INHIBITORS OF LYSINE SPECIFIC DEMETHYLASE-1

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application 62/020,758, filed July 3, 2014, which is incorporated herein by reference in its entirety.

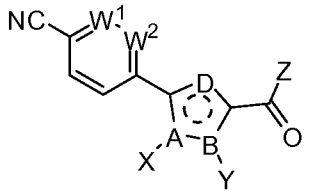
BACKGROUND

[0002] A need exists in the art for an effective treatment of cancer and neoplastic disease.

BRIEF SUMMARY OF THE INVENTION

[0003] Provided herein are substituted heterocyclic derivative compounds and pharmaceutical compositions comprising said compounds. The subject compounds and compositions are useful for the inhibition of the enzyme lysine specific demethylase-1 (LSD-1). Furthermore, the subject compounds and compositions are useful for the treatment of cancer, such as prostate cancer, breast cancer, bladder cancer, lung cancer and/or melanoma and the like. The substituted heterocyclic derivative compounds described herein are based upon a central heterocyclic ring system, such as pyrrole or imidazole, or the like. Said central heterocyclic ring system is further substituted with a 4-cyanophenyl group and a substituted amide group.

[0004] One embodiment provides a compound having the structure of Formula (I), or a pharmaceutically acceptable salt thereof,



(I)

wherein,

A is C; B is N; and D is C-R^3; or A is N; B is C; and D is N;

each R^3 is independently chosen from hydrogen or optionally substituted alkyl;

W^1 and W^2 are independently chosen from N, C-H, or C-F;

X is chosen from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted alkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclylalkyl, optionally substituted aralkyl, or optionally substituted heteroarylalkyl;

Y is chosen from hydrogen, halogen, optionally substituted alkyl, optionally substituted cycloalkyl, or optionally substituted cycloalkylalkyl; and

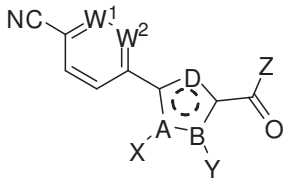
Z is chosen from an optionally substituted *N*-heterocyclyl, optionally substituted -N(H)-heterocyclylalkyl, optionally substituted -N(Me)-heterocyclylalkyl, or $–N(R^3)_2$.

[0005] One embodiment provides a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0006] One embodiment provides a method of regulating gene transcription in a cell comprising inhibiting lysine-specific demethylase 1 activity by exposing the lysine-specific demethylase 1 enzyme to a compound of Formula (I).

[0007] One embodiment provides a method of treating cancer in a patient in need thereof, comprising administering to the patient a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0007a] One embodiment provides a compound having the structure of Formula (I), or a pharmaceutically acceptable salt thereof,



(I)

wherein,

A is C; B is N; and D is CH; or A is N; B is C; and D is N;

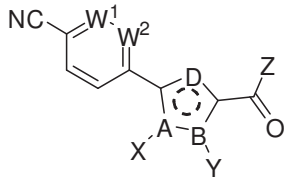
W^1 and W^2 are independently chosen from N, C-H, or C-F;

X is chosen from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclylalkyl, optionally substituted aralkyl, or optionally substituted heteroarylalkyl;

Y is chosen from hydrogen, halogen, optionally substituted alkyl, optionally substituted cycloalkyl, or optionally substituted cycloalkylalkyl; and

Z is chosen from an optionally substituted *N*-heterocyclyl, optionally substituted -N(H)-heterocyclylalkyl, optionally substituted -N(Me)-heterocyclylalkyl, or $–N(R^3)_2$, wherein each R^3 is independently chosen from hydrogen or optionally substituted alkyl.

[0007b] One embodiment provides a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof,



(I)

wherein,

A is C; B is N; and D is CH; or A is N; B is C; and D is N;

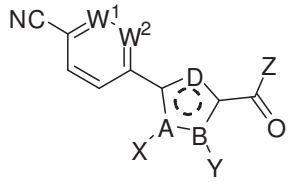
W^1 and W^2 are independently chosen from N, C-H, or C-F;

X is chosen from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclylalkyl, optionally substituted aralkyl, or optionally substituted heteroarylalkyl;

Y is chosen from hydrogen, halogen, optionally substituted alkyl, optionally substituted cycloalkyl, or optionally substituted cycloalkylalkyl; and

Z is chosen from an optionally substituted *N*-heterocyclyl, optionally substituted -N(H)-heterocyclylalkyl, optionally substituted -N(Me)-heterocyclylalkyl, or $-N(R^3)_2$, wherein each R^3 is independently chosen from hydrogen or optionally substituted alkyl, and a pharmaceutically acceptable excipient.

[0007c] One embodiment provides a use of a compound of Formula (I)



(I)

wherein,

A is C; B is N; and D is CH; or A is N; B is C; and D is N;

W^1 and W^2 are independently chosen from N, C-H, or C-F;

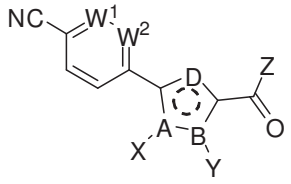
X is chosen from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclylalkyl, optionally substituted aralkyl, or optionally substituted heteroarylalkyl;

Y is chosen from hydrogen, halogen, optionally substituted alkyl, optionally substituted cycloalkyl, or optionally substituted cycloalkylalkyl; and

Z is chosen from an optionally substituted *N*-heterocyclyl, optionally substituted -N(H)-heterocyclylalkyl, optionally substituted -N(Me)-heterocyclylalkyl, or $–N(R^3)_2$, wherein

each R^3 is independently chosen from hydrogen or optionally substituted alkyl, in the manufacture of a medicament for regulating gene transcription in a cell comprising inhibiting lysine-specific demethylase 1 activity.

[0007d] One embodiment provides a use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof,



(I)

wherein,

A is C; B is N; and D is CH; or A is N; B is C; and D is N;

W^1 and W^2 are independently chosen from N, C-H, or C-F;

X is chosen from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclylalkyl, optionally substituted aralkyl, or optionally substituted heteroarylalkyl;

Y is chosen from hydrogen, halogen, optionally substituted alkyl, optionally substituted cycloalkyl, or optionally substituted cycloalkylalkyl; and

Z is chosen from an optionally substituted *N*-heterocyclyl, optionally substituted -N(H)-heterocyclylalkyl, optionally substituted -N(Me)-heterocyclylalkyl, or $–N(R^3)_2$, wherein each R^3 is independently chosen from hydrogen or optionally substituted alkyl,

in the manufacture of a medicament for treating acute myeloid leukemia, breast or prostate cancer in a patient in need thereof.

INCORPORATION BY REFERENCE

[0008] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

DETAILED DESCRIPTION OF THE INVENTION

[0009] As used herein and in the appended claims, the singular forms "a," "and," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an agent" includes a plurality of such agents, and reference to "the cell" includes reference to one or more cells (or to a plurality of cells) and equivalents thereof known to those skilled in the art, and so forth. When ranges are used herein for physical properties, such as molecular weight, or chemical properties, such as chemical formulae, all combinations and subcombinations of ranges and specific embodiments therein are intended to be included. The term "about" when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range may vary between 1% and 15% of the stated number or numerical range. The term "comprising" (and related terms such as "comprise" or "comprises" or "having" or "including") is not intended to exclude that in other certain embodiments, for example, an embodiment of any composition of matter,

composition, method, or process, or the like, described herein, may "consist of" or "consist essentially of" the described features.

Definitions

[0010] As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated below.

[0011] "Amino" refers to the $-NH_2$ radical.

[0012] "Cyano" refers to the -CN radical.

[0013] "Nitro" refers to the $-NO_2$ radical.

[0014] "Oxa" refers to the -O- radical.

[0015] "Oxo" refers to the =O radical.

[0016] "Thioxo" refers to the =S radical.

[0017] "Imino" refers to the =N-H radical.

[0018] "Oximo" refers to the =N-OH radical.

[0019] "Hydrazino" refers to the $=N-NH_2$ radical.

[0020] "Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from 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 one to five carbon atoms (*e.g.*, C_1-C_5 alkyl). In other embodiments, an alkyl comprises one to four carbon atoms (*e.g.*, C_1-C_4 alkyl). In other embodiments, an alkyl comprises one to three carbon atoms (*e.g.*, C_1-C_3 alkyl). In other embodiments, an alkyl comprises one to two carbon atoms (*e.g.*, C_1-C_2 alkyl). In other embodiments, an alkyl comprises one carbon atom (*e.g.*, C_1 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). In other embodiments, an alkyl comprises two to five carbon atoms (*e.g.*, C_2-C_5 alkyl). In other embodiments, an alkyl comprises three to five carbon atoms (*e.g.*, C_3-C_5 alkyl). In other embodiments, the alkyl group is selected from methyl, ethyl, 1-propyl (*n*-propyl), 1-methylethyl (*iso*-propyl), 1-butyl (*n*-butyl), 1-methylpropyl (*sec*-butyl), 2-methylpropyl (*iso*-butyl), 1,1-dimethylethyl (*tert*-butyl), 1-pentyl (*n*-pentyl). The alkyl is attached to the rest of the molecule by a single bond. Unless stated otherwise specifically in the specification, an alkyl group is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilanyl, $-OR^a$, -

SR^a, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-OC(O)-N(R^a)_2$, $-N(R^a)C(O)R^a$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tR^a$ (where t is 1 or 2) and $-S(O)_tN(R^a)_2$ (where t is 1 or 2) where each R^a is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, carbocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), carbocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl).

[0021] "Alkoxy" refers to a radical bonded through an oxygen atom of the formula –O-alkyl, where alkyl is an alkyl chain as defined above.

[0022] "Alkenyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one carbon-carbon double bond, and having from two to twelve carbon atoms. In certain embodiments, an alkenyl comprises two to eight carbon atoms. In other embodiments, an alkenyl comprises two to four carbon atoms. 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. Unless stated otherwise specifically in the specification, an alkenyl group is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-OC(O)-N(R^a)_2$, $-N(R^a)C(O)R^a$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tR^a$ (where t is 1 or 2) and $-S(O)_tN(R^a)_2$ (where t is 1 or 2) where each R^a is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, carbocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), carbocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted

with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl).

[0023] "Alkynyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one carbon-carbon triple bond, having from two to twelve carbon atoms. In certain embodiments, an alkynyl comprises two to eight carbon atoms. In other embodiments, an alkynyl comprises two to six carbon atoms. In other embodiments, an alkynyl comprises two to four carbon atoms. The alkynyl is attached to the rest of the molecule by a single bond, for example, ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like. Unless stated otherwise specifically in the specification, an alkynyl group is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-OC(O)-N(R^a)_2$, $-N(R^a)C(O)R^a$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tR^a$ (where t is 1 or 2) and $-S(O)_tN(R^a)_2$ (where t is 1 or 2) where each R^a is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, carbocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), carbocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl).

[0024] "Alkylene" or "alkylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing no unsaturation and having from one to twelve carbon atoms, for example, methylene, ethylene, propylene, *n*-butylene, and the like. The alkylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. The points of attachment of the alkylene chain to the rest of the molecule and to the radical group can be through one carbon in the alkylene chain or through any two carbons within the chain. In certain embodiments, an

alkylene comprises one to eight carbon atoms (*e.g.*, C_1-C_8 alkylene). In other embodiments, an alkylene comprises one to five carbon atoms (*e.g.*, C_1-C_5 alkylene). In other embodiments, an alkylene comprises one to four carbon atoms (*e.g.*, C_1-C_4 alkylene). In other embodiments, an alkylene comprises one to three carbon atoms (*e.g.*, C_1-C_3 alkylene). In other embodiments, an alkylene comprises one to two carbon atoms (*e.g.*, C_1-C_2 alkylene). In other embodiments, an alkylene comprises one carbon atom (*e.g.*, C_1 alkylene). In other embodiments, an alkylene comprises five to eight carbon atoms (*e.g.*, C_5-C_8 alkylene). In other embodiments, an alkylene comprises two to five carbon atoms (*e.g.*, C_2-C_5 alkylene). In other embodiments, an alkylene comprises three to five carbon atoms (*e.g.*, C_3-C_5 alkylene). Unless stated otherwise specifically in the specification, an alkylene chain is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-OC(O)-N(R^a)_2$, $-N(R^a)C(O)R^a$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tR^a$ (where t is 1 or 2) and $-S(O)_tN(R^a)_2$ (where t is 1 or 2) where each R^a is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, carbocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), carbocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl).

[0025] "Alkynylene" or "alkynylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing at least one carbon-carbon triple bond, and having from two to twelve carbon atoms. The alkynylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. In certain embodiments, an alkynylene comprises two to eight carbon atoms (*e.g.*, C_2-C_8 alkynylene). In other embodiments, an alkynylene comprises two to five carbon atoms (*e.g.*, C_2-C_5 alkynylene). In other embodiments, an alkynylene comprises two to four carbon atoms (*e.g.*, C_2-C_4 alkynylene). In other embodiments, an alkynylene comprises

two to three carbon atoms (*e.g.*, C_2-C_3 alkynylene). In other embodiments, an alkynylene comprises two carbon atom (*e.g.*, C_2 alkylene). In other embodiments, an alkynylene comprises five to eight carbon atoms (*e.g.*, C_5-C_8 alkynylene). In other embodiments, an alkynylene comprises three to five carbon atoms (*e.g.*, C_3-C_5 alkynylene). Unless stated otherwise specifically in the specification, an alkynylene chain is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-OC(O)-N(R^a)_2$, $-N(R^a)C(O)R^a$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tR^a$ (where t is 1 or 2) and $-S(O)_tN(R^a)_2$ (where t is 1 or 2) where each R^a is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, carbocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), carbocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl).

[0026] "Aryl" 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 from five 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. The ring system from which aryl groups are derived include, but are not limited to, groups such as benzene, fluorene, indane, indene, tetralin and naphthalene. Unless stated otherwise specifically in the specification, the term "aryl" or the prefix "ar-" (such as in "aralkyl") is meant to include aryl radicals optionally substituted by one or more substituents independently selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted carbocyclyl, optionally substituted carbocyclylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally

substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2) and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, cycloalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), cycloalkylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), each R^b is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^c is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

[0027] "Aralkyl" refers to a radical of the formula $-R^c$-aryl where R^c is an alkylene chain as defined above, for example, methylene, ethylene, and the like. The alkylene chain part of the aralkyl radical is optionally substituted as described above for an alkylene chain. The aryl part of the aralkyl radical is optionally substituted as described above for an aryl group.

[0028] "Aralkenyl" refers to a radical of the formula $-R^d$-aryl where R^d is an alkenylene chain as defined above. The aryl part of the aralkenyl radical is optionally substituted as described above for an aryl group. The alkenylene chain part of the aralkenyl radical is optionally substituted as defined above for an alkenylene group.

[0029] "Aralkynyl" refers to a radical of the formula $-R^e$-aryl, where R^e is an alkynylene chain as defined above. The aryl part of the aralkynyl radical is optionally substituted as described above for an aryl group. The alkynylene chain part of the aralkynyl radical is optionally substituted as defined above for an alkynylene chain.

[0030] "Aralkoxy" refers to a radical bonded through an oxygen atom of the formula $-O-R^c$-aryl where R^c is an alkylene chain as defined above, for example, methylene, ethylene, and the like. The alkylene chain part of the aralkyl radical is optionally

substituted as described above for an alkylene chain. The aryl part of the aralkyl radical is optionally substituted as described above for an aryl group.

[0031] "Carbocyclyl" refers to a stable non-aromatic monocyclic or polycyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, which includes fused or bridged ring systems, having from three to fifteen carbon atoms. In certain embodiments, a carbocyclyl comprises three to ten carbon atoms. In other embodiments, a carbocyclyl comprises five to seven carbon atoms. The carbocyclyl is attached to the rest of the molecule by a single bond. Carbocyclyl may be saturated, (*i.e.*, containing single C-C bonds only) or unsaturated (*i.e.*, containing one or more double bonds or triple bonds.) A fully saturated carbocyclyl radical is also referred to as "cycloalkyl." Examples of monocyclic cycloalkyls include, *e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. An unsaturated carbocyclyl is also referred to as "cycloalkenyl." Examples of monocyclic cycloalkenyls include, *e.g.*, cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. Polycyclic carbocyclyl radicals include, for example, adamantyl, norbornyl (*i.e.*, bicyclo[2.2.1]heptanyl), norbornenyl, decalinyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl, and the like. Unless otherwise stated specifically in the specification, the term "carbocyclyl" is meant to include carbocyclyl radicals that are optionally substituted by one or more substituents independently selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted carbocyclyl, optionally substituted carbocyclylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2) and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, cycloalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), cycloalkylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted

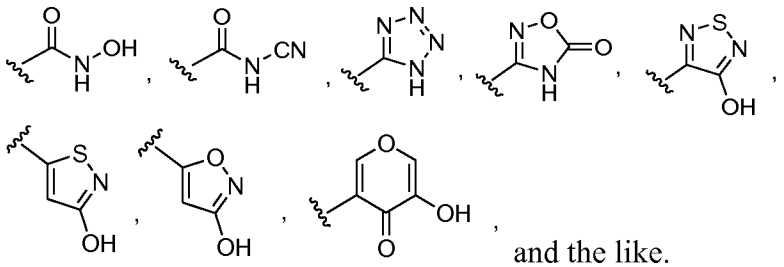
with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), each R^b is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^c is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

[0032] "Carbocyclylalkyl" refers to a radical of the formula $-R^c$-carbocyclyl where R^c is an alkylene chain as defined above. The alkylene chain and the carbocyclyl radical is optionally substituted as defined above.

[0033] "Carbocyclylalkynyl" refers to a radical of the formula $-R^c$-carbocyclyl where R^c is an alkynylene chain as defined above. The alkynylene chain and the carbocyclyl radical is optionally substituted as defined above.

[0034] "Carbocyclylalkoxy" refers to a radical bonded through an oxygen atom of the formula $-O-R^c$-carbocyclyl where R^c is an alkylene chain as defined above. The alkylene chain and the carbocyclyl radical is optionally substituted as defined above.

[0035] As used herein, "carboxylic acid bioisostere" refers to a functional group or moiety that exhibits similar physical, biological and/or chemical properties as a carboxylic acid moiety. Examples of carboxylic acid bioisosteres include, but are not limited to,



and the like.

[0036] "Halo" or "halogen" refers to bromo, chloro, fluoro or iodo substituents.

[0037] "Fluoroalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more fluoro radicals, as defined above, for example, trifluoromethyl, difluoromethyl, fluoromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and the like. The alkyl part of the fluoroalkyl radical may be optionally substituted as defined above for an alkyl group.

[0038] "Heterocyclyl" refers to a stable 3- to 18-membered non-aromatic ring radical that comprises two to twelve carbon atoms and from one to six heteroatoms selected from nitrogen, oxygen and sulfur. Unless stated otherwise specifically in the specification, the heterocyclyl radical is a monocyclic, bicyclic, tricyclic or tetracyclic

ring system, which may include fused or bridged ring systems. The heteroatoms in the heterocyclyl radical may be optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heterocyclyl radical is partially or fully saturated. The heterocyclyl may be attached to the rest of the molecule through any atom of the ring(s). Examples of such heterocyclyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, and 1,1-dioxo-thiomorpholinyl. Unless stated otherwise specifically in the specification, the term "heterocyclyl" is meant to include heterocyclyl radicals as defined above that are optionally substituted by one or more substituents selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted carbocyclyl, optionally substituted carbocyclylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2) and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, cycloalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), cycloalkylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), each R^b is independently a direct bond or a straight or branched alkylene or alkenylene chain, and

R^c is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

[0039] "*N*-heterocyclyl" or "N-attached heterocyclyl" refers to a heterocyclyl radical as defined above containing at least one nitrogen and where the point of attachment of the heterocyclyl radical to the rest of the molecule is through a nitrogen atom in the heterocyclyl radical. An *N*-heterocyclyl radical is optionally substituted as described above for heterocyclyl radicals. Examples of such *N*-heterocyclyl radicals include, but are not limited to, 1-morpholinyl, 1-piperidinyl, 1-piperazinyl, 1-pyrrolidinyl, pyrazolidinyl, imidazolinyl, and imidazolidinyl.

[0040] "*C*-heterocyclyl" or "C-attached heterocyclyl" refers to a heterocyclyl radical as defined above containing at least one heteroatom and where the point of attachment of the heterocyclyl radical to the rest of the molecule is through a carbon atom in the heterocyclyl radical. A *C*-heterocyclyl radical is optionally substituted as described above for heterocyclyl radicals. Examples of such *C*-heterocyclyl radicals include, but are not limited to, 2-morpholinyl, 2- or 3- or 4-piperidinyl, 2-piperazinyl, 2- or 3-pyrrolidinyl, and the like.

[0041] "Heterocyclylalkyl" refers to a radical of the formula $-R^c$-heterocyclyl where R^c is an alkylene chain as defined above. If the heterocyclyl is a nitrogen-containing heterocyclyl, the heterocyclyl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heterocyclylalkyl radical is optionally substituted as defined above for an alkylene chain. The heterocyclyl part of the heterocyclylalkyl radical is optionally substituted as defined above for a heterocyclyl group.

[0042] "Heterocyclylalkoxy" refers to a radical bonded through an oxygen atom of the formula $-O-R^c$-heterocyclyl where R^c is an alkylene chain as defined above. If the heterocyclyl is a nitrogen-containing heterocyclyl, the heterocyclyl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heterocyclylalkoxy radical is optionally substituted as defined above for an alkylene chain. The heterocyclyl part of the heterocyclylalkoxy radical is optionally substituted as defined above for a heterocyclyl group.

[0043] "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 heteroaryls include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzindolyl, 1,3-benzodioxolyl, benzofuranyl, benzooxazolyl, benzo[d]thiazolyl, benzothiadiazolyl, benzo[*b*][1,4]dioxepinyl, benzo[b][1,4]oxazinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzothieno[3,2-d]pyrimidinyl, benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, cyclopenta[d]pyrimidinyl, 6,7-dihydro-5H-cyclopenta[4,5]thieno[2,3-d]pyrimidinyl, 5,6-dihydrobenzo[h]quinazolinyl, 5,6-dihydrobenzo[h]cinnolinyl, 6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, furo[3,2-c]pyridinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyrimidinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridazinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridinyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, 5,8-methano-5,6,7,8-tetrahydroquinazolinyl, naphthyridinyl, 1,6-naphthyridinonyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 5,6,6a,7,8,9,10,10a-octahydrobenzo[h]quinazolinyl, 1-phenyl-1*H*-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyrazolo[3,4-d]pyrimidinyl, pyridinyl, pyrido[3,2-d]pyrimidinyl, pyrido[3,4-d]pyrimidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, 5,6,7,8-tetrahydroquinazolinyl, 5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidinyl, 6,7,8,9-tetrahydro-5H-cyclohepta[4,5]thieno[2,3-d]pyrimidinyl, 5,6,7,8-tetrahydropyrido[4,5-c]pyridazinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, thieno[2,3-d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, thieno[2,3-c]pridinyl, and thiophenyl (*i.e.* thienyl). Unless stated otherwise specifically in the specification, the term "heteroaryl" is meant to include heteroaryl radicals as defined above which are optionally substituted by one or more substituents selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl,

optionally substituted aralkynyl, optionally substituted carbocyclyl, optionally substituted carbocyclylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2) and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, cycloalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), cycloalkylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), each R^b is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^c is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

[0044] "*N*-heteroaryl" refers to a heteroaryl radical as defined above containing at least one nitrogen and where the point of attachment of the heteroaryl radical to the rest of the molecule is through a nitrogen atom in the heteroaryl radical. An *N*-heteroaryl radical is optionally substituted as described above for heteroaryl radicals.

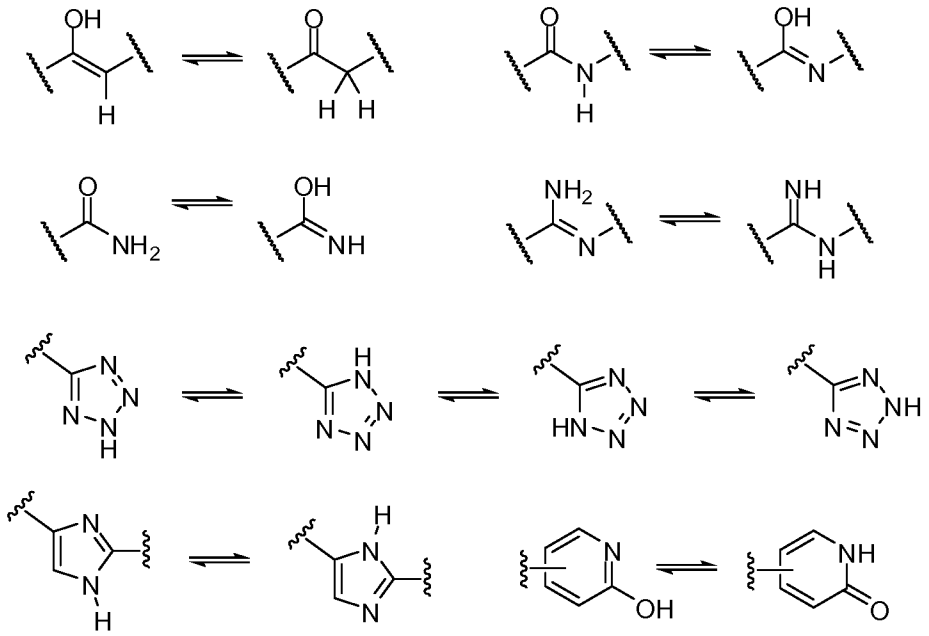
[0045] "*C*-heteroaryl" refers to a heteroaryl radical as defined above and where the point of attachment of the heteroaryl radical to the rest of the molecule is through a carbon atom in the heteroaryl radical. A *C*-heteroaryl radical is optionally substituted as described above for heteroaryl radicals.

[0046] "Heteroarylalkyl" refers to a radical of the formula $-R^c$-heteroaryl, where R^c is an alkylene chain as defined above. If the heteroaryl is a nitrogen-containing heteroaryl, the heteroaryl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heteroarylalkyl radical is optionally substituted as defined above for an alkylene chain. The heteroaryl part of the heteroarylalkyl radical is optionally substituted as defined above for a heteroaryl group.

[0047] "Heteroarylalkoxy" refers to a radical bonded through an oxygen atom of the formula –O-R^c-heteroaryl, where R^c is an alkylene chain as defined above. If the heteroaryl is a nitrogen-containing heteroaryl, the heteroaryl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heteroarylalkoxy radical is optionally substituted as defined above for an alkylene chain. The heteroaryl part of the heteroarylalkoxy radical is optionally substituted as defined above for a heteroaryl group.

[0048] The compounds disclosed herein may contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)-. Unless stated otherwise, it is intended that all stereoisomeric forms of the compounds disclosed herein are contemplated by this disclosure. When the compounds described herein contain alkene double bonds, and unless specified otherwise, it is intended that this disclosure includes both *E* and Z geometric isomers (*e.g., cis* or *trans*.) Likewise, all possible isomers, as well as their racemic and optically pure forms, and all tautomeric forms are also intended to be included. The term "geometric isomer" refers to *E* or Z geometric isomers (*e.g., cis* or *trans*) of an alkene double bond. The term "positional isomer" refers to structural isomers around a central ring, such as *ortho*-, *meta*-, and *para*- isomers around a benzene ring.

[0049] A "tautomer" refers to a molecule wherein a proton shift from one atom of a molecule to another atom of the same molecule is possible. The compounds presented herein may, in certain embodiments, exist as tautomers. In circumstances where tautomerization is possible, a chemical equilibrium of the tautomers will exist. The exact ratio of the tautomers depends on several factors, including physical state, temperature, solvent, and pH. Some examples of tautomeric equilibrium include:



[0050] "Optional" or "optionally" means that a subsequently described event or circumstance may or may not occur and that the description includes instances when the event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" means that the aryl radical may or may not be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution.

[0051] "Pharmaceutically acceptable salt" includes both acid and base addition salts. A pharmaceutically acceptable salt of any one of the substituted heterocyclic derivative 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.

[0052] "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.

[0053] "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*.

[0054] As used herein, "treatment" or "treating," or "palliating" or "ameliorating" are used interchangeably herein. These terms refers to an approach for obtaining beneficial or desired results including but not limited to therapeutic benefit and/or a prophylactic benefit. By "therapeutic benefit" is meant eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the

underlying disorder such that an improvement is observed in the patient, notwithstanding that the patient may still be afflicted with the underlying disorder. For prophylactic benefit, the compositions may be administered to a patient at risk of developing a particular disease, or to a patient reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease may not have been made.

[0055] "Prodrug" is meant to indicate a compound that may be converted under physiological conditions or by solvolysis to a biologically active compound described herein. Thus, the term "prodrug" refers to a precursor of a biologically active compound that is pharmaceutically acceptable. A prodrug may be inactive when administered to a subject, but is converted *in vivo* to an active compound, for example, by hydrolysis. The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism (*see, e.g.,* Bundgard, H., Design of Prodrugs (1985), pp. 7-9, 21-24 (Elsevier, Amsterdam).

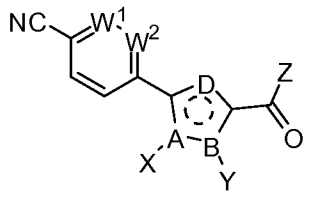
[0056] A discussion of prodrugs is provided in Higuchi, T., et al., "Pro-drugs as Novel Delivery Systems," A.C.S. Symposium Series, Vol. 14, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated in full by reference herein.

[0057] The term "prodrug" is also meant to include any covalently bonded carriers, which release the active compound *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of an active compound, as described herein, may be prepared by modifying functional groups present in the active compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent active compound. Prodrugs include compounds wherein a hydroxy, amino or mercapto group is bonded to any group that, when the prodrug of the active compound is administered to a mammalian subject, cleaves to form a free hydroxy, free amino or free mercapto group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol or amine functional groups in the active compounds and the like.

Substituted Heterocyclic Derivative Compounds

[0058] Substituted heterocyclic derivative compounds are described herein that are lysine specific demethylase-1 inhibitors. These compounds, and compositions comprising these compounds, are useful for the treatment of cancer and neoplastic disease. The compounds described herein are useful for treating prostate cancer, breast cancer, bladder cancer, lung cancer and/or melanoma and the like.

[0059] One embodiment provides a compound having the structure of Formula (I), or a pharmaceutically acceptable salt thereof,



(I)

wherein,

A is C; B is N; and D is C-R^3; or A is N; B is C; and D is N;

each R^3 is independently chosen from hydrogen or optionally substituted alkyl;

W^1 and W^2 are independently chosen from N, C-H, or C-F;

X is chosen from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted alkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclylalkyl, optionally substituted aralkyl, or optionally substituted heteroarylalkyl;

Y is chosen from hydrogen, halogen, optionally substituted alkyl, optionally substituted cycloalkyl, or optionally substituted cycloalkylalkyl; and

Z is chosen from an optionally substituted *N*-heterocyclyl, optionally substituted -N(H)-heterocyclylalkyl, optionally substituted -N(Me)-heterocyclylalkyl, or $-N(R^3)_2$.

[0060] Another embodiment provides the compound or pharmaceutically acceptable salt of Formula (I), wherein A is N; B is C; and D is N.

[0061] Another embodiment provides the compound or pharmaceutically acceptable salt of Formula (I), wherein A is C; B is N; and D is C-R^3.

[0062] Another embodiment provides the compound or pharmaceutically acceptable salt of Formula (I), wherein A is C; B is N; and D is C-R^3, and R^3 is hydrogen.

[0063] Another embodiment provides the compound or pharmaceutically acceptable salt of Formula (I), wherein A is C; B is N; and D is C-R^3, and R^3 is optionally substituted alkyl.

[0064] Another embodiment provides the compound or pharmaceutically acceptable salt of Formula (I), wherein W^2 is C-H. Another embodiment provides the compound or pharmaceutically acceptable salt of Formula (I), wherein W^1 is C-F. Another embodiment provides the compound or pharmaceutically acceptable salt of Formula (I), wherein W^1 is C-H. Another embodiment provides the compound or pharmaceutically acceptable salt of Formula (I), wherein W^1 is N.

[0065] Another embodiment provides the compound or pharmaceutically acceptable salt of Formula (I), wherein X is optionally substituted aryl. Another embodiment provides the compound or pharmaceutically acceptable salt of Formula (I), wherein X is optionally substituted aryl and the optionally substituted aryl is an optionally substituted phenyl.

[0066] Another embodiment provides the compound or pharmaceutically acceptable salt of Formula (I), wherein X is optionally substituted heteroaryl. Another embodiment provides the compound or pharmaceutically acceptable salt of Formula (I), wherein X is optionally substituted heteroaryl and the optionally substituted heteroaryl is chosen from an optionally substituted pyridinyl, optionally substituted pyrimidinyl, optionally substituted pyrazinyl, optionally substituted pyrazolyl, optionally substituted indazolyl, optionally substituted azaindazolyl, optionally substituted isoindazolyl, optionally substituted indolyl, or optionally substituted azaindolyl.

[0067] Another embodiment provides the compound or pharmaceutically acceptable salt of Formula (I), wherein Z is an optionally substituted *N*-heterocyclyl. Another embodiment provides the compound or pharmaceutically acceptable salt of Formula (I), wherein Z is an optionally substituted *N*-heterocyclyl and the optionally substituted *N*-heterocyclyl is a 4-, 5-, 6-, or 7-membered N-heterocyclyl. Another embodiment provides the compound or pharmaceutically acceptable salt of Formula (I), wherein Z is an optionally substituted *N*-heterocyclyl, and the optionally substituted *N*-heterocyclyl is a 6-membered N-heterocyclyl. Another embodiment provides the compound or pharmaceutically acceptable salt of Formula (I), wherein Z is an optionally substituted *N*-heterocyclyl, the optionally substituted *N*-heterocyclyl is an optionally substituted piperidine. Another embodiment provides the compound or pharmaceutically acceptable salt of Formula (I), wherein Z is an optionally substituted *N*-heterocyclyl, the optionally substituted *N*-heterocyclyl is an optionally substituted piperidine, and the optionally substituted piperidine is an optionally substituted 3-aminopiperidine. Another embodiment provides the compound or pharmaceutically acceptable salt of Formula (I), wherein Z is an optionally substituted *N*-heterocyclyl and the optionally substituted *N*-heterocyclyl is a 5-membered N-heterocyclyl. Another embodiment provides the compound or pharmaceutically acceptable salt of Formula (I), wherein Z is an optionally substituted *N*-heterocyclyl, and the optionally substituted *N*-heterocyclyl is an optionally substituted pyrrolidine. Another embodiment provides the compound or pharmaceutically acceptable salt of Formula (I), wherein Z is an optionally substituted *N*-

heterocyclyl, the optionally substituted *N*-heterocyclyl is an optionally substituted pyrrolidine and the optionally substituted pyrrolidine is an optionally substituted 3-aminopyrrolidine.

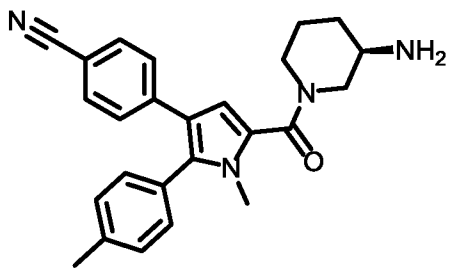
[0068] Another embodiment provides the compound or pharmaceutically acceptable salt of Formula (I), wherein Y is hydrogen. Another embodiment provides the compound or pharmaceutically acceptable salt of Formula (I), wherein Y is halogen.

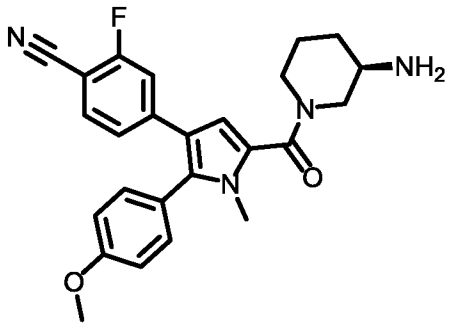
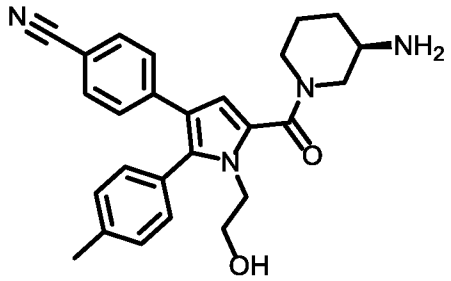
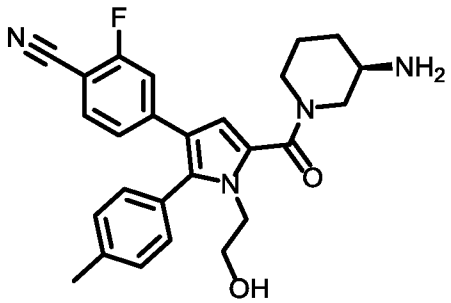
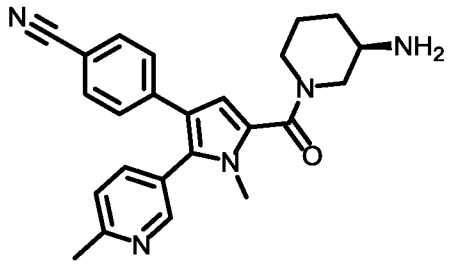
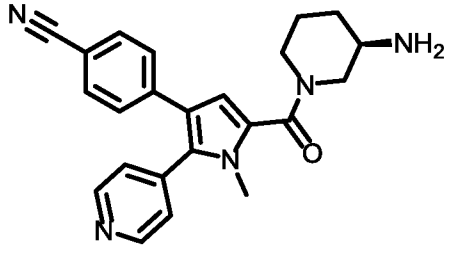
[0069] Another embodiment provides the compound or pharmaceutically acceptable salt of Formula (I), wherein Y is optionally substituted alkyl. Another embodiment provides the compound or pharmaceutically acceptable salt of Formula (I), wherein Y is optionally substituted alkyl, and the optionally substituted alkyl is an optionally substituted C_1-C_3 alkyl. Another embodiment provides the compound or pharmaceutically acceptable salt of Formula (I), wherein Y is optionally substituted alkyl, and the optionally substituted alkyl is an optionally substituted C_1 alkyl. Another embodiment provides the compound or pharmaceutically acceptable salt of Formula (I), wherein Y is optionally substituted alkyl, and the optionally substituted alkyl is a methyl group.

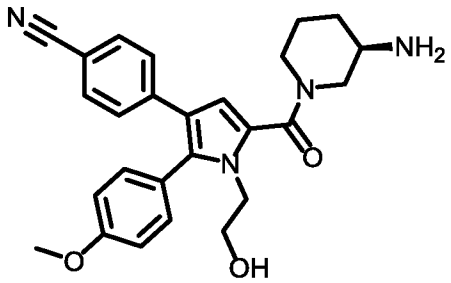
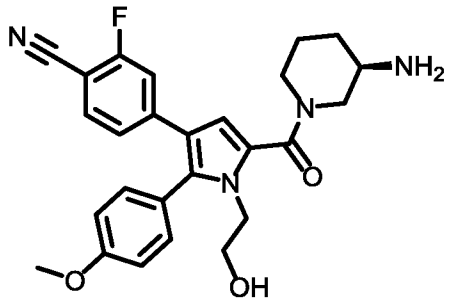
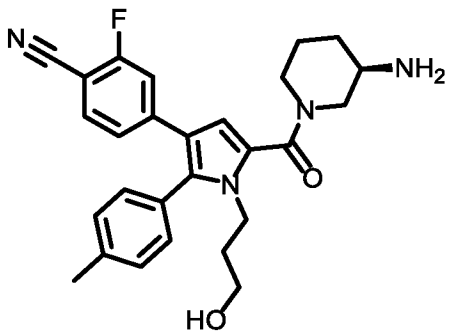
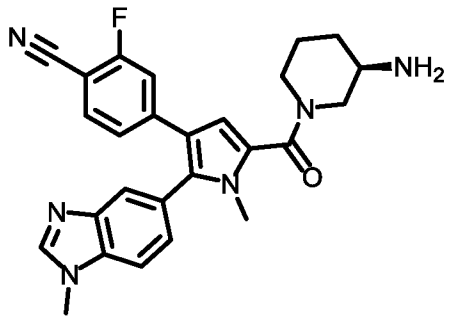
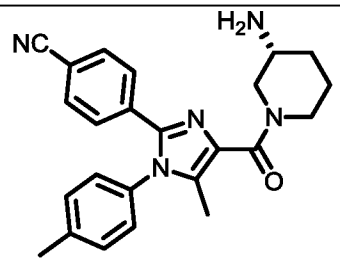
[0070] Another embodiment provides the compound or pharmaceutically acceptable salt of Formula (I), wherein Y is optionally substituted cycloalkyl. Another embodiment provides the compound or pharmaceutically acceptable salt of Formula (I), wherein Y is optionally substituted cycloalkylalkyl.

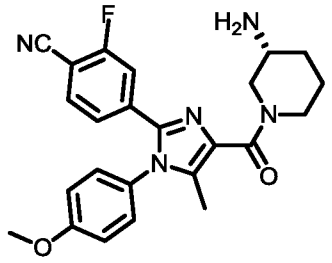
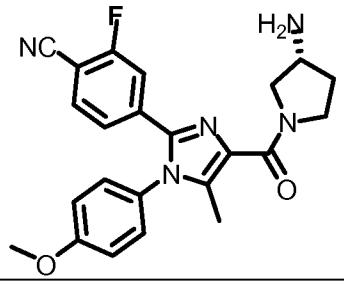
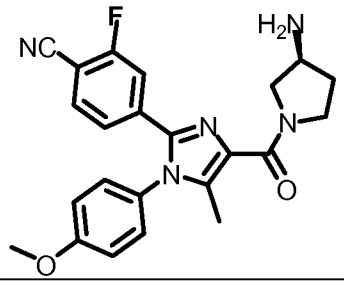
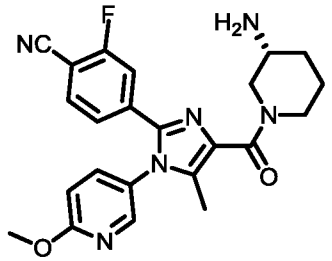
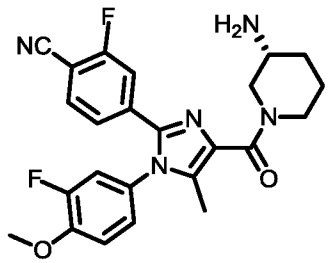
[0071] In some embodiments, the substituted heterocyclic derivative compound described herein has the structure provided in Table 1.

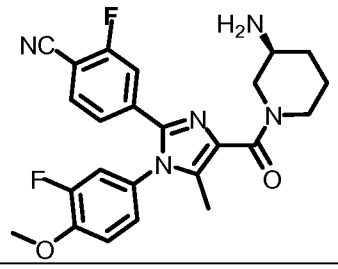
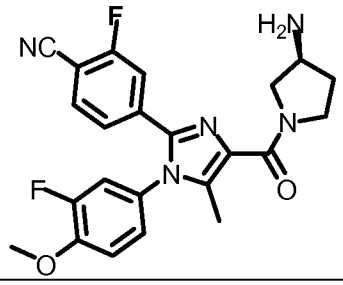
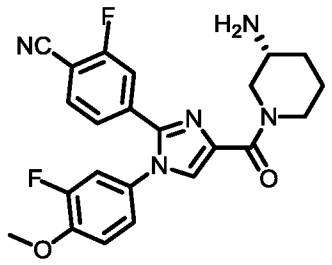
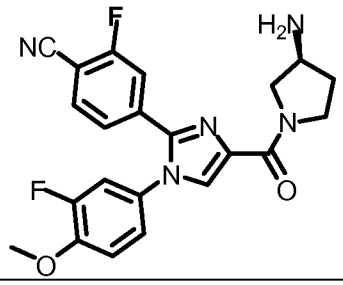
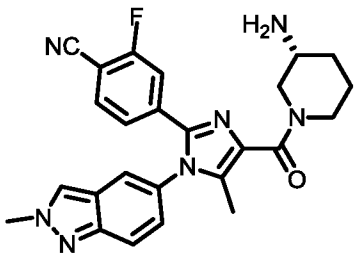
TABLE 1

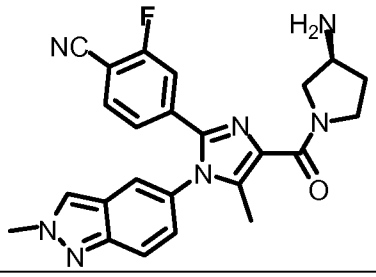
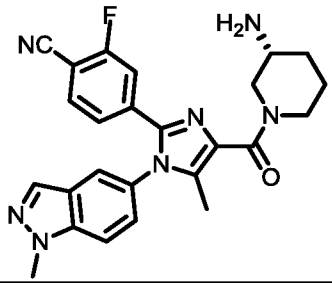
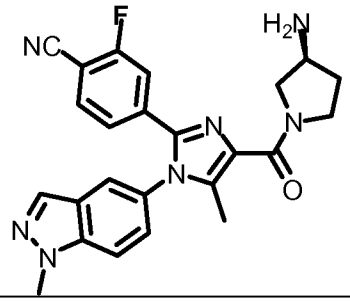
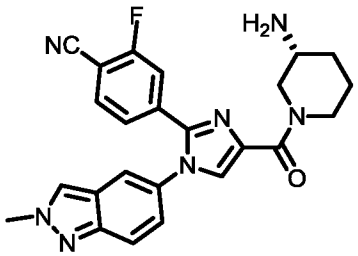
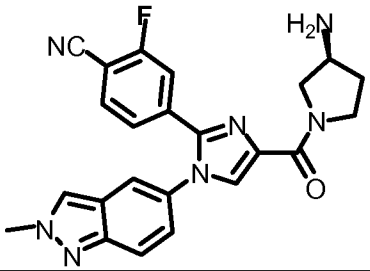
Chemical Synthesis Example	Structure	Name
1		4-[5-(3-(R)-amino-piperidine-1-carbonyl)-1-methyl-2-p-tolyl-1H-pyrrol-3-yl]-benzonitrile

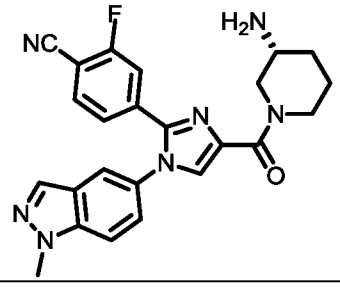
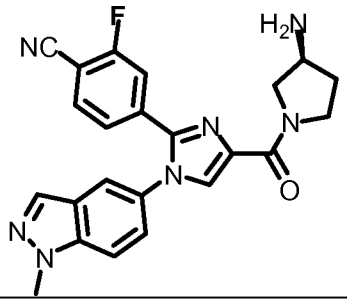
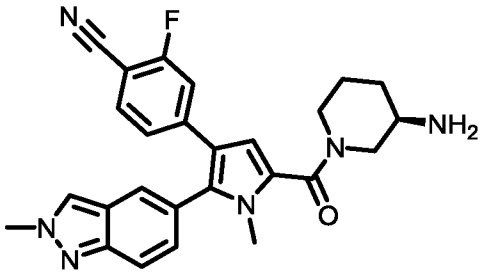
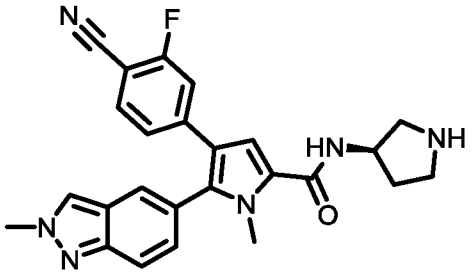
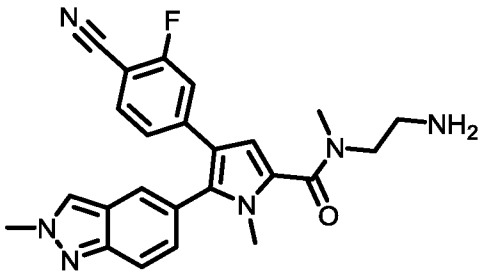
Chemical Synthesis Example	Structure	Name
2		4-[5-(3-(R)-amino-piperidine-1-carbonyl)-2-(4-methoxy-phenyl)-1-methyl-1H-pyrrol-3-yl]-2-fluoro-benzonitrile
3		4-[5-(3-(R)-amino-piperidine-1-carbonyl)-1-(2-hydroxy-ethyl)-2-p-tolyl-1H-pyrrol-3-yl]-benzonitrile
4		4-[5-(3-(R)-amino-piperidine-1-carbonyl)-1-(2-hydroxy-ethyl)-2-p-tolyl-1H-pyrrol-3-yl]-2-fluoro-benzonitrile
5		4-[5-(3-(R)-amino-piperidine-1-carbonyl)-1-methyl-2-(6-methyl-pyridin-3-yl)-1H-pyrrol-3-yl]-benzonitrile
6		4-[5-(3-(R)-amino-piperidine-1-carbonyl)-1-methyl-2-pyridin-4-yl-1H-pyrrol-3-yl]-benzonitrile

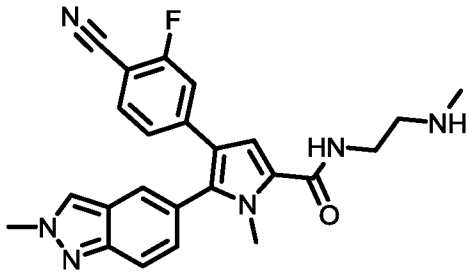
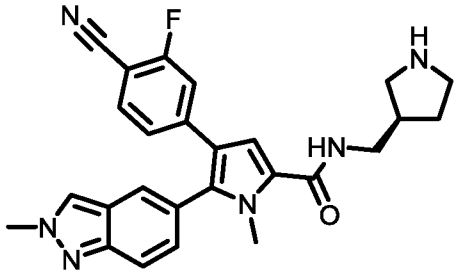
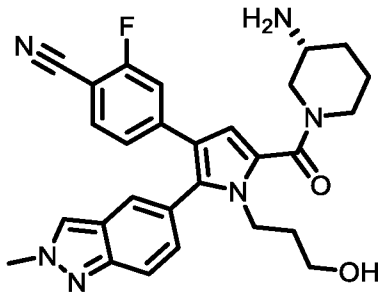
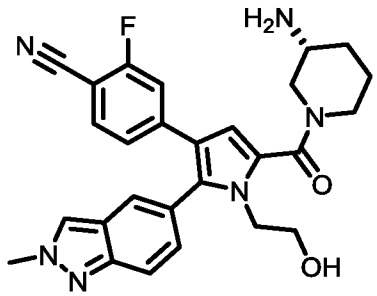
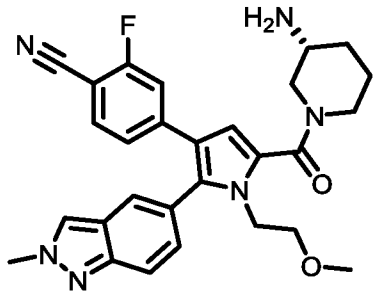
Chemical Synthesis Example	Structure	Name
7		4-[5-(3-(R)-amino-piperidine-1-carbonyl)-1-(2-hydroxy-ethyl)-2-(4-methoxy-phenyl)-1H-pyrrol-3-yl]-benzonitrile
8		4-[5-(3-(R)-amino-piperidine-1-carbonyl)-1-(2-hydroxy-ethyl)-2-(4-methoxy-phenyl)-1H-pyrrol-3-yl]-2-fluoro-benzonitrile
9		4-[5-(3-(R)-amino-piperidine-1-carbonyl)-1-(3-hydroxy-propyl)-2-(4-methoxy-phenyl)-1H-pyrrol-3-yl]-2-fluoro-benzonitrile
10		4-[5-(3-(R)-amino-piperidine-1-carbonyl)-1-methyl-2-(1-methyl-1H-benzoimidazol-5-yl)-1H-pyrrol-3-yl]-2-fluoro-benzonitrile
11		4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-5-methyl-1-(4-methylphenyl)imidazol-2-yl]benzonitrile

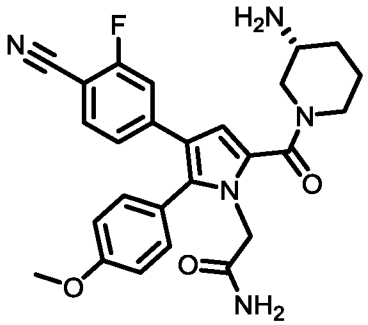
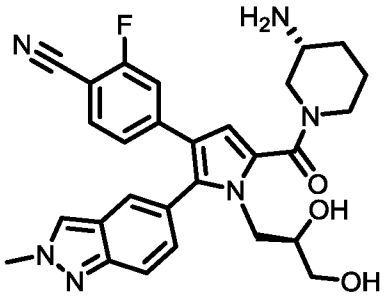
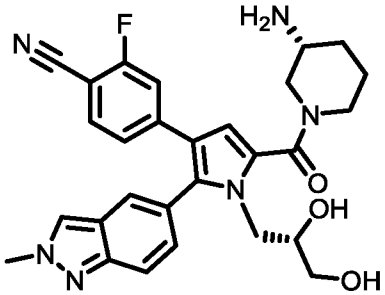
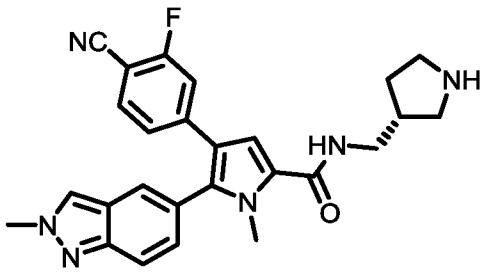
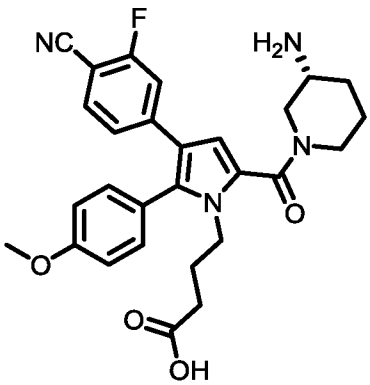
Chemical Synthesis Example	Structure	Name
12		4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-1-(4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile
13		4-[4-[(3R)-3-aminopyrrolidine-1-carbonyl]-1-(4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile
14		4-[4-[(3S)-3-aminopyrrolidine-1-carbonyl]-1-(4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile
15		4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-1-(6-methoxypyridin-3-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile
16		4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-1-(3-fluoro-4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile

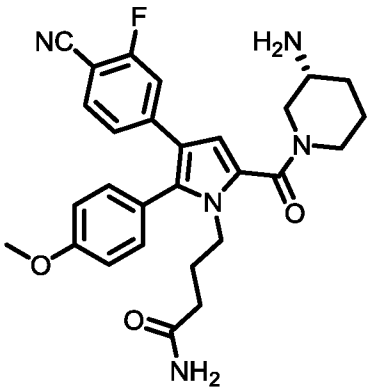
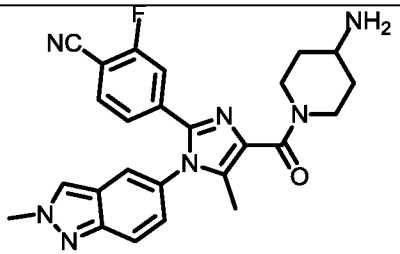
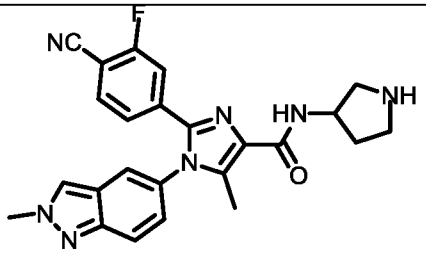
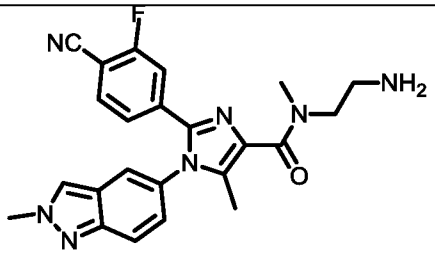
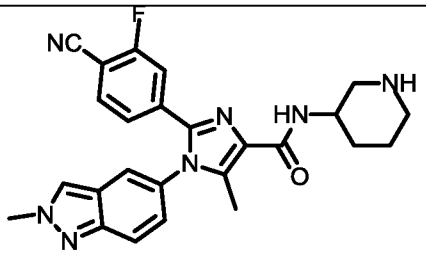
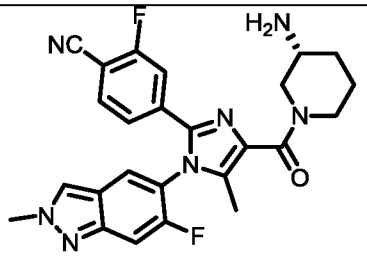
Chemical Synthesis Example	Structure	Name
17		4-[4-[(3S)-3-aminopiperidine-1-carbonyl]-1-(3-fluoro-4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile
18		4-[4-[(3S)-3-aminopyrrolidine-1-carbonyl]-1-(3-fluoro-4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile
19		4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-1-(3-fluoro-4-methoxyphenyl)imidazol-2-yl]-2-fluorobenzonitrile
20		4-[4-[(3S)-3-aminopyrrolidine-1-carbonyl]-1-(3-fluoro-4-methoxyphenyl)imidazol-2-yl]-2-fluorobenzonitrile
21		4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-5-methyl-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile

