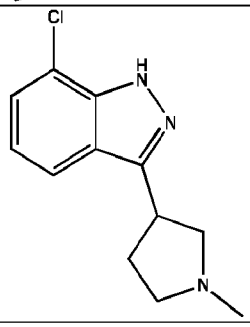
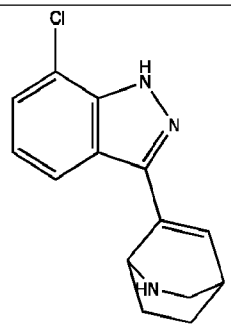
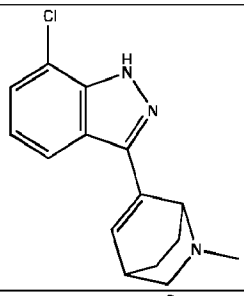
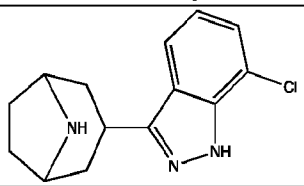
189	ZX162-126		3-(7,7-difluoro-3-azabicyclo[4.1.0]heptan-1-yl)-7-methyl-1*H*-indazole
190	ZX162-127		3-(7,7-difluoro-3-azabicyclo[4.1.0]heptan-1-yl)-7-fluoro-1*H*-indazole
191	ZX162-128		7-chloro-3-(7,7-difluoro-3-azabicyclo[4.1.0]heptan-1-yl)-5-fluoro-1*H*-indazole
192	ZX162-129		3-(7,7-difluoro-3-azabicyclo[4.1.0]heptan-1-yl)-1*H*-indazole-7-carbonitrile
193	ZX162-138		3-(3-azabicyclo[4.1.0]heptan-1-yl)-7-methyl-1*H*-indazole
194	ZX162-139		3-(3-azabicyclo[4.1.0]heptan-1-yl)-7-fluoro-1*H*-indazole

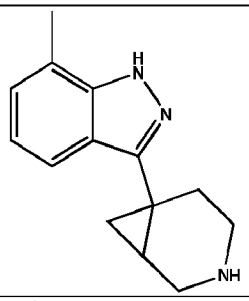
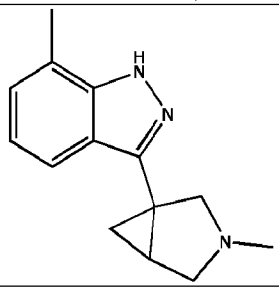
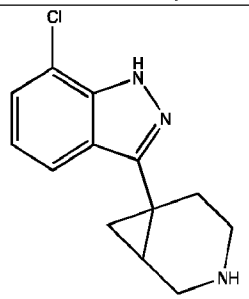
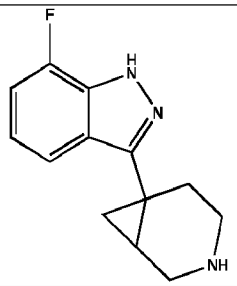
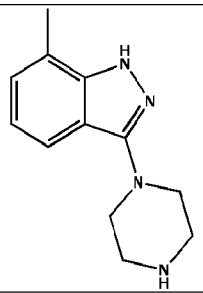
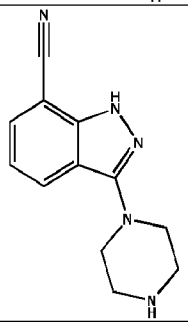
195	ZX162-140		3-(3-azabicyclo[4.1.0]heptan-1-yl)-1*H*-indazole-7-carbonitrile
196	ZX162-141		3-(3-azabicyclo[4.1.0]heptan-1-yl)-7-chloro-5-fluoro-1*H*-indazole
197	ZX162-147		7-chloro-3-(3-methyl-3-azabicyclo[4.1.0]heptan-1-yl)-1*H*-indazole
198	ZX162-148		7-chloro-5-fluoro-3-(3-methyl-3-azabicyclo[4.1.0]heptan-1-yl)-1*H*-indazole
199	ZX162-151		7-chloro-3-(6,6-difluoro-3-azabicyclo[3.1.0]hexan-1-yl)-1*H*-indazole
200	ZX162-173		3-(6,6-difluoro-3-azabicyclo[3.1.0]hexan-1-yl)-7-methyl-1*H*-indazole

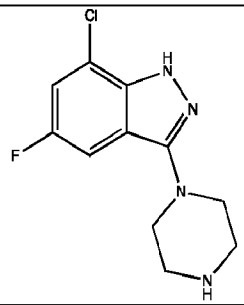
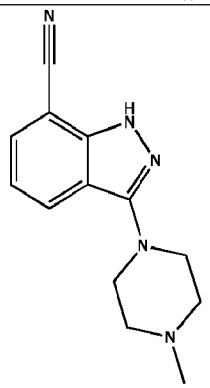
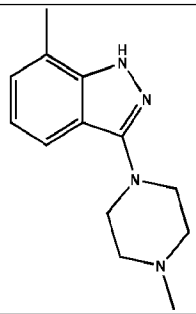
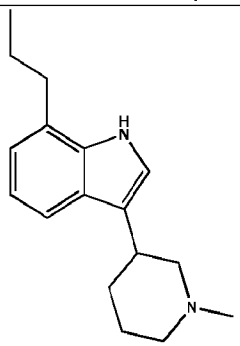
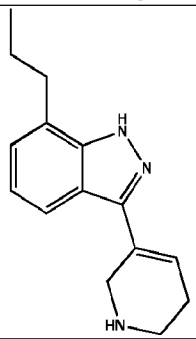
201	ZX162-174		3-(6,6-difluoro-3-azabicyclo[3.1.0]hexan-1-yl)-7-fluoro-1*H*-indazole
202	ZX162-175		3-(6,6-difluoro-3-azabicyclo[3.1.0]hexan-1-yl)-1*H*-indazole-7-carbonitrile
203	ZX162-176		7-chloro-3-(6,6-difluoro-3-azabicyclo[3.1.0]hexan-1-yl)-5-fluoro-1*H*-indazole
204	YX143-103B		7-methyl-3-(2,5,6,7-tetrahydro-1*H*-azepin-4-yl)-1*H*-indazole
205	YX143-103C		7-methyl-3-(1-methyl-2,5,6,7-tetrahydro-1*H*-azepin-4-yl)-1*H*-indazole
206	YX143-105C		7-chloro-3-(2,5-dihydro-1*H*-pyrrol-3-yl)-1*H*-indazole

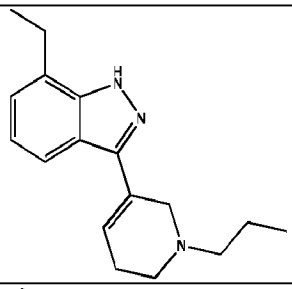
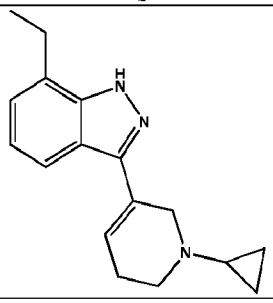
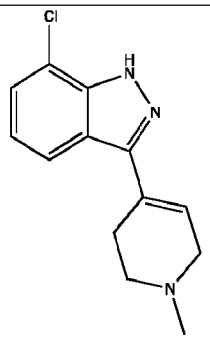
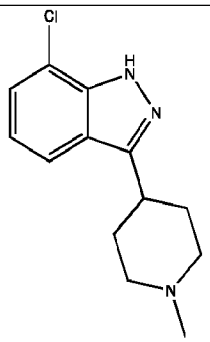
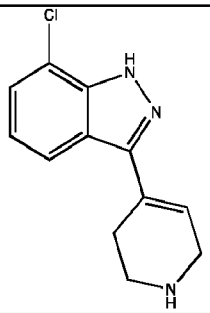
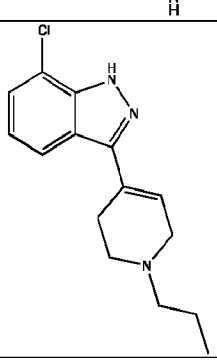
207	YX143-108		7-chloro-3-(1-methyl-2,5-dihydro-1*H*-pyrrol-3-yl)-1*H*-indazole
208	YX143-110B		7-chloro-3-(2,5,6,7-tetrahydro-1*H*-azepin-3-yl)-1*H*-indazole
209	YX143-112B		7-chloro-3-(2,5-dihydro-1*H*-pyrrol-3-yl)-1*H*-indole
210	YX143-129		7-chloro-3-(1-methyl-2,5-dihydro-1*H*-pyrrol-3-yl)-1*H*-indole
211	YX143-134C		7-chloro-3-(1-methyl-2,5,6,7-tetrahydro-1*H*-azepin-3-yl)-1*H*-indazole
212	YX143-138C		7-chloro-3-(2,5,6,7-tetrahydro-1*H*-azepin-3-yl)-1*H*-indole

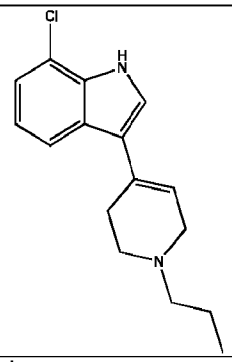
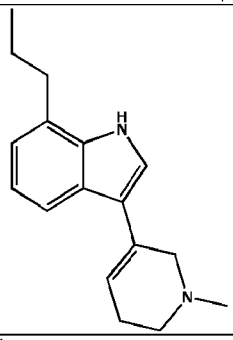
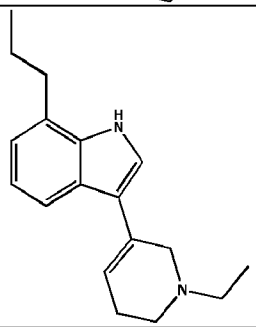
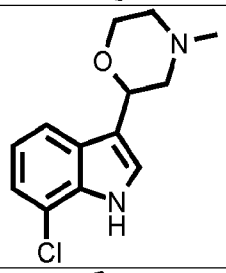
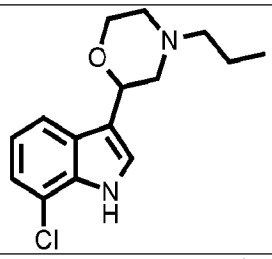
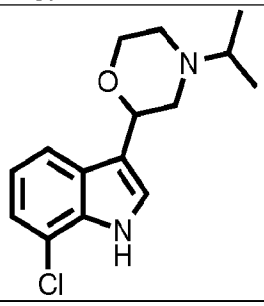
213	YX143-182C-1		7-chloro-3-(1-propyl-2,5-dihydro-1*H*-pyrrol-3-yl)-1*H*-indazole
214	YX143-183A		7-chloro-3-(pyridin-3-yl)-1*H*-indazole
215	YX143-184B-1		3,7-di(pyrimidin-5-yl)-1*H*-indazole
216	YX143-184B-2		7-chloro-3-(pyrimidin-5-yl)-1*H*-indazole
217	YX143-185B		7-chloro-3-(1*H*-imidazol-5-yl)-1*H*-indazole
218	YX143-186B		7-chloro-3-(1*H*-pyrazol-4-yl)-1*H*-indazole

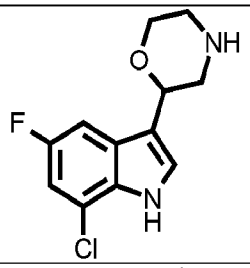
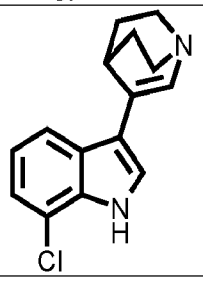
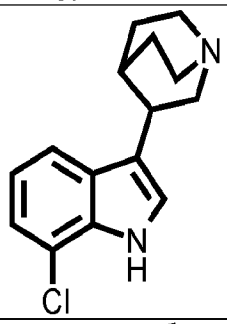
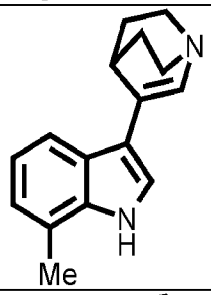
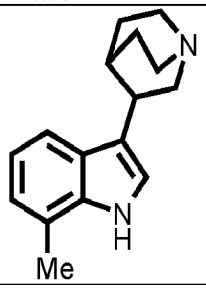
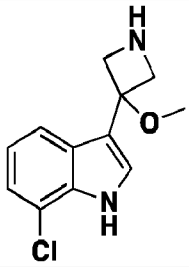
219	YX157-19A		7-chloro-3-(1-isopropyl-2,5-dihydro-1*H*-pyrrol-3-yl)-1*H*-indazole
220	YX157-20A		7-chloro-3-(3,6-dihydro-2*H*-pyran-4-yl)-1*H*-indazole
221	YX157-29B		3-(8-azabicyclo[3.2.1]oct-2-en-3-yl)-7-chloro-1*H*-indazole
222	YX157-42B		7-chloro-3-(1-methylpyrrolidin-3-yl)-1*H*-indazole
223	YX157-51B		6-(7-chloro-1*H*-indazol-3-yl)-2-azabicyclo[2.2.2]oct-5-ene
224	YX157-51C		6-(7-chloro-1*H*-indazol-3-yl)-2-methyl-2-azabicyclo[2.2.2]oct-5-ene
225	YX157-55A		3-(8-azabicyclo[3.2.1]octan-3-yl)-7-chloro-1*H*-indazole

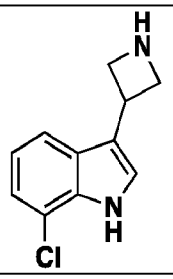
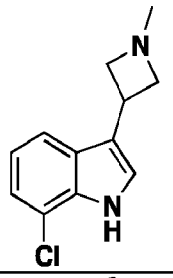
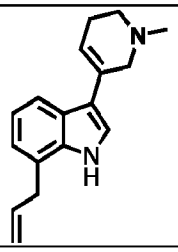
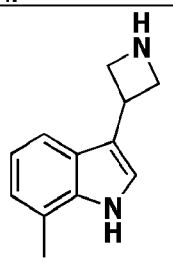
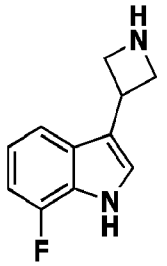
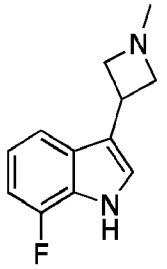
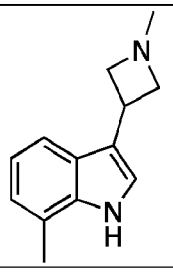
226	XS159-153		3-(3-azabicyclo[4.1.0]heptan-6-yl)-7-methyl-1*H*-indazole
227	XS159-155		7-methyl-3-(3-methyl-3-azabicyclo[3.1.0]hexan-1-yl)-1*H*-indazole
228	XS159-160		3-(3-azabicyclo[4.1.0]heptan-6-yl)-7-chloro-1*H*-indazole
229	XS159-163		3-(3-azabicyclo[4.1.0]heptan-6-yl)-7-fluoro-1*H*-indazole
230	XS159-180		7-methyl-3-(piperazin-1-yl)-1*H*-indazole
231	XS159-186		3-(piperazin-1-yl)-1*H*-indazole-7-carbonitrile

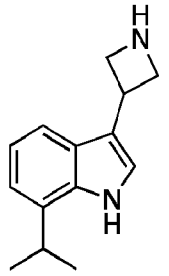
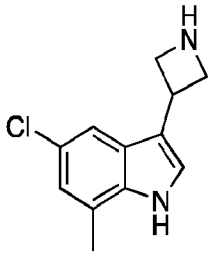
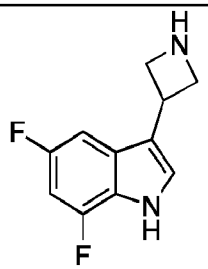
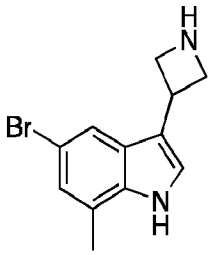
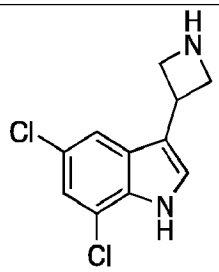
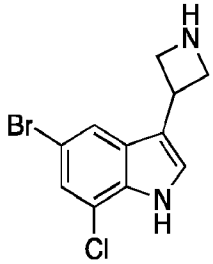
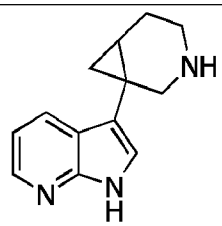
232	XS165-3		7-chloro-5-fluoro-3-(piperazin-1-yl)-1*H*-indazole
233	XS165-5		3-(4-methylpiperazin-1-yl)-1*H*-indazole-7-carbonitrile
234	XS165-8		7-methyl-3-(4-methylpiperazin-1-yl)-1*H*-indazole
235	XQ148-93		3-(1-methylpiperidin-3-yl)-7-propyl-1*H*-indole
236	XQ158-012		7-propyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole

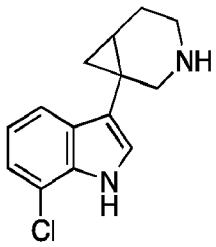
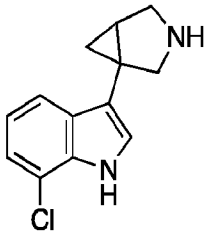
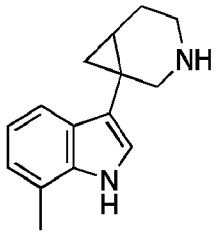
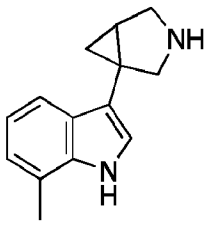
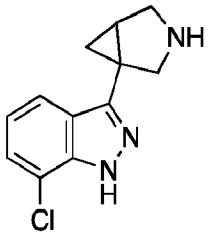
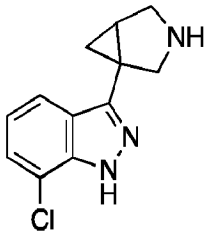
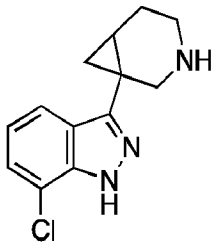
237	XQ158-055		7-ethyl-3-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indazole
238	XQ158-056		3-(1-cyclopropyl-1,2,5,6-tetrahydropyridin-3-yl)-7-ethyl-1*H*-indazole
239	XQ158-078		7-chloro-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indazole
240	XQ158-093A		7-chloro-3-(1-methylpiperidin-4-yl)-1*H*-indazole
241	XQ158-082		7-chloro-3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indazole
242	XQ158-115		7-chloro-3-(1-propyl-1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indazole

