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(71) Applicant: **NUPHASE THERAPEUTICS (HANGZHOU) LIMITED., CO.** [CN/CN]; Room 1219, 21 Building, Hexiang Tech Center, Qiantang District, Hangzhou, Zhejiang 310020 (CN).

(72) Inventors: **LIU, Kun Chin**; Room 902, Building 2, Shengda Tiandi Yuanchuanggu, Lane 88, Shengrong Road, Pudong New Area, Shanghai 201203 (CN). **QUAN, Weiguo**; Room 902, Building 2, Shengda Tiandi Yuanchuanggu, Lane 88, Shengrong Road, Pudong New Area, Shanghai 201203 (CN). **JIANG, Xiangqing**; Room 902, Building 2, Shengda Tiandi Yuanchuanggu, Lane 88, Shengrong Road, Pudong New Area, Shanghai 201203 (CN).

(74) Agent: **XU & PARTNERS, LLC.**; Room No.106, Building No.1, Universal High-Tech Plaza., 958 Zhen Bei Road, Putuo District, Shanghai 200333 (CN).

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(54) Title: NOVEL COMPOUNDS, COMPOSITIONS COMPRISING THE SAME AND USES THEREOF

(57) Abstract: Provided are novel compounds, compositions comprising the same and uses thereof. In particular, it provides bicyclic compounds and analogues and derivatives thereof, the use thereof for inhibiting Werner Syndrome RecQ DNA helicase (WRN) and methods of treating disease using said compounds, in particular the use in treating cancer.

NOVEL COMPOUNDS, COMPOSITIONS COMPRISING THE SAME AND USES THEREOF

Field of Invention

The invention relates to the field of medicinal chemistry, and in particular, it provides bicyclic compounds and analogues and derivatives thereof, the use thereof for inhibiting Werner Syndrome RecQ DNA helicase (WRN) and methods of treating disease using said compounds, in particular the use in treating cancer, and in particular the treatment of cancer characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), including colorectal, gastric and endometrial cancer. The invention also provides the use of said compounds as research chemicals, intermediate compounds, combinations, processes and formulations.

Background of the Invention

Werner Syndrome helicase (WRN) is a member of the RecQ DNA helicase subfamily (Croteau et al., 2014). RecQ helicases and WRN are involved in multiple DNA processing steps, including DNA replication, double-strand break repair, transcription, and telomere maintenance, and are therefore considered as "genome guardians" (Chu and Hickson, 2009). Defects in DNA mismatch repair (MMR) promote microsatellite instability (MSI), characterized by frequent insertion and/or deletion mutations in repetitive nucleotide sequences. MSI-induced genomic instability causes the occurrence and development of various cancers, including colorectal cancer, gastric cancer, endometrial cancer, and ovarian cancer (Kim et al., 2013; Kunitomi, H et al., 2017). CRISPR-CAS9-mediated large-scale silencing revealed that RecQ DNA helicase WRN is selectively essential in MSI models but not necessary in microsatellite-stable models. Knocking out WRN in MSI models induces DNA double-strand breaks and selectively promotes cell apoptosis and cell cycle arrest (Chan et al., 2019). These findings suggest that WRN is a synthetic lethal drug target for specific targeting of MSI-related cancers.

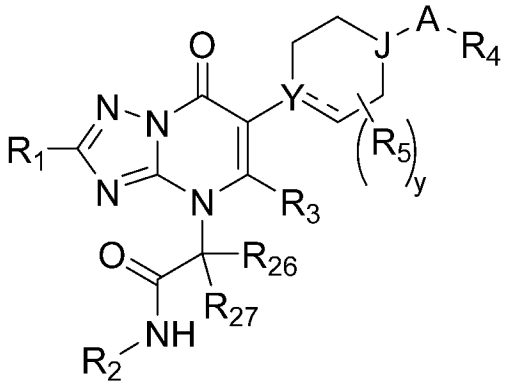
Summary of the description

There remains a need for new treatments and therapies for the treatment of cancer, and in particular cancers characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), including colorectal, gastric or endometrial cancer. The invention provides compounds, pharmaceutically acceptable salts thereof, pharmaceutical compositions thereof and combinations thereof, said compounds being inhibitors of Werner Syndrome RecQ DNA Helicase (WRN). The invention further provides methods of treating, preventing, or ameliorating a disease or condition, comprising administering to a subject in need thereof an effective amount of a WRN inhibitor. The invention also provides compounds, pharmaceutically acceptable salts thereof, pharmaceutical compositions thereof and combinations thereof, said compounds being useful for the treatment of cancer, in particular cancers characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). Also provided are compounds that bind to, and/or inhibit WRN, and are therefore useful as research chemicals, e.g. as a chemical probe, and as tool compounds. Various embodiments of the invention are described herein.

The present invention relates to a nitrogenous compound, pharmaceutical composition and use thereof, the compound of the present disclosure shows a good inhibitory effect on Werner

Syndrome helicase (WRN), which can be used as Werner Syndrome helicase (WRN) inhibitor to treat cancers.

In the first aspect, the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt, a hydrate, a solvate, a prodrug, a stereoisomer, a deuterated product or a tautomer thereof:



(I)

wherein

A is a linker selected from -C(O)-, -S(O)-, -S(O)$_2$-, and  ;

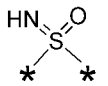
Y is N, C, or CH;

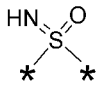
y is 0, 1, 2, 3 or 4;

Y^{---} means Y is linked via a single bond to the adjacent carbon atom when Y is CH, or Y is linked via a double bond to the adjacent atom when Y is C, and when Y^{---} is a single bond, Y is carbon unsubstituted or substituted by OH or F;

when Y is N, Y^{---} is a single bond;

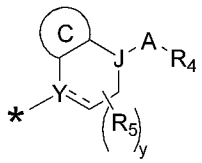
J is N or CH;

when J is N, and A is a linker selected from -C(O)-, -S(O)-, -S(O)$_2$-, and  ;

when J is CH, and A is a linker selected from-S(O)-, -S(O)$_2$-, and  ;

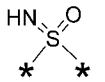
R_5 is independently selected from:

- H,
- -(C_1-C_4)alkyl,
- -(C_3-C_5)cycloalkyl,
- or two R_5 substituents on the same ring carbon atom may join, together with the carbon atom to which they are attached, to form a (C_3-C_4)cycloalkyl spiro ring or a 3 or 4-membered heterocyclyl spiro ring, wherein said heterocyclyl spiro ring contains ring carbon ring atoms and one ring heteroatom selected from O, N and S,
- when J is N, a R_5 substituent form ring C:

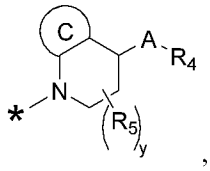


wherein ring C is a fused (C_3-C_6)cycloalkyl ring, a fused (C_3-C_6)heterocyclyl ring or a fused phenyl ring, wherein said fused (C_3-C_6)heterocyclyl ring contains ring carbon atoms and one ring heteroatom selected from O, N and S,

- when J is CH, Y is N, ⩬ is a single bond, and



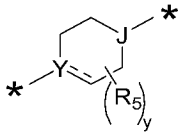
A is a linker selected from -S(O)-, -S(O)$_2$-, and , a R_5 substituent form ring C:



,

- when J is N, two R_5 substituents may join to form a (C_1-C_3)alkylene bridge or a heteroalkylene bridge, wherein said heteroalkylene bridge is one heteroatom selected from N and O, or is -CH_2-O-CH_2-;

and wherein one or more H atoms on the ring:



may be replaced by deuterium;

R_1 is:

(C_3-C_4)cycloalkyl

- (C_3-C_4)cycloalkyl is unsubstituted or substituted by 1 or 2 R_{33}, wherein R_{33} is halo, and wherein said (C_3-C_4)cycloalkyl or halo-substituted (C_3-C_4)cycloalkyl is substituted by 0, 1 or 2 R_{15} substituents,
- (C_3-C_4)cycloalkyl has 2 substituents at the same ring carbon atom which join to form a (C_3-C_6)cycloalkyl spiro ring, or 3, 4, 5, or 6 membered heterocyclyl spiro ring contains ring carbon atoms and 1 or 2 ring heteroatom selected from O, N and S, and wherein said cycloalkyl or heterocyclyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23},
- (C_3-C_4)cycloalkyl is fused to (C_3-C_6)cycloalkyl ring, or 3, 4, 5, or 6 membered heterocyclyl ring contains ring carbon atoms and 1-4 ring heteroatom selected from O, N and S, and wherein said cycloalkyl or heterocyclyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23},
- For C_4 cycloalkyl, it can be bridged by 1 or 2 carbon atoms, and wherein said bridged C_4 cycloalkyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23};

or cycloalkenyl

- a partially unsaturated monocyclic ring containing 5 or 6 ring carbon atoms containing 0, 1 or 2 R_{33}, wherein R_{33} is halo, and the cycloalkenyl
  - ✧ contains one =CF_2 substituent and 0, 1 or 2 R_{15} substituents,
  - ✧ contains one substituent selected from =CCl_2, -S(O)C_{1-4}alkyl, -S(O)$_2$(C_{1-4}alkyl), and CN, and contains 0, 1 or 2 R_{15} substituents which is not =CCl_2, -S(O)C_{1-4}alkyl, -S(O)$_2$(C_{1-4}alkyl), or CN,

- ✧ has 2 substituents at the same ring carbon atom which join to form a (C_3-C_6) cycloalkyl spiro ring, or 3, 4, 5, or 6 membered heterocyclyl spiro ring containing ring carbon atoms and 1 or 2 ring heteroatom selected from O, N and S, and wherein said cycloalkyl or heterocyclyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23},
- ✧ is fused to (C_3-C_6)cycloalkyl ring, or 3, 4, 5, or 6 membered heterocyclyl ring containing ring carbon atoms and 1-4 ring heteroatom selected from O, N and S, and wherein said cycloalkyl or heterocyclyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23},
- ✧ is bridged, and said bridge contains 1 or 2 carbon atoms, and substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23};

- a partially unsaturated monocyclic ring containing 7 ring carbon atoms is substituted by 0, 1 or 2 R_{15} substituents;
  - ✧ contains 0 or 1 $=CF_2$ substituent,
  - ✧ has 2 substitutents at the same ring carbon atom which join to form a (C_3-C_6)cycloalkyl spiro ring, or 3, 4, 5, or 6 membered heterocyclyl spiro ring contains ring carbon atoms and 1 or 2 ring heteroatoms selected from O, N and S, and wherein said cycloalkyl or heterocyclyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23},
  - ✧ is fused to (C_3-C_6)cycloalkyl ring, or 3, 4, 5, or 6 membered heterocyclyl ring contains ring carbon atoms and 1-4 ring heteroatoms selected from O, N and S, and wherein said cycloalkyl or heterocyclyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23};

or heterocyclyl

- heterocyclyl is a 4 or 7 membered fully saturated or partially unsaturated group comprising ring carbon atoms and 1 or 2 ring heteroatoms independently selected from N, O and S, wherein said heterocyclyl is unsubstituted or substituted by 1, 2, 3 or 4, preferably 1 or 2, R_{33}, wherein R_{33} is halo, wherein said heterocyclyl or halo-substituted heterocyclyl
  - ✧ contains 0, 1 or 2 R_{15} substituents and 0 or 1 $=CF_2$ substituent,
  - ✧ contains one substituent selected from CN, $-S(O)C_{1-4}$alkyl, and $-S(O)_2C_{1-4}$ alkyl, and contains 0, 1 or 2 substituents selected from halogen, C_{1-4}alkyl, C_{1-4} haloalkyl and C_{3-4} cycloalkyl,
  - ✧ has 2 substitutents at the same ring carbon atom which join to form a (C_3-C_6)cycloalkyl spiro ring, or 3, 4, 5, or 6 membered heterocyclyl spiro ring contains ring carbon atoms and 1 or 2 ring heteroatoms selected from O, N and S, and wherein said cycloalkyl or heterocyclyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23},
  - ✧ is fused to (C_3-C_6)cycloalkyl ring, or 3, 4, 5, or 6 membered heterocyclyl ring contains ring carbon atoms and 1-4 ring heteroatoms selected from O, N and S, and wherein said cycloalkyl or heterocyclyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23};
  - ✧ is fused to phenyl, wherein said phenyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23};
- heterocyclyl is a 5 or 6 membered fully saturated or partially unsaturated group

comprising ring carbon atoms and 1 or 2 ring heteroatoms independently selected from N, O and S, wherein said heterocyclyl is unsubstituted or substituted by 1, 2, 3 or 4, preferably 1 or 2 R_{33}, wherein R_{33} is halo, wherein said heterocyclyl or halo-substituted heterocyclyl

- ✧ contains one $=CF_2$ substituent and 0, 1 or 2 R_{15} substituents,
- ✧ contains one substituent selected from $=CCl_2$, CN, and $-S(O)_2C_{1-4}$ alkyl and contains 0, 1 or 2 R_{15} substituents which is not $=CCl_2$, CN, or $-S(O)_2C_{1-4}$ alkyl,
- ✧ has 2 substituents at the same ring carbon atom which join to form a (C_4-C_7)cycloalkyl spiro ring, or 4, 5, 6 or 7 membered heterocyclyl spiro ring containing ring carbon atoms and 1 or 2 ring heteroatoms selected from O, N and S, and wherein said cycloalkyl or heterocyclyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23},
- ✧ is fused to (C_4-C_6)cycloalkyl ring, or 4, 5, or 6 membered heterocyclyl ring containing ring carbon atoms and 1-3 ring heteroatoms selected from N and S, or 5-6 membered heteroaryl ring containing ring carbon atoms and 1-3 ring heteroatoms selected from N and S, or 1 ring O atom and 1 or 2 ring heteroatoms selected from N and S; and wherein said cycloalkyl, heterocyclyl or heteroaryl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23};
- ✧ is fused to phenyl, wherein said phenyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23};

or heteroaryl, wherein said heteroaryl is a 5 or 6 membered fully unsaturated monocyclic group comprising ring carbon atoms and 1, 2, 3 or 4 ring heteroatoms independently selected from N, O and S, preferably 1 or 2 ring heteratoms, wherein the total number of ring S atoms does not exceed 1, and the total number of ring O atoms does not exceed 1, the heteroaryl is substituted by one or more substituents selected from CN, $-S(O)_2C_{1-4}$ alkyl, $-S(O)C_{1-4}$alkyl, $R_{25}(R_{24})N-$ and C_{1-4}alkoxy and contains 0, 1 or 2 R_{15} substituents which is not CN,or $-S(O)_2C_{1-4}$ alkyl, $-S(O)C_{1-4}$alkyl, $R_{25}(R_{24})N-$ or C_{1-4}alkoxy;

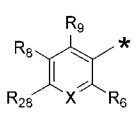
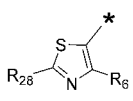
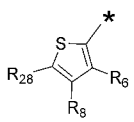
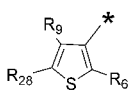
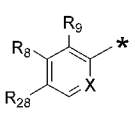
or wherein said heteroaryl is a 5 or 6 membered fully unsaturated monocyclic group comprising ring carbon atoms and 1, 2, 3 or 4 ring heteroatoms independently selected from N, O and S, preferably 1 or 2 ring heteratoms, wherein the total number of ring S atoms does not exceed 1, and the total number of ring O atoms does not exceed 1; said heteroaryl contains 0, 1 or 2 R_{15} substituents and is fused to 4, 5 or 6 membered heterocyclyl or 5-6 membered heteroaryl, wherein the heterocyclyl ring contains ring carbon atoms and 1-4 ring heteroatom selected from N, O and S and the heteroaryl ring contains ring carbon atoms and 1, 2, 3 or 4 ring heteroatoms independently selected from N, O and S, and wherein the heterocyclyl and heteroaryl are substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23};

or phenyl, wherein said phenyl is unsubstituted or substituted by 1, 2, 3 or 4, preferably 1 or 2, R_{33}, wherein R_{33} is halo, and wherein said phenyl or halo-substituted phenyl contains 1 or 2 substituents selected from CN, $-S(O)_2C_{1-4}$alkyl, $-S(O)C_{1-4}$alkyl, halogenated $-S(O)C_{1-4}$alkyl, halogenated $-S(O)_2C_{1-4}$alkyl, $-S(O)C_{3-6}$cycloalkyl and $-PO(C_{1-4}alkyl)_2$,
or wherein said phenyl is unsubstituted or substituted by 1, 2, 3 or 4 R_{15}, and is fused to 4, 5 or 6 membered monocyclic ring or 6, 7, 8, 9 or 10 membered di-cyclic ring, wherein said 4, 5 or 6

membered monocyclic ring or 6, 7, 8, 9 or 10 membered di-cyclic ring contains ring carbon atoms and 0-3 ring heteroatoms selected from N, O and S and is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23};
wherein, the 4, 5 or 6 membered ring or 6, 7, 8, 9 or 10 membered di-cyclic ring is saturated, partially saturated or unsaturated heterocycle or carbocycle,
each R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23} is independently selected from:

- halo,
- CN,
- $-S(O)_2C_{1-4}$alkyl, unsubstituted or substituted by 1,2 or 3 halo,
- $-PO(C_{1-4}$ alkyl$)_2$,
- (C_1-C_4)alkyl-O- unsubstituted or substituted by 1,2 or 3 halo,
- (C_1-C_4)alkyl unsubstituted or substituted by deuterium, OH, -O-(C_1-C_2)alkyl or 1,2 or 3 halo,
- (C_3-C_4)cycloalkyl unsubstituted or substituted by deuterium, OH, -O-(C_1-C_2)alkyl or 1,2 or 3 halo,
- $HOC(O)-(CH_2)_n-$,
- $H_3C-C(O)(CH_2)_n-$,
- (C_1-C_4)alkyl-O-$C(O)(CH_2)_n$,
- =O,
- azetidinyl or pyrrolidinyl, wherein said azetidinyl and pyrrolidinyl are linked to the rest of the molecule via the N atom, and are each unsubstituted or substituted by 1 or 2 F,
- $R_{25}(R_{24})N-$, wherein R_{24} is H or (C_1-C_4)alkyl unsubstituted or substituted by 1, 2 or 3 halo, R_{25} is H or (C_1-C_4)alkyl unsubstituted or substituted by 1,2 or 3 halo,
- $=CF_2$,
- $=CCl_2$,
- $-S(O)C_{1-4}$alkyl, unsubstituted or substituted by 1,2 or 3 halo,
- $-S(O)C_{3-6}$cycloalkyl,
- $-S(O)_2C_{3-6}$cycloalkyl,

wherein n is 0, 1 or 2,
R_{26} is CH_3, H, halogen or deuterium;
R_{27} is CH_3, H, halogen or deuterium;
or R_{26} and R_{27} join, together with the carbon atom to which they are attached, to form a cyclopropyl ring;
R_2 is the moiety selected from:






;

R_6 is selected from:

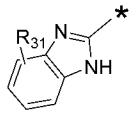
- H,
- halo,

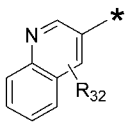
- $(C_1$-$C_4)$alkyl unsubstituted or substituted by 1, 2 or 3 halo,
- $(C_3$-$C_5)$cycloalkyl unsubstituted or substituted by 1, 2 or 3 halo,
- -O-$(C_1$-$C_4)$alkyl unsubstituted or substituted by 1, 2 or 3 halo,
- OH, and
- CN;

R_8 is selected from H, halo, and $(C_1$-$C_4)$alkyl unsubstituted or substituted by 1,2 or 3 halo;
R_9 is selected from H, O-CH_3, OH, CN, CH_3 and halo;
R_{28} is selected from:

- SF_5,
- Deuterium,
- H,
- -C(O)H,
- halo,
- $(C_1$-$C_4)$alkyl unsubstituted or substituted by 1, 2 or 3 halo or deuterium,
- $(C_2$-$C_4)$alkynyl,
- $(C_2$-$C_4)$alkenyl,
- $(C_3$-$C_5)$cycloalkyl unsubstituted or substituted by 1, 2 or 3 halo or deuterium,
- OCF_3;

X is selected from C-R_7 and N, wherein R_7 is H or halo, or R_7 can join, together with R_{28} or R_6, and the atoms to which they are attached, to form a fused $(C_4$-$C_6)$cycloalkyl ring, wherein said fused $(C_4$-$C_6)$cycloalkyl ring is unsubstituted or substituted by 1, 2 or 3 halo,
or
R_2 is selected from:

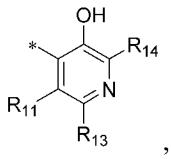


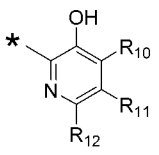
and


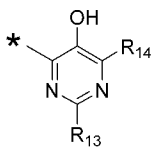
wherein
R_{31} is selected from H, halo and CH_3,
R_{32} is selected from H, halo and CH_3,
R_3 is:

- O-CH_3,
- $N(CH_3)_2$,
- S-CH_3,
- $(C_1$-$C_4)$alkyl unsubstituted or substituted by 1, 2 or 3 substituents independently selected from halo and OH;

R_4 is selected from:



,


and


wherein

R_{10}, R_{11}, R_{12}, R_{13} and R_{14} are each independently selected from:

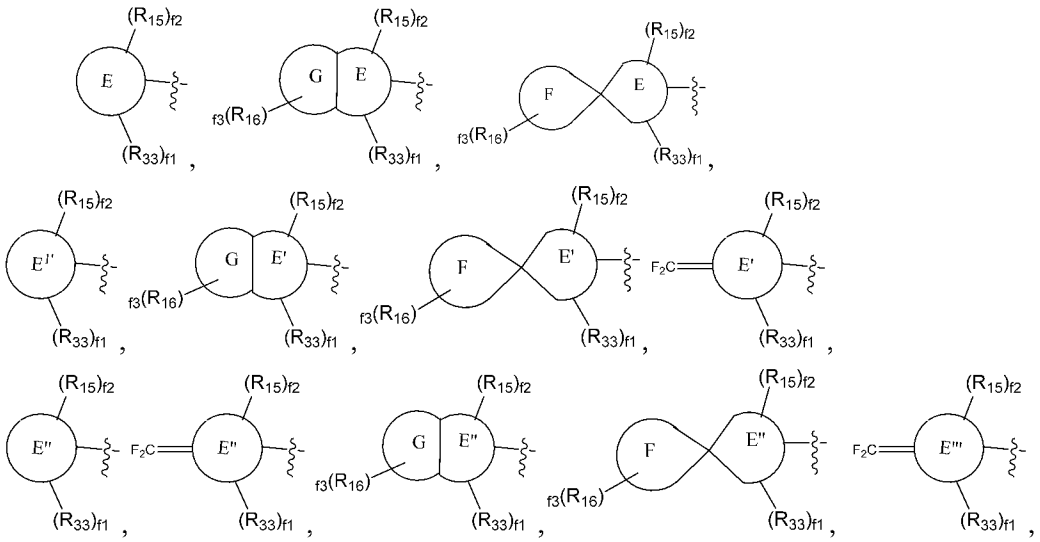
- H,
- Deuterium,
- halo,
- $(C_1$-$C_4)$alkyl unsubstituted or substituted by 1, 2 or 3 halo or deuterium substituents,
- $(C_1$-$C_2)$alkyl substituted by -O-(C_1-$C_2)$alkyl or OH,
- -S-$(C_1$-$C_3)$alkyl,
- -O-$(C_1$-$C_4)$alkyl unsubstituted or substituted by 1,2 or 3 halo or deuterium substituents,
- OH,
- $(C_3$-$C_5)$cycloalkyl, wherein said $(C_3$-$C_5)$Cycloalkyl is unsubstituted or substituted by 1 or 2 halo or deuterium,
- -O-$(C_3$-$C_5)$cycloalkyl,
- $-NR_{34}R_{35}$, wherein R_{34} and R_{35} are each independently selected from:
  - ✧ H,
  - ✧ Deuterium,
  - ✧ $(C_1$-$C_4)$alkyl, wherein said $(C_1$-$C_4)$alkyl is unsubstituted or substituted by OH or -O$(C_1$-$C_2)$alkyl,

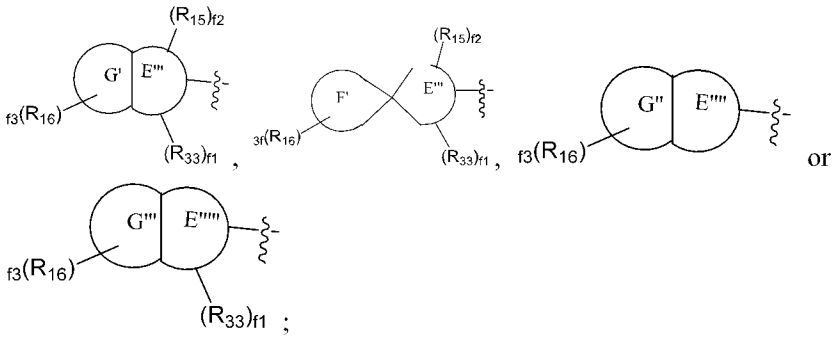
  or R_{34} and R_{35} can join, together with the atom to which they are attached, to form an azetidinyl, pyrrolidinyl or piperidinyl ring, wherein said azetidinyl, pyrrolidinyl and piperidinyl are unsubstituted or substituted with CH_3;
- CN,
- -$(C_2$-$C_4)$alkenyl,
- -$(C_2$-$C_4)$alkynyl,
- -C(O)H, and
- -C(O)$(C_1$-$C_4)$alkyl;

and

* indicates a point of attachment.

In another preferred embodiment, R_1 is





or

wherein, ring E is (C_3-C_4)cycloalkyl which contains 0, 1, or 2 R_{15} substituents;

or E is a substituted 5-6-membered cycloalkenyl, or a substituted 5-6-membered heterocyclyl, which is substituted by 1 or 2 substituents selected from $=CF_2$, CN, $-S(O)_2C_{1-4}$alkyl, and $=CCl_2$, and 0, 1, or 2 R_{15} substituents which are not $=CF_2$, CN, $-S(O)_2C_{1-4}$alkyl, or $=CCl_2$;

or E is a phenyl substituted by 1 or 2 substituents selected from CN, $-S(O)_2C_{1-4}$alkyl, $-S(O)C_{1-4}$alkyl, $-S(O)C_{3-6}$cycloalkyl, halogenated $-S(O)C_{1-4}$alkyl, halogenated $-S(O)_2C_{1-4}$alkyl and $-PO(C_{1-4}alkyl)_2$ and 0, 1, or 2 R_{15} substituents which are not CN, $-S(O)_2C_{1-4}$alkyl, $-S(O)C_{1-4}$alkyl, $-S(O)C_{3-6}$cycloalkyl, halogenated $-S(O)C_{1-4}$alkyl, halogenated $-S(O)_2C_{1-4}$alkyl or $-PO(C_{1-4}alkyl)_2$;

or E is a 5-6-membered heteroaryl substituted by 1 or 2 substituents selected from CN, $R_{25}(R_{24})N$- and $-OC_{1-4}$alkyl and 0, 1, or 2 R_{15} substituents which are not CN, $R_{25}(R_{24})N$- or $-OC_{1-4}$alkyl;

ring E' is independently selected from partially unsaturated monocyclic ring C5-C7 cycloalkenyl;

ring E$^{I'}$ is independently selected from partially unsaturated monocyclic ring C7 cycloalkenyl;

ring E'' is independently selected from 4 or 7 membered fully saturated or partially unsaturated heterocyclyl comprising ring carbon atoms and 1 or 2 ring heteroatoms independently selected from N, O and S;

ring E''' is independently selected from 5 or 6 membered fully saturated or partially unsaturated heterocyclyl;

ring E'''' is independently selected from 5-6 membered heteroaryl comprising ring carbon atoms and 1, 2, 3 or 4 ring heteroatoms independently selected from N, O and S, preferably 1 or 2 ring heteraoms, wherein the total number of ring S atoms does not exceed 1, and the total number of ring O atoms does not exceed 1;

ring E''''' is independently selected from phenyl;

ring F is independently selected from (C_3-C_6)cycloalkyl, or 3, 4, 5, or 6 membered heterocyclyl comprising ring carbon atoms and 1 or 2 ring heteroatom selected from O, N and S;

ring F' is independently selected from (C_4-C_5)cycloalkyl, or 4, 5, 6 or 7 membered heterocyclyl comprising ring carbon atoms and 1 or 2 ring heteroatoms selected from O, N and S;

ring G is independently selected from (C_3-C_6)cycloalkyl, or 3, 4, 5, or 6 membered heterocyclyl comprising ring carbon atoms and 1-4 ring heteroatom selected from O, N and S;

ring G' is independently selected from (C_4-C_6)cycloalkyl, or 4, 5, or 6 membered heterocyclyl comprising ring carbon atoms and 1-3 ring heteroatoms selected from N and S, or 5-6 membered heteroaryl comprising ring carbon atoms and 1-3 ring heteroatom selected from N and S, or 1 ring O atom and 1 or 2 ring heteroatoms selected from N and S;

ring G'' is independently selected from 4, 5 or 6 membered heterocyclyl or 5-6 membered heteroaryl, wherein the heterocyclyl ring contains ring carbon atoms and 1-4 ring heteroatoms selected from N, O and S and the heteroaryl ring contains ring carbon atoms and 1, 2, 3 or 4 ring

heteroatoms independently selected from N, O and S;

ring G''' is independently selected from 4, 5 or 6 membered ring contains ring carbon atoms and 0-3 ring heteroatoms selected from N, O and S; preferably G''' is independently selected from (C_4-C_6)cycloalkyl, 4, 5, or 6 membered heterocyclyl comprising ring carbon atoms and 1-3 ring heteroatom selected from N and S, or 1 ring O atom and 1 or 2 ring heteroatoms selected from N and S, or 5-6 membered heteroaryl comprising ring carbon atoms and 1-3 ring heteroatoms selected from N and S, or 1 ring O atom and 1 or 2 ring heteroatoms selected from N and S;

R_{33} is halo;

each R_{15} and R_{16} is independently selected from:

- halo,
- CN,
- -S(O)$_2$$C_{1-4}$alkyl, unsubstituted or substituted by 1,2 or 3 halo,
- -PO(C_{1-4} alkyl)$_2$,
- (C_1-C_4)alkyl-O- unsubstituted or substituted by 1,2 or 3 halo,
- (C_1-C_4)alkyl unsubstituted or substituted by deuterium, OH, -O-(C_1-C_2)alkyl or 1,2 or 3 halo,
- HOC(O)-(CH_2)$_n$-,
- H_3C-C(O)(CH_2)$_n$-,
- (C_1-C_4)alkyl-O-C(O)(CH_2)$_n$,
- =O,
- azetidinyl or pyrrolidinyl, wherein said azetidinyl and pyrrolidinyl are linked to the rest of the molecule via the N atom, and are each unsubstituted or substituted by 1 or 2 F,
- R_{25}(R_{24})N-, wherein R_{24} is H or (C_1-C_4)alkyl unsubstituted or substituted by 1, 2 or 3 halo, R_{25} is H or (C_1-C_4)alkyl unsubstituted or substituted by 1,2 or 3 halo,
- =CF_2,
- =CCl_2,
- -S(O)C_{1-4}alkyl, unsubstituted or substituted by 1,2 or 3 halo,
- -S(O)C_{3-6}cycloalkyl,
- -S(O)$_2$$C_{3-6}$cycloalkyl,

wherein n is 0, 1 or 2,

f1 is 0, 1 or 2,

f2 is 0, 1 or 2,

f3 is 0, 1 or 2.

In another preferred embodiment, R_1 is:

cycloalkenyl

- a partially unsaturated monocyclic ring containing 5 or 6 ring carbon atoms containing 0, 1 or 2 R_{33}, wherein R_{33} is halo, and the cycloalkenyl
  - ✧ contains one =CF_2 substituent and 0, 1 or 2 R_{15} substituents,
  - ✧ contains one substituent selected from =CCl_2, -S(O)$_2$(C_{1-4}alkyl), -S(O)C_{1-4}alkyl, and CN, and contains 0, 1 or 2 R_{15} substituents which is not =CCl_2, -S(O)$_2$(C_{1-4}alkyl), -S(O)C_{1-4}alkyl, or CN,

- ✧ has 2 substituents at the same ring carbon atom which join to form a (C_3-C_6) cycloalkyl spiro ring, or 3, 4, 5, or 6 membered heterocyclyl spiro ring containing ring carbon atoms and 1 or 2 ring heteroatom selected from O, N and S, and wherein said cycloalkyl or heterocyclyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23},
- ✧ is fused to (C_3-C_6)cycloalkyl ring, or 3, 4, 5, or 6 membered heterocyclyl ring contains ring carbon atoms and 1-4 ring heteroatom selected from O, N and S, and wherein said cycloalkyl or heterocyclyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23},
- ✧ is bridged, and said bridge contains 1 or 2 carbon atoms, and substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23};

- a partially unsaturated monocyclic ring containing 7 ring carbon atoms is substituted by 0, 1 or 2 R_{15} substituents;
  - ✧ contains 0 or 1 $=CF_2$ substituent,
  - ✧ has 2 substitutents at the same ring carbon atom which join to form a (C_3-C_6)cycloalkyl spiro ring, or 3, 4, 5, or 6 membered heterocyclyl spiro ring contains ring carbon atoms and 1 or 2 ring heteroatoms selected from O, N and S, and wherein said cycloalkyl or heterocyclyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23},
  - ✧ is fused to (C_3-C_6)cycloalkyl ring, or 3, 4, 5, or 6 membered heterocyclyl ring contains ring carbon atoms and 1-4 ring heteroatoms selected from O, N and S, and wherein said cycloalkyl or heterocyclyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23};

or heterocyclyl

- heterocyclyl is a 4 or 7 membered fully saturated or partially unsaturated group comprising ring carbon atoms and 1 or 2 ring heteroatoms independently selected from N, O and S, wherein said heterocyclyl is unsubstituted or substituted by 1, 2, 3 or 4, preferably 1 or 2, R_{33}, wherein R_{33} is halo, wherein said heterocyclyl or halo-substituted heterocyclyl
  - ✧ contains 0, 1 or 2 R_{15} substituents and 0 or 1 $=CF_2$ substituent,
  - ✧ contains one substituent selected from CN, $-S(O)C_{1-4}$alkyl, and $-S(O)_2C_{1-4}$ alkyl, and contains 0, 1 or 2 substituents selected from halogen, C_{1-4}alkyl, C_{1-4} haloalkyl and C_{3-4} cycloalkyl,
  - ✧ has 2 substitutents at the same ring carbon atom which join to form a (C_3-C_6)cycloalkyl spiro ring, or 3, 4, 5, or 6 membered heterocyclyl spiro ring contains ring carbon atoms and 1 or 2 ring heteroatoms selected from O, N and S, and wherein said cycloalkyl or heterocyclyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23},
  - ✧ is fused to (C_3-C_6)cycloalkyl ring, or 3, 4, 5, or 6 membered heterocyclyl ring contains ring carbon atoms and 1-4 ring heteroatoms selected from O, N and S, and wherein said cycloalkyl or heterocyclyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23};
  - ✧ is fused to phenyl, wherein said phenyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23};
- heterocyclyl is a 5 or 6 membered fully saturated or partially unsaturated group

comprising ring carbon atoms and 1 or 2 ring heteroatoms independently selected from N, O and S, wherein said heterocyclyl is unsubstituted or substituted by 1, 2, 3 or 4, preferably 1 or 2 R_{33}, wherein R_{33} is halo, wherein said heterocyclyl or halo-substituted heterocyclyl

- ✧ contains one $=CF_2$ substituent and 0, 1 or 2 R_{15} substituents,
- ✧ contains one substituent selected from $=CCl_2$, CN, and $-S(O)_2C_{1-4}$ alkyl, and contains 0, 1 or 2 R_{15} substituents which is not $=CCl_2$, CN, or $-S(O)_2C_{1-4}$ alkyl,
- ✧ has 2 substituents at the same ring carbon atom which join to form a (C_4-C_7)cycloalkyl spiro ring, or 4, 5, 6 or 7 membered heterocyclyl spiro ring containing ring carbon atoms and 1 or 2 ring heteroatoms selected from O, N and S, and wherein said cycloalkyl or heterocyclyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23},
- ✧ is fused to (C_4-C_6)cycloalkyl ring, 4, 5, or 6 membered heterocyclyl ring contains ring carbon atoms and 1-3 ring heteroatoms selected from N and S, or 5-6 membered heteroaryl ring containing ring carbon atoms and 1-3 ring heteroatoms selected from N and S, or 1 ring O atom and 1 or 2 ring heteroatoms selected from N and S; and wherein said cycloalkyl, heterocyclyl or heteroaryl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23};
- ✧ is fused to phenyl, wherein said phenyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23};

or heteroaryl, wherein said heteroaryl is a 5 or 6 membered fully unsaturated monocyclic group comprising ring carbon atoms and 1, 2, 3 or 4 ring heteroatoms independently selected from N, O and S, preferably 1 or 2 ring heteratoms, wherein the total number of ring S atoms does not exceed 1, and the total number of ring O atoms does not exceed 1, the heteroaryl is substituted by one or more substituents selected from CN, $-S(O)_2C_{1-4}$ alkyl, $-S(O)C_{1-4}$ alkyl, $R_{25}(R_{24})N-$ and C_{1-4}alkoxy and contains 0, 1 or 2 R_{15} substituents which is not CN,or $-S(O)_2C_{1-4}$ alkyl, $-S(O)_2C_{1-4}$ alkyl or $R_{25}(R_{24})N-$ or C_{1-4}alkoxy;

or wherein said heteroaryl is a 5 or 6 membered fully unsaturated monocyclic group comprising ring carbon atoms and 1, 2, 3 or 4 ring heteroatoms independently selected from N, O and S, preferably 1 or 2 ring heteratoms, wherein the total number of ring S atoms does not exceed 1, and the total number of ring O atoms does not exceed 1; said heteroaryl contains 0, 1 or 2 R_{15} substituents and is fused to 4, 5 or 6 membered heterocyclyl or 5-6 membered heteroaryl, wherein the heterocyclyl ring contains ring carbon atoms and 1-4 ring heteroatom selected from N, O and S and the heteroaryl ring contains ring carbon atoms and 1, 2, 3 or 4 ring heteroatoms independently selected from N, O and S, and wherein the heterocyclyl and heteroaryl are substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23};

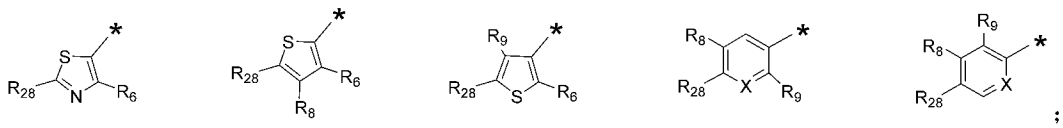
or phenyl, wherein said phenyl is unsubstituted or substituted by 1, 2, 3 or 4, preferably 1 or 2, R_{33}, wherein R_{33} is halo, and wherein said phenyl or halo-substituted phenyl contains 1 or 2 substituents selected from CN, $-S(O)_2C_{1-4}$alkyl, $-S(O)C_{1-4}$ alkyl, $-S(O)C_{3-6}$cycloalkyl and $-PO(C_{1-4}alkyl)_2$,
or wherein said phenyl is unsubstituted or substituted by 1, 2, 3 or 4 R_{15}, and is fused to 4, 5 or 6 membered monocyclic ring or 6, 7, 8, 9 or 10 membered di-cyclic ring, wherein said 4, 5 or 6

membered monocyclic ring or 6, 7, 8, 9 or 10 membered di-cyclic ring contains ring carbon atoms and 0-3 ring heteroatoms selected from N, O and S, and is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23};
wherein, the 4, 5 or 6 membered ring or 6, 7, 8, 9 or 10 membered di-cyclic ring is saturated, partially saturated or unsaturated heterocycle or carbocycle,
each R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23} is independently selected from:

- halo,
- CN,
- $-S(O)_2C_{1-4}$alkyl, unsubstituted or substituted by 1,2 or 3 halo,
- $-PO(C_{1-4}$ alkyl$)_2$,
- (C_1-C_4)alkyl-O- unsubstituted or substituted by 1,2 or 3 halo,
- (C_1-C_4)alkyl unsubstituted or substituted by deuterium, OH, -O-(C_1-C_2)alkyl or 1,2 or 3 halo,
- (C_3-C_4)cycloalkyl unsubstituted or substituted by deuterium, OH, -O-(C_1-C_2)alkyl or 1,2 or 3 halo,
- $HOC(O)-(CH_2)_n-$,
- $H_3C-C(O)(CH_2)_n-$,
- (C_1-C_4)alkyl-O-$C(O)(CH_2)_n$,
- =O,
- azetidinyl or pyrrolidinyl, wherein said azetidinyl and pyrrolidinyl are linked to the rest of the molecule via the N atom, and are each unsubstituted or substituted by 1 or 2 F,
- $R_{25}(R_{24})N-$, wherein R_{24} is H or (C_1-C_4)alkyl unsubstituted or substituted by 1, 2 or 3 halo, R_{25} is H or (C_1-C_4)alkyl unsubstituted or substituted by 1,2 or 3 halo,
- $=CF_2$,
- $=CCl_2$,
- $-S(O)C_{1-4}$alkyl, unsubstituted or substituted by 1,2 or 3 halo,
- $-S(O)C_{3-6}$cycloalkyl,
- $-S(O)_2C_{3-6}$cycloalkyl,

wherein n is 0, 1 or 2.