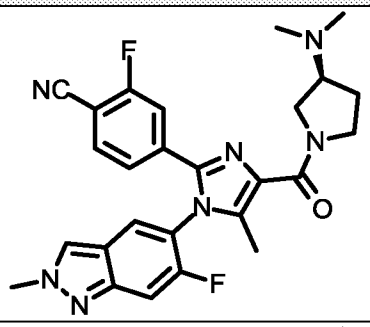
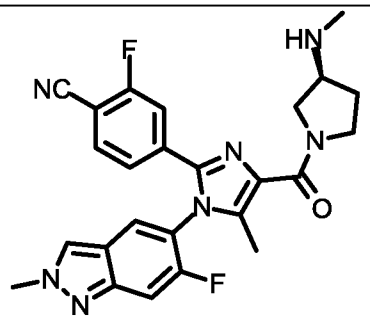
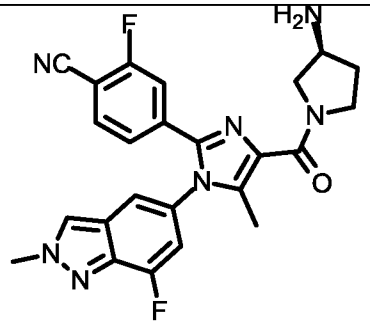
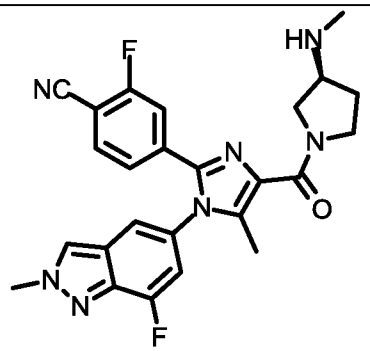
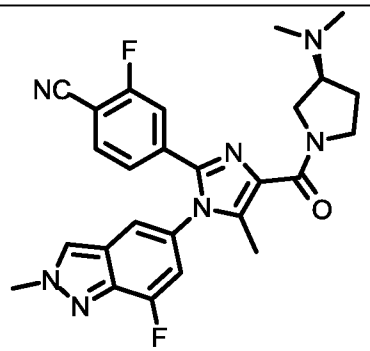
Chemical Synthesis Example	Structure	Name
22		4-[4-[(3S)-3-aminopyrrolidine-1-carbonyl]-5-methyl-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile
23		4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-5-methyl-1-(1-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile
24		4-[4-[(3S)-3-aminopyrrolidine-1-carbonyl]-5-methyl-1-(1-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile
25		4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile
26		4-[4-[(3S)-3-aminopyrrolidine-1-carbonyl]-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile

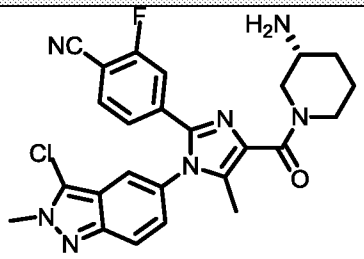
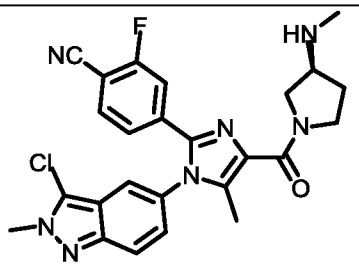
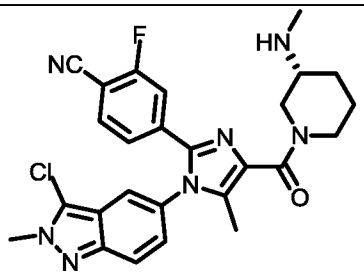
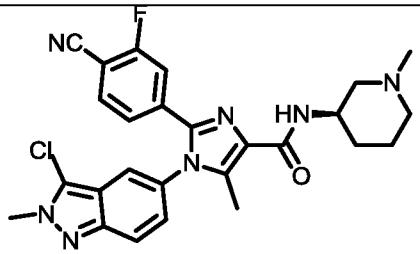
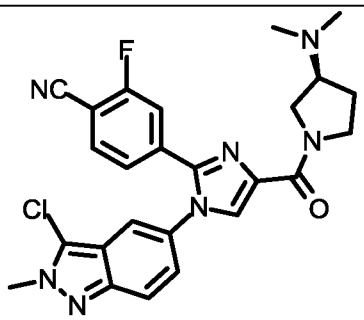
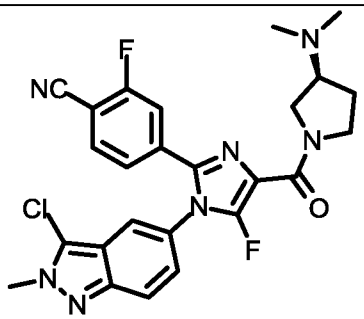
Chemical Synthesis Example	Structure	Name
27		4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-1-(1-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile
28		4-[4-[(3S)-3-aminopyrrolidine-1-carbonyl]-1-(1-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile
29		4-{5-[((3R)-3-aminopiperidyl)carbonyl]-1-methyl-2-(2-methyl(2H-indazol-5-yl))pyrrol-3-yl}-2-fluorobenzenecarbonitrile
30		N-((3R)pyrrolidin-3-yl)[4-(4-cyano-3-fluorophenyl)-1-methyl-5-(2-methyl(2H-indazol-5-yl))pyrrol-2-yl]carboxamide
31		N-(2-aminoethyl)[4-(4-cyano-3-fluorophenyl)-1-methyl-5-(2-methyl(2H-indazol-5-yl))pyrrol-2-yl]-N-methylcarboxamide

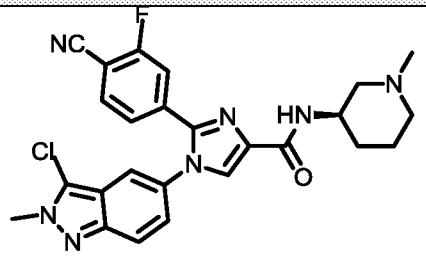
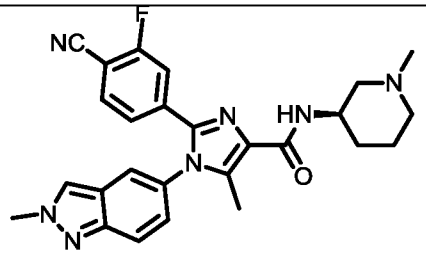
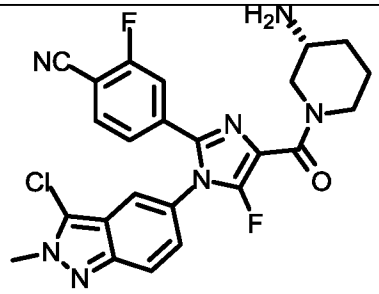
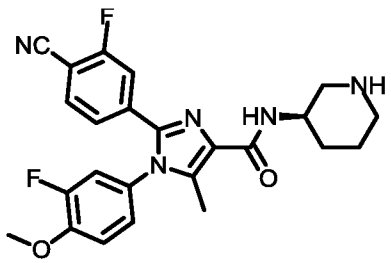
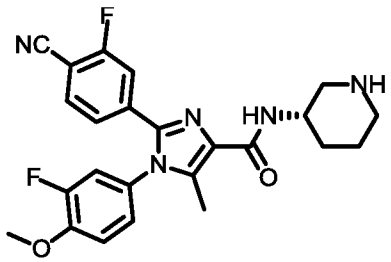
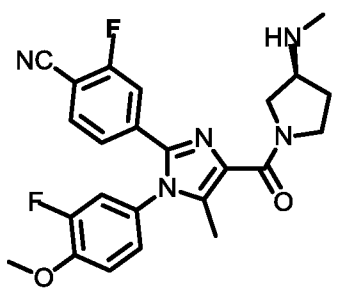
Chemical Synthesis Example	Structure	Name
32		[4-(4-cyano-3-fluorophenyl)-1-methyl-5-(2-methyl(2H-indazol-5-yl))pyrrol-2-yl]-N-[2-(methylamino)ethyl]carboxamide
33		N-[((3S)pyrrolidin-3-yl)methyl][4-(4-cyano-3-fluorophenyl)-1-methyl-5-(2-methyl(2H-indazol-5-yl))pyrrol-2-yl]carboxamide
34		(R)-4-(5-(3-aminopiperidine-1-carbonyl)-1-(3-hydroxypropyl)-2-(2-methyl-2H-indazol-5-yl)-1H-pyrrol-3-yl)-2-fluorobenzonitrile
35		(R)-4-(5-(3-aminopiperidine-1-carbonyl)-1-(2-hydroxyethyl)-2-(2-methyl-2H-indazol-5-yl)-1H-pyrrol-3-yl)-2-fluorobenzonitrile
36		(R)-4-(5-(3-aminopiperidine-1-carbonyl)-1-(2-methoxyethyl)-2-(2-methyl-2H-indazol-5-yl)-1H-pyrrol-3-yl)-2-fluorobenzonitrile

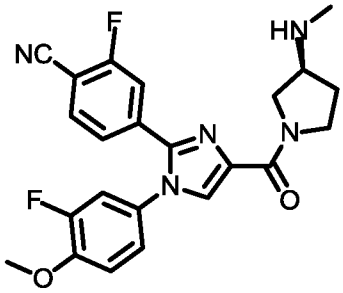
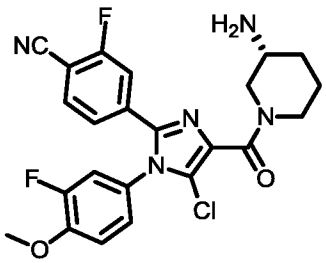
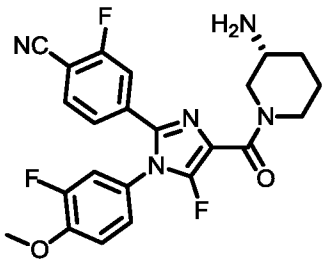
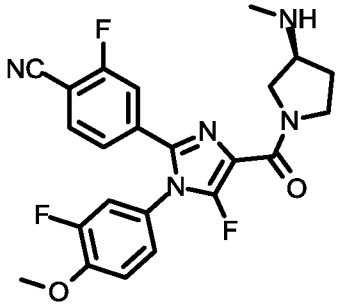
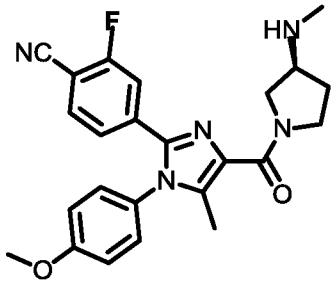
Chemical Synthesis Example	Structure	Name
37		(R)-2-(5-(3-aminopiperidine-1-carbonyl)-3-(4-cyano-3-fluorophenyl)-2-(4-methoxyphenyl)-1H-pyrrol-1-yl)acetamide
38		4-(5-((R)-3-aminopiperidine-1-carbonyl)-1-((R)-2,3-dihydroxypropyl)-2-(2-methyl-2H-indazol-5-yl)-1H-pyrrol-3-yl)-2-fluorobenzonitrile
39		4-(5-((R)-3-aminopiperidine-1-carbonyl)-1-((S)-2,3-dihydroxypropyl)-2-(2-methyl-2H-indazol-5-yl)-1H-pyrrol-3-yl)-2-fluorobenzonitrile
40		N-[((3R)pyrrolidin-3-yl)methyl][4-(4-cyano-3-fluorophenyl)-1-methyl-5-(2-methyl(2H-indazol-5-yl))pyrrol-2-yl]carboxamide
41		4-{5-[((3R)-3-aminopiperidyl)carbonyl]-3-(4-cyano-3-fluorophenyl)-2-(4-methoxyphenyl)pyrrolyl}butanoic acid

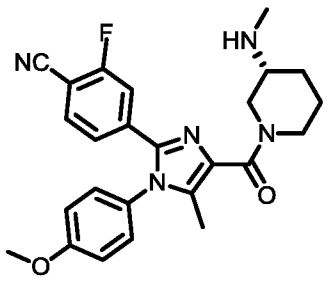
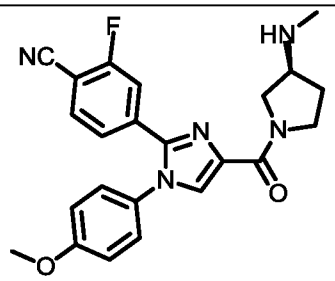
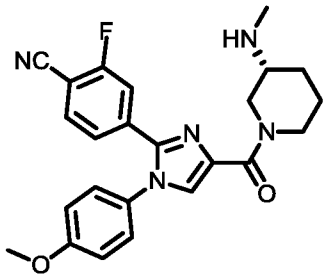
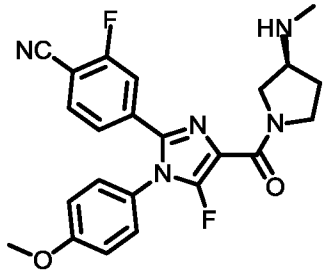
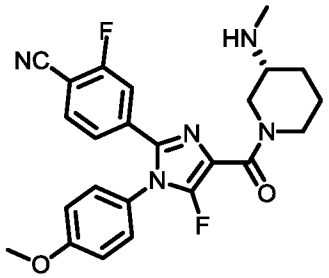
Chemical Synthesis Example	Structure	Name
42		4-{5-[((3R)-3-aminopiperidyl)carbonyl]-3-(4-cyano-3-fluorophenyl)-2-(4-methoxyphenyl)pyrrolyl}butanamide
43		4-[4-(4-Aminopiperidine-1-carbonyl)-5-methyl-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile
44		N-(2-Aminoethyl)-2-(4-cyano-3-fluorophenyl)-N,5-dimethyl-1-(2-methylindazol-5-yl)imidazole-4-carboxamide
45		2-(4-Cyano-3-fluorophenyl)-5-methyl-1-(2-methylindazol-5-yl)-N-piperidin-3-ylimidazole-4-carboxamide
46		2-(4-Cyano-3-fluorophenyl)-5-methyl-1-(2-methylindazol-5-yl)-N-pyrrolidin-3-ylimidazole-4-carboxamide
47		4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-1-(6-fluoro-2-methylindazol-5-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile

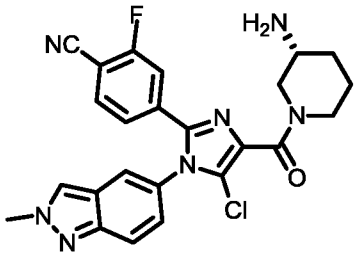
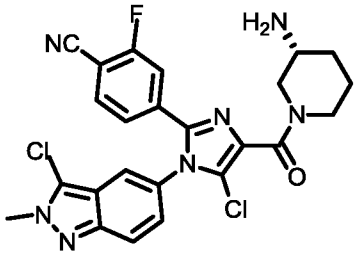
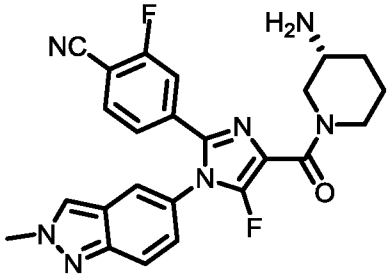
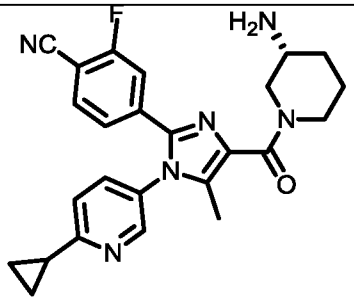
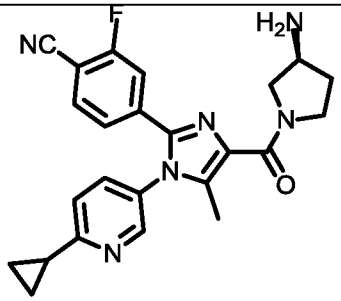
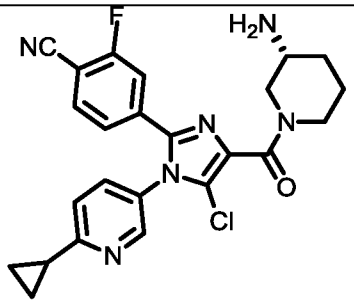
Chemical Synthesis Example	Structure	Name
48		4-[4-[(3S)-3-(Dimethylamino)pyrrolidine-1-carbonyl]-1-(6-fluoro-2-methylindazol-5-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile
49		2-Fluoro-4-[1-(6-fluoro-2-methylindazol-5-yl)-5-methyl-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile
50		4-[4-[(3S)-3-Aminopyrrolidine-1-carbonyl]-1-(7-fluoro-2-methylindazol-5-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile
51		2-Fluoro-4-[1-(7-fluoro-2-methylindazol-5-yl)-5-methyl-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile
52		4-[4-[(3S)-3-(Dimethylamino)pyrrolidine-1-carbonyl]-1-(7-fluoro-2-methylindazol-5-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile

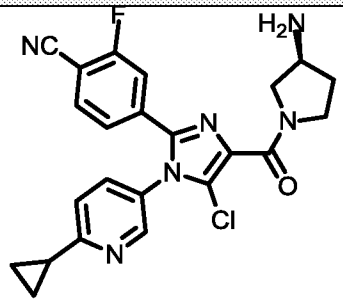
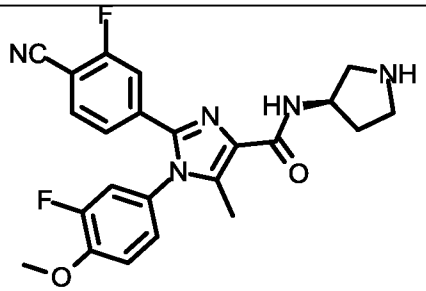
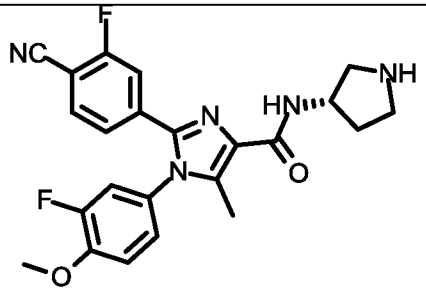
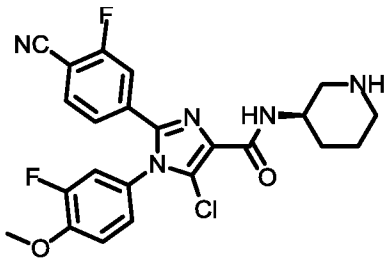
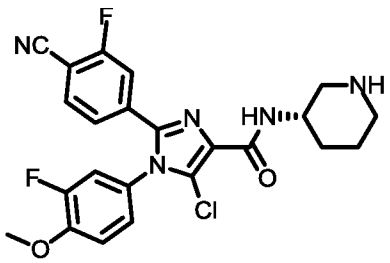
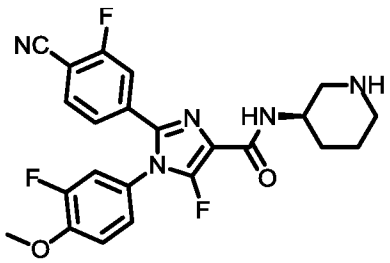
Chemical Synthesis Example	Structure	Name
53		4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-1-(3-chloro-2-methylindazol-5-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile
54		4-[1-(3-Chloro-2-methylindazol-5-yl)-5-methyl-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile
55		4-[1-(3-Chloro-2-methylindazol-5-yl)-5-methyl-4-[(3R)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile
56		1-(3-Chloro-2-methylindazol-5-yl)-2-(4-cyano-3-fluorophenyl)-5-methyl-N-[(3R)-1-methylpiperidin-3-yl]imidazole-4-carboxamide
57		4-[1-(3-Chloro-2-methylindazol-5-yl)-4-[(3S)-3-(dimethylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile
58		4-[1-(3-Chloro-2-methylindazol-5-yl)-4-[(3S)-3-(dimethylamino)pyrrolidine-1-carbonyl]-5-fluoroimidazol-2-yl]-2-fluorobenzonitrile

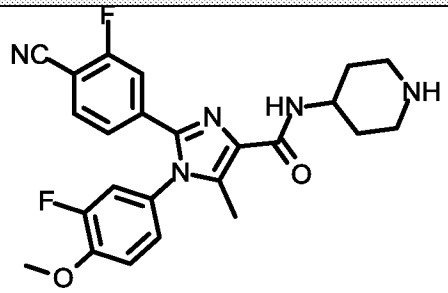
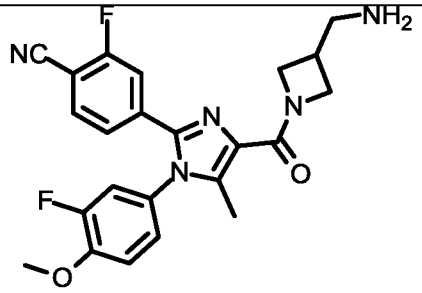
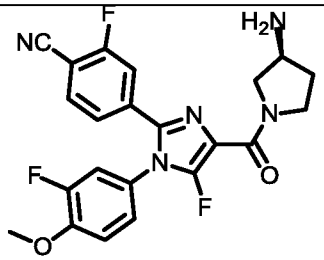
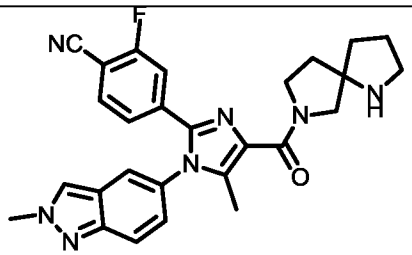
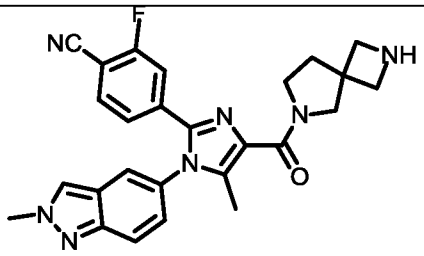
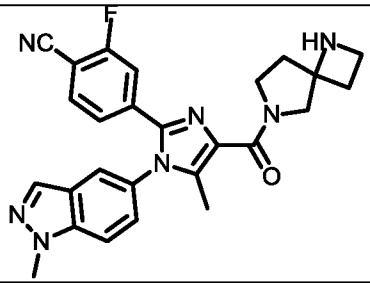
Chemical Synthesis Example	Structure	Name
59		1-(3-Chloro-2-methylindazol-5-yl)-2-(4-cyano-3-fluorophenyl)-N-[(3R)-1-methylpiperidin-3-yl]imidazole-4-carboxamide
60		2-(4-Cyano-3-fluorophenyl)-5-methyl-1-(2-methylindazol-5-yl)-N-[(3R)-1-methylpiperidin-3-yl]imidazole-4-carboxamide
61		4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-1-(3-chloro-2-methylindazol-5-yl)-5-fluoroimidazol-2-yl]-2-fluorobenzonitrile
62		2-(4-Cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)-5-methyl-N-[(3R)-piperidin-3-yl]imidazole-4-carboxamide
63		2-(4-Cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)-5-methyl-N-[(3S)-piperidin-3-yl]imidazole-4-carboxamide
64		2-Fluoro-4-[1-(3-fluoro-4-methoxyphenyl)-5-methyl-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile

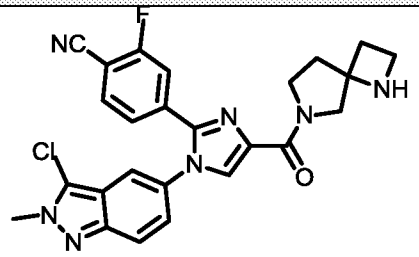
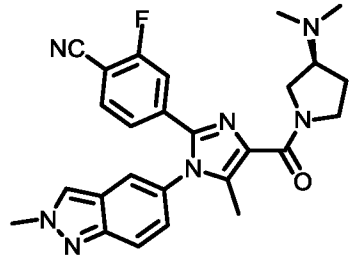
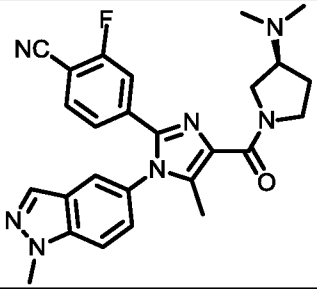
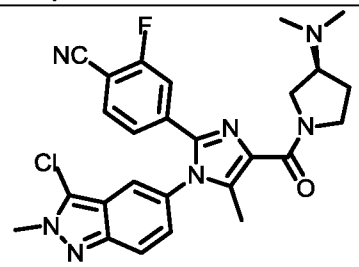
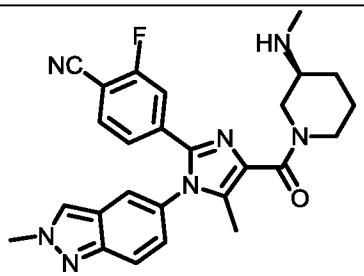
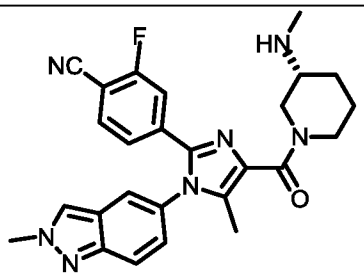
Chemical Synthesis Example	Structure	Name
65		2-Fluoro-4-[1-(3-fluoro-4-methoxyphenyl)-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile
66		4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-5-chloro-1-(3-fluoro-4-methoxyphenyl)imidazol-2-yl]-2-fluorobenzonitrile
67		4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-5-fluoro-1-(3-fluoro-4-methoxyphenyl)imidazol-2-yl]-2-fluorobenzonitrile
68		2-Fluoro-4-[5-fluoro-1-(3-fluoro-4-methoxyphenyl)-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile
69		2-Fluoro-4-[1-(4-methoxyphenyl)-5-methyl-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile

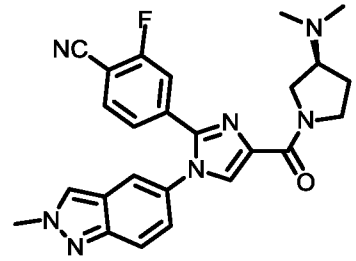
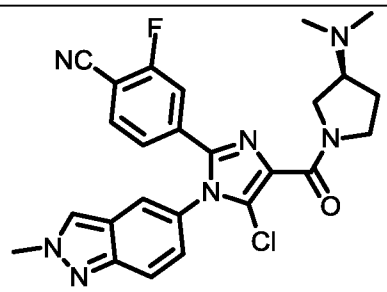
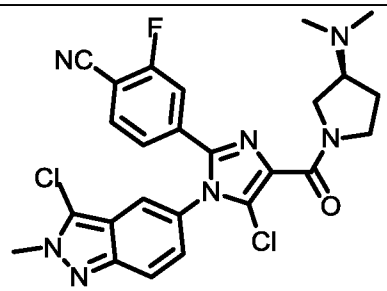
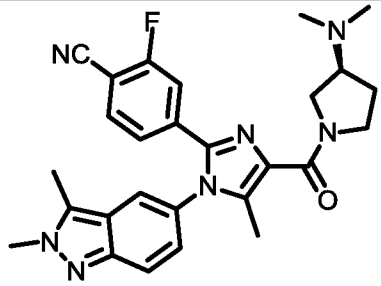
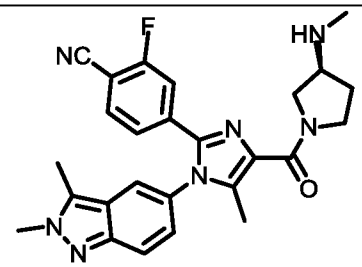
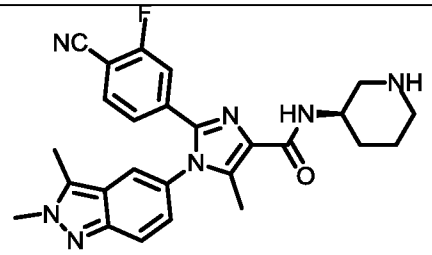
Chemical Synthesis Example	Structure	Name
70		2-Fluoro-4-[1-(4-methoxyphenyl)-5-methyl-4-[(3R)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]benzonitrile
71		2-Fluoro-4-[1-(4-methoxyphenyl)-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile
72		2-Fluoro-4-[1-(4-methoxyphenyl)-4-[(3R)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]benzonitrile
73		2-Fluoro-4-[5-fluoro-1-(4-methoxyphenyl)-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile
74		2-Fluoro-4-[5-fluoro-1-(4-methoxyphenyl)-4-[(3R)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]benzonitrile

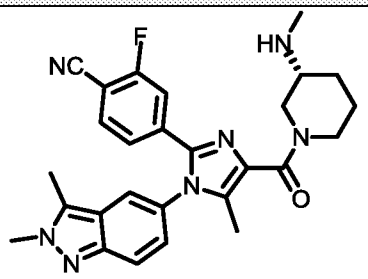
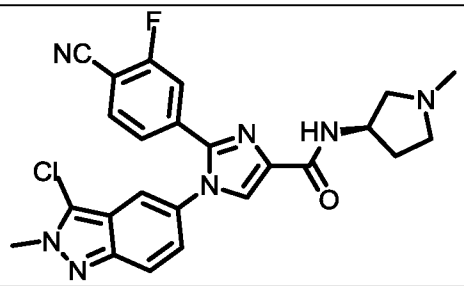
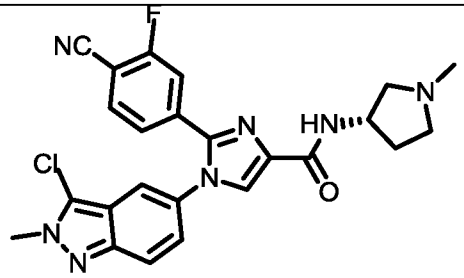
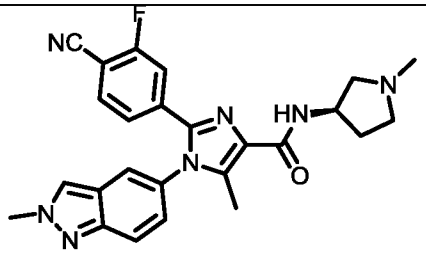
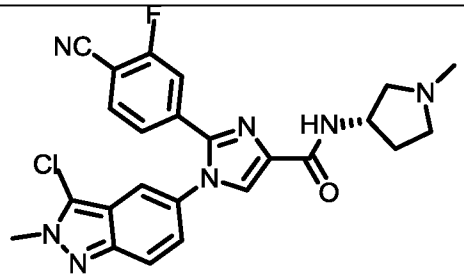
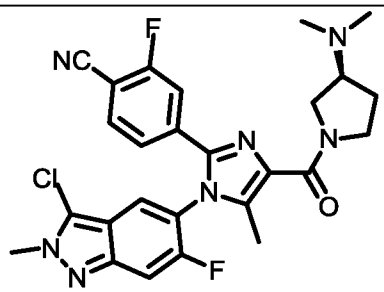
Chemical Synthesis Example	Structure	Name
75		4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-5-chloro-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile
76		4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-5-chloro-1-(3-chloro-2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile
77		4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-5-fluoro-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile
78		4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-1-(6-cyclopropylpyridin-3-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile
79		4-[4-[(3S)-3-Aminopyrrolidine-1-carbonyl]-1-(6-cyclopropylpyridin-3-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile
80		4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-5-chloro-1-(6-cyclopropylpyridin-3-yl)imidazol-2-yl]-2-fluorobenzonitrile

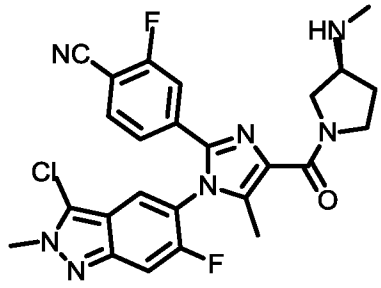
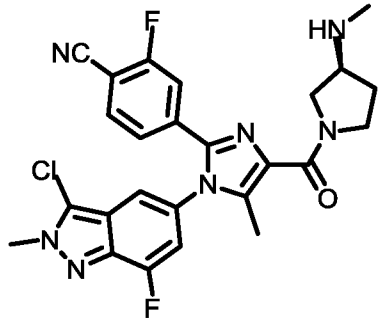
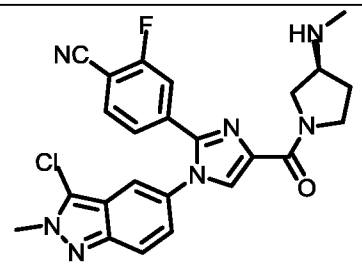
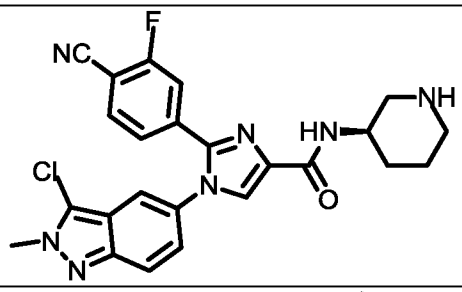
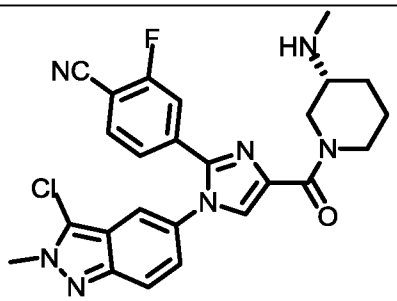
Chemical Synthesis Example	Structure	Name
81		4-[4-[(3S)-3-Aminopyrrolidine-1-carbonyl]-5-chloro-1-(6-cyclopropylpyridin-3-yl)imidazol-2-yl]-2-fluorobenzonitrile
82		2-(4-Cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)-5-methyl-N-[(3R)-pyrrolidin-3-yl]imidazole-4-carboxamide
83		2-(4-Cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)-5-methyl-N-[(3S)-pyrrolidin-3-yl]imidazole-4-carboxamide
84		5-Chloro-2-(4-cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)-N-[(3R)-piperidin-3-yl]imidazole-4-carboxamide
85		5-Chloro-2-(4-cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)-N-[(3S)-piperidin-3-yl]imidazole-4-carboxamide
86		2-(4-Cyano-3-fluorophenyl)-5-fluoro-1-(3-fluoro-4-methoxyphenyl)-N-[(3R)-piperidin-3-yl]imidazole-4-carboxamide

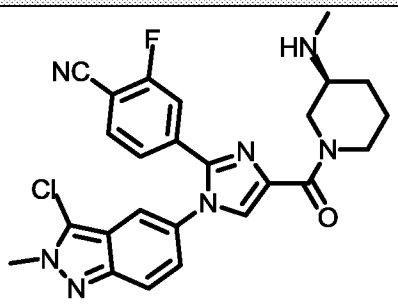
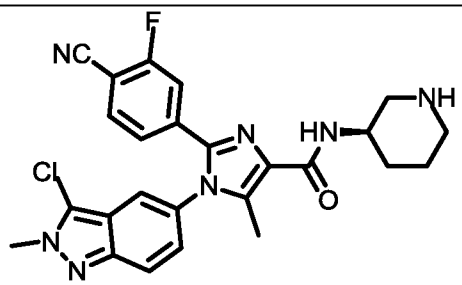
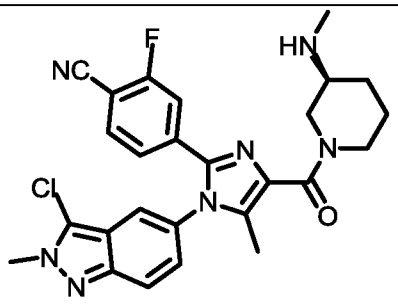
Chemical Synthesis Example	Structure	Name
87		2-(4-Cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)-5-methyl-N-piperidin-4-ylimidazole-4-carboxamide
88		4-[4-[3-(Aminomethyl)azetidine-1-carbonyl]-1-(3-fluoro-4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile
89		4-[4-[(3S)-3-Aminopyrrolidine-1-carbonyl]-5-fluoro-1-(3-fluoro-4-methoxyphenyl)imidazol-2-yl]-2-fluorobenzonitrile
90		4-[4-(1,7-Diazaspiro[4.4]nonane-7-carbonyl)-5-methyl-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile
91		4-[4-(2,6-Diazaspiro[3.4]octane-6-carbonyl)-5-methyl-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile
92		4-[4-(1,7-Diazaspiro[3.4]octane-7-carbonyl)-5-methyl-1-(1-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile

Chemical Synthesis Example	Structure	Name
93		4-[1-(3-Chloro-2-methylindazol-5-yl)-4-(1,7-diazaspiro[3.4]octane-7-carbonyl)imidazol-2-yl]-2-fluorobenzonitrile
94		4-[4-[(3S)-3-(Dimethylamino)pyrrolidine-1-carbonyl]-5-methyl-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile
95		4-[4-[(3S)-3-(Dimethylamino)pyrrolidine-1-carbonyl]-5-methyl-1-(1-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile
96		4-[1-(3-Chloro-2-methylindazol-5-yl)-4-[(3S)-3-(dimethylamino)pyrrolidine-1-carbonyl]-5-methylimidazol-2-yl]-2-fluorobenzonitrile
97		2-Fluoro-4-[5-methyl-4-[(3S)-3-(methylamino)piperidine-1-carbonyl]-1-(2-methylindazol-5-yl)imidazol-2-yl]benzonitrile
98		2-Fluoro-4-[5-methyl-4-[(3R)-3-(methylamino)piperidine-1-carbonyl]-1-(2-methylindazol-5-yl)imidazol-2-yl]benzonitrile

Chemical Synthesis Example	Structure	Name
99		4-[4-[(3S)-3-(Dimethylamino)pyrrolidine-1-carbonyl]-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile
100		4-[5-Chloro-4-[(3S)-3-(dimethylamino)pyrrolidine-1-carbonyl]-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile
101		4-[5-Chloro-1-(3-chloro-2-methylindazol-5-yl)-4-[(3S)-3-(dimethylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile
102		4-[4-[(3S)-3-(Dimethylamino)pyrrolidine-1-carbonyl]-1-(2,3-dimethylindazol-5-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile
103		4-[1-(2,3-Dimethylindazol-5-yl)-5-methyl-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile
104		2-(4-Cyano-3-fluorophenyl)-1-(2,3-dimethylindazol-5-yl)-5-methyl-N-[(3R)-piperidin-3-yl]imidazole-4-carboxamide

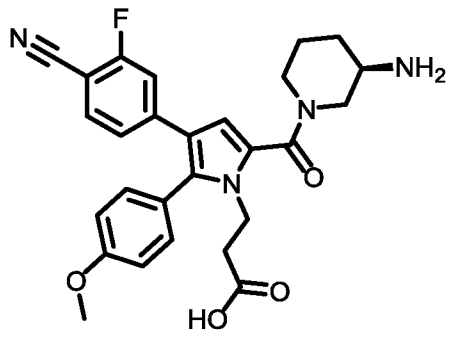
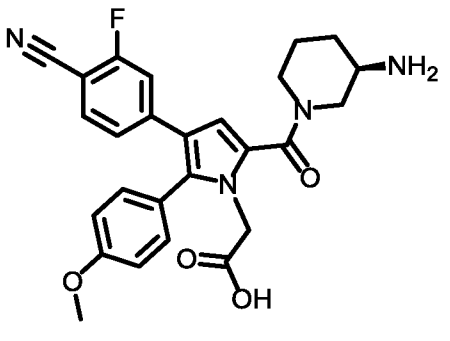
Chemical Synthesis Example	Structure	Name
105		4-[1-(2,3-Dimethylindazol-5-yl)-5-methyl-4-[(3R)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile
106		1-(3-Chloro-2-methylindazol-5-yl)-2-(4-cyano-3-fluorophenyl)-N-[(3R)-1-methylpyrrolidin-3-yl]imidazole-4-carboxamide
107		1-(3-Chloro-2-methylindazol-5-yl)-2-(4-cyano-3-fluorophenyl)-N-[(3S)-1-methylpyrrolidin-3-yl]imidazole-4-carboxamide
108		2-(4-Cyano-3-fluorophenyl)-5-methyl-1-(2-methylindazol-5-yl)-N-[(3R)-1-methylpyrrolidin-3-yl]imidazole-4-carboxamide
109		2-(4-Cyano-3-fluorophenyl)-5-methyl-1-(2-methylindazol-5-yl)-N-[(3S)-1-methylpyrrolidin-3-yl]imidazole-4-carboxamide
110		4-[1-(3-Chloro-6-fluoro-2-methylindazol-5-yl)-4-[(3S)-3-(dimethylamino)pyrrolidine-1-carbonyl]-5-methylimidazol-2-yl]-2-fluorobenzonitrile

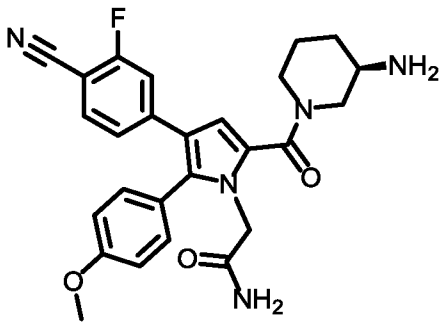
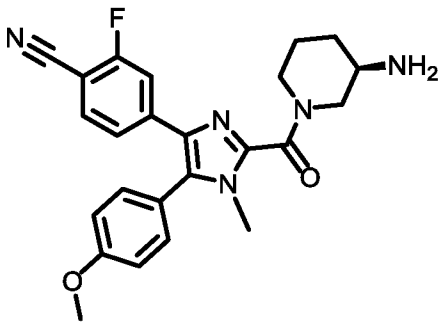
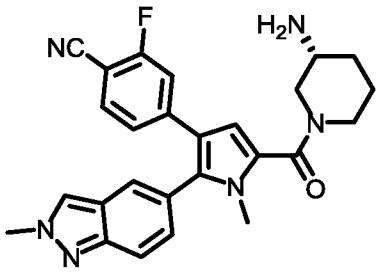
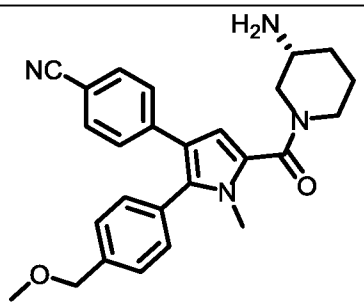
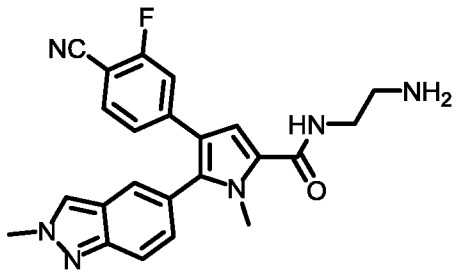
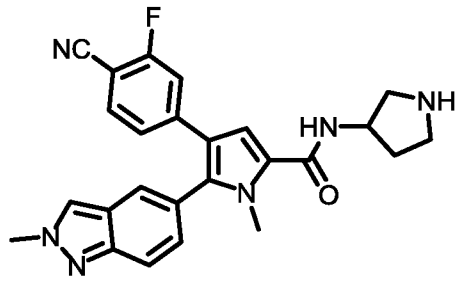
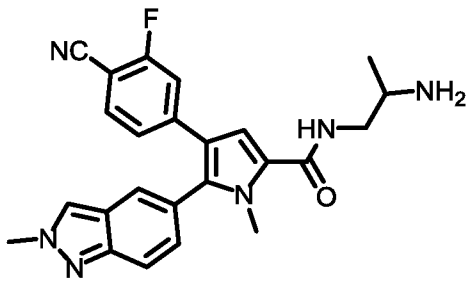
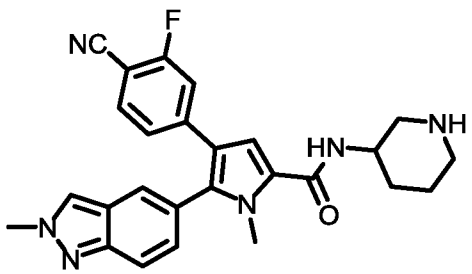
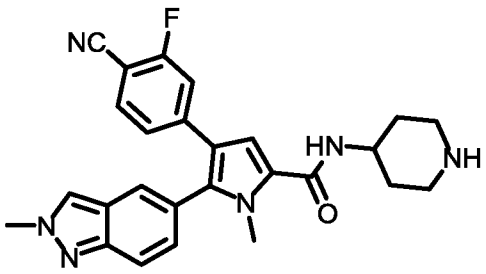
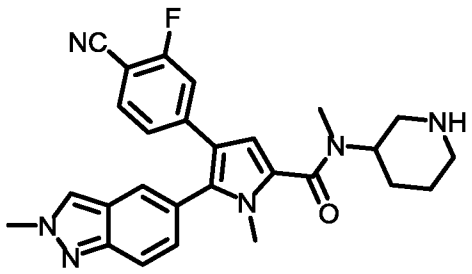
Chemical Synthesis Example	Structure	Name
111		4-[1-(3-Chloro-6-fluoro-2-methylindazol-5-yl)-5-methyl-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile
112		4-[1-(3-Chloro-6-fluoro-2-methylindazol-5-yl)-4-[(3S)-3-(dimethylamino)pyrrolidine-1-carbonyl]-5-methylimidazol-2-yl]-2-fluorobenzonitrile
113		4-[1-(3-Chloro-2-methylindazol-5-yl)-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile
114		1-(3-Chloro-2-methylindazol-5-yl)-2-(4-cyano-3-fluorophenyl)-N-[(3R)-piperidin-3-yl]imidazole-4-carboxamide
115		4-[1-(3-Chloro-2-methylindazol-5-yl)-4-[(3R)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile

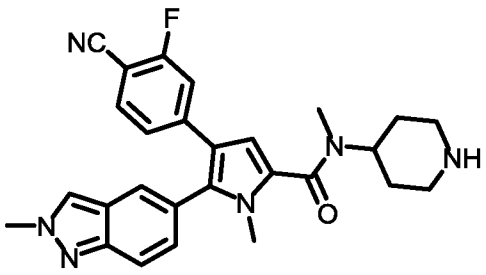
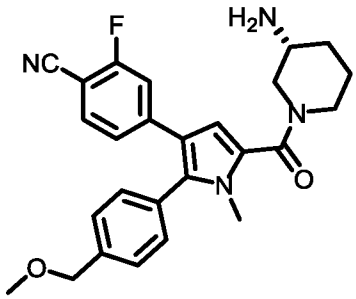
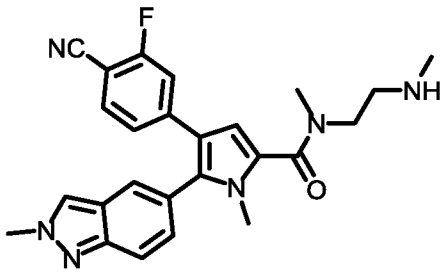
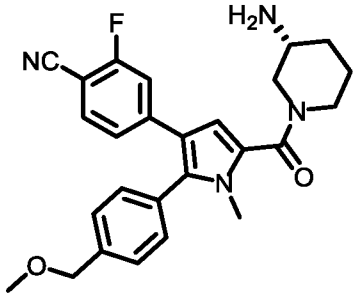
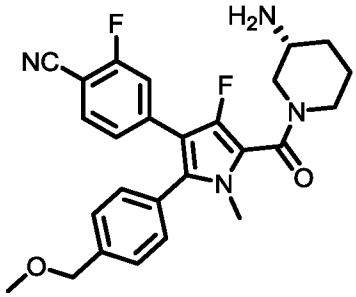
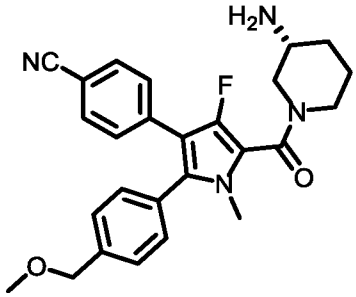
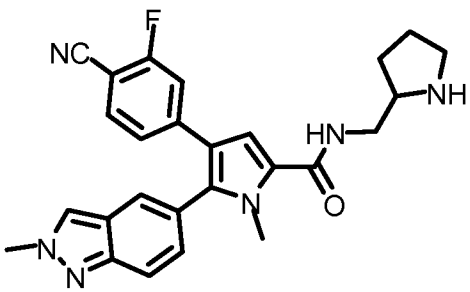
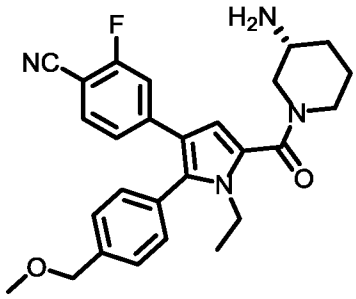
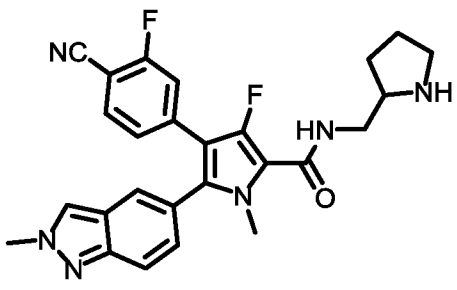
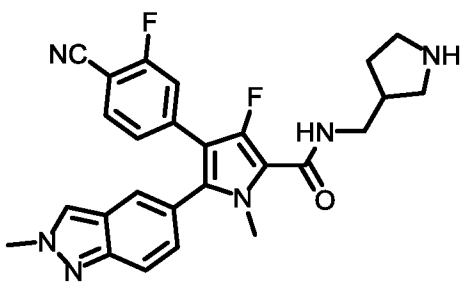
Chemical Synthesis Example	Structure	Name
116		4-[1-(3-Chloro-2-methylindazol-5-yl)-4-[(3S)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile
117		1-(3-Chloro-2-methylindazol-5-yl)-2-(4-cyano-3-fluorophenyl)-5-methyl-N-[(3R)-piperidin-3-yl]imidazole-4-carboxamide
118		4-[1-(3-Chloro-2-methylindazol-5-yl)-5-methyl-4-[(3S)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile

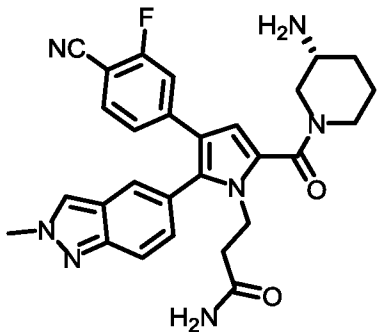
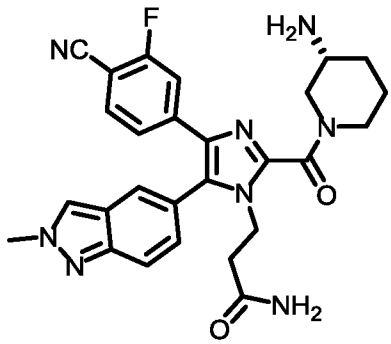
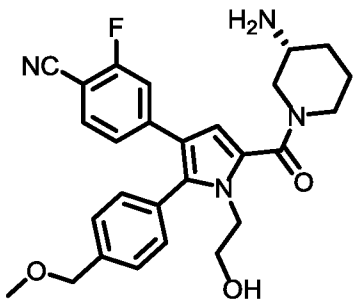
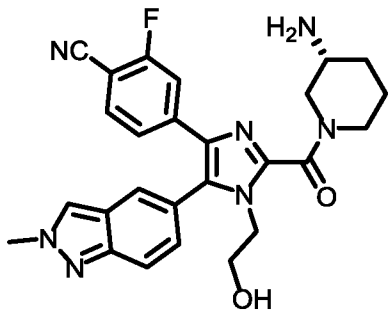
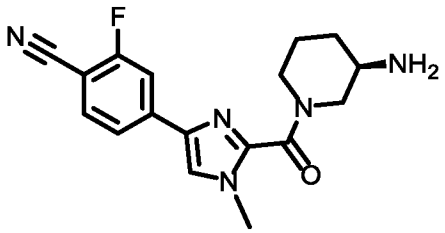
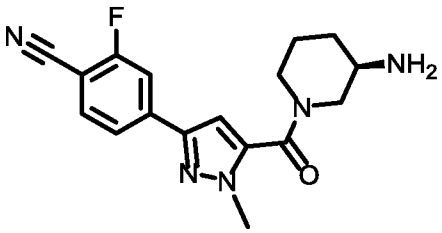
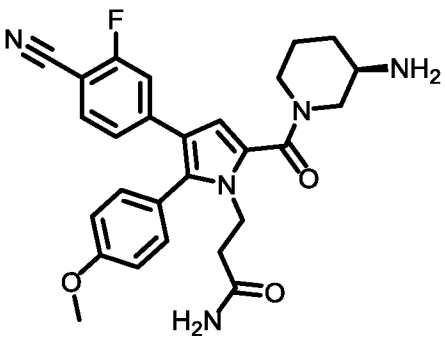
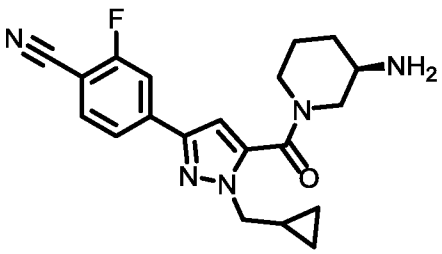
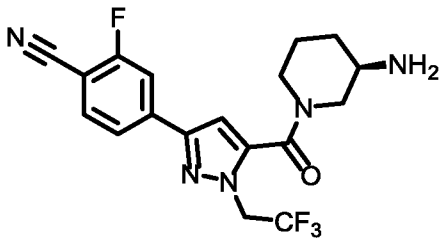
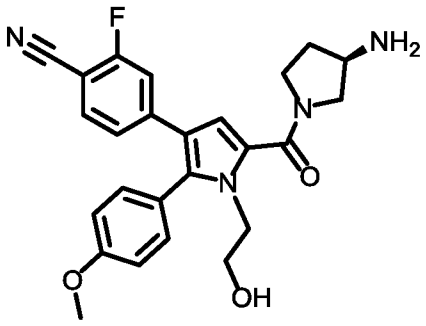
[0072] In some embodiments, the substituted heterocyclic derivative compound described herein has the structure provided in Table 2.