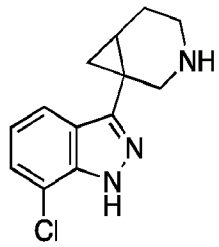
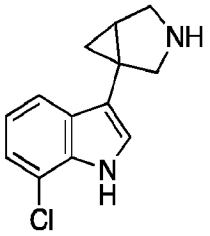
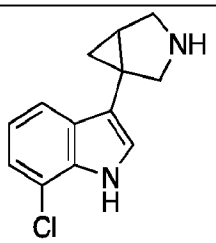
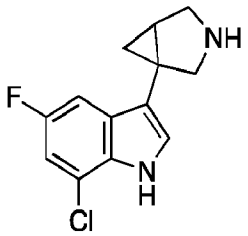
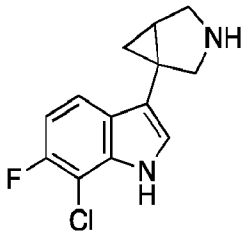
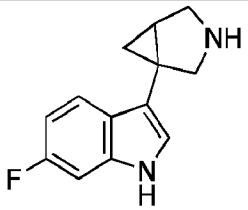
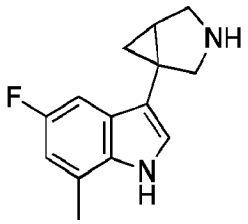
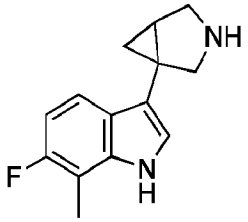
243	XQ158-164		7-chloro-3-(1-propyl-1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole
244	XQ158-167		3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-7-propyl-1*H*-indole
245	XQ158-168		3-(1-ethyl-1,2,5,6-tetrahydropyridin-3-yl)-7-propyl-1*H*-indole
246	ZD160-34		2-(7-chloro-1*H*-indol-3-yl)-4-methylmorpholine
247	ZD160-140		2-(7-chloro-1*H*-indol-3-yl)-4-propylmorpholine
248	ZD160-141		2-(7-chloro-1*H*-indol-3-yl)-4-isopropylmorpholine

249	ZD160-149		2-(7-chloro-5-fluoro-1*H*-indol-3-yl)morpholine
250	ZD160-11		3-(7-chloro-1*H*-indol-3-yl)-1-azabicyclo[2.2.2]oct-2-ene
251	ZD160-133		3-(7-chloro-1*H*-indol-3-yl)quinuclidine
252	ZD160-130		3-(7-methyl-1*H*-indol-3-yl)-1-azabicyclo[2.2.2]oct-2-ene
253	ZD160-131		3-(7-methyl-1*H*-indol-3-yl)quinuclidine
254	QC166-005		7-chloro-3-(3-methoxyazetidin-3-yl)-1H-indole

255	QC166-008		3-(azetidin-3-yl)-7-chloro-1H-indole
256	QC-166-032		7-chloro-3-(1-methylazetidin-3-yl)-1H-indole
257	XQ148-86		7-allyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole
258	QC166-096		3-(azetidin-3-yl)-7-methyl-1*H*-indole
259	QC166-097		3-(azetidin-3-yl)-7-fluoro-1*H*-indole
260	QC179-001		7-fluoro-3-(1-methylazetidin-3-yl)-1*H*-indole
261	QC179-002		7-methyl-3-(1-methylazetidin-3-yl)-1*H*-indole

262	QC179-025		3-(azetidin-3-yl)-7-isopropyl-1*H*-indole
263	QC-179-032		3-(azetidin-3-yl)-5-chloro-7-methyl-1*H*-indole
264	QC-179-033		3-(azetidin-3-yl)-5,7-difluoro-1*H*-indole
265	QC179-038		3-(azetidin-3-yl)-5-bromo-7-methyl-1*H*-indole
266	QC179-039		3-(azetidin-3-yl)-5,7-dichloro-1*H*-indole
267	QC179-040		3-(azetidin-3-yl)-5-bromo-7-chloro-1*H*-indole
268	ZX167-072		3-(3-azabicyclo[4.1.0]heptan-1-yl)-1H-pyrrolo[2,3-b]pyridine

269	ZX167-077		3-(3-azabicyclo[4.1.0]heptan-1-yl)-7-chloro-1H-indole
270	ZX167-074		3-(3-azabicyclo[3.1.0]hexan-1-yl)-7-chloro-1H-indole
271	ZX167-090		3-(3-azabicyclo[4.1.0]heptan-1-yl)-7-methyl-1H-indole
272	ZX167-091		3-(3-azabicyclo[3.1.0]hexan-1-yl)-7-methyl-1H-indole
273	ZX162-100-1 (Enantiomer 1 of ZX162-100)		3-(3-azabicyclo[3.1.0]hexan-1-yl)-7-chloro-1H-indazole
274	ZX162-100-2 (Enantiomer 2 of ZX162-100)		3-(3-azabicyclo[3.1.0]hexan-1-yl)-7-chloro-1H-indazole
275	ZX162-031-1 (Enantiomer 1 of ZX162-031)		3-(3-azabicyclo[4.1.0]heptan-1-yl)-7-chloro-1H-indazole

276	ZX162-031-2 (Enantiomer 2 of ZX162-031)		3-(3-azabicyclo[4.1.0]heptan-1-yl)-7-chloro-1H-indazole
277	ZX167-074-1 (Enantiomer 1 of ZX167-074)		3-(3-azabicyclo[3.1.0]hexan-1-yl)-7-chloro-1H-indole
278	ZX167-074-2 (Enantiomer 2 of ZX167-074)		3-(3-azabicyclo[3.1.0]hexan-1-yl)-7-chloro-1H-indole
279	ZX177-057		3-(3-azabicyclo[3.1.0]hexan-1-yl)-7-chloro-5-fluoro-1H-indole
280	ZX177-058		3-(3-azabicyclo[3.1.0]hexan-1-yl)-7-chloro-6-fluoro-1H-indole
281	ZX177-058BY		3-(3-azabicyclo[3.1.0]hexan-1-yl)-6-fluoro-1H-indole
282	ZX177-059		3-(3-azabicyclo[3.1.0]hexan-1-yl)-5-fluoro-7-methyl-1H-indole
283	ZX177-060		3-(3-azabicyclo[3.1.0]hexan-1-yl)-6-fluoro-7-methyl-1H-indole

Compounds corresponding to Examples 1 - 126 have been synthesized and are provided with a Compound Code in Table 1.

Compounds corresponding to Examples 127 - 283 have been synthesized and are provided with a Compound Code in Table 2.

As used herein, in case of discrepancy between the structure and chemical name provided for a particular compound, the given structure shall control.

General Chemistry Methods

For the synthesis of intermediates and examples, HPLC spectra for all compounds were acquired using an Agilent 1200 Series system with DAD detector. Chromatography was performed on a 2.1×150 mm Zorbax 300SB-C18 5 µm column with water containing 0.1% formic acid as solvent A and acetonitrile containing 0.1% formic acid as solvent B at a flow rate of 0.4 ml/min. The gradient program was as follows: 1% B (0−1 min), 1−99% B (1−4 min), and 99% B (4−8 min). High-resolution mass spectra (HRMS) data were acquired in positive ion mode using an Agilent G1969A API-TOF with an electrospray ionization (ESI) source. Nuclear Magnetic Resonance (NMR) spectra were acquired on a Bruker DRX-600 spectrometer with 600 MHz for proton (^{1}H NMR) and 150 MHz for carbon (^{13}C NMR); chemical shifts are reported in (δ). Preparative HPLC was performed on Agilent Prep 1200 series with UV detector set to 254 nm. Samples were injected onto a Phenomenex Luna 250 x 30 mm, 5 µm, C_{18} column at room temperature. The flow rate was 40 ml/min. A linear gradient was used with 10% (or 50%) of MeOH (A) in H_2O (with 0.1 % TFA) (B) to 100% of MeOH (A). HPLC was used to establish the purity of target compounds. All final compounds had > 95% purity using the HPLC methods described above.

Example 284:

Biological Methods:

All biological assays are performed in HEK 293T cells (bioluminescence resonance energy transfer (BRET) assays) or Flp-In T-REx 293 cells (binding and calcium flux assays).

Binding assays: Two binding assays, referred to as primary and secondary binding assays, are used to identify compounds that bind and to measure the affinities of their binding, respectively, to 5HT2A, 5HT2B, and 5HT2C receptors. Crude membranes are prepared from Flp-In T Rex 293 cells stably expressing the receptor of interest in a doxycycline/tetracycline-inducible manner.

For primary binding assays, membranes are co-incubated with compound (10 μM) and radioligand (0.5 – 1.0 K_d; for the 5HT2A and 5HT2B receptors, the radioligand is [3H]-LSD, and for the 5-HT2C receptor the radioligand is [3H]-mesulergine) in standard binding buffer (50 mM Tris HCl, 10 mM $MgCl_2$, 0.1 mM EDTA, pH 7.4). Total binding is determined by replacing compound with buffer only, and non-specific binding is determined by replacing compound with a positive control, a known high-affinity binder (either clozapine or LSD). All conditions are tested in technical quadruplicate. Compounds, radioligands, and membranes are incubated at room temperature prior to harvesting via vacuum filtration onto 0.3% polyethylimine-soaked filter mats and subsequent washing/vacuuming with wash buffer (50 mM Tris HCl, pH 7.4, cold). Scintillation wax is then melted onto the filter mats, and measurements are taken using a microbeta counter. Compounds that show at least 50% displacement of radioligand relative to the total specific binding are then assessed in secondary assays to determine their binding affinities.

Secondary assays are performed similarly to primary binding assays, except in the set up of the conditions. Here, compounds are half-logarithmically diluted to yield final concentrations between 10 μM and 0.1 μM with a final well supplemented with buffer instead of drug (i.e., total binding). Each well is incubated with radioligand, as described for primary assays. Compounds are tested in technical triplicate, with the exception of the positive control, which is tested in technical duplicate, and in biological triplicate. The highest concentration of the psotive control yields the non-specific binding. Binding curves are analyzed in GraphPad Prism, with K_is determined from the experimental IC_{50}s using the Cheng-Prusoff equation.

BRET assays: Two complimentary BRET assays are used to quantitatively measure 5-HT2A activation of Gαq heterotrimeric G proteins and recruitment of beta-arrestin2 in response to compounds. The G protein assay is from the BRET2-based TRUPATH platform, in which *Renilla* luciferase (RLuc) has been fused to Gαq and GFP2 has been fused to Gγ9. These plasmids, along with those encoding 5HT2A receptor and Gβ3, are co-transfected in HEK293T cells. 96-well plates containing transfected cells are then aspirated of media, and incubated for 30 minutes at 37 °C with compound (logarithmically diluted to yield final concentrations between 10 μM and 0.1 μM) in assay buffer (HBSS, 20 mM HEPES, pH 7.4) (each plate contains a 5-HT dilution series as a positive control to which values are normalized during analysis). 10 minutes prior to reading (20 minutes after incubation begins), the BRET2 substrate coelenterazine 400a (5 μM final concentration) is added. Reading takes place in a microplate reader to measure RLuc luminescence and GFP2 fluorescence. The beta-arrestin2 assay is BRET1-based, with RLuc fused to the C-

terminus of the receptor and mVenus fused to the N-terminus of beta-arrestin2. Plasmids encoding these constructs, along with a plasmid encoding G protein-coupled receptor kinase 2, are co-transfected. Procedurally, the BRET1 assay is performed the same as the BRET2 assays, but uses a different substrate, coelenterazine h, to account for the different acceptor fluorophore. Data are analyzed in GraphPad Prism, and the responses of all compounds on a given plate are normalized to that produced by 5-HT on the same plate to yield measurements of potency and relative efficacy.

Calcium flux assay (calcium mobilization assay): Calcium flux assay: Flp-In TREx 293 cells stably expressing GPCR (5HT2A, 5HT2B, or 5HT2C) were plated in black 384-well plates in 40uL/well Pro293 medium (Lonza) supplemented with 20mM L-glutamine (Gibco) and incubated at 37C and 5% CO2 overnight. Prior to running the experiment, medium was removed from the plates and replaced with Fluo-4 dye (Fisher) prepared according to vendor protocols and returned to incubation for 1 hour. Drug dilutions were prepared in HBSS with 0.1% bovine serum albumin. Plates were run using a FLIPR TETRA (Molecular Devices) with 384-well liquid handling system. Baseline fluorescence was recorded for ten seconds prior to drug addition, and fluorescence was recorded once per second for two minutes after drug addition. The maximum fluorescence signal during those two minutes was plotted against delivered drug concentration to obtain concentration-response curves, which were then analyzed in Prism (GraphPad).

Table 3 & 4. Binding affinities and functional activities of synthesized compounds for 5HT2A receptor.

Table 3.

Examples	Compound code	5HT2A K_i (nM)	5HT2A Gq		5HT2A β-Arr	
			E_{max} (%)	EC_{50} (nM)	E_{max} (%)	EC_{50} (nM)
1	NS131-179	1719.0	N.D.	N.D.	N.D.	N.D.
2	NS131-178	293.8	73.7	135.1	61.6	1043.0
3	NS131-177	142.7	82.0	29.4	43.8	229.4
4	NS136-006	613.40	67.0	294.2	N.D.	N.D.
5	NS131-169	716.8	N.D.	N.D.	N.D.	N.D.
6	NS131-168	694.7	65.9	44.1	33.4	792.1
7	NS131-167	208.6	73.4	56.9	20.7	18.7
8	NS131-173	155.7	95.5	67.0	58.3	811.5
9	NS131-180	8507.0	74.2	489.1	72.8	748.8
10	RS134-52	311.6	66.5	124.6	N.D.	N.D.
11	RS134-48	272.5	84.7	79.9	43.7	903.6
12	NS131-185	190.8	N.D.	N.D.	N.D.	N.D.
13	NS131-170	63.5	68.7	105.8	38.9	764.7

14	RS134-45	43.0	67.1	72.7	32.2	74.1
15	RS134-40	465.0	68.8	23.5	31.5	683.3
16	NS131-184	163.8	N.D.	N.D.	49.6	2136.0
17	RS134-49	11.5	85.7	22.0	42.0	147.4
18	RS134-53	50.5	96.1	3.9	51.8	71.2
19	RS134-41	136.0	75.9	9.0	40.4	101.5
20	RS134-46	60.0	91.0	3.0	47.7	61.8
21	NS131-172	14.0	59.6	874.3	15.1	358.4
22	RS134-38	44.3	102.5	7.2	77.3	78.4
23	RS134-65	98.6	58.8	65.7	31.4	734.9
24	RS134-62	104.5	N.D.	N.D.	N.D.	N.D.
25	RS134-70	940.7	73.3	592.1	N.D.	N.D.
26	NS136-081	165.8	64.2	176.6	N.D.	N.D.
27	RS134-73	1476.0	N.D.	N.D.	N.D.	N.D.
28	RS134-72	497.5	N.D.	N.D.	N.D.	N.D.
29	NS136-092	1201.0	N.D.	N.D.	N.D.	N.D.
30	NS136-091	646.9	N.D.	N.D.	N.D.	N.D.
31	NS136-096	160.1	93.0	106.2	111.7	1497.0
32	NS136-095	236.5	77.5	303.8	45.5	709.4
33	NS136-102	1263.0	N.D.	N.D.	N.D.	N.D.
34	NS136-101	486.3	N.D.	N.D.	N.D.	N.D.
35	NS136-115	>10,000	N.D.	N.D.	N.D.	N.D.
36	NS136-116	8495.0	N.D.	N.D.	N.D.	N.D.
37	NS136-117	9909.0	N.D.	N.D.	N.D.	N.D.
38	NS136-118	7883.0	N.D.	N.D.	N.D.	N.D.
39	NS136-119	6755.0	N.D.	N.D.	N.D.	N.D.
40	NS136-120	1332.0	N.D.	N.D.	N.D.	N.D.
41	NS136-109	1376.0	92.6	234.1.	83.2	1410.00
42	NS136-110	144.9	101.6	15.8	76.5	180.0
43	NS136-111	405.2	86.8	68.1	48.9	486.7
44	NS136-112	76.3	86.6	18.9	37.6	78.8
45	RS134-37	112.5	98.3	9.9	68.1	138.2
46	RS134-56	87.3	62.6	3.3	21.9	114.8
47	NS136-002	795.9	48.7	378.6	N.D.	N.D.
48	NS136-004	423.4	N.D.	N.D.	N.D.	N.D.
49	RS130-132	5583.0	N.D.	N.D.	N.D.	N.D.
50	YX129-177C	244.3	92.6	4.7	79.1	67.0
51	YX129-180C	>10,000	N.D.	N.D.	N.D.	N.D.
52	YX143-19	42.0	89.3	25.0	73.4	880.0
53	YX143-20	373.7	77.8	165.7	N.D.	N.D.
54	YX143-2	510.2	N.D.	N.D.	N.D.	N.D.
55	YX143-21	373.7	N.D.	N.D.	N.D.	N.D.
56	NS144-042	59.8	96.9	16.8	49.5	57.7
57	NS144-043	>10,000	N.D.	N.D.	N.D.	N.D.
58	NS144-044	>10,000	N.D.	N.D.	N.D.	N.D.
59	YS135-44	25.8	81.7	17.8	56.9	75.5
60	YS135-45	795.4	64.3	439.9	N.D.	N.D.