In another preferred embodiment, R_2 is selected from:



;

X is selected form: N, or CH;

R_6 is selected from:

- H,
- halo,
- (C_1-C_4)alkyl unsubstituted or substituted by 1, 2 or 3 halo,
- (C_3-C_5)cycloalkyl unsubstituted or substituted by 1, 2 or 3 halo,

- -O-(C_1-C_4)alkyl unsubstituted or substituted by 1, 2 or 3 halo,
- OH, and
- CN;

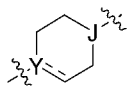
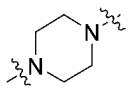
R_8 is selected from H, halo, and (C_1-C_4)alkyl unsubstituted or substituted by 1,2 or 3 halo;

R_9 is selected from H, O-CH_3, OH, CN, CH_3 and halo;

R_{28} is selected from:

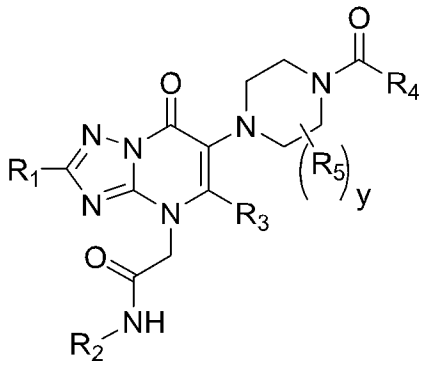
- SF_5,
- Deuterium,
- H,
- -C(O)H,
- halo,
- (C_1-C_4)alkyl unsubstituted or substituted by 1, 2 or 3 halo or deuterium,
- (C_2-C_4)alkynyl,
- (C_2-C_4)alkenyl,
- (C_3-C_5)cycloalkyl unsubstituted or substituted by 1, 2 or 3 halo or deuterium,
- OCF_3.

In another preferred embodiment, A is -C(O)-.

In another preferred embodiment,  is .

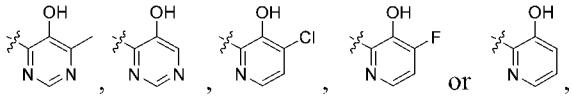
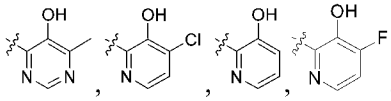
In another preferred embodiment, R_{33} is F.

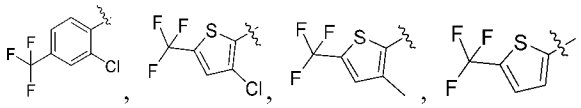
In another preferred embodiment, the compound has a structure of formula (II)

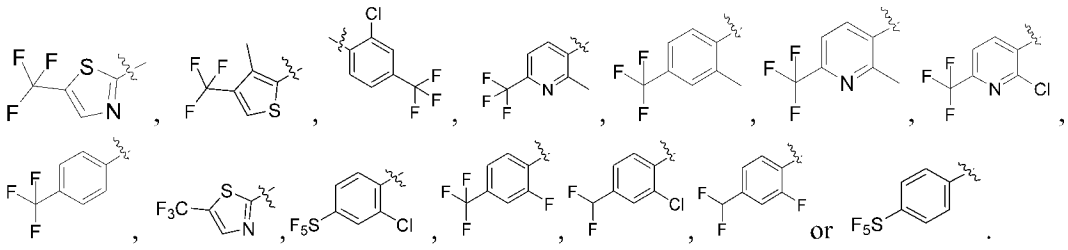


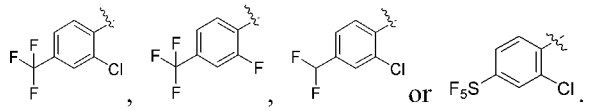
(II)

wherein, R_1, R_2, R_3, R_4, R_5 and y is defined as above.

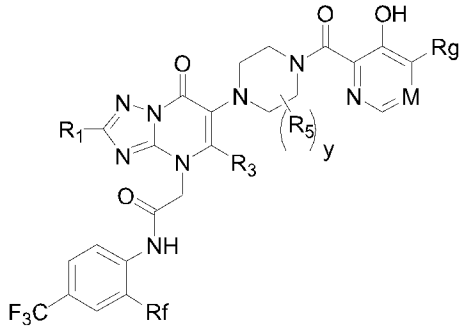
In another preferred embodiment, R_4 is , preferably R_4 is .

In another preferred embodiment, R_2 is ,



In another preferred embodiment, R_2 is .

In another preferred embodiment, the compound has a structure of formula (III)



(III)

Wherein

M is N or CH;

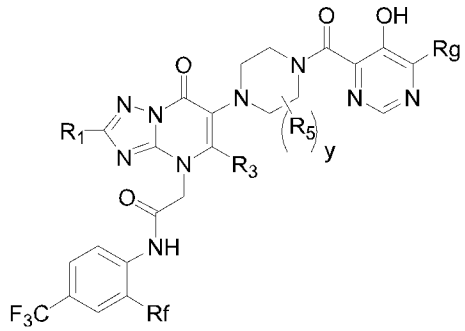
Rf is selected from H, halogen, C_{1-6} alkyl, and halogenated C_{1-6} alkyl; preferably Rf is halogen;

Rg is selected from H, halogen, C_{1-6} alkyl, and halogenated C_{1-6} alkyl;

and R_1, R_3, R_5 and y are defined as above.

In another preferred embodiment, R_3 is methyl, ethyl, or propyl.

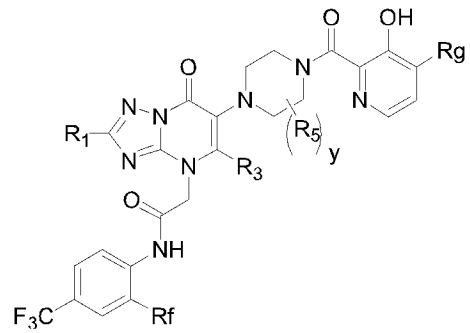
In another preferred embodiment, when M is N, the compound has a structure of formula (III-A):



(III-A)

wherein Rf, Rg, R_1, R_3, R_5 and y are defined as above.

In another preferred embodiment, when M is CH, the compound has a structure of formula (III-B):

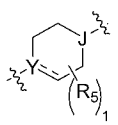
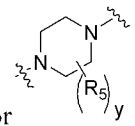
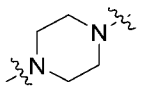


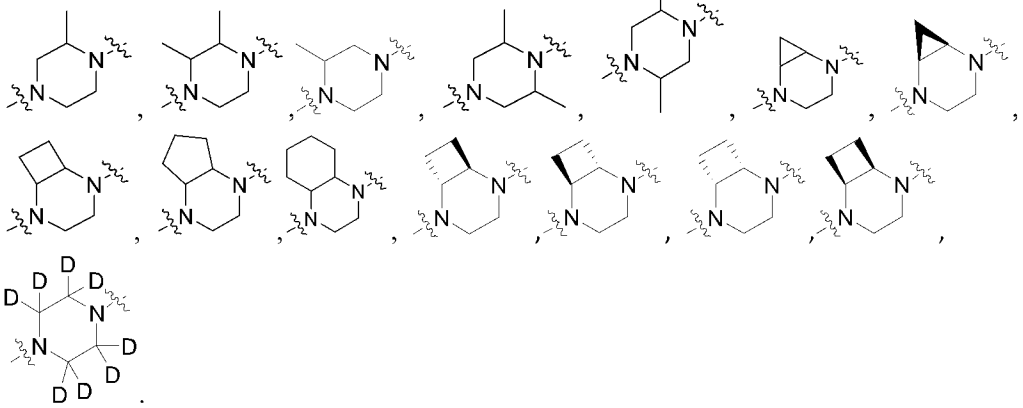
(III-B)

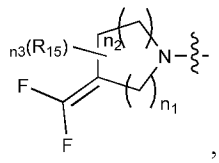
wherein Rf, Rg, R_1, R_3, R_5 and y are defined as above.

In another preferred embodiment, Rf is selected from Cl and F.

In another preferred embodiment, Rg is selected from H, methyl, Cl, F, CHF_2 and CF_3.

In another preferred embodiment,  or  is selected from: ,

.



In another preferred embodiment, R_1 is independently selected from , wherein n_1 and n_2 are each independently selected from 1, 2, or 3;

n_3 independently selected from 0, 1, or 2;

R_{15} is defined as above.

In another preferred embodiment, R_1 is independently selected from oxacycloheptenyl, wherein said oxacycloheptenyl is unsubstituted or substituted by 1, 2, 3 or 4, preferably 1 or 2, R_{33}, wherein R_{33} is halo, wherein said oxacycloheptenyl or halo-substituted oxacycloheptenyl

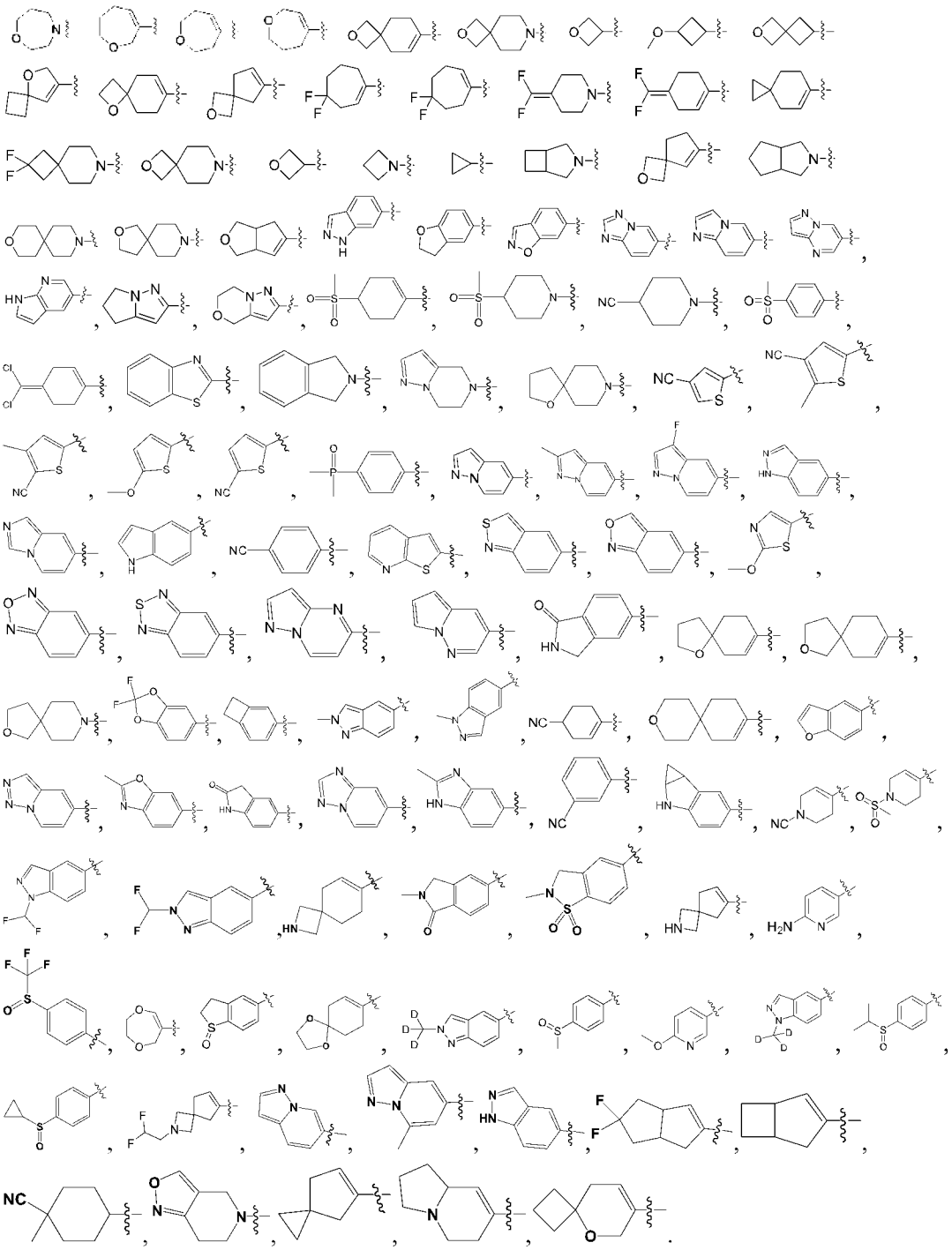
✧ contains 0, 1 or 2 R_{15} substituents and 0 or 1 $=CF_2$ substituent,

✧ has 2 substituents at the same ring carbon atom which join to form a (C_3-C_6)cycloalkyl spiro ring, or 3, 4, 5 ,6 membered heterocyclyl spiro ring containing ring carbon atoms and one ring heteroatom selected from O, N and S, and wherein said cycloalkyl or heterocyclyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23},

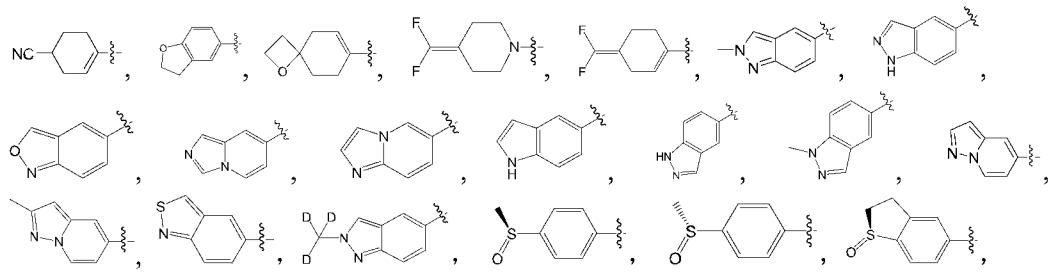
✧ is fused to (C_3-C_6)cycloalkyl ring, or 3, 4, 5 ,6 membered heterocyclyl ring containing ring carbon atoms and one ring heteroatom selected from O, N and S, and wherein said cycloalkyl or heterocyclyl is substituted by 0, 1 or 2 substituents independently selected from

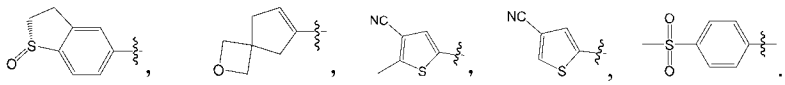
R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23}.

In another preferred embodiment, R_1 is independently selected from:

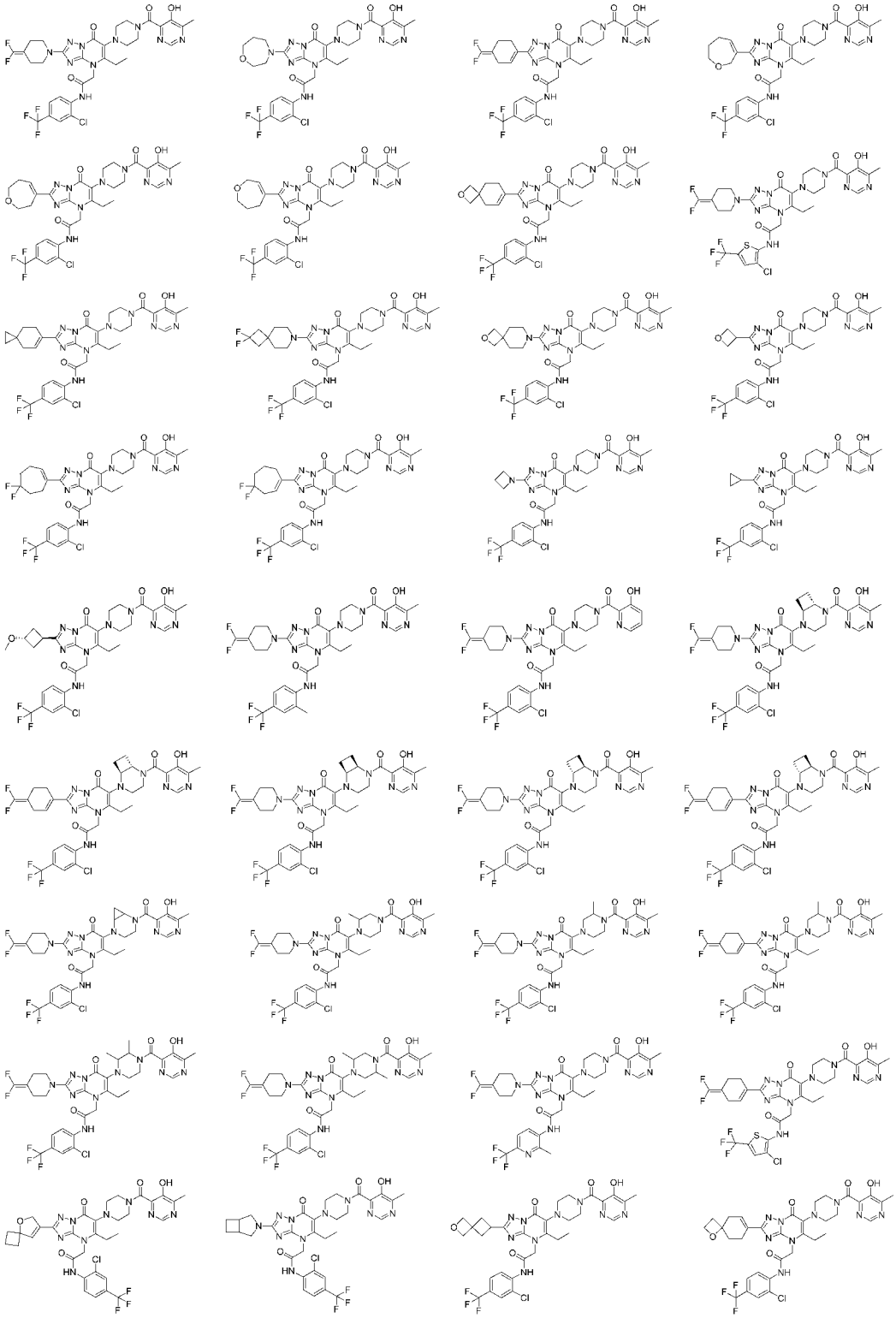


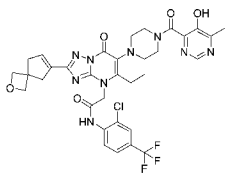
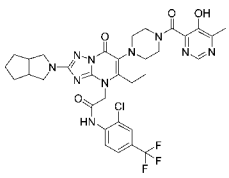
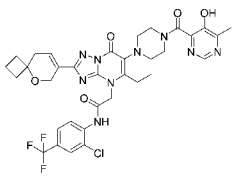
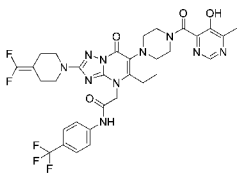
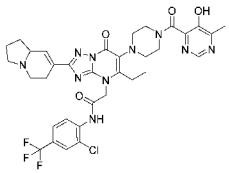
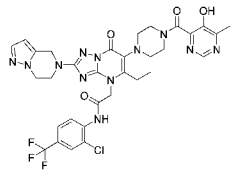
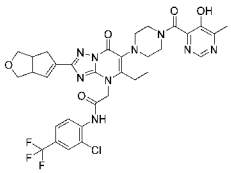
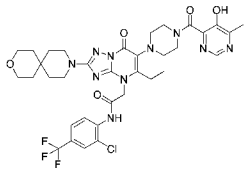
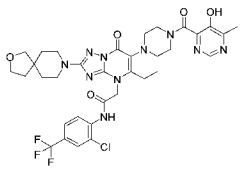
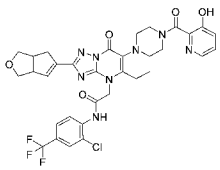
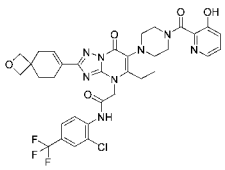
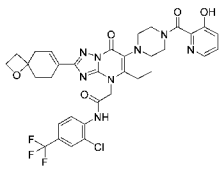
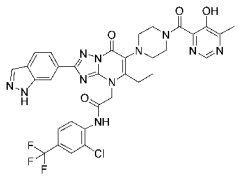
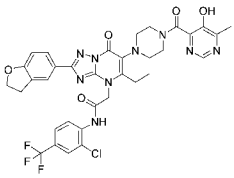
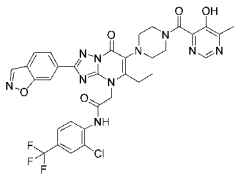
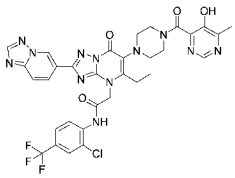
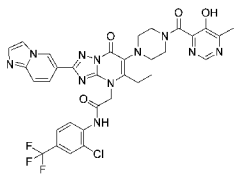
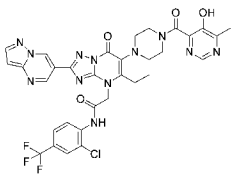
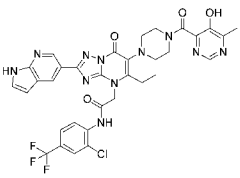
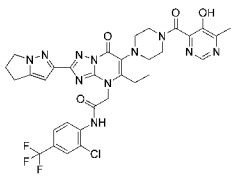
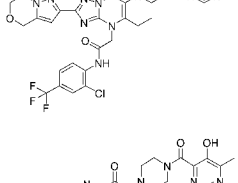
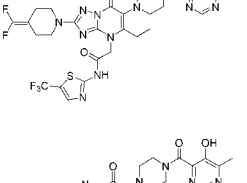
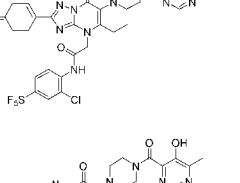
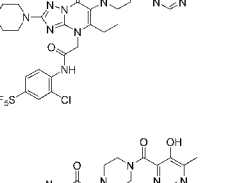
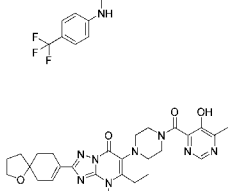
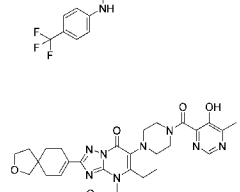
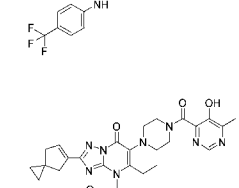
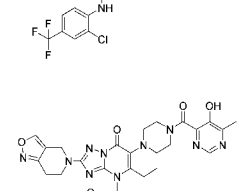
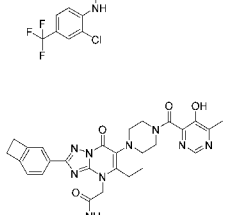
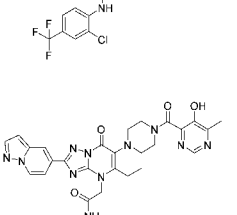
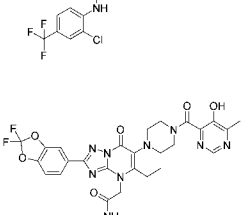
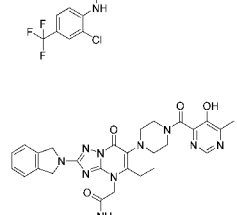
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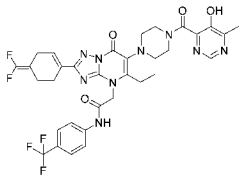
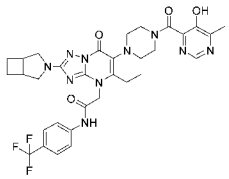
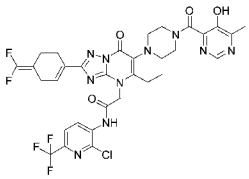
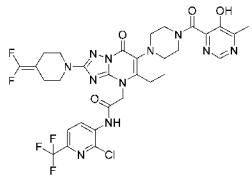
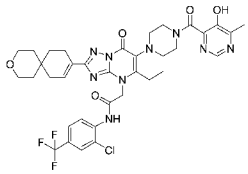
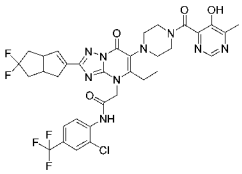
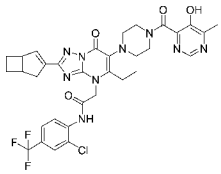
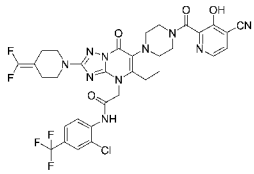
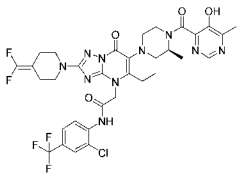
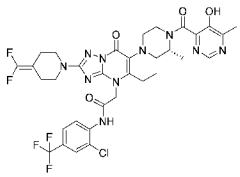
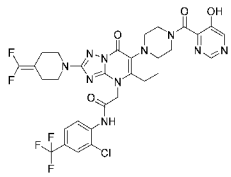
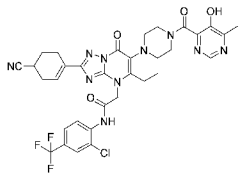
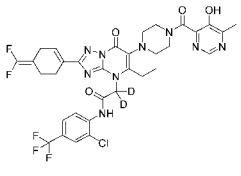
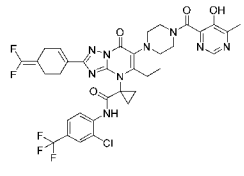
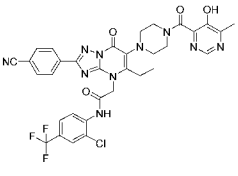
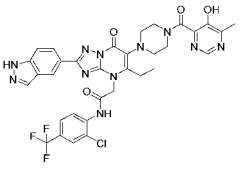
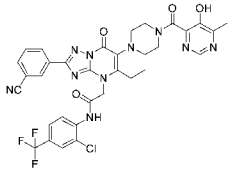
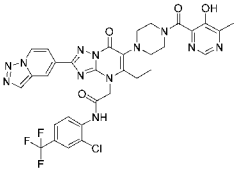
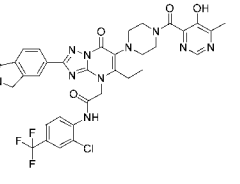
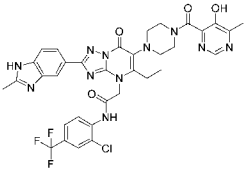
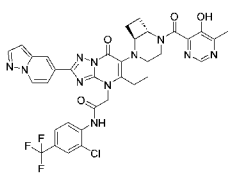
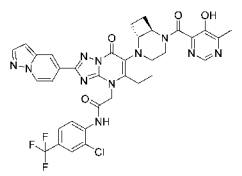
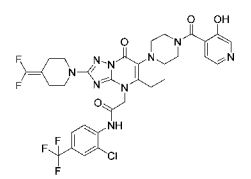
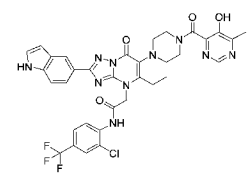
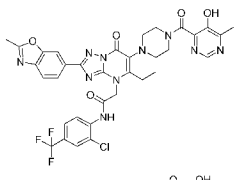
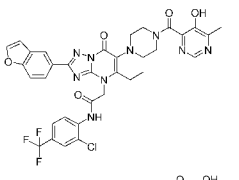
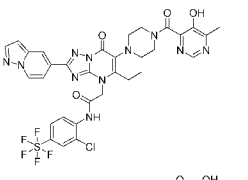
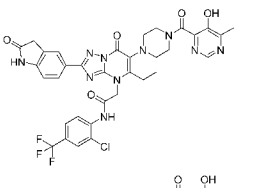
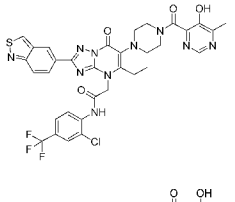
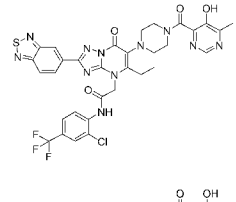
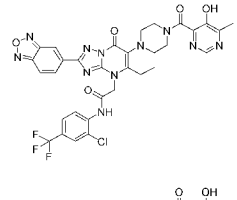
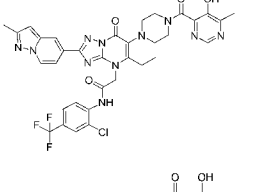
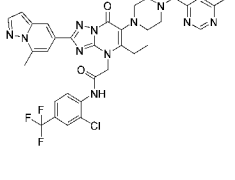
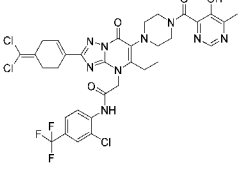
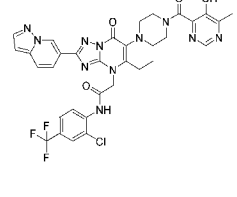
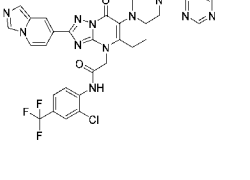




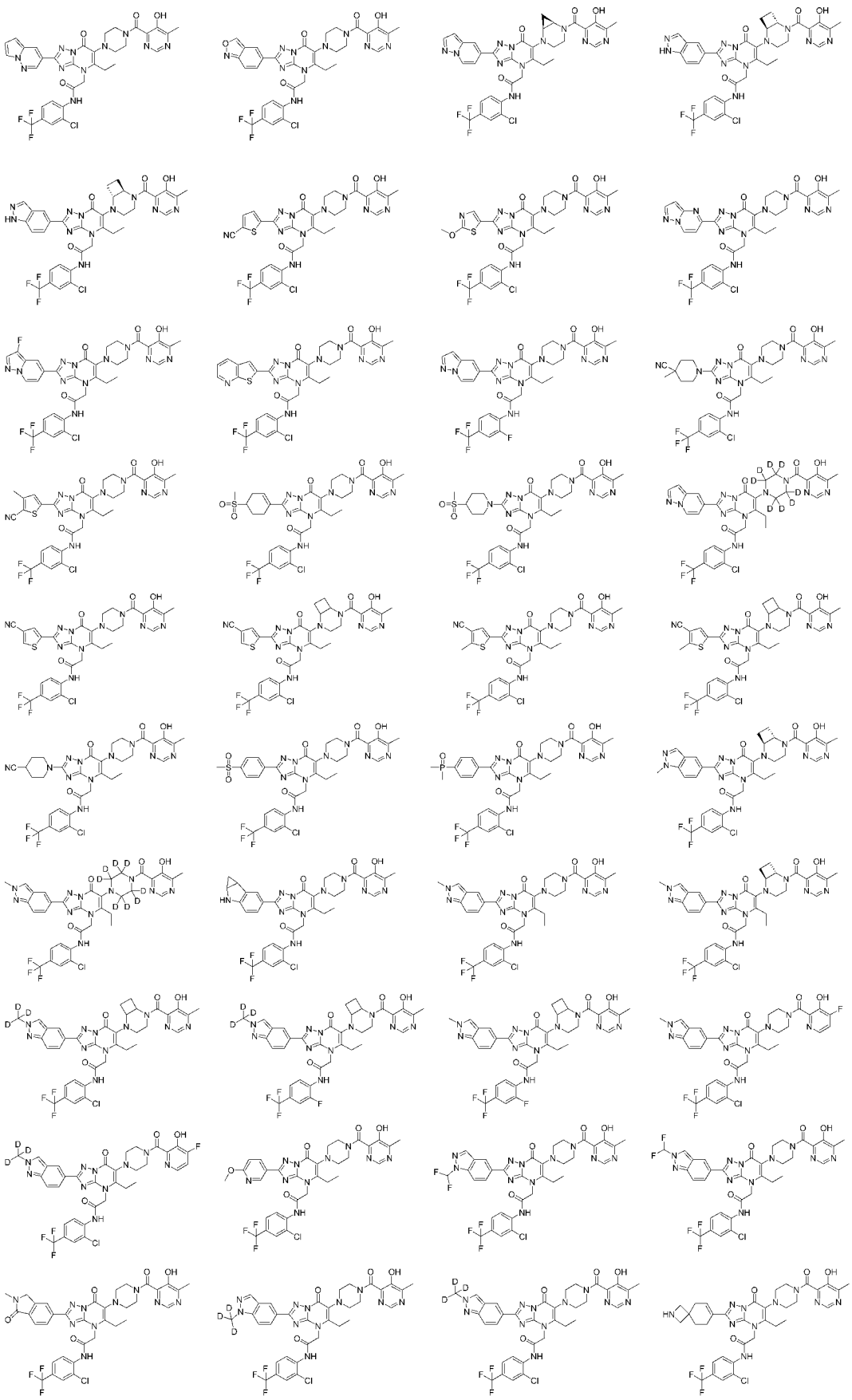
In another preferred embodiment, the compound is selected from:

