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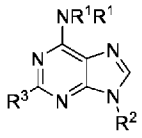
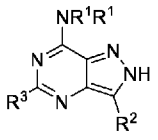
(54) Title: LIGANDS OF THE M6A-RNA READERS



(I)



(II)

(57) Abstract: The present invention relates to a compound of formula (I) or (II), (I), (II) for use as a medicament in the treatment of cancer.

Ligands of the m6A-RNA readers

Cross-Reference to Related Applications

This application claims the benefit of EP Patent Application No. 22207923.8, filed on November 16, 2022, which is incorporated herein by reference in its entirety.

Field

The present invention relates to a compound for use as a ligand of m6a-RNA readers.

Background

N6-Methyladenosine (m6A) is an abundant modification in mRNA and DNA. It is found within some viruses, and most eukaryotes including mammals, insects, plants and yeast. It is also found in tRNA, rRNA, and small nuclear RNA (snRNA) as well as several long non-coding RNA, such as Xist. The biological functions of m6A are mediated through a group of RNA binding proteins that specifically recognize the methylated adenosine on RNA. These binding proteins are named m6A readers. The YT521-B homology (YTH) domain family of proteins (YTHDF1, YTHDF2, YTHDF3 and YTHDC1) have been characterized as direct m6A readers and have a conserved m6A-binding pocket. YTH domain-containing protein 1 is a protein that in humans is encoded by the YTHDC1 gene. YTHDC1 is a nuclear protein involved in splice site selection that localises to YT bodies; dynamic subnuclear compartments, which first appear at the beginning of S-phase in the cell cycle and disperse during mitosis. Alternative splicing, however is known to be altered in a number of diseases and is particularly relevant to cancer. YTHDC1 has been shown to splice mRNA transcripts which have oncological importance, regulating tumour functions such as hypoxia associated vascular endothelial growth factor (VEGF), DNA damage associated breast cancer 1 (BRCA1) and hormonal growth driver; the progesterone receptor (PGR). It has further been shown that YTHDC1 is overexpressed in acute myeloid leukemia (AML) and that it is required for the proliferation and survival of AML cells, while knockout of YTHDC1 blocks AML development and maintenance as well as self-renewal of leukemia stem cells (LSCs) in vivo.

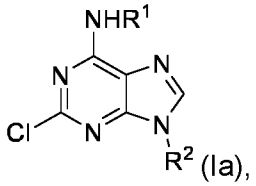
However, there are no potent YTHDC1 inhibitors known, much less with sufficient efficacy for the treatment of cancer.

Based on the above-mentioned state of the art, the objective of the present invention is to provide novel ligands of m6A-RNA readers, particularly of YTDC1. This objective is attained by the subject-matter of the independent claims of the present disclosure, with further

advantageous embodiments described in the dependent claims, examples, figures and general description of this specification.

Summary

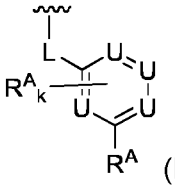
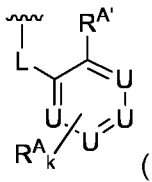
In some embodiments, disclosed herein is a compound of formula (Ia), or a pharmaceutically acceptable salt thereof,


(Ia),

wherein

R^1 is -C_1-C_3-alkyl;

R^2 is -L-A or a moiety of formula (IIIb) or (IIIc),


(IIIb),

(IIIc),

each R^A is independently selected from halogen, -CN, -NO_2, -OH, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -C(=O)O-C_1-C_3-alkyl, -C(=O)OH, -O-C_1-C_3-alkyl, -C(=O)-NR^6R^6, -C(=O)-C_1-C_3-alkyl, -NR^6R^6, -NH-SO_2-C_1-C_3-alkyl, -NH-SO_2-$(CH_2)_s$-OH, -NH-SO_2-$(CH_2)_s$-R^7, -SO_2-NH-R^7, -$SO_2NR^6R^6$, -$(CH_2)_s$-R^8, -$(CH_2)_s$-cycloalkyl, -$(CH_2)_s$-aryl, -$(CH_2)_s$-heteroaryl, and -$(CH_2)_s$-heterocycloalkyl; wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, or 3 R;

$R^{A'}$ is selected from -CN, -NO_2, -OH, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -C(=O)O-C_1-C_3-alkyl, -C(=O)OH, -O-C_1-C_3-alkyl, -C(=O)-NR^6R^6, -C(=O)-C_1-C_3-alkyl, -NR^6R^6, -NH-SO_2-C_1-C_3-alkyl, -NH-SO_2-$(CH_2)_s$-OH, -NH-SO_2-$(CH_2)_s$-R^7, -SO_2-NH-R^7, -$SO_2NR^6R^6$, -$(CH_2)_s$-R^8, -$(CH_2)_s$-cycloalkyl, -$(CH_2)_s$-aryl, -$(CH_2)_s$-heteroaryl, and -$(CH_2)_s$-heterocycloalkyl; wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, or 3 R;

each R is independently halogen, -CN, -OH, oxo, -S(=O)CH_3, -$S(=O)_2CH_3$, -$S(=O)_2NH_2$, -$S(=O)_2OH$, -$S(=O)_2NHCH_3$, -$S(=O)_2N(CH_3)_2$, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -C(=O)CH_3, -C(=O)OH, -C(=O)OCH_3, C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, or C_3-C_6cycloalkyl;

k is 0, 1, 2, or 3;

L is -$(CH_2)_n$- or –$(CH_2)_n$-Y-,

n is 0, 1, 2 or 3;

wherein Y is selected from -O-, -S-, -SO_2-, -NH- and -C(=O)-NH-;

A is a bicyclic aryl, bicyclic cycloalkyl, or bicyclic heterocycle, each of which is unsubstituted or substituted with 1, 2, 3 or 4 R^A;

each U is independently CH or N;

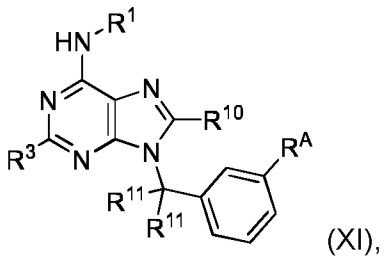
each R^6 is independently selected from -H, -C(=O)-O-tert-butyl, -C_1-C_3-alkyl, and -C(=O)-CF_3;

s is 0, 1, 2, or 3;

R^7 is aryl or five or six-membered heterocycle, each of which is optionally substituted with 1, 2, or 3 R; and

R^8 is a four or five membered ring, each of which is optionally substituted with 1, 2, or 3 R.

In some embodiments, disclosed herein is a compound of formula (XI), or a pharmaceutically acceptable salt thereof,



(XI),

wherein

R^1 is C_1-C_3-alkyl;

R^3 is selected from -Br, -Cl, -NO_2, CN, -O-C_1-C_3-alkyl, C_1-C_3-alkyl, C_2-C_3-haloalkyl, -NR^6R^6, -OH, -CH_2F, and -CHF_2;

each R^A is independently selected from halogen, -CN, -NO_2, -OH, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -C(=O)O-C_1-C_3-alkyl, -C(=O)O-$(CH_2)_s$-R^7, -C(=O)OH, -O-C_1-C_3-alkyl, -C(=O)-NR^6R^6, -NR^6R^6, -NH-SO_2-C_1-C_3-alkyl, -NH-SO_2-$(CH_2)_s$-R^7, -SO_2-NH-R^7, -$SO_2NR^6R^6$, -$(CH_2)_s$-R^8, -$(CH_2)_s$-cycloalkyl, -$(CH_2)_s$-aryl, -$(CH_2)_s$-heteroaryl, or -$(CH_2)_s$-heterocycloalkyl; wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, or 3 R;

each R is independently halogen, -CN, -OH, oxo, -S(=O)CH_3, -$S(=O)_2CH_3$, -$S(=O)_2NH_2$, -$S(=O)_2OH$, -$S(=O)_2NHCH_3$, -$S(=O)_2N(CH_3)_2$, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -C(=O)CH_3, -C(=O)OH, -C(=O)OCH_3, C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, or C_3-C_6cycloalkyl;

each R^6 is independently selected from -H, -C(=O)-O-tert-butyl, -C_1-C_3-alkyl, and -C(=O)-CF_3;

s is 0, 1, 2, or 3;

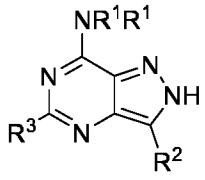
R^7 is aryl or five or six-membered heterocycle, each of which is optionally substituted with 1, 2, or 3 R;

R^8 is a four or five membered ring, each of which is optionally substituted with 1, 2, or 3 R;

R^{10} is -CN, -NO_2, -OH, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -C(=O)O-C_1-C_3-alkyl, -C(=O)-C_1-C_3-alkyl, -C(=O)OH, -O-C_1-C_3-alkyl, -C(=O)-NR^6R^6, -NR^6R^6, -NH-SO_2-C_1-C_3-alkyl, -NH-SO_2-$(CH_2)_s$-R^7, or -$SO_2NR^6R^6$, wherein the alkyl is optionally substituted with 1, 2, or 3 R; and

R^{11} is selected from -H, -F, -Br, -Cl, -CN, -C_1-C_3-alkyl, and NO_2.

In some embodiments, disclosed herein is a compound of formula (II), or a pharmaceutically acceptable salt thereof,



(II),

wherein

each R^1 is independently selected from -H and -C_1-C_3-alkyl, R^3 is selected from -F, -Cl, -Br, -CN, -NO_2, C_1-C_3-haloalkyl, and -NR^6R^6; R^2 is C_1-C_3-alkyl or -L-A;

A is an aryl, heteroaryl, cycloalkyl, or a nitrogen-containing heterocycloalkyl, each of which is unsubstituted or substituted with 1, 2, 3, or 4 R^A;

each R^A is independently selected from halogen, -CN, -NO_2, -OH, C_1-C_6alkyl, C_1-C_3-haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_3heteroalkyl, -C(=O)O-C_1-C_3-alkyl, -C(=O)-C_1-C_3-alkyl, -C(=O)OH, -O-C_1-C_3-alkyl, -C(=O)-NR^6R^6, -NR^6R^6, -NH-SO_2-C_1-C_3-alkyl, -NH-SO_2-$(CH_2)_s$-OH, -NH-SO_2-$(CH_2)_s$-R^7, -SO_2-NH-R^7, -$SO_2NR^6R^6$, and -$(CH_2)_s$-R^8; wherein the alkyl is optionally substituted with 1, 2, or 3 R;

each R^6 is independently selected from -H, -C(=O)-O-tert-butyl, -C_1-C_3-alkyl, and -C(=O)-CF_3;

R^7 is aryl or five or six-membered heterocycle, each of which is optionally substituted with 1, 2, or 3 R;

R^8 is a four or five membered ring, each of which is optionally substituted with 1, 2, or 3 R;

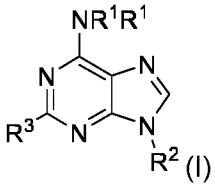
L is $–(CH_2)_n$- or -Y-$(CH_2)_n$-, wherein Y is selected from -O-, -S-, $-SO_2$-, -NH- and -C(=O)-NH-;

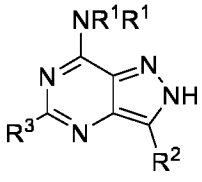
each R is independently halogen, -CN, -OH, oxo, $-S(=O)CH_3$, $-S(=O)_2CH_3$, $-S(=O)_2NH_2$, $-S(=O)_2NHCH_3$, $-S(=O)_2N(CH_3)_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-C(=O)CH_3$, -C(=O)OH, $-C(=O)OCH_3$, C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, or C_3-C_6cycloalkyl;

n is 0, 1, 2, or 3; and

s is 0 to 3.

One aspect of the invention relates to a compound of formula (I) or (II), particularly of (I)


(I)

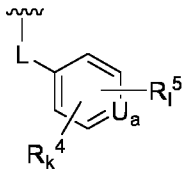

(II),

wherein

R^1 is independently selected from -H and -C_1-C_3-alkyl, particularly -H and -Me or cyclopropyl, more particularly -H and -Me, wherein at least one of R^1 is H,

R^3 is selected from -Br, -Cl, -CN, -F and $-NO_2$, particularly -Cl,

R^2 is selected from -C_1-C_3-alkyl and a moiety of formula (III) or (IV), particularly R^2 is a moiety of formula (III) or (IV),

- 
(III), wherein

L of formula (I) is a linker comprising -$(CH_2)_n$- or $–(CH_2)_n$-Y- and L of formula (II) is a linker comprising $–(CH_2)_n$- or -Y-$(CH_2)_n$-, wherein Y is selected from -O-, -S-, $-SO_2$-, -NH- and -C(=O)-NH-, and

n is 0 to 3, k is 0 to 3, particularly 0 to 2, more particularly 1 or 2, l is 0 or 1,

U is CH or a heteroatom, particularly CH or N, more particularly CH,

a is 0 or 1, particularly 1,

R^4 is independently selected from

- -Cl, -Br, $-CH_2F$, $-CHF_2$, $-CF_3$ and
- -C(=O)O-C_1-C_3-alkyl, -C(=O)OH, -O-C_1-C_3-alkyl, -C(=O)-NR^6R^6, -C_1-C_3-alkyl-OH, and

- -NR^6R^6,

wherein R^6 is independently selected from

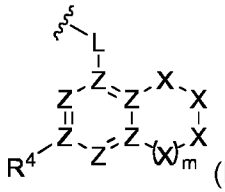
- -H, -C(=O)-O-tert-butyl, -C_1-C_3-alkyl, and -C(=O)-CF_3, particularly from -H and Me,

R^5 is selected from

- -NH-SO_2-C_1-C_3-alkyl, -NH-SO_2-$(CH_2)_s$-OH and
- -NH-SO_2-$(CH_2)_s$-R^7, wherein R^7 is selected from an aryl and a heterocycle, wherein the heterocycle is a five or six-membered heterocycle and wherein the heterocycle is an aliphatic heterocycle or an aromatic heterocycle, and
- -$(CH_2)_s$-R^8, wherein R^8 is a four or five membered ring,

s is 0 to 3,

or

-  (IV), wherein

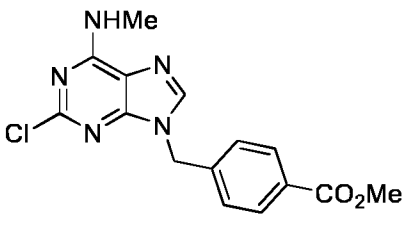
L of formula (I) is a linker comprising -$(CH_2)_n$- or –$(CH_2)_n$-Y- and L of formula (II) is a linker comprising –$(CH_2)_n$- or -Y-$(CH_2)_n$-, wherein Y is selected from -O-, -S-, -SO_2-, -NH- and -C(=O)-NH-, and

n is 0 to 3, m is 0 or 1,

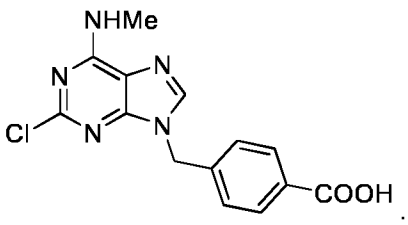
each X and Z are selected from C, NR^3 , SO_2 and O, wherein R^3 is -H or -C_1-C_3-alkyl-NH_2 and wherein Z is particularly C,

R^4 is defined as above,

with the exception of



and



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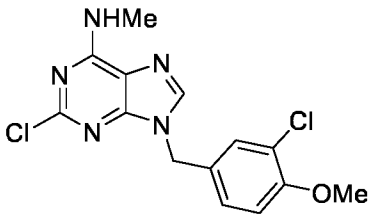
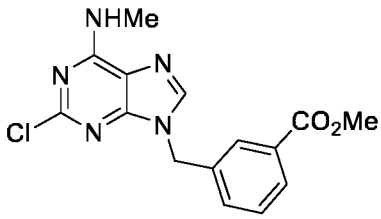
Another aspect of the invention relates to a compound selected from any one of (V) to (XI) for use as a medicament


(V),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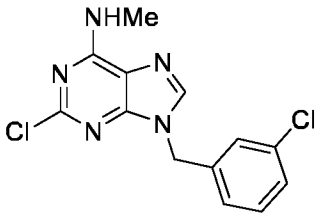
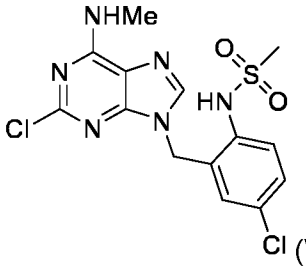
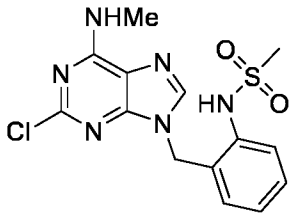
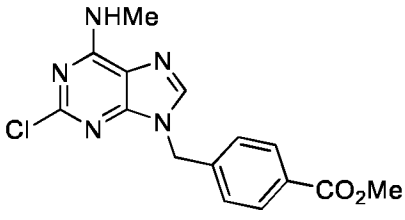
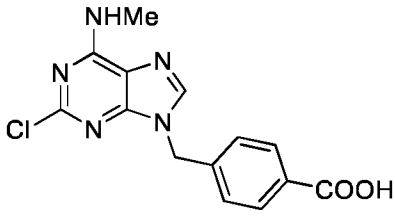

(VII),


(VIII),


(IX)


(X),


(XI).

Another aspect of the invention relates to a compound described herein for use in the treatment of a disease, wherein the disease is cancer.

Terms and definitions

For purposes of interpreting this specification, the following definitions will apply and whenever appropriate, terms used in the singular will also include the plural and vice versa. In the eventthat any definition set forth below conflicts with any document incorporated herein by reference, the definition set forth shall control.

The terms “comprising”, “having”, “containing”, and “including”, and other similar forms, and grammatical equivalents thereof, as used herein, are intended to be equivalent in meaning and to be open-ended in that an item or items following any one of these words is not meant to be an exhaustive listing of such item or items, or meant to be limited to only the listed item or items. For example, an article “comprising” components A, B, and C can consist of (i.e., contain only) components A, B, and C, or can contain not only components A, B, and C but also one or more other components. As such, it is intended and understood that “comprises” and similar forms thereof, and grammatical equivalents thereof, include disclosure of embodiments of “consisting essentially of” or “consisting of.”

Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit, unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range, is encompassed within the disclosure, subject to any specifically excluded limit in the stated

range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the disclosure.

Reference to “about” a value or parameter herein includes (and describes) variations that are directed to that value or parameter per se. For example, description referring to “about X” includes description of “X.”

As used herein, including in the appended claims, the singular forms “a”, “or” and “the” include plural referents unless the context clearly dictates otherwise.

"And/or" where used herein is to be taken as specific recitation of each of the two specified features or components with or without the other. Thus, the term "and/or" as used in a phrase such as "A and/or B" herein is intended to include "A and B," "A or B," "A" (alone), and "B" (alone). Likewise, the term "and/or" as used in a phrase such as "A, B, and/or C" is intended to encompass each of the following aspects: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art (e.g., in cell culture, molecular genetics, nucleic acid chemistry, hybridization techniques and biochemistry, organic synthesis). Standard techniques are used for molecular, genetic, and biochemical methods (see generally, Sambrook et al., Molecular Cloning: A Laboratory Manual, 4th ed. (2012) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. and Ausubel et al., Short Protocols in Molecular Biology (2002) 5th Ed, John Wiley & Sons, Inc.) and chemical methods.

The term *TR-FRET* in the context of the present disclosure relates to time-resolved fluorescence energy transfer.

The term *TSA* in the context of the present disclosure relates to thermal shift assay which measures the thermal denaturation temperature and hence stability of a protein under varying conditions such as variations in drug concentration, buffer pH, ionic strength, redox potential or sequence mutation. The thermal denaturation temperature is measured via differential scanning fluorimetry (DSF) using specialised fluorogenic dyes. The binding of low molecular weight ligands can increase the thermal stability of a protein.

The term IC_{50} in the context of the present disclosure relates to the half maximal inhibitory concentration which states the potency if a substance in inhibiting a specific biochemical function. IC_{50} is a quantitative measure that indicates the concentration of a particular inhibitor required to inhibit a biological process or biological component by 50%.

The term GI_{50} in the context of the present disclosure relates to the half maximal growth inhibition. GI_{50} is a quantitative measure that indicates the concentration of a particular inhibitor required to inhibit the cell proliferation by 50%.

Any patent document cited herein shall be deemed incorporated by reference herein in its entirety.

The term *alkyl* in the context of the present disclosure relates to a saturated linear or branched hydrocarbon, or unsaturated linear or branched hydrocarbon.

The term *cycloalkyl* in the context of the present disclosure relates to a partially or fully saturated, monocyclic, or polycyclic carbocyclic ring, which may include fused (when fused with an aryl or a heteroaryl ring, the cycloalkyl is bonded through a non-aromatic ring atom), spiro, or bridged ring systems. In some embodiments, the cycloalkyl is fully saturated. Representative cycloalkyls include, but are not limited to, cycloalkyls having from three to fifteen carbon atoms (C_3-C_{15} fully saturated cycloalkyl or C_3-C_{15} cycloalkenyl), from three to ten carbon atoms (C_3-C_{10} fully saturated cycloalkyl or C_3-C_{10} cycloalkenyl), from three to eight carbon atoms (C_3-C_8 fully saturated cycloalkyl or C_3-C_8 cycloalkenyl), from three to six carbon atoms (C_3-C_6 fully saturated cycloalkyl or C_3-C_6 cycloalkenyl), from three to five carbon atoms (C_3-C_5 fully saturated cycloalkyl or C_3-C_5 cycloalkenyl), or three to four carbon atoms (C_3-C_4 fully saturated cycloalkyl or C_3-C_4 cycloalkenyl). In some embodiments, the cycloalkyl is a 3- to 10-membered fully saturated cycloalkyl or a 3- to 10-membered cycloalkenyl. In some embodiments, the cycloalkyl is a 3- to 6-membered fully saturated cycloalkyl or a 3- to 6-membered cycloalkenyl. In some embodiments, the cycloalkyl is a 5- to 6-membered fully saturated cycloalkyl or a 5- to 6-membered cycloalkenyl. Monocyclic cycloalkyls include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyls include, for example, adamantyl, norbornyl, decalinyl, bicyclo[3.3.0]octane, bicyclo[4.3.0]nonane, cis-decalin, trans-decalin, bicyclo[2.1.1]hexane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, and bicyclo[3.3.2]decane, and 7,7-dimethyl-bicyclo[2.2.1]heptanyl. Partially saturated cycloalkyls include, for example cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl.

The term C_3-C_6cycloalkyl in the context of the present disclosure refers to cycloalkyl having three to six carbon atoms (C_3-C_6 fully saturated cycloalkyl or C_3-C_6 cycloalkenyl).

The term *C_1-C_3 alkyl* in the context of the present disclosure relates to a saturated linear or branched hydrocarbon having 1, 2 or 3 carbon atoms. Non-limiting examples for a C_1-C_3 alkyl are methyl, ethyl, propyl, and prop-2-enyl, cyclopropyl. In certain embodiments, a C_1-C_3 alkyl is a methyl, ethyl or propyl moiety. In some embodiments, the alkyl is a linear alkyl. In some embodiments, the alkyl is a branched alkyl.

Where used in the context of chemical formulae, the following abbreviations may be used: *Me* is methyl CH_3, *Et* is ethyl -CH_2CH_3, *Prop* is propyl (including –$(CH_2)_2CH_3$ (n-propyl, n-pr) or -$CH(CH_3)_2$ (iso-propyl, i-pr)), *but* is butyl -C_4H_9 (including -$(CH_2)_3CH_3$, -$CHCH_3CH_2CH_3$, -$CH_2CH(CH_3)_2$ or -$C(CH_3)_3$).

The term *haloalkyl* in the context of the present disclosure refers to alkyl, as defined above, that is substituted by one or more halo radicals, *e.g.*, trifluoromethyl, difluoromethyl, fluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like.

The term *hydroxyalkyl* in the context of the present disclosure refers to alkyl, as defined above, that is substituted by one or more hydroxyls. In some embodiments, the alkyl is substituted with one hydroxyl. In some embodiments, the alkyl is substituted with one, two, or three hydroxyls. Hydroxyalkyl include, for example, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, or hydroxypentyl. In some embodiments, the hydroxyalkyl is hydroxymethyl.

The term *aminoalkyl* in the context of the present disclosure refers to alkyl, as defined above, that is substituted by one or more amines. In some embodiments, the alkyl is substituted with one amine. In some embodiments, the alkyl is substituted with one, two, or three amines. Aminoalkyl include, for example, aminomethyl, aminoethyl, aminopropyl, aminobutyl, or aminopentyl. In some embodiments, the aminoalkyl is aminomethyl.

The term *heteroalkyl* in the context of the present disclosure refers to alkyl, as defined above, in which one or more skeletal atoms of the alkyl are selected from an atom other than carbon, e.g., oxygen, nitrogen (e.g., -NH-, -N(alkyl)-), sulfur, phosphorus, or combinations thereof. A heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. In one aspect, a heteroalkyl is a C_1-C_6 heteroalkyl wherein the heteroalkyl is comprised of 1 to 6 carbon atoms and one or more atoms other than carbon, e.g., oxygen, nitrogen (e.g. -NH-, -N(alkyl)-), sulfur, phosphorus, or combinations thereof wherein the heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. Examples of such heteroalkyl are, for example, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, $-CH_2CH_2OCH_2CH_2OCH_3$, $-CH(CH_3)OCH_3$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CH_2CH_2NHCH_3$, or $-CH_2CH_2N(CH_3)_2$.

In the context of the present disclosure, the term alkyl also comprises unsaturated hydrocarbons like alkene and alkyne.

The term *alkene* in the context of the present disclosure relates to a hydrocarbon comprising a double bond. Unsubstituted alkene is of formula -CH=CH- when being located intramolecularly, and of formula $-CH=CH_2$ when being a terminal moiety. An unsubstituted alkene consists of C and H only. A substituted alkene may comprise substituents as defined herein for substituted alkyl.

The term *alkyne* in the context of the present disclosure relates to a hydrocarbon comprising a triple bond. Unsubstituted alkyne is of formula -CΞC- when being located intramolecularly, and of formula -CΞCH (-C_2H) when being a terminal moiety. An unsubstituted alkyne consists

of C and H only. A substituted alkyne may comprise substituents as defined herein for substituted alkyl.

The term *aryl* in the context of the present disclosure relates to a cyclic aromatic C_5-C_{10} hydrocarbon. Examples of aryl include, without being restricted to, phenyl and naphthyl.

The term *halo* or *halogen* in the context of the present disclosure refers to bromo, chloro, fluoro or iodo. In some embodiments, halogen is fluoro or chloro. In some embodiments, halogen is fluoro.The term *heterocycle* in the context of the present disclosure relates to a cyclic aromatic or aliphatic C_3-C_9 hydrocarbon that comprises at least one heteroatom (e.g. N, O, S). Examples for heteroaryl include, without being restricted to, pyrrole, thiophene, furan, imidazole, pyrazole, thiazole, oxazole, pyridine, pyrimidine, thiazin, quinoline, benzofuran and indole. In some embodiments, the heterocycle is a heteroaryl. In some embodiments, the heterocycle is a heterocycloalkyl.The term *heteroaryl* in the context of the present disclosure relates to a 5- to 14-membered ring system radical comprising one to thirteen carbon atoms, one to six heteroatoms selected from the group consisting of nitrogen, oxygen, phosphorous, and sulfur, and at least one aromatic ring. In some embodiments, the heteroaryl comprises one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur. In some embodiments, the heteroaryl comprises one to three heteroatoms selected from the group consisting of nitrogen and oxygen. In some embodiments, the heteroaryl comprises one to three nitrogens. In some embodiments, the heteroaryl comprises one or two nitrogens. In some embodiments, the heteroaryl comprises one nitrogen. The heteroaryl radical may be a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may include fused (when fused with a cycloalkyl or heterocycloalkyl ring, the heteroaryl is bonded through an aromatic ring atom) or bridged ring systems; and the nitrogen, carbon, or sulfur atoms in the heteroaryl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. In some embodiments, the heteroaryl is a 5- to 10-membered heteroaryl. In some embodiments, the heteroaryl is a 5- to 6-membered heteroaryl. In some embodiments, the heteroaryl is a 6-membered heteroaryl. In some embodiments, the heteroaryl is a 5-membered heteroaryl. Examples include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzodioxolyl, benzofuranyl, benzooxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[b][1,4]dioxepinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, isothiazolyl, imidazolyl, indazolyl, indolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, 1-phenyl-1H-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl,

pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, tetrahydroquinolinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, and thiophenyl (i.e., thienyl).The term *heterocycloalkyl* in the context of the present disclosure relates refers to a 3- to 24-membered partially or fully saturated ring radical comprising 2 to 23 carbon atoms and from one to 8 heteroatoms selected from the group consisting of nitrogen, oxygen, phosphorous, silicon, and sulfur. In some embodiments, the heterocycloalkyl is fully saturated. In some embodiments, the heterocycloalkyl comprises one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur. In some embodiments, the heterocycloalkyl comprises one to three heteroatoms selected from the group consisting of nitrogen and oxygen. In some embodiments, the heterocycloalkyl comprises one to three nitrogens. In some embodiments, the heterocycloalkyl comprises one or two nitrogens. In some embodiments, the heterocycloalkyl comprises one nitrogen. In some embodiments, the heterocycloalkyl comprises one nitrogen and one oxygen. Unless stated otherwise specifically in the specification, the heterocycloalkyl radical may be a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may include fused (when fused with an aryl or a heteroaryl ring, the heterocycloalkyl is bonded through a non-aromatic ring atom), spiro, or bridged ring systems; and the nitrogen, carbon, or sulfur atoms in the heterocycloalkyl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. Representative heterocycloalkyls include, but are not limited to, heterocycloalkyls having from two to fifteen carbon atoms (C_2-C_{15} fully saturated heterocycloalkyl or C_2-C_{15} heterocycloalkenyl), from two to ten carbon atoms (C_2-C_{10} fully saturated heterocycloalkyl or C_2-C_{10} heterocycloalkenyl), from two to eight carbon atoms (C_2-C_8 fully saturated heterocycloalkyl or C_2-C_8 heterocycloalkenyl), from two to seven carbon atoms (C_2-C_7 fully saturated heterocycloalkyl or C_2-C_7 heterocycloalkenyl), from two to six carbon atoms (C_2-C_6 fully saturated heterocycloalkyl or C_2-C_6 heterocycloalkenyl), from two to five carbon atoms (C_2-C_5 fully saturated heterocycloalkyl or C_2-C_5 heterocycloalkenyl), or two to four carbon atoms (C_2-C_4 fully saturated heterocycloalkyl or C_2-C_4 heterocycloalkenyl). Examples of such heterocycloalkyl radicals include, but are not limited to, aziridinyl, azetidinyl, oxetanyl, 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, 1,1-dioxo-thiomorpholinyl, 1,3-dihydroisobenzofuran-1-yl, 3-oxo-1,3-dihydroisobenzofuran-1-yl, methyl-2-oxo-1,3-dioxol-4-yl, and 2-oxo-1,3-dioxol-4-yl. The term heterocycloalkyl also includes all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides, and the oligosaccharides. In some embodiments, heterocycloalkyls have from 2 to 10 carbons in the ring. It is understood that when referring to

the number of carbon atoms in a heterocycloalkyl, the number of carbon atoms in the heterocycloalkyl is not the same as the total number of atoms (including the heteroatoms) that make up the heterocycloalkyl (i.e. skeletal atoms of the heterocycloalkyl ring). In some embodiments, the heterocycloalkyl is a 3- to 8-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 3- to 7-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 3- to 6-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 3- to 8-membered heterocycloalkenyl.

The term *oxo* in the context of the present disclosure refers to =O.

The term *cyano* in the context of the present disclosure refers to -CN.

The term *carboxyl* in the context of the present disclosure refers to -COOH.

The term "optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted alkyl" means either "alkyl" or "substituted alkyl" as defined above. Further, an optionally substituted group may be un-substituted (e.g., $-CH_2CH_3$), fully substituted (e.g., $-CF_2CF_3$), mono-substituted (e.g., $-CH_2CH_2F$) or substituted at a level anywhere in-between fully substituted and mono-substituted (e.g., $-CH_2CHF_2$, $-CH_2CF_3$, $-CF_2CH_3$, $-CFHCHF_2$, etc.). It will be understood by those skilled in the art with respect to any group containing one or more substituents that such groups are not intended to introduce any substitution or substitution patterns that are sterically impractical and/or synthetically non-feasible. Thus, any substituents described should generally be understood as having a maximum molecular weight of about 1,000 daltons, and more typically, up to about 500 daltons.

As used herein, the term *pharmaceutically acceptable carrier* includes any solvents, dispersion media, coatings, surfactants, antioxidants, preservatives (for example, antibacterial agents, antifungal agents), isotonic agents, absorption delaying agents, salts, preservatives, drugs, drug stabilizers, binders, excipients, disintegration agents, lubricants, sweetening agents, flavoring agents, dyes, and the like and combinations thereof, as would be known to those skilled in the art (see, for example, Remington: the Science and Practice of Pharmacy, ISBN 0857110624).

The term *cancer* as used in the context of the present disclosure relates to malignant neoplastic disease; the terms "cancer" and "malignant neoplastic disease" are used synonymously herein. They specifically include carcinoma (epithelial derived cancer), sarcoma (connective tissue derived cancer), lymphoma and leukemia, germ-cell derived tumours and blastomas. Particular alternatives of any of the aspects and embodiments disclosed herein are directed at the use of the compounds and compositions of the invention in treatment of solid tumours.

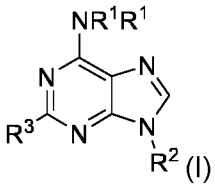
Other alternatives of any of the aspects and embodiments disclosed herein are directed at the use of the combinations of the invention in treatment of cancers such as renal cancer, breast cancer, acute myeloid leukemia, hepatocellular carcinoma, and lung adenocarcinoma.

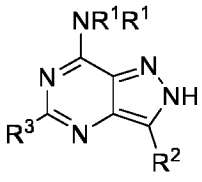
The term *inhibitor* in the context of the present disclosure relates to any pharmaceutically acceptable agent or compound that may be used to interact with and specifically interfere with the biological activity of its designated target, in case of the present invention YTH protein domain, particularly ZTH domain-containing protein 1 (YTHDC1).

As used herein, the term *treating* or *treatment* of any disease or disorder (e.g. cancer) refers in one embodiment, to ameliorating the disease or disorder (e.g. slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment "treating" or "treatment" refers to alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient. In yet another embodiment, "treating" or "treatment" refers to modulating the disease or disorder, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both. Methods for assessing treatment and/or prevention of disease are generally known in the art, unless specifically described herein below.

Detailed Description

One aspect of the invention relates to a compound of formula (I) or (II), particularly of (I)


(I)

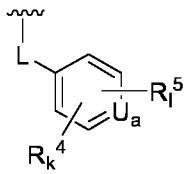

(II),

wherein

R^1 is independently selected from -H and -C_1-C_3-alkyl, particularly -H and -Me or cyclopropyl, more particularly -H and -Me, wherein at least one of R^1 is H,

R^3 is selected from -Br, -Cl, -CN, -F and -NO_2, particularly -Cl,

R^2 is selected from -C_1-C_3-alkyl and a moiety of formula (III) or (IV), particularly R^2 is a moiety of formula (III) or (IV),


(III), wherein

L of formula (I) is a linker comprising -$(CH_2)_n$- or –$(CH_2)_n$-Y- and

L of formula (II) is a linker comprising $-(CH_2)_n-$ or $-Y-(CH_2)_n-$, wherein Y is selected from -O-, -S-, $-SO_2-$, -NH- and -C(=O)-NH-, and

n is 0 to 3, k is 0 to 3, particularly 0 to 2, more particularly 1 or 2,

l is 0 or 1,

U is CH or a heteroatom, particularly CH or N, more particularly CH,

a is 0 or 1, particularly 1,

R^4 is independently selected from

- -Cl, -Br, $-CH_2F$, $-CHF_2$, $-CF_3$ and
- $-C(=O)O-C_1-C_3$-alkyl, -C(=O)OH, $-O-C_1-C_3$-alkyl, $-C(=O)-NR^6R^6$, $-C_1-C_3$-alkyl-OH, and
- $-NR^6R^6$,

wherein R^6 is independently selected from

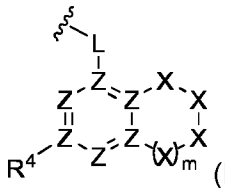
- -H, $-C(=O)-O$-tert-butyl, $-C_1-C_3$-alkyl, and $-C(=O)-CF_3$, particularly from -H and Me,

R^5 is selected from

- $-NH-SO_2-C_1-C_3$-alkyl, $-NH-SO_2-(CH_2)_s$-OH and
- $-NH-SO_2-(CH_2)_s-R^7$, wherein R^7 is selected from an aryl and a heterocycle, wherein the heterocycle is a five or six-membered heterocycle and wherein the heterocycle is an aliphatic heterocycle or an aromatic heterocycle, and
- $-(CH_2)_s-R^8$, wherein R^8 is a four or five membered ring,

s is 0 to 3,

or

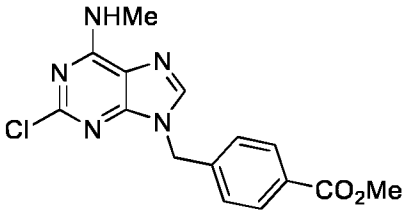
-  (IV), wherein

L of formula (I) is a linker comprising $-(CH_2)_n-$ or $-(CH_2)_n-Y-$ and L of formula (II) is a linker comprising $-(CH_2)_n-$ or $-Y-(CH_2)_n-$, wherein Y is selected from -O-, -S-, $-SO_2-$, -NH- and -C(=O)-NH-, and

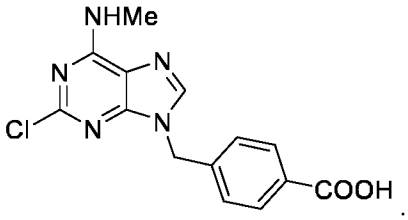
n is 0 to 3, m is 0 or 1,

each X and Z are selected from C, NR^3 , SO_2 and O, wherein R^3 is -H or -C_1-C_3-alkyl-NH_2 and wherein Z is particularly C,
R^4 is defined as above,

with the exception of



and



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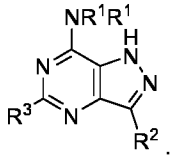
Formula (II) includes all resonance structures of said formula, e.g.



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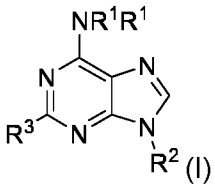
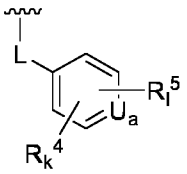
In certain embodiments, the compound is a compound of formula (I)



(I)

wherein

R^1 is independently selected from -H and -C_1-C_3-alkyl, particularly -H and -Me or cyclopropyl, more particularly -H and -Me, wherein at least one of R^1 is H,
R^3 is selected from -Br, -Cl, -CN, -F and -NO_2, particularly -Cl,
R^2 is selected from -C_1-C_3-alkyl and a moiety of formula (III) or (IV), particularly R^2 is a moiety of formula (III) or (IV),

- 

(III), wherein

L is a linker comprising -$(CH_2)_n$- or –$(CH_2)_n$-Y- wherein Y is selected from -O-, -S-, -SO_2-, -NH- and -C(=O)-NH-, and
n is 0 to 3, k is 0 to 3, particularly 0 to 2, more particularly 1 or 2,
l is 0 or 1,
U is CH or a heteroatom, particularly CH or N, more particularly CH,
a is 0 or 1, particularly 1,
R^4 is independently selected from

- -Cl, -Br, -CH_2F, -CHF_2, -CF_3 and
- -C(=O)O-C_1-C_3-alkyl, -C(=O)OH, -O-C_1-C_3-alkyl, -C(=O)-NR^6R^6, -C_1-C_3-alkyl-OH, and
- -NR^6R^6,

wherein R^6 is independently selected from

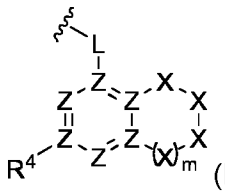
- -H, -C(=O)-O-tert-butyl, -C_1-C_3-alkyl, and -C(=O)-CF_3, particularly from -H and Me,

R^5 is selected from

- -NH-SO_2-C_1-C_3-alkyl, -NH-SO_2-$(CH_2)_s$-OH and
- -NH-SO_2-$(CH_2)_s$-R^7, wherein R^7 is selected from an aryl and a heterocycle, wherein the heterocycle is a five or six-membered heterocycle and wherein the heterocycle is an aliphatic heterocycle or an aromatic heterocycle, and
- -$(CH_2)_s$-R^8, wherein R^8 is a four or five membered ring,

s is 0 to 3,

or

-  (IV), wherein

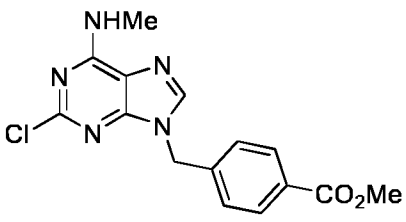
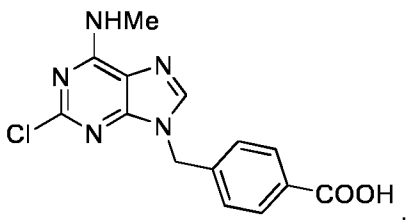
L is a linker comprising -$(CH_2)_n$- or –$(CH_2)_n$-Y- and

wherein Y is selected from -O-, -S-, -SO_2-, -NH- and -C(=O)-NH-, and n is 0 to 3, m is 0 or 1,

each X and Z are selected from C, NR^3 , SO_2 and O, wherein R^3 is -H or -C_1-C_3-alkyl-NH_2 and wherein Z is particularly C,

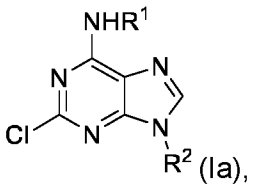
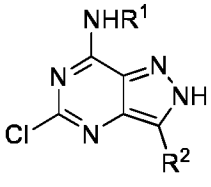
R^4 is defined as above,

with the exception of

 and  .

In certain embodiments, R^2 is a moiety of formula (III) or (IV).

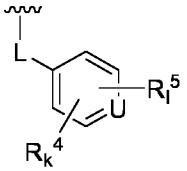
In certain embodiments the compound is a compound of formula (Ia) or (IIa), particularly of (Ia)


(Ia),

(IIa)

wherein

R^1 is selected from -H and -C_1-C_3-alkyl, particularly -H and -Me or cyclopropyl, more particularly -Me,

R^2 is selected from -C_1-C_3-alkyl and a moiety of formula (IIIa) or (IVa), particularly R^2 is a moiety of formula (IIIa) or (IVa),

- 
(IIIa),

wherein

L of formula (I) is a linker comprising -$(CH_2)_n$- or –$(CH_2)_n$-Y- and L of formula (II) is a linker comprising –$(CH_2)_n$- or -Y-$(CH_2)_n$-, wherein Y is selected from -O-, -S-, -SO_2-, -NH- and -C(=O)-NH-, and

and n is 0 to 3,

k is 0 to 3, particularly 0 to 2, more particularly 1 or 2,

l is 0 or 1,

U is CH or a heteroatom, particularly CH or N, more particularly CH,

R^4 is selected from

- -Cl, -Br, -CH_2F, -CHF_2, -CF_3, and
- -C(=O)O-C_1-C_3-alkyl, -C(=O)OH, -O-C_1-C_3-alkyl, -C(=O)-N R^6R^6, -C_1-C_3-alkyl-OH, and
- -NR^6R^6,

wherein R^6 is independently selected from

- -H, -C(=O)-O-tert-butyl, -C_1-C_3-alkyl and -C(=O)-CF_3, particularly from -H and Me,

R^5 is selected from

- -NH-SO_2-C_1-C_3-alkyl, -NH-SO_2-$(CH_2)_s$-OH, and
- -NH-SO_2-$(CH_2)_s$-R^7,

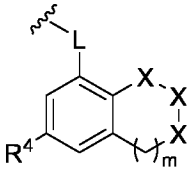
wherein R^7 is selected from an aryl or a heterocycle, wherein the heterocycle is a five or six-membered

heterocycle and wherein the heterocycle is an aliphatic heterocycle or an aromatic heterocycle, and

- $-(CH_2)_s-R^8$,

wherein R^8 is a four or five membered ring,

s is 0 to 3,

-  (IVa),

wherein

L of formula (I) is a linker comprising $-(CH_2)_n-$ or $-(CH_2)_n-Y-$ and L of formula (II) is a linker comprising $-(CH_2)_n-$ or $-Y-(CH_2)_n-$, wherein Y is selected from -O-, -S-, $-SO_2-$, -NH- and -C(=O)-NH-, and

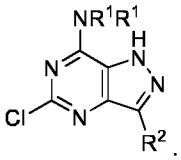
n is 0 to 3,

n is 0 or 1,

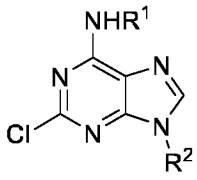
m is 0 or 1,

X is independently selected from CH, NR^{13}, SO_2 and O, wherein R^{13} is selected from -H and $-C_1-C_3$-alkyl-NH_2,

R^4 is defined as above.

Formula (IIa) includes all resonance structures of said formula, e.g.,  .

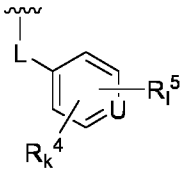
In certain embodiments the compound is a compound of formula (Ia)

 (Ia),

wherein

R^1 is selected from -H and $-C_1-C_3$-alkyl, particularly -H and -Me or cyclopropyl, more particularly -Me,

R^2 is selected from $-C_1-C_3$-alkyl and a moiety of formula (IIIa) or (IVa), particularly R^2 is a moiety of formula (IIIa) or (IVa),

-  (IIIa),

wherein

L is a linker comprising $-(CH_2)_n-$ or $-(CH_2)_n-Y-$ and

wherein Y is selected from -O-, -S-, $-SO_2-$, -NH- and -C(=O)-NH-, and

and n is 0 to 3,

k is 0 to 3, particularly 0 to 2, more particularly 1 or 2,

l is 0 or 1,

U is CH or a heteroatom, particularly CH or N, more particularly CH,

R^4 is selected from

- -Cl, -Br, $-CH_2F$, $-CHF_2$, $-CF_3$, and
- $-C(=O)O-C_1-C_3$-alkyl, -C(=O)OH, $-O-C_1-C_3$-alkyl, -C(=O)-N R^6R^6, $-C_1-C_3$-alkyl-OH, and
- $-NR^6R^6$,

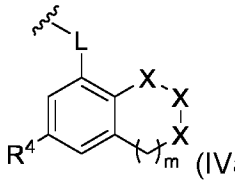
wherein R^6 is independently selected from

- -H, -C(=O)-O-tert-butyl, $-C_1-C_3$-alkyl and $-C(=O)-CF_3$, particularly from -H and Me,

R^5 is selected from

- $-NH-SO_2-C_1-C_3$-alkyl, $-NH-SO_2-(CH_2)_s-OH$, and
- $-NH-SO_2-(CH_2)_s-R^7$,
  wherein R^7 is selected from an aryl or a heterocycle, wherein the heterocycle is a five or six-membered heterocycle and wherein the heterocycle is an aliphatic heterocycle or an aromatic heterocycle, and
- $-(CH_2)_s-R^8$,
  wherein R^8 is a four or five membered ring,

s is 0 to 3,

-  (IVa),

wherein

L is a linker comprising -$(CH_2)_n$- or –$(CH_2)_n$-Y- and

wherein Y is selected from -O-, -S-, -SO_2-, -NH- and -C(=O)-NH-, and

n is 0 to 3,

n is 0 or 1,

m is 0 or 1,

X is independently selected from CH, NR^{13}, SO_2 and O, wherein R^{13} is selected from -H and -C_1-C_3-alkyl-NH_2,

R^4 is defined as above.

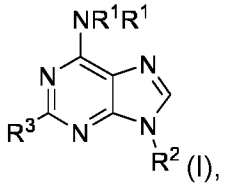
In certain embodiments, L of formula (I) is a linker comprising -$(CH_2)_n$- or –$(CH_2)_n$-Y-, and L of formula (II) is a linker comprising –$(CH_2)_n$- or -Y-$(CH_2)_n$-, wherein Y is selected from -O-, -S-, -SO_2-, -NH- and -C(=O)-NH-, wherein n is 0 or 1, particularly 1.

In certain embodiments L is a linker comprising -$(CH_2)_n$- or –$(CH_2)_n$-Y-, wherein Y is selected from -O-, -S-, -SO_2-, -NH- and -C(=O)-NH-, wherein n is 0 or 1, particularly 1.

In certain embodiments, L is a linker comprising -$(CH_2)_n$-. In certain embodiments, L is -$(CH_2)_n$- and n is 0 or 1.

In certain embodiments, L is –$(CH_2)_n$-Y-, and Y is selected from -O-, -S-, -SO_2-, -NH- and -C(=O)-NH-. In certain embodiments, L is –$(CH_2)_n$-Y- or -Y-$(CH_2)_n$-, and Y is selected from -O-, -S-, -SO_2-, -NH- and -C(=O)-NH-. In certain embodiments, Y is O. In certain embodiments, Y is S. In certain embodiments, Y is -SO_2-. In certain embodiments, Y is -NH-. In certain embodiments, Y is -C(=O)-NH-.

In some embodiments, disclosed herein is a compound of Formula (I), or a pharmaceutically acceptable salt thereof,

 (I),

wherein

each R^1 is independently -H or C_1-C_6-alkyl;

R^3 is -Br, -Cl, -CN, -F, or -NO_2;

R^2 is C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, or -L-A, wherein alkyl is optionally substituted with 1, 2, or 3 R;

each R^A is independently selected from halogen, -CN, -NO_2, -OH, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -C(=O)O-C_1-C_3-alkyl, -C(=O)OH, -O-C_1-C_3-alkyl, -C(=O)-NR^6R^6, -C(=O)-C_1-C_3-alkyl, -NR^6R^6, -NH-SO_2-C_1-C_3-alkyl, -NH-SO_2-$(CH_2)_s$-OH, -NH-SO_2-$(CH_2)_s$-R^7, -SO_2-NH-R^7, -$SO_2NR^6R^6$, -$(CH_2)_s$-R^8, -$(CH_2)_s$-cycloalkyl, -$(CH_2)_s$-aryl, -$(CH_2)_s$-heteroaryl, and -$(CH_2)_s$-heterocycloalkyl; wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, or 3 R;

each R is independently halogen, -CN, -OH, oxo, -S(=O)CH_3, -S(=O)$_2CH_3$, -S(=O)$_2NH_2$, -S(=O)$_2$OH, -S(=O)$_2NHCH_3$, -S(=O)$_2N(CH_3)_2$, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -C(=O)CH_3, -C(=O)OH, -C(=O)OCH_3, C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, or C_3-C_6cycloalkyl;

k is 0, 1, 2, or 3;

L is -$(CH_2)_n$- or –$(CH_2)_n$-Y-,

n is 0, 1, 2, 3, or 4;

wherein Y is selected from -O-, -S-, -SO_2-, -NH-, -C(=O), and -C(=O)-NH-;

A is H, phenyl, bicyclic aryl, monocyclic cycloalkyl, bicyclic cycloalkyl, monocyclic heterocycle, or bicyclic heterocycle, each of which is unsubstituted or substituted with 1, 2, 3 or 4 R^A;

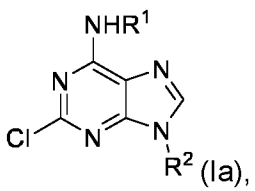
each R^6 is independently selected from -H, -C(=O)-O-tert-butyl, -C_1-C_3-alkyl, and -C(=O)-CF_3;

s is 0, 1, 2, or 3;

R^7 is aryl or five or six-membered heterocycle, each of which is optionally substituted with 1, 2, or 3 R; and

R^8 is a four or five membered ring, each of which is optionally substituted with 1, 2, or 3 R.

In some embodiments, disclosed herein is a compound of formula (Ia), or a pharmaceutically acceptable salt thereof,

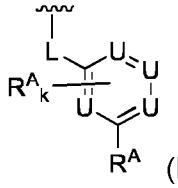
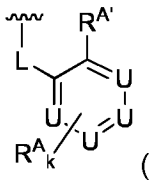


(Ia),

wherein

R^1 is -C_1-C_3-alkyl;

R^2 is -L-A or a moiety of formula (IIIb) or (IIIc),


(IIIb),

(IIIc),

each R^A is independently selected from halogen, -CN, -NO_2, -OH, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -C(=O)O-C_1-C_3-alkyl, -C(=O)OH, -O-C_1-C_3-alkyl, -C(=O)-NR^6R^6, -C(=O)-C_1-C_3-alkyl, -NR^6R^6, -NH-SO_2-C_1-C_3-alkyl, -NH-SO_2-$(CH_2)_s$-OH, -NH-SO_2-$(CH_2)_s$-R^7, -SO_2-NH-R^7, -$SO_2NR^6R^6$, -$(CH_2)_s$-R^8, -$(CH_2)_s$-cycloalkyl, -$(CH_2)_s$-aryl, -$(CH_2)_s$-heteroaryl, and -$(CH_2)_s$-heterocycloalkyl; wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, or 3 R;

$R^{A'}$ is selected from -CN, -NO_2, -OH, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -C(=O)O-C_1-C_3-alkyl, -C(=O)OH, -O-C_1-C_3-alkyl, -C(=O)-NR^6R^6, -C(=O)-C_1-C_3-alkyl, -NR^6R^6, -NH-SO_2-C_1-C_3-alkyl, -NH-SO_2-$(CH_2)_s$-OH, -NH-SO_2-$(CH_2)_s$-R^7, -SO_2-NH-R^7, -$SO_2NR^6R^6$, -$(CH_2)_s$-R^8, -$(CH_2)_s$-cycloalkyl, -$(CH_2)_s$-aryl, -$(CH_2)_s$-heteroaryl, and -$(CH_2)_s$-heterocycloalkyl; wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, or 3 R;

each R is independently halogen, -CN, -OH, oxo, -S(=O)CH_3, -$S(=O)_2CH_3$, -$S(=O)_2NH_2$, -$S(=O)_2$OH, -$S(=O)_2NHCH_3$, -$S(=O)_2N(CH_3)_2$, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -C(=O)CH_3, -C(=O)OH, -C(=O)OCH_3, C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, or C_3-C_6cycloalkyl;

k is 0, 1, 2, or 3;

L is -$(CH_2)_n$- or –$(CH_2)_n$-Y-,

n is 0, 1, 2 or 3;

wherein Y is selected from -O-, -S-, -SO_2-, -NH- and -C(=O)-NH-;

A is a bicyclic aryl, bicyclic cycloalkyl, or bicyclic heterocycle, each of which is unsubstituted or substituted with 1, 2, 3 or 4 R^A;

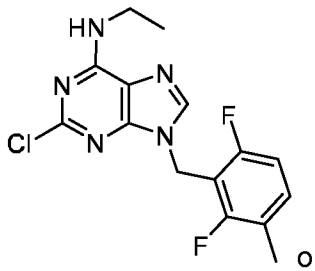
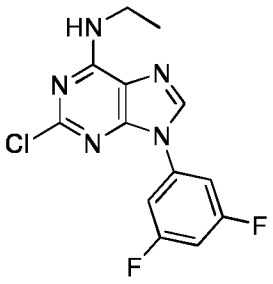
each U is independently CH or N;

each R^6 is independently selected from -H, -C(=O)-O-tert-butyl, -C_1-C_3-alkyl, and -C(=O)-CF_3;

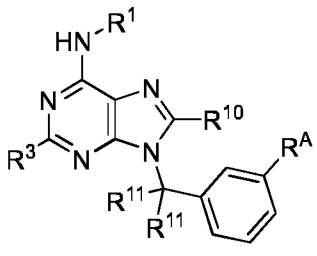
s is 0, 1, 2, or 3;

R^7 is aryl or five or six-membered heterocycle, each of which is optionally substituted with 1, 2, or 3 R; and

R^8 is a four or five membered ring, each of which is optionally substituted with 1, 2, or 3 R.

In some embodiments, disclosed herein is a compound of formula (Ia), or a pharmaceutically acceptable salt thereof, provided that the compound is not  or  .

In some embodiments, disclosed herein is a compound of formula (XI), or a pharmaceutically acceptable salt thereof,

 (XI),

wherein

R^1 is C_1-C_3-alkyl;

R^3 is selected from -Br, -Cl, -NO_2, CN, -O-C_1-C_3-alkyl, C_1-C_3-alkyl, C_2-C_3-haloalkyl, -NR^6R^6, -OH, -CH_2F, and -CHF_2;

each R^A is independently selected from halogen, -CN, -NO_2, -OH, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -C(=O)O-C_1-C_3-alkyl, -C(=O)O-$(CH_2)_s$-R^7, -C(=O)OH, -O-C_1-C_3-alkyl, -C(=O)-NR^6R^6, -NR^6R^6, -NH-SO_2-C_1-C_3-alkyl, -NH-SO_2-$(CH_2)_s$-R^7, -SO_2-NH-R^7, -$SO_2NR^6R^6$, -$(CH_2)_s$-R^8, -$(CH_2)_s$-cycloalkyl, -$(CH_2)_s$-aryl, -$(CH_2)_s$-heteroaryl, or -$(CH_2)_s$-heterocycloalkyl; wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, or 3 R;

each R is independently halogen, -CN, -OH, oxo, -S(=O)CH_3, -$S(=O)_2CH_3$, -$S(=O)_2NH_2$, -$S(=O)_2OH$, -$S(=O)_2NHCH_3$, -$S(=O)_2N(CH_3)_2$, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -C(=O)CH_3, -

C(=O)OH, -C(=O)OCH$_3$, C$_1$-C$_6$alkyl, C$_1$-C$_6$alkoxy, C$_1$-C$_6$haloalkyl, C$_1$-C$_6$hydroxyalkyl, C$_1$-C$_6$aminoalkyl, C$_1$-C$_6$heteroalkyl, or C$_3$-C$_6$cycloalkyl;

each R^6 is independently selected from -H, -C(=O)-O-tert-butyl, -C$_1$-C$_3$-alkyl, and -C(=O)-CF$_3$;

s is 0, 1, 2, or 3;

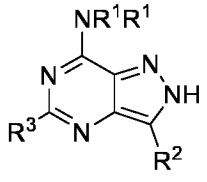
R^7 is aryl or five or six-membered heterocycle, each of which is optionally substituted with 1, 2, or 3 R;

R^8 is a four or five membered ring, each of which is optionally substituted with 1, 2, or 3 R;

R^{10} is -CN, -NO$_2$, -OH, C$_1$-C$_6$alkyl, C$_1$-C$_6$haloalkyl, C$_1$-C$_6$hydroxyalkyl, C$_1$-C$_6$aminoalkyl, C$_1$-C$_6$heteroalkyl, -C(=O)O-C$_1$-C$_3$-alkyl, -C(=O)-C$_1$-C$_3$-alkyl, -C(=O)OH, -O-C$_1$-C$_3$-alkyl, -C(=O)-NR^{6}R^6, -NR^{6}R^6, -NH-SO$_2$-C$_1$-C$_3$-alkyl, -NH-SO$_2$-(CH$_2$)$_s$-R^7, or -SO$_2$NR^{6}R^6, wherein the alkyl is optionally substituted with 1, 2, or 3 R; and

R^{11} is selected from -H, -F, -Br, -Cl, -CN, -C$_1$-C$_3$-alkyl, and NO$_2$.

In some embodiments, disclosed herein is a compound of formula (II), or a pharmaceutically acceptable salt thereof,



(II),

wherein

each R^1 is independently selected from -H and -C$_1$-C$_3$-alkyl, R^3 is selected from -F, -Cl, -Br, -CN, -NO$_2$, C$_1$-C$_3$-haloalkyl, and -NR^{6}R^6; R^2 is C$_1$-C$_3$-alkyl or -L-A;

A is an aryl, heteroaryl, cycloalkyl, or a nitrogen-containing heterocycloalkyl, each of which is unsubstituted or substituted with 1, 2, 3, or 4 R^A;

each R^A is independently selected from halogen, -CN, -NO$_2$, -OH, C$_1$-C$_6$alkyl, C$_1$-C$_3$-haloalkyl, C$_1$-C$_6$hydroxyalkyl, C$_1$-C$_6$aminoalkyl, C$_1$-C$_3$heteroalkyl, -C(=O)O-C$_1$-C$_3$-alkyl, -C(=O)-C$_1$-C$_3$-alkyl, -C(=O)OH, -O-C$_1$-C$_3$-alkyl, -C(=O)-NR^{6}R^6, -NR^{6}R^6, -NH-SO$_2$-C$_1$-C$_3$-alkyl, -NH-SO$_2$-(CH$_2$)$_s$-OH, -NH-SO$_2$-(CH$_2$)$_s$-R^7, -SO$_2$-NH-R^7, -SO$_2$NR^{6}R^6, and -(CH$_2$)$_s$-R^8; wherein the alkyl is optionally substituted with 1, 2, or 3 R;

each R^6 is independently selected from -H, -C(=O)-O-tert-butyl, -C$_1$-C$_3$-alkyl, and -C(=O)-CF$_3$;

R^7 is aryl or five or six-membered heterocycle, each of which is optionally substituted with 1, 2, or 3 R;

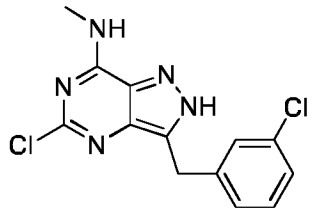
R^8 is a four or five membered ring, each of which is optionally substituted with 1, 2, or 3 R;

L is $-(CH_2)_n-$ or $-Y-(CH_2)_n-$, wherein Y is selected from -O-, -S-, $-SO_2-$, -NH- and -C(=O)-NH-;

each R is independently halogen, -CN, -OH, oxo, $-S(=O)CH_3$, $-S(=O)_2CH_3$, $-S(=O)_2NH_2$, $-S(=O)_2NHCH_3$, $-S(=O)_2N(CH_3)_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-C(=O)CH_3$, $-C(=O)OH$, $-C(=O)OCH_3$, C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, or C_3-C_6cycloalkyl;

n is 0, 1, 2, or 3; and

s is 0 to 3.