61	YS135-34	804.6	67.4	363.0	N.D.	N.D.
62	YS135-32	809.6	49.1	75.7	45.1	633.3
63	YS135-38	822.6	79.0	162.1	N.D.	N.D.
64	YS135-41	185.6	91.8	61.9	60.2	218.9
65	YS135-39	221.3	51.2	124.5	N.D.	N.D.
66	YX143-14A-2	115.0	79.0	212.9	N.D.	N.D.
67	NS144-019	90.2	48.8	44.1	46.6	756.0
68	NS144-021	115.3	40.2	127.3	42.4	489.8
69	YX143-15	199.2	49.7	98.2	63.5	1743.0
70	YX143-16	2050.0	N.D.	N.D.	N.D.	N.D.
71	YX143-17C	448.4	65.2	530.2	N.D.	N.D.
72	YX143-18C	733.9	N.D.	N.D.	N.D.	N.D.
73	NS144-047	150.9	81.9	116.3	56.5	331.3
74	NS144-048	>10,000	N.D.	N.D.	N.D.	N.D.
75	NS144-049	>10,000	N.D.	N.D.	N.D.	N.D.
76	NS136-128	2462.0	93.6	117.6	88.7	1503.0
77	NS136-129	438.9	93.9	38.9	76.7	429.5
78	NS136-130	57.6	79.4	11.5	59.4	115.3
79	NS136-131	441.2	48.6	874.3	82.1	1711.0
80	NS136-150	254.5	83.4	73.8	71.8	697.8
81	NS136-151	348.1	92.3	26.5	75.7	210.6
82	NS136-152	153.4	95.9	12.0	87.9	561.7
83	NS136-166	78.8	81.7	12.5	75.9	108.6
84	NS144-011	25.3	94.8	3.4	97.0	52.4
85	NS136-158	33.4	88.3	2.8	96.0	68.6
86	NS136-167	370.4	90.2	15.9	95.1	354.5
87	NS136-159	119.3	84.2	17.8	80.0	241.3
88	NS136-135	211.4	72.6	52.8	64.8	227.3
89	NS136-136	85.2	93.7	11.4	85.1	83.5
90	NS136-137	1393.0	95.6	9.2	70.0	86.0
91	NS144-046	236.9	126.3	17.2	86.0	105.1
92	NS144-045	1089.0	N.D.	N.D.	N.D.	N.D.
93	NS136-140	2920.0	N.D.	N.D.	N.D.	N.D.
94	NS136-141	1301.0	72.1	308.7	N.D.	N.D.
95	NS136-142	47.3	47.1	21.1	27.0	466.8
96	NS136-143	5466.0	N.D.	N.D.	N.D.	N.D.
97	NS136-153	786.0	69.0	80.4	64.6	604.8
98	NS136-154	835.3	58.5	105.3	54.0	483.2
99	NS136-155	491.2	80.0	96.4	43.8	1013.0
100	NS136-175	348.9	63.9	91.6	52.4	460.2
101	NS144-016	141.1	74.2	16.2	80.7	292.3
102	NS136-160	245.8	84.5	9.0	79.8	128.7
103	NS136-176	1390.0	64.9	611.9	N.D.	N.D.
104	NS136-161	500.5	88.2	82.8	83.7	681.4
105	NS136-144	1338.0	75.4	35.4	45.7	432.4
106	NS136-145	332.4	85.5	39.1	66.8	176.4
107	NS136-146	882.7	68.1	34.5	36.3	212.8

108	NS144-051	1375	101.9	108.1	72.5	494.1
109	NS144-050	>10,000	N.D.	N.D.	N.D.	N.D.
110	YX143-41C	>10,000	N.D.	N.D.	N.D.	N.D.
111	YX143-42C	>10,000	N.D.	N.D.	N.D.	N.D.
112	YX143-43D	9036	N.D.	N.D.	N.D.	N.D.
113	NS144-059-2	1426.	84.9	279.2	62.6	1524.0
114	NS144-054-2	1237	74.5	289.8	29.3	468.4
115	NS144-067	20.8	113.6	51.1	59.7	575.8
116	NS144-085	99.6	125.2	74.0	56.1	129.4
117	NS144-093	1365.0	110.2	252.9	51.1	865.2
118	NS144-094	80.3	109.0	31.6	56.7	49.4
119	NS144-095	844.4	88.2	193.1	53.83	1524
120	NS144-096	53.6	100.4	21.5	60.4	67.4
121	XQ148-012	422.3	102.6	20.2	85.7	75.8
122	XQ148-023	816.4	102.1	151.1	42.9	247.2
123	ZX147-015	139.8	66.9	142.1	N.D.	N.D.
124	ZX147-016	159.1	64.9	49.6	35.3	1008
125	ZX147-017	1970.0	93.5	75.0	63.3	290.9
126	ZX147-019	42.6	96.6	40.2	62.9	74.9

Table 4.

Examples	Compound code	5HT2A K_i (nM)	5HTA Gq		5HT2A β-Arr	
			E_{max} (%)	EC_{50} (nM)	E_{max} (%)	EC_{50} (nM)
127	NS144-097	120.8	90.2	26.6	48.9	62.9
128	NS144-098	15.3	89.2	11.9	56.5	66.1
129	NS144-102	162.4	88.8	3.1	95.0	20.1
130	NS144-101	19.5	91.4	12.9	88.5	165.2
131	NS144-107	47.5	106.3	7.2	72.7	17.4
132	NS144-108	84.6	95.4	24.0	50.9	93.0
133	NS144-109	291.6	77.2	166.5	38.1	896.8
134	NS144-110	283.6	87.4	139.9	51.1	1046.0
135	YS135-52	3538.0	77.8	1611.0	N.D.	N.D.
136	YS135-53	1809.0	92.5	529.5	N.D.	N.D.
137	YS135-54	530.9	74.4	57.6	44.6	372.4
138	YS135-80	147.3	79.0	118.1	100.9	1421.0
139	YS135-81	4180.0	112.0	784.9	N.D.	N.D.
140	YS135-82	1131.0	62.6	247.0	N.D.	N.D.
141	YS135-96	739.0	91.3	630.9	N.D.	N.D.
142	YS135-98	152.3	N.D.	N.D.	N.D.	N.D.
143	YS135-99	9760.0	N.D.	N.D.	N.D.	N.D.
144	YS135-100	8248.9	67.2	1181.0	N.D.	N.D.
145	ZX147-026-01	123.0	64.4	23.3	42.4	77.0
146	ZX147-026-02	170.8	54.5	51.7	56.7	1529.0
147	ZX147-027	>10,000	62.2	1367.0	N.D.	N.D.
148	ZX147-028	221.6	78.0	51.7	33.60	153.7
149	ZX147-029	363.7	49.8	10.1	24.2	113.5

150	ZX147-031	842.5	95.3	13.3	60.9	29.9
151	ZX147-054	198.4	38.8	61.1	N.D.	N.D.
152	ZX147-055	389.0	89.8	1574.0	66.45	1050
153	ZX147-056	634.0	83.9	1243.0	77.42	1197
153	ZX147-092	196.9	66.8	58.9	27.40	142.0
155	ZX147-093	539.4	68.5	29.5	34.38	532.4
156	ZX147-094	163.8	103.2	20.2	58.43	61.18
157	ZX147-095	163.9	78.0	93.0	39.30	500.0
158	ZX147-096	368.3	82.2	78.4	32.60	120.3
159	ZX147-097	125.5	90.3	17.5	39.66	66.88
160	ZX147-098	150.6	84.1	74.5	30.93	144.3
161	ZX147-099	488.2	93.2	84.1	35.22	311.3
162	ZX147-100	1137.0	80.6	260.1	23.38	302.6
163	ZX147-128	>10,000	82.4	604.4	N.D.	N.D.
164	ZX147-129	>10,000	52.9	517.8	23.28	836.4
165	ZX147-130	342.3	65.0	85.8	28.67	157.2
166	ZX147-131	306.6	64.0	47.1	24.85	120.2
167	ZX147-137	524.5	25.7	173.2	N.D.	N.D.
168	ZX147-183	8636.0	68.2	183.2	41.60	1052
169	ZX156-011	>10,000	N.D.	N.D.	N.D.	N.D.
170	ZX156-012	>10,000	N.D.	N.D.	N.D.	N.D.
171	ZX156-014-1	>10,000	N.D.	N.D.	N.D.	N.D.
172	ZX156-014-2	>10,000	66.4	4016.0	N.D.	N.D.
173	ZX156-019	838.8	57.3	84.6	N.D.	N.D.
174	ZX156-059	9760.0	N.D.	N.D.	N.D.	N.D.
175	ZX156-069	8249.0	46.3	88.8	31.6	343.4
176	ZX156-070	>10,000	N.D.	N.D.	N.D.	N.D.
177	ZX156-071	1831.0	N.D.	N.D.	N.D.	N.D.
178	ZX156-089	>10,000	N.D.	N.D.	N.D.	N.D.
179	ZX156-090	8616.0	N.D.	N.D.	N.D.	N.D.
180	ZX162-100	227.3	109.0	174.4	N.D.	N.D.
181	ZX162-031	842.5	61.26	120.0	N.D.	N.D.
182	ZX162-104	2465.0	78.9	786.4	N.D.	N.D.
183	ZX162-105	595.4	69.7	251.0	N.D.	N.D.
184	ZX162-110	5676.0	102.9	423.4	68.2	1972.0
185	ZX162-111	6743.0	78.1	289.9	46.07	542.3
186	ZX162-112	748.5	98.8	231.0	46.85	481.3
187	ZX162-113	699.1	71.6	136.4	34.96	647.8
188	ZX162-124	2105.0	83.7	1456.0	N.D.	N.D.
189	ZX162-126	6925.0	N.D.	N.D.	N.D.	N.D.
190	ZX162-127	5368.0	N.D.	N.D.	N.D.	N.D.
191	ZX162-128	3044.0	83.0	1617.0	N.D.	N.D.
192	ZX162-129	>10,000	N.D.	N.D.	N.D.	N.D.
193	ZX162-138	>10,000	N.D.	N.D.	N.D.	N.D.
194	ZX162-139	2476.0	64.4	794.7	N.D.	N.D.
195	ZX162-140	>10,000	77.4	1086.0	21.66	1040.0
196	ZX162-141	910.0	67.0	220.4	N.D.	N.D.

197	ZX162-147	1197.0	N.D.	N.D.	N.D.	N.D.
198	ZX162-148	1453.0	45.1	1159.0	N.D.	N.D.
199	ZX162-151	3435.0	87.1	173.9	76.5	955.9
200	ZX162-173	>10,000	N.D.	N.D.	N.D.	N.D.
201	ZX162-174	4308	N.D.	N.D.	N.D.	N.D.
202	ZX162-175	>10,000	N.D.	N.D.	N.D.	N.D.
203	ZX162-176	1080.0	39.5	700.5	N.D.	N.D.
204	YX143-103B	158.3	N.D.	N.D.	N.D.	N.D.
205	YX143-103C	216.6	N.D.	N.D.	N.D.	N.D.
206	YX143-105C	272.1	116.7	14.4	107.8	44.8
207	YX143-108	203.0	94.7	50.9	47.8	128.9
208	YX143-110B	>10,000	95.7	849.3	48.9	1898.0
209	YX143-112B	160.4	100.5	8.1	88.1	60.7
210	YX143-129	86.1	74.9	33.1	33.6	119.0
211	YX143-134C	1184.0	59.9	732.0	N.D.	N.D.
212	YX143-138C	6236.0	72.5	654.5	N.D.	N.D.
213	YX143-182C-1	1768.0	61.3	72.7	31.5	210.7
214	YX143-183A	>10,000	N.D.	N.D.	N.D.	N.D.
215	YX143-184B-1	3278.0	N.D.	N.D.	N.D.	N.D.
216	YX143-184B-2	4386.0	85.1	27.5	53.8	729.3
217	YX143-185B	>10,000	N.D.	N.D.	N.D.	N.D.
218	YX143-186B	1723.0	N.D.	N.D.	N.D.	N.D.
219	YX157-19A	312.8	55.5	25.5	71.9	536.6
220	YX157-20A	>10,000	N.D.	N.D.	N.D.	N.D.
221	YX157-29B	1397.0	59.3	108.4	66.89	1316
222	YX157-42B	6976.0	N.D.	N.D.	N.D.	N.D.
223	YX157-51B	1918.0	89.7	717.3	N.D.	N.D.
224	YX157-51C	8879.0	N.D.	N.D.	N.D.	N.D.
225	YX157-55A	2113.0	105.0	500.4	N.D.	N.D.
226	XS159-153	4629.0	91.0	1350	52.13	2005
227	XS159-155	1450.0	32.5	684.1	N.D.	N.D.
228	XS159-160	5241.0	76.4	1073	N.D.	N.D.
229	XS159-163	1900.0	83.7	235.9	90.2	2067.0
230	XS159-180	714.8	66.1	248.1	45.3	917.3
231	XS159-186	3014.0	N.D.	N.D.	N.D.	N.D.
232	XS165-3	1540.0	48.4	170.0	29.0	1973.0
233	XS165-5	4832.0	N.D.	N.D.	N.D.	N.D.
234	XS165-8	259.4	N.D.	N.D.	N.D.	N.D.
235	XQ148-93	5548.0	N.D.	N.D.	N.D.	N.D.
236	XQ158-012	293.6	N.D.	N.D.	N.D.	N.D.
237	XQ158-055	389.0	37.7	33.6	39.8	1581.0
238	XQ158-056	634.0	42.2	100.7	50.0	1023.0
239	XQ158-078	603.1	N.D.	N.D.	N.D.	N.D.
240	XQ158-093A	378.4	N.D.	N.D.	N.D.	N.D.
241	XQ158-082	375.7	63.4	65.00	N.D.	N.D.
242	XQ158-115	329.6	N.D.	N.D.	N.D.	N.D.
243	XQ158-164	27.18	41.9	104.4	N.D.	N.D.

244	XQ158-167	1555.0	77.2	397.3	N.D.	N.D.
245	XQ158-168	600.4	87.5	391.8	44.79	1302
246	ZD160-34	2141.0	69.6	620.0	N.D.	N.D.
247	ZD160-140	2558.0	N.D.	N.D.	N.D.	N.D.
248	ZD160-141	5888.0	N.D.	N.D.	N.D.	N.D.
249	ZD160-149	1015.0	72.2	118.4	N.D.	N.D.
250	ZD160-11	1628.0	73.1	1286.0	N.D.	N.D.
251	ZD160-133	1103.0	N.D.	N.D.	N.D.	N.D.
252	ZD160-130	6017.0	N.D.	N.D.	N.D.	N.D.
253	ZD160-131	>10,000	N.D.	N.D.	N.D.	N.D.
254	QC166-005	1085.0	88.3	294.3	77.6	1456.0
255	QC166-008	158.9	81.1	68.18	42.30	302.4
256	QC-166-032	2014.0	97.5	366.6	31.68	1003.0
257	XQ148-86	97.0	90.7	44.9	52.1	104.6
258	QC166-096	674.4	82.1	444.2	N.D.	N.D.
259	QC166-097	168.2	81.6	943.8	N.D.	N.D.
260	QC179-001	356.5	63.1	422.0	N.D.	N.D.
261	QC179-002	1684.0	69.3	195.6	26.1	1647.0
262	QC179-025	1907.0	114.0	316.0	N.D.	N.D.
263	QC-179-032	244.3	63.7	127.1	N.D.	N.D.
264	QC-179-033	98.75	44.7	164.8	N.D.	N.D.
265	QC179-038	217.1	N.D.	N.D.	N.D.	N.D.
266	QC179-039	244.3	N.D.	N.D.	N.D.	N.D.
267	QC179-040	174.9	64.0	948.6	20.8	1055.0
268	ZX167-072	5936.0	98.0	740.3	N.D.	N.D.
269	ZX167-077	743.4	88.8	257.2	29.96	1378
270	ZX167-074	133.9	93.8	29.79	21.22	821.6
271	ZX167-090	3151.0	80.1	326.7	N.D.	N.D.
272	ZX167-091	890.2	89.5	100.2	37.99	1496.0
273	ZX162-100-1	6301.0	81.0	226.2	20.73	1298.0
274	ZX162-100-2	1583.0	117.2	61.47	50.96	733.3
275	ZX162-031-1	2772.0	91.5	654.6	24.07	1817.0
276	ZX162-031-2	3131.0	97.5	366.6	31.68	1003.0
277	ZX167-074-1	80.5	86.5	83.75	25.45	212.1
278	ZX167-074-2	33.0	58.2	9.227	N.D.	N.D.
279	ZX177-057	75.2	98.6	109.6	60.90	380.2
280	ZX177-058	63.8	81.6	38.1	55.6	255.9
281	ZX177-058BY	61.9	66.3	52.06	27.90	368.7
282	ZX177-059	257.3	96.8	165.0	44.8	1284.0
283	ZX177-060	140.9	104.4	88.2	41.5	797.0

N.D.: Not Determined; is used for compounds that did either not produce a response or did not produce a response from which reliable measurements of the E_{max} and/or EC_{50} could be determined over the tested concentration range.

Example 285: Several compounds display 5HT2A biased signaling towards Gαq (blue) versus beta-arrestin2 (red) signaling as measured in the BRET assays (Figure 2). Biased signaling is

represented by either preferential efficacy, potency, or both through the G protein over beta-arrestin2 pathway.

Example 286: Several compounds display selective activation 5HT2A alone as compared by compound-induced calcium flux (calcium mobilization assay) at 5HT2A (blue), 5HT2B (red), 5HT2C (green) (Figure 4).

OTHER EMBODIMENTS

It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

References:

Hutcheson, J.D., Setola, V., Roth, B.L., and Merryman, W.D. (2011). Serotonin receptors and heart valve disease--it was meant 2B. Pharmacol Ther *132*, 146-157. 10.1016/j.pharmthera.2011.03.008.

Kim, K., Che, T., Panova, O., DiBerto, J.F., Lyu, J., Krumm, B.E., Wacker, D., Robertson, M.J., Seven, A.B., Nichols, D.E., et al. (2020). Structure of a Hallucinogen-Activated Gq-Coupled 5-HT2A Serotonin Receptor. Cell *182*, 1574-1588 e1519. 10.1016/j.cell.2020.08.024.

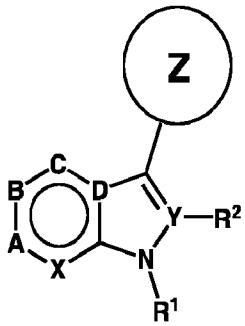
McCorvy, J.D., and Roth, B.L. (2015). Structure and function of serotonin G protein-coupled receptors. Pharmacol Ther *150*, 129-142. 10.1016/j.pharmthera.2015.01.009.