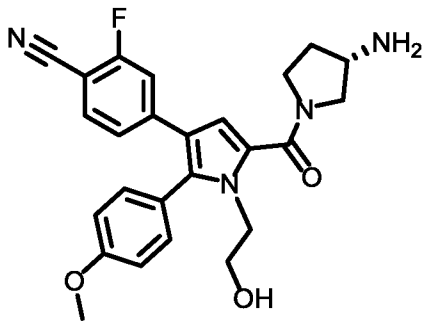
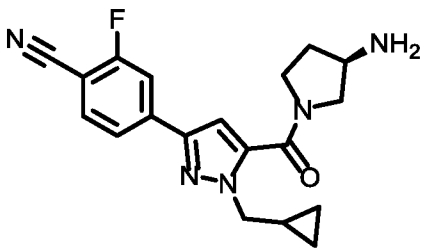
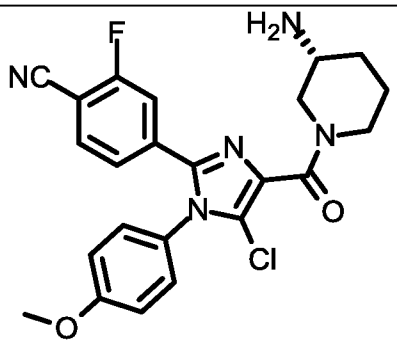
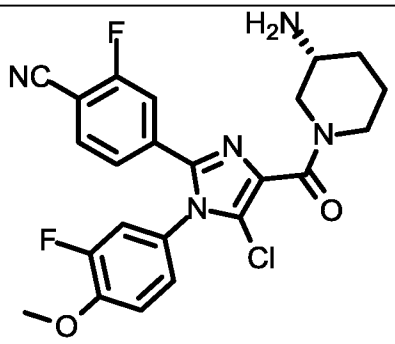
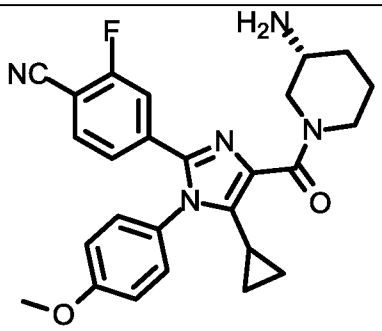
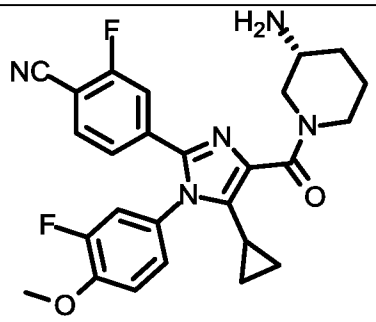
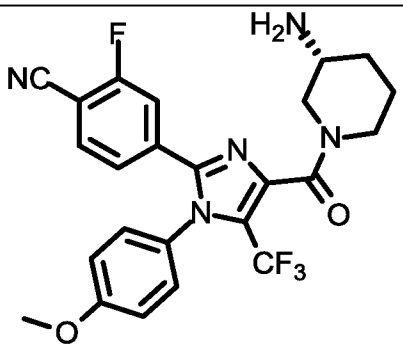
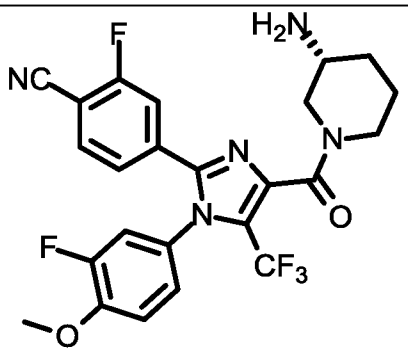
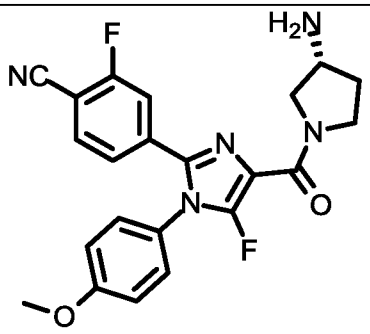
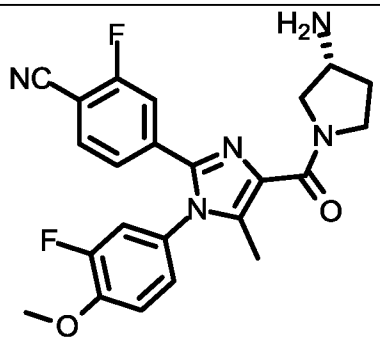
TABLE 2

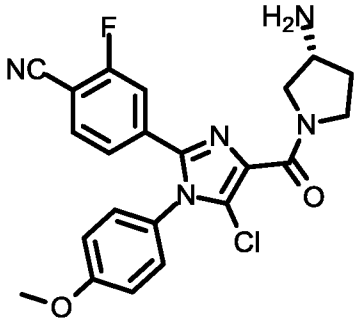
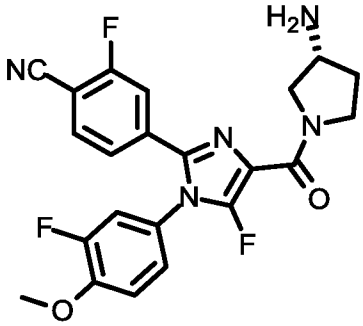
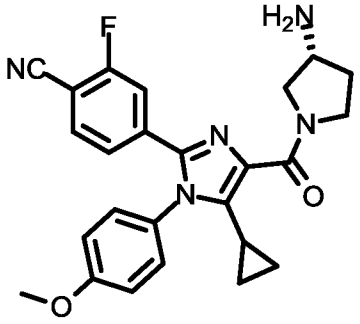
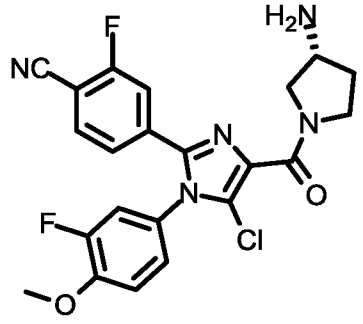
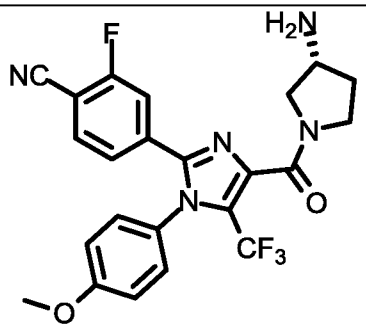
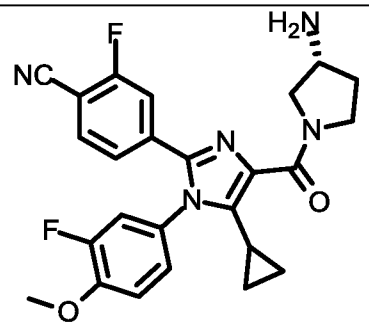
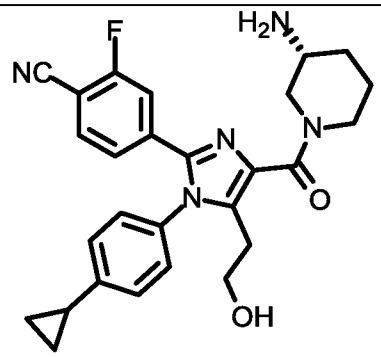
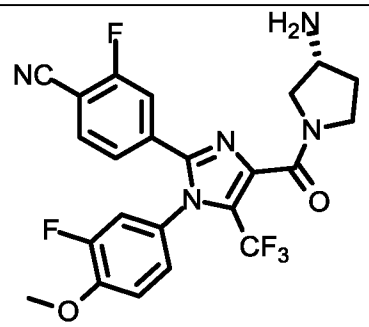
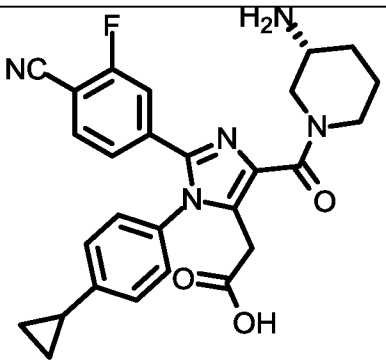
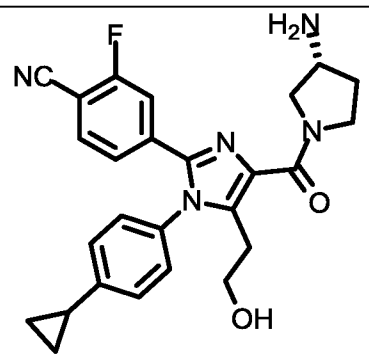
	

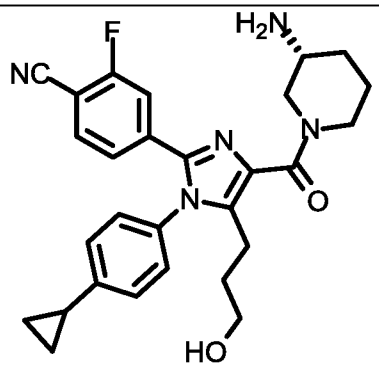
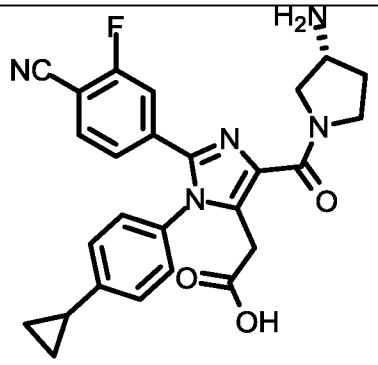
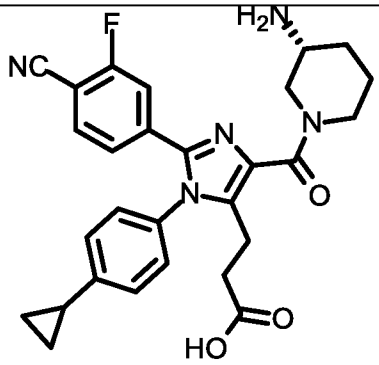
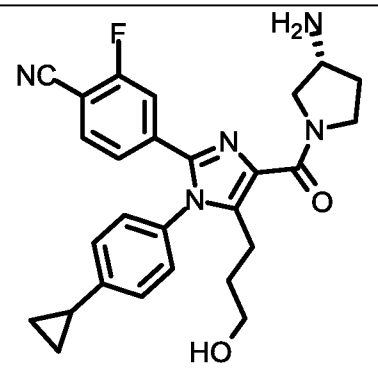
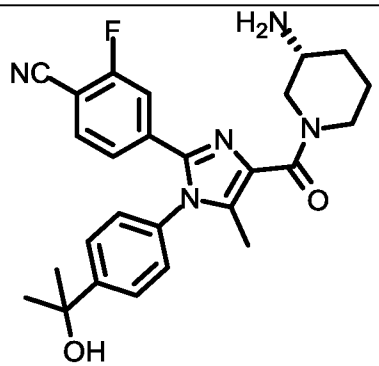
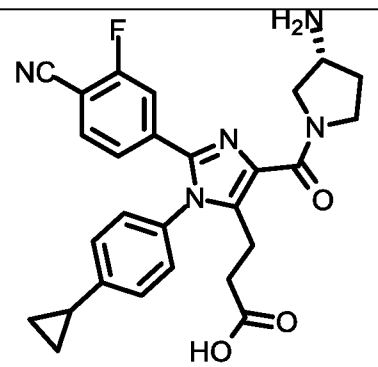
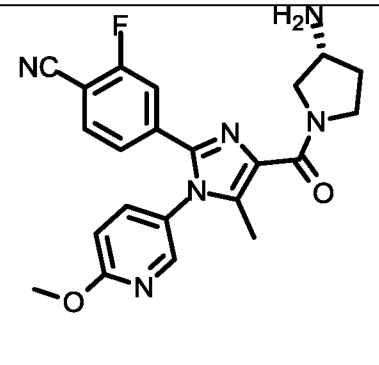
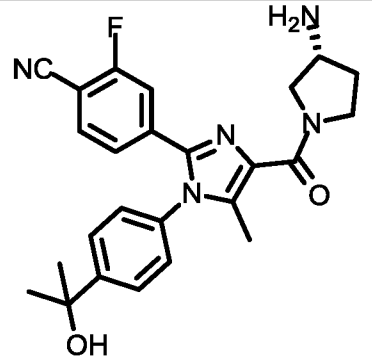
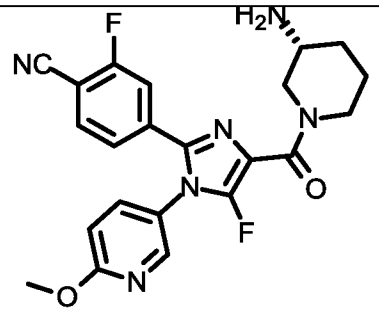
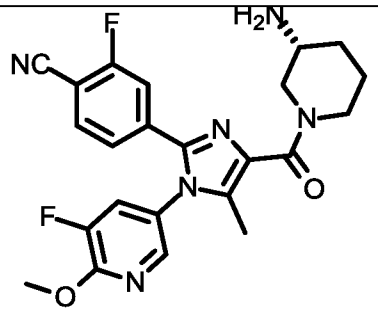
	
	
	
	
	

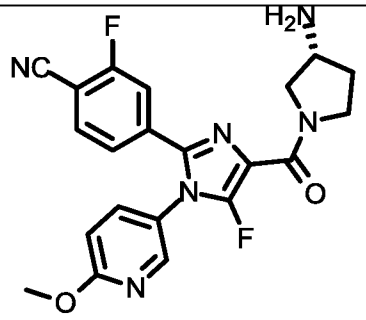
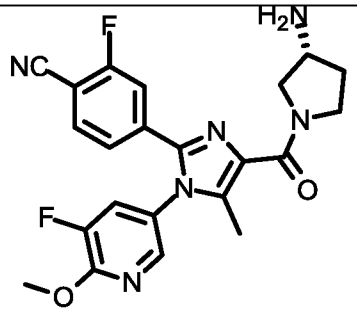
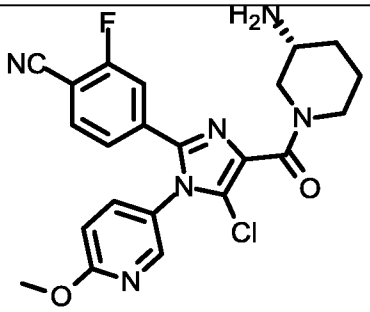
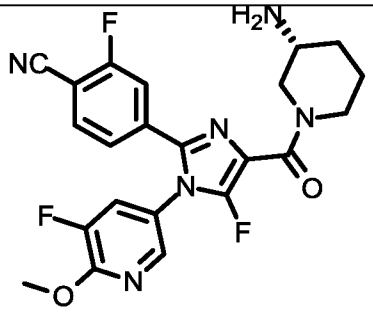
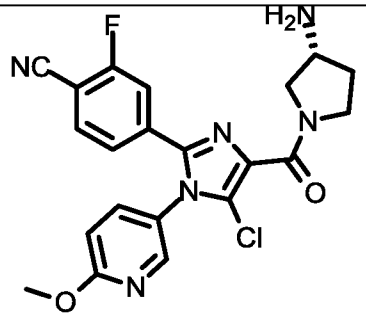
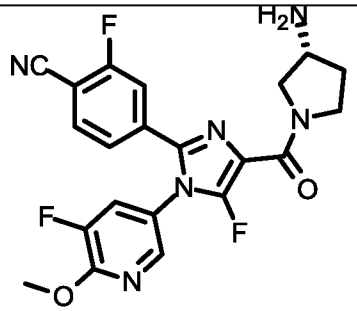
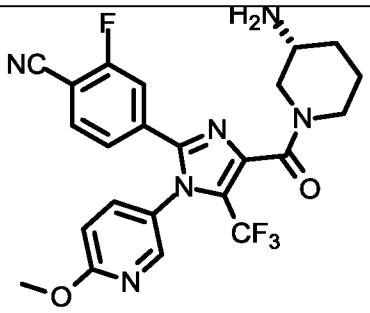
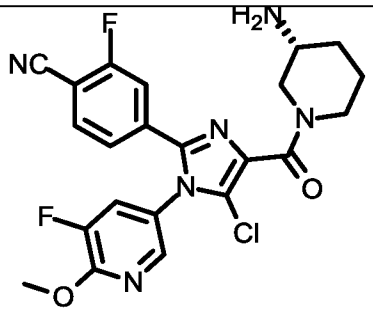
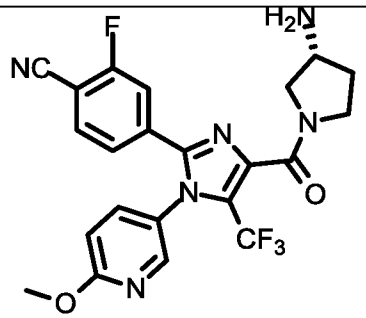
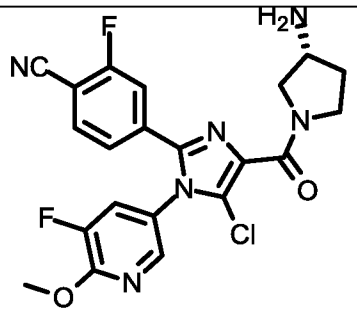
	
	
	
	
	

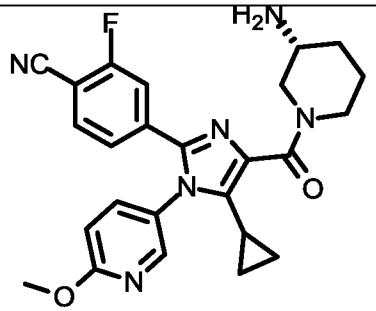
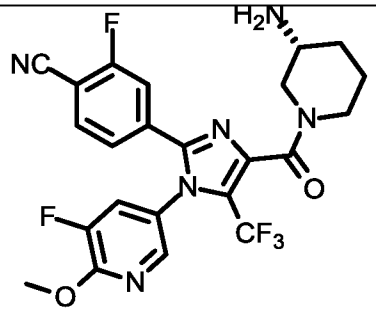
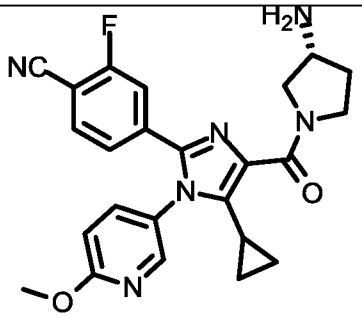
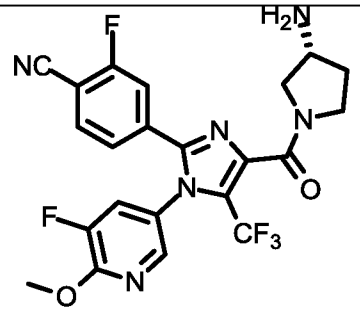
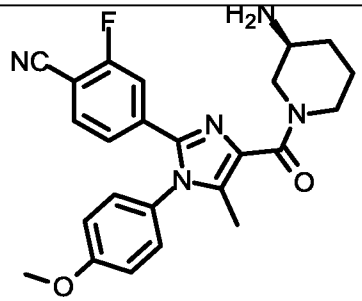
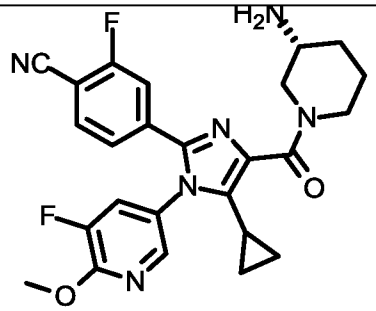
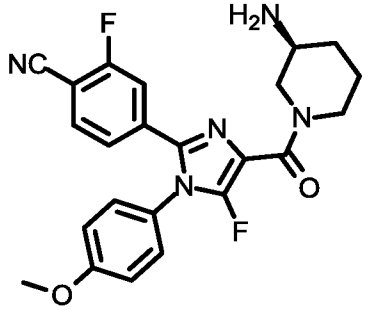
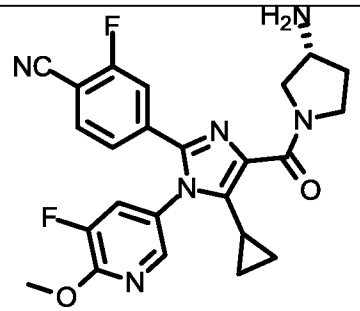
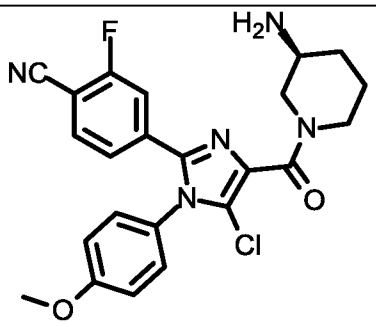
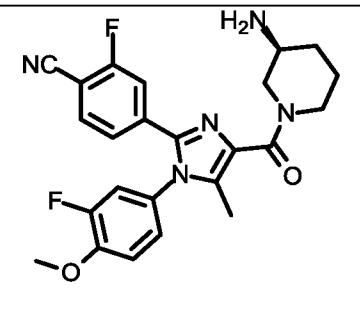
	
	
	
	
	

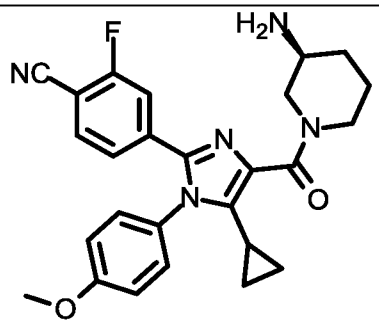
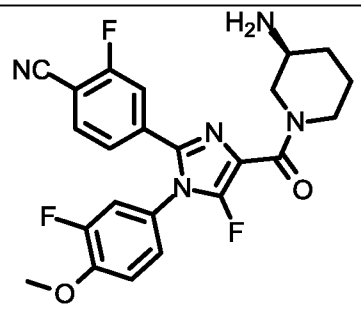
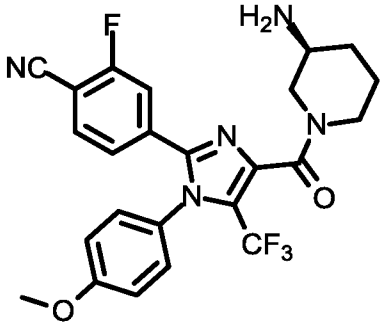
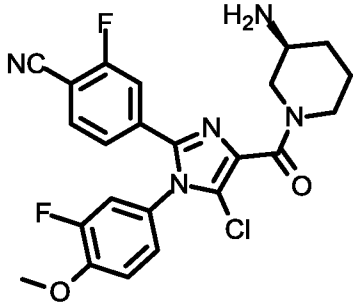
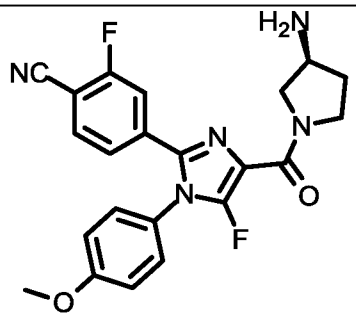
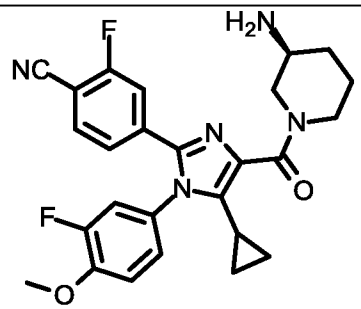
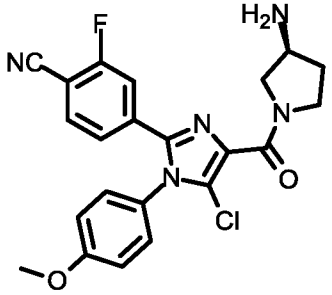
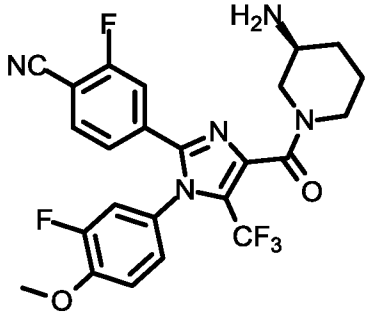
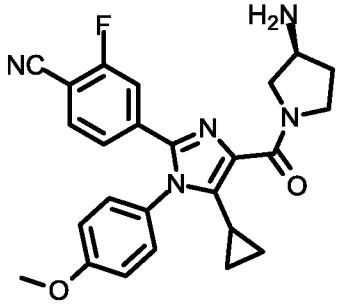
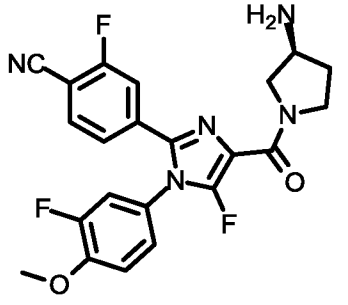
	
	
	
	
	

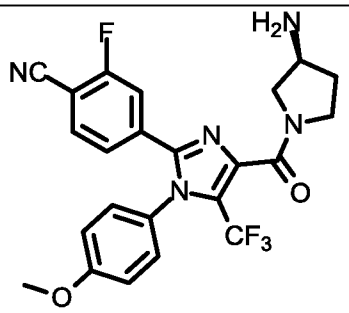
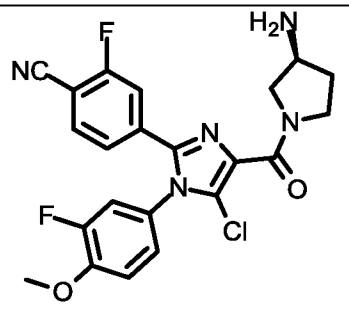
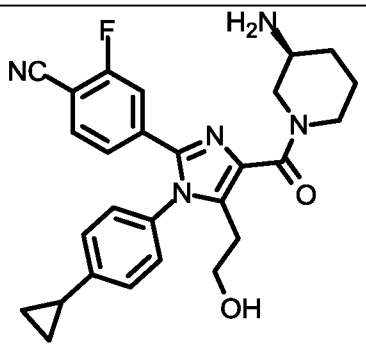
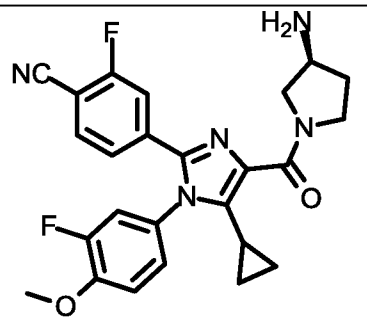
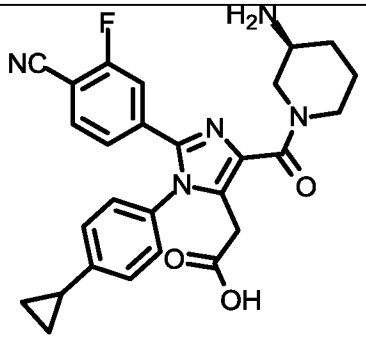
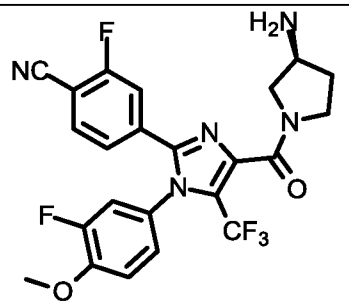
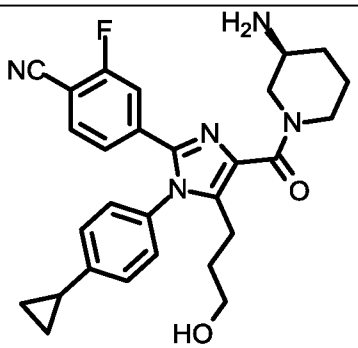
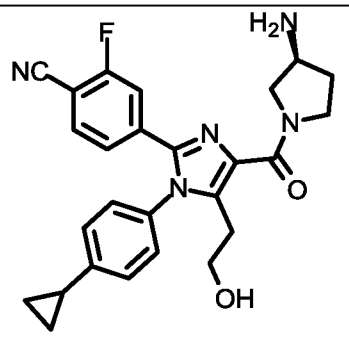
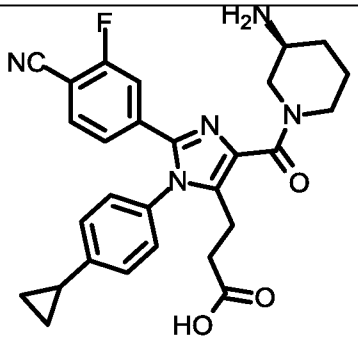
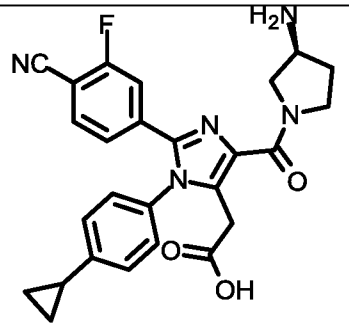
	
	
	
	
	

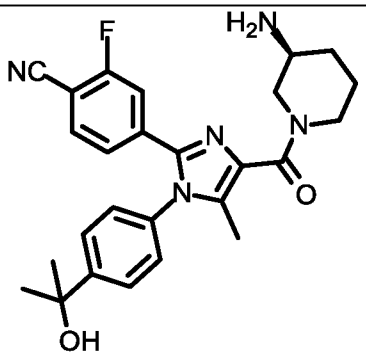
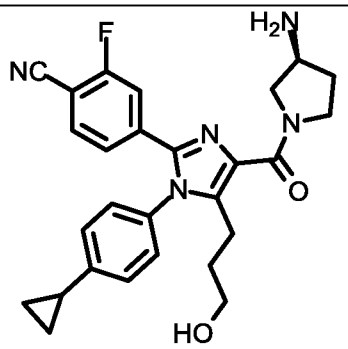
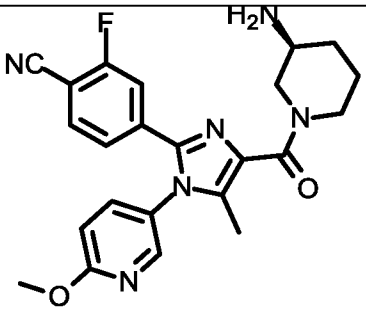
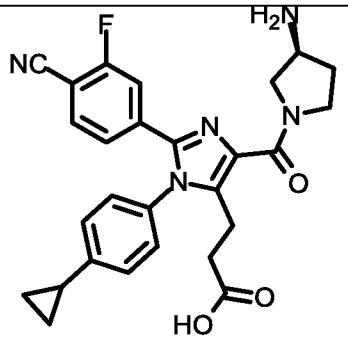
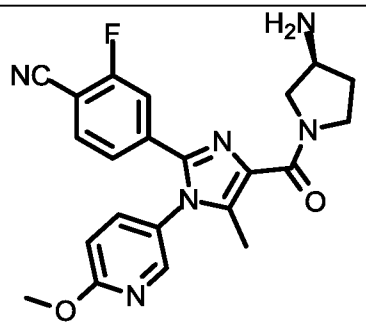
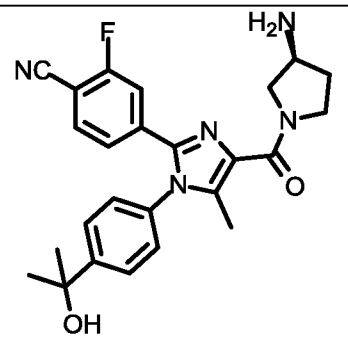
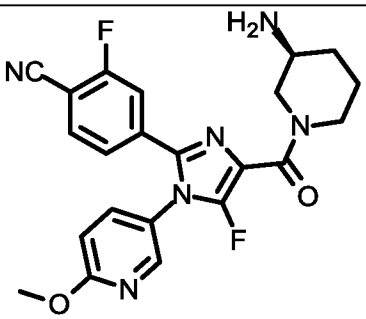
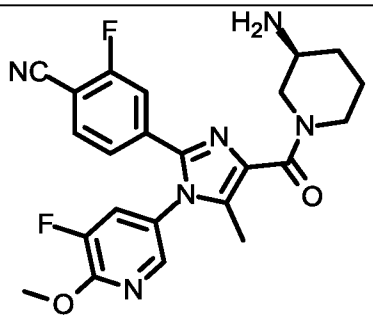
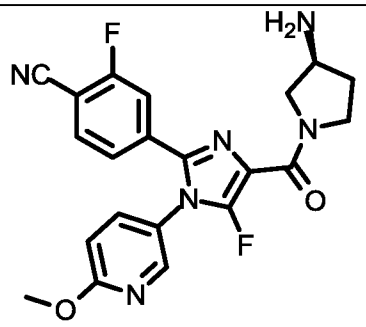
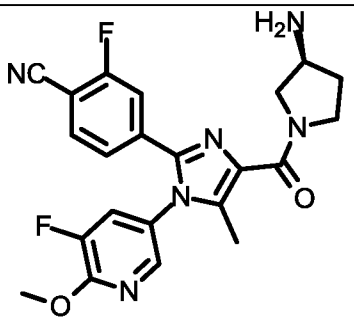
	
	
	
	
	

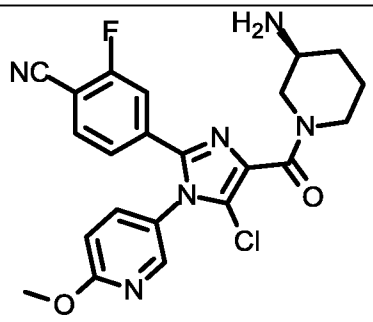
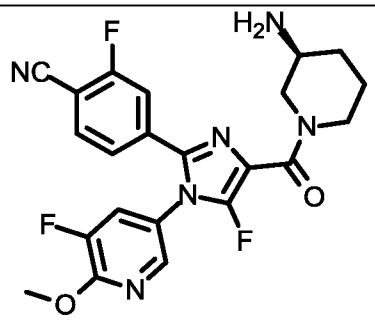
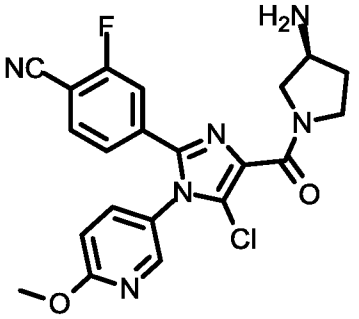
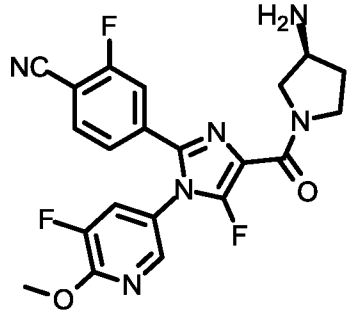
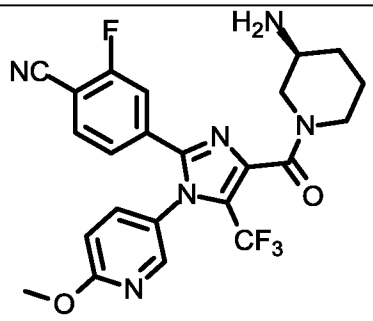
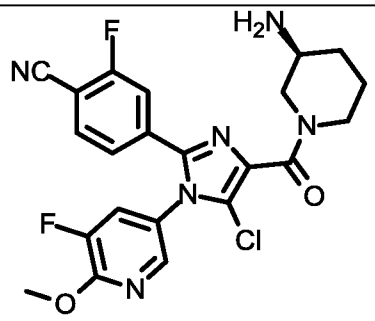
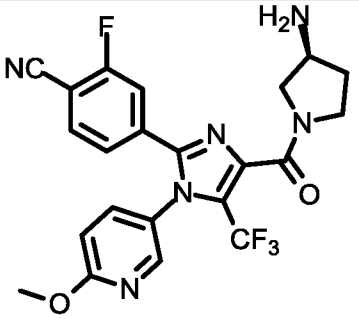
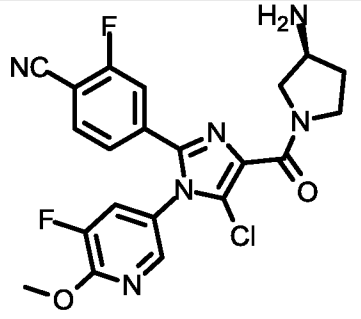
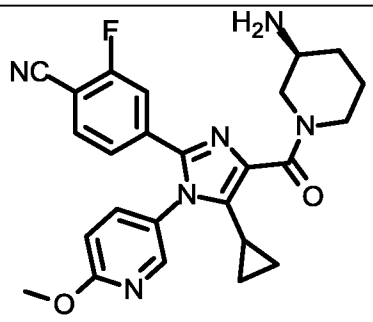
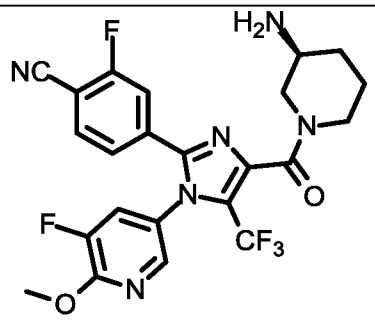
	
	
	
	
	

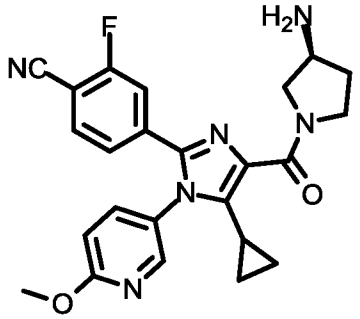
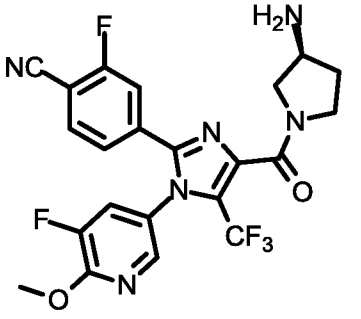
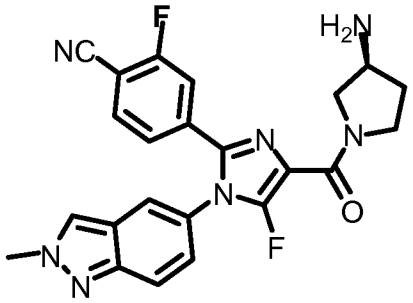
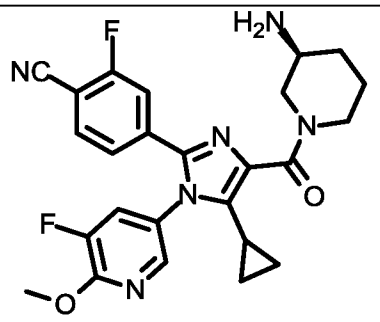
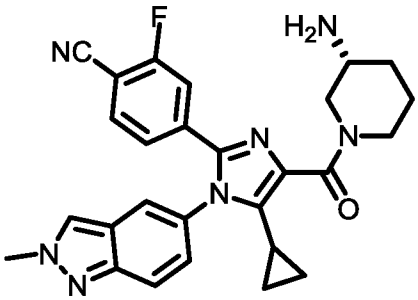
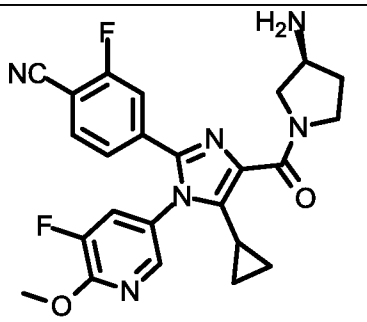
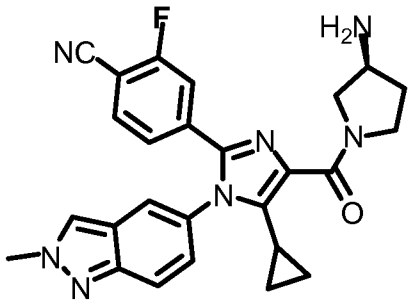
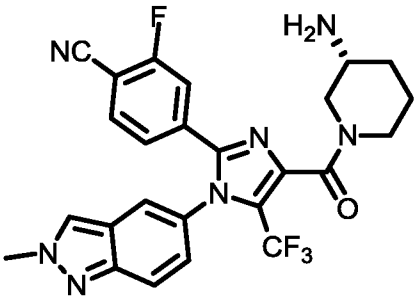
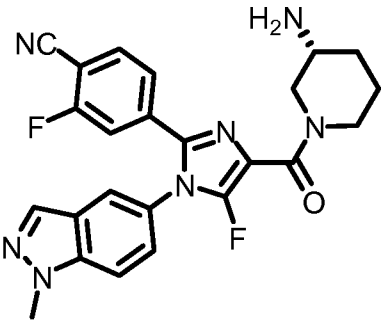
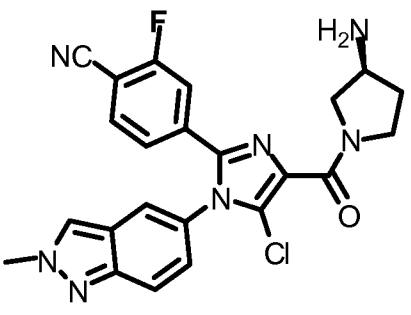
	
	
	
	
	

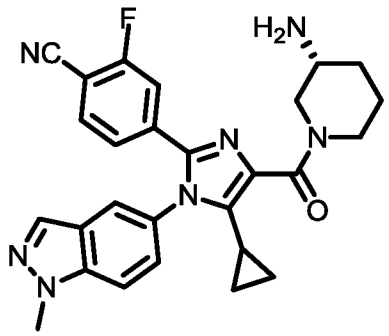
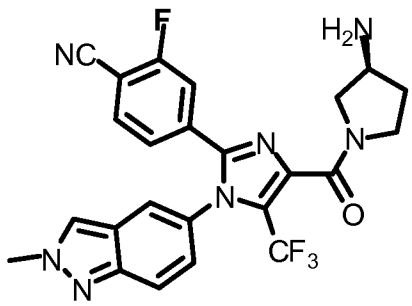
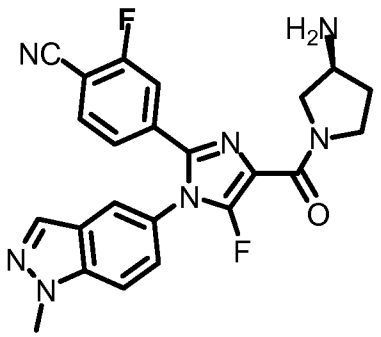
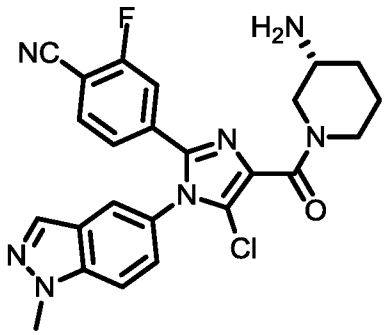
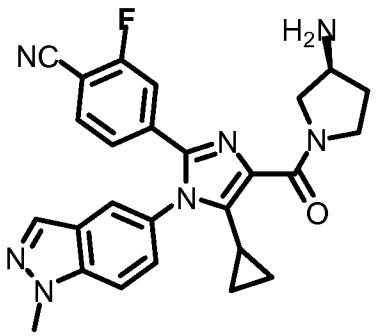
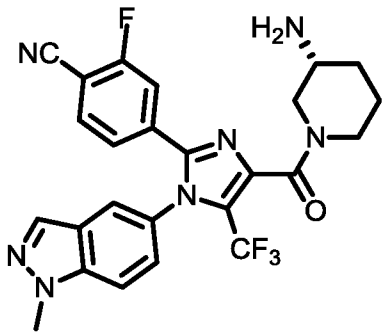
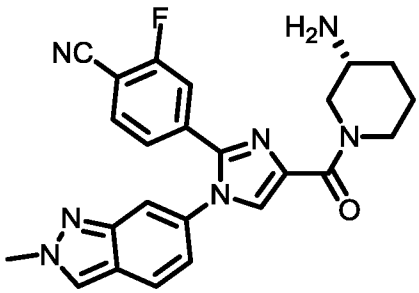
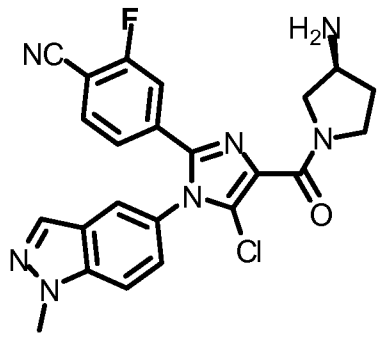
	
	
	
	
	

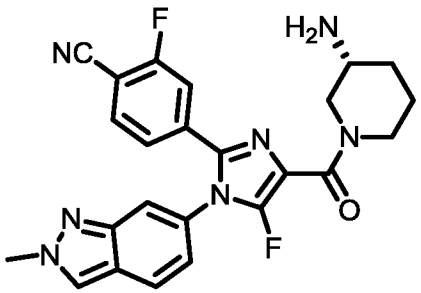
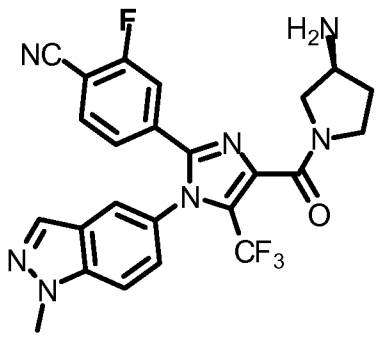
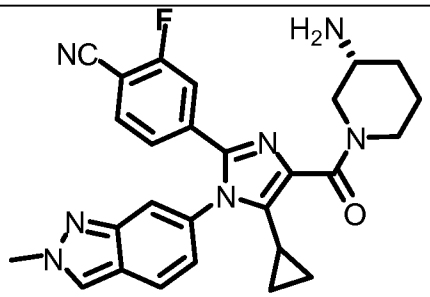
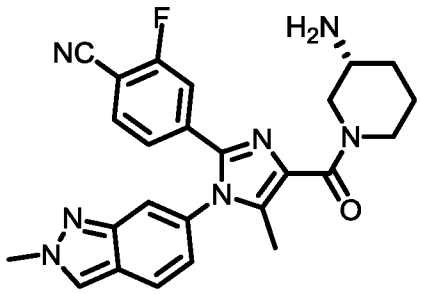
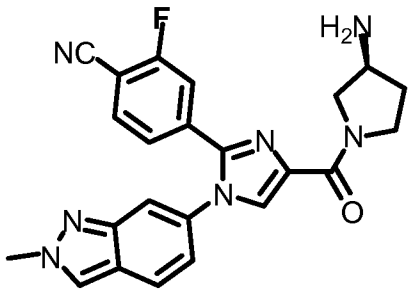
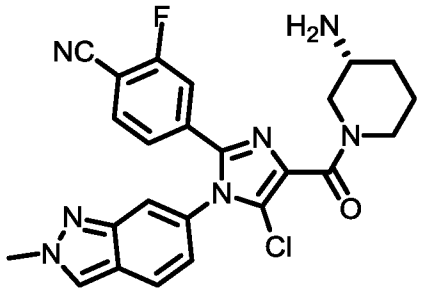
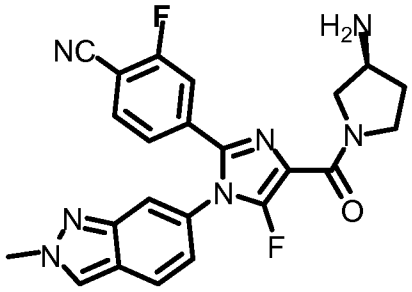
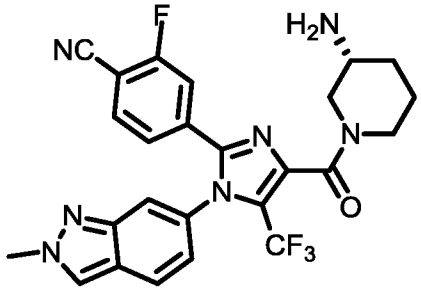
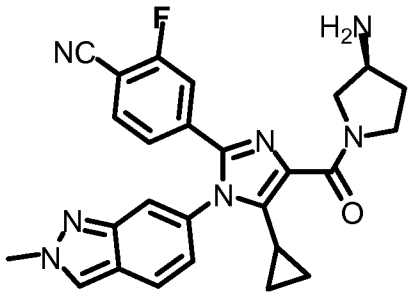
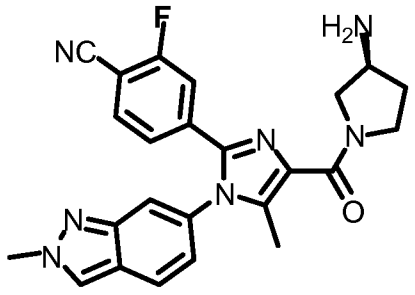
	
	
	
	
	

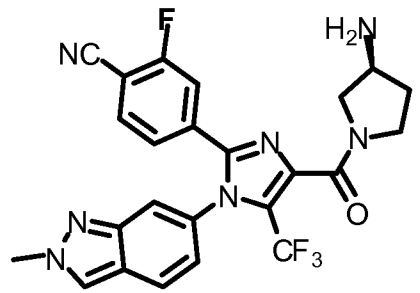
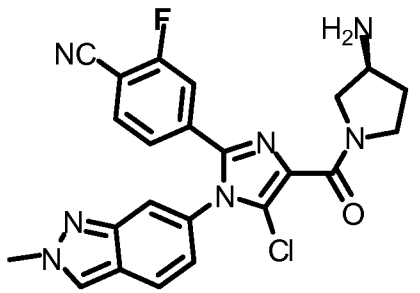
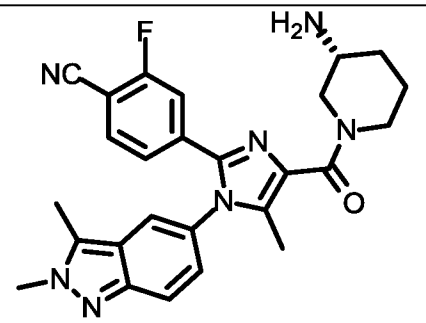
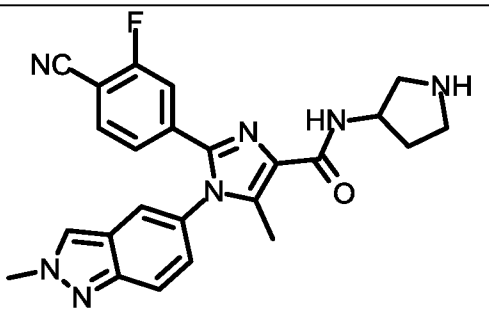
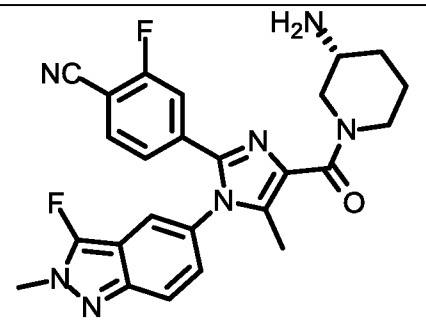
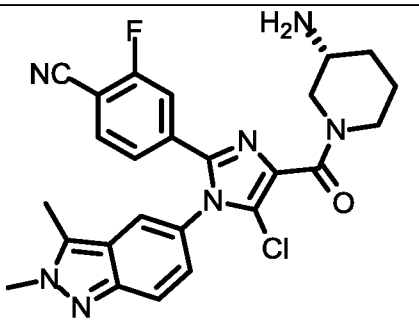
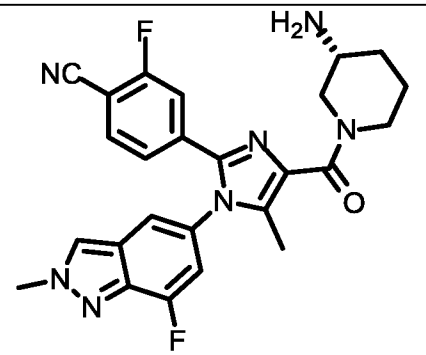
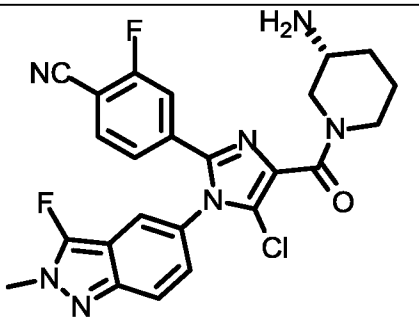
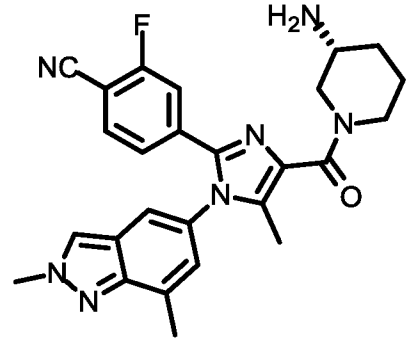
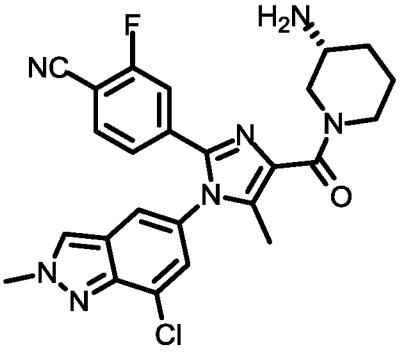
	
	
	
	
	

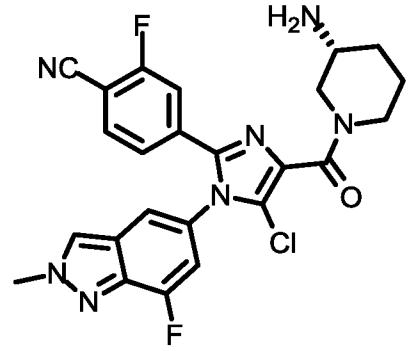
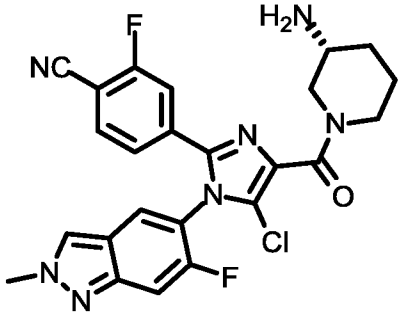
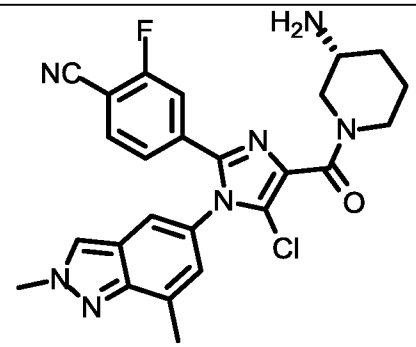
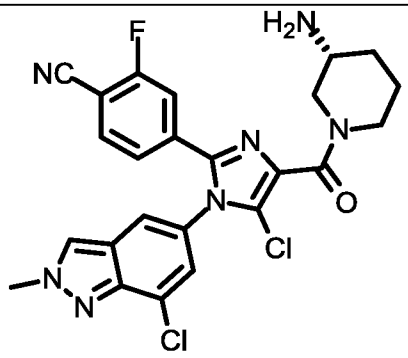
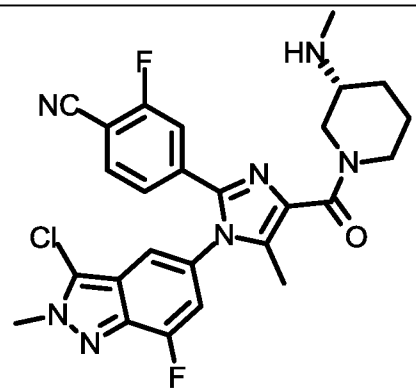
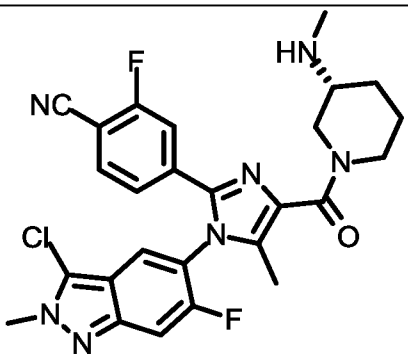
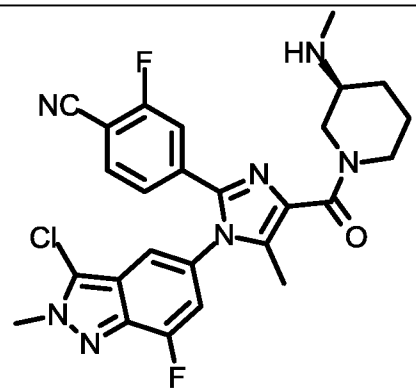
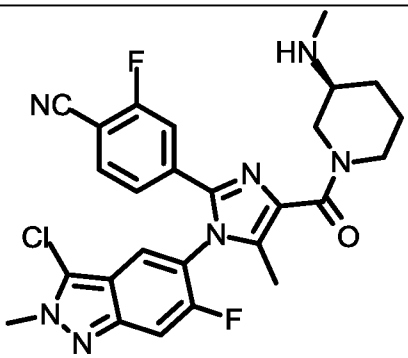
	
	
	
	
	

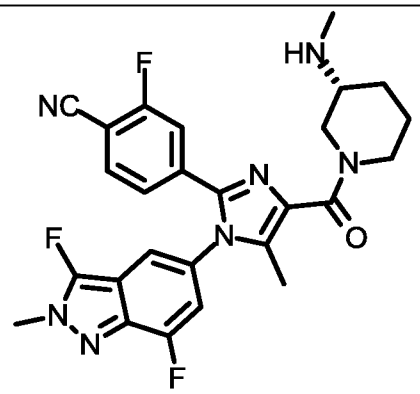
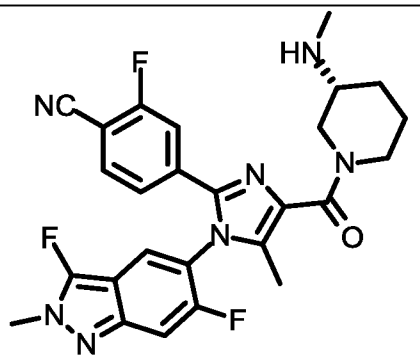
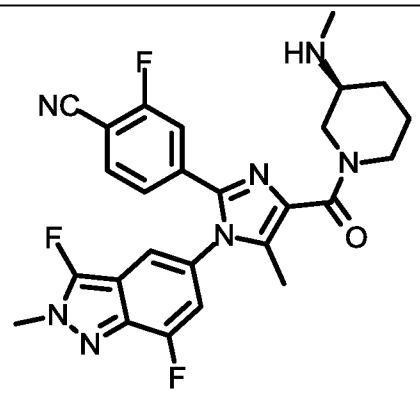
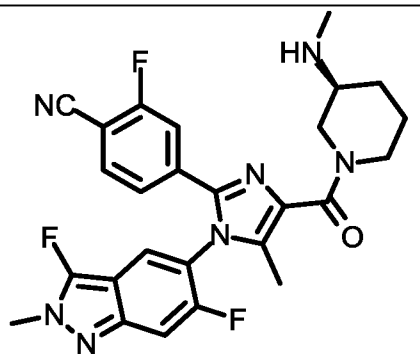
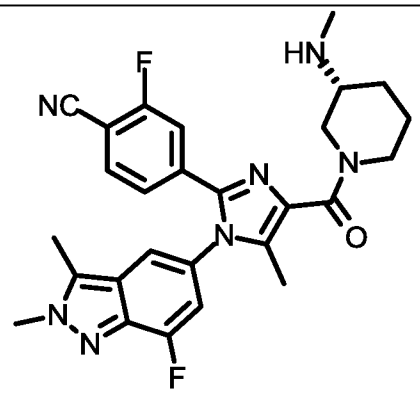
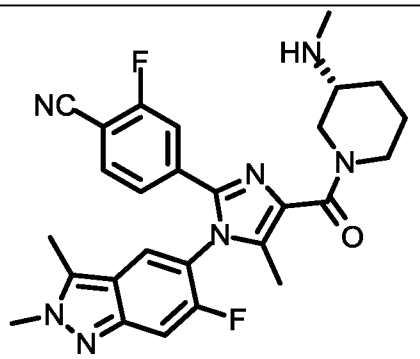
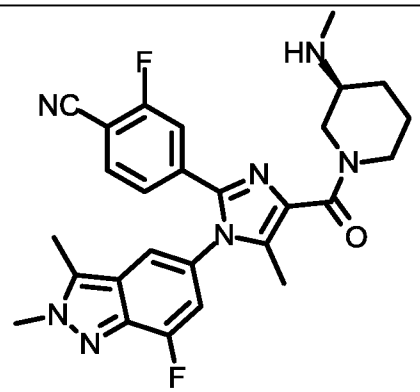
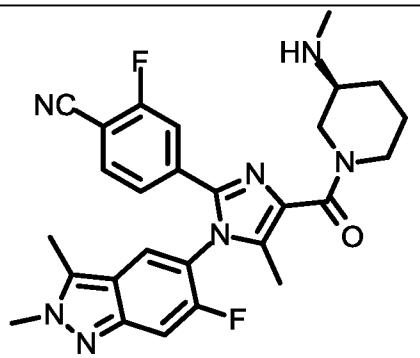
	
	
	
	
	

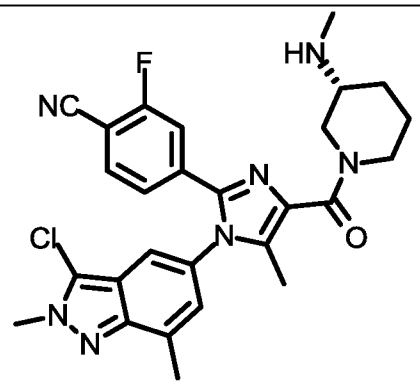
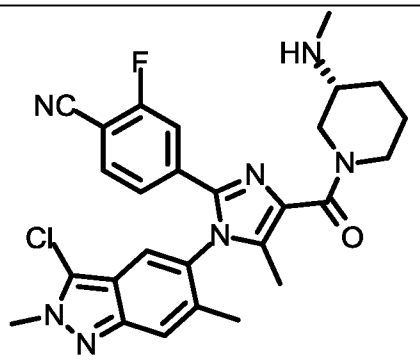
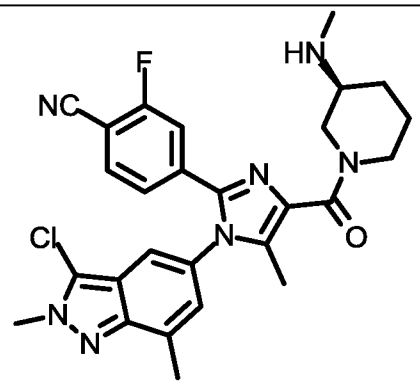
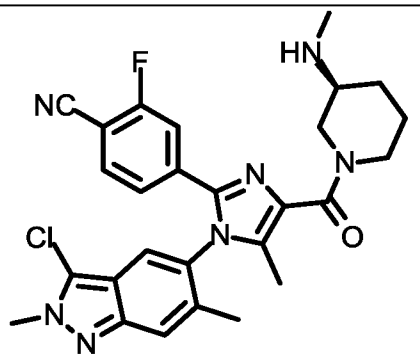
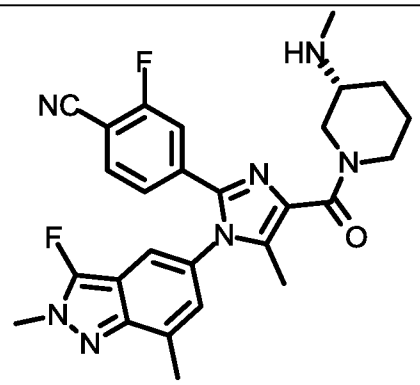
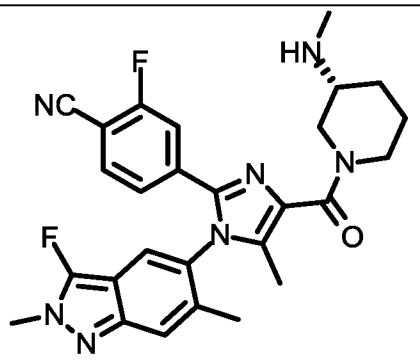
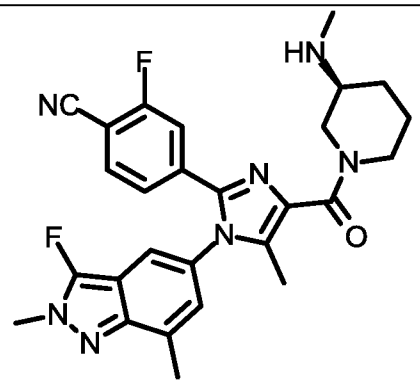
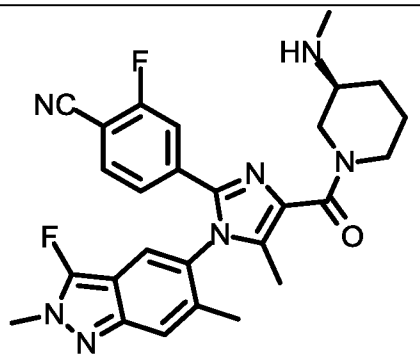
	