In some embodiments, disclosed herein is a compound of formula (XI), or a pharmaceutically acceptable salt thereof, provided that the compound is not  .

In some embodiments of Formula (I) or (II), each R^1 is independently selected from -H and -C_1-C_3-alkyl. In some embodiments, each R^1 is hydrogen. In some embodiments, each R^1 is -C_1-C_3-alkyl. In some embodiments of Formula (I) or (II), at least one of R^1 is H.

In some embodiments of Formula (Ia), (IIa), or (XI), R^1 is -H or -C_1-C_3-alkyl. In some embodiments, R^1 is hydrogen. In some embodiments, R^1 is -C_1-C_3-alkyl. In some embodiments, the -C_1-C_3-alkyl is linear C_1-C_3-alkyl. In some embodiments, the -C_1-C_3-alkyl is branched C_1-C_3-alkyl. In some embodiments, the -C_1-C_3-alkyl is methyl. In some embodiments, the -C_1-C_3-alkyl is ethyl. In some embodiments, R^1 is methyl or ethyl.

In some embodiments of Formula (I), (II), or (XI), R^3 is selected from -Br, -Cl, $-NO_2$, CN, -O-C_1-C_3-alkyl, C_1-C_3-alkyl, C_2-C_3-haloalkyl, $-NR^6R^6$, -OH, $-CH_2F$, and $-CHF_2$. In some embodiments, R^3 is -Br, -Cl, -O-C_1-C_3-alkyl, linear or branched C_1-C_3-alkyl, or $-NH_2$. In some embodiments of Formula (I), (II), (XI), R^3 is selected from -F, -Cl, -Br, -CN, $-NO_2$, C_1-C_3-haloalkyl, and $-NR^6R^6$. In some embodiments of Formula (I), (II), (XI), R^3 is selected from -F, -Cl, -Br, and $-NO_2$. In some embodiments, R^3 is -F, -Cl, -Br, C_1-C_3-haloalkyl, or $-NH_2$. In some embodiments, R^3 is -Cl, C_1-C_3-haloalkyl, and $-NH_2$. In some embodiments, R^3 is -F. In some embodiments, R^3 is -Cl. In some embodiments, R^3 is -Br. In some embodiments, R^3 is $-NO_2$. In some embodiments, R^3 is CN. In some embodiments, R^3 is -O-C_1-C_3-alkyl such as O-methyl. In some embodiments, R^3 is C_1-C_3-alkyl. In some embodiments, R^3 is methyl, ethyl, propyl. In some embodiments, R^3 is  . In some embodiments, R^3 is C_2-C_3-haloalkyl. In some embodiments, R^3 is C_1-C_3-haloalkyl. In some embodiments, R^3 is not methyl. In some embodiments, R^3 is not CF_3.

In some embodiments of a compound of Formula (I), (Ia), (II), or (IIa), R^2 is -L-A.

In some embodiments of a compound of Formula (I), (Ia), (II), or (IIa), L is $–(CH_2)_n$-, -Y-$(CH_2)_n$-, or -$(CH_2)_n$-Y-, wherein Y is selected from -O-, -S-, -SO_2-, -NH- and -C(=O)-NH- and n is 0, 1, 2, or 3. In some embodiments of a compound of Formula (I), (Ia), (II), or (IIa), L is $–(CH_2)_n$- or -Y-$(CH_2)_n$-, wherein Y is selected from -O-, -S-, -SO_2-, -NH- and -C(=O)-NH- and n is 0, 1, 2, or 3. In some embodiments, L is -Y-$(CH_2)_n$-, or -$(CH_2)_n$-Y-, wherein Y is selected from -O-, -S-, -SO_2-, -NH- and -C(=O)-NH- and n is 0, 1, 2, or 3. In some embodiments, L is $–(CH_2)_n$- wherein n is 0, 1, 2, or 3. In some embodiments, L is absent. In some embodiments, L is CH_2. In some embodiments, L is -$(CH_2)_2$-.

In some embodiments of a compound of Formula (I), (Ia), (II), or (IIa), A is phenyl, 5-6 membered heteroaryl, C_3-C_6 cycloalkyl, naphthyl, or bicyclic heteroaryl, each of which is unsubstituted or substituted. In some embodiments, A is phenyl, 5-6 membered heteroaryl, naphthyl, or bicyclic heteroaryl, each of which is unsubstituted or substituted. In some embodiments, A is phenyl or 5-6 membered heteroaryl, each of which is unsubstituted or substituted. In some embodiments, A is naphthyl, or bicyclic heteroaryl, each of which is unsubstituted or substituted. In some embodiments, A is phenyl, which is unsubstituted or substituted. In some embodiments, A is 5-6 membered heteroaryl, which is unsubstituted or substituted. In some embodiments, A is C_3-C_6 cycloalkyl, which is unsubstituted or substituted. In some embodiments, A is naphthyl, which is unsubstituted or substituted. In some embodiments, A is bicyclic heteroaryl, which is unsubstituted or substituted.

In some embodiments of a compound of Formula (Ia) or (II), A is unsubstituted or substituted with 1, 2, 3, or 4 R^A. In some embodiments, A is unsubstituted. In some embodiments, A is substituted with 1, 2, 3, or 4 R^A. In some embodiments, A is substituted with 1, 2, or 3 R^A. In some embodiments, A is substituted with 1 or 2 R^A. In some embodiments, A is substituted with 1 R^A.

In some embodiments of a compound of Formula (Ia), (II), or (XI), each R^A is independently selected from halogen, -CN, -NO_2, -OH, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, -C(=O)O-C_1-C_3-alkyl, -C(=O)OH, -O-C_1-C_3-alkyl, -C(=O)-NR^6R^6, -C(=O)-C_1-C_3-alkyl, -NR^6R^6, -NH-SO_2-C_1-C_3-alkyl, -NH-SO_2-$(CH_2)_s$-OH, -NH-SO_2-$(CH_2)_s$-R^7, -SO_2-NH-R^7, -$SO_2NR^6R^6$, -cycloalkyl, -aryl, -heteroaryl, and -heterocycloalkyl; wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, or 3 R. In some embodiments, each R^A is independently selected from halogen, -CN, -NO_2, -OH, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, -C(=O)O-C_1-C_3-alkyl, -C(=O)OH, -O-C_1-C_3-alkyl, -C(=O)-NR^6R^6, -C(=O)-C_1-C_3-alkyl, -NH_2, -NH-SO_2-C_1-C_3-alkyl, -NH-SO_2-$(CH_2)_s$-OH, -NH-SO_2-$(CH_2)_s$-R^7, -SO_2-NH-R^7, and -$SO_2NR^6R^6$; wherein the alkyl is optionally substituted with 1, 2, or 3 R. In some embodiments, each R^A is selected from halogen, -CN, -NO_2, -OH,

C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, -C(=O)O-C_1-C_3-alkyl, -C(=O)O-$(CH_2)_s$-R^7, -C(=O)OH, -O-C_1-C_3-alkyl, and -NH_2; wherein the alkyl is optionally substituted with 1, 2, or 3 R. In some embodiments, R^A is not F. In some embodiments, R^A is not Cl. In some embodiments, R^A is not halogen. In some embodiments of a compound of Formula (Ia), (II), or (XI), each R^A is independently selected from F, Cl, Br, I, -CN, -NO_2, -OH, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, -C(=O)O-C_1-C_3-alkyl, -C(=O)OH, C(=O)-NR^6R^6, -NH-SO_2-$(CH_2)_s$-R^7, -$SO_2NR^6R^6$, or heteroaryl, wherein the alkyl or heteroaryl is optionally substituted with 1, 2, or 3 R. In some embodiments, each R^A is independently selected from F, Cl, Br, I, -CN, -NO_2, -OH, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, or C_1-C_6aminoalkyl, wherein the alkyl is optionally substituted with 1, 2, or 3 R. In some embodiments, each R^A is independently selected from -C(=O)O-C_1-C_3-alkyl, -C(=O)OH, C(=O)-NR^6R^6, -NH-SO_2-$(CH_2)_s$-R^7, -$SO_2NR^6R^6$, or heteroaryl, wherein the alkyl or heteroaryl is optionally substituted with 1, 2, or 3 R. In some embodiments, each R^A is independently selected from F, Cl, Br, I, -CN, -NO_2, -OH, -OMe, -OEt, -CF_3, -CHF_2, -CH_2NH_2, -$(CH_2)_2NH_2$, -$(CH_2)_3NH_2$, -C(=O)OH, -CH_2C(=O)OH, -$(CH_2)_2$C(=O)OH, -$(CH_2)_3$C(=O)OH, -$(CH_2)_4$C(=O)OH, -C(=O)OMe, -C(=O)NH_2, -SO_2NH_2, -NH-SO_2-CH_2-phenyl, or tetrazole, wherein phenyl is optionally substituted with 1 or 2 R.In some embodiments, R^A is C_1-C_6alkyl. In some embodiments, the C_1-C_6alkyl is linear C_1-C_6alkyl. In some embodiments, the C_1-C_6alkyl is branched C_1-C_6alkyl. In some embodiments, the C_1-C_6alkyl is methyl, ethyl, n-propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neopentyl, tert-amyl and hexyl. In some embodiments, R^A is -C(=O)O-C_1-C_3-alkyl, -C(=O)OH, or -O-C_1-C_3-alkyl. In some embodiments, the C_1-C_3-alkyl is linear C_1-C_3-alkyl. In some embodiments, the C_1-C_3-alkyl is branched C_1-C_3-alkyl. In some embodiments, the C_1-C_3-alkyl is methyl, ethyl, n-propyl, or isopropyl.

In some embodiments, R^A is R^4. In some embodiments, R^A is R^5. In some embodiments, at least one R^A is R^5.

In some embodiments, R^2 is substituted with -COOH or an ester or amide thereof. In some embodiments, R^2 is substituted with -COOH. In some embodiments, at least one R^A is -C(=O)OH. In some embodiments, at least one R^A is an ester of -C(=O)OH. In some embodiments, R^A is C(=O)O-C_1-C_3-alkyl. In some embodiments, R^4 is -C(=O)OH. In some embodiments, R^4 is an ester of -C(=O)OH. In some embodiments, R^4 is C(=O)O-C_1-C_3-alkyl. Without being bound by theory, for some compounds of this disclosure, the difference between the compounds' biochemical IC50 and biological GI50 values can be a result of a prodrug/drug

complementarity (carboxylic acid group-drug vs ester group-prodrug). For example, ZA590 (comprising a -$COOCH_3$) can be considered a prodrug of ZA591 (comprising COOH).

In some embodiments, R^A is C_1-C_6haloalkyl. In some embodiments, the C_1-C_6haloalkyl is linear C_1-C_6haloalkyl. In some embodiments, the C_1-C_6haloalkyl is branched C_1-C_6haloalkyl. In some embodiments, the C_1-C_6haloalkyl is trifluoromethyl, difluoromethyl, fluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, or 1,2-dibromoethyl.

In some embodiments, R^A is C_1-C_6hydroxyalkyl. In some embodiments, the C_1-C_6hydroxyalkyl is linear C_1-C_6hydroxyalkyl. In some embodiments, the C_1-C_6hydroxyalkyl is branched C_1-C_6hydroxyalkyl. In some embodiments, the C_1-C_6hydroxyalkyl is hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, or hydroxypentyl.

In some embodiments, R^A is C_1-C_6aminoalkyl. In some embodiments, the C_1-C_6aminoalkyl is linear C_1-C_6aminoalkyl. In some embodiments, the C_1-C_6aminoalkyl is branched C_1-C_6aminoalkyl. In some embodiments, the C_1-C_6aminoalkyl is aminomethyl, aminoethyl, aminopropyl, aminobutyl, or aminopentyl.

In some embodiments of a compound of Formula (Ia), $R^{A'}$ is -CN, -NO_2, -OH, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, -C(=O)O-C_1-C_3-alkyl, -C(=O)OH, -O-C_1-C_3-alkyl, -C(=O)-NR^6R^6, -C(=O)-C_1-C_3-alkyl, -NR^6R^6, -NH-SO_2-C_1-C_3-alkyl, -NH-SO_2-$(CH_2)_s$-OH, -NH-SO_2-$(CH_2)_s$-R^7, -SO_2-NH-R^7, -$SO_2NR^6R^6$, -cycloalkyl, -aryl, -heteroaryl, and -heterocycloalkyl; wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, or 3 R. In some embodiments, $R^{A'}$ is -CN, C_1-C_6alkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, -NH-SO_2-C_1-C_3-alkyl, -NH-SO_2-$(CH_2)_s$-OH, -NH-SO_2-$(CH_2)_s$-R^7, aryl or heteroaryl, wherein the alkyl, aryl, or heteroaryl is optionally substituted with 1, 2, or 3 R.

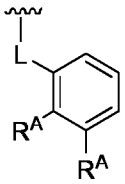
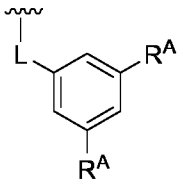
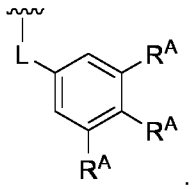
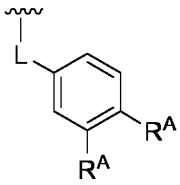
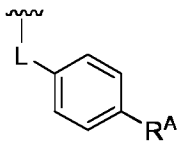
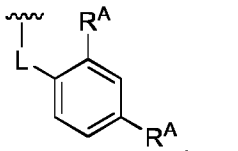
In some embodiments, $R^{A'}$ is C_1-C_6alkyl. In some embodiments, the C_1-C_6alkyl is linear C_1-C_6alkyl. In some embodiments, the C_1-C_6alkyl is branched C_1-C_6alkyl. In some embodiments, the C_1-C_6alkyl is methyl, ethyl, n-propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neopentyl, tert-amyl and hexyl. In some embodiments, $R^{A'}$ is -C(=O)O-C_1-C_3-alkyl, -C(=O)OH, -O-C_1-C_3-alkyl. In some embodiments, the C_1-C_3-alkyl is linear C_1-C_3-alkyl. In some embodiments, the C_1-C_3-alkyl is branched C_1-C_3-alkyl. In some embodiments, the C_1-C_3-alkyl is methyl, ethyl, n-propyl, or isopropyl.

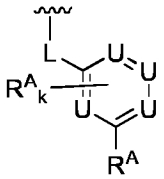
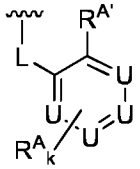
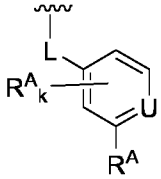
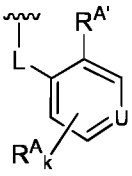
In some embodiments, $R^{A'}$ is C_1-C_6haloalkyl. In some embodiments, the C_1-C_6haloalkyl is linear C_1-C_6haloalkyl. In some embodiments, the C_1-C_6haloalkyl is branched C_1-C_6haloalkyl. In some

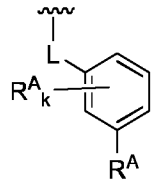
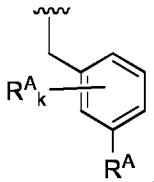
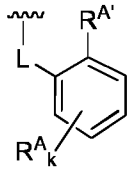
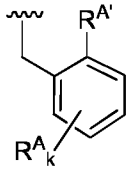
embodiments, the C_1-C_6haloalkyl is trifluoromethyl, difluoromethyl, fluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, or 1,2-dibromoethyl.

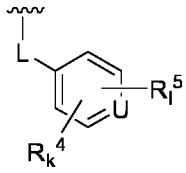
In some embodiments, $R^{A'}$ is C_1-C_6hydroxyalkyl. In some embodiments, the C_1-C_6hydroxyalkyl is linear C_1-C_6hydroxyalkyl. In some embodiments, the C_1-C_6hydroxyalkyl is branched C_1-C_6hydroxyalkyl. In some embodiments, the C_1-C_6hydroxyalkyl is hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, or hydroxypentyl.

In some embodiments, $R^{A'}$ is C_1-C_6aminoalkyl. In some embodiments, the C_1-C_6aminoalkyl is linear C_1-C_6aminoalkyl. In some embodiments, the C_1-C_6aminoalkyl is branched C_1-C_6aminoalkyl. In some embodiments, the C_1-C_6aminoalkyl is aminomethyl, aminoethyl, aminopropyl, aminobutyl, or aminopentyl.

In some embodiments, R^2 is  . In some embodiments, R^2 is  . In some embodiments, R^2 is  . In some embodiments, R^2 is  . In some embodiments, R^2 is  . In some embodiments, R^2 is  .

In some embodiments of a compound of Formula (I), (Ia), (II), or (IIa), R^2 is a moiety of  (IIIb) or  (IIIc). In some embodiments, R^2 is a moiety of  (IIIb') or  (IIIc'). In some embodiments, U is CH. In some embodiments, U is N.

In some embodiments of a compound of Formula (I), (Ia), (II), or (IIa), R^2 is  . In some embodiments, R^2 is  . In some embodiments, R^2 is  . In some embodiments, R^2 is  .In some embodiments a compound of Formula (I), (Ia), (II), or (IIa), R^2 is a moiety of formula (III) or (IV),



(III),

wherein

L is a linker comprising $-(CH_2)_n-$ or $-Y-(CH_2)_n-$;

Y is selected from -O-, -S-, $-SO_2-$, -NH- and -C(=O)-NH-;

n is 0 to 3, k is 0 to 3, particularly 0 to 2, more particularly 1 or 2;

l is 0 or 1;

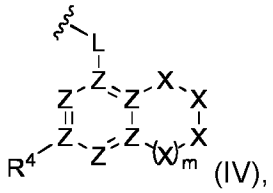
U is CH or a heteroatom, particularly CH or N, more particularly CH;

R^4 is independently selected from -Cl, -Br, $-CH_2F$, $-CHF_2$, $-CF_3$, $-C(=O)O-C_1-C_3$-alkyl, $-C(=O)OH$, $-O-C_1-C_3$-alkyl, $-C(=O)-NR^6R^6$, $-C_1-C_3$-alkyl-OH, and $-NR^6R^6$, wherein R^6 is independently selected from -H, $-C(=O)-O$-tert-butyl, $-C_1-C_3$-alkyl, and $-C(=O)-CF_3$, particularly from -H and Me;

R^5 is selected from $-NH-SO_2-C_1-C_3$-alkyl, $-NH-SO_2-(CH_2)_s-OH$ and $NH-SO_2-(CH_2)_s-R^7$, wherein R^7 is selected from an aryl and a heterocycle, wherein the heterocycle is a five or six-membered heterocycle and wherein the heterocycle is an aliphatic heterocycle or an aromatic heterocycle, and $-(CH_2)_s-R^8$, wherein R^8 is a four or five membered ring,

s is 0 to 3,

or



(IV),

wherein

L of formula (I) is a linker comprising -$(CH_2)_n$- or –$(CH_2)_n$-Y- and

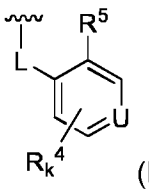
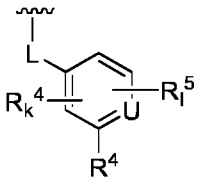
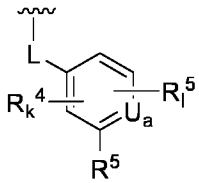
L is –$(CH_2)_n$- or -Y-$(CH_2)_n$-, wherein Y is selected from -O-, -S-, -SO_2-, -NH- and -C(=O)-NH-;

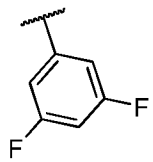
n is 0 to 3, m is 0 or 1;

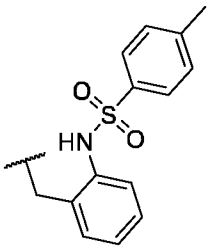
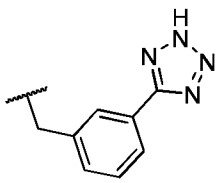
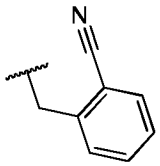
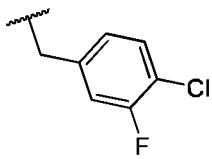
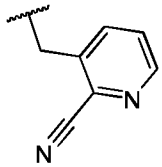
each X and Z are selected from C, NR^3, SO_2 and O, wherein R^3 is -H or -C_1-C_3-alkyl-NH_2 and wherein Z is particularly C;

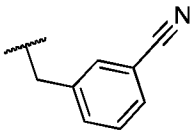
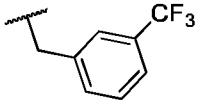
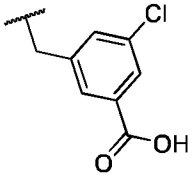
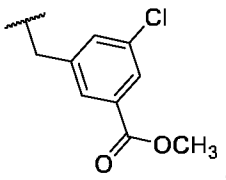
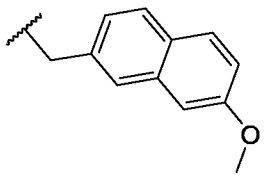
R^4 is defined as above.

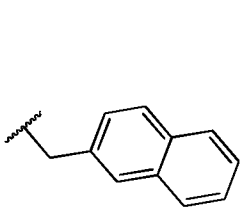
In some embodiments of a compound of Formula (I), (Ia), (II), or (IIa), R^2 is para or meta substituted.

In some embodiments of a compound of Formula (I), (Ia), (II), or (IIa), R^2 is a moiety of formula (IIIb''), (IIIc''), or (IIId'):  (IIIb''),  (IIIc''), or  (IIId').

In some embodiments of a compound of Formula (I), (Ia), (II), or (IIa), R^2 is  ,

 ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,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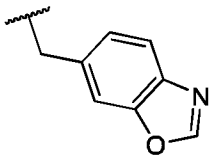
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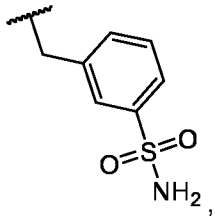
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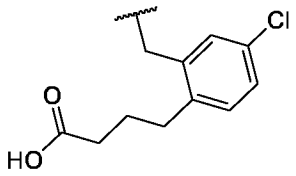
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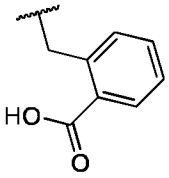
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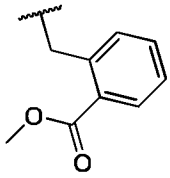
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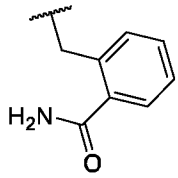
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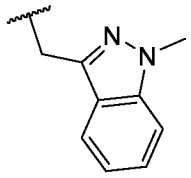
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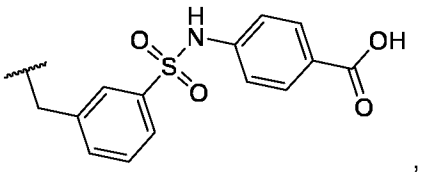
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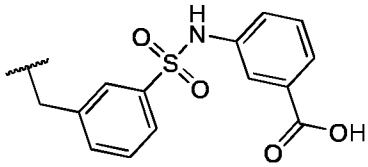
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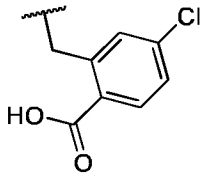
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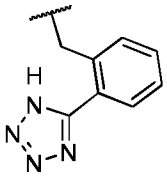
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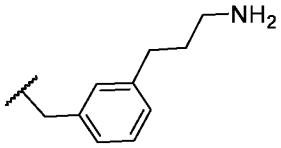
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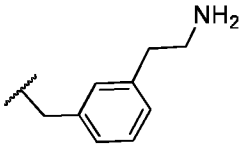
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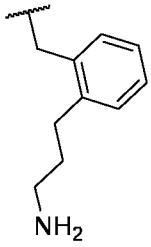
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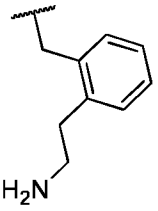
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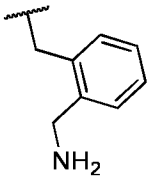
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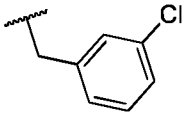
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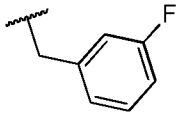
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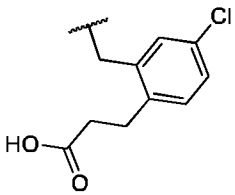
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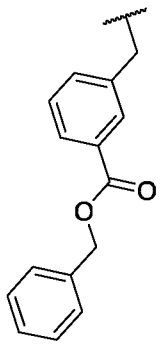
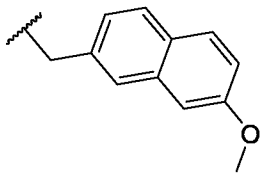

. In some embodiments of a compound of Formula (I), (Ia), (II), or (IIa), R^2 is

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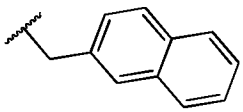
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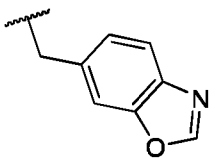
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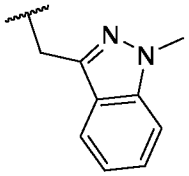
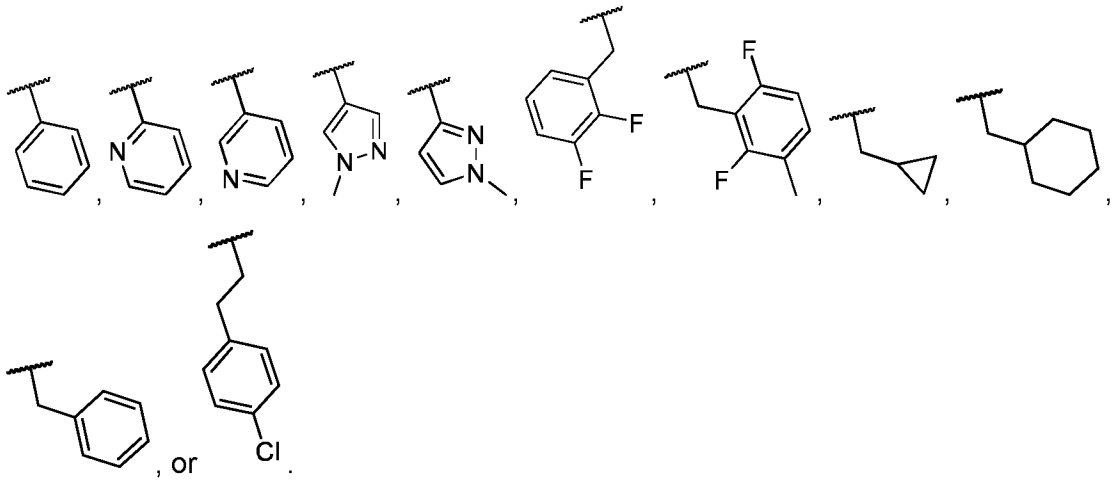

. In some embodiments, R^2 is



In some embodiments of a compound of Formula (I), R^2 is C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, or -L-A, wherein alkyl is optionally substituted with 1, 2, or 3 R;

each R^A is independently selected from halogen, -CN, -NO_2, -OH, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -C(=O)O-C_1-C_3-alkyl, -C(=O)OH, -O-C_1-C_3-alkyl, -C(=O)-NR^6R^6, -C(=O)-C_1-C_3-alkyl, -NR^6R^6, -NH-SO_2-C_1-C_3-alkyl, -NH-SO_2-$(CH_2)_s$-OH, -NH-SO_2-$(CH_2)_s$-R^7, -SO_2-NH-R^7, -$SO_2NR^6R^6$, -$(CH_2)_s$-R^8, -$(CH_2)_s$-cycloalkyl, -$(CH_2)_s$-aryl, -$(CH_2)_s$-heteroaryl, and -$(CH_2)_s$-heterocycloalkyl; wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, or 3 R;

each R is independently halogen, -CN, -OH, oxo, -S(=O)CH_3, -$S(=O)_2CH_3$, -$S(=O)_2NH_2$, -$S(=O)_2$OH, -$S(=O)_2NHCH_3$, -$S(=O)_2N(CH_3)_2$, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -C(=O)CH_3, -C(=O)OH, -C(=O)OCH_3, C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, or C_3-C_6cycloalkyl;

k is 0, 1, 2, or 3;

L is -$(CH_2)_n$- or –$(CH_2)_n$-Y-,

n is 0, 1, 2, 3, or 4;

wherein Y is selected from -O-, -S-, -SO_2-, -NH-, -C(=O), and -C(=O)-NH-;

A is H, phenyl, bicyclic aryl, monocyclic cycloalkyl, bicyclic cycloalkyl, monocyclic heterocycle, or bicyclic heterocycle, each of which is unsubstituted or substituted with 1, 2, 3 or 4 R^A;

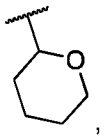
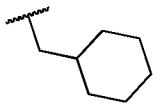
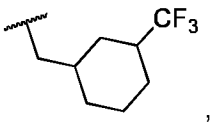
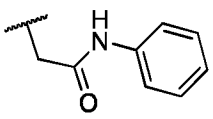
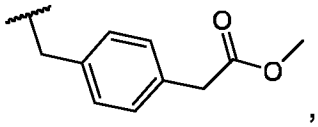
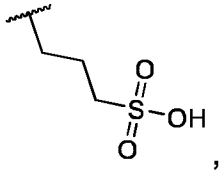
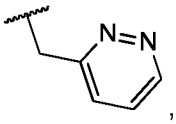
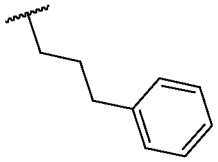
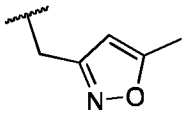
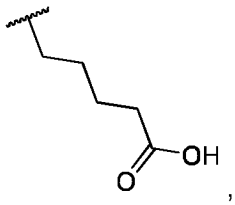
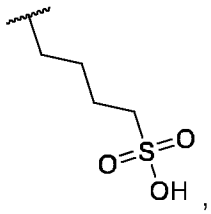
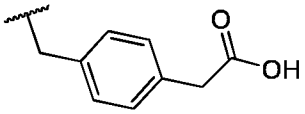
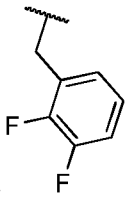
each R^6 is independently selected from -H, -C(=O)-O-tert-butyl, -C_1-C_3-alkyl, and -C(=O)-CF_3;

s is 0, 1, 2, or 3;

R^7 is aryl or five or six-membered heterocycle, each of which is optionally substituted with 1, 2, or 3 R; and

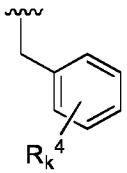
R^8 is a four or five membered ring, each of which is optionally substituted with 1, 2, or 3 R.

In some embodiments of a compound of Formula (Ia), R^2 is a moiety of formula (IIIb). In some embodiments of a compound of Formula (Ia), R^2 is a moiety of formula (IIIc),

In some embodiments of a compound of Formula (Ia), R^2 is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or

In certain embodiments of a compound of Formula (I), (II), (Ia) or (IIa), R^2 is a moiety of formula (IIIa) or (IVa). In certain embodiments, R^2 is a moiety of formula (IIIc). In certain embodiments, R^2 is a moiety of formula (IIIc'). In certain embodiments, R^2 is a moiety of formula (IIIc'). In certain embodiments, R^2 is a moiety of formula (IIIc''). In certain embodiments, R^2 is a moiety of formula (IIIb). In certain embodiments, R^2 is a moiety of formula (IIIb'). In certain embodiments, R^2 is a moiety of formula (IIIb''). In certain embodiments, R^2 is a moiety of formula (IIId').

In certain embodiments, the formula (IIIa) of R^2 is

 , wherein

k is 0 to 3, particularly 0 to 2, more particularly 1 or 2

R^4 is selected from

- -Cl, -Br, $-CH_2F$, $-CHF_2$, $-CF_3$, and
- $-C(=O)O-C_1-C_3$-alkyl, $-C(=O)OH$, $-C_1-C_3$-alkyl, $-C(=O)-NR^6R^6$, $-C_1-C_3$-alkyl-OH, and
- $-NR^6R^6$,

wherein R^6 is independently selected from

-H, -C(=O)-O-tert-butyl, -C_1-C_3-alkyl and -C(=O)-CF_3, particularly from -H and Me.

In certain embodiments, R^4 is selected from

- -Cl, -Br, -CH_2F, -CHF_2, -CF_3,
- -OMe, -C(=O)OMe, -C(=O)OH, -CH_2OH, - NH_2, -C(=O)-NH-Me and -C(=O)-NH_2.

In certain embodiments, R^4 is selected from

- -Cl, -Br, -CH_2F, -CHF_2, -CF_3,
- -OMe, -CH_2OH, - NH_2, -C(=O)-NH-Me and -C(=O)-NH_2.

In certain embodiments, R^4 is selected from

-Cl, -OMe, -C(=O)OH, -C(=O)OMe, -C(=O)NHMe and -C(=O)NH_2.

In certain embodiments, R^4 is selected from

-Cl, -OMe, -C(=O)NHMe and -C(=O)NH_2.

In certain embodiments, R^4 is selected from

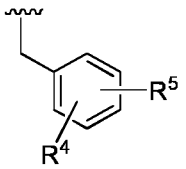
-Cl, -OMe, -C(=O)OH and -C(=O)OMe.

In certain embodiments, R^4 is -Cl or -C(=O)OMe.

In certain embodiments, R^4 is -OMe and -Cl.

In certain embodiments, one R^4 is in meta position to L.

In certain embodiments, the formula (IIIa) of R^2 is



,

wherein

R^5 is selected from

- -NH-SO_2-C_1-C_3-alkyl, -NH-SO_2-$(CH_2)_s$-OH, particularly -NH-SO_2-Me or -NH-SO_2-$(CH_2)_2$-OH, and
- -NH-SO_2-$(CH_2)_s$-R^7, wherein R^7 is selected from an aryl or a heterocycle, wherein the heterocycle is a five or six-membered heterocycle and wherein the heterocycle is an aliphatic heterocycle or an aromatic heterocycle, and
- -$(CH_2)_s$-R^8, wherein R^8 is a four or five membered ring,

s is 0 to 3,

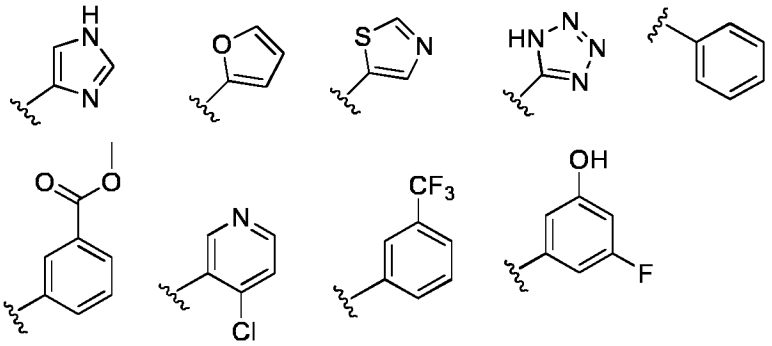
R^4 being as defined above.

In some embodiments of a compound of Formula (XI), R^{10} is -CN, -OH, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -C(=O)O-C_1-C_3-alkyl, -C(=O)-C_1-C_3-alkyl, -C(=O)OH, wherein the alkyl is optionally substituted with 1, 2, or 3 R. In some embodiments, R^{10} is -C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl,

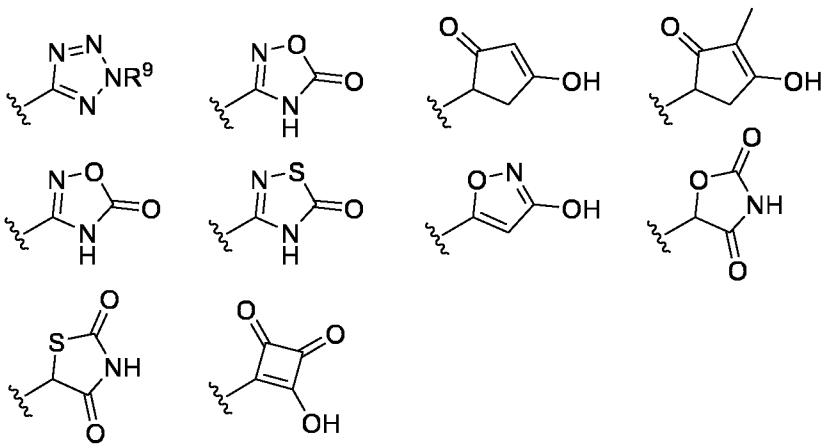
C_1-C_6heteroalkyl, -C(=O)O-C_1-C_3-alkyl, or -C(=O)-C_1-C_3-alkyl, wherein the alkyl is linear alkyl and is optionally substituted with 1, 2, or 3 R. In some embodiments, R^{10} is -C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -C(=O)O-C_1-C_3-alkyl, or -C(=O)-C_1-C_3-alkyl, wherein the alkyl is branched alkyl and is optionally substituted with 1, 2, or 3 R.

In some embodiments of a compound of Formula (XI), each R^{11} is independently -H, -F, -Br, -Cl, -CN, or -C_1-C_3-alkyl. In some embodiments, each R^{11} is independently -H, -F, -CN, or -C_1-C_3-alkyl. In some embodiments, each R^{11} is independently -H or linear -C_1-C_3-alkyl. In some embodiments, each R^{11} is independently -H or branched -C_1-C_3-alkyl.

In certain embodiments, R^7 is selected from any one of the moieties

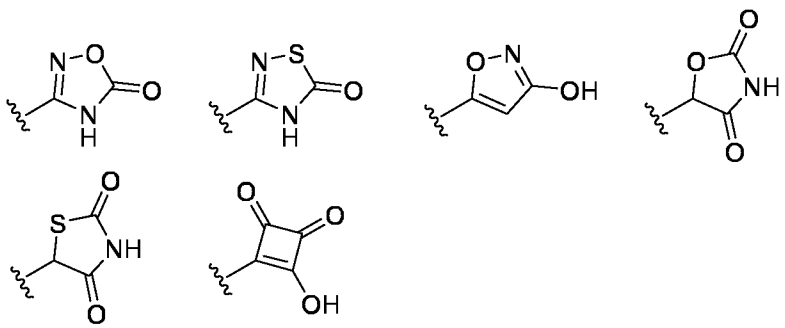


In certain embodiments, R^8 is selected from any one of the moieties



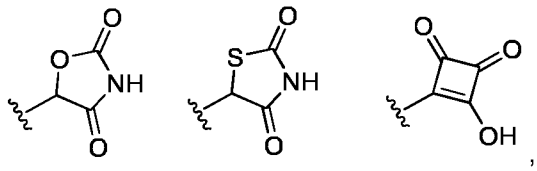
wherein R^9 is selected from -H or -C_1-C_6-alkyl.

In certain embodiments, R^8 is selected from any one of the moieties



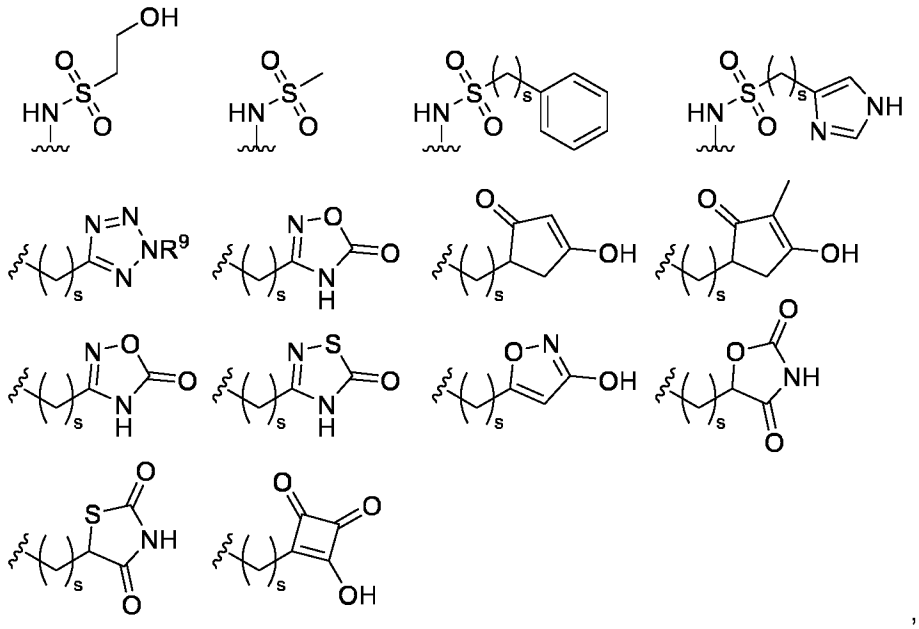
wherein R^9 is selected from -H or -C_1-C_6-alkyl.

In certain embodiments, R^8 is selected from any one of the moieties



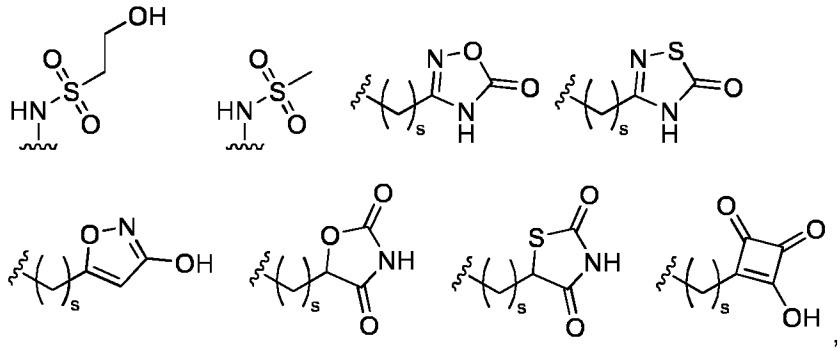
wherein R^9 is selected from -H or -C_1-C_6-alkyl.

In certain embodiments, R^5 is selected from any one of the moieties



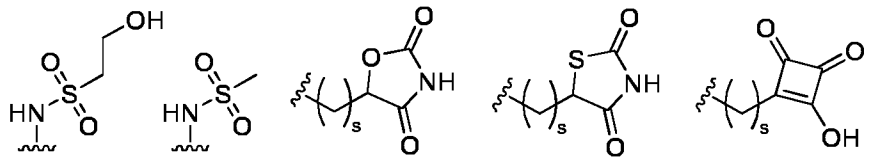
wherein R^9 is selected from -H or -C_1-C_6-alkyl and wherein s is 0 to 3.

In certain embodiments, R^5 is selected from any one of the moieties



wherein R^9 is selected from -H or -C_1-C_6-alkyl and wherein s is 0 to 3.

In certain embodiments, R^5 is selected from any one of the moieties

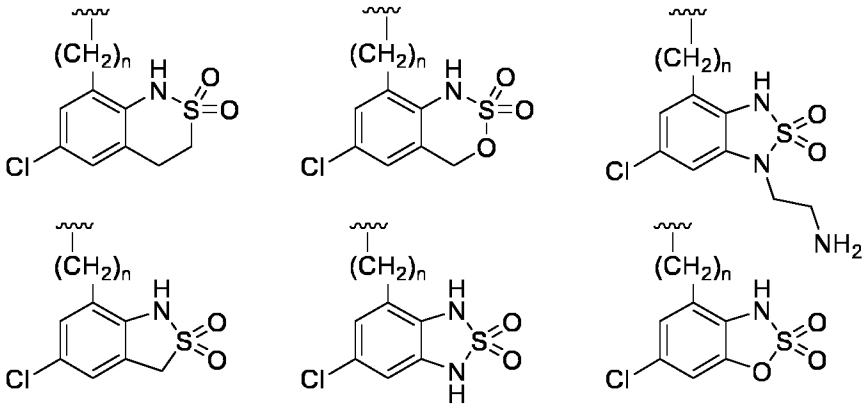


wherein R^9 is selected from -H or -C_1-C_6-alkyl and wherein s is 0 to 3.

In certain embodiments, one of X is SO_2.

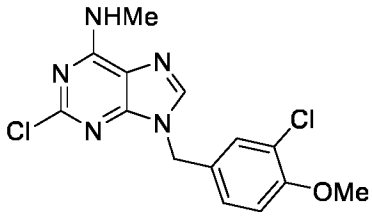
In certain embodiments, at least one of X is NH.

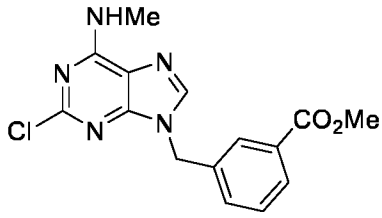
In certain embodiments, the compound of formula (IVa) of R^2 is selected from any one of the moieties

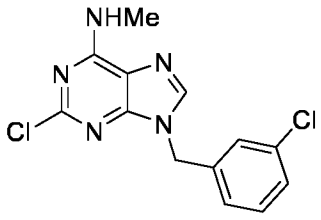


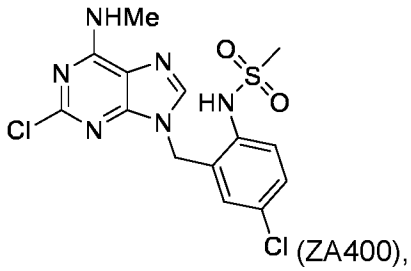
wherein n is 0 or 1.

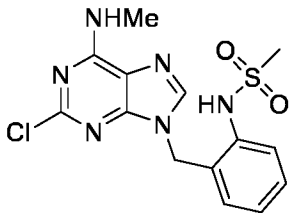
In certain embodiments, the compound is selected from a compound of formula (FE150), (ZA347), (ZA349), (ZA400) or (ZA364)


(FE150),


(ZA347),

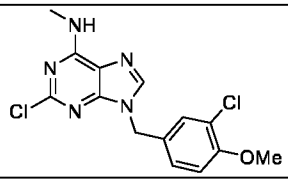
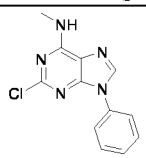
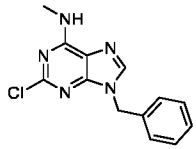
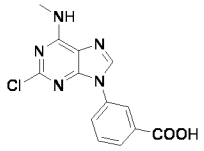
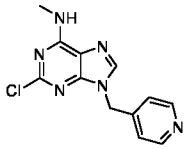
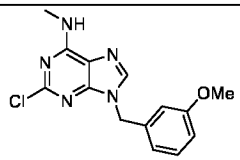
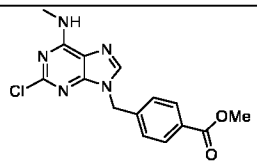
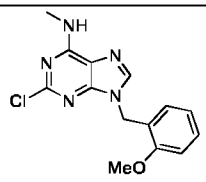
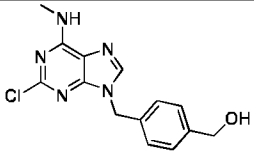
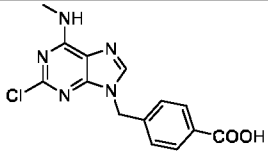

(ZA349),

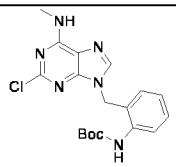
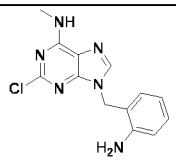
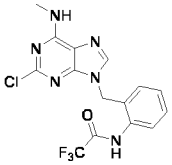
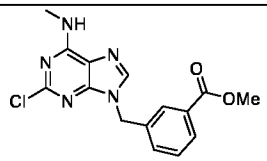
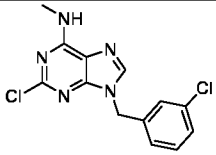
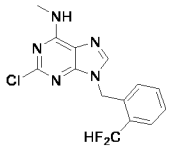
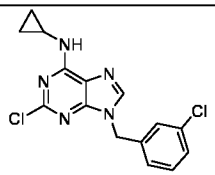
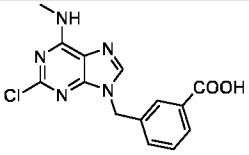
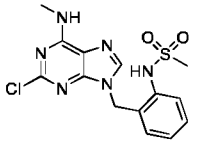
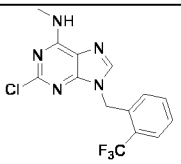

(ZA400),

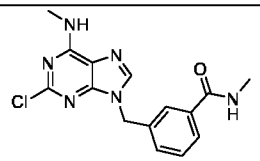
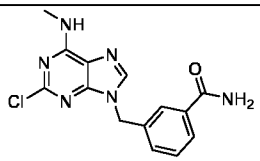
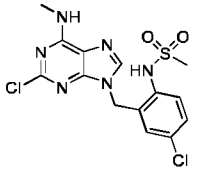
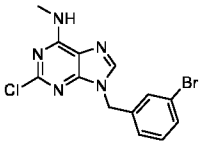
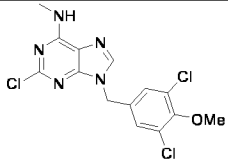
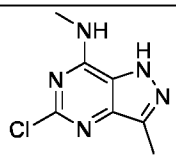
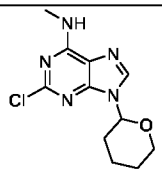
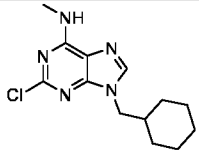
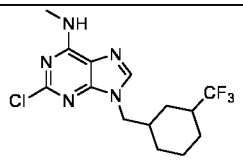
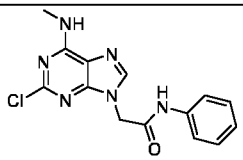

(ZA364).

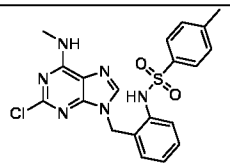
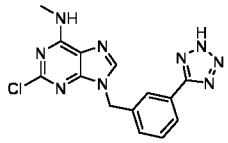
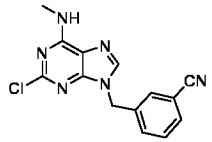
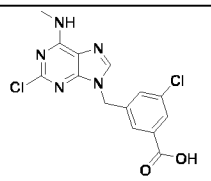
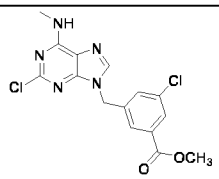
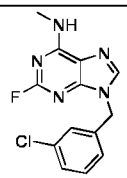
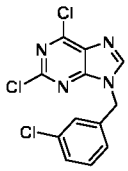
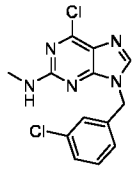
In some embodiments, a compound disclosed herein is a compound of Table 1 or a salt thereof.

Table 1.

Compound	Structure
FE150	
ZA232	
ZA236	
ZA294	
ZA308	
ZA309	
ZA311	
ZA312	
ZA326	
ZA337	

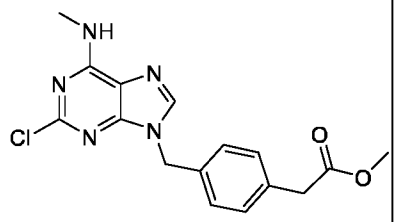
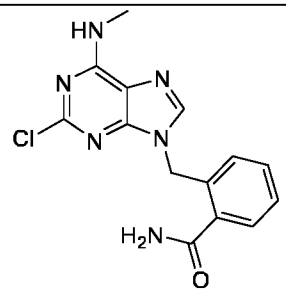
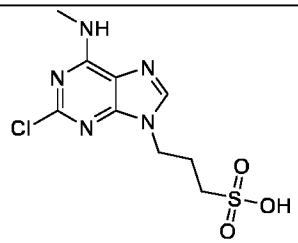
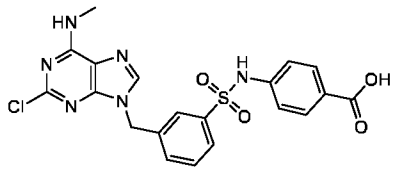
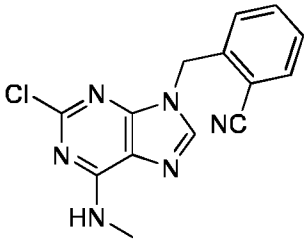
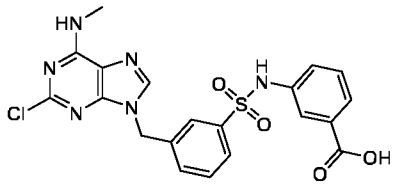
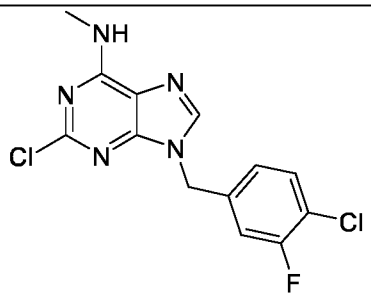
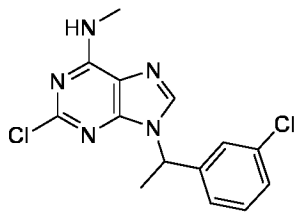
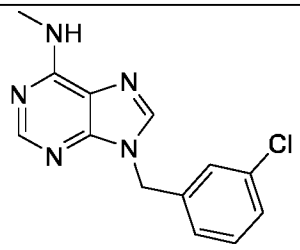
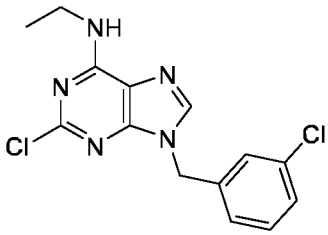
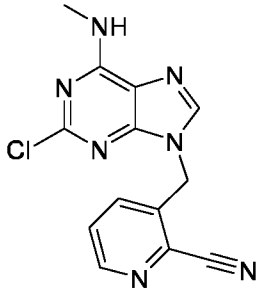
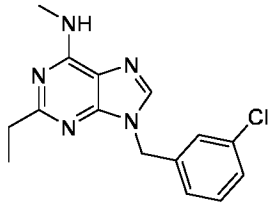
Compound	Structure
ZA340	
ZA341	
ZA343	
ZA347	
ZA349	
ZA354	
ZA356	
ZA360	
ZA364	
ZA366	

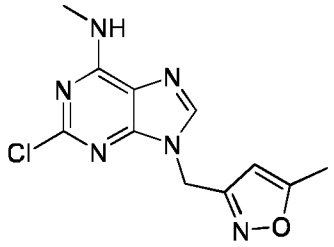
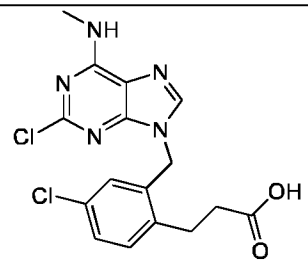
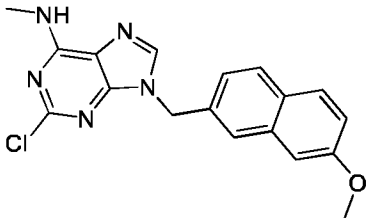
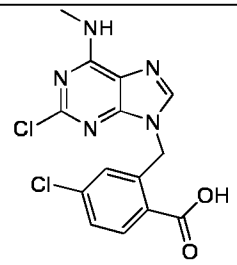
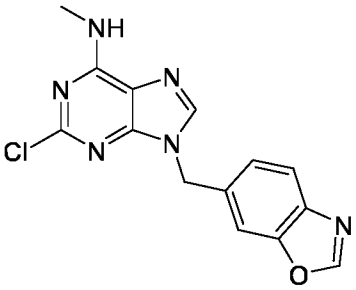
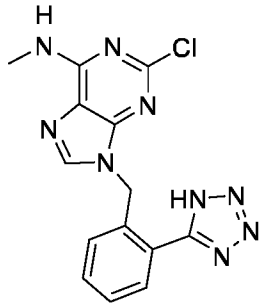
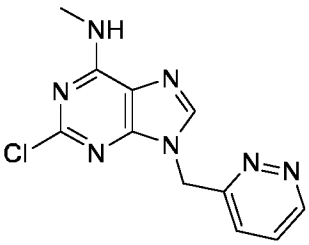
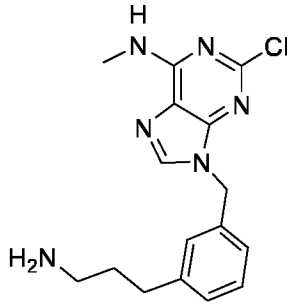
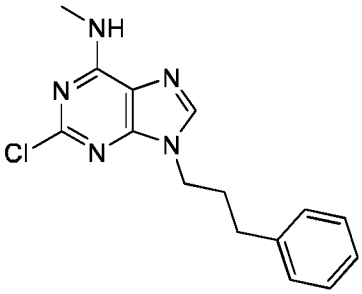
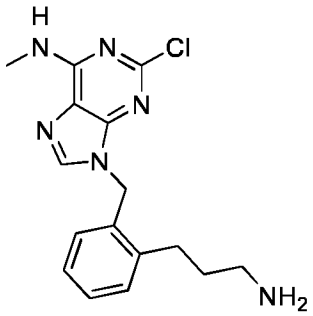
Compound	Structure
ZA385	
ZA393	
ZA400	
ZA409	
ZA410	
ZA431	
ZA560	
CSDC1-001	
CSDC1-002	
ZA572	

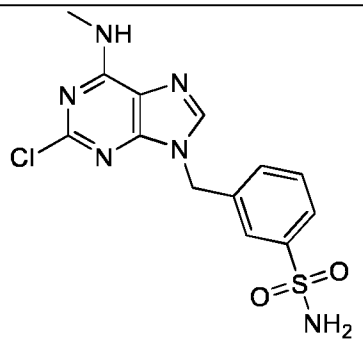
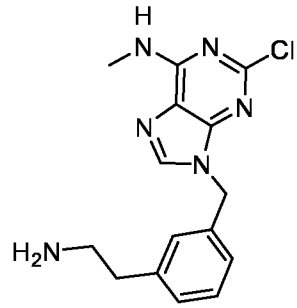
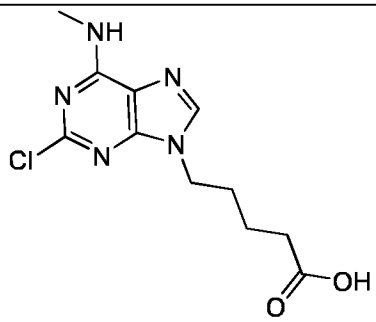
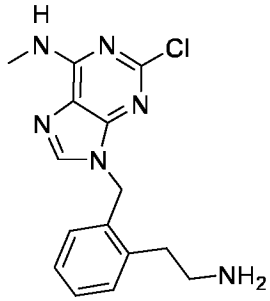
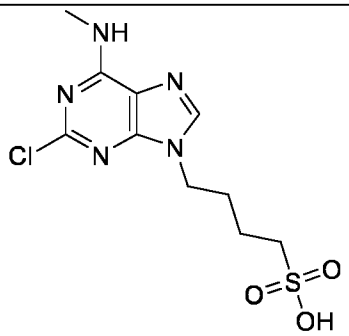
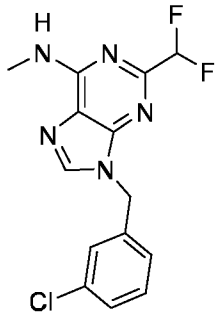
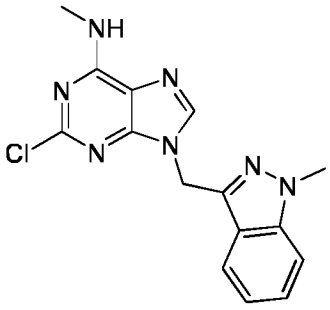
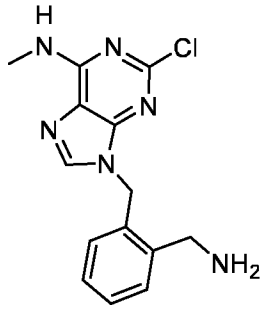
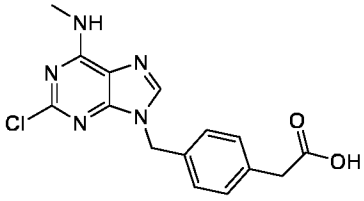
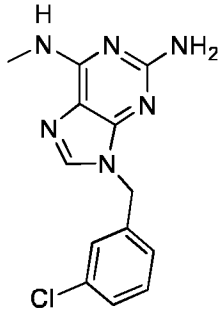
Compound	Structure
ZA480	
ZA515	
ZA513	
ZA591	
ZA590	
ZA540b	
ZA348	
ZA540a	

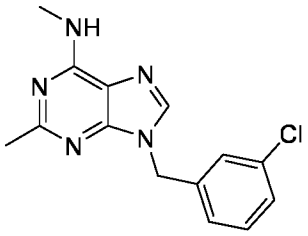
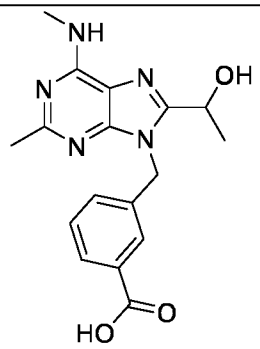
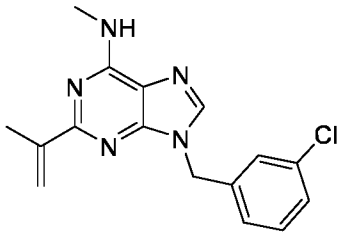
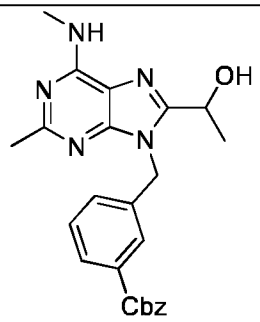
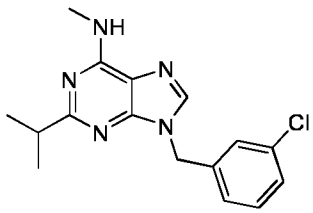
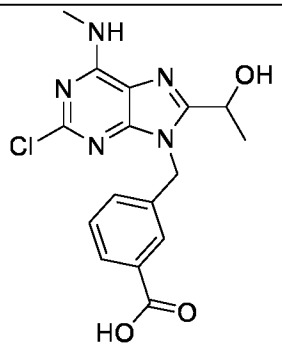
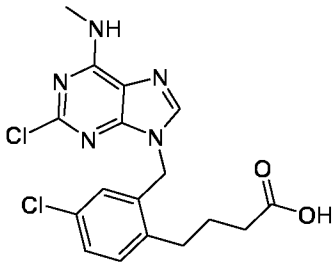
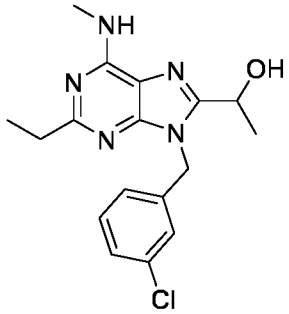
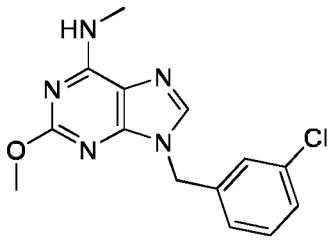
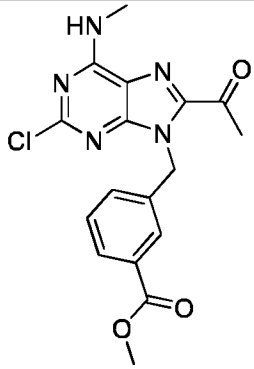
In some embodiments, a compound disclosed herein is a compound of Table 2, or a salt thereof.