Roth, B.L. (2007). Drugs and valvular heart disease. N Engl J Med *356*, 6-9. 10.1056/NEJMp068265.

Slocum, S.T., DiBerto, J.F., and Roth, B.L. (2021). Molecular Insights into Psychedelic Drug Action. J Neurochem. 10.1111/jnc.15540.

WHAT IS CLAIMED IS:

1. A 5HT2A agonist, comprising a compound having the structure of FORMULA 1,



FORMULA 1

wherein,

A is selected from N, CH or CR^6;

B is selected from N, CH or CR^5;

C is selected from N, CH or CR^4;

D is selected from N or C;

X is selected from N, CH or CR^7;

Y is selected from N or C;

$R^1$and R^2 at each occurrence, are independently selected from null, hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, $C(O)R^{21}$, $C(O)OR^{21}$, $C(O)NR^{21}R^{22}$, $S(O)R^{21}$, $S(O)_2R^{21}$, $S(O)_2NR^{21}R^{22}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

R^{21} and R^{22} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl,

optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{21} and R^{22}, together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring;

R^4, R^5, R^6 and R^7 at each occurrence, are independently selected from hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, CN, NO_2, OR^{23}, SR^{23}, $NR^{23}R^{24}$, $C(O)R^{23}$, $C(O)OR^{23}$, $C(O)NR^{23}R^{24}$, $S(O)R^{23}$, $S(O)_2R^{23}$, $S(O)_2NR^{23}R^{24}$, $NR^{25}C(O)OR^{23}$, $NR^{25}C(O)R^{23}$, $NR^{25}C(O)NR^{23}R^{24}$, $NR^{25}S(O)R^{23}$, $NR^{25}S(O)_2R^{23}$, $NR^{25}S(O)_2NR^{23}R^{24}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

R^{23}, R^{24}, and R^{25} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

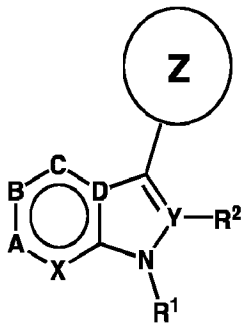
R^{23} and R^{24}, R^{23} and R^{25}, R^{24} and R^{25} together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring; and

is at each occurrence independently selected from an optionally substituted 3-10 membered carbocyclyl, optionally substituted 3-10 membered heterocyclyl, optionally substituted 4-13 membered fused carbocyclyl, optionally substituted 4-13 membered fused heterocyclyl, optionally substituted 4-13 membered bridged carbocyclyl, optionally substituted 4-13 membered bridged heterocyclyl, optionally substituted 4-13 membered spiro carbocyclyl, optionally substituted 4-13 membered spiro heterocyclyl, optionally substituted aryl, optionally substituted bicyclic fused aryl, optionally substituted tricyclic fused aryl, and optionally substituted heteroaryl,

optionally substituted bicyclic fused heteroaryl, and optionally substituted tricyclic fused heteroaryl, and

pharmaceutically acceptable salts thereof.

2. A 5HT2A agonist, comprising a compound having the structure of FORMULA 1,



FORMULA 1

wherein,

A is selected from N, CH or CR^6;

B is selected from N, CH or CR^5;

C is selected from N, CH or CR^4;

D is selected from N or C;

X is selected from N, CH or CR^7;

Y is selected from N or C;

R^1 and R^2 at each occurrence, are independently selected from null, hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, $C(O)R^{21}$, $C(O)OR^{21}$, $C(O)NR^{21}R^{22}$, $S(O)R^{21}$, $S(O)_2R^{21}$, $S(O)_2NR^{21}R^{22}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

R^{21} and R^{22} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl,

optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{21} and R^{22}, together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring;

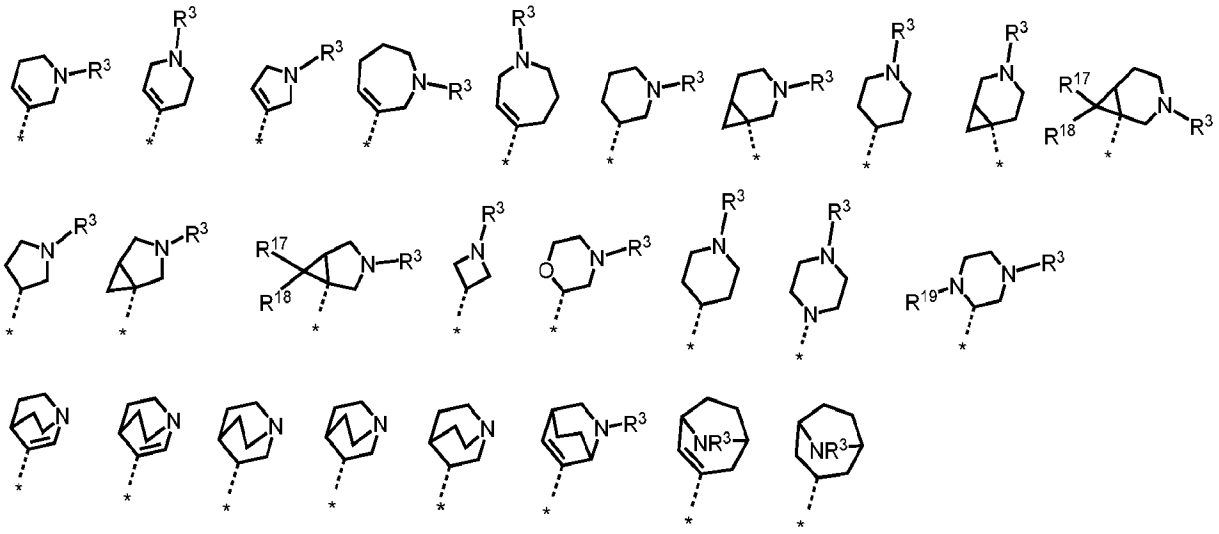
R^4, R^5, R^6 and R^7 at each occurrence, are independently selected from hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, CN, NO_2, OR^{23}, SR^{23}, $NR^{23}R^{24}$, $C(O)R^{23}$, $C(O)OR^{23}$, $C(O)NR^{23}R^{24}$, $S(O)R^{23}$, $S(O)_2R^{23}$, $S(O)_2NR^{23}R^{24}$, $NR^{25}C(O)OR^{23}$, $NR^{25}C(O)R^{23}$, $NR^{25}C(O)NR^{23}R^{24}$, $NR^{25}S(O)R^{23}$, $NR^{25}S(O)_2R^{23}$, $NR^{25}S(O)_2NR^{23}R^{24}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

R^{23}, R^{24}, and R^{25} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{23} and R^{24}, R^{23} and R^{25}, R^{24} and R^{25} together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring; and

(z) at each occurrence is selected from the following groups, or their optionally substituted analogs, wherein * denotes the point of attachment:



wherein,

R^3 at each occurrence, are independently selected from hydrogen, methyl, ethyl, n-propyl, C_1-C_8 alkyl, CD_3, Ph, $C(O)R^{26}$, $C(O)OR^{26}$, $C(O)NR^{26}R^{27}$, $S(O)R^{26}$, $S(O)_2R^{26}$, $S(O)_2NR^{26}R^{27}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

R^{26} and R^{27} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{26} and R^{27}, together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring;

R^{17} and R^{18} at each occurrence, are independently selected from hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, CN, NO_2, OR^{28}, SR^{28}, $NR^{28}R^{29}$, $C(O)R^{28}$, $C(O)OR^{29}$, $C(O)NR^{28}R^{29}$, $S(O)R^{28}$, $S(O)_2R^{28}$, $S(O)_2NR^{28}R^{29}$, $NR^{30}C(O)OR^{28}$, $NR^{30}C(O)R^{28}$, $NR^{30}C(O)NR^{28}R^{29}$, $NR^{30}S(O)R^{28}$, $NR^{30}S(O)_2R^{28}$, $NR^{30}S(O)_2NR^{28}R^{29}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally

substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

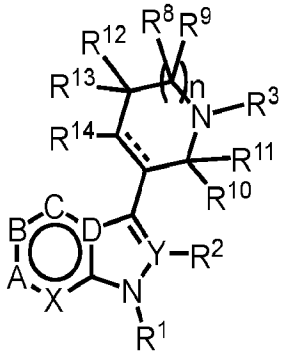
wherein;

R^{28}, R^{29}, and R^{30} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{28} and R^{29}, R^{28} and R^{30}, R^{29} and R^{30} together with the atom to which they are connected form an optionally substituted 3-20 membered cycloalkyl or heterocyclyl ring; and

pharmaceutically acceptable salts thereof.

3. A 5HT2A agonist, comprising a compound having the structure of FORMULA 2,



FORMULA 2

wherein

A is selected from N, CH or CR^6;

B is selected from N, CH or CR^5;

C is selected from N, CH or CR^4;

D is selected from N or C;

X is selected from N, CH or CR^7;

Y is selected from N or C;

n is selected from 0, 1 or 2;

R^1 and R^2 at each occurrence, are independently selected from null, hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, $C(O)R^{21}$, $C(O)OR^{21}$, $C(O)NR^{21}R^{22}$, $S(O)R^{21}$, $S(O)_2R^{21}$, $S(O)_2NR^{21}R^{22}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

R^{21} and R^{22} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{21} and R^{22}, together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring;

R^4, R^5, R^6 and R^7 at each occurrence, are independently selected from hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, CN, NO_2, OR^{23}, SR^{23}, $NR^{23}R^{24}$, $C(O)R^{23}$, $C(O)OR^{23}$, $C(O)NR^{23}R^{24}$, $S(O)R^{23}$, $S(O)_2R^{23}$, $S(O)_2NR^{23}R^{24}$, $NR^{25}C(O)OR^{23}$, $NR^{25}C(O)R^{23}$, $NR^{25}C(O)NR^{23}R^{24}$, $NR^{25}S(O)R^{23}$, $NR^{25}S(O)_2R^{23}$, $NR^{25}S(O)_2NR^{23}R^{24}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

R^{23}, R^{24}, and R^{25} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{23} and R^{24}, R^{23} and R^{25}, R^{24} and R^{25} together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring;

R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14}, at each occurrence, are independently selected from hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, CN, NO_2, OR^{31}, SR^{31}, $NR^{31}R^{32}$, $C(O)R^{31}$, $C(O)OR^{31}$, $C(O)NR^{31}R^{32}$, $S(O)R^{31}$, $S(O)_2R^{31}$, $S(O)_2NR^{31}R^{32}$, $NR^{33}C(O)OR^{31}$, $NR^{33}C(O)R^{31}$, $NR^{33}C(O)NR^{31}R^{32}$, $NR^{33}S(O)R^{31}$, $NR^{33}S(O)_2R^{31}$, $NR^{33}S(O)_2NR^{31}R^{32}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

R^{31}, R^{32}, and R^{33} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{31} and R^{32}, R^{31} and R^{33}, R^{32} and R^{33} together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring;

R^3 is selected from hydrogen, methyl, ethyl, n-propyl, C_1-C_8 alkyl, CD_3, Ph, $C(O)R^{26}$, $C(O)OR^{26}$, $C(O)NR^{26}R^{27}$, $S(O)R^{26}$, $S(O)_2R^{26}$, $S(O)_2NR^{26}R^{27}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

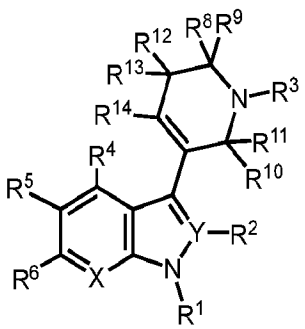
R^{26} and R^{27} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl,

optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

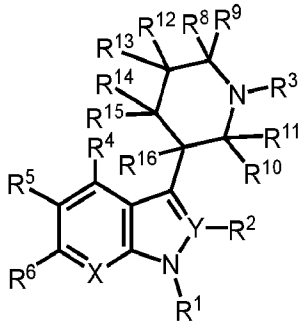
R^{26} and R^{27}, together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring; and

pharmaceutically acceptable salts thereof.

4. A 5HT2A agonist, comprising a compound having the structure of FORMULA 2A or FORMULA 2B,



FORMULA 2A



FORMULA 2B

wherein;

X is selected from N, CH or CR^7;

Y is selected from N or C;

R^1 and R^2 at each occurrence, are independently selected from null, hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, $C(O)R^{21}$, $C(O)OR^{21}$, $C(O)NR^{21}R^{22}$, $S(O)R^{21}$, $S(O)_2R^{21}$, $S(O)_2NR^{21}R^{22}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

R^{21} and R^{22} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl,

optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{21} and R^{22}, together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring;

R^4, R^5, R^6 and R^7 at each occurrence, are independently selected from hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, CN, NO_2, OR^{23}, SR^{23}, $NR^{23}R^{24}$, $C(O)R^{23}$, $C(O)OR^{23}$, $C(O)NR^{23}R^{24}$, $S(O)R^{23}$, $S(O)_2R^{23}$, $S(O)_2NR^{23}R^{24}$, $NR^{25}C(O)OR^{23}$, $NR^{25}C(O)R^{23}$, $NR^{25}C(O)NR^{23}R^{24}$, $NR^{25}S(O)R^{23}$, $NR^{25}S(O)_2R^{23}$, $NR^{25}S(O)_2NR^{23}R^{24}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

R^{23}, R^{24}, and R^{25} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{23} and R^{24}, R^{23} and R^{25}, R^{24} and R^{25} together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring;

R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14}, at each occurrence, are independently selected from hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, CN, NO_2, OR^{31}, SR^{31}, $NR^{31}R^{32}$, $C(O)R^{31}$, $C(O)OR^{31}$, $C(O)NR^{31}R^{32}$, $S(O)R^{31}$, $S(O)_2R^{31}$, $S(O)_2NR^{31}R^{32}$, $NR^{33}C(O)OR^{31}$, $NR^{33}C(O)R^{31}$, $NR^{33}C(O)NR^{31}R^{32}$, $NR^{33}S(O)R^{31}$, $NR^{33}S(O)_2R^{31}$, $NR^{33}S(O)_2NR^{31}R^{32}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

R^{31}, R^{32}, and R^{33} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{31} and R^{32}, R^{31} and R^{33}, R^{32} and R^{33} together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring;

R^3 is selected from hydrogen, methyl, ethyl, n-propyl, C_1-C_8 alkyl, CD_3, Ph, $C(O)R^{26}$, $C(O)OR^{26}$, $C(O)NR^{26}R^{27}$, $S(O)R^{26}$, $S(O)_2R^{26}$, $S(O)_2NR^{26}R^{27}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

R^{26} and R^{27} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{26} and R^{27}, together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring;

R^{15} and R^{16}, at each occurrence, are independently selected from hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, CN, NO_2, OR^{34}, SR^{34}, $NR^{34}R^{35}$, $C(O)R^{34}$, $C(O)OR^{34}$, $C(O)NR^{34}R^{35}$, $S(O)R^{34}$, $S(O)_2R^{34}$, $S(O)_2NR^{34}R^{35}$, $NR^{36}C(O)OR^{34}$, $NR^{36}C(O)R^{34}$, $NR^{36}C(O)NR^{34}R^{35}$, $NR^{36}S(O)R^{34}$, $NR^{36}S(O)_2R^{34}$, $NR^{36}S(O)_2NR^{34}R^{35}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

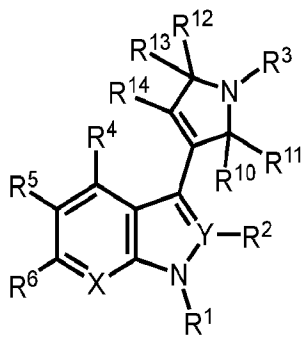
R^{34}, R^{35}, and R^{36} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{34} and R^{35}, R^{34} and R^{36}, R^{35} and R^{36} together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring;

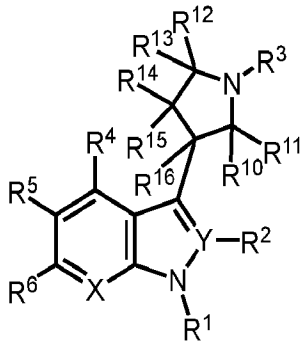
optionally, R^{15} and R^{16} together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring; and

pharmaceutically acceptable salts thereof.