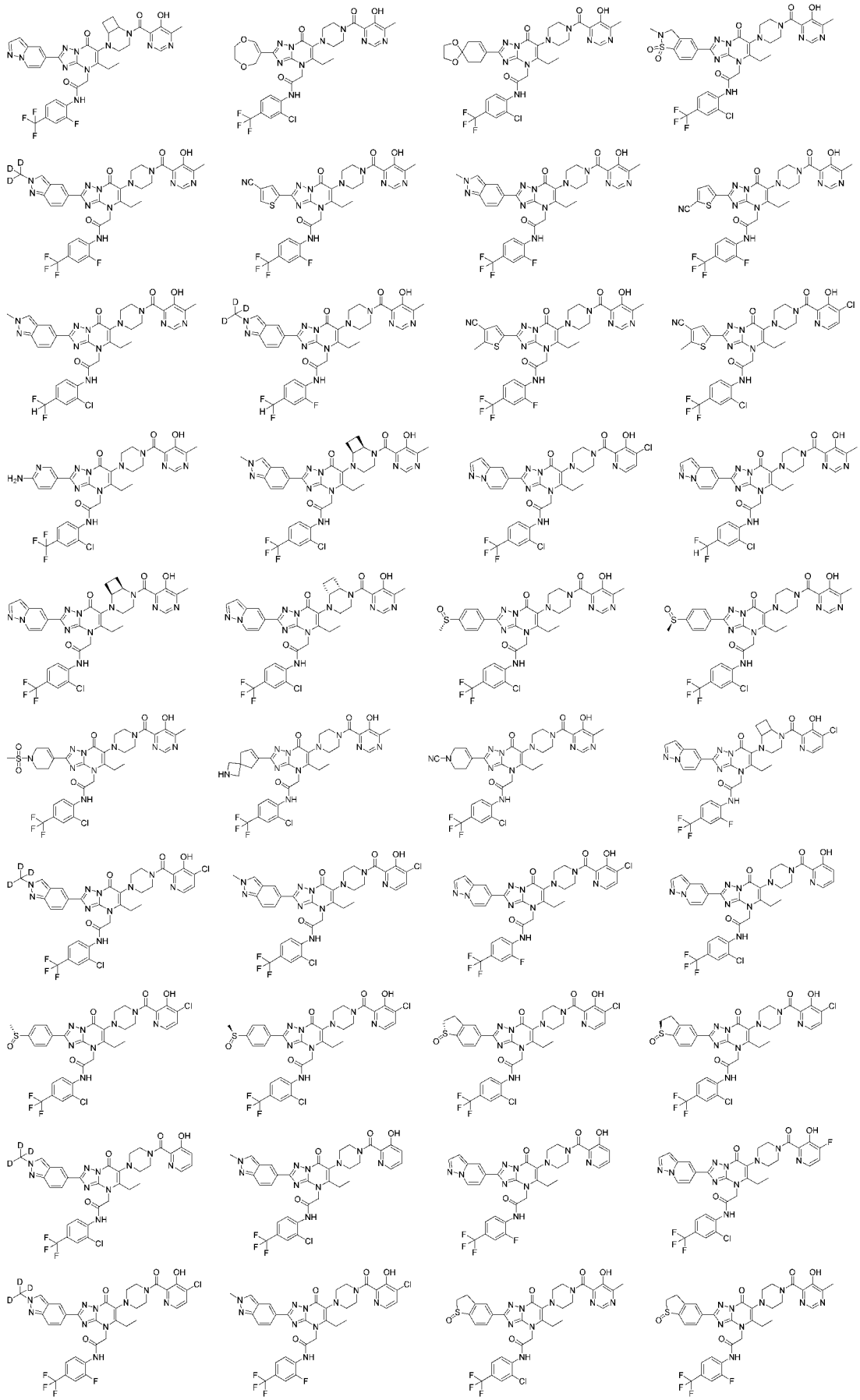


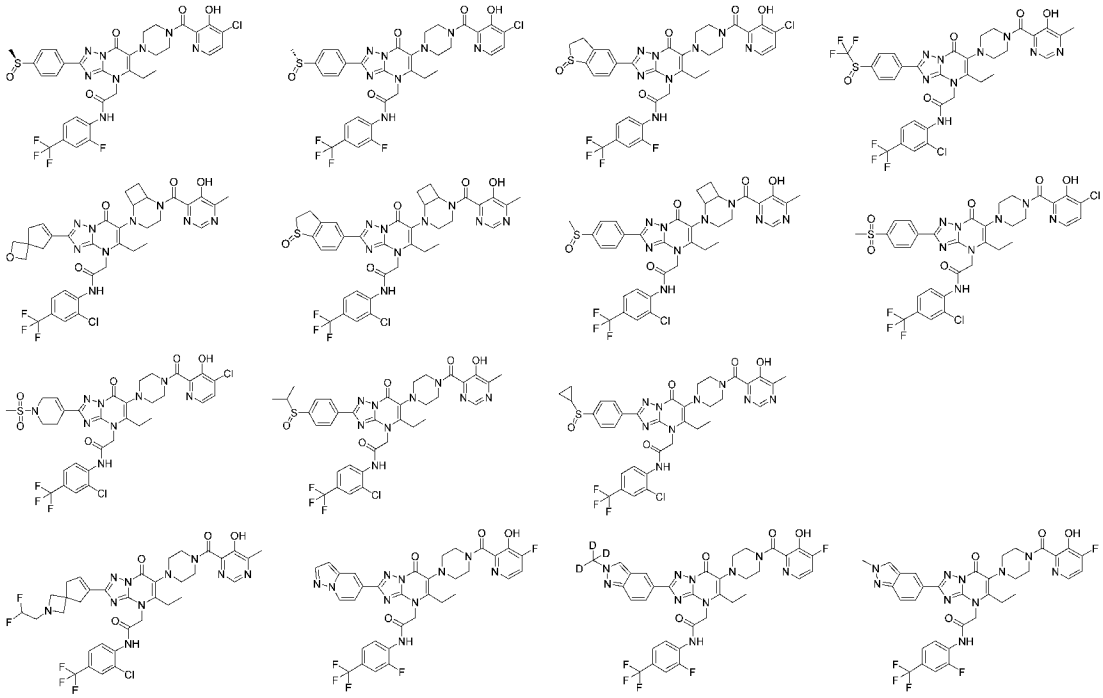









































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In another preferred embodiment, said heterocyclyl and carbocyclyl can be saturated or partially unsaturated, or unsaturated, substituted or unsubstituted, aromatic or non aromatic.

In some preferred embodiments, said heterocyclyl and carbocyclyl may be in fused, bridged or spiro-connected fashion.

In another preferred embodiment, each group is the corresponding group in the specific compound in the example.

In another preferred embodiment, the compound is the compound prepared in examples 1-328.

In another preferred embodiment, the compound is the compound of examples 1，7，45，46，51，52，77，78, 127，131，200，201，202，224，232，238，245，246，250，254，256，257，259，260，264，265，270，272, 273, 274, 276, 277, 278, 279a, 279b, 281, 282a, 282b, 283, 284, 285, 286a, 286b, 287a, 287b, 302, 304, 308, 311, 314, 316, 317, 325, 326, 327, 328.

In the second aspect, the present application relates to a pharmaceutical composition comprising the compound of the first aspect of the present invention, or a pharmaceutically acceptable salt, a hydrate, a solvate, a prodrug, a stereoisomer, a deuterated product or a tautomer thereof and one or more pharmaceutically acceptable carriers or excipients.

In some embodiments, pharmaceutical compositions can be used to prepare individual, single-unit dosage forms. In some embodiments, single unit dosage forms provided herein are suitable for oral, mucosal, parenteral, topical, transdermal, or transcutaneous administration to a patient. Examples of dosage forms include, but are not limited to: tablets; caplets; capsules, such as soft elastic gelatin capsules; cachets; troches; lozenges; dispersions; suppositories; powders; aerosols; gels; liquid dosage forms suitable for oral or mucosal administration to a patient, including suspensions, solutions, and elixirs; liquid dosage forms suitable for parenteral administration to a patient; eye drops or other ophthalmic preparations suitable for topical administration; and sterile solids that can be reconstituted to provide liquid dosage forms suitable for parenteral administration to a patient. In some embodiments, dosage forms comprise the compound provided herein, or the enantiomer, stereoisomer, solvate or pharmaceutically

acceptable salt thereof in an amount of 1 to about 1000 mg, from about 5 to about 500 mg, from about 10 to about 350 mg, or from about 50 to about 200 mg. The specific amount of the compound provided herein, or the enantiomer, stereoisomer, solvate or pharmaceutically acceptable salt thereof will depend on the specific agent used, the diseases or conditions being treated or prevented.

The compounds of formula (I) of the present invention in free form or in pharmaceutically acceptable salt form, exhibit valuable pharmacological properties, e.g. WRN inhibiting properties, e.g. as indicated in vitro and in vivo tests as provided in the next sections, and are therefore indicated for therapy, or for use as research chemicals, e.g. as a chemical probe, and as tool compounds.

In some embodiments, pharmaceutical compositions comprise a compound provided herein, or an enantiomer, a stereoisomer, a solvate, a deuterated product or a pharmaceutically acceptable salt thereof, and optionally a second active agent used for treating cancer, and in particular the treatment of cancer characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), including colorectal, gastric and endometrial cancer.

In the third aspect, the present application relates to a method of:

- modulating WRN activity in a subject, wherein the method comprises administering to the subject a therapeutically effective amount of the compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof,
- inhibiting WRN in a subject, wherein the method comprises administering to the subject a therapeutically effective amount of the compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof,
- treating a disorder or disease which can be treated by WRN inhibition in a subject, comprising administering to the subject a therapeutically effective amount of the compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof,
- treating cancer in a subject, comprising administering to the subject a therapeutically effective amount of the compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof,
- treating cancer in a subject, comprising administering a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein the cancer is characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). In particular, the cancer characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) is selected from colorectal, gastric, prostate, endometrial, adrenocortical, uterine, cervical, esophageal, breast, kidney and ovarian cancer. More particularly, the cancer characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) is selected from colorectal, gastric, prostate and endometrial cancer. Examples include uterine corpus endometrial carcinoma, colon adenocarcinoma, stomach adenocarcinoma, rectal adenocarcinoma, adrenocortical carcinoma, uterine carcinosarcoma, cervical squamous cell carcinoma, endocervical adenocarcinoma, esophageal carcinoma, breast carcinoma, kidney renal clear cell carcinoma, prostate cancer and ovarian serous cystadenocarcinoma.

In the fourth aspect, there is also provided a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, for use as a medicament. In particular, said use is:

- for the treatment of a disease that is treated by WRN inhibition,
- for the treatment of cancer,

- for the treatment of cancer that is characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR),
- for the treatment of cancer that is characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), such as colorectal, gastric, prostate, endometrial, adrenocortical, uterine, cervical, esophageal, breast, kidney and ovarian cancer,
- for the treatment of cancer that is characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) is selected from colorectal, gastric, prostate and endometrial cancer, or
- for the treatment of cancer wherein the cancer characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) is selected from uterine corpus endometrial carcinoma, colon adenocarcinoma, stomach adenocarcinoma, rectal adenocarcinoma, adrenocortical carcinoma, uterine carcinosarcoma, cervical squamous cell carcinoma, endocervical adenocarcinoma, esophageal carcinoma, breast carcinoma, kidney renal clear cell carcinoma, prostate cancer and ovarian serous cystadenocarcinoma.

In the fifth aspect, there is also provided the use of a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof:

- in therapy,
- in the manufacture of a medicament,
- in the manufacture of a medicament for the treatment of cancer. In particular, said cancer is characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR),
- in the manufacture of a medicament for treatment of a disease which may be treated by WRN inhibition,

wherein in particular, the cancer is characterized by microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), for example colorectal, gastric, prostate, endometrial, adrenocortical, uterine, cervical, esophageal, breast, kidney and ovarian cancer, in particular, colorectal, gastric, prostate or endometrial cancer, or uterine corpus endometrial carcinoma, colon adenocarcinoma, stomach adenocarcinoma, rectal adenocarcinoma, adrenocortical carcinoma, uterine carcinosarcoma, cervical squamous cell carcinoma, endocervical adenocarcinoma, esophageal carcinoma, breast carcinoma, kidney renal clear cell carcinoma and ovarian serous cystadenocarcinoma.

In some embodiments, the subject has or is identified as having a microsatellite instable (MSI-H) cancer, e.g., in reference to a control, e.g., a normal, subject. In one embodiment, the subject has MSI-H advanced solid tumors, a colorectal cancer (CRC), endometrial, uterine, stomach or other MSI-H cancer. In some embodiments, the subject has a colorectal (CRC), endometrial or stomach cancer, which cancer has or is identified as having a microsatellite instability (MSI-H), e.g., in reference to a control, e.g., a normal, subject. Such identification techiques are known in the art.

In another aspect, the invention provides a combination, in particular a pharmaceutical combination, comprising a compound of the first aspect of the present invention, or a pharmaceutically acceptable salt, a hydrate, a solvate, a deuterated product, a prodrug, a stereoisomer, or a tautomer thereof and one or more therapeutically active agents.

In another aspect, the invention provides a compound of the first aspect of the present invention or a pharmaceutically acceptable salt, a hydrate, a solvate, a deuterated product, a prodrug, a stereoisomer, or a tautomer thereof for use as a research chemical, for example as a

chemical probe or as a tool compound.

In another aspect, the invention provides a solid form, process or intermediate as described herein.

DETAILED DESCRIPTION OF THE INVENTION

After a long and intensive study, the inventor had accidentally prepared a new class of compounds which can be used as Werner Syndrome helicase (WRN) inhibitor to treat cancers. On this basis, the inventor has completed the present invention.

Term

In the present invention, unless otherwise specified, the terms used have the general meanings known to those skilled in the art.

The term used herein, "alkyl" refers to a branched or straight chain saturated aliphatic hydrocarbon group. In one embodiment, the alkyl contains from 1 to about 12 (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12) carbon atoms, more generally from 1 to about 6 carbon atoms($(C_1$-$C_6)$alkyl) or from 1 to about 4 carbon atoms($(C_1$-$C_4)$alkyl). The specified ranges as used herein indicate an alkyl group having each member of the range described as an independent species. For example, the term $(C_1$-$C_4)$alkyl as used herein indicates a straight or branched alkyl group having from 1, 2, 3 or 4 carbon atoms and is intended to mean that each of these is described as an independent species. Examples of alkyl include, but are not limited to, methyl, ethyl, npropyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl. In one embodiment, the alkyl group is optionally substituted as described herein.

The term used herein, "alkenyl" refers to a branched or straight chain aliphatic hydrocarbon group having one or more carbon-carbon double bonds that may occur at a stable point along the chain. Nonlimiting example is $(C_2$-$C_4)$alkenyl (such as C_2, C_3, C_4). The specified ranges as used herein indicate an alkenyl group having each member of the range described as an independent species, as described herein for the alkyl moiety. Examples of alkenyl include, but are not limited to, ethenyl, propenyl, and butadienyl (including 1,2-butadienyl and 1,3-butadienyl). In one embodiment, the alkenyl group is optionally substituted as described herein.

The term used herein, "alkynyl" refers to a branched or straight chain aliphatic hydrocarbon group having one or more carbon-carbon triple bonds that may occur at any stable point along the chain, for example, $(C_2$-$C_4)$alkynyl (such as C_2, C_3, C_4). The specified ranges as used herein indicate an alkynyl group having each member of the range described as anindependent species, as described herein for the alkyl moiety. Examples of alkynyl include, but are not limited to, ethynyl, propynyl, 1-butynyl, 2-butynyl, and 3-butynyl. In one embodiment, the alkynyl group is optionally substituted as described herein.

The term used herein, "cycloalkyl" refers to a saturated cyclic alkyl group having a single ring or multiple rings including fused, bridged, and spiro ring systems. As used herein, C3-8 cycloalkyl has from 3 to 8 ring carbon atoms (such as, 3, 4, 5, 6, 7 or 8 ring carbon atoms). Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl.

The term used herein, "cycloalkenyl" refers to a partially unsaturated monocyclic ring alkyl group having a single ring or multiple rings including fused, bridged, and spiro ring systems, for example, 5 or 6 ring carbon atoms. Examples of cycloalkenyl include, but are not limited to, cyclopentenyl and cyclohexenyl.

The term used herein, "haloalkyl" refers to both branched and straight-chain alkyl groups substituted with 1 or more halogen atoms, up to the maximum allowable number of halogen atoms.

Examples of haloalkyl include, but are not limited to, trifluoromethyl, monofluoromethyl, difluoromethyl, 2-fluoroethyl, and penta-fluoroethyl.

The term used herein, "halo" or "halogen" refers to independently any of fluoro, chloro, bromo, and iodo.

The term used herein, "heterocyclyl" refers to a saturated or a partially unsaturated (i.e., having one or more double and/or triple bonds within the ring without aromaticity) monocyclic or bicyclic radical of 4, 5, 6, 7, 8, 9, or 10 ring atoms in which at least one ring atom is a heteroatom selected from nitrogen, oxygen, and sulfur, the remaining ring atoms being C, where one or more ring atoms is optionally substituted independently with one or more substituents described above. In one embodiment, the only heteroatom is oxygen. A heterocyclyl may be a monocycle having 4 to 7 ring members (2 to 6 carbon atoms and 1 to 4 heteroatoms selected from N, O, and S) or a bicycle having 6 to 10 ring members (4 to 9 carbon atoms and 1 to 6 heteroatoms selected from N, O, and S), for example: a bicyclo [4,5], [5,5], [5,6], or [6,6] system. In one embodiment, the only heteroatom is sulfur. Examples of heterocyclic rings include, but are not limited to, pyrrolidinyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, piperidonyl, morpholino, thiomorpholino, thioxanyl, piperazinyl, homopiperazinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, dihydroisoquinolinyl, tetrahydroisoquinolinyl, pyrazolidinylimidazolinyl, imidazolidinyl, 2-oxa-5-azabicyclo[2.2.2]octane, 3-oxa-8-azabicyclo[3.2.1]octane, 8-oxa-3-azabicyclo[3.2.1]octane, 6-oxa-3-azabicyclo[3.1.1]heptane, 2-oxa-5-azabicyclo[2.2.1]heptane, 3-azabicyco[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, azabicyclo[2.2.2]hexanyl, 3H-indolyl, quinolizinyl, N-pyridyl ureas, and pyrrolopyrimidine. Spiro moieties are also included within the scope of this definition. Examples of a heterocyclic group wherein 1 or 2 ring carbon atoms are substituted with oxo (=O) moieties are pyrimidinonyl and 1,1-dioxothiomorpholinyl. The heterocycle groups herein are optionally substituted independently with one or more substituents described herein.

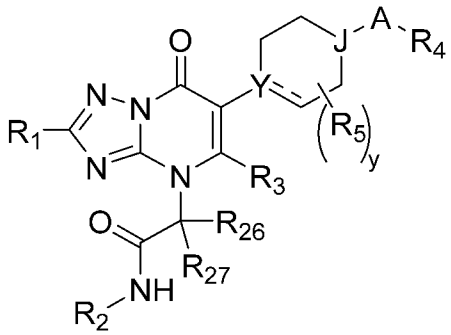
The term "substituted", as used herein, means that any one or more hydrogens on the designated atom or group is replaced with a moiety selected from the indicated group, provided that the designated atom's normal valence is not exceeded.

Unless otherwise stated, it is assumed that any heteroatom with a lower valence state has enough hydrogen atoms to replenish its valence state.

Active ingredient

As used herein, "the compound of the present invention" refers to the compound represented by the formula I, and further comprises the pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

The invention therefore provides a compound of formula (I):



(I).

Unless specified otherwise, the term "compounds of the present invention" or "compound of the present invention" or "a compound of formula (I)", refers to a compound or compounds of formula (I), subformulae thereof, exemplified compounds, and salts thereof, as well as all zwitterions, stereoisomers (including diastereoisomers and enantiomers), rotamers, tautomers and isotopically labeled compounds (including deuterium substitutions), as well as inherently formed moieties, and combinations or mixtures of the above-mentioned aspects thereof.

Various (enumerated) embodiments of the invention are described herein. It will be recognized that features specified in each embodiment may be combined with other specified features to provide further embodiments of the present invention.

Embodiment 1. A compound of formula (I) or a pharmaceutically acceptable salt thereof, as described above.

Embodiment 2: A compound of formula (I) or a pharmaceutically acceptable salt thereof, according to Embodiment 1, wherein when R_1 is a ring, then:

each R_1 ring atom adjacent to the R_1 ring atom to which said R_1 ring is joined to the remainder of the molecule, is independently unsubstituted or substituted by halo only, in particular, independently unsubstituted or substituted with one F substituent, and

- R_1 is 3, 4, 5, 6 or 7 membered ring, said R_1 ring is linked to the remainder of the molecule via a R_1 ring nitrogen atom, or a R_1 ring carbon atom to an adjacent ring atom. Optionally, said R_1 ring carbon atom has one double bond.

It should be understood that the compounds of the present invention are not limited to the above-listed compounds.

The salt of the compound in the present invention may be formed which are also within the scope of the present invention. Unless otherwise stated, the compound in the present invention is understood to include its salt. The term "salt" as used herein refers to a salt formed in the form of acid or base from inorganic or organic acid and base. Further, when the compound in the present invention contains a base fragment which includes, but is not limited to pyridine or imidazole, when contains an acid segment which includes, but is not limited to carboxylic acid. The zwitter-ion that may form "inner salt" is included within the range of the term "salt". Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salt is preferred, although other salts are also useful and may be used, for example, in the separation or purification steps of the preparation process. The compound of the present invention may form a salt, for example, compound I is reacted with a certain amount (such as an equivalent amount) of an acid or base, and precipitated in a medium, or freeze-dried in aqueous solution.

The compounds in the present invention containing base fragment which includes but is not limited to amines or pyridine or imidazole rings, may form salt with organic or inorganic acid. Typical acids that form salts include acetate (such as acetate or trihalogenated acetic acid, such as trifluoroacetic acid), adipate, alginate, ascorbate, aspartate, benzoate, benzene sulfonate, disulfate,

borate, butyrate, citrate, camphorate, camphor sulfonate, cyclopentane propionate, diethylene glycolate, lauryl sulfate, ethanesulphonate, fumarate, gluceptate, glycerophosphate, hemisulphate, enanthate, caproate, hydrochloride, hydrobromide, hydriodate, isethionate(e.g., 2-hydroxy-ethesulfonate), lactate, maleate, mesylate, naphthalenesulfonate (e.g., 2-naphthalenesulfonate), nicotinate, nitrate, oxalate, pectate, persulfate, phenylpropionate (e.g., 3-phenylpropionate), phosphate, picrate, pivalate, propionate, salicylate, succinate, sulfate (e.g., formed with sulfuric acid), sulfonate, tartrate, thiocyanate, toluenesulfonate(e.g., tosilate), dodecanoate, etc..

Some compounds of the invention may contain acidic fragments including, but not limited to carboxylic acid may form salts with various o$_{rg}$anic or inorganic bases. Salt formed by typical base includes ammonium salt, alkali metal salt (such as sodium, lithium and potassium salts), alkaline earth metal salt (such as calcium and magnesium salts), and salt formed by organic bases (such as organic amines), such as benzathine, dicyclohexylamine, hydrabamine (salt formed with N,N-bis(dehydroabietyl) ethylenediamine), *N*-methyl-D-glucanamine, N-methyl-D-glucoamide, tert-butyllamine, and the salt formed with amino acids such as arginine, lysine, etc.. Basic nitrogen-containing groups can form quaternary ammonium salts with halides, such as small molecular alkyl halides (such as chlorides, bromides and iodides of methyl, ethyl, propyl and butyl), dialkyl sulfate (such as dimethyl, diethyl, dibutyl, and dipentyl sulfates), long chain halides (such as asuch as chlorides, bromides and iodides of decyl, dodecyl, tetradecyl, and tetradecyl), aralkyl halides (such as bromides of benzyl and phenyl), etc..

The prodrug and solvate of the compound in the present invention are also included within the scope of the present invention. The term "prodrug" herein refers to a compound resulting from the chemical transformation of a metabolic or chemical process to produce a compound, salt, or solvate in the present invention for the treatment of an associated disease. The compounds of the invention include solvates such as hydrates.

Compound, salt or solvate in the present invention, may be present in tautomeric forms such as amide and imino ether. All of these tautomers are part of the present invention.

Stereisomers of all compounds (e.g., those asymmetric carbon atoms that may be present due to various substitutions), including their enantiomeric forms and non-enantiomed forms, all belong to the protection scope of the present invention. The independent stereoisomer in the present invention may not coexist with other isomers (e.g., as a pure or substantially pure optical isomer with special activity), or may be a mixture (e.g., racemate), or a mixture formed with all other stereoisomers or a part thereof. The chiral center of the present invention has two configurations of S or R, which is defined by International Union of Pure and Applied Chemistry (IUPAC) founded in 1974. The racemization form can be solved by physical methods, such as fractional crystallization, or separation crystallization by derivation into diastereomers, or separation by chiral column chromatography. Individual optical isomer can be obtained from racemate by appropriate methods, including but not limited to conventional methods, such as recrystallization after salting with optically active acids.

Weight content of compound in the present invention obtained by preparation, separation and purification in turn is equal to or greater than 90%, such as equal to or greater than 95%, equal to or greater than 99% ("very pure" compound), and listed in the description of the text. In addition, the "very pure" compound of the present invention is also part of the present invention.

All configuration isomers of the compound of the present invention are within the scope, whether in mixture, pure or very pure form. The definition of the compound of the present invention comprises cis (*Z*) and trans (*E*) olefin isomers, and cis and trans isomers of carbocyclic

and heterocyclic.

In the entire specification, the groups and substituents can be selected to provide stable fragments and compounds.

Specific functional groups and chemical term definitions are described in detail. For the purposes of the present invention, the chemical elements are consistent with Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed. The definition of a particular functional group is also described. In addition, the basic principles of Organic Chemistry as well as specific functional groups and reactivity described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, the entire content of which is incorporated herein by reference.

Some compounds of the present invention may exist in specific geometric or stereoisomer forms. The present invention covers all compounds, including their cis and trans isomers, R and S enantiomers, diastereomers, (D) type isomers, (L) type isomers, racemic mixtures and other mixtures. In addition, asymmetric carbon atom can represent substituent, such as alkyl. All isomers and mixtures thereof are included in the present invention.

According to the invention, mixtures of isomers may contain a variety ratios of isomers. For example, mixtures with only two isomers may have the following combinations: 50:50, 60:40, 70:30, 80:20, 90:10, 95:5, 96:4, 97:3, 98:2, 99:1, or 100:0, all ratios of the isomers are within the scope of the present invention. Similar ratio and the ratio of mixtures of more complex isomers, which are readily understood by general skill of the art are also within the scope of the invention.

The present invention also includes the isotope labeled compound, which is equivalent to the original compound herein. However, in fact, the substitution of one or more atoms by an atom with a different atomic weight or mass number usually occurs. Examples of compound isotopes that may be listed in the present invention include hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, and chlorine isotopes such as ^{2}H, ^{3}H, ^{13}C, ^{11}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F and ^{36}Cl, respectively. Compound, or enantiomer, diastereomer, isomer, or pharmaceutically acceptable salt or solvate, the above compound containing isotopes or other isotope atoms are all within the scope of the invention. Some isotope-labeled compounds in the present invention, such as the radioactive isotopes of ^{3}H and ^{14}C, are also included and are useful in experiments on the tissue distribution of drugs and substrates. Tritium (^{3}H) and Carbon-14 (^{14}C), are relatively easy to prepare and detect. In addition, heavier isotope substitutions such as deuterium, i.e. ^{2}H, have advantages in certain therapies due to their good metabolic stability, such as increased half-life or reduced dosage in vivo, and thus may be preferred in certain situations. Isotope-labeled compounds can be prepared by conventional methods through replacing readily available isotope-labeled reagents with non-isotopic reagents that can be prepared using the disclosed scheme shown in the Example.

If the synthesis of the compound of the invention is to be designed, it can be prepared by asymmetric synthesis, or derivatized with chiral auxiliary reagent, separating the resulting diastereomeric mixture and removing the chiral adjunct to obtain a pure enantiomer. In addition, if a molecule contains a basic functional group, such as an amino acid, or an acidic functional group, such as a carboxyl group, a diastereomer can be formed with a salt of suitable optically active acids or bases, which can be separated by conventional means, such as crystallization or chromatography, to obtain a pure enantiomer.

As described herein, the compound in the present invention may be substituted with any number of substituents or functional groups to extend its scope. In general, whether the term "substituted" appears before or after the term "optional", the general formula that includes

substituents in the compound of the present invention means the substitution of a specified structural substituent for a hydrogen radical. When multiple locations in a particular structure are replaced by multiple specific substituents, each location of the substituents can be the same or different. The term "substituted" as used herein includes all substitution that allows organic compounds to be substituted. Broadly speaking, the allowable substituents include non-annular, cyclic, branched, non-branched, carbocyclic and heterocyclic, aromatic ring and non-aromatic organic compounds. In the present invention, such as heteroatomic nitrogen, its valence state may be supplemented by a hydrogen substituent or by any permitted organic compound described above. Furthermore, the invention is unintentionally limited to the substituted organic compounds. The present invention considers that a combination of substituents and variable groups is good for the treatment of diseases (such as infectious or hypertrophic diseases) in the form of stable compounds. The term "stable" herein refers to a stable compound which is sufficient for maintaining the integrity of the compound structure within a sufficiently long time, preferably in a sufficiently long time, which is hereby used for the above purposes.

The metabolite of the compounds of the present application and their pharmaceutically acceptable salts, and prodrugs that can be converted into the compounds of the present application and their pharmaceutically acceptable salts in vivo, also included in the claims.

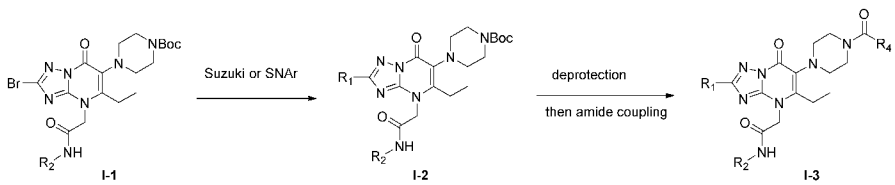
Preparation method

The preparation method of the compound of the formula (I) of the present invention is more specifically described below, but these specific methods do not constitute any limitation of the invention. The compound of the invention may also optionally be conveniently prepared by combining the various synthetic methods described in this specification or known in the art, such a combination may be easily performed by a skilled person in the art to which the invention belongs.

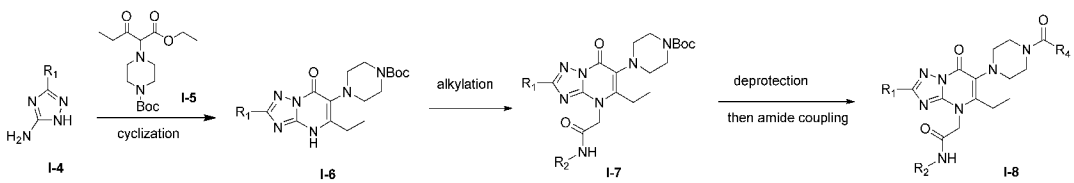
Typically, the preparation process for the compounds of the present invention is as follows, in which the raw materials and reagents used may be commercially purchased unless otherwise specified.

General procedure for preparation of the claimed inhibitors is as shown below.

Scheme 1:



Scheme 2:



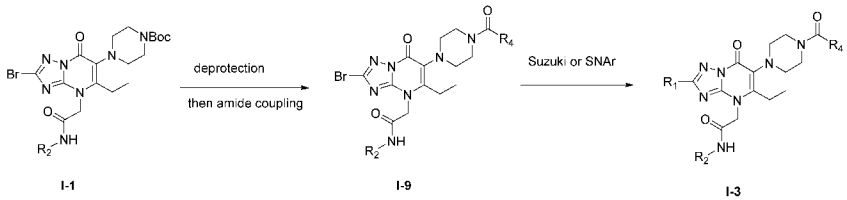
Step 1: the compound **I-6** was obtained by cyclization of compound **I-4** and tert-butyl 4-(1-ethoxy-1,3-dioxopentan-2-yl)piperazine-1-carboxylate (compound **I-5**).

Step 2: the compound **I-6** was alkylated with the various intermediate in the base condition to afford compound **I-7**.

Step 3: the compound **I-7** was then deprotected and the resulting amine was coupled with the

corresponding acid to get the final compound **I-8**.

Scheme 3:



Pharmaceutical composition and method of administration

The pharmaceutical compositions of the present invention are used to prevent and / or treat cancer.

The compounds of the formula (I) may be used in combination with other drugs known to treat or improve similar conditions. When administered in combination, the original administration for the drug can remain unchanged, while compound of formula I may be administered simultaneously or subsequently. Pharmaceutical composition containing one or more known drugs and the compound of formula I may be preferred when administered in combination with one or more other drugs. The drug combination also includes administering the compound of formula I and other one or more known drugs at overlapping time. When the compound of formula I is combined with other one or more drugs, the dose of the compound or known drug may be lower than that of their individual use.

In some embodiments, a compound provided herein, or an enantiomer, a stereoisomer, a solvate or a pharmaceutically acceptable salt thereof, is administered in combination with another drug ("second active agent") or treatment. Second active agents include small molecules and large molecules (e.g., proteins and antibodies). Other therapies that can be used in combination with the administration of compounds provided herein include, but are not limited to, surgery, immunotherapy, biological therapy, radiation therapy, and other non-drug-based therapies useful for treating or preventing various diseases described herein.

The dosage forms of the pharmaceutical composition of the present invention include (but are not limited to): injection, tablet, capsule, aerosol, suppository, pellicle, pill, liniment for external use, controlled release or sustained-release or nano formulation.

The pharmaceutical composition of the present invention comprises a compound of the present invention or a pharmaceutically acceptable salt and a pharmaceutically acceptable excipient or carrier with safe and effective amount. wherein "safe and effective amount" refers to the amount of compound is sufficient to significantly improve the condition, not to produce severe side effects. Typically, the pharmaceutical composition contains 1-2000 mg of the compound / dosage of the present invention, and preferably contains 10-1000 mg of the compound / dosage of the present invention. Preferably, "one dosage" is a capsule or a pill.

"Pharmaceutically acceptable carrier" refers to one or more compatible solid or liquid filler or gel substances, which are suitable for human use, and must be sufficiently pure and of sufficiently low toxicity. "Compatible" herein refers to ability of each component of a composition can be mixed with the compound of the present invention and can be mixed with each other without appreciably reducing the efficacy of the compound. Examples of pharmaceutically acceptable carrier include cellulose and derivatives thereof (such as sodium carboxymethylcellulose, sodium ethylcellulose, cellulose acetate, etc.), gelatin, talc, solid lubricant (such as stearic acid, magnesium stearate), calcium sulfate, vegetable oil

(such as soybean oil, sesame oil, peanut oil, olive oil, etc.), polyol (such as propylene glycol, glycerol, mannitol, sorbitol, etc.), emulsifier (such as Tween®), wetting agent (such as lauryl sodium sulfate), colorant, flavoring, stabilizer, antioxidant, preservative, pyrogen-free water, etc..

There is no special limitation of administration mode for the compound or pharmaceutical compositions of the present invention, and the representative administration mode includes (but is not limited to): oral, intratumorally, rectal, parenteral (intravenous, intramuscular or subcutaneous), and topical administration.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In these solid dosage forms, the active compounds are mixed with at least one conventional inert excipient (or carrier), such as sodium citrate or dicalcium phosphate, or mixed with any of the following components: (a) fillers or compatibilizer, such as starch, lactose, sucrose, glucose, mannitol and silicic acid; (b) binders, such as hydroxymethyl cellulose, alginate, gelatin, polyvinylpyrrolidone, sucrose and arabic gum; (c) humectant, such as glycerol; (d) disintegrating agent, such as agar, calcium carbonate, potato starch or tapioca starch, alginic acid, certain composite silicates, and sodium carbonate; (e) dissolution-retarding agents, such as paraffin; (f) absorption accelerators, such as quaternary ammonium compounds; (g) wetting agents, such as cetyl alcohol and glyceryl monostearate; (h) adsorbents, such as kaolin; and (i) lubricants, such as talc, stearin calcium, magnesium stearate, solid polyethylene glycol, lauryl sodium sulfate, or the mixtures thereof. In capsules, tablets and pills, the dosage forms may also contain buffering agents.

The solid dosage forms such as tablets, sugar pills, capsules, pills and granules can be prepared by using coating and shell materials, such as enteric coatings and any other materials known in the art. They can contain an opaque agent. The release of the active compounds or compounds in the compositions can be released in a delayed mode in a given portion of the digestive tract. Examples of the embedding components include polymers and waxes. If necessary, the active compounds and one or more above excipients can form microcapsules.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups or tinctures. In addition to the active compounds, the liquid dosage forms may contain any conventional inert diluents known in the art such as water or other solvents, solubilizers and emulsifiers, such as ethanol, isopropanol, ethyl carbonate, ethyl acetate, propylene glycol, 1,3-butanediol, dimethyl formamide, as well as oil, in particular, cottonseed oil, peanut oil, corn germ oil, olive oil, castor oil and sesame oil, or the combination thereof.

Besides these inert diluents, the composition may also contain additives such as wetting agents, emulsifiers, and suspending agent, sweetener, flavoring agents and perfume.