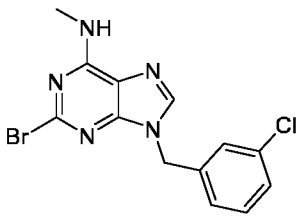
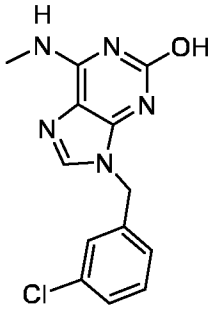
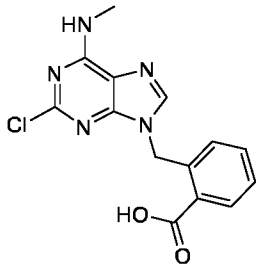
Table 2.

Compound	Structure	Compound	Structure
2		36	
3		40	
5		43	
6		45	
7		47	
8		49	

Compound	Structure	Compound	Structure
9		54	
10		56	
11		57	
12		58	
13		59	

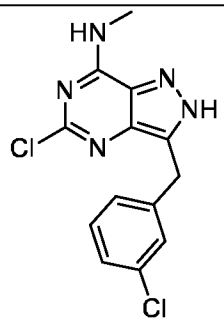
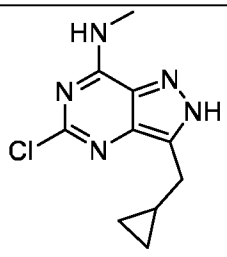
Compound	Structure	Compound	Structure
14		60	
15		61	
16		62	
17		63	
18		64	

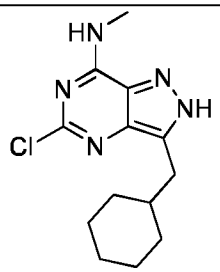
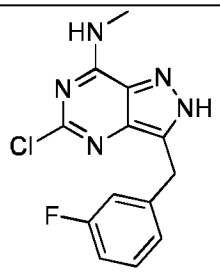
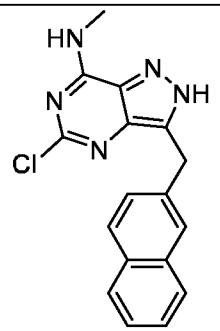
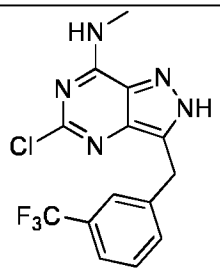
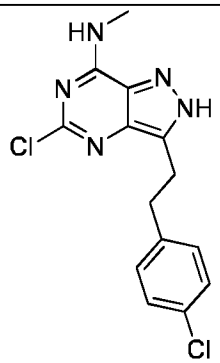
Compound	Structure	Compound	Structure
20		65	
22		66	
24		67	
29		68	
30		69	

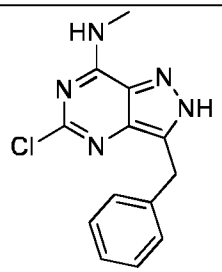
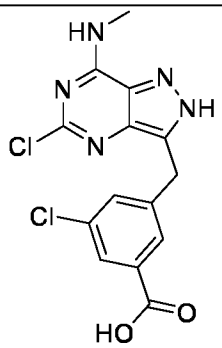
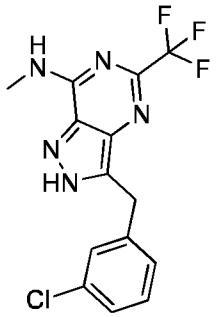
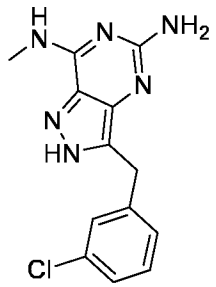
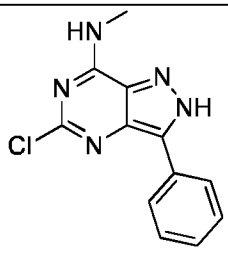
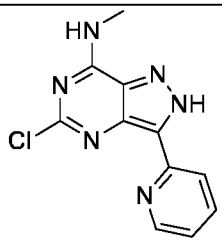
Compound	Structure	Compound	Structure
33		70	
35		71	

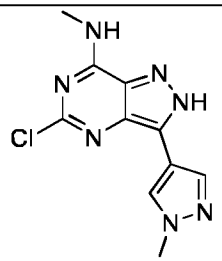
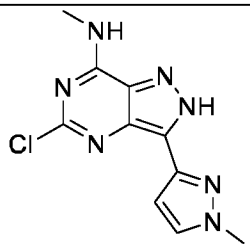
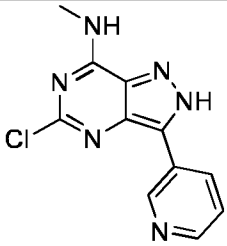
In some embodiments, a compound disclosed herein is a compound of Table 3, or a salt thereof.

Table 3.

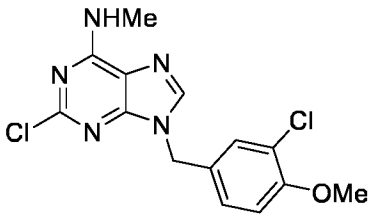
Compound	Structure
72	
73	

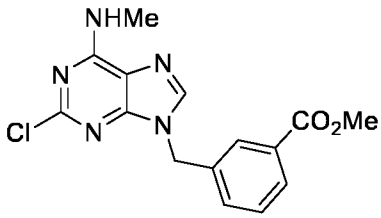
Compound	Structure
74	
75	
76	
77	
78	

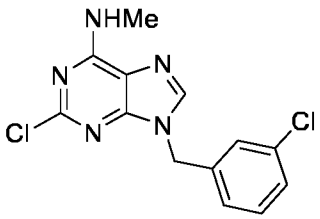
Compound	Structure
79	
80	
81	
82	
83	
84	

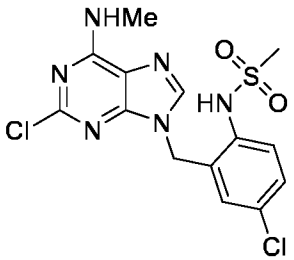
Compound	Structure
85	
86	
87	

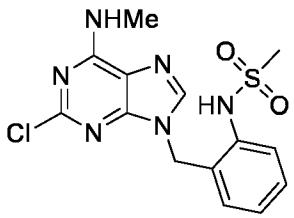
Another aspect of the invention relates to a compound selected from any one of (FE150), (ZA347), (ZA349), (ZA400), (ZA364), (ZA311) and (ZA337) for use as a medicament

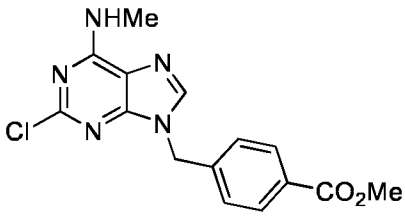
 (V),

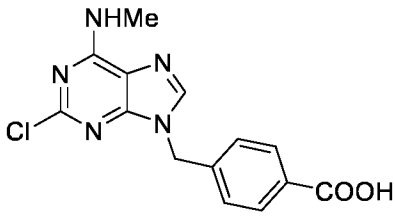
 (VI),

 (VII),

 (VIII),

 (IX)

 (X),

 (XI).

Another aspect of the invention relates to a compound described herein for use in the treatment of a disease, wherein the disease is cancer.

In certain embodiments, the cancer is selected from renal cancer, breast cancer, acute myeloid leukemia, hepatocellular carcinoma, and lung adenocarcinoma.

Further forms of compounds

Isomers/Stereoisomers

In some embodiments, the compounds described herein exist as geometric isomers. In some embodiments, the compounds described herein possess one or more double bonds. The compounds presented herein include all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the corresponding mixtures thereof. In some situations, the compounds described herein possess one or more chiral centers and each center exists in the R configuration, or S configuration. The compounds described herein include all diastereomeric, enantiomeric, and epimeric forms as well as the corresponding mixtures thereof. In additional embodiments of the compounds and methods provided herein, mixtures of enantiomers and/or diastereoisomers, resulting from a single preparative step, combination, or interconversion are useful for the applications described herein. In some embodiments, the compounds described herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomers. In some embodiments, dissociable complexes are preferred. In some embodiments, the diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and are separated by taking advantage of these dissimilarities. In some embodiments, the diastereomers are separated by chiral chromatography, or preferably, by separation/resolution techniques based upon differences in solubility. In some embodiments, the optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization.

Isotopically enriched compounds

Unless otherwise stated, compounds described herein may exhibit their natural isotopic abundance, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. All isotopic variations of the compounds of the present disclosure, whether radioactive or not, are encompassed within the scope of the present disclosure. For example, hydrogen has three naturally occurring isotopes, denoted ^{1}H

(protium), ^{2}H (deuterium), and ^{3}H (tritium). Protium is the most abundant isotope of hydrogen in nature. Enriching for deuterium may afford some therapeutic advantages, such as increased *in vivo* half-life and/or exposure, or may provide a compound useful for investigating *in vivo* routes of drug elimination and metabolism.

For example, the compounds described herein may be artificially enriched in one or more particular isotopes. In some embodiments, the compounds described herein may be artificially enriched in one or more isotopes that are not predominantly found in nature. In some embodiments, the compounds described herein may be artificially enriched in one or more isotopes selected from deuterium (^{2}H), tritium (^{3}H), iodine-125 (^{125}I) or carbon-14 (^{14}C). In some embodiments, the compounds described herein are artificially enriched in one or more isotopes selected from ^{2}H, ^{11}C, ^{13}C, ^{14}C, ^{15}C, ^{12}N, ^{13}N, ^{15}N, ^{16}N, ^{16}O, ^{17}O, ^{14}F, ^{15}F, ^{16}F, ^{17}F, ^{18}F, ^{33}S, ^{34}S, ^{35}S, ^{36}S, ^{35}Cl, ^{37}Cl, ^{79}Br, ^{81}Br, ^{131}I, and ^{125}I. In some embodiments, the abundance of the enriched isotopes is independently at least 1%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or 100% by molar.

In some embodiments, the compound is deuterated in at least one position. In some embodiments, the compounds disclosed herein have some or all of the ^{1}H atoms replaced with ^{2}H atoms.

The methods of synthesis for deuterium-containing compounds are known in the art and include, by way of non-limiting example only, the procedure described in U.S. Patent Nos. 5,846,514 and 6,334,997, and the following synthetic methods. For example, deuterium substituted compounds may be synthesized using various methods such as described in: Dean, Dennis C.; Editor. Recent Advances in the Synthesis and Applications of Radiolabeled Compounds for Drug Discovery and Development. [In: Curr., Pharm. Des., 2000; 6(10)] **2000**, 110 pp; George W.; Varma, Rajender S. The Synthesis of Radiolabeled Compounds via Organometallic Intermediates, Tetrahedron, **1989**, 45(21), 6601-21; and Evans, E. Anthony. Synthesis of radiolabeled compounds, J. Radioanal. Chem., **1981**, 64(1-2), 9-32.

Deuterated starting materials are readily available and are subjected to the synthetic methods described herein to provide for the synthesis of deuterium-containing compounds. Large numbers of deuterium-containing reagents and building blocks are available commercially from chemical vendors, such as Aldrich Chemical Co.

Tautomers

In some situations, compounds exist as tautomers. The compounds described herein include all possible tautomers within the formulas described herein. Tautomers are compounds that are interconvertible by migration of a hydrogen atom, accompanied by a switch of a single bond and adjacent double bond. In bonding arrangements where tautomerization is possible, a chemical equilibrium of the tautomers will exist. All tautomeric forms of the compounds disclosed herein are contemplated. The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH.

Medical treatment

Similarly, within the scope of the present invention is a method or treating cancer in a patient in need thereof, comprising administering to the patient a compound according to the above description.

Pharmaceutical Compositions, Administration/Dosage Forms and Salts

According to one aspect of the compound according to the invention, the compound according to the invention is provided as a pharmaceutical composition, pharmaceutical administration form, or pharmaceutical dosage form, said pharmaceutical composition, pharmaceutical administration form, or pharmaceutical dosage form comprising at least one of the compounds of the present invention or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable carrier, diluent or excipient.

The skilled person is aware that any specifically mentioned drug compound mentioned herein may be present as a pharmaceutically acceptable salt of said drug. Pharmaceutically acceptable salts comprise the ionized drug and an oppositely charged counterion. Non-limiting examples of pharmaceutically acceptable anionic salt forms include acetate, benzoate, besylate, bitatrate, bromide, carbonate, chloride, citrate, edetate, edisylate, embonate, estolate, fumarate, gluceptate, gluconate, hydrobromide, hydrochloride, iodide, lactate, lactobionate, malate, maleate, mandelate, mesylate, methyl bromide, methyl sulfate, mucate, napsylate, nitrate, pamoate, phosphate, diphosphate, salicylate, disalicylate, stearate, succinate, sulfate, tartrate, tosylate, triethiodide and valerate. Non-limiting examples of pharmaceutically acceptable cationic salt forms include aluminium, benzathine, calcium, ethylene diamine, lysine, magnesium, meglumine, potassium, procaine, sodium, tromethamine and zinc.

In certain embodiments of the invention, the compound of the present invention is typically formulated into pharmaceutical dosage forms to provide an easily controllable dosage of the drug and to give the patient an elegant and easily handleable product.

Similarly, a dosage form for the prevention or treatment of cancer is provided, comprising a non-agonist ligand or antisense molecule according to any of the above aspects or embodiments of the invention.

The invention further encompasses a pharmaceutical composition comprising a compound of the present invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In further embodiments, the composition comprises at least two pharmaceutically acceptable carriers, such as those described herein.

Certain embodiments of the invention relate to a dosage form for enteral administration, such as nasal, buccal, rectal, transdermal or oral administration, or as an inhalation form or suppository. In addition, the pharmaceutical compositions of the present invention can be made up in a solid form (including without limitation capsules, tablets, pills, granules, powders or suppositories), or in a liquid form (including without limitation solutions, suspensions or emulsions).

Certain embodiments of the invention relate to a dosage form for parenteral administration, such as subcutaneous, intravenous, intrahepatic or intramuscular injection forms. Optionally, a pharmaceutically acceptable carrier and/or excipient may be present.

The dosage regimen for the compounds of the present invention will vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient, and the effect desired. In certain embodiments, the compounds of the invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

In certain embodiments, the pharmaceutical composition or combination of the present invention can be in unit dosage of about 1-1000 mg of active ingredient(s) for a subject of about 50-70 kg. The therapeutically effective dosage of a compound, the pharmaceutical composition, or the combinations thereof, is dependent on the species of the subject, the body weight, age and individual condition, the disorder or disease or the severity thereof being treated. A physician, clinician or veterinarian of ordinary skill can readily determine the effective amount of each of the active ingredients necessary to prevent, treat or inhibit the progress of the disorder or disease.

The pharmaceutical compositions of the present invention can be subjected to conventional pharmaceutical operations such as sterilization and/or can contain conventional inert diluents, lubricating agents, or buffering agents, as well as adjuvants, such as preservatives, stabilizers,

wetting agents, emulsifiers and buffers, etc. They may be produced by standard processes, for instance by conventional mixing, granulating, dissolving or lyophilizing processes. Many such procedures and methods for preparing pharmaceutical compositions are known in the art, see for example L. Lachman et al. The Theory and Practice of Industrial Pharmacy, 4th Ed, 2013 (ISBN 8123922892).

Method of Manufacture and Method of Treatment according to the invention

The invention further encompasses, as an additional aspect, the use of a compound as identified herein, or its pharmaceutically acceptable salt, as specified in detail above, for use in a method of manufacture of a medicament for the treatment or prevention of cancer.

Similarly, the invention encompasses methods of treatment of a patient having been diagnosed with a disease associated with cancer. This method entails administering to the patient an effective amount of compound as identified herein, or its pharmaceutically acceptable salt, as specified in detail herein.

The invention is further illustrated by the following examples and figures, from which further embodiments and advantages can be drawn. These examples are meant to illustrate the invention but not to limit its scope.

Examples

Biochemical assays

Example 1: TR-FRET

The IC_{50} values were obtained through an HTRF-based assay. The assay evaluates the binding interaction of the YTHDC1 YTH domain (amino acids 345–509) and a methylated RNA (sequence: 5'-Biotin-AAGAACCGG(m^6A)CUAAGCU-30). The YTH domain of YTHDC1 is expressed as a GST-fusion protein that is recognized by an anti-GST antibody labelled with Eu^{3+}, acting as the Förster resonance energy transfer (FRET) donor. The biotinylated RNA is bound by Streptavidin conjugated to XL665, the FRET acceptor. The binding of the methylated RNA to the YTH binding site leads to the formation of a four-member complex constituted by the GST-tagged YTH domain of YTHDC1, anti-GST Eu^{3+}-labelled antibody, biotinylated RNA, and Streptavidin conjugated to XL665. This complex formation subsequently leads to the proximity between the FRET donor and acceptor, resulting in a signal emission. Suppose the tested compound can compete with the methylated RNA for the occupation of the YTH active site, the emitted signal decreases. The assay mix includes 25 nM YTHDC1 YTH domain-GST fusion protein, 15 nM biotinylated RNA (Dharmacon), 0.8 nM anti-GST Eu^{3+}-conjugated antibody (Cisbio, 61GSTKLB), 1.875 nM XL665-conjugated

streptavidin (Cisbio, 610SAXLB), and the compound of interest. The compound concentration in the final mix strictly depends on the assay's aims. It is fixed at 1 mM to investigate the residual signal or set as an array of 1 mM 2-fold dilutions to determine the IC_{50} values. The assay's components are diluted in a buffer composed of 50 mM HEPES pH 7.5, 150 mM NaCl, 100 mM kF, and 0.1% BSA. The reagents mix is incubated for 3 h at 24 C, transferred into a white, low volume 384-well plate (Corning, 4513), and measured using an Infinite M1000 plate reader (Tecan). Eu^{3+} is excited at a wavelength of 317 nm, and fluorescence emissions are measured at 620 and 665 nm, with an excitation/emission lag time of 60 µs. The IC_{50} values were obtained by analyzing the dose-response data.

Example 2: TSA assay

Protein sample was buffered in 25 mM HEPES pH 7.2, 150 mM NaCl and assayed in a 96-well plate at a final concentration of 2 µM in 20 µl volume. Fluorescent dye was added as a fluorescence probe at a dilution of 1:1000. Compound concentrations tested were 12.5 µM, 25 µM, 50 µM, 100 µM and 200 µM. The temperature was raised with a step of 0.5 °C starting from 20 °C to 80 °C and fluorescence readings were taken at each interval. The reported values (ΔTm) are calculated as the difference between the transition midpoints of an individual sample and the average of the reference wells (containing the protein and the DMSO only) in the same plate. The DMSO concentration was kept at 1% (v/v).

Example 3: Cytotoxicity

Cells were seeded in white clear-bottom 96-well plates at a density of 6×10^3 cells/well in 50 µL of the complete RPMI medium and treated with 50 µL of increasing concentrations of the indicated compounds dissolved in DMSO (final concentration of compounds 1.25 − 160 µM) or DMSO only (0.5 % (v/v)) as a negative control and incubated for 72 h at 37°C with 5 % CO_2. Cell viability was determined using a CellTiter-Glo luminescent cell viability assay (Promega) based on the detection of ATP according to manufacturer's instructions. 100 µL of the reagent was added to each well and incubated for 10 min at room temperature on an orbital shaker. The luminescence was recorded using a Tecan Infinite 3046 M1000 microplate reader from the top. Background luminescence value was obtained from wells containing the CellTiter-Glo reagent and medium without cells. Cell viability curves were plotted in GraphPad Prism 9 and fitted with nonlinear regression, from which GI_{50} values were determined.

Table 4 IC_{50}, GI_{50} and ΔT_m data of YTHDC1 inhibitors.

The activity for representative examples is shown in the following table, wherein:

A: 0< IC_{50} ≤ 1 µM; B: 1 µM < IC_{50} ≤ 10 µM; C: 10 µM < IC_{50} ≤ 100 µM; D: IC_{50} > 100 µM

A*: 0< GI_{50} ≤ 1 µM; B*: 1 µM < GI_{50} ≤ 10 µM; C*: 10 µM < GI_{50} ≤ 100 µM; D*: GI_{50} > 100 µM

E: 0 °C < ΔT_m ≤ 1 °C; F: 1 °C < ΔT_m ≤ 10 °C

Compound	TR-FRET IC_{50} (μM)	TSA ΔT_m (°C), @ 100 μM comp conc.	Antiprolif. activity GI_{50} (μM)
FE150	A	F	B*
ZA232	D		
ZA236	B	F	C*
ZA294	B	E	
ZA308	B	F	C*
ZA309	B	F	
ZA311	B	F	B*
ZA312	B	F	
ZA326	B		C*
ZA337	A	F	
ZA340	C	E	
ZA341	B	F	
ZA343	D		
ZA347	B	F	B*
ZA349	A	F	B*
ZA354	B	F	C*
ZA356	C	F	
ZA360	A		D*
ZA364	A		C*
ZA366	B		
ZA385	A		C*
ZA393	B		
ZA400	A		C*
ZA409	B		
ZA410	B		
ZA431	B		
ZA560	C		
CSDC1-001	B		
CSDC1-002	C		
ZA572	B		
ZA480	B		
ZA515	B		
ZA513	B		
ZA591	A		D*
ZA590	B		B*
ZA540b	B		
ZA348	D		
ZA540a	D		

Table 5. IC_{50} data

The activity for representative examples is shown in the following table, wherein A: 0< IC_{50} ≤ 1 μM; B: 1 μM < IC_{50} ≤ 10 μM; C: 10 μM < IC_{50} ≤ 100 μM; D: IC_{50} > 100 μM.

Compound	IC50 (μM)
2	A
3	B

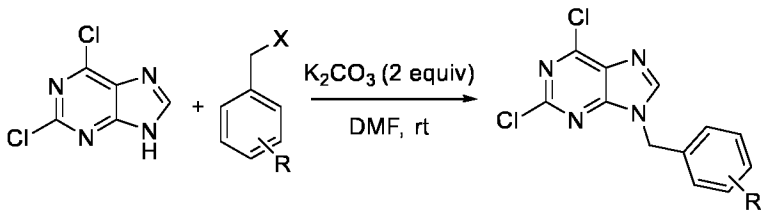
5	B
6	B
7	B
8	B
9	B
10	B
11	A
12	B
13	B
14	B
15	B
16	B
17	B
18	A
20	C
22	D
24	D
29	A
30	D
33	A
35	A
36	B
40	A
43	A
45	B
47	B
49	C
54	A
56	A
57	A
58	C
59	D
60	C
61	D
62	B
63	C
64	C
65	D
66	D
67	D
68	D
69	C
70	D
71	B
72	A
73	A
74	A
75	A
76	A
77	A
78	A
79	A
80	A

81	C
82	C
83	B
84	C
85	B
86	B
87	B

Chemistry

All reagents were purchased from commercial suppliers and used as received. Reactions run at elevated temperature were carried out in the oil bath. All reactions were monitored by thin-layer chromatography (Aluminium plates coated with silica gel 60 F_{254}). Flash column chromatography was carried out over silica gel (0.040-0.063 mm). ^{1}H and ^{13}C $\{^{1}H\}$ NMR spectra were recorded on AV2 400 MHz and AV600 Bruker spectrometers (400 MHz, 101 MHz and 600 MHz, 150 MHz, respectively) in DMSO or $CDCl_3$ Chemical shifts are given in ppm and their calibration was performed to the residual ^{1}H and ^{13}C signals of the deuterated solvents. Multiplicities are abbreviated as follows: singlet (s), doublet (d) multiplet (m), and broad signal (bs). The purity was acquired by Liquid chromatography high resolution electrospray ionization mass spectrometry (LC-HR- ESI-MS): Acquity UPLC (Waters, Milford, USA) connected to an Acquity eλ diode array detector and a Synapt G2 HR-ESI-QTOF-MS (Waters, Milford, USA); injection of 1 μL sample (c = ca. 10-100 μg mL−1 in the indicated solvent); Acquity BEH C18 HPLC column (1.7 μm particle size, 2 × 50 mm, Waters) kept at 30 °C;* elution at a flow rate of 400 μL min−1 with A: H_2O + 1% HCO_2H and B: CH_3CN + 0.1% HCO_2H, linear gradient from 5–98% B within 5 min, then isocratic for 1 min;* UV spectra recorded from 200–600 nm at 1.2 nm resolution and 20 points s−1; ESI: positive ionization mode, capillary voltage 3.0 kV, sampling cone 40V, extraction cone 4V, N_2 cone gas 4 L h−1, N_2 desolvation gas 800 L min−1, source temperature 120°C; mass analyzer in resolution mode: mass range 100–2'000 m/z with a scan rate of 1 Hz; mass calibration to <2 ppm within 50–2'500 m/z with a 5mM aq. soln. of HCO_2Na, lockmasses: m/z 195.0882 (caffein, 0.7 ng mL−1) and 556.2771(Leucine-enkephalin, 2 ng mL−1).

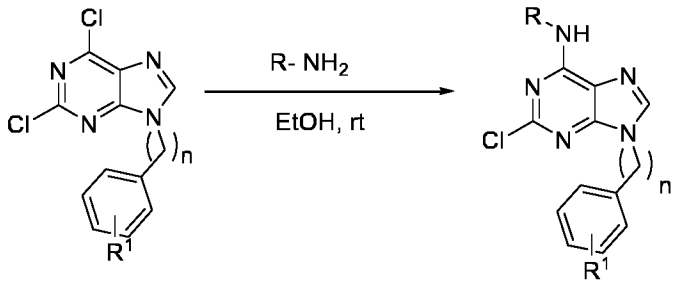
Example 4: General procedure for 2,5-dichloropurine alkylation



2,6-dichloropurine (1 equiv) was dissolved in DMF (0.5 M) and K_2CO_3 (2 equiv) was added. To a stirred mixture was added alkylhalide (1 equiv). The resulting reaction mixture was stirred at

rt until a reaction completion (Monitored by TLC). The reaction mixture was quenched by an addition of water and extracted into EtOAc. Combined organic layers were washed by 10 % aq. sol. of LiCl. Then dried over $MgSO_4$, filtrated and evaporated.

Example 5: General procedure for nucleophilic aromatic substitution (S_nAr) with $MeNH_2$



n = 0, 1

9-alkyl-2,6-dichloropurine (1 mmol) was suspended in EtOH (0.5 M) and 33 % $MeNH_2$ in EtOH (2 mL) and stirred at rt. After the reaction completion (TLC) the volatiles were removed *in vacuo.* The crude product was purified using flash column chromatography.

N-(2-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)phenyl)methanesulfonamide (ZA364)

tert-butyl (2-((2,6-dichloro-9H-purin-9-yl)methyl)phenyl)carbamate (0.47 g, 1.19 mmol) was dissolved in DCM (5 mL) followed by addition of TFA (0.45 mL). The reaction mixture was stirred at rt for 16 hours. After the reaction completion, the reaction was quenched by aq. sol. Na_2CO_3 and extracted into DCM. Combined organic layers were dried over $MgSO_4$ and the volatiles were removed *in vacuo.*. The crude product was purified using flash column chromatography (SiO2; EtOAc/Hept = 1 : 1) and the intermediate 2-((2,6-dichloro-9H-purin-9-yl)methyl)aniline was obtained as a white solid (0.346 g, 31 %). 1H NMR (400 MHz, DMSO) δ 8.93 (s, 1H), 8.62 (s, 1H), 7.33 – 7.28 (m, 2H), 7.15 – 7.10 (m, 1H), 7.08 (d, *J* = 7.0 Hz, 1H), 5.48 (s, 2H), 1.41 (s, 9H); 13C NMR (101 MHz, DMSO) δ 154.1, 154.0, 151.5, 150.2, 148.9, 136.5, 130.8, 130.2, 129.1, 129.0, 126.6, 125.9, 79.6, 44.4, 28.5.

To a solution of Compound 2-((2,6-dichloro-9H-purin-9-yl)methyl)aniline (0.067 g, 0.227 mmol) in DCM (2.2 mL) was added pyridine (0.024 mL, 0.295 mmol). The solution was cooled down to 0 ℃ and MsCl (0.021 mL, 0.274 mmol) was added dropwise after 30 min. After the reaction completion (TLC), the volatiles were removed *in vacuo*. The crude product was subsequently used in the next step without further purification. The final product was prepared following Example 5. The crude product was purified using flash column chromatography (SiO_2; EtOAc/MeOH = 4 : 1 → 4 : 0) and the desired compound was obtained (0.025 g, 30 % after two steps). 1H NMR (400 MHz, DMSO) δ 9.50 (s, 1H), 8.31-8.25 (m, 1H), 8.18 (s, 1H), 7.40 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.35 (td, *J* = 7.5, 1.5 Hz, 1H), 7.22 (td, *J* = 7.4, 1.5 Hz, 1H), 6.87 (dd, *J* = 7.8, 1.5 Hz, 1H), 5.45 (s, 2H), 3.09 (s, 3H), 2.92 (d, *J* = 4.6 Hz, 2H); 13C NMR (101 MHz, DMSO) δ 155.6, 153.3, 149.6, 141.4, 134.8, 133.2, 128.7,

128.0, 127.0, 126.8, 118.2, 42.9, 27.2. LRMS (ESI) m/z: [M + H]+ calcd for C12H12N5; 367.073 found, 367.075.

N-(4-chloro-2-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)phenyl) methanesulfonamide (ZA400)

To a solution of N-(4-chloro-2-(hydroxymethyl)phenyl)methanesulfonamide (0.747 g, 3.17 mmol), prepared the procedure reported in *Angewandte Chemie International Edition* **2019**, *58* (51), 18410–18413, in DCM (6.3 mL) was added dropwise $SOCl_2$ (0.342 mL, 4.75 mmol). The reaction mixture was stirred at rt for 90 min. The volatiles were removed *in vacuo* and the crude product was dissolved in DMF (6.2 mL) and added to a stirred solution of 2,6-dichloropurine (0.599 g, 3.17 mmol) and K_2CO_3 (0.649 g, 4.71 mmol). The reaction was quenched by aq. sol. of NH_4Cl after 5 hours. The reaction mixture was extracted into EtOAc (3 x 12 mL) and combined organic layers were dried over $MgSO_4$, filtrated and evaporated. The residue was dissolved in EtOH (4 mL) and 33 % $MeNH_2$ in EtOH (1 mL) was added. The reaction mixture was stirred at rt for 1 hour. After the reaction completion, the volatiles were removed *in vacuo*. The crude compound was purified using flash column chromatography (SiO2; EtOAc/Hept = 4 : 1 → 6 : 1) and the desired compound was obtained (0.074 g, 6 % after three steps). 1H NMR (400 MHz, DMSO) δ 9.61 (s, 1H), 8.32 - 8.27 (m, 1H), 8.21 (s, 1H), 7.45 – 7.40 (m, 2H), 5.43 (s, 2H), 3.10 (s, 3H), 2.93 (d, *J* = 4.6 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 155.6, 153.3, 149.6, 141.4, 134.6, 133.3, 128.7, 128.0, 127.1, 126.9, 118.2, 42.9, 27.2. LRMS (ESI) m/z: [M + H]+ calcd for C14H15Cl2N6O2S; 401.035 found, 401.035.

2-chloro-9-(3-chloro-4-methoxybenzyl)-N-methyl-9H-purin-6-amine (FE150)

The compound was prepared following Example 4 using 2,6-dichloropurine (0.566 g, 3.00 mmol) and 2-chloro-4-(chloromethyl)-1-methoxybenzene (0.573 g, 3.00 mmol). The crude product was purified using flash column chromatography (SiO2; EtOAc/Hept = 3 : 2) and the desired compound was obtained. (0.71 g, 69 %). 1H NMR (400 MHz, DMSO) δ 8.05 (s, 1H), 7.34 (d, J = 2.2 Hz, 1H), 7.21 (dd, J = 8.5, 2.3 Hz, 1H), 6.90 (d, J = 8.5 Hz, 1H), 5.32 (s, 2H), 3.88 (s, 3H); 13C NMR (101 MHz, CDCl3) δ 155.7, 153.3, 153.1, 152.0, 145.5, 130.8, 130.2, 128.0, 127.0, 123.4, 112.6, 56.4, 47.2. The final compound was prepared following Example 5 from corresponding 9-alkyl-2,6-dichloro-9H-purine (0.134 g, 0.397 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/Hept = 2 : 3 → 1 : 4) and the desired compound was obtained (0.08 g, 59 %). %). 1H NMR (400 MHz, DMSO) δ 8.24 (s, 1H), 8.26 – 8.18 (bs, 1H), 7.44 (d, *J* = 2.2 Hz, 1H), 7.25 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.12 (d, *J* = 8.5 Hz, 1H), 5.26 (s, 2H), 3.82 (s, 3H), 2.91 (d, *J* = 4.6 Hz, 3H); 13C NMR (101 MHz, DMSO) δ 155.5, 154.2, 153.4, 149.3, 141.0, 129.8, 129.3, 127.9, 121.0, 118.3, 113.0, 56.1, 45.3, 27.2. LRMS (ESI) m/z: [M + H]+ calcd for C14H14Cl2N5O; 338.057 found, 338.057.

methyl 3-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzoate (ZA347)

The N^9 alkylation was performed following Example 4 using 2,6-dichloropurine (0.825 g, 4.37 mmol) and methyl-3-bromomethylbenzoate (1.0 g, 4.37 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/Hept = 2 : 1) and the desired compound was obtained as a white solid (0.465 g, 31 %). 1H NMR (400 MHz, CDCl3) δ 8.08 (s, 1H), 8.04 (dt, J = 7.3, 1.7 Hz, 1H), 8.01 – 8.00 (bs, 1H), 5.46 (s, 2H), 3.92 (s, 3H); 13C NMR (101 MHz, CDCl3) δ 166.2, 153.4, 153.1, 152.1, 145.4, 134.5, 132.5, 131.4, 130.7, 130.3, 129.6, 129.1, 52.4, 47.6.

The final compound was prepared following Example 5 from corresponding 9-alkyl-2,6-dichloro-9H-purine (0.465 g, 1.38 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/Hept = 3 : 1) and the desired compound was obtained (0.374g, 82 %). ^{1}H NMR (400 MHz, DMSO) δ 8.28 (s, 1H), 8.29 – 8.21 (m, 1H), 7.90 – 7.87 (m, 2H), 7.56 – 7.49 (m, 2H), 5.43 (s, 2H), 3.83 (s, 3H), 2.92 (d, *J* = 4.6 Hz, 1H); 13C NMR (101 MHz, DMSO) δ 165.9, 155.6, 153.5, 149.5, 141.2, 137.5, 132.3, 130.1, 129.4, 128.6, 128.0, 118.3, 52.3, 45.9, 27.2. LRMS (ESI) m/z: [M + H]+ calcd for C15H15ClN5O2; 332.091 found, 332.091.

2-chloro-9-(3-chlorobenzyl)-N-methyl-9H-purin-6-amine (ZA349)

The final compound was prepared following Examples 5 starting from ZA348 (0.272 g, 0.867 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/Hept = 3 : 1) and the desired compound was obtained (0.191 g, 71 %). ^{1}H NMR (400 MHz, DMSO) δ 8.26 (s, 1H), 8.28 – 8.21 (bs, 1H), 7.40 – 7.35 (m, 3H), 7.23 – 7.18 (m, 1H), 5.35 (s, 2H), 2.92 (d, *J* = 4.7 Hz, 3H); 13C NMR (101 MHz, DMSO) δ 155.6, 153.5, 149.4, 141.2, 139.2, 133.3, 130.8, 127.9, 127.4, 126.1, 118.3, 45.7, 27.2. LRMS (ESI) m/z: [M + H]+ calcd for C13H12Cl2N5; 308.045 found, 308.046.

Methyl 4-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzoate (ZA311)

The N^9 alkylation was performed following Example 4 using 2,6-dichloropurine (0.2 g, 1.06 mmol) and methyl-4-(bromomethyl)benzoate (0.242 g, 1.06 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/Hept = 1 : 2) and the desired compound was obtained as a white solid (0.145 g, 40 %). 1H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 8.05 – 8.03 (m, 2H), 7.38 – 7.34 (m, 2H), 5.47 (s, 2H), 3.91 (s, 3H). 13C NMR (101 MHz, CDCl3) δ 166.3, 153.5, 153.3, 152.2, 145.5, 138.9, 131.0, 130.8, 130.7, 128.0, 52.5, 47.7.

The final compound was prepared following Example 5 from corresponding 9-alkyl-2,6-dichloro-9H-purine (0.052 g, 0.154 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/Hept = 2 : 1) and the desired compound was obtained (0.038

g, 74 %). ^{1}H NMR (400 MHz, DMSO) δ 8.26 (s, 2H), 7.93 (d, 2H), 7.35 (d, 2H), 5.45 (s, 2H), 3.83 (s, 3H), 2.92 (bs, 3H); 13C NMR (101 MHz, DMSO) δ 165.9, 155.6, 153.5, 149.5, 142.0, 141.3, 129.6, 129.0, 127.4, 118.3, 52.2, 45.9, 27.2. HRMS (ESI) m/z: [M + H]+ calcd for C15H15ClN5O2; 332.091 found, 332.091.

3-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzoic acid (ZA337)

The corresponding methyl ester ZA311 (0.2 g, 0.602 mmol) was dissolved in dioxane (6 mL) followed by the addition of 38 % HCl (4 mL). The reaction mixture was refluxed for 5 hours. The reaction mixture was cooled to 0 °C and left for 4 hours at this temperature. The precipitate was filtered off and dried on air providing the final compound (164 mg, 85 %). 1H NMR (400 MHz, DMSO) δ 8.52 (s, 1H), 8.48 – 8.38 (bs, 1H), 7.92 – 7.88 (m, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 5.47 (s, 2H), 2.93 (s, 3H); 13C NMR (101 MHz, DMSO) δ 13C NMR (101 MHz, DMSO) 13C NMR (101 MHz, DMSO) δ 167.0, 155.1, 154.0, 149.3, 141.2, 141.0, 130.4, 129.8, 127.5, 116.8, 46.4, 27.3. LRMS (ESI) m/z: [M + H]+ calcd for C14H13ClN5O2 318.075 found, 318.075.

5-chloro-N,3-dimethyl-1H-pyrazolo[4,3-d]pyrimidin-7-amine (ZA431)

To a powder of 4-amino-3-methyl-1H-pyrazole-5-carboxamide (0.13 g, 0.97 mmol), which was prepared following the procedure reported in *J. Org. Chem.* 1956, 21, 8, 833–836, was added urea (389 mg, 6.4 mmol). The neat reaction mixture was heated and stirred at 195 °C for 5 h. Upon the temperature increase, the solid reactants melted and after the product formation, the reaction mixture solidified. The reaction vessel was cooled to rt and the crude product was used in the next step without further purification.

The pyrazolo[4,3-d]pyrimidine-5,7(6H)-dione was suspended in $POCl_3$ (4.6 mL) followed by the addition of DIPEA (0.403 mL, 2.3 mmol). The reaction mixture was heated at 70 °C for 14 hours. The volatiles were removed *in vacuo* and the residue was poured over ice. The mixture was extracted into EtOAc (3 x 6 mL) and the combined organic layers were dried over $MgSO_4$ and filtered. Activated charcoal was added to the filtrate and the mixture was stirred for 10 minutes. After the charcoal removal (filtration paper), the solvent was removed under reduced pressure. The crude product was dissolved in EtOH and 33% $MeNH_2$ in EtOH (0.2 mL) was added into the reaction vessel. The reaction mixture was stirred at rt for 1 hour and after the reaction completion (TLC), the volatiles were removed *in vacuo*. The crude product of ZA431 was purified using flash column chromatography (SiO_2; EtOAc/MeOH = 10 : 1) and the desired compound was obtained (0.018 g, 9 % after three steps). ^{1}H NMR (400 MHz, MeOH -d^4) δ 3.12 (s, 3H), 2.49 (s, 3H). ^{13}C NMR (126 MHz, MeOD) δ 155.83, 154.20, 138.56, 136.67, 128.31, 27.83, 9.34. LRMS (ESI) m/z: [M + H]+ calcd for C7H9ClN5; 198.054 found, 198.019.

5,7-dichloro-3-methyl-1H-pyrazolo[4,3-d]pyrimidine was prepared according to 5).

2-chloro-N-methyl-9-phenyl-9H-purin-6-amine (ZA232)

The final compound was prepared following Example 5 from corresponding 9-phenyl-2,6-dichloro-9H-purine (0.02 g, 0.075 mmol) that was prepared according to the procedure reported in *Tetrahedron Lett* **2003**, *44* (16), 3359–3362. The crude product was purified using flash column chromatography (SiO_2; EtOAc/Hept = 1.2 : 1) and the desired compound was obtained (0.017 g, 87 %). 1H NMR (400 MHz, CDCl3) δ 7.98 (s, 1H), 7.67 – 7.64 (m, 2H), 7.57 – 7.53 (m, 2H), 7.46 – 7.42 (m, 1H), 6.05 – 5.93 (bs, 1H), 3.22 (s, 3H); 13C NMR (101 MHz, CDCl3) δ 156.4, 155.5, 149.7, 139.3, 134.6, 130.1, 128.4, 123.6, 119.6, 27.9. LRMS (ESI) m/z: [M + H]+ calcd for C12H11ClN5; 260.070 found, 260.070.

9-benzyl-2-chloro-N-methyl-9H-purin-6-amine (ZA236)

The N^9 alkylation was performed following Example 4 using 2,6-dichloropurine (0.2 g, 1.06 mmol) and BnBr (0.126 mL, 1.06 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/Hept = 1.2 : 2) and the desired compound was obtained. as a white solid (0.160 g, 54 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.43 – 7.36 (m, 3H), 7.31 (m, 2H), 5.41 (s, 2H); 13C NMR (101 MHz, $CDCl_3$) δ 153.4, 153.3, 152.1, 145.7, 134.1, 130.8, 129.6, 129.3, 128.3, 48.2.

The final compound was prepared following Example 5 from corresponding 9-benzyl-2,6-dichloro-9H-purine (0.08 g, 0.286 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/Hept = 2.5 : 1 -> 4 : 1) and the desired compound was obtained (0.06 g, 76 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (bs, 1H), 7.38 – 7.32 (m, 3H), 7.31 (m, 2H), 5.89 (bs, 1H), 5.32 (s, 2H), 3.19 (bs, 3H); 13C NMR (101 MHz, CDCl3) δ 156.1, 154.9, 150.1, 139.8, 135.3, 129.1, 128.5, 128.0, 118.7, 47.2, 29.7. LRMS (ESI) m/z: [M + H]+ calcd for C13H13ClN5; 274.085 found, 274.085.

2-chloro-N-methyl-9-(pyridin-4-ylmethyl)-9H-purin-6-amine (ZA308)

The N^9 alkylation was performed following Example 4 using 2,6-dichloropurine (0.2 g, 1.06 mmol) and 4-bromoethylpyridine hydrobromide (0.267 g, 1.06 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/MeOH = 2 : 0.2) and the desired compound was obtained as a white solid (0.094 g, 32 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 – 8.55 (m, 2H), 8.05 (s, 1H), 7.11 – 7.06 (m, 2H), 5.39 (s, 2H). 13C NMR (101 MHz, $CDCl_3$) δ 153.7, 153.3, 152.5, 151.0, 145.4, 143.0, 130.8, 122.2, 46.8.

The final compound was prepared following Example 5 from corresponding 9-alkyl-2,6-dichloro-9H-purine (0.069 g, 0.246 mmol). The crude product was purified using flash column

chromatography (SiO_2; EtOAc/MeOH = 2 : 0.2 -> 2 : 0.8) and the desired compound was obtained (0.045 g, 66 %). ^{1}H NMR (400 MHz, DMSO) δ 8.53 – 8.52 (m, 2H), 8.29 – 8.27 (m, 1H), 8.26 (s, 1H), 8.16 – 8.15 (m, 2H), 5.42 (s, 2H), 2.93 (d, *J* = 4.6 Hz, 3H); 13C NMR (101 MHz, DMSO) δ 155.6, 153.5, 150.0, 149.5, 145.5, 141.3, 121.8, 118.3, 45.2, 27.2. LRMS (ESI) m/z: [M + H]+ calcd for C12H12ClN6; 275.081 found, 275.081.

2-chloro-N-methyl-9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-amine (ZA560)

The final compound was prepared following Example 5 from corresponding 9-alkyl-2,6-dichloro-9H-purine (0.2 g, 0.073 mmol) that was prepared according to the procedure reported in Eur. J. Med. Chem. 2019, 184, 111728. The crude product was purified using flash column chromatography (SiO_2; EtOAc/Hept = 2 : 1) and the desired compound was obtained (0.165 g, 84 %). 1H NMR (400 MHz, DMSO) δ 8.35 (s, 1H), 8.27 – 8.22 (m, 1H), 5.56 (dd, *J* = 11.0, 2.2 Hz, 1H), 4.03 – 3.96 (m, 1H), 3.75 – 3.61 (m, 1H), 2.92 (d, *J* = 4.6 Hz, 3H), 2.37 – 2.18 (m, 1H), 2.08 – 1.92 (m, 2H), 1.86 – 1.72 (m, 1H), 1.68 – 1.56 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 155.5, 153.4, 148.9, 139.2, 118.2, 80.9, 67.7, 30.0, 27.2, 24.5, 22.3. LRMS (ESI) m/z: [M + H]+ calcd for C11H15ClN5O; 268.096 found, 268.097.

3-(2-chloro-6-(methylamino)-9H-purin-9-yl)benzoic acid (ZA294)

The final compound was prepared following Example 5 from corresponding tert-butyl 3-(2,6-dichloro-9H-purin-9-yl)benzoate (0.02 g, 0.055 mmol) that was prepared according to the procedure reported in *Tetrahedron Lett* **2003**, *44* (16), 3359–3362. The crude product was purified using flash column chromatography (SiO_2; EtOAc/Hept = 2 : 1). and the desired compound was obtained as a white solid (0.018 g, 91 %). 1H NMR (400 MHz CDCl3) δ 8.21 (t, *J* = 1.9 Hz, 1H), 8.07 – 8.02 (m, 2H), 7.93 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.61 (t, *J* = 7.9 Hz, 1H), 6.14 – 6.03 (bs, 1H), 3.29 – 3.15 (bs, 3H), 1.62 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.60, 156.39, 155.63, 139.01, 134.76, 134.02, 130.05, 129.21, 127.53, 124.10, 119.67, 82.12, 77.36, 28.29.

The tert-butyl ester (0.014, 0.039 mmol) was dissolved in DCM (0.5 mL) and TFA was added (0.02 mL). The reaction was stirred at rt overnight and neutralized with DIPEA. The volatiles were evaporated *in vacuo* and the crude product was recrystalized from H_2O. The final product was obtained (0.011 g, 93 %). 1H NMR (400 MHz, DMSO) δ 8.64 (s, 1H), 8.41 – 8.37 (m, 1H), 8.35 – 8.34 (bs, 1H), 8.07 – 8.01 (m, 2H), 7.76 – 7.72 (m, 1H), 2.96 (d, *J* = 4.5 Hz, 3H); 13C NMR (101 MHz, DMSO) δ 166.5, 155.8, 153.9, 149.0, 140.1, 134.9, 132.3, 130.0, 128.5, 127.6, 123.9, 118.9, 27.3.LRMS (ESI) m/z: [M + H]+ calcd for C13H11ClN5O2; 304.057 found, 304.039.

2-(2-chloro-6-(methylamino)-9H-purin-9-yl)-N-phenylacetamide (ZA572)

The N^9 alkylation was performed following Example 4 using 2,6-dichloropurine (0.2 g, 1.06 mmol) and *N*-phenylchloroacetamide (1.0 g , 5.9 mmol), that was prepared according to the procedure reported in *Eur J Med Chem* **2022**, *238*, 114444. The crude product was purified using flash column chromatography (SiO_2; EtOAc/Hept = 2:1 to 4:1) and the desired compound was obtained as a white solid (0.54 g, 28 %). ^{1}H NMR (400 MHz, DMSO) δ 10.53 (s, 1H), 8.88 (s, 1H), 7.61 – 7.50 (m, 2H), 7.36 – 7.29 (m, 2H), 7.14 – 7.05 (m, 1H), 5.42 (s, 1H). 13C NMR (101 MHz, $CDCl_3$) δ 153.4, 153.3, 152.1, 145.7, 134.1, 130.8, 129.6, 129.3, 128.3, 48.2. ^{13}C NMR (101 MHz, DMSO) δ 164.8, 163.1, 153.5, 151.0, 143.4, 138.3, 128.9, 123.9, 122.4, 119.3, 49.4.

The final compound was prepared following Example 5 from corresponding 9-alkyl-2,6-dichloro-9H-purine (0.05 g, 0.155 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/Hept = 4 : 1 to 10:1) and the desired compound was obtained (0.038 g, 77 %). ^{1}H NMR (400 MHz, DMSO) δ 9.63 (bs, 1H), 7.41 – 7.39 (m, 1H), 7.31 (s, 1H), 6.75 (d, *J* = 7.3 Hz, 2H), 6.54 – 6.45 (m, 2H), 6.25 (t, *J* = 7.4 Hz, 1H), 4.22 (s, 2H), 2.10 (d, *J* = 4.6 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 164.87, 155.52, 153.25, 149.83, 142.16, 138.47, 128.90, 123.67, 119.13, 117.87, 45.68, 27.19. LRMS (ESI) m/z: [M + H]+ calcd for C14H14ClN6O; 317.091 found, 317.092.

9-(2-aminobenzyl)-2-chloro-N-methyl-9H-purin-6-amine (ZA341)

The N^9 alkylation was performed following Example 4 using 2,6-dichloropurine (0.531 g, 2.81 mmol) and tert-butyl (2-(chloromethyl)phenyl)carbamate that was prepared according to the procedure reported in *Angewandte Chemie* **2014**, 126 (36), 9757–9761.. The crude product was purified using flash column chromatography (SiO2; EtOAc/Hept = 1 : 1) and the desired compound was obtained as a white solid (0.346 g, 31 %). 1H NMR (400 MHz, DMSO) δ 8.93 (s, 1H), 8.62 (s, 1H), 7.33 – 7.28 (m, 2H), 7.15 – 7.10 (m, 1H), 7.08 (d, *J* = 7.0 Hz, 1H), 5.48 (s, 2H), 1.41 (s, 9H); 13C NMR (101 MHz, DMSO) δ 154.1, 154.0, 151.5, 150.2, 148.9, 136.5, 130.8, 130.2, 129.1, 129.0, 126.6, 125.9, 79.6, 44.4, 28.5.

The next step was performed using Example 5 from corresponding 9-alkyl-2,6-dichloro-9H-purine (0.15 g, 0.38 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/Hept = 2 : 1) and the desired compound was obtained as a white solid (0.121 g, 81 %). ^{1}H NMR (400 MHz, DMSO) 9.06 (s, 1H), 8.28 – 8.22 (m, 1H), 8.11 (s, 1H), 7.38 (d, *J* = 8.7 Hz, 1H), 7.29 (td, *J* = 7.6, 1.6 Hz, 1H), 7.11 (td, *J* = 7.5, 1.4 Hz, 1H), 7.00 (d, *J* = 6.8 Hz, 1H), 5.32 (s, 2H), 2.92 (d, *J* = 4.6 Hz, 3H), 1.46 (s, 9H). ^{13}C NMR (101 MHz, DMSO) δ 155.6, 153.6, 153.3, 149.5, 141.1, 136.0, 130.1, 128.4, 125.6, 125.2, 118.1, 79.2, 43.0, 28.1, 27.3.

The final compound was prepared by deprotection (0.05 g, 0.128 mmol) in DCM (0.6 mL) using TFA (0.097 mL, 1.28 mmol). The reaction mixture was stirred at room temperature for 6 h. The volatiles were removed *in vacuo* and the crude product was purified using flash column chromatography (SiO_2; EtOAc/MeOH = 2 : 1 → 10 : 1) and the desired compound was obtained (0.024 g, 64 %). ^{13}C NMR (101 MHz, DMSO) δ 155.54, 153.23, 149.44, 145.93, 141.10, 128.80, 128.62, 119.68, 118.11, 116.53, 115.46, 43.09, 27.18. LRMS (ESI) m/z: [M + H]+ calcd for C13H14ClN6; 289.096 found, 289.096.

N-(2-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)phenyl)-4-methylbenzene sulfonamide (ZA480)

To a solution of ZA341 (0.1 g, 0.339 mmol) in DCM (2 mL) was added pyridine (0.032 mL, 0.407 mmol). The solution was cooled down to 0 ℃ and TsCl (0.064 mL, 0.339 mmol) was added portion wise after 30 min. After the reaction completion (TLC), the volatiles were removed *in vacuo*. The crude product was subsequently used in the next step without further purification. The final product was prepared following Example 5. The crude product was purified using flash column chromatography (SiO_2; EtOAc:Hept = 2 : 1) and the desired compound was obtained (0.078 g, 52 % after two steps). 1H NMR (400 MHz, CDCl3) 7.74 (d, *J* = 8.0 Hz, 2H), 7.72 – 7.68 (bs, 1H), 7.29 – 7.21 (m, 4H), 7.18 – 7.10 (m, 1H), 6.27 – 6.13 (bs, 1H), 4.93 (s, 2H), 3.20 – 3.03 (bs, 3H), 2.40 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.0, 154.7, 149.0, 143.5, 139.4, 138.2, 135.9, 130.7, 130.5, 130.2, 129.8, 127.5, 127.2, 1276.0, 118.7, 44.2, 27.8, 21.7. LRMS (ESI) m/z: [M + H]+ calcd for C20H20ClN6O2S; 443.105 found, 443.099.

N-(2-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)phenyl)-2,2,2-trifluoroacetamide (ZA343)

To a solution ZA341 (0.07 g, 0.237 mmol) in DCM (2 mL) was added pyridine (0.024 mL, 0.308 mmol). The solution was cooled down to 0 ℃ and trifluoroacetic anhydride (0.039 mL, 0.280 mmol) was added dropwise after 30 min. After the reaction completion (TLC), the volatiles were removed *in vacuo*. The crude product was subsequently used in the next step without further purification. The final compound was prepared following Example 5. The crude product was purified using flash column chromatography (SiO2; EtOAc/MeOH = 2 : 1 → 3 : 1) and the desired compound was obtained (0.030 g, 30 % after two steps). 1H NMR (400 MHz, DMSO) δ 11.32 (s, 1H), 8.37 – 8.28 (m, 1H), 8.16 (s, 1H), 7.50 – 7.38 (m, 3H), 7.18 (dd, J = 7.6, 1.5 Hz, 1H), 5.40 (s, 2H), 2.98 (d, J = 4.5 Hz, 1H); 13C NMR (101 MHz, DMSO) δ 156.05 (q, J = 36.7 Hz), 155.9, 153.8, 149.8, 141.5, 133.1, 132.8, 129.3, 129.2, 128.6, 127.9, 118.2 (q, 70.7 Hz), 115.0, 43.1, 27.7. LRMS (ESI) m/z: [M + H]+ calcd for C15H12ClF3N6O; 385.079 found, 385.078.

2-chloro-9-(2-(difluoromethyl)benzyl)-N-methyl-9H-purin-6-amine (ZA354)

2-(difluoromethyl)benzoic acid (0.500 g, 2.90 mmol) was dissolved in THF (5 mL) and BH_3 . DMS (0.687 mL, 7.25 mmol) was added dropwise. The reaction mixture was stirred under dinitrogen atmosphere at rt overnight. After the reaction completion (monitored by TLC), the reaction was quenched by aq. sol. of $NaHCO_3$. The mixture was extracted into EtOAc (3 x 7 mL). The combined organic layers were dried over $MgSO_4$, filtrated and evaporated. The resulting alcohol was dissolved in DCM (5.2 mL) together with one drop of DMF, followed by addition of $SOCl_2$ (0.315 mL, 4.35 mmol). The reaction mixture was stirred at rt overnight. The volatiles were removed *in vacuo* and the resulting alkyl chloride was used in the next step without further purification.

The N^9 alkylation was performed following Example 4 using 2,6-dichloropurine (0.48 g, 2.54 mmol) and 1-chloromethyl-2-difluoromethylbenzene (0.449 g, 2.54 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/Hept = 1 : 1) and the desired compound was obtained as a white solid (0.210 g, 25 %). 1H NMR (400 MHz, CDCl3) δ 8.06 (s, 1H), 7.54 – 7.46 (m, 3H), 7.34 – 7.32 (m, 1H), 6.84 (t, *J* = 54.8 Hz, 1H), 5.63 (s, 2H); 13C NMR (101 MHz, CDCl3) δ 153.4, 152.2, 145.9 (t, *J* = 2.6 Hz), 132.7, 132.1 (t, *J* = 2.0 Hz) , 131.9 (t, *J* = 21.6 Hz), 130.8, 130.7, 129.4, 128.3 (t, *J* = 8.2 Hz), 116.0 (t, *J* = 238.9 Hz), 44.4 (t, *J* = 2.7 Hz).

The final compound was prepared following Example 5 starting from corresponding 9-alkyl-2,6-dichloro-9H-purine (0.080 g, 0.243 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/Hept = 1.1 : 1) and the desired compound was obtained (0.071g, 90 %). ^{1}H NMR (400 MHz, , $CDCl_3$) δ 7.65 (s, 1H), 7.54 – 7.51 (m, 1H), 7.47 – 7.40 (m, 2H), 7.23 (d, *J* = 8.3 Hz, 1H), 6.87 (t, *J* = 54.9 Hz, 1H), 6.09 – 5.94 (bs, 1H), 5.52 (s, 2H), 3.28 – 3.08 (bs, 3H); 13C NMR (101 MHz, CDC3) δ 156.2, 150.2, 140.1, 133.92 (t, *J* = 2.2 Hz), 131.97 (t, *J* = 21.4 Hz), 131.8, 130.1, 128.9, 118.6, 127.65 (t, *J* = 8.1 Hz), 115.50 (t, *J* = 238.8 Hz), 43.5. LRMS (ESI) m/z: [M + H]+ calcd for C14H13ClF2N5; 324.082 found, 324.082.

2-chloro-N-methyl-9-(2-(trifluoromethyl)benzyl)-9H-purin-6-amine (ZA366)

2-(trifluoromethyl)benzoic acid (0.500 g, 2.63 mmol) was dissolved in THF (5.2 mL) and BH_3 . DMS (0.748 mL, 7.89 mmol) was added dropwise. The reaction mixture was stirred under dinitrogen atmosphere at rt overnight. After the reaction completion (monitored by TLC), the reaction was quenched by aq. sol. of $NaHCO_3$. The mixture was extracted into EtOAc (3 x 7mL). The combined organic layers were dried over $MgSO_4$, filtrated and evaporated. The resulting alcohol was dissolved in DCM (5.2 mL) together with one drop of DMF, followed by addition of $SOCl_2$ (0.504 mL, 6.95 mmol). The reaction mixture was stirred at rt overnight. The

volatiles were removed *in vacuo* and the resulting alkylchloride was used in the next step without further purification.