5. A 5HT2A agonist, comprising a compound having the structure of FORMULA 2C or FORMULA 2D,



FORMULA 2C



FORMULA 2D

wherein,

X is selected from N, CH or CR^7;

Y is selected from N or C;

R^1 and R^2 at each occurrence, are independently selected from null, hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, $C(O)R^{21}$, $C(O)OR^{21}$, $C(O)NR^{21}R^{22}$, $S(O)R^{21}$, $S(O)_2R^{21}$, $S(O)_2NR^{21}R^{22}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally

substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

R^{21} and R^{22} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{21} and R^{22}, together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring;

R^4, R^5, R^6 and R^7 at each occurrence, are independently selected from hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, CN, NO_2, OR^{23}, SR^{23}, $NR^{23}R^{24}$, $C(O)R^{23}$, $C(O)OR^{23}$, $C(O)NR^{23}R^{24}$, $S(O)R^{23}$, $S(O)_2R^{23}$, $S(O)_2NR^{23}R^{24}$, $NR^{25}C(O)OR^{23}$, $NR^{25}C(O)R^{23}$, $NR^{25}C(O)NR^{23}R^{24}$, $NR^{25}S(O)R^{23}$, $NR^{25}S(O)_2R^{23}$, $NR^{25}S(O)_2NR^{23}R^{24}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

R^{23}, R^{24}, and R^{25} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{23} and R^{24}, R^{23} and R^{25}, R^{24} and R^{25} together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring;

R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14}, at each occurrence, are independently selected from hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, CN, NO_2, OR^{31}, SR^{31}, $NR^{31}R^{32}$, $C(O)R^{31}$, $C(O)OR^{31}$, $C(O)NR^{31}R^{32}$, $S(O)R^{31}$, $S(O)_2R^{31}$, $S(O)_2NR^{31}R^{32}$, $NR^{33}C(O)OR^{31}$, $NR^{33}C(O)R^{31}$, $NR^{33}C(O)NR^{31}R^{32}$,

$NR^{33}S(O)R^{31}$, $NR^{33}S(O)_2R^{31}$, $NR^{33}S(O)_2NR^{31}R^{32}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

R^{31}, R^{32}, and R^{33} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{31} and R^{32}, R^{31} and R^{33}, R^{32} and R^{33} together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring;

R^3 is selected from hydrogen, methyl, ethyl, n-propyl, C_1-C_8 alkyl, CD_3, Ph, $C(O)R^{26}$, $C(O)OR^{26}$, $C(O)NR^{26}R^{27}$, $S(O)R^{26}$, $S(O)_2R^{26}$, $S(O)_2NR^{26}R^{27}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

R^{26} and R^{27} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{26} and R^{27}, together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring;

R^{15} and R^{16}, at each occurrence, are independently selected from hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, CN, NO_2, OR^{34}, SR^{34}, $NR^{34}R^{35}$, $C(O)R^{34}$, $C(O)OR^{34}$, $C(O)NR^{34}R^{35}$, $S(O)R^{34}$, $S(O)_2R^{34}$,

$S(O)_2NR^{34}R^{35}$, $NR^{36}C(O)OR^{34}$, $NR^{36}C(O)R^{34}$, $NR^{36}C(O)NR^{34}R^{35}$, $NR^{36}S(O)R^{34}$, $NR^{36}S(O)_2R^{34}$, $NR^{36}S(O)_2NR^{34}R^{35}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

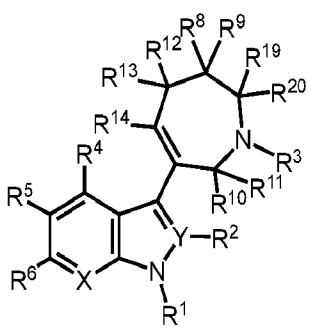
R^{34}, and R^{35}, and R^{36} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{34} and R^{35}, R^{34} and R^{36}, R^{35} and R^{36} together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring;

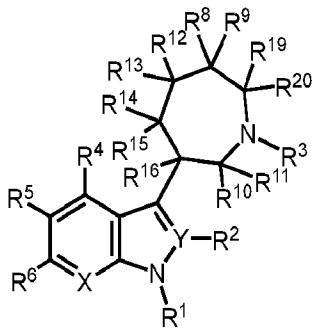
optionally, R^{15} and R^{16} together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring; and

pharmaceutically acceptable salts thereof.

6. A 5HT2A agonist, comprising a compound having the structure of FORMULA 2E or FORMULA 2F



FORMULA 2E



FORMULA 2F

wherein,

X is selected from N, CH or CR^7;

Y is selected from N or C;

R^1 and R^2 at each occurrence, are independently selected from null, hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, $C(O)R^{21}$, $C(O)OR^{21}$, $C(O)NR^{21}R^{22}$, $S(O)R^{21}$, $S(O)_2R^{21}$, $S(O)_2NR^{21}R^{22}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

R^{21} and R^{22} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{21} and R^{22}, together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring;

R^4, R^5, R^6 and R^7 at each occurrence, are independently selected from hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, CN, NO_2, OR^{23}, SR^{23}, $NR^{23}R^{24}$, $C(O)R^{23}$, $C(O)OR^{23}$, $C(O)NR^{23}R^{24}$, $S(O)R^{23}$, $S(O)_2R^{23}$, $S(O)_2NR^{23}R^{24}$, $NR^{25}C(O)OR^{23}$, $NR^{25}C(O)R^{23}$, $NR^{25}C(O)NR^{23}R^{24}$, $NR^{25}S(O)R^{23}$, $NR^{25}S(O)_2R^{23}$, $NR^{25}S(O)_2NR^{23}R^{24}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

R^{23}, R^{24}, and R^{25} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{23} and R^{24}, R^{23} and R^{25}, R^{24} and R^{25} together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring;

R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14}, at each occurrence, are independently selected from hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, CN, NO_2, OR^{31}, SR^{31}, $NR^{31}R^{32}$, $C(O)R^{31}$, $C(O)OR^{31}$, $C(O)NR^{31}R^{32}$, $S(O)R^{31}$, $S(O)_2R^{31}$, $S(O)_2NR^{31}R^{32}$, $NR^{33}C(O)OR^{31}$, $NR^{33}C(O)R^{31}$, $NR^{33}C(O)NR^{31}R^{32}$, $NR^{33}S(O)R^{31}$, $NR^{33}S(O)_2R^{31}$, $NR^{33}S(O)_2NR^{31}R^{32}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

R^{31}, R^{32}, and R^{33} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{31} and R^{32}, R^{31} and R^{33}, R^{32} and R^{33} together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring;

R^3 is selected from hydrogen, methyl, ethyl, n-propyl, C_1-C_8 alkyl, CD_3, Ph, $C(O)R^{26}$, $C(O)OR^{26}$, $C(O)NR^{26}R^{27}$, $S(O)R^{26}$, $S(O)_2R^{26}$, $S(O)_2NR^{26}R^{27}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

R^{26} and R^{27} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl,

optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{26} and R^{27}, together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring;

R^{15} and R^{16}, at each occurrence, are independently selected from hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, CN, NO_2, OR^{34}, SR^{34}, $NR^{34}R^{35}$, $C(O)R^{34}$, $C(O)OR^{34}$, $C(O)NR^{34}R^{35}$, $S(O)R^{34}$, $S(O)_2R^{34}$, $S(O)_2NR^{34}R^{35}$, $NR^{36}C(O)OR^{34}$, $NR^{36}C(O)R^{34}$, $NR^{36}C(O)NR^{34}R^{35}$, $NR^{36}S(O)R^{34}$, $NR^{36}S(O)_2R^{34}$, $NR^{36}S(O)_2NR^{34}R^{35}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

R^{34}, and R^{35}, and R^{36} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{34} and R^{35}, R^{34} and R^{36}, R^{35} and R^{36} together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring;

optionally, R^{15} and R^{16} together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring;

R^{19} and R^{20}, at each occurrence, are independently selected from hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, CN, NO_2, OR^{37}, SR^{37}, $NR^{37}R^{38}$, $C(O)R^{37}$, $C(O)OR^{38}$, $C(O)NR^{37}R^{38}$, $S(O)R^{37}$, $S(O)_2R^{37}$, $S(O)_2NR^{37}R^{38}$, $NR^{39}C(O)OR^{37}$, $NR^{39}C(O)R^{37}$, $NR^{39}C(O)NR^{37}R^{38}$, $NR^{39}S(O)R^{37}$, $NR^{39}S(O)_2R^{37}$, $NR^{36}S(O)_2NR^{37}R^{38}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally

substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

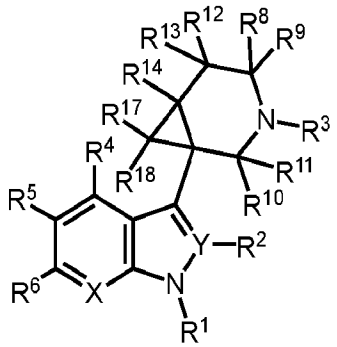
wherein

R^{37}, R^{38}, and R^{39} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{37} and R^{38}, R^{37} and R^{39}, $R^{38}$and R^{39} together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring; and

pharmaceutically acceptable salts thereof.

7. A 5HT2A agonist, comprising a compound having the structure of FORMULA 3



FORMULA 3

wherein;

X is selected from N, CH or CR^7;

Y is selected from N or C;

R^1 and R^2 at each occurrence, are independently selected from null, hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, $C(O)R^{21}$, $C(O)OR^{21}$, $C(O)NR^{21}R^{22}$, $S(O)R^{21}$, $S(O)_2R^{21}$, $S(O)_2NR^{21}R^{22}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

R^{21} and R^{22} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{21} and R^{22}, together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring;

R^4, R^5, R^6 and R^7 at each occurrence, are independently selected from hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, CN, NO_2, OR^{23}, SR^{23}, $NR^{23}R^{24}$, $C(O)R^{23}$, $C(O)OR^{23}$, $C(O)NR^{23}R^{24}$, $S(O)R^{23}$, $S(O)_2R^{23}$, $S(O)_2NR^{23}R^{24}$, $NR^{25}C(O)OR^{23}$, $NR^{25}C(O)R^{23}$, $NR^{25}C(O)NR^{23}R^{24}$, $NR^{25}S(O)R^{23}$, $NR^{25}S(O)_2R^{23}$, $NR^{25}S(O)_2NR^{23}R^{24}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

R^{23}, R^{24}, and R^{25} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{23} and R^{24}, R^{23} and R^{25}, R^{24} and R^{25} together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring;

R^3 is selected from hydrogen, methyl, ethyl, n-propyl, C_1-C_8 alkyl, CD_3, Ph, $C(O)R^{26}$, $C(O)OR^{26}$, $C(O)NR^{26}R^{27}$, $S(O)R^{26}$, $S(O)_2R^{26}$, $S(O)_2NR^{26}R^{27}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-

C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

R^{26} and R^{27} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{26} and R^{27}, together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring; and

R^{17} and R^{18} at each occurrence, are independently selected from hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, CN, NO_2, OR^{28}, SR^{28}, $NR^{28}R^{29}$, $C(O)R^{28}$, $C(O)OR^{29}$, $C(O)NR^{28}R^{29}$, $S(O)R^{28}$, $S(O)_2R^{28}$, $S(O)_2NR^{28}R^{29}$, $NR^{30}C(O)OR^{28}$, $NR^{30}C(O)R^{28}$, $NR^{30}C(O)NR^{28}R^{29}$, $NR^{30}S(O)R^{28}$, $NR^{30}S(O)_2R^{28}$, $NR^{30}S(O)_2NR^{28}R^{29}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein;

R^{28}, R^{29}, and R^{30} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{28} and R^{29}, R^{28} and R^{30}, R^{29} and R^{30} together with the atom to which they are connected form an optionally substituted 3-20 membered cycloalkyl or heterocyclyl ring;

R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14}, at each occurrence, are independently selected from hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, CN, NO_2, OR^{31}, SR^{31}, $NR^{31}R^{32}$, $C(O)R^{31}$, $C(O)OR^{31}$, $C(O)NR^{31}R^{32}$, $S(O)R^{31}$, $S(O)_2R^{31}$, $S(O)_2NR^{31}R^{32}$, $NR^{33}C(O)OR^{31}$, $NR^{33}C(O)R^{31}$, $NR^{33}C(O)NR^{31}R^{32}$, $NR^{33}S(O)R^{31}$, $NR^{33}S(O)_2R^{31}$, $NR^{33}S(O)_2NR^{31}R^{32}$, optionally substituted C_1-C_8 alkyl, optionally

substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

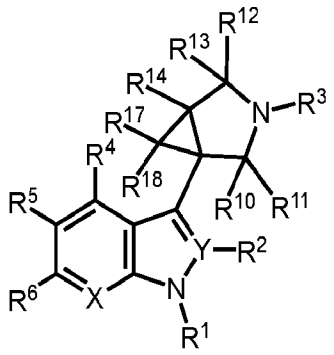
wherein

R^{31}, R^{32}, and R^{33} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{31} and R^{32}, R^{31} and R^{33}, R^{32} and R^{33} together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring; and

pharmaceutically acceptable salts thereof.

8. A 5HT2A agonist, comprising a compound having the structure of FORMULA 4



FORMULA 4

wherein;

X is selected from N, CH or CR^7;

Y is selected from N or C;

R^1 and R^2 at each occurrence, are independently selected from null, hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, $C(O)R^{21}$, $C(O)OR^{21}$, $C(O)NR^{21}R^{22}$, $S(O)R^{21}$, $S(O)_2R^{21}$, $S(O)_2NR^{21}R^{22}$, optionally

substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

R^{21} and R^{22} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{21} and R^{22}, together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring;

R^4, R^5, R^6 and R^7 at each occurrence, are independently selected from hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, CN, NO_2, OR^{23}, SR^{23}, $NR^{23}R^{24}$, $C(O)R^{23}$, $C(O)OR^{23}$, $C(O)NR^{23}R^{24}$, $S(O)R^{23}$, $S(O)_2R^{23}$, $S(O)_2NR^{23}R^{24}$, $NR^{25}C(O)OR^{23}$, $NR^{25}C(O)R^{23}$, $NR^{25}C(O)NR^{23}R^{24}$, $NR^{25}S(O)R^{23}$, $NR^{25}S(O)_2R^{23}$, $NR^{25}S(O)_2NR^{23}R^{24}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

R^{23}, R^{24}, and R^{25} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{23} and R^{24}, R^{23} and R^{25}, R^{24} and R^{25} together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring;

R^3 is selected from hydrogen, methyl, ethyl, n-propyl, C_1-C_8 alkyl, CD_3, Ph, $C(O)R^{26}$, $C(O)OR^{26}$, $C(O)NR^{26}R^{27}$, $S(O)R^{26}$, $S(O)_2R^{26}$, $S(O)_2NR^{26}R^{27}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

R^{26} and R^{27} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{26} and R^{27}, together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring; and

R^{17} and R^{18} at each occurrence, are independently selected from hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, CN, NO_2, OR^{28}, SR^{28}, $NR^{28}R^{29}$, $C(O)R^{28}$, $C(O)OR^{29}$, $C(O)NR^{28}R^{29}$, $S(O)R^{28}$, $S(O)_2R^{28}$, $S(O)_2NR^{28}R^{29}$, $NR^{30}C(O)OR^{28}$, $NR^{30}C(O)R^{28}$, $NR^{30}C(O)NR^{28}R^{29}$, $NR^{30}S(O)R^{28}$, $NR^{30}S(O)_2R^{28}$, $NR^{30}S(O)_2NR^{28}R^{29}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein;

R^{28}, R^{29}, and R^{30} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{28} and R^{29}, R^{28} and R^{30}, R^{29} and R^{30} together with the atom to which they are connected form an optionally substituted 3-20 membered cycloalkyl or heterocyclyl ring;

R^{10}, R^{11}, R^{12}, R^{13} and R^{14}, at each occurrence, are independently selected from hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, CN, NO_2, OR^{31}, SR^{31}, $NR^{31}R^{32}$, $C(O)R^{31}$, $C(O)OR^{31}$, $C(O)NR^{31}R^{32}$, $S(O)R^{31}$, $S(O)_2R^{31}$, $S(O)_2NR^{31}R^{32}$, $NR^{33}C(O)OR^{31}$, $NR^{33}C(O)R^{31}$, $NR^{33}C(O)NR^{31}R^{32}$, $NR^{33}S(O)R^{31}$, $NR^{33}S(O)_2R^{31}$, $NR^{33}S(O)_2NR^{31}R^{32}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

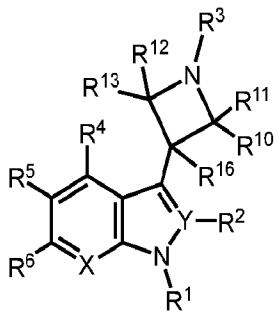
wherein

R^{31}, R^{32}, and R^{33} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{31} and R^{32}, R^{31} and R^{33}, R^{32} and R^{33} together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring; and

pharmaceutically acceptable salts thereof.

9. A 5HT2A agonist, comprising a compound having the structure of FORMULA 5



FORMULA 5

wherein;

X is selected from N, CH or CR^7;

Y is selected from N or C;

R^1 and R^2 at each occurrence, are independently selected from null, hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, $C(O)R^{21}$, $C(O)OR^{21}$, $C(O)NR^{21}R^{22}$, $S(O)R^{21}$, $S(O)_2R^{21}$, $S(O)_2NR^{21}R^{22}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

R^{21} and R^{22} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{21} and R^{22}, together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring;

R^4, R^5, R^6 and R^7 at each occurrence, are independently selected from hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, CN, NO_2, OR^{23}, SR^{23}, $NR^{23}R^{24}$, $C(O)R^{23}$, $C(O)OR^{23}$, $C(O)NR^{23}R^{24}$, $S(O)R^{23}$, $S(O)_2R^{23}$, $S(O)_2NR^{23}R^{24}$, $NR^{25}C(O)OR^{23}$, $NR^{25}C(O)R^{23}$, $NR^{25}C(O)NR^{23}R^{24}$, $NR^{25}S(O)R^{23}$, $NR^{25}S(O)_2R^{23}$, $NR^{25}S(O)_2NR^{23}R^{24}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

R^{23}, R^{24}, and R^{25} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{23} and R^{24}, R^{23} and R^{25}, R^{24} and R^{25} together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring;

R^3 is selected from hydrogen, methyl, ethyl, n-propyl, C_1-C_8 alkyl, CD_3, Ph, $C(O)R^{26}$, $C(O)OR^{26}$, $C(O)NR^{26}R^{27}$, $S(O)R^{26}$, $S(O)_2R^{26}$, $S(O)_2NR^{26}R^{27}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

R^{26} and R^{27} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{26} and R^{27}, together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring; and

R^{10}, R^{11}, R^{12} and R^{13}, at each occurrence, are independently selected from hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, CN, NO_2, OR^{31}, SR^{31}, $NR^{31}R^{32}$, $C(O)R^{31}$, $C(O)OR^{31}$, $C(O)NR^{31}R^{32}$, $S(O)R^{31}$, $S(O)_2R^{31}$, $S(O)_2NR^{31}R^{32}$, $NR^{33}C(O)OR^{31}$, $NR^{33}C(O)R^{31}$, $NR^{33}C(O)NR^{31}R^{32}$, $NR^{33}S(O)R^{31}$, $NR^{33}S(O)_2R^{31}$, $NR^{33}S(O)_2NR^{31}R^{32}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

R^{31}, R^{32}, and R^{33} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered

heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{31} and R^{32}, R^{31} and R^{33}, R^{32} and R^{33} together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring;

R^{16}, at each occurrence, is independently selected from hydrogen, halogen, C_1-C_8 alkyl, oxo, Ph, CN, NO_2, OR^{34}, SR^{34}, $NR^{34}R^{35}$, $C(O)R^{34}$, $C(O)OR^{34}$, $C(O)NR^{34}R^{35}$, $S(O)R^{34}$, $S(O)_2R^{34}$, $S(O)_2NR^{34}R^{35}$, $NR^{36}C(O)OR^{34}$, $NR^{36}C(O)R^{34}$, $NR^{36}C(O)NR^{34}R^{35}$, $NR^{36}S(O)R^{34}$, $NR^{36}S(O)_2R^{34}$, $NR^{36}S(O)_2NR^{34}R^{35}$, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted C_1-C_8 alkoxy, optionally substituted C_1-C_8alkoxyC_1-C_8 alkyl, optionally substituted C_1-C_8 alkylaminoC_1-C_8 alkyl, optionally substituted 3-8 membered cycloalkyl, optionally substituted C_3-C_8 cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

wherein

R^{34}, and R^{35}, and R^{36} are independently selected from hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8alkoxyC_1-C_8alkyl, optionally substituted C_1-C_8alkylaminoC_1-C_8alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-20 membered heterocyclyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{34} and R^{35}, R^{34} and R^{36}, R^{35} and R^{36} together with the atom to which they are connected form an optionally substituted 3-8 membered cycloalkyl or heterocyclyl ring;

and pharmaceutically acceptable salts thereof.