	
	
	

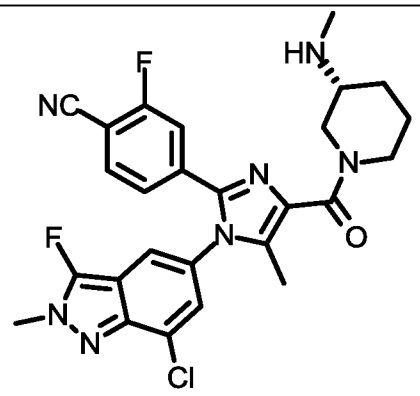
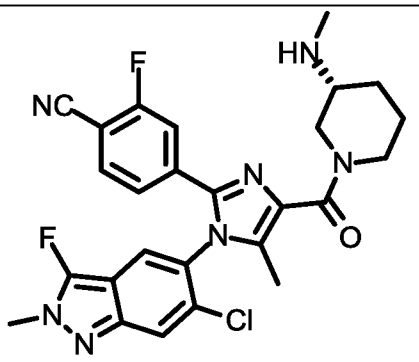
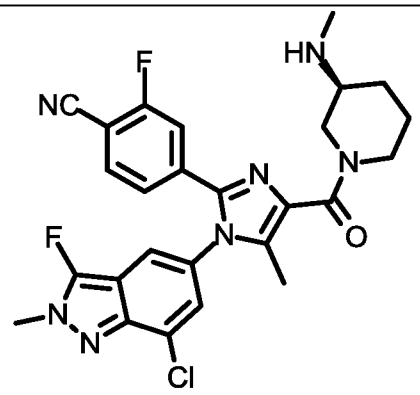
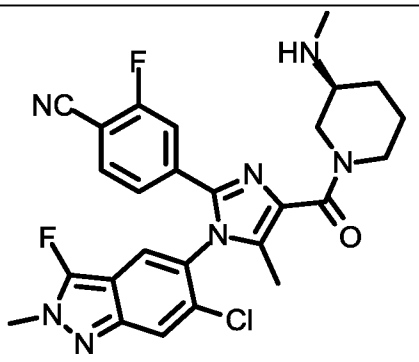
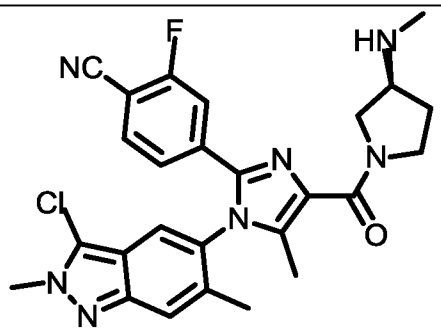
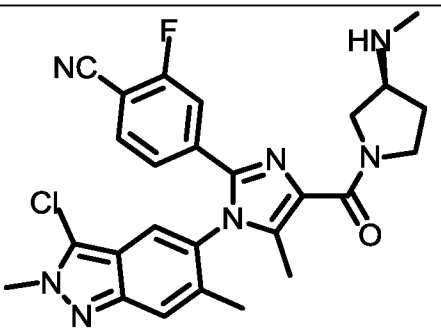
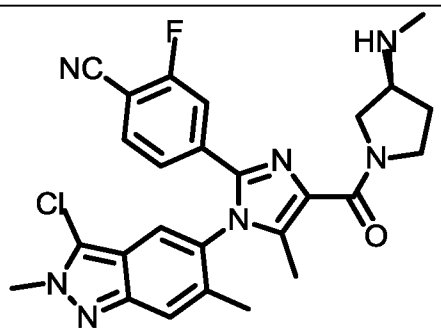
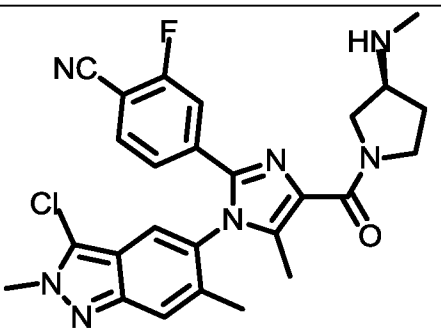
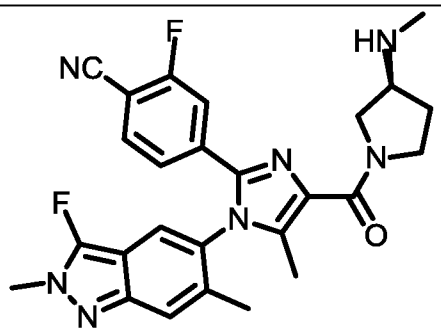
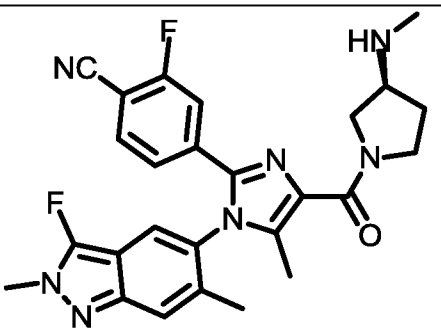
	
	
	
	
	

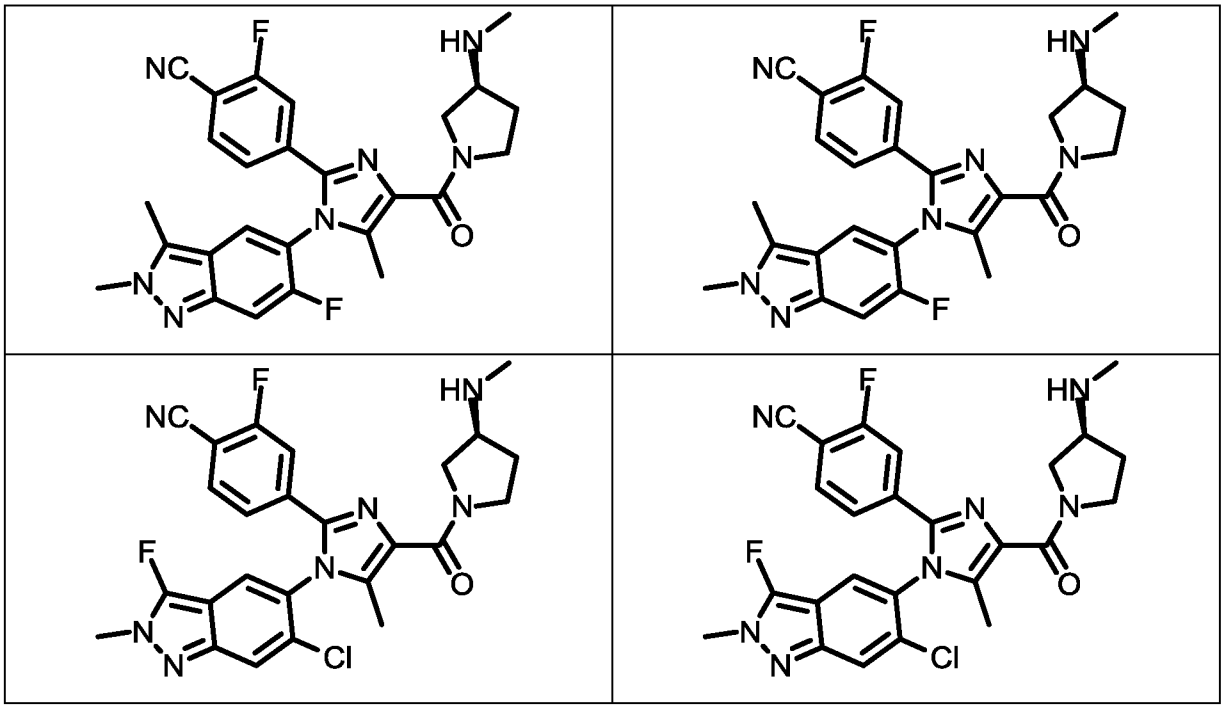
	
	
	
	
	



Preparation of the Substituted Heterocyclic Derivative Compounds

[0073] The compounds used in the reactions described herein are made according to organic synthesis techniques known to those skilled in this art, starting from commercially available chemicals and/or from compounds described in the chemical literature. "Commercially available chemicals" are obtained from standard commercial sources including Acros Organics (Pittsburgh, PA), Aldrich Chemical (Milwaukee, WI, including Sigma Chemical and Fluka), Apin Chemicals Ltd. (Milton Park, UK), Avocado Research (Lancashire, U.K.), BDH Inc. (Toronto, Canada), Bionet (Cornwall, U.K.), Chemservice Inc. (West Chester, PA), Crescent Chemical Co. (Hauppauge, NY), Eastman Organic Chemicals, Eastman Kodak Company (Rochester, NY), Fisher Scientific Co. (Pittsburgh, PA), Fisons Chemicals (Leicestershire, UK), Frontier Scientific (Logan, UT), ICN Biomedicals, Inc. (Costa Mesa, CA), Key Organics (Cornwall, U.K.), Lancaster Synthesis (Windham, NH), Maybridge Chemical Co. Ltd. (Cornwall, U.K.), Parish Chemical Co. (Orem, UT), Pfaltz & Bauer, Inc. (Waterbury, CN), Polyorganix (Houston, TX), Pierce Chemical Co. (Rockford, IL), Riedel de Haen AG (Hanover, Germany), Spectrum Quality Product, Inc. (New Brunswick, NJ), TCI America (Portland, OR), Trans World Chemicals, Inc. (Rockville, MD), and Wako Chemicals USA, Inc. (Richmond, VA).

[0074] Methods known to one of ordinary skill in the art are identified through various reference books and databases. Suitable reference books and treatise that detail the synthesis of reactants useful in the preparation of compounds described herein, or provide references to articles that describe the preparation, include for example, "Synthetic Organic

Chemistry", John Wiley & Sons, Inc., New York; S. R. Sandler et al., "Organic Functional Group Preparations," 2nd Ed., Academic Press, New York, 1983; H. O. House, "Modern Synthetic Reactions", 2nd Ed., W. A. Benjamin, Inc. Menlo Park, Calif. 1972; T. L. Gilchrist, "Heterocyclic Chemistry", 2nd Ed., John Wiley & Sons, New York, 1992; J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure", 4th Ed., Wiley-Interscience, New York, 1992. Additional suitable reference books and treatise that detail the synthesis of reactants useful in the preparation of compounds described herein, or provide references to articles that describe the preparation, include for example, Fuhrhop, J. and Penzlin G. "Organic Synthesis: Concepts, Methods, Starting Materials", Second, Revised and Enlarged Edition (1994) John Wiley & Sons ISBN: 3-527-29074-5; Hoffman, R.V. "Organic Chemistry, An Intermediate Text" (1996) Oxford University Press, ISBN 0-19-509618-5; Larock, R. C. "Comprehensive Organic Transformations: A Guide to Functional Group Preparations" 2nd Edition (1999) Wiley-VCH, ISBN: 0-471-19031-4; March, J. "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure" 4th Edition (1992) John Wiley & Sons, ISBN: 0-471-60180-2; Otera, J. (editor) "Modern Carbonyl Chemistry" (2000) Wiley-VCH, ISBN: 3-527-29871-1; Patai, S. "Patai's 1992 Guide to the Chemistry of Functional Groups" (1992) Interscience ISBN: 0-471-93022-9; Solomons, T. W. G. "Organic Chemistry" 7th Edition (2000) John Wiley & Sons, ISBN: 0-471-19095-0; Stowell, J.C., "Intermediate Organic Chemistry" 2nd Edition (1993) Wiley-Interscience, ISBN: 0-471-57456-2; "Industrial Organic Chemicals: Starting Materials and Intermediates: An Ullmann's Encyclopedia" (1999) John Wiley & Sons, ISBN: 3-527-29645-X, in 8 volumes; "Organic Reactions" (1942-2000) John Wiley & Sons, in over 55 volumes; and "Chemistry of Functional Groups" John Wiley & Sons, in 73 volumes.

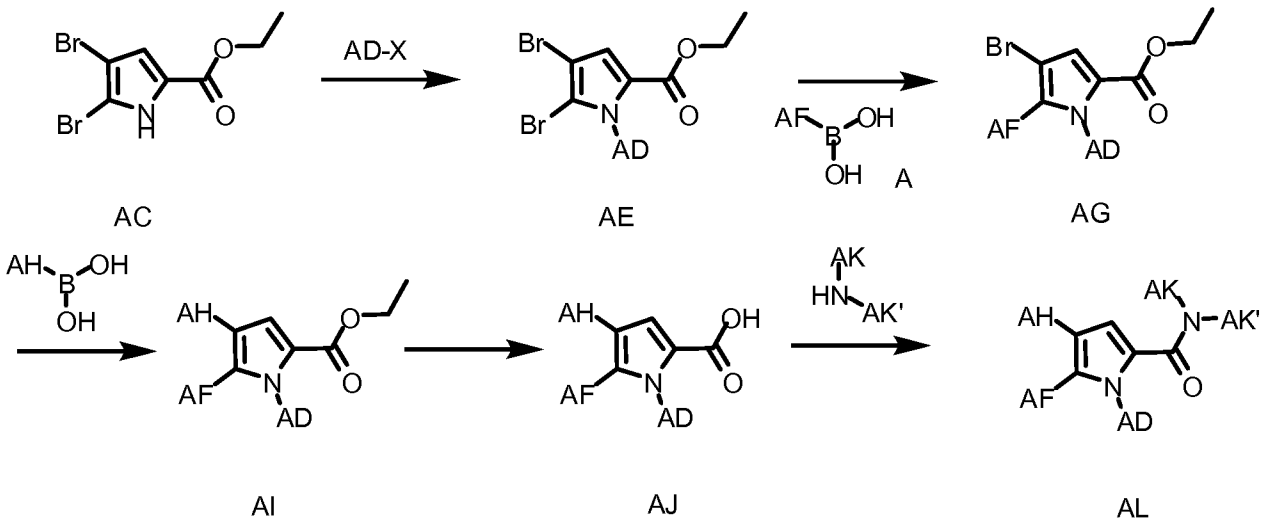
[0075] Specific and analogous reactants may also be identified through the indices of known chemicals prepared by the Chemical Abstract Service of the American Chemical Society, which are available in most public and university libraries, as well as through on-line databases (the American Chemical Society, Washington, D.C., may be contacted for more details). Chemicals that are known but not commercially available in catalogs may be prepared by custom chemical synthesis houses, where many of the standard chemical supply houses (*e.g.*, those listed above) provide custom synthesis services. A reference for the preparation and selection of pharmaceutical salts of the substituted heterocyclic derivative compounds described herein is P. H. Stahl & C. G. Wermuth "Handbook of Pharmaceutical Salts", Verlag Helvetica Chimica Acta, Zurich, 2002.

[0076] The substituted heterocyclic derivative compounds are prepared by the general synthetic routes described below in Schemes 1-2.

[0077] The substituted pyrrole derivative compounds are prepared by the general synthetic route described below in Scheme 1.

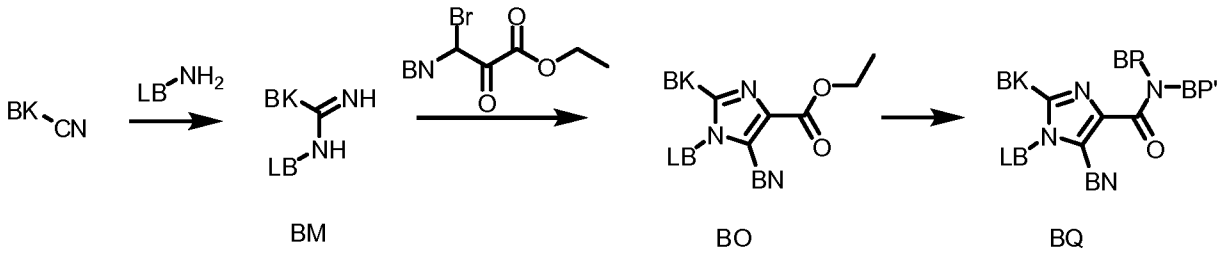
[0078] Referring to Scheme 1, compound AE is obtained from N-alkylation of compound AC with a variety of alkyl halides AD-X. Compound AG is prepared from aryl halide compound AE using palladium-mediated aryl cross coupling conditions with boronic acids AF-$B(OH)_2$. Compound AI is prepared from aryl halide compound AG using palladium-mediated aryl cross coupling conditions with boronic acids AH-$B(OH)_2$. Hydrolysis of compound AI affords compound AJ. Amide coupling is carried out with a variety of amines AKAK'-NH and compound AJ to form compound AL.

Scheme 1



[0079] The substituted imidazole derivative compounds are prepared by the general synthetic route described below in Scheme 2.

Scheme 2



[0080] Referring to Scheme 2, substituted aniline (BL-NH_2) is first treated with a base followed by reaction with an aromatic nitrile (BK-CN) to form amidine intermediate BM.

Compound BM is then treated with α-bromo-oxobutanoate in presence of a base at room temperature or under heating condition. After the first alkylation intermediate is formed, treatment with an acid affects the cyclization to give compound BO. Saponification followed by HATU coupling with an amine to affords the final product BQ.

Pharmaceutical Compositions

[0081] In certain embodiments, the substituted heterocyclic derivative compound as described herein is administered as a pure chemical. In other embodiments, the substituted heterocyclic derivative compound described herein is combined with a pharmaceutically suitable or acceptable carrier (also referred to herein as a pharmaceutically suitable (or acceptable) excipient, physiologically suitable (or acceptable) excipient, or physiologically suitable (or acceptable) carrier) selected on the basis of a chosen route of administration and standard pharmaceutical practice as described, for example, in *Remington: The Science and Practice of Pharmacy* (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005)), the disclosure of which is hereby incorporated herein by reference in its entirety.

[0082] Accordingly, provided herein is a pharmaceutical composition comprising at least one substituted heterocyclic derivative compound, or a stereoisomer, pharmaceutically acceptable salt, hydrate, solvate, or N-oxide thereof, together with one or more pharmaceutically acceptable carriers. The carrier(s) (or excipient(s)) is acceptable or suitable if the carrier is compatible with the other ingredients of the composition and not deleterious to the recipient (*i.e.,* the subject) of the composition.

[0083] One embodiment provides a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0084] In certain embodiments, the substituted heterocyclic derivative compound as described by Formula (I) is substantially pure, in that it contains less than about 5%, or less than about 1%, or less than about 0.1%, of other organic small molecules, such as contaminating intermediates or by-products that are created, for example, in one or more of the steps of a synthesis method.

[0085] Suitable oral dosage forms include, for example, tablets, pills, sachets, or capsules of hard or soft gelatin, methylcellulose or of another suitable material easily dissolved in the digestive tract. Suitable nontoxic solid carriers can be used which include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate,

and the like. (*See, e.g., Remington: The Science and Practice of Pharmacy* (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005)).

[0086] The dose of the composition comprising at least one substituted heterocyclic derivative compound as described herein may differ, depending upon the patient's (*e.g.,* human) condition, that is, stage of the disease, general health status, age, and other factors that a person skilled in the medical art will use to determine dose.

[0087] Pharmaceutical compositions may be administered in a manner appropriate to the disease to be treated (or prevented) as determined by persons skilled in the medical arts. An appropriate dose and a suitable duration and frequency of administration will be determined by such factors as the condition of the patient, the type and severity of the patient's disease, the particular form of the active ingredient, and the method of administration. In general, an appropriate dose and treatment regimen provides the composition(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit (*e.g.,* an improved clinical outcome, such as more frequent complete or partial remissions, or longer disease-free and/or overall survival, or a lessening of symptom severity. Optimal doses may generally be determined using experimental models and/or clinical trials. The optimal dose may depend upon the body mass, weight, or blood volume of the patient.

[0088] Oral doses can typically range from about 1.0 mg to about 1000 mg, one to four times, or more, per day.

Biology

[0089] Epigenetics is the study of heritable changes in gene expression caused by mechanisms other than the underlying DNA sequence. Molecular mechanisms that play a role in epigenetic regulation include DNA methylation and chromatin/histone modifications.

[0090] The genomes of eukaryotic organisms are highly organized within the nucleus of the cell. Tremendous compaction is required to package the 3 billion nucleotides of the human genome into the nucleus of a cell. Chromatin is the complex of DNA and protein that makes up chromosomes. Histones are the major protein component of chromatin, acting as spools around which DNA winds. Changes in chromatin structure are affected by covalent modifications of histone proteins and by non-histone binding proteins. Several classes of enzymes are known which can modify histones at various sites.

[0091] There are a total of six classes of histones (HI, H2A, H2B, H3, H4, and H5) organized into two groups: core histones (H2A, H2B, H3, and H4) and linker histones

(HI and H5). The basic unit of chromatin is the nucleosome, which consists of about 147 base pairs of DNA wrapped around the core histone octamer, consisting of two copies each of the core histones H2A, H2B, H3, and H4.

[0092] Basic nucleosome units are then further organized and condensed by the aggregation and folding of nucleosomes to form a highly condensed chromatin structure. A range of different states of condensation are possible, and the tightness of chromatin structure varies during the cell cycle, being most compact during the process of cell division.

[0093] Chromatin structure plays a critical role in regulating gene transcription, which cannot occur efficiently from highly condensed chromatin. The chromatin structure is controlled by a series of post translational modifications to histone proteins, notably histones H3 and H4, and most commonly within the histone tails which extend beyond the core nucleosome structure. These modifications acetylation, methylation, phosphorylation, ribosylation sumoylation, ubiquitination, citrullination, deimination, and biotinylation. The core of histones H2A and H3 can also be modified. Histone modifications are integral to diverse biological processes such as gene regulation, DNA repair, and chromosome condensation.

[0094] Histone methylation is one of the most important chromatin marks; these play important roles in transcriptional regulation, DNA-damage response, heterochromatin formation and maintenance, and X-chromosome inactivation. A recent discovery also revealed that histone methylation affects the splicing outcome of pre-mRNA by influencing the recruitment of splicing regulators. Histone methylation includes mono-, di-, and tri-methylation of lysines, and mono-, symmetric di-, and asymmetric di-methylation of arginines. These modifications can be either an activating or repressing mark, depending on the site and degree of methylation.

Histone Demethylases

[0095] A "demethylase" or "protein demethylase," as referred to herein, refers to an enzyme that removes at least one methyl group from polypeptide. Demethylases comprise a JmjC domain, and can be a methyl-lysine or methyl-arginine demethylase. Some demethylases act on histones, e.g., act as a histone H3 or H4 demethylase. For example, an H3 demethylase may demethylate one or more of H3K4, H3K9, H3K27, H3K36 and/or H3K79. Alternately, an H4 demethylase may demethylate histone H4K20. Demethylases are known which can demethylate either a mono-, di- and/or a tri-methylated substrate. Further, histone demethylases can act on a methylated core histone

substrate, a mononucleosome substrate, a dinucleosome substrate and/or an oligonucleosome substrate, peptide substrate and/or chromatin (e.g., in a cell-based assay).

[0096] The first lysine demethylase discovered was lysine specific demethylase 1 (LSD1/KDM1), which demethylates both mono- and di-methylated H3K4 or H3K9, using flavin as a cofactor. A second class of Jumonji C (JmjC) domain containing histone demethylases were predicted, and confirmed when a H3K36 demethylase was found used a formaldehyde release assay, which was named JmjC domain containing histone demethylase 1 (JHDM1/KDM2A).

[0097] More JmjC domain-containing proteins were subsequently identified and they can be phylogenetically clustered into seven subfamilies: JHDM1, JHDM2, JHDM3, JMJD2, JARID, PHF2/PHF8, UTX/UTY, and JmjC domain only.

LSD-1

[0098] Lysine-specific demethylase 1 (LSD1) is a histone lysine demethylase that specifically demethylates monomethylated and dimethylated histone H3 at K4 and also demethylates dimethylated histone H3 at K9. Although the main target of LSDl appears to be mono- and di-methylated histone lysines, specifically H3K4 and H3K9, there is evidence in the literature that LSD l can demethylate methylated lysines on non-histone proteins like p53, E2F1 , Dnmtl and STAT3.

[0099] LSD l has a fair degree of structural similarity and amino acid identity/homology to polyamine oxidases and monoamine oxidases, all of which (i. e., MAO-A, MAO-B and LSDl) are flavin dependent amine oxidases which catalyze the oxidation of nitrogen-hydrogen bonds and/or nitrogen-carbon bonds. LSD1 also includes an N-terminal SWRIM domain. There are two transcript variants of LSD1 produced by alternative splicing.

Methods of Use

[00100] In some embodiments, the compounds disclosed herein are capable of inhibiting LSD1 activity in a biological sample by contacting the biological sample with a substituted heterocyclic compound as disclosed herein. In some embodiments, a substituted heterocyclic compound as disclosed herein is capable of modulating the level of histone 4 lysine 3 methylation in the biological sample. In some embodiments, a substituted heterocyclic compound as disclosed herein is capable of modulating histone-3 lysine-9 methylation levels in the biological sample.

[00101] In some embodiments, a substituted heterocyclic compound as disclosed herein inhibits LSD1 activity to a greater extent than MAO-A and/or MAO-B.

[00102] One embodiment provides a method of regulating gene transcription in a cell comprising inhibiting lysine-specific demethylase 1 activity by exposing the lysine-specific demethylase 1 enzyme to a compound of Formula (I).

Methods of Treatment

[00103] Disclosed herein are methods of modulating demethylation in a cell or in a subject, either generally or with respect to one or more specific target genes. Demethylation can be modulated to control a variety of cellular functions, including without limitation: differentiation; proliferation; apoptosis; tumorigenesis, leukemogenesis or other oncogenic transformation events; hair loss; or sexual differentiation.

[00104] One embodiment provides a method of treating cancer in a patient in need thereof, comprising administering to the patient a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[00105] In a further embodiment is the method for treating cancer in a subject wherein the cancer is selected from prostate cancer, breast cancer, bladder cancer, lung cancer or melanoma.

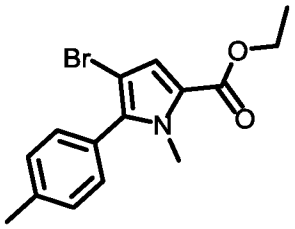
[00106] Other embodiments and uses will be apparent to one skilled in the art in light of the present disclosures. The following examples are provided merely as illustrative of various embodiments and shall not be construed to limit the invention in any way.

EXAMPLES

I. Chemical Synthesis

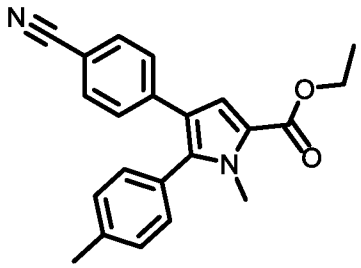
[00107] Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Anhydrous solvents and oven-dried glassware were used for synthetic transformations sensitive to moisture and/or oxygen. Yields were not optimized. Reaction times are approximate and were not optimized. Column chromatography and thin layer chromatography (TLC) were performed on silica gel unless otherwise noted. Spectra are given in ppm (δ) and coupling constants, J are reported in Hertz. For proton spectra the solvent peak was used as the reference peak.

Preparation 1A: ethyl 4-bromo-1-methyl-5-p-tolyl-1H-pyrrole-2-carboxylate



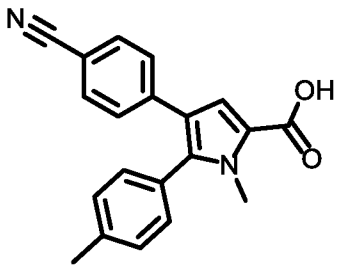
[00108] A mixture of ethyl 4,5-dibromo-1-methyl-1H-pyrrole-2-carboxylate (3.7 g, 11.9 mmol), p-tolylboronic acid (1.62 g, 11.9 mmol), $Pd(PPh_3)_4$ (275 mg, 0.24 mmol) and 2M Na_2CO_3 (2.5 g, 23.8 mmol) in in toluene/ethanol (30/10 mL) was flushed with nitrogen and stirred at 90 °C for 3 h. Water was added and the solution was extracted with EA (3x). The organics were combined, washed with water, washed with brine, dried and concentrated. The residue was purified by silica gel chromatography (1:1, EA:PE) to give 530 mg (14%) of the title compound. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 1.36 (t, *J* = 7.2 Hz , 3H), 2.42 (s, 3H), 3.78 (s, 3H), 4.27-4.32 (m, 2H), 7.06 (s, 1H), 7.24-7.30 (m, 4H). [M+H] Calc'd for $C_{15}H_{16}BrNO_2$, 322-324; Found, 322-324.

Preparation 1B: ethyl 4-(4-cyanophenyl)-1-methyl-5-p-tolyl-1H-pyrrole-2-carboxylate



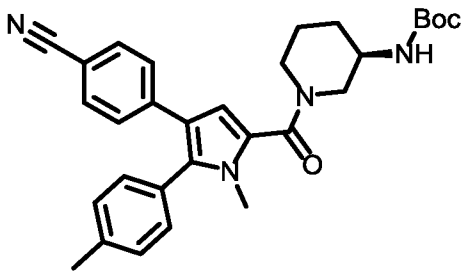
[00109] A mixture of ethyl 4-bromo-1-methyl-5-p-tolyl-1H-pyrrole-2-carboxylate (530 mg, 1.65 mmol) was added 4-cyanophenylboronic acid (371 mg, 2.48 mmol), $Pd(PPh_3)_4$ (190 mg, 0.17 mmol) and 2M Na_2CO_3 (1.7 mL, 3.4 mmol) in DMF (5 mL) was flushed with nitrogen and stirred at 90 °C for 4 h. Water was added and the solution was extracted with EA (3x). The organics were combined, washed with water, washed with brine, dried and concentrated. The residue was purified by silica gel chromatography (1:5, EA:PE) to give 200 mg (35%) of the title compound. ^1H NMR (300 MHz, $CDCl_3$): δ ppm 1.39 (t, *J* = 7.1 Hz , 3H), 2.43 (s, 3H), 3.75 (s, 3H), 4.30-4.37 (m, 2H), 7.13 (d, *J* = 7.8 Hz , 2H), 7.18-7.26 (m, 5H), 7.43 (d, *J* = 8.4 Hz , 2H). [M+H] Calc'd for $C_{22}H_{20}N_2O_2$, 345; Found, 345.

Preparation 1C: 4-(4-cyanophenyl)-1-methyl-5-p-tolyl-1H-pyrrole-2-carboxylic acid



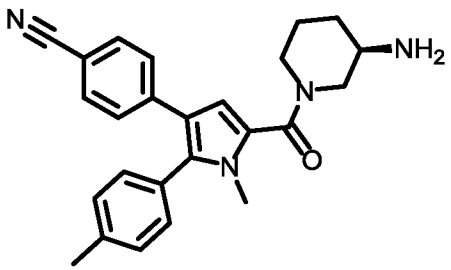
[00110] 2M NaOH solution (4 mL) was added to a solution of ethyl 4-(4-cyanophenyl)-1-methyl-5-p-tolyl-1H-pyrrole-2-carboxylate (200 mg, 0.58 mmol) in ethanol/THF (6/2 mL), and the mixture was stirred at RT overnight. The solution was adjusted to PH=2-3 and extracted with DCM (3x). The organics were combined, washed with water, washed with brine, dried and concentrated to give 160 mg (87%) of the title compound. [M-H] Calc'd for $C_{20}H_{16}N_2O_2$, 315; Found, 315.

Preparation 1D: (*R*)-*tert*-butyl 1-(3-(4-cyanophenyl)-1-methyl-2-p-tolyl-1H-pyrrole-5-carbonyl)piperidin-3-ylcarbamate



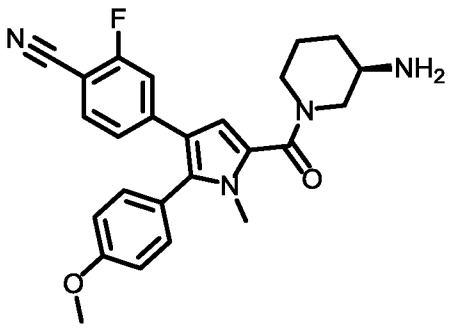
[00111] To a mixture of 4-(4-cyanophenyl)-1-methyl-5-p-tolyl-1H-pyrrole-2-carboxylic acid (160 mg, 0.5 mmol) in DCM (10 mL) was added EDCI (144 mg, 0.55 mmol), HOBT (68 mg, 0.75 mmol), (*R*)-*tert*-butyl piperidin-3-ylcarbamate (110 mg, 0.55 mmol) and DIEA (129 mg, 2.0 mmol), and the solution was stirred at RT overnight. Water was added and the solution was extracted with DCM (3x). The organics were combined, washed with water, washed with brine, dried and concentrated. The residue was purified by silica gel chromatography (1:5, EA:PE) to give 130 mg (53%) of the title compound. [M+H] Calc'd for $C_{30}H_{34}N_4O_3$, 499; Found, 499.

Example 1: 4-[5-(3-(*R*)-amino-piperidine-1-carbonyl)-1-methyl-2-p-tolyl-1H-pyrrol-3-yl]-benzonitrile



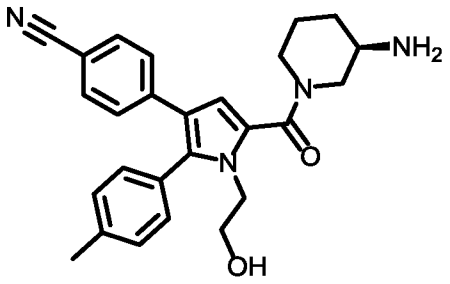
[00112] To a solution of (*R*)-tert-butyl 1-(3-(4-cyanophenyl)-1-methyl-2-p-tolyl-1H-pyrrole-5-carbonyl)piperidin-3-ylcarbamate (130 mg, 0.26 mmol) in EA (1 mL) was added a 4N HCl solution in EA (2 mL), and the mixture was stirred at RT for 1h. The solvent was concentrated *in vacuo* to give 108 mg (96%) of the title compound as the HCl salt. ^{1}H NMR (CD_3OD, 400 MHz): δ ppm 1.67-1.71 (m, 2H), 1.87-1.90 (m, 1H), 2.17-2.19 (m, 1H), 2.39 (s, 3H), 3.30-3.37 (m, 3H), 3.49 (s, 3H), 4.21 (d, J = 13.6 Hz , 1H), 4.46-4.49 (m, 1H), 6.79 (s, 1H), 7.14 (d, J = 7.6 Hz, 2H), 7.26-7.29 (m, 4H), 7.46 (d, J = 8.0 Hz, 2H). [M+H] Calc'd for $C_{25}H_{26}N_4O$, 399; Found, 399.

Example 2: 4-[5-(3-(*R*)-amino-piperidine-1-carbonyl)-2-(4-methoxy-phenyl)-1-methyl-1H-pyrrol-3-yl]-2-fluoro-benzonitrile



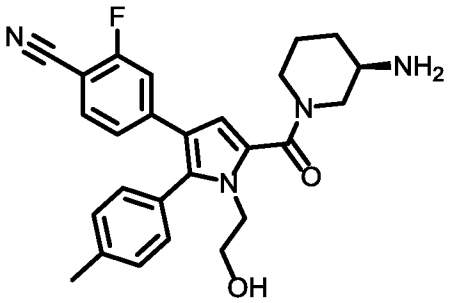
[00113] The title compound was prepared as the HCl salt in 7% overall yield according to the general procedure for the preparation of Example 1. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 1.70-1.73 (m, 2H), 1.88-1.91 (m, 1H), 2.20-2.22 (m, 1H), 3.35-3.37 (m, 3H), 3.50 (s, 3H), 3.85 (s, 3H), 4.22 (d, *J* = 11.6 Hz , 1H), 4.47-4.50 (m, 1H), 6.84 (s, 1H), 7.05-7.10 (m, 4H), 7.21 (d, *J* = 7.6 Hz, 2H), 7.47 (t, *J* = 7.4 Hz, 1H). [M+H] Calc'd for $C_{25}H_{25}N_4O_2$, 433; Found, 433.

Example 3: 4-[5-(3-(*R*)-amino-piperidine-1-carbonyl)-1-(2-hydroxy-ethyl)-2-p-tolyl-1H-pyrrol-3-yl]-benzonitrile



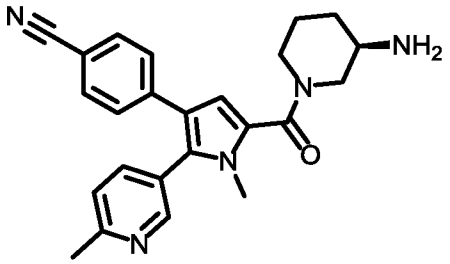
[00114] The title compound was prepared as the HCl salt in 14% overall yield according to the general procedure for the preparation of Example 1. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 1.71-1.74 (m, 2H), 1.86-1.87 (m, 1H), 2.17-2.20 (m, 1H), 2.41 (s, 3H), 3.36-3.42 (m, 5H), 4.17-4.49 (m, 1H), 3.85 (s, 3H), 6.79 (s, 1H), 7.18 (d, J = 8.0 Hz, 2H), 7.25-7.30 (m, 4H), 7.45 (t, J = 8.8 Hz, 2H). [M+H] Calc'd for $C_{26}H_{28}N_4O_2$, 429; Found, 429.

Example 4: 4-[5-(3-(*R*)-amino-piperidine-1-carbonyl)-1-(2-hydroxy-ethyl)-2-p-tolyl-1H-pyrrol-3-yl]-2-fluoro-benzonitrile



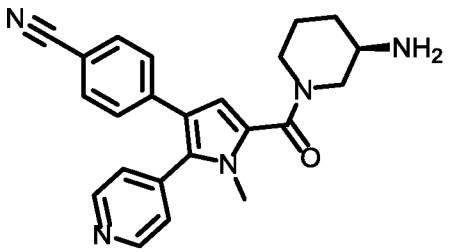
[00115] The title compound was prepared as the HCl salt in 13% overall yield according to the general procedure for the preparation of Example 1. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 1.70-1.73 (m, 2H), 1.83-1.86 (m, 1H), 2.15-2.20 (m, 1H), 2.40 (s, 3H), 3.31-3.42 (m, 5H), 4.14-4.23 (m, 3H), 4.45-4.48 (m, 1H), 6.82 (s, 1H), 6.99-7.07 (m, 2H), 7.19 (d, J = 7.6 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 7.45 (t, J = 7.6 Hz, 1H). [M+H] Calc'd for $C_{26}H_{27}FN_4O_2$, 447; Found, 447.

Example 5: 4-[5-(3-(*R*)-amino-piperidine-1-carbonyl)-1-methyl-2-(6-methyl-pyridin-3-yl)-1H-pyrrol-3-yl]-benzonitrile



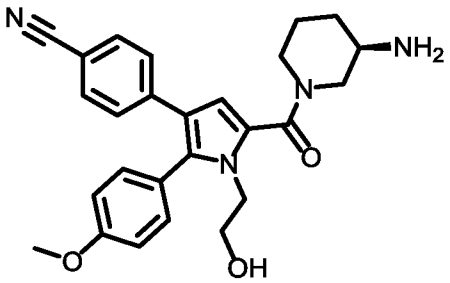
[00116] The title compound was prepared as the HCl salt in 21% overall yield according to the general procedure for the preparation of Example 1. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 1.67-1.76 (m, 2H), 1.89-1.92 (m, 1H), 2.19-2.21 (m, 1H), 2.84 (s, 3H), 3.32-3.39 (m, 3H), 3.63 (s, 3H), 4.16-4.20 (m, 1H), 4.48-4.51 (m, 1H), 6.81 (s, 1H), 7.34 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.98 (d, J = 8.4 Hz, 1H), 8.40-8.43 (m, 1H), 8.74 (d, J = 2.0 Hz, 1H). [M+H] Calc'd for $C_{24}H_{25}N_5O$, 400; Found, 400.

Example 6: 4-[5-(3-(*R*)-amino-piperidine-1-carbonyl)-1-methyl-2-pyridin-4-yl-1H-pyrrol-3-yl]-benzonitrile



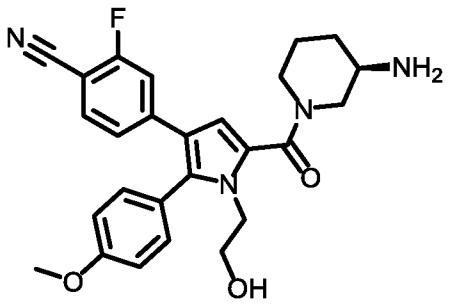
[00117] The title compound was prepared as the HCl salt in 25% overall yield according to the general procedure for the preparation of Example 1. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 1.67-1.73 (m, 2H), 1.88-1.92 (m, 1H), 2.18-2.20 (m, 1H), 3.30-3.39 (m, 3H), 3.73 (s, 3H), 4.13-4.16 (m, 1H), 4.45-4.49 (m, 1H), 6.77 (s, 1H), 7.38 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H), 7.94 (d, J = 8.6 Hz, 2H), 8.77 (d, J = 6.8 Hz, 2H). [M+H] Calc'd for $C_{23}H_{23}N_5O$, 386; Found, 386.

Example 7: 4-[5-(3-(*R*)-amino-piperidine-1-carbonyl)-1-(2-hydroxy-ethyl)-2-(4-methoxy-phenyl)-1H-pyrrol-3-yl]-benzonitrile



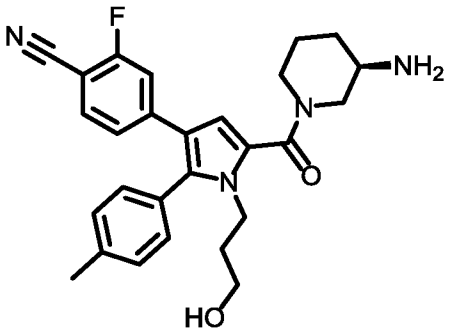
[00118] The title compound was prepared as the HCl salt in 16% overall yield according to the general procedure for the preparation of Example 1. ^{1}H NMR (300 MHz, CD_3OD): δ ppm 1.67-1.73 (m, 2H), 1.82-1.86 (m, 1H), 2.13-2.15 (m, 1H), 3.32-3.42 (m, 5H), 3.81 (s, 3H), 4.14-4.25 (m, 3H), 4.43-4.49 (m, 1H), 6.77 (s, 1H), 7.00 (d, J = 8.7 Hz, 2H), 7.17-7.26 (m, 4H), 7.44 (d, J = 8.7 Hz, 2H). [M+H] Calc'd for $C_{26}H_{28}N_4O_3$, 445; Found, 445.

Example 8: 4-[5-(3-(*R*)-amino-piperidine-1-carbonyl)-1-(2-hydroxy-ethyl)-2-(4-methoxy-phenyl)-1H-pyrrol-3-yl]-2-fluoro-benzonitrile



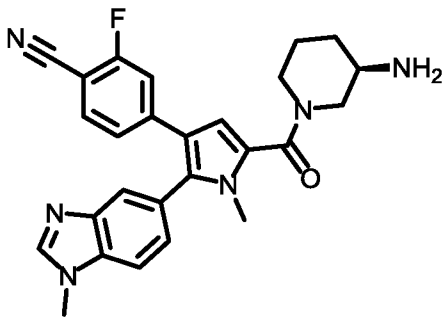
[00119] The title compound was prepared as the HCl salt in 15% overall yield according to the general procedure for the preparation of Example 1. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 1.70-1.76 (m, 2H), 1.86-1.89 (m, 1H), 2.01-2.06 (m, 1H), 3.36-3.48 (m, 5H), 3.87 (s, 3H), 4.18-4.26 (m, 3H), 4.86-4.51 (m, 1H), 6.84 (s, 1H), 7.04-7.10 (m, 4H), 7.24 (d, *J* = 8.8 Hz, 2H),7.46-7.50 (m, 1H). [M+H] Calc'd for $C_{26}H_{27}FN_4O_3$, 463; Found, 463.

Example 9: 4-[5-(3-(*R*)-amino-piperidine-1-carbonyl)-1-(3-hydroxy-propyl)-2-(4-methoxy-phenyl)-1H-pyrrol-3-yl]-2-fluoro-benzonitrile



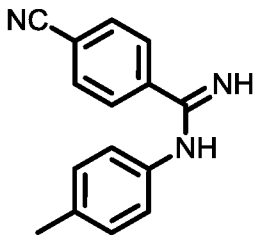
[00120] The title compound was prepared as the HCl salt in 13% overall yield according to the general procedure for the preparation of Example 1. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 1.54-1.61 (m, 2H), 1.73-1.78 (m, 2H), 1.87-1.92 (m, 1H), 2.18-2.22 (m, 1H), 2.42 (s, 3H), 3.24-3.49 (m, 5H), 4.11-4.21 (m, 3H), 4.38-4.41 (m, 1H) ، 6.85 (s, 1H), 7.01-7.08 (m, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.44-7.48 (m, 1H). [M+H] Calc'd for $C_{27}H_{29}FN_4O_2$, 461; Found, 461.

Example 10: 4-[5-(3-(*R*)-amino-piperidine-1-carbonyl)-1-methyl-2-(1-methyl-1H-benzoimidazol-5-yl)-1H-pyrrol-3-yl]-2-fluoro-benzonitrile



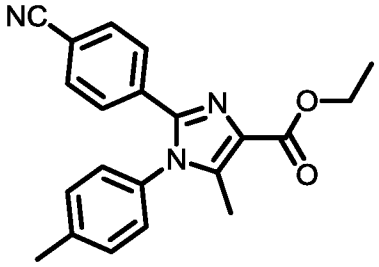
[00121] The title compound was prepared as the HCl salt in 21% overall yield according to the general procedure for the preparation of Example 1. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 1.69-1.77 (m, 2H), 1.90-1.96 (m, 1H), 2.00-2.22 (m, 1H), 3.33-3.42 (m, 3H), 3.53 (s, 3H), 4.17-4.24 (m, 4H), 4.50-4.53 (m, 1H), 6.87 (s, 1H), 7.04-7.07 (m, 2H), 7.43-7.47 (m, 1H), 7.61-7.63 (m, 1H), 7.84 (s, 1H), 8.06 (d, J = 8.4 Hz, 1H), 9.50 (s, 1H). [M+H] Calc'd for $C_{26}H_{25}FN_6O$, 457; Found, 457.

Preparation 11A: 4-Cyano-N-(4-methylphenyl)benzenecarboximidamide



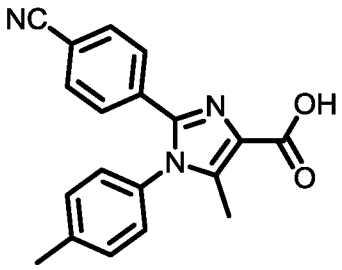
[00122] To a suspension of NaH (60% in mineral oil) (2.34 g, 58.5 mmol, 60%, 1.5 equiv) in DMSO (80 mL) at 0 °C was added p-toluidine (4.6 g, 43.0 mmol, 1.1 equiv) and 1,4-dicyanobenzene (5.0 g, 39.0 mmol). The mixture was kept at 0 °C for 15 min and then stirred at rt for 1 h. Ice-water (500 mL) was added while maintaining vigorous stirring. The precipitate was filtered, washed with water and dried to give 6.11 g of the desired product as a yellow solid (67%). [M+H] Calc'd for $C_{15}H_{13}N_3$, 236; Found, 236.

Preparation 11B: Ethyl 2-(4-cyanophenyl)-5-methyl-1-(4-methylphenyl)imidazole-4-carboxylate



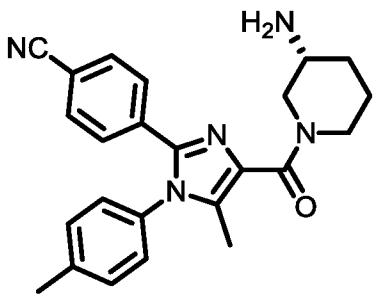
[00123] To a mixture of 4-cyano-N-(4-methylphenyl)benzenecarboximidamide (470 mg, 2 mmol) in EtOH (10 mL) was added ethyl-3-bromo-2-oxobutanoate (500 mg, 2.4 mmol), followed by sodium bicarbonate (252 mg, 3 mmol). The reaction mixture was heated at 90 °C overnight. The solid was filtered and filtrate was concentrated to a residue, which was dissolved in acetic acid (5 mL) and heated to 120 °C for 3 h. The reaction mixture was then concentrated and purified by flash column (EtOAc/Hexane) to give the title compound as an orange solid (270 mg, 40%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.31 (3H, t, J = 7.4 Hz), 2.29 (3H, s), 2.39 (3H, s), 4.29 (2H, q, J = 7.1 Hz), 7.29 (2H, d, J= 8.2 Hz), 7.37 (2H, d, J = 8.2 Hz), 7.45 (2H, d, J = 8.3 Hz), 7.75 (2H, d, J = 8.4 Hz). [M+H] Calc'd for $C_{21}H_{19}N_3O_2$, 346; Found, 346.

Preparation 11C: 2-(4-Cyanophenyl)-5-methyl-1-(4-methylphenyl)imidazole-4-carboxylic acid



[00124] A solution of ethyl 2-(4-cyanophenyl)-5-methyl-1-(4-methylphenyl)imidazole-4-carboxylate (240 mg, 0.8 mmol) in a mixture of THF (2 mL) and EtOH (6 mL) was treated with 2M NaOH (2 mL). The reaction mixture was stirred at rt overnight. It was then acidified by 1N HCl, followed by extraction with EtOAc. Organic layer was separated, dried and concentrated to give the title compound as an orange solid (120 mg, 48%). [M+H] Calc'd for $C_{19}H_{15}N_3O_2$, 318; Found, 318.

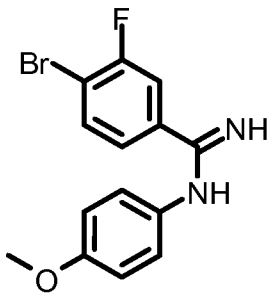
Example 11: 4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-5-methyl-1-(4-methylphenyl)imidazol-2-yl]benzonitrile



[00125] To a mixture of 2-(4-cyanophenyl)-5-methyl-1-(4-methylphenyl)imidazole-4-carboxylic acid (120 mg, 0.38 mmol), (R)-3-boc-aminopiperidine (114 mg, 0.57 mmol)

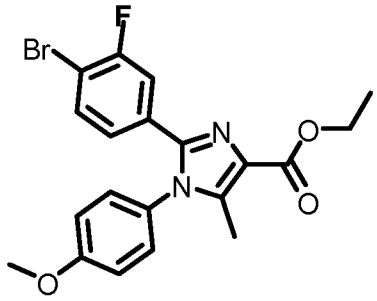
and DIEA (126 uL, 0.57 mmol) in DMF was added HATU (217 mg, 0.57 mmol). The reaction mixture was stirred at rt for 2 h. It was then separated between water and EtOAc. The organic extract was dried and concentrated to a residue, which was dissolved in CH_2Cl_2 (5 mL) and treated with TFA (2 mL). After 2 h, the reaction mixture was concentrated and purified by prep-HPLC to afford the title compound as the formic acid salt (20 mg, 16%) as a white solid. ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.35-1.52 (2H, m), 1.74 (1H, m), 1.95 (1H, m), 2.16 (3H, s), 2.40 (3H, s), 2.89 (1H, m), 3.20 (2H, m), 4.57 (2H. m), 7.28 (2H, d, J= 7.8 Hz), 7.37 (2H, d, J = 8.2 Hz), 7.45 (2H, m), 7.75 (2H, d, J = 8.4 Hz), 8.28 (1H, s). [M+H] Calc'd for $C_{24}H_{25}N_5O$, 400; Found, 400.

Preparation 12A: 4-Bromo-3-fluoro-N-(4-methoxyphenyl)benzenecarboximidamide



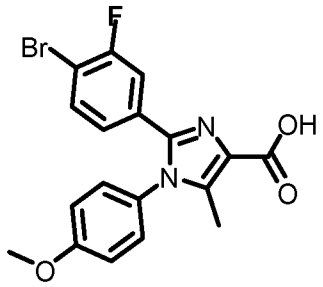
[00126] To 20 mL of EtMgBr (1M in THF) in 10 mL of THF, under nitrogen, was carefully added p-anisidine (1.23 g, 10 mmol). After 30 minutes of stirring at rt, 4-bromo-3-fluorobenzene nitrile (2.2 g, 11 mmol) in 5 mL THF was added dropwise. The mixture was stirred at rt for 20 h. Ice-water (10 mL) was carefully added while maintaining vigorous stirring. The reaction mixture was separated between water and EtOAc. Organic extract was dried and concentrated to a residue which was purified by ISCO flash column (EtOAc/Hexane). Fractions collected, concentrated and triturated with acetone and EtOAc to give 1.5 g of the desired product as a reddish solid (46%). [M+H] Calc'd for $C_{14}H_{12}BrFN_2O$, 324; Found, 324.

Preparation 12B: Ethyl 2-(4-bromo-3-fluorophenyl)-5-methyl-1-(4-methoxyphenyl)imidazole-4-carboxylate



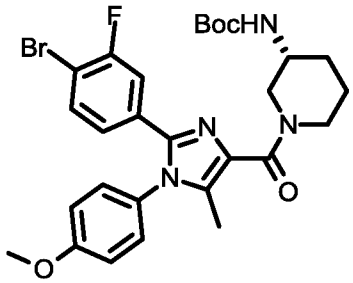
[00127] The title compound was prepared in 97% yield according to the procedure of Preparation 11B, except the product was formed in one pot without treatment with acid. [M+H] Calc'd for $C_{20}H_{18}BrFN_2O_3$, 434; Found, 434.

Preparation 12C: 2-(4-Bromo-3-fluorophenyl)-5-methyl-1-(4-methoxyphenyl)imidazole-4-carboxylic acid



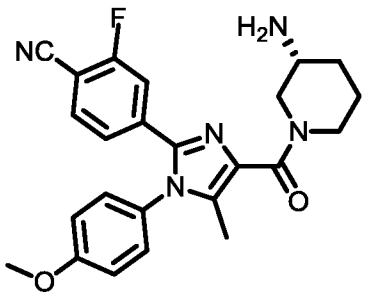
[00128] The title compound was prepared in 88% yield according to the procedure of Preparation 11C. [M+H] Calc'd for $C_{18}H_{14}BrFN_2O_3$, 406; Found, 406.

Preparation 12D: N-[(3R)-1-[2-(4-bromo-3-fluorophenyl)-1-(4-methoxyphenyl)-5-methylimidazole-4-carbonyl]piperidin-3-yl]carbamate



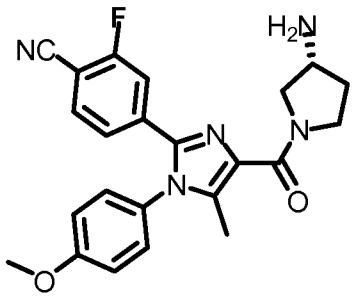
[00129] To a mixture of 2-(4-bromo-3-fluorophenyl)-5-methyl-1-(4-methoxyphenyl)imidazole-4-carboxylic acid (405 mg, 1 mmol), (R)-3-boc-aminopiperidine (300 mg, 1.5 mmol) and DIEA (331 μL, 2 mmol) in DMF was added HATU (570 mg, 1.5 mmol). The reaction mixture was stirred at rt for 2 h. It was then separated between water and EtOAc. The organic extract was dried and concentrated to a residue, which was purified by ISCO flash column (EtOAc/Hexane) to afford the title compound (460 mg, 78%). [M+H] Calc'd for $C_{28}H_{32}BrFN_4O_4$, 588; Found, 588.

Example 12: 4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-1-(4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile



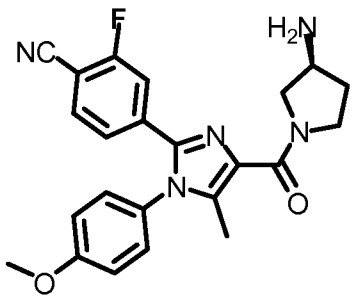
[00130] In a microwave vessel, was added N-[(3R)-1-[2-(4-bromo-3-fluorophenyl)-1-(4-methoxyphenyl)-5-methylimidazole-4-carbonyl]piperidin-3-yl]carbamate (400 mg, 0.68 mmol), zinc cyanide (400 mg, 3.4 mmol) and $Pd(PPh_3)_4$ (92 mg, 0.08 mmol) in 5 mL DMF. The reaction mixture was heated at 120 °C for 1 h in a microwave oven. It was then purified by ISCO flash column (EtOAc/Hexane). The fractions were concentrated to a residue, which was dissolved in CH_2Cl_2 (5 mL) and treated with TFA (2 mL). After 2 h, the reaction mixture was concentrated and purified by prep-HPLC to afford the title compound as the formic acid salt (40 mg, 15%) as a light yellow solid. ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.44 (2H, m), 1.75 (1H, m), 1.97 (1H, m), 2.15 (3H, s), 2.73 (2H, s), 2.89 (2H, m), 3.84 (3H, s), 4.56 (1H, m), 7.12 (2H, d, J= 8.7 Hz), 7.21 (1H, d, J = 8.2 Hz), 7.36 (2H, d, J = 8.2 Hz), 7.84 (1H, t, J = 7.7 Hz), 7.95 (1H, s), 8.30 (1H, br s). [M+H] Calc'd for $C_{24}H_{24}FN_5O_2$, 434; Found, 434.