In addition to the active compounds, the suspension may contain suspending agent, for example, ethoxylated isooctadecanol, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, methanol aluminum and agar, or the combination thereof.

The compositions for parenteral injection may comprise physiologically acceptable sterile aqueous or anhydrous solutions, dispersions, suspensions or emulsions, and sterile powders which can be re-dissolved into sterile injectable solutions or dispersions. Suitable aqueous and non-aqueous carriers, diluents, solvents or excipients include water, ethanol, polyols and any suitable mixtures thereof.

The dosage forms for topical administration of compounds of the invention include

ointments, powders, patches, aerosol, and inhalants. The active ingredients are mixed with physiologically acceptable carriers and any preservatives, buffers, or propellant if necessary, under sterile conditions.

Compounds of the present invention can be administrated alone, or in combination with any other pharmaceutically acceptable compounds.

When the pharmaceutical compositions are used, a safe and effective amount of compound of the present invention is administrated to a mammal (such as human) in need thereof, wherein the dose of administration is a pharmaceutically effective dose. For a person weighed 60 kg, the daily dose is usually 1-2000 mg, preferably 50-1000mg. Of course, the particular dose should also depend on various factors, such as the route of administration, patient healthy status, which are well within the skills of an experienced physician.

The present invention also provides a preparation method of pharmaceutical composition comprising the step of mixing a pharmaceutically acceptable carrier with the compound of formula (I) or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof of the present invention.

The main advantages of the present invention include:

1. The compound of the present invention is a new class of Werner Syndrome helicase inhibitor.

2. The compound of the present disclosure shows a good inhibitory effect on Werner Syndrome helicase, which can be used as Werner Syndrome helicase (WRN) inhibitor to treat cancers.

3. The compound of the present disclosure possesses good druggability (including but not limited to: solubility, safety, etc.).

Examples

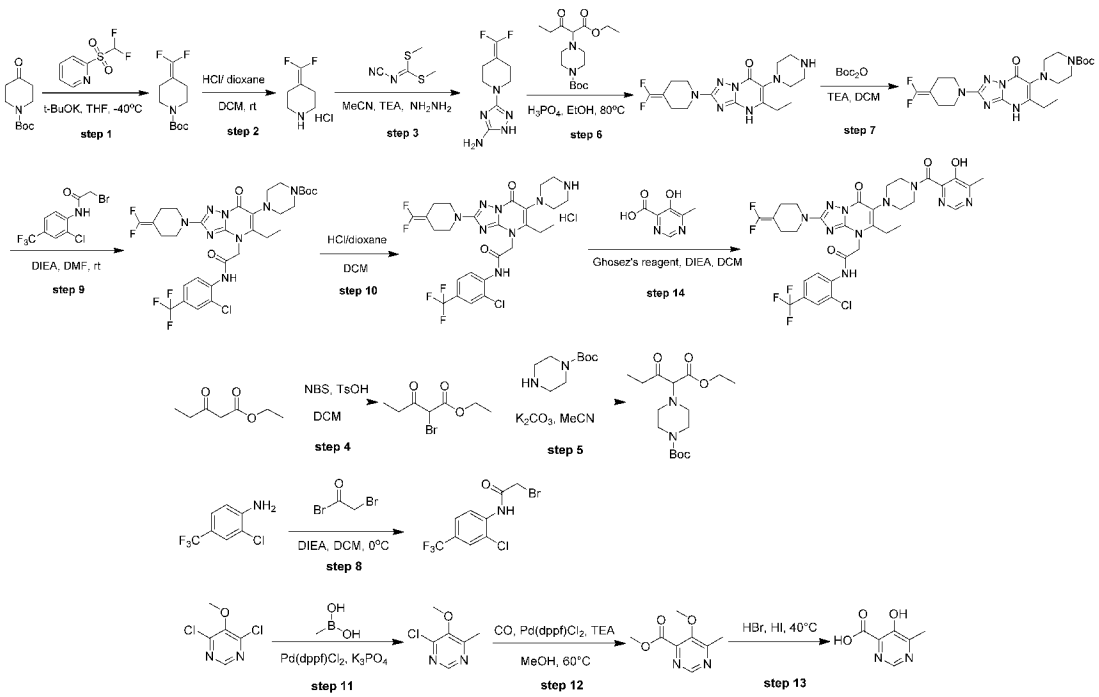
Certain embodiments of the claimed subject matter are illustrated by the following non-limiting examples.

The disclosed compounds can generally be synthesized by the above general procedure or by an appropriate combination of generally well-known synthetic methods. Techniques useful in synthesizing these compounds are both readily apparent and accessible to those of skill in the relevant art, based on the instant disclosure. Many of the optionally substituted starting compounds and other reactants are commercially available or can be readily prepared by those skilled in the art using commonly employed synthetic method.

The example below is to illustrate certain methods for making the disclosed compounds and is not intended to limit the scope of reactions or reaction sequences that can be used in preparing the compounds provided herein.

Example 1:

***N*-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(4-(difluoromethylene)piperidin-1-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7*H*)-yl)acetamide**



Step 1: To the solution of tert-butyl 4-oxopiperidine-1-carboxylate (1.25 g, 6.2 mmol) and 2-(difluoromethane)sulfonylpyridine (1 g, 5.2 mmol) in DMF (30 mL) was added the solution of t-BuOK (1.05 g, 9.3 mmol) in DMF (10 mL) dropwise at -40°C. Then the mixture was stirred under nitrogen at -40°C for 2 hrs. The reaction mixture was warmed to room temperature, poured into water (50 mL), adjusted PH to 3 with 2N HCl, then extracted with EtOAc (50 mL * 3). The organic layers were washed with brine (50 mL * 2), dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford crude product. The crude product was purified by flash silica chromatography (elution gradient: 0 to 20% EtOAc in Hexane, v/v) to afford tert-butyl 4-(difluoromethylene)piperidine-1-carboxylate (1.1 g, 4.7 mmol, yield: 90.4%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 3.38 – 3.37 (m, 4H), 2.12 – 2.10 (m, 4H), 1.42 (s, 9H). **MS** (ESI) m/z = 178.2 $[M-56]^+$.

Step 2: To a solution of tert-butyl 4-(difluoromethylene)piperidine-1-carboxylate (1.1 g, 4.7 mmol) in DCM (10 mL) stirred under nitrogen was added 4M HCl in dioxane (10 mL, 40 mmol) dropwise. The reaction mixture was stirred at 25°C for 2 hrs. The mixture was concentrated under reduced pressure to afford 4-(difluoromethylene)piperidine hydrochloride (0.6 g, 3.5 mmol, yield: 74.47 %) as a white solid. The product was used directly without any further purification. **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 9.31–9.17 (m, 2H), 3.06–3.05 (m, 4H), 2.38–2.37 (m, 4H).

Step 3: The mixture of 4-(difluoromethylidene)piperidine hydrochloride (133 mg, 1 mmol), [bis(methylsulfanyl)methylidene](cyano)amine (146 mg, 1 mmol) and TEA (106 mg, 1.04 mmol) in MeCN (5 mL) was stirred at 90°C for 16 hrs. Then it was cooled to 0°C. Hydrazine hydrate (625.12 mg, 10 mmol) was added dropwise and the resulting mixture was stirred at 90°C for 20 hrs. The mixture was concentrated under vacuum and purified by Flash Chromatography (MeOH-DCM = 0-10%) to give the product 3-(4-(difluoromethylene)piperidin-1-yl)-1*H*-1,2,4-triazol-5-amine (215 mg, 1 mmol, 100% yield) as a yellow oil. **MS** (ESI) m/z = 216.1 $[M+H]^+$.

Step 4: To a solution of ethyl 3-oxopentanoate (30 g, 208.1 mmol) in DCM (200 mL) were added N-Bromosuccinimide (38.89 g,218.5 mmol) and $TsOH.H_2O$ (7.91 g, 41.6 mmol). The mixture was stirred at room temperature for 2.5 hrs. The mixture was diluted with water (200 mL), extracted with DCM (200 mL * 3). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, concentrated under vacuum and purified by Flash Chromatography (EtOAc/hexanes = 0-1%) to give the product ethyl 2-bromo-3-oxopentanoate (19 g, 85.2 mmol, yield: 40%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.80 (s, 1H), 4.28 (t, J = 7.1 Hz, 2H), 2.80 (q, J = 7.2 Hz, 2H), 1.31 (t, J = 7.1 Hz, 3H), 1.14 (t, J = 7.2 Hz, 3H).

Step 5: The mixture of ethyl 2-bromo-3-oxopentanoate (19 g, 85.2 mmol), tert-butyl piperazine-1-carboxylate (31.74 g, 170.4 mmol) and K_2CO_3 (35.33 g, 0.25 mmol) in CH_3CN (100 mL) was stirred at 50°C for 2 hrs. The mixture was filtered, the cake was washed with CH_3CN.

The filtrate was concentrated under vacuum and purified by Flash Chromatography (EtOAc-hexanes = 0-3%) to give the product tert-butyl 4-(1-ethoxy-1,3-dioxopentan-2-yl)piperazine-1-carboxylate (18 g, 54.8 mmol, yield: 64%) as a yellow oil. **MS** (ESI) m/z = 329.1 $[M+H]^+$.

Step 6: To a solution of 5-[4-(difluoromethylidene)piperidin-1-yl]-2*H*-1,2,4-triazol-3-amine (215 mg, 1 mmol) in EtOH (10 mL) were added tert-butyl 4-(1-ethoxy-1,3-dioxopentan-2-yl) piperazine-1-carboxylate (328.11 mg, 1 mmol) and H_3PO_4 (293.74 mg,3 mmol). The reaction mixture was stirred at 80°C for 72 hrs under N_2. The mixture was basified with $NaHCO_3$ to pH=9, diluted with water, extracted with EtOAc (20 mL * 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, concentrated under vacuum and purified by Flash Chromatography (5%$NH_3.H_2O$ in MeOH-DCM = 0-20%) to give the product 2-(4-(difluoro methylene)piperidin-1-yl)-5-ethyl-6-(piperazin-1-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-7(4H)-one (140 mg, 0.369 mmol, 36% yield) as an off-white solid. **MS** (ESI) m/z = 380.2 $[M+H]^+$.

Step 7: To a solution of 2-[4-(difluoromethylidene)piperidin-1-yl]-5-ethyl-6-(piperazin-1-yl)-4*H*-[1,2,4]triazolo[1,5-a]pyrimidin-7-one (140 mg, 0.37 mmol) in DCM (10 mL) were added Boc_2O (96.64 mg, 0.44 mmol) and TEA (112.02 mg, 1.1 mmol). The mixture was stirred at room temperature for 16 hrs. The mixture was concentrated under vacuum and the residue was purified by Flash Chromatography (EtOAc-Hexanes = 0-60%) to give the product tert-butyl 4-(2-(4-(difluoromethylene)piperidin-1-yl)-5-ethyl-7-oxo-4,7-dihydro-[1,2,4]triazolo[1,5-a] pyrimidin-6-yl)piperazine-1-carboxylate (120 mg, 0.22 mmol, 61% yield) as a pale-yellow solid. **^{1}H NMR** (400 MHz, CD_3OD) δ 4.05 (d, *J* = 12.5 Hz, 2H), 3.64 – 3.59 (m, 4H), 3.55 (t, *J* = 11.5 Hz, 2H), 3.01 (s, 2H), 2.86 (q, *J* = 7.6 Hz, 2H), 2.68 (d, *J* = 11.0 Hz, 2H), 2.28 (t, *J* = 5.5 Hz, 4H), 1.51 (s, 9H), 1.28 (t, *J* = 7.6 Hz, 3H). **MS** (ESI) m/z = 480.2 $[M+H]^+$

Step 8: To a solution of 2-chloro-4-(trifluoromethyl)aniline (10 g, 50.9 mmol) in DCM (50 mL) were added DIPEA (19.73 g, 152.7 mmol) and 2-bromoacetyl bromide (30.82 g, 152.7 mmol) at 0°C. The mixture was stirred at room temperature for 16 hrs. The mixture was diluted with water (50 mL), extracted with DCM (50 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, concentrated under vacuum and purified by Flash Chromatography (EtOAc-Hxanes = 0-20%) to give the product 2-bromo-*N*-(2-chloro-4- (trifluoro methyl)phenyl) acetamide (12 g, 37.8 mmol, 74 % yield) as a yellow solid. **MS** (ESI) m/z = 315.9, 317.9 $[M+H]^+$.

Step 9: To a solution of tert-butyl 4-{2-[4-(difluoromethylidene)piperidin-1-yl]-5-ethyl-7-oxo-4H-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl}piperazine-1-carboxylate (120 mg, 0.25 mmol) in DMF (10 mL) were added 2-bromo-*N*-[2-chloro-4-(trifluoromethyl)phenyl]acetamide (79 mg, 0.25 mmol) and DIPEA (97 mg, 0.75 mmol). The mixture was stirred at room temperature for 4 hrs. The mixture was diluted with water (20 mL), extracted with EtOAc (20 mL*3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, concentrated under vacuum and purified by Flash Chromatography (MeOH/DCM = 0-1%) to give the product tert-butyl 4-(4-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-2-(4-(difluoromethylene)piperidin-1-yl)-5-ethyl-7-oxo-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)piperazine-1-carboxylate (133 mg, 0.186 mmol, 74% yield) as a colorless oil. **MS** (ESI) m/z = 715.2, 717.2 $[M+H]^+$.

Step 10: To the solution of tert-butyl 4-[4-({[2-chloro-4-(trifluoromethyl) phenyl] carbamoyl} methyl)-2-[4-(difluoromethylidene)piperidin-1-yl]-5-ethyl-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl] piperazine-1-carboxylate (133 mg, 0.186 mmol) in DCM (5 mL) was added HCl in dioxane (4 mL). The mixture was stirred at room temperature for 2 hrs. The mixture was concentrated under vacuum to give the crude product N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(4-(difluoro methylene)piperidin-1-yl)-5-ethyl-7-oxo-6-(piperazin-1-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide hydrochloride (110 mg, 0.1789 mmol, 98% yield) as an off white solid. **MS** (ESI) m/z = 615.3, 617.3 $[M+H]^+$.

Step 11: The mixture of 4,6-dichloro-5-methoxypyrimidine (20 g, 111.7 mmol), methylboranediol (10.03 g, 167.55 mmol), $Pd(dppf)Cl_2$ (3.27 g, 4.46 mmol) and K_3PO_4 (47.42 g. 223.4 mmol) in tuluene (60 mL), dioxane (8 mL) and H_2O (20 mL) was stirred at 105°C for 16 hrs under N_2 atmosphere. The mixture was diluted with water (100 mL), extracted with EtOAc (100 mL*3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, concentrated under vacuum and purified by Chromatography (EtOAc-hexanes = 0-20%) to give the product 4-chloro-5-methoxy-6-methylpyrimidine (9.8 g, 61.8 mmol, 55 % yield) as colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 3.91 (s, 3H), 2.56 (s, 3H). **MS** (ESI) m/z = 159.0, 161.0 $[M+H]^+$.

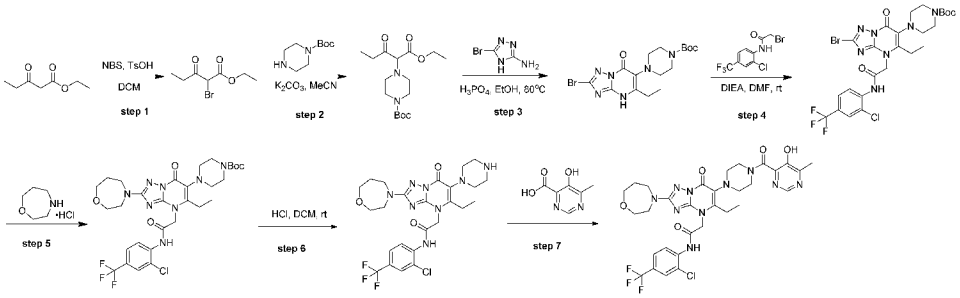
Step 12: To a solution of 4-chloro-5-methoxy-6-methylpyrimidine (9.8 g, 61.8 mmol) in MeOH (100 mL) were added $Pd(dppf)Cl_2$ (2.24 g, 3 mmol) and TEA (18.76 g, 185.4 mmol). The reaction mixture was stirred at 60°C for 48 hrs under CO. The mixture was concentrated under vacuum, purified by silica (EtOAc/hexanes = 0-30%) to give the product methyl 5-methoxy-6-methylpyrimidine-4-carboxylate (7.9 g, 43.4 mmol, 70 % yield) as a yellow oil. **MS** (ESI) m/z = 183.1 $[M+H]^+$.

Step 13: A mixture of methyl 5-methoxy-6-methylpyrimidine-4-carboxylate (7.9 g, 43.4 mmol) in HBr (25 mL, 48 wt. % in H_2O) was stirred at 40°C for 16 hrs. Then HI (25 mL, 55-57 wt.% aqueous) was added to the solution and stirred for 16 hrs. The PH was adjusted to 3-4 with NaOH (50% in water) at 0 - 20°C. The mixture was filtered to give the product 5-hydroxy-6-methylpyrimidine-4-carboxylic acid (3.1 g, 20.1 mmol, 46% yield) as yellow solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.50 (s, 1H), 6.31 (s, 3H), 2.42 (s, 3H).

Step 14: To a solution of 5-hydroxy-6-methylpyrimidine-4-carboxylic acid（27.06 mg, 0.17 mmol) in DCM (5 mL) was added (1-chloro-2-methylprop-1-en-1-yl)dimethylamine (29.32 mg, 0.22 mmol). The mixture was stirred at room temperature for 30 min. Then *N*-[2-chloro-4-(trifluoromethyl)phenyl]-2-{2-[4-(difluoromethylidene)piperidin-1-yl]-5-ethyl-7- oxo-6-(piperazin -1-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4-yl}acetamide hydrochloride (90 mg, 0.146 mmol) was added and the resulting mixture was stirred at room temperature for 30 min. Then DIPEA (56.72 mg, 0.43 mmol) in DCM (1 mL) was added dropwise and the resulting mixture was stirred at room temperature for 1 hr. The mixture was diluted with water (10 mL), extracted with DCM (10 mL * 3). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4, then concentrated under vacuum, purified by Flash Chromatography (MeOH/DCM = 0-2%) to give the product *N*-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(4-(difluoromethylene)piperidin-1-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo [1,5-a]pyrimidin-4(7*H*)-yl)acetamide (24.1 mg, 0.03 mmol, 20% yield) as a white solid. **^{1}H NMR** (400 MHz,CD_3OD) δ 8.54 (s, 1H), 8.13 (d, J = 8.6 Hz, 1H), 7.79 (s, 1H), 7.59 (d, J = 8.6 Hz, 1H), 5.26 (s, 2H), 4.66 (d, J = 12.0 Hz, 1H), 4.06 (d, J = 11.1 Hz, 1H), 3.70 (t, J = 13.4 Hz, 2H), 3.62 - 3.52 (m, 4H), 3.39 (t, J = 11.1 Hz, 1H), 3.16 - 2.96 (m, 3H), 2.88 (d, J = 10.4 Hz, 1H), 2.73 (d, J = 11.2 Hz, 1H), 2.49 (s, 3H), 2.21 (s, 4H), 1.26 (t, J = 7.4 Hz, 3H). **MS** (ESI) m/z = 751.1 $[M+H]^+$.

Example 6:

N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(1,4-oxazepan-4-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide



Step 1: To a solution of ethyl 3-oxopentanoate (30 g, 208.1 mmol) in DCM (200 mL) were added N-Bromosuccinimide (38.89 g, 218.5 mmol) and $TsOH.H_2O$ (7.91 g, 41.6 mmol). The mixture was stirred at room temperature for 2.5 hrs. The mixture was diluted with water (200 mL), extracted with DCM (200 mL * 3). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, concentrated under vacuum and purified by Flash Chromatography (EtOAc/hexanes = 0-1%) to give the product ethyl 2-bromo-3-oxopentanoate (19 g, 85.2 mmol, yield: 40%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.80 (s, 1H), 4.28 (t, J = 7.1 Hz, 2H), 2.80 (q, J = 7.2 Hz, 2H), 1.31 (t, J = 7.1 Hz, 3H), 1.14 (t, J = 7.2 Hz, 3H).

Step 2: The mixture of ethyl 2-bromo-3-oxopentanoate (19 g, 85.2 mmol), tert-butyl piperazine-1-carboxylate (31.74 g, 170.4 mmol) and K_2CO_3 (35.33 g, 0.25 mmol) in CH_3CN (100 mL) was stirred at 50°C for 2 hrs. The mixture was filtered, the cake was washed with CH_3CN. The filtrate was concentrated under vacuum and purified by Flash Chromatography (EtOAc/ hexanes = 0-3%) to give the product tert-butyl 4-(1-ethoxy-1,3-dioxopentan-2-yl)piperazine-1-carboxylate (18 g, 54.8 mmol, yield: 64%) as a yellow oil. **MS** (ESI) m/z = 329.1 $[M+H]^+$.

Step 3: To a solution of tert-butyl 4-(1-ethoxy-1,3-dioxopentan-2-yl)piperazine-1-

carboxylate (3 g, 9.1 mmol) in EtOH (20 mL) were added 5-bromo-4H-1,2,4-triazol-3-amine (1.48 g, 9.1 mmol) and H_3PO_4 (1.78 g, 18.2 mmol). The reaction mixture was stirred at room temperature 80°C for 16 hrs under N_2. The mixture was basified with $NaHCO_3$ solution to pH=9, diluted with water, extracted with EA (20 mL * 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, concentrated under vacuum and purified by Flash Chromatography (MeOH/DCM = 0-3%) to give the product tert-butyl 4-(2-bromo-5-ethyl-7-oxo-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)piperazine-1-carboxylate (310 mg, 0.7 mmol, yield: 7%) as a yellow solid. **MS** (ESI) m/z = 427.1, 429.1 $[M+H]^+$.

Step 4: To a solution of tert-butyl 4-{2-bromo-5-ethyl-7-oxo-4H-[1,2,4]triazolo [1,5-a] pyrimidin-6-yl}piperazine-1-carboxylate (310 mg, 0.72 mmol) in DMF (6 mL) were added 2-bromo-N-[2-chloro-4-(trifluoromethyl)phenyl]acetamide (252.58 mg, 0.79 mmol) and DIPEA (281.29 mg, 2.17 mmol). The mixture was stirred at room temperature for 16 hrs. The mixture was diluted with water (20 mL), extracted with EtOAc (20 mL * 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, concentrated under vacuum and purified by Flash Chromatography (EtOAc/hexanes = 0-60%) to give the product tert-butyl 4-(2-bromo-4-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-5-ethyl-7-oxo-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)piperazine-1-carboxylate (350 mg, 0.52 mmol, yield: 72%) as a yellow solid. **MS** (ESI) m/z = 606.0, 608.0 $[M+H-56]^+$.

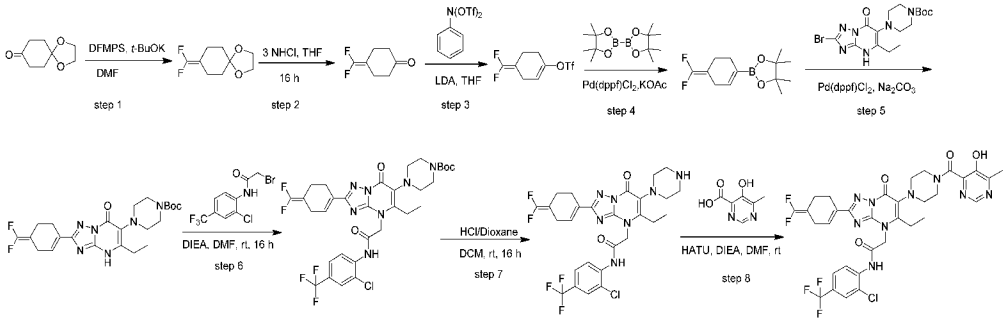
Step 5: The mixture of tert-butyl 4-[2-bromo-4-({[2-chloro-4-(trifluoromethyl)phenyl]carbamoyl}methyl)-5-ethyl-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl]piperazine-1-carboxylate (100 mg, 0.15 mmol), 1,4-oxazepane hydrochloride (208 mg, 1.5 mmol) and DIEA (97 mg, 0.75 mmol) in DMSO (5 mL) was stirred at 100°C for 48 hrs. The reaction mixture was quenched with water (5 mL) and extracted with EtOAc (10 mL * 3). The organic layers were combined, washed with brine (80 mL), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford the crude product, which was purified by flash chromatography (Methanol/DCM: 0~10%) to afford the compound tert-butyl 4-(4-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-5-ethyl-2-(1,4-oxazepan-4-yl)-7-oxo-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)piperazine-1-carboxylate (20 mg, 0.03 mmol, yield: 19.4%) as solid. **MS** (ESI) m/z = 627.3 $[M+H]^+$.

Step 6: To a solution of tert-butyl 4-(4-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-5-ethyl-2-(1,4-oxazepan-4-yl)-7-oxo-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)piperazine-1-carboxylate (20 mg, 0.03 mmol) in DCM (3 mL) was added HCl/dioxane (1 mL). The mixture was stirred at room temperature for 1 hour, then concentrated under vacuum to afford the crude product N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-2-(1,4-oxazepan-4-yl)-7-oxo-6-(piperazin-1-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide (20 mg, 0.03 mmol, yield: 117%) as a yellow solid. **MS** (ESI) m/z = 583.3 $[M+H]^+$.

Step 7: To a solution of 5-hydroxy-6-methylpyrimidine-4-carboxylic acid (7 mg, 0.04 mmol) in DCM (2 mL) was added 1-chloro-*N*,*N*,2-trimethyl-1-propen-1-amine (7 mg, 0.05 mmol), the mixture was stirred at room temperature for 30 mins, then *N*-[2-chloro-4-(trifluoromethyl)phenyl]-2-[5-ethyl-2-(1,4-oxazepan-4-yl)-7-oxo-6-(piperazin-1-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4-yl] acetamide (20 mg, 0.03 mmol) was added and the mixture was stirred at room temperature for 30 mins. DIEA (13 mg, 0.1 mmol) in DCM (1 mL) was added dropwise and the resulting mixture was stirred at room temperature for 1 hr. The mixture was concentrated and purified by Prep-TLC (Methanol/DCM: 0~10%) to get the product *N*-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(1,4-oxazepan-4-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7*H*)-yl) acetamide (3.6 mg, 0.005 mmol, yield: 16.6%) as a white solid. **^{1}H NMR** (400 MHz, CD_3OD) δ 8.59 (s, 1H), 8.16 (d, J = 8.5 Hz, 1H), 7.83 (s, 1H), 7.64 (d, J = 8.5 Hz, 1H), 5.30 (s, 2H), 4.71 (d, J = 11.9 Hz, 1H), 4.10 (d, J = 13.0 Hz, 1H), 3.83 – 3.70 (m, 10H), 3.44 (t, J = 10.7 Hz, 1H), 3.08 (d, J = 7.7 Hz, 3H), 2.92 (d, J = 11.8 Hz, 1H), 2.78 (d, J = 10.7 Hz, 1H), 2.54 (s, 3H), 2.00 – 1.92 (m, 2H), 1.29 (d, J = 7.5 Hz, 3H). **MS** (ESI) m/z = 719.3 $[M+H]^+$.

Example 7:

***N*-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(4-(difluoromethylene)cyclohex-1-en-1-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7*H*)-yl)acetamide**



Step 1: To a solution of 1,4-dioxaspiro[4.5]decan-8-one (5000 mg, 32.0 mmol) and DFMPS (5565 mg, 28.8 mmol) in DMF (20 mL) stirred under nitrogen at -60 °C was added *t*-BuOK (6466 mg, 57.6 mmol). The reaction mixture was stirred at -60 to -25 °C for 2 hrs. The reaction was quenched with water (20 mL). The crude mixture was extracted with EtOAc (50 mL * 3), and the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to get the product 8-(difluoromethylene)-1,4-dioxaspiro[4.5]decane (2000 mg, 10.5 mmol, yield: 32.8 %) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.96 (s, 4H), 2.27-2.22 (m, 4H), 1.72- 1.61 (m, 4H).

Step 2: To a solution of 8-(difluoromethylene)-1,4-dioxaspiro[4.5]decane (2000 mg, 10.5 mmol) in THF(10 mL) was added 3*N* HCl (10 mL). The reaction mixture was stirred at room temperature for 16 hrs. The crude mixture was extracted with DCM (50 mL * 3), and the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to get the crude product. Then purified by Flash Chromatography (elution gradient: EtOAc/hexanes, 0-3%) to get the product 4-(difluoromethylene) cyclohexan-1-one (600 mg, 4.1 mmol, yield: 39.0%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.55-2.46 (m, 4H), 2.46-2.37 (m, 4H).

Step 3: To a solution of 4-(difluoromethylene) cyclohexan-1-one (600 mg, 4.1 mmol) in THF (20 mL) stirred at -78 °C was added LDA (2 M, 4.1 mL, 8.2 mmol). The solution was stirred at -78 °C 30 mins under nitrogen. Then *N*-phenyl-O-((trifluoromethyl)sulfonyl)-*N*- (((trifluoromethyl) sulfonyl)oxy)hydroxylamine (1591 mg, 4.1 mmol) was added to the solution. The mixture was stirred at room temperature for 16 hrs. The reaction was quenched with NH_4Cl. The crude mixture was extracted with DCM (50 mL * 3), and the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated in *vacuo* to get the crude product. Then purified by Flash Chromatography (elution gradient: hexanes) to get the product 4-(difluoro methylene)cyclohex-1-en-1-yl trifluoromethanesulfonate (350 mg, 1.25 mmol, yield: 30.5 %) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.77 (s, 1H), 2.89 (s, 2H), 2.43 (s, 4H).

Step 4: To a solution of 4-(difluoromethylene)cyclohex-1-en-1-yl trifluoro methanesulfonate (350 mg, 1.25 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (383 mg, 1.5 mmol) and KOAc (247 mg, 2.5 mmol) in dioxane (3 mL) was added $Pd(dppf)Cl_2$ (92 mg, 0.12 mmol). The reaction mixture was stirred at 80°C for 5 hrs under nitrogen. The mixture was concentrated in *vacuo* and purified by Flash Chromatography (elution gradient: EtOAc-hexanes, 0-5%) to get the product 2-(4-(difluoromethylene)cyclohex-1-en-1-yl)-4,4,5,5-tetramethyl -1,3,2-dioxaborolane (90 mg, 0.35 mmol, yield: 28.0%) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.51 (s, 1H), 2.78 (s, 2H), 2.20 (s, 4H), 1.26 (s, 12H).

Step 5: To a solution of 2-(4-(difluoromethylene)cyclohex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (90 mg, 0.35 mmol), tert-butyl 4-(2-bromo-5-ethyl-7-oxo-4,7-dihydro-[1,2,4] triazolo[1,5-a]pyrimidin-6-yl)piperazine-1-carboxylate (165 mg, 0.38 mmol) and Na_2CO_3 in Dioxane (3 mL)/H_2O (0.5 mL) was added $Pd(dppf)Cl_2$ (25.17 mg, 0.1 mmol). The mixture was stirred at 100 °C for 16 hrs under nitrogen. The mixture was concentrated in *vacuo* and purified by Flash Chromatography (elution gradient: MeOH/DCM, 0-3%) to get the product *tert*-butyl 4-(2-(4-(difluoromethylene)cyclohex-1-en-1-yl)-5-ethyl-7-oxo-4,7-dihydro-[1,2,4]triazolo[1,5-a] pyrimidin-6-yl)piperazine-1-carboxylate (95 mg, 0.20 mmol, yield: 57.1%) as a yellow oil. **MS** (ESI) m/z = 477.3 $[M+H]^+$.

Step 6: To a solution of *tert*-butyl 4-(2-(4-(difluoromethylene)cyclohex-1-en-1-yl)-5-ethyl-7-oxo-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)piperazine-1-carboxylate (95 mg, 0.20 mmol), 2-bromo-*N*-(2-chloro-4-(trifluoromethyl) phenyl)acetamide (80 mg, 0.25 mmol) in DMF (3 mL) was added DIEA (81 mg, 0.63 mmol). The mixture was stirred at room temperature for 16

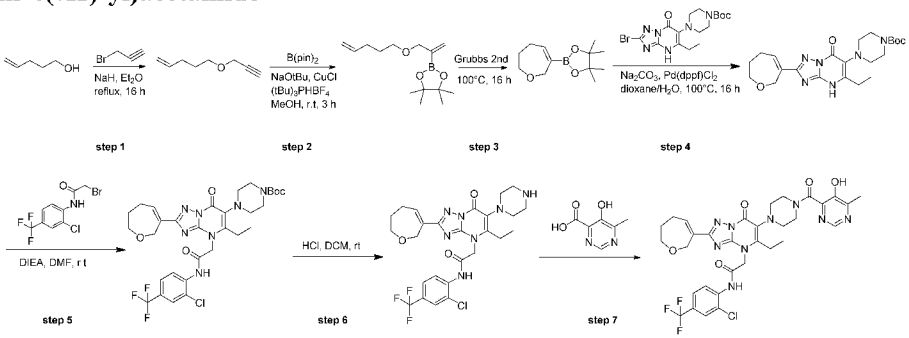
hrs. The mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL * 3). The organic layers were combined, washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford the crude product, which was purified by flash chromatography (elution gradient: MeOH/DCM = 0-20%) to afford the compound *tert*-butyl 4-(4-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-2-(4-(difluoromethylene) cyclohex-1-en-1-yl)-5-ethyl-7-oxo-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)piperazine-1-carboxylate (100 mg, 0.14 mmol, yield: 70.0%) as a yellow solid. **MS** (ESI) m/z = 656.3 $[M+H-56]^+$.

Step 7: A solution of *tert*-butyl 4-(4-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-2-(4-(difluoromethylene)cyclohex-1-en-1-yl)-5-ethyl-7-oxo-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)piperazine-1-carboxylate (100 mg, 0.14 mmol) in DCM (1 mL) was added HCl/Dioxane (4 M, 1 mL). The mixture was stirred at room temperature for 16 hrs. The mixture was concentrated under vacuum to afford the product *N*-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(4-(difluoromethylene)cyclohex-1-en-1-yl)-5-ethyl-7-oxo-6-(piperazin-1-yl)-[1,2,4]triazolo [1,5-a]pyrimidin-4(7*H*)-yl)acetamide (70 mg, 0.11 mmol, 78.6 % yield) as a white solid. **MS** (ESI) m/z = 612.3 $[M+H]^+$.

Step 8: To a solution of 5-hydroxy-6-methylpyrimidine-4-carboxylic acid (20 mg, 0.13 mmol) in DCM (3 mL) was added (1-chloro-2-methylprop-1-en-1-yl) dimethylamine (22 mg, 0.17 mmol). The mixture was stirred at room temperature for 30 mins. Then *N*-(2-chloro-4- (trifluoromethyl) phenyl)-2-(2-(4-(difluoromethylene)cyclohex-1-en-1-yl)-5-ethyl-7-oxo-6- (piperazin-1-yl)- [1,2,4] triazolo[1,5-a]pyrimidin-4(7*H*)-yl)acetamide (70 mg, 0.11 mmol) was added and the mixture was stirred at the room temperature for 30 mins. Then DIPEA (42 mg, 0.33 mmol) in DCM (1 mL) was added dropwise and the mixture was stirred at room temperature for 1 hour. The mixture was diluted with water (10 mL), extracted with DCM (10 mL * 3). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4, then concentrated under vacuum, purified by Prep-TLC (PE/EtOAc = 1/1) to get the product *N*-(2-chloro-4-(trifluoromethyl) phenyl)-2- (2-(4-(difluoromethylene)cyclohex-1-en-1-yl)-5-ethyl- 6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl) piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7*H*)-yl)acetamide (2.1 mg, 0.003 mmol, 2.7% yield) as a white solid. **^{1}H NMR** (400 MHz, CD_3OD) δ 8.59 (s, 1H), 8.18 (d, J = 8.6 Hz, 1H), 7.84 (s, 1H), 7.64 (d, J = 7.2 Hz, 1H), 6.99 (s, 1H), 5.40 (s, 2H), 4.72 (d, J = 12.0 Hz, 1H), 4.10 (d, J = 13.0 Hz, 1H), 3.76 (t, J = 13.0 Hz, 2H), 3.45 (t, J = 11.3 Hz, 1H), 3.22-3.08 (m, 3H), 2.96 (d, J = 19.3 Hz, 3H), 2.80 (d, J = 11.2 Hz, 1H), 2.68 (s, 2H), 2.54 (s, 3H), 2.42 (t, J = 6.4 Hz, 2H), 1.34 (d, J = 7.5 Hz, 3H). **MS** (ESI) m/z = 748.2 $[M+H]^+$.