10. A 5HT2A agonist comprising a compound selected from the group consisting of: NS131-179, NS131-178, NS131-177, NS136-006, NS131-169, NS131-168, NS131-167, NS131-173, NS131-180, RS134-52, RS134-48, NS131-185, NS131-170, RS134-45, RS134-40, NS131-184, RS134-49, RS134-53, RS134-41, RS134-46, NS131-172, RS134-38, RS134-65, RS134-62, RS134-70, NS136-081, RS134-73, RS134-72, NS136-092, NS136-091, NS136-096, NS136-095, NS136-102, NS136-101, NS136-115, NS136-116, NS136-117, NS136-118, NS136-119, NS136-120, NS136-109, NS136-110, NS136-111, NS136-112, RS134-37, RS134-56, NS136-002, NS136-004, RS130-132, YX129-177C, YX129-180C, YX143-19, YX143-20, YX143-2, YX143-

21, NS144-042, NS144-043, NS144-044, YS135-44, YS135-45, YS135-34, YS135-32, YS135-38, YS135-41, YS135-39, YX143-14A-2, NS144-019, NS144-021, YX143-15, YX143-16, YX143-17C, YX143-18C, NS144-047, NS144-048, NS144-049, NS136-128, NS136-129, NS136-130, NS136-131, NS136-150, NS136-151, NS136-152, NS136-166, NS144-011, NS136-158, NS136-167, NS136-159, NS136-135, NS136-136, NS136-137, NS144-046, NS144-045, NS136-140, NS136-141, NS136-142, NS136-143, NS136-153, NS136-154, NS136-155, NS136-175, NS144-016, NS136-160, NS136-176, NS136-161, NS136-144, NS136-145, NS136-146, NS144-051, NS144-050, YX143-41C, YX143-42C, YX143-43D, NS144-059-2, NS144-054-2, NS144-067, NS144-085, NS144-093, NS144-094, NS144-095, NS144-096, XQ148-012, XQ148-023, ZX147-015, ZX147-016, ZX147-017, ZX147-019, NS144-097, NS144-098, NS144-102, NS144-101, NS144-107, NS144-108, NS144-109, NS144-110, YS135-52, YS135-53, YS135-54, YS135-80, YS135-81, YS135-82, YS135-96, YS135-98, YS135-99, YS135-100, ZX147-026-01, ZX147-026-02, ZX147-027, ZX147-028, ZX147-029, ZX147-031, ZX147-054, ZX147-055, ZX147-056, ZX147-092, ZX147-093, ZX147-094, ZX147-095, ZX147-096, ZX147-097, ZX147-098, ZX147-099, ZX147-100, ZX147-128, ZX147-129, ZX147-130, ZX147-131, ZX147-137, ZX147-183, ZX156-011, ZX156-012, ZX156-014-1, ZX156-014-2, ZX156-019, ZX156-059, ZX156-069, ZX156-070, ZX156-071, ZX156-089, ZX156-090, ZX162-100, ZX162-031, ZX162-104, ZX162-105, ZX162-110, ZX162-111, ZX162-112, ZX162-113, ZX162-124, ZX162-126, ZX162-127, ZX162-128, ZX162-129, ZX162-138, ZX162-139, ZX162-140, ZX162-141, ZX162-147, ZX162-148, ZX162-151, ZX162-173, ZX162-174, ZX162-175, ZX162-176, YX143-103B, YX143-103C, YX143-105C, YX143-108, YX143-110B, YX143-112B, YX143-129, YX143-134C, YX143-138C, YX143-182C-1, YX143-183A, YX143-184B-1, YX143-184B-2, YX143-185B, YX143-186B, YX157-19A, YX157-20A, YX157-29B, YX157-42B, YX157-51B, YX157-51C, YX157-55A, XS159-153, XS159-155, XS159-160, XS159-163, XS159-180, XS159-186, XS165-3, XS165-5, XS165-8, XQ148-93, XQ158-012, XQ158-055, XQ158-056, XQ158-078, XQ158-093A, XQ158-082, XQ158-115, XQ158-164, XQ158-167, XQ158-168, ZD160-34, ZD160-140, ZD160-141, ZD160-149, ZD160-11, ZD160-133, ZD160-130, ZD160-131, QC166-005, QC166-008, QC-166-032, XQ148-86, QC166-096, QC166-097, QC179-001, QC179-002, QC179-025, QC-179-032, QC-179-033, QC179-038, QC179-039, QC179-040, ZX167-072, ZX167-077, ZX167-074, ZX167-090, ZX167-091, ZX162-100-1 (Enantiomer 1 of ZX162-100), ZX162-100-2 (Enantiomer 2 of ZX162-100), ZX162-031-1 (Enantiomer 1 of ZX162-031), ZX162-031-2 (Enantiomer 2 of ZX162-031), ZX167-074-1 (Enantiomer 1 of ZX167-074),

ZX167-074-2 (Enantiomer 2 of ZX167-074), ZX177-057, ZX177-058, ZX177-058BY, ZX177-059 and ZX177-060 and pharmaceutically acceptable salts thereof.

11. A 5HT2A agonist comprising a compound selected from the group consisting of: NS131-179, NS131-178, NS131-177, NS136-006, NS131-169, NS131-168, NS131-167, NS131-173, NS131-180, RS134-52, RS134-48, NS131-185, NS131-170, RS134-45, RS134-40, NS131-184, RS134-49, RS134-53, RS134-41, RS134-46, NS131-172, RS134-38, RS134-65, RS134-62, RS134-70, NS136-081, RS134-73, RS134-72, NS136-092, NS136-091, NS136-096, NS136-095, NS136-102, NS136-101, NS136-115, NS136-116, NS136-117, NS136-118, NS136-119, NS136-120, RS134-37, RS134-56, NS136-002, NS136-004, YS135-34, YS135-32, YS135-38, YS135-41, YS135-39, YX143-14A-2, NS144-019, NS144-021, YX143-15, YX143-16, YX143-17C, YX143-18C, NS144-047, NS144-048, NS144-049, NS136-128, NS136-129, NS136-130, NS136-131, NS136-150, NS136-151, NS136-152, NS136-166, NS144-011, NS136-158, NS136-167, NS136-159, NS136-140, NS136-141, NS136-142, NS136-143, NS136-153, NS136-154, NS136-155, NS136-175, NS144-016, NS136-160, NS136-176, NS136-161, NS144-093, NS144-094, NS144-095, NS144-096, YS135-80, YS135-81, YS135-82, YS135-96, YS135-98 and ZX156-069, and pharmaceutically acceptable salts thereof.

12. A 5HT2A agonist comprising a compound selected from the group consisting of: RS130-132, YX129-177C, YX129-180C, YX143-19, YX143-20, YX143-2, YX143-21, NS144-042, NS144-043, NS144-044, YS135-44, YS135-45, NS136-135, NS136-136, NS136-137, NS144-046, NS144-045, NS136-144, NS136-145, NS136-146, NS144-051, NS144-050, YX143-41C, YX143-42C, YX143-43D, NS144-059-2, NS144-054-2, NS144-067, NS144-085, XQ148-012, XQ148-023, ZX147-015, ZX147-016, ZX147-017, ZX147-019, NS144-097, NS144-098, NS144-102, NS144-101, NS144-107, NS144-108, NS144-109, NS144-110, YS135-52, YS135-53, YS135-54, YS135-99, YS135-100, ZX147-026-01, ZX147-026-02, ZX147-027, ZX147-028, ZX147-029, ZX147-054, ZX147-055, ZX147-056, ZX147-092, ZX147-093, ZX147-094, ZX147-095, ZX147-096, ZX147-097, ZX147-098, ZX147-099, ZX147-100, ZX147-128, ZX147-129, ZX147-130, ZX147-137, ZX147-183, ZX156-019, ZX156-059, ZX156-070, ZX156-071, ZX156-089, ZX156-090, XQ148-93, XQ158-012, XQ158-055, XQ158-056, XQ148-86, and pharmaceutically acceptable salts thereof.

13. A 5HT2A agonist comprising a compound selected from the group consisting of:

YX143-103B, YX143-103C, YX143-105C, YX143-108, YX143-110B, YX143-112B, YX143-129, YX143-134C, YX143-138C, YX143-182C-1, YX143-183A, YX143-184B-1, YX143-184B-2, YX143-185B, YX143-186B, YX157-19A, YX157-20A, YX157-29B, YX157-42B, YX157-51B, YX157-51C, YX157-55A, and pharmaceutically acceptable salts thereof.

14. A 5HT2A agonist comprising a compound selected from the group consisting of:

XS159-180, XS159-186, XS165-3, XS165-5, XS165-8, XQ158-078, XQ158-093A, XQ158-082, XQ158-115, XQ158-164, XQ158-167, XQ158-168, ZD160-34, ZD160-140, ZD160-141, ZD160-149, ZD160-11, ZD160-133, ZD160-130, ZD160-131, and pharmaceutically acceptable salts thereof.

15. A 5HT2A agonist comprising a compound selected from the group consisting of:

QC166-005, QC166-008, QC-166-032, QC166-096, QC166-097, QC179-001, QC179-002, QC179-025, QC-179-032, QC-179-033, QC179-038, QC179-039, QC179-040, and pharmaceutically acceptable salts thereof.

16. A 5HT2A agonist comprising a compound selected from the group consisting of: ZX162-100, ZX162-031, ZX162-104, ZX162-105, ZX162-110, ZX162-111, ZX162-112, ZX162-113, ZX162-124, ZX162-126, ZX162-127, ZX162-128, ZX162-129, ZX162-138, ZX162-139, ZX162-140, ZX162-141, ZX162-147, ZX162-148, ZX162-151, ZX162-173, ZX162-174, ZX162-175, ZX162-176, XS159-153, XS159-155, XS159-160, XS159-163, ZX167-072, ZX167-077, ZX167-074, ZX167-090, ZX167-091, ZX162-100-1 (Enantiomer 1 of ZX162-100), ZX162-100-2 (Enantiomer 2 of ZX162-100), ZX162-031-1 (Enantiomer 1 of ZX162-031), ZX162-031-2 (Enantiomer 2 of ZX162-031), ZX167-074-1 (Enantiomer 1 of ZX167-074), ZX167-074-2 (Enantiomer 2 of ZX167-074), ZX177-057, ZX177-058, ZX177-058BY, ZX177-059, ZX177-060, and pharmaceutically acceptable salts thereof.

17. A 5HT2A agonist comprising a compound selected from the group consisting of: NS136-109, NS136-110, NS136-111, NS136-112, NS136-145, RS134-40, RS134-45, RS134-48, RS134-46, YX143-19, and pharmaceutically acceptable salts thereof.

18. A 5HT2A agonist comprising a compound selected from the group consisting of:

YX143-108, YX143-129, YX143-134C, ZX147-031, ZX147-131, ZX162-031, ZX162-031-1, ZX162-100, ZX162-100-2, ZX162-105, ZX167-074, ZX167-091, QC166-008, QC166-096, QC166-097, and pharmaceutically acceptable salts thereof.

19. A 5HT2A agonist comprising a compound selected from the group consisting of: ZX162-031, ZX162-031-1, ZX162-100, ZX162-100-2, ZX162-105, ZX167-074, ZX167-091, QC166-008, QC166-096, QC166-097, and pharmaceutically acceptable salts thereof.

20. A 5HT2A agonist comprising a compound selected from the group consisting of: 3-(3-azabicyclo[4.1.0]heptan-1-yl)-7-chloro-1H-indazole (ZX162-031); 3-(3-azabicyclo[3.1.0]hexan-1-yl)-7-chloro-1H-indazole (ZX162-100); 3-(3-azabicyclo[3.1.0]hexan-1-yl)-7-chloro-1H-indole (ZX167-074); and 3-(3-azabicyclo[3.1.0]hexan-1-yl)-7-methyl-1H-indole (ZX167-091) and enantiomers, pharmaceutically acceptable salts, solvent complexes, morphological forms, and deuterated and fluorinated derivatives thereof.

21. A 5HT2A agonist comprising a compound selected from the group consisting of: 3-(azetidin-3-yl)-7-chloro-1H-indole (QC166-008), 3-(azetidin-3-yl)-7-methyl-1H-indole (QC166-096), 3-(azetidin-3-yl)-7-fluoro-1H-indole (QC166-097), and enantiomers, pharmaceutically acceptable salts, solvent complexes, morphological forms, and deuterated and fluorinated derivatives thereof.

22. A pharmaceutical composition, comprising:
    a. a 5HT2A agonist according to any one of claims 1 – 21; and
    b. a pharmaceutically acceptable carrier.

23. The pharmaceutical composition of claim 22, formulated to be administered orally, parenterally, intradermally, subcutaneously, topically, and/or rectally.

24. A method of treating a psychiatric disorder, comprising administering to a subject in need thereof, a 5HT2A agonist according to any one of claims 1 – 23.

25. The method of claim 24, wherein the psychiatric disorder is depression, anxiety, psychosis, dyskinesias, hallucination or substance abuse.

26. A Gq-biased 5HT2A agonist selective for 5HT2A over 5HT2B and SERT, according to any one of claims 1 – 23.

27. Use of a 5HT2A agonist according to any one of claims 1 – 20 for the treatment of a psychiatric disorder.

28. A compound according to any one of claims 1 – 9, wherein Y is N and R^2 is null.

29. A compound according to any one of claims 1 – 9, wherein Y is C and R^2 is hydrogen.

30. A compound according to any one of claims 1 – 9, 28 and 29, wherein R^4, R^5, R^6 and R^7 at each occurrence, are independently selected from hydrogen, halogen, C_1-C_8 alkyl, Ph, CN, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_1-C_8 alkoxy, optionally substituted heteroaryl and hydroxy.

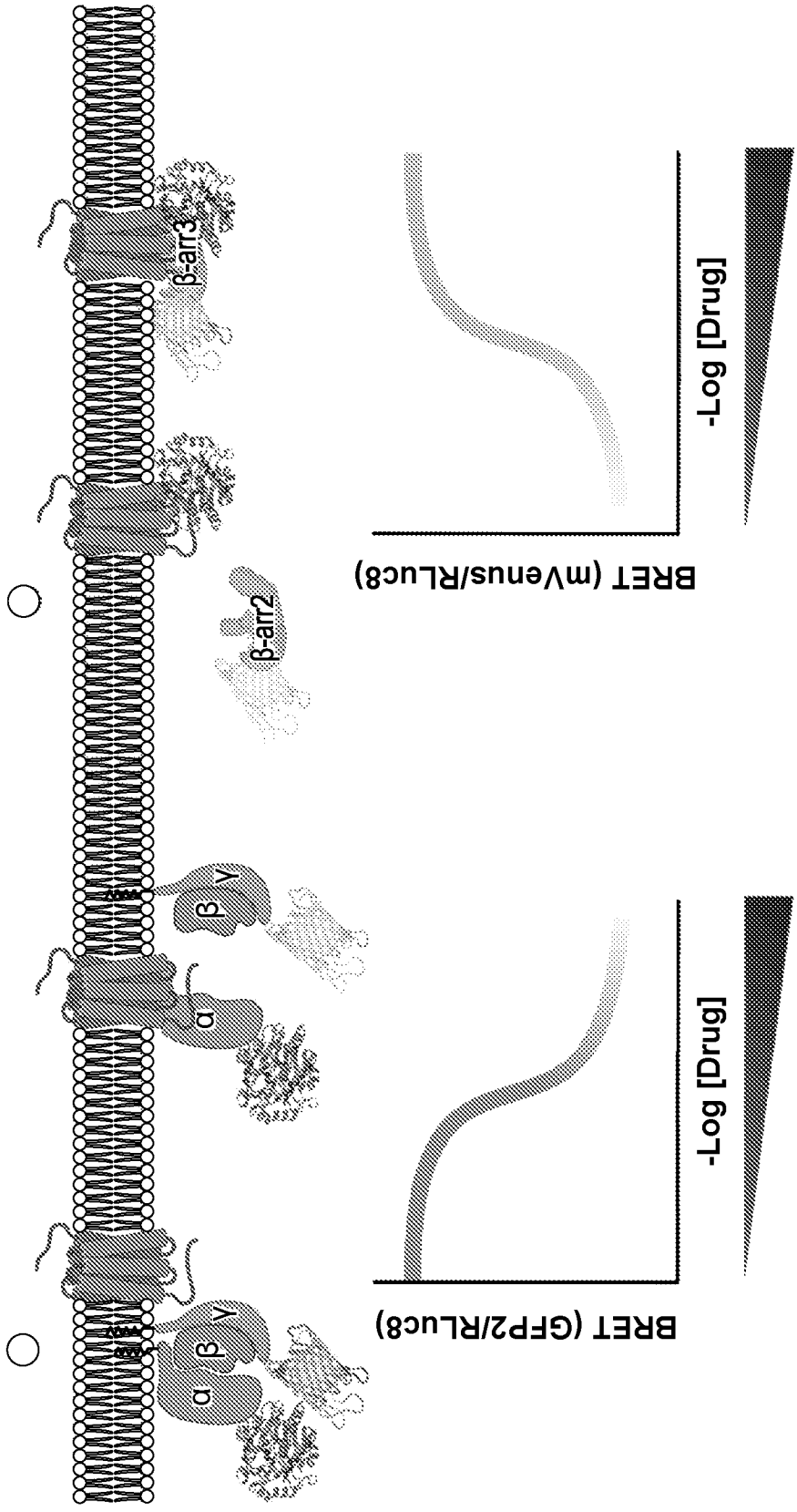

β-arr3
β-arr2
α
β γ
α
β γ
BRET (GFP2/RLuc8)
-Log [Drug]
BRET (mVenus/RLuc8)
-Log [Drug]