The N^9 alkylation was performed following Example 4 using 2,6-dichloropurine (0.525 g, 2.78 mmol) and 1-chloromethyl-2-trifluoromethylbenzen (0.540 g, 2.78 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/Hept = 1 : 1.2) and the desired compound was obtained as a white solid (0.234 g, 24 % after three steps). 1H NMR (400 MHz, CDCl3) δ 8.02 (s, 1H), 7.77 (d, *J* = 7.0 Hz, 1H), 7.58 – 7.47 (m, 2H), 7.29 (d, *J* = 7.6 Hz, 1H), 5.63 (s, 2H); 13C NMR (101 MHz, CDCl3) δ 153.6, 153.5, 152.3, 133.1, 132.5, 130.7, 130.5, 129.4, 128.5 (q, *J* = 30.7 Hz), 128.3, 126.9 (q, *J* = 5.6 Hz), 125.6, 122.9, 44.5 (q, *J* = 2.9 Hz).

The final compound was prepared following Example 5 from corresponding 9-alkyl-2,6-dichloro-9H-purine (0.1 g, 0.288 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/Hept = 1 : 1) and the desired compound was obtained (0.045 g, 46 %). ^{1}H NMR (400 MHz, DMSO) δ 8.33 – 8.27 (m, 1H), 8.17 (s, 1H), 7.82 (d, *J* = 7.7 Hz, 1H), 7.61 (t, J = 7.7 Hz, 1H), 7.54 (t, J = 7.8 Hz, 1H), 6.85 (d, J = 7.7 Hz, 1H), 5.55 (s, 2H), 2.94 (d, J = 4.6 Hz, 3H); 13C NMR (101 MHz, DMSO) δ 156.1, 154.01, 150.1, 141.9, 135.0, 133.7, 128.8, 128.5, 126.77 (q, J = 5.7 Hz), 126.6, 126.3, 126.1, 126.0, 123.4, 118.8, 43.6, 27.7. LRMS (ESI) m/z: [M + H]+ calcd for C14H12ClF3N5; 342.073 found, 342.074.

2-chloro-9-(2-methoxybenzyl)-N-methyl-9H-purin-6-amine (ZA312)

The N^9 alkylation was performed following Example 4 using 2,6-dichloropurine (0.2 g, 1.06 mmol) and 1-chloromethyl-2-methoxybenzen (0.165 g, 1.06 mmol) that was prepared according to the procedure reported in *J Org Chem* **2002**, *46* (11), 2394–2398. The crude product was purified using flash column chromatography (SiO_2; EtOAc/Hept = 1.2 : 1) and the desired compound was obtained as a white solid (0.103 g, 31 %). 1H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.39 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.35 (td, *J* = 7.9, 1.7 Hz, 1H), 6.96 (td, *J* = 7.5, 1.1 Hz, 1H), 6.91 (d, *J* = 8.2 Hz, 1H), 5.38 (s, 2H), 3.86 (s, 3H); 13C NMR (101 MHz, $CDCl_3$) δ 157.5, 153.4, 152.9, 151.5, 146.6, 131.1, 131.0, 130.7, 122.3, 121.2, 110.9, 55.6, 43.8.

The final compound was prepared following Example 5 starting from corresponding 9-alkyl-2,6-dichloro-9H-purine (0.048 g, 0.155 mmol). The crude product was purified using flash column chromatography (SiO2; EtOAc/Hept = 3 : 1) and the desired compound was obtained (0.036 g, 76 %). 1H NMR (400 MHz, CDCl3) δ 7.72 (s, 1H), 7.31 (td, J = 7.9, 1.7 Hz, 1H), 7.26 (dd, J = 7.5, 1.7 Hz, 1H), 6.94 – 6.8 (m, 2H), 6.22 – 6.02 (bs, 1H), 5.30 (s, 2H), 3.86 (s, 3H), 3.27 – 3.06 (bs, 3H); 13C NMR (101 MHz, CDCl3) δ 157.4, 156.1, 140.6, 130.6, 130.6, 130.5, 130.3, 127.7, 123.5, 121.0, 118.6, 110.7, 55.5, 42.7, 27.8. LRMS (ESI) m/z: [M + H]+ calcd for C14H15ClN5O; 304.096 found, 304.097.

3-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzoic acid (ZA360)

The corresponding methyl ester (0.1 g, 0.301 mmol) was dissolved in dioxane (3 mL) followed by the addition of 38 % HCl (2 mL). The reaction mixture was refluxed for 5 hours. The reaction mixture was cooled to 0 °C and left for 4 hours at this temperature. The white precipitate was filtered off and dried on air. The carboxylic acid was isolated (60 mg, 63 %). ^{1}H NMR (400 MHz, DMSO) δ 8.32 (s, 1H), 8.32 – 8.25 (bs, 1H), 7.88 – 7.83 (m, 2H), 7.54 – 7.47 (m, 2H), 5.43 (s, 2H), 2.92 (d, *J* = 3.9 Hz, 3H). 13C NMR (101 MHz, DMSO) δ 13C NMR (101 MHz, DMSO) δ 166.9, 155.4, 153.6, 149.4, 141.2, 137.2, 131.9, 131.2, 129.1, 128.8, 128.1, 117.9, 46.0, 27.2. LRMS (ESI) m/z: [M + H]+ calcd for C14H13ClN5O2 318.075 found, 318.075.

9-(3-(2H-tetrazol-5-yl)benzyl)-2-chloro-N-methyl-9H-purin-6-amine (ZA515)

To a solution of the nitrile (0.05 g, 0.167 mmol) in DMSO (1.6 mL) was added anhydrous $CuSO_4$ (0.066 g, 0.417 mmol) and NaN_3 (0.010 g, 0.167 mmol). The reaction mixture was heated at 100 °C for 16 h. The reaction mixture was quenched with 10 % HCl and extracted into EtOAc. Combined organic layers were washed with 10 % aq. sol. of LiCl and dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified using flash column chromatography (SiO_2; DCM/MeOH = 5 : 1 → 1 : 1) and the desired compound was obtained (0.021 g, 36 %). 1H NMR (400 MHz, DMSO) δ 8.28 (s, 1H), 8.26 – 8.23 (m, 1H), 7.89 (d, *J* = 7.7 Hz, 1H), 7.84 (s, 1H), 7.35 (t, *J* = 7.7 Hz, 1H), 7.15 (d, *J* = 7.6 Hz, 1H), 5.39 (s, 2H), 2.92 (d, *J* = 4.7 Hz, 2H).^{13}C NMR (101 MHz, DMSO) δ 160.29, 155.60, 153.45, 149.53, 141.30, 136.79, 133.11, 128.78, 125.81, 125.18, 124.47, 118.27, 46.34, 27.20.

3-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzamide (ZA393)

Corresponding carboxylic acid (0.064 g, 0.201 mmol) was suspended in dry DMF (1.6 mL) followed by the addition of DIPEA (0.052 mL, 0.301 mmol). The reaction mixture was cooled to 0 °C and COMU (0.128 g, 0.301 mmol) was added after 30 min. To the reaction mixture was added 7N NH_3 in THF (0.2 mL) after additional 30 min. The reaction was slowly warmed to rt and stirred overnight. The reaction mixture was then extracted into EtOAc and combined organic layers were dried over $MgSO_4$ and evaporated. The crude product was purified using flash column chromatography (SiO_2; EtOAc/MeOH = 2 : 0.1 → 2 : 0.2) and the desired compound was obtained (0.015 g, 24 %). 1H NMR (400 MHz, DMSO) δ 8.25 (s, 1H), 8.27 – 8.20 (bs, 1H), 7.98 (s, 1H), 7.79 (dt, *J* = 7.3, 1.7 Hz, 1H), 7.75 (s, 1H), 7.46 – 7.35 (m, 3H), 5.39 (s, 2H), 2.92 (d, *J* = 4.6 Hz, 2H); 13C NMR (101 MHz, DMSO) δ 168.0, 156.0, 153.9, 149.9, 141.7, 137.4, 135.2, 130.6, 129.2, 127.2, 127.0, 118.7, 46.5, 27.7. LRMS (ESI) m/z: [M + H]+ calcd for C14H14ClN6O; 317.091 found, 317.091.

3-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)-N-methylbenzamide (ZA385)

Corresponding carboxylic acid (0.027 g, 0.084 mmol) was suspended in dry DMF (0.6 mL) followed by the addition of DIPEA (0.021 mL, 0.126 mmol). The reaction mixture was cooled to 0 °C and COMU (0.053 g, 0.126 mmol) was added after 30 min. To the reaction mixture was added 2M $MeNH_2$ in THF (0.15 mL) after additional 30 min. The reaction was slowly warmed to rt and stirred overnight. The reaction mixture was then extracted into EtOAc and combined organic layers were dried over $MgSO_4$ and evaporated. The crude product was purified using flash column chromatography (SiO_2; EtOAc/MeOH = 2 : 0.1 → 2 : 0.2) and the desired compound was obtained (0.017 g, 60 %). 1H NMR (400 MHz, DMSO) δ 8.47 – 8.39 (m, 1H), 8.28 (s, 2H), 7.75 – 7.71 (m, 2H), 7.44 (t, *J* = 7.4 Hz, 1H), 7.39 (dt, *J* = 7.7, 1.6 Hz, 1H), 5.39 (s, 2H), 2.92 (d, *J* = 4.7 Hz, 3H), 2.76 (d, *J* = 4.6 Hz, 3H). 13C NMR (101 MHz, DMSO) δ 166.8, 156.0, 153.9, 149.9, 141.7, 137.4, 135.5, 130.4, 129.2, 126.7, 126.6, 118.7, 46.5, 27.7, 26.7. LRMS (ESI) m/z: [M + H]+ calcd for C15H16ClN6; 331.107 found, 331.106.

9-(3-bromobenzyl)-2-chloro-N-methyl-9H-purin-6-amine (ZA409)

The N^9 alkylation was performed following Example 4 using 2,6-dichloropurine (0.5 g, 2.65 mmol) and 1-bromo-3-bromomethylbenzen (0.661 g, 2.65 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/Hept = 1.2 : 2) and the desired compound was obtained as a white solid (0.35 g, 37 %). 1H NMR (400 MHz, DMSO) δ 8.84 (s, 1H), 7.63 – 7.61 (bs, 1H), 7.54 – 7.49 (m, 1H), 7.34 – 7.29 (m, 2H), 5.50 (s, 2H); 13C NMR (101 MHz, DMSO) δ 153.4, 151.1, 149.8, 148.4, 138.2, 131.0, 131.0, 130.6, 130.5, 126.8, 121.9, 46.4.

The final compound was prepared following Example 5 starting from corresponding 9-alkyl-2,6-dichloro-9H-purine (0.150 g, 0.419 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/Hept = 1 : 1) and the desired compound was obtained (0.12 g, 81 %). 1H NMR (400 MHz, DMSO) δ 8.26 (s, 1H), 7.54 – 7.49 (m, 2H), 7.32 (t, J = 7.7 Hz, 1H), 7.24 (d, J = 7.8 Hz, 1H), 5.35 (s, 2H), 2.92 (d, J = 4.7 Hz, 3H). 13C NMR (101 MHz, DMSO) δ 155.6, 153.5, 149.4, 141.1, 139.4, 131.0, 130.7, 130.2, 126.5, 121.9, 118.3, 45.6, 27.2. LRMS (ESI) m/z: [M + H]+ calcd for C13H12BrClN5; 351.995 found, 351.996.

3-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzonitrile (ZA513)

The N^9 alkylation was performed following Example 4 using 2,6-dichloropurine (0.337 g, 1.79 mmol) and 3-(bromomethyl)benzonitrile (0.35 g, 1.79 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/Hept = 2.5 : 1) and the desired compound was obtained as a white solid (0.15 g, 28 %). ^{1}H NMR (400 MHz, CDCl3) δ 8.11 (s, 1H), 7.67 (dt, *J* = 7.1, 1.7 Hz, 1H), 7.61 – 7.60 (m, 1H), 7.57 – 7.41 (m, 2H), 5.47 (s, 2H). ^{13}C NMR (101

MHz, $CDCl_3$) δ 153.7, 153.2, 152.5, 145.2, 135.9, 132.8, 132.3, 131.4, 130.8, 130.5, 117.9, 113.8, 47.2.

The final compound was prepared following Example 5 from corresponding 9-alkyl-2,6-dichloro-9H-purine (0.082 g, 0.262 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/MeOH = 10 : 1) and the desired compound was obtained (0.057 g, 71 %). ^{1}H NMR (400 MHz, DMSO) δ 8.29 – 8.21 (m, 2H), 7.80 – 7.75 (m, 2H), 7.58 – 7.55 (m, 2H), 5.41 (s, 2H), 2.92 (d, *J* = 4.6 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 155.6, 153.4, 149.4, 141.1, 138.2, 132.3, 131.7, 131.1, 130.0, 118.5, 118.3, 111.6, 45.5, 27.2. LRMS (ESI) m/z: [M + H]+ calcd for C14H12ClN6; 299.081 found, 299.080.

2-chloro-9-(3-methoxybenzyl)-N-methyl-9H-purin-6-amine (ZA309)

The *N*^{9} alkylation was performed following Example 4 using 2,6-dichloropurine (0.2 g, 1.06 mmol) and 1-bromomethyl-3-methoxybenzen (0.212 g, 1.06 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/Hept = 2 : 1.2) and the desired compound was obtained as a white solid (0.115 g, 35 %). 1H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.25 (d, *J* = 13.5, 5.6 Hz, 1H), 6.87 – 6.80 (m, 3H), 5.33 (s, 2H), 3.75 (s, 3H); 13C NMR (101 MHz, $CDCl_3$) δ 160.4, 153.3, 153.3, 152.0, 145.7, 135.5, 130.8, 130.6, 120.3, 114.4, 114.1, 55.5, 48.1. 393

The final compound was prepared following Example 5 starting from corresponding 9-alkyl-2,6-dichloro-9H-purine (0.050 g, 0.161 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/Hept = 2 : 1) and the desired compound was obtained (0.034 g, 69 %). ^{1}H NMR (400 MHz, , $CDCl_3$) δ 7.64 (s, 1H), 7.28 – 7.24 (m, 1H), 6.87 – 6.81 (m, 3H), 6.20 – 6.01 (bs, 1H), 5.27 (s, 2H), 3.77 (s, 3H), 3.25 – 3.08 (bs, 3H). 13C NMR (101 MHz, CDCl3) δ 160.2, 156.2, 155.0, 150.2, 139.9, 136.8, 130.3, 120.2, 118.7, 114.0, 113.8, 55.4, 47.3, 27.8. LRMS (ESI) m/z: [M + H]+ calcd for C14H15ClN5O; 304.096 found, 304.097.

(4-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)phenyl)methanol (ZA326)

The *N*^{9} alkylation was performed following Example 4 using 2,6-dichloropurine (0.2 g, 1.06 mmol) and (4-(bromomethyl)phenyl)methanol (0.212 g, 1.06 mmol) that was prepared according to the procedure reported in *Org Lett* **2003**, *5* (13), 2239–2242. The crude product was purified using flash column chromatography (SiO2; EtOAc/Hept = 3 : 1 → 5 : 1) and the desired compound was obtained as a white solid (0.12 g, 37 %). 1H NMR (400 MHz, DMSO) δ 8.83 (s, 1H), 7.32 – 7.27 (m, 4H), 5.47 (s, 2H), 5.24 – 5.07 (bs, 1H), 4.47 (s, 2H); 13C NMR (101 MHz, DMSO) δ 153.4, 151.1, 149.8, 148.4, 142.6, 133.9, 130.5, 127.5, 126.8, 62.5, 47.0.

The final compound was prepared following Example 5 from corresponding 9-alkyl-2,6-dichloro-9H-purine (0.05 g, 0.264 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/MeOH = 1 : 0.1) and the desired compound was obtained

(0.075 g, 92 %). 1H NMR (400 MHz, DMSO) δ 8.22 (s, 1H), 8.23 – 8.18 (bs, 1H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.22 (d, *J* = 8.2 Hz, 2H), 5.31 (s, 2H), 5.17 (t, J = 5.7 Hz, 1H), 4.45 (d, J = 5.7 Hz, 1H), 2.91 (d, J = 4.6 Hz, 3H); 13C NMR (101 MHz, DMSO) δ 13C NMR (101 MHz, DMSO) δ 155.6, 153.4, 149.5, 142.2, 141.2, 135.1, 127.2, 126.8, 118.3, 62.6, 46.2, 27.2. LRMS (ESI) m/z: [M + H]+ calcd for C14H14ClN5O; 304.096 found, 304.096

3-chloro-5-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzoic acid (ZA591)

The corresponding methyl ester (0.06 g, 0.161 mmol) was dissolved in dioxane (2.5 mL) followed by the addition of 38 % HCl (1 mL). The reaction mixture was refluxed for 5 hours. The reaction mixture was cooled to 0 ℃ and left for 4 hours at this temperature. The white precipitate was filtered off and dried on air. The carboxylic acid was isolated (0.045 g, 79 %). 1H NMR (400 MHz, DMSO) δ 8.36 (s, 1H), 8.35 – 8.28 (bs, 1H), 7.83 (t, *J* = 1.8 Hz, 1H), 7.77 (t, *J* = 1.6 Hz, 1H), 7.68 (t, *J* = 1.9 Hz, 1H), 5.45 (s, 2H). ^{13}C NMR (101 MHz, DMSO) δ 166.15, 155.87, 154.09, 149.79, 141.56, 139.99, 134.04, 133.74, 132.18, 128.79, 127.36, 118.31, 45.96, 27.68. LRMS (ESI) m/z: [M + H]+ calcd for C14H12Cl2N5O2; 352.036 found, 352.036.

methyl 3-chloro-5-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzoate (ZA590)

The N^9 alkylation was performed following Example 4 using 2,6-dichloropurine (0.459 g, 2.43 mmol) and methyl 3-(bromomethyl)-5-chlorobenzoate (0.641 g, 2.43 mmol) that was prepared according to the procedure reported in *Molecules* **2023**, *28* (2), 768. The crude product was purified using flash column chromatography (SiO2; EtOAc/Hept = 1:1) and the desired compound was obtained as a white solid (0.51 g, 56 %). 1H NMR (400 MHz, CDCl3) δ 8.10 (s, 1H), 8.02 – 8.00 (m, 1H), 7.88 – 7.86 (m, 1H), 7.48 (t, *J* = 1.9 Hz, 1H), 5.44 (s, 2H), 3.92 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.15, 153.71, 153.18, 152.44, 145.26, 136.46, 135.86, 133.07, 132.34, 130.82, 130.49, 127.23, 52.87, 47.15.

The final compound was prepared following Example 5 from corresponding 9-alkyl-2,6-dichloro-9H-purine (0.337 g, 0.906 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/Hept = 4 : 1) and the desired compound was obtained (0.176 g, 53 %). %). 1H NMR (400 MHz, DMSO) δ 8.32 – 8.24 (m, 2H), 8.86 – 8.81 (m, 2H), 7.70 – 7.69 (m, 1H), 5.44 (s, 2H), 3.84 (s, 3H), 2.92 (d, *J* = 4.6 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 165.18, 156.03, 153.96, 149.86, 141.60, 140.28, 134.20, 132.63, 132.46, 128.65, 127.30, 118.78, 53.09, 45.86, 27.66. LRMS (ESI) m/z: [M + H]+ calcd for C15H14Cl2N5O2; 366.052 found, 366.052.

2-chloro-9-(3,5-dichloro-4-methoxybenzyl)-N-methyl-9H-purin-6-amine (ZA410)

3,5-dichloro-4-methoxybenzoic acid (0.500 g, 2.26 mmol) was dissolved in THF (5 mL) and BH_3. DMS (0.529 mL, 5.65 mmol) was added dropwise. The reaction mixture was stirred under dinitrogen atmosphere at rt overnight. After the reaction completion (monitored by TLC), the

reaction was quenched by aq. sol. of $NaHCO_3$. The mixture was extracted into EtOAc (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtrated and evaporated. The resulting alcohol was dissolved in DCM (3 mL) together with one drop of DMF, followed by addition of $SOCl_2$ (0.261 mL, 3.63 mmol). The reaction mixture was stirred at rt overnight. The volatiles were removed *in vacuo* and the resulting 1,3-dichloro-5-(chloromethyl)-2-methoxybenzene was used in the next step without further purification.

The N^9 alkylation was performed following Example 4 using 2,6-dichloropurine (0.457 g, 2.42 mmol) and 1,3-dichloro-5-(chloromethyl)-2-methoxybenzene (0.449 g, 2.54 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/Hept = 1 : 1) and the desired compound was obtained as a white solid (0.325 g, 35 %). 1H NMR (400 MHz, DMSO) δ 8.81 (s, 1H), 7.54 (s, 2H), 5.46 (s, 2H), 3.80 (t, 3H); ^{13}C NMR (101 MHz, DMSO) δ 153.49, 151.36, 151.10, 149.75, 148.26, 133.69, 130.66, 128.79, 128.50, 60.61, 45.62.

The final compound was prepared following Example 5 for S_nAr starting from corresponding 9-alkyl-2,6-dichloro-9H-purine (0.080 g, 0.211 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/Hept = 1.1 : 1) and the desired compound was obtained (0.064g, 81 %). ^1H NMR (400 MHz, DMSO) δ 8.29 – 8.23 (bs, 1H), 8.25 (s, 1H), 7.45 (s, 2H), 5.31 (s, 2H), 3.80 (s, 3H), 2.92 (d, *J* = 4.7 Hz, 1H. ^{13}C NMR (101 MHz, DMSO) δ 155.6, 153.5, 151.2, 149.3, 141.1, 134.8, 128.5, 128.5, 118.3, 60.6, 44.9, 27.2. LRMS (ESI) m/z: [M + H]+ calcd for C14H13Cl3N5O; 372.018 found, 372.018.

9-(3-chlorobenzyl)-2-fluoro-N-methyl-9H-purin-6-amine ZA540b and 6-chloro-9-(3-chloro-benzyl)-N-methyl-9H-purin-2-amine (540a)

The N^9 alkylation was performed following Example 4 using 6-chloro-2-fluoro-9H-purine (0.578 g, 3.35 mmol) and 1-(bromomethyl)-3-chlorobenzene (0.688 g, 3.35 mmol). The crude product was purified using flash column chromatography (SiO2; EtOAc/Hept = 1 : 1) and the desired compound was obtained as a white solid (0.178 g, 18 %). 1H NMR (400 MHz, DMSO) δ 8.08 (s, 1H), 7.36 – 7.28 (m, 3H), 7.20 (dt, J = 6.7, 1.9 Hz, 1H), 5.36 (s, 2H). 13C NMR (101 MHz, CDCl3) δ 158.6, 156.4, 153.7, 153.5, 153.2, 153.0, 145.3, 145.3, 136.0, 135.3, 130.7, 130.2, 130.2, 129.3, 128.1, 126.1, 47.4.

The final compounds and were prepared following Example 5 starting from corresponding 9-alkyl-2,6-dichloro-9H-purine (0.080 g, 0.211 mmol). The reaction provided both products that were separated using flash column chromatography (SiO_2; EtOAc/Hept = 1.2 : 1 to 2:1) and the desired compounds were obtained (**ZA540b:** 0.021 g, 20 %, **ZA540a**: 0.042 g, 40 %). **ZA540b:** ^1H NMR (400 MHz, CDCl3) δ 7.66 (s, 1H), 7.30 – 7.15 (m, 3H), 7.17 – 7.14 (m, 1H), 6.16 – 6.02 (bs, 1H), 5.26 (s, 2H), 3.23 – 3.10 (bs, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.88, 158.81, 157.28, 157.07, 139.51, 139.48, 137.34, 135.00, 130.40, 128.73, 127.82, 125.91, 118.05, 46.56. ^{19}F NMR (376 MHz, $CDCl_3$) δ -49.37. LRMS (ESI) m/z: [M + H]+ calcd for

C13H12ClFN5; 292.076 found, 292.077. **ZA540a**: ^{1}H NMR (400 MHz, CDCl3) δ 7.70 (s, 1H), 7.34 – 7.27 (m, 3H), 7.18 – 7.14 (m, 1H), 5.28 – 5.22 (bs, 1H), 5.23 (s, 2H), 3.04 (d, *J* = 5.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.0, 154.0, 151.5, 141.2, 137.5, 135.1, 130.5, 128.9, 128.3, 126.1, 124.4, 46.7, 29.0. LRMS (ESI) m/z: [M + H]+ calcd for C13H12Cl2N5; 308.046 found, 308.048.

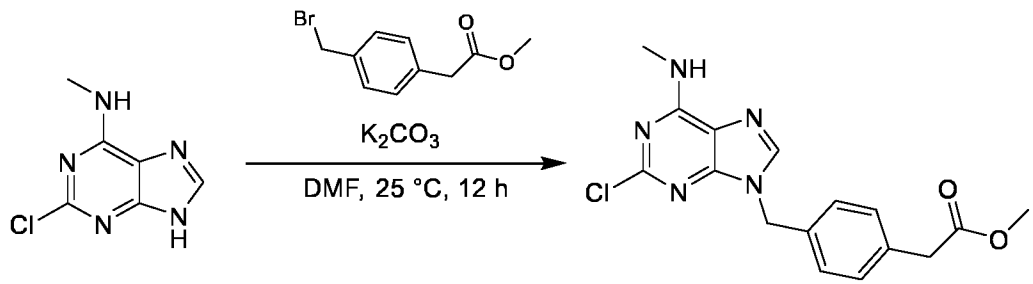
2-chloro-9-(3-chlorobenzyl)-N-cyclopropyl-9H-purin-6-amine (ZA356)

The compound was prepared following Example 5 starting from corresponding 9-alkyl-2,6-dichloro-9H-purine (0.07 g, 0.223 mmol) and cyclopropylamine (0.03 mL, 0.433 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/Hept = 3 : 1) and the desired compound was obtained (0.071 g, 95 %). ^{1}H NMR (400 MHz, DMSO) δ 7.66 (s, 1H), 7.32 – 7.28 (m, 2H), 7.24 (s, 1H), 7.17 – 7.12 (m, 1H), 6.18 – 5.95 (bs, 1H), 5.29 (s, 2H), 3.25 – 2.98 (bs, 1H), 1.87 (s, 1H), 0.96 – 0.91 (m, 2H), 0.67 – 0.63 (m, 2H); 13C NMR (101 MHz, CDCl3) δ 156.6, 155.0, 140.00, 137.4, 135.1, 130.6, 128.9, 128.0, 126.1, 118.7, 46.7, 24.2, 7.7. LRMS (ESI) m/z: [M + H]+ calcd for C15H14Cl2N5; 334.062 found, 334.062.

2,6-dichloro-9-(3-chlorobenzyl)-9H-purine (ZA348)

The *N*^{9} alkylation was performed following Example 4 using 2,6-dichloropurine (0.5 g, 2.65 mmol) and 1-bromomethyl-3-chlorbenzen (0.543 g, 2.65 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/Hept = 2 : 1) and the desired compound was obtained (0.495 g, 59 %). 1H NMR (400 MHz, CDCl3) δ 8.07 (s, 1H), 7.37 – 7.29 (m, 3H), 7.19 (dt, J = 6.8, 1.8 Hz, 1H), 5.39 (s, 2H). 13C NMR (101 MHz, CDCl3) δ 153.4, 153.1, 152.2, 145.3, 136.0, 135.3, 130.7, 130.7, 129.4, 128.1, 126.1, 47.3. LRMS (ESI) m/z: [M + H]+ calcd for C12H8Cl3N4; 312.981 found, 312.982.

Synthesis of methyl 2-(4-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)phenyl)acetate (Compound 2)

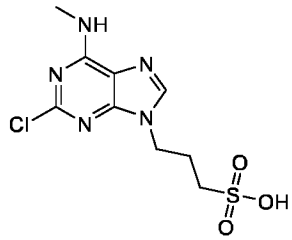
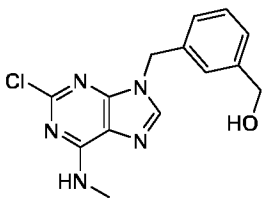
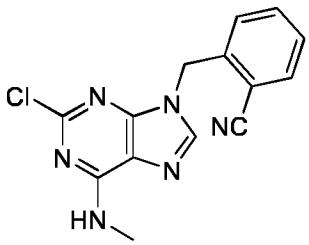


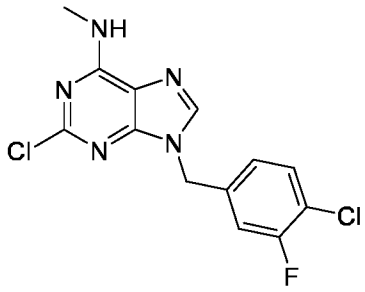
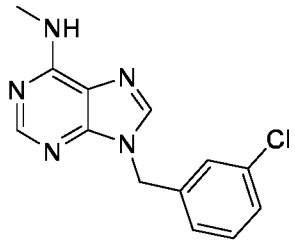
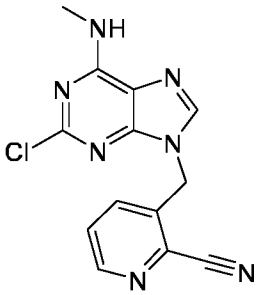
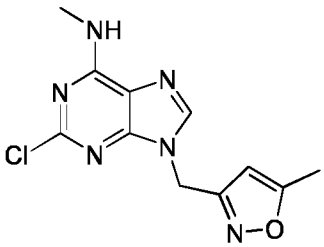
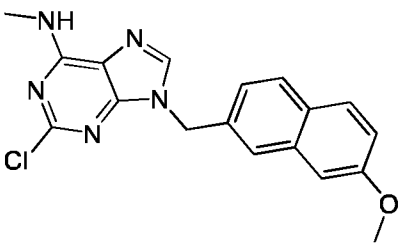
1 **2**

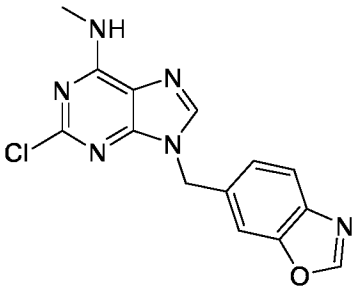
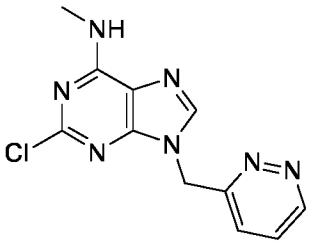
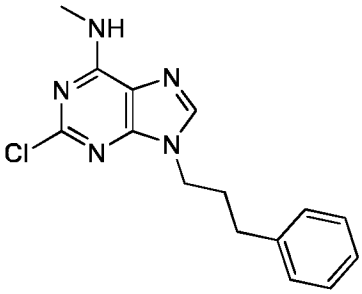
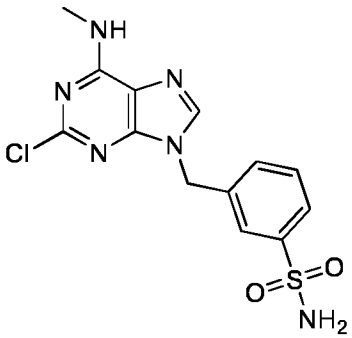
To a solution of 2-chloro-*N*-methyl-9*H*-purin-6-amine (**1**) (260 mg, 1 eq) and methyl 2-(4-(bromomethyl)phenyl)acetate (200 mg, 1 eq) in DMF (5 mL) was added K_2CO_3 (301 mg, 2 eq) at 25 °C. The mixture was stirred at 25 °C for 12 hr. The reaction mixture was poured into

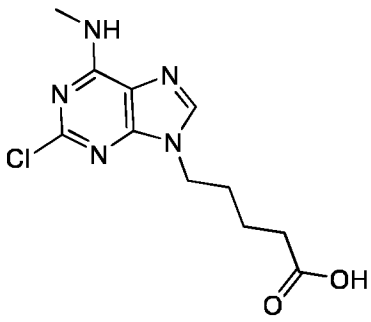
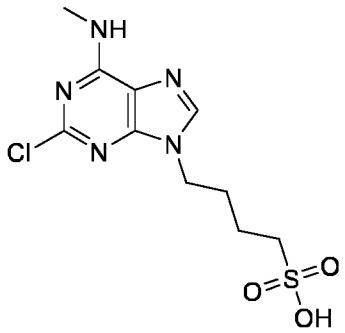
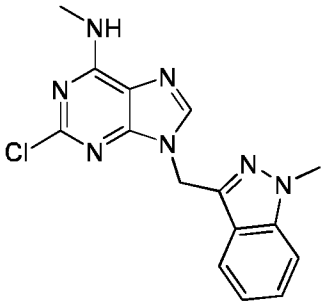
H_2O (10 mL) and extracted with ethyl acetate (10 mL × 2). The combined organic layers were washed with H_2O (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate / petroleum ether) to afford the desired compound (370 mg). LCMS ESI $[M+1]^+$: 346.2. ^1H NMR (400 MHz, MeOH-d_4) δ = 8.03 (s, 1H) 7.25-7.29 (m, 4H) 5.35 (s, 2H) 3.66 (s, 3H) 3.64 (s, 2H) 3.07 (br s, 3H).

The following analogs were prepared via a similar procedure and purified either via column chromatography or reversed phase HPLC.

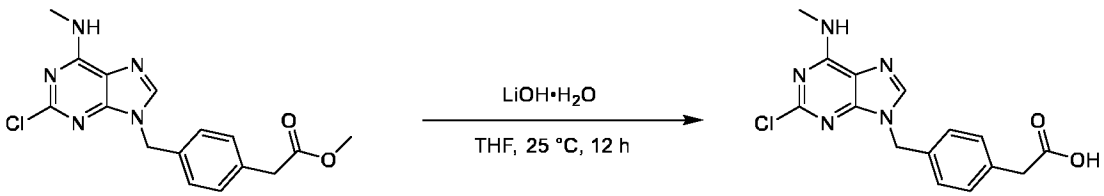
Compound ID	Structure	LCMS	^1H NMR
3		ESI $[M+1]^+$: 306.0	^1H NMR (400 MHz, MeOH-d_4) δ = 8.08 (s, 1H), 4.36 (t, *J*=7.2 Hz, 2H), 3.02-3.14 (m, 3H), 2.80 (t, *J*=7.2 Hz, 2H), 2.29–2.36 (m, 2H)
4		ESI $[M+1]^+$: 304.0	^1H NMR (400 MHz, DMSO-d_6) δ = 8.23 (s, 2H), 7.29 (t, *J*=7.2 Hz, 1H), 7.23 (d, *J*=7.2 Hz, 2H), 7.13 (d, *J*=7.6 Hz, 1H), 5.33 (m, 2H), 5.16 (t, *J*=5.6 Hz, 1H), 4.45 (d, *J*=4.4, Hz, 2H), 2.93 (br s, 3H)
5		ESI $[M+1]^+$: 299.1	^1H NMR (400 MHz, DMSO-d_6) δ = 8.29 (m, 1H), 8.20 (br s, 1H), 7.92-7.90 (d, *J*=7.6 Hz, 1H), 7.69-7.67 (t, *J*=7.6 Hz, 1H), 7.54-7.52 (t, *J*=7.6 Hz, 1H), 7.13 (d, *J*=7.6 Hz, 1H), 5.57 (s, 2H), 2.93 (br s, 3H)

Compound ID	Structure	LCMS	^{1}H NMR
6		ESI $[M+1]^+$: 325.7	^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.24 (s, 2H), 7.61-7.54 (m, 1H), 7.41-7.35 (m, 1H), 7.12-7.06 (m, 1H), 5.36 (s, 2H), 2.92 (br d, *J*=4.4 Hz, 3H)
7		ESI $[M+1]^+$: 274.2	^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.33-8.15 (m, 2H), 7.73 (br s, 1H), 7.39 (br s, 1H), 7.34 (br d, *J*=2.0 Hz, 1H), 7.28-7.22 (m, 1H), 5.39 (s, 2H), 2.95 (br s, 3H)
8		ESI $[M+1]^+$: 300.2	^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.72-8.68 (m, 1H), 8.29 (br d, *J*=4.4 Hz, 1H), 8.23 (s, 1H), 7.72-7.65 (m, 2H), 5.61 (s, 2H), 2.92 (br d, *J*=4.4 Hz, 3H)
9		ESI $[M+1]^+$: 278.8	^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.22-8.23 (m, 2H), 6.18 (s, 1H), 5.40 (s, 2H), 2.92 (br d, *J*=4.4 Hz, 3H), 2.36 (s, 3H)
10		ESI $[M+1]^+$: 353.8	^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.32-8.22 (m, 2H), 7.81 (d, *J*=8.8, Hz, 2H), 7.54 (s, 1H), 7.30-7.25 (m, 2H), 7.14 (d, *J*= 8.8 Hz, 1H), 5.49 (s, 2H), 3.84 (s, 3H), 2.93 (br d, *J*=4.4 Hz, 3H)

Compound ID	Structure	LCMS	^{1}H NMR
11		ESI $[M+1]^+$: 314.8	^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.74 (s, 1H), 8.30-8.25 (m, 1H), 8.23 (br s, 1H), 7.81-7.76 (m, 1H), 7.74 (s, 1H), 7.35 (d, *J*=8.4 Hz, 1H), 5.48 (s, 2H), 2.92 (br d, *J*=4.4 Hz, 3H)
12		ESI $[M+1]^+$:276.2	^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.15 (s, 1H), 7.93 (s, 1H), 7.62-7.58 (m, 1H), 7.52-7.26 (m, 1H), 6.10 (br s, 1H), 5.67 (s, 2H), 3.18 (br d, *J*=4.4 Hz, 3H)
13		ESI $[M+1]^+$:302.2	^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.16 (s, 1H), 7.30-7.24 (m, 2H), 7.22-7.15 (m, 3H), 4.13 (t, *J*=6.8 Hz, 2H), 2.92(d, *J*=4.4 Hz, 3H), 2.61-2.55 (m, 2H), 2.16-2.06 (d, *J*=4.4 Hz, 3H)
14		ESI $[M+1]^+$:353.0	^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.27 (s, 1H), 7.78-7.74 (m, 1H), 7.69-7.58 (m, 1H), 7.57-7.54 (m, 1H), 7.50-7.46 (m, 1H), 7.37 (s, 2H), 5.45 (s, 2H), 2.92 (d, *J*=4.8 Hz, 3H)

Compound ID	Structure	LCMS	^{1}H NMR
15		ESI $[M+1]^+$:284.1	^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.02 (s, 1H), 8.18-8.14 (m, 2H), 4.10 (t, *J*=6.8 Hz, 2H), 2.91 (d, *J*=4.4 Hz, 3H), 2.50-2.22 (m, 2H), 1.82-1.73 (m, 2H), 1.48-1.41 (m, 2H)
16		ESI $[M+1]^+$:320.0	^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.44-8.29 (m, 1H), 4.28 (t, *J*=6.8 Hz, 2H), 3.20-3.01 (m, 3H), 2.96-2.77 (m, 2H), 2.11-1.97 (m, 2H), 1.86-1.74 (m, 2H)
17		ESI $[M+1]^+$:328.0	^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.21 (br s, 2H), 7.70 (br d, *J*=8.0 Hz, 1H), 7.61 (d, *J*=8.4 Hz, 1H), 7.40 (t, *J*=7.6 Hz, 1H), 7.13 (t, *J*=7.6 Hz, 1H), 5.67 (s, H), 4.00 (s, 3H), 2.91 (br d, *J* = 4.0 Hz, 3H)

Synthesis of 2-(4-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)phenyl)acetic acid ***(Compound 18)***

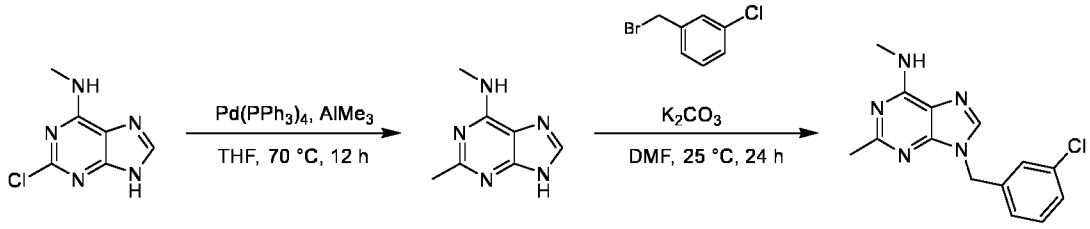


2 **18**

Scheme 2

To a solution of compound **2** (100 mg, 1 eq) in THF (2.5 mL) was added $LiOH \cdot H_2O$ (30 mg, 2.5 eq). The mixture was stirred at 25 °C for 12 hr. HCl (1 N, 5 mL) was added to the reaction mixture, then filtered and the collected solid was washed with DCM/MeOH (1:1, 5 mL). The solid was dried in vacuo to afford the desired product (34.5 mg). LCMS ESI $[M+1]^+$: 332.2. ^1H NMR (400 MHz, DMSO-d_6) δ = 12.31 (s, 1H), 8.23 (s, 2H), 7.20-7.25 (m, 4H), 5.31 (s, 2H), 3.53 (s, 2H), 2.91 (br d, *J*=4.4 Hz, 3H).

*Synthesis of 9-(3-chlorobenzyl)-N,2-dimethyl-9H-purin-6-amine (**Compound 20**)*



1 **19** **20**

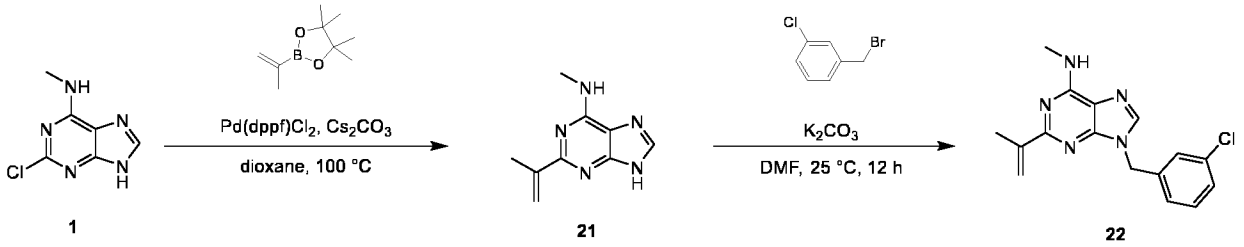
Step 1: N,2-dimethyl-9H-purin-6-amine (**19**)

To a solution of 2-chloro-*N*-methyl-9*H*-purin-6-amine (**1**) (300 mg, 1 eq) and $Pd(PPh_3)_4$ (37 mg, 0.2 eq) in THF (5 mL) was added $AlMe_3$ (1.1 mL, 1M, 1.5 eq) at 25 °C under a nitrogen atmosphere. The mixture was stirred at 70 °C for 12 hr. The reaction mixture was treated with H_2O (5 mL) at 25 °C, and then extracted with ethyl acetate (10 mL × 2). The combined organic layers were washed with H_2O (5 mL), dried over Na_2SO_4, filtered and then concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex C18 150 × 25 mm × 10 μm; mobile phase: [water (NH_4HCO_3)-MeCN]; gradient: 30%-50% B over 10 min) to afford the desired product (80 mg) as a yellow solid. LCMS ESI $[M+1]^+$: 164.5

Step 2: 9-(3-chlorobenzyl)-N,2-dimethyl-9H-purin-6-amine (**20**)

To a solution of compound **19** (80 mg, 1 eq) in DMF (2 mL) was added 1-(bromomethyl)-3-chlorobenzene (111 mg, 1.1 eq) and K_2CO_3 (136 mg, 2 eq). The mixture was stirred at 25 °C for 24 hr. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex C18 150 × 25 mm × 10 μm; mobile phase: [water (FA)-MeCN]; gradient: 50%-65% B over 10 min) to afford the desired product (16.4 mg). LCMS ESI $[M+1]^+$: 288.1. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.42 (s, 1H) 7.29-7.49 (m, 4H) 5.48 (s, 2H) 3.32 (br s, 3H) 2.62 (s, 3H)

Synthesis of 9-(3-chlorobenzyl)-N-methyl-2-(prop-1-en-2-yl)-9H-purin-6-amine ***(Compound 22)***



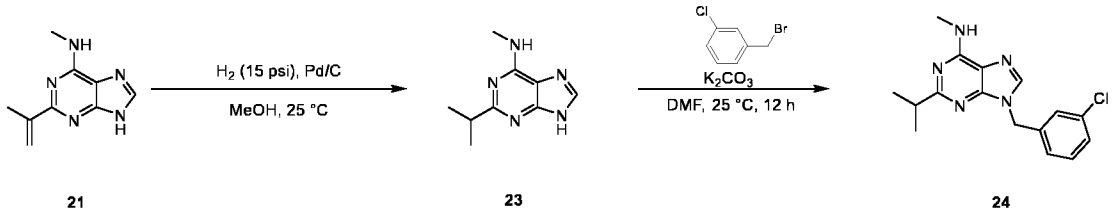
Step 1: N-methyl-2-(prop-1-en-2-yl)-9H-purin-6-amine (**21**)

To a solution of 2-chloro-*N*-methyl-9*H*-purin-6-amine (**1**) (0.5 g, 1 eq) in 1,4-dioxane (5 mL) and water (0.5 mL) was added 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (686 mg, 1.5 eq) and Cs_2CO_3 (1.77 g, 2 eq) and $Pd(dppf)Cl_2$ (199 mg, 0.1 eq). The mixture was evacuated and backfilled with N_2 three times. The mixture was stirred at 100 °C for 12 hr. The reaction mixture was diluted with H_2O (20 mL) and extracted with DCM (30 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (DCM/methanol=1/0 to 6/1) to afford the desired product (0.3 g, crude) as a white solid. LCMS ESI $[M+1]^+$: 190.4

Step 2: 9-(3-chlorobenzyl)-N-methyl-2-(prop-1-en-2-yl)-9H-purin-6-amine (**22**)

To a solution of compound **21** (50 mg, 1 eq) in DMF (1 mL) was added 1-(bromomethyl)-3-chlorobenzene (54 mg, 1 eq). The mixture was stirred at 25 °C for 12 hr. The reaction mixture was diluted with H_2O (10 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150 × 25mm × 10 μm; mobile phase: [water (NH_4HCO_3)-MeCN]; gradient:42%-72% B over 11 min) to afford the desired product (10.1 mg). LCMS ESI $[M+1]^+$: 313.9. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.27-8.20 (m, 1H), 7.65-7.55 (m, 1H), 7.53 (s, 1H), 7.40-7.31 (m, 3H), 6.29 (br s, 1H), 5.37 (s, 2H), 5.36-5.32 (m, 1H), 3.10-2.86 (m, 3H), 2.17 (s, 3H).

Synthesis of 9-(3-chlorobenzyl)-2-isopropyl-N-methyl-9H-purin-6-amine ***(Compound 24)***



Step 1: 2-isopropyl-N-methyl-9H-purin-6-amine (**23**)

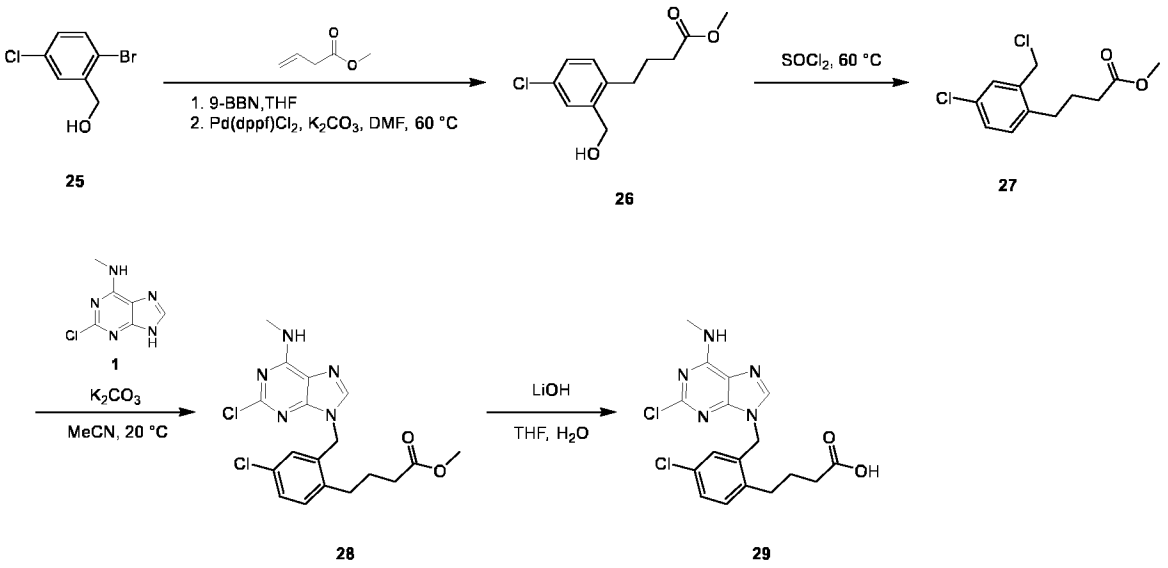
To a solution of compound **21** (0.1 g, 1 eq) in THF (5 mL) was added Pd/C (56 mg, 10 wt. %) under a nitrogen atmosphere. The suspension was degassed and purged with H_2 three

times. The mixture was stirred under H_2 (15 Psi) at 25 °C for 1 hr. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-TLC to afford the desired compound (80 mg) as a yellow oil.

Step 2: 9-(3-chlorobenzyl)-2-isopropyl-N-methyl-9H-purin-6-amine (**24**)

To a solution of compound **23** (80 mg, 1 eq) in DMF (1 mL) was added 1-(bromomethyl)-3-chlorobenzene (86 mg, 1 eq) and K_2CO_3 (116 mg, 2 eq). The mixture was stirred at 25 °C for 12 hr. The reaction mixture was diluted with H_2O (10 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150 × 25mm × 10 μm; mobile phase: [water (NH_4HCO_3)-MeCN]; gradient:45%-75% B over 11 min) to afford the desired product (11.3 mg). LCMS ESI $[M+1]^+$: 315.9. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.16 (s, 1H), 7.51 (s, 2H), 7.39-7.33 (m, 2H), 7.33-7.29 (m, 1H), 5.36-5.32 (m, 2H), 3.01-2.89 (m, 3H), 1.25 (d, *J*=6.8 Hz, 6H).

*Synthesis of 4-(4-chloro-2-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)phenyl)butanoic acid (**Compound 29**)*



Step 1: methyl 4-(4-chloro-2-(hydroxymethyl)phenyl)butanoate (**26**)

To an ice cooled solution of methyl but-3-enoate (1 g, 1 eq) in THF (10 mL) was added 9-BBN (30 mL, 0.5 M in THF) at 0 °C. After additional stirring for 4.5 hr, K_2CO_3 (4.14 g, 3 eq), (2-bromo-5-chlorophenyl)methanol (**25**) (2.65 g, 1 eq), DMF (30 mL) and Pd(dppf)Cl_2 (365 mg, 0.05 eq) were added to the mixture. The mixture was stirred at 60 °C for 12 hr. The reaction mixture was filtered and then concentrated under reduced pressure. The residue was purified by flash chromatography (eluent of 0 ~ 30% petroleum ether / ethyl acetate) to afford the desired compound (280 mg) as a yellow oil. ^1H NMR (400 MHz, DMSO-d_6) δ =

7.49 (d, *J*=8.0 Hz, 1H), 7.41 (d, *J*=2.4 Hz, 1H), 7.24-7.20 (m, 1H), 5.34-5.29 (m, 1H), 4.52 (d, *J*=3.2 Hz, 2H), 3.59 (s, 3H), 2.57-2.52 (m, 2H), 2.34 (s, 2H), 1.80-1.71 (m, 2H).

Step 2: methyl 4-(4-chloro-2-(chloromethyl)phenyl)butanoate (**27**)

To a stirred mixture of compound **26** (0.6 g, 1 eq) was added $SOCl_2$ (5 mL) at 25 °C. The mixture was stirred at 60 °C for 2 hr. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluent of 0 ~ 30% petroleum ether / ethyl acetate) to afford the desired compound (0.3 g) as a yellow oil.

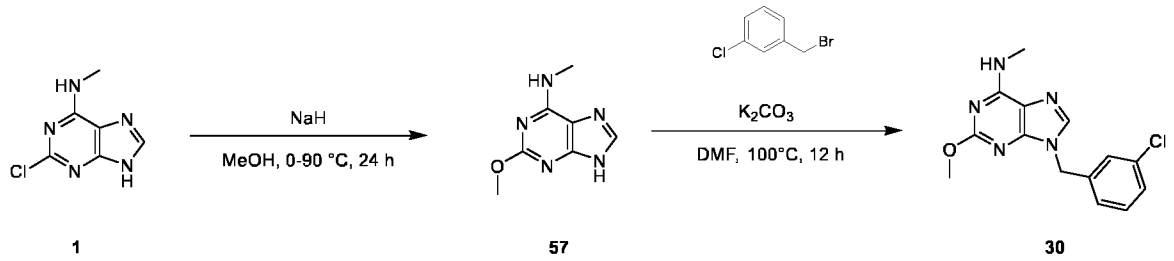
Step 3: methyl 4-(4-chloro-2-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)phenyl)-butanoate (**28**)

To a solution of compound **27** (0.3 g, 1 eq) in MeCN (5 mL) was added K_2CO_3 (318 mg, 2 eq) and 2-chloro-*N*-methyl-9*H*-purin-6-amine (**1**) (211 mg, 1 eq). The mixture was stirred at 25 °C for 12 hr. The reaction mixture was diluted with H_2O (10 mL) and extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150 × 25 mm × 10 μm; mobile phase: [water (NH_4HCO_3)-MeCN]; gradient:38%-68% B over 11 min) to afford the desired compound (60 mg) as a white solid. LCMS ESI $[M+1]^+$: 407.8. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.31-8.24 (m, 1H), 8.17 (s, 1H), 7.37-7.31 (m, 1H), 7.28 (s, 1H), 6.98 (s, 1H), 5.37 (s, 2H), 3.59-3.56 (m, 3H), 2.93 (br d, *J*=3.6 Hz, 3H), 2.71 (br s, 2H), 2.38-2.31 (m, 2H), 1.68 (quin, *J* = 7.6 Hz, 2H).

Step 4: 4-(4-chloro-2-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)phenyl)butanoic acid (**29**)

To a solution of compound **28** (30 mg, 1 eq) in THF (1 mL) and water (0.1 mL) was added $LiOH•H_2O$ (3 mg, 1 eq). The mixture was stirred at 25 °C for 12 hr. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150 × 25 mm × 10 μm; mobile phase: [water (FA)-MeCN]; gradient:30%-60% B over 10 min) to afford the desired product (11.1 mg). LCMS ESI $[M+1]^+$: 394.0. ^1H NMR (400 MHz, DMSO-d_6) δ = 12.15 (s, 1H), δ = 8.31-8.24 (m, 1H), 8.17 (s, 1H), 7.37-7.31 (m, 1H), 7.28 (s, 1H), 6.98 (s, 1H), 5.38 (s, 2H), 2.93 (br d, *J*=3.6 Hz, 3H), 2.73-2.71 (m, 2H), 2.30-2.20 (m, 2H), 1.68 (t, *J*=7.6 Hz, 2H).

Synthesis of 9-(3-chlorobenzyl)-2-methoxy-N-methyl-9H-purin-6-amine ***(Compound 30)***



1 57 30

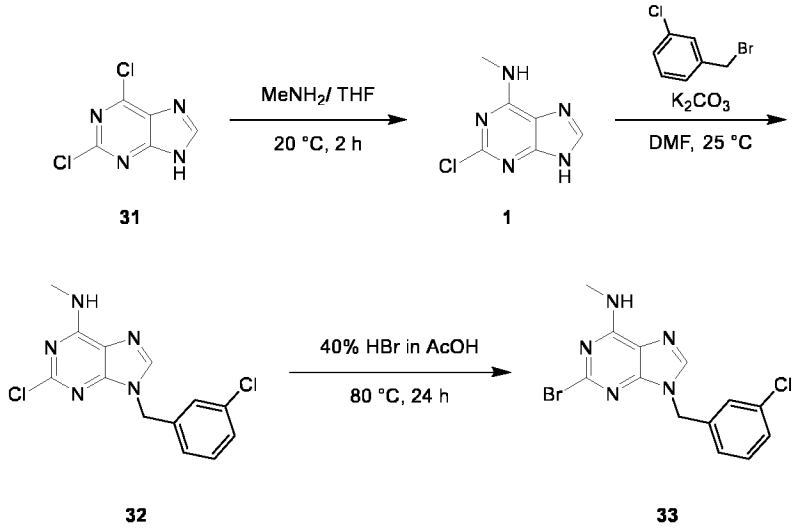
Step 1: 2-methoxy-N-methyl-9H-purin-6-amine (**57**)

To stirred MeOH (10 mL) at 0 °C was added NaH (1.09 g, 10 eq, 60 wt. %). The mixture was stirred for 30 min at 0 °C, then 2-chloro-*N*-methyl-9*H*-purin-6-amine (**1**) (0.5 g, 1 eq) was added. The mixture was stirred at 90 °C for 24 hr. The reaction mixture was poured into sat. NH_4Cl (30 mL) at room temperature, then was diluted with H_2O (20 mL) and extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with brine (100 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150 × 25 mm × 10 μm; mobile phase: [water (NH_4HCO_3)-MeCN]; gradient:1%-30% B over 10 min) to afford the desired compound (0.2 g) as a white solid. LCMS ESI $[M+1]^+$: 179.9

Step 2: 9-(3-chlorobenzyl)-2-methoxy-N-methyl-9H-purin-6-amine (**30**)

To a solution of compound **57** (60 mg, 1 eq) and K_2CO_3 (139 mg, 2 eq) in DMF (2 mL) was added 1-(bromomethyl)-3-chlorobenzene (75 mg, 1.1 eq) at 25 °C. The reaction mixture was heated to 100 °C and stirred for 16 hr. The reaction mixture was diluted with H_2O (20 mL) and extracted with ethyl acetate (20 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150 × 25 mm × 10 μm; mobile phase: [water (NH_4HCO_3)-MeCN]; gradient:25%-55% B over 8 min) to afford the desired product (60 mg). LCMS ESI $[M+1]^+$: 303.9. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.05 (s, 1H), 7.80-7.69 (m, 1H), 7.46-7.42 (m, 1H), 7.40-7.34 (m, 2H), 7.30-7.26 (m, 1H), 5.28 (s, 2H), 3.83 (s, 3H), 2.91 (br s, 3H).

Synthesis of 2-bromo-9-(3-chlorobenzyl)-N-methyl-9H-purin-6-amine ***(Compound 33)***



Step 1: 2-chloro-N-methyl-9H-purin-6-amine (**1**)

To a solution of 2,6-dichloro-9*H*-purine (**31**) (5 g, 1 eq) in THF (10 mL) was added methylamine (30 g, 2M in THF, 2 eq). The mixture was stirred at 20 °C for 2 hr. The reaction mixture was concentrated under reduced pressure. The residue was triturated in ethyl acetate (5 mL) and collected by filtration to afford the desired product (5 g) as a yellow solid. LCMS ESI $[M+1]^+$: 184.1

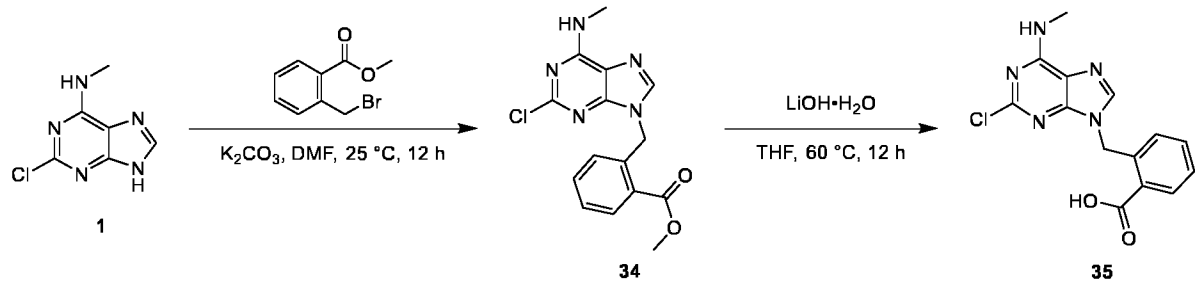
Step 2: 2-chloro-9-(3-chlorobenzyl)-N-methyl-9H-purin-6-amine (**32**)

To a solution of 2-chloro-*N*-methyl-9*H*-purin-6-amine (**1**) (1 g, 1 eq) in DMF (15 mL) was added K_2CO_3 (2.26 g, 3 eq) and 1-(bromomethyl)-3-chlorobenzene (1.34 g, 1.2 eq). The mixture was stirred at 20 °C for 2 hr. The reaction mixture was diluted with H_2O (30 mL) and extracted with ethyl acetate (30 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (eluent of 0~50% petroleum ether / ethyl acetate) to afford the desired product (0.7 g) as a white solid. LCMS ESI $[M+1]^+$: 307.9

Step 3: 2-bromo-9-(3-chlorobenzyl)-N-methyl-9H-purin-6-amine (**33**)

A solution of compound **32** (0.1 g, 1 eq) in 40% HBr in AcOH (5 mL) was stirred at 80 °C for 24 hr. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150 × 25 mm × 10 μm; mobile phase: [water (FA)-MeCN]; gradient:36%-66% B over 10 min) to afford the desired product (10.8 mg). LCMS ESI $[M+1]^+$: 353.8. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.24 (s, 2H), 7.40-7.36 (m, 3H), 7.23-7.17 (m, 1H), 5.35 (s, 2H), 2.91 (br d, *J*=4.0 Hz, 3H).