Example 8:

***N*-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-2-(2,5,6,7-tetrahydrooxepin-3-yl)-[1,2,4]triazolo[1,5-a] pyrimidin-4(7*H*)-yl)acetamide**



Step 1: To a solution of NaH (1.68 g, 60%, 0.04 mol) in Et_2O (30 mL) was added pent-4-en-1-ol (3 g, 0.035 mol) dropwise, the reaction mixture was stirred at 30°C for 1 hr. 3-bromoprop-1-yne was added dropwise at room temperature, the reaction mixture was refluxed overnight. The mixture was quenched with ice-water (20 mL), extracted with EtOAc (20 mL* 3). The organic layers were combined, washed with brine (80 mL), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford the crude product, which was purified by flash chromatography (EtOAc/hexanes: 0~5%) to afford the compound 5-(prop-2-yn-1-yloxy) pent-1-ene (2 g, 0.016 mol, yield: 45.7%) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.83 – 5.77 (m, 1H), 5.05 – 4.93 (m, 2H), 4.17 – 4.07 (m, 2H), 3.51 (t, J = 6.5 Hz, 2H), 2.40 (t, J = 2.4 Hz, 1H), 2.22 – 2.05 (m, 2H), 1.72 – 1.64 (m, 2H).

Step 2: To a solution of 5-(prop-2-yn-1-yloxy)pent-1-ene (2 g, 0.016 mol) in toluene (10

mL), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (4.91 g, 0.019 mol), CuCl (0.16 g, 1.61 mmol), NaOtBu (0.46 g, 4.83 mmol) and $(tBu)_3PHBF_4$ (0.56 g, 1.93 mmol) were added at room temperature under argon, then methanol (2 mL) was added, the reaction mixture was stirred at room temperature for 3 hrs. Then concentrated under vacuum to afford the crude product, which was purified by flash chromatography (EtOAc/hexanes: 0~10%) to afford the compound 4,4,5,5-tetramethyl-2-(3-(pent-4-en-1-yloxy)prop-1-en-2-yl)-1,3,2-dioxaborolane (1.1 g, 4.36 mmol, yield: 27.2%) as yellow oil. **MS** (ESI) m/z = 253.3 $[M+H]^+$.

Step 3: A solution of 4,4,5,5-tetramethyl-2-[3-(pent-4-en-1-yloxy)prop-1-en-2-yl]-1,3,2-dioxaborolane (1.1 g, 4.4 mmol) in toluene (10 mL) was refluxed for 1 hr under argon, then cool to room temperature. Grubbs 2nd generation catalyst (190 mg, 0.2 mmol) was added, the reaction mixture was refluxed overnight. Then concentrated under vacuum to afford the crude product, which was purified by flash chromatography (EtOAc/hexanes: 0~10%) to afford the compound 4,4,5,5-tetramethyl-2-(2,5,6,7-tetrahydrooxepin-3-yl)-1,3,2-dioxaborolane (700 mg, 3.125 mmol, yield: 71.02%) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.73 (s, 1H), 4.27 (d, J = 1.1 Hz, 2H), 3.83 (t, J = 5.7 Hz, 2H), 2.39 (d, J = 5.8 Hz, 2H), 1.80 (m, 2H), 1.22 (s, 12H).

Step 4: The mixture of 4,4,5,5-tetramethyl-2-(2,5,6,7-tetrahydrooxepin-3-yl)-1,3,2-dioxaborolane (100 mg, 0.44 mmol), tert-butyl 4-{2-bromo-5-ethyl-7-oxo-4*H*-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl}piperazine-1-carboxylate (190 mg, 0.44 mmol), Na_2CO_3 (94 mg, 0.89 mmol) and $Pd(dppf)Cl_2$ (16 mg, 0.022 mmol) in Dioxane/H_2O = 5:1 (4 mL) was stirred at 100°C for 16 hrs. Then concentrated under vacuum to afford the crude product, which was purified by flash chromatography (Methanol/DCM: 0~10%) to afford the compound tert-butyl 4-(5-ethyl-7-oxo- 2-(2,5,6,7-tetrahydrooxepin-3-yl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)piperazine-1-carboxylate (80 mg, 0.18 mmol, yield: 40.95%) as a yellow oil. **MS** (ESI) m/z = 445.3 $[M+H]^+$.

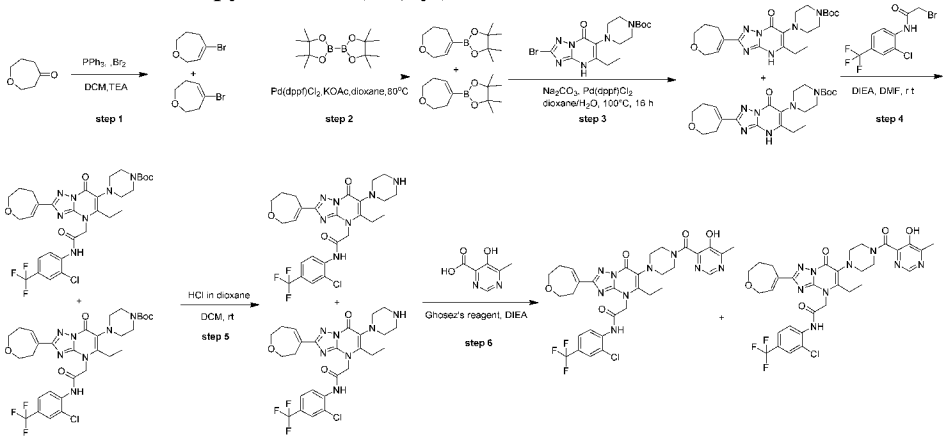
Step 5: The mixture of tert-butyl 4-[5-ethyl-7-oxo-2-(2,5,6,7-tetrahydrooxepin-3-yl)-4*H*-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl]piperazine-1-carboxylate (80 mg, 0.18 mmol), 2-bromo-*N*-[2-chloro-4-(trifluoromethyl)phenyl]acetamide (68 mg, 0.21 mmol) and DIEA (70 mg, 0.54 mmol) in DMF (5 mL) was stirred at room temperature for 16 hrs. The mixture was quenched with ice-water (20 mL) and extracted with EtOAc (10 mL * 3). The organic layers were combined, washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford the crude product, which was purified by flash chromatography (Methanol/DCM 0~10%) to afford the compound tert-butyl 4-(4-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino) -2-oxoethyl)-5-ethyl-7-oxo-2-(2,5,6,7-tetrahydrooxepin-3-yl)-4,7-dihydro-[1,2,4]triazolo[1,5-a] pyrimidin-6-yl)piperazine-1-carboxylate (100 mg, 0.14 mmol, yield: 81.8%) as a yellow oil. **MS** (ESI) m/z = 624.1 $[M+H]^+$.

Step 6: To a solution of tert-butyl 4-[4-({[2-chloro-4-(trifluoromethyl)phenyl] carbamoyl} methyl)-5-ethyl-7-oxo-2-(2,5,6,7-tetrahydrooxepin-3-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl]piperazine-1-carboxylate (100 mg, 0.14 mmol) in DCM (2 mL) was added HCl/dioxane (1 mL) and stirred at room temperature for 1 hr. Then concentrated under vacuum to afford the crude product *N*-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-7-oxo-6-(piperazin-1-yl)-2-(2,5,6,7- tetrahydrooxepin-3-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7*H*)-yl)acetamide (80 mg, 0.138 mmol, 98.69 %) as a pale yellow solid. **MS** (ESI) m/z = 580.3 $[M+H]^+$.

Step 7: To a solution of 5-hydroxy-6-methylpyrimidine-4-carboxylic acid (32 mg, 0.2 mmol) in DCM (3 mL) was added 1-chloro-*N*,*N*,2-trimethyl-1-propen-1-amine (35 mg, 0.25 mmol), the mixture was stirred at room temperature for 30 mins, then *N*-[2-chloro-4-(trifluoromethyl)phenyl] -2-[5-ethyl-7-oxo-6-(piperazin-1-yl)-2-(2,5,6,7-tetrahydrooxepin-3-yl)-[1,2,4]triazolo[1,5-a] pyrimidin-4-yl]acetamide (100 mg, 0.17 mmol) was added and the mixture was stirred at room temperature for 30 mins. DIEA (67 mg, 0.51 mmol) in DCM (1 mL) was added dropwise and the resulting mixture was stirred at room temperature for 1 hr. The mixture was concentrated and purified by Flash Chromatography (Methanol/DCM = 0~2%) and Prep-HPLC (Gemini-C18 150 * 21.2 mm 5um: ACN--H_2O (0.1%FA):55-85) to get the product *N*-(2-chloro-4-(trifluoromethyl) phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-2-(2,5,6,7-tetrahydrooxepin-3-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7*H*)-yl) acetamide (2 mg, 0.0026 mmol, yield: 1.51%) as a white solid. **^{1}H NMR** (400 MHz, CD_3OD) δ 8.51 (d, J = 24.4 Hz, 2H), 8.17 (d, J = 8.4 Hz, 1H), 7.84 (s, 1H), 7.64 (d, J = 8.3 Hz, 1H), 7.23 (t, J = 5.7 Hz, 1H), 5.39 (s, 2H), 4.77 (s, 2H), 4.07 (s, 1H), 3.95 (s, 2H), 3.73 (s, 2H), 3.43 (d, J = 53.4 Hz, 2H), 3.24-3.06 (m, 3H), 2.96 (s, 1H), 2.81 (s, 1H), 2.53 (s, 3H), 2.05 (s, 1H), 1.92 (d, J = 4.8 Hz, 2H), 1.62 (s, 1H), 1.31 (s, 3H). **MS** (ESI) m/z = 716.3 $[M+H]^+$.

Example 9 and Example 10:

***N*-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-2-(2,3,6,7-tetrahydrooxepin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-4(7*H*)-yl)acetamide and *N*-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6- (4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-2-(2,5,6,7-tetrahydrooxepin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-4(7*H*)-yl)acetamide**



Step 1: To a solution of Triphenyl phosphite (1631 mg, 5.257 mmol) in DCM (15 mL) stirred under nitrogen at -60 °C was added Br_2 (728 mg, 4.556 mmol). The reaction mixture was stirred at -60°C for 30 minutes. Then added TEA (709 mg, 7.009 mmol) and stirred at -60°C for 30 minutes. Then added oxepan-4-one (400 mg, 3.504 mmol). The reaction mixture was stirred at the room temperature for 16 hrs. The reaction mixture was quenched with water (20 mL). The crude mixture was extracted with DCM (50 mL * 3), and the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated in vacuo, then purified by Flash Chromatography (EtOAc/hexanes = 0-10%) to get the mixture 5-bromo-2,3,4,7-tetrahydrooxepine and 4-bromo-2,3,6,7-tetrahydrooxepine (150 mg, 0.847 mmol, yield: 24.2%) as a brown oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.16 (dt, *J* = 9.3, 5.3 Hz, 1H), 4.03 (dt, *J* = 4.6, 1.6 Hz, 0.6H), 3.84 – 3.76 (m, 1H), 3.70 (dd, *J* = 10.0, 4.6 Hz, 2H), 3.58 (dd, *J* = 5.5, 4.2 Hz, 0.3H), 2.92 – 2.68 (m, 2H), 2.28 – 2.24 (m, 1H), 1.97 – 1.86 (m, 1H).

Step 2: To a solution of mixture 5-bromo-2,3,4,7-tetrahydrooxepine and 4-bromo-2,3,6,7-tetrahydrooxepine (150 mg, 0.847 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-1,3,2-dioxaborolane (322.74 mg, 1.271 mmol) and [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (61.49 mg, 0.085 mmol) in dioxane (10 mL) was added KOAc (166.31 mg, 1.695 mmol). The reaction mixture was stirred under nitrogen at 80 °C for 10 hrs. The mixture was concentrated under vacuum. Then purified by Flash Chromatography (EtOAc/hexanes = 0-3%) to get the mixture of 4,4,5,5-tetramethyl-2-(2,5,6,7-tetrahydrooxepin-4-yl)-1,3,2-dioxaborolane; 4,4,5,5-tetramethyl-2-(2,3,6,7-tetrahydrooxepin-4-yl)-1,3,2-dioxaborolane (160 mg, 0.714 mmol, yield: 84.3%) as yellow oil. **MS** (ESI)m/z =225.3 $[M+H]^+$.

Step 3: To a solution of mixture 4,4,5,5-tetramethyl-2-(2,3,6,7-tetrahydrooxepin-4-yl)-1,3,2-dioxaborolane and 4,4,5,5-tetramethyl-2-(2,5,6,7-tetrahydrooxepin-4-yl)-1,3,2-dioxaborolane (160 mg, 0.714 mmol), *tert*-butyl 4-{2-bromo-5-ethyl-7-oxo-4*H*-[1,2,4]triazolo[1,5-*a*]pyrimidin-6-yl}piperazine-1-carboxylate (152.61 mg, 0.357 mmol) and Na_2CO_3 (151.41 mg, 1.429 mmol) in dioxane (6 mL)/H_2O (1 mL) was added $Pd(dppf)Cl_2$ (0.5 mg, 0.0714 mmol). The reaction mixture was stirred under nitrogen at 100°C for 16 hrs. The mixture was concentrated in vacuo and purified by Flash Chromatography (MeOH/DCM = 0-5%) to get the mixture of *tert*-butyl 4-(5-ethyl-7-oxo-2-(2,5,6,7-tetrahydrooxepin-4-yl)-4,7-dihydro-[1,2,4]triazolo[1,5-*a*]pyrimidin-6-yl)piperazine-1-carboxylate and *tert*-butyl 4-(5-ethyl-7-oxo-2-(2,3,6,7-tetrahydrooxepin-4-yl)-4,7-dihydro-[1,2,4]triazolo[1,5-*a*]pyrimidin-6-yl)piperazine-1-carboxylate (120 mg, 0.270 mmol, yield: 37.8%) as a yellow oil. **MS** (ESI) m/z = 445.3 $[M+H]^+$.

Step 4: To a solution of mixture *tert*-butyl 4-[5-ethyl-7-oxo-2-(2,3,6,7-tetrahydrooxepin-4-yl)-4*H*-[1,2,4]triazolo[1,5-*a*]pyrimidin-6-yl]piperazine-1-carboxylate and *tert*-butyl 4-[5-ethyl-7-oxo-2-(2,5,6,7-tetrahydrooxepin-4-yl)-4*H*-[1,2,4]triazolo[1,5-*a*]pyrimidin-6-yl]piperazine-1-carboxylate (120 mg, 0.270 mmol) and 2-bromo-*N*-[2-chloro-4-(trifluoromethyl)phenyl]acetamide (85.42 mg, 0.270 mmol) in DMF (10 mL) was added DIPEA (104.65 mg, 0.810 mmol).

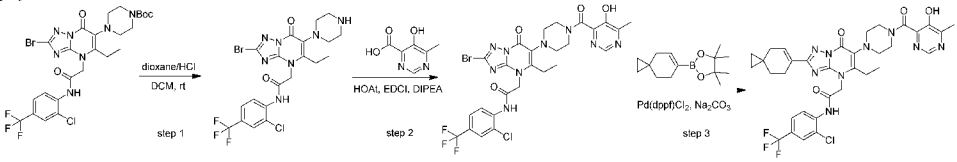
The reaction mixture was stirred at 25 °C for 16 hrs. The mixture was diluted with water (20 mL), extracted with EtOAc (20 mL * 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, concentrated under vacuum and purified by Flash Chromatography (EtOAc/hexanes = 50-80%) to give the mixture of *tert*-butyl 4-(4-(2-((2-chloro-4- (trifluoromethyl) phenyl)amino)-2-oxoethyl)-5-ethyl-7-oxo-2-(2,5,6,7-tetrahydrooxepin-4-yl)-4,7-dihydro-[1,2,4]tri azolo[1,5-*a*]pyrimidin-6-yl)piperazine-1-carboxylate and *tert*-butyl 4-(4-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-5-ethyl-7-oxo-2-(2,3,6,7-tetrahydrooxepin-4-yl)- 4,7-dihydro-[1,2,4]triazolo[1,5-*a*]pyrimidin-6-yl)piperazine-1-carboxylate (30 mg, 0.044 mmol, yield: 16.3%) as a yellow oil. **MS** (ESI) m/z = 680.2 $[M+H]^+$.

Step 5: To a solution of mixture *tert*-butyl 4-[4-({[2-chloro-4-(trifluoromethyl)phenyl] carbamoyl}methyl)-5-ethyl-7-oxo-2-(2,3,6,7-tetrahydrooxepin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyrimid in-6-yl]piperazine-1-carboxylate and *tert*-butyl 4-[4-({[2-chloro-4-(trifluoromethyl)phenyl] carbamoyl}methyl)-5-ethyl-7-oxo-2-(2,5,6,7-tetrahydrooxepin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyrimid in-6-yl]piperazine-1-carboxylate (30 mg, 0.044 mmol) in DCM (3 mL) was added HCl in 1,4-dioxane (4 N, 1 mL). The reaction mixture was stirred at 25 °C for 3 hrs. The mixture was concentrated under vacuo to get the mixture *N*-(2-chloro-4-(trifluoromethyl)phenyl)-2- (5-ethyl -7-oxo-6-(piperazin-1-yl)-2-(2,5,6,7-tetrahydrooxepin-4-yl)-[1,2,4]triazolo[1,5-*a*] pyrimidin- 4(7*H*) -yl)acetamide and *N*-(2-chloro-4- (trifluoromethyl) phenyl)-2-(5-ethyl-7-oxo-6-(piperazin-1-yl) -2-(2,3,6,7-tetrahydrooxepin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-4(7*H*)-yl)acetamide (35 mg, 0.042 mmol, yield: 95.7%) as a yellow oil. **MS** (ESI) m/z =580.3 $[M+H]^+$.

Step 6: To a solution of 5-hydroxy-6-methylpyrimidine-4-carboxylic acid (11.15 mg, 0.072 mmol) in DCM (4 mL) was added (1-chloro-2-methylprop-1-en-1-yl)dimethylamine (12.09 mg, 0.0904 mmol). The mixture was stirred at the room temperature for 30 minutes. Then the mixture of *N*-[2-chloro-4-(trifluoromethyl)phenyl]-2-[5-ethyl-7-oxo-6-(piperazin-1-yl)-2-(2,3,6,7-tetrahy drooxepin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-4-yl]acetamide and *N*-[2-chloro-4-(trifluoro methyl)phenyl]-2-[5-ethyl-7-oxo-6-(piperazin-1-yl)-2-(2,5,6,7-tetrahydrooxepin-4-yl)-[1,2,4]triaz olo[1,5-*a*]pyrimidin-4-yl]acetamide (35 mg, 0.060 mmol) was added and the mixture was stirred at the room temperature for 30 minutes. Then DIPEA (23.38 mg, 0.181 mmol) in DCM (1 mL) was added dropwise and the mixture was stirred at the room temperature for 1 hr. The mixture was diluted with water (10 mL), extracted with DCM (10 mL * 3). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4, then concentrated under vacuum, purified by Flash Chromatography (MeOH/DCM = 0-2%) and Prep-HPLC (Gemini-C18 150 * 21.2 mm 5um: ACN--H_2O (0.1%FA):55-85) to get the mixture *N*-(2-chloro-4-(trifluoromethyl) phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-2-(2,3,6,7-tetrahydr ooxepin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-4(7*H*)-yl)acetamide and *N*-(2-chloro-4-(trifluoro methyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo -2-(2,5,6,7-tetrahydrooxepin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-4(7*H*)-yl)acetamide (11.7 mg, 0.016 mmol, 27.0 % yield) as a yellow solid. **^{1}H NMR** (400 MHz, CD_3OD) δ 8.49 (s, 1H), 8.13 (d, *J* = 7.8 Hz, 1H), 7.79 (s, 1H), 7.59 (d, *J* = 6.7 Hz, 1H), 7.23 (d, *J* = 5.3 Hz, 0.6H), 7.00 (s, 0.2H), 5.35 (s, 2H), 4.67 (d, *J* = 11.4 Hz, 1H), 4.30 (s, 0.4H), 4.03 (d, *J* = 9.0 Hz, 1H), 3.88 (t, *J* = 5.0 Hz, 0.4H), 3.71 (d, *J* = 17.5 Hz, 4.5H), 3.41 (t, *J* = 12.0 Hz, 1H), 3.16 – 2.82 (m, 6H), 2.75 (d, *J* = 8.9 Hz, 1H), 2.51 (s, 1H), 2.48 (s, 3H), 2.04 – 1.85 (m, 0.8H), 1.57 (s, 0.2H), 1.28 (s, 2H), 1.27 (d, *J* = 6.5 Hz, 3H). **MS** (ESI) m/z = 716.3 $[M+H]^+$.

Example 11:

_N_-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-2-(spiro[2.5]oct-5-en-6-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7*H*)-yl)acetamide



Step 1: **:** To a solution of tert-butyl 4-(2-bromo-4-(2-((2-chloro-4-(trifluoromethyl)phenyl) amino)-2-oxoethyl)-5-ethyl-7-oxo-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)piperazine-1-c arboxylate (480 mg, 0.72 mmol) in DCM (5 mL) was added HCl/dioxane (2 mL) and stirred at room temperature for 1 hr. Then concentrated under vacuum to afford the crude product 2-(2-bromo-5-ethyl-7-oxo-6-(piperazin-1-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chlor

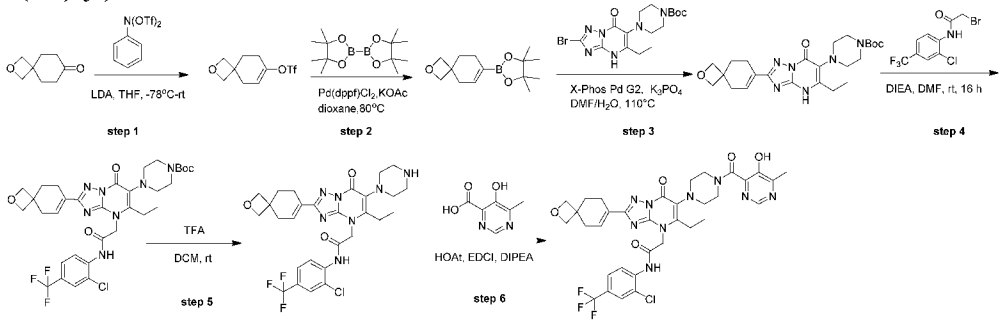
o-4-(trifluoromethyl)phenyl)acetamide (450 mg, crude) as solid. **MS** (ESI) m/z = 562.0 $[M+H]^+$.

Step 2: The mixture of 5-hydroxy-6-methylpyrimidine-4-carboxylic acid (248 mg, 1.6 mmol), HOAt (163 mg, 1.2 mmol) and EDCI (229 mg, 1.2 mmol) in ACN (10 mL) was stirred at room temperature for 1 hr under argon, then 2-(2-bromo-5-ethyl-7-oxo-6-(piperazin-1-yl)-[1,2,4] triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (450 mg, 0.8 mmol) and DIEA (310 mg, 2.4 mmol) in ACN (5 mL) was added, the mixture was stirred at room temperature for 1 hr. The mixture was concentrated and purified by Flash Chromatography (Methanol/DCM = 0~10%) to get the product 2-(2-bromo-5-ethyl-6-(4-(5-hydroxy-6-methyl pyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chlor o-4-(trifluoromethyl)phenyl)acetamide (360 mg, 0.51 mmol, yield: 64.4%) as a white solid. **MS** (ESI) m/z = 698.0/700.0 $[M]^+/[M+2]^+$.

Step 3: The mixture of 2-(2-bromo-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4- carbonyl) piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(trifluoromethyl)p henyl)acetamide (90 mg, 0.13 mmol), 4,4,5,5-tetramethyl-2-{spiro[2.5]oct-5-en-6-yl}-1,3,2-dioxaborolane (45 mg, 0.19 mmol), $Pd(dppf)Cl_2$ (9 mg, 0.013 mmol) and sodium carbonate (41 mg, 0.39 mmol) in dioxane/water=10:1 (4 mL) was stirred at 90°C overnight under nitrogen. Then the mixture was concentrated under vacuum to afford the crude product, which was purified by prep-HPLC (HPLC (Mobile Phase: ACN-H_2O (0.1%FA), 45/55-85/15)) to afford the compound *N*-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbon yl)piperazin-1-yl)-7-oxo-2-(spiro[2.5]oct-5-en-6-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7*H*)-yl)acet amide (18 mg, 0.025 mmol, yield: 19.2%) as a white solid. **^{1}H NMR** (400 MHz, CD_3OD) δ 8.59 (s, 1H), 8.18 (d, *J* = 8.6 Hz, 1H), 7.82 (s, 1H), 7.63 (d, *J* = 7.3 Hz, 1H), 7.04 (s, 1H), 5.40 (s, 2H), 4.72 (d, *J* = 12.3 Hz, 1H), 4.12 (d, *J* = 12.7 Hz, 1H), 3.76 (t, *J* = 11.5 Hz, 2H), 3.51 - 3.39 (m, 1H), 3.22 – 3.05 (m, 3H), 2.95 (d, *J* = 11.4 Hz, 1H), 2.80 (d, *J* = 11.0 Hz, 1H), 2.64 (s, 2H), 2.55 (s, 3H), 2.14 (s, 2H), 1.56 (t, *J* = 6.1 Hz, 2H), 1.33 (t, *J* = 7.5 Hz, 3H), 0.44 – 0.34 (m, 4H). **MS** (ESI) m/z = 726.2 $[M+H]^+$.

Example 12:

N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-2-(2-oxaspiro[3.5]non-6-en-7-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide



Step 1: To a solution of 2-oxaspiro[3.5]nonan-7-one (200 mg, 1.42 mmol) and phenyl [(trifluoromethane)sulfonyloxy]amino trifluoromethanesulfonate (555 mg, 1.42 mmol) in THF (5 mL) was added LDA (1.5 mL, 3 mmol) at -78°C, the mixture was stirred at room temperature for 16 hrs under argon, then concentrated under vacuum to afford the crude product, which was purified by flash chromatography (EtOAc/hexanes: 0~5%) to afford the compound 2-oxaspiro[3.5] non-6-en-7-yl trifluoromethanesulfonate (200 mg, 0.73 mmol, yield:51.7%) as a yellow oil. **^{1}H NMR** NMR (400 MHz, $CDCl_3$) δ 5.70-5.65 (m, 1H), 4.47 (d, *J* = 6.0 Hz, 2H), 4.43 (d, *J* = 6.0 Hz, 2H), 2.55-2.50 (m, 2H), 2.39 (dtd, *J* = 6.4, 4.0, 2.0 Hz, 2H), 2.10-2.05 (m, 2H).

Step 2: The mixture of 2-oxaspiro[3.5]non-6-en-7-yl trifluoromethanesulfonate (200 mg, 0.73 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (205 mg, 0.8 mmol), $Pd(dppf)Cl_2$ (52 mg, 0.07 mmol) and KOAc (144 mg, 1.46 mmol) in dioxane (5 mL) was stirred at 80°C for 16 hrs under argon, then concentrated under vacuum to afford the crude product, which was purified by flash chromatography (EtOAc/ hexanes: 0~5%) to afford the compound 4,4,5,5-tetramethyl-2-(2-oxaspiro[3.5]non-6-en-7-yl)-1,3,2-dioxaborolane (100 mg, 0.4 mmol, yield: 54.7%) as a pale yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.45 (d, *J* = 1.8 Hz, 1H), 4.40 (dd, *J* = 19.2, 5.7 Hz, 4H), 2.45-2.40 (m, 2H), 2.18 (d, *J* = 2.3 Hz, 2H), 1.85 (t, *J* = 6.3 Hz, 2H), 1.24 (s, 12H).

Step 3: The mixture of 4,4,5,5-tetramethyl-2-(2-oxaspiro[3.5]non-6-en-7-yl)-1,3,2-dioxaborolane (60 mg, 0.24 mmol), tert-butyl 4-{2-bromo-5-ethyl-7-oxo-4H-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl}piperazine-1-carboxylate (68 mg, 0.16 mmol), X-Phos Pd G2 (12 mg, 0.016 mmol) and K_3PO_4 (101 mg, 0.48 mmol) in DMF (5 mL) and H_2O (0.5 mL) was stirred at 110°C for 16 hrs under argon. The mixture was quenched with ice-water (20 mL) and extracted with EtOAc (10 mL * 3). The organic layers were combined, washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford the crude product, which was purified by flash chromatography (Methanol /DCM: 0~10%) to afford the compound tert-butyl 4-(5-ethyl-7-oxo-2-(2-oxaspiro[3.5]non-6-en-7-yl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)piperazine-1-carboxylate (30 mg, 0.06 mmol, yield: 39.8%) as a yellow oil. **MS** (ESI) m/z = 471.4 $[M+H]^+$.

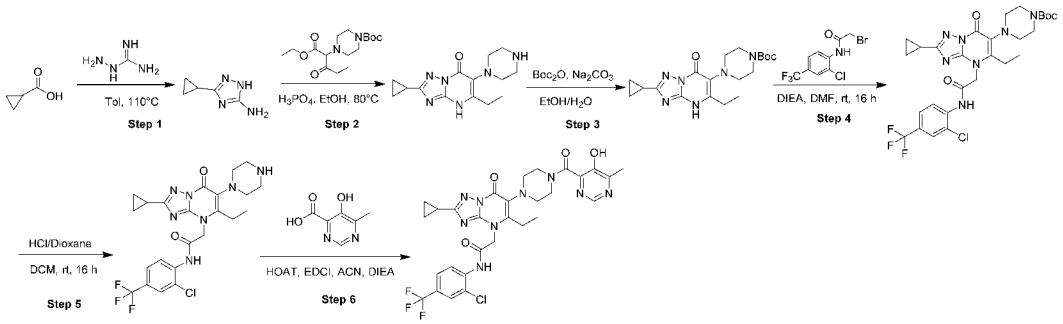
Step 4: The mixture of tert-butyl 4-(5-ethyl-7-oxo-2-(2-oxaspiro[3.5]non-6-en-7-yl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)piperazine-1-carboxylate (30 mg, 0.06 mmol), 2-bromo-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (23 mg, 0.07 mmol) and DIPEA (23 mg, 0.18 mmol) in DMF (3 mL) was stirred at room temperature for 6 hrs. The mixture was quenched with ice-water (20 mL) and extracted with EtOAc (10 mL * 3). The organic layers were combined, washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford the crude product, which was purified by flash chromatography (Methanol/DCM: 0~10%) to afford the compound tert-butyl 4-(4-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-5-ethyl-7-oxo-2-(2-oxaspiro[3.5]non-6-en-7-yl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)piperazine-1-carboxylate (20 mg, 0.03 mmol, yield: 47.2%) as a yellow oil. **MS** (ESI) m/z = 650.3 $[M-56+H]^+$.

Step 5: To a solution of tert-butyl 4-(4-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-5-ethyl-7-oxo-2-(2-oxaspiro[3.5]non-6-en-7-yl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)piperazine-1-carboxylate (20 mg, 0.03 mmol) in DCM (2 mL) was added TFA (1 mL) and stirred at room temperature for 1 hr. The mixture was quenched by $NaHCO_3$ and extracted with EtOAc (10 mL * 3). The organic layers were combined, washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford the crude product N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-7-oxo-6-(piperazin-1-yl)-2-(2-oxaspiro[3.5]non-6-en-7-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide (15 mg, 0.024 mmol, yield: 82.6%) as a pale yellow solid. **MS** (ESI) m/z = 606.0 $[M+H]^+$.

Step 6: The mixture of 5-hydroxy-6-methylpyrimidine-4-carboxylic acid (8 mg, 0.048 mmol), HOAt (5 mg, 0.036 mmol) and EDCI (7 mg, 0.036 mmol) in ACN (5 mL) was stirred at room temperature for 1 hr under argon, then N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-7-oxo-6-(piperazin-1-yl)-2-(2-oxaspiro[3.5]non-6-en-7-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide (15 mg, 0.024 mmol) and DIEA (10 mg, 0.072 mmol) in ACN (3 mL) was added, the mixture was stirred at room temperature for 1 hr. The mixture was concentrated and purified by Flash Chromatography (Methanol/DCM = 0~2%) and Prep-HPLC (Gemini-C18 150 x 21.2 mm 5um: ACN--H_2O (0.1%FA):55-85) to get the product N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-2-(2-oxaspiro[3.5]non-6-en-7-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide (6.4 mg, 0.008 mmol, yield: 35.9%) as a white solid. **^{1}H NMR** (400 MHz, CD_3OD) δ 8.46 (s, 1H), 8.05 (d, J=8.5 Hz, 1H), 7.71 (s, 1H), 7.51 (d, J=7.3 Hz, 1H), 6.82 (s, 1H), 5.27 (s, 2H), 4.60 (d, J=12.4 Hz, 1H), 4.42 (d, J=5.8 Hz, 2H), 4.33 (d, J=5.8 Hz, 2H), 4.00 (d, J=12.4 Hz, 1H), 3.63 (s, 2H), 3.33 (t, J=11.5 Hz, 1H), 3.20-3.10 (m, 3H), 2.82 (d, J=10.5 Hz, 1H), 2.68 (d, J=10.5 Hz, 1H), 2.51 (d, J=11.3 Hz, 4H), 2.42 (s, 3H), 1.95 (t, J=6.2 Hz, 2H), 1.20 (t, J=7.4 Hz, 3H). **MS** (ESI) m/z = 742.3 $[M+H]^+$.

Example 14:

***N*-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-cyclopropyl-5-ethyl-6-(4-(5-hydroxy-6-methyl pyrimidine -4- carbonyl) piperazin-1-yl) -7-oxo- [1,2,4] triazolo [1,5-a] pyrimidin -4(7*H*)-yl) acetamide**



Step 1: A mixture of cyclopropanecarboxylic acid (2.5 g, 29 mmol), Aminoguanidine bicarbonate (3.95 g, 29 mmol) in Tol (40 mL) was stirred at 110°C for 16 hrs under dean stark apparatus. The mixture was concentrated and purified by flash (MeOH:DCM = 0~10%) to get the product 5-cyclopropyl-2*H*-1,2,4-triazol-3-amine (0.44 g, 2.8 mmol, yield: 9.66%) as oil. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.82 (s, 1H), 5.51 (s, 2H), 1.77-1.70 (m, 1H), 0.82-0.76 (m, 4H).

Step 2 & 3: To a solution of 5-cyclopropyl-2*H*-1,2,4-triazol-3-amine (150 mg, 1.2 mmol) in EtOH (5 mL) were added tert-butyl 4-(1-ethoxy-1,3-dioxopentan-2-yl)piperazine-1-carboxylate (397 mg, 1.2 mmol) and H_3PO_4 (355 mg, 3.6 mmol). The reaction mixture was stirred at 80°C for 72 hrs under N_2. Then the mixture was added Sat.Na_2CO_3 to pH=10 with Boc_2O (1.3 g, 6.0 mmol). The mixture was stirred at 25°C for 3 hrs. The mixture was concentrated under vacuum and purified by Flash Chromatography (MeOH-DCM = 0~3%) to give the product tert-butyl 4-{2-cyclopropyl-5-ethyl-7-oxo-4*H*-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl}piperazine-1-carboxylate (50 mg, 0.12 mmol, yield: 10.1%) as a colorless oil. **MS** (ESI) m/z = 389.1 $[M+H]^+$.

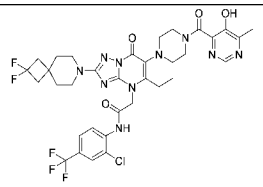
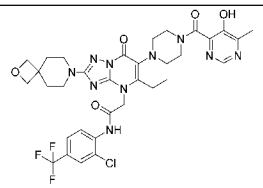
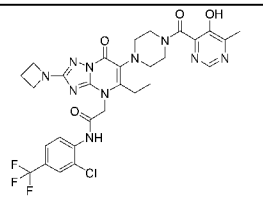
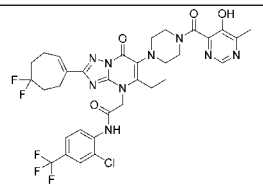
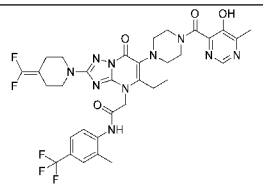
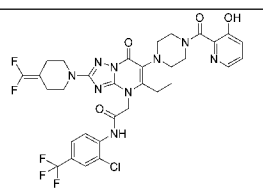
Step 4: To a solution of tert-butyl 4-{2-cyclopropyl-5-ethyl-7-oxo-4*H*-[1,2,4]triazolo[1,5-a] pyrimidin-6-yl}piperazine-1-carboxylate (50 mg, 0.13 mmol) in DMF (4 mL) were added 2-bromo-*N*-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (49 mg, 0.15 mmol) and DIPEA (50 mg, 0.39 mmol). The mixture was diluted with water (20 mL), extracted with EtOAc (20 mLx3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, concentrated under vacuum and purified by Flash Chromatography (MeOH-DCM = 0~3%) to give the product tert-butyl 4-[4-({[2-chloro-4-(trifluoromethyl)phenyl]carbamoyl}methyl)-2-cyclopropyl-5-ethyl -7 -oxo-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl]piperazine-1-carboxylate (50 mg, 0.064 mmol, yield: 49.8%) as a yellow solid. **MS** (ESI) m/z = 624.0 $[M+H]^+$.