FIG. 1A

FIG. 1B

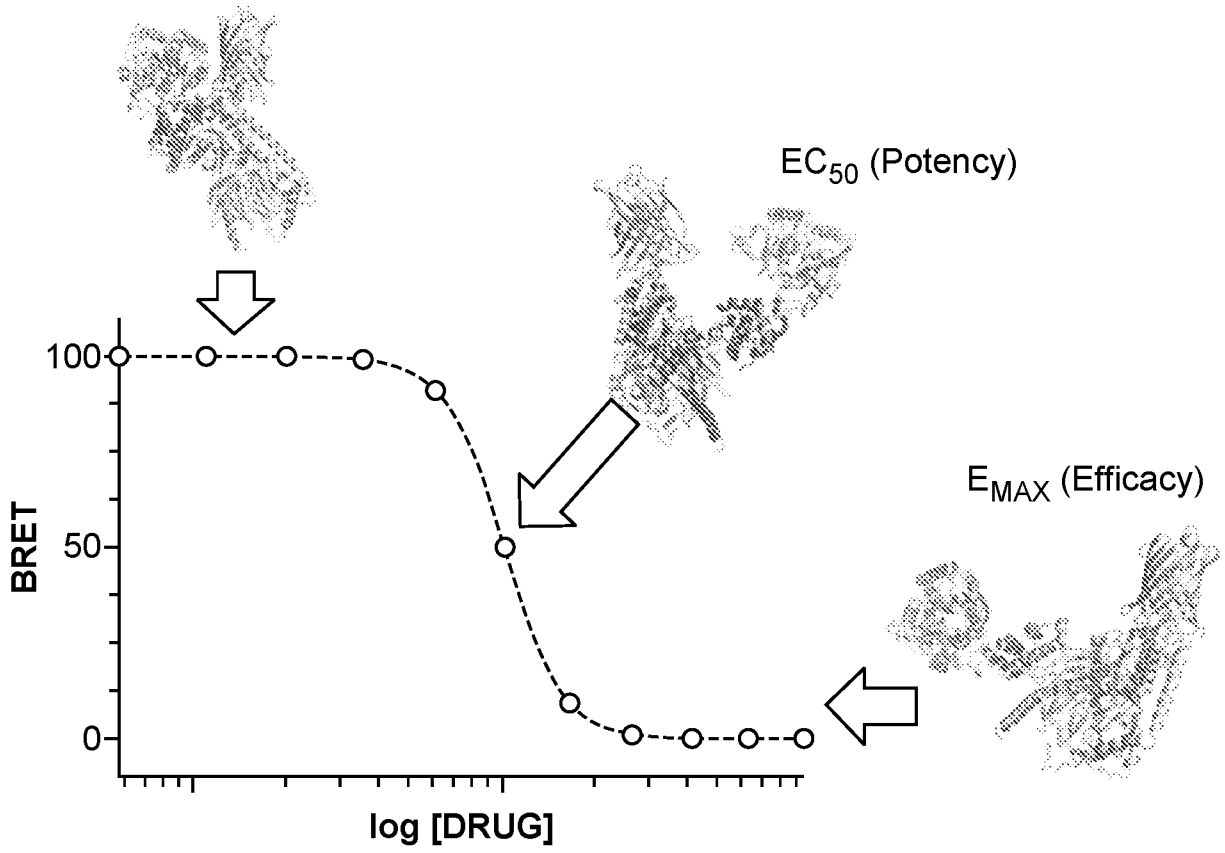


FIG. 1C

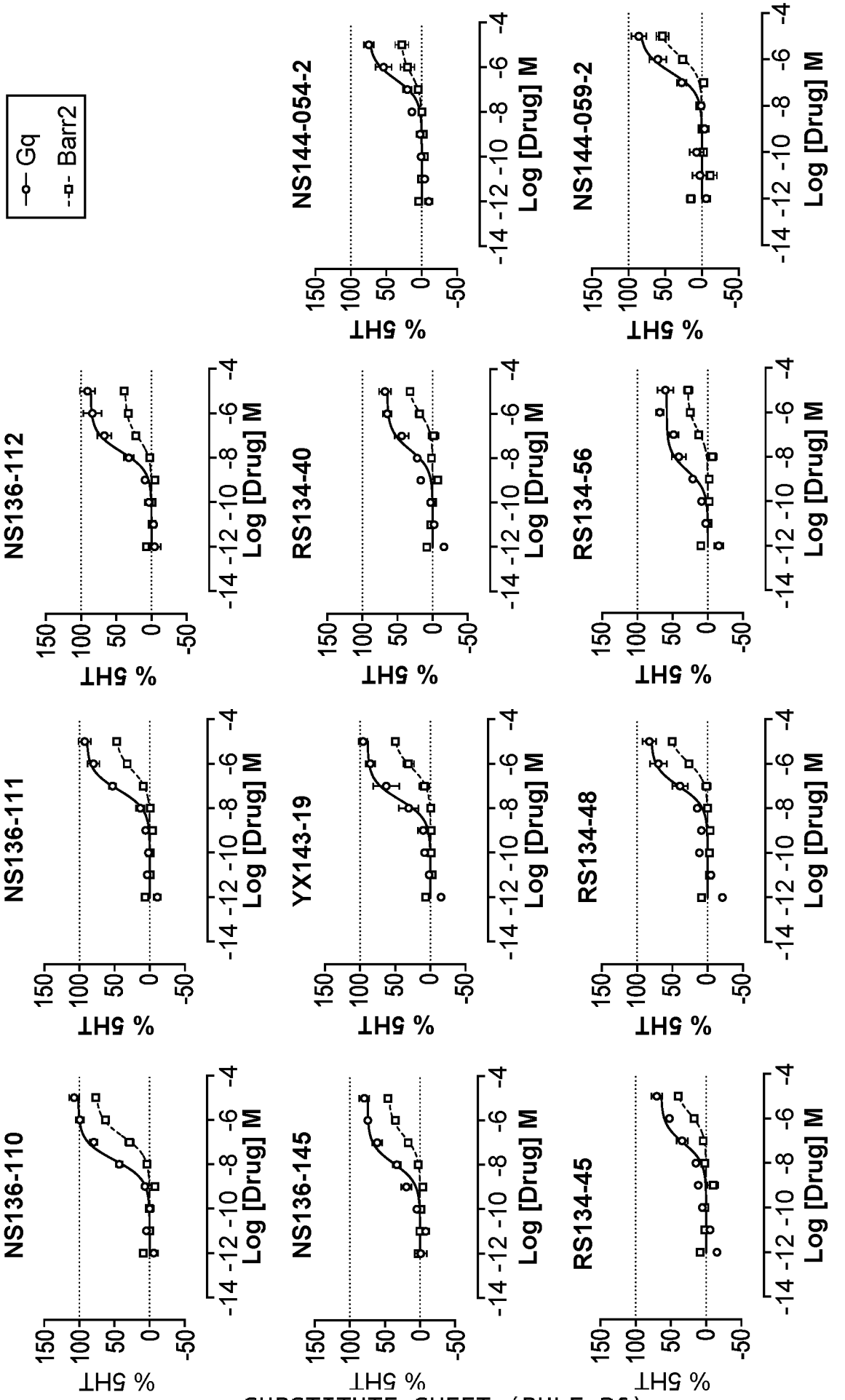

Gq
Barr2
NS136-110
NS136-111
NS136-112
YX143-19
NS136-145
RS134-40
RS134-48
RS134-56
RS134-45
NS144-054-2
NS144-059-2
% 5HT
Log [Drug] M

FIG. 2A

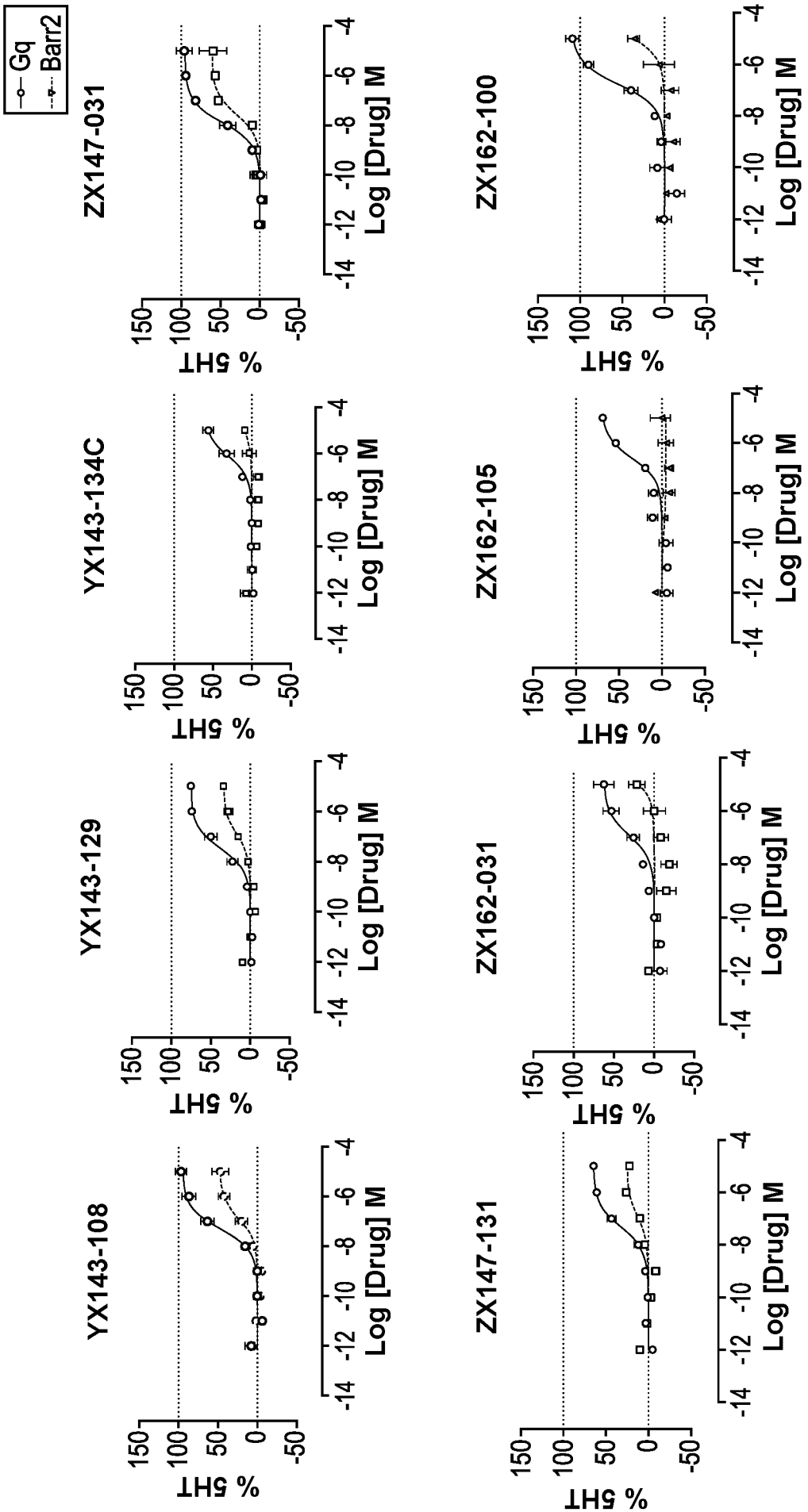

Gq
Barr2
ZX147-031
YX143-134C
ZX162-100
ZX162-105
YX143-129
ZX162-031
YX143-108
ZX147-131
% 5HT
Log [Drug] M

FIG. 2B

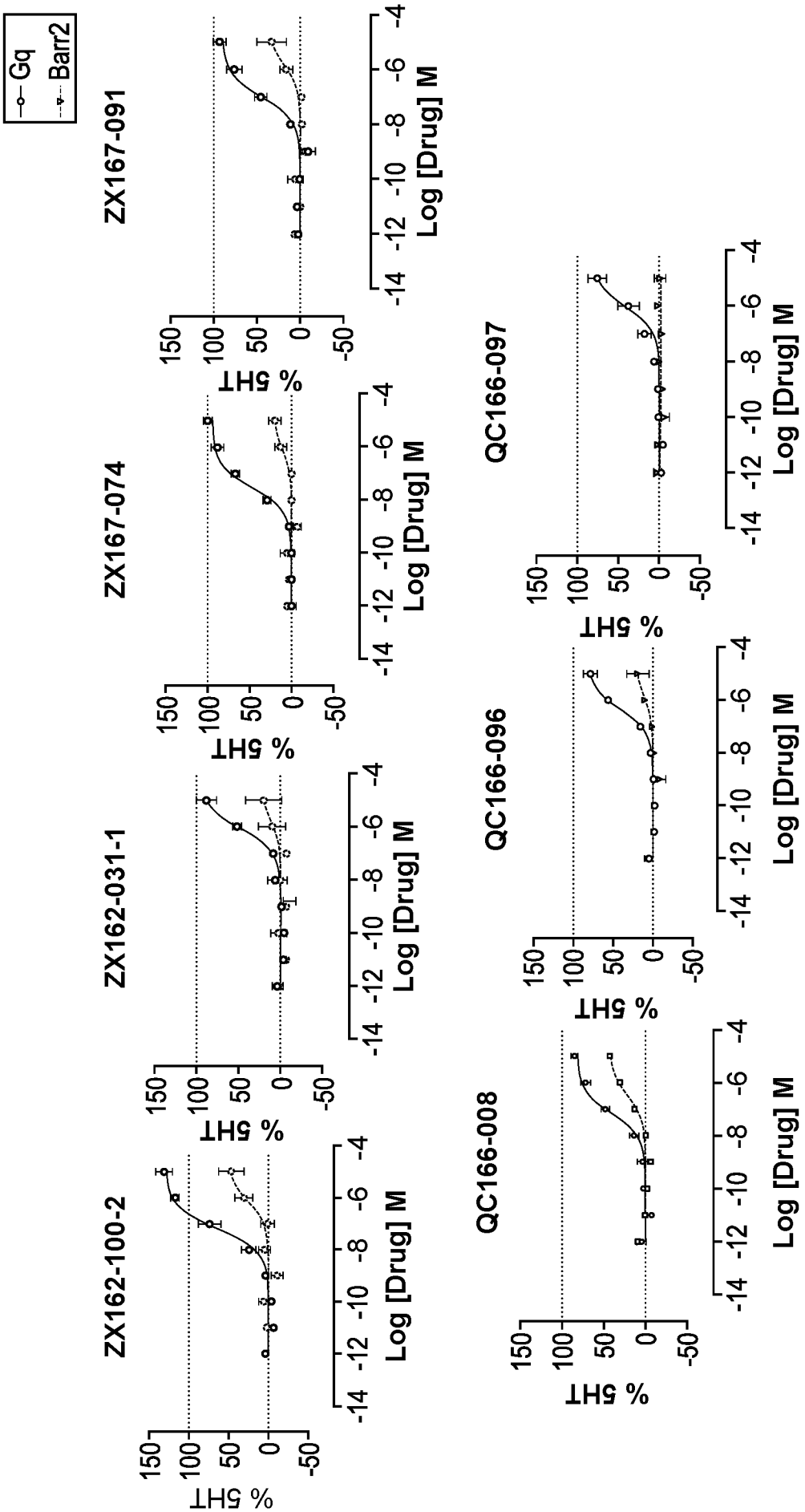

Gq
Barr2
ZX167-091
ZX167-074
QC166-097
ZX162-031-1
QC166-096
ZX162-100-2
QC166-008
% 5HT
Log [Drug] M