Example 13: 4-[4-[(3R)-3-aminopyrrolidine-1-carbonyl]-1-(4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile



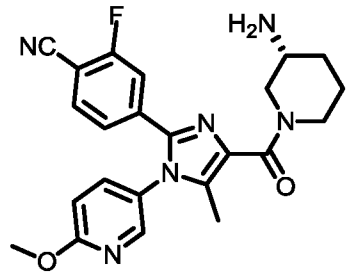
[00131] The title compound was prepared as the formic acid salt in 7% yield according to the general procedure for the preparation of Example 12 starting from 2-(4-bromo-3-fluorophenyl)-5-methyl-1-(4-methoxyphenyl)imidazole-4-carboxylic acid. ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.78 (1H, m), 2.03 (1H, m), 2.19 (3H, s), 3.30 (1H, m), 3.60 (2H, m), 3.78 (1H, m), 3.85 (3H, s), 4.14 (2H, m), 7.13 (2H, d, J= 8.8 Hz), 7.22 (1H, t, J = 7.8 Hz), 7.33-7.38 (3H, m), 7.85 (1H, m), 8.28 (1H, br s). [M+H] Calc'd for $C_{23}H_{22}FN_5O_2$, 420; Found, 420.

Example 14: 4-[4-[(3S)-3-aminopyrrolidine-1-carbonyl]-1-(4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile



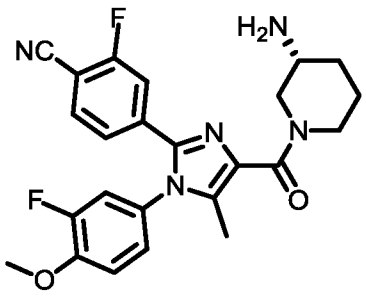
[00132] The title compound was prepared as the formic acid salt in 10% yield according to the general procedure for the preparation of Example 12 starting from 2-(4-bromo-3-fluorophenyl)-5-methyl-1-(4-methoxyphenyl)imidazole-4-carboxylic acid. ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.78 (1H, m), 2.03 (1H, m), 2.19 (3H, s), 3.30 (1H, m), 3.60 (2H, m), 3.78 (1H, m), 3.85 (3H, s), 4.14 (2H, m), 7.13 (2H, d, J= 8.8 Hz), 7.22 (1H, t, J = 7.8 Hz), 7.33-7.38 (3H, m), 7.85 (1H, m), 8.28 (1H, br s). [M+H] Calc'd for $C_{23}H_{22}FN_5O_2$, 420; Found, 420.

Example 15: 4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-1-(6-methoxypyridin-3-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile



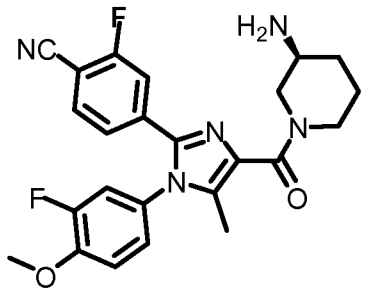
[00133] The title compound was prepared as the formic acid salt in 22% overall yield according to the general procedure for the preparation of Example 12. ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.58 (2H, m), 1.81 (1H, m), 2.06 (1H, m), 2.20 (3H, s), 2.98 (2H, m), 3.21 (2H, m), 3.95 (3H, s), 4.51 (1H, m), 7.05 (1H, d, J= 8.8 Hz), 7.19 (1H, d, J = 7.7 Hz), 7.88 (2H, m), 7.98 (2H, m), 8.26 (1H, br s). [M+H] Calc'd for $C_{23}H_{23}FN_6O_2$, 435; Found, 435.

Example 16: 4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-1-(3-fluoro-4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile



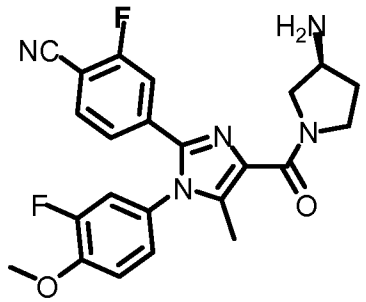
[00134] The title compound was prepared as the formic acid salt in 15% overall yield according to the general procedure for the preparation of Example 12. ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.58 (2H, m), 1.81 (1H, m), 2.04 (1H, m), 2.19 (3H, s), 2.73 (2H, s), 3.18-3.31 (2H, m), 3.93 (3H, s), 4.52 (1H, m), 7.19 (2H, m), 7.37 (2H, d, J = 9.0 Hz), 7.54 (1H, m), 7.86 (1H, t, J = 8.0 Hz), 8.00 (2H, br s). [M+H] Calc'd for $C_{24}H_{23}F_2N_5O_2$, 452; Found, 452.

Example 17: 4-[4-[(3S)-3-aminopiperidine-1-carbonyl]-1-(3-fluoro-4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile



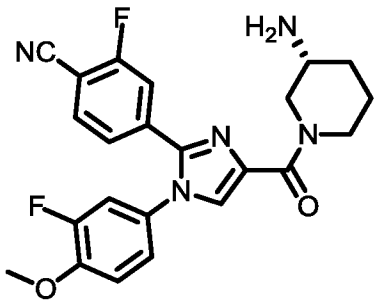
[00135] The title compound was prepared as the formic acid salt in 6% overall yield according to the general procedure for the preparation of Example 12. ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.42 (2H, m), 1.78 (1H, m), 1.98 (2H, m), 2.16 (3H, s), 2.90 (1H, m), 3.15 (1H, m), 3.92 (3H, s), 4.54 (1H, m), 7.19 (1H, d, J= 8.1 Hz), 7.21 (1H, m), 7.34 (1H, t, J = 8.8 Hz), 7.56 (1H, d, J = 10.4 Hz), 7.86 (1H, t, J = 7.3 Hz), 8.28 (1H, br s). [M+H] Calc'd for $C_{24}H_{23}F_2N_5O_2$, 452; Found, 452.

Example 18: 4-[4-[(3S)-3-aminopyrrolidine-1-carbonyl]-1-(3-fluoro-4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile



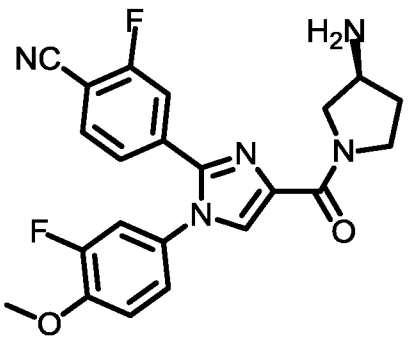
[00136] The title compound was prepared as the formic acid salt in 5% overall yield according to the general procedure for the preparation of Example 12. ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.71 (1H, m), 2.04 (2H, m), 2.25 (3H, s), 3.49 (1H, m), 3.76 (1H, m), 3.92 (3H, s), 4.16 (1H, m), 7.16 (1H, d, J= 8.4 Hz), 7.25 (1H, m), 7.31 (1H, m), 7.39 (1H, t, J = 7.7 Hz), 7.55 (1H, d, J = 11.5 Hz), 7.86 (1H, m), 8.26 (1H, s). [M+H] Calc'd for $C_{23}H_{21}F_2N_5O_2$, 438; Found, 438.

Example 19: 4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-1-(3-fluoro-4-methoxyphenyl)imidazol-2-yl]-2-fluorobenzonitrile



[00137] The title compound was prepared as the formic acid salt in 15% overall yield according to the general procedure for the preparation of Example 12 using ethyl bromopyruvate. ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.38 (2H, m), 1.75 (2H, m), 1.93 (2H, m), 2.86 (2H, m), 3.90 (3H, s), 4.69 (1H, m), 7.19-7.31 (3H, m), 7.52 (2H, dd, J = 11.5 and 2.4 Hz), 7.90 (1H, t, J = 7.9 Hz), 7.97 (1H, s), 8.24 (1H, s). [M+H] Calc'd for $C_{23}H_{21}F_2N_5O_2$, 438; Found, 438.

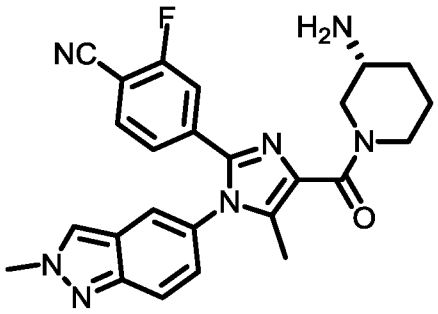
Example 20: 4-[4-[(3S)-3-aminopyrrolidine-1-carbonyl]-1-(3-fluoro-4-methoxyphenyl)imidazol-2-yl]-2-fluorobenzonitrile



[00138] The title compound was prepared as the formic acid salt in 8% overall yield according to the general procedure for the preparation of Example 12 using ethyl bromopyruvate. ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.71-1.84 (1H, m), 1.99-2.08 (1H, m), 3.37 (2H, m), 3.50 (1H, m), 3.71 (2H, m), 3.91 (3H, s), 4.06-4.18 (1H, m), 7.19-7.31

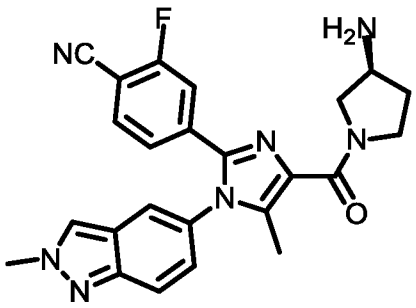
(3H, m), 7.54 (2H, dd, J = 11.5 Hz), 7.93 (1H, m), 8.02 (1H, s), 8.25 (1H, s). [M+H] Calc'd for $C_{22}H_{19}F_2N_5O_2$, 424; Found, 424.

Example 21: 4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-5-methyl-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile



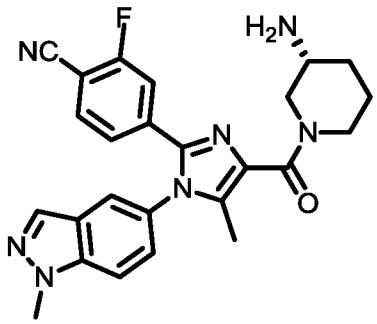
[00139] The title compound was prepared as the formic acid salt in 6% overall yield according to the general procedure for the preparation of Example 12. ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.45 (2H, m), 1.75 (1H, m), 1.97 (1H, m), 2.17 (3H, s), 2.93 (2H, m), 3.20 (1H, m), 4.16 (1H, m), 4.23 (3H, s), 4.46-4.62 (1H, m), 7.19 (2H, d, J= 8.2 Hz), 7.39 (1H, m), 7.76-7.86 (2H, m), 8.27 (1H, s), 8.49 (1H, s). [M+H] Calc'd for $C_{25}H_{24}FN_7O$, 458; Found, 458.

Example 22: 4-[4-[(3S)-3-aminopyrrolidine-1-carbonyl]-5-methyl-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile



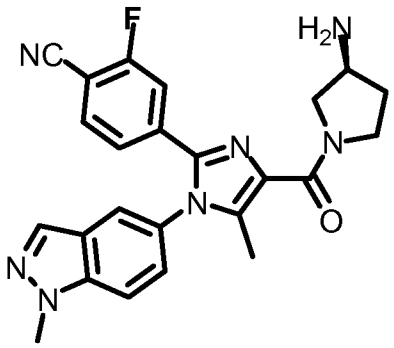
[00140] The title compound was prepared as the formic acid salt in 7% overall yield according to the general procedure for the preparation of Example 12. ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.92 (1H, m), 2.05 (1H, m), 2.16 (1H, m), 2.21 (4H, s & m), 3.70 (1H, m), 3.75 (1H, m), 3.81 (1H, m), 4.29 (3H, s), 7.11-7.21 (2H, m), 7.41 (1H, t, J = 9.7 Hz), 7.74-7.95 (4H, m), 8.48 (1H, s). [M+H] Calc'd for $C_{24}H_{22}FN_7O$, 444; Found, 444.

Example 23: 4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-5-methyl-1-(1-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile



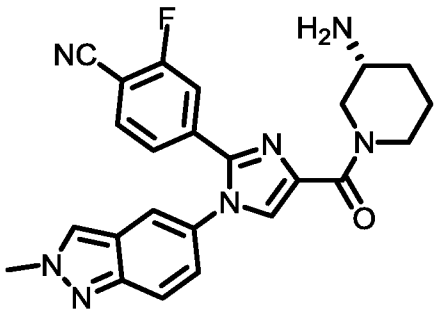
[00141] The title compound was prepared as the formic acid salt in 4% overall yield according to the general procedure for the preparation of Example 12. ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.46 (2H, m), 1.77 (1H, m), 1.98 (1H, m), 2.15 (3H, s), 2.97 (2H, m), 3.29 (2H, m), 4.13 (3H, s), 4.59 (1H, m), 7.14 (1H, d, J= 8.2 Hz), 7.42 (2H, m), 7.77 (1H, t, J = 7.6 Hz), 7.86-7.91 (2H, m), 8.17 (1H, s), 8.27 (1H, s). [M+H] Calc'd for $C_{25}H_{24}FN_7O$, 458; Found, 458.

Example 24: 4-[4-[(3S)-3-aminopyrrolidine-1-carbonyl]-5-methyl-1-(1-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile



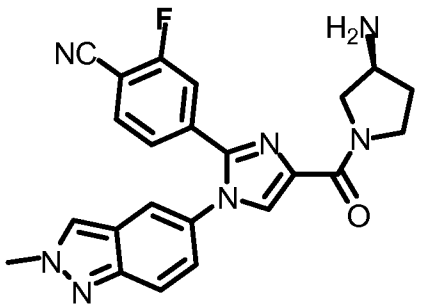
[00142] The title compound was prepared as the formic acid salt in 2% overall yield according to the general procedure for the preparation of Example 12. ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.71-1.84 (1H, m), 2.00-2.09 (1H, m), 2.33 (3H, s), 3.53 (1H, m), 3.66 (2H, m), 3.84 (1H, m), 4.16 (4H, s & m), 7.14 (1H, t, J = 9.7 Hz), 7.36-7.42 (2H, m), 7.76 (1H, m), 7.87 (1H, d, J = 8.6 Hz), 7.90 (1H, s), 8.17 (1H, s), 8.24 (1H, s). [M+H] Calc'd for $C_{24}H_{22}FN_7O$, 444; Found, 444.

Example 25: 4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile



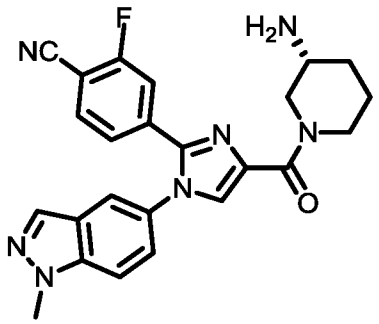
[00143] The title compound was prepared as the formic acid salt in 4% overall yield according to the general procedure for the preparation of Example 12 using ethyl bromopyruvate. ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.49 (2H, m), 1.78 (1H, m), 1.99 (1H, m), 3.01 (1H, m), 3.19 (1H, m), 4.22 (3H, s), 4.42-4.96 (2H, m), 7.11 (1H, dd, J= 9.0 and 2.0 Hz), 7.24 (1H, dd, J = 8.2 and 1.4 Hz), 7.51 (1H, m), 7.73 (1H, d, J = 9 Hz), 7.82 (1H, t, J = 7.3 Hz), 7.87 (1H, d, J = 1.6 Hz), 8.02 (1H, s), 8.25 (1H, br s), 8.48 (1H, s). [M+H] Calc'd for $C_{24}H_{22}FN_7O$, 444; Found, 444.

Example 26: 4-[4-[(3S)-3-aminopyrrolidine-1-carbonyl]-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile



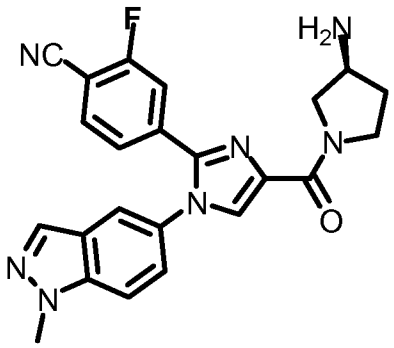
[00144] The title compound was prepared as the formic acid salt in 2% overall yield according to the general procedure for the preparation of Example 12 using ethyl bromopyruvate. ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.68-1.85 (1H, m), 2.01-2.13 (1H, m), 3.30-3.41 (2H, m), 3.51-3.86 (3H, m), 3.89 (1H, m), 4.20 (4H, s & m), 7.18 (1H, dd, J = 9.1 and 2.1 Hz), 7.25 (1H, m), 7.46 (1H, dd, J = 10.7 and 1.4 Hz), 7.73 (1H, d, J = 9.0 Hz), 7.81 (1H, m), 7.87 (1H, d, J = 1.6 Hz), 8.04 (1H, s), 8.25 (1H, br s), 8.48 (1H, s). [M+H] Calc'd for $C_{23}H_{20}FN_7O$, 430; Found, 430.

Example 27: 4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-1-(1-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile



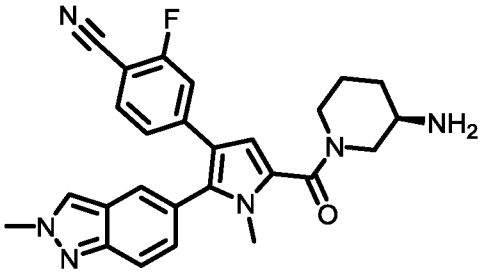
[00145] The title compound was prepared as the formic acid salt in 2% overall yield according to the general procedure for the preparation of Example 12 using ethyl bromopyruvate. ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.59 (2H, m), 1.81 (1H, m), 2.03 (1H, m), 3.20 (1H, m), 4.11 (3H, s), 7.17 (1H, d, J= 8.2 Hz), 7.37 (1H, d, J = 9.8 Hz), 7.53 (1H, br s), 7.76-7.85 (3H, t & m, J = 8.6 Hz), 7.98 (1H, s), 8.09 (1H, s), 8.16 (1H, s). [M+H] Calc'd for $C_{24}H_{22}FN_7O$, 444; Found, 444.

Example 28: 4-[4-[(3S)-3-aminopyrrolidine-1-carbonyl]-1-(1-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile



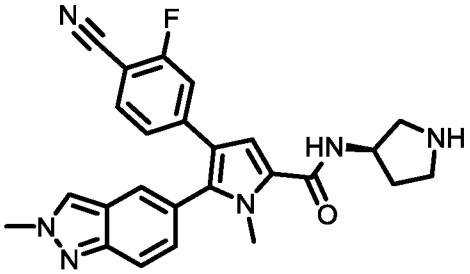
[00146] The title compound was prepared as the formic acid salt in 4% overall yield according to the general procedure for the preparation of Example 12 using ethyl bromopyruvate. ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.80-1.94 (1H, m), 2.07-2.19 (1H, m), 3.32-3.46 (2H, m), 3.54-3.82 (3H, m), 4.03 (1H, m), 4.21 (4H, s & m), 7.19 (1H, t, J = 7.3 Hz), 7.39 (1H, dd, J = 8.9 and 2.0 Hz), 7.47 (1H, d, J = 10.6 Hz), 7.80 (1H, d, J = 8.9 Hz), 7.86 (1H, m), 7.91 (1H, d, J = 1.8 Hz), 8.07 (1H, s), 8.16 (1H, s), 8.27 (1H, s). [M+H] Calc'd for $C_{23}H_{20}FN_7O$, 430; Found, 430.

Example 29: 4-{5-[((3R)-3-aminopiperidyl)carbonyl]-1-methyl-2-(2-methyl(2H-indazol-5-yl))pyrrol-3-yl}-2-fluorobenzenecarbonitrile



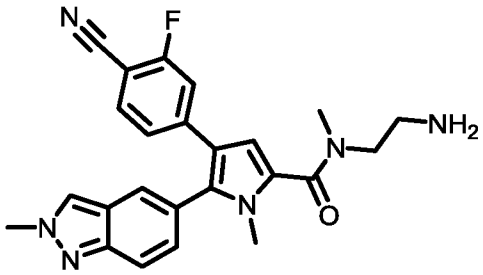
The title compound was prepared as the HCl salt in 24% overall yield according to the general procedure for the preparation of Example 1. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 1.76-1.80 (m, 2H), 1.95-1.96 (m, 1H), 2.23-2.25 (m, 1H), 3.32-3.46 (m, 3H), 3.58 (s, 3H), 4.30 (s, 3H), 4.26-4.33 (m, 1H), 4.55 (d, J = 10.0 Hz 1H), 6.91 (s, 1H), 7.10-7.14 (m, 2H), 7.29 (dd, J = 8.8 Hz, 1.6 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 7.77- 7.80 (m, 2H), 8.41 (s, 1H). [M+H] Calc'd for $C_{26}H_{25}FN_6O$, 457; Found, 457.

Example 30: N-((3R)pyrrolidin-3-yl)[4-(4-cyano-3-fluorophenyl)-1-methyl-5-(2-methyl(2H-indazol-5-yl))pyrrol-2-yl]carboxamide



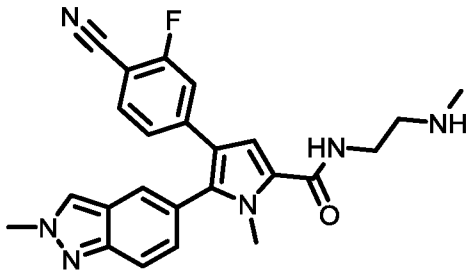
The title compound was prepared as the HCl salt in 18% overall yield according to the general procedure for the preparation of Example 1. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 2.20-2.25 (m, 1H), 2.40-2.46 (m, 1H),3.38-3.44 (m, 2H), 3.56-3.63 (m, 2H), 3.73 (s, 3H), 4.32 (s, 3H), 4.58-4.62 (m, 1H), 7.02 (dd, J = 1.6, 11.2 Hz, 1H), 7.09 (dd, J = 1.6, 8.0 Hz, 1H), 7.30-7.33 (m, 2H), 7.46 (t, J = 8.0 Hz, 1H)), 7.77-7.79 (m, 2H), 8.46 (s, 1H). [M+H] Calc'd for $C_{25}H_{23}FN_6O$, 443; Found, 443.

Example 31: N-(2-aminoethyl)[4-(4-cyano-3-fluorophenyl)-1-methyl-5-(2-methyl(2H-indazol-5-yl))pyrrol-2-yl]-N-methylcarboxamide



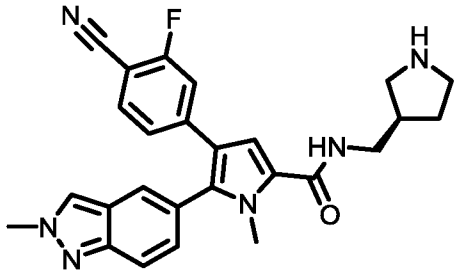
The title compound was prepared as the HCl salt in 16% overall yield according to the general procedure for the preparation of Example 1. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 3.27-3.28 (m, 2H), 3.38 (s, 3H), 3.59 (s, 3H), 3.86 (t, J = 5.6 Hz, 2H), 4.33 (s, 3H), 7.00 (s, 1H), 7.09 (t, J = 10.0 Hz, 2H), 7.36(d, t, J = 8.4 Hz, 1H), 7.46 (t, J = 10.0 Hz, 1H), 7.78-7.81 (m, 2H), 8.50 (s, 1H). [M+H] Calc'd for $C_{24}H_{23}FN_6O$, 431; Found, 431.

Example 32: [4-(4-cyano-3-fluorophenyl)-1-methyl-5-(2-methyl(2H-indazol-5-yl))pyrrol-2-yl]-N-[2-(methylamino)ethyl]carboxamide



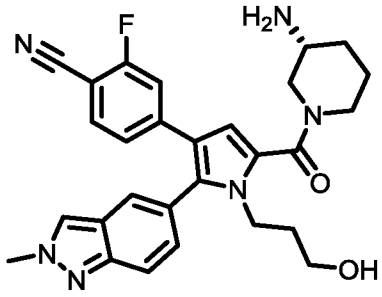
The title compound was prepared as the HCl salt in 21% overall yield according to the general procedure for the preparation of Example 1. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 2.78 (s, 3H), 3.24-3.27 (t, J = 6.0 Hz, 2H), 3.68 (t, J = 6.0 Hz, 2H), 3.76 (s, 3H), 4.30 (s, 3H), 7.02 (dd, J = 2.0, 9.0 Hz, 1H), 7.08 (dd, J = 1.2, 10.0 Hz, 1H), 7.24 (s, 1H), 7.27 (dd, J = 1.6, 8.8 Hz, 1H), 7.47 (t, J = 8.0 Hz, 1H), 7.74-7.79 (m, 2H), 8.41 (s, 1H). [M+H] Calc'd for $C_{24}H_{23}FN_6O$, 431; Found, 431.

Example 33: N-[((3S)pyrrolidin-3-yl)methyl][4-(4-cyano-3-fluorophenyl)-1-methyl-5-(2-methyl(2H-indazol-5-yl))pyrrol-2-yl]carboxamide



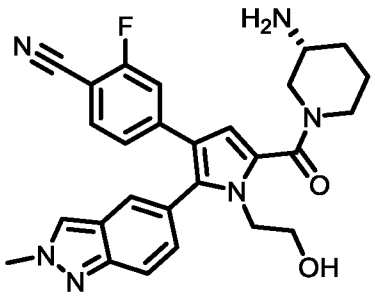
The title compound was prepared as the HCl salt in 19% overall yield according to the general procedure for the preparation of Example 1. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 1.84-1.89 (m, 1H), 2.20-2.25 (m, 1H), 2.70-2.73 (m, 1H),3.07-3.12 (m, 1H), 3.30-3.31 (m, 1H), 3.40-3.44 (m, 1H), 3.46-3.49 (m, 3H), 3.73 (s, 3H), 4.34 (s, 3H), 7.02 (dd, J = 1.6, 11.2 Hz, 1H), 7.08 (dd, J = 2.0, 8.0 Hz, 1H), 7.20-7.22 (m, 1H), 7.37-7.49 (m, 2H), 7.78-7.82 (m, 2H), 8.50 (s, 1H). [M+H] Calc'd for $C_{26}H_{25}FN_6O$, 457; Found, 457.

Example 34: (R)-4-(5-(3-aminopiperidine-1-carbonyl)-1-(3-hydroxypropyl)-2-(2-methyl-2H-indazol-5-yl)-1H-pyrrol-3-yl)-2-fluorobenzonitrile



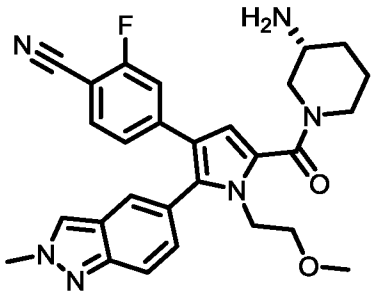
The title compound was prepared as the HCl salt in 25 % overall yield according to the general procedure for the preparation of Example 1. ^{1}H NMR (400 MHz, CD_3OD): δ 1.61-1.65 (m, 2H), 1.78-1.98 (m, 3H), 2.20-2.30 (m, 1H), 3.28-3.37 (m, 2H), 3.48-3.53 (m, 3H), 4.22-4.27 (m, 3H), 4.42 (s, 3H), 4.48-4.51 (m, 1H), 6.93 (s, 1H), 7.07-7.13 (m, 2H), 7.46-7.58 (m, 2H), 7.87 (d, J = 8.8 Hz, 1H), 7.98 (s, 1H), 8.76 (s, 1H). [M+H] Calc'd for $C_{28}H_{29}FN_6O_2$, 501; Found, 501.

Example 35: (R)-4-(5-(3-aminopiperidine-1-carbonyl)-1-(2-hydroxyethyl)-2-(2-methyl-2H-indazol-5-yl)-1H-pyrrol-3-yl)-2-fluorobenzonitrile



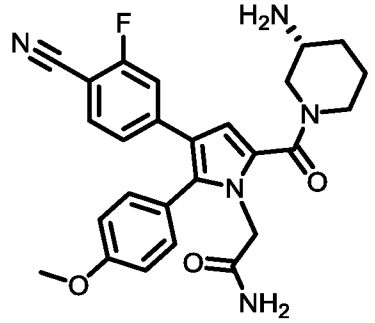
The title compound was prepared as the HCl salt in 20 % overall yield according to the general procedure for the preparation of Example 1. ^{1}H NMR (400 MHz, CD_3OD): δ 1.74-1.92 (m, 3H), 2.20-2.22 (m, 1H), 3.30-3.47 (m, 5H), 4.21-4.29 (m, 3H), 4.35 (s, 3H), 4.53-4.55 (m, 1H), 6.88 (s, 1H), 7.04-7.10 (m, 2H), 7.42-7.46 (m, 2H), 7.81 (d, J = 8.8 Hz,1H), 7.88 (s, 1H), 8.60 (s, 1H). [M+H] Calc'd for $C_{27}H_{27}FN_6O_2$, 487; Found, 487.

Example 36: (R)-4-(5-(3-aminopiperidine-1-carbonyl)-1-(2-methoxyethyl)-2-(2-methyl-2H-indazol-5-yl)-1H-pyrrol-3-yl)-2-fluorobenzonitrile



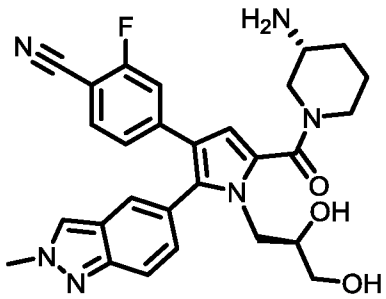
The title compound was prepared as the free base in 26 % overall yield according to the general procedure for the preparation of Example 1. ^{1}H NMR (400 MHz, CD_3OD): δ 1.76-1.80 (m, 2H), 1.97-1.99 (m, 1H), 2.27-2.29 (m, 1H), 3.18 (s, 3H), 3.25-3.42 (m, 5H), 4.28-4.34 (m, 3H), 4.37 (s, 3H), 4.62-4.65 (m,1H), 6.91 (s, 1H), 7.09-7.13 (m, 2H), 7.42-7.49 (m, 2H), 7.82 (d, J = 8.8 Hz,1H), 7.88 (s, 1H), 8.59 (s, 1H). [M+H] Calc'd for $C_{28}H_{29}FN_6O_2$, 501; Found, 501.

Example 37: (R)-2-(5-(3-aminopiperidine-1-carbonyl)-3-(4-cyano-3-fluorophenyl)-2-(4-methoxyphenyl)-1H-pyrrol-1-yl)acetamide



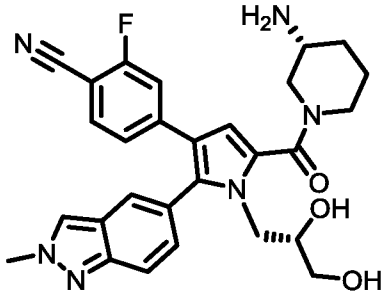
The title compound was prepared as the free base in 25 % overall yield according to the general procedure for the preparation of Example 1. ^{1}H NMR (400 MHz, CD3OD): δ 1.64-1.68 (m, 1H), 1.88-2.14 (m, 3H), 3.41-3.43 (m, 2H), 3.55-3.57 (m, 1H), 3.71-3.75 (m, 1H), 3.88-3.92 (m, 4H), 4.76-4.78 (m,1H), 5.22-5.25 (m, 1H), 7.04-7.07 (m, 3H), 7.12-7.15 (m, 1H), 7.25 (d, J = 8.4 Hz, 2H), 7.38 (s, 1H), 7.52-7.55 (m, 1H). [M+H] Calc'd for $C_{26}H_{26}FN_5O_3$, 476; Found, 476.

Example 38: 4-(5-((R)-3-aminopiperidine-1-carbonyl)-1-((R)-2,3-dihydroxypropyl)-2-(2-methyl-2H-indazol-5-yl)-1H-pyrrol-3-yl)-2-fluorobenzonitrile



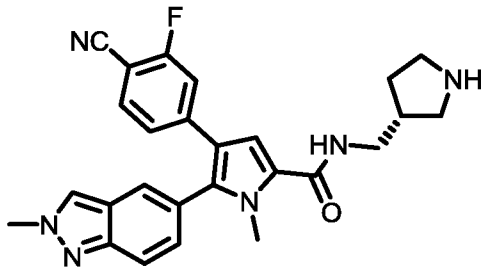
The title compound was prepared as the free base in 21 % overall yield according to the general procedure for the preparation of Example 1. ^{1}H NMR (400 MHz, CD_3OD): δ 1.75-1.79 (m, 2H), 1.88-1.91 (m, 1H), 2.20-2.22 (m, 1H), 3.21 (d, J = 5.2 Hz, 2H), 3.38-3.48 (m, 4H), 4.16-4.27 (m, 3H), 4.37 (s, 3H), 4.49-4.52 (m, 1H), 6.88 (s, 1H), 7.04-7.10 (m, 2H), 7.43-7.51 (m, 2H), 7.81 (d, J = 8.4 Hz, 1H), 7.93 (s, 1H), 8.67 (s, 1H). [M+H] Calc'd for $C_{28}H_{29}FN_6O_3$, 517; Found, 517.

Example 39: 4-(5-((R)-3-aminopiperidine-1-carbonyl)-1-((S)-2,3-dihydroxypropyl)-2-(2-methyl-2H-indazol-5-yl)-1H-pyrrol-3-yl)-2-fluorobenzonitrile



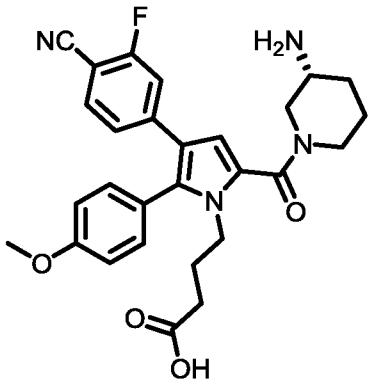
The title compound was prepared as the free base in 18 % overall yield according to the general procedure for the preparation of Example 1. ^{1}H NMR (400 MHz, CD_3OD): δ 1.75-1.91 (m, 3H), 2.20-2.22 (m, 1H), 3.23 (d, J = 5.2 Hz, 2H), 3.38-3.48 (m, 4H), 4.16-4.29 (m, 4H), 4.37 (s, 3H), 6.88 (s, 1H), 7.04-7.10 (m, 2H), 7.43-7.51 (m, 2H), 7.81 (d, J = 8.4 Hz, 1H), 7.92 (s, 1H), 8.65(s, 1H). [M+H] Calc'd for $C_{28}H_{29}FN_6O_3$, 517; Found, 517.

Example 40: N-[((3R)pyrrolidin-3-yl)methyl][4-(4-cyano-3-fluorophenyl)-1-methyl-5-(2-methyl(2H-indazol-5-yl))pyrrol-2-yl]carboxamide



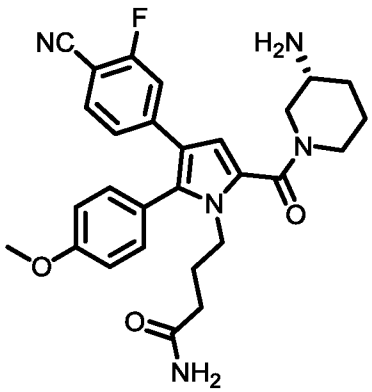
The title compound was prepared as the hydrochloride salt in 4% overall yield according to the general procedure for the preparation of Example 1. ^{1}H NMR (400 MHz, CD_3OD): δ 1.86-1.92 (m, 1H), 2.22-2.27 (m, 1H), 2.72-2.75 (m, 1H), 3.09-3.14 (m, 1H), 3.31-3.34 (m, 1H), 3.42-3.51 (m, 4H), 3.74 (s, 3H), 4.31 (s, 3H), 7.04 (dd, *J* = 1.6,11.6 Hz, 1H), 7.10 (dd, *J* = 1.6,8.4 Hz, 1H),7.22 (s, 1H), 7.26 (d, *J* = 8.8 Hz, 1H), 7.46-7.50 (m, 1H), 7.75-7.80 (m, 2H), 8.40 (s, 1H). [M-H] Calc'd for $C_{26}H_{25}FN_6O$, 457; Found, 457.

Example 41: 4-{5-[((3R)-3-aminopiperidyl)carbonyl]-3-(4-cyano-3-fluorophenyl)-2-(4-methoxyphenyl)pyrrolyl}butanoic acid



The title compound was prepared as the TFA salt in 3% overall yield according to the general procedure for the preparation of Example 1. ^{1}H NMR (400 MHz, CD_3OD): δ 1.60-1.67 (m, 4H), 1.82-1.84 (m, 1H), 1.93-1.97 (m, 2H), 2.10-2.13 (m, 1H), 3.30-3.32 (m, 3H), 3.78 (s, 3H), 3.95-4.02 (m, 2H), 4.18-4.20 (m, 1H), 4.44-4.78 (m, 1 H), 6.76 (s, 1H), 6.94-7.00 (m, 4H), 7.13-7.16 (m, 2H), 7.37-7.41 (m, 1H). [M+H] Calc'd for $C_{28}H_{29}FN_4O_4$, 505; Found, 505.

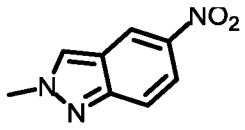
Example 42: 4-{5-[((3R)-3-aminopiperidyl)carbonyl]-3-(4-cyano-3-fluorophenyl)-2-(4-methoxyphenyl)pyrrolyl}butanamide



The title compound was prepared as the hydrochloride salt in 2% overall yield according to the general procedure for the preparation of Example 1. ^{1}H NMR (400 MHz, CD_3OD):

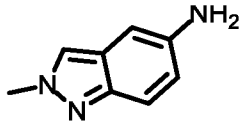
δ 1.58-1.71 (m, 4H), 1.82-1.92 (m, 3H), 2.10-2.13 (m, 1H), 3.33-3.45 (m, 3H), 3.76 (s, 3H), 3.93-3.99 (m, 2H), 4.05-4.09 (m, 1H), 4.29-4.33 (m, 1H), 6.77 (s, 1H), 6.94-7.00 (m, 4H), 7.13-7.16 (m, 2H), 7.36-7.40 (m, 1H). [M+H] Calc'd for $C_{28}H_{30}FN_5O_3$, 504; Found, 504.

Preparation 43A: 2-Methyl-5-nitroindazole



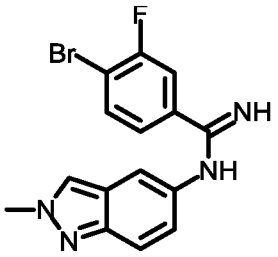
To a solution of 5-nitroindazole (15 g, 91.95 mmol) in ethylacetate (150 mL), was added BF_4OMe_3 (17.68 g, 119.54 mmol) at r.t. The mixture was stirred for 5 hr at r.t. aq $NaHCO_3$ was added to adjust the pH to 7-8, extracted with ethylacetate, dried, concentrated to afford the title compound (15 g, 92.5%). [M+H] Calc'd for $C_8H_7N_3O_2$, 178; Found, 178.

Preparation 43B: 2-Methylindazol-5-amine



A mixture of 2-methyl-5-nitroindazole (12 g, 0.0678 mol) and Pd/C (1.2 g, 10%) in DCM/MeOH (120/120 mL) was stirred for 3 hr at 50 °C with 50psi of H_2. The reaction mixture was then filtered, concentrated and purified by flash column chromatography on silica gel (DCM/MeOH=20/1) to afford the title compound (8.414 g, 85%). [M+H] Calc'd for $C_8H_9N_3$, 148; Found, 148.

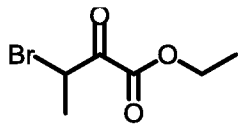
Preparation 43C: 4-Bromo-3-fluoro-N-(2-methylindazol-5-yl)benzenecarboximidamide



To a solution of EtMgBr (30 mL, 27.21 mmol, 0.9 M) in THF (15 mL) was added a solution of 2-methylindazol-5-amine (2 g, 13.61 mmol) in THF (20 mL) at r.t. The reaction mixture was stirred for 30 min at r.t. A solution of 4-bromo-3-fluoro-benzonitrile (2.978 g, 14.97 mmol) in THF (20 mL) was added dropwise at r.t. and stirred overnight. LC/MS showed the reaction was completed. H_2O was added and extracted with ethylacetate, dried, concentrated and purified by flash column chromatography on silica gel (PE/EA=3/1 to EA) to afford the title compound (3.3 g,

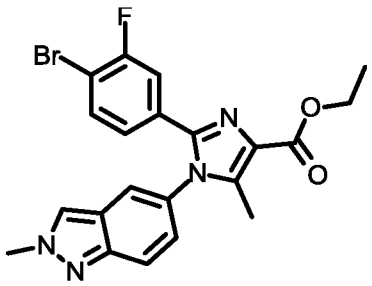
70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.21 (3H, s), 6.98 (1H, dd, J=9.0 Hz, J=1.8 Hz), 7.13-7.14 (1H, m), 7.60-7.72 (4H, m), 7.80 (1H, s). [M+H] Calc'd for $C_{15}H_{12}BrFN_4$, 347; Found, 347.

Preparation 43D: Ethyl 3-bromo-2-oxobutanoate



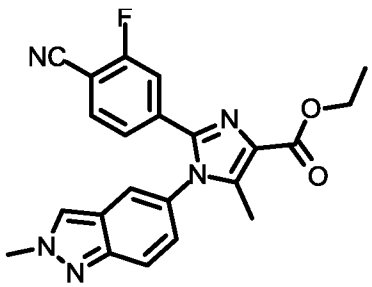
To a solution of ethyl 2-oxobutanoate (5 g, 38.46 mmol) in DCM was added Br_2 (6.15 g, 38.46 mmol) dropwise at 0°C, then stirred for 2 hr at r.t. The reaction mixture was concentrated, the residue was dissolved in DCM and washed with aq $NaHCO_3$, dried and concentrated to give the title compound (7 g, 88 %).

Preparation 43E: Ethyl 2-(4-bromo-3-fluorophenyl)-5-methyl-1-(2-methylindazol-5-yl)imidazole-4-carboxylate



A mixture of 4-bromo-3-fluoro-N-(2-methylindazol-5-yl)benzenecarboximidamide (3.3 g, 9.54 mmol), ethyl 3-bromo-2-oxobutanoate (1.983 g, 9.54 mmol) and Na_2CO_3 (1.011 g, 9.54 mmol) in toluene/EtOH (50 mL, 1/1) was stirred overnight at 100 °C. It was then filtered and concentrated. The residue was dissolved in AcOH (20 mL) and stirred for 1h at 120 °C. It was then concentrated and purified by flash column chromatography on silica gel (PE/EA=3/1 to EA) to afford the title compound (1.4 g, 32%). [M+H] Calc'd for $C_{21}H_{18}BrFN_4O_2$, 457; Found, 457.

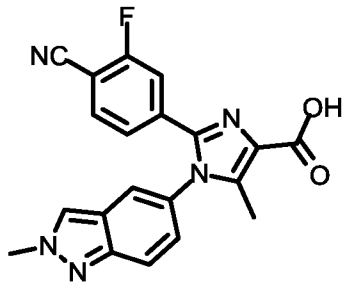
Preparation 43F: Ethyl 2-(4-cyano-3-fluorophenyl)-5-methyl-1-(2-methylindazol-5-yl)imidazole-4-carboxylate



A mixture of ethyl 2-(4-bromo-3-fluorophenyl)-5-methyl-1-(2-methylindazol-5-yl)imidazole-4-carboxylate (1.1 g, 2.41 mmol), $Zn(CN)_2$ (1.41 g, 12.05 mmol) and

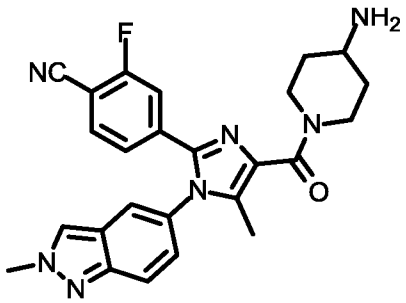
$Pd(PPh_3)_4$ (278 mg, 0.241 mmol) in DMA (10 mL) was stirred overnight at 110 °C in a sealed tube. LC/MS showed the reaction was completed, concentrated and purified by flash column chromatography on silica gel (PE/EA=3/1 to EA) to afford the tile compound (364 mg, 38%). [M+H] Calc'd for $C_{22}H_{18}FN_5O_2$, 404; Found, 404.

Preparation 43G: 2-(4-Cyano-3-fluorophenyl)-5-methyl-1-(2-methylindazol-5-yl)imidazole-4-carboxylic acid



To a solution of ethyl 2-(4-cyano-3-fluorophenyl)-5-methyl-1-(2-methylindazol-5-yl)imidazole-4-carboxylate (360 mg, 0.89 mmol) in THF/H_2O (6 mL/2 mL) was added $LiOH{\cdot}H_2O$ (187 mg, 4.45 mmol) at r.t, then stirred overnight at r.t, acidified to pH 3-4, extracted with EA, dried and concentrated to give the title compound (334 mg, 100%). [M+H] Calc'd for $C_{20}H_{14}FN_5O_2$, 376; Found, 376.

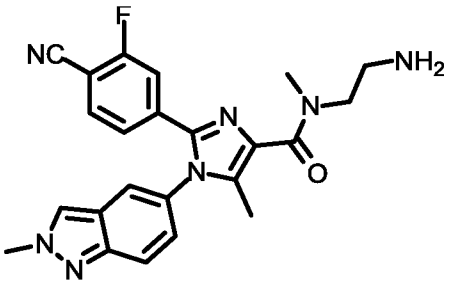
Example 43: 4-[4-(4-Aminopiperidine-1-carbonyl)-5-methyl-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile



A mixture of 2-(4-cyano-3-fluorophenyl)-5-methyl-1-(2-methylindazol-5-yl)imidazole-4-carboxylic acid (160 mg, 0.43 mmol), piperidin-4-yl-carbamic acid tert -butyl ester (85 mg, 0.43 mmol), HATU (178 mg, 0.47 mmol) and NMM (86 mg, 0.86 mmol) in DMF (5 mL) was stirred for 1 hr at r.t, LC/MS showed the reaction was completed, concentrated to afford the boc protected intermediate (239 mg, 100%). A solution of the intermediate (239 mg, 0.43 mmol) in HCl/EA (5 mL) was stirred for 1 hr at r.t. LC/MS showed the reaction was completed, concentrated and purified by *prep*-HPLC to afford the title compound (107 mg, 55%). ^1H NMR (400 MHz, CD_3OD): δ 1.61-1.64 (2H, m), 2.07-2.10 (2H, m), 2.20 (3H, s), 3.20-3.22 (2H, m), 3.40-3.42 (1H, m), 4.19 (3H, s), 4.20-4.60 (2H, m), 7.32-7.46 (3H, m), 7.66-7.74 (2H, m), 7.95 (1 H, s), 8.37 (1 H, s). [M+H] Calc'd

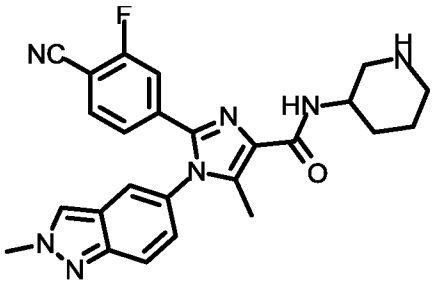
for $C_{25}H_{24}FN_7O$, 458; Found, 458.

Example 44: N-(2-Aminoethyl)-2-(4-cyano-3-fluorophenyl)-N,5-dimethyl-1-(2-methylindazol-5-yl)imidazole-4-carboxamide



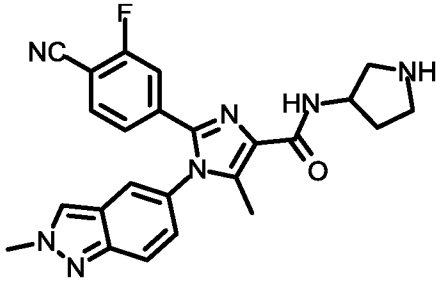
The title compound was prepared as TFA salt in 3% overall yield according to the general procedure for the preparation of Example 43. ^{1}H NMR (400 MHz, CD_3OD): δ 2.34 (3H, s), 3.33-3.40 (5H, m), 3.94-3.95 (2H, m), 4.33 (3H, s), 7.47-7.60 (3H, m), 7.85-7.88 (2H, m), 8.08 (1 H, s), 8.53 (1 H, s). [M+H] Calc'd for $C_{23}H_{22}FN_7O$, 432; Found, 432.

Example 45: 2-(4-Cyano-3-fluorophenyl)-5-methyl-1-(2-methylindazol-5-yl)-N-piperidin-3-ylimidazole-4-carboxamide



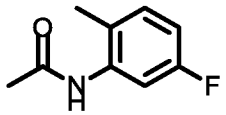
The title compound was prepared as TFA salt in 2% overall yield according to the general procedure for the preparation of Example 43. ^{1}H NMR (400 MHz, CD_3OD): δ 1.89-1.94 (2H, m), 2.17-2.18 (2H, m), 2.49 (3H, s), 3.15-3.20 (2H, m), 3.33-3.36 (1H, m), 3.55-3.59 (1H, m), 4.35-4.37 (4H, m), 7.44-7.50 (2H, m), 7.61-7.64 (1H, m), 7.77-7.80 (1H, m), 7.88-7.91 (1H, m), 8.04 (1 H, s), 8.59 (1 H, s). [M+H] Calc'd for $C_{25}H_{24}FN_7O$, 458; Found, 458.

Example 46: 2-(4-Cyano-3-fluorophenyl)-5-methyl-1-(2-methylindazol-5-yl)-N-pyrrolidin-3-ylimidazole-4-carboxamide



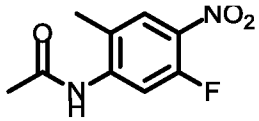
The title compound was prepared as TFA salt in 3% overall yield according to the general procedure for the preparation of Example 43. ^{1}H NMR (400 MHz, CD_3OD): δ 2.27-2.28 (1H, m), 2.43-2.48 (4H, m), 3.43-3.50 (2H, m), 3.61-3.65 (2H, m), 4.31 (3H, s), 4.70-4.72 (1H, m), 7.38 (1H, d, *J* = 9.2 Hz), 7.43 (1H, d, *J* = 8.0 Hz), 7.58 (1H, d, *J* = 9.6 Hz), 7.74 (1H, t, *J* = 7.2 Hz), 7.85 (1H, d, *J* = 9.2 Hz), 7.96 (1 H, s), 8.52 (1 H, s). [M+H] Calc'd for $C_{24}H_{22}FN_7O$, 444; Found, 444.

Preparation 47A: N-(5-Fluoro-2-methylphenyl)acetamide



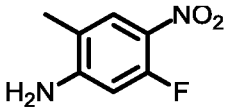
A solution of 5-fluoro-2-methylaniline (5g, 0.04 mol), Ac_2O (4.08 g, 0.04 mol) and TEA (4.848 g, 0.048 mol) in DCM (20 mL) was stirred overnight at rt. H_2O was added, extracted with DCM, dried, concentrated to afford the title copound (6 g, 90%). [M+H] Calc'd for $C_9H_{10}FNO$, 168; Found, 168.

Prepration 47B: N-(5-Fluoro-2-methyl-4-nitrophenyl)acetamide



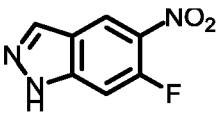
To a solution of N-(5-fluoro-2-methylphenyl)acetamide (6 g, 3.593 mmol) in 98% H_2SO_4 (36 mL) was added 70% HNO_3 (3.23 g, 3.593 mmol) at 0°C, then the mixture was stirred for 1 hr at this temperature. TLC showed the reaction was completed, poured into ice water and extracted with DCM, dried, concentrated to afford the title compound (6 g, 79%). [M+H] Calc'd for $C_9H_9FN_2O_3$, 213; Found, 213.

Preparation 47C: 5-Fluoro-2-methyl-4-nitroaniline



A solution of N-(5-fluoro-2-methyl-4-nitrophenyl)acetamide (6g, 35.93 mmol) in 5N HCl (30 mL) was stirred for 1 hr at 100°C, TLC showed the reaction was completed, cooled and adjusted to pH = 7-8 with Na_2CO_3, extracted with EA, dried, concentrated to afford the title compound (4.9 g, 80%). [M+H] Calc'd for $C_7H_7FN_2O_2$, 171; Found, 171

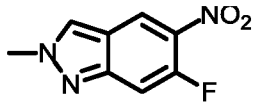
Preparation 47D: 6-Fluoro-5-nitro-1H-indazole



To a solution of 5-fluoro-2-methyl-4-nitroaniline (4.9 g, 28.82 mmol) in AcOH (50 mL) was added $NaNO_2$ (2.18 g, 31.71 mmol) in water (5 mL) in ice-bath. The mixture was

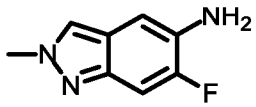
stirred for 2 hr in ice-bath. H_2O was added and extracted with EA, dried, concentrated and purified by flash chromatography on silica gel (PE/EA=3/1) to afford the title compound (1.14 g, 21%). ^{1}H NMR (300 MHz, DMSO): δ 7.86 (1H, d, *J* =12.0 Hz), 8.36 (1H, s), 8.76 (1H, d, *J* = 7.2 Hz), 13.71 (1H, s). [M+H] Calc'd for $C_7H_4FN_3O_2$, 182; Found, 182.

Preparation 47E: 6-Fluoro-2-methyl-5-nitroindazole



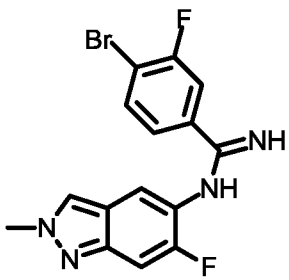
To a solution of 6-fluoro-5-nitro-1H-indazole (1.14 g, 6.30 mmol) in EA (150 mL) was added BF_4-OMe_3 (1.397 g, 9.45 mmol) at rt. The mixture was stirred for 5 hr at r.t. aq $NaHCO_3$ was added to adjust pH = 7-8, extracted with EA, dried, concentrated to afford the title compound (1 g, 81%). [M+H] Calc'd for $C_8H_6FN_3O_2$, 196; Found, 196.

Preparation 47F: 6-Fluoro-2-methylindazol-5-amine



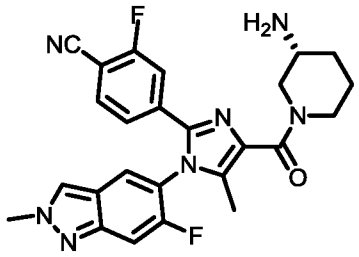
A mixture of 6-fluoro-2-methyl-5-nitroindazole (1 g, 5.128 mol) and Pd/C (200 mg, 10%) in DCM/MeOH (10/10 mL) was stirred overnight at r.t. under H_2. LC/MS showed the reaction was completed, filtered, concentrated and purified by flash chromatography on silica gel (DCM/MeOH=20/1) to afford the title compound (400 mg, 47%). [M+H] Calc'd for $C_8H_8FN_3$, 166; Found, 166.

Preparation 47G: 4-Bromo-3-fluoro-N-(6-fluoro-2-methylindazol-5-yl)benzenecarboximidamide



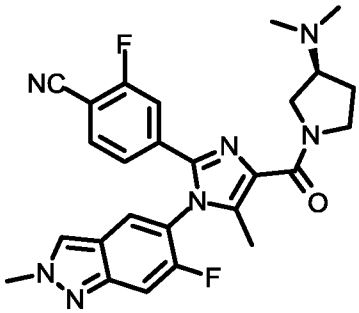
To a solution of 6-fluoro-2-methylindazol-5-amine (100 mg, 0.61 mmol) in toluene (5 mL) was added a solution of $Al(CH_3)_3$ (0.5 mL, 0.91 mmol) in THF at 0°C, then the mixture was stirred for 3.5 hr at r.t. A solution of 4-bromo-3-fluoro-benzonitrile (241 mg, 1.21 mmol) in THF (5 mL) was added dropwised at r.t. and stirred overnight at 75°C. LC/MS showed the reaction was completed, after concentration, the residue was purified by flash chromatography on silica gel (PE/EA=3/1 to EA) to afford the title compound (120 g, 54%). [M+H] Calc'd for $C_{15}H_{11}BrF_2N_4$, 365; Found, 365.

Example 47: 4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-1-(6-fluoro-2-methylindazol-5-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile



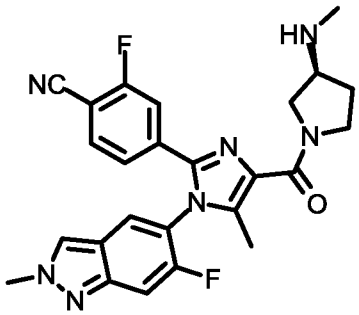
The title compound was prepared as TFA salt in 1% overall yield according to the general procedure for the preparation of Example 43 using 4-bromo-3-fluoro-N-(6-fluoro-2-methylindazol-5-yl)benzenecarboximidamide. ^{1}H NMR (400 MHz, CD_3OD): δ 1.74-2.00 (3H, m), 2.19-2.29 (4H, m), 3.40-3.54 (3H, m), 4.12-4.48 (5H, m), 7.39-7.42 (1H, m), 7.56-7.60 (2H, m), 7.72-7.77 (1H, m), 8.17-8.20 (1 H, m), 8.48 (1 H, s). [M+H] Calc'd for $C_{25}H_{23}F_2N_7O$, 476; Found, 476.