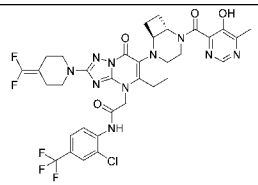
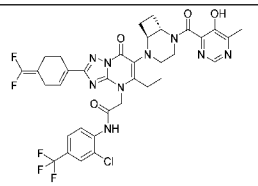
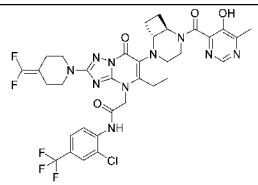
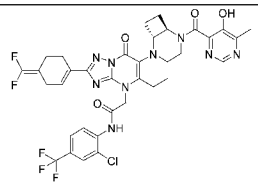
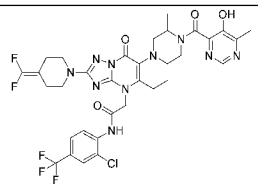
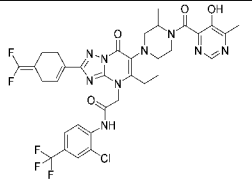
Step 5: A mixture of tert-butyl 4-[4-({[2-chloro-4-(trifluoromethyl)phenyl]carbamoyl} methyl)-2-cyclopropyl-5-ethyl-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl]piperazine-1-carboxylat e (50 mg, 0.08 mmol) in HCl/Dioxane (1 mL) and DCM (1 mL) was stirred at 25°C for 1 hr. The mixture was concentrated to give *N*-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-cyclopropyl-5-ethyl-7-oxo-6-(piperazin-1-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4-yl]acetamide (40 mg, crude) as a yellow oil. **MS** (ESI) m/z = 524.0 $[M+H]^+$.

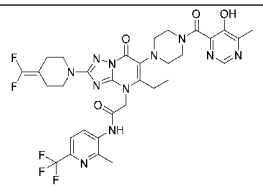
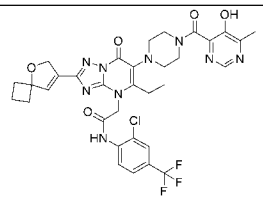
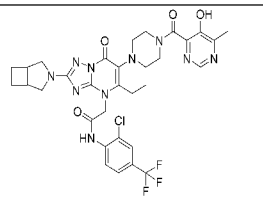
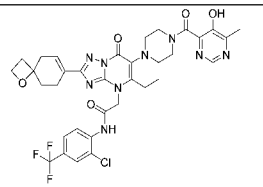
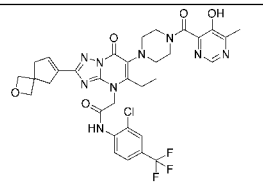
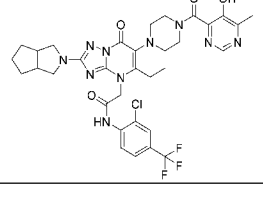
Step 6: The mixture of 5-hydroxy-6-methylpyrimidine-4-carboxylic acid (18 mg, 0.11 mmol), HOAt (10 mg, 0.076 mmol) and EDCI (22 mg, 0.11 mmol) was stirred in ACN at 25°C for 1 hr under N_2, then *N*-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-cyclopropyl-5-ethyl-7-oxo-6-(piperazin-1-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4-yl]acetamide (40 mg, 0.076 mmol) and DIEA (49 mg, 0.38 mmol) was added and further stirred for 15 hrs. The mixture was concentrated and purified by Prep-HPLC (Gemini-C18 150 * 21.2 mm, 5um: ACN--H_2O(0.1%FA):45-75) to get the product *N*-[2-chloro-4-(trifluoromethyl)phenyl]-2-(2-cyclopropyl-5-ethyl-6-{4-[(5-hydroxy-6-methylpyrimidin-4-yl)carbonyl]piperazin-1-yl}-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4-yl) acetamide (6.0 mg, 0.009 mmol, yield: 11.8%) as a white solid. **^{1}H NMR** (400 MHz, CD_3OD) δ 8.51 (s, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.81 (d, *J* = 1.1 Hz, 1H), 7.61 (d, *J* = 8.7 Hz, 1H), 5.31 (s, 2H), 4.69 (d, *J* = 12.4 Hz, 1H), 4.13 - 3.94 (m, 1H), 3.78 – 3.62 (m, 2H), 3.52- 3.36 (m, 1H), 3.15 - 2.92 (m, 3H), 2.95 – 2.72 (m, 2H), 2.50 (s, 3H), 2.09 - 2.02 (m, 1H), 1.33 - 1.17 (m, 5H), 1.03 - 0.98 (m, 2H). **MS** (ESI) m/z = 660.2 $[M+H]^+$.

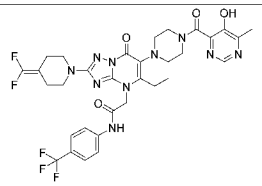
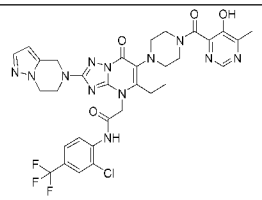
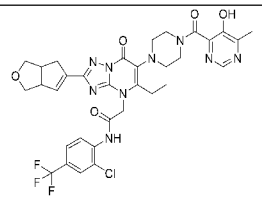
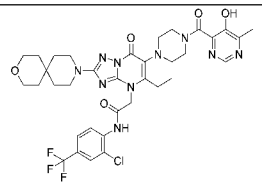
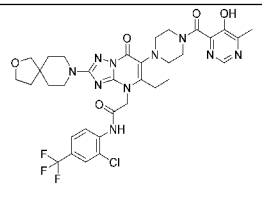
The following compounds were synthesized by using the similar methods as above procedure or reference. The start material is commercially available or prepared in house.

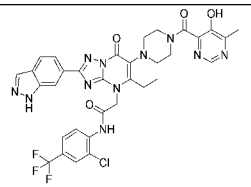
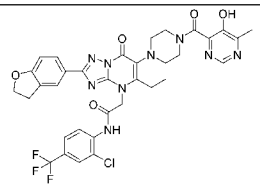
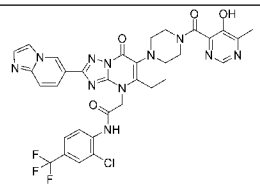
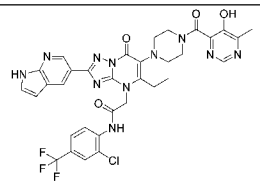
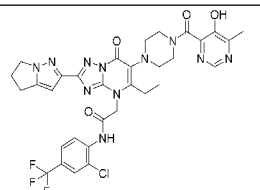
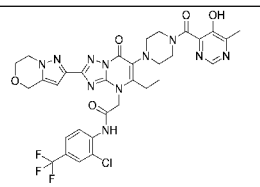
Example number	Structure	Name of structure	Data (NMR and LCMS)

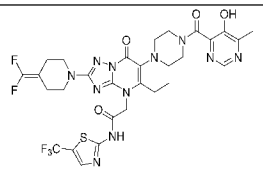
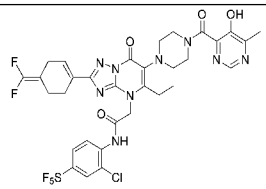
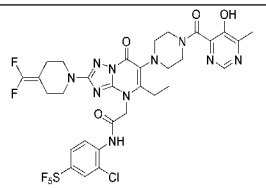
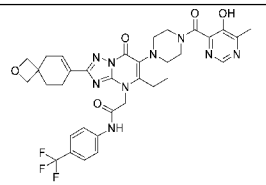
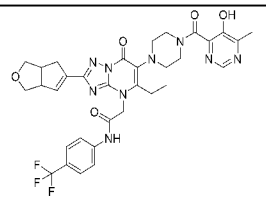
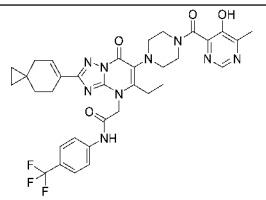
25		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(2,2-difluoro-7-azaspiro[3.5]nonan-7-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.53 (s, 1H), 8.13 (d, J=8.6 Hz, 1H), 7.79 (s, 1H), 7.65-7.55 (m, 1H), 5.25 (s, 2H), 4.66 (d, J=11.6 Hz, 1H), 4.05 (d, J=13.3 Hz, 1H), 3.75-3.65 (m, 2H), 3.50-3.45 (m, 4H), 3.39 (t, J=11.8 Hz, 1H), 3.06 (dt, J=14.7, 8.5 Hz, 3H), 2.87 (d, J=10.5 Hz, 1H), 2.72 (d, J=10.3 Hz, 1H), 2.49 (s, 3H), 2.35 (t, J=12.7 Hz, 4H), 1.70 - 1.64 (m, 4H), 1.24 (d, J=7.6 Hz, 3H). **MS** (ESI) m/z = 779.2 $[M+H]^+$.
26		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-2-(2-oxa-7-azaspiro[3.5]nonan-7-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.42 (s, 1H), 8.05 (d, J=8.5 Hz, 1H), 7.72 (s, 1H), 7.52 (d, J=8.5 Hz, 1H), 5.18 (s, 2H), 4.59 (d, J=12 Hz, 1H), 4.36 (s, 4H), 3.98 (d, J=12 Hz, 1H), 3.62 (d, J=6.5 Hz, 2H), 3.40-3.25 (m, 5H), 3.05- 2.90 (m, 3H), 2.79 (d, J=11 Hz, 1H), 2.64 (d, J=11.1 Hz, 1H), 2.41 (s, 3H), 1.80-1.75 (m, 4H), 1.17 (t, J=7.2 Hz, 3H). **MS** (ESI) m/z = 745.2 $[M+H]^+$.
34		2-(2-(azetidin-1-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(trifluoromethyl) phenyl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.51 (s, 1H), 8.14 (d, *J* = 8.5 Hz, 1H), 7.78 (s, 1H), 7.59 (d, *J* = 8.5 Hz, 1H), 5.25 (s, 2H), 4.66 (d, *J* = 12.2 Hz, 1H), 4.05 (t, *J* = 7.4 Hz, 5H), 3.68 (s, 2H), 3.37 (dd, *J* = 24.8, 13.8 Hz, 1H), 3.15-2.95 (m, 3H), 2.86 (d, *J* = 11.1 Hz, 1H), 2.72 (d, *J* = 11.3 Hz, 1H), 2.49 (s, 3H), 2.45-2.35 (m, 2H), 1.24 (t, *J* = 7.3 Hz, 3H). **MS** (ESI) m/z = 675.2 $[M+H]^+$.
37		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(5,5-difluorocyclohept-1-en-1-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.58 (s, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 7.84 (s, 1H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.26 (t, *J* = 6.8 Hz, 1H), 5.40 (s, 2H), 4.73 (d, *J* = 10.1 Hz, 1H), 4.10 (d, *J* = 12.8 Hz, 1H), 3.80 - 3.72 (m, 2H), 3.50 - 3.43 (m, 1H), 3.28 – 3.05 (m, 3H), 2.99 – 2.76 (m, 4H), 2.70 - 2.54 (m, 3 H), 2.47 – 2.32 (m, 2H), 2.17 – 1.89 (m, 4H), 1.33 (t, *J* = 7.4 Hz, 3H). **MS** (ESI) m/z = 750.2 $[M+H]^+$.
41		2-(2-(4-(difluoromethylene)piperidin-1-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-methyl-4-(trifluoromethyl) phenyl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.55 (s, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.58 (s, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 5.25 (s, 2H), 4.70 (d, *J* = 12.0 Hz, 1H), 4.08 (d, *J* = 12.2 Hz, 1H), 3.82 - 3.68 (m, 2H), 3.67 - 3.56 (m, 4H), 3.44 (t, *J* = 11.6 Hz, 1H), 3.20 – 3.02 (m, 3H), 2.92 (d, *J* = 11.8 Hz, 1H), 2.77 (d, *J* = 10.1 Hz, 1H), 2.53 (s, 3H), 2.41 (s, 3H), 2.32 - 2.16(m, 4H), 1.31 (t, *J* = 7.4 Hz, 3H). **MS** (ESI) m/z = 731.2 $[M+H]^+$.
43		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(4-(difluoromethylene)piperidin-1-yl)-5-ethyl-6-(4-(3-hydroxypicolinoyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.12 (d, *J* = 8.6 Hz, 1H), 8.08 – 8.02 (m, 1H), 7.79 (d, *J* = 1.4 Hz, 1H), 7.60 (d, *J* = 8.7 Hz, 1H), 7.32 (d, *J* = 2.8 Hz, 2H), 5.25 (s, 2H), 4.68 (d, *J* = 11.0 Hz, 1H), 3.68 (dd, *J* = 25.4, 12.9 Hz, 3H), 3.61 – 3.52 (m, 4H), 3.46 - 3.32 (m, 1H), 3.15 – 2.97 (m, 3H), 2.87 (d, *J* = 8.2 Hz, 1H), 2.70 (s, 1H), 2.25 - 2.17 (m, 4H), 1.25 (t, *J* = 7.6 Hz, 3H). **MS** (ESI) m/z = 736.2 $[M+H]^+$.

45		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(4-(difluoromethylene)piperidin-1-yl)-5-ethyl-6-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.51 (s, 1H), 8.12 (d, J = 8.5 Hz, 1H), 7.79 (s, 1H), 7.60 (d, J = 8.7 Hz, 1H), 5.25 (s, 2H), 4.62 (s, 1H), 3.84 (d, J = 7.6 Hz, 1H), 3.73 – 3.34 (m, 8H), 3.17 - 3.07 (m, 1H), 3.04 - 2.92 (m, 1H), 2.48 (s, 3H), 2.25 - 2.16 (m, 4H), 1.68 (d, J = 28.3 Hz, 2H), 1.53 – 1.40 (m, 1H), 1.36 - 1.22 (m, 4H). **MS** (ESI) m/z = 777.2 $[M+H]^+$.
46		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(4-(difluoromethylene)cyclohex-1-en-1-yl)-5-ethyl-6-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.54 (s, 1H), 8.17 (d, *J* = 8.6 Hz, 1H), 7.83 (s, 1H), 7.63 (d, *J* = 8.3 Hz, 1H), 6.98 (s, 1H), 5.39 (s, 2H), 4.67 (s, 1H), 3.90 (s, 1H), 3.70 (d, *J* = 23.4 Hz, 2H), 3.53 (d, *J* = 19.1 Hz, 2H), 3.22 (dd, *J* = 13.8, 7.3 Hz, 1H), 3.07 (dd, *J* = 13.7, 7.1 Hz, 1H), 2.98 (s, 2H), 2.74 - 2.62 (m, 2H), 2.52 (s, 3H), 2.45 - 2.37 (m, 2H), 1.74 (d, *J* = 25.4 Hz, 2H), 1.51 (s, 1H), 1.33 (t, *J* = 7.5 Hz, 4H). **MS** (ESI) m/z = 774.2 $[M+H]^+$.
51		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(4-(difluoromethylene)piperidin-1-yl)-5-ethyl-6-((1R,6R)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.48 (s, 1H), 8.12 (d, J = 8.6 Hz, 1H), 7.79 (s, 1H), 7.59 (d, J = 8.8 Hz, 1H), 5.35 – 5.19 (m, 2H), 4.63 (s, 1H), 3.83 (d, J = 7.0 Hz, 1H), 3.74 – 3.35 (m, 8H), 3.11 (dt, J = 14.7, 7.4 Hz, 1H), 2.99 (dd, J = 13.9, 7.3 Hz, 1H), 2.47 (s, 3H), 2.25 - 2.15 (m, 4H), 1.67 (d, J = 29.0 Hz, 2H), 1.45 (s, 1H), 1.29 - 1.22 (m ,4H). **MS** (ESI) m/z = 777.2 $[M+H]^+$.
52		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(4-(difluoromethylene)cyclohex-1-en-1-yl)-5-ethyl-6-((1R,6R)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.39 (s, 1H), 8.05 (d, *J* = 8.6 Hz, 1H), 7.71 (s, 1H), 7.51 (d, *J* = 8.7 Hz, 1H), 6.86 (s, 1H), 5.27 (s, 2H), 4.55 (s, 1H), 3.77 (d, *J* = 10.8 Hz, 1H), 3.49 (dd, *J* = 66.2, 19.4 Hz, 4H), 3.10 (dd, *J* = 13.9, 7.5 Hz, 1H), 2.95 (dd, *J* = 13.8, 7.4 Hz, 1H), 2.86 (s, 2H), 2.56 (s, 2H), 2.40 (s, 3H), 2.30 (t, *J* = 6.1 Hz, 2H), 1.60 (d, *J* = 32.3 Hz, 2H), 1.39 (s, 1H), 1.23 – 1.18 (m, 4H). **MS** (ESI) m/z = 774.2 $[M+H]^+$.
57		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(4-(difluoromethylene)piperidin-1-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-3-methylpiperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz,CD_3OD) δ 8.54 (d, *J* = 1.2 Hz, 1H), 8.12 (d, *J* = 8.7 Hz, 1H), 7.79 (s, 1H), 7.59 (d, *J* = 8.5 Hz, 1H), 5.26 (s, 2H), 4.96 – 4.85 (m, 0.5H), 4.53 (d, *J* = 13.3 Hz, 0.5H), 4.18 - 4.10 (m, 0.5H), 3.92 - 3.86 (m, 1H), 3.80 – 3.59 (m, 2H), 3.57 (t, *J* = 5.6 Hz, 4H), 3.39 – 3.30 (m, 0.5H), 3.21 – 3.09 (m, 1H), 3.06 – 2.95 (m, 1H), 2.87 (d, *J* = 10.9 Hz, 0.5H), 2.73 (t, *J* = 12.3 Hz, 1H), 2.62 (d, *J* = 11.7 Hz, 0.5H), 2.50 (s, 3H), 2.25 – 2.17 (m, 4H), 1.55 – 1.48 (m, 3H), 1.28 (t, *J* = 7.2 Hz, 3H). **MS** (ESI) m/z = 765.0 $[M+H]^+$.
58		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(4-(difluoromethylene)cyclohex-1-en-1-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-3-methylpiperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.14 (d, J = 8.6 Hz, 1H), 7.80 (s, 1H), 7.60 (d, J = 8.6 Hz, 1H), 6.95 (s, 1H), 5.37 (s, 2H), 4.96 - 4.91 (m, 0.5H), 4.57 - 4.54(m, 1H), 4.19 - 4.12 (m, 0.5H), 3.94 - 3.88 (m, 1H), 3.79 – 3.63 (m, 2H), 3.41 – 3.35 (m, 0.5H), 3.24 - 3.16 (m, 1H), 3.09 – 3.00 (m, 1H), 2.97 – 2.89 (m, 2.5H), 2.83 – 2.73 (m, 1H),

			2.67 - 2.61 (m, 2H), 2.51 (s, 3H), 2.42 - 2.35 (m, 2H), 1.54 (t, J = 6.2 Hz, 3H), 1.32 (t, J = 7.4 Hz, 3H). **MS** (ESI) m/z = 761.9 $[M+H]^+$.
63		2-(2-(4-(difluoromethylene)piperidin-1-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-methyl-6-(trifluoromethyl) pyridin-3-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.57 (s, 1H), 8.25 (d, *J* = 8.3 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 5.29 (s, 2H), 4.71 (d, *J* = 11.7 Hz, 1H), 4.10 (d, *J* = 11.9 Hz, 1H), 3.83 - 3.68 (m, 2H), 3.62 (t, *J* = 5.4 Hz, 4H), 3.44 (t, *J* = 12.1 Hz, 1H), 3.21 - 3.02 (m, 3H), 2.92 (d, *J* = 9.9 Hz, 1H), 2.78 (d, *J* = 10.9 Hz, 1H), 2.64 (s, 3H), 2.54 (s, 3H), 2.30 - 2.20 (m, 4H), 1.31 (t, *J* = 7.5 Hz, 3H). **MS** (ESI) m/z = 732.2 $[M+H]^+$.
73		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-2-(5-oxaspiro[3.4]oct-7-en-7-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.50 (d, *J* = 17.6 Hz, 1H), 8.21 (s, 1H), 7.85 (s, 1H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.05 (s, 1H), 5.43 (s, 2H), 4.98 (s, 2H), 4.75 (s, 1H), 4.10 (s, 1H), 3.74 (d, *J* = 9.8 Hz, 2H), 3.50 (s, 2H), 3.13 (d, *J* = 7.2 Hz, 3H), 2.94 (s, 1H), 2.79 (s, 1H), 2.52 (s, 2H), 2.50-2.45 (m, 2H), 2.26 (d, *J* = 8.5 Hz, 2H), 1.72 (dd, *J* = 27.0, 9.6 Hz, 2H), 1.34 (s, 3H). **MS** (ESI) m/z = 728.2 $[M+H]^+$.
76		2-(2-(3-azabicyclo[3.2.0]heptan-3-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(trifluoromethyl) phenyl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.44 (s, 1H), 8.07 (d, *J* = 8.6 Hz, 1H), 7.71 (s, 1H), 7.52 (d, *J* = 8.7 Hz, 1H), 5.21 (s, 2H), 4.60 (d, *J* = 12.0 Hz, 1H), 3.98 (d, *J* = 13.0 Hz, 1H), 3.61 (dd, *J* = 20.7, 10.7 Hz, 4H), 3.34 (d, *J* = 11.3 Hz, 1H), 3.17 (dd, *J* = 10.8, 6.1 Hz, 2H), 3.07 – 2.89 (m, 5H), 2.81 (d, *J* = 10.5 Hz, 1H), 2.66 (d, *J* = 10.7 Hz, 1H), 2.41 (s, 3H), 2.21 – 2.08 (m, 2H), 1.62 (d, *J* = 10.2 Hz, 2H), 1.18 (t, *J* = 7.1 Hz, 3H). **MS** (ESI) m/z = 715.2 $[M+H]^+$.
77		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-2-(1-oxaspiro[3.5]non-6-en-7-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.49 (s, 1H), 8.17 (d, *J* = 8.5 Hz, 1H), 7.84 (s, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 6.87 (s, 1H), 5.39 (s, 2H), 4.80 – 4.68 (m, 1H), 4.66 – 4.55 (m, 2H), 4.15 – 4.03 (m, 1H), 3.75 (dd, *J* = 22.8, 12.3 Hz, 2H), 3.55 – 3.40 (m, 1H), 3.22 – 3.06 (m, 3H), 2.95 (d, *J* = 11.5 Hz, 1H), 2.82 – 2.63 (m, 4H), 2.58 – 2.42 (m, 4H), 2.17 – 2.01 (m, 2H), 1.40 – 1.24 (m, 5H). **MS** (ESI) m/z = 742.2 $[M+H]^+$.
78		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-2-(2-oxaspiro[3.4]oct-6-en-6-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.44 (s, 1H), 8.06 (t, J = 7.5 Hz, 1H), 7.72 (s, 1H), 7.51 (d, J = 8.6 Hz, 1H), 6.86 (s, 0.7H), 6.52 (s, 0.3H), 5.30 - 5.28 (m, 2H), 4.67 – 4.54 (m, 5H), 4.00 - 3.96 (m, 1H), 3.65 - 3.60 (m, 2H), 3.3 5 - 3.31 (m, 1H), 3.07 - 2.98 (m, 4H), 2.86 – 2.66 (m, 4H), 2.41 (s, 3H), 2.31 (t, J = 7.0 Hz, 1H), 1.19 (t, J = 9.2 Hz, 3H). **MS** (ESI) m/z = 727.9 $[M+H]^+$.
79		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-2-(hexahydrocyclopenta[c]pyrrol-2(1H)-yl)-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]p	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.44 (s, 1H), 8.06 (d, *J* = 8.5 Hz, 1H), 7.71 (s, 1H), 7.51 (d, *J* = 8.3 Hz, 1H), 5.19 (s, 2H), 4.59 (d, *J* = 11.8 Hz, 1H), 3.98 (d, *J* = 12.1 Hz, 1H), 3.62 (s, 2H), 3.55 – 3.42 (m, 2H), 3.32 (s, 1H), 3.16 (d, *J* = 8.6 Hz, 2H), 3.08 – 2.88 (m, 3H), 2.79 (d, *J*

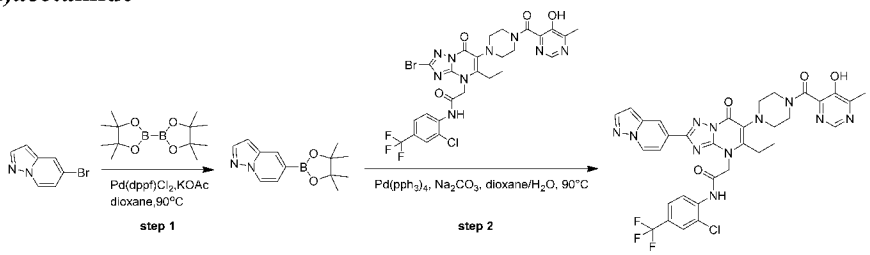
		yrimidin-4(7H)-yl)acetamide	= 11.1 Hz, 1H), 2.66 (s, 3H), 2.41 (s, 3H), 1.76 (dd, *J* = 12.4, 7.0 Hz, 2H), 1.68 – 1.57 (m, 1H), 1.49 (dt, *J* = 12.8, 6.4 Hz, 1H), 1.38 (d, *J* = 6.3 Hz, 2H), 1.21 – 1.15 (m, 3H). **MS** (ESI) m/z = 729.2 $[M+H]^+$.
89		2-(2-(4-(difluoromethylene)piperidin-1-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(4-(trifluoromethyl)phenyl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.57 (s, 1H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 8.5 Hz, 2H), 5.19 (s, 2H), 4.71 (d, *J* = 11.2 Hz, 1H), 4.09 (d, *J* = 14.1 Hz, 1H), 3.83 - 3.69 (m, 2H), 3.65 – 3.51 (m, 4H), 3.50 – 3.38 (m, 1H), 3.18 – 2.99 (m, 3H), 2.93 (d, *J* = 11.3 Hz, 1H), 2.78 (d, *J* = 10.0 Hz, 1H), 2.54 (s, 3H), 2.30 - 2.15 (m, 4H), 1.29 (t, *J* = 7.5 Hz, 3H). **MS** (ESI) m/z = 717.1 $[M+H]^+$.
95		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.51 (d, *J* = 17.6 Hz, 1H), 8.18 (d, *J* = 8.6 Hz, 1H), 7.86 (s, 1H), 7.65 (d, *J* = 8.8 Hz, 1H), 7.48 (d, *J* = 1.8 Hz, 1H), 6.19 (s, 1H), 5.35 (s, 2H), 4.84 (s, 1H), 4.73 (d, *J* = 11.4 Hz, 1H), 4.25 (t, *J* = 5.2 Hz, 2H), 4.12 (t, *J* = 5.2 Hz, 2H), 3.87 – 3.62 (m, 2H), 3.46 (s, 1H), 3.13 (dd, *J* = 29.3, 9.6 Hz, 3H), 2.94 (d, *J* = 11.3 Hz, 1H), 2.79 (d, *J* = 10.2 Hz, 1H), 2.53 (s, 3H), 2.21 (dd, *J* = 15.8, 8.4 Hz, 1H), 1.63 (s, 1H), 1.32 (t, *J* = 7.4 Hz, 3H). **MS** (ESI) m/z = 741.2 $[M+H]^+$.
97		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-2-(3,3a,4,6a-tetrahydro-1H-cyclopenta[c]furan-5-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) *δ* 8.44 (s, 1H), 8.07 (d, *J* = 7.4 Hz, 1H), 7.71 (s, 1H), 7.51 (d, *J* = 8.2 Hz, 1H), 6.47 (s, 1H), 5.28 (s, 2H), 4.60 (s, 1H), 3.98 (s, 1H), 3.64 (t, *J* = 49.3 Hz, 7H), 3.36 (d, *J* = 16.7 Hz, 1H), 3.00 (s, 5H), 2.84 (s, 1H), 2.62 (dd, *J* = 20.8, 16.4 Hz, 2H), 2.41 (s, 3H), 1.21 (s, 3H). **MS** (ESI) m/z = 728.2 [M+H]+.
107		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-2-(3-oxa-9-azaspiro[5.5]undecan-9-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.52 (s, 1H), 8.17 (d, J = 8.6 Hz, 1H), 7.83 (d, J = 1.1 Hz, 1H), 7.64 (d, J = 8.7 Hz, 1H), 5.30 (s, 2H), 4.71 (d, J = 11.6 Hz, 1H), 4.11 (d, J = 11.1 Hz, 1H), 3.70 (dd, J = 13.9, 8.8 Hz, 6H), 3.60 – 3.51 (m, 4H), 3.46 (d, J = 11.1 Hz, 1H), 3.21 – 2.99 (m, 3H), 2.91 (d, J = 11.3 Hz, 1H), 2.77 (d, J = 10.2 Hz, 1H), 2.52 (s, 3H), 1.63 – 1.53 (m, 8H), 1.30 (t, J = 5.4 Hz, 3H). **MS** (ESI) m/z = 773.2 $[M+H]^+$.
108		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-2-(2-oxa-8-azaspiro[4.5]decan-8-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.57 (s, 1H), 8.17 (d, *J* = 8.5 Hz, 1H), 7.83 (s, 1H), 7.64 (d, *J* = 7.6 Hz, 1H), 5.29 (s, 2H), 4.71 (d, *J* = 11.2 Hz, 1H), 4.10 (d, *J* = 12.8 Hz, 1H), 3.89 (t, *J* = 7.1 Hz, 2H), 3.75 (d, *J* = 9.0 Hz, 2H), 3.63 (dd, *J* = 12.1, 6.3 Hz, 2H), 3.59 (s, 2H), 3.55-3.35 (m, 3H), 3.10 (dd, *J* = 19.2, 11.8 Hz, 3H), 2.90 (s, 1H), 2.77 (d, *J* = 11.3 Hz, 1H), 2.54 (s, 3H), 1.85 (t, *J* = 7.2 Hz, 2H), 1.64 (t, *J* = 5.6 Hz, 4H), 1.31 (d, *J* = 7.2 Hz, 3H). **MS** (ESI) m/z = 759.2 $[M+H]^+$.

126		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(1H-indazol-6-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.38 (s, 2H), 8.30 (s, 1H), 8.08 (d, J = 7.0 Hz, 1H), 7.99 (s, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 16.5 Hz, 2H), 7.52 (s, 1H), 5.39 (s, 2H), 4.64 (s, 1H), 3.99 (s, 1H), 3.75-3.60 (m, 2H), 3.42 - 3.32 (m, 1H), 3.08 - 3.01 (m, 3H), 2.90 - 2.84 (m, 1H), 2.76 - 2.68 (m, 1H), 2.42 (s, 3H), 1.25 - 1.22 (m, 3H). **MS** (ESI) m/z = 736.2 [M+H]+.
127		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(2,3-dihydrobenzofuran-5-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.80 (s, 1H), 9.22 (s, 1H), 8.59 (s, 1H), 8.50 (d, J = 8.7 Hz, 1H), 8.14 (s, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.58 (s, 1H), 7.53 (d, J = 8.8 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 5.67 (d, J = 12.7 Hz, 1H), 5.16 (s, 2H), 4.80 (d, J = 11.1 Hz, 1H), 4.65 (t, J = 8.8 Hz, 2H), 3.84 (t, J = 11.1 Hz, 2H), 3.50 (t, J = 12.0 Hz, 1H), 3.34 – 3.16 (m, 4H), 3.08 (t, J = 14.8 Hz, 1H), 2.81 (dd, J = 34.2, 10.6 Hz, 2H), 2.57 (s, 3H), 1.35 (t, J = 7.5 Hz, 3H). **MS** (ESI) m/z = 738.2 $[M+H]^+$.
131		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(imidazo[1,2-a]pyridin-6-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.13 (s, 2H), 8.58 (s, 1H), 8.43 (d, J = 8.7 Hz, 1H), 8.07 (d, J = 8.8 Hz, 1H), 7.81 (d, J = 8.1 Hz, 1H), 7.70 (d, J = 10.8 Hz, 2H), 7.61 (s, 1H), 7.52 (d, J = 8.1 Hz, 1H), 5.68 (d, J = 10.8 Hz, 1H), 5.25 (s, 2H), 4.80 (d, J = 11.9 Hz, 1H), 3.82 (t, J = 11.5 Hz, 2H), 3.49 (t, J = 13.2 Hz, 1H), 3.17 (dd, J = 14.4, 7.2 Hz, 2H), 3.07 (t, J = 14.1 Hz, 1H), 2.83 (dd, J = 31.9, 10.4 Hz, 2H), 2.56 (s, 3H), 1.35 (t, J = 7.5 Hz, 3H). **MS** (ESI) m/z = 736.0 [M+H]+.
133		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-2-(1H-pyrrolo[2,3-b]pyridin-5-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.82 (s, 1H), 9.85 (s, 1H), 9.20 (d, J = 19.8 Hz, 2H), 8.84 (s, 1H), 8.60 (s, 1H), 8.50 (d, J = 8.7 Hz, 1H), 7.57 (s, 1H), 7.52 (d, J = 8.6 Hz, 1H), 7.40 (s, 1H), 6.60 (s, 1H), 5.68 (d, J = 11.8 Hz, 1H), 5.23 (s, 2H), 4.81 (d, J = 11.1 Hz, 1H), 3.95-3.80 (m, 2H), 3.51 (s, 1H), 3.23 (d, J = 7.1 Hz, 2H), 3.09 (s, 1H), 2.83 (d, J = 21.7 Hz, 2H), 2.57 (s, 3H), 1.40-1.30 (m, 3H). **MS** (ESI) m/z = 736.2 [M+H]+.
134		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-2-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.54 (s, 1H), 8.20 (d, J = 8.5 Hz, 1H), 7.82 (s, 1H), 7.61 (d, J = 8.4 Hz, 1H), 6.66 (s, 1H), 5.48 (s, 2H), 4.73 – 4.55 (m, 2H), 4.25 – 4.09 (m, 3H), 3.83 – 3.71 (m, 2H), 3.54 – 3.42 (m, 1H), 3.19 – 3.07 (m, 3H), 2.99 – 2.96 (m, 2H), 2.83 (d, J = 9.8 Hz, 1H), 2.72 – 2.64 (m, 2H), 2.53 (s, 3H), 1.34 - 1.30 (m, 3H). **MS** (ESI) m/z = 726.2 $[M+H]^+$.
136		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-2-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.80 (s, 1H), 9.11 (s, 1H), 8.59 (s, 1H), 8.43 (d, J = 8.2 Hz, 1H), 7.58 (s, 1H), 7.45 (d, J = 8.2 Hz, 1H), 6.80 (s, 1H), 5.68 (d, J = 11.4 Hz, 1H), 5.46 – 5.25 (m, 2H), 4.96 – 4.78 (m, 3H), 4.34 - 4.22 (m, 2H), 4.20 - 4.09 (m, 2H), 3.92 – 3.75 (m, 2H), 3.57 – 3.43 (m, 1H), 3.23 – 2.99 (m, 3H), 2.83 (d, J = 20.7 Hz, 2H),

			2.57 (s, 3H), 1.39 - 1.29 (m, 3H). **MS** (ESI) m/z = 742.2 $[M+H]^+$.
140		2-(2-(4-(difluoromethylene)piperidin-1-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(5-(trifluoromethyl)thiazol-2-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.56 (s, 1H), 7.93 (s, 1H), 5.29 (s, 2H), 4.72 (d, J=11.5 Hz, 1H), 4.08 (d, J=11.6 Hz, 1H), 3.80 - 3.68 (m, 2H), 3.63 – 3.54 (m, 4H), 3.49 - 3.40 (m, 1H), 3.18 – 3.02 (m, 3H), 2.97 – 2.90 (m, 1H), 2.79 (d, J=10.1 Hz, 1H), 2.54 (s, 3H), 2.27 - 2.18 (m, 4H), 1.27 (t, J=7.2 Hz, 3H). **MS** (ESI) m/z = 723.9 $[M+H]^+$.
148		N-(2-chloro-4-(pentafluoro-l6-sulfaneyl)phenyl)-2-(2-(4-(difluoromethylene)cyclohex-1-en-1-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD)δ 8.59 (s, 1H), 8.22 (d, J = 9.1 Hz, 1H), 8.01 (d, J = 2.4 Hz, 1H), 7.80 (dd, J = 9.2, 2.4 Hz, 1H), 6.98 (s, 1H), 5.41 (s, 2H), 4.72 (d, J = 12.4 Hz, 1H), 4.11 (d, J = 12.5 Hz, 1H), 3.75 (s, 2H), 3.53 – 3.40 (m, 1H), 3.14 (t, J = 16.5 Hz, 3H), 2.96 (d, J = 18.8 Hz, 3H), 2.80 (d, J = 10.4 Hz, 1H), 2.67 (s, 2H), 2.54 (s, 3H), 2.41 (s, 2H), 1.31 (d, J = 7.1 Hz, 3H). **MS** (ESI) m/z = 806.2 $[M+H]^+$.
149		N-(2-chloro-4-(pentafluoro-l6-sulfaneyl)phenyl)-2-(2-(4-(difluoromethylene)piperidin-1-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD)δ 8.52 (s, 1H), 8.16 (d, J = 9.1 Hz, 1H), 7.97 (d, J = 2.4 Hz, 1H), 7.76 (dd, J = 9.2, 2.4 Hz, 1H), 5.27 (s, 2H), 4.67 (d, J = 12.0 Hz, 1H), 4.07 (d, J = 12.2 Hz, 1H), 3.71 (s, 2H), 3.56 (t, J = 5.6 Hz, 4H), 3.40 (t, J = 11.8 Hz, 1H), 3.06 (dt, J = 14.6, 9.6 Hz, 3H), 2.87 (d, J = 10.0 Hz, 1H), 2.73 (d, J = 11.2 Hz, 1H), 2.49 (s, 3H), 2.21 (s, 4H), 1.25 (t, J = 7.4 Hz, 3H). **MS** (ESI) m/z = 809.2 $[M+H]^+$.
181		2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-2-(2-oxaspiro[3.5]non-6-en-7-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(4-(trifluoromethyl)phenyl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.53 (s, 1H), 7.85-7.75 (m, 2H), 7.70-7.55 (m, 2H), 6.90 (s, 1H), 5.27 (s, 2H), 4.73 (d, J = 12.0 Hz, 1H), 4.53 (d, J = 5.8 Hz, 2H), 4.44 (d, J = 5.9 Hz, 2H), 4.07 (s, 1H), 3.75 (d, J = 8.9 Hz, 2H), 3.46 (s, 1H), 3.20-3.05 (m, 3H), 2.95 (d, J = 8.9 Hz, 1H), 2.80 (d, J = 9.7 Hz, 1H), 2.62 (d, J = 15.5 Hz, 4H), 2.53 (s, 3H), 2.05 (d, J = 5.6 Hz, 2H), 1.45-1.30 (m, 3H). **MS** (ESI) m/z = 708.2 [M+H]+.
184		2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-2-(3,3a,4,6a-tetrahydro-1H-cyclopenta[c]furan-5-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(4-(trifluoromethyl)phenyl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.44 (s, 1H), 7.67 (d, J = 8.5 Hz, 2H), 7.53 (d, J = 8.6 Hz, 2H), 6.45 (d, J = 1.9 Hz, 1H), 5.16 (s, 2H), 4.61 (d, J = 12.0 Hz, 1H), 4.01 (d, J = 11.4 Hz, 1H), 3.79 – 3.72 (m, 1H), 3.69 – 3.58 (m, 4H), 3.50 (ddd, J = 9.5, 7.9, 2.9 Hz, 2H), 3.34 (t, J = 12.4 Hz, 1H), 3.07 – 2.92 (m, 5H), 2.84 (d, J = 9.9 Hz, 1H), 2.69 (d, J = 10.8 Hz, 1H), 2.59 (q, J = 7.8 Hz, 1H), 2.42 (s, 3H), 1.18 (d, J = 7.5 Hz, 3H). **MS** (ESI) m/z = 694.3 $[M+H]^+$.
185		2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-2-(spiro[2.5]oct-5-en-6-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(4-(trifluoromethyl)phenyl)acetamide	**^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.81 (s, 1H), 9.31 (s, 1H), 8.58 (s, 1H), 7.70 – 7.51 (m, 4H), 7.03 (s, 1H), 5.66 (d, J = 13.0 Hz, 1H), 5.05 (s, 2H), 4.79 (d, J = 11.5 Hz, 1H), 3.81 (t, J = 11.1 Hz, 2H), 3.48 (s, 1H), 3.22 - 2.98 (m, 3H), 2.89 – 2.64 (m, 4H), 2.56 (s, 3H), 2.16 (s, 2H), 1.53 (t, J = 5.6 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H), 0.37 (q, J = 6.2 Hz, 4H). **MS** (ESI) m/z = 692.3 $[M+H]^+$.