Synthesis of 2-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzoic acid ***(Compound 35)***



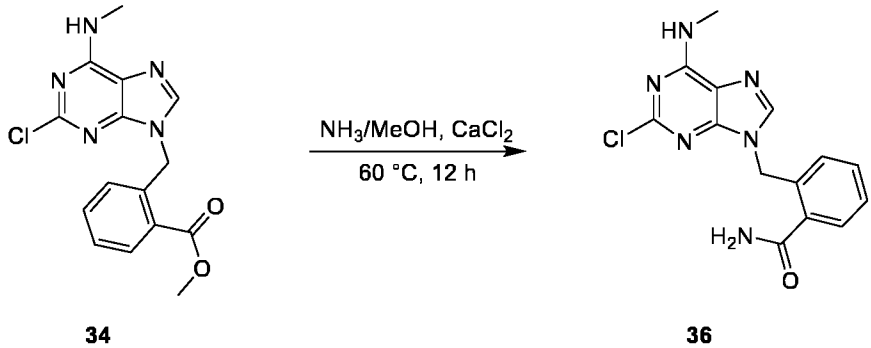
Step 1: methyl 2-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzoate (**34**)

To a solution of 2-chloro-*N*-methyl-9*H*-purin-6-amine (**1**) (0.4 g, 1 eq) in DMF (4 mL) was added K_2CO_3 (903 mg, 3 eq) and methyl 2-(bromomethyl)benzoate (599 mg, 1.2 eq). The mixture was stirred at 20 °C for 12 hr. The reaction mixture was diluted with H_2O (30 mL) and extracted with ethyl acetate (30 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150 × 25 mm × 10 μm; mobile phase: [water (FA)-MeCN]; gradient:36%-66% B over 10 min) to afford the desired product (120 mg) as a white solid. LCMS ESI $[M+1]^+$: 332.2.

Step 2: 2-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzoic acid (**35**)

To a solution of compound **34** (50 mg, 1 eq) in THF (1 mL) was added LiOH•H_2O (16 mg, 2.5 eq). The mixture was stirred at 60 °C for 12 hr. The reaction mixture was diluted with H_2O (5 mL), then HCl (2 M) was added to adjust the pH to 8. The mixture was filtered and then concentrated under reduced pressure to afford the desired product (22.3 mg). LCMS ESI $[M+1]^+$: 317.9. ^1H NMR (400 MHz, DMSO-d_6) δ = 13.33 (s, 1H), 8.27 (br s, 1H), 8.15-8.13 (m, 1H), 7.99-7.97 (m, 1H), 7.51-7.40 (m, 2H), 6.72-6.70 (m, 1H), 5.73 (s, 2H), 2.93 (s, 3H).

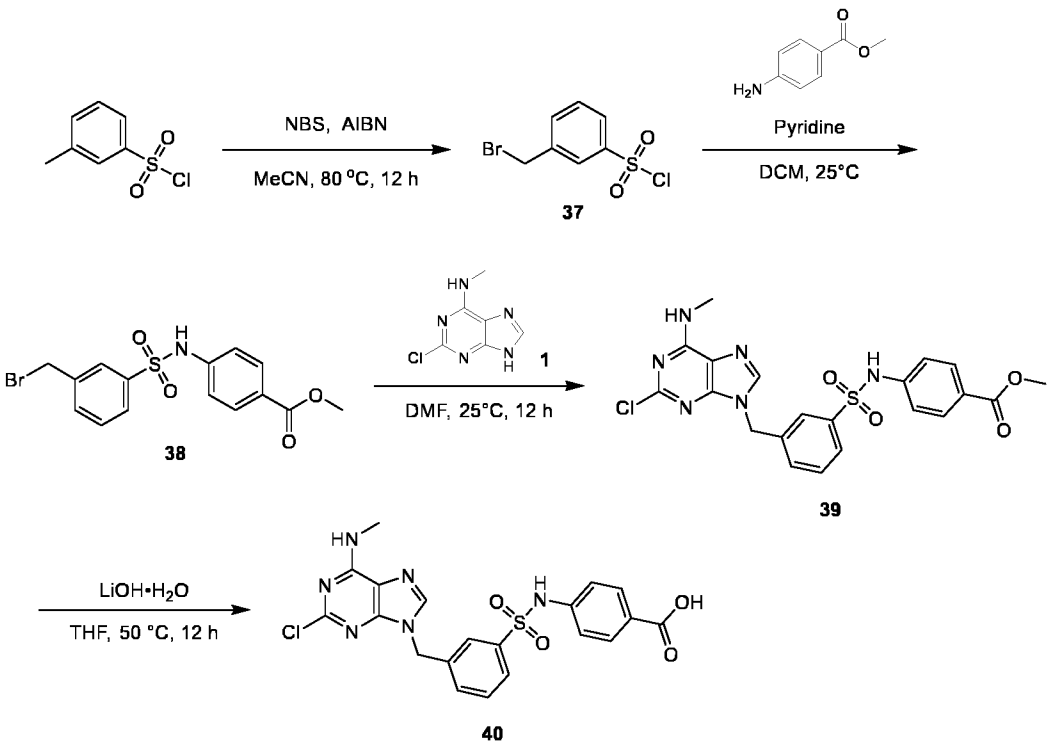
Synthesis of 2-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzamide ***(Compound 36)***



To a solution of compound **34** (60 mg, 1 eq) in NH_3•MeOH (7 M, 3 mL) was added $CaCl_2$ (40 mg, 2 eq). The mixture was stirred at 60 °C for 12 hr. The reaction mixture was concentrated under reduced pressure and the residue was purified by prep-HPLC (column: Phenomenex

luna C18 150 × 25 mm × 10 μm; mobile phase: [water(FA)-MeCN]; gradient:15%-45% B over 10 min) to afford the desired product (21.1 mg). LCMS ESI $[M+1]^+$: 316.9. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.13 (br s, 1H), 8.0 (s, 1H), 7.58 (s, 1H), 7.58-7.55 (m, 2H), 7.41-7.33 (m, 2H), 6.91 (d, *J*=8.4 Hz, 1H), 5.53 (s, 2H), 2.92 (d, J=4.0 Hz, 3H).

Synthesis of 4-((3-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)phenyl)sulfonamido)benzoic acid ***(Compound 40)***



Step 1: 3-(bromomethyl)benzenesulfonyl chloride (**37**)

To a solution of 3-methylbenzenesulfonyl chloride (5 g, 1 eq) and NBS (6 g, 1.3 eq) in MeCN (75 mL) was added AIBN (431 mg,0.1 eq). The mixture was stirred at 80 °C for 12 hr. The reaction mixture was cooled and then concentrated under reduced pressure. The residue was diluted with H_2O (40 mL) and extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (eluent of 0~20% ethyl acetate / petroleum ether) to afford the desired product (4 g) as a white solid.

Step 2: methyl 4-((3-(bromomethyl)phenyl)sulfonamido)benzoate (**38**)

To a solution of compound **37** (0.5 g, 1 eq) in DCM (5 mL) was added methyl 4-aminobenzoate (280 mg, 1 eq) and pyridine (176 mg, 1.2 eq) at 0 °C. The mixture was stirred at 25 °C for 12 hr. The reaction mixture was diluted with H_2O (10 mL) and extracted with DCM (20 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered and

concentrated under reduced pressure. The residue was purified by flash chromatography (eluent of 0~25% ethyl acetate / petroleum ether) to afford the desired product (310 mg) as a white solid. LCMS ESI $[M+1]^+$:386.1

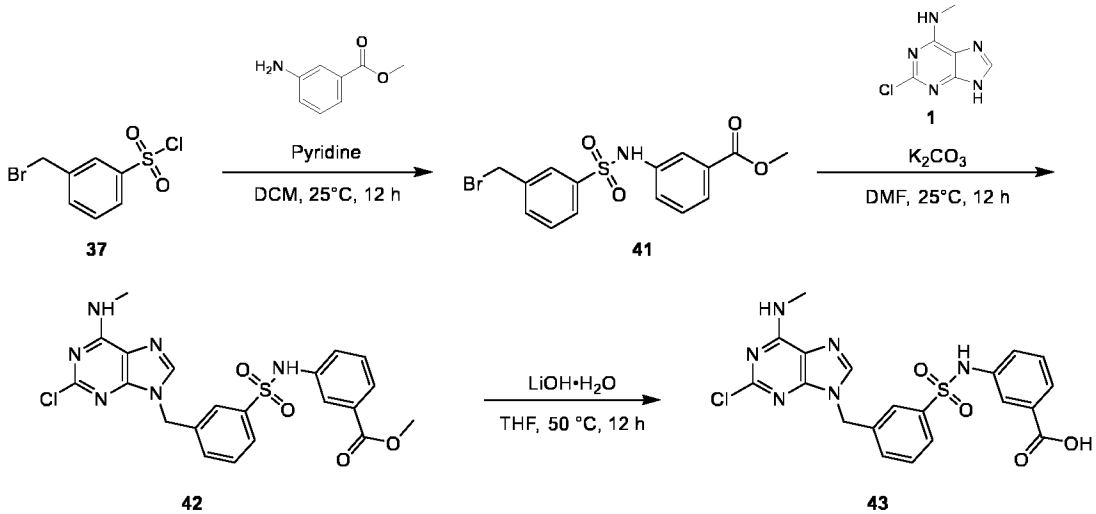
Step 3: methyl 4-((3-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)phenyl)sulfonamido)benzoate (**39**)

To a solution of 2-chloro-*N*-methyl-9*H*-purin-6-amine (**1**) (148 mg, 1 eq) and compound **38** (310 mg, 1 eq) in DMF (5 mL) was added K_2CO_3 (526 mg, 2 eq) at 25 °C. The mixture was stirred at 25 °C for 24 hr. The reaction mixture was poured into H_2O (10 mL) and extracted with ethyl acetate (10 mL × 2). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (eluent of 0~60% ethyl acetate / petroleum ether) to afford the desired product (200 mg) as a white solid. LCMS ESI $[M+1]^+$:487.0

Step 4: 4-((3-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)phenyl)sulfonamido)benzoic acid (**40**)

To a solution of methyl compound **39** (150 mg, 1 eq) in THF (1.5 mL) was added $LiOH•H_2O$ (32 mg, 2.5 eq). The mixture was stirred at 50 ℃ for 12 hr. The reaction mixture was treated with HCl (2 M) to adjust the pH to 8, was filtered and then concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Waters xbridge 150 × 25 mm × 10 μm; mobile phase: water (NH_4HCO_3)-MeCN; B: 8%-38%, 30 min) to afford the desired product (55.7 mg). LCMS ESI $[M+1]^+$:473.1. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.26 (s, 1H), 8.21 (s, 1H), 7.68-7.61 (m, 2H), 7.60-7.55 (m, 2H), 7.44-7.35 (m, 2H), 6.87 (d, *J*=8.4 Hz, 2H), 5.40 (s, 2H), 2.94 (br d, *J*=4.4 Hz, 3H)

Synthesis of 3-((3-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)phenyl)sulfonamido)benzoic acid ***(Compound 43)***



Step 1: methyl 3-((3-(bromomethyl)phenyl)sulfonamido)benzoate (**41**)

To a solution of compound **37** (0.5 g, 1 eq) in DCM (5 mL) was added methyl 3-aminobenzoate (280 mg, 1 eq) and pyridine (176 mg, 1.2 eq) at 0 °C. The mixture was stirred at 25 °C for 12 hr. The reaction mixture was diluted with H_2O (10 mL) and extracted with DCM (20 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (eluent of 0~25% ethyl acetate / petroleum ether) to afford the desired compound (440 mg) as a white solid. LCMS ESI $[M-1]^+$:383.2

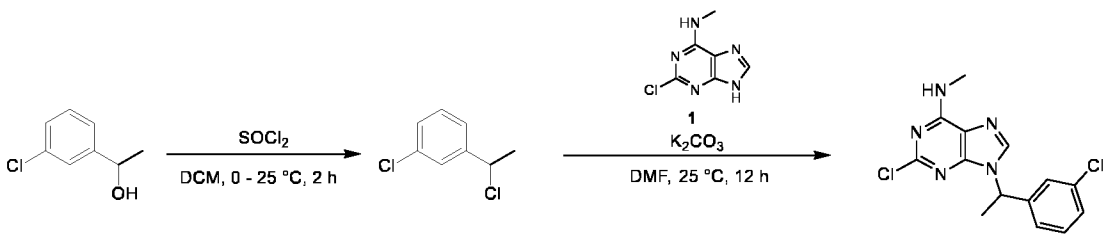
Step 2: methyl 3-((3-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)phenyl)sulfonamido)benzoate (**42**)

To a solution of 2-chloro-*N*-methyl-9*H*-purin-6-amine (**1**) (210 mg, 1 eq) and compound **41** (440 mg, 1 eq) in DMF (7 mL) was added K_2CO_3 (746 mg, 2 eq) at 25 °C. The mixture was stirred at 25 °C for 48 hr. The reaction mixture was treated with H_2O (10 mL) and extracted with ethyl acetate (10 mL × 2). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (eluent of 0~60% ethyl acetate / petroleum ether) to afford the desired compound (300 mg) as a white solid. LCMS ESI $[M+1]^+$:487.1

Step 3: 3-((3-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)phenyl)sulfonamido)benzoic acid (**43**)

To a solution of methyl compound **42** (150 mg, 1 eq) in THF (1.5 mL) was added $LiOH•H_2O$ (32 mg, 2.5 eq). The mixture was stirred at 50 ℃ for 12 hr. The reaction mixture was treated with HCl (2 M) to adjust the pH to 8, then was filtered and then concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Waters xbridge 150 × 25 mm × 10 μm; mobile phase: water (NH_4HCO_3)-MeCN; B%: 8%-38%, 30 min) to afford the desired product (56.1 mg). LCMS ESI $[M+1]^+$:473.2. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.26 (s, 1H), 8.24-8.19 (m, 1H), 7.65-7.49 (m, 3H), 7.48-7.44 (m, 3H), 7.21-6.91(m, 2H), 5.40 (s, 2H), 2.96 (br d, *J*=4.4 Hz, 3H)

Synthesis of 2-chloro-9-(1-(3-chlorophenyl)ethyl)-N-methyl-9H-purin-6-amine ***(Compound 45)***



44 45

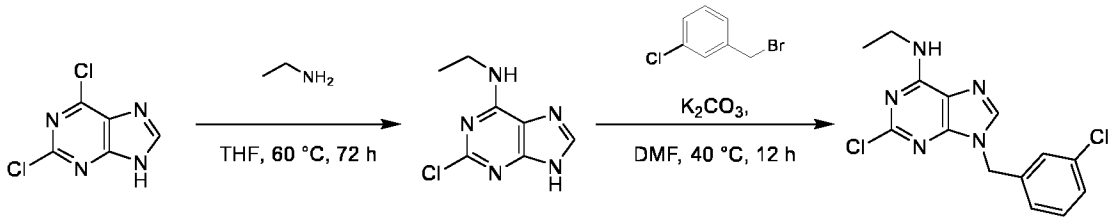
Step 1: 1-chloro-3-(1-chloroethyl)benzene (**44**)

To a solution of 1-(3-chlorophenyl)ethan-1-ol (300 mg, 1 eq) in DCM (6 mL) was added $SOCl_2$ (273 mg, 1.2 eq) slowly at 0 °C. The mixture was stirred at 25 °C for 2 hr. The reaction mixture was concentrated under reduced pressure to remove solvent to afford the desired product (305 mg, crude) as a yellow solid.

Step 2: 2-chloro-9-(1-(3-chlorophenyl)ethyl)-N-methyl-9H-purin-6-amine (**45**)

To a solution of 2-chloro-*N*-methyl-9*H*-purin-6-amine (**1**) (100 mg, 1 eq) and compound **44** (124 mg, 1.3 eq) in DMF (1 mL) was added K_2CO_3 (226 mg, 2 eq) at 25 °C. The mixture was stirred at 25 °C for 12 hr. The reaction mixture was filtered and then was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Waters xbridge 150 × 25 mm × 10 μm; mobile phase: water (NH_4HCO_3)-MeCN; B%: 20%-50%, 10 min) to afford the desired product (29.8 mg). LCMS ESI $[M+1]^+$:322.0. ^1H NMR (400 MHz, MeOH-d_4) δ = 8.18 (s, 1H), 7.42-7.21 (m, 4H), 5.81 (q, *J*=7.2 Hz, 1H), 3.06 (br s, 3H), 1.96 (br d, *J*=7.6 Hz, 3H)

Synthesis of 2-chloro-9-(3-chlorobenzyl)-N-ethyl-9H-purin-6-amine ***(Compound 47)***



31 **46** **47**

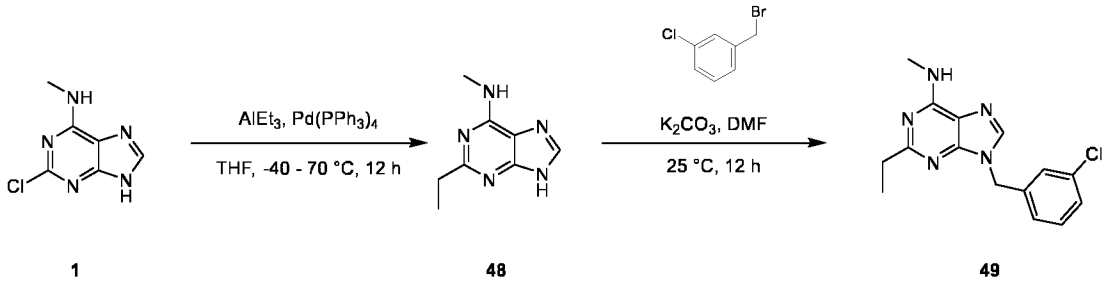
Step 1: 2-chloro-N-ethyl-9H-purin-6-amine (**46**)

To a solution of 2,6-dichloro-9*H*-purine (**31**) (500 mg, 1 eq) in THF (4 mL) was added ethanamine (596 mg, 5 eq) at 25 °C. The mixture was stirred at 60 °C for 72 hr. The reaction mixture was filtered and the collected residue was washed with ethyl acetate (20 mL) to afford the desired product (400 mg) as a yellow solid. LCMS ESI $[M+1]^+$:198.1

Step 2: 2-chloro-9-(3-chlorobenzyl)-N-ethyl-9H-purin-6-amine (**47**)

To a solution of compound **46** (100 mg, 1 eq) and 1-(bromomethyl)-3-chlorobenzene (125 mg, 1.2 eq) in DMF (1 mL) was added K_2CO_3 (226 mg, 2 eq) at 25 °C. The mixture was stirred at 40 °C for 12 hr. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Waters xbridge 150 × 25 mm × 10 μm; mobile phase : water (NH_4HCO_3)-MeCN; B%: 33%-63%, 10 min) to afford the desired product (19.7 mg). LCMS ESI $[M+1]^+$:322.0. ^1H NMR (400 MHz, MeOH-d_4) δ = 8.07 (s, 1H), 7.38-7.29 (m, 3H), 7.25-7.20 (m, 1H), 5.36 (s, 2H), 3.59 (br d, *J*=5.2 Hz, 2H), 1.28 (t, *J*=7.6 Hz, 3H)

Synthesis of 9-(3-chlorobenzyl)-2-ethyl-N-methyl-9H-purin-6-amine ***(Compound 49)***



1 48 49

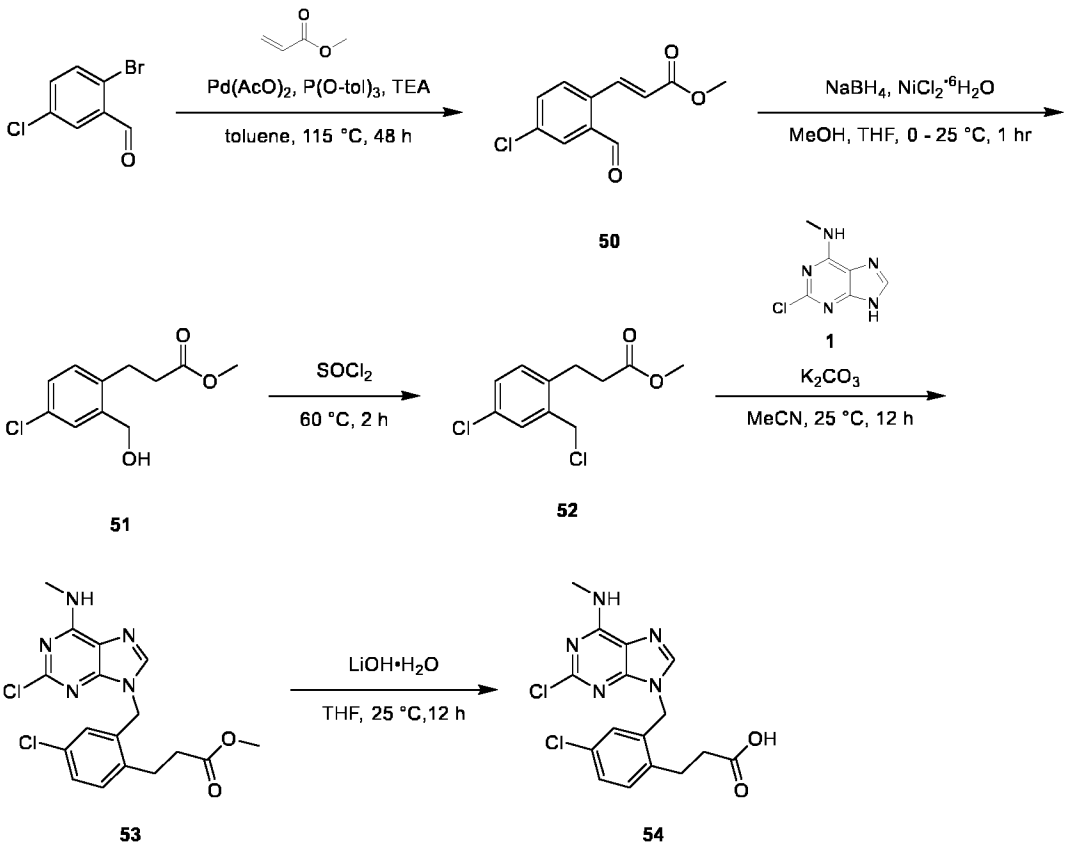
Step 1: 2-ethyl-N-methyl-9H-purin-6-amine (**48**)

To a solution of 2-chloro-*N*-methyl-9*H*-purin-6-amine (**1**) (300 mg,1 eq) and $Pd(PPh_3)_4$ (189 mg, 0.1 eq) in THF (5 mL) was degassed and purged with nitrogen three times, and then $AlEt_3$ (560 mg, 3 eq) was added at -40 °C. The mixture was then heated 70 ℃ and stirred for 12 hr. The reaction mixture was cooled, then treated with MeOH (10 mL) at 0 °C. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Waters xbridge 150 × 25 mm × 10 μm; mobile phase: water (FA)-MeCN; B%: 5%-35%, 10 min) to afford the desired product (100 mg) as a white solid. LCMS ESI $[M+1]^+$:178.3

Step 2: 9-(3-chlorobenzyl)-2-ethyl-N-methyl-9H-purin-6-amine (**49**)

To a solution of compound **48** (50 mg, 1 eq) and 1-(bromomethyl)-3-chlorobenzene (58 mg, 1 eq) in DMF (1 mL) was added K_2CO_3 (78 mg, 2 eq) at 25 °C. The mixture was stirred at 25 °C for 12 hr. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Waters xbridge 150 × 25 mm × 10 μm; mobile phase: water (HCl)-MeCN; B%: 12%-42%, 10 min) to afford the desired product (10.7 mg). LCMS ESI $[M+1]^+$:302.0. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.15 (s, 1H), 7.57 (br s, 1H), 7.44 (s, 1H), 7.39-7.33 (m, 2H), 7.29-7.22 (m, 1H), 5.35 (s, 2H), 2.94 (br s, 3H), 2.70 (q, *J*=7.2 Hz, 2H), 1.25 (t, *J*=7.6 Hz, 3H)

Synthesis of 3-(4-chloro-2-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)phenyl)propanoic acid ***(Compound 54)***



Step 1: methyl (E)-3-(4-chloro-2-formylphenyl)acrylate (**50**)

A mixture of 2-bromo-5-chlorobenzaldehyde (5 g, 1 eq), methyl acrylate (2.94 g, 1.5 eq) in toluene (10 mL) was added $Pd(AcO)_2$ (256 mg, 0.05 eq), $P(O\text{-}tol)_3$ (693 mg, 0.1 eq) and TEA (4.61 g, 2 eq) and then was purged with nitrogen three times. The mixture was stirred at 115 °C for 48 hr under a N_2 atmosphere. The reaction mixture was diluted with H_2O (50 mL) and extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with brine (150 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (eluent of 0~10% ethyl acetate / petroleum ether) to afford the desired product (2.5 g) as a yellow solid. LCMS ESI $[M+23]^+$:246.7. ^1H NMR (400 MHz, $CDCl_3$) δ = 10.27 (s, 1H), 8.45 (d, *J*=16.0 Hz, 1H), 7.87 (s, 1H), 7.59 (d, *J*=1.2 Hz, 2H), 6.39 (d, *J*=16.0 Hz, 1H), 3.85 (s, 3H)

Step 2: methyl 3-(4-chloro-2-(hydroxymethyl)phenyl)propanoate (**51**)

To a solution of compound **50** (2.3 g, 1 eq) in MeOH (15 mL) and THF (15 mL) was degassed and purged with nitrogen three times. The reaction mixture was cooled to 0 °C, then $NaBH_4$ (1.55 g, 4 eq) was added at 0 °C in three portions. The reaction mixture was stirred for 15 minutes, then $NiCl_2•6H_2O$ (1.22 g, 0.5 eq) was added in three portions. The mixture was stirred at 25 °C for 2 hr under a N_2 atmosphere. The reaction mixture was

poured into aqueous NH_4Cl (30 mL aq) at 0 °C, then H_2O (10 mL) was added and then extracted with DCM (50 mL × 3). The combined organic layers were washed with brine (150 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (eluent of 0~20% ethyl acetate / petroleum ether gradient) to afford the desired product (1.8 g) as a colorless oil. LCMS ESI $[M+23]^+$:250.8. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.40 (d, *J*=2.0 Hz, 1H), 7.25-7.21 (m, 1H), 7.16-7.12 (m, 1H), 4.71 (d, *J*=5.6 Hz, 2H), 3.67 (s, 3H), 2.98 (t, *J*=7.6 Hz, 2H), 2.70-2.65 (m, 2H), 2.22 (t, *J*=5.6 Hz, 1H)

Step 3: methyl 3-(4-chloro-2-(chloromethyl)phenyl)propanoate (**52**)

A stirred solution of compound **51** (1.8 g, 1 eq) in $SOCl_2$ (15 mL) was purged with nitrogen three times. The mixture was stirred at 60 °C for 2 hr. The reaction mixture was treated with H_2O (40 mL) and then extracted with ethyl acetate (40 mL × 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (eluent of 0~20% ethyl acetate / petroleum ether gradient) to afford the desired compound (1.8 g) as a colorless oil. LCMS ESI $[M+23]^+$:270.2. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.35 (d, *J*=2.0 Hz, 1H), 7.27 (s, 1H), 7.19-7.15 (m, 1H), 4.61 (s, 2H), 3.69 (s, 3H), 3.04 (t, *J*=8.0 Hz, 2H), 2.67 (t, *J*=8.0 Hz, 2H)

Step 4: methyl 3-(4-chloro-2-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)phenyl)-propanoate (**53**)

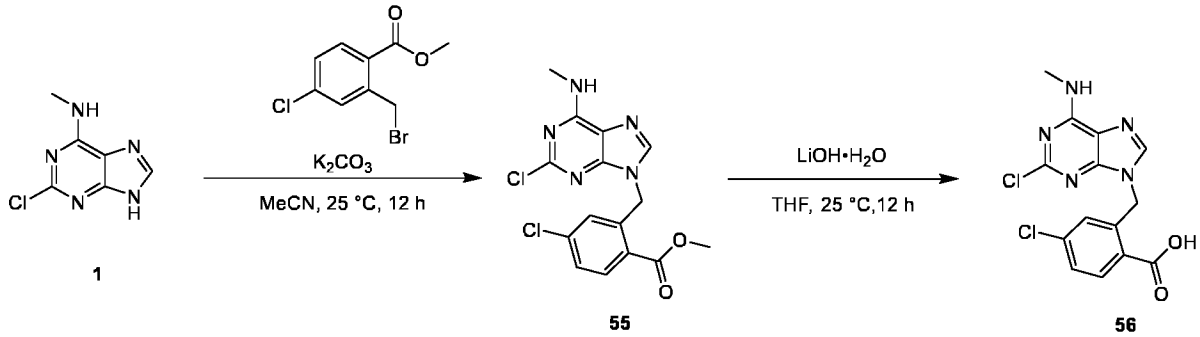
To a solution of compound **52** (0.5 g, 1 eq) in MeCN (6 mL) was added 2-chloro-*N*-methyl-9*H*-purin-6-amine (**1**) (371 mg, 1 eq) and K_2CO_3 (559 mg, 2 eq). The mixture was stirred at 25 °C for 12 hr. The reaction mixture was filtered and then the filtrate was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Daisogel SP ODS RPS 150 × 25 mm × 5 μm; mobile phase: (water (NH_4HCO_3)-MeCN; B%: 32%-62%, 12 min) to afford the desired compound (76 mg) as a white solid. LCMS ESI $[M+1]^+$:394.0. ^1H NMR (400 MHz, MeOH-d_4) δ = 7.94 (s, 1H), 7.31-7.25 (m, 2H), 7.05 (s, 1H), 5.43 (s, 2H), 3.63 (s, 3H), 3.09 (br s, 3H), 3.00 (br t, *J*=7.6 Hz, 2H), 2.46 (br t, *J*=7.6 Hz, 2H)

Step 5: 3-(4-chloro-2-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)phenyl)propanoic acid (**54**)

To a solution of compound **53** (65 mg, 1 eq) in THF (1 mL) was added $LiOH•H_2O$ (21 mg, 2.5 eq). The mixture was stirred at 25 ℃ for 12 hr. The reaction mixture was treated with H_2O (2 mL) and the reaction mixture was filtered. HCl (1.2 M) was added to the filtrate and the pH was adjusted to 6. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was washed with H_2O (3 mL), MeCN (3 mL), and filtered to afford the desired product (17.7 mg). LCMS ESI $[M+1]^+$:379.9. ^1H NMR (400 MHz, DMSO-d_6) δ = 12.20

(br s, 1H), 8.28 (br d, *J*=4.4 Hz, 1H), 8.15 (s, 1H), 7.37-7.26 (m, 2H), 6.91 (s, 1H), 5.40 (s, 2H), 2.99-2.84 (m, 5H), 2.49-2.44 (m, 2H)

Synthesis of 4-chloro-3-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzoic acid ***(Compound 56)***



Step 1: methyl 4-chloro-2-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzoate (**55**)

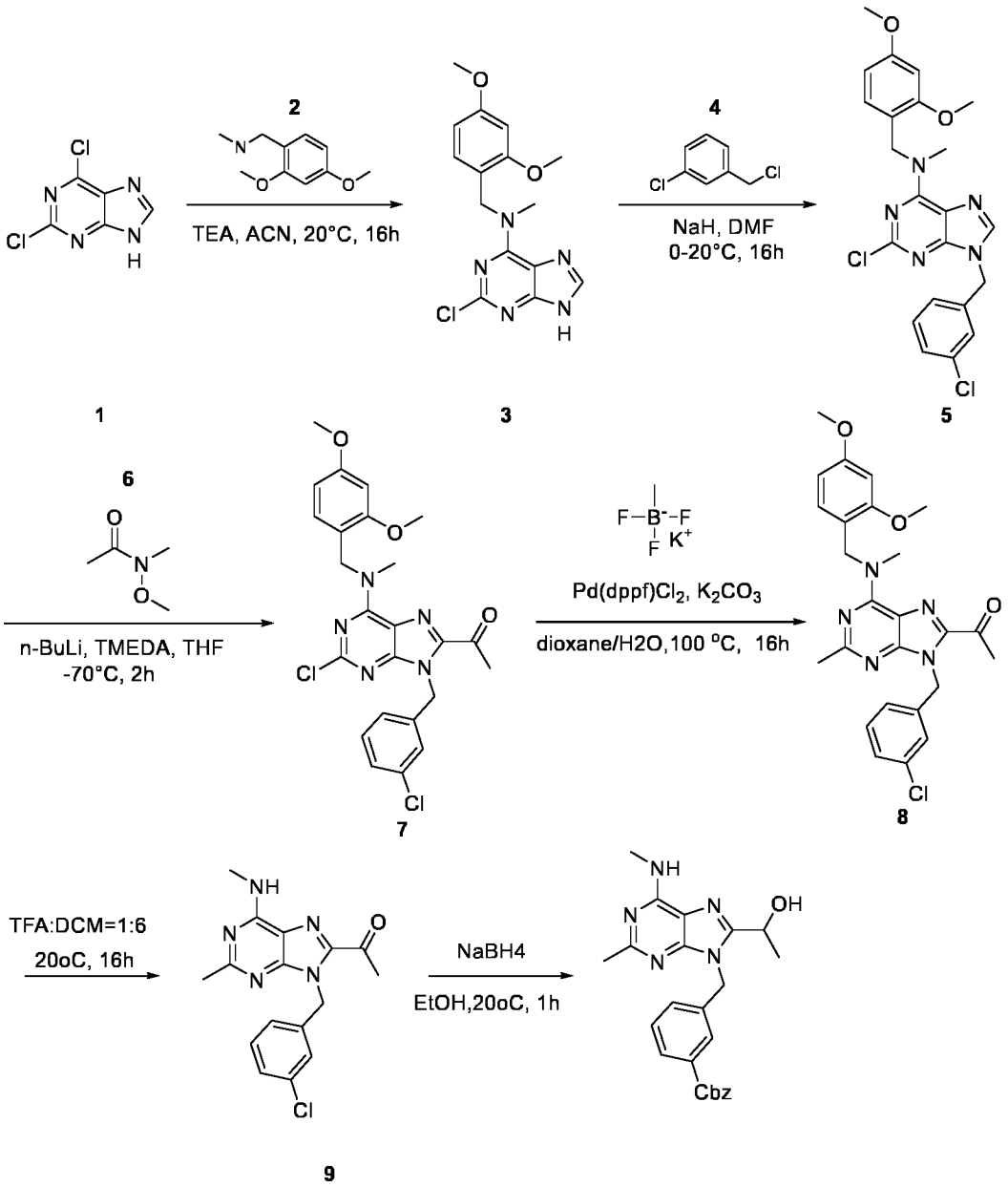
To a mixture of 2-chloro-*N*-methyl-9*H*-purin-6-amine (**1**) (200 mg, 1.09 mmol, 1 eq) in DMF (2 ml) was added methyl 3-(bromomethyl)-4-chlorobenzoate(316 mg, 1.1 eq) and potassium carbonate (301 mg, 2 eq). The mixture was stirred at 25 °C for 12 hr. The reaction mixture was treated with H_2O (15 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (eluent of 0~100% ethyl acetate / petroleum ether) to afford the desired compound (300 mg) as a white solid. LCMS ESI $[M+1]^+$:366.0

Step 2: 4-chloro-3-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzoic acid (**56**)

To a solution of methyl 4-chloro-3-((2-chloro-6-(methylamino)-9*H*-purin-9-yl)methyl)benzoate (100 mg, 1 eq) in THF (1 mL) was added LiOH•H_2O (29 mg, 2.5 eq). The mixture was stirred at 25 °C for 12 hr. The reaction mixture was treated with HCl (2 M) and adjusted to pH 8, was filtered and then concentrated under reduced pressure. The residue was purified by prep-HPLC (water (NH_4HCO_3)-MeCN; Waters xbridge 150 × 25 mm × 10 μm) to afford the desired product (60.7 mg). LCMS ESI $[M+1]^+$:352.0. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.31 (d, *J*=4.4 Hz, 1H), 8.19 (s, 1H), 7.87 (d, *J*=8.4 Hz, 1H), 7.63 (d, *J*=8.4 Hz, 1H), 7.47 (s, 1H), 5.47 (s, 2H), 2.93(d, *J*=4.4 Hz, 3H)

Synthesis of 1-{9-[(m-chlorophenyl)methyl]-2,9a-dimethyl-8-adenineyl}-1-ethanol

(Compound 66)



Step 1: Synthesis of 2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyladenine.

To a mixture of 2,6-dichloropurine (10 g, 52.9 mmol, 1.0 eq., cas:5451-40-1) and N-methyl[(2,4-dimethoxyphenyl)methyl]amine (9.68 g, 53.4 mmol, 1.0 eq., cas:102502-23-1) in acetonitrile (0.1 L) was added TEA (16.1 g, 159 mmol, 3 eq.) at 20℃. The mixture was stirred at 20℃ for 16h. After completion, the mixture was concentrated in vacuo to give a residue. The residue was purified by SGC (UV254, Petroleum ether: EtOAc = 1:1) to afford 2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyladenine (16 g, yield:90.6%) as a yellow solid. ESI-MS m/z =334.2[M-H]+. Calculated MW: 333.78

Step 2: Synthesis of 2-chloro-9-[(m-chlorophenyl)methyl]-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyladenine.

To 2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyladenine (1 g, 3 mmol, 1.0 eq.) in dimethylformamide (16.7 mL) was added NaH (1.11 g, 8.99 mmol, 3 eq., 60% in mineral oil) at 0℃. After stirring at 0℃ for 30 min, m-chloro(chloromethyl)benzene (1.93 g, 12 mmol, 4 eq.) was added and the mixture continued stirring at 20℃ for 3h. The mixture was quenched with NH_4Cl aq. (10 mL), extracted with EtOAc (10 mL*3). The organic layer was washed with H_2O (10 mL), brine (10 mL), dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo to give a residue. The residue was purified by SGC (UV254, Petroleum ether: EtOAc = 4:1) to afford 2-chloro-9-[(m-chlorophenyl)methyl]-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyladenine (960 mg, yield:69.91%) as a white solid. ESI-MS m/z =458.0 $[M-H]^+$. Calculated MW: 458.34

Step 3: Synthesis of 1-{2-chloro-9-[(m-chlorophenyl)methyl]-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-8-adenineyl}-1-ethanone.

To a mixture of 2-chloro-9-[(m-chlorophenyl)methyl]-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyladenine (960 mg, 2.09 mmol, 1.0 eq.) and TMEDA (365 mg, 3.14 mmol, 1.5 eq.) in tetrahydrofuran (10 mL) was cooled to -70 °C, n-BuLi (268 mg, 4.19 mmol , 2 eq. 2.5M in Hexene) was added dropwise and the mixture was stirred at -70 °C for 40 min, N-methoxy-N-methylacetamide (324 mg, 3.14 mmol , 1.5 eq.) was added dropwise and the mixture was stirred at -70 °C for 1.5 h, then allowed to warm to -30 °C. Water was added followed by NH4Cl aq. and the mixture was 3 times with ethyl acetate. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo to give a residue. The residue was purified by SGC (UV254, Petroleum ether: EtOAc = 10:1) to afford 1-{2-chloro-9-[(m-chlorophenyl)methyl]-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-8-adenineyl}-1-ethanone (436 mg, yield:41.6%) as a white solid. ESI-MS m/z =500.1 $[M-H]^+$. Calculated MW: 500.38

Step 4: Synthesis of 1-{9-[(m-chlorophenyl)methyl]-9a-[(2,4-dimethoxyphenyl)methyl]-2,9a-dimethyl-8-adenineyl}-1-ethanone.

To a mixture of 1-{2-chloro-9-[(m-chlorophenyl)methyl]-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-8-adenineyl}-1-ethanone (140 mg, 0.280 mmol, 1.0 eq.) and potassium trifluoro(methyl)boranuide (341 mg, 2.8 mmol, 10 eq.) in 1,4-dioxane (4 mL)/water (1 mL)=4/1 was added at 20℃. The mixture was stirred at 100℃ for 60h under N_2. After completion, the mixture was filtrated and concentrated in vacuo to give a residue. The residue was purified by SGC (UV254, Petroleum ether: EtOAc = 10:1) to afford 1-{9-[(m-chlorophenyl)methyl]-9a-[(2,4-dimethoxyphenyl)methyl]-2,9a-dimethyl-8-adenineyl}-1-ethanone (85 mg,yield:63.3%) as a colorless oil. ESI-MS m/z =480.2 $[M-H]^+$. Calculated MW: 479.97

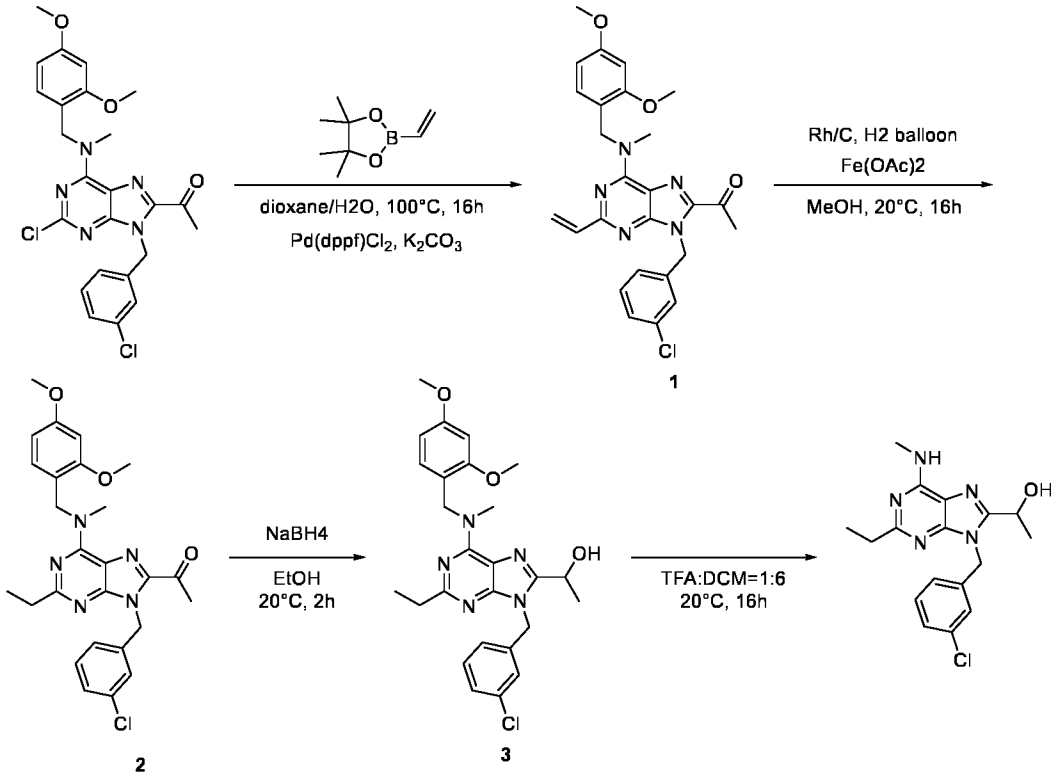
Step 5: Synthesis of 1-{9-[(m-chlorophenyl)methyl]-2,9a-dimethyl-8-adenineyl}-1-ethanone.

To 1-{9-[(m-chlorophenyl)methyl]-9a-[(2,4-dimethoxyphenyl)methyl]-2,9a-dimethyl-8-adenineyl}-1-ethanone (85 mg, 0.177 mmol, 1.0 eq.) in dichloromethane (0.6 mL) was added TFA (0.1 mL) at 20℃. The mixture was stirred at 20℃ for 16h. After completion, the mixture was filtrated and concentrated in vacuo to give a residue. The residue was purified by Prep-HPLC (Mobile Phase: ACN---H_2O (0.1% $NH_3.H_2O$) to afford 1-{9-[(m-chlorophenyl)methyl]-2,9a-dimethyl-8-adenineyl}-1-ethanone (24 mg, yield:41.09%) as a white solid. ESI-MS m/z =330.1 $[M-H]^+$. Calculated MW: 329.79

Step 6: Synthesis of 1-{9-[(m-chlorophenyl)methyl]-2,9a-dimethyl-8-adenineyl}-1-ethanol.

To 1-{9-[(m-chlorophenyl)methyl]-2,9a-dimethyl-8-adenineyl}-1-ethanone–ethanol (1/1) (20 mg, 0.532 mmol, 1.0 eq.) in ethanol (1 mL) was added NaBH4 (4.03 mg, 0.106 mmol, 2 eq.) at 20℃. The mixture was stirred at 20℃ for 2 h. After completion, the mixture was filtrated and purified by Prep-HPLC (Mobile Phase: ACN---H_2O (0.1% $NH_3.H_2O$) to afford 1-{9-[(m-chlorophenyl)methyl]-2,9a-dimethyl-8-adenineyl}-1-ethanol (11.7 mg, yield:65.25%). ESI-MS m/z =332.2 [M-H]+. Calculated MW: 331.80. ^1H NMR (400 MHz, DMSO) δ 7.52 (s, 1H), 7.36 – 7.30 (m, 2H), 7.24 (s, 1H), 7.10 – 7.05 (m, 1H), 5.65 (d, J = 6.0 Hz, 1H), 5.48 (q, J = 16.3 Hz, 2H), 4.84 (p, J = 6.4 Hz, 1H), 2.94 (s, 3H), 2.41 (s, 3H), 1.46 (d, J = 6.5 Hz, 3H).

Synthesis of 1-{9-[(m-chlorophenyl)methyl]-2-ethyl-9a-methyl-8-adenineyl}-1-ethanol ***(Compound 68)***



Step 1: Synthesis of 1-{9-[(m-chlorophenyl)methyl]-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-2-vinyl-8-adenineyl}-1-ethanone.

To a mixture of 1-{2-chloro-9-[(m-chlorophenyl)methyl]-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-8-adenineyl}-1-ethanone (0.2 g, 0.4 mmol, 1.0 eq., synthesized according to procedure described in synthesis of **Compound 66**) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (73.9 mg, 0.48 mmol, 1.2 eq., cas: 75927-49-0) in 1,4-dioxane (4 mL)/water (1 mL)=4/1 was added Pd(dppf)Cl2 (58.5 mg, 0.0799 mmol, 0.2 eq.) and K_2CO_3 (166 mg, 1.2 mmol, 3 eq.) at 20℃. The mixture was stirred at 100℃ for 16 h under N_2. After completion, the mixture was concentrated in vacuo to give a residue. The residue was purified by SGC (UV254, Petroleum ether: EtOAc = 10:1) to afford 1-{9-[(m-chlorophenyl)methyl]-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-2-vinyl-8-adenineyl}-1-ethanone (74 mg, 150 μmol, yield:37.63%) as a colorless oil. ESI-MS m/z =492.2 [M-H]+. Calculated MW: 491.98

Step 2: Synthesis of 1-{9-[(m-chlorophenyl)methyl]-9a-[(2,4-dimethoxyphenyl)methyl]-2-ethyl-9a-methyl-8-adenineyl}-1-ethanone.

To 1-{9-[(m-chlorophenyl)methyl]-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-2-vinyl-8-adenineyl}-1-ethanone (74 mg, 0.150 mmol, 1.0 eq.) in methanol (10 mL) was added Rh/C (50 mg) and Fe(OAc)2 (50 mg) at 20℃. The mixture was stirred at 20℃ for 16 h under H_2 balloon. After completion, the mixture was filtrated and concentrated in vacuo to afford 1-{9-[(m-chlorophenyl)methyl]-9a-[(2,4-dimethoxyphenyl)methyl]-2-ethyl-9a-methyl-8-adenineyl}-1-ethanone (78 mg, yield:105%) as a yellow oil. ESI-MS m/z =494.1 [M-H]+. Calculated MW: 493.99

Step 3: Synthesis of 1-{9-[(m-chlorophenyl)methyl]-9a-[(2,4-dimethoxyphenyl)methyl]-2-ethyl-9a-methyl-8-adenineyl}-1-ethanol.

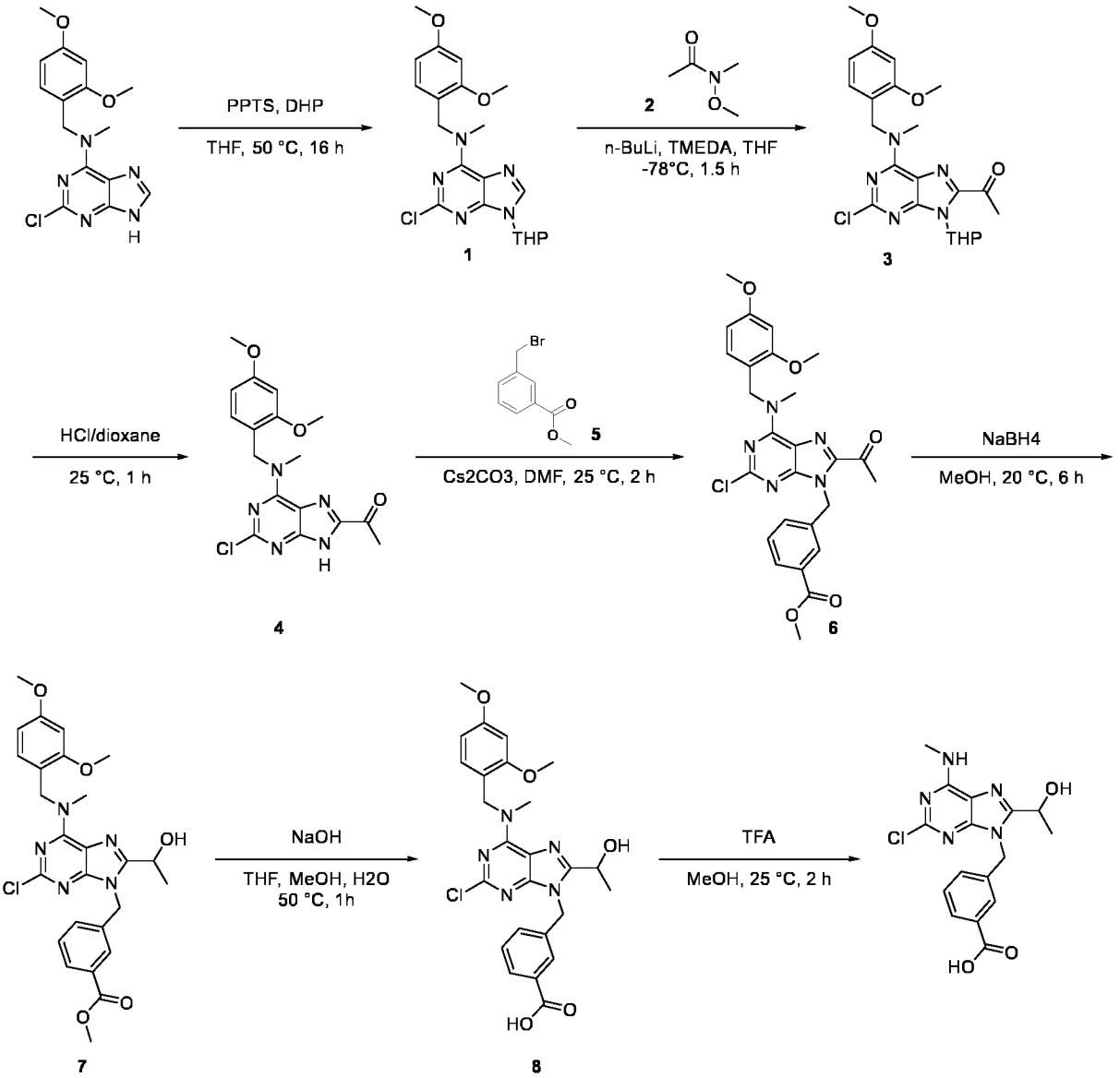
To 1-{9-[(m-chlorophenyl)methyl]-9a-[(2,4-dimethoxyphenyl)methyl]-2-ethyl-9a-methyl-8-adenineyl}-1-ethanone (80 mg, 0.162 mmol, 1.0 eq.) in ethanol (16 mL) was added NaBH4 (12.3 mg, 0.324 mmol, 2 eq.) at 20℃. The mixture was stirred at 20℃ for 2h. After completion, the mixture was quenched with H2O (10 mL), extracted with EtOAc (10 mL*3). The organic layer was washed with H_2O (10 mL), brine (10 mL), dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo to afford 1-{9-[(m-chlorophenyl)methyl]-9a-[(2,4-dimethoxyphenyl)methyl]-2-ethyl-9a-methyl-8-adenineyl}-1-ethanol (58 mg, yield:72.21%) as a colorless oil. ESI-MS m/z =496.2 [M-H]+. Calculated MW: 496.01

Step 4: Synthesis of 1-{9-[(m-chlorophenyl)methyl]-2-ethyl-9a-methyl-8-adenineyl}-1-ethanol.

To 1-{9-[(m-chlorophenyl)methyl]-9a-[(2,4-dimethoxyphenyl)methyl]-2-ethyl-9a-methyl-8-adenineyl}-1-ethanol (53 mg, 0.107 mmol, 1.0 eq.) in dichloromethane (4 mL) was added TFA (0.7 mL) at 20℃. The mixture was stirred at 20℃ for 16h. After completion, the mixture

was concentrated in vacuo to give a residue. The residue was purified by Prep-HPLC (Mobile Phase: ACN---H_2O (0.1% $NH_3.H_2O$) to afford 1-{9-[(m-chlorophenyl)methyl]-2-ethyl-9a-methyl-8-adenineyl}-1-ethanol (13.3 mg, yield:35.82%). ESI-MS m/z =346.2 [M-H]+. Calculated MW: 345.83. ^{1}H NMR (400 MHz, DMSO) δ 7.49 (s, 1H), 7.33 (dd, J = 6.7, 3.9 Hz, 3H), 7.15 (dd, J = 5.5, 2.3 Hz, 1H), 5.66 (d, J = 6.1 Hz, 1H), 5.47 (q, J = 16.0 Hz, 2H), 4.87 (p, J = 6.4 Hz, 1H), 2.95 (s, 3H), 2.72 – 2.65 (m, 2H), 1.47 (d, J = 6.5 Hz, 3H), 1.23 (t, J = 7.6 Hz, 3H).

Synthesis of 1-{2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-8-adenineyl}-1-ethanone ***(Compound 67)***



Step 1: Synthesis of 2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-9-(tetrahydro-2H-pyran-2-yl)adenine.

To a mixture of 2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyladenine (2 g, 5.99 mmol, synthesized according to procedure described in synthesis of **Compound 66**) in tetrahydrofuran (20 mL) was added 3,4-dihydro-2H-pyran (1.51 g, 18 mmol, 3 eq.) and 1-pyridylium p-toluenesulfonate (1.51 g, 5.99 mmol) at 20℃. The mixture was stirred at 50℃ for 16h. After completion, the mixture was quenched with H2O (25 mL), extracted with EtOAc (20 mL*3). The organic layer was washed with H2O (20 mL), brine (20 mL), dried over anhydrous Na2SO4, filtrated and concentrated in vacuo to give a residue. The residue was purified by SGC (UV254, Petroleum ether: EtOAc = 4:1) to afford 2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-9-(tetrahydro-2H-pyran-2-yl)adenine (2.4 g, purity: 100%, yield:95.85%) as a white solid. MS (ESI, pos. ion) m/z: 418.1. (M+1). Calculated MW: 417.89.

Step 2: Synthesis of 1-{2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-9-(tetrahydro-2H-pyran-2-yl)-8-adenineyl}-1-ethanone.

To a mixture of 2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-9-(tetrahydro-2H-pyran-2-yl)adenine (2.4 g, 5.74 mmol) in tetrahydrofuran (96 mL) was added 1,2-bis(dimethylamino)ethane (1 g, 8.61 mmol, 1.5 eq.) and lithium 1-butanide (736 mg, 11.5 mmol, 2 eq.) at -78℃ stirred for 30 min . The mixture was added N-methoxy-N-methylacetamide (888 mg, 8.61 mmol, 1.5 eq.) stirred at -78℃ for 1h. After completion, the mixture was quenched with H2O (15 mL), extracted with EtOAc (15 mL*3). The organic layer was washed with H2O (15 mL), brine (15 mL), dried over anhydrous Na2SO4, filtrated and concentrated in vacuo to give a residue. The residue was purified by SGC (UV254 Petroleum ether: EtOAc = 5:1) to afford 1-{2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-9-(tetrahydro-2H-pyran-2-yl)-8-adenineyl}-1-ethanone (1.04 g, purity: 100%, yield:39.37%) as a white solid. MS (ESI, pos. ion) m/z: 460.1. (M+1). Calculated MW: 459.93.

Step 3: Synthesis of 1-{2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-8-adenineyl}-1-ethanone.

A mixture of 1-{2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-9-(tetrahydro-2H-pyran-2-yl)-8-adenineyl}-1-ethanone (1.07 g, 2.33 mmol) in 2N hydrogen chloride (170 mg, 4.65 mmol, 2 eq.)/dioxane(10 ml) was stirred at 25℃ for 1h. The solvent was removed in vacuo to afford crude product 1-{2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-8-adenineyl}-1-ethanone—hydrogen chloride (1/1) (1 g, purity: 100%, yield:39.37%) and used into next step without further purification. MS (ESI, pos. ion) m/z: 376.1. (M+1). Calculated MW: 375.81.

Step 4: Synthesis of methyl m-({8-acetyl-2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-9-adenineyl}methyl)benzoate.

To a mixture of 1-{2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-8-adenineyl}-1-ethanone (136 mg, 0.20 mmol) in dimethylformamide (8 mL) was added methyl m-(bromomethyl)benzoate (550 mg, 2.4 mmol, 1.1 eq.) and dicaesium carbonate (1.07 g, 3.27 mmol, 1.5 eq.) at 25℃. The mixture was stirred at 25℃ for 2h. After completion, the mixture was quenched with H2O (10 mL), extracted with EtOAc(10 mL*3). The organic layer was washed with H2O (10 mL), brine (10 mL), dried over anhydrous Na2SO4, filtrated and concentrated in vacuo to give a residue. The residue was purified by Pre-TLC (UV254, Petroleumether: EtOAc = 3:1) to afford methyl m-({8-acetyl-2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-9-adenineyl}methyl)benzoate (360 mg, purity: 100%, yield:31.47%) as a colorless oil. MS (ESI, pos. ion) m/z: 524.2. (M+1). Calculated MW: 523.97.

Step 5: Synthesis of methyl m-({2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-8-(1-hydroxyethyl)-9a-methyl-9-adenineyl}methyl)benzoate.

To a mixture of methyl m-({8-acetyl-2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-9-adenineyl}methyl)benzoate (160 mg, 0.31 mmol) in methanol (2 mL) was added sodium boranuide (11.6 mg, 0.31 mmol) at 25℃. The mixture was stirred at 25℃ for 6h. After completion, the mixture was quenched with H2O (5 mL), extracted with EtOAc (5 mL*3). The organic layer was washed with H2O (5 mL), brine (5 mL), dried over anhydrous Na2SO4, filtrated and concentrated in vacuo to give a residue. The residue was purified by Pre-TLC (Petroleumether: EtOAc = 3:1) to afford methyl m-({2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-8-(1-hydroxyethyl)-9a-methyl-9-adenineyl}methyl)benzoate (80 mg, purity: 100%, yield:49.81%) as a white solid. MS (ESI, pos. ion) m/z: 526.2. (M+1). Calculated MW: 525.99.

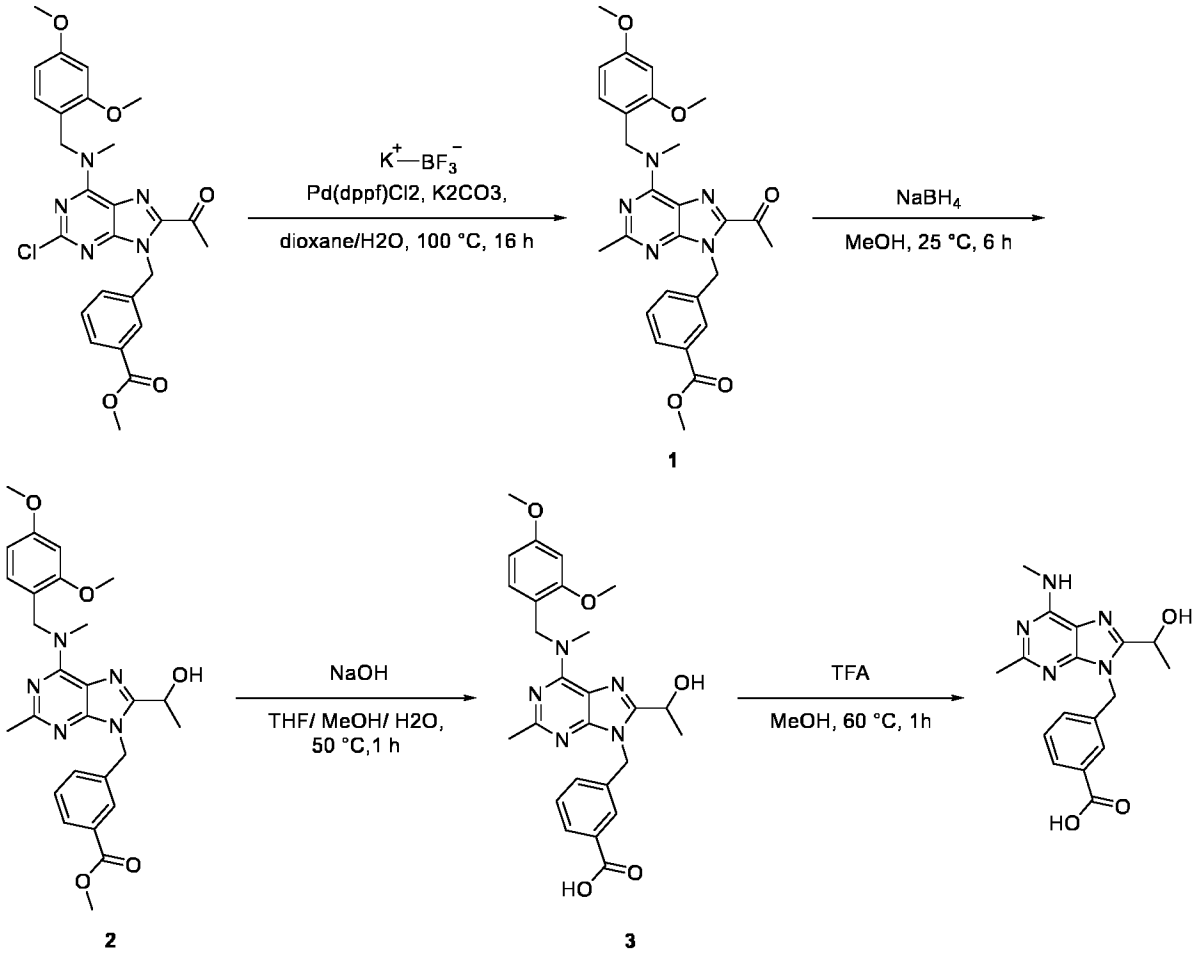
Step 6: Synthesis of purificationm-({2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-8-(1-hydroxyethyl)-9a-methyl-9-adenineyl}methyl)benzoic acid.