Example 48: 4-[4-[(3S)-3-(Dimethylamino)pyrrolidine-1-carbonyl]-1-(6-fluoro-2-methylindazol-5-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile



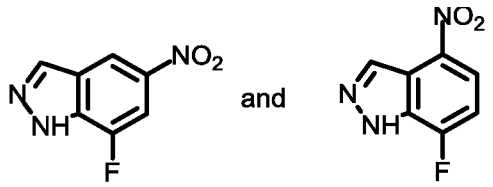
The title compound was prepared as TFA salt in 0.4% overall yield according to the procedure for the preparation of Example 47. ^{1}H NMR (300 MHz, CD_3OD): δ 2.25-2.29 (4H, m), 2.53-2.55 (1H, m), 3.01 (6H, s), 4.00-4.15 (4H, m), 4.25 (3H, s), 4.49-4.55 (1H, m), 7.27-7.29 (1H, m), 7.42-7.62 (3H, m), 7.91-7.97 (1 H, m), 8.41 (1 H, s). [M+H] Calc'd for $C_{26}H_{25}F_2N_7O$, 490; Found, 490.

Example 49: 2-Fluoro-4-[1-(6-fluoro-2-methylindazol-5-yl)-5-methyl-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile



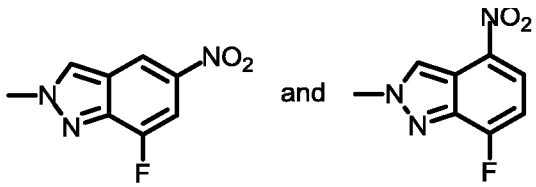
The title compound was prepared as TFA salt in 0.2% overall yield according to the procedure for the preparation of example 47. ^{1}H NMR (300 MHz, CD_3OD): δ 2.30-2.51 (5H, m), 2.82 (3H, s), 3.91-4.41 (8H, m), 7.37-7.70 (4H, m), 8.15 (1H, br), 8.52 (1 H, s). [M+H] Calc'd for $C_{25}H_{23}F_2N_7O$, 476; Found, 476.

Preparation 50A: 7-Fluoro-5-nitro-1H-indazole and 7-fluoro-4-nitro-1H-indazole



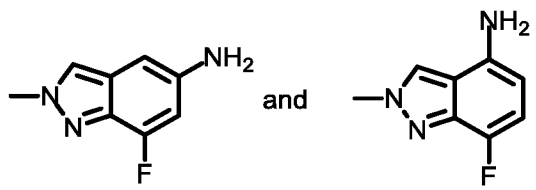
To a solution of 7-fluoro-1H-indazole (7.2g, 52.99 mmol) in 98% H_2SO_4 (70 mL) was added KNO_3 (5.62 g, 55.64 mmol) portionwise at 0 °C, allow the reaction mixture to stir for 4 hr at the same temperature; then poured into ice-water, extracted with EA, the combined organic layers were washed by H_2O, aq $NaHCO_3$, and dried over Na_2SO_4, after concentration the residue was purified by flash chromatography on silica gel (PE/EA=3/1) to afford a mixture of 7-fluoro-5-nitro-1H-indazole and 7-fluoro-4-nitro-1H-indazole (8.23 g, 86%).

Preparation 50B: 7-Fluoro-2-methyl-5-nitroindazole and 7-fluoro-2-methyl-4-nitroindazole



To a solution of a mixture of 7-fluoro-5-nitro-1H-indazole and 7-fluoro-4-nitro-1H-indazole (8.23 g, 45.47 mmol) in EA (100 mL) was added BF_4-OMe_3 (10.08 g, 68.20 mmol) at r.t. The mixture was stirred for 5 hr at r.t. aq $NaHCO_3$ was added to adjust pH = 7-8, the reaction mixture was extracted with EA, the combined organic layers were dried over Na_2SO_4, the solvent was removed in vacuum to afford a mixture of compound 7-fluoro-2-methyl-5-nitroindazole and 7-fluoro-2-methyl-4-nitroindazole (3.2 g, 36%). [M+H] Calc'd for $C_8H_6FN_3O_2$, 196; Found, 196.

Preparation 50C: 7-Fluoro-2-methylindazol-5-amine and 7-fluoro-2-methylindazol-4-amine



A mixture of 7-fluoro-2-methyl-5-nitroindazole and 7-fluoro-2-methyl-4-nitroindazole (3.2 g, 16.41 mol), Fe (9.2 g, 164 mmol), and NH_4Cl (439 mg, 8.20 mmol) in 80% EtOH (30 mL) was refluxed for 4 hr. LC/MS showed the reaction was completed. The mixture was filtered and concentrated, the residue was purified by flash chromatography on silica gel (PE/EA=1/1) to afford a mixture of 7-fluoro-2-methylindazol-5-amine (326 mg) and 7-fluoro-2-methylindazol-4-amine (724 mg).

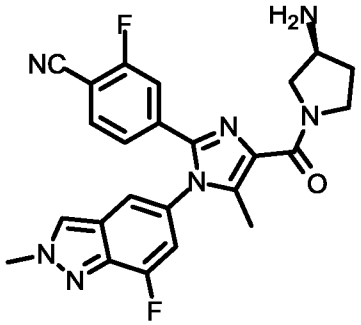
7-Fluoro-2-methylindazol-5-amine: ^{1}H NMR (400 MHz, DMSO): δ 4.06 (3H, s), 4.96 (2H, s), 6.39 (1H, *J* = 1.2 Hz, d), 6.53 (1H, *J* = 13.6 Hz, 1.2 Hz, dd), 7.96 (1H, *J* = 2.8 Hz, d).

[M+H] Calc'd for $C_8H_8FN_3$, 166; Found, 166.

7-fluoro-2-methylindazol-4-amine: ^{1}H NMR (400 MHz, DMSO): δ 4.12 (3H, s), 5.41 (2H, s), 5.84 (1H, *J* = 8.0 Hz, 2.8 Hz, dd), 6.67 (1H, *J* = 12 Hz, 7.6 Hz, dd), 8.32 (1H, *J* = 2.8 Hz, d).

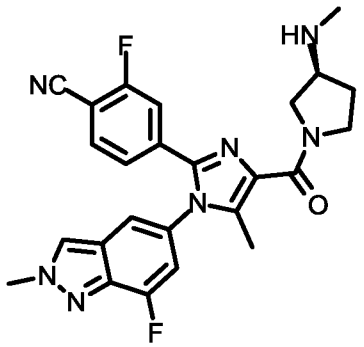
[M+H] Calc'd for $C_8H_8FN_3$, 166; Found, 166.

Example 50: 4-[4-[(3S)-3-Aminopyrrolidine-1-carbonyl]-1-(7-fluoro-2-methylindazol-5-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile



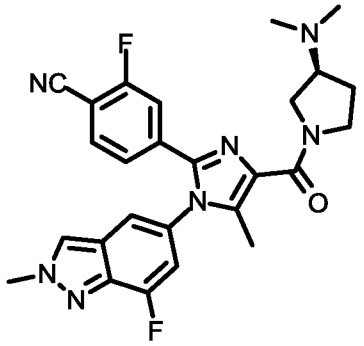
The title compound was prepared as TFA salt in 0.2% overall yield according to the procedure for the preparation of example 47 using 7-fluoro-2-methylindazol-5-amine. ^{1}H NMR (400 MHz, CD_3OD): δ 2.15-2.23 (1H, m), 2.36 (3H, s), 2.47-2.48 (1H, m), 3.77-4.34 (8H, m), 7.18 (1H, d, *J* = 11.1 Hz), 7.38 (1H, d, *J* =7.8 Hz),, 7.54 (1H, d, *J* =10.2 Hz), 7.67-7.74 (2 H, m), 8.49 (1 H, s). [M+H] Calc'd for $C_{24}H_{21}F_2N_7O$, 462; Found, 462.

Example 51: 2-Fluoro-4-[1-(7-fluoro-2-methylindazol-5-yl)-5-methyl-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile



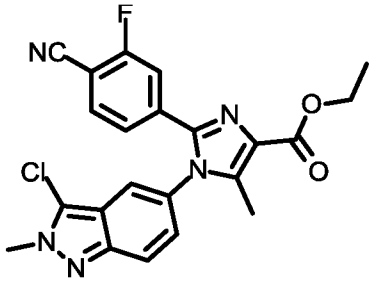
The title compound was prepared as TFA salt in 0.2% overall yield according to the procedure for the preparation of example 47 7-fluoro-2-methylindazol-5-amine. ^{1}H NMR (400 MHz, CD_3OD): δ 2.22-2.52 (2H, m), 2.36 (3H, s), 2.79 (3H, s), 3.85-4.40 (8H, m), 7.13-7.17 (1H, m), 7.35-7.37 (1H, m), 7.49-7.74 (3H, m), 8.48 (1 H, s). [M+H] Calc'd for $C_{25}H_{23}F_2N_7O$, 476; Found, 476.

Example 52: 4-[4-[(3S)-3-(Dimethylamino)pyrrolidine-1-carbonyl]-1-(7-fluoro-2-methylindazol-5-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile



The title compound was prepared as TFA salt in 0.2% overall yield according to the procedure for the preparation of example 47 using 7-fluoro-2-methylindazol-5-amine. 1H NMR (400 MHz, CD_3OD): δ 2.22-2.52 (4H, m), 2.50-2.70 (1H, m), 3.03 (6H, s), 3.76-4.57 (8H, m), 7.22-7.24 (1H, m), 7.46-7.59 (2H, m), 7.75-7.90 (2H, m), 8.53 (1 H, s). [M+H] Calc'd for $C_{26}H_{25}F_2N_7O$, 490; Found, 490.

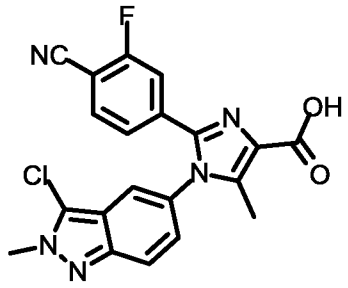
Preparation 53A: Ethyl 1-(3-chloro-2-methylindazol-5-yl)-2-(4-cyano-3-fluorophenyl)-5-methylimidazole-4-carboxylate



To a solution of ethyl 2-(4-cyano-3-fluorophenyl)-5-methyl-1-(2-methylindazol-5-yl)imidazole-4-carboxylate (100 mg, 0.248 mmol) in ACN (10 mL) was added NCS (33

mg, 0.248 mmol) at r.t. The mixture was stirred overnight at 50°C. H_2O was added and extracted with DCM, dried, concentrated to afford the title compound (90 mg, 83%). ^1H NMR (300 MHz, $CDCl_3$): δ 1.46 (3H, t, J = 7.2 Hz), 2.43 (3H, s), 4.25 (3H, s), 4.47 (2H, q, J = 7.2 Hz), 7.28-7.29 (1H, m), 7.41-7.45 (4H, m), 7.81-7.84 (1H, m). [M+H] Calc'd for $C_{22}H_{17}ClFN_5O_2$, 438; Found, 438.

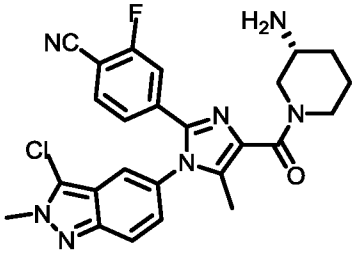
Prepration 53B: 1-(3-Chloro-2-methylindazol-5-yl)-2-(4-cyano-3-fluorophenyl)-5-methylimidazole-4-carboxylic acid



To a solution of ethyl 1-(3-chloro-2-methylindazol-5-yl)-2-(4-cyano-3-fluorophenyl)-5-methylimidazole-4-carboxylate (180 mg, 0.41 mmol) in THF/H_2O (6 mL/2 mL) was added $LiOH{\cdot}H_2O$ (35 mg, 0.82 mmol) at rt, then stirred for overnight at rt, acidified to pH= 3-4, and extracted with EA, dried and concentrated to give the title compound (170 mg, 100%).

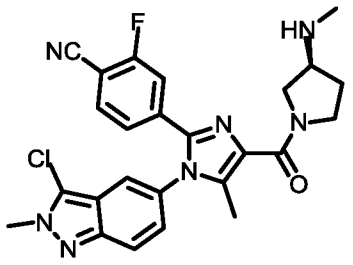
[M+H] Calc'd for $C_{20}H_{13}ClFN_5O_2$, 410; Found, 410.

Example 53: 4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-1-(3-chloro-2-methylindazol-5-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile



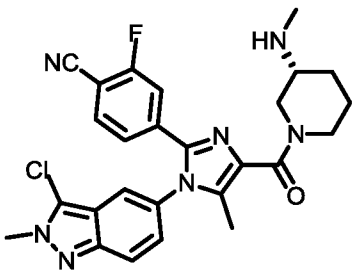
The title compound was prepared as TFA salt in 37% overall yield according to the procedure for the preparation of example 47 starting from ethyl 1-(2-methylindazol-5-yl)-2-(4-cyano-3-fluorophenyl)-5-methylimidazole-4-carboxylate. ^1H NMR (400 MHz, CD_3OD): δ 1.63-1.66 (2H, m), 1.70-1.75 (1H, m), 2.05-2.06 (1H, m), 2.14 (3H, s), 3.29-3.33 (3H, m), 3.99-4.07 (1H, m), 4.08 (3H, s), 4.20-4.30 (1H, m), 7.19-7.24 (2H, m), 7.30-7.40 (1H, m), 7.54-7.57 (1H, m), 7.66-7.71 (2 H, m). [M+H] Calc'd for $C_{25}H_{23}ClFN_7O$, 492; Found, 492.

Example 54: 4-[1-(3-Chloro-2-methylindazol-5-yl)-5-methyl-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile



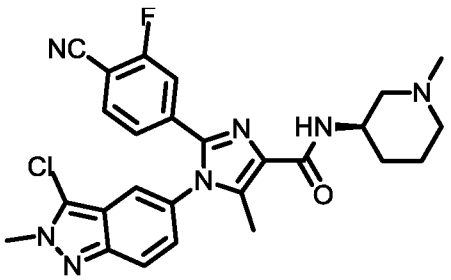
The title compound was prepared as TFA salt in 23% overall yield according to the procedure for the preparation of example 53. ^{1}HNMR (400 MHz, CD_3OD): δ 2.37-2.39 (4H, m), 2.55-2.64 (1H, m), 2.85 (3H, s), 3.79-4.38 (5H, m), 4.25 (3H, s), 7.49-7.63 (3H, m), 7.80-7.86 (2H, m), 7.99 (1H, s). [M+H] Calc'd for $C_{25}H_{23}ClFN_7O$, 492; Found, 492.

Example 55: 4-[1-(3-Chloro-2-methylindazol-5-yl)-5-methyl-4-[(3R)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile



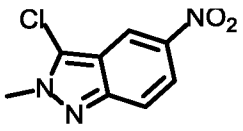
The title compound was prepared as TFA salt in 7% overall yield according to the procedure for the preparation of example 53. ^{1}HNMR (400 MHz, CD_3OD): δ 1.77-2.07 (3H, m), 2.33-2.34 (4H, m), 2.83 (3H, s), 3.40-3.41 (1H, m), 3.79-4.50 (4H, m), 4.25 (3H, s), 7.50-7.64 (3H, m), 7.81-7.85 (2H, m), 8.03 (1H, s). [M+H] Calc'd for $C_{26}H_{25}ClFN_7O$, 506; Found, 506.

Example 56: 1-(3-Chloro-2-methylindazol-5-yl)-2-(4-cyano-3-fluorophenyl)-5-methyl-N-[(3R)-1-methylpiperidin-3-yl]imidazole-4-carboxamide



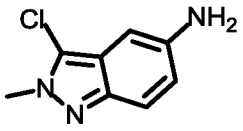
The title compound was prepared as TFA salt in 7% overall yield according to the procedure for the preparation of example 53. ^{1}HNMR (300 MHz, CD_3OD): δ 1.70-2.14 (4H, m), 2.41 (3H, s), 2.88-2.99 (2H, m), 2.94 (3H, s), 3.53-3.68 (2H, m), 4.21 (3H, s), 4.22-4.28 (1H, m), 7.20-7.28 (2H, m), 7.49-7.60 (2H, m), 7.70 (1H, s), 7.80 (1H, d, *J* =9.0 Hz). [M+H] Calc'd for $C_{26}H_{25}ClFN_7O$, 506; Found, 506.

Preparation 57A: 3-Chloro-2-methyl-5-nitroindazole



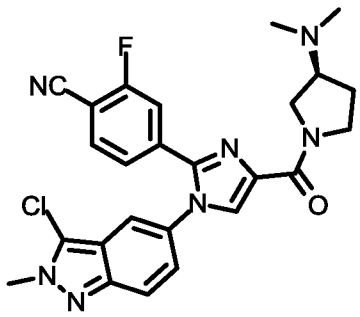
A solution of 2-methyl-5-nitroindazole (9 g, 50.85 mmol) and NCS (6.79 g, 50.85 mmol) in AcOH (60 mL) was stirred overnight at 70°C. Concentrated and dissolved in EA, washed by aq $NaHCO_3$ and H_2O, dried over Na_2SO_4, concentrated in vacuum to afford the title compound (10.7 g, 100%). ^{1}HNMR (300 MHz, $CDCl_3$): δ 4.22 (3H, s), 7.69 (1H, d, J = 9.6 Hz), 8.10 (1H, dd, J = 9.6 Hz, 2.1 Hz), 8.62 (1H, d, J = 1.8 Hz).

Preparation 57B: 3-Chloro-2-methylindazol-5-amine



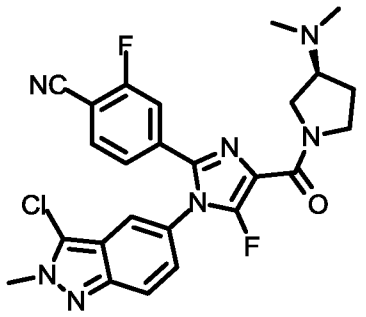
A mixture of 3-chloro-2-methyl-5-nitroindazole (10.7 g, 50.85 mmol), Fe (28.40 g, 508.5 mmol) and NH_4Cl (1.36 g, 25.35 mmol) in 80% EtOH (100 mL) was refluxed for 4 hr. LCMS showed the reaction was completed, after filtration, the residue was concentrated to afford the title compound (9.2 g, 100%). [M+H] Calc'd for $C_8H_8ClN_3$, 182; Found, 182.

Example 57: 4-[1-(3-Chloro-2-methylindazol-5-yl)-4-[(3S)-3-(dimethylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile



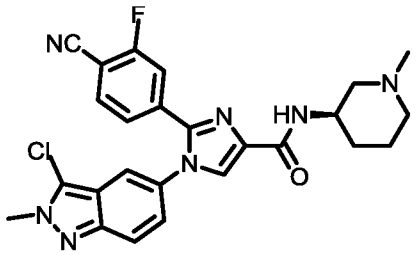
The title compound was prepared as TFA salt in 23% overall yield according to the procedure for the preparation of Example 47 using 3-chloro-2-methylindazol-5-amine. ^{1}HNMR (400 MHz, CD_3OD): δ 2.36-2.65 (2H, m), 3.08 (6H, s), 3.86-4.25 (4H, m), 4.25 (3H, s), 4.62-4.90 (1H, m), 7.23-7.38 (2H, m), 7.52-7.69 (2H, m), 7.74-7.78 (2H, m), 8.12-8.15 (1H, m). [M+H] Calc'd for $C_{25}H_{23}ClFN_7O$, 492; Found, 492.

Example 58: 4-[1-(3-Chloro-2-methylindazol-5-yl)-4-[(3S)-3-(dimethylamino)pyrrolidine-1-carbonyl]-5-fluoroimidazol-2-yl]-2-fluorobenzonitrile



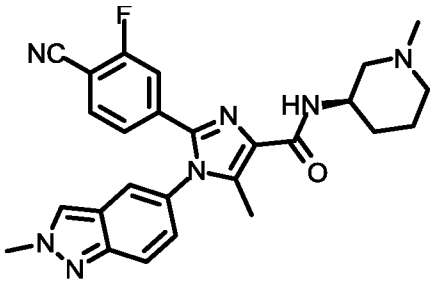
A solution of 4-[1-(3-chloro-2-methylindazol-5-yl)-4-[(3S)-3-(dimethylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile (500 mg, 1.02 mmol) and selectflour (720 mg, 2.04 mmol) in ACN was stirred overnight at 70 °C under N_2, after concentration the residue was purified by *prep*-HPLC to give the title compound (7 mg, 1%) . ^{1}HNMR (400 MHz, CD_3OD): δ 2.20-2.28 (2H, m), 3.01 (6H, s), 3.55-4.71 (5H, m), 4.22 (3H, s), 7.24-7.29 (2H, m), 7.46-7.47 (1H, m), 7.58-7.63 (1H, m), 7.77-7.84 (2H, m). [M+H] Calc'd for $C_{25}H_{22}ClF_2N_7O$, 510; Found, 510.

Example 59: 1-(3-Chloro-2-methylindazol-5-yl)-2-(4-cyano-3-fluorophenyl)-N-[(3R)-1-methylpiperidin-3-yl]imidazole-4-carboxamide



The title compound was prepared as TFA salt in 5% overall yield according to the procedure for the preparation of Example 57. ^{1}HNMR (300 MHz, CD_3OD): δ 1.70-2.14 (4H, m), 2.89-2.99 (2H, m), 2.94 (3H, s), 3.52-3.70 (2H, m), 4.21 (3H, s), 4.30-4.32 (1H, m), 7.19-7.33 (2H, m), 7.52-7.75 (4H, m), 8.02 (1 H, s). [M+H] Calc'd for $C_{25}H_{23}ClFN_7O$, 492; Found, 492.

Example 60: 2-(4-Cyano-3-fluorophenyl)-5-methyl-1-(2-methylindazol-5-yl)-N-[(3R)-1-methylpiperidin-3-yl]imidazole-4-carboxamide

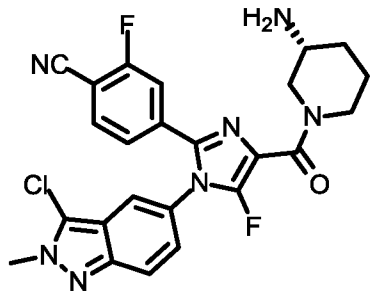


The title compound was prepared as TFA salt in 5% overall yield according to the general procedure for the preparation of Example 43. ^{1}HNMR (400 MHz, CD_3OD): δ

1.64-2.15 (4H, m), 2.41 (3H, s), 2.93-2.97 (2H, m), 2.94 (3H, s), 3.56-3.67 (2H, m), 4.26 (3H, s), 4.26-4.28 (1H, m), 7.16-7.29 (2H, m), 7.45-7.59 (2H, m), 7.74-7.93 (2H, m), 8.35 (1H, s).

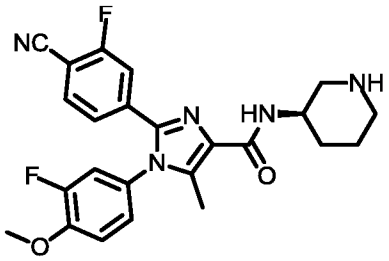
[M+H] Calc'd for $C_{26}H_{26}FN_7O$, 472; Found, 472.

Example 61: 4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-1-(3-chloro-2-methylindazol-5-yl)-5-fluoroimidazol-2-yl]-2-fluorobenzonitrile



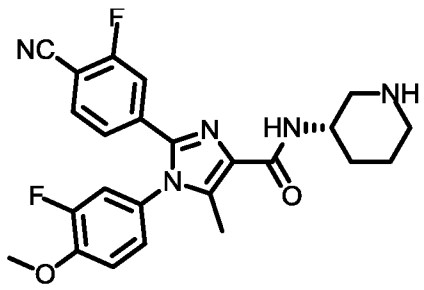
The title compound was prepared as TFA salt in 3% yield according to the procedure for the preparation of Example 58. ^{1}H NMR (400 MHz, CD_3OD): δ 1.30-1.43 (2H, m), 1.77-1.80 (1H, m), 1.97-2.02 (1H, m), 2.85-2.88 (2H, m), 3.20-3.25 (1H, m), 4.13 (3H, s), 4.13-4.61 (2H, m), 7.16-7.22 (2H, m), 7.13-7.14 (1H, m), 7.52 (1H, t, J = 7.4 Hz), 7.68 (1H, d, J = 8.8 Hz), 7.76 (1H, s) . [M+H] Calc'd for $C_{24}H_{20}ClF_2N_7O$, 496; Found, 496.

Example 62: 2-(4-Cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)-5-methyl-N-[(3R)-piperidin-3-yl]imidazole-4-carboxamide



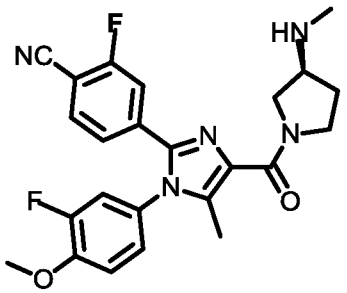
The title compound was prepared as TFA salt in 0.2% overall yield according to the general procedure for the preparation of Example 12. ^{1}H NMR (400 MHz, CD_3OD): δ 1.87-1.88 (2H, m), 2.11-2.14 (2H, m), 2.43 (3H, s), 3.09-3.12 (2H, m), 3.30-3.33 (2H, m), 3.96 (3H, s), 4.25-4.40 (1H, m), 7.25-7.42 (4H, m), 7.57-7.60 (1H, m), 7.77-7.81 (1H, m). [M+H] Calc'd for $C_{24}H_{23}F_2N_5O_2$, 452; Found, 452.

Example 63: 2-(4-Cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)-5-methyl-N-[(3S)-piperidin-3-yl]imidazole-4-carboxamide



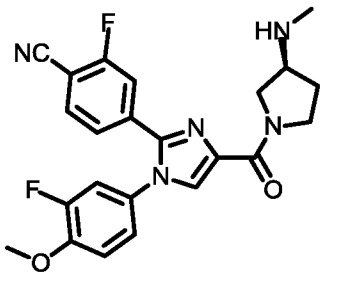
The title compound was prepared as TFA salt in 0.2% overall yield according to the general procedure for the preparation of Example 12. ^{1}H NMR (400 MHz, CD_3OD): δ 1.87-1.88 (2H, m), 2.11-2.14 (2H, m), 2.43 (3H, s), 3.09-3.12 (2H, m), 3.30-3.33 (2H, m), 3.96 (3H, s), 4.25-4.40 (1H, m), 7.25-7.42 (4H, m), 7.57-7.60 (1H, m), 7.77-7.81 (1H, m). [M+H] Calc'd for $C_{24}H_{23}F_2N_5O_2$, 452; Found, 452.

Example 64: 2-Fluoro-4-[1-(3-fluoro-4-methoxyphenyl)-5-methyl-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile



The title compound was prepared as TFA salt in 1% overall yield according to the general procedure for the preparation of Example 12. ^{1}H NMR (300 MHz, CD_3OD): δ 2.18-2.32 (4H, m), 2.50-2.52 (1H, m), 2.80 (3H, s), 3.93-4.35 (5H, m), 3.96 (3H, s), 7.24-7.38 (4H, m), 7.49-7.52 (1H, m), 7.72-7.77 (1H, m). [M+H] Calc'd for $C_{24}H_{23}F_2N_5O_2$, 452; Found, 452.

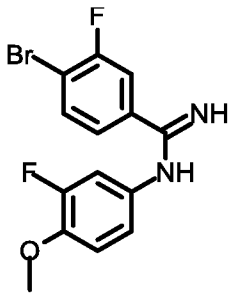
Example 65: 2-Fluoro-4-[1-(3-fluoro-4-methoxyphenyl)-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile



The title compound was prepared as TFA salt in 0.6% overall yield according to the general procedure for the preparation of Example 12 using ethyl bromopyruvate. ^{1}H NMR (300 MHz, CD_3OD): δ 2.18-2.32 (2H, m), 2.81 (3H, s), 3.93-4.35 (5H, m), 3.94

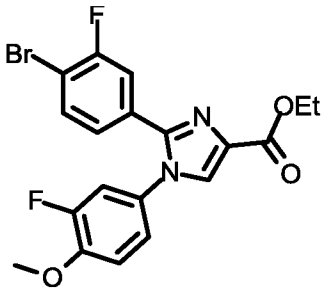
(3H, s), 7.23-7.40 (4H, m), 7.55-7.58 (1H, m), 7.80-7.82 (1H, m), 8.23-8.27 (1H, m). [M+H] Calc'd for $C_{23}H_{21}F_2N_5O_2$, 438; Found, 438.

Preparation 66A: 4-Bromo-3-fluoro-N-(3-fluoro-4-methoxyphenyl)benzenecarboximidamide



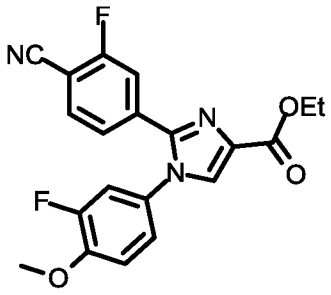
To a solution of EtMgBr (48 mL, 42.55 mmol, 0.9 M) in THF (24 mL) was added a solution of 3-fluoro-4-methoxyaniline (3 g, 21.28 mmol) in THF (30 mL) at r.t. The mixture was stirred for 30 min at r.t. A solution of 4-bromo-3-fluorobenzonitrile (4.657 g, 23.40 mmol) in THF (20 mL) was added dropwise at r.t. and stirred overnight at r.t. LC/MS showed the reaction was completed, H_2O was added and extracted with EA, dried, concentrated and purified by flash chromatography on silica gel (PE/EA=3/1 to EA) to afford 4-bromo-3-fluoro-N-(3-fluoro-4-methoxyphenyl)benzenecarboximidamide (4.68 g, 65%). [M+H] Calc'd for $C_{14}H_{11}BrF_2N_2O$, 341; Found, 341.

Preparation 66B: Ethyl 2-(4-bromo-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)imidazole-4-carboxylate



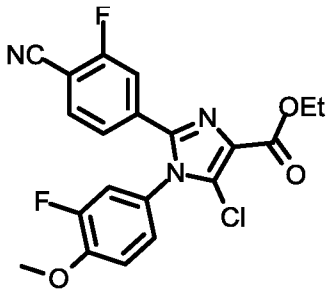
A mixture of 4-bromo-3-fluoro-N-(3-fluoro-4-methoxyphenyl)benzenecarboximidamide (4.68 g, 13.76 mmol), ethyl 3-bromo-2-oxopropanoate (2.684 g, 13.76 mmol) and Na_2CO_3 (1.459 g, 13.76 mmol) in toluene/EtOH (100 mL, 1/1) was stirred overnight at 100 °C; filtered, concentrated, the residue was dissolved in AcOH (50 mL) and stirred for 1h at 120 °C, concentrated and purified by flash chromatography on silica gel (PE/EA=3/1 to EA) to afford the title compound (1.1 g, 18%). [M+H] Calc'd for $C_{19}H_{15}BrF_2N_2O_3$, 437; Found, 437.

Preparation 66C: Ethyl 2-(4-cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)imidazole-4-carboxylate



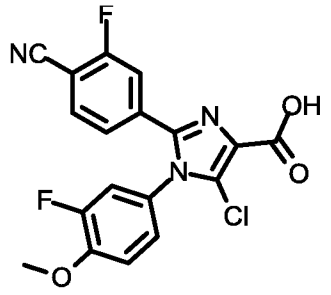
A mixture of ethyl 2-(4-bromo-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)imidazole-4-carboxylate (1.1 g, 2.58 mmol), Zn(CN)2 (1.51 g, 12.89 mmol) and $Pd(PPh_3)_4$ (298 mg, 0.258 mmol) in DMA (5 mL) was stirred overnight at 110 °C in a sealed tube. LC/MS showed the reaction was completed, concentrated and purified by flash chromatography on silica gel (PE/EA=3/1 to EA) to afford the title compound (600 mg, 60%). [M+H] Calc'd for $C_{20}H_{15}F_2N_3O_3$, 384; Found, 384.

Preparation 66D: Ethyl 5-chloro-2-(4-cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)imidazole-4-carboxylate



To a solution of ethyl 2-(4-cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)imidazole-4-carboxylate (200 mg, 0.522 mmol) in AcOH (5 mL) was added NCS (70 mg, 0.522 mmol) at r.t, then stirred overnight at 50 °C; concentrated, H_2O was added and extracted with DCM, dried and concentrated to give the title compound (196 mg, 90%). [M+H] Calc'd for $C_{20}H_{14}ClF_2N_3O_3$, 418; Found, 418.

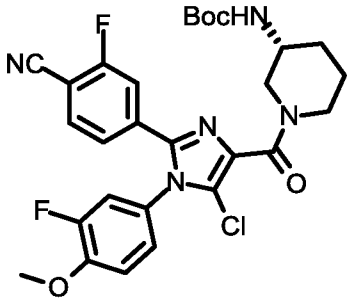
Preparation 66E: 5-Chloro-2-(4-cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)imidazole-4-carboxylic acid



To a solution of Ethyl 5-chloro-2-(4-cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)imidazole-4-carboxylate (196 mg, 0.47 mmol) in THF/H_2O (6 mL/2 mL) was added $LiOH{\cdot}H_2O$ (100 mg, 2.35 mmol) at r.t, stirred overnight at r.t, acidified to pH=

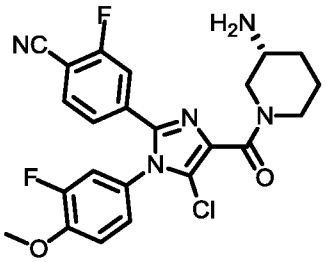
3-4, extracted with EA, dried and concentrated to give the title compound (182 mg, 100%). [M+H] Calc'd for $C_{18}H_{10}ClF_2N_3O_3$, 390; Found, 390.

Preparation 66F: tert-butyl N-[(3R)-1-[5-Chloro-2-(4-cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)imidazole-4-carbonyl]piperidin-3-yl]carbamate



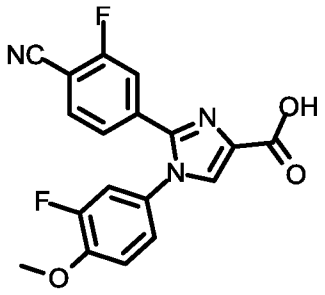
A mixture of 5-chloro-2-(4-cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)imidazole-4-carboxylic acid (180 mg, 0.46 mmol), N-((3R)(3-piperidyl))(tert-butoxy) carboxamide (93 mg, 0.46 mmol), HATU (194 mg, 0.51 mmol) and NMM (94 mg, 0.93 mmol) in DMF (5 mL) was stirred for 1 hr at r.t. LC/MS showed the reaction was completed, concentrated to afford the title compound (260 mg, 100%). [M+H] Calc'd for $C_{28}H_{28}ClF_2N_5O_4$, 572; Found, 572

Example 66: 4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-5-chloro-1-(3-fluoro-4-methoxyphenyl)imidazol-2-yl]-2-fluorobenzonitrile



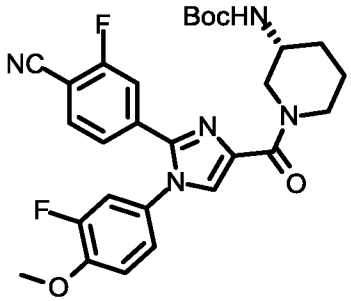
A solution of tert-butyl N-[(3R)-1-[5-Chloro-2-(4-cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)imidazole-4-carbonyl]piperidin-3-yl]carbamate (260 mg, 0.46 mmol) in HCl/EA (5 mL) was stirred for 1 hr at r.t. LC/MS showed the reaction was completed, concentrated and purified by *prep*-HPLC to afford the title compound (117 mg, 54%). ^{1}H NMR (400 MHz, CD_3OD): δ 1.65-1.67 (2H, m), 1.83-1.84 (1H, m), 2.08-2.09 (1H, m), 3.19-3.30 (3H, m), 3.86 (3H, s), 3.90-4.37 (2H, m), 7.06-7.37 (5H, m), 7.60 (1H, t, *J* =7.2 Hz). [M+H] Calc'd for $C_{23}H_{20}ClF_2N_5O_2$, 472; Found, 472.

Preparation 67A: 2-(4-Cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)imidazole-4-carboxylic acid



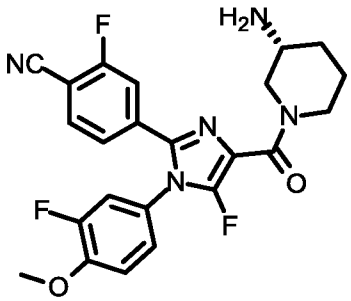
To a solution of ethyl 2-(4-cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)imidazole-4-carboxylate (300 mg, 0.78 mmol) in THF/H_2O (9 mL/3 mL) was added LiOH·H_2O (165 mg, 3.92 mmol) at r.t, stirred overnight at r.t, acidified to pH= 3-4; extracted with EA, dried and concentrated to give the title compound (278 mg, 100%). [M+H] Calc'd for $C_{18}H_{11}F_2N_3O_3$, 356; Found, 356.

Preparation 67B: tert-butyl N-[(3R)-1-[2-(4-Cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)imidazole-4-carbonyl]piperidin-3-yl]carbamate



A mixture of 2-(4-cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)imidazole-4-carboxylic acid (300 mg, 0.78 mmol), N-((3R)(3-piperidyl))(tert-butoxy) carboxamide (157 mg, 0.78 mmol), HATU (327 mg, 0.86 mmol) and NMM (158 mg, 1.566 mmol) in DMF (5 mL) was stirred for 1 hr at r.t. LC/MS showed the reaction was completed, concentrated to afford the title compound (420 mg, 100%). [M+H] Calc'd for $C_{28}H_{29}F_2N_5O_4$, 538; Found, 538.

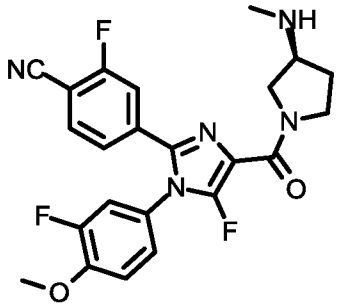
Example 67: 4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-5-fluoro-1-(3-fluoro-4-methoxyphenyl)imidazol-2-yl]-2-fluorobenzonitrile



To a solution of tert-butyl N-[(3R)-1-[2-(4-cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)imidazole-4-carbonyl]piperidin-3-yl]carbamate (420 mg, 0.78 mmol) in

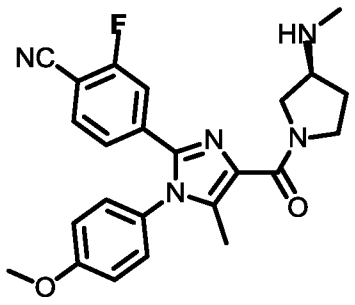
ACN (10 mL) was added selectfluor (554 mg, 1.566 mmol) and 0.5 mL AcOH was stirred for overnight at 90 °C, concentrated and purified by *prep*-HPLC to afford the title compound (17 mg, 4.7%). ^{1}H NMR (400 MHz, CD_3OD): δ 1.98-2.30 (3H, m), 2.40-2.42 (1H, m), 3.53-3.55 (3H, m), 4.20 (3H, s), 4.62-4.73 (2H, m), 7.43-7.59 (5H, m), 7.91-7.94 (1H, m). [M+H] Calc'd for $C_{23}H_{20}F_3N_5O_2$, 456; Found, 456.

Example 68: 2-Fluoro-4-[5-fluoro-1-(3-fluoro-4-methoxyphenyl)-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile



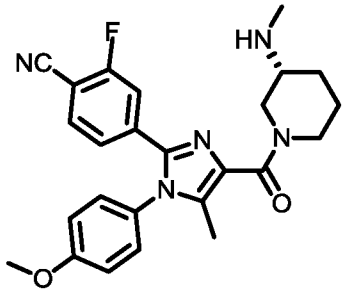
A solution of tert-butyl N-[(3S)-1-[2-(4-cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)imidazole-4-carbonyl]pyrrolidin-3-yl]-N-methylcarbamate (400 mg, 0.74 mmol) in ACN (10 mL) was added selectfluor (528 mg, 1.49 mmol) and 0.5 mL AcOH, which was stirred overnight at 90 °C. It was then concentrated and purified by *prep*-HPLC to afford the title compound (11 mg, 3%). ^{1}H NMR (400 MHz, DMSO-*d6*): δ 2.00-2.30 (2H, m), 2.63 (3H, d, J = 5.6 Hz), 3.55-4.29 (5H, m), 3.94 (3H, s), 7.20-7.21 (1H, m), 7.25-7.30 (1H, m), 7.38-7.39 (2H, m), 7.66-7.69 (1H, m), 7.90-7.91 (1H, m), 8.75-8.94 (2 H, m). [M+H] Calc'd for $C_{23}H_{20}F_3N_5O_2$, 456; Found, 456.

Example 69: 2-Fluoro-4-[1-(4-methoxyphenyl)-5-methyl-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile



The title compound was prepared as TFA salt in 4% overall yield according to the general procedure for the preparation of Example 12. 1H NMR (300 MHz, CD_3OD): δ 2.30-2.32 (1H, m), 2.31 (3H, s), 2.47-2.48 (1H, m), 2.81 (3H, s), 3.88-4.39 (5H, m), 3.92 (3H, s), 7.11-7.14 (2H, m), 7.34-7.48 (3H, m), 7.46 (1H, d. J = 9.9 Hz), 7.73 (1H, t, J = 7.2 Hz). [M+H] Calc'd for $C_{24}H_{24}FN_5O_2$, 434; Found, 434.

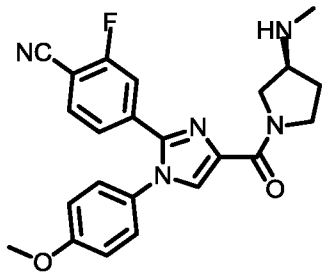
Example 70: 2-Fluoro-4-[1-(4-methoxyphenyl)-5-methyl-4-[(3R)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]benzonitrile



The title compound was prepared as TFA salt in 2% overall yield according to the general procedure for the preparation of Example 12. ^{1}H NMR (300 MHz, CD_3OD): δ 1.74-2.02 (3H, m), 2.26 (3H, s), 2.26-2.27 (1H, m), 2.79 (3H, s), 3.30-3.31 (2H, m), 3.67-3.74 (1H, m), 3.86 (3H, s), 3.97-4.08 (2H, m), 7.11-7.14 (2H, m), 7.41-7.45 (4H, m), 7.79-7.81 (1H, m).

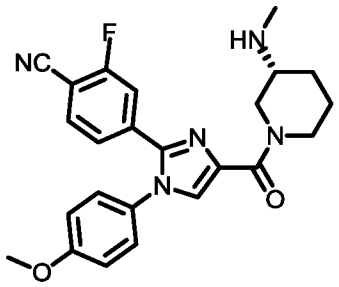
[M+H] Calc'd for $C_{25}H_{26}FN_5O_2$, 448; Found, 448.

Example 71: 2-Fluoro-4-[1-(4-methoxyphenyl)-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile



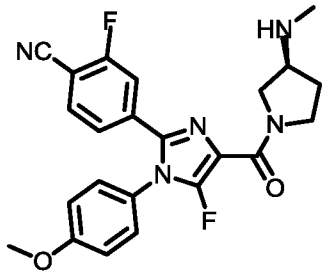
The title compound was prepared as TFA salt in 6% overall yield according to the general procedure for the preparation of Example 12 using ethyl bromopyruvate. ^{1}H NMR (400 MHz, CD_3OD): δ 2.44-2.64 (2H, m), 2.84 (3H, s), 3.96 (3H, m), 3.85-4.38 (5H, m), 7.10-7.13 (2H, m), 7.48-7.52 (3H, m), 7.62-7.65 (1H, m), 7.93 (1H, t, J=7.2 Hz), 8.50 (1H, s).[M+H] Calc'd for $C_{23}H_{22}FN_5O_2$, 420; Found, 420.

Example 72: 2-Fluoro-4-[1-(4-methoxyphenyl)-4-[(3R)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]benzonitrile



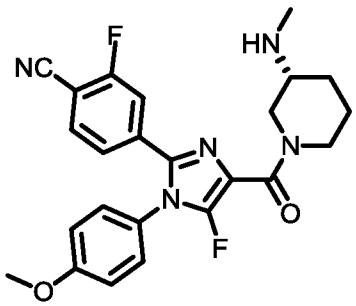
The title compound was prepared as TFA salt in 6% overall yield according to the general procedure for the preparation of Example 12 using ethyl bromopyruvate. ^{1}H NMR (300 MHz, CD_3OD): δ 1.70-2.27 (4H, m), 2.80 (3H, s), 2.30-2.43 (3H, m), 3.85 (3H, s), 3.85-4.13 (2H, m), 7.06-7.08 (2H, m), 7.41-7.45 (3H, m), 7.55 (1H, d, J = 9.9 Hz), 7.84 (1H, t, J =7.2 Hz), 8.27 (1H, s). [M+H] Calc'd for $C_{24}H_{24}FN_5O_2$, 434; Found, 434.

Example 73: 2-Fluoro-4-[5-fluoro-1-(4-methoxyphenyl)-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile



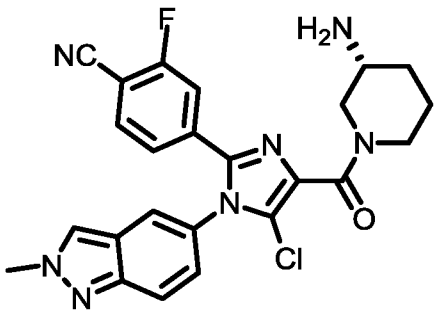
The title compound was prepared as TFA salt in 0.1% overall yield according to the general procedure for the preparation of Example 58. ^{1}H NMR (400 MHz, CD_3OD): δ 1.74-2.15 (2H, m), 2.33 (3H, d, J = 5.2 Hz), 3.20-4.23 (5H, m), 3.89 (3H, s), 7.02-7.04 (2H, m), 7.20-7.32 (4H, m), 7.56 (1H, t, J = 7.2 Hz). [M+H] Calc'd for $C_{23}H_{21}F_2N_5O_2$, 438; Found, 438.

Example 74: 2-Fluoro-4-[5-fluoro-1-(4-methoxyphenyl)-4-[(3R)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]benzonitrile



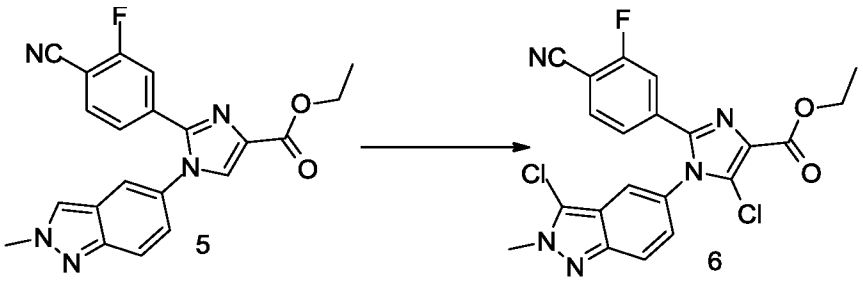
The title compound was prepared as TFA salt in 0.5% overall yield according to the general procedure for the preparation of Example 68. ^{1}H NMR (400 MHz, CD_3OD): δ 1.68-2.18 (4H, m), 2.63 (3H, s), 2.99-3.02 (1H, m), 3.54-3.70 (2H, m), 3.87 (3H, s), 3.87-4.48 (2H, m), 7.11-7.14 (2H, m), 7.30-7.37 (4H, m), 7.68 (1H, t, J = 7.6 Hz). [M+H] Calc'd for $C_{24}H_{23}F_2N_5O_2$, 452; Found, 452.

Example 75: 4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-5-chloro-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile



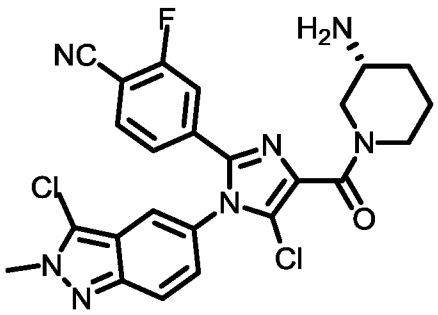
[00147] The title compound was prepared as the formic acid salt in 0.4% overall yield according to the general procedure for the preparation of Example 66. ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.43 (2H, m), 1.78 (1H, m), 1.95 (1H, m), 3.01 (1H, m), 4.25 (3H, s), 4.44 (1H, br s), 4.81 (1H, br s), 7.19 (1H, d, J= 8.7 Hz), 7.25 (1H, d, J = 8.4 Hz), 7.50 (1H, br s), 7.75 (1H, d, J = 9 Hz), 7.84 (1H, t, J = 7.4 Hz), 7.86 (1H, s), 8.05 (1H, s), 8.26 (1H, br s). [M+H] Calc'd for $C_{24}H_{21}ClFN_7O$, 478; Found, 478.

Preparation 76A: Ethyl 5-chloro-1-(3-chloro-2-methylindazol-5-yl)-2-(4-cyano-3-fluorophenyl)imidazole-4-carboxylate



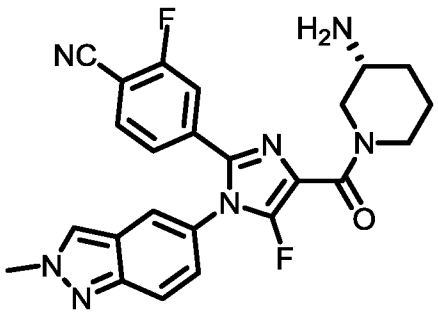
To a solution of ethyl 2-(4-cyano-3-fluorophenyl)-1-(2-methylindazol-5-yl)imidazole-4-carboxylate (800 mg, 2.06 mmol) in ACN/AcOH (10/1 mL) was added NCS (550 mg, 4.12 mmol) at r.t. The mixture was stirred overnight at 50°C. H_2O was added and extracted with DCM, dried, concentrated and purified by flash chromatography on silica gel (PE/EA=2/1) to afford the title compound (140 mg, 15%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (3H, t, J = 7.2 Hz), 4.24 (3H, s), 4.49 (2H, q, J = 7.2 Hz), 7.07-7.09 (1H, m), 7.26-7.29 (1H, m), 7.39-7.50 (3H, m), 7.82 (1H, d, J = 9.2 Hz). [M+H] Calc'd for $C_{21}H_{14}Cl_2FN_5O_2$, 458; Found, 458.

Example 76: 4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-5-chloro-1-(3-chloro-2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile



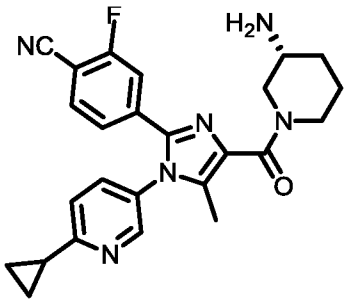
The title compound was prepared as TFA salt in 3% overall yield according to the procedure for the preparation of example 53 starting from ethyl 2-(4-cyano-3-fluorophenyl)-1-(2-methylindazol-5-yl)imidazole-4-carboxylate. ^{1}H NMR (400 MHz, CD_3OD): δ 1.77-1.81 (2H, m), 1.95-1.96 (1H, m), 2.20-2.21 (1H, m), 3.34-3.69 (3H, m), 4.20-4.22 (4H, m), 4.46-4.69 (1H, m), 7.27-7.33 (2H, m), 7.40-7.46 (1H, m), 7.61-7.65 (1H, m), 7.79-7.81 (2 H, m). [M+H] Calc'd for $C_{24}H_{20}Cl_2FN_7O$, 512; Found, 512.

Example 77: 4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-5-fluoro-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile



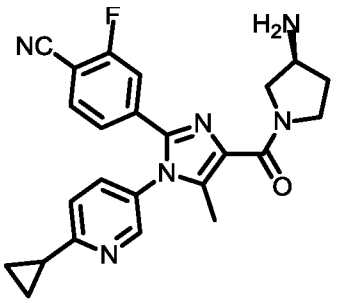
[00148] The title compound was prepared as the formic acid salt in 0.1% overall yield according to the general procedure for the preparation of Example 58. ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.28 (2H, m), 1.75 (1H, m), 1.89 (1H, m), 3.01 (1H, m), 4.25 (3H, s), 4.24 (1H, br s), 6.65 (1H, br s), 7.16 (1H, dd, J= 2 and 8.9 Hz), 7.27 (1H, d, J = 9.7 Hz), 7.50 (1H, br s), 7.60 (1H, d, J = 8.6 Hz), 7.85 (1H, t, J = 7.8 Hz), 7.89 (1H, s), 7.98 (1H, s), 8.36 (1H, br s). [M+H] Calc'd for $C_{24}H_{21}F_2N_7O$, 462; Found, 462.

Example 78: 4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-1-(6-cyclopropylpyridin-3-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile



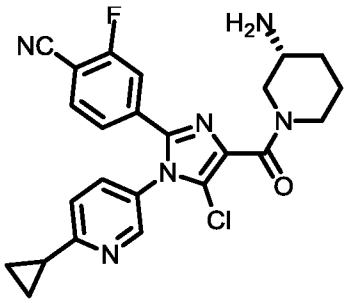
The title compound was prepared as formic acid salt in 2% overall yield according to the general procedure for the preparation of Example 12 using 6-cyclopropylpyridin-3-amine. ^{1}H NMR (400 MHz, DMSO- d_6): δ 0.99 (2H, s), 1.16 (2H, d, J = 6.3 Hz), 1.49 (2H, m), 1.75 (1H, m), 1.97 (1H, m), 2.17 (3H, s), 2.24 (1H, m), 2.92 (2H, m), 3.07 (2H, m), 4.14 (1H, m), 4.50 (1H, m), 7.16 (1H, d, J = 7.7 Hz), 7.36 (1H, m), 7.52 (1H, d, J = 8.2 Hz), 7.80 (1H, d, J = 6.4 Hz), 7.87 (1H, t, J = 8.0 Hz), 8.43 (1H, br s). [M+H] Calc'd for $C_{25}H_{25}FN_6O$, 445; Found, 445.

Example 79: 4-[4-[(3S)-3-Aminopyrrolidine-1-carbonyl]-1-(6-cyclopropylpyridin-3-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile



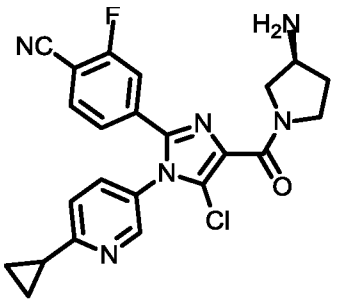
The title compound was prepared as formic acid salt in 0.8% overall yield according to the general procedure for the preparation of Example 12 using 6-cyclopropylpyridin-3-amine. ^{1}H NMR (400 MHz, DMSO- d_6): δ 0.99 (2H, s), 1.05 (2H, d, J = 10.1 Hz), 1.76 (1H, m), 1.85 (1H, m), 2.12 (1H, m), 2.22 (3H, s), 3.37 (1H, m), 3.56 (1H, m), 3.66 (1H, m), 3.85 (1H, m), 4.06-4.15 (1H, m), 7.16 (1H, t, J = 8.8 Hz), 7.38 (1H, d, J = 10.7 Hz), 7.53 (1H, d, J = 8.3 Hz), 7.79 (1H, d, J = 5.8 Hz), 7.86 (1H, m), 8.44 (1H, br s). [M+H] Calc'd for $C_{24}H_{23}FN_6O$, 431; Found, 431.

Example 80: 4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-5-chloro-1-(6-cyclopropylpyridin-3-yl)imidazol-2-yl]-2-fluorobenzonitrile



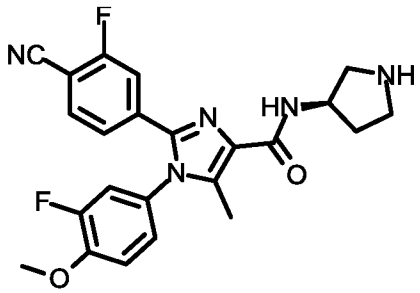
The title compound was prepared as formic acid salt in 4% overall yield according to the general procedure for the preparation of Example 66 using 6-cyclopropylpyridin-3-amine. ^{1}H NMR (400 MHz, DMSO- d_6): δ 0.99 (2H, s), 1.12 (2H, s), 1.52 (2H, m), 1.82 (1H, m), 1.99 (1H, m), 2.24 (1H, m), 2.92 (1H, m), 3.17 (2H, m), 4.12 (1H, m), 4.25 (1H, m), 4.45 (1H, m), 7.21 (1H, d, J = 8.0 Hz), 7.43 (1H, m), 7.55 (1H, d, J = 8.2 Hz), 7.85 (1H, m), 7.94 (1H, t, J = 6.8 Hz), 8.48 (1H, br s). [M+H] Calc'd for $C_{24}H_{22}ClFN_6O$, 465; Found, 465.

Example 81: 4-[4-[(3S)-3-Aminopyrrolidine-1-carbonyl]-5-chloro-1-(6-cyclopropylpyridin-3-yl)imidazol-2-yl]-2-fluorobenzonitrile



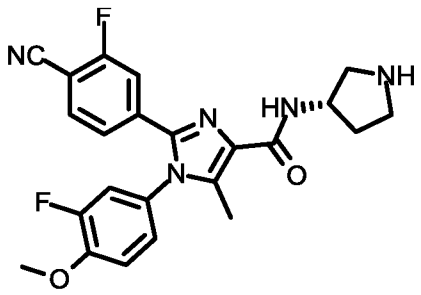
The title compound was prepared as formic acid salt in 3% overall yield according to the general procedure for the preparation of Example 66 using 6-cyclopropylpyridin-3-amine. ^{1}H NMR (400 MHz, DMSO- d_6): δ 0.99 (2H, s), 2.03 (1H, m), 2.22 (3H, m), 3.65 (1H, m), 3.68 (1H, m), 3.73 (1H, m), 3.88 (1H, m), 4.11 (1H, m), 4.25 (1H, m), 7.20 (1H, d, J = 6.9 Hz), 7.46 (1H, d, J = 10.4 HJz), 7.56 (1H, d, J = 8.0 Hz), 7.85 (1H, m), 7.93 (1H, m), 8.49 (1H, br s). [M+H] Calc'd for $C_{23}H_{20}ClFN_6O$, 451; Found, 451.