Example 200:

N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-2-(pyrazolo[1,5-a]pyridin-5-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide

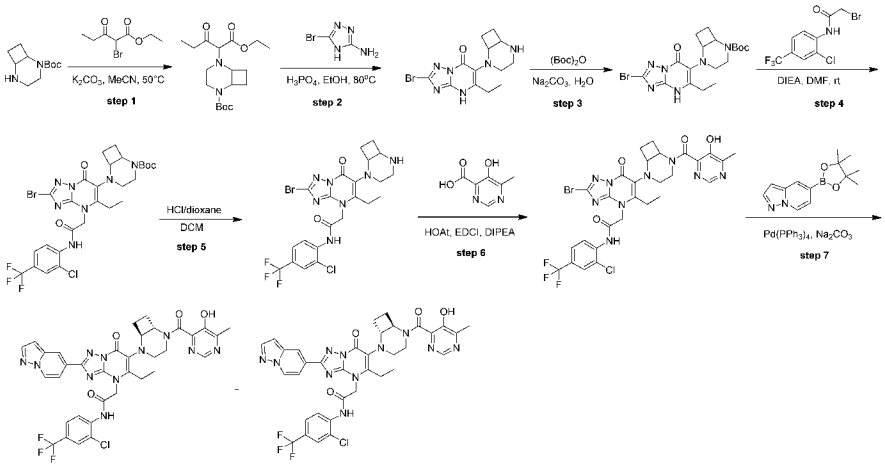


Step 1: The mixture of 5-bromopyrazolo[1,5-a]pyridine (200 mg, 1 mmol), $(BPin)_2$ (309 mg, 1.22 mmol), KOAc (299 mg, 3.04 mmol) and $Pd(dppf)Cl_2$ (74 mg. 0.1 mmol) in dioxane (5 mL) was stirred at 90°C for 16 hrs under N_2 atmosphere. The mixture was concentrated under vacuum and purified by flash to give the product 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo [1,5-a]pyridine (100 mg, 0.41 mmol, yield: 41%) as a yellow oil. **MS** (ESI) m/z = 245.2 $[M+H]^+$.

Step 2: The mixture of 2-(2-bromo-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl) piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(trifluoromethyl)p henyl)acetamide (70 mg, 0.1 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)pyrazolo [1,5-a]pyridine (37 mg, 0.15 mmol), $Pd(PPh_3)_4$ (12 mg, 0.01 mmol) and Na_2CO_3 (32 mg, 0.3 mmol) in dioxane (5 mL) and H_2O (0.5 mL) was stirred at 90°C for 16 hrs under N_2 atmosphere. The mixture was concentrated under vacuum and purified by Flash Chromatography (DCM/ MeOH = 0-3%) and then Prep-HPLC to give the product N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-2-(pyrazolo[1,5 -a]pyridin-5-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide (8.3 mg, 0.011 mmol, yield: 11.2%) as white solid. **^{1}H NMR** (400 MHz, CD_3OD) δ 8.58 (d, J = 7.4 Hz, 1H), 8.55-8.45 (m, 2H), 8.40 (s, 1H), 8.15 (d, J = 8.3 Hz, 1H), 7.97 (d, J = 2.1 Hz, 1H), 7.81 (s, 1H), 7.65-7.55 (m, 2H), 6.73 (s, 1H), 5.46 (s, 2H), 4.71 (d, J = 11.6 Hz, 1H), 4.08 (d, J = 15.0 Hz, 1H), 3.80-3.70 (m, 2H), 3.43 (d, J = 11.6 Hz, 1H), 3.12 (d, J = 7.5 Hz, 3H), 2.95 (d, J = 9.6 Hz, 1H), 2.80 (d, J = 11.1 Hz, 1H), 2.49 (s, 3H), 1.40-1.30 (m, 3H). **MS** (ESI) m/z = 736.2 $[M+H]^+$.

Example 201 and example 202:

N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-7-oxo-2-(pyrazolo[1,5-a]pyridin-5-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide and N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-((1R,6R)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-7-oxo-2-(pyrazolo[1,5-a]pyridin-5-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide



Step 1: The mixture of ethyl 2-bromo-3-oxopentanoate (800 mg, 3.60 mmol), trans tert-butyl 2,5-diazabicyclo[4.2.0]octane-2-carboxylate (761 mg, 3.58 mmol) and K_2CO_3 (1.48 g,10.75 mmol) in CH_3CN (20 mL) was stirred at 50°C for 2 hrs. The mixture was filtered, the cake was washed with CH_3CN. The filtrate was concentrated under vacuum and purified by Flash Chromatography

(PE/EtOAc = 0-5%) to give the product trans tert-butyl 5-(1-ethoxy-1,3-dioxopentan-2-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (1 g, 2.82 mmol, 78% yield) as yellow oil. **MS** (ESI) m/z = 355.1 $[M+H]^+$.

Step 2 & Step 3: To a solution of trans tert-butyl 5-(1-ethoxy-1,3-dioxopentan-2-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (500 mg, 1.41 mmol) in EtOH (10 mL) were added 5-bromo-4H-1,2,4-triazol-3-amine (344 mg, 2.11 mmol) and H_3PO_4 (1.38 g, 14.1 mmol). The reaction mixture was stirred at room temperature at 85°C for 48 hrs under N_2. Then the mixture was added Sat. Na_2CO_3 to pH=10 and the Boc_2O (1.54 g, 7.05 mmol) was added. The mixture was stirred at 25°C for 2 hrs. The mixture was diluted with water (20 mL), extracted with EtOAc (20 mL * 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, concentrated under vacuum and purified by Flash Chromatography (MeOH/DCM = 0-3%) to give the product trans tert-butyl 5-(2-bromo-5-ethyl-7-oxo-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (157 mg, 0.34 mmol, 25% yield) as a yellow solid. **MS** (ESI) m/z = 453.0, 455.0 $[M+H]^+$.

Step 4: To the solution of trans tert-butyl 5-(2-bromo-5-ethyl-7-oxo-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (157 mg, 0.34 mmol) in MeCN (10 mL) were added 2-bromo-N-[2-chloro-4-(trifluoromethyl)phenyl]acetamide (164 mg, 0.51 mmol) and DIPEA (137 mg, 1.03 mmol). The mixture was stirred at 25°C for 16 hrs. The mixture was concentrated under vacuum and purified by Flash Chromatography (PE/EtOAc = 0-45%) to give the product trans tert-butyl 5-(2-bromo-4-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-5-ethyl-7-oxo-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (130 mg, 0.188 mmol, 55% yield) as white solid. **MS** (ESI) m/z = 632.0, 633.9 $[M+H-56]^+$.

Step 5: To a solution of trans tert-butyl 5-(2-bromo-4-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-5-ethyl-7-oxo-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (130 mg, 0.1887 mmol) in DCM (5 mL) was added HCl in dioxane (2 mL，4M). The mixture was stirred at room temperature for 1 hr. The mixture was concentrated under vacuum to give the crude product trans 2-(6-(2,5-diazabicyclo[4.2.0]octan-2-yl)-2-bromo-5-ethyl-7-oxo-[1,2,4]triazolo[1,5-a] pyrimidin-4(7H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (110 mg, 0.187 mmol, 99% yield) as a white solid. **MS** (ESI) m/z = 587.9, 590.0 $[M+H]^+$.

Step 6: The mixture of 5-hydroxy-6-methylpyrimidine-4-carboxylic acid (54 mg, 0.35 mmol), HOAt (60 mg, 0.44 mmol) and EDCI (84 mg, 0.44 mmol) in MeCN (80 mL) was stirred at room temperature for 1 hr under argon, then trans 2-(6-(2,5-diazabicyclo[4.2.0]octan-2-yl)-2-bromo-5-ethyl-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (110 mg, 0.187 mmol) and DIEA (136 mg, 1.05 mmol) in MeCN (20 mL) was added, the mixture was stirred at room temperature for 1 hr. The mixture was concentrated to remove MeCN, diluted with water (20 mL), extracted with EtOAc (20 mL * 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, concentrated under vacuum and purified by Flash Chromatography (MeOH-DCM = 0-3%) to give the product trans 2-(2-bromo-5-ethyl-6-(5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0] octan-2-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (90 mg, 0.124 mmol, 66.3% yield) as white solid. **MS** (ESI) m/z = 723.8, 725.9 $[M+H]^+$

Step 7: The mixture of trans 2-(2-bromo-5-ethyl-6-(5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (90 mg, 0.124 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan -2-yl)pyrazolo[1,5-a]pyridine (45.48 mg, 0.1863 mmol), $Pd(PPh_3)_4$ (14.35 mg, 0.0124 mmol) and Na_2CO_3 (39.49 mg, 0.37 mmol) in dioxane (10 mL) and H_2O (1 mL) was stirred at 90°C for 16 hrs under Ar_2 atmosphere. The mixture was concentrated under vacuum and purified by Prep-HPLC to give the racemic product. The product was purified by SFC (Separation Conditions：Apparatus：SFC Thar prep 80, Column：CHIRALPAK AD-H 250mm×20 mm，5μm, Modifier ：40% IPA (NH_4OH 0.2%):60%CO_2, Total Flow：40g/min) to give the N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-7-oxo-2-(pyrazolo[1,5-a]pyridin-5-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide & N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-((1R,6R)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-7-oxo-2-(pyrazolo[1,5-a]pyridin-5-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide as a white solid.

The first peak from the SFC (Rt = 2.46 min, 17.3 mg, 0.022 mmol, 18% yield):

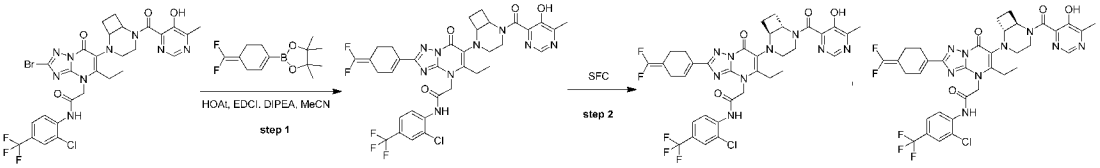
^{1}H NMR (400 MHz, CD_3OD) δ 8.64 (d, J = 7.1 Hz, 1H), 8.52 (s, 2H), 8.20 (d, J = 8.7 Hz, 1H), 8.02 (d, J = 2.1 Hz, 1H), 7.85 (s, 1H), 7.65 (dd, J = 17.0, 7.9 Hz, 2H), 6.78 (s, 1H), 5.50 (s, 2H), 4.69 (s, 1H), 3.93 (s, 1H), 3.79 – 3.43 (m, 4H), 3.28 – 3.20 (m, 1H), 3.16 – 3.06 (m, 1H), 2.52 (s, 3H), 1.90 – 1.49 (m, 4H), 1.37 (t, J = 7.5 Hz, 3H). **MS** (ESI) m/z = 762.1, 764.2 $[M+H]^+$.

The second peak from the SFC (Rt = 6.65 min, 11.3 mg, 0.0145 mmol, 11% yield):

^{1}H NMR (400 MHz, CD_3OD) δ 8.63 (d, J = 7.0 Hz, 1H), 8.51 (s, 1H), 8.44 - 8.16 (m, 2H), 8.02 (s, 1H), 7.85 (s, 1H), 7.65 (dd, J = 16.8, 8.2 Hz, 2H), 6.77 (s, 1H), 5.49 (s, 2H), 4.66 (s, 1H), 3.90 (s, 1H), 3.78 - 3.40 (m, 4H), 3.29 – 3.19 (m, 1H), 3.11 (dd, J = 14.0, 7.4 Hz, 1H), 2.49 (s, 3H), 1.85 – 1.42 (m, 4H), 1.38 – 1.34 (m, 3H). **MS** (ESI) m/z = 762.2, 764.2 $[M+H]^+$.

Example 46 and example 52:

N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(4-(difluoromethylene)cyclohex-1-en-1-yl)-5-ethyl-6-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide and N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(4-(difluoromethylene)cyclohex-1-en-1-yl)-5-ethyl-6-((1R,6R)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide



Step 1: The mixture of trans 2-(2-bromo-5-ethyl-6-(5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (97 mg, 0.1338 mmol), 2-[4-(difluoromethylidene) cyclohex-1-en-1-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (51.4 mg, 0.2 mmol), $Pd(dppf)Cl_2$ (9.79 mg, 0.0133 mmol) and Na_2CO_3 (42.54 mg, 0.4 mmol)in dioxane (10 mL) and H_2O (1 mL) was stirred at 90°C for 16 hrs under N_2 atmosphere. The mixture was concentrated under vacuum and purified by Prep-HPLC to give the trans product N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(4-(difluoromethylene)cyclohex-1-en-1-yl)-5-ethyl-6-(5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide (25 mg, 0.032 mmol, 24% yield) as a white solid. **^{1}H NMR** (400 MHz, CD_3OD) δ 8.43 (d, J = 8.3 Hz, 1H), 8.08 (d, J = 8.6 Hz, 1H), 7.74 (d, J = 1.5 Hz, 1H), 7.57 – 7.49 (m, 1H), 6.89 (d, J = 2.1 Hz, 1H), 5.30 (d, J = 1.7 Hz, 2H), 4.58 (s, 1H), 3.79 (s, 1H), 3.52 (dd, J = 65.1, 22.2 Hz, 4H), 3.18 - 3.07 (m, 1H), 2.97 (dd, J = 13.9, 7.3 Hz, 1H), 2.89 (s, 2H), 2.59 (s, 2H), 2.43 (s, 3H), 2.33 (t, J = 6.2 Hz, 2H), 1.64 (d, J = 31.0 Hz, 2H), 1.42 (s, 1H), 1.27 - 1.22 (m, 4H). **MS** (ESI) m/z = 774.2, 776.3 $[M+H]^+$.

Step 2: The trans N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(4-(difluoromethylene)cyclohex-1-en-1-yl)-5-ethyl-6-(5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide (25 mg, 0.032 mmol) was purified by SFC (Apparatus: SFC Thar prep 80, Column:CHIRALPAK AD-H 250mm×20 mm, 5 μm, Modifier:40% IPA (NH_4OH 0.2%): 60% CO_2, Total Flow: 40g/min) to give N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(4-(difluoromethylene)cyclohex-1-en-1-yl)-5-ethyl-6-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide and N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(4-(difluoromethylene)cyclohex-1-en-1-yl)-5-ethyl-6-((1R,6R)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide.

The first peak from the SFC (Rt = 3.00 min, 10.7 mg, 0.013 mmol, 43% yield):

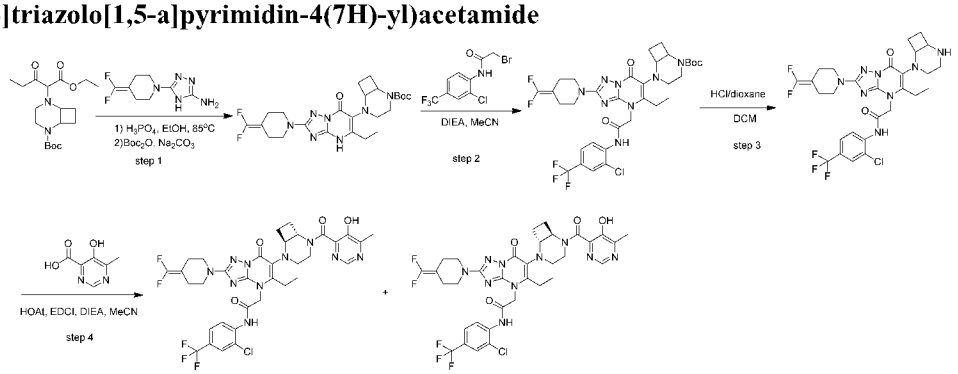
^{1}H NMR (400 MHz, CD_3OD) δ 8.54 (s, 1H), 8.17 (d, J = 8.6 Hz, 1H), 7.83 (s, 1H), 7.63 (d, J = 8.3 Hz, 1H), 6.98 (s, 1H), 5.39 (s, 2H), 4.67 (s, 1H), 3.90 (s, 1H), 3.70 (d, J = 23.4 Hz, 2H), 3.53 (d, J = 19.1 Hz, 2H), 3.22 (dd, J = 13.8, 7.3 Hz, 1H), 3.07 (dd, J = 13.7, 7.1 Hz, 1H), 2.98 (s, 2H), 2.74 - 2.62 (m, 2H), 2.52 (s, 3H), 2.45 - 2.37 (m, 2H), 1.74 (d, J = 25.4 Hz, 2H), 1.51 (s, 1H), 1.33 (t, J = 7.5 Hz, 4H). **MS** (ESI) m/z = 774.1, 776.1 $[M+H]^+$.

The second peak from the SFC (Rt = 9.46 min, 5.3 mg, 0.0068 mmol, 21% yield):

^{1}H NMR (400 MHz, CD_3OD) δ 8.39 (s, 1H), 8.05 (d, J = 8.6 Hz, 1H), 7.71 (s, 1H), 7.51 (d, J = 8.7 Hz, 1H), 6.86 (s, 1H), 5.27 (s, 2H), 4.55 (s, 1H), 3.77 (d, J = 10.8 Hz, 1H), 3.49 (dd, J = 66.2, 19.4 Hz, 4H), 3.10 (dd, J = 13.9, 7.5 Hz, 1H), 2.95 (dd, J = 13.8, 7.4 Hz, 1H), 2.86 (s, 2H), 2.56 (s, 2H), 2.40 (s, 3H), 2.30 (t, J = 6.1 Hz, 2H), 1.60 (d, J = 32.3 Hz, 2H), 1.39 (s, 1H), 1.23 – 1.18 (m, 4H). **MS** (ESI) m/z = 774.1, 776.0 $[M+H]^+$.

Example 45 and example 51:

N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(4-(difluoromethylene)piperidin-1-yl)-5-ethyl-6-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide & N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(4-(difluoromethylene)piperidin-1-yl)-5-ethyl-6-((1R,6R)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide



Step 1: To a solution of trans tert-butyl 5-(1-ethoxy-1,3-dioxopentan-2-yl)-2,5-diazabicyclo [4.2.0]octane-2-carboxylate (66 mg, 0.186 mmol) in EtOH (5 mL) were added 5-[4-(difluoro methylidene)piperidin-1-yl]-4H-1,2,4-triazol-3-amine (40 mg, 0.186 mmol) and H_3PO_4 (182.48 mg, 1.86 mmol). The reaction mixture was stirred at 85°C for 48 hrs under N_2. Then the mixture was added Sat.Na_2CO_3 to pH=10 and the Boc_2O (203.19 mg, 0.93 mmol) was added into. The resulting mixture was stirred at 25°C for another 2 hrs. The mixture was diluted with water (20 mL), extracted with EtOAc (20 mL * 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, concentrated under vacuum and purified by Flash Chromatography (MeOH-DCM = 0-3%) to give the product trans tert-butyl 5-(2-(4-(difluoromethylene)piperidin-1-yl)-5-ethyl-7-oxo-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (20 mg, 0.04 mmol, 21% yield) as yellow solid. **MS** (ESI) m/z = 506.2$[M+H]^+$.

Step 2: To a solution of trans tert-butyl 5-(2-(4-(difluoromethylene)piperidin-1-yl)-5-ethyl-7-oxo-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (20 mg, 0.04 mmol) in MeCN (10 mL) were added 2-bromo-N-[2-chloro-4-(trifluoromethyl)phenyl]acetamide (18.86 mg, 0.06 mmol) and DIPEA (15.35 mg, 0.11 mmol). The mixture was stirred at 25°C for 16 hrs. The mixture was concentrated under vacuum and the crude residue was purified by Flash Chromatography (EtOAc/Hexanes = 0-65%) to give the product trans *tert*-butyl 5-(4-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-2-(4-(difluoromethylene)piperidin-1-yl)-5-ethyl-7-oxo-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (21mg, 0.028 mmol, 71% yield) as yellow solid. **MS** (ESI) m/z = 741.2, 743.0 $[M+H]^+$.

Step 3: To the solution of trans *tert*-butyl 5-(4-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-2-(4-(difluoromethylene)piperidin-1-yl)-5-ethyl-7-oxo-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (21 mg, 0.0283 mmol) in DCM (5 mL) was added HCl in dioxane (2 mL, 4M). The mixture was stirred at room temperature for 1 hr. The mixture was concentrated under vacuum to give the crude product trans 2-(6-(2,5-diazabicyclo[4.2.0]octan-2-yl)-2-(4-(difluoromethylene)piperidin-1-yl)-5-ethyl-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (19 mg, 0.028 mmol, 98% yield) as yellow solid. **MS** (ESI) m/z = 641.0, 643.2 $[M+H]^+$.

Step 4: The mixture of 5-hydroxy-6-methylpyrimidine-4-carboxylic acid (97.13 mg, 0.63 mmol), HOAt (107.22 mg, 0.78 mmol) and EDCI (151.01 mg,0.78 mmol) in MeCN (80 mL) was stirred at room temperature for 1 hr under argon, then the reagent trans 2-(6-(2,5-diazabicyclo[4.2.0]octan-2-yl)-2-(4-(difluoromethylene)piperidin-1-yl)-5-ethyl-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (202 mg, 0.31 mmol) and

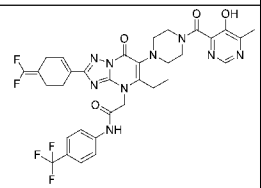
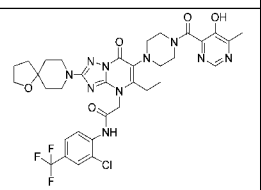
DIEA (407.24 mg, 3.15 mmol) in MeCN (10 mL) was added, the mixture was stirred at room temperature for 1 hr. The mixture was concentrated to remove MeCN, diluted with water (20 mL), extracted with EtOAc (20 mL * 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, concentrated under vacuum and the residue was purified by Flash Chromatography (MeOH/DCM = 0-3%) to give the trans product N-(2-chloro-4-(trifluoromethyl) phenyl)-2-(2-(4-(difluoromethylene)piperidin-1-yl)-5-ethyl-6-(5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)ac etamide as yellow solid. **^{1}H NMR** (400 MHz,CD_3OD) δ 8.51 (d, J = 12.1 Hz, 1H), 8.39 (s, 1H), 8.13 (s, 1H), 7.80 (s, 1H), 7.60 (s, 1H), 5.25 (s, 2H), 3.82 (s, 1H), 3.75 – 3.35 (m, 8H), 3.05 (d, J = 43.6 Hz, 3H), 2.48 (s, 3H), 2.21 (s, 5H), 1.64 (d, J = 48.6 Hz, 2H), 1.45 (d, J = 10.5 Hz, 1H), 1.26 (s, 3H). **MS** (ESI) m/z = 777.1, 779.2 $[M+H]^+$

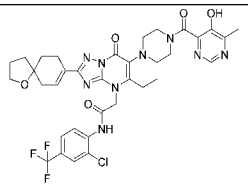
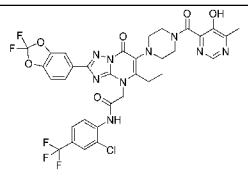
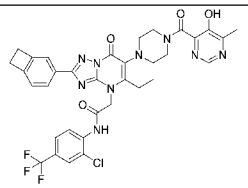
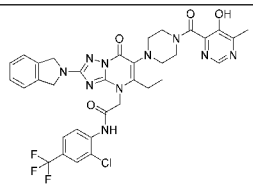
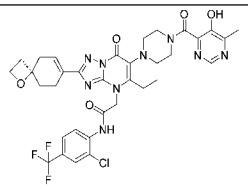
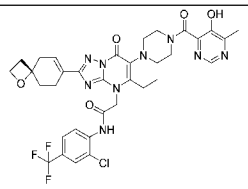
The product was then purified by SFC (Separation Conditions: Apparatus: SFC Thar prep 80, Column: CHIRALPAK AD-H 250mm × 20 mm, 5μm, Modifier: 40% IPA (NH_4OH 0.2%): 60% CO_2, Total Flow: 40g/min) to give the N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(4-(difluoro methylene)piperidin-1-yl)-5-ethyl-6-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-d iazabicyclo[4.2.0]octan-2-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide and N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(4-(difluoromethylene)piperidin-1-yl)-5-ethyl-6-((1R,6R)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-7-oxo -[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide.

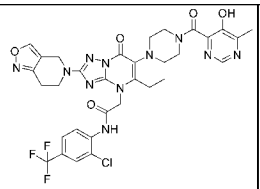
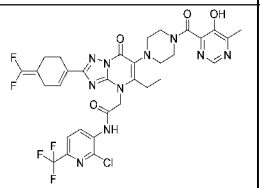
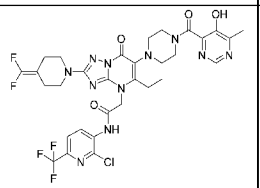
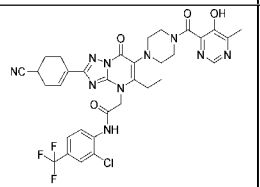
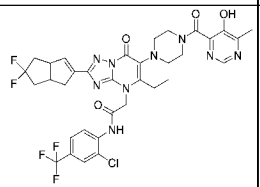
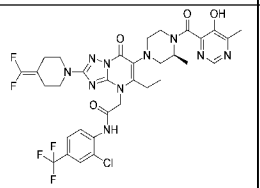
The first peak from the SFC (Rt = 4.08 min, 38.7 mg, 0.05 mmol, 15% yield): **^{1}H NMR** (400 MHz, CD_3OD) δ 8.51 (s, 1H), 8.12 (d, J = 8.5 Hz, 1H), 7.79 (s, 1H), 7.60 (d, J = 8.7 Hz, 1H), 5.25 (s, 2H), 4.62 (s, 1H), 3.84 (d, J = 7.6 Hz, 1H), 3.73 – 3.34 (m, 8H), 3.17 - 3.07 (m, 1H), 3.04 - 2.92 (m, 1H), 2.48 (s, 3H), 2.25 - 2.16 (m, 4H), 1.68 (d, J = 28.3 Hz, 2H), 1.53 – 1.40 (m, 1H), 1.36 - 1.22 (m, 4H). **MS** (ESI) m/z = 777.2, 779.2 $[M+H]^+$

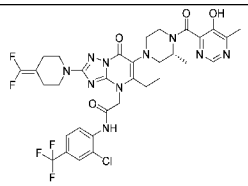
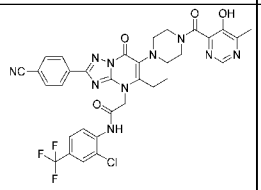
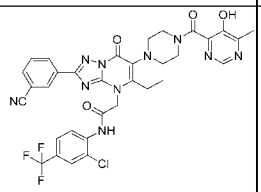
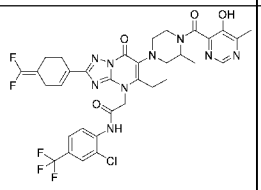
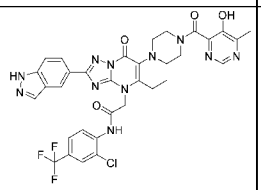
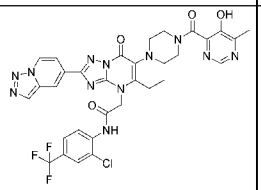
The second peak from the SFC (Rt = 15.25 min, 25.1 mg, 0.03 mmol, 10% yield): **^{1}H NMR** (400 MHz, CD_3OD) δ 8.48 (s, 1H), 8.12 (d, J = 8.6 Hz, 1H), 7.79 (s, 1H), 7.59 (d, J = 8.8 Hz, 1H), 5.35 – 5.19 (m, 2H), 4.63 (s, 1H), 3.83 (d, J = 7.0 Hz, 1H), 3.74 – 3.35 (m, 8H), 3.11 (dt, J = 14.7, 7.4 Hz, 1H), 2.99 (dd, J = 13.9, 7.3 Hz, 1H), 2.47 (s, 3H), 2.25 - 2.15 (m, 4H), 1.67 (d, J = 29.0 Hz, 2H), 1.45 (s, 1H), 1.29 - 1.22 (m ,4H). **MS** (ESI) m/z = 777.2, 779.2 $[M+H]^+$

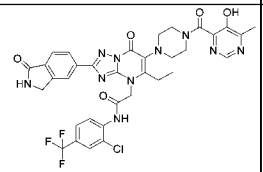
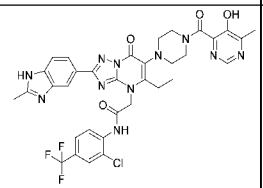
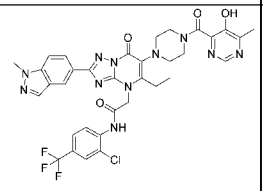
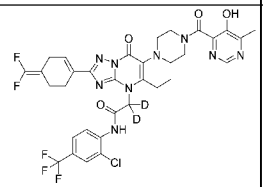
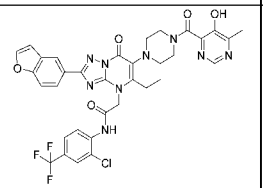
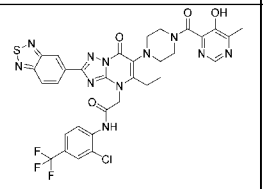
The following compounds were synthesized by using the similar methods as above procedure or reference. The start material is commercially available or prepared in house.

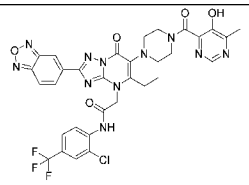
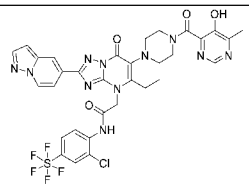
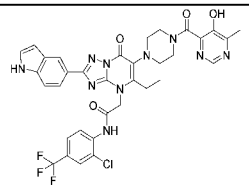
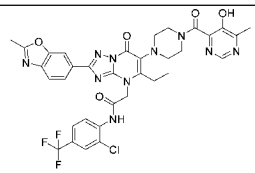
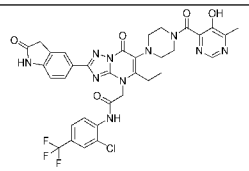
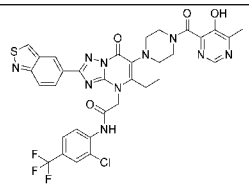
Example number	Structure	Name of structure	Data (NMR and LCMS)
208		2-(2-(4-(difluoromethylene)cyclohex-1-en-1-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(4-(trifluoromethyl)phenyl)acetamide	**^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.80 (s, 1H), 9.04 (s, 1H), 8.59 (s, 1H), 7.59 (s, 4H), 6.95 (s, 1H), 5.67 (d, J = 12.3 Hz, 1H), 5.04 (s, 2H), 4.79 (d, J = 12.7 Hz, 1H), 3.80 (t, J = 11.3 Hz, 2H), 3.48 (t, J = 11.7 Hz, 1H), 3.17 (dd, J = 14.7, 7.2 Hz, 2H), 3.12 – 3.02 (m, 1H), 2.98 (s, 2H), 2.89 - 2.66 (m, 4H), 2.57 (s, 3H), 2.38 (t, J = 5.6 Hz, 2H), 1.33 (t, J = 7.5 Hz, 3H). **MS** (ESI) m/z = 714.2 $[M+H]^+$.
211		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-2-(1-oxa-8-azaspiro[4.5]decan-8-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.53 (s, 1H), 8.12 (d, J = 8.8 Hz, 1H), 7.79 (s, 1H), 7.60 (d, J = 8.6 Hz, 1H), 5.25 (s, 2H), 4.67 (d, J = 12.0 Hz, 1H), 4.04 (d, J = 11.5 Hz, 1H), 3.82 (t, J = 6.8 Hz, 2H), 3.77 – 3.61 (m, 4H), 3.45 (ddd, J = 35.7, 18.0, 9.1 Hz, 3H), 3.06 (dt, J = 14.4, 9.0 Hz, 3H), 2.87 (d, J = 10.5 Hz, 1H), 2.77 – 2.67 (m, 1H), 2.49 (s, 3H), 2.00 – 1.87 (m, 2H), 1.73 (t, J = 7.4 Hz, 2H), 1.62 (t, J = 5.6 Hz, 4H), 1.25 (t, J = 5.3 Hz, 3H). **MS** (ESI) m/z = 758.9 $[M+H]^+$.