To a mixture of methyl m-({2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-8-(1-hydroxyethyl)-9a-methyl-9-adenineyl}methyl)benzoate (70 mg, 0.13 mmol) in methanol (0.4 mL)/tetrahydrofuran (0.8 mL) was added sodium hydroxide (26.6 mg, 0.67 mmol, 5 eq.)/water (0.2 mL) at 25℃. The mixture was stirred at 50℃ for 1h. The solvent was removed in vacuo to afford crude product purificationm-({2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-8-(1-hydroxyethyl)-9a-methyl-9-adenineyl}methyl)benzoic acid(70 mg, purity: 100%, yield:100%) and used into next step without further. MS (ESI, pos. ion) m/z: 512.2. (M+1). Calculated MW: 511.96.

Step 7: Synthesis of 1-{2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-8-adenineyl}-1-ethanone.

To a mixture of m-({2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-8-(1-hydroxyethyl)-9a-methyl-9-adenineyl}methyl)benzoic acid (70 mg, 0.14 mmol) in methanol (1.2 mL) was added trifluoroacetic acid (0.2 mL) at 25℃. The mixture was stirred at 25℃ for 2h. The residue was purified by Pre-HPLC (MeCN/H2O, 0.1 %NH3/H2O) to afford m-{[2-chloro-8-(1-hydroxyethyl)-9a-methyl-9-adenineyl]methyl}benzoic acid (33 mg, purity: 96.79%, yield:64.57%). MS (ESI, pos. ion) m/z: 362.1. (M+1). Calculated MW: 361.79. ^{1}H NMR (400 MHz, DMSO) δ 8.21 (d, J = 4.3 Hz, 1H), 7.80 (d, J = 7.7 Hz, 1H), 7.69 (s, 1H), 7.37 (t, J = 7.6 Hz, 1H), 7.27 (d, J = 7.9 Hz, 1H), 5.74 (s, 1H), 5.52 (q, J = 16.2 Hz, 2H), 4.83 (q, J = 6.3 Hz, 1H), 2.92 (d, J = 4.2 Hz, 3H), 2.53 (dd, J = 4.2, 2.5 Hz, 1H), 1.44 (d, J = 6.5 Hz, 3H).

Synthesis of m-{[8-(1-hydroxyethyl)-2,9a-dimethyl-9-adenineyl]methyl}benzoic acid ***(Compound 65)***



Step 1: Synthesis of methyl m-({8-acetyl-9a-[(2,4-dimethoxyphenyl)methyl]-2,9a-dimethyl-9-adenineyl}methyl)benzoate.

To a mixture of methyl m-({8-acetyl-2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-9-adenineyl}methyl)benzoate (0.2 g, 0.38 mmol, 1 eq, synthesized according to procedure described in synthesis of **Compound 67**) in 1,4-dioxane (2 mL)/water (0.4 mL) was added potassium trifluoro(methyl)boranuide (931 mg, 7.63 mmol, 20 eq.), [1,1'-

Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (55.9 mg, 0.08 mmol, 0.2 eq.) and dipotassium carbonate (158 mg, 1.15 mmol, 3 eq.) at 20℃. The mixture was stirred at 100℃ for 16h under N2. After completion, the mixture was concentrated in vacuo to give a residue. The residue was purified by SGC (UV254, Petroleum ether: EtOAc = 4:1) to afford methyl m-({8-acetyl-9a-[(2,4-dimethoxyphenyl)methyl]-2,9a-dimethyl-9-adenineyl}methyl)benzoate (135 mg, purity: 100%, yield:70.24%) as a white solid. MS (ESI, pos. ion) m/z: 504.2. (M+1). Calculated MW: 503.56.

Step 2: Synthesis of methyl m-({9a-[(2,4-dimethoxyphenyl)methyl]-8-(1-hydroxyethyl)-2,9a-dimethyl-9-adenineyl}methyl)benzoate.

To a mixture of methyl m-({8-acetyl-9a-[(2,4-dimethoxyphenyl)methyl]-2,9a-dimethyl-9-adenineyl}methyl)benzoate (115 mg, 0.23 mmol, 1 eq) in methanol (2 mL) was added sodium boranuide (17.3 mg, 0.46 mmol, 2 eq.) at 25℃. The mixture was stirred at 25℃ for 6h. The residue was purified by Prep-TLC (Petroleum ether: EtOAc = 3:1) to afford methyl m-({9a-[(2,4-dimethoxyphenyl)methyl]-8-(1-hydroxyethyl)-2,9a-dimethyl-9-adenineyl}methyl)benzoate (95 mg, purity: 100%, yield: 82.28%). MS (ESI, pos. ion) m/z: 506.2. (M+1). Calculated MW: 505.58.

Step 3: Synthesis of m-({9a-[(2,4-dimethoxyphenyl)methyl]-8-(1-hydroxyethyl)-2,9a-dimethyl-9-adenineyl}methyl)benzoic acid.

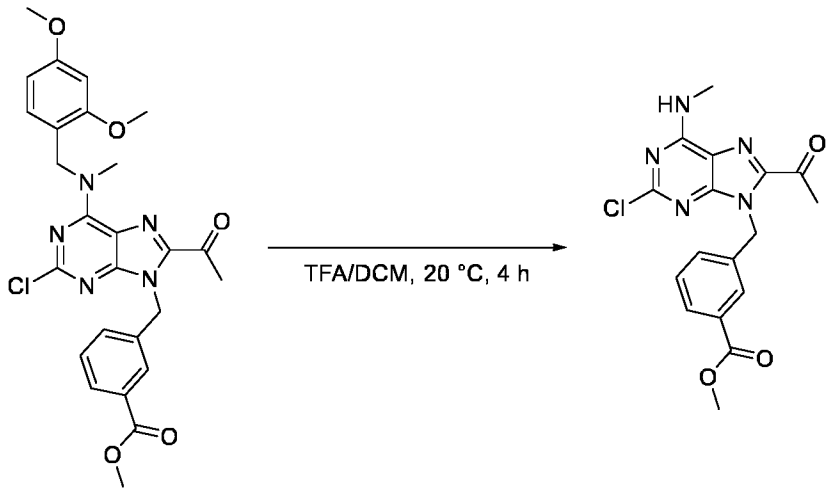
To a mixture of methyl m-({9a-[(2,4-dimethoxyphenyl)methyl]-8-(1-hydroxyethyl)-2,9a-dimethyl-9-adenineyl}methyl)benzoate (95 mg, 0.19 mmol, 1 eq) in methanol (2 mL)/tetrahydrofuran (4 mL) was added solution of sodium hydroxide (37.6 mg, 0.94 mmol, 5 eq.) in water (0.5 mL) at 25℃. The mixture was stirred at 50℃ for 1h. The solvent was removed in vacuo to afford crude product m-({9a-[(2,4-dimethoxyphenyl)methyl]-8-(1-hydroxyethyl)-2,9a-dimethyl-9-adenineyl}methyl)benzoic acid (95 mg, purity: 95%, yield: 97.71%) and used into next step without further purification. MS (ESI, pos. ion) m/z: 492.2. (M+1). Calculated MW: 491.55.

Step 4: Synthesis of m-{[8-(1-hydroxyethyl)-2,9a-dimethyl-9-adenineyl]methyl}benzoic acid.

To the crude mixture of m-({9a-[(2,4-dimethoxyphenyl)methyl]-8-(1-hydroxyethyl)-2,9a-dimethyl-9-adenineyl}methyl)benzoic acid (95 mg, 0.19 mmol, 1 eq) in methanol (2 mL) was added trifluoroacetic acid to pH=1 at 25℃. The mixture was stirred at 60℃ for 1h. The residue was purified by Pre-HPLC (MeCN/H2O, 0.05%NH3/H2O) to afford m-{[8-(1-hydroxyethyl)-2,9a-dimethyl-9-adenineyl]methyl} benzoic acid (25.7 mg, purity: 99.11%, yield:38.55%). MS (ESI, pos. ion) m/z: 342.1. (M+1). Calculated MW: 341.37. ^{1}H NMR (400 MHz, DMSO) δ 7.81 (d, J = 7.6 Hz, 1H), 7.71 (s, 1H), 7.51 (s, 1H), 7.40 (t, J = 7.6 Hz, 1H),

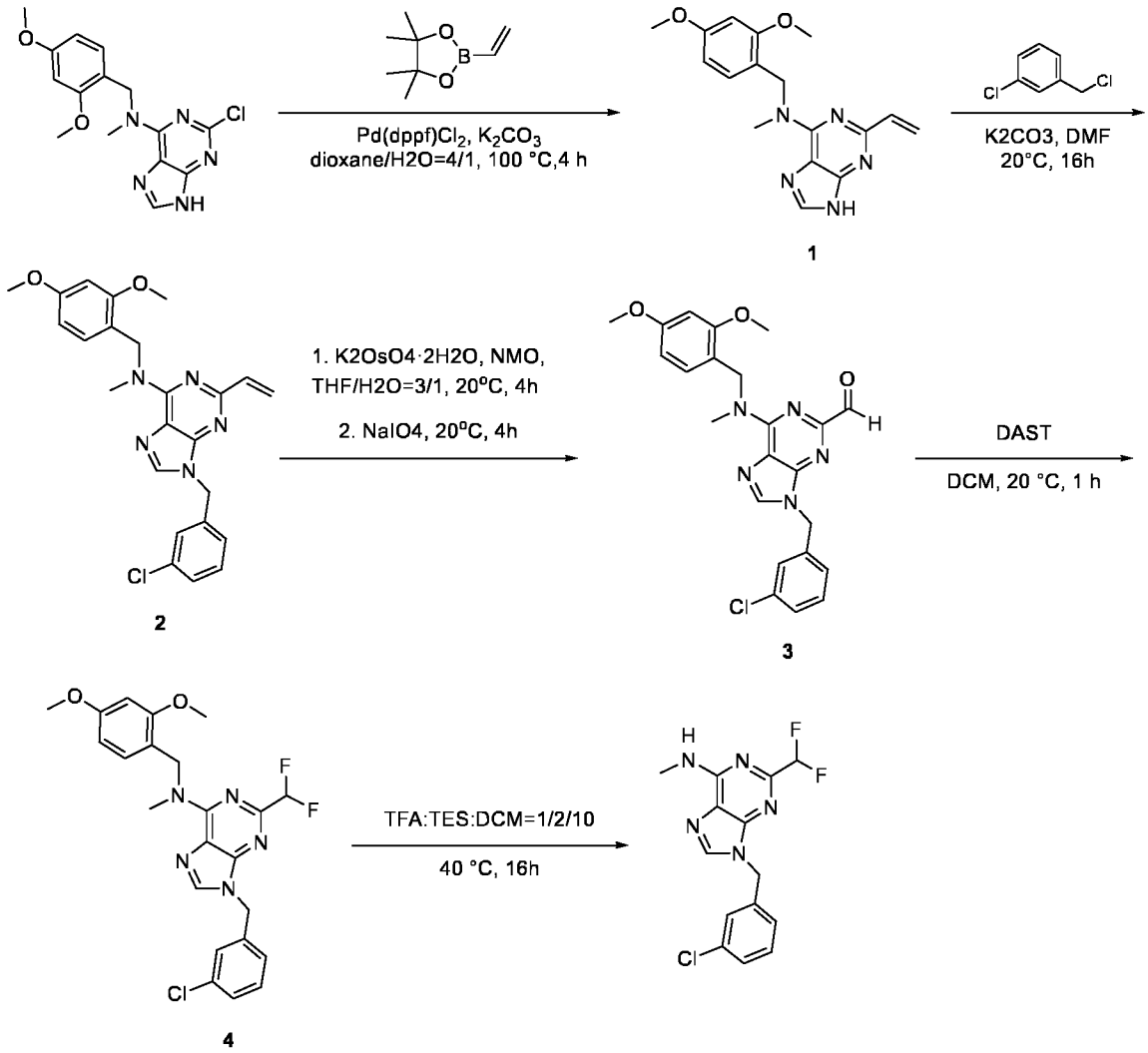
7.32 (d, J = 7.7 Hz, 1H), 5.54 (dd, J = 39.7, 16.2 Hz, 2H), 4.81 (q, J = 6.5 Hz, 1H), 2.95 (s, 3H), 2.41 (s, 3H), 1.44 (d, J = 6.5 Hz, 3H).

Synthesis of 4-(4-{[4-(dimethylamino)-1-piperidyl]methyl}-2,5-difluorophenyl)-9-[6-(methylamino)-4-pyrimidinyl]-1,4,9-triaza-2-spiro[5.5]undecanone ***(Compound 69)***



To a mixture of methyl m-({8-acetyl-2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-9-adenineyl}methyl)benzoate (10 mg, 0.019 mmol, synthesized according to procedure described in synthesis of **Compound 67**) in dichloromethane (0.6 mL) was added trifluoroacetic acid (0.1 mL) at 25℃. The mixture was stirred at 25℃ for 4h. After completion, the mixture was concentrated in vacuo to give a residue. The residue was purified by Pre-HPLC (MeCN/H2O, 0.1 %NH3/H2O) to afford methyl m-[(8-acetyl-2-chloro-9a-methyl-9-adenineyl)methyl]benzoate (3.4 mg, purity: 96.86%, yield:46.16%). MS (ESI, pos. ion) m/z: 374.0. (M+1). Calculated MW: 373.8. ^{1}H NMR (400 MHz, MeOD) δ 7.93 (d, J = 7.1 Hz, 2H), 7.53 (d, J = 7.9 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 5.78 (s, 2H), 3.90 (s, 3H), 3.17 – 3.09 (m, 3H), 2.69 (s, 3H).

Synthesis of 9-[(m-chlorophenyl)methyl]-2-(difluoromethyl)-9a-methyladenine ***(Compound 62)***



Step 1: Synthesis of 9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-2-vinyladenine

To a mixture of 2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyladenine (2 g, 5.99 mmol, 1.0 eq., synthesized according to procedure described in synthesis of **Compound 66**) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (2.21 g, 14.4 mmol, 2.4 eq., cas:75927-49-0.) in 1,4-dioxane (20 mL)/water (5 mL)=4/1 was added $Pd(dppf)Cl_2$ (877 mg, 1.2 mmol, 0.2 eq.) and K_2CO_3 (2.48 g, 18 mmol, 3 eq.) at 20℃. The mixture was stirred at 100℃ for 16 h under N_2. After completion, the mixture was filtrated and concentrated in vacuo to give a residue. The residue was purified by SGC (UV254, DCM: MeOH= 20:1) to afford 9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-2-vinyladenine (1.4 g, yield:71.81%) as a brown solid. ESI-MS m/z = 326.1 $[M-H]^+$. Calculated MW: 325.37

Step 2: Synthesis of 9-[(m-chlorophenyl)methyl]-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-2-vinyladenine.

To a mixture of 9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-2-vinyladenine (1 g, 3.07 mmol, 1.0 eq.) and m-chloro(chloromethyl)benzene (544 mg, 3.38 mmol, 1.1 eq., cas:620-20-2) in dimethylformamide (10 mL) was added K_2CO_3 (1.27 g, 9.22 mmol, 3 eq.) at 20℃. The mixture was stirred at 20℃ for 16h. After completion, the mixture was quenched with H_2O (20 mL), extracted with EtOAc (20 mL*3). The organic layer was washed with H_2O (20 mL), brine (20 mL), dried over anhydrous Na2SO4, filtrated and concentrated in vacuo to give a residue. The residue was purified by SGC (UV254, Petroleum ether: EtOAc = 4:1) to afford 9-[(m-chlorophenyl)methyl]-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-2-vinyladenine (390 mg, yield:28.2%) as a colorless oil. ESI-MS m/z =450.2 $[M-H]^+$. Calculated MW: 449.94

Step 3: Synthesis of 9-[(m-chlorophenyl)methyl]-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-2-adenineecarbaldehyde.

To 9-[(m-chlorophenyl)methyl]-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-2-vinyladenine (260 mg, 0.58 mmol, 1.0 eq.) in tetrahydrofuran (9 mL)/water (3 mL)=3/1 was added dipotassium tetraoxidoosmate(2-) dihydrate (21.3 mg, 0.06 mmol, 0.1 eq.) and NMO (203 mg, 1.73 mmol, 3 eq.) at 20℃. After stirring at 20℃ for 4h, sodium tetraoxidoiodate(1-) (371 mg, 1.73 mmol, 3 eq.) was added and the mixture continued stirring for 4 h. After completion, the mixture was washed with Na_2SO_3 aq.(10 ml) and quenched with H_2O (10 mL), extracted with EtOAc (10 mL*3). The organic layer was washed with H_2O (10 mL), brine (10 mL), dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo to give a residue. The residue was purified by SGC (UV254, Petroleum ether: EtOAc = 10:1) to afford 9-[(m-chlorophenyl)methyl]-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-2-adenineecarbaldehyde (150 mg, yield:57.44%) as a yellow oil. ESI-MS m/z =452.0 $[M-H]^+$. Calculated MW: 451.91

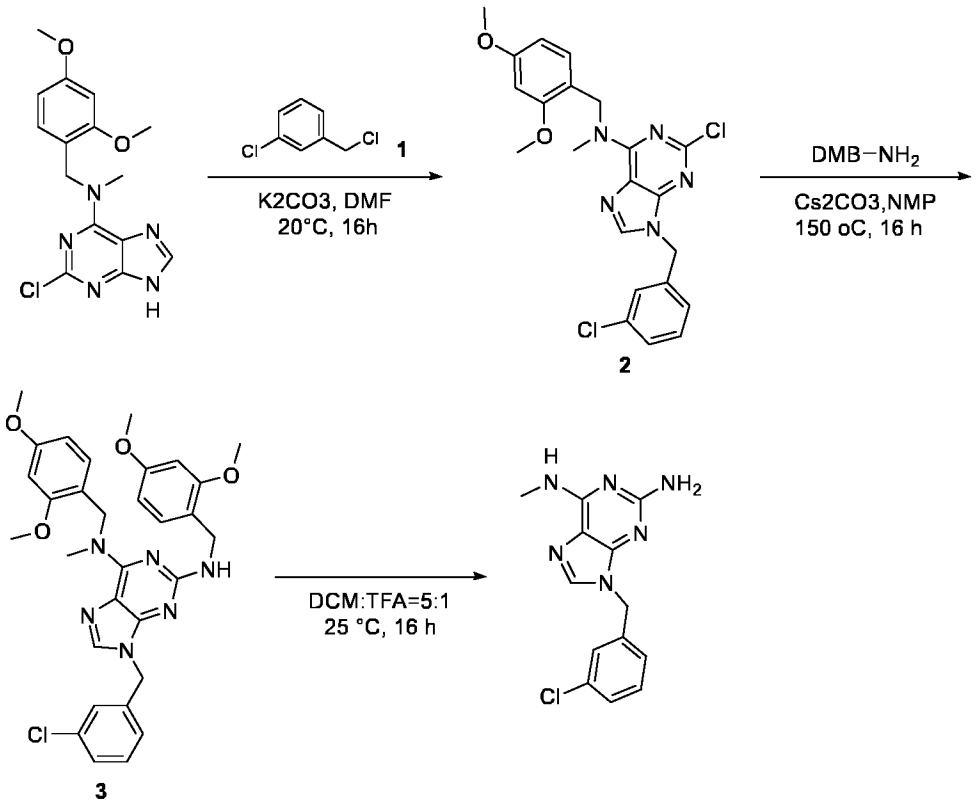
Step 4: Synthesis of 9-[(m-chlorophenyl)methyl]-2-(difluoromethyl)-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyladenine.

To 9-[(m-chlorophenyl)methyl]-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-2-adenineecarbaldehyde (130 mg, 0.29 mmol, 1.0 eq.) in dichloromethane (4 mL) was added DAST (162 mg, 1.01 mmol, 3.5 eq.cas:38078-09-0) at 20℃. The mixture was stirred at 20℃ for 1h. The mixture was diluted with dichloromethane, washed with NaHCO3 aq. (10 mL), H_2O (10 mL), brine (10 mL), dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo to give a residue. The residue was purified by SGC (UV254, Petroleum ether: EtOAc = 10:1) to afford 9-[(m-chlorophenyl)methyl]-2-(difluoromethyl)-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyladenine (76 mg, yield:55.75%) as a colorless oil. ESI-MS m/z =474.0 $[M-H]^+$. Calculated MW: 473.91

Step 5: Synthesis of 9-[(m-chlorophenyl)methyl]-2-(difluoromethyl)-9a-methyladenine.

To 9-[(m-chlorophenyl)methyl]-2-(difluoromethyl)-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyladenine (66 mg, 0.14 mmol,1.0 eq.) in dichloromethane (0.5 mL) was added TFA (0.1 mL) at 20℃. The mixture was stirred at 20℃ for 16h. After completion, the mixture was filtrated and purified by Prep-HPLC (Mobile Phase: ACN---H_2O (0.1% $NH_3.H_2O$) to afford 9-[(m-chlorophenyl)methyl]-2-(difluoromethyl)-9a-methyladenine (23.1 mg, yield:98.74%). ESI-MS m/z =324.0 $[M-H]^+$. Calculated MW: 323.73. ^1H NMR (400 MHz, DMSO) δ 8.37 (s, 1H), 8.11 (s, 1H), 7.41 (d, J = 4.6 Hz, 1H), 7.39 – 7.35 (m, 2H), 7.25 – 7.20 (m, 1H), 6.70 (t, J = 56.0 Hz, 1H), 5.43 (s, 2H), 2.98 (d, J = 3.7 Hz, 3H).

Synthesis of 9-[(m-chlorophenyl)methyl]-9a-methyl-2-adenineamine ***(Compound 64)***



Step 1: Synthesis of 2-chloro-9-[(m-chlorophenyl)methyl]-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyladenine.

To a mixture of 2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyladenine (0.5 g, 1.5 mmol) in dimethylformamide (5 mL) was added m-chloro(chloromethyl)benzene (265 mg, 1.65 mmol, 1.1 eq.) and dipotassium carbonate (621 mg, 4.49 mmol, 3 eq.) at 25℃. The mixture was stirred at 25℃ for 16h. After completion, the mixture was quenched with H2O (5 mL), extracted with EtOAc(5 mL*3). The organic layer was washed with H2O (5 mL), brine (5 mL), dried over anhydrous Na2SO4, filtrated and concentrated in vacuo to give a residue. The residue was purified by SGC (UV254, Petroleumether: EtOAc = 8:1) to afford 2-chloro-9-[(m-chlorophenyl)methyl]-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyladenine (0.6 g, purity:

100%, yield:87.39%) as a white solid. MS (ESI, pos. ion) m/z: 458.1. (M+1). Calculated MW: 458.34.

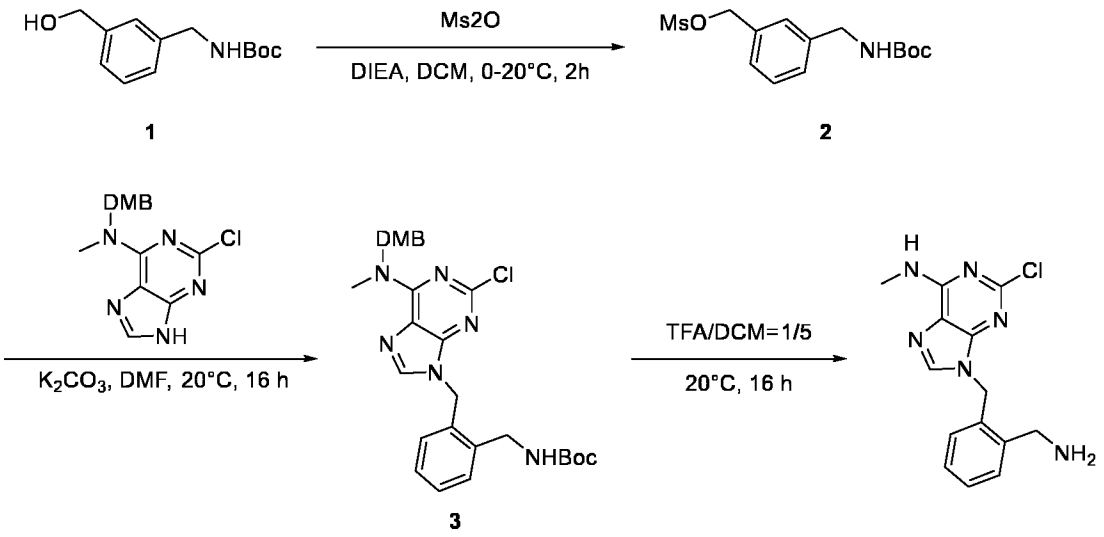
Step 2: Synthesis of 9-[(m-chlorophenyl)methyl]-9a-[(2,4-dimethoxyphenyl)methyl]-2-{[(2,4-dimethoxyphenyl)methyl]amino}-9a-methyladenine.

To a mixture of 2-chloro-9-[(m-chlorophenyl)methyl]-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyladenine (0.1 g, 0.22 mmol) in N-Methyl-2-pyrrolidone (1 mL) was added [(2,4-dimethoxyphenyl)methyl]amine (182 mg, 1.09 mmol, 5 eq.) and dicaesium carbonate (213 mg, 0.66 mmol, 3 eq.) at 25℃. The mixture was stirred at 150℃ for 16h. After completion, the mixture was quenched with H2O (5 mL), extracted with EtOAc (5 mL*3). The organic layer was washed with H2O (5 mL), brine (5 mL), dried over anhydrous Na2SO4, filtrated and concentrated in vacuo to give a residue. The residue was purified by Pre-TLC (Petroleum ether: EtOAc = 3:1) to afford 9-[(m-chlorophenyl)methyl]-9a-[(2,4-dimethoxyphenyl)methyl]-2-{[(2,4-dimethoxyphenyl)methyl]amino}-9a-methyladenine (110 mg, purity: 100%, yield:85.59%) as a colorless oil. MS (ESI, pos. ion) m/z: 589.2. (M+1). Calculated MW: 589.09.

Step 3: Synthesis of 9-[(m-chlorophenyl)methyl]-9a-methyl-2-adenineamine.

To a mixture of 9-[(m-chlorophenyl)methyl]-9a-[(2,4-dimethoxyphenyl)methyl]-2-{[(2,4-dimethoxyphenyl)methyl]amino}-9a-methyladenine (0.1 g, 0.17 mmol) in dichloromethane (2 mL) was added trifluoroacetic acid (0.4 mL) at 25℃. The mixture was stirred at 25℃ for 16h. After completion, the mixture was purified by Pre-HPLC (MeCN/H2O, 0.1 %NH3/H2O) to afford 9-[(m-chlorophenyl)methyl]-9a-methyl-2-adenineamine (29.3 mg, purity: 100%, yield:59.86%). MS (ESI, pos. ion) m/z: 289.1. (M+1). Calculated MW: 288.74. ^{1}H NMR (400 MHz, cd3od) δ 7.75 (s, 1H), 7.35 – 7.23 (m, 3H), 7.16 (d, J = 6.8 Hz, 1H), 5.26 (s, 2H), 3.05 (s, 3H).

Synthesis of {o-[(2-chloro-9a-methyl-9-adenineyl)methyl]phenyl}methanamine ***(Compound 63)***



Step 1: Synthesis of tert-butyl ({m-[(mesyloxy)methyl]phenyl}methyl)carbamate .

To a mixture of [m-(hydroxymethyl)phenyl]methyl 2-methyl-2-propanecarbamate (1 g, 4.21 mmol) and MS2O (1.47 g, 8.43 mmol, 2 eq.) in dichloromethane (10 mL) was added DIEA (1.63 g, 12.6 mmol, 3 eq.) at 0℃. The mixture was stirred at 20℃ for 2h. The mixture was quenched with H2O (20 mL), extracted with DCM (20 mL*3). The organic layer was washed with H2O (20 mL), brine (20 mL), dried over anhydrous Na2SO4, filtrated and concentrated in vacuo to afford tert-butyl ({m-[(mesyloxy)methyl]phenyl}methyl)carbamate (1.32 g, yield: 99.32%) as a brown oil. ESI-MS m/z =338.1[M+ Na]+. Calculated MW: 315.38

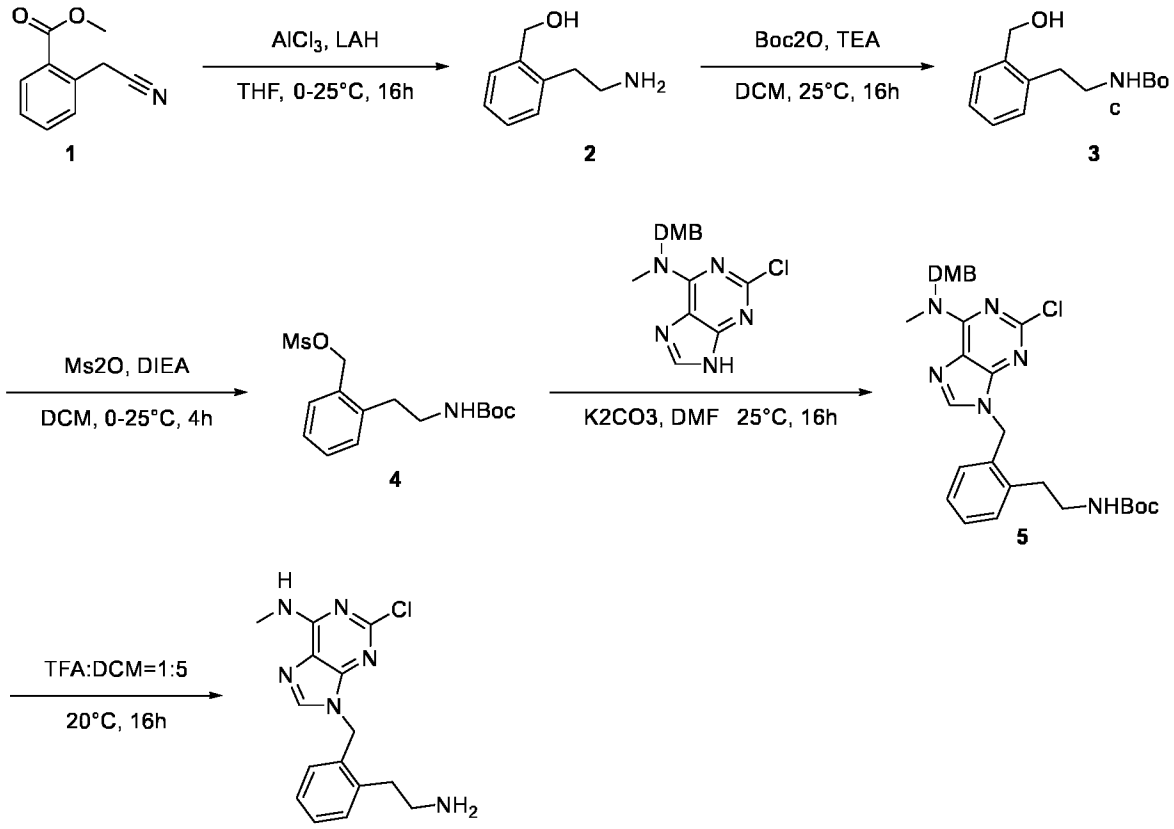
Step 2: Synthesis of [o-({2-chloro-9a-methyl-9a-[(3,4-xylyl)methyl]-9-adenineyl}methyl)phenyl]methyl 2-methyl-2-propanecarbamate.

To a mixture of tert-butyl ({m-[(mesyloxy)methyl]phenyl}methyl)carbamate (1.32 g, 4.19 mmol, 1.0 eq.) and 2-chloro-9a-methyl-9a-[(3,4-xylyl)methyl]adenine (1.26 g, 4.19 mmol, 1.0 eq., synthesized according to procedure described in synthesis of **Compound 66**) in dimethylformamide (10 mL) was added dipotassium carbonate (1.74 g, 12.6 mmol, 3 eq.) at 20℃. The mixture was stirred at 20℃ for 16h. After completion, the mixture was quenched with H_2O (20 mL), extracted with EtOAc (20 mL*3). The organic layer was washed with H_2O (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo to give a residue. The residue was purified by SGC (UV254, Petroleum ether: EtOAc = 4:1) to afford [o-({2-chloro-9a-methyl-9a-[(3,4-xylyl)methyl]-9-adenineyl}methyl)phenyl]methyl 2-methyl-2-propanecarbamate (1.14 g, yield:52.27%) as a yellow oil. ESI-MS m/z =553.3 $[M-H]^+$. Calculated MW: 553.06

Step 3: Synthesis of {o-[(2-chloro-9a-methyl-9-adenineyl)methyl]phenyl}methanamine.

To [o-({2-chloro-9a-methyl-9a-[(3,4-xylyl)methyl]-9-adenineyl}methyl)phenyl]methyl 2-methyl-2-propanecarbamate (1 g, 1.92 mmol, 1.0 eq.) in dichloromethane (5 mL) was added TFA (1 mL) at 20℃. The mixture was stirred at 20℃ for 16h. After completion, the mixture was filtrated and purified by Prep-HPLC (Mobile Phase: ACN---H_2O (0.1% $NH_3.H_2O$) to afford {o-[(2-chloro-9a-methyl-9-adenineyl)methyl]phenyl}methanamine (530 mg, yield:91.28%). ESI-MS m/z = 303.2[M-H]+. Calculated MW: 302.77. ^{1}H NMR (400 MHz, MeOD) δ 8.01 (s, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.36 – 7.31 (m, 1H), 7.28 – 7.21 (m, 1H), 7.02 (d, J = 7.6 Hz, 1H), 5.47 (s, 2H), 3.95 (s, 2H), 3.08 (s, 3H).

Synthesis of 2-{o-[(2-chloro-9a-methyl-9-adenineyl)methyl]phenyl}ethanamine ***(Compound 61)***



Step 1: Synthesis of [o-(2-aminoethyl)phenyl]methanol.

To a suspension of trichloroalumane (3.04 g, 22.8 mmol, 2.5 eq.) in THF (100 mL) was added dropwised a solution of aluminium(3+) lithium tetrahydride (22.8 mL, 22.8 mmol, 2.5 eq.) in THF at 0°C. Then a solution of methyl o-(cyanomethyl)benzoate (1.6 g, 9.13 mmol, 1.0 eq., cas: 5597-04-6) in THF (5 mL) was added. The mixture was stirred at 0-25°C for 16h. LCMS showed the reaction was completed. The mixture was quenched by 10% NaOH (1 mL) and ice water, filtered by celite and the filter cake was washed with MeOH. The filtrate was extracted with DCM (100 mL*3). The product was in aqueous layer as crude product which was used to the next step directly. ESI-MS m/z =152.2 $[M-H]^+$. Calculated MW: 151.21

Step 2: Synthesis of 2-[o-(hydroxymethyl)phenyl]ethyl 2-methyl-2-propanecarbamate.

To the crude solution of [o-(2-aminoethyl)phenyl]methanol (1.38 g, 9.13 mmol, 1.0 eq.) from previous step was added 10% NaOH solution to pH=13-14 and then tert-butyl (tert-butyl)(oxycarbonyloxy)formylate (3.98 g, 18.3 mmol, 2 eq.) was added. The mixture was stirred at 25°C for 16h. LCMS showed the reaction was completed. The mixture was extracted with DCM (100 mL*2). The organic layer was dried over Na_2SO_4 and concentrated. The crude was purified by flash column (10% EtOAc in PE) to give 2-[o-(hydroxymethyl)phenyl]ethyl 2-methyl-2-propanecarbamate (2 g, yield:87.19%)as yellow oil. ESI-MS m/z = 274.2 $[M+Na]^+$. Calculated MW: 251.33

Step 3: Synthesis of tert-butyl (2-{o-[(mesyloxy)methyl]phenyl}ethyl)carbamate.

To a mixture of 2-[o-(hydroxymethyl)phenyl]ethyl 2-methyl-2-propanecarbamate (1.97 g, 7.83 mmol, 1.0 eq.) and Ms_2O (6.82 g, 39.2 mmol, 5 eq.) in dichloromethane (20 mL) was added DIEA (6.07 g, 47 mmol, 6 eq.) at 0℃. The mixture was stirred at 20℃ for 4h. After completion, the mixture was quenched with H_2O (10 mL), extracted with DCM (10 mL*3). The organic layer was washed with H_2O (10 mL), brine (10 mL), dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo to afford tert-butyl (2-{o-[(mesyloxy)methyl]phenyl}ethyl)carbamate (2.58 g, yield:100%) as a yellow oil. ESI-MS m/z =352.2 $[M+Na]^+$. Calculated MW: 329.41

Step 4: Synthesis of 2-[o-({2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-9-adenineyl}methyl)phenyl]ethyl 2-methyl-2-propanecarbamate.

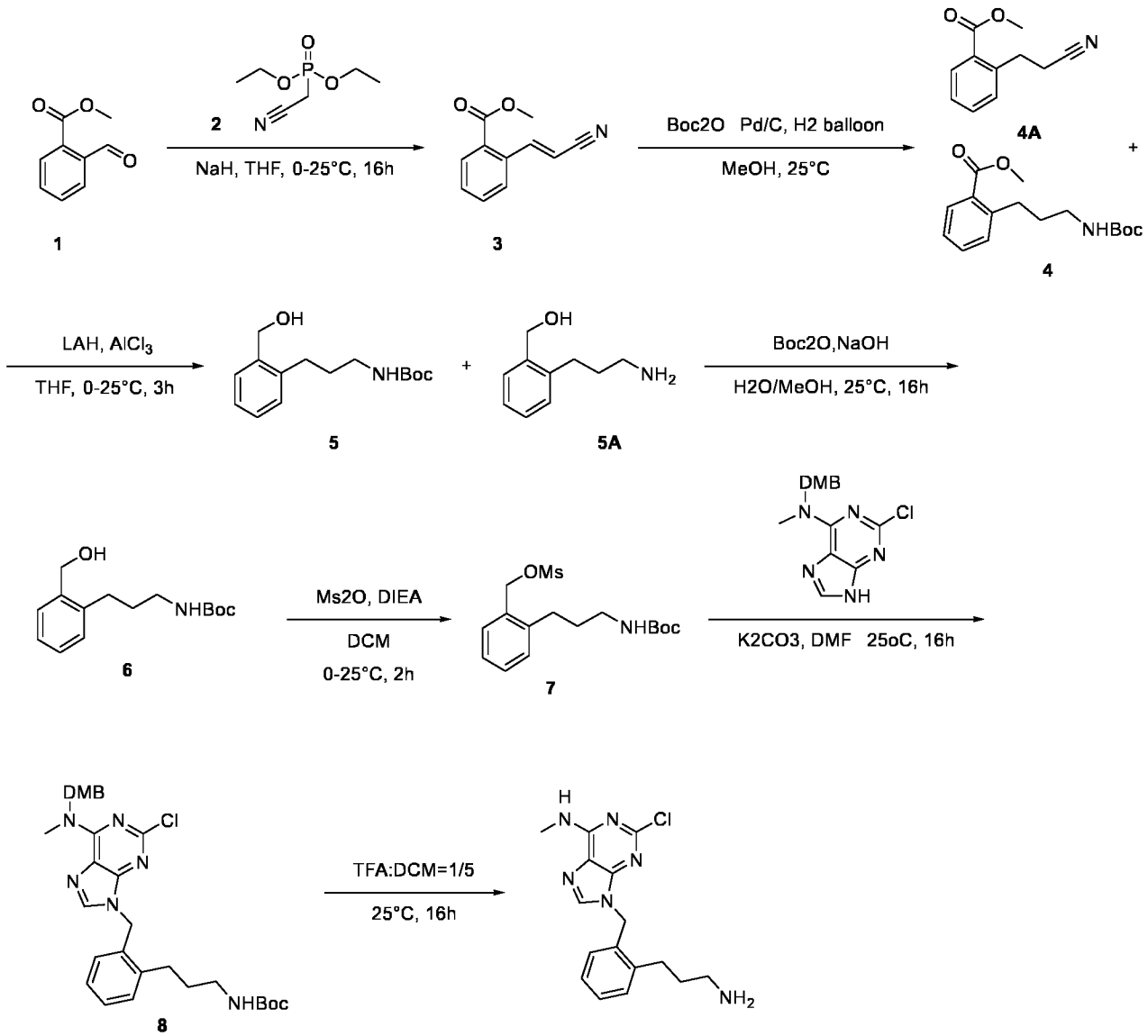
To a mixture of [o-(2-aminoethyl)phenyl]methanol (2.5 g, 16.5 mmol, 1.0 eq.) and 2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyladenine (5.52 g, 16.5 mmol, 1.0 eq., synthesized according to procedure described in synthesis of **Compound 66**) in dimethylformamide (20 mL) was added dipotassium carbonate (6.85 g, 49.6 mmol, 3 eq.) at 20℃. The mixture was stirred at 20℃ for 16h. After completion, the mixture was quenched with H_2O (10 mL), extracted with EtOAc (10 mL*3). The organic layer was washed with H_2O (10 mL), brine (10 mL), dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo to give a residue. The residue was purified by SGC (UV254, Petroleum ether: EtOAc = 20:1) to afford 2-[o-({2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-9-adenineyl}methyl)phenyl]ethyl 2-methyl-2-propanecarbamate (1.3 g, yield:13.87%) as a yellow oil. ESI-MS m/z =567.2 $[M-H]^+$. Calculated MW: 567.09

Step 5: Synthesis of 2-{o-[(2-chloro-9a-methyl-9-adenineyl)methyl]phenyl}ethanamine.

To 2-{o-[(2-chloro-9a,9a-dimethyl-9-adenineyl)methyl]phenyl}ethanamine in dichloromethane (5 mL, 78.1 mmol) was added TFA (1 mL) at 20℃. The mixture was stirred at 20℃ for 16 h .After completion, the mixture was filtrated and purified by reversed phase column

chromatograph (Mobile Phase: ACN---H2O (0.1% NH3.H2O) to afford 2-{o-[(2-chloro-9a-methyl-9-adenineyl)methyl]phenyl}ethanamine (646 mg, yield:88.36%). ESI-MS m/z =317.1 $[M-H]^+$. Calculated MW: 316.79. ^1H NMR (400 MHz, DMSO) δ 8.26 (d, J = 4.4 Hz, 1H), 8.14 (d, J = 8.4 Hz, 1H), 7.24 (d, J = 4.1 Hz, 2H), 7.17 – 7.13 (m, 1H), 6.83 (d, J = 7.8 Hz, 1H), 5.40 (s, 2H), 2.92 (t, J = 5.7 Hz, 3H), 2.87 – 2.78 (m, 2H), 2.77 – 2.67 (m, 2H).

Synthesis of 3-{o-[(2-chloro-9a-methyl-9-adenineyl)methyl]phenyl}-1-propanamine ***(Compound 59)***



Step 1: Synthesis of methyl o-[(E)-2-cyanoethenyl]benzoate.

To a mixture of (diethoxyphosphoryl)acetonitrile (3.56 g, 20.1 mmol, 1.1 eq., cas:2537-48-6) in tetrahydrofuran (30 mL) was added sodium hydride (570 mg, 23.8 mmol, 1.3 eq.) in portions at 0°C. The mixture was stirred for 0.5h and methyl o-formylbenzoate (3 g, 18.3 mmol,1.0 eq., cas:4122-56-9) was added dropwise and the mixture continued stirring at 25°C for 16h. After completion, the mixture was quenched with H2O (20 mL), extracted with EtOAc

(20 mL*3). The organic layer was washed with H_2O (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo to give a residue. The residue was purified by SGC (UV254, Petroleum ether: EtOAc = 10:1) to afford methyl o-[(E)-2-cyanoethenyl]benzoate (2.24 g, yield:65.45%) as a white solid. ESI-MS m/z =210.1 $[M+Na]^+$. Calculated MW: 187.20

Step 2: Synthesis of methyl o-{3-[(tert-butyl)(oxycarbonylamino)]propyl}benzoate and methyl o-(2-cyanoethyl)benzoate.

To a mixture of methyl o-[(E)-2-cyanoethenyl]benzoate (1.47 g, 7.85 mmol, 1.0 eq.) in methanol (110 mL) was added Pd/C (1 g) and Boc_2O (2.57 g, 11.8 mmol, 1.5 eq.) at 20℃. The mixture was stirred at 20℃ for 16 h under H2(0.4MPa). After completion, LCMS showed 48% 4A, 39% 4, the mixture was filtrated and concentrated in vacuo to afford the crude product and was used directly in the next step. 4: ESI-MS m/z =316.1 $[M+Na]^+$. Calculated MW: 293.36; 4A:ESI-MS m/z =212.0 $[M+Na]^+$. Calculated MW: 189.21

Step 3: Synthesis of tert-butyl (3-(2-(hydroxymethyl)phenyl)propyl)carbamate and [o-(3-aminopropyl)phenyl]methanol .

To a suspension of $AlCl_3$ (3.71 g, 27.8 mmol, 3 eq.) in tetrahydrofuran (20 mL) was added dropwised a solution of LAH (1.05 g, 27.8 mmol, 3 eq.) at 0°C. Then a solution of mixture methyl o-{3-[(tert-butyl)(oxycarbonylamino)]propyl}benzoate and methyl o-(2-cyanoethyl)benzoate (1.75 g, 9.26 mmol, 1.0 eq.) in THF (5 mL) was added. The mixture was stirred at 0-25°C for 3h. LCMS showed the reaction was completed. The mixture was quenched by 10% NaOH (1 mL) and ice water. The crude product was used to the next step directly. ESI-MS m/z =166.2 $[M-H]^+$. Calculated MW: 165.24

Step 4: Synthesis of 3-[o-(hydroxymethyl)phenyl]propyl 2-methyl-2-propanecarbamate.

To [o-(3-aminopropyl)phenyl]methanol (1 g, 6.05 mmol, 1.0 eq., crude from previous step) in water (5 mL)/methanol (5 mL)=1/1 was added sodium hydroxide (726 mg, 18.2 mmol, 3 eq.) and Boc_2O (2.64 g, 12.1 mmol, 2 eq.) at 20℃. The mixture was stirred at 20℃ for 16h. After completion, the mixture was quenched with H_2O (20 mL), extracted with EtOAc (20 mL*3). The organic layer was washed with H_2O (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo to give a residue. The residue was purified by SGC (UV254, Petroleum ether: EtOAc = 10:1) to afford 3-[o-(hydroxymethyl)phenyl]propyl 2-methyl-2-propanecarbamate (1.5 g, yield:93.41%) as a colorless oil. ESI-MS m/z =288.1 $[M+Na]^+$. Calculated MW: 265.35

Step 5: Synthesis of tert-butyl (3-{o-[(mesyloxy)methyl]phenyl}propyl)carbamate.

To a mixture of 3-[o-(hydroxymethyl)phenyl]propyl 2-methyl-2-propanecarbamate (1.47 g, 5.54 mmol, 1.0 eq.) and DIEA (4.3 g, 33.2 mmol, 6 eq.) in dichloromethane (14 mL) was

added Ms_2O (3.86 g, 22.2 mmol, 4 eq.) at 0℃. The mixture was stirred at 20℃ for 4h. After completion, the mixture was quenched with H_2O (20 mL), extracted with EtOAc (20 mL*3). The organic layer was washed with H_2O (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo to afford tert-butyl (3-{o-[(mesyloxy)methyl]phenyl}propyl)carbamate (1.9 g, yield:99.86%) as a yellow oil. ESI-MS m/z =366.1 [M+Na]+. Calculated MW: 343.44

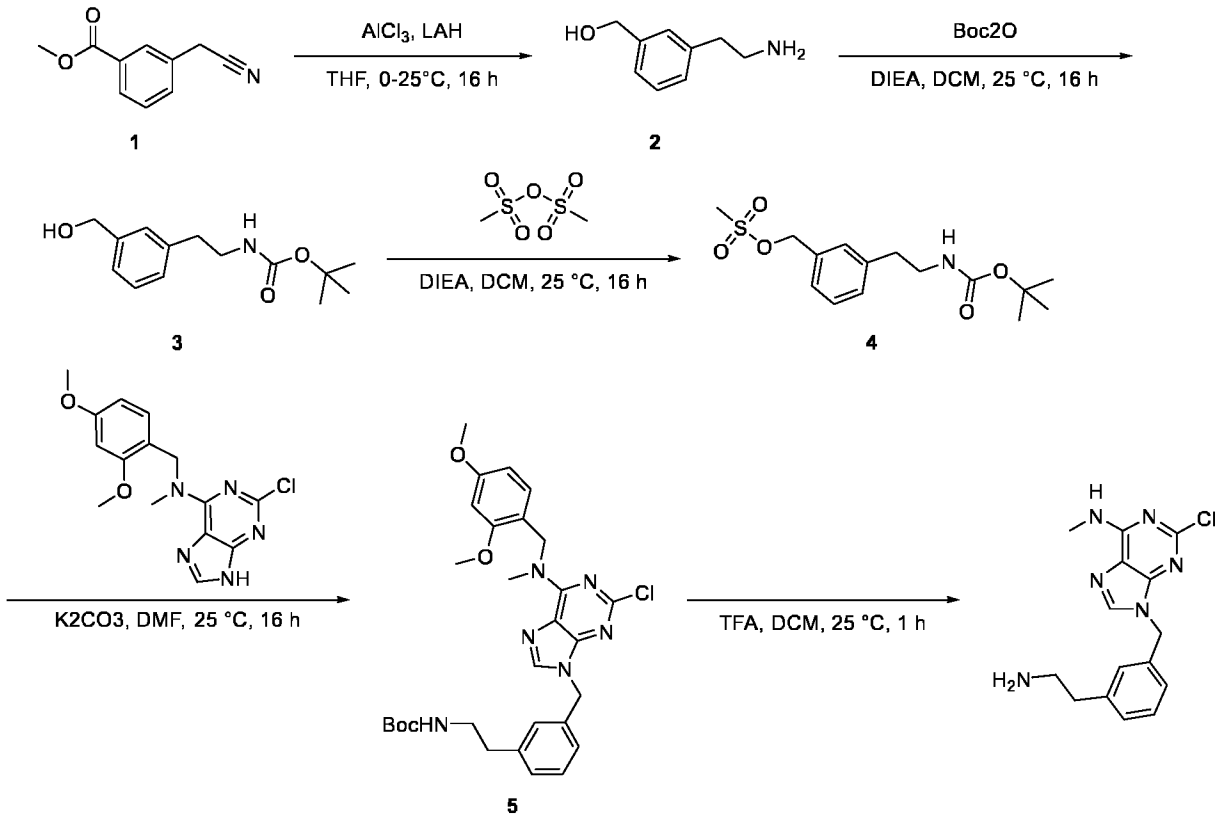
Step 6: Synthesis of 3-[o-({2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-9-adenineyl}methyl)phenyl]propyl 2-methyl-2-propanecarbamate.

To a mixture of tert-butyl (3-{o-[(mesyloxy)methyl]phenyl}propyl)carbamate (1.9 g, 5.53 mmol, 1.0 eq.) and 2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyladenine (1.85 g, 5.53 mmol, 1.0 eq., synthesized according to procedure described in synthesis of **Compound 66**) in dimethylformamide (10 mL) was added dipotassium carbonate (2.29 g, 16.6 mmol, 3 eq.) at 20℃. The mixture was stirred at 20℃ for 16h. After completion, the mixture was quenched with H_2O (20 mL), extracted with EtOAc (20 mL*3). The organic layer was washed with H_2O (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo to give a residue. The residue was purified by SGC (UV254, Petroleum ether: EtOAc = 4:1) to afford 3-[o-({2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-9-adenineyl}methyl)phenyl] propyl 2-methyl-2-propanecarbamate (1.51 g, yield:46.97%) as a yellow oil. ESI-MS m/z =581.3 [M-H]+. Calculated MW: 581.11

Step 7: Synthesis of 3-{o-[(2-chloro-9a-methyl-9-adenineyl)methyl]phenyl}-1-propanamine.

To a mixture of 3-[o-({2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-9-adenineyl}methyl)phenyl]propyl 2-methyl-2-propanecarbamate (1.5 g, 2.58 mmol) in dichloromethane (5 mL) was added TFA (1 mL) at 20℃. The mixture was stirred at 20℃ for 16h. After completion, the mixture was adjusted pH=8 with NaHCO3 aq. and then concentrated in vacuo to give a residue. The residue was purified SGC (UV254, DCM: MeOH = 10:1) to afford 3-{o-[(2-chloro-9a-methyl-9-adenineyl)methyl]phenyl}-1-propanamine (729 mg, yield:83.23%). ESI-MS m/z =331.2 $[M-H]^+$. Calculated MW: 330.82. ^1H NMR (400 MHz, DMSO) δ 8.28 (d, J = 4.6 Hz, 1H), 8.13 (s, 1H), 7.71 (s, 2H), 7.32 – 7.25 (m, 2H), 7.21 – 7.16 (m, 1H), 6.87 (d, J = 7.5 Hz, 1H), 5.38 (s, 2H), 2.93 (d, J = 4.6 Hz, 3H), 2.87 (d, J = 7.6 Hz, 2H), 2.82 – 2.76 (m, 2H), 1.82 (dd, J = 15.1, 7.8 Hz, 2H).

Synthesis of 2-{m-[(2-chloro-9a-methyl-9-adenineyl)methyl]phenyl}ethanamine ***(Compound 60)***



Step 1: Synthesis of [m-(2-aminoethyl)phenyl]methanol.

To a suspension of trichloroalumane (1.9 g, 14.3 mmol, 2.5 eq.) in THF (10 mL) was added dropwise a solution of aluminium(3+) lithium tetrahydride (5.7 mL, 14.3 mmol, 2.5 eq.) in THF at -15°C. Then a solution of methyl m-(cyanomethyl)benzoate (1 g, 5.71 mmol)in THF (5 mL) was added. The mixture was stirred at -15-25°C for 16h. LCMS showed the reaction was completed. The mixture was quenched by water at 0°C and then acidified by 1M HCl to pH=2-3, extracted with EtOAc (50 mL*2). The aqueous layer was basified by NaOH to pH=12 and extracted with DCM (50 mL*2). The organic layer was dried over Na2SO4 and concentrated to give [m-(2-aminoethyl)phenyl]methanol (0.8 g, purity: 100%, yield:92.69%) as crude product which was used to the next step directly. MS (ESI, pos. ion) m/z: 152.3. (M+1). Calculated MW: 151.21.

Step 2: Synthesis of 2-[m-(hydroxymethyl)phenyl]ethyl 2-methyl-2-propanecarbamate.

To a mixture of [m-(2-aminoethyl)phenyl]methanol (0.7 g, 4.63 mmol) in dichloromethane (8 mL) was added tert-butyl (tert-butyl)(oxycarbonyloxy)formylate (1.52 g, 6.94 mmol, 1.5 eq.) and N-ethylbis(isopropyl)amine (1.79 g, 13.9 mmol, 3 eq.) at 25℃. The mixture was stirred at 25℃ for 16h. After completion, the mixture was quenched with H2O (8 mL), extracted with DCM (8 mL*3). The organic layer was washed with H2O (8 mL), brine (8 mL), dried over

anhydrous Na2SO4, filtrated and concentrated in vacuo to give a residue. The residue was purified by SGC (UV254, Petroleum ether: EtOAc = 10:1) to afford 2-[m-(hydroxymethyl)-phenyl]ethyl 2-methyl-2-propanecarbamate (0.7 g, purity: 100%, yield:60.16%) as a colorless oil. MS (ESI, pos. ion) m/z: 274.1. (M+Na). Calculated MW: 251.33.

Step 3: Synthesis of tert-butyl (2-{m-[(mesyloxy)methyl]phenyl}ethyl)carbamate.

To a mixture of 2-[m-(hydroxymethyl)phenyl]ethyl 2-methyl-2-propanecarbamate (0.7 g, 2.79 mmol) in dichloromethane (7 mL) was added N-ethylbis(isopropyl)amine (1.44 g, 11.1 mmol, 4 eq.) and (mesyloxysulfonyl)methane (1.46 g, 8.36 mmol, 3 eq.) at 0℃. The mixture was stirred at 25℃ for 2h. After completion, the mixture was quenched with H2O (10 mL), extracted with DCM (10 mL*3). The organic layer was washed with H2O (10 mL), brine (10 mL), dried over anhydrous Na2SO4, filtrated and concentrated to afford crude product tert-butyl (2-{m-[(mesyloxy)methyl]phenyl}ethyl)carbamate (0.9 g, purity: 72%, yield:70.63%) and used into next step without further purification. MS (ESI, pos. ion) m/z: 352.1. (M+Na). Calculated MW: 329.41.

Step 4: Synthesis of 2-[m-({2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-9-adenineyl}methyl)phenyl]ethanamine.

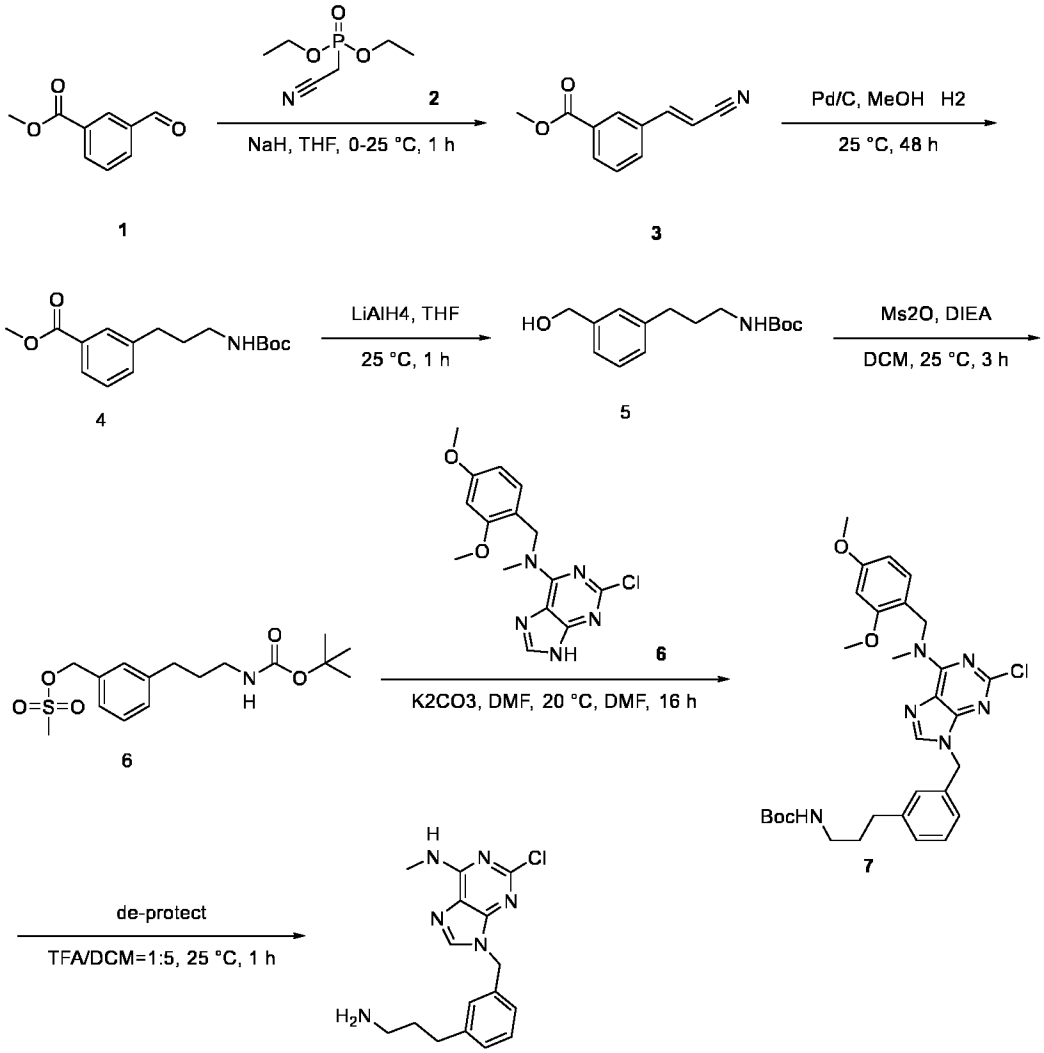
To a mixture of tert-butyl (2-{m-[(mesyloxy)methyl]phenyl}ethyl)carbamate (0.9 g, 2.73 mmol) in dimethylformamide (9 mL) was added 2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyladenine (912 mg, 2.73 mmol, synthesized according to procedure described in synthesis of **Compound 66**) and dipotassium carbonate (1.13 g, 8.2 mmol, 3 eq.) at 25℃. The mixture was stirred at 25℃ for 16h. After completion, the mixture was quenched with H2O (10 mL), extracted with EtOAc (10 mL*3). The organic layer was washed with H2O (10 mL), brine (10 mL), dried over anhydrous Na2SO4, filtrated and concentrated in vacuo to give a residue. The residue was purified by SGC (UV254, Petroleum ether: EtOAc = 4:1) to afford 2-[m-({2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-9-adenineyl}methyl)phenyl] ethanamine (1.2 g, purity: 92%, yield:86.53%) as a colorless oil. MS (ESI, pos. ion) m/z: 567.2. (M+1). Calculated MW: 567.09.