Example 82: 2-(4-Cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)-5-methyl-N-[(3R)-pyrrolidin-3-yl]imidazole-4-carboxamide



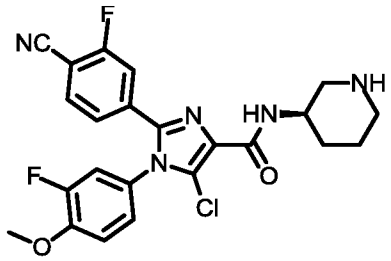
The title compound was prepared as formic acid salt in 2% overall yield according to the general procedure for the preparation of Example 12. ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.98-2.05 (1H, m), 2.18-2.26 (1H, m), 2.32 (3H, s), 3.17-3.22 (2H, m), 3.36-3.42 (2H, m), 3.92 (3H, s), 4.58-4.64 (1H, m), 7.18 (1H, dd, J = 1.5 and 8.2 Hz), 7.25 (1H, dd, J = 1.5 and 8.7 Hz), 7.35 (1H, t, J = 8.9 Hz), 7.54 (1H, dd, J = 2.4 and 11.5 Hz), 7.58 (1H, dd, J = 1.3 and 8.0 Hz), 7.88 (1H, t, J = 7.0 Hz), 8.45 (1H, d, J = 7.6 Hz), 9.09 (1H, br s). [M+H] Calc'd for $C_{23}H_{21}F_2N_5O_2$, 438; Found, 438.

Example 83: 2-(4-Cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)-5-methyl-N-[(3S)-pyrrolidin-3-yl]imidazole-4-carboxamide



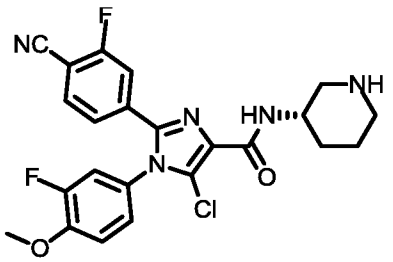
The title compound was prepared as formic acid salt in 5% overall yield according to the general procedure for the preparation of Example 12. ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.99-2.07 (1H, m), 2.19-2.24 (1H, m), 2.32 (3H, s), 3.20 (2H, m), 3.38 (2H, m), 3.92 (3H, s), 4.61 (1H, m), 7.19 (1H, d, J = 8.2 Hz), 7.24 (1H, d, J = 8.7 Hz), 7.35 (1H, t, J = 8.8 Hz), 7.57 (2H, t, J = 11.2Hz), 7.87 (1H, t, J = 6.8 Hz), 8.47 (1H, d, J = 7.3 Hz), 9.16 (1H, br s). [M+H] Calc'd for $C_{23}H_{21}F_2N_5O_2$, 438; Found, 438.

Example 84: 5-Chloro-2-(4-cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)-N-[(3R)-piperidin-3-yl]imidazole-4-carboxamide



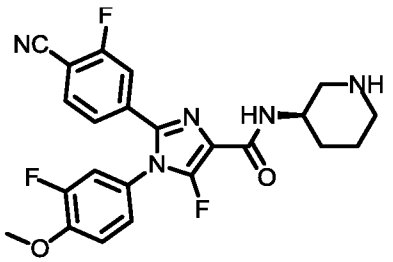
The title compound was prepared as formic acid salt in 4% overall yield according to the general procedure for the preparation of Example 66. ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.56-1.65 (2H, m), 1.74-1.81 (2H, m), 2.64 (1H, t, J = 10.6 Hz), 2.75 (1H, t, J = 10.7 Hz), 2.98 (1H, d, J = 11.8 Hz), 3.08 (1H, d, J = 11.6 Hz), 3.93 (3H, s), 4.06 (1H, m), 7.23 (1H, d, J = 8.0 Hz), 7.37 (1H, m), 7.60 (2H, d, J = 10.4 Hz), 7.89 (1H, t, J = 7.6 Hz), 8.23 (1H, d, J = 8.6 Hz), 8.29 (1H, s). [M+H] Calc'd for $C_{23}H_{20}ClF_2N_5O_2$, 472; Found, 472.

Example 85: 5-Chloro-2-(4-cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)-N-[(3S)-piperidin-3-yl]imidazole-4-carboxamide



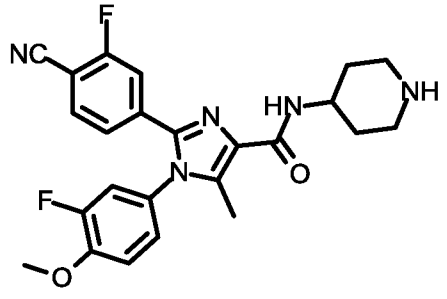
The title compound was prepared as formic acid salt in 3% overall yield according to the general procedure for the preparation of Example 66. ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.55-1.61 (2H, m), 1.64-1.81 (2H, m), 2.60 (1H, t, J = 12.1 Hz), 2.69 (1H, t, J = 9.8 Hz), 2.93 (1H, d, J = 10.8 Hz), 3.03 (1H, d, J = 11.1 Hz), 3.93 (3H, s), 4.00 (1H, m), 7.23 (1H, d, J = 8.3 Hz), 7.35 (1H, m), 7.60 (2H, m), 7.91 (1H, t, J = 7.1 Hz), 8.16 (1H, d, J = 8.5 Hz), 8.23 (1H, s). [M+H] Calc'd for $C_{23}H_{20}ClF_2N_5O_2$, 472; Found, 472.

Example 86: 2-(4-Cyano-3-fluorophenyl)-5-fluoro-1-(3-fluoro-4-methoxyphenyl)-N-[(3R)-piperidin-3-yl]imidazole-4-carboxamide



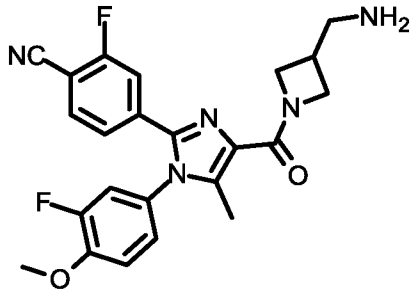
The title compound was prepared as formic acid salt in 4% overall yield according to the general procedure for the preparation of Example 68. ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.09 (2H, m), 1.23 (1H, m), 1.44 (1H, m), 1.76 (1H, m), 2.76 (1H, m), 2.93 (1H, m), 3.92 (3H, s), 6.27 (1H, s), 7.21 (1H, m), 7.39 (1H, m), 7.58 (2H, m), 7.91 (1H, m), 8.38 (1H, m). [M+H] Calc'd for $C_{23}H_{20}F_3N_5O_2$, 456; Found, 456.

Example 87: 2-(4-Cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)-5-methyl-N-piperidin-4-ylimidazole-4-carboxamide



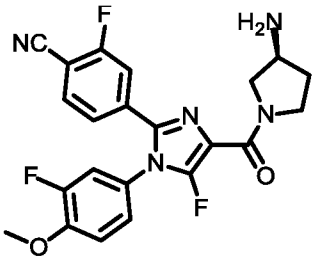
The title compound was prepared as formic acid salt in 2% overall yield according to the general procedure for the preparation of Example 12. ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.63-1.68 (1H, m), 1.82 (1H, m), 2.31 (3H, s), 2.73 (1H, t, J = 11.1 Hz), 3.14 (1H, d, J = 11.7 Hz), 3.92 (3H, s), 7.18 (1H, dd, J = 1.4 and 8.2 Hz), 7.34 (1H, t, J = 8.9 Hz), 7.59 (1H, dd, J = 2.4 and 11.6 Hz), 7.59 (1H, dd, J = 1.4 and 10.9 Hz), 7.87 (1H, t, J = 6.6 Hz), 7.95 (1H, d, J = 8.2 Hz), 8.27 (1H, br s), 8.34 (1H, br s). [M+H] Calc'd for $C_{24}H_{23}F_2N_5O_2$, 452; Found, 452.

Example 88: 4-[4-[3-(Aminomethyl)azetidine-1-carbonyl]-1-(3-fluoro-4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile



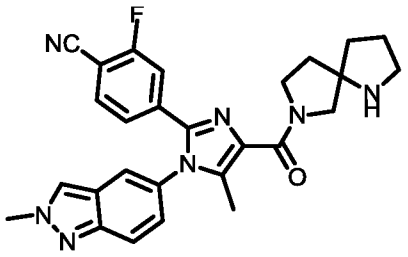
The title compound was prepared as formic acid salt in 0.9% overall yield according to the general procedure for the preparation of Example 12. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.35 (3H, s), 2.72 (1H, m), 2.91 (2H, m), 3.75 (1H, m), 3.91 (3H, s), 4.06 (1H, t, J = 9.6 Hz), 4.36 (1H, m), 4.66 (1H, t, J = 9.1 Hz), 7.17 (1H, dd, J = 1.4 and 8.3 Hz), 7.23 (1H, d, J = 7.5 Hz), 7.35 (2H, t, J = 8.9 Hz), 7.40 (1H, d, J = 10.8 Hz), 7.54 (1H, dd, J = 2.4 and 11.6 Hz), 7.85 (1H, t, J = 7.8 Hz), 8.32 (1H, br s). [M+H] Calc'd for $C_{23}H_{21}F_2N_5O_2$, 438; Found, 438.

Example 89: 4-[4-[(3S)-3-Aminopyrrolidine-1-carbonyl]-5-fluoro-1-(3-fluoro-4-methoxyphenyl)imidazol-2-yl]-2-fluorobenzonitrile



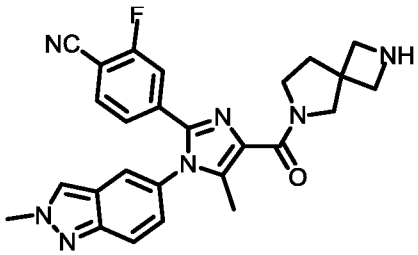
The title compound was prepared as formic acid salt in 0.1% overall yield according to the general procedure for the preparation of Example 68. Calc'd for $C_{22}H_{18}F_3N_5O_2$, 442; Found, 442.

Example 90: 4-[4-(1,7-Diazaspiro[4.4]nonane-7-carbonyl)-5-methyl-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile



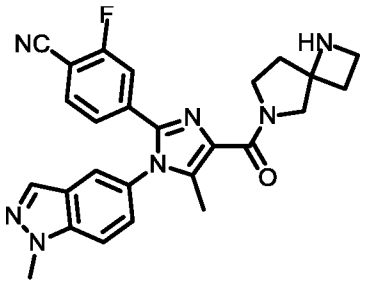
The title compound was prepared as the formic acid salt in 1% overall yield according to the general procedure for the preparation of Example 12. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.77-1.92 (6H, m), 2.27 (3H, s), 2.95 (2H, m), 3.73 (1H, m), 3.99 (1H, m), 4.14 (1H, m), 4.23 (3H, s), 7.20 (2H, m), 7.37 (1H, m), 7.83 (3H, m), 8.18 (1H, m), 8.50 (1H, m). [M+H] Calc'd for $C_{27}H_{26}FN_7O$, 484; Found, 484.

Example 91: 4-[4-(2,6-Diazaspiro[3.4]octane-6-carbonyl)-5-methyl-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile



The title compound was prepared as the formic acid salt in 2.3% overall yield according to the general procedure for the preparation of Example 12. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.06-2.22 (2H, m), 2.26 (3H, s), 2.32 (1H, m), 2.42 (1H, m), 3.51-3.58 (2H, m), 4.06 (1H, m), 4.14 (1H, m), 4.23 (3H, s), 7.22 (2H, m), 7.39 (1H, t, J = 11.2 Hz), 7.76-7.85 (3H, m), 8.29 (1H, s), 8.49 (1H, s). [M+H] Calc'd for $C_{26}H_{24}FN_7O$, 470; Found, 470.

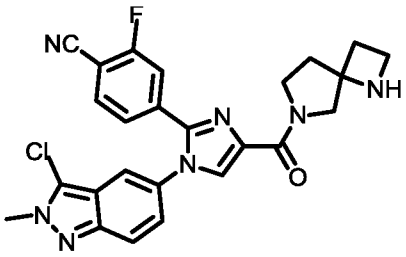
Example 92: 4-[4-(1,7-Diazaspiro[3.4]octane-7-carbonyl)-5-methyl-1-(1-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile



The title compound was prepared as the formic acid salt in 0.2% overall yield according to the general procedure for the preparation of Example 12. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.15 (1H, m), 2.06-2.22 (2H, m), 2.26 (3H, s), 2.60 (1H, m), 3.51-3.58 (2H, m),

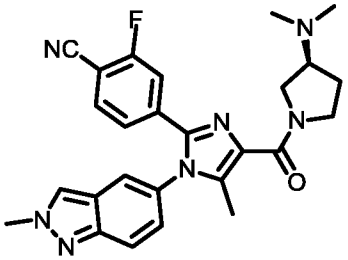
4.06 (1H, m), 4.14 (1H, m), 4.23 (3H, s), 7.22 (2H, m), 7.39 (1H, t, J = 11.2 Hz), 7.76-7.85 (3H, m), 8.29 (1H, s), 8.49 (1H, s). [M+H] Calc'd for $C_{26}H_{24}FN_7O$, 470; Found, 470.

Example 93: 4-[1-(3-Chloro-2-methylindazol-5-yl)-4-(1,7-diazaspiro[3.4]octane-7-carbonyl)imidazol-2-yl]-2-fluorobenzonitrile



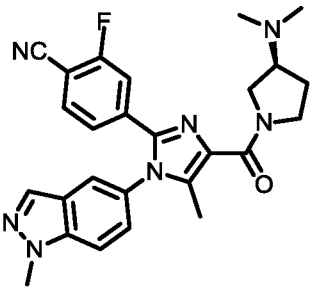
The title compound was prepared as the formic acid salt in 0.8% overall yield according to the general procedure for the preparation of Example 57. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.14 (1H, m), 2.22 (2H, m), 2.67 (1H, m), 3.69 (1H, m), 3.89 (2H, m), 4.14 (1H, m), 4.22 (3H, s), 4.39 (1H, m), 7.16 (1H, d, J = 10.6 Hz), 7.26 (1H, t, J = 7.5 Hz), 7.75 (1H, d, J = 9.0 Hz), 7.85 (2H, m), 8.16 (1H, s). [M+H] Calc'd for $C_{25}H_{21}ClFN_7O$, 490; Found, 490.

Example 94: 4-[4-[(3S)-3-(Dimethylamino)pyrrolidine-1-carbonyl]-5-methyl-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile



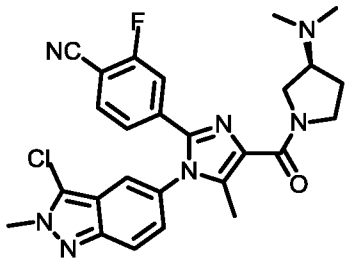
The title compound was prepared as the formic acid salt in 3% overall yield according to the general procedure for the preparation of Example 12. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.71-1.79 (1H, m), 1.99-2.13 (1H, m), 2.21 (3H, s), 2.26 (3H, s), 2.67-2.74 (1H, m), 3.21-3.26 (1H, m), 3.46 (1H, m), 3.68-3.79 (2H, m), 3.94 (1H, m), 4.23 (3H, s), 4.23 (1H, m), 7.22 (1H, m), 7.35 (1H, dd, J = 1.4 and 11.2 Hz), 7.76-7.85 (2H, m), 8.47 (1H, s). [M+H] Calc'd for $C_{26}H_{26}FN_7O$, 472; Found, 472.

Example 95: 4-[4-[(3S)-3-(Dimethylamino)pyrrolidine-1-carbonyl]-5-methyl-1-(1-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile



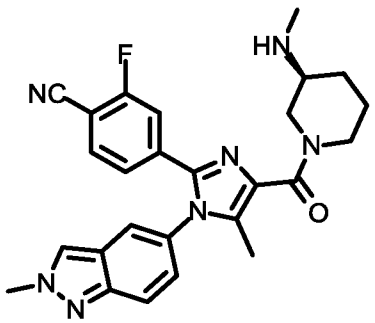
The title compound was prepared as the formic acid salt in 3.5% overall yield according to the general procedure for the preparation of Example 12. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.71-1.78 (1H, m), 2.06-2.11 (1H, m), 2.21 (3H, s), 2.25 (3H, s), 2.43 (1H, m), 3.68 (1H, m), 3.94 (1H, m), 4.24 (3H, s), 4.27 (1H, m), 7.08 (1H, m), 7.16 (1H, m), 7.31-7.41 (2H, m), 7.76 (1H, m), 7.86 (2H, m), 8.17 (1H, s). [M+H] Calc'd for $C_{26}H_{26}FN_7O$, 472; Found, 472.

Example 96: 4-[1-(3-Chloro-2-methylindazol-5-yl)-4-[(3S)-3-(dimethylamino)pyrrolidine-1-carbonyl]-5-methylimidazol-2-yl]-2-fluorobenzonitrile



The title compound was prepared as formic acid salt in 11% overall yield according to the procedure for the preparation of example 53. ^{1}HNMR (400 MHz, DMSO- d_6): δ 1.79-1.92 (2H, m), 2.13 (1H, m), 2.26 (3H, s), 3.45-3.48 (1H, m), 3.68 (1H, m), 3.83 (1H, m), 3.93 (1H, m), 4.19 (3H, s), 4.26 (1H, m), 7.19-7.29 (2H, m), 7.39-7.44 (1H, m), 7.79-7.85 (3H, m). [M+H] Calc'd for $C_{26}H_{25}ClFN_7O$, 506; Found, 506.

Example 97: 2-Fluoro-4-[5-methyl-4-[(3S)-3-(methylamino)piperidine-1-carbonyl]-1-(2-methylindazol-5-yl)imidazol-2-yl]benzonitrile

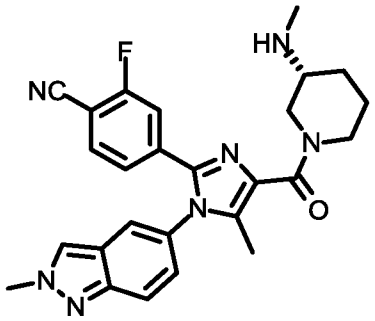


The title compound was prepared as formic acid salt in 2.5% overall yield according to the general procedure for the preparation of Example 12. ^{1}HNMR (400 MHz, DMSO-d_6): δ 1.39-1.48 (2H, m), 1.76-1.78 (1H, m), 1.98 (1H, m), 2.17 (3H, s), 2.36 (3H, d, J =

22.6 Hz), 2.66 (1H, m), 2.99-3.13 (2H, m), 4.15 (1H, m), 4.25 (3H, s), 4.40 (1H, m), 4.63 (1H, m), 7.20 (2H, d, J = 8.0 Hz), 7.38 (1H, m), 7.78 (2H, t, J = 9.6 Hz), 7.86 (1H, s), 8.24 (1H, s), 8.49 (1H, s).

[M+H] Calc'd for $C_{26}H_{26}FN_7O$, 472; Found, 472.

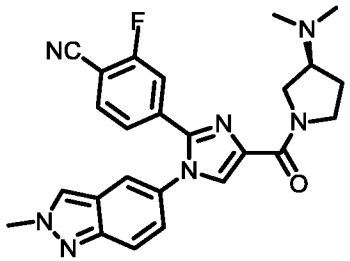
Example 98: 2-Fluoro-4-[5-methyl-4-[(3R)-3-(methylamino)piperidine-1-carbonyl]-1-(2-methylindazol-5-yl)imidazol-2-yl]benzonitrile



The title compound was prepared as formic acid salt in 2% overall yield according to the general procedure for the preparation of Example 12. ^{1}HNMR (400 MHz, DMSO- d_6): δ 1.47 (2H, m), 1.79 (1H, m), 2.05 (1H, m), 2.18 (3H, s), 2.44 (3H, d, J = 17.2 Hz), 2.76 (2H, m), 3.04 (1H, m), 4.14 (1H, m), 4.22 (3H, s), 4.41 (1H, m), 4.65 (1H, m), 7.21 (2H, d, J = 8.3 Hz), 7.38 (1H, m), 7.78 (2H, t, J = 9.1 Hz), 7.86 (1H, s), 8.20 (1H, br s), 8.48 (1H, s).

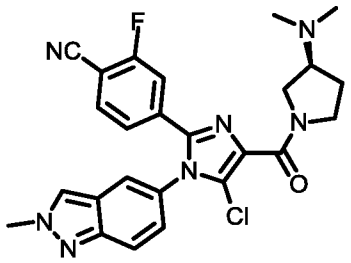
[M+H] Calc'd for $C_{26}H_{26}FN_7O$, 472; Found, 472.

Example 99: 4-[4-[(3S)-3-(Dimethylamino)pyrrolidine-1-carbonyl]-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile



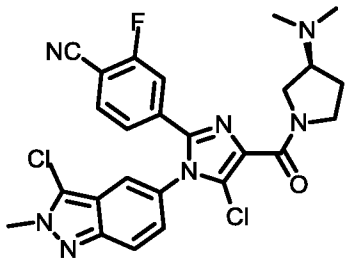
The title compound was prepared as the formic acid salt in 0.5% overall yield according to the general procedure for the preparation of Example 12. [M+H] Calc'd for $C_{25}H_{24}FN_7O$, 458; Found, 458.

Example 100: 4-[5-Chloro-4-[(3S)-3-(dimethylamino)pyrrolidine-1-carbonyl]-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile



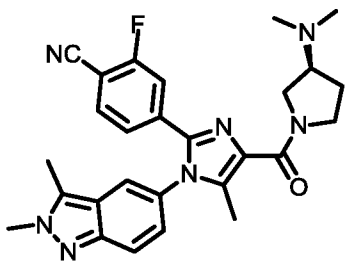
The title compound was prepared as the formic acid salt in 9% yield starting from 4-[4-[(3S)-3-(dimethylamino)pyrrolidine-1-carbonyl]-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile using NCS. ^{1}HNMR (400 MHz, DMSO- d_6): δ 1.68-1.83 (1H, m), 2.13 (1H, m), 2.20 (6H, s), 2.67-2.75 (1H, m), 3.67-3.80 (2H, m), 3.94 (1H, m), 4.20 (3H, s), 4.32 (1H, m), 7.20 (1H, m), 7.27 (1H, t, J = 6.6 Hz), 7.48 (1H, t, J = 11.1 Hz), 7.73 (1H, d, J = 9.4 Hz), 7.84 (1H, s), 7.87 (1H, s), 8.10 (1H, s), 8.45 (1H, br s). [M+H] Calc'd for $C_{25}H_{23}ClFN_7O$, 492; Found, 492.

Example 101: 4-[5-Chloro-1-(3-chloro-2-methylindazol-5-yl)-4-[(3S)-3-(dimethylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile



The title compound was prepared as the formic acid salt in 10% yield starting from 4-[4-[(3S)-3-(dimethylamino)pyrrolidine-1-carbonyl]-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile with excess of NCS. [M+H] Calc'd for $C_{25}H_{22}Cl_2FN_7O$, 526; Found, 526.

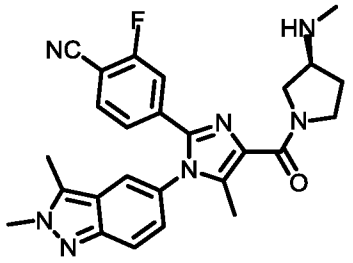
Example 102: 4-[4-[(3S)-3-(Dimethylamino)pyrrolidine-1-carbonyl]-1-(2,3-dimethylindazol-5-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile



The title compound was prepared as the formic acid salt in 0.6% overall yield according to the general procedure for the preparation of Example 12. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.95-2.07 (1H, m), 2.25 (1H, m), 2.26 (3H, s), 2.69 (3H, s), 3.32 (3H, s), 3.51 (2H, m), 3.57 (1H, m), 3.88 (1H, m), 4.02 (3H, s), 4.37 (1H, m), 7.01-7.09 (1H, m), 7.25 (1H,

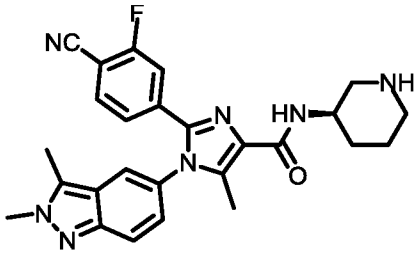
m), 7.41 (1H, d, J = 10.8 Hz), 7.71 (1H, d, J = 8.6 Hz), 7.79 (1H, m), 7.86 (1H, s), 8.14 (1H, s). [M+H] Calc'd for $C_{27}H_{28}FN_7O$, 486; Found, 486.

Example 103: 4-[1-(2,3-Dimethylindazol-5-yl)-5-methyl-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile



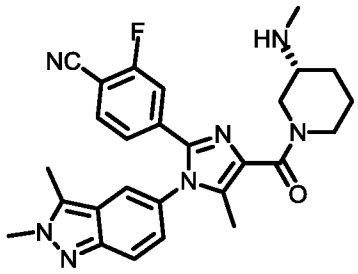
The title compound was prepared as the formic acid salt in 1.7% overall yield according to the general procedure for the preparation of Example 12. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.81 (1H, m), 1.90 (1H, m), 2.03-2.08 (1H, m), 2.26 (3H, s), 2.39 (3H, d, J = 7.6 Hz), 2.61 (3H, s), 3.34-3.70 (4H, m), 3.93 (1H, m), 4.13 (3H, s), 4.16 (1H, m), 7.14 (1H, d, J = 8.5 Hz), 7.24 (1H, m), 7.41 (1H, m), 7.70 (1H, d, J = 8.9 Hz), 7.79 (1H, m), 7.88 (1H, s), 8.19 (1H, s). [M+H] Calc'd for $C_{26}H_{26}FN_7O$, 472; Found, 472.

Example 104: 2-(4-Cyano-3-fluorophenyl)-1-(2,3-dimethylindazol-5-yl)-5-methyl-N-[(3R)-piperidin-3-yl]imidazole-4-carboxamide



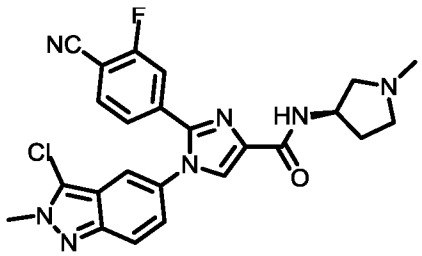
The title compound was prepared as the formic acid salt in 0.2% overall yield according to the general procedure for the preparation of Example 12. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.58-1.68 (2H, m), 1.84 (2H, m), 2.32 (3H, s), 2.60 (3H, s), 2.67 (1H, m), 2.81 (1H, m), 3.04 (1H, m), 3.15 (1H, m), 4.10 (3H, s), 7.15 (1H, m), 7.21 (1H, d, J = 8.4 Hz), 7.56 (1H, d, J = 9.9 Hz), 7.70 (1H, d, J = 9.7 Hz), 7.80 (1H, m), 7.87 (1H, s), 8.10 (1H, d, J = 7.9 Hz), 8.16 (1H, s). [M+H] Calc'd for $C_{26}H_{26}FN_7O$, 472; Found, 472.

Example 105: 4-[1-(2,3-Dimethylindazol-5-yl)-5-methyl-4-[(3R)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile



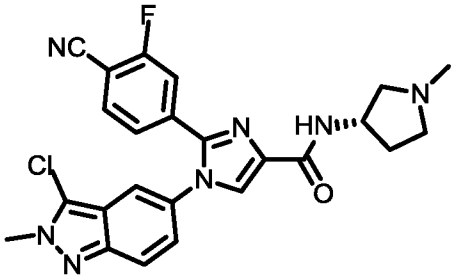
The title compound was prepared as the formic acid salt in 0.6% overall yield according to the general procedure for the preparation of Example 12. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.55 (2H, m), 1.82 (1H, m), 2.08 (1H, m), 2.19 (3H, s), 2.59 (3H, s), 2.61 (3H, s), 3.05 (2H, m), 3.47 (1H, m), 4.10 (3H, s), 4.42 (1H, m), 7.24 (1H, d, J = 10.8 Hz), 7.37-7.48 (1H, m), 7.70 (1H, d, J = 8.7 Hz), 7.79 (1H, t, J = 6.6 Hz), 7.88 (1H, s), 8.15 (1H, s). [M+H] Calc'd for $C_{28}H_{27}FN_7O$, 486; Found, 486.

Example 106: 1-(3-Chloro-2-methylindazol-5-yl)-2-(4-cyano-3-fluorophenyl)-N-[(3R)-1-methylpyrrolidin-3-yl]imidazole-4-carboxamide



The title compound was prepared as the formic acid salt in 14% overall yield according to the general procedure for the preparation of Example 57. ^{1}H NMR (400 MHz, DMSO-d_6): 1.81 (1H, m), 2.21 (1H, m), 2.34 (3H, s), 2.57 (1H, d, J = 9.9 Hz), 2.75 (2H, m), 4.18 (3H, s), 4.46 (1H, m), 7.20 (1H, d, J = 9.2 Hz), 7.24 (1H, d, J = 8.2 Hz), 7.62 (1H, d, J = 10.7 Hz), 7.73 (1H, d, J = 8.9 Hz), 7.83 (1H, d, J = 7.8 Hz), 7.86 (1H, s), 8.10 (2H, s), 8.20 (1H, s). [M+H] Calc'd for $C_{24}H_{21}ClFN_7O$, 478; Found, 478.

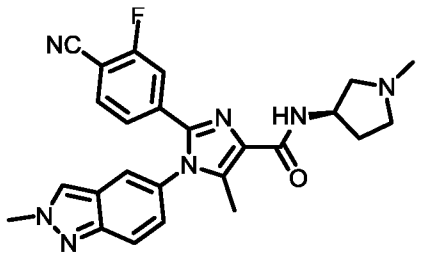
Example 107: 1-(3-Chloro-2-methylindazol-5-yl)-2-(4-cyano-3-fluorophenyl)-N-[(3S)-1-methylpyrrolidin-3-yl]imidazole-4-carboxamide



The title compound was prepared as the formic acid salt in 14% overall yield according to the general procedure for the preparation of Example 57. ^{1}H NMR (400 MHz, DMSO-

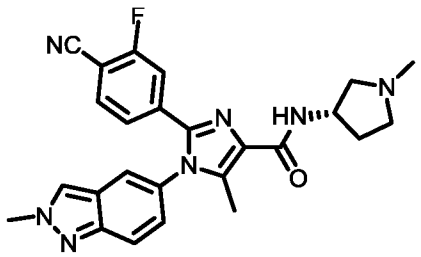
d$_6$): 1.87-1.94 (1H, m), 2.08-2.32 (1H, m), 2.51 (3H, s), 2.76 (1H, m), 2.83 (1H, m), 3.01 (2H, m), 4.17 (3H, s), 4.54 (1H, m), 7.20 (1H, dd, J = 2 and 9.1 Hz), 7.61 (1H, dd, J = 1.1 and 10.6 Hz), 7.83 (1H, s), 7.85 (1H, t, J = 16.5 Hz), 8.13 (1H, s), 8.25 (1H, d, J = 7.7 Hz). [M+H] Calc'd for $C_{24}H_{21}ClFN_7O$, 478; Found, 478.

Example 108: 2-(4-Cyano-3-fluorophenyl)-5-methyl-1-(2-methylindazol-5-yl)-N-[(3R)-1-methylpyrrolidin-3-yl]imidazole-4-carboxamide



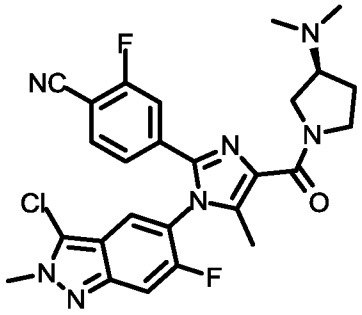
The title compound was prepared as the formic acid salt in 3% overall yield according to the general procedure for the preparation of Example 12. ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 1.78 (1H, m), 2.20 (1H, m), 2.29 (3H, s), 2.31 (3H, s), 2.37 (1H, m), 2.64-2.69 (2H, m), 4.23 (3H, s), 4.44 (1H, m), 7.19 (2H, m), 7.57 (1H, d, J = 10.6 Hz), 7.77 (1H, d, J = 11.1 Hz), 7.82 (1H, d, J = 9.9 Hz), 7.85 (1H, s), 7.96 (1H, d, J = 7.4 Hz), 8.22 (1H, br s), 8.50 (1H, s). [M+H] Calc'd for $C_{25}H_{24}FN_7O$, 458; Found, 458.

Example 109: 2-(4-Cyano-3-fluorophenyl)-5-methyl-1-(2-methylindazol-5-yl)-N-[(3S)-1-methylpyrrolidin-3-yl]imidazole-4-carboxamide



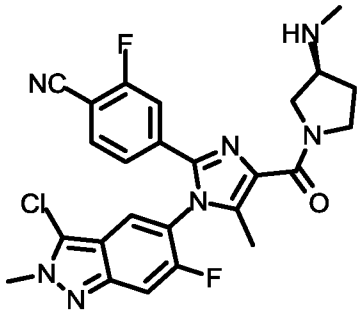
The title compound was prepared as the formic acid salt in 4% overall yield according to the general procedure for the preparation of Example 12. ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 1.78 (1H, m), 2.19 (1H, m), 2.30 (6H, s), 2.41 (1H, m), 2.54 (1H, m), 2.68-2.73 (2H, m), 4.22 (3H, s), 4.44 (1H, m), 7.19 (2H, m), 7.57 (1H, d, J = 10.8 Hz), 7.76 (1H, d, J = 11.2 Hz), 7.80 (1H, d, J = 9.7 Hz), 7.85 (1H, s), 7.99 (1H, d, J = 7.9 Hz), 8.21 (1H, br s), 8.50 (1H, s). [M+H] Calc'd for $C_{25}H_{24}FN_7O$, 458; Found, 458.

Example 110: 4-[1-(3-Chloro-6-fluoro-2-methylindazol-5-yl)-4-[(3S)-3-(dimethylamino)pyrrolidine-1-carbonyl]-5-methylimidazol-2-yl]-2-fluorobenzonitrile



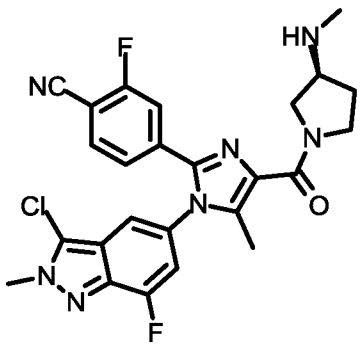
The title compound was prepared as formic acid salt in 9% yield by treating Example 48 with 1 equiv. of NCS. [M+H] Calc'd for $C_{26}H_{24}ClF_2N_7O$, 510; Found, 510.

Example 111: 4-[1-(3-Chloro-6-fluoro-2-methylindazol-5-yl)-5-methyl-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile



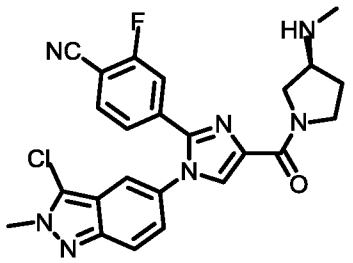
The title compound was prepared as formic acid salt in 15% yield by treating Example 49 with 1 equiv. of NCS. [M+H] Calc'd for $C_{25}H_{22}ClF_2N_7O$, 524; Found, 524.

Example 112: 4-[1-(3-Chloro-6-fluoro-2-methylindazol-5-yl)-4-[(3S)-3-(dimethylamino)pyrrolidine-1-carbonyl]-5-methylimidazol-2-yl]-2-fluorobenzonitrile



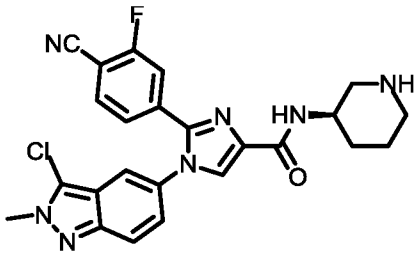
The title compound was prepared as formic acid salt in 15% yield by treating Example 51 with 1 equiv. of NCS. [M+H] Calc'd for $C_{25}H_{22}ClF_2N_7O$, 524; Found, 524.

Example 113: 4-[1-(3-Chloro-2-methylindazol-5-yl)-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile



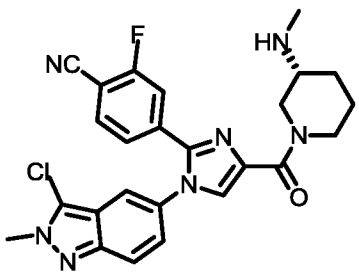
The title compound was prepared as the formic acid salt in 6% overall yield according to the general procedure for the preparation of Example 57. ^{1}H NMR (400 MHz, DMSO-d_6): 2.08-2.39 (3H, m), 2.66 (3H, s), 3.61 (1H, m), 3.72 (1H, m), 3.83 (1H, m), 4.19 (3H, s), 4.31 (1H, m), 7.19 (1H, d, J = 9.0 Hz), 7.24 (1H, br s), 7.54 (1H, d, J = 11.2 Hz), 7.75 (1H, d, J = 9.2 Hz), 7.84 (1H, s), 7.87 (1H, s), 8.17 (1H, s), 8.72 (1H, br s). [M+H] Calc'd for $C_{24}H_{21}ClFN_7O$, 478; Found, 478.

Example 114: 1-(3-Chloro-2-methylindazol-5-yl)-2-(4-cyano-3-fluorophenyl)-N-[(3R)-piperidin-3-yl]imidazole-4-carboxamide



The title compound was prepared as the formic acid salt in 4.6% overall yield according to the general procedure for the preparation of Example 57. ^{1}H NMR (400 MHz, DMSO-d_6): 1.70 (2H, m), 1.89 (2H, m), 2.74 (1H, m), 2.94 (1H, m), 3.23 (2H, m), 4.19 (3H, s), 4.20 (1H, m), 7.20 (1H, d, J = 9.1 Hz), 7.24 (1H, d, J = 8.0 Hz), 7.60 (1H, d, J = 10.4 Hz), 7.74 (1H, d, J = 8.6 Hz), 7.85 (1H, s), 7.86 (1H, s), 8.15 (1H, s), 8.34 (1H, d, J = 8.0 Hz), 8.65 (1H, br s). [M+H] Calc'd for $C_{24}H_{21}ClFN_7O$, 478; Found, 478.

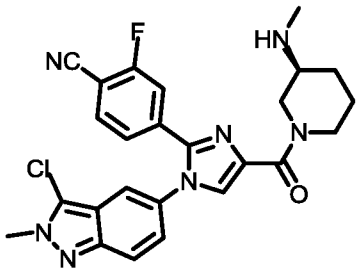
Example 115: 4-[1-(3-Chloro-2-methylindazol-5-yl)-4-[(3R)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile



The title compound was prepared as the formic acid salt in 6% overall yield according to the general procedure for the preparation of Example 57. ^{1}H NMR (400 MHz, DMSO-d_6): 1.56 (1H, m), 1.68 (1H, m), 1.83 (1H, m), 2.11 (1H, m), 2.66 (3H, s), 3.25 (1H, m),

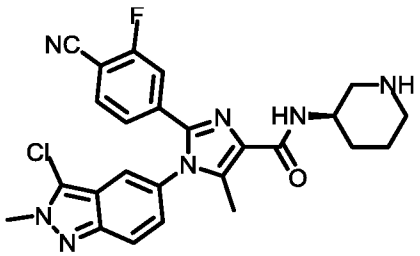
3.32 (2H, s), 4.19 (3H, s), 7.19 (1H, d, J = 9.2 Hz), 7.25 (1H, d, J = 8.5 Hz), 7.53 (1H, m), 7.75 (1H, d, J = 9.2 Hz), 7.86 (2H, s), 8.13 (1H, s), 8.64 (1H, s). [M+H] Calc'd for $C_{25}H_{23}ClFN_7O$, 492; Found, 492.

Example 116: 4-[1-(3-Chloro-2-methylindazol-5-yl)-4-[(3S)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile



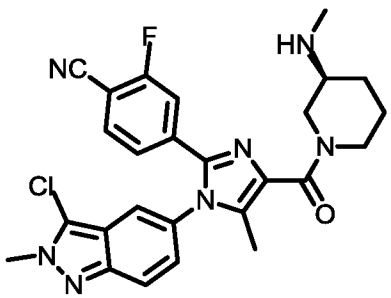
The title compound was prepared as the formic acid salt in 6% overall yield according to the general procedure for the preparation of Example 57. ^{1}H NMR (400 MHz, DMSO-d_6): 1.54 (1H, m), 1.64 (1H, m), 1.82 (1H, m), 2.07 (1H, m), 2.62 (3H, s), 3.14 (1H, m), 3.32 (3H, s), 4.19 (3H, s), 7.19 (1H, d, J = 8.9 Hz), 7.25 (1H, d, J = 7.8 Hz), 7.53 (1H, m), 7.75 (1H, d, J = 9.2 Hz), 7.86 (2H, s), 8.12 (1H, s). [M+H] Calc'd for $C_{25}H_{23}ClFN_7O$, 492; Found, 492.

Example 117: 1-(3-Chloro-2-methylindazol-5-yl)-2-(4-cyano-3-fluorophenyl)-5-methyl-N-[(3R)-piperidin-3-yl]imidazole-4-carboxamide



The title compound was prepared as the formic acid salt in 2% overall yield treating Boc protected Example 97 with 1 equiv. of NCS followed by deprotection. ^{1}H NMR (400 MHz, DMSO- d_6): 1.65 (2H, m), 1.78 (2H, m), 2.33 (3H, s), 2.65 (1H, m), 2.78 (1H, t, J = 10.3 Hz), 3.00 (1H, m), 3.10 (1H, d, J = 10.4 Hz), 4.09 (1H, m), 4.19 (3H, s), 4.21 (1H, s), 7.17 (1H, d, J = 8.3 Hz), 7.27 (1H, d, J = 8.7 Hz), 7.59 (1H, d, J = 9.2 Hz), 7.76-7.85 (3H, m), 8.12 (1H, d, J = 8.1 Hz), 8.29 (1H, m). [M+H] Calc'd for $C_{25}H_{23}ClFN_7O$, 492; Found, 492.

Example 118: 4-[1-(3-Chloro-2-methylindazol-5-yl)-5-methyl-4-[(3S)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile



The title compound was prepared as the formic acid salt in 2.5% overall yield treating Boc protected Example 98 with 1 equiv. of NCS followed by deprotection. ^{1}H NMR (400 MHz, DMSO- d_6): 1.14 (1H, s), 1.40 (2H, m), 1.76 (1H, m), 1.98 (1H, m), 2.19 (3H, s), 2.35 (3H, d, J = 25.9 Hz), 3.00 (2H, m), 4.15 (3H, s), 4.43 (1H, m), 4.66 (1H, m), 7.19 (1H, d, J = 7.5 Hz), 7.28 (1H, d, J = 9.2 Hz), 7.42 (1H, m), 7.79 (1H, d, J = 7.9 Hz), 7.84 (1H, s), 7.86 (1H, s), 8.23 (1H, s). [M+H] Calc'd for $C_{26}H_{25}ClFN_7O$, 506; Found, 506.

II. Biological Evaluation

Example 1: In Vitro Enzyme Inhibition Assay – LSD-1

[00149] This assay determines the ability of a test compound to inhibit LSD1 demethylase activity. E.coli expressed full-length human LSD1 (Accession number O60341) was purchased from Active Motif (Cat#31334).

[00150] The enzymatic assay of LSD1 activity is based on Time Resolved-Fluorescence Resonance Energy Transfer (TR-FRET) detection. The inhibitory properties of compounds to LSD1 were determined in 384-well plate format under the following reaction conditions: 0.1- 0.5 nM LSD1, 50 nM H3K4me1-biotin labeled peptide (Anaspec cat # 64355), 2 μM FAD in assay buffer of 50 mM HEPES, pH7.3, 10 mM NaCl, 0.005% Brij35, 0.5 mM TCEP, 0.2 mg/ml BSA. Reaction product was determined quantitatively by TR-FRET after the addition of detection reagent Phycolink Streptavidin-allophycocyanin (Prozyme) and Europium-anti-unmodified histone H3 lysine 4 (H3K4) antibody (PerkinElmer) in the presence of LSD1 inhibitor such as 1.8 mM of Tranylcypromine hydrochloride (2-PCPA) in LANCE detection buffer (PerkinElmer) to final concentration of 12.5 nM and 0.25 nM respectively.

[00151] The assay reaction was performed according to the following procedure: 2 μL of the mixture of 150 nM H3K4me1-biotin labeled peptide with 2 μL of 11-point serial diluted test compound in 3% DMSO were added to each well of plate, followed by the addition of 2 μL of 0.3 nM LSD1 and 6 μM of FAD to initiate the reaction. The reaction mixture was then incubated at room temperature for one hour, and terminated by the addition of 6 μL of 1.8 mM 2-PCPA in LANCE detection buffer containing 25 nM

Phycolink Streptavidin-allophycocyanin and 0.5 nM Europium-anti-unmodified H3K4 antibody. Enzymatic reaction is terminated within 15 minutes if 0.5 LSD1 enzyme is used in the plate. Plates were read by EnVision Multilabel Reader in TR-FRET mode (excitation at 320nm, emission at 615nm and 665nm) after 1 hour incubation at room temperature. A ratio was calculated (665/615) for each well and fitted to determine inhibition constant (IC_{50}).

[00152] The ability of the compounds disclosed herein to inhibit LSD1 activity was quantified and the respective IC_{50} value was determined. Table 3 provides the IC_{50} values of various substituted heterocyclic compounds disclosed herein.

TABLE 3

Chemical Synthesis Example	Name	LSD1 IC_{50} (μM)
1	4-[5-(3-(R)-amino-piperidine-1-carbonyl)-1-methyl-2-p-tolyl-1H-pyrrol-3-yl]-benzonitrile	A
2	4-[5-(3-(R)-amino-piperidine-1-carbonyl)-2-(4-methoxy-phenyl)-1-methyl-1H-pyrrol-3-yl]-2-fluoro-benzonitrile	A
3	4-[5-(3-(R)-amino-piperidine-1-carbonyl)-1-(2-hydroxy-ethyl)-2-p-tolyl-1H-pyrrol-3-yl]-benzonitrile	A
4	4-[5-(3-(R)-amino-piperidine-1-carbonyl)-1-(2-hydroxy-ethyl)-2-p-tolyl-1H-pyrrol-3-yl]-2-fluoro-benzonitrile	A
5	4-[5-(3-(R)-amino-piperidine-1-carbonyl)-1-methyl-2-(6-methyl-pyridin-3-yl)-1H-pyrrol-3-yl]-benzonitrile	A
6	4-[5-(3-(R)-amino-piperidine-1-carbonyl)-1-methyl-2-pyridin-4-yl-1H-pyrrol-3-yl]-benzonitrile	A
7	4-[5-(3-(R)-amino-piperidine-1-carbonyl)-1-(2-hydroxy-ethyl)-2-(4-methoxy-phenyl)-1H-pyrrol-3-yl]-benzonitrile	A
8	4-[5-(3-(R)-amino-piperidine-1-carbonyl)-1-(2-hydroxy-ethyl)-2-(4-methoxy-phenyl)-1H-pyrrol-3-yl]-2-fluoro-benzonitrile	A
9	4-[5-(3-(R)-amino-piperidine-1-carbonyl)-1-(3-hydroxy-propyl)-2-(4-methoxy-phenyl)-1H-pyrrol-3-yl]-2-fluoro-benzonitrile	A
10	4-[5-(3-(R)-amino-piperidine-1-carbonyl)-1-methyl-2-(1-methyl-1H-benzoimidazol-5-yl)-1H-pyrrol-3-yl]-2-fluoro-benzonitrile	A

Chemical Synthesis Example	Name	LSD1 IC_{50} (μM)
11	4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-5-methyl-1-(4-methylphenyl)imidazol-2-yl]benzonitrile	A
12	4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-1-(4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A
13	4-[4-[(3R)-3-aminopyrrolidine-1-carbonyl]-1-(4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A
14	4-[4-[(3S)-3-aminopyrrolidine-1-carbonyl]-1-(4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A
15	4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-1-(6-methoxypyridin-3-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A
16	4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-1-(3-fluoro-4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A
17	4-[4-[(3S)-3-aminopiperidine-1-carbonyl]-1-(3-fluoro-4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A
18	4-[4-[(3S)-3-aminopyrrolidine-1-carbonyl]-1-(3-fluoro-4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A
19	4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-1-(3-fluoro-4-methoxyphenyl)imidazol-2-yl]-2-fluorobenzonitrile	A
20	4-[4-[(3S)-3-aminopyrrolidine-1-carbonyl]-1-(3-fluoro-4-methoxyphenyl)imidazol-2-yl]-2-fluorobenzonitrile	A
21	4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-5-methyl-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile	A
22	4-[4-[(3S)-3-aminopyrrolidine-1-carbonyl]-5-methyl-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile	A
23	4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-5-methyl-1-(1-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile	A
24	4-[4-[(3S)-3-aminopyrrolidine-1-carbonyl]-5-methyl-1-(1-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile	A
25	4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile	A
26	4-[4-[(3S)-3-aminopyrrolidine-1-carbonyl]-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile	A
27	4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-1-(1-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile	A

Chemical Synthesis Example	Name	LSD1 IC_{50} (μM)
28	4-[4-[(3S)-3-aminopyrrolidine-1-carbonyl]-1-(1-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile	A
29	4-{5-[((3R)-3-aminopiperidyl)carbonyl]-1-methyl-2-(2-methyl(2H-indazol-5-yl))pyrrol-3-yl}-2-fluorobenzenecarbonitrile	A
30	N-((3R)pyrrolidin-3-yl)[4-(4-cyano-3-fluorophenyl)-1-methyl-5-(2-methyl(2H-indazol-5-yl))pyrrol-2-yl]carboxamide	A
31	N-(2-aminoethyl)[4-(4-cyano-3-fluorophenyl)-1-methyl-5-(2-methyl(2H-indazol-5-yl))pyrrol-2-yl]-N-methylcarboxamide	A
32	[4-(4-cyano-3-fluorophenyl)-1-methyl-5-(2-methyl(2H-indazol-5-yl))pyrrol-2-yl]-N-[2-(methylamino)ethyl]carboxamide	A
33	N-[((3S)pyrrolidin-3-yl)methyl][4-(4-cyano-3-fluorophenyl)-1-methyl-5-(2-methyl(2H-indazol-5-yl))pyrrol-2-yl]carboxamide	A
34	(R)-4-(5-(3-aminopiperidine-1-carbonyl)-1-(3-hydroxypropyl)-2-(2-methyl-2H-indazol-5-yl)-1H-pyrrol-3-yl)-2-fluorobenzonitrile	A
35	(R)-4-(5-(3-aminopiperidine-1-carbonyl)-1-(2-hydroxyethyl)-2-(2-methyl-2H-indazol-5-yl)-1H-pyrrol-3-yl)-2-fluorobenzonitrile	A
36	(R)-4-(5-(3-aminopiperidine-1-carbonyl)-1-(2-methoxyethyl)-2-(2-methyl-2H-indazol-5-yl)-1H-pyrrol-3-yl)-2-fluorobenzonitrile	A
37	(R)-2-(5-(3-aminopiperidine-1-carbonyl)-3-(4-cyano-3-fluorophenyl)-2-(4-methoxyphenyl)-1H-pyrrol-1-yl)acetamide	A
38	4-(5-((R)-3-aminopiperidine-1-carbonyl)-1-((R)-2,3-dihydroxypropyl)-2-(2-methyl-2H-indazol-5-yl)-1H-pyrrol-3-yl)-2-fluorobenzonitrile	A
39	4-(5-((R)-3-aminopiperidine-1-carbonyl)-1-((S)-2,3-dihydroxypropyl)-2-(2-methyl-2H-indazol-5-yl)-1H-pyrrol-3-yl)-2-fluorobenzonitrile	A
40	N-[((3R)pyrrolidin-3-yl)methyl][4-(4-cyano-3-fluorophenyl)-1-methyl-5-(2-methyl(2H-indazol-5-yl))pyrrol-2-yl]carboxamide	A
41	4-{5-[((3R)-3-aminopiperidyl)carbonyl]-3-(4-cyano-3-fluorophenyl)-2-(4-methoxyphenyl)pyrrolyl}butanoic acid	A

Chemical Synthesis Example	Name	LSD1 IC_{50} (μM)
42	4-{5-[((3R)-3-aminopiperidyl)carbonyl]-3-(4-cyano-3-fluorophenyl)-2-(4-methoxyphenyl)pyrrolyl}butanamide	A
43	4-[4-(4-Aminopiperidine-1-carbonyl)-5-methyl-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile	A
44	N-(2-Aminoethyl)-2-(4-cyano-3-fluorophenyl)-N,5-dimethyl-1-(2-methylindazol-5-yl)imidazole-4-carboxamide	A
45	2-(4-Cyano-3-fluorophenyl)-5-methyl-1-(2-methylindazol-5-yl)-N-piperidin-3-ylimidazole-4-carboxamide	A
46	2-(4-Cyano-3-fluorophenyl)-5-methyl-1-(2-methylindazol-5-yl)-N-pyrrolidin-3-ylimidazole-4-carboxamide	A
47	4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-1-(6-fluoro-2-methylindazol-5-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A
48	4-[4-[(3S)-3-(Dimethylamino)pyrrolidine-1-carbonyl]-1-(6-fluoro-2-methylindazol-5-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A
49	2-Fluoro-4-[1-(6-fluoro-2-methylindazol-5-yl)-5-methyl-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile	A
50	4-[4-[(3S)-3-Aminopyrrolidine-1-carbonyl]-1-(7-fluoro-2-methylindazol-5-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A
51	2-Fluoro-4-[1-(7-fluoro-2-methylindazol-5-yl)-5-methyl-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile	A
52	4-[4-[(3S)-3-(Dimethylamino)pyrrolidine-1-carbonyl]-1-(7-fluoro-2-methylindazol-5-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A
53	4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-1-(3-chloro-2-methylindazol-5-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A
54	4-[1-(3-Chloro-2-methylindazol-5-yl)-5-methyl-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile	A
55	4-[1-(3-Chloro-2-methylindazol-5-yl)-5-methyl-4-[(3R)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile	A

Chemical Synthesis Example	Name	LSD1 IC_{50} (μM)
56	1-(3-Chloro-2-methylindazol-5-yl)-2-(4-cyano-3-fluorophenyl)-5-methyl-N-[(3R)-1-methylpiperidin-3-yl]imidazole-4-carboxamide	A
57	4-[1-(3-Chloro-2-methylindazol-5-yl)-4-[(3S)-3-(dimethylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile	A
58	4-[1-(3-Chloro-2-methylindazol-5-yl)-4-[(3S)-3-(dimethylamino)pyrrolidine-1-carbonyl]-5-fluoroimidazol-2-yl]-2-fluorobenzonitrile	A
59	1-(3-Chloro-2-methylindazol-5-yl)-2-(4-cyano-3-fluorophenyl)-N-[(3R)-1-methylpiperidin-3-yl]imidazole-4-carboxamide	A
60	2-(4-Cyano-3-fluorophenyl)-5-methyl-1-(2-methylindazol-5-yl)-N-[(3R)-1-methylpiperidin-3-yl]imidazole-4-carboxamide	A
61	4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-1-(3-chloro-2-methylindazol-5-yl)-5-fluoroimidazol-2-yl]-2-fluorobenzonitrile	A
62	2-(4-Cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)-5-methyl-N-[(3R)-piperidin-3-yl]imidazole-4-carboxamide	A
63	2-(4-Cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)-5-methyl-N-[(3S)-piperidin-3-yl]imidazole-4-carboxamide	A
64	2-Fluoro-4-[1-(3-fluoro-4-methoxyphenyl)-5-methyl-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile	A
65	2-Fluoro-4-[1-(3-fluoro-4-methoxyphenyl)-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile	A
66	4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-5-chloro-1-(3-fluoro-4-methoxyphenyl)imidazol-2-yl]-2-fluorobenzonitrile	A
67	4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-5-fluoro-1-(3-fluoro-4-methoxyphenyl)imidazol-2-yl]-2-fluorobenzonitrile	A
68	2-Fluoro-4-[5-fluoro-1-(3-fluoro-4-methoxyphenyl)-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile	A
69	2-Fluoro-4-[1-(4-methoxyphenyl)-5-methyl-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile	A

Chemical Synthesis Example	Name	LSD1 IC_{50} (μM)
70	2-Fluoro-4-[1-(4-methoxyphenyl)-5-methyl-4-[(3R)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]benzonitrile	A
71	2-Fluoro-4-[1-(4-methoxyphenyl)-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile	A
72	2-Fluoro-4-[1-(4-methoxyphenyl)-4-[(3R)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]benzonitrile	A
73	2-Fluoro-4-[5-fluoro-1-(4-methoxyphenyl)-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile	A
74	2-Fluoro-4-[5-fluoro-1-(4-methoxyphenyl)-4-[(3R)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]benzonitrile	A
75	4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-5-chloro-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile	A
76	4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-5-chloro-1-(3-chloro-2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile	A
77	4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-5-fluoro-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile	A
78	4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-1-(6-cyclopropylpyridin-3-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A
79	4-[4-[(3S)-3-Aminopyrrolidine-1-carbonyl]-1-(6-cyclopropylpyridin-3-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A
80	4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-5-chloro-1-(6-cyclopropylpyridin-3-yl)imidazol-2-yl]-2-fluorobenzonitrile	A
81	4-[4-[(3S)-3-Aminopyrrolidine-1-carbonyl]-5-chloro-1-(6-cyclopropylpyridin-3-yl)imidazol-2-yl]-2-fluorobenzonitrile	A
82	2-(4-Cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)-5-methyl-N-[(3R)-pyrrolidin-3-yl]imidazole-4-carboxamide	A
83	2-(4-Cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)-5-methyl-N-[(3S)-pyrrolidin-3-yl]imidazole-4-carboxamide	A

Chemical Synthesis Example	Name	LSD1 IC_{50} (μM)
84	5-Chloro-2-(4-cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)-N-[(3R)-piperidin-3-yl]imidazole-4-carboxamide	A
85	5-Chloro-2-(4-cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)-N-[(3S)-piperidin-3-yl]imidazole-4-carboxamide	A
86	2-(4-Cyano-3-fluorophenyl)-5-fluoro-1-(3-fluoro-4-methoxyphenyl)-N-[(3R)-piperidin-3-yl]imidazole-4-carboxamide	A
87	2-(4-Cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)-5-methyl-N-piperidin-4-ylimidazole-4-carboxamide	A
88	4-[4-[3-(Aminomethyl)azetidine-1-carbonyl]-1-(3-fluoro-4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A
89	4-[4-[(3S)-3-Aminopyrrolidine-1-carbonyl]-5-fluoro-1-(3-fluoro-4-methoxyphenyl)imidazol-2-yl]-2-fluorobenzonitrile	A
90	4-[4-(1,7-Diazaspiro[4.4]nonane-7-carbonyl)-5-methyl-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile	A
91	4-[4-(2,6-Diazaspiro[3.4]octane-6-carbonyl)-5-methyl-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile	A
92	4-[4-(1,7-Diazaspiro[3.4]octane-7-carbonyl)-5-methyl-1-(1-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile	A
93	4-[1-(3-Chloro-2-methylindazol-5-yl)-4-(1,7-diazaspiro[3.4]octane-7-carbonyl)imidazol-2-yl]-2-fluorobenzonitrile	A
94	4-[4-[(3S)-3-(Dimethylamino)pyrrolidine-1-carbonyl]-5-methyl-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile	A
95	4-[4-[(3S)-3-(Dimethylamino)pyrrolidine-1-carbonyl]-5-methyl-1-(1-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile	A
96	4-[1-(3-Chloro-2-methylindazol-5-yl)-4-[(3S)-3-(dimethylamino)pyrrolidine-1-carbonyl]-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A
97	2-Fluoro-4-[5-methyl-4-[(3S)-3-(methylamino)piperidine-1-carbonyl]-1-(2-methylindazol-5-yl)imidazol-2-yl]benzonitrile	A

Chemical Synthesis Example	Name	LSD1 IC_{50} (μM)
98	2-Fluoro-4-[5-methyl-4-[(3R)-3-(methylamino)piperidine-1-carbonyl]-1-(2-methylindazol-5-yl)imidazol-2-yl]benzonitrile	A
99	4-[4-[(3S)-3-(Dimethylamino)pyrrolidine-1-carbonyl]-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile	A
100	4-[5-Chloro-4-[(3S)-3-(dimethylamino)pyrrolidine-1-carbonyl]-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile	A
101	4-[5-Chloro-1-(3-chloro-2-methylindazol-5-yl)-4-[(3S)-3-(dimethylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile	A
102	4-[4-[(3S)-3-(Dimethylamino)pyrrolidine-1-carbonyl]-1-(2,3-dimethylindazol-5-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A
103	4-[1-(2,3-Dimethylindazol-5-yl)-5-methyl-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile	A
104	2-(4-Cyano-3-fluorophenyl)-1-(2,3-dimethylindazol-5-yl)-5-methyl-N-[(3R)-piperidin-3-yl]imidazole-4-carboxamide	A
105	4-[1-(2,3-Dimethylindazol-5-yl)-5-methyl-4-[(3R)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile	A
106	1-(3-Chloro-2-methylindazol-5-yl)-2-(4-cyano-3-fluorophenyl)-N-[(3R)-1-methylpyrrolidin-3-yl]imidazole-4-carboxamide	A
107	1-(3-Chloro-2-methylindazol-5-yl)-2-(4-cyano-3-fluorophenyl)-N-[(3S)-1-methylpyrrolidin-3-yl]imidazole-4-carboxamide	A
108	2-(4-Cyano-3-fluorophenyl)-5-methyl-1-(2-methylindazol-5-yl)-N-[(3R)-1-methylpyrrolidin-3-yl]imidazole-4-carboxamide	A
109	2-(4-Cyano-3-fluorophenyl)-5-methyl-1-(2-methylindazol-5-yl)-N-[(3S)-1-methylpyrrolidin-3-yl]imidazole-4-carboxamide	A
110	4-[1-(3-Chloro-6-fluoro-2-methylindazol-5-yl)-4-[(3S)-3-(dimethylamino)pyrrolidine-1-carbonyl]-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A
111	4-[1-(3-Chloro-6-fluoro-2-methylindazol-5-yl)-5-methyl-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile	A

Chemical Synthesis Example	Name	LSD1 IC_{50} (μM)
112	4-[1-(3-Chloro-6-fluoro-2-methylindazol-5-yl)-4-[(3S)-3-(dimethylamino)pyrrolidine-1-carbonyl]-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A
113	4-[1-(3-Chloro-2-methylindazol-5-yl)-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile	A
114	1-(3-Chloro-2-methylindazol-5-yl)-2-(4-cyano-3-fluorophenyl)-N-[(3R)-piperidin-3-yl]imidazole-4-carboxamide	A
115	4-[1-(3-Chloro-2-methylindazol-5-yl)-4-[(3R)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile	A
116	4-[1-(3-Chloro-2-methylindazol-5-yl)-4-[(3S)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile	A
117	1-(3-Chloro-2-methylindazol-5-yl)-2-(4-cyano-3-fluorophenyl)-5-methyl-N-[(3R)-piperidin-3-yl]imidazole-4-carboxamide	A
118	4-[1-(3-Chloro-2-methylindazol-5-yl)-5-methyl-4-[(3S)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile	A

Note: Biochemical assay IC_{50} data are designated within the following ranges:

A: ≤ 0.10 μM C: > 1.0 μM to ≤ 10 μM

B: > 0.10 μM to ≤ 1.0 μM D: > 10 μM

Example 2: In Vitro Enzyme Inhibition Assay – MAO selectivity

[00153] Human recombinant monoamine oxidase proteins MAO-A and MAO-B are obtained. MAOs catalyze the oxidative deamination of primary, secondary and tertiary amines. In order to monitor MAO enzymatic activities and/or their inhibition rate by inhibitor(s) of interest, a fluorescent-based (inhibitor)-screening assay is performed. 3-(2-Aminophenyl)-3-oxopropanamine (kynuramine dihydrobromide, Sigma Aldrich), a non-fluorescent compound is chosen as a substrate. Kynuramine is a non-specific substrate for both MAOs activities. While undergoing oxidative deamination by MAO activities, kynuramine is converted into 4-hydroxyquinoline (4-HQ), a resulting fluorescent product.