FIG. 2C

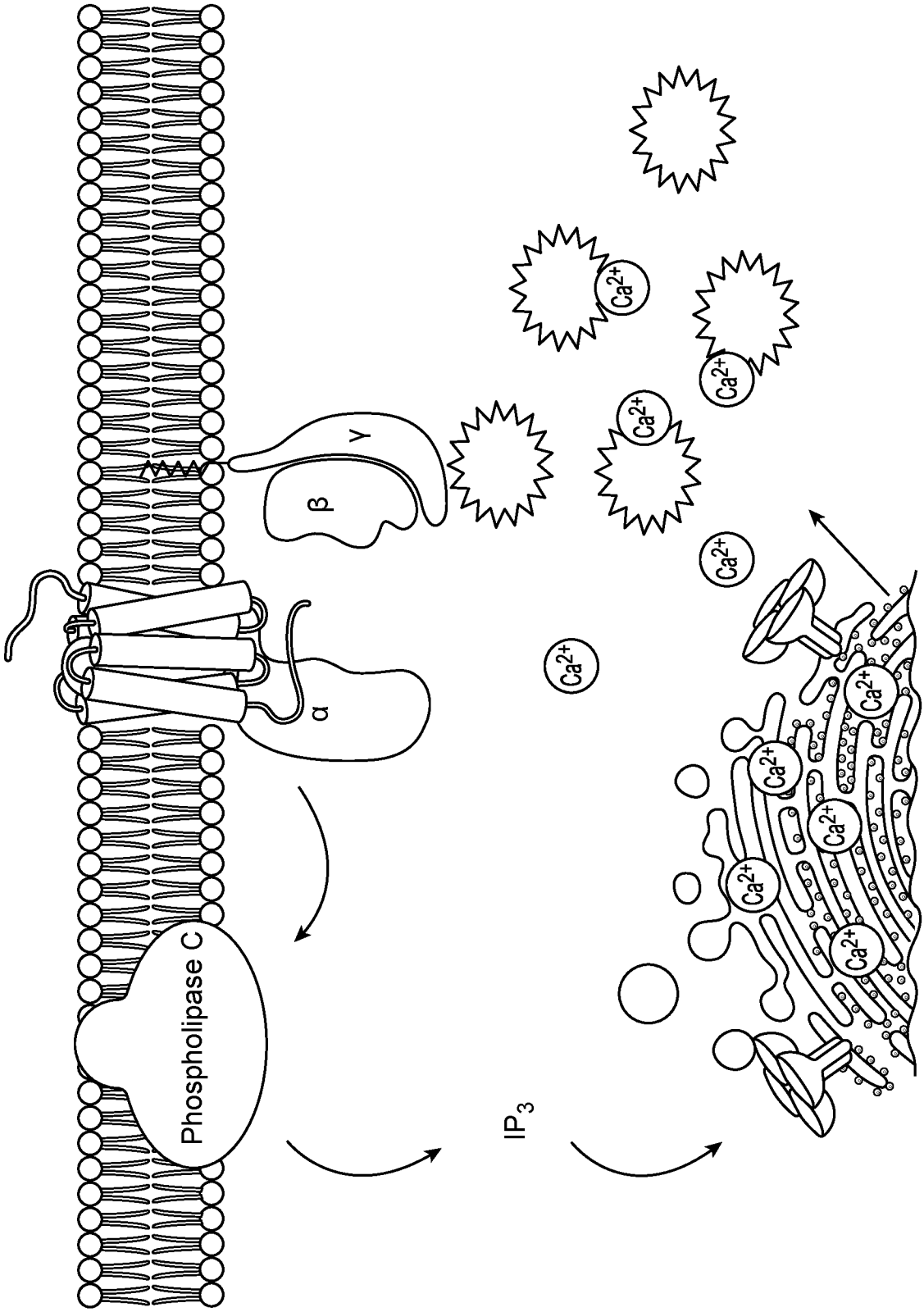


FIG. 3

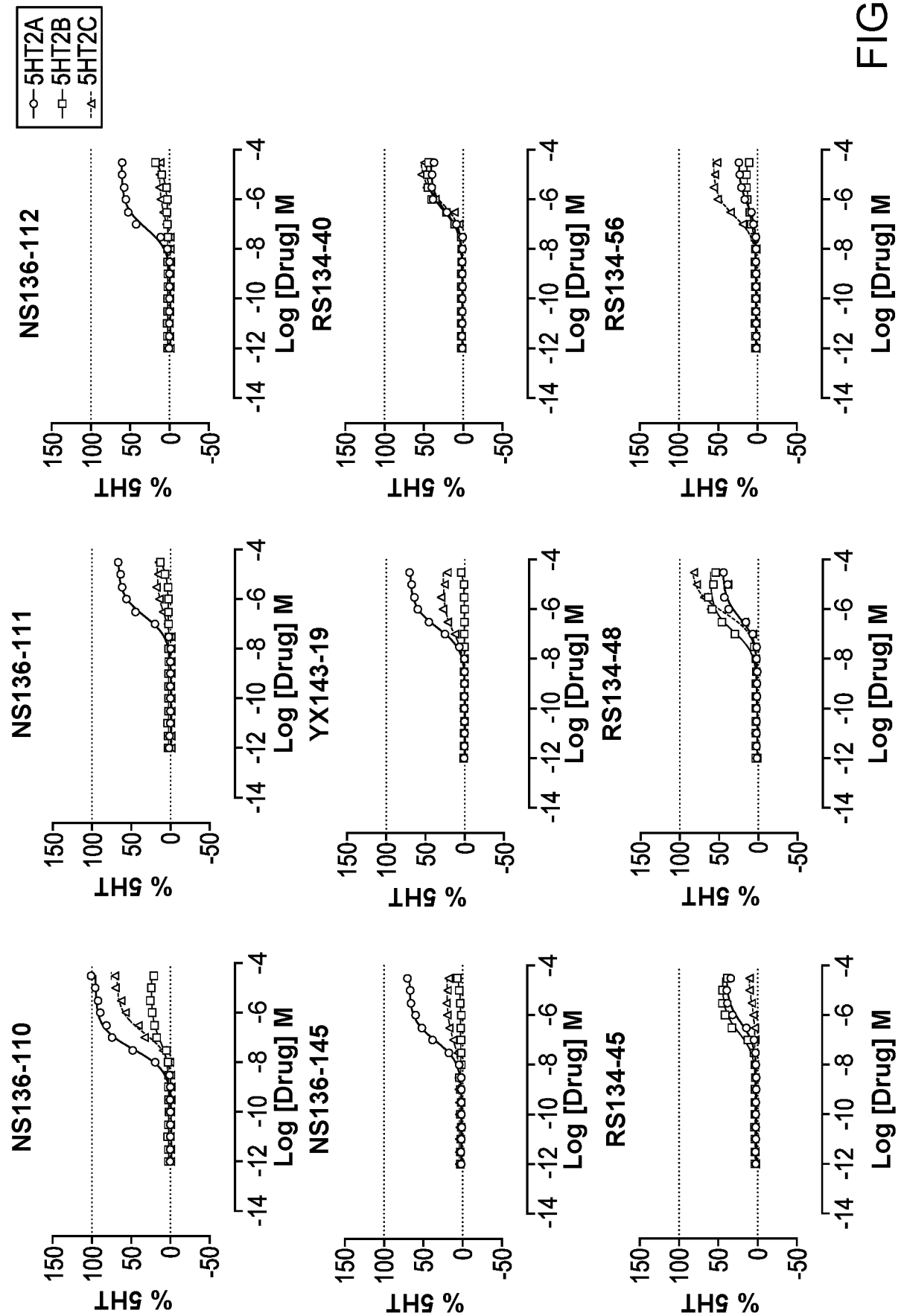

5HT2A
5HT2B
5HT2C
NS136-112
RS134-40
RS134-56
NS136-111
YX143-19
RS134-48
NS136-110
NS136-145
RS134-45
% 5HT
Log [Drug] M
150
100
50
0
-50
-14
-12
-10
-8
-6
-4

FIG. 4A

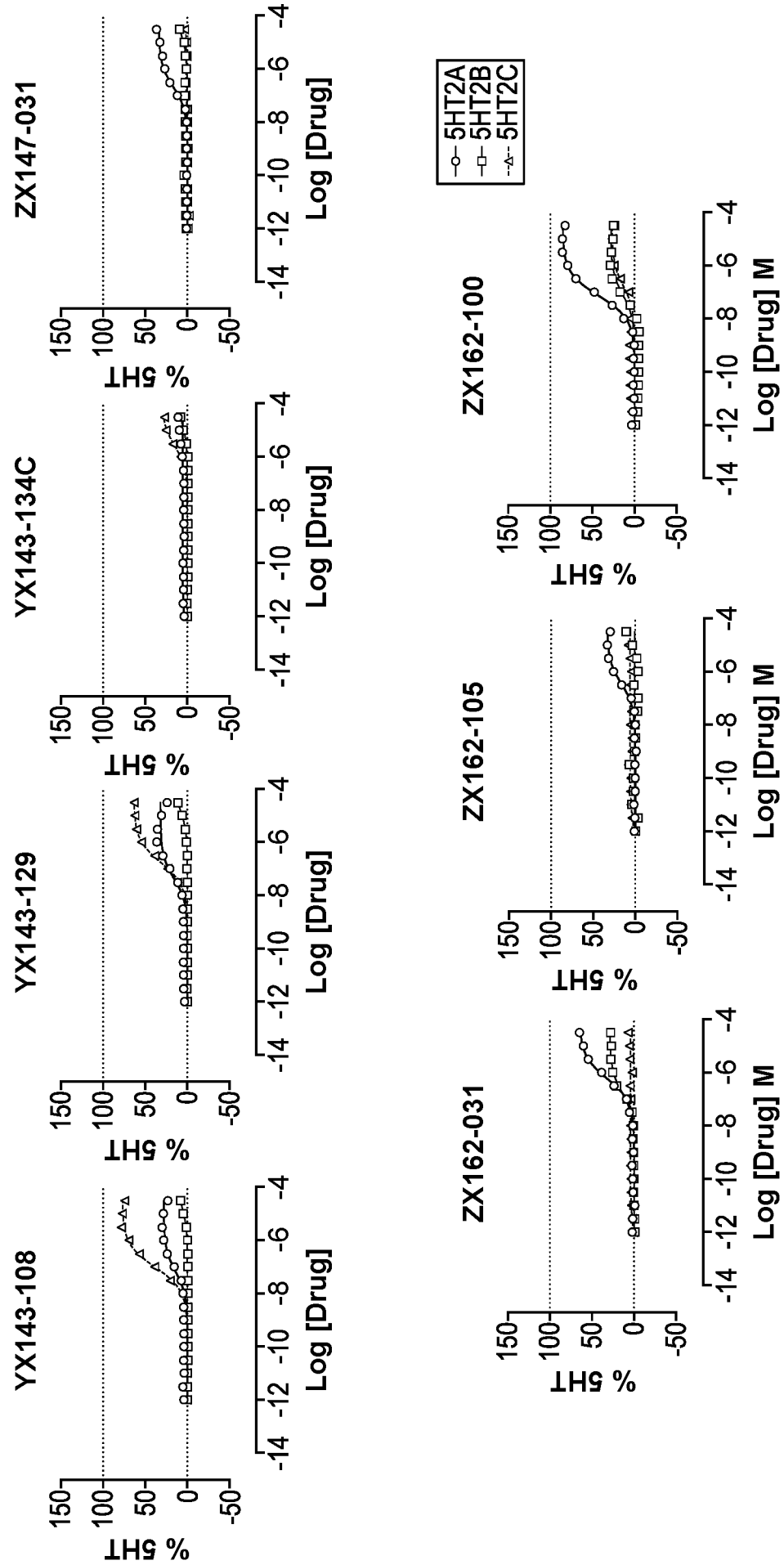

YX143-108
YX143-129
YX143-134C
ZX147-031
ZX162-031
ZX162-105
ZX162-100
% 5HT
Log [Drug]
Log [Drug] M
5HT2A
5HT2B
5HT2C

FIG. 4B

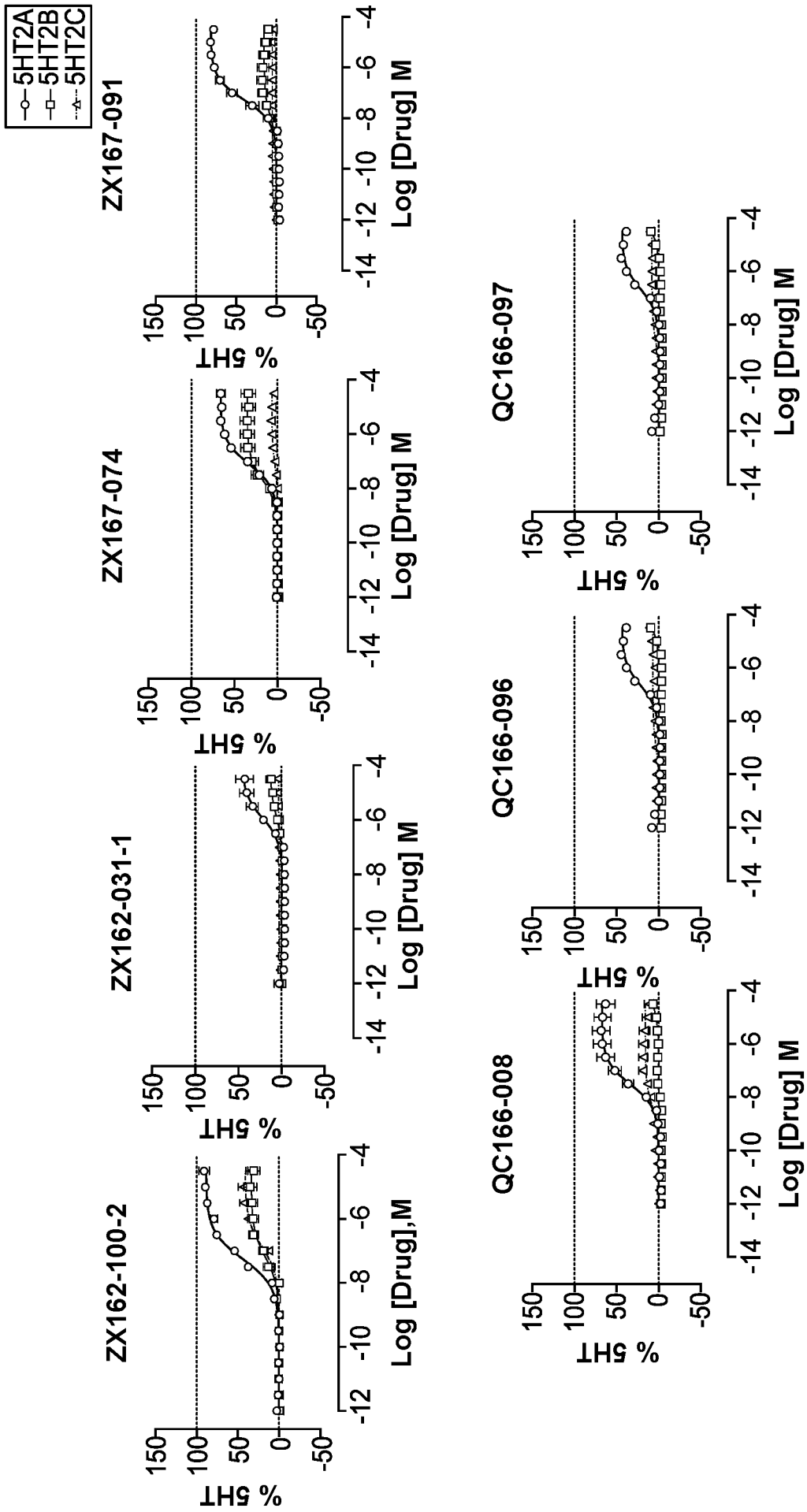

5HT2A
5HT2B
5HT2C
ZX167-091
ZX167-074
QC166-097
ZX162-031-1
QC166-096
ZX162-100-2
QC166-008
% 5HT
Log [Drug] M
Log [Drug],M

FIG. 4C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 22/53168

A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. A61K 31/33, A61K 31/395, A61K 31/40 (2023.01)
ADD. A61K 31/407 (2023.01)

CPC - INV. A61K 31/33, A61K 31/395, A61K 31/40
ADD. A61K 31/407

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DAHLGREN et al. "SYNTHESIS AND SEROTONIN RECEPTOR BINDING PROPERTIES OF 5 -SUBSTITUTED 3-(1',2',5',6'-TETRAHYDROPYRIDIN-3'-YL) INDOLES", Bioorganic & Medicinal Chemistry Letters. 1995. Vol. 5, No. 24, pp. 2963-2968, especially: abstract; pg 2963, para 1; pg 2963, middle, formula RU28253.	1,22-23,27-28
A	PubChem-SID-377336608, Modify Date: 4 May 2021 (04.05.2021), pg 2 figure, this is a purchasable chemical.	1,22-23,27-28
A	US 2010/0120731 A1 (VIAL JUAN et al.) 13 May 2010 (13.05.2010), especially: para [0205] Intermediate 4.	1,22-23,27-28
A	WO 2019/149657 A1 (BOEHRINGER INGELHEIM INTERNATIONAL GMBH) 8 August 2019 (08.08.2019), especially: pg 87, ln 10-14, Intermediate 4.13b.	1,22-23,27-28

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 April 2023	MAY 08 2023
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Kari Rodriquez Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 22/53168

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 24-26 and 30
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1,22-23,27-28

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 22/53168

--Box III - Lack of Unity--

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I+: Claims 1-23 and 27-29 directed to a 5HT2A agonist, comprising a compound having the structure of FORMULA 1, or a pharmaceutically acceptable salt thereof. The compound of FORMULA 1 will be searched to the extent that it encompasses the first species of claim 1, wherein A is N; B is N; C is N; D is N; X is N; Y is N; R1 and R2 are null; and Z is an unsubstituted 3 membered carbocyclyl. It is believed that claims 1, 22-23 and 27-28 encompass this first named invention, and thus these claims will be searched without fee to the extent that they encompass the first species of claim 1. This first named invention has been selected based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines. Applicant is invited to elect additional compounds of FORMULA 1, wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched. Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be a compound of claim 1, wherein A is N; B is N; C is N; D is N; X is N; Y is N; R1 and R2 are null; and Z is an unsubstituted 4 membered carbocyclyl (i.e. claims 1, 22-23 and 27-28).

The groups of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Group I+ includes the technical feature of a unique compound of FORMULA 1, which is not required by any other invention of Group I+.

Common technical features:

The inventions of Groups I+ share the technical feature of a 5HT2A agonist, comprising a compound having the structure of FORMULA 1, or a pharmaceutically acceptable salt thereof.

These shared technical features, however, do not provide a contribution over the prior art, as being obvious over the article entitled "SYNTHESIS AND SEROTONIN RECEPTOR BINDING PROPERTIES OF 5-SUBSTITUTED 3-(1',2',5',6'-TETRAHYDROPYRIDIN-3'-YL) INDOLES" by Dahlgren et al. (hereinafter 'Dahlgren').

Dahlgren teaches a 5HT2 agonist (abstract, A semi-rigid 5-hydroxytryptamine (5-HT) analogue, RU28253 [5-methoxy-3-(l',2',5',6'-tetrahydropyridin-3'-yl) indole], is a potent 5-HT1 and 5-HT2 agonist), comprising a compound having the structure of FORMULA 1, wherein A is CH; B is CR5, R5 is OR23, R23 is unsubstituted C1 alkyl; C is CH; D is C; X is CH; Y is C (pg 2963, middle, formula RU28253), and Dahlgren further teaches a 5HT1A agonist (pg 2963, para 1, RU28253 was also found to be more potent than RU24969 at the 5-HT2 receptors, in addition to having potency at 5-HT1A receptor), but Dahlgren doesn't specifically teach wherein the compound is a 5HT2A agonist. However, it would have been obvious to a person having ordinary skill in the art to determine that the compound is a 5HT2A agonist by routine experimentation in order to fully characterize the activity of the compound in the course of development and commercialization.

As said compound was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the inventions of Group I+.

The inventions of Group I+ thus lack unity under PCT Rule 13.

Item 4 continued: Claims 24-26 and 30 are unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a). These claims are therefore, not included in the above analysis.