Step: Synthesis of 2-{m-[(2-chloro-9a-methyl-9-adenineyl)methyl]phenyl}ethanamine.

To a mixture of 2-[m-({2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-9-adenineyl}methyl)phenyl]ethyl 2-methyl-2-propanecarbamate (1.2 g, 2.12 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (2 mL) at 25℃. The mixture was stirred at 25℃ for 1h. After completion, the mixture was concentrated in vacuo to give a residue. The residue was purified by reversed phase column chromatograph (MeCN/H2O, 0.1 %NH3/H2O) to afford 2-{m-[(2-chloro-9a-methyl-9-adenineyl)methyl]phenyl}ethanamine (495 mg, purity: 98.41%, yield:72.72%). MS (ESI, pos. ion) m/z: 317.2. (M+1). Calculated

MW: 316.79. ^{1}H NMR (400 MHz, dmso) δ 8.23 (s, 2H), 7.25 (t, J = 7.9 Hz, 1H), 7.14 (t, J = 10.3 Hz, 2H), 7.05 (d, J = 7.6 Hz, 1H), 5.31 (s, 2H), 2.92 (d, J = 4.4 Hz, 3H), 2.71 (d, J = 7.5 Hz, 2H), 2.62 – 2.57 (m, 2H).

Synthesis of 3-{m-[(2-chloro-9a-methyl-9-adenineyl)methyl]phenyl}-1-propanamine ***(Compound 58)***



Step 1: Synthesis of methyl m-[(E)-2-cyanoethenyl]benzoate.

To a solution of (diethoxyphosphoryl)acetonitrile (2.37 g, 13.4 mmol, 1.1 eq.) in tetrahydrofuran (20 mL) was added sodium hydride (633 mg, 15.8 mmol, 1.3 eq.) in portions at 0°C. The mixture was stirred for 0.5h and methyl m-formylbenzoate (2 g, 12.2 mmol) was added dropwise. After completion, the mixture was quenched with H2O (20 mL), extracted with EtOAc (20 mL*3). The organic layer was washed with H2O (20 mL), brine (20 mL), dried over anhydrous Na2SO4, filtrated and concentrated in vacuo to give a residue to afford crude product methyl m-[(E)-2-cyanoethenyl]benzoate (2.5 g, purity: 91%, yield:99.75%) and used into next step without further purification. MS (ESI, pos. ion) m/z: 188.1. [M+H]. Calculated MW: 187.2.

Step 2: Synthesis of methyl m-{3-[(tert-butyl)(oxycarbonylamino)]propyl}benzoate.

To a mixture of methyl m-[(E)-2-cyanoethenyl]benzoate (0.8 g, 4.27 mmol) in methanol (8 mL) was added palladium/C (455 mg, 4.27 mmol) and tert-butoxycarbonyl -tert-butyl carbonate (1.12 g, 5.13 mmol, 1.2 eq.) at 25℃. The mixture was stirred at 25℃ for 48h under H_2(1 atm). After completion, the mixture was filtrated and concentrated in vacuo to give a residue. The residue was purified by SGC (UV254, Petroleum ether:EtOAc = 10:1) to afford methyl m-{3-[(tert-butyl)(oxycarbonylamino)]propyl}benzoate (720 mg, purity: 65%, yield:37.33%) as a colorless oil. MS (ESI, pos. ion) m/z: 316.2[M+Na]. Calculated MW: 293.36.

Step 3: Synthesis of 3-[m-(hydroxymethyl)phenyl]propyl 2-methyl-2-propanecarbamate.

To a mixture of methyl m-{3-[(tert-butyl)(oxycarbonylamino)]propyl}benzoate (720 mg, 1.23 mmol) in tetrahydrofuran (7 mL) was added aluminium(3+) lithium tetrahydride (48.9 mg, 1.29 mmol, 1.1 eq.) at 0℃. The mixture was stirred at 25℃ for 1h. After completion, the mixture was quenched with H2O (7 mL), extracted with EtOAc (10 mL*3). The organic layer was washed with H2O (7 mL), brine (7 mL), dried over anhydrous Na2SO4, filtrated and concentrated in vacuo to give a residue. The residue was purified by SGC (UV254, Petroleumether: EtOAc = 5:1) to afford 3-[m-(hydroxymethyl)phenyl]propyl 2-methyl-2-propanecarbamate (390 mg, purity: 95%, yield:97.71%) as a colorless oil. MS (ESI, pos. ion) m/z: 288.2 [M+Na]. Calculated MW: 265.35.

Step 4: Synthesis of tert-butyl (3-{m-[(mesyloxy)methyl]phenyl}propyl)carbamate.

To a mixture of 3-[m-(hydroxymethyl)phenyl]propyl 2-methyl-2-propanecarbamate (390 mg, 1.47 mmol) in dichloromethane (4 mL) was added N-ethylbis(isopropyl)amine (570 mg, 4.41 mmol, 3 eq.) and (mesyloxysulfonyl)methane (512 mg, 2.94 mmol, 2 eq.) at 25℃. The mixture was stirred at 25℃ for 3h. After completion, the mixture was quenched with H2O (5 mL), extracted with DCM (5 mL*3). The organic layer was washed with H2O (5 mL), brine (5 mL), dried over anhydrous Na2SO4, filtrated and concentrated in vacuo to give a residue to afford crude product tert-butyl (3-{m-[(mesyloxy)methyl]phenyl}propyl)carbamate (0.5 g, purity: 70%, yield:69.34%) and used into next step without further purification. MS (ESI, pos. ion) m/z: 366.1 [M+H]. Calculated MW: 343.44.

Step 5: Synthesis of 3-[m-({2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-9-adenineyl}methyl)phenyl]-1-propanamine.

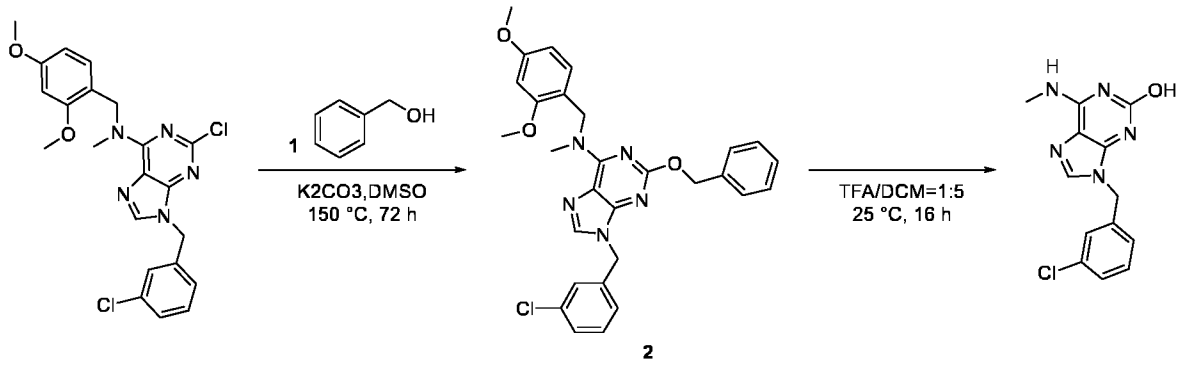
To a mixture of tert-butyl (3-{m-[(mesyloxy)methyl]phenyl}propyl)carbamate (0.5 g, 1.46 mmol) in dimethylformamide (5 mL) was added 2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyladenine (510 mg, 1.53 mmol, 1.1 eq.) and dipotassium carbonate (604 mg, 4.37 mmol, 3 eq.) at 25℃. The mixture was stirred at 20℃ for 16h. After completion, the mixture

was quenched with H2O (5 mL), extracted with EtOAc (5 mL*3). The organic layer was washed with H2O (5 mL), brine (5 mL), dried over anhydrous Na2SO4, filtrated and concentrated in vacuo to give a residue. The residue was purified by SGC (UV254, Petroleum ether: EtOAc = 2:1) to afford 3-[m-({2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-9-adenineyl}methyl)phenyl]-1-propanamine (710 mg, purity: 95%, yield:96.32%) as a colorless oil. MS (ESI, pos. ion) m/z: 581.2 [M+H]. Calculated MW: 581.11.

Step 6: Synthesis of 3-{m-[(2-chloro-9a-methyl-9-adenineyl)methyl]phenyl}-1-propanamine.

To a mixture of 3-[m-({2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-9-adenineyl}methyl)phenyl]propyl 2-methyl-2-propanecarbamate (710 mg, 1.22 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (1 mL) at 25℃. The mixture was stirred at 25℃ for 1h. After completion, the mixture was adjusted pH=8 with NaHCO3 and concentrated in vacuo to give a residue. The residue was purified by SGC (UV254, DCM: MeOH = 10:1) to afford 3-{m-[(2-chloro-9a-methyl-9-adenineyl)methyl]phenyl}-1-propanamine (410 mg, purity: 70%, yield:69.34%). MS (ESI, pos. ion) m/z: 331.1. (M+1). Calculated MW: 330.82. ^{1}H NMR (400 MHz, dmso) δ 8.23 (s, 1H), 7.63 (s, 3H), 7.30 (t, J = 7.5 Hz, 1H), 7.12-7.08 (m, 3H), 5.32 (s, 2H), 2.92 (d, J = 4.5 Hz, 3H), 2.80 – 2.75 (m, 2H), 2.62 – 2.58 (m, 2H), 1.78 (dt, J = 15.3, 7.7 Hz, 2H).

Synthesis of 9-[(m-chlorophenyl)methyl]-9a-methyl-2-adenineol ***(Compound 70)***



Step 1: Synthesis of 2-(benzyloxy)-9-[(m-chlorophenyl)methyl]-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyladenine.

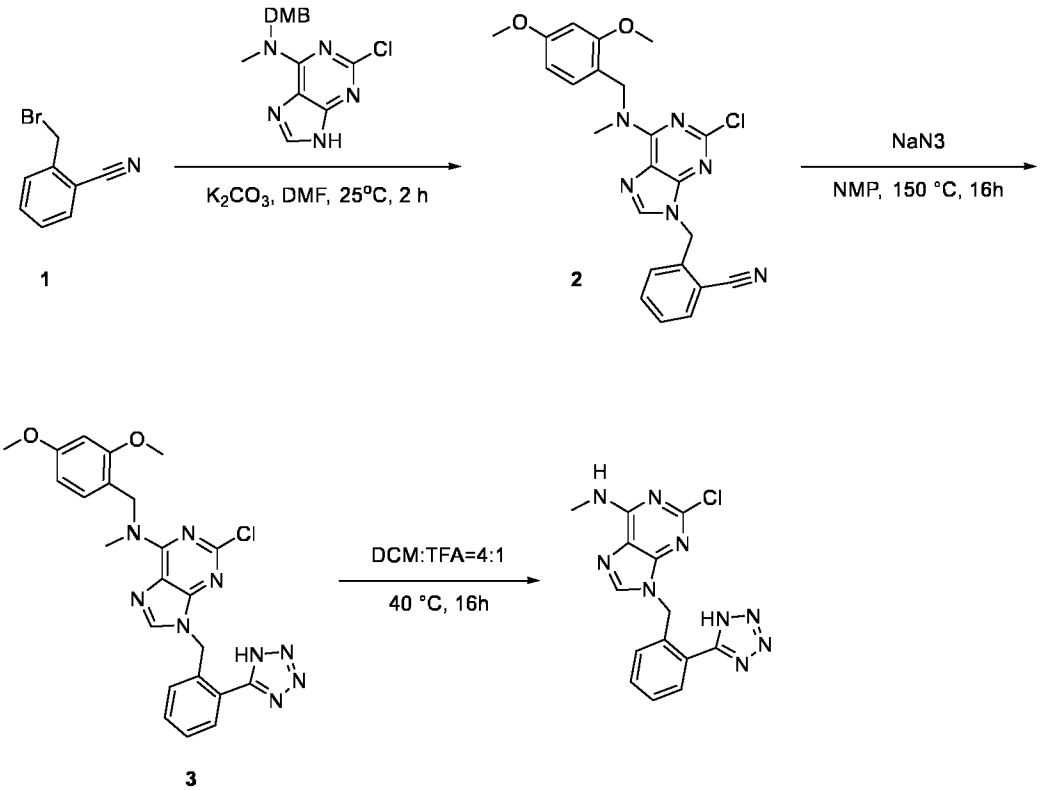
To a mixture of 2-chloro-9-[(m-chlorophenyl)methyl]-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyladenine (0.5 g, 1.09 mmol) in dimethyl sulfoxide (10 mL) was added benzyl alcohol (590 mg, 5.45 mmol, 5 eq.) and dipotassium carbonate (452 mg, 3.27 mmol, 3 eq.) at 25℃. The mixture was stirred at 150℃ for 72h. After completion, the mixture was quenched with H2O (10 mL), extracted with EtOAc (10 mL*3). The organic layer was washed with H2O (10 mL), brine (10 mL), dried over anhydrous Na2SO4, filtrated and concentrated in vacuo to give a residue. The residue was purified by SGC (UV254, Petroleum ether: EtOAc = 94:6) to afford 2-(benzyloxy)-9-[(m-chlorophenyl)methyl]-9a-[(2,4-dimethoxyphenyl)methyl]-9a-

methyladenine (290 mg, purity: 90%, yield:45.14%) as a colorless oil. MS (ESI, pos. ion) m/z: 530.1 [M+H]. Calculated MW: 530.03.

Step 2: Synthesis of 9-[(m-chlorophenyl)methyl]-9a-methyl-2-adenineol.

To a mixture of 2-(benzyloxy)-9-[(m-chlorophenyl)methyl]-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyladenine (30 mg, 0.057mmol, 1.0 eq) in dichloromethane (1 mL) was added trifluoroacetic acid (0.2 mL) at 25℃. The mixture was stirred at 25℃ for 16h. After completion, the mixture was concentrated in vacuo to give a residue. The residue was purified by Pre-HPLC (MeCN/H2O, 0.1 %FA/H2O) to afford 9-[(m-chlorophenyl)methyl]-9a-methyl-2-adenineol (3.8 mg, purity: 98.56%, yield:22.84%). MS (ESI, pos. ion) m/z: 290.0. (M+1). Calculated MW: 289.72. ^{1}H NMR (400 MHz, DMSO) δ 10.73 (br s, 1H), 7.88 (s, 1H), 7.43 – 7.37 (m, 1H), 7.37 (d, J = 1.5 Hz, 1H), 7.35 (d, J = 1.8 Hz, 1H), 7.21 (d, J = 6.4 Hz, 1H), 5.19 (s, 2H), 2.90 (s, 3H).

Synthesis of 9-(2-(1H-tetrazol-5-yl)benzyl)-2-chloro-N-methyl-9H-purin-6-amine ***(Compound 57)***



Step 1: Synthesis of 2-((2-chloro-6-((2,4-dimethoxybenzyl)(methyl)amino)-9H-purin-9-yl)methyl)benzonitrile.

To a solution of o-(bromomethyl)benzonitrile (0.5 g, 2.55 mmol, 1eq, CAS: 22115-41-9) and 2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyladenine (851 mg, 2.55 mmol, 1.0 eq, synthesized according to procedure described in synthesis of **Compound 66**) in

dimethylformamide (10 mL) was added dipotassium carbonate (529 mg, 3.83 mmol,1.5 eq), the mixture was stirred at 25 °C for 2 h. Then the mixture was diluted with EtOAc (50 mL), washed with brine (50 mL*2). The EA layer was dried, evaporated to dryness and the residue was purified by flash column (20% EA/PE) to afford the desired product (1.0 g, yield:87.34%) as white solid. ESI-MS m/z = 449.1$[M+H]^+$, Calculated MW: 448.91.

Step 2: Synthesis of 9-(2-(1H-tetrazol-5-yl)benzyl)-2-chloro-N-(2,4-dimethoxybenzyl)-N-methyl-9H-purin-6-amine.

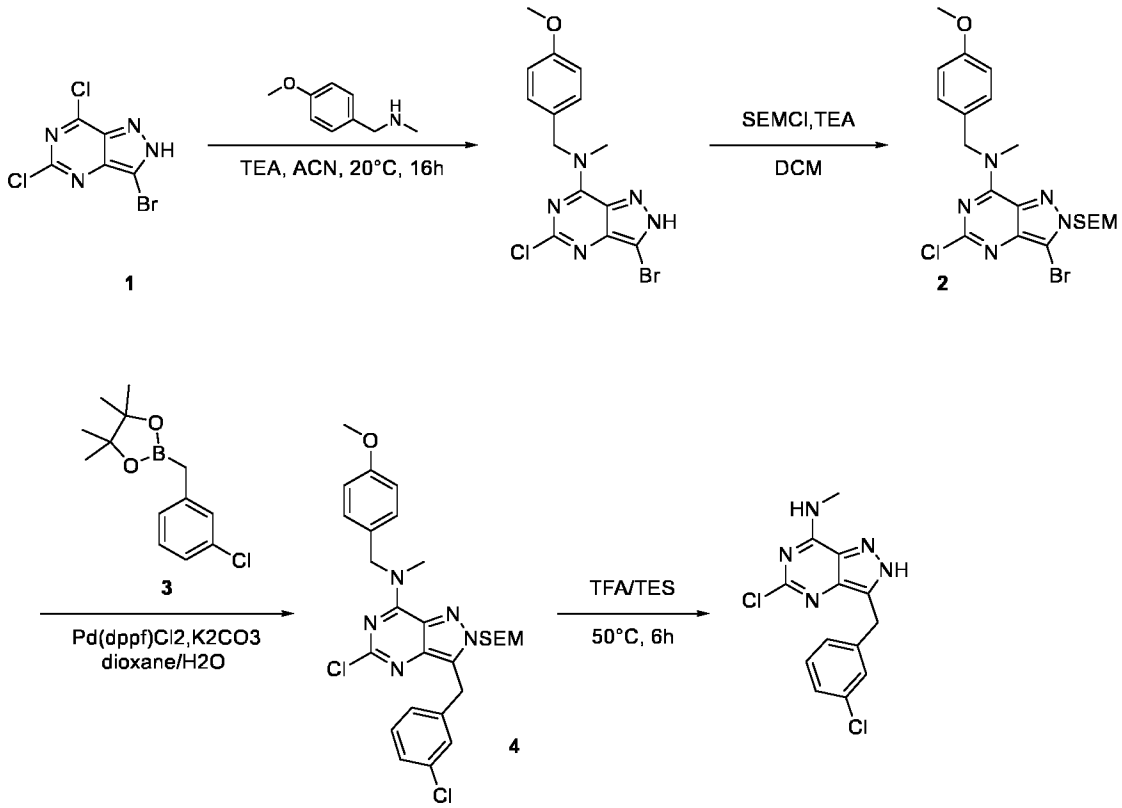
To a solution of o-({2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-9-adenineyl}methyl)benzonitrile (0.2 g, 0.45 mmol, 1.0 eq) in NMP (5 mL) was added sodium azide (57.9 mg, 0.89 mmol, 2.0 eq), the mixture was stirred at 150 °C for 16 h. Then the mixture was purified by reversed phase column (35% ACN/H2O) to afford the desired product (88 mg, yield:34.13%) as colorless oil. ESI-MS m/z = 492.1$[M+H]^+$, Calculated MW: 491.94.

Step 3: Synthesis of 9-(2-(1H-tetrazol-5-yl)benzyl)-2-chloro-N-methyl-9H-purin-6-amine.

To a solution of 2-chloro-9a-[(2,4-dimethoxyphenyl)methyl]-9a-methyl-9-{[o-(1H-tetraazol-5-yl)phenyl]methyl}adenine (75 mg, 0.12 mmol) in dichloromethane (2 mL) was added trifluoroacetic acid (0.5 mL), the mixture was stirred at 40 °C for 16 h. Then the mixture was evaporated to dryness and the residue was purified by prep-HPLC to afford 2-chloro-9a-methyl-9-{[o-(1H-tetraazol-5-yl)phenyl]methyl}adenine (15 mg, yield:35.99%). ESI-MS m/z = 342.1$[M+H]^+$, Calculated MW: 341.76. HNMR (400 MHz, DMSO) δ 8.27 (d, J = 4.6 Hz, 1H), 8.14 (s, 1H), 7.87 (d, J = 6.2 Hz, 1H), 7.59 – 7.49 (m, 2H), 6.98 (d, J = 6.6 Hz, 1H), 5.70 (s, 2H), 2.92 (d, J = 4.4 Hz, 3H).

Synthesis of 5-chloro-3-(3-chlorobenzyl)-N-methyl-2H-pyrazolo[4,3-d]pyrimidin-7-amine

(Compound 72)



Step 1: Synthesis of 3-bromo-5-chloro-N-(2,4-dimethoxybenzyl)-N-methyl-2H-pyrazolo[4,3-d]pyrimidin-7-amine.

To a solution of 3-bromo-5,7-dichloro-2H-1,2,4,6-tetraazaindene (950 mg, 3.55 mmol, 1 eq,CAS:1934543-12-0) and TEA (1.07 g, 10.6 mmol, 3eq) in acetonitrile (20 mL) was added N-methyl[(p-methoxyphenyl)methyl]amine (643 mg, 4.26 mmol, 1.2 eq,CAS:702-24-9), the mixture was stirred at 20 °C for 16 h. Then the mixture was evaporated to dryness and the residue was purified by flash column (40% EA/PE) to afford the desired product (1.2 g, yield:88.44%) as yellow solid. ESI-MS m/z = 384.0 [M+H]+. Calculated MW: 382.65

Step 2: Synthesis of 3-bromo-5-chloro-N-(2,4-dimethoxybenzyl)-N-methyl-2-((2-(trimethylsilyl)ethoxy)methyl)-2H-pyrazolo[4,3-d]pyrimidin-7-amine.

To a mixture of [(p-methoxyphenyl)methyl]-N-methyl(3-bromo-5-chloro-2H-1,2,4,6-tetraazainden-7-yl)amine (0.2 g, 0.52 mmol,1 eq) and (2-chloromethoxyethyl)tris(methyl)silane (131 mg, 0.78 mmol, 1.5 eq) in DCM (5 mL) was added triethylamine (159 mg, 1.57 mmol, 3 eq) at 20 ℃. The mixture was stirred at 40oC for 16 h. After completion, the mixture was concentrated in vacuo to give a residue. The residue was purified by flash column(Petroleum ether: EtOAc = 10:1) to afford [(p-methoxyphenyl)methyl]-N-methyl(3-bromo-5-chloro-2-{[2-(trimethylsilyl)ethoxy]methyl}-2H-

1,2,4,6-tetraazainden-7-yl)amine (150 mg, yield:55.95%) as a colorless oil. ESI-MS m/z = 514.1[M+H]+. Calculated MW: 512.91

Step 3: Synthesis of 5-chloro-3-(3-chlorobenzyl)-N-(2,4-dimethoxybenzyl)-N-methyl-2-((2-(trimethylsilyl)ethoxy)methyl)-2H-pyrazolo[4,3-d]pyrimidin-7-amine.

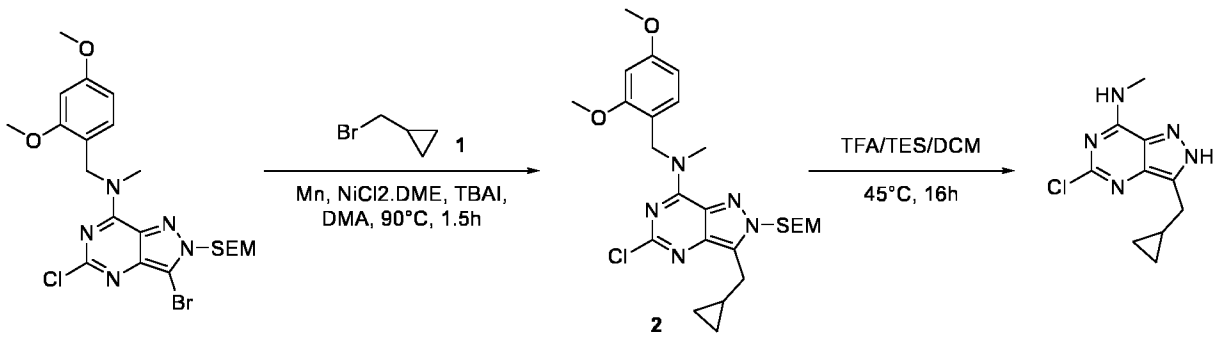
To a mixture of [(p-methoxyphenyl)methyl]-N-methyl(3-bromo-5-chloro-2-{[2-(trimethylsilyl)ethoxy]methyl}-2H-1,2,4,6-tetraazainden-7-yl)amine (130 mg, 0.25 mmol) and 2-[(m-chlorophenyl)methyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (96 mg, 0.38 mmol, 1.5 eq,CAS:517950-59-1) in 1,4-dioxane (6 mL)/water (1.5 mL)=4/1 was added Pd(dppf)Cl2 (36.8 mg, 0.051 mmol, 0.2 eq.) and dipotassium carbonate (70.1 mg, 0.51 mmol, 2 eq) at 20℃. The mixture was stirred at 110℃ for 5 h under N2. After completion, the mixture was concentrated in vacuo to give a residue. The residue was purified by SGC (UV254, Petroleum ether: EtOAc = 10:1) to afford [(p-methoxyphenyl)methyl]-N-methyl{5-chloro-3-[(m-chlorophenyl)methyl]-2-{[2-(trimethylsilyl)ethoxy]methyl}-2H-1,2,4,6-tetraazainden-7-yl}amine (70 mg, yield:39.55%) as a colorless oil. ESI-MS m/z = 558.2[M+H]+, Calculated MW: 558.58.

Step 4: Synthesis of 5-chloro-3-(3-chlorobenzyl)-N-methyl-2H-pyrazolo[4,3-d]pyrimidin-7-amine.

To a solution of [(p-methoxyphenyl)methyl]-N-methyl{5-chloro-3-[(m-chlorophenyl)methyl]-2H-1,2,4,6-tetraazainden-7-yl}amine (20 mg, 46.7 μmol) in TFA (0.5 mL) was added triethylsilane (1 mL), the mixture was stirred at 50 °C for 6 h. Then the mixture was evaporated to dryness and the residue was purified by prep-HPLC (MeCN/H2O+0.05% FA) to afford the N-methyl{5-chloro-3-[(m-chlorophenyl)methyl]-2H-1,2,4,6-tetraazainden-7-yl}amine (2.5 mg, yield:). ESI-MS m/z = 544.3[M+H]+, Calculated MW: 543.66.

1H NMR (400 MHz, MeOD) δ 7.21 (s, 1H), 7.18 – 7.03 (m, 3H), 4.15 (s, 2H), 3.02 (s, 3H).

Synthesis of N-methyl[5-chloro-3-(cyclopropylmethyl)-2H-1,2,4,6-tetraazainden-7-yl]amine ***(Compound 73)***



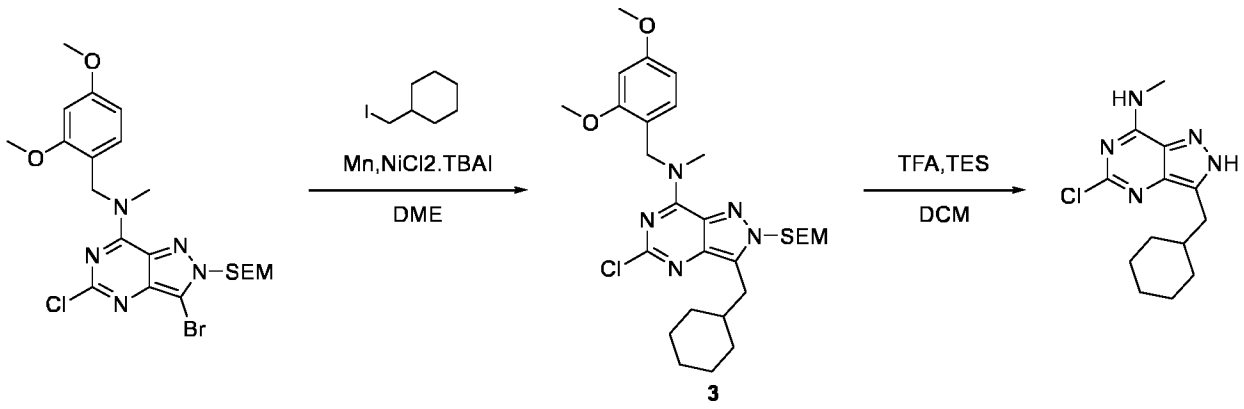
Step 1: Synthesis of [(2,4-dimethoxyphenyl)methyl]-N-methyl{5-chloro-3-[(2-naphthyl)methyl]-2-{[2-(trimethylsilyl)ethoxy]methyl}-2H-1,2,4,6-tetraazainden-7-yl}amine

A mixture of 1-(bromomethyl)cyclopropane (1.5 g, 11.1 mmol, 25 eq.), [(2,4-dimethoxyphenyl)methyl]-N-methyl(3-bromo-5-chloro-2-{[2-(trimethylsilyl)ethoxy]methyl}-2H-1,2,4,6-tetraazainden-7-yl)amine (240 mg, 0.44 mmol, 1.0 eq., synthesized according to procedure described in synthesis of **Compound 72**), manganese (121 mg, 2.21 mmol, 5 eq.), NiCl2.DME (96 mg, 442 mmol, 1.0 eq.), tetrabutylammonium iodide (49 mg, 0.14 mmol, 0.3 eq.), 2-pyridinecarboxamidine—hydrogen chloride (1/1) (69.7 mg, 0.44 mmol, 1.0 eq.) in dimethylacetamide (4 mL)was degassed and purged with N2 for several times. The mixture was stirred at 90oC for 2h. The mixture was diluted with EtOAc (100 mL) and washed with water (100 mL) and brine (100 mL). The organic layer was dried over Na2SO4 and concentrated. The crude was purified by prep-TLC (PE:EA=4:1) to give [(2,4-dimethoxyphenyl)methyl]-N-methyl[5-chloro-3-(cyclopropylmethyl)-2-{[2-(trimethylsilyl)ethoxy]methyl}-2H-1,2,4,6-tetraazainden-7-yl]amine (60 mg, 99.6 μmol) as yellow gum. ESI-MS m/z =518.2 [M-H]+. Calculated MW: 518.13

Step 2: Synthesis of N-methyl[5-chloro-3-(cyclopropylmethyl)-2H-1,2,4,6-tetraazainden-7-yl]amine

A mixture of [(2,4-dimethoxyphenyl)methyl]-N-methyl[5-chloro-3-(cyclopropylmethyl)-2-{[2-(trimethylsilyl)ethoxy]methyl}-2H-1,2,4,6-tetraazainden-7-yl]amine (40 mg, 0.08 mmol), dichloromethane (2 mL, 31.2 mmol), trifluoroacetic acid (0.1 mL), triethylsilane (0.2 mL) was stirred at 45oC for 16h. The mixture was concentrated. The crude was purified by basic prep-HPLC (ACN-H2O (0.05%NH3)) to give N-methyl[5-chloro-3-(cyclopropylmethyl)-2H-1,2,4,6-tetraazainden-7-yl]amine (12 mg, 50.5 μmol). ESI-MS m/z =238.2 [M-H]+. Calculated MW: 237.69. 1H NMR (400 MHz, MeOD) δ 5.76 (ddt, J = 17.0, 10.2, 6.7 Hz, 1H), 4.96 - 4.84 (m, 2H), 3.01 (s, 3H), 2.94 -2.86 (m, 2H), 2.40 (dt, J = 14.0, 6.9 Hz, 2H).

Synthesis of 5-chloro-3-(cyclohexylmethyl)-N-methyl-2H-pyrazolo[4,3-d]pyrimidin-7-amine (Compound 74)



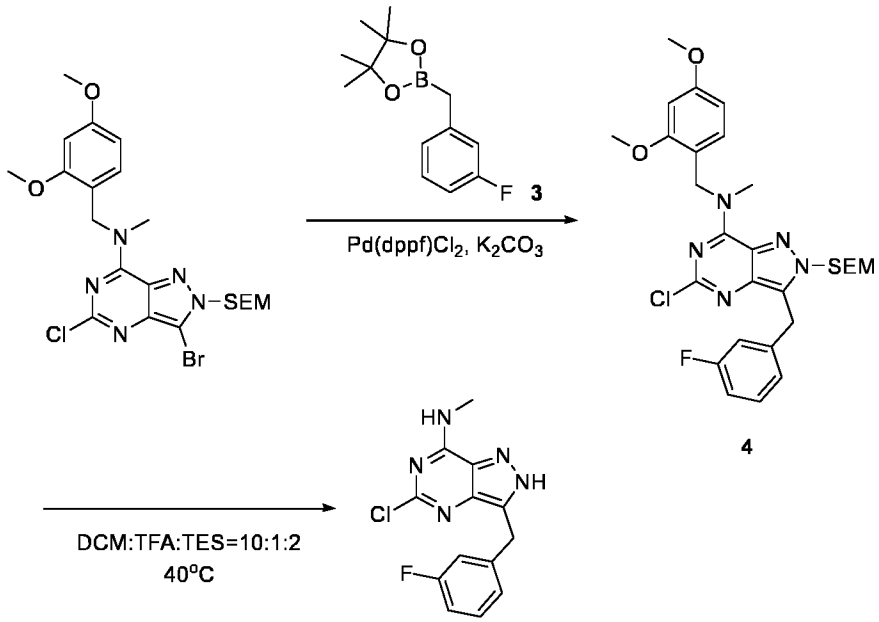
Step 1: Synthesis of 5-chloro-3-(cyclohexylmethyl)-N-(2,4-dimethoxybenzyl)-N-methyl-2-((2-(trimethylsilyl)ethoxy)methyl)-2H-pyrazolo[4,3-d]pyrimidin-7-amine

To a solution of [(2,4-dimethoxyphenyl)methyl]-N-methyl(3-bromo-5-chloro-2-{[2-(trimethylsilyl)ethoxy]methyl}-2H-1,2,4,6-tetraazainden-7-yl)amine (190 mg, 0.35 mmol, synthesized according to procedure described in synthesis of **Compound 72**), 1-(iodomethyl)cyclohexane (471 mg, 2.1 mmol, 6 eq, CAS:5469-33-0), manganese (96 mg, 1.75 mmol, 5 eq), Nickel(II) chloride ethylene glycol dimethyl ether (2.4 mg) and tetrabutylammonium iodide (32.3 mg, 0.09 mmol, 0.25 eq) in dimethylacetamide (10 mL) was added 2-pyridinecarboxamidine—hydrogen chloride (1/1) (55 mg, 0.35 mol, 1eq, CAS:51285-26-8), the mixture was stirred under N_2 at 90 °C for 16 h. Then the mixture was diluted with EA (50 mL), washed with brine (50 mL*2). The EA layer dried, evaporated to dryness and the residue was purified by flash column (10% EtOAc in PE) to afford 5-chloro-3-(cyclohexylmethyl)-N-(2,4-dimethoxybenzyl)-N-methyl-2-((2-(trimethylsilyl)ethoxy)methyl)-2H-pyrazolo[4,3-d]pyrimidin-7-amine (45 mg, 22.95% yield) as colorless oil. ESI-MS m/z = 560.2$[M+H]^+$, Calculated MW: 560.21.

Step 2: Synthesis of 5-chloro-3-(cyclohexylmethyl)-N-methyl-2H-pyrazolo[4,3-d]pyrimidin-7-amine.

To a solution of 5-chloro-3-(cyclohexylmethyl)-N-(2,4-dimethoxybenzyl)-N-methyl-2-((2-(trimethylsilyl)ethoxy)methyl)-2H-pyrazolo[4,3-d]pyrimidin-7-amine (55 mg, 0.10 mmol) and triethylsilane (0.2 mL) in dichloromethane (1 mL) was added trifluoroacetic acid (0.1 mL), the mixture was stirred at 45°C for 16 h. Then the mixture was evaporated to dryness and the residue was purified by prep-HPLC (MeCN/H2O-0.05% NH3.H2O) to afford the desired product (17 mg, yield: 61.89%). ESI-MS m/z = 280.0$[M+H]^+$, Calculated MW: 279.77. 1H NMR (400 MHz, MeOD) δ 3.11 (s, 3H), 2.80 (d, *J* = 8.0 Hz, 2H), 1.77 – 1.61 (m, 6H), 1.30 – 1.16 (m, 3H), 1.08 – 0.96 (m, 2H).

Synthesis of 5-chloro-3-(3-fluorobenzyl)-N-methyl-2H-pyrazolo[4,3-d]pyrimidin-7-amine ***(Compound 75)***



Step 1: Synthesis of 5-chloro-N-(2,4-dimethoxybenzyl)-3-(3-fluorobenzyl)-N-methyl-2-((2-(trimethylsilyl)ethoxy)methyl)-2H-pyrazolo[4,3-d]pyrimidin-7-amine.

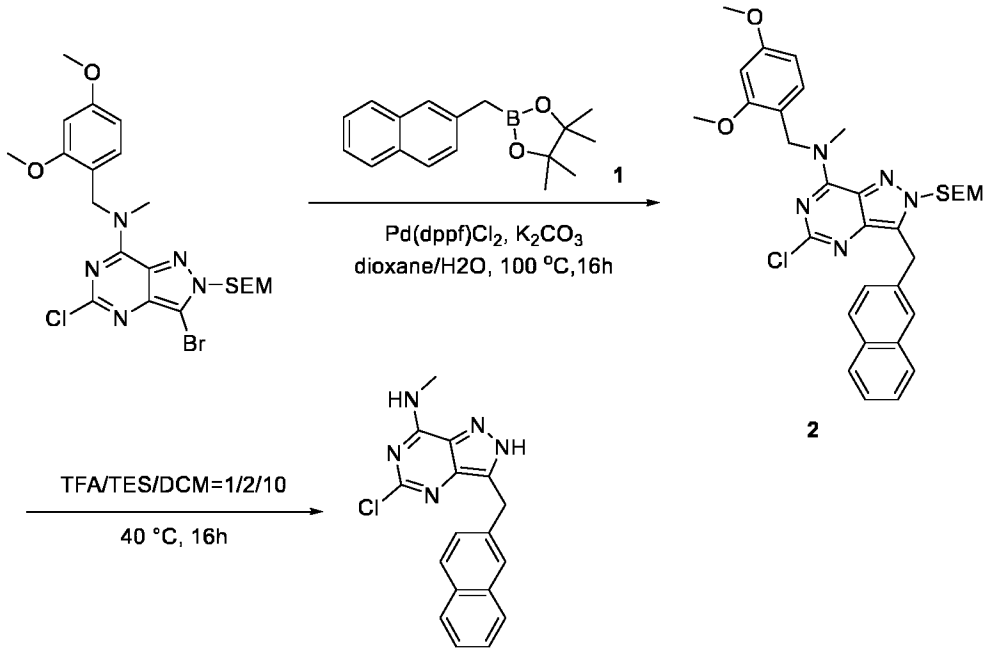
To a solution of [(2,4-dimethoxyphenyl)methyl]-N-methyl(3-bromo-5-chloro-2-{[2-(trimethylsilyl)ethoxy]methyl}-2H-1,2,4,6-tetraazainden-7-yl)amine (70 mg, 0.13 mmol, synthesized according to procedure described in synthesis of **Compound 72**), 2-[(m-fluorophenyl)methyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (45.7 mg, 0.19 mmol, 1.5 eq, CAS:517920-60-4) and iron bis[3-(diphenylphosphino)-2,4-cyclopentadien-1-ide]—dichloro-palladamethane—dichloromethane (1/1/1) (10.5 mg, 0.013 mmol, 0.1 eq) in 1,4-dioxane (2 mL) and water (0.5 mL) was added dipotassium carbonate (35.6 mg, 0.26 mmol,2 eq), the mixture was stirred under N2 at 100 °C for 16 h. Then the mixture was diluted with EtOAc (20 mL), washed with brine (20 mL). The EtOAc layer was dried, evaporated to dryness and the residue was purified by flash column (10% EA/PE) to afford the desired product (28 mg, yield:37.96%) as colorless syrup. ESI-MS m/z = 572.2$[M+H]^+$, Calculated MW: 572.15.

Step 2: Synthesis of 5-chloro-3-(3-fluorobenzyl)-N-methyl-2H-pyrazolo[4,3-d]pyrimidin-7-amine.

To a solution of [(2,4-dimethoxyphenyl)methyl]-N-methyl{5-chloro-3-[(m-fluorophenyl)methyl]-2-{[2-(trimethylsilyl)ethoxy]methyl}-2H-1,2,4,6-tetraazainden-7-yl}amine (25 mg, 0.044 mmol) and triethylsilane (0.2 mL) in dichloromethane (1 mL, 15.6 mmol) was added trifluoroacetic acid (0.1 mL), the mixture was stirred at 40 °C for 16 h. Then the mixture was evaporated to dryness and the residue was purified by basic prep-HPLC to afford the desired product. ESI-MS m/z = 292.0$[M+H]^+$, Calculated MW: 291.71. 1H NMR (400 MHz, MeOD) δ 7.30 – 7.16

(m, 2H), 7.08 (t, J = 8.3 Hz, 2H), 4.32 (s, 2H), 3.14 (s, 3H). 1H NMR (400 MHz, MeOD) δ -119.78.

Synthesis of N-methyl{5-chloro-3-[(2-naphthyl)methyl]-2H-1,2,4,6-tetraazainden-7-yl}amine ***(Compound 76)***



Step 1: Synthesis of [(2,4-dimethoxyphenyl)methyl]-N-methyl{5-chloro-3-[(2-naphthyl)methyl]-2-{[2-(trimethylsilyl)ethoxy]methyl}-2H-1,2,4,6-tetraazainden-7-yl}amine.

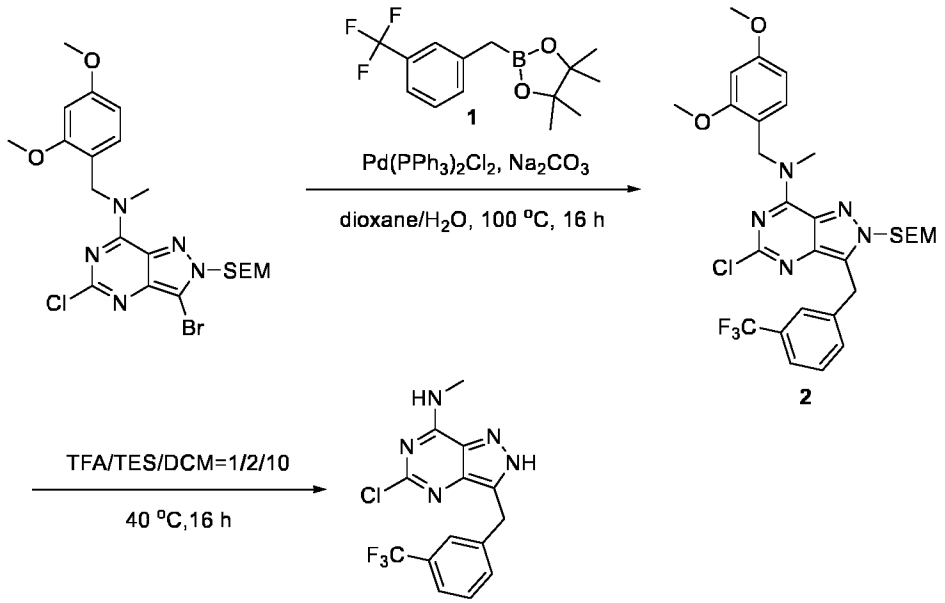
To a mixture of [(2,4-dimethoxyphenyl)methyl]-N-methyl(3-bromo-5-chloro-2-{[2-(trimethylsilyl)ethoxy]methyl}-2H-1,2,4,6-tetraazainden-7-yl)amine (40 mg, 0.074 mmol, 1.0 eq., synthesized according to procedure described in synthesis of **Compound 72**) and 4,4,5,5-tetramethyl-2-[(2-naphthyl)methyl]-1,3,2-dioxaborolane (21.7 mg, 0.08 mmol, 1.1 eq., cas:1379610-55-5) in 1,4-dioxane (4 mL)/water (1 mL)=4/1 was added $Pd(dppf)Cl_2$ (10.8 mg, 0.015 mmol, 0.2 eq.) and K_2CO_3 (20.4 mg, 0.15 mmol, 2 eq.) at 20℃. The mixture was stirred at 100℃ for 16h under N_2. After completion, the mixture was filtrated and concentrated in vacuo to give a residue. The residue was purified by SGC (UV254, Petroleum ether: EtOAc = 4:1) to afford [(2,4-dimethoxyphenyl)methyl]-N-methyl{5-chloro-3-[(2-naphthyl)methyl]-2-{[2-(trimethylsilyl)ethoxy]methyl}-2H-1,2,4,6-tetraazainden-7-yl}amine (30 mg, yield:67.39%) as a colorless oil. ESI-MS m/z =604.3 [M-H]+. Calculated MW: 604.22

Step 2: Synthesis of N-methyl{5-chloro-3-[(2-naphthyl)methyl]-2H-1,2,4,6-tetraazainden-7-yl}amine.

To [(2,4-dimethoxyphenyl)methyl]-N-methyl{5-chloro-3-[(2-naphthyl)methyl]-2-{[2-(trimethylsilyl)ethoxy]methyl}-2H-1,2,4,6-tetraazainden-7-yl}amine (25 mg, 0.04 mmol, 1.0 eq.) in dichloromethane (1 mL) was added TFA (0.1 mL)/TES (0.2 mL)=1/2 at 20℃. The

mixture was stirred at 40℃ for 16h. After completion, the mixture was concentrated in vacuo to give a residue. The residue was purified by Prep-HPLC (Mobile Phase: ACN---H_2O (0.1% $NH_3.H_2O$) to afford N-methyl{5-chloro-3-[(2-naphthyl)methyl]-2H-1,2,4,6-tetraazainden-7-yl}amine (5.76 mg, yield:42.54%). ESI-MS m/z =324.1 [M-H]+. Calculated MW: 323.78. ^{1}H NMR (400 MHz, DMSO) δ 8.34 (s, 1H), 7.84 (t, J = 7.9 Hz, 3H), 7.73 (s, 1H), 7.52 – 7.40 (m, 3H), 4.35 (s, 2H), 2.98 (s, 3H).

Synthesis of 5-chloro-N-methyl-3-(3-(trifluoromethyl)benzyl)-2H-pyrazolo[4,3-d]pyrimidin-7-amine ***(Compound 77)***



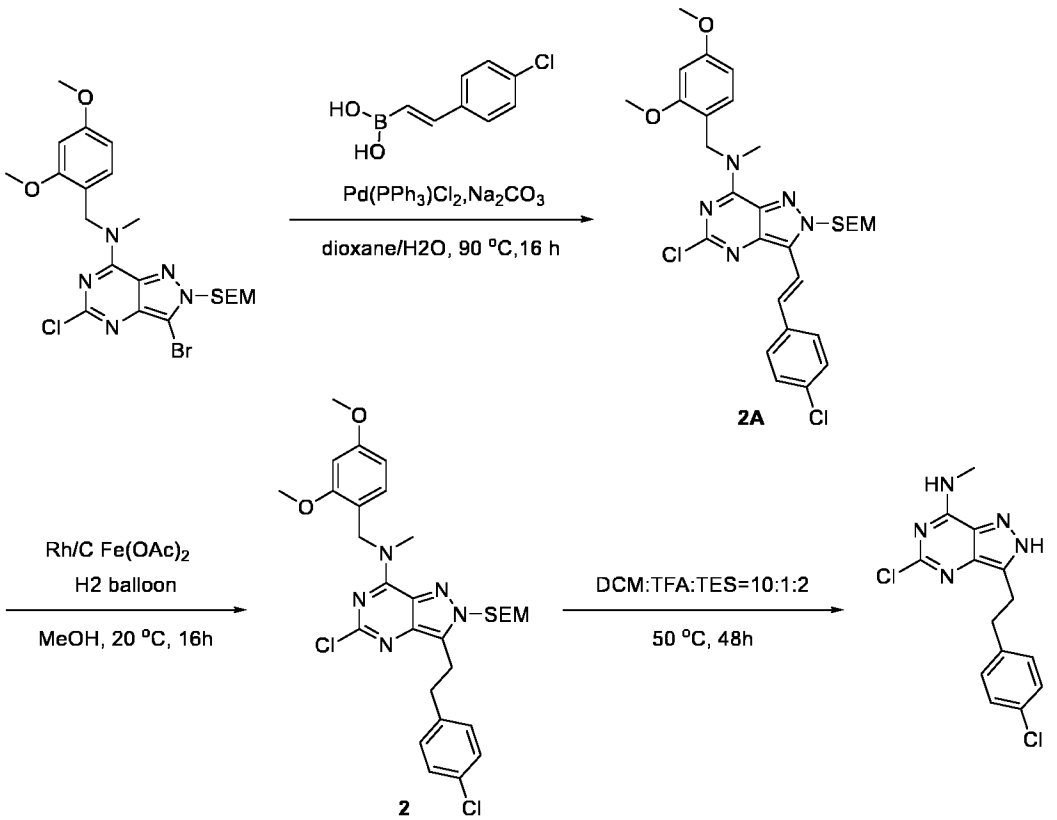
Step 1: Synthesis of 5-chloro-N-(2,4-dimethoxybenzyl)-N-methyl-3-(3-(trifluoromethyl)benzyl)-2-((2-(trimethylsilyl)ethoxy)methyl)-2H-pyrazolo[4,3-d]pyrimidin-7-amine.

To a mixture of [(2,4-dimethoxyphenyl)methyl]-N-methyl(3-bromo-5-chloro-2-{[2-(trimethylsilyl)ethoxy]methyl}-2H-1,2,4,6-tetraazainden-7-yl)amine (20 mg, 0.04 mmol, 1.0 eq., synthesized according to procedure described in synthesis of **Compound 72**) and 4,4,5,5-tetramethyl-2-(3-(trifluoromethyl)benzyl)-1,3,2-dioxaborolane (34.6 mg, 0.11 mmol, 3 eq., cas:1190235-39-2) in 1,4-dioxane (4 mL)/water (0.4 mL) was added $Pd(PPh_3)_2Cl_2$ (2.6 mg, 0.004 mmol, 0.1 eq.) and disodium carbonate (11.7 mg, 0.221 mmol, 3 eq.) at 20℃. The mixture was stirred at 100℃ for 16h under N_2. After completion, the mixture was filtrated and concentrated in vacuo to give a residue. The residue was purified by SGC (UV254, Petroleum ether: EtOAc = 5:1) to afford 5-chloro-N-(2,4-dimethoxybenzyl)-N-methyl-3-(3-(trifluoromethyl)benzyl)-2-((2-(trimethylsilyl)ethoxy)methyl)-2H-pyrazolo[4,3-d]pyrimidin-7-amine (14 mg, yield:61.1%) as a yellow oil. ESI-MS m/z =622.2 $[M+H]^+$. Calculated MW: 621.21

Step 2: Synthesis of 5-chloro-N-methyl-3-(3-(trifluoromethyl)benzyl)-2H-pyrazolo[4,3-d]pyrimidin-7-amine.

To 3-benzyl-5-chloro-N-(2,4-dimethoxybenzyl)-N-methyl-2-((2-(trimethylsilyl)ethoxy)methyl)-2H-pyrazolo[4,3-d]pyrimidin-7-amine (14 mg, 0.023 mmol, 1.0 eq.) in dichloromethane (1 mL) was added TFA (0.1 mL)/TES (0.2 mL) at 20℃. The mixture was stirred at 40℃ for 16h. After completion, the mixture was concentrated in vacuo to give a residue. The residue was purified by Prep-HPLC (Mobile Phase: ACN-H_2O (0.1% $NH_3.H_2O$) to afford 5-chloro-N-methyl-3-(3-(trifluoromethyl)benzyl)-2H-pyrazolo[4,3-d]pyrimidin-7-amine (2.59 mg, yield:33.7%). ESI-MS m/z =342.1 $[M+H]^+$. Calculated MW: 341.07. ^1H NMR (400 MHz, CDCl3) δ 7.46 (m, 4H), 6.09 (s, 1H), 4.37 (s, 2H), 3.21 (d, J = 4.0 Hz, 3H).

Synthesis of 5-chloro-3-(4-chlorophenethyl)-N-methyl-2H-pyrazolo[4,3-d]pyrimidin-7-amine (Compound 78)



Step 1: Synthesis of (E)-5-chloro-3-(4-chlorostyryl)-N-(2,4-dimethoxybenzyl)-N-methyl-2-((2-(trimethylsilyl)ethoxy)methyl)-2H-pyrazolo[4,3-d]pyrimidin-7-amine.

To a mixture of [(2,4-dimethoxyphenyl)methyl]-N-methyl(3-bromo-5-chloro-2-{[2-(trimethylsilyl)ethoxy]methyl}-2H-1,2,4,6-tetraazainden-7-yl)amine (80 mg, 0.147 mmol, 1.0 eq., synthesized according to procedure described in synthesis of **Compound 72**) and [(E)-2-(p-chlorophenyl)ethenyl]boranediol (40 mg, 0.221 mmol, 1.5 eq., cas:154230-29-2) in 1,4-dioxane (2 mL)/water (0.2 mL) was added $Pd(PPh_3)_2Cl_2$ (10.4 mg, 0.014 mmol, 0.1 eq.) and

disodium carbonate (46.9 mg, 0.442 mmol, 3 eq.) at 20℃. The mixture was stirred at 90℃ for 16h under N_2. After completion, the mixture was filtrated and concentrated in vacuo to give a residue. The residue was purified by SGC (UV254, Petroleum ether: EtOAc = 5:1) to afford (E)-5-chloro-3-(4-chlorostyryl)-N-(2,4-dimethoxybenzyl)-N-methyl-2-((2-(trimethylsilyl)ethoxy)methyl)-2H-pyrazolo[4,3-d]pyrimidin-7-amine (70 mg, yield:79.1%) as a yellow oil. ESI-MS m/z =600.2 $[M+H]^+$. Calculated MW: 599.19

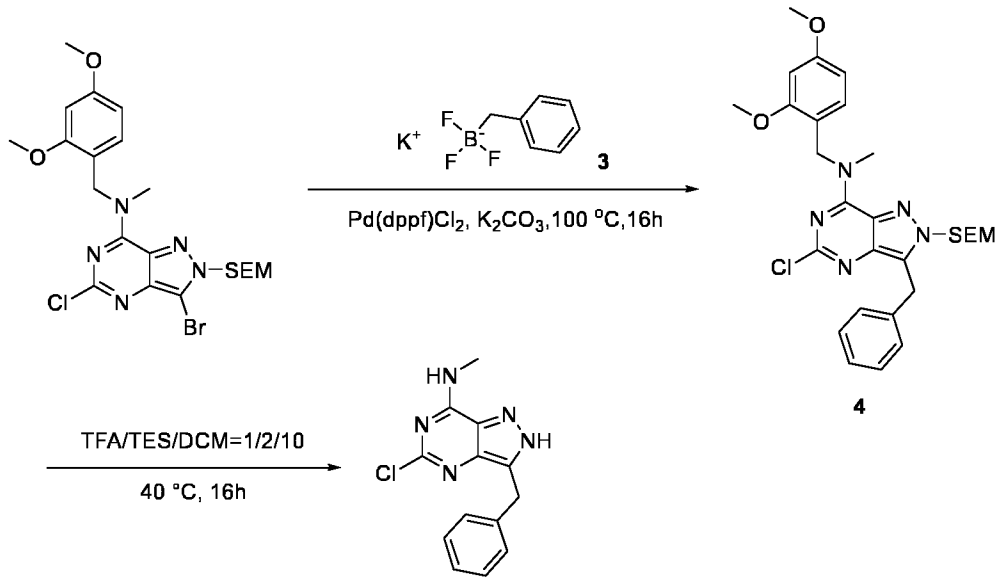
Step 2: Synthesis of 5-chloro-3-(4-chlorophenethyl)-N-(2,4-dimethoxybenzyl)-N-methyl-2-((2-(trimethylsilyl)ethoxy)methyl)-2H-pyrazolo[4,3-d]pyrimidin-7-amine.

A mixture of (E)-5-chloro-3-(4-chlorostyryl)-N-(2,4-dimethoxybenzyl)-N-methyl-2-((2-(trimethylsilyl)ethoxy)methyl)-2H-pyrazolo[4,3-d]pyrimidin-7-amine (70 mg, 0.117 mmol, 1.0 eq.), Rh/C (55%, 22 mg, 0.117 mmol, 1.0 eq.) and $Fe(OAc)_2$ (20.3 mg, 0.117 mmol, 1 eq.) in MeOH (5 mL) was degassed under vacuum and purged with H_2 several times. The reaction mixture was stirred under H_2 balloon for 48 h at 20℃. After completion, the mixture was filtrated and concentrated in vacuo to give a residue which was used in the next step without further purification. ESI-MS m/z =602.1 $[M+H]^+$. Calculated MW: 601.20

Step 3: Synthesis of 5-chloro-3-(4-chlorophenethyl)-N-methyl-2H-pyrazolo[4,3-d]pyrimidin-7-amine.

To 5-chloro-3-(4-chlorophenethyl)-N-(2,4-dimethoxybenzyl)-N-methyl-2-((2-(trimethylsilyl)ethoxy)methyl)-2H-pyrazolo[4,3-d]pyrimidin-7-amine (50 mg, 0.083 mmol, 1.0 eq.) in dichloromethane (1 mL) was added TFA (0.1 mL) and TES (0.2 mL) at 20℃. The mixture was stirred at 40℃ for 16h. After completion, the mixture was concentrated in vacuo to give a residue. The residue was purified by Prep-HPLC (Mobile Phase: ACN-H_2O (0.1% $NH_3.H_2O$) to afford 5-chloro-3-(4-chlorophenethyl)-N-methyl-2H-pyrazolo[4,3-d]pyrimidin-7-amine (2.82 mg, yield:10.5%). ESI-MS m/z =322.1 $[M+H]^+$. Calculated MW: 321.05. ^1H NMR (400 MHz, CDCl3) δ 7.23 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 8.0 Hz, 2H), 6.09 (s, 1H), 3.28 (t, J = 7.2 Hz, 2H), 3.23 (s, 3H), 3.08 (t, J = 7.2 Hz, 2H).

Synthesis of N-methyl(3-benzyl-5-chloro-2H-1,2,4,6-tetraazainden-7-yl)amine ***(Compound 79)***



Step 1: Synthesis of [(2,4-dimethoxyphenyl)methyl]-N-methyl(3-benzyl-5-chloro-2-{[2-(trimethylsilyl)ethoxy]methyl}-2H-1,2,4,6-tetraazainden-7-yl)amine.

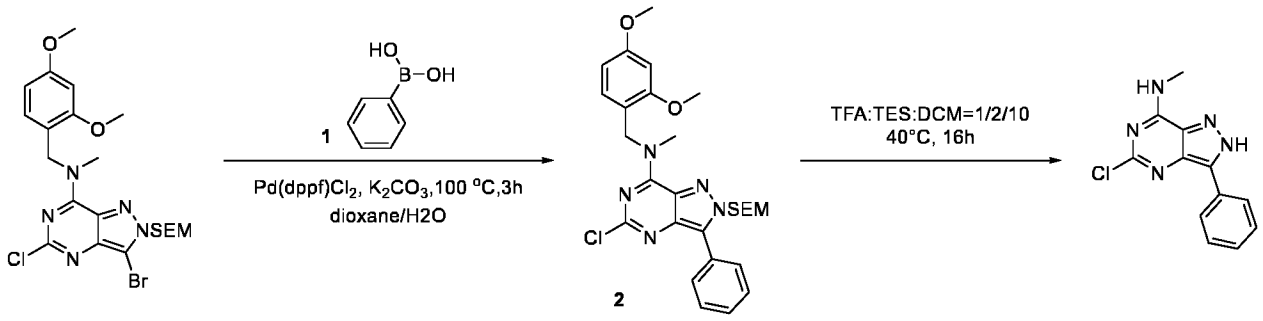
To a mixture of [(2,4-dimethoxyphenyl)methyl]-N-methyl(3-bromo-5-chloro-2-{[2-(trimethylsilyl)ethoxy]methyl}-2H-1,2,4,6-tetraazainden-7-yl)amine (40 mg, 0.737 mmol, 1.0 eq., synthesized according to procedure described in synthesis of **Compound 72**) and potassium benzyltris(fluoro)boranuide (58.4 mg, 0.295 mmol, 4 eq., cas:329976-73-0) in 1,4-dioxane (4 mL)/water (1 mL)=4/1 ws added $Pd(dppf)Cl_2$ (10.8 mg, 0.147 mmol, 0.2 eq.) and dipotassium carbonate (30.5 mg, 0.221 mmol, 3 eq.) at 20℃. The mixture was stirred at 100℃ for 16h under N_2. After completion, the mixture was filtrated and concentrated in vacuo to give a residue. The residue was purified by SGC (UV254, Petroleum ether: EtOAc = 3:1) to afford [(2,4-dimethoxyphenyl)methyl]-N-methyl(3-benzyl-5-chloro-2-{[2-(trimethylsilyl)-ethoxy]methyl}-2H-1,2,4,6-tetraazainden-7-yl)amine (30 mg, yield:99.13%) as a yellow oil. ESI-MS m/z =554.4 [M-H]+. Calculated MW: 554.16

Step 2: Synthesis of N-methyl(3-benzyl-5-chloro-2H-1,2,4,6-tetraazainden-7-yl)amine.