[00154] The monoamine oxidase activity is estimated by measuring the conversion of

kynuramine into 4-hydroxyquinoline. Assays are conducted in 96-well black plates with clear bottom (Corning) in a final volume of 100 µl. The assay buffer is 100 mM HEPES, pH 7.5. Each experiment is performed in triplicate within the same experiment.

[00155] Briefly, a fixed amount of MAO (0.25 µg for MAO-A and 0.5 µg for AO-B) is incubated on ice for 15 minutes in the reaction buffer, in the absence and/or in the presence of various concentrations of compounds as disclosed herein (e.g., from 0 to 50 µM, depending on the inhibitor strength). Tranylcypromine (Biomol International) is used as a control for inhibition.

[00156] After leaving the enzyme(s) interacting with the test compound, 60 to 90 µM of kynuramine is added to each reaction for MAO-B and MAO-A assay respectively, and the reaction is left for 1 hour at 37 °C in the dark. The oxidative deamination of the substrate is stopped by adding 50 µl of 2N NaOH. The conversion of kynuramine to 4-hydroxyquinoline, is monitored by fluorescence (excitation at 320 nm, emission at 360 nm) using a microplate reader (Infinite 200, Tecan). Arbitrary units are used to measure levels of fluorescence produced in the absence and/or in the presence of test compound.

[00157] The maximum of oxidative deamination activity is obtained by measuring the amount of 4-hydroxyquinoline formed from kynuramine deamination in the absence of test compound and corrected for background fluorescence. The Ki (IC_{50}) of each inhibitor is determined at Vmax/2.

Example 3: LSD1 CD11b cellular assay

[00158] To analyze LSD1 inhibitor efficacy in cells, a CD11b flow cytometry assay was performed. LSD1 inhibition induces CD11b expression in THP-1 (AML) cells which can be measured by flow cytometry. THP-1 cells were seeded at 100,000 cells/well in 10% Fetal Bovine Serum containing RPMI 1640 media in a 24 well plate with a final volume of 500 µL per well. LSD1 test compounds were serially diluted in DMSO. The dilutions were added to each well accordingly to a final concentration of 0.2% DMSO. The cells were incubated at 37 degrees Celsius in 5% CO_2 for 4 days. 250 µL of each well was transferred to a well in a 96 well round bottom plate. The plate was centrifuged at 1200 rpm at 4 degrees Celsius in a Beckman Coulter Alegra 6KR centrifuge for 5 minutes. The media was removed leaving the cells at the bottom of the wells. The cells were washed in 100 µL cold HBSS (Hank's Balanced Salt Solution) plus 2% BSA (Bovine Serum Albumin) solution and centrifuged at 1200 rpm at 4 degrees Celsius for 5 minutes. The wash was removed. The cells were resuspended in 100 µL HBSS plus 2% BSA containing 1:15 dilution of APC conjugated mouse anti-CD11b antibody (BD

Pharmingen Cat# 555751) and incubated on ice for 25 minutes. The cells were centrifuged and washed two times in 100 µl HBSS plus 2% BSA. After the final spin the cells were resuspended in 100 µL HBSS plus 2% BSA containing 1ug/mL DAPI (4',6-diamidino-2-phenylindole). The cells were then analyzed by flow cytometry in a BD FACSAria machine. Cells were analyzed for CD11b expression. The percent of CD11b expressing cells for each inhibitor concentration was used to determine an IC_{50} curve for each compound analyzed.

[00159] Table 4 provides the cellular IC_{50} values of various substituted heterocyclic compounds disclosed herein.

Table 4

Chemical Synthesis Example	Name	Cellular IC_{50} (µM)
1	4-[5-(3-(R)-amino-piperidine-1-carbonyl)-1-methyl-2-p-tolyl-1H-pyrrol-3-yl]-benzonitrile	A
2	4-[5-(3-(R)-amino-piperidine-1-carbonyl)-2-(4-methoxy-phenyl)-1-methyl-1H-pyrrol-3-yl]-2-fluoro-benzonitrile	A
3	4-[5-(3-(R)-amino-piperidine-1-carbonyl)-1-(2-hydroxy-ethyl)-2-p-tolyl-1H-pyrrol-3-yl]-benzonitrile	A
4	4-[5-(3-(R)-amino-piperidine-1-carbonyl)-1-(2-hydroxy-ethyl)-2-p-tolyl-1H-pyrrol-3-yl]-2-fluoro-benzonitrile	A
5	4-[5-(3-(R)-amino-piperidine-1-carbonyl)-1-methyl-2-(6-methyl-pyridin-3-yl)-1H-pyrrol-3-yl]-benzonitrile	A
6	4-[5-(3-(R)-amino-piperidine-1-carbonyl)-1-methyl-2-pyridin-4-yl-1H-pyrrol-3-yl]-benzonitrile	A
7	4-[5-(3-(R)-amino-piperidine-1-carbonyl)-1-(2-hydroxy-ethyl)-2-(4-methoxy-phenyl)-1H-pyrrol-3-yl]-benzonitrile	A
8	4-[5-(3-(R)-amino-piperidine-1-carbonyl)-1-(2-hydroxy-ethyl)-2-(4-methoxy-phenyl)-1H-pyrrol-3-yl]-2-fluoro-benzonitrile	A
9	4-[5-(3-(R)-amino-piperidine-1-carbonyl)-1-(3-hydroxy-propyl)-2-(4-methoxy-phenyl)-1H-pyrrol-3-yl]-2-fluoro-benzonitrile	A

Chemical Synthesis Example	Name	Cellular IC_{50} (μM)
10	4-[5-(3-(R)-amino-piperidine-1-carbonyl)-1-methyl-2-(1-methyl-1H-benzoimidazol-5-yl)-1H-pyrrol-3-yl]-2-fluoro-benzonitrile	A
11	4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-5-methyl-1-(4-methylphenyl)imidazol-2-yl]benzonitrile	A
12	4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-1-(4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A
13	4-[4-[(3R)-3-aminopyrrolidine-1-carbonyl]-1-(4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile	B
14	4-[4-[(3S)-3-aminopyrrolidine-1-carbonyl]-1-(4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A
15	4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-1-(6-methoxypyridin-3-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile	B
16	4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-1-(3-fluoro-4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A
17	4-[4-[(3S)-3-aminopiperidine-1-carbonyl]-1-(3-fluoro-4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile	B
18	4-[4-[(3S)-3-aminopyrrolidine-1-carbonyl]-1-(3-fluoro-4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A
19	4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-1-(3-fluoro-4-methoxyphenyl)imidazol-2-yl]-2-fluorobenzonitrile	A
20	4-[4-[(3S)-3-aminopyrrolidine-1-carbonyl]-1-(3-fluoro-4-methoxyphenyl)imidazol-2-yl]-2-fluorobenzonitrile	A
21	4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-5-methyl-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile	A
22	4-[4-[(3S)-3-aminopyrrolidine-1-carbonyl]-5-methyl-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile	A

Chemical Synthesis Example	Name	Cellular IC_{50} (μM)
23	4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-5-methyl-1-(1-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile	A
24	4-[4-[(3S)-3-aminopyrrolidine-1-carbonyl]-5-methyl-1-(1-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile	A
29	4-{5-[((3R)-3-aminopiperidyl)carbonyl]-1-methyl-2-(2-methyl(2H-indazol-5-yl))pyrrol-3-yl}-2-fluorobenzenecarbonitrile	A
30	N-((3R)pyrrolidin-3-yl)[4-(4-cyano-3-fluorophenyl)-1-methyl-5-(2-methyl(2H-indazol-5-yl))pyrrol-2-yl]carboxamide	A
31	N-(2-aminoethyl)[4-(4-cyano-3-fluorophenyl)-1-methyl-5-(2-methyl(2H-indazol-5-yl))pyrrol-2-yl]-N-methylcarboxamide	A
32	[4-(4-cyano-3-fluorophenyl)-1-methyl-5-(2-methyl(2H-indazol-5-yl))pyrrol-2-yl]-N-[2-(methylamino)ethyl]carboxamide	A
33	N-[((3S)pyrrolidin-3-yl)methyl][4-(4-cyano-3-fluorophenyl)-1-methyl-5-(2-methyl(2H-indazol-5-yl))pyrrol-2-yl]carboxamide	A
34	(R)-4-(5-(3-aminopiperidine-1-carbonyl)-1-(3-hydroxypropyl)-2-(2-methyl-2H-indazol-5-yl)-1H-pyrrol-3-yl)-2-fluorobenzonitrile	A
35	(R)-4-(5-(3-aminopiperidine-1-carbonyl)-1-(2-hydroxyethyl)-2-(2-methyl-2H-indazol-5-yl)-1H-pyrrol-3-yl)-2-fluorobenzonitrile	A
36	(R)-4-(5-(3-aminopiperidine-1-carbonyl)-1-(2-methoxyethyl)-2-(2-methyl-2H-indazol-5-yl)-1H-pyrrol-3-yl)-2-fluorobenzonitrile	A
38	4-(5-((R)-3-aminopiperidine-1-carbonyl)-1-((R)-2,3-dihydroxypropyl)-2-(2-methyl-2H-indazol-5-yl)-1H-pyrrol-3-yl)-2-fluorobenzonitrile	A
39	4-(5-((R)-3-aminopiperidine-1-carbonyl)-1-((S)-2,3-dihydroxypropyl)-2-(2-methyl-2H-indazol-5-yl)-1H-pyrrol-3-yl)-2-fluorobenzonitrile	A

Chemical Synthesis Example	Name	Cellular IC_{50} (μM)
40	N-[((3R)pyrrolidin-3-yl)methyl][4-(4-cyano-3-fluorophenyl)-1-methyl-5-(2-methyl(2H-indazol-5-yl))pyrrol-2-yl]carboxamide	A
41	4-{5-[((3R)-3-aminopiperidyl)carbonyl]-3-(4-cyano-3-fluorophenyl)-2-(4-methoxyphenyl)pyrrolyl}butanoic acid	B
42	4-{5-[((3R)-3-aminopiperidyl)carbonyl]-3-(4-cyano-3-fluorophenyl)-2-(4-methoxyphenyl)pyrrolyl}butanamide	A
43	4-[4-(4-Aminopiperidine-1-carbonyl)-5-methyl-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile	B
44	N-(2-Aminoethyl)-2-(4-cyano-3-fluorophenyl)-N,5-dimethyl-1-(2-methylindazol-5-yl)imidazole-4-carboxamide	
45	2-(4-Cyano-3-fluorophenyl)-5-methyl-1-(2-methylindazol-5-yl)-N-piperidin-3-ylimidazole-4-carboxamide	A
46	2-(4-Cyano-3-fluorophenyl)-5-methyl-1-(2-methylindazol-5-yl)-N-pyrrolidin-3-ylimidazole-4-carboxamide	A
47	4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-1-(6-fluoro-2-methylindazol-5-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A
48	4-[4-[(3S)-3-(Dimethylamino)pyrrolidine-1-carbonyl]-1-(6-fluoro-2-methylindazol-5-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A
49	2-Fluoro-4-[1-(6-fluoro-2-methylindazol-5-yl)-5-methyl-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile	A
50	4-[4-[(3S)-3-Aminopyrrolidine-1-carbonyl]-1-(7-fluoro-2-methylindazol-5-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A
51	2-Fluoro-4-[1-(7-fluoro-2-methylindazol-5-yl)-5-methyl-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile	A
52	4-[4-[(3S)-3-(Dimethylamino)pyrrolidine-1-carbonyl]-1-(7-fluoro-2-methylindazol-5-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A

Chemical Synthesis Example	Name	Cellular IC_{50} (μM)
53	4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-1-(3-chloro-2-methylindazol-5-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A
54	4-[1-(3-Chloro-2-methylindazol-5-yl)-5-methyl-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile	A
55	4-[1-(3-Chloro-2-methylindazol-5-yl)-5-methyl-4-[(3R)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile	A
56	1-(3-Chloro-2-methylindazol-5-yl)-2-(4-cyano-3-fluorophenyl)-5-methyl-N-[(3R)-1-methylpiperidin-3-yl]imidazole-4-carboxamide	A
57	4-[1-(3-Chloro-2-methylindazol-5-yl)-4-[(3S)-3-(dimethylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile	A
58	4-[1-(3-Chloro-2-methylindazol-5-yl)-4-[(3S)-3-(dimethylamino)pyrrolidine-1-carbonyl]-5-fluoroimidazol-2-yl]-2-fluorobenzonitrile	A
59	1-(3-Chloro-2-methylindazol-5-yl)-2-(4-cyano-3-fluorophenyl)-N-[(3R)-1-methylpiperidin-3-yl]imidazole-4-carboxamide	A
60	2-(4-Cyano-3-fluorophenyl)-5-methyl-1-(2-methylindazol-5-yl)-N-[(3R)-1-methylpiperidin-3-yl]imidazole-4-carboxamide	A
61	4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-1-(3-chloro-2-methylindazol-5-yl)-5-fluoroimidazol-2-yl]-2-fluorobenzonitrile	A
62	2-(4-Cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)-5-methyl-N-[(3R)-piperidin-3-yl]imidazole-4-carboxamide	A
63	2-(4-Cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)-5-methyl-N-[(3S)-piperidin-3-yl]imidazole-4-carboxamide	A
64	2-Fluoro-4-[1-(3-fluoro-4-methoxyphenyl)-5-methyl-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile	A

Chemical Synthesis Example	Name	Cellular IC_{50} (μM)
65	2-Fluoro-4-[1-(3-fluoro-4-methoxyphenyl)-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile	A
66	4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-5-chloro-1-(3-fluoro-4-methoxyphenyl)imidazol-2-yl]-2-fluorobenzonitrile	A
67	4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-5-fluoro-1-(3-fluoro-4-methoxyphenyl)imidazol-2-yl]-2-fluorobenzonitrile	A
68	2-Fluoro-4-[5-fluoro-1-(3-fluoro-4-methoxyphenyl)-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile	A
69	2-Fluoro-4-[1-(4-methoxyphenyl)-5-methyl-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile	A
70	2-Fluoro-4-[1-(4-methoxyphenyl)-5-methyl-4-[(3R)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]benzonitrile	A
71	2-Fluoro-4-[1-(4-methoxyphenyl)-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile	A
72	2-Fluoro-4-[1-(4-methoxyphenyl)-4-[(3R)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]benzonitrile	A
73	2-Fluoro-4-[5-fluoro-1-(4-methoxyphenyl)-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile	A
74	2-Fluoro-4-[5-fluoro-1-(4-methoxyphenyl)-4-[(3R)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]benzonitrile	A
75	4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-5-chloro-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile	A
76	4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-5-chloro-1-(3-chloro-2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile	A

Chemical Synthesis Example	Name	Cellular IC_{50} (μM)
77	4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-5-fluoro-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile	A
78	4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-1-(6-cyclopropylpyridin-3-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile	B
79	4-[4-[(3S)-3-Aminopyrrolidine-1-carbonyl]-1-(6-cyclopropylpyridin-3-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A
80	4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-5-chloro-1-(6-cyclopropylpyridin-3-yl)imidazol-2-yl]-2-fluorobenzonitrile	B
81	4-[4-[(3S)-3-Aminopyrrolidine-1-carbonyl]-5-chloro-1-(6-cyclopropylpyridin-3-yl)imidazol-2-yl]-2-fluorobenzonitrile	A
82	2-(4-Cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)-5-methyl-N-[(3R)-pyrrolidin-3-yl]imidazole-4-carboxamide	B
83	2-(4-Cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)-5-methyl-N-[(3S)-pyrrolidin-3-yl]imidazole-4-carboxamide	B
84	5-Chloro-2-(4-cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)-N-[(3R)-piperidin-3-yl]imidazole-4-carboxamide	A
85	5-Chloro-2-(4-cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)-N-[(3S)-piperidin-3-yl]imidazole-4-carboxamide	B
86	2-(4-Cyano-3-fluorophenyl)-5-fluoro-1-(3-fluoro-4-methoxyphenyl)-N-[(3R)-piperidin-3-yl]imidazole-4-carboxamide	B
87	2-(4-Cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)-5-methyl-N-piperidin-4-ylimidazole-4-carboxamide	B
88	4-[4-[3-(Aminomethyl)azetidine-1-carbonyl]-1-(3-fluoro-4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A

Chemical Synthesis Example	Name	Cellular IC_{50} (μM)
89	4-[4-[(3S)-3-Aminopyrrolidine-1-carbonyl]-5-fluoro-1-(3-fluoro-4-methoxyphenyl)imidazol-2-yl]-2-fluorobenzonitrile	B
90	4-[4-(1,7-Diazaspiro[4.4]nonane-7-carbonyl)-5-methyl-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile	B
91	4-[4-(2,6-Diazaspiro[3.4]octane-6-carbonyl)-5-methyl-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile	A
92	4-[4-(1,7-Diazaspiro[3.4]octane-7-carbonyl)-5-methyl-1-(1-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile	B
93	4-[1-(3-Chloro-2-methylindazol-5-yl)-4-(1,7-diazaspiro[3.4]octane-7-carbonyl)imidazol-2-yl]-2-fluorobenzonitrile	B
94	4-[4-[(3S)-3-(Dimethylamino)pyrrolidine-1-carbonyl]-5-methyl-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile	A
95	4-[4-[(3S)-3-(Dimethylamino)pyrrolidine-1-carbonyl]-5-methyl-1-(1-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile	A
96	4-[1-(3-Chloro-2-methylindazol-5-yl)-4-[(3S)-3-(dimethylamino)pyrrolidine-1-carbonyl]-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A
97	2-Fluoro-4-[5-methyl-4-[(3S)-3-(methylamino)piperidine-1-carbonyl]-1-(2-methylindazol-5-yl)imidazol-2-yl]benzonitrile	A
98	2-Fluoro-4-[5-methyl-4-[(3R)-3-(methylamino)piperidine-1-carbonyl]-1-(2-methylindazol-5-yl)imidazol-2-yl]benzonitrile	A
99	4-[4-[(3S)-3-(Dimethylamino)pyrrolidine-1-carbonyl]-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile	B
100	4-[5-Chloro-4-[(3S)-3-(dimethylamino)pyrrolidine-1-carbonyl]-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile	B

Chemical Synthesis Example	Name	Cellular IC_{50} (μM)
101	4-[5-Chloro-1-(3-chloro-2-methylindazol-5-yl)-4-[(3S)-3-(dimethylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile	A
102	4-[4-[(3S)-3-(Dimethylamino)pyrrolidine-1-carbonyl]-1-(2,3-dimethylindazol-5-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A
103	4-[1-(2,3-Dimethylindazol-5-yl)-5-methyl-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile	A
104	2-(4-Cyano-3-fluorophenyl)-1-(2,3-dimethylindazol-5-yl)-5-methyl-N-[(3R)-piperidin-3-yl]imidazole-4-carboxamide	A
105	4-[1-(2,3-Dimethylindazol-5-yl)-5-methyl-4-[(3R)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile	A
110	4-[1-(3-Chloro-6-fluoro-2-methylindazol-5-yl)-4-[(3S)-3-(dimethylamino)pyrrolidine-1-carbonyl]-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A
111	4-[1-(3-Chloro-6-fluoro-2-methylindazol-5-yl)-5-methyl-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile	A
112	4-[1-(3-Chloro-6-fluoro-2-methylindazol-5-yl)-4-[(3S)-3-(dimethylamino)pyrrolidine-1-carbonyl]-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A
113	4-[1-(3-Chloro-2-methylindazol-5-yl)-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile	A
114	1-(3-Chloro-2-methylindazol-5-yl)-2-(4-cyano-3-fluorophenyl)-N-[(3R)-piperidin-3-yl]imidazole-4-carboxamide	A
115	4-[1-(3-Chloro-2-methylindazol-5-yl)-4-[(3R)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile	A
116	4-[1-(3-Chloro-2-methylindazol-5-yl)-4-[(3S)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile	A

Chemical Synthesis Example	Name	Cellular IC_{50} (μM)
117	1-(3-Chloro-2-methylindazol-5-yl)-2-(4-cyano-3-fluorophenyl)-5-methyl-N-[(3R)-piperidin-3-yl]imidazole-4-carboxamide	A
118	4-[1-(3-Chloro-2-methylindazol-5-yl)-5-methyl-4-[(3S)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile	A

Note: Assay IC_{50} data are designated within the following ranges:

A: ≤ 0.10 μM C: > 1.0 μM to ≤ 10 μM

B: > 0.10 μM to ≤ 1.0 μM D: > 10 μM

Example 4: Kasumi-1 AML Cell Line Proliferation Assay (Cell-MTS Assay)

[0001] Colorimetric cellular assay to assess the ability of LSD-1 small molecule inhibitors to effect the proliferation of the established AML cancer cell line Kasumi-1.

Assay Background

[0002] The LSD-1 protein has been shown to play a key role in the biology of a variety of cancer types including SCLC and AML. To demonstrate small molecule inhibition of LSD-1 as a potential anti-cancer therapy, an assay to measure the degree of proliferative inhibition in an established cancer cell line of AML was implemented.

Assay Principle

[0003] This Cell-MTS assay is a 7-day plate based colorimetric assay which quantifies the amount of newly generated NADH in the presence and absence of test compound. These NADH levels are used as a proxy for the quantification of cancer cell proliferation.

Assay Method in Brief

[0004] The established cancer cell line Kasumi-1 with a verified p53 mutation were purchased from *American Type Culture Collection* (ATCC) and routinely passaged according to ATCC published protocols. For routine assay these cells were seeded at a density of 20,000 cells per 96-well. 24 hours after plating, cells received an 11 point dilution of test compound with final concentration ranges from 100 μM to 2.0 nM. Cells are incubated in the presence of compound for 168 hours at 37 °C, 5% CO_2. At the end of this compound incubation period, 80 μl of media is removed and 20 μL of CellTiter 96® AQueous Non-Radioactive Cell Proliferation Assay solution (Promega) is added. The cells are incubated until the OD490 is >0.6. IC_{50} values are calculated using the

IDBS XLfit software package and include background subtracted OD490 values and normalization to DMSO controls.

[0005] Table 5 provides the Kasumi-1 cellular IC_{50} values of various substituted heterocyclic compounds disclosed herein.

Table 5

Chemical Synthesis Example	Name	Kasumi-1 IC_{50} (μM)
12	4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-1-(4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A
14	4-[4-[(3S)-3-aminopyrrolidine-1-carbonyl]-1-(4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A
16	4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-1-(3-fluoro-4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A
18	4-[4-[(3S)-3-aminopyrrolidine-1-carbonyl]-1-(3-fluoro-4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A
64	2-Fluoro-4-[1-(3-fluoro-4-methoxyphenyl)-5-methyl-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile	A
67	4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-5-fluoro-1-(3-fluoro-4-methoxyphenyl)imidazol-2-yl]-2-fluorobenzonitrile	A
70	2-Fluoro-4-[1-(4-methoxyphenyl)-5-methyl-4-[(3R)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]benzonitrile	A
76	4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-5-chloro-1-(3-chloro-2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile	A
88	4-[4-[3-(Aminomethyl)azetidine-1-carbonyl]-1-(3-fluoro-4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A
94	4-[4-[(3S)-3-(Dimethylamino)pyrrolidine-1-carbonyl]-5-methyl-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile	A

Chemical Synthesis Example	Name	Kasumi-1 IC_{50} (μM)
96	4-[1-(3-Chloro-2-methylindazol-5-yl)-4-[(3S)-3-(dimethylamino)pyrrolidine-1-carbonyl]-5-methylimidazol-2-yl]-2-fluorobenzonitrile	A

Note: Assay IC_{50} data are designated within the following ranges:

A: ≤ 0.10 μM C: > 1.0 μM to ≤ 10 μM

B: > 0.10 μM to ≤ 1.0 μM D: > 10 μM

Example 5: In Vivo Xenograph Study – MCF-7 Xenograph

[0006] Time release pellets containing 0.72 mg 17-β Estradiol are subcutaneously implanted into nu/nu mice. MCF-7 cells are grown in RPMI containing 10% FBS at 5% CO_2, 37 °C. Cells are spun down and re-suspended in 50% RPMI (serum free) and 50% Matrigel at $1X10^7$ cells/mL. MCF-7 cells are subcutaneously injected (100μL/animal) on the right flank 2-3 days post pellet implantation and tumor volume (length x $width^2/2$) is monitored bi-weekly. When tumors reach an average volume of ~200 mm^3 animals are randomized and treatment is started. Animals are treated with vehicle or compound daily for 4 weeks. Tumor volume and body weight are monitored bi-weekly throughout the study. At the conclusion of the treatment period, plasma and tumor samples are taken for pharmacokinetic and pharmacodynamic analyses, respectively.

Example 6: In Vivo Xenograph Study – LNCaP Xenograph

[0007] LNCaP cells with a stable knockdown of LSDl (shLSDl cells) or control cells (such as shNTC cells) are inoculated in the dorsal flank of nude mice by subcutaneous injection (such as 3 x 10^6 cells in 100 μl of 50% RPMI 1640/BD Matrigel). Mouse weight and tumor size are measured once per week and tumor volume is estimated using the formula (7i/6)(LxW), where L = length of tumor and W = width of tumor. A two sample t-test is performed to determine statistical differences in mean tumor volume between the two groups.

[0008] Unmodified LNCaP cells are inoculated by subcutaneous injection into the dorsal flank of nude mice (such as 3 x 10^6 cells in 100 μl of 50% RPMI 1640/BD Matrigel). After three weeks, mice are injected intraperitoneally once per day with water (control), pargyline (0.53 mg or 1.59 mg; 1 or 3 mM final concentration, assuming 70% bioavailability), or XB154 (4 or 20 μg; 1 or 5 μM final concentration, assuming 70% bioavailability) or treated with a test compound (5 mg/kg each week or 10 mg/kg each week). Treatment continues for three weeks, during which time mouse weight and tumor

volume are measured as above.

[0009] shLSDl LNCaP cells or control cells are injected in nude mice as above. After three weeks, mice are treated with 2.6 μg mitomycin C (predicted final concentration of 1 μM assuming 40% bioavailability), olaparib (for example, about 0.5 mg/kg to 25 mg/kg), or vehicle intraperitoneally once per day for three weeks. In other examples, unmodified LNCaP cells are injected in nude mice as above.

[0010] After three weeks, mice are treated with test compounds, or vehicle as above, plus MMC or olaparib. Treatment continues for three weeks, during which time mouse weight and tumor volume are measured as above.

[0011] A decrease in tumor volume compared to control in mice injected with shLSDl cells indicates that LSDl inhibition decreases tumor growth in vivo.

[0012] Similarly, a decrease in tumor volume compared to control in mice injected with LNCaP cells and treated with a compound disclosed herein indicates that LSDl inhibition decreases tumor growth in vivo. Finally, a decrease in tumor volume in mice injected with LNCaP cells and treated with a compound disclosed herein plus olaparib as compared to mice treated with a compound disclosed herein alone indicates that inhibition of LSDl plus inhibition of PARP decreases tumor growth in vivo.

[0013] The harvested xenograft tissue is examined for evidence of LSDl inhibition. This is assessed with Western blots to examine global levels of the 2MK4 and 2MK9 histone marks, expression of FA/BRCA genes, FANCD2 ubiquitination, and LSDl protein levels in the cases of the shRNA cells. A decrease in one or more of these parameters indicates the effective inhibition of LSD 1. Additionally, effects on DNA damage repair are assessed with staining for H2AX foci.

III. Preparation of Pharmaceutical Dosage Forms

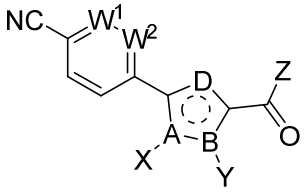
Example 1: Oral Tablet

[0014] A tablet is prepared by mixing 48% by weight of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, 45% by weight of microcrystalline cellulose, 5% by weight of low-substituted hydroxypropyl cellulose, and 2% by weight of magnesium stearate. Tablets are prepared by direct compression. The total weight of the compressed tablets is maintained at 250-500 mg.

CLAIMS

We Claim:

1. A compound having the structure of Formula (I), or a pharmaceutically acceptable salt thereof,



(I)

wherein,

A is C; B is N; and D is CH; or A is N; B is C; and D is N;

W^1 and W^2 are independently chosen from N, C-H, or C-F;

X is chosen from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclylalkyl, optionally substituted aralkyl, or optionally substituted heteroarylalkyl;

Y is chosen from hydrogen, halogen, optionally substituted alkyl, optionally substituted cycloalkyl, or optionally substituted cycloalkylalkyl; and

Z is chosen from an optionally substituted *N*-heterocyclyl, optionally substituted -N(H)-heterocyclylalkyl, optionally substituted -N(Me)-heterocyclylalkyl, or $–N(R^3)_2$, wherein each R^3 is independently chosen from hydrogen or optionally substituted alkyl.

2. The compound or pharmaceutically acceptable salt of claim 1, wherein W^2 is C-H.

3. The compound or pharmaceutically acceptable salt of claim 1 or 2, wherein W^1 is C-F.

4. The compound or pharmaceutically acceptable salt of claim 1 or 2, wherein W^1 is C-H.

5. The compound or pharmaceutically acceptable salt of claim 1 or 2, wherein W^1 is N.

6. The compound or pharmaceutically acceptable salt of any one of claims 1-5, wherein X is optionally substituted aryl.

7. The compound or pharmaceutically acceptable salt of claim 6, wherein the optionally substituted aryl is an optionally substituted phenyl.

8. The compound or pharmaceutically acceptable salt of any one of claims 1-5, wherein X is optionally substituted heteroaryl.

9. The compound or pharmaceutically acceptable salt of claim 8, wherein the optionally substituted heteroaryl is chosen from an optionally substituted pyridinyl, optionally substituted pyrimidinyl, optionally substituted pyrazinyl, optionally substituted pyrazolyl, optionally substituted indazolyl, optionally substituted azaindazolyl, optionally substituted isoindazolyl, optionally substituted indolyl, or optionally substituted azaindolyl.

10. The compound or pharmaceutically acceptable salt of any one of claims 1-9, wherein Z is an optionally substituted *N*-heterocyclyl and the optionally substituted *N*-heterocyclyl is a 4-, 5-, 6-, or 7-membered N-heterocyclyl.

11. The compound or pharmaceutically acceptable salt of claim 10, wherein the optionally substituted *N*-heterocyclyl is a 6-membered N-heterocyclyl.

12. The compound or pharmaceutically acceptable salt of claim 11, wherein the optionally substituted *N*-heterocyclyl is an optionally substituted piperidine.

13. The compound or pharmaceutically acceptable salt of claim 12, wherein the optionally substituted piperidine is an optionally substituted 3-aminopiperidine.

14. The compound or pharmaceutically acceptable salt of claim 10, wherein the optionally substituted *N*-heterocyclyl is a 5-membered N-heterocyclyl.

15. The compound or pharmaceutically acceptable salt of claim 14, wherein the optionally substituted *N*-heterocyclyl is an optionally substituted pyrrolidine.

16. The compound or pharmaceutically acceptable salt of claim 15, wherein the optionally substituted pyrrolidine is an optionally substituted 3-aminopyrrolidine.

17. The compound or pharmaceutically acceptable salt of any one of claims 1-16, wherein Y is hydrogen.

18. The compound or pharmaceutically acceptable salt of any one of claims 1-16, wherein Y is halogen.

19. The compound or pharmaceutically acceptable salt of any one of claims 1-16, wherein Y is optionally substituted alkyl.

20. The compound or pharmaceutically acceptable salt of any one of claims 1-16, wherein Y is optionally substituted cycloalkyl.

21. The compound or pharmaceutically acceptable salt of any one of claims 1-16, wherein Y is optionally substituted cycloalkylalkyl.

22. The compound or pharmaceutically acceptable salt of claim 19, wherein the optionally substituted alkyl is an optionally substituted C_1-C_3 alkyl.

23. The compound or pharmaceutically acceptable salt of claim 19, wherein the optionally substituted alkyl is an optionally substituted C_1 alkyl.

24. The compound or pharmaceutically acceptable salt of claim 19, wherein the optionally substituted alkyl is a methyl group.

25. The compound or pharmaceutically acceptable salt of any one of claims 1-24, wherein A is N; B is C; and D is N.

26. The compound or pharmaceutically acceptable salt of any one of claims 1-24, wherein A is C; B is N; and D is CH.

27. The compound or pharmaceutically acceptable salt of claim 26, wherein R^3 is hydrogen.

28. The compound or pharmaceutically acceptable salt of claim 26, wherein R^3 is optionally substituted alkyl.

29. The compound or pharmaceutically acceptable salt of claim 1, wherein the compound is any one of the following:

4-[5-(3-(R)-amino-piperidine-1-carbonyl)-1-methyl-2-p-tolyl-1H-pyrrol-3-yl]-benzonitrile;

4-[5-(3-(R)-amino-piperidine-1-carbonyl)-2-(4-methoxy-phenyl)-1-methyl-1H-pyrrol-3-yl]-2-fluoro-benzonitrile;

4-[5-(3-(R)-amino-piperidine-1-carbonyl)-1-(2-hydroxy-ethyl)-2-p-tolyl-1H-pyrrol-3-yl]-benzonitrile;

4-[5-(3-(R)-amino-piperidine-1-carbonyl)-1-(2-hydroxy-ethyl)-2-p-tolyl-1H-pyrrol-3-yl]-2-fluoro-benzonitrile;

4-[5-(3-(R)-amino-piperidine-1-carbonyl)-1-methyl-2-(6-methyl-pyridin-3-yl)-1H-pyrrol-3-yl]-benzonitrile;

4-[5-(3-(R)-amino-piperidine-1-carbonyl)-1-methyl-2-pyridin-4-yl-1H-pyrrol-3-yl]-benzonitrile;

4-[5-(3-(R)-amino-piperidine-1-carbonyl)-1-(2-hydroxy-ethyl)-2-(4-methoxy-phenyl)-1H-pyrrol-3-yl]-benzonitrile;

4-[5-(3-(R)-amino-piperidine-1-carbonyl)-1-(2-hydroxy-ethyl)-2-(4-methoxy-phenyl)-1H-pyrrol-3-yl]-2-fluoro-benzonitrile;

4-[5-(3-(R)-amino-piperidine-1-carbonyl)-1-(3-hydroxy-propyl)-2-(4-methoxy-phenyl)-1H-pyrrol-3-yl]-2-fluoro-benzonitrile;

4-[5-(3-(R)-amino-piperidine-1-carbonyl)-1-methyl-2-(1-methyl-1H-benzoimidazol-5-yl)-1H-pyrrol-3-yl]-2-fluoro-benzonitrile;

4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-5-methyl-1-(4-methylphenyl)imidazol-2-yl]benzonitrile;

4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-1-(4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile;

4-[4-[(3R)-3-aminopyrrolidine-1-carbonyl]-1-(4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile;

4-[4-[(3S)-3-aminopyrrolidine-1-carbonyl]-1-(4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile;

4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-1-(6-methoxypyridin-3-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile;

4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-1-(3-fluoro-4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile;

4-[4-[(3S)-3-aminopiperidine-1-carbonyl]-1-(3-fluoro-4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile;

4-[4-[(3S)-3-aminopyrrolidine-1-carbonyl]-1-(3-fluoro-4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile;

4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-1-(3-fluoro-4-methoxyphenyl)imidazol-2-yl]-2-fluorobenzonitrile;

4-[4-[(3S)-3-aminopyrrolidine-1-carbonyl]-1-(3-fluoro-4-methoxyphenyl)imidazol-2-yl]-2-fluorobenzonitrile;

4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-5-methyl-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile;

4-[4-[(3S)-3-aminopyrrolidine-1-carbonyl]-5-methyl-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile;

4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-5-methyl-1-(1-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile;

4-[4-[(3S)-3-aminopyrrolidine-1-carbonyl]-5-methyl-1-(1-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile;

4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile;

4-[4-[(3S)-3-aminopyrrolidine-1-carbonyl]-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile;

4-[4-[(3R)-3-aminopiperidine-1-carbonyl]-1-(1-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile;

4-[4-[(3S)-3-aminopyrrolidine-1-carbonyl]-1-(1-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile;

4-{5-[((3R)-3-aminopiperidyl)carbonyl]-1-methyl-2-(2-methyl(2H-indazol-5-yl))pyrrol-3-yl}-2-fluorobenzenecarbonitrile;

N-((3R)pyrrolidin-3-yl)[4-(4-cyano-3-fluorophenyl)-1-methyl-5-(2-methyl(2H-indazol-5-yl))pyrrol-2-yl]carboxamide;

N-(2-aminoethyl)[4-(4-cyano-3-fluorophenyl)-1-methyl-5-(2-methyl(2H-indazol-5-yl))pyrrol-2-yl]-N-methylcarboxamide;

[4-(4-cyano-3-fluorophenyl)-1-methyl-5-(2-methyl(2H-indazol-5-yl))pyrrol-2-yl]-N-[2-(methylamino)ethyl]carboxamide;

N-[((3S)pyrrolidin-3-yl)methyl][4-(4-cyano-3-fluorophenyl)-1-methyl-5-(2-methyl(2H-indazol-5-yl))pyrrol-2-yl]carboxamide;

(R)-4-(5-(3-aminopiperidine-1-carbonyl)-1-(3-hydroxypropyl)-2-(2-methyl-2H-indazol-5-yl)-1H-pyrrol-3-yl)-2-fluorobenzonitrile;

(R)-4-(5-(3-aminopiperidine-1-carbonyl)-1-(2-hydroxyethyl)-2-(2-methyl-2H-indazol-5-yl)-1H-pyrrol-3-yl)-2-fluorobenzonitrile;

(R)-4-(5-(3-aminopiperidine-1-carbonyl)-1-(2-methoxyethyl)-2-(2-methyl-2H-indazol-5-yl)-1H-pyrrol-3-yl)-2-fluorobenzonitrile;

(R)-2-(5-(3-aminopiperidine-1-carbonyl)-3-(4-cyano-3-fluorophenyl)-2-(4-methoxyphenyl)-1H-pyrrol-1-yl)acetamide;

4-(5-((R)-3-aminopiperidine-1-carbonyl)-1-((R)-2,3-dihydroxypropyl)-2-(2-methyl-2H-indazol-5-yl)-1H-pyrrol-3-yl)-2-fluorobenzonitrile;

4-(5-((R)-3-aminopiperidine-1-carbonyl)-1-((S)-2,3-dihydroxypropyl)-2-(2-methyl-2H-indazol-5-yl)-1H-pyrrol-3-yl)-2-fluorobenzonitrile;

N-[((3R)pyrrolidin-3-yl)methyl][4-(4-cyano-3-fluorophenyl)-1-methyl-5-(2-methyl(2H-indazol-5-yl))pyrrol-2-yl]carboxamide;

4-{5-[((3R)-3-aminopiperidyl)carbonyl]-3-(4-cyano-3-fluorophenyl)-2-(4-methoxyphenyl)pyrrolyl}butanoic acid;

4-{5-[((3R)-3-aminopiperidyl)carbonyl]-3-(4-cyano-3-fluorophenyl)-2-(4-methoxyphenyl)pyrrolyl}butanamide;

4-[4-(4-Aminopiperidine-1-carbonyl)-5-methyl-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile;

N-(2-Aminoethyl)-2-(4-cyano-3-fluorophenyl)-N,5-dimethyl-1-(2-methylindazol-5-yl)imidazole-4-carboxamide;

2-(4-Cyano-3-fluorophenyl)-5-methyl-1-(2-methylindazol-5-yl)-N-piperidin-3-ylimidazole-4-carboxamide;

2-(4-Cyano-3-fluorophenyl)-5-methyl-1-(2-methylindazol-5-yl)-N-pyrrolidin-3-ylimidazole-4-carboxamide;

4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-1-(6-fluoro-2-methylindazol-5-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile;

4-[4-[(3S)-3-(Dimethylamino)pyrrolidine-1-carbonyl]-1-(6-fluoro-2-methylindazol-5-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile;

2-Fluoro-4-[1-(6-fluoro-2-methylindazol-5-yl)-5-methyl-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile;

4-[4-[(3S)-3-Aminopyrrolidine-1-carbonyl]-1-(7-fluoro-2-methylindazol-5-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile;

2-Fluoro-4-[1-(7-fluoro-2-methylindazol-5-yl)-5-methyl-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile;

4-[4-[(3S)-3-(Dimethylamino)pyrrolidine-1-carbonyl]-1-(7-fluoro-2-methylindazol-5-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile;

4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-1-(3-chloro-2-methylindazol-5-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile;

4-[1-(3-Chloro-2-methylindazol-5-yl)-5-methyl-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile;

4-[1-(3-Chloro-2-methylindazol-5-yl)-5-methyl-4-[(3R)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile;

1-(3-Chloro-2-methylindazol-5-yl)-2-(4-cyano-3-fluorophenyl)-5-methyl-N-[(3R)-1-methylpiperidin-3-yl]imidazole-4-carboxamide;

4-[1-(3-Chloro-2-methylindazol-5-yl)-4-[(3S)-3-(dimethylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile;

4-[1-(3-Chloro-2-methylindazol-5-yl)-4-[(3S)-3-(dimethylamino)pyrrolidine-1-carbonyl]-5-fluoroimidazol-2-yl]-2-fluorobenzonitrile;

1-(3-Chloro-2-methylindazol-5-yl)-2-(4-cyano-3-fluorophenyl)-N-[(3R)-1-methylpiperidin-3-yl]imidazole-4-carboxamide;

2-(4-Cyano-3-fluorophenyl)-5-methyl-1-(2-methylindazol-5-yl)-N-[(3R)-1-methylpiperidin-3-yl]imidazole-4-carboxamide;

4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-1-(3-chloro-2-methylindazol-5-yl)-5-fluoroimidazol-2-yl]-2-fluorobenzonitrile;

2-(4-Cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)-5-methyl-N-[(3R)-piperidin-3-yl]imidazole-4-carboxamide;

2-(4-Cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)-5-methyl-N-[(3S)-piperidin-3-yl]imidazole-4-carboxamide;

2-Fluoro-4-[1-(3-fluoro-4-methoxyphenyl)-5-methyl-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile;

2-Fluoro-4-[1-(3-fluoro-4-methoxyphenyl)-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile;

4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-5-chloro-1-(3-fluoro-4-methoxyphenyl)imidazol-2-yl]-2-fluorobenzonitrile;

4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-5-fluoro-1-(3-fluoro-4-methoxyphenyl)imidazol-2-yl]-2-fluorobenzonitrile;

2-Fluoro-4-[5-fluoro-1-(3-fluoro-4-methoxyphenyl)-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile;

2-Fluoro-4-[1-(4-methoxyphenyl)-5-methyl-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile**;**

2-Fluoro-4-[1-(4-methoxyphenyl)-5-methyl-4-[(3R)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]benzonitrile;

2-Fluoro-4-[1-(4-methoxyphenyl)-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile;

2-Fluoro-4-[1-(4-methoxyphenyl)-4-[(3R)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]benzonitrile;

2-Fluoro-4-[5-fluoro-1-(4-methoxyphenyl)-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]benzonitrile;

2-Fluoro-4-[5-fluoro-1-(4-methoxyphenyl)-4-[(3R)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]benzonitrile;

4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-5-chloro-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile;

4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-5-chloro-1-(3-chloro-2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile;

4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-5-fluoro-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile;

4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-1-(6-cyclopropylpyridin-3-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile;

4-[4-[(3S)-3-Aminopyrrolidine-1-carbonyl]-1-(6-cyclopropylpyridin-3-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile;

4-[4-[(3R)-3-Aminopiperidine-1-carbonyl]-5-chloro-1-(6-cyclopropylpyridin-3-yl)imidazol-2-yl]-2-fluorobenzonitrile;

4-[4-[(3S)-3-Aminopyrrolidine-1-carbonyl]-5-chloro-1-(6-cyclopropylpyridin-3-yl)imidazol-2-yl]-2-fluorobenzonitrile;

2-(4-Cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)-5-methyl-N-[(3R)-pyrrolidin-3-yl]imidazole-4-carboxamide;

2-(4-Cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)-5-methyl-N-[(3S)-pyrrolidin-3-yl]imidazole-4-carboxamide;

5-Chloro-2-(4-cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)-N-[(3R)-piperidin-3-yl]imidazole-4-carboxamide;

5-Chloro-2-(4-cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)-N-[(3S)-piperidin-3-yl]imidazole-4-carboxamide;

2-(4-Cyano-3-fluorophenyl)-5-fluoro-1-(3-fluoro-4-methoxyphenyl)-N-[(3R)-piperidin-3-yl]imidazole-4-carboxamide;

2-(4-Cyano-3-fluorophenyl)-1-(3-fluoro-4-methoxyphenyl)-5-methyl-N-piperidin-4-ylimidazole-4-carboxamide;

4-[4-[3-(Aminomethyl)azetidine-1-carbonyl]-1-(3-fluoro-4-methoxyphenyl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile;

4-[4-[(3S)-3-Aminopyrrolidine-1-carbonyl]-5-fluoro-1-(3-fluoro-4-methoxyphenyl)imidazol-2-yl]-2-fluorobenzonitrile;

4-[4-(1,7-Diazaspiro[4.4]nonane-7-carbonyl)-5-methyl-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile;

4-[4-(2,6-Diazaspiro[3.4]octane-6-carbonyl)-5-methyl-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile;

4-[4-(1,7-Diazaspiro[3.4]octane-7-carbonyl)-5-methyl-1-(1-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile;

4-[1-(3-Chloro-2-methylindazol-5-yl)-4-(1,7-diazaspiro[3.4]octane-7-carbonyl)imidazol-2-yl]-2-fluorobenzonitrile;

4-[4-[(3S)-3-(Dimethylamino)pyrrolidine-1-carbonyl]-5-methyl-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile;

4-[4-[(3S)-3-(Dimethylamino)pyrrolidine-1-carbonyl]-5-methyl-1-(1-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile;

4-[1-(3-Chloro-2-methylindazol-5-yl)-4-[(3S)-3-(dimethylamino)pyrrolidine-1-carbonyl]-5-methylimidazol-2-yl]-2-fluorobenzonitrile;

2-Fluoro-4-[5-methyl-4-[(3S)-3-(methylamino)piperidine-1-carbonyl]-1-(2-methylindazol-5-yl)imidazol-2-yl]benzonitrile;

2-Fluoro-4-[5-methyl-4-[(3R)-3-(methylamino)piperidine-1-carbonyl]-1-(2-methylindazol-5-yl)imidazol-2-yl]benzonitrile;

4-[4-[(3S)-3-(Dimethylamino)pyrrolidine-1-carbonyl]-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile;

4-[5-Chloro-4-[(3S)-3-(dimethylamino)pyrrolidine-1-carbonyl]-1-(2-methylindazol-5-yl)imidazol-2-yl]-2-fluorobenzonitrile;

4-[5-Chloro-1-(3-chloro-2-methylindazol-5-yl)-4-[(3S)-3-(dimethylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile;

4-[4-[(3S)-3-(Dimethylamino)pyrrolidine-1-carbonyl]-1-(2,3-dimethylindazol-5-yl)-5-methylimidazol-2-yl]-2-fluorobenzonitrile;

4-[1-(2,3-Dimethylindazol-5-yl)-5-methyl-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile;

2-(4-Cyano-3-fluorophenyl)-1-(2,3-dimethylindazol-5-yl)-5-methyl-N-[(3R)-piperidin-3-yl]imidazole-4-carboxamide;

4-[1-(2,3-Dimethylindazol-5-yl)-5-methyl-4-[(3R)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile;

1-(3-Chloro-2-methylindazol-5-yl)-2-(4-cyano-3-fluorophenyl)-N-[(3R)-1-methylpyrrolidin-3-yl]imidazole-4-carboxamide;

1-(3-Chloro-2-methylindazol-5-yl)-2-(4-cyano-3-fluorophenyl)-N-[(3S)-1-methylpyrrolidin-3-yl]imidazole-4-carboxamide;

2-(4-Cyano-3-fluorophenyl)-5-methyl-1-(2-methylindazol-5-yl)-N-[(3R)-1-methylpyrrolidin-3-yl]imidazole-4-carboxamide;

2-(4-Cyano-3-fluorophenyl)-5-methyl-1-(2-methylindazol-5-yl)-N-[(3S)-1-methylpyrrolidin-3-yl]imidazole-4-carboxamide;

4-[1-(3-Chloro-6-fluoro-2-methylindazol-5-yl)-4-[(3S)-3-(dimethylamino)pyrrolidine-1-carbonyl]-5-methylimidazol-2-yl]-2-fluorobenzonitrile;

4-[1-(3-Chloro-6-fluoro-2-methylindazol-5-yl)-5-methyl-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile;

4-[1-(3-Chloro-6-fluoro-2-methylindazol-5-yl)-4-[(3S)-3-(dimethylamino)pyrrolidine-1-carbonyl]-5-methylimidazol-2-yl]-2-fluorobenzonitrile;

4-[1-(3-Chloro-2-methylindazol-5-yl)-4-[(3S)-3-(methylamino)pyrrolidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile;

1-(3-Chloro-2-methylindazol-5-yl)-2-(4-cyano-3-fluorophenyl)-N-[(3R)-piperidin-3-yl]imidazole-4-carboxamide;

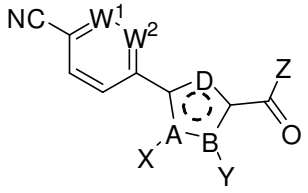
4-[1-(3-Chloro-2-methylindazol-5-yl)-4-[(3R)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile;

4-[1-(3-Chloro-2-methylindazol-5-yl)-4-[(3S)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile;

1-(3-Chloro-2-methylindazol-5-yl)-2-(4-cyano-3-fluorophenyl)-5-methyl-N-[(3R)-piperidin-3-yl]imidazole-4-carboxamide; or

4-[1-(3-Chloro-2-methylindazol-5-yl)-5-methyl-4-[(3S)-3-(methylamino)piperidine-1-carbonyl]imidazol-2-yl]-2-fluorobenzonitrile.

30. A pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof,



(I)

wherein,

A is C; B is N; and D is CH; or A is N; B is C; and D is N;

W^1 and W^2 are independently chosen from N, C-H, or C-F;

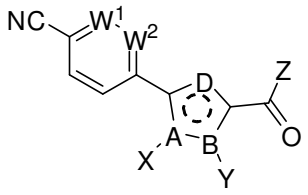
X is chosen from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclylalkyl, optionally substituted aralkyl, or optionally substituted heteroarylalkyl;

Y is chosen from hydrogen, halogen, optionally substituted alkyl, optionally substituted cycloalkyl, or optionally substituted cycloalkylalkyl; and

Z is chosen from an optionally substituted *N*-heterocyclyl, optionally substituted -N(H)-heterocyclylalkyl, optionally substituted -N(Me)-heterocyclylalkyl, or $–N(R^3)_2$, wherein each R^3 is independently chosen from hydrogen or optionally substituted alkyl, and

a pharmaceutically acceptable excipient.

31. Use of a compound of Formula (I)



(I)

wherein,

A is C; B is N; and D is CH; or A is N; B is C; and D is N;

W^1 and W^2 are independently chosen from N, C-H, or C-F;

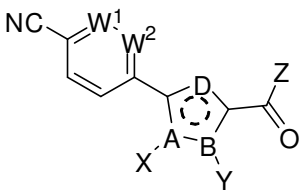
X is chosen from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclylalkyl, optionally substituted aralkyl, or optionally substituted heteroarylalkyl;

Y is chosen from hydrogen, halogen, optionally substituted alkyl, optionally substituted cycloalkyl, or optionally substituted cycloalkylalkyl; and

Z is chosen from an optionally substituted *N*-heterocyclyl, optionally substituted -N(H)-heterocyclylalkyl, optionally substituted -N(Me)-heterocyclylalkyl, or $–N(R^3)_2$, wherein each R^3 is independently chosen from hydrogen or optionally substituted alkyl,

in the manufacture of a medicament for regulating gene transcription in a cell comprising inhibiting lysine-specific demethylase 1 activity.

32. Use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof,



(I)

wherein,

A is C; B is N; and D is CH; or A is N; B is C; and D is N;

W^1 and W^2 are independently chosen from N, C-H, or C-F;

X is chosen from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclylalkyl, optionally substituted aralkyl, or optionally substituted heteroarylalkyl;

Y is chosen from hydrogen, halogen, optionally substituted alkyl, optionally substituted cycloalkyl, or optionally substituted cycloalkylalkyl; and

Z is chosen from an optionally substituted *N*-heterocyclyl, optionally substituted -N(H)-heterocyclylalkyl, optionally substituted -N(Me)-heterocyclylalkyl, or $–N(R^3)_2$; wherein each R^3 is independently chosen from hydrogen or optionally substituted alkyl,

in the manufacture of a medicament for treating acute myeloid leukemia, breast or prostate cancer in a patient in need thereof.