To [(2,4-dimethoxyphenyl)methyl]-N-methyl(3-benzyl-5-chloro-2-{[2-(trimethylsilyl)ethoxy]methyl}-2H-1,2,4,6-tetraazainden-7-yl)amine (30 mg, 0.54 mmol, 1.0 eq.) in dichloromethane (3 mL) was added TFA (0.1 mL) and TES (0.2 mL)=1/2 at 20℃. The mixture was stirred at 40℃ for 16h. After completion, the mixture was concentrated in vacuo to give a residue. The residue was purified by Prep-HPLC (Mobile Phase: ACN---H_2O (0.1% $NH_3.H_2O$) to afford N-methyl(3-benzyl-5-chloro-2H-1,2,4,6-tetraazainden-7-yl)amine (2.86 mg, yield:19.3%). ESI-MS m/z =274.1 [M-H]+. Calculated MW: 273.72. ^1H NMR (400 MHz,

DMSO) δ 8.33 (s, 1H), 7.30 – 7.24 (m, 5H), 7.18 (td, J = 6.0, 2.6 Hz, 1H), 4.17 (s, 2H), 2.97 (s, 3H).

Synthesis of N-methyl(5-chloro-3-phenyl-2H-1,2,4,6-tetraazainden-7-yl)amine ***(Compound 83)***



Step 1: Synthesis of [(2,4-dimethoxyphenyl)methyl]-N-methyl(5-chloro-3-phenyl-2-{[2-(trimethylsilyl)ethoxy]methyl}-2H-1,2,4,6-tetraazainden-7-yl)amine.

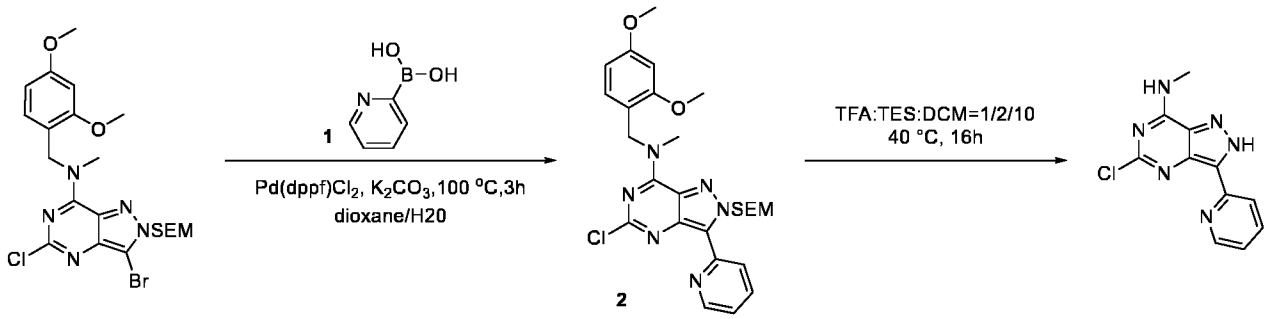
To a mixture of [(2,4-dimethoxyphenyl)methyl]-N-methyl(3-bromo-5-chloro-2-{[2-(trimethylsilyl)ethoxy]methyl}-2H-1,2,4,6-tetraazainden-7-yl)amine (50 mg, 0.09 mmol, 1.0 eq., synthesized according to procedure described in synthesis of **Compound 72**) and phenylboranediol (11.2 mg, 0.09 mmol, 1.0 eq. cas:98-80-6) in 1,4-dioxane (1.6 mL)/water (0.4 mL) = 4/1 was added $Pd(dppf)Cl_2$ (13.5 mg, 0.02 mmol, 0.2 eq.) and K_2CO_3 (38.2 mg, 0.28 mmol, 3 eq.) at 20℃. The mixture was stirred at 100℃ for 3h under N_2. After completion, the mixture was filtrated and concentrated in vacuo to give a residue. The residue was purified by SGC (UV254, Petroleum ether: EtOAc = 10:1) to afford [(2,4-dimethoxyphenyl)methyl]-N-methyl(5-chloro-3-phenyl-2-{[2-(trimethylsilyl)ethoxy]methyl}-2H-1,2,4,6-tetraazainden-7-yl)amine (50 mg, yield:100%) as a white solid. ESI-MS m/z =540.2 $[M-H]^+$. Calculated MW: 540.14

Step 2: Synthesis of N-methyl(5-chloro-3-phenyl-2H-1,2,4,6-tetraazainden-7-yl)amine.

To [(2,4-dimethoxyphenyl)methyl]-N-methyl(5-chloro-3-phenyl-2-{[2-(trimethylsilyl)ethoxy]methyl}-2H-1,2,4,6-tetraazainden-7-yl)amine (45 mg, 0.08 mmol, 1.0 eq.) in dichloromethane (1 mL) was added TFA (0.1 mL)/TES (0.2 mL)=1/2 at 20℃.The mixture was stirred at 40℃ for 16h .After completion, the mixture was filtrated and purified by Prep-HPLC (Mobile Phase: ACN---H_2O (0.1% $NH_3.H_2O$) to afford N-methyl(5-chloro-3-phenyl-2H-1,2,4,6-tetraazainden-7-yl)amine (3.93 mg, yield:18.04%). ESI-MS m/z =260.1 $[M-H]^+$. Calculated MW: 259.70. ^1H NMR (400 MHz, dmso) δ 8.45 (s, 1H), 8.24 (d, J = 7.6 Hz, 2H), 7.52 (t, J = 7.7 Hz, 2H), 7.39 (t, J = 7.4 Hz, 1H), 3.02 (d, J = 3.1 Hz, 3H).

Synthesis of N-methyl[5-chloro-3-(2-pyridyl)-2H-1,2,4,6-tetraazainden-7-yl]amine

(Compound 84)



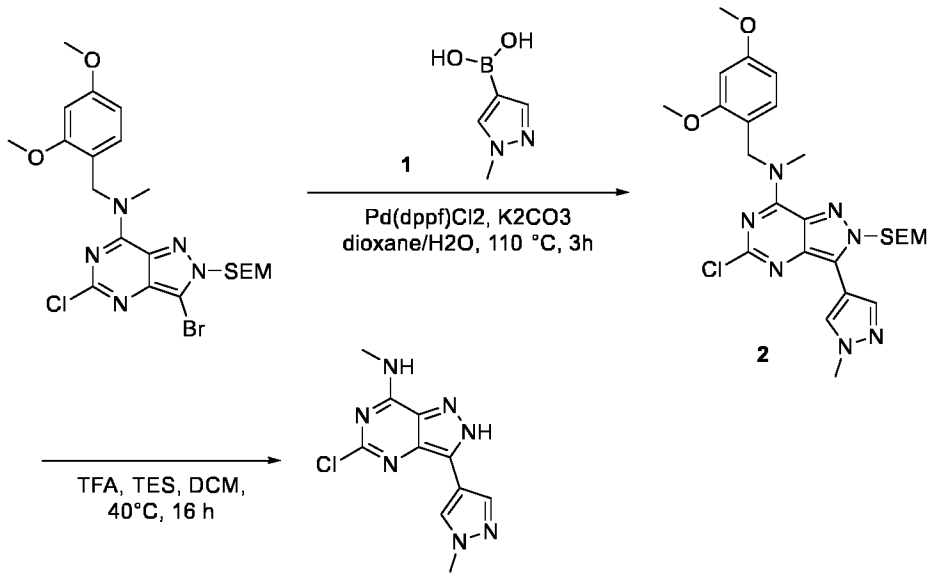
Step 1: Synthesis of [(2,4-dimethoxyphenyl)methyl]-N-methyl[5-chloro-3-(2-pyridyl)-2-{[2-(trimethylsilyl)ethoxy]methyl}-2H-1,2,4,6-tetraazainden-7-yl]amine.

To a mixture of [(2,4-dimethoxyphenyl)methyl]-N-methyl(3-bromo-5-chloro-2-{[2-(trimethylsilyl)ethoxy]methyl}-2H-1,2,4,6-tetraazainden-7-yl)amine (0.1 g, 0.18 mmol, 1.0 eq., synthesized according to procedure described in synthesis of **Compound 72**) and (2-pyridyl)boranediol (113 mg, 0.92 mmol, 5 eq.) in 1,4-dioxane (1 mL)/water (0.25 mL)=4/1 was added $Pd(dppf)Cl_2$ (27 mg, 0.04 mmol, 0.2 eq.) and K_2CO_3 (76.4 mg, 0.55 mmol, 3 eq.) at 20℃. The mixture was stirred at 100℃ for 4h under N_2. After completion, the mixture was filtrated and concentrated in vacuo to give a residue. The residue was purified by SGC (UV254, Petroleum ether: EtOAc = 6:1) to afford [(2,4-dimethoxyphenyl)methyl]-N-methyl[5-chloro-3-(2-pyridyl)-2-{[2-(trimethylsilyl)ethoxy]methyl}-2H-1,2,4,6-tetraazainden-7-yl]amine (45 mg, yield:45.15%) as a colorless oil. ESI-MS m/z =541.3$[M-H]^+$. Calculated MW: 541.12

Step 2: Synthesis of N-methyl[5-chloro-3-(2-pyridyl)-2H-1,2,4,6-tetraazainden-7-yl]amine.

To [(2,4-dimethoxyphenyl)methyl]-N-methyl[5-chloro-3-(2-pyridyl)-2-{[2-(trimethylsilyl)-ethoxy]methyl}-2H-1,2,4,6-tetraazainden-7-yl]amine (40 mg, 0.74 mmol, 1.0 eq.) in dichloromethane (8 mL) was added TFA (0.1 mL)/TES (0.2 mL)=1/2 at 20℃. The mixture was stirred at 40℃ for 16h. After completion, the mixture was filtrated and purified by Prep-HPLC (Mobile Phase: ACN---H2O (0.1% $NH_3.H_2O$) to afford N-methyl[5-chloro-3-(2-pyridyl)-2H-1,2,4,6-tetraazainden-7-yl]amine (3.36 mg, yield:16.37%). ESI-MS m/z =261.0 $[M-H]^+$. Calculated MW: 260.69. ^1H NMR (400 MHz, DMSO) δ 8.65 (d, J = 4.1 Hz, 2H), 8.37 (d, J = 7.9 Hz, 1H), 7.95 (t, J = 7.1 Hz, 1H), 7.37 – 7.31 (m, 1H), 2.98 (s, 3H).

Synthesis of N-methyl[5-chloro-3-(1-methyl-4-pyrazolyl)-2H-1,2,4,6-tetraazainden-7-yl]amine ***(Compound 85)***



Step 1: Synthesis of [(2,4-dimethoxyphenyl)methyl]-N-methyl[5-chloro-3-(1-methyl-4-pyrazolyl)-2-{[2-(trimethylsilyl)ethoxy]methyl}-2H-1,2,4,6-tetraazainden-7-yl]amine.

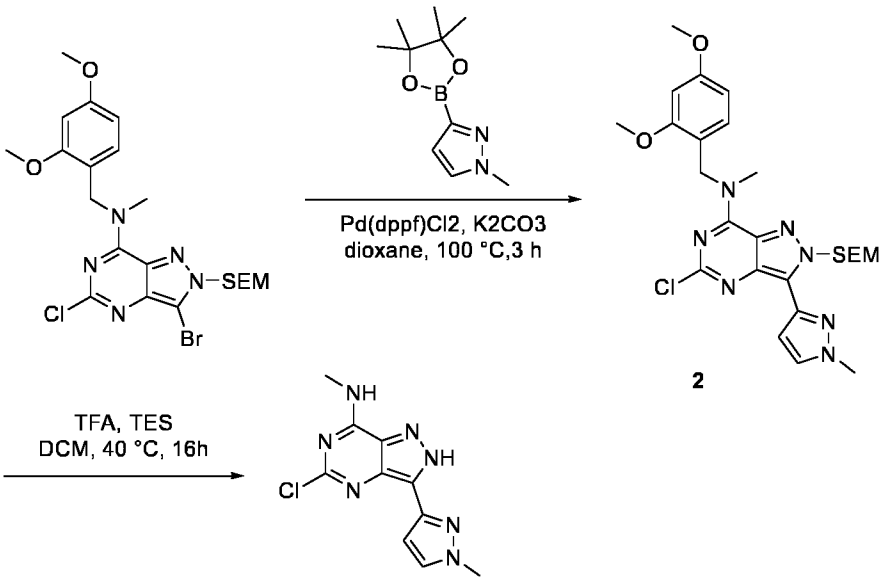
To a mixture of [(2,4-dimethoxyphenyl)methyl]-N-methyl(3-bromo-5-chloro-2-{[2-(trimethylsilyl)ethoxy]methyl}-2H-1,2,4,6-tetraazainden-7-yl)amine (90 mg, 0.17 mmol, 1 eq., synthesized according to procedure described in synthesis of **Compound 72**) in 1,4-dioxane (0.8 mL)/water (0.2 mL) was added (1-methyl-4-pyrazolyl)boranediol (21.3 mg, 0.17 mmol, 1 eq.), Pd(dppf)Cl_2 (24.3 mg, 0.03 mmol, 0.2 eq.) and dipotassium carbonate (68.7 mg, 0.05 mmol, 3 eq.) at 25℃. The mixture was stirred at 110℃ for 3h under N2. After completion, the mixture was purified by Prep-TLC (Petroleum ether: EtOAc = 5:1) to afford [(2,4-dimethoxyphenyl)methyl]-N-methyl[5-chloro-3-(1-methyl-4-pyrazolyl)-2-{[2-(trimethylsilyl)ethoxy]methyl}-2H-1,2,4,6-tetraazainden-7-yl]amine (65 mg, purity: 80%, yield:57.65%) as a colorless oil. MS (ESI, pos. ion) m/z: 544.2. (M+1). Calculated MW: 544.13.

Step 2: Synthesis of N-methyl[5-chloro-3-(1-methyl-4-pyrazolyl)-2H-1,2,4,6-tetraazainden-7-yl]amine.

To a mixture of [(2,4-dimethoxyphenyl)methyl]-N-methyl[5-chloro-3-(1-methyl-4-pyrazolyl)-2-{[2-(trimethylsilyl)ethoxy]methyl}-2H-1,2,4,6-tetraazainden-7-yl]amine (55 mg, 0.10 mmol) in dichloromethane (1 mL) was added trifluoroacetic acid (0.1 mL) and Et3SiH (0.2 mL) at 25℃. The mixture was stirred at 40℃ for 16h . After completion, the mixture was purified by Prep-HPLC (MeCN/H2O, 0.1 %NH3/H2O) to afford N-methyl[5-chloro-3-(1-methyl-4-pyrazolyl)-2H-1,2,4,6-tetraazainden-7-yl]amine (10.9 mg, purity: 98.62%, yield:40.33%). MS (ESI, pos. ion)

m/z: 264.1. (M+1). Calculated MW: 263.69. ^{1}H NMR (400 MHz, dmso) δ 8.38 (brs, 1H), 8.26 (s, 1H), 7.98 (s, 1H), 3.94 (s, 3H), 3.00 (s, 3H).

Synthesis of N-methyl[5-chloro-3-(1-methyl-3-pyrazolyl)-2H-1,2,4,6-tetraazainden-7-yl]amine ***(Compound 86)***



Step 1: Synthesis of [(2,4-dimethoxyphenyl)methyl]-N-methyl[5-chloro-3-(1-methyl-3-pyrazolyl)-2-{[2-(trimethylsilyl)ethoxy]methyl}-2H-1,2,4,6-tetraazainden-7-yl]amine.

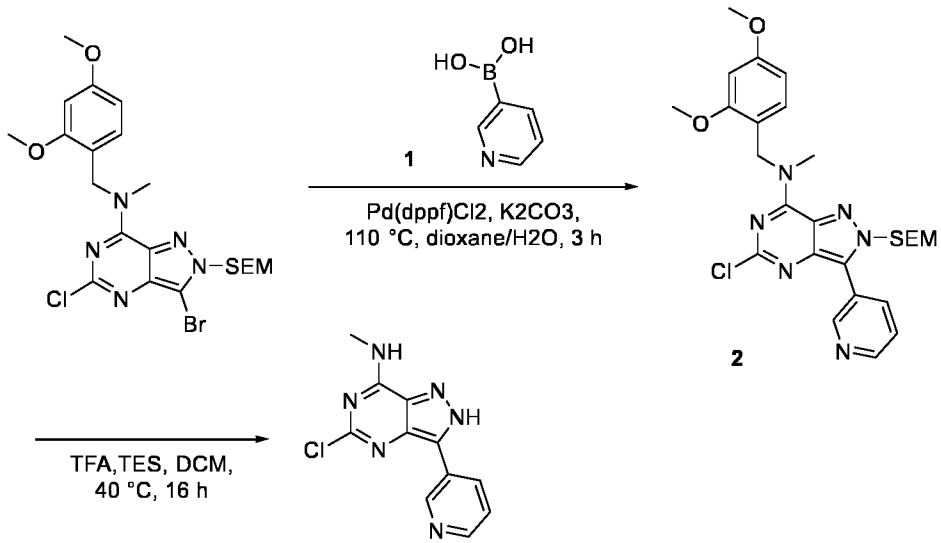
To a mixture of [(2,4-dimethoxyphenyl)methyl]-N-methyl(3-bromo-5-chloro-2-{[2-(trimethylsilyl)ethoxy]methyl}-2H-1,2,4,6-tetraazainden-7-yl)amine (90 mg, 0.17 mmol, 1 eq., synthesized according to procedure described in synthesis of **Compound 72**) in 1,4-dioxane (2 mL) was added 4,4,5,5-tetramethyl-2-(1-methyl-3-pyrazolyl)-1,3,2-dioxaborolane (34.5 mg, 0.17 mmol, 1 eq), Pd(dppf)Cl2 (12.1 mg, 0.017 mmol, 0.1 eq.) and dipotassium carbonate (68.7 mg, 0.50 mmol, 3 eq.) at 25℃. The mixture was stirred at 100℃ for 3h under N2. After completion, the mixture was concentrated in vacuo to give a residue. The residue was purified by Pre-TLC (PE:EA=4:1) to afford [(2,4-dimethoxyphenyl)methyl]-N-methyl[5-chloro-3-(1-methyl-3-pyrazolyl)-2-{[2-(trimethylsilyl)ethoxy]methyl}-2H-1,2,4,6-tetraazainden-7-yl]amine (60 mg, purity: 80%, yield:66.52%) as a white solid. MS (ESI, pos. ion) m/z: 544.2. (M+1). Calculated MW: 544.13.

Step 2: Synthesis of N-methyl[5-chloro-3-(1-methyl-3-pyrazolyl)-2H-1,2,4,6-tetraazainden-7-yl]amine

To a mixture of [(2,4-dimethoxyphenyl)methyl]-N-methyl[5-chloro-3-(1-methyl-3-pyrazolyl)-2-{[2-(trimethylsilyl)ethoxy]methyl}-2H-1,2,4,6-tetraazainden-7-yl]amine (50 mg, 0.092 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (0.1 mL) and Et3SiH (0.2 mL) at 25℃. The mixture was stirred at 40℃ for 16h. After completion, the mixture was purified by Pre-

HPLC (MeCN/H2O, 0.1 %NH3/H2O) to afford N-methyl[5-chloro-3-(1-methyl-3-pyrazolyl)-2H-1,2,4,6-tetraazainden-7-yl]amine (10.6 mg, purity: 99.55%, yield:43.51%). MS (ESI, pos. ion) m/z: 264.0. (M+1). Calculated MW: 263.69. ^{1}H NMR (400 MHz, DMSO) δ 8.55 (brs, 1H), 7.84 (s, 1H), 6.84 (s, 1H), 3.95 (s, 3H), 2.98 (s, 3H).

Synthesis of N-methyl[5-chloro-3-(3-pyridyl)-2H-1,2,4,6-tetraazainden-7-yl]amine ***(Compound 87)***



Step 1: Synthesis of [(2,4-dimethoxyphenyl)methyl]-N-methyl[5-chloro-3-(3-pyridyl)-2-{[2-(trimethylsilyl)ethoxy]methyl}-2H-1,2,4,6-tetraazainden-7-yl]amine.

To a mixture of [(2,4-dimethoxyphenyl)methyl]-N-methyl(3-bromo-5-chloro-2-{[2-(trimethylsilyl)ethoxy]methyl}-2H-1,2,4,6-tetraazainden-7-yl)amine (90 mg, 0.17 mmol, 1 eq, synthesized according to procedure described in synthesis of **Compound 72**) in 1,4-dioxane (0.8 mL)/water (0.2 mL) was added (3-pyridyl)boranediol (20.4 mg, 0.17 mmol, 1eq), Pd(dppf)Cl2 (12.1 mg, 0.017 mmol, 0.1 eq.) and dipotassium carbonate (68.7 mg, 0.50 mmol, 3 eq.) at 25℃. The mixture was stirred at 110℃ for 3h under N2. After completion, the mixture was purified by Pre-TLC (Petroleum ether: EtOAc = 5:1) to afford [(2,4-dimethoxyphenyl)methyl]-N-methyl[5-chloro-3-(3-pyridyl)-2-{[2-(trimethylsilyl)ethoxy]methyl}-2H-1,2,4,6-tetraazainden-7-yl]amine (40 mg, purity: 100%, yield:44.59%) as a colorless oil. MS (ESI, pos. ion) m/z: 541.2. (M+1). Calculated MW: 541.12.

Step 2: Synthesis of N-methyl[5-chloro-3-(3-pyridyl)-2H-1,2,4,6-tetraazainden-7-yl]amine.

To a mixture of [(2,4-dimethoxyphenyl)methyl]-N-methyl[5-chloro-3-(3-pyridyl)-2-{[2-(trimethylsilyl)ethoxy]methyl}-2H-1,2,4,6-tetraazainden-7-yl]amine (35 mg, 0.065 mmol) in dichloromethane (7 mL) was added trifluoroacetic acid (0.1 mL) and Et3SiH (0.2 mL) at 25℃. The mixture was stirred at 40℃ for 16h. After completion, the mixture was purified by Pre-HPLC (MeCN/H2O, 0.1 %NH3/H2O) to afford N-methyl[5-chloro-3-(3-pyridyl)-2H-1,2,4,6-

tetraazainden-7-yl]amine (5.2 mg, purity: 99.55%, yield:43.51%). MS (ESI, pos. ion) m/z: 261.1. (M+1). Calculated MW: 260.69. ^{1}H NMR (400 MHz, dmso) δ 9.43 (s, 1H), 8.62 (dd, *J* = 4.7, 1.4 Hz, 1H), 8.58 (d, *J* = 8.0 Hz, 1H), 8.43 (s, 1H), 7.59 (dd, *J* = 7.9, 4.8 Hz, 1H), 3.06 (d, *J* = 3.6 Hz, 3H).

Cited prior art documents:

1) Sambrook et al., Molecular Cloning: A Laboratory Manual, 4th ed. (2012) Cold Spring Harbor Laboratory Press.

2) Ausubel et al., Short Protocols in Molecular Biology (2002) 5th Ed, John Wiley & Sons, Inc.

3) L. Lachman et al. The Theory and Practice of Industrial Pharmacy, 4th Ed, 2013 (ISBN 8123922892).

4) Wu, Shuquan; Liu, Changyi; Luo, Guoyong; Jin, Zhichao; Zheng, Pengcheng; Chi, Yonggui Robin[Angewandte Chemie - International Edition, 2019, vol. 58, # 51, p. 18410 - 18413][Angew. Chem., 2019, vol. 131, p. 18581 - 18584,4].

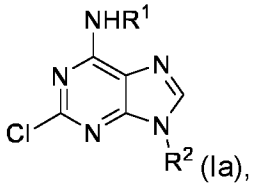
5) Pfizer Limited, WO 2004/96810 A1.

All scientific publications and patent documents cited in the present disclosure are incorporated by reference herein.

CLAIMS

We claim:

1. A compound of formula (Ia), or a pharmaceutically acceptable salt thereof,

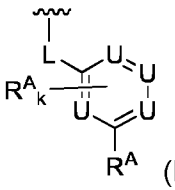


(Ia),

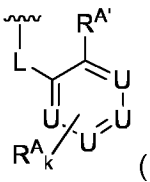
wherein

R^1 is -C_1-C_3-alkyl;

R^2 is -L-A or a moiety of formula (IIIb) or (IIIc),



(IIIb),



(IIIc),

each R^A is independently selected from halogen, -CN, -NO_2, -OH, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -C(=O)O-C_1-C_3-alkyl, -C(=O)OH, -O-C_1-C_3-alkyl, -C(=O)-NR^6R^6, -C(=O)-C_1-C_3-alkyl, -NR^6R^6, -NH-SO_2-C_1-C_3-alkyl, -NH-SO_2-$(CH_2)_s$-OH, -NH-SO_2-$(CH_2)_s$-R^7, -SO_2-NH-R^7, -$SO_2NR^6R^6$, -$(CH_2)_s$-R^8, -$(CH_2)_s$-cycloalkyl, -$(CH_2)_s$-aryl, -$(CH_2)_s$-heteroaryl, and -$(CH_2)_s$-heterocycloalkyl; wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, or 3 R;

$R^{A'}$ is selected from -CN, -NO_2, -OH, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -C(=O)O-C_1-C_3-alkyl, -C(=O)OH, -O-C_1-C_3-alkyl, -C(=O)-NR^6R^6, -C(=O)-C_1-C_3-alkyl, -NR^6R^6, -NH-SO_2-C_1-C_3-alkyl, -NH-SO_2-$(CH_2)_s$-OH, -NH-SO_2-$(CH_2)_s$-R^7, -SO_2-NH-R^7, -$SO_2NR^6R^6$, -$(CH_2)_s$-R^8, -$(CH_2)_s$-cycloalkyl, -$(CH_2)_s$-aryl, -$(CH_2)_s$-heteroaryl, and -$(CH_2)_s$-heterocycloalkyl; wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, or 3 R;

each R is independently halogen, -CN, -OH, oxo, -S(=O)CH_3, -$S(=O)_2CH_3$, -$S(=O)_2NH_2$, -$S(=O)_2$OH, -$S(=O)_2NHCH_3$, -$S(=O)_2N(CH_3)_2$, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -C(=O)CH_3, -C(=O)OH, -C(=O)OCH_3, C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, or C_3-C_6cycloalkyl;

k is 0, 1, 2, or 3;

L is -$(CH_2)_n$- or –$(CH_2)_n$-Y-,

n is 0, 1, 2 or 3;

wherein Y is selected from -O-, -S-, -SO_2-, -NH- and -C(=O)-NH-;

A is a bicyclic aryl, bicyclic cycloalkyl, or bicyclic heterocycle, each of which is unsubstituted or substituted with 1, 2, 3 or 4 R^A;

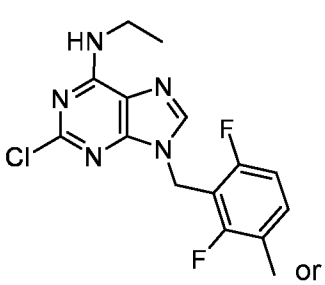
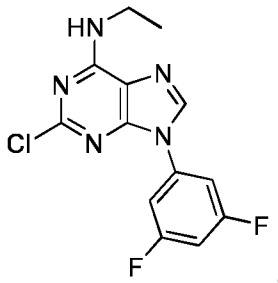
each U is independently CH or N;

each R^6 is independently selected from -H, -C(=O)-O-tert-butyl, -C_1-C_3-alkyl, and -C(=O)-CF_3;

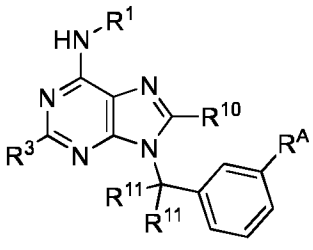
s is 0, 1, 2, or 3;

R^7 is aryl or five or six-membered heterocycle, each of which is optionally substituted with 1, 2, or 3 R;

R^8 is a four or five membered ring, each of which is optionally substituted with 1, 2, or 3 R;

provided that the compound is not  or  .

2. A compound of formula (XI), or a pharmaceutically acceptable salt thereof,


(XI),

wherein

R^1 is C_1-C_3-alkyl;

R^3 is selected from -Br, -Cl, -NO_2, CN, -O-C_1-C_3-alkyl, C_1-C_3-alkyl, C_2-C_3-haloalkyl, -NR^6R^6, -OH, -CH_2F, and -CHF_2;

each R^A is independently selected from halogen, -CN, -NO_2, -OH, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -C(=O)O-C_1-C_3-alkyl, -C(=O)O-$(CH_2)_s$-R^7, -C(=O)OH, -O-C_1-C_3-alkyl, -C(=O)-NR^6R^6, -NR^6R^6, -NH-SO_2-C_1-C_3-alkyl, -NH-SO_2-$(CH_2)_s$-R^7, -SO_2-NH-R^7, -$SO_2NR^6R^6$, -$(CH_2)_s$-R^8, -$(CH_2)_s$-cycloalkyl, -$(CH_2)_s$-aryl, -$(CH_2)_s$-heteroaryl, or -$(CH_2)_s$-heterocycloalkyl; wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, or 3 R;

each R is independently halogen, -CN, -OH, oxo, -S(=O)CH_3, -S(=O)$_2CH_3$, -S(=O)$_2NH_2$, -S(=O)$_2$OH, -S(=O)$_2NHCH_3$, -S(=O)$_2N(CH_3)_2$, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -C(=O)CH_3, -C(=O)OH, -C(=O)OCH_3, C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, or C_3-C_6cycloalkyl;

each R^6 is independently selected from -H, -C(=O)-O-tert-butyl, -C_1-C_3-alkyl, and -C(=O)-CF_3;

s is 0, 1, 2, or 3;

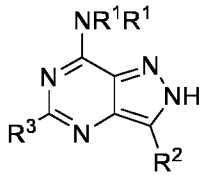
R^7 is aryl or five or six-membered heterocycle, each of which is optionally substituted with 1, 2, or 3 R;

R^8 is a four or five membered ring, each of which is optionally substituted with 1, 2, or 3 R;

R^{10} is -CN, -NO_2, -OH, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -C(=O)O-C_1-C_3-alkyl, -C(=O)-C_1-C_3-alkyl, -C(=O)OH, -O-C_1-C_3-alkyl, -C(=O)-NR^6R^6, -NR^6R^6, -NH-SO_2-C_1-C_3-alkyl, -NH-SO_2-$(CH_2)_s$-R^7, or -$SO_2NR^6R^6$, wherein the alkyl is optionally substituted with 1, 2, or 3 R; and

R^{11} is selected from -H, -F, -Br, -Cl, -CN, -C_1-C_3-alkyl, and NO_2.

3. A compound of formula (II), or a pharmaceutically acceptable salt thereof,



(II),

wherein

each R^1 is independently selected from -H and -C_1-C_3-alkyl,

R^3 is selected from -F, -Cl, -Br, -CN, -NO_2, C_1-C_3-haloalkyl, and -NR^6R^6;

R^2 is C_1-C_3-alkyl or -L-A;

A is an aryl, heteroaryl, cycloalkyl, or a nitrogen-containing heterocycloalkyl, each of which is unsubstituted or substituted with 1, 2, 3, or 4 R^A;

each R^A is independently selected from halogen, -CN, -NO_2, -OH, C_1-C_6alkyl, C_1-C_3-haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_3heteroalkyl, -C(=O)O-C_1-C_3-alkyl, -C(=O)-C_1-C_3-alkyl, -C(=O)OH, -O-C_1-C_3-alkyl, -C(=O)-NR^6R^6, -NR^6R^6, -NH-SO_2-C_1-C_3-alkyl, -NH-SO_2-$(CH_2)_s$-OH, -NH-SO_2-$(CH_2)_s$-R^7, -SO_2-NH-R^7, -$SO_2NR^6R^6$, and -$(CH_2)_s$-R^8; wherein the alkyl is optionally substituted with 1, 2, or 3 R;

each R^6 is independently selected from -H, -C(=O)-O-tert-butyl, -C_1-C_3-alkyl, and -C(=O)-CF_3;

R^7 is aryl or five or six-membered heterocycle, each of which is optionally substituted with 1, 2, or 3 R;

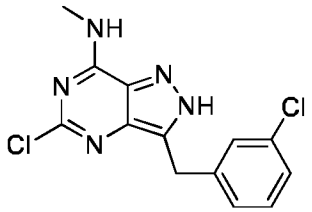
R^8 is a four or five membered ring, each of which is optionally substituted with 1, 2, or 3 R;

L is $–(CH_2)_n$- or -Y-$(CH_2)_n$-, wherein Y is selected from -O-, -S-, -SO_2-, -NH- and -C(=O)-NH-;

each R is independently halogen, -CN, -OH, oxo, -S(=O)CH_3, -S(=O)$_2CH_3$, -S(=O)$_2NH_2$, -S(=O)$_2NHCH_3$, -S(=O)$_2N(CH_3)_2$, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -C(=O)CH_3, -C(=O)OH, -C(=O)OCH_3, C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, or C_3-C_6cycloalkyl;

n is 0, 1, 2, or 3;

s is 0 to 3;

provided that the compound is not 

.

4. The compound of claim 3, or a pharmaceutically acceptable salt thereof, wherein at least one of R^1 is H.
5. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein R^1 is methyl or ethyl.
6. The compound of any one of claims 2 to 5, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from -Cl.
7. The compound of any one of claims 2 or 5, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from -Br, -Cl, -O-C_1-C_3-alkyl, C_1-C_3-alkyl (e.g., methyl, ) and -NH_2.
8. The compound of any one of claims 3 to 5, or a pharmaceutically acceptable salt thereof, wherein R^3 is -Cl, C_1-C_3-haloalkyl, and -NH_2.
9. The compound of any one of claims 1 or 3 to 8, or a pharmaceutically acceptable salt thereof, wherein R^2 is -L-A.
10. The compound of any one of claims 3 to 9, or a pharmaceutically acceptable salt thereof, wherein A is phenyl, which is unsubstituted or substituted.
11. The compound of any one of claims 3 to 9, or a pharmaceutically acceptable salt thereof, wherein A is 5-6 membered heteroaryl, which is unsubstituted or substituted.

12. The compound of any one of claims 3 to 9, or a pharmaceutically acceptable salt thereof, wherein A is C_3-C_6 cycloalkyl, which is unsubstituted or substituted.

13. The compound of any one of claims 1 or 3 to 9, or a pharmaceutically acceptable salt thereof, wherein A is naphthyl, which is unsubstituted or substituted.

14. The compound of any one of claims 1 or 3 to 9, or a pharmaceutically acceptable salt thereof, wherein A is bicyclic heteroaryl, which is unsubstituted or substituted.

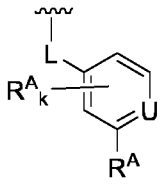
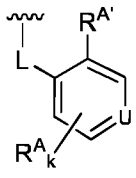
15. The compound of any one of claims 1 or 3 to 14, or a pharmaceutically acceptable salt thereof, wherein each R^A is independently selected from halogen, -CN, -NO_2, -OH, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, -C(=O)O-C_1-C_3-alkyl, -C(=O)OH, -O-C_1-C_3-alkyl, -C(=O)-NR^6R^6, -C(=O)-C_1-C_3-alkyl, -NR^6R^6, -NH-SO_2-C_1-C_3-alkyl, -NH-SO_2-$(CH_2)_s$-OH, -NH-SO_2-$(CH_2)_s$-R^7, -SO_2-NH-R^7, -$SO_2NR^6R^6$, -cycloalkyl, -aryl, -heteroaryl, and -heterocycloalkyl; wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, or 3 R.

16. The compound of any one of claims 1 or 3 to 14, or a pharmaceutically acceptable salt thereof, wherein each R^A is independently selected from halogen, -CN, -NO_2, -OH, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, -C(=O)O-C_1-C_3-alkyl, -C(=O)OH, -O-C_1-C_3-alkyl, -C(=O)-NR^6R^6, -C(=O)-C_1-C_3-alkyl, -NH_2, -NH-SO_2-C_1-C_3-alkyl, -NH-SO_2-$(CH_2)_s$-OH, -NH-SO_2-$(CH_2)_s$-R^7, -SO_2-NH-R^7, and -$SO_2NR^6R^6$; wherein the alkyl is optionally substituted with 1, 2, or 3 R.

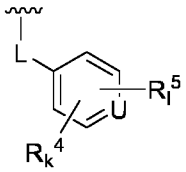
17. The compound of any one of claims 2 or 5 to 14, or a pharmaceutically acceptable salt thereof, wherein R^A is selected from halogen, -CN, -NO_2, -OH, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, -C(=O)O-C_1-C_3-alkyl, -C(=O)O-$(CH_2)_s$-R^7, -C(=O)OH, -O-C_1-C_3-alkyl, and -NH_2; wherein the alkyl is optionally substituted with 1, 2, or 3 R.

18. The compound of any one of claims 1 or 3 to 16, or a pharmaceutically acceptable salt thereof, wherein R^2 is a moiety of formula (IIIb) or (IIIc).

19. The compound of claim 18, or a pharmaceutically acceptable salt thereof, wherein the moiety of (IIIb) or (IIIc) is moiety (IIIb') or (IIIc'), respectively,


(IIIb'),

(IIIc').

20. The compound of any one of claims 3 to 16, or a pharmaceutically acceptable salt thereof, wherein R2 is a moiety of formula (III) or (IV),



(III), wherein

L is a linker comprising -$(CH_2)_n$- or -Y-$(CH_2)_n$-;

Y is selected from -O-, -S-, -SO_2-, -NH- and -C(=O)-NH-;

n is 0 to 3, k is 0 to 3, particularly 0 to 2, more particularly 1 or 2;

l is 0 or 1;

U is CH or a heteroatom, particularly CH or N, more particularly CH;

R^4 is independently selected from

- -Cl, -Br, -CH_2F, -CHF_2, -CF_3 and
- -C(=O)O-C_1-C_3-alkyl, -C(=O)OH, -O-C_1-C_3-alkyl, -C(=O)-NR^6R^6, -C_1-C_3-alkyl-OH, and
- -NR^6R^6,

wherein R^6 is independently selected from

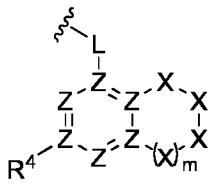
- -H, -C(=O)-O-tert-butyl, -C_1-C_3-alkyl, and -C(=O)-CF_3, particularly from -H and Me,

R^5 is selected from

- -NH-SO_2-C_1-C_3-alkyl, -NH-SO_2-$(CH_2)_s$-OH and
- -NH-SO_2-$(CH_2)_s$-R^7, wherein R^7 is selected from an aryl and a heterocycle, wherein the heterocycle is a five or six-membered heterocycle and wherein the heterocycle is an aliphatic heterocycle or an aromatic heterocycle, and
- -$(CH_2)_s$-R^8, wherein R^8 is a four or five membered ring,

s is 0 to 3,

or



(IV), wherein

L of formula (I) is a linker comprising -$(CH_2)_n$- or –$(CH_2)_n$-Y- and

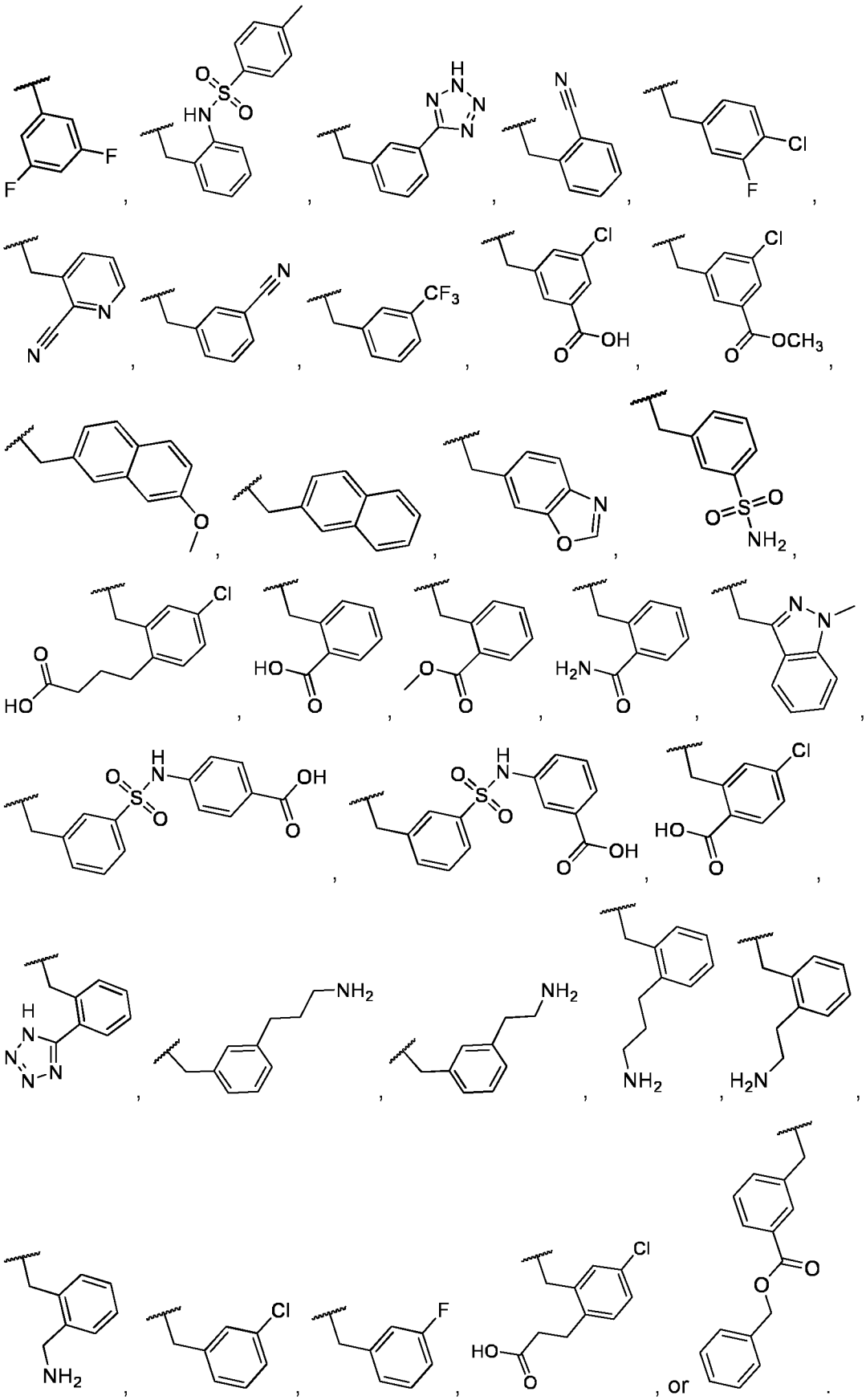
L is –$(CH_2)_n$- or -Y-$(CH_2)_n$-, wherein Y is selected from -O-, -S-, -SO_2-, -NH- and -C(=O)-NH-;

n is 0 to 3, m is 0 or 1;

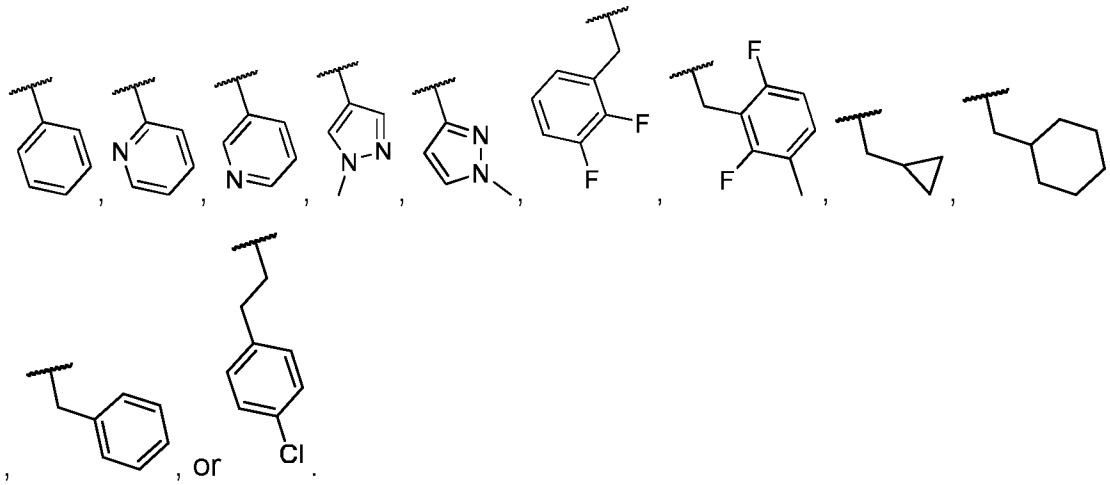
each X and Z are selected from C, NR^3 , SO_2 and O, wherein R^3 is -H or -C_1-C_3-alkyl-NH_2 and wherein Z is particularly C;

R^4 is defined as above.

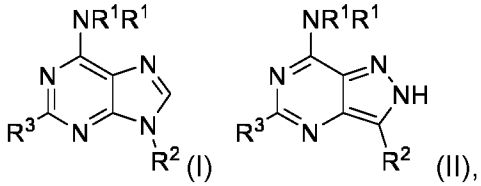
21. The compound of any one of claims 1 or 3 to 16, or a pharmaceutically acceptable salt thereof, wherein R^2 is:



22. The compound of any one of claims 3 to 16, or a pharmaceutically acceptable salt thereof, wherein R^2 is:



23. A compound of formula (I) or (II), particularly of (I)

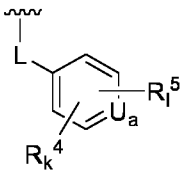


wherein

R^1 is independently selected from -H and -C_1-C_3-alkyl, particularly -H and -Me or cyclopropyl, more particularly -H and -Me, wherein at least one of R^1 is H,

R^3 is selected from -Br, -Cl, -CN, -F and -NO_2, particularly -Cl,

R^2 is selected from -C_1-C_3-alkyl and a moiety of formula (III) or (IV), particularly R^2 is a moiety of formula (III) or (IV),

-  (III), wherein

L of formula (I) is a linker comprising -$(CH_2)_n$- or –$(CH_2)_n$-Y- and

L of formula (II) is a linker comprising –$(CH_2)_n$- or -Y-$(CH_2)_n$-, wherein Y is selected from -O-, -S-, -SO_2-, -NH- and -C(=O)-NH-, and

n is 0 to 3, k is 0 to 3, particularly 0 to 2, more particularly 1 or 2,

l is 0 or 1,

U is CH or a heteroatom, particularly CH or N, more particularly CH,

a is 0 or 1, particularly 1,

R^4 is independently selected from

- -Cl, -Br, -CH_2F, -CHF_2, -CF_3 and
- -C(=O)O-C_1-C_3-alkyl, -C(=O)OH, -O-C_1-C_3-alkyl, -C(=O)-NR^6R^6, -C_1-C_3-alkyl-OH, and
- -NR^6R^6,

wherein R^6 is independently selected from

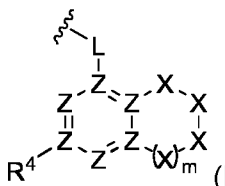
- -H, -C(=O)-O-tert-butyl, -C_1-C_3-alkyl, and -C(=O)-CF_3, particularly from -H and Me,

R^5 is selected from

- -NH-SO_2-C_1-C_3-alkyl, -NH-SO_2-$(CH_2)_s$-OH and
- -NH-SO_2-$(CH_2)_s$-R^7, wherein R^7 is selected from an aryl and a heterocycle, wherein the heterocycle is a five or six-membered heterocycle and wherein the heterocycle is an aliphatic heterocycle or an aromatic heterocycle, and
- -$(CH_2)_s$-R^8, wherein R^8 is a four or five membered ring,

s is 0 to 3,

or

-  (IV), wherein

L of formula (I) is a linker comprising -$(CH_2)_n$- or –$(CH_2)_n$-Y- and

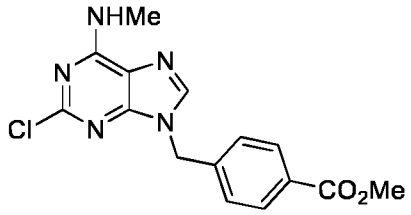
L of formula (II) is a linker comprising –$(CH_2)_n$- or -Y-$(CH_2)_n$-, wherein Y is selected from -O-, -S-, -SO_2-, -NH- and -C(=O)-NH-, and

n is 0 to 3, m is 0 or 1,

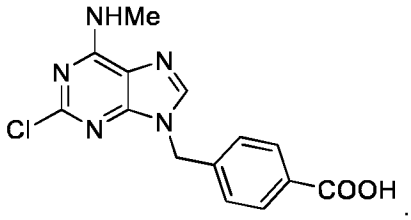
each X and Z are selected from C, NR^3 , SO_2 and O, wherein R^3 is -H or -C_1-C_3-alkyl-NH_2 and wherein Z is particularly C,

R^4 is defined as above,

with the exception of



and



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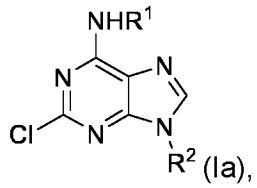
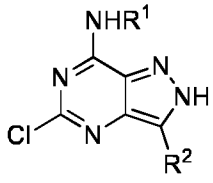
24. The compound according to claim 23 is a compound of formula (Ia) or (IIa), particularly of (Ia)



(Ia),

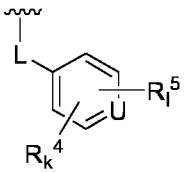


(IIa)

wherein

R^1 is selected from -H and -C_1-C_3-alkyl, particularly -H and -Me or cyclopropyl, more particularly -Me,

R^2 is selected from -C_1-C_3-alkyl and a moiety of formula (IIIa) or (IVa), particularly R^2 is a moiety of formula (IIIa) or (IVa),

- 

(IIIa),

wherein

L of formula (I) is a linker comprising -$(CH_2)_n$- or –$(CH_2)_n$-Y- and

L of formula (II) is a linker comprising –$(CH_2)_n$- or -Y-$(CH_2)_n$-, wherein Y is selected from -O-, -S-, -SO_2-, -NH- and -C(=O)-NH- , and

and n is 0 to 3,

k is 0 to 3, particularly 0 to 2, more particularly 1 or 2,

l is 0 or 1,

U is CH or a heteroatom, particularly CH or N, more particularly CH,

R^4 is selected from

- -Cl, -Br, $-CH_2F$, $-CHF_2$, $-CF_3$, and
- $-C(=O)O-C_1-C_3$-alkyl, -C(=O)OH, $-O-C_1-C_3$-alkyl, -C(=O)-N R^6R^6, $-C_1-C_3$-alkyl-OH, and
- $-NR^6R^6$,

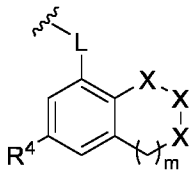
wherein R^6 is independently selected from

- -H, $-C(=O)-O$-tert-butyl, $-C_1-C_3$-alkyl and $-C(=O)-CF_3$, particularly from -H and Me,

R^5 is selected from

- $-NH-SO_2-C_1-C_3$-alkyl, $-NH-SO_2-(CH_2)_s$-OH, and
- $-NH-SO_2-(CH_2)_s-R^7$,
  wherein R^7 is selected from an aryl or a heterocycle, wherein the heterocycle is a five or six-membered heterocycle and wherein the heterocycle is an aliphatic heterocycle or an aromatic heterocycle, and
- $-(CH_2)_s-R^8$,
  wherein R^8 is a four or five membered ring,

s is 0 to 3,

-  (IVa),

wherein

L of formula (I) is a linker comprising $-(CH_2)_n-$ or $-(CH_2)_n-Y-$ and

L of formula (II) is a linker comprising $-(CH_2)_n-$ or $-Y-(CH_2)_n-$, wherein Y is selected from -O-, -S-, $-SO_2-$, -NH- and -C(=O)-NH-, and

n is 0 to 3,

n is 0 or 1,

m is 0 or 1,

X is independently selected from CH, NR^{13}, SO_2 and O, wherein R^{13} is selected from -H and -C_1-C_3-alkyl-NH_2,

R^4 is defined as above.

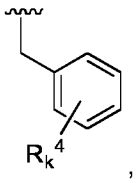
25. The compound according to claim 23 or 24, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from -Br, -Cl, -F and -NO_2.

26. The compound according to any one of claims 23-25, or a pharmaceutically acceptable salt thereof, wherein R^2 is para or meta substituted.

27. The compound according to any one of claims 23-25, or a pharmaceutically acceptable salt thereof, wherein L is -$(CH_2)_n$- and n is 0 or 1.

28. The compound according to any one of claims 23-27, or a pharmaceutically acceptable salt thereof, wherein L is –$(CH_2)_n$-Y-, and Y is selected from -O-, -S-, -SO_2-, -NH- and -C(=O)-NH-,

29. The compound according to any one of claims 23-28, or a pharmaceutically acceptable salt thereof, wherein formula (IIIa) of R^2 is



, wherein

k is 0 to 3, particularly 0 to 2, more particularly 1 or 2

R^4 is selected from

- -Cl, -Br, -CH_2F, -CHF_2, -CF_3, and
- -C(=O)O-C_1-C_3-alkyl, -C(=O)OH, -C_1-C_3-alkyl, -C(=O)-NR^6R^6, -C_1-C_3-alkyl-OH, and
- -NR^6R^6,

wherein R^6 is independently selected from

-H, -C(=O)-O-tert-butyl, -C_1-C_3-alkyl and -C(=O)-CF_3, particularly from -H and Me.

30. The compound according to any one of claims 23-29, or a pharmaceutically acceptable salt thereof, wherein R^4 is selected from

- -Cl, -Br, -CH_2F, -CHF_2, -CF_3,

- -OMe, -C(=O)OMe, -C(=O)OH, -CH_2OH, - NH_2, -C(=O)-NH-Me and -C(=O)-NH_2,

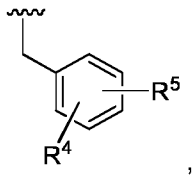
particularly from

-Cl, -OMe, -C(=O)OH, -C(=O)OMe, -C(=O)NHMe and -$C(=O)NH_2$,

more particularly from

-Cl, -OMe, -C(=O)OH and -C(=O)OMe.

31. The compound according to any one of claims 1, 3, 23-30, or a pharmaceutically acceptable salt thereof, wherein formula (IIIa) of R^2 is



,

wherein

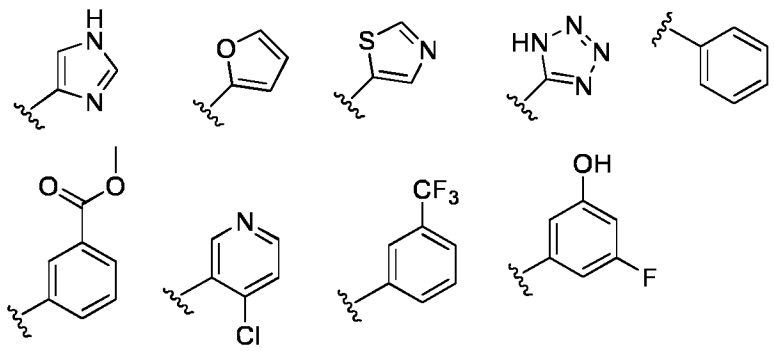
R^5 is selected from

- -NH-SO_2-C_1-C_3-alkyl, -NH-SO_2-$(CH_2)_s$-OH, particularly -NH-SO_2-Me or -NH-SO_2-$(CH_2)_2$-OH, and
- -NH-SO_2-$(CH_2)_s$-R^7, wherein R^7 is selected from an aryl or a heterocycle, wherein the heterocycle is a five or six-membered heterocycle and wherein the heterocycle is an aliphatic heterocycle or an aromatic heterocycle, and
- -$(CH_2)_s$-R^8, wherein R^8 is a four or five membered ring,

s is 0 to 3,

R^4 being as defined above.

32. The compound according to any one of claims 23-31, or a pharmaceutically acceptable salt thereof, wherein R^7 is selected from any one of the moieties



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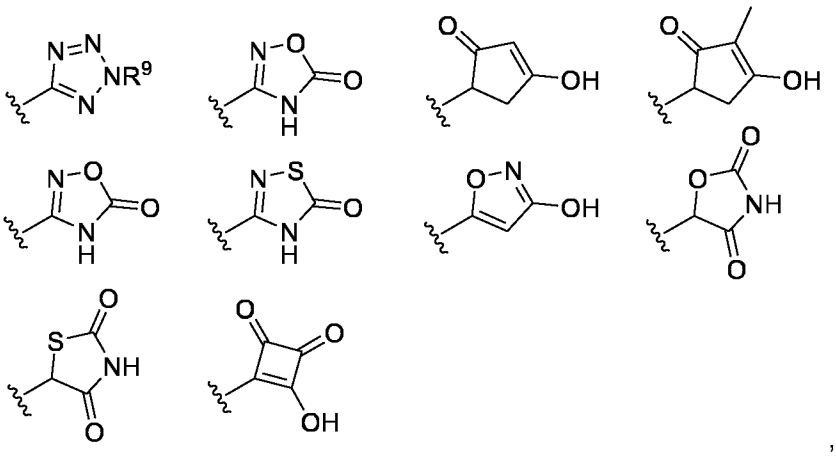
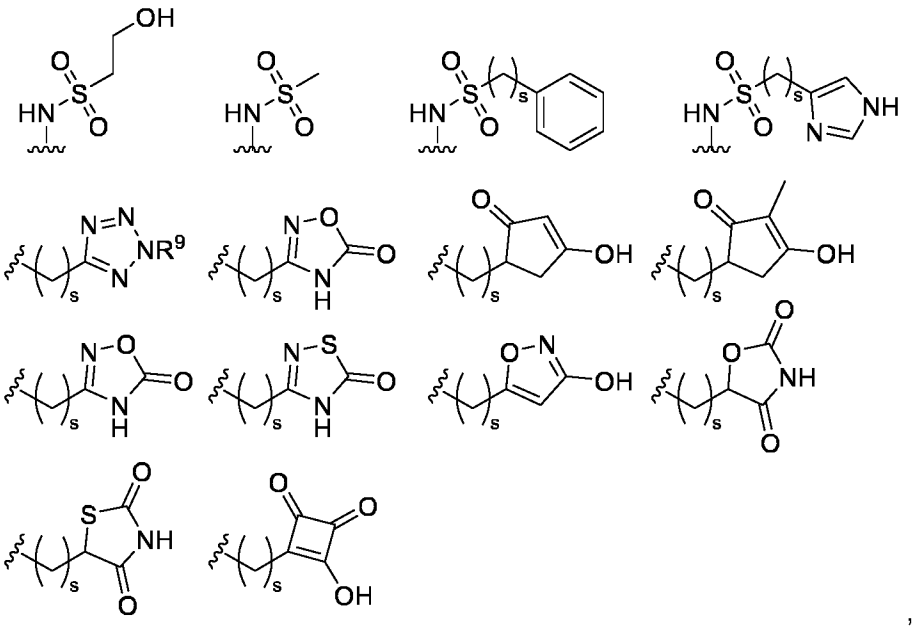
33. The compound according to any one of claims 23-32, or a pharmaceutically acceptable salt thereof, wherein R^8 is selected from any one of the moieties



wherein R^9 is selected from -H or -C_1-C_6-alkyl.

34. The compound according to any one of claims 23-33, or a pharmaceutically acceptable salt thereof, wherein R^5 is selected from any one of the moieties

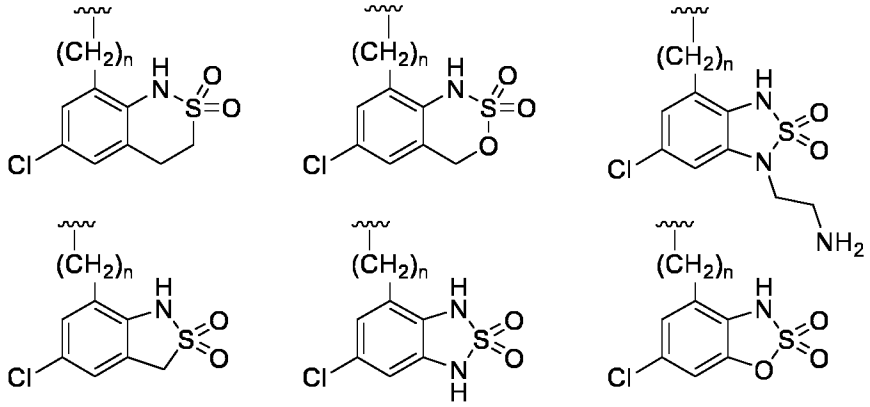


wherein R^9 is selected from -H or -C_1-C_6-alkyl and wherein s is 0 to 3.

35. The compound according to any one of claims 23-34, or a pharmaceutically acceptable salt thereof, wherein one of X is SO_2.

36. The compound according to any one of claims 23-34, or a pharmaceutically acceptable salt thereof, wherein at least one of X is NH.

37. The compound according to any one of claims 23-36, or a pharmaceutically acceptable salt thereof, wherein formula (IVa) of R^2 is selected from any one of the moieties



wherein n is 0 or 1.

38. A compound, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from Table 1, Table 2, and Table 3.
39. A pharmaceutical composition, comparing a compound of any one of claims 1 to 38, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.
40. A compound according to any one of claims 1 to 38, or a pharmaceutically acceptable salt thereof, for use as a medicament.
41. A compound according to any one of claims 1 to 38, or a pharmaceutically acceptable salt thereof,

    for use in the treatment of a disease, wherein the disease is cancer, in particular the cancer is selected from breast cancer, renal cancer, acute myeloid leukemia, hepatocellular carcinoma, and lung adenocarcinoma.
42. A method of treating cancer in a subject in need thereof, comprising administering to the subject a compound of any one of claims 1 to 38, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 39.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2023/082044

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D473/34 C07D473/40 C07D487/04 C07D519/00 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	WO 2014/083327 A1 (MD PHARMA AB) 5 June 2014 (2014-06-05) pages 33, 34, 46, 47; claims	23-25, 39,40

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 January 2024	15/02/2024

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Helps, Ian

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Form PCT/ISA/210 (second sheet) (April 2005)

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