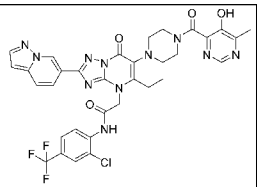
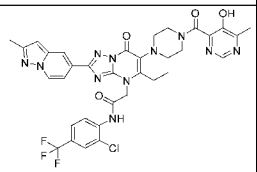
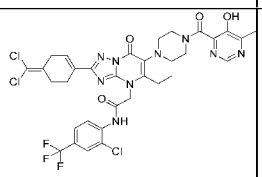
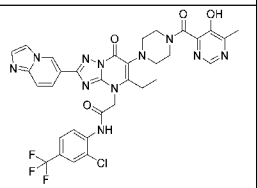
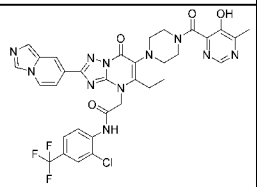
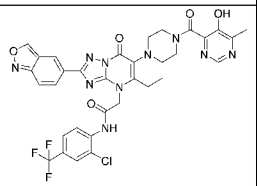
212		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-2-(1-oxaspiro[4.5]dec-7-en-8-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.79 (s, 1H), 9.10 (s, 1H), 8.59 (s, 1H), 8.49 (d, J = 8.6 Hz, 1H), 7.63 (s, 1H), 7.53 (d, J = 8.8 Hz, 1H), 6.94 (s, 1H), 5.65 (d, J = 10.6 Hz, 1H), 5.09 (dd, J = 36.8, 15.4 Hz, 2H), 4.79 (d, J = 10.7 Hz, 1H), 3.95-3.85 (m, 2H), 3.84-3.74 (m, 2H), 3.49 (s, 1H), 3.25-3.10 (m, 2H), 3.06 (s, 1H), 2.85 (d, J = 17.5 Hz, 2H), 2.80-2.65 (m, 2H), 2.56 (s, 3H), 2.45-2.30 (m, 2H), 1.99 (dd, J = 14.1, 7.1 Hz, 2H), 1.95-1.85 (m, 1H), 1.80-1.70 (m, 3H), 1.40-1.30 (m, 3H). **MS** (ESI) m/z = 756.3 $[M+H]^+$.
214		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.52 (s, 1H), 8.13 (d, J=8.7 Hz, 1H), 8.05 (d, J=8.5 Hz, 1H), 7.97 (s, 1H), 7.80 (s, 1H), 7.59 (d, J=8.8 Hz, 1H), 7.29 (d, J=8.4 Hz, 1H), 5.44 (s, 2H), 4.70 (d, J=11.8 Hz, 1H), 4.09 (d, J=11.5 Hz, 1H), 3.79 – 3.67 (m, 2H), 3.44 (d, J=9.3 Hz, 1H), 3.11 (d, J=7.7 Hz, 3H), 2.97 – 2.90 (m, 1H), 2.79 (d, J=11.5 Hz, 1H), 2.50 (s, 3H), 1.35 - 1.25 (m, 3H). **MS** (ESI) m/z = 776.0 $[M+H]^+$.
215		2-(2-(bicyclo[4.2.0]octa-1(6),2,4-trien-3-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide	**^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.79 (s, 1H), 9.19 (s, 1H), 8.58 (s, 1H), 8.48 (d, J = 8.8 Hz, 1H), 8.20-8.10 (m, 1H), 7.94 (s, 1H), 7.56 (s, 1H), 7.51 (d, J = 8.9 Hz, 1H), 7.12 (d, J = 7.5 Hz, 1H), 5.66 (d, J = 10.5 Hz, 1H), 5.16 (s, 2H), 4.79 (d, J = 11.2 Hz, 1H), 3.85-3.75 (m, 2H), 3.47 (d, J = 13.1 Hz, 1H), 3.20 (d, J = 10.6 Hz, 6H), 3.08 (d, J = 11.1 Hz, 1H), 2.85-2.70 (m, 2H), 2.56 (s, 3H), 1.35-1.30 (m, 3H). **MS** (ESI) m/z = 722.1 $[M+H]^+$.
216		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(isoindolin-2-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.51 (s, 1H), 8.15 (d, J = 8.9 Hz, 1H), 7.81 (s, 1H), 7.60 (d, J = 8.9 Hz, 1H), 7.31-7.29 (m, 2H), 7.28-7.24 (m, 2H), 5.32 (s, 2H), 4.79 (s, 4H), 4.69 (d, J = 13.0 Hz, 1H), 4.06 (d, J = 14.0 Hz, 1H), 3.80-3.65 (m, 2H), 3.45-3.35 (m, 1H), 3.15-3.00 (m, 3H), 2.95-2.85 (m, 1H), 2.75 (d, J = 8.2 Hz, 1H), 2.49 (s, 3H), 1.27 (d, J = 5.6 Hz, 3H). **MS** (ESI) m/z = 737.1 $[M+H]^+$.
219		(R)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-2-(1-oxaspiro[3.5]non-6-en-7-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.55 (s, 1H), 8.17 (d, J = 8.6 Hz, 1H), 7.83 (s, 1H), 7.63 (d, J = 8.5 Hz, 1H), 6.86 (s, 1H), 5.39 (s, 2H), 4.72 (d, J = 12.9 Hz, 1H), 4.58 (t, J = 7.8 Hz, 2H), 4.09 (d, J = 12.2 Hz, 1H), 3.75 (t, J = 12.1 Hz, 2H), 3.45 (t, J = 11.7 Hz, 1H), 3.23 - 3.06 (m, 3H), 2.94 (d, J = 10.9 Hz, 1H), 2.87 – 2.60 (m, 5H), 2.59 – 2.44 (m, 5H), 2.18 - 2.09 (m, 1H), 2.08 – 2.01 (m, 1H), 1.35 - 1.29 (m, 3H). **MS** (ESI) m/z = 742.2 $[M+H]^+$.
220		(S)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-2-(1-oxaspiro[3.5]non-6-en-7-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, MeOD) δ 8.56 (s, 1H), 8.17 (d, J = 8.6 Hz, 1H), 7.83 (s, 1H), 7.63 (d, J = 8.6 Hz, 1H), 6.86 (s, 1H), 5.39 (s, 2H), 4.72 (d, J = 12.5 Hz, 1H), 4.58 (t, J = 7.7 Hz, 2H), 4.10 (d, J = 12.7 Hz, 1H), 3.75 (t, J = 11.0 Hz, 2H), 3.45 (t, J = 11.8 Hz, 1H), 3.23 - 3.04 (m, 3H), 2.94 (d, J = 11.3 Hz, 1H), 2.84 – 2.61 (m, 5H), 2.59 – 2.46 (m, 5H), 2.18 - 2.09 (m, 1H), 2.08 - 2.00 (m, 1H), 1.32 (t, J = 7.5 Hz, 3H). **MS** (ESI) m/z = 742.0 $[M+H]^+$.

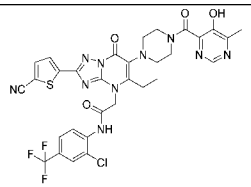
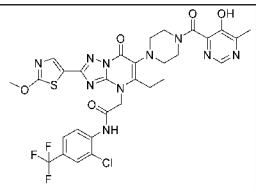
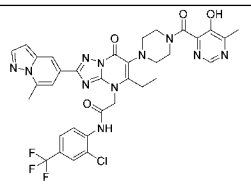
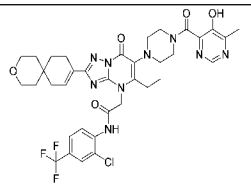
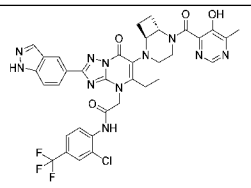
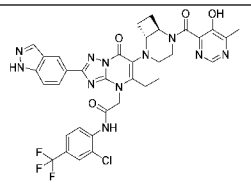
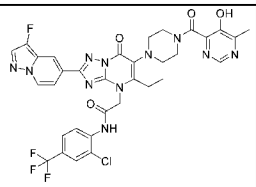
221		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(6,7-dihydroisoxazolo[4,3-c]pyridin-5(4H)-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD)δ 8.55 (s, 1H), 8.48 (s, 1H), 8.16 (d, J = 8.6 Hz, 1H), 7.85 (s, 1H), 7.64 (d, J = 8.7 Hz, 1H), 5.32 (s, 2H), 4.71 (d, J = 17.6 Hz, 3H), 4.10 (d, J = 12.4 Hz, 1H), 3.93 (t, J = 5.9 Hz, 2H), 3.74 (d, J = 9.4 Hz, 2H), 3.50 – 3.39 (m, 1H), 3.11 (dt, J = 14.7, 9.0 Hz, 3H), 2.93 (t, J = 5.9 Hz, 3H), 2.78 (d, J = 10.6 Hz, 1H), 2.53 (s, 3H), 1.30 (s, 3H). **MS** (ESI) m/z = 741.9 $[M+H]^+$.
222		N-(2-chloro-6-(trifluoromethyl)pyridin-3-yl)-2-(2-(4-(difluoromethylene)cyclohex-1-en-1-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.67 (d, J = 8.4 Hz, 1H), 8.58 (s, 1H), 7.81 (d, J = 8.4 Hz, 1H), 6.98 (s, 1H), 5.44 (s, 2H), 4.72 (d, J = 10.7 Hz, 1H), 4.10 (d, J = 11.7 Hz, 1H), 3.75 (s, 2H), 3.46 (s, 1H), 3.12 (dd, J = 15.6, 8.0 Hz, 4H), 2.98 (s, 2H), 2.80 (d, J = 10.4 Hz, 1H), 2.67 (s, 2H), 2.54 (s, 3H), 2.42 (d, J = 6.3 Hz, 2H), 1.32 (d, J = 6.5 Hz, 3H). **MS** (ESI) m/z = 749.1 $[M+H]^+$.
223		N-(2-chloro-6-(trifluoromethyl)pyridin-3-yl)-2-(2-(4-(difluoromethylene)piperidin-1-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.67 (d, J = 8.4 Hz, 1H), 8.56 (s, 1H), 7.81 (d, J = 8.4 Hz, 1H), 5.34 (s, 2H), 4.71 (d, J = 12.4 Hz, 1H), 4.10 (d, J = 12.5 Hz, 1H), 3.75 (d, J = 6.7 Hz, 2H), 3.61 (t, J = 5.6 Hz, 4H), 3.44 (t, J = 11.8 Hz, 1H), 3.16 (d, J = 10.8 Hz, 1H), 3.07 (dd, J = 15.1, 7.5 Hz, 2H), 2.92 (d, J = 10.9 Hz, 1H), 2.77 (d, J = 11.8 Hz, 1H), 2.54 (s, 3H), 2.25 (s, 4H), 1.35 - 1.25 (m, 3H). **MS** (ESI) m/z = 752.2 $[M+H]^+$.
224		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(4-cyanocyclohex-1-en-1-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.79 (s, 1H), 8.96 (s, 1H), 8.59 (s, 1H), 8.48 (d, J= 8.5 Hz, 1H), 7.65 (s, 1H), 7.54 (d, J=8.6 Hz, 1H), 6.95 (s, 1H), 5.66 (d, J=11.9 Hz, 1H), 5.11 (s, 2H), 4.79 (d, J=10.7 Hz, 1H), 3.85-3.75 (m, 2H), 3.49 (s, 1H), 3.25-3.05 (m, 3H), 2.88 (d, J=23.9 Hz, 3H), 2.76 - 2.56 (m, 4H), 2.56 (s, 3H), 2.07 (dd, J = 24.4, 18.5 Hz, 2H), 1.35-1.25 (m, 3H). **MS** (ESI) m/z = 725.1 $[M+H]^+$.
225		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(5,5-difluoro-1,3a,4,5,6,6a-hexahydropentalen-2-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.54 (s, 1H), 8.14 (d, J = 8.6 Hz, 1H), 7.79 (s, 1H), 7.59 (dd, J = 8.5, 1.6 Hz, 1H), 6.60 (s, 1H), 5.36 (s, 2H), 4.68 (d, J = 10.7 Hz, 1H), 4.06 (d, J = 13.1 Hz, 1H), 3.71 (t, J = 12.7 Hz, 2H), 3.43 (dd, J = 29.3, 15.9 Hz, 2H), 3.15 – 2.99 (m, 5H), 2.91 (d, J = 10.5 Hz, 1H), 2.72 (dd, J = 30.0, 13.2 Hz, 2H), 2.50 (s, 3H), 2.41 – 2.28 (m, 2H), 2.02 – 1.81 (m, 2H), 1.29 (d, J = 7.4 Hz, 3H). **MS** (ESI) m/z = 762.2 $[M+H]^+$.
227		N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{2-[4-(difluoromethylidene)piperidin-1-yl]-5-ethyl-6-[(3S)-4-[(5-hydroxy-6-methylpyrimidin-4-yl)carbonyl]-3-methylpiperazin-1-yl]-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4-yl}acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.56 (d, J=4.7 Hz, 1H), 8.17 (d, J=8.6 Hz, 1H), 7.84 (s, 1H), 7.64 (d, J=8.4 Hz, 1H), 5.31 (s, 2H), 4.97–4.93 (m, 0.5H), 4.57 (d, J=13.2 Hz, 0.5H), 4.20–4.13 (m, 0.5H), 3.98–3.89 (m, 1H), 3.81-3.64 (m, 2H), 3.61 (t, J=5.4 Hz, 4H), 3.44-3.35 (m, 0.5H), 3.25–3.14 (m, 1H), 3.09–2.98 (m, 1H), 2.91 (d, J=10.5 Hz, 0.5H), 2.81–2.73 (m, 1H), 2.66 (d, J=11.7 Hz, 0.5H), 2.53 (d, J=1.7 Hz, 3H), 2.31–2.18 (m, 4H), 1.56 (t, J = 6.0 Hz, 3H), 1.32 (t, J=6.4 Hz, 3H). **MS** (ESI) m/z = 765.2 $[M+H]^+$.

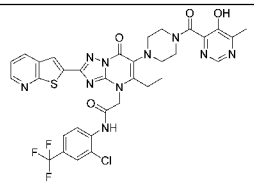
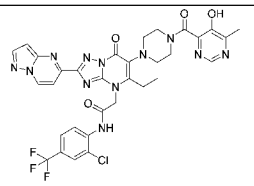
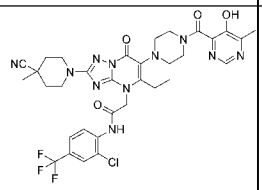
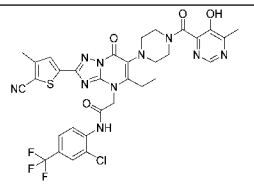
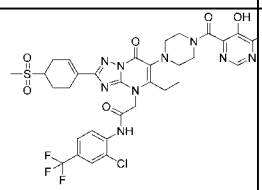
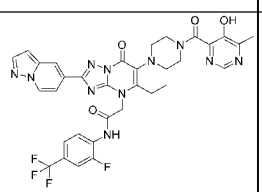
228		N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{2-[4-(difluoromethylidene)piperidin-1-yl]-5-ethyl-6-[(3R)-4-[(5-hydroxy-6-methylpyrimidin-4-yl)carbonyl]-3-methylpiperazin-1-yl]-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4-yl}acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.54 (d, J = 1.2 Hz, 1H), 8.12 (d, J = 8.7 Hz, 1H), 7.79 (s, 1H), 7.59 (d, J = 8.5 Hz, 1H), 5.26 (s, 2H), 4.96–4.85 (m, 0.5H), 4.53 (d, J = 13.3 Hz, 0.5H), 4.18-4.10 (m, 0.5H), 3.92 - 3.86 (m, 1H), 3.80–3.59 (m, 2H), 3.57 (t, J = 5.6 Hz, 4H), 3.39–3.30 (m, 0.5H), 3.21–3.09 (m, 1H), 3.06–2.95 (m, 1H), 2.87 (d, J = 10.9 Hz, 0.5H), 2.73 (t, J = 12.3 Hz, 1H), 2.62 (d, J = 11.7 Hz, 0.5H), 2.50 (s, 3H), 2.25–2.17 (m, 4H), 1.55–1.48 (m, 3H), 1.28 (t, J = 7.2 Hz, 3H). **MS** (ESI) m/z = 765.0 $[M+H]^+$.
229		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(4-cyanophenyl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.80 (s, 1H), 8.85 (s, 1H), 8.60 (s, 1H), 8.50 (d, J= 8.7 Hz, 1H), 8.45-8.35 (m, 2H), 7.80-7.70 (m, 2H), 7.62 (s, 1H), 7.54 (d, J=8.3 Hz, 1H), 5.69 (s, 1H), 5.20 (s, 2H), 4.81 (d, J= 11.7 Hz, 1H), 3.82 (d, J=10.9 Hz, 2H), 3.50 (d, J=6.9 Hz, 1H), 3.21 (d, J=7.3 Hz, 2H), 3.09 (s, 1H), 2.87 (d, J=9.8 Hz, 1H), 2.81 (s, 1H), 2.57 (s, 3H), 1.40-1.30 (m, 3H). **MS** (ESI) m/z = 721.0 $[M+H]^+$.
230		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(3-cyanophenyl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.55 (d, J = 17.5 Hz, 2H), 8.49 (d, J = 7.9 Hz, 1H), 8.17 (d, J = 8.5 Hz, 1H), 7.85 (d, J = 9.5 Hz, 2H), 7.69 (t, J = 7.8 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 5.50 (s, 2H), 4.74 (d, J = 12.5 Hz, 1H), 4.15 (d, J = 11.2 Hz, 1H), 3.78 (t, J = 11.7 Hz, 2H), 3.48 (t, J = 12.0 Hz, 1H), 3.25 - 3.10 (m, 3H), 2.99 (d, J = 10.4 Hz, 1H), 2.84 (d, J = 10.4 Hz, 1H), 2.54 (s, 3H), 1.36 (t, J = 7.4 Hz, 3H). **MS** (ESI) m/z = 721.1 $[M+H]^+$.
231		N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{2-[4-(difluoromethylidene)cyclohex-1-en-1-yl]-5-ethyl-6-{4-[(5-hydroxy-6-methylpyrimidin-4-yl)carbonyl]-3-methylpiperazin-1-yl}-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4-yl}acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.14 (d, J = 8.6 Hz, 1H), 7.80 (s, 1H), 7.60 (d, J = 8.6 Hz, 1H), 6.95 (s, 1H), 5.37 (s, 2H), 4.96 - 4.91 (m, 0.5H), 4.57 - 4.54(m, 1H), 4.19 - 4.12 (m, 0.5H), 3.94 - 3.88 (m, 1H), 3.79 – 3.63 (m, 2H), 3.41 – 3.35 (m, 0.5H), 3.24 - 3.16 (m, 1H), 3.09 – 3.00 (m, 1H), 2.97 – 2.89 (m, 2.5H), 2.83 – 2.73 (m, 1H), 2.67 - 2.61 (m, 2H), 2.51 (s, 3H), 2.42 - 2.35 (m, 2H), 1.54 (t, J = 6.2 Hz, 3H), 1.32 (t, J = 7.4 Hz, 3H). **MS** (ESI) m/z = 761.9 $[M+H]^+$.
232		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(1H-indazol-5-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.55 (s, 1H), 8.46 (s, 1H), 8.14 (d, J=8.8 Hz, 1H), 8.10-8.03 (m, 2H), 7.72 (s, 1H), 7.55-7.48 (m, 2H), 5.38 (s, 2H), 4.63 (d, J=11.6 Hz, 1H), 4.50 (s, 1H), 3.99 (s, 1H), 3.67 (d, J=8.9 Hz, 2H), 3.36 (s, 1H), 3.03 (d, J=7.0 Hz, 2H), 2.87 (d, J=10.9 Hz, 1H), 2.72 (d, J=10.8 Hz, 1H), 2.42 (s, 3H), 1.32-1.20 (m, 3H). **MS** (ESI) m/z = 736.2 $[M+H]^+$.
234		2-(2-([1,2,3]triazolo[1,5-a]pyridin-5-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 9.01 (d, J = 7.3 Hz, 1H), 8.72 (s, 1H), 8.58 (s, 1H), 8.29 (s, 1H), 8.20 (d, J = 8.6 Hz, 1H), 7.93 (dd, J = 7.4, 1.6 Hz, 1H), 7.85 (d, J = 1.7 Hz, 1H), 7.63 (dd, J = 8.7, 1.6 Hz, 1H), 5.52 (s, 2H), 4.75 (d, J = 12.2 Hz, 1H), 4.14 (d, J = 13.2 Hz, 1H), 3.79 (t, J = 12.0 Hz, 2H), 3.48 (t, J = 11.7 Hz, 1H), 3.24 - 3.11 (m, 3H), 3.00 (d, J = 11.1 Hz, 1H), 2.85 (d, J = 11.9 Hz, 1H), 2.55 (s, 3H), 1.37 (t, J = 7.5 Hz, 3H).

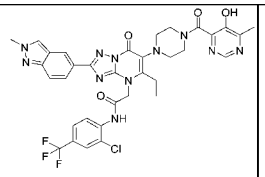
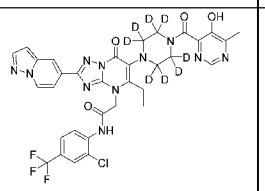
			MS (ESI) m/z = 737.1 $[M+H]^+$.
235		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-2-(1-oxoisoindolin-5-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.59 (s, 1H), 8.43 (s, 1H), 8.38 (d, J = 8.1 Hz, 1H), 8.19 (d, J = 8.5 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.85 (s, 1H), 7.63 (d, J = 8.5 Hz, 1H), 5.51 (s, 2H), 4.75 (d, J = 11.1 Hz, 1H), 4.56 (s, 2H), 4.13 (d, J = 13.1 Hz, 1H), 3.79 (t, J = 12.3 Hz, 2H), 3.48 (t, J = 10.6 Hz, 1H), 3.23 – 3.10 (m, 3H), 2.99 (d, J = 7.7 Hz, 1H), 2.85 (d, J = 9.3 Hz, 1H), 2.54 (d, J = 8.4 Hz, 3H), 1.36 (t, J = 7.3 Hz, 3H). **MS** (ESI) m/z = 751.3 $[M+H]^+$.
236		N-[2-chloro-4-(trifluoromethyl)phenyl]-2-(5-ethyl-6-{4-[(5-hydroxy-6-methylpyrimidin-4-yl)carbonyl]piperazin-1-yl}-2-(2-methyl-1H-1,3-benzodiazol-5-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.44 (s, 1H), 8.23 (s, 1H), 8.06 (d, J = 8.5 Hz, 1H), 7.98 (d, J = 7.6 Hz, 1H), 7.70 (s, 1H), 7.49 (d, J = 8.5 Hz, 1H), 7.44 (d, J = 8.5 Hz, 1H), 5.36 (s, 2H), 4.62 (d, J = 11.9 Hz, 1H), 4.03 (d, J = 11.1 Hz, 1H), 3.66 (s, 2H), 3.36 (d, J = 12.2 Hz, 1H), 3.10 – 2.95 (m, 3H), 2.85 (d, J = 10.4 Hz, 1H), 2.71 (d, J = 10.7 Hz, 1H), 2.48 (s, 3H), 2.42 (s, 3H), 1.22 (s, 3H). **MS** (ESI) m/z = 749.9 $[M+H]^+$.
238		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(1-methyl-1H-indazol-5-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.63 (s, 1H), 8.57 (s, 1H), 8.29 (d, J = 8.8 Hz, 1H), 8.19 (d, J = 8.5 Hz, 1H), 8.11 (s, 1H), 7.84 (s, 1H), 7.67-7.60 (m, 2H), 5.50 (s, 2H), 4.74 (d, J = 11.5 Hz, 1H), 4.12 (d, J = 7.6 Hz, 4H), 3.79 (s, 2H), 3.49 (d, J = 11.1 Hz, 1H), 3.15 (d, J = 7.1 Hz, 3H), 2.99 (d, J = 10.0 Hz, 1H), 2.84 (d, J = 9.7 Hz, 1H), 2.54 (s, 3H), 1.40-1.30 (m, 3H). **MS** (ESI) m/z = 750.3 $[M+H]^+$.
240		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(4-(difluoromethylene)cyclohex-1-en-1-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide-2,2-d2	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.58 (s, 1H), 8.17 (d, J = 8.5 Hz, 1H), 7.83 (s, 1H), 7.62 (d, J = 8.4 Hz, 1H), 6.98 (s, 1H), 4.71 (d, J = 12.8 Hz, 1H), 4.11 (d, J = 12.8 Hz, 1H), 3.79 - 3.69 (m, 2H), 3.48 – 3.40 (m, 1H), 3.19 – 3.07 (m, 3H), 3.00 – 2.90 (m, 3H), 2.79 (d, J = 11.2 Hz, 1H), 2.70 - 2.62 (m, 2H), 2.53 (s, 3H), 2.45 – 2.37 (m, 2H), 1.32 (t, J = 7.4 Hz, 3H). **MS** (ESI) m/z = 749.9 $[M+H]^+$.
241		2-(2-(benzofuran-5-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.61 – 8.38 (m, 2H), 8.19 (d, *J* = 8.6 Hz, 2H), 7.84 (s, 2H), 7.61 (t, *J* = 8.1 Hz, 2H), 6.94 (s, 1H), 5.49 (s, 2H), 4.77 (s, 1H), 4.14 (s, 1H), 3.88 - 3.68 (m, 2H), 3.48 (s, 1H), 3.25 - 3.10 (m, 3H), 2.98 (d, *J* = 9.7 Hz, 1H), 2.84 (d, *J* = 9.8 Hz, 1H), 2.54 (s, 3H), 1.36 (t, *J* = 7.3 Hz, 3H). **MS** (ESI) m/z = 736.0 $[M+H]^+$.
243		2-(2-(benzo[c][1,2,5]thiadiazol-5-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide	**^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.81 (s, 1H), 8.97 (s, 1H), 8.92 (s, 1H), 8.60 (s, 1H), 8.56 (d, *J* = 9.2 Hz, 1H), 8.50 (d, *J* = 8.7 Hz, 1H), 8.09 (d, *J* = 9.2 Hz, 1H), 7.60 (s, 1H), 7.53 (d, *J* = 9.3 Hz, 1H), 5.71 (d, *J* = 12.8 Hz, 1H), 5.24 (s, 2H), 4.82 (d, *J* = 9.9 Hz, 1H), 3.86 (t, *J* = 11.2 Hz, 2H), 3.52 (s, 1H), 3.24 (d, *J* = 7.4 Hz, 2H), 3.09 (s, 1H), 2.85 (d, *J* = 22.6 Hz, 2H), 2.58 (s, 3H), 1.38 (t, *J* = 7.4 Hz, 3H). **MS** (ESI) m/z = 753.9 $[M+H]^+$.

244		2-(2-(benzo[c][1,2,5]oxadiazol-5-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.72 (s, 1H), 8.58 (s, 1H), 8.36 (d, *J* = 9.5 Hz, 1H), 8.18 (d, *J* = 8.6 Hz, 1H), 8.04 (d, *J* = 9.4 Hz, 1H), 7.84 (s, 1H), 7.62 (d, *J* = 8.6 Hz, 1H), 5.52 (s, 2H), 4.75 (d, *J* = 12.4 Hz, 1H), 4.15 (d, *J* = 11.5 Hz, 1H), 3.79 (t, *J* = 11.7 Hz, 2H), 3.48 (t, *J* = 11.6 Hz, 1H), 3.18 (dd, *J* = 14.6, 7.0 Hz, 3H), 3.00 (d, *J* = 10.4 Hz, 1H), 2.85 (d, *J* = 10.6 Hz, 1H), 2.55 (s, 3H), 1.37 (t, *J* = 7.5 Hz, 3H). **MS** (ESI) m/z = 738.2 $[M+H]^+$.
245		N-(2-chloro-4-(pentafluoro-λ^6-sulfaneyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-2-(pyrazolo[1,5-a]pyridin-5-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.49 (d, J= 6.5 Hz, 1H), 8.43 (s, 1H), 8.33 (d, J=17.6 Hz, 1H), 8.11 (d, J=8.3 Hz, 1H), 7.89 (d, J=3.4 Hz, 2H), 7.66 (d, J=7.5 Hz, 1H), 7.51 (d, J=5.8 Hz, 1H), 6.63 (s, 1H), 5.39 (s, 2H), 4.63 (d, J=12.0 Hz, 1H), 4.04 (s, 1H), 3.66 (s, 2H), 3.36 (s, 1H), 3.04 (d, J=6.9 Hz, 3H), 2.87 (d, J=10.8 Hz, 1H), 2.72 (d, J=10.5 Hz, 1H), 2.41 (s, 3H), 1.21 (d, J=21.9 Hz, 3H). **MS** (ESI) m/z = 793.9 $[M+H]^+$.
246		N-[2-chloro-4-(trifluoromethyl)phenyl]-2-(5-ethyl-6-{4-[(5-hydroxy-6-methylpyrimidin-4-yl)carbonyl]piperazin-1-yl}-2-(1H-indol-5-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.51 (s, 1H), 8.40 (d, J = 6.5 Hz, 1H), 8.14 (d, J = 8.7 Hz, 1H), 7.95 (d, J = 8.6 Hz, 1H), 7.79 (s, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.26 (d, J = 2.7 Hz, 1H), 6.50 (d, J = 2.4 Hz, 1H), 5.43 (s, 2H), 4.69 (d, J = 11.7 Hz, 1H), 4.07 (d, J = 11.4 Hz, 1H), 3.74 (d, J = 8.7 Hz, 2H), 3.49 – 3.38 (m, 1H), 3.11 (t, J = 14.7 Hz, 3H), 2.92 (d, J = 10.6 Hz, 1H), 2.77 (d, J = 9.9 Hz, 1H), 2.50 (s, 3H), 1.27 (d, J = 7.7 Hz, 3H). **MS** (ESI) m/z = 735.1 $[M+H]^+$.
247		N-[2-chloro-4-(trifluoromethyl)phenyl]-2-(5-ethyl-6-{4-[(5-hydroxy-6-methylpyrimidin-4-yl)carbonyl]piperazin-1-yl}-2-(2-methyl-1,3-benzoxazol-6-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4-yl)acetamide	**^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.74 (s, 1H), 9.02 (s, 1H), 8.53 (s, 1H), 8.43 (d, J=8.7 Hz, 1H), 8.33 (s, 1H), 8.19 (d, J=8.3 Hz, 1H), 7.64 (d, J=8.3 Hz, 1H), 7.51 (s, 1H), 7.46 (d, J=8.8 Hz, 1H), 5.62 (d, J=11.1 Hz, 1H), 5.14 (s, 2H), 4.74 (d, J=11.9 Hz, 1H), 3.78 (t, J=11.3 Hz, 2H), 3.50–3.39 (m, 1H), 3.16-3.10 (m, 2H), 3.08–2.94 (m, 1H), 2.84–2.69 (m, 2H), 2.61 (s, 3H), 2.50 (s, 3H), 1.29 (t, J=7.5 Hz, 3H). **MS** (ESI) m/z = 750.9 $[M+H]^+$.
248		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-2-(2-oxoindolin-5-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.64 (s, 1H), 10.43 (s, 1H), 8.55 (s, 1H), 8.07 (d, J=8.6 Hz, 1H), 7.96 (d, J=13.8 Hz, 3H), 7.72 (d, J=8.6 Hz, 1H), 6.93 (d, J=8.0 Hz, 1H), 5.39 (s, 2H), 4.54 (d, J=11.8 Hz, 1H), 3.57 (s, 2H), 3.55–3.46 (m, 3H), 3.25 (d, J=13.1 Hz, 1H), 3.00 (t, J=7.9 Hz, 3H), 2.84 (d, J=9.8 Hz, 1H), 2.66 (d, J=9.3 Hz, 1H), 2.44 (s, 3H), 1.21 (t, J=7.5 Hz, 3H). **MS** (ESI) m/z = 751.2 $[M+H]^+$.
250		2-(2-(benzo[c]isothiazol-5-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide	**^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.81 (s, 1H), 9.34 (s, 1H), 9.10 (s, 1H), 8.76 (s, 1H), 8.60 (s, 1H), 8.51 (d, J = 8.7 Hz, 1H), 8.36 (d, J = 9.3 Hz, 1H), 7.93 (d, J = 9.3 Hz, 1H), 7.58 (s, 1H), 7.53 (d, J = 8.6 Hz, 1H), 5.70 (d, J = 12.3 Hz, 1H), 5.23 (s, 2H), 4.82 (d, J = 11.1 Hz, 1H), 3.85 (t, J = 11.2 Hz, 2H), 3.51 (t, J = 13.2 Hz, 1H), 3.23 (d, J = 6.9 Hz, 2H), 3.09 (t, J = 12.7 Hz, 1H), 2.84 (dd, J = 33.7, 10.9 Hz, 2H), 2.58 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H). **MS** (ESI) m/z = 753.2 $[M+H]^+$.

253		N-[2-chloro-4-(trifluoromethyl)phenyl]-2-(5-ethyl-6-{4-[(5-hydroxy-6-methylpyrimidin-4-yl)carbonyl]piperazin-1-yl}-7-oxo-2-{pyrazolo[1,5-a]pyridin-6-yl}-[1,2,4]triazolo[1,5-a]pyrimidin-4-yl)acetamide	**^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.81 (s, 1H), 9.37 (s, 1H), 8.93 (s, 1H), 8.60 (s, 1H), 8.48 (d, J = 8.7 Hz, 1H), 8.03 (d, J = 2.1 Hz, 1H), 7.97 (d, J = 9.7 Hz, 1H), 7.65 – 7.58 (m, 2H), 7.53 (d, J = 8.7 Hz, 1H), 6.58 (d, J = 1.9 Hz, 1H), 5.69 (d, J = 12.1 Hz, 1H), 5.21 (s, 2H), 4.81 (d, J = 11.5 Hz, 1H), 3.84 (t, J = 11.1 Hz, 2H), 3.51 (s, 1H), 3.28 – 3.02 (m, 3H), 2.94 – 2.72 (m, 2H), 2.57 (s, 3H), 1.37 (t, J=7.4 Hz, 3H). **MS** (ESI) m/z = 753.9 $[M+H]^+$.
254		N-[2-chloro-4-(trifluoromethyl)phenyl]-2-(5-ethyl-6-{4-[(5-hydroxy-6-methylpyrimidin-4-yl)carbonyl]piperazin-1-yl}-2-{2-methylpyrazolo[1,5-a]pyridin-5-yl}-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4-yl)acetamide	**^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.80 (s, 1H), 9.01 (s, 1H), 8.60 (s, 1H), 8.51 (d, J= 8.7 Hz, 1H), 8.42 (d, J=7.3 Hz, 1H), 8.36 (s, 1H), 7.60 (s, 1H), 7.56-7.52 (m, 2H), 6.43 (s, 1H), 5.69 (d, J=11.4 Hz, 1H), 5.20 (s, 2H), 4.81 (d, J=11.9 Hz, 1H), 3.90-3.80 (m, 2H), 3.52 (d, J=11.5 Hz, 1H), 3.22 (d, J=7.6 Hz, 2H), 3.10 (d, J=12.4 Hz, 1H), 2.83 (dd, J=33.3, 11.3 Hz, 2H), 2.57 (s, 3H), 2.51 (s, 3H), 1.39-1.34 (m, 3H). **MS** (ESI) m/z = 750.2 $[M+H]^+$.
255		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(4-(dichloromethylene)cyclohex-1-en-1-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.42 (s, 1H), 8.13 (d, *J* = 8.7 Hz, 1H), 7.79 (s, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 6.91 (t, *J* = 2.8 Hz, 1H), 5.36 (s, 2H), 4.67 (d, *J* = 11.4 Hz, 1H), 4.03-4.00 (m, 1H), 3.70 (dd, *J* = 16.1, 11.5 Hz, 2H), 3.49 – 3.36 (m, 1H), 3.18 (d, *J* = 3.1 Hz, 2H), 3.15 – 3.01 (m, 3H), 2.90 (d, *J* = 12.2 Hz, 1H), 2.75 (d, *J* = 10.5 Hz, 1H), 2.66 (s, 4H), 2.47 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H). **MS** (ESI) m/z = 780.0 $[M+H]^+$.
256		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(imidazo[1,2-*a*]pyridin-6-yl)-7-oxo-[1,2,4]triazolo[1,5-*a*]pyrimidin-4(7*H*)-yl)acetamide	**^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.13 (s, 2H), 8.58 (s, 1H), 8.43 (d, J = 8.7 Hz, 1H), 8.07 (d, J = 8.8 Hz, 1H), 7.81 (d, J=8.1 Hz, 1H), 7.70 (d, J = 10.8 Hz, 2H), 7.61 (s, 1H), 7.52 (d, J = 8.1 Hz, 1H), 5.68 (d, J = 10.8 Hz, 1H), 5.25 (s, 2H), 4.80 (d, J = 11.9 Hz, 1H), 3.82 (t, J = 11.5 Hz, 2H), 3.49 (t, J = 13.2 Hz, 1H), 3.17 (dd, J = 14.4, 7.2 Hz, 2H), 3.07 (t, J = 14.1 Hz, 1H), 2.83 (dd, J = 31.9, 10.4 Hz, 2H), 2.56 (s, 3H), 1.35 (t, J = 7.5 Hz, 3H). **MS** (ESI) m/z = 736.0 $[M+H]^+$.
257		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(imidazo[1,5-a]pyridin-7-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.47 (s, 1H), 8.38 (s, 2H), 8.29 (d, J = 7.1 Hz, 1H), 8.15 (d, J = 8.6 Hz, 1H), 7.81 (s, 1H), 7.59 (d, J = 9.5 Hz, 1H), 7.53 (s, 1H), 7.42 (d, J = 7.6 Hz, 1H), 5.45 (s, 2H), 4.75-4.68 (m, 1H), 4.57-4.47 (m, 1H), 3.84–3.65 (m, 2H), 3.55–3.40 (m, 1H), 3.19–3.08 (m, 3H), 2.95 (d, J = 8.7 Hz, 1H), 2.79 (d, J = 13.3 Hz, 1H), 2.48 (s, 3H), 1.33 (m, 3H). **MS** (ESI) m/z = 736.0 $[M+H]^+$.
259		2-(2-(benzo[c]isoxazol-5-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide	**^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.83 (s, 1H), 9.26 (s, 1H), 8.98 (s, 1H), 8.73 – 8.47 (m, 3H), 8.24 (d, J=9.2 Hz, 1H), 7.73 (d, J=9.0 Hz, 1H), 7.61 (s, 1H), 7.54 (d, J=8.6 Hz, 1H), 5.69 (d, J=11.9 Hz, 1H), 5.22 (s, 2H), 4.82 (d, J=10.8 Hz, 1H), 3.90 - 3.76 (m, 2H), 3.58 - 3.44 (m, 1H), 3.26 - 3.02 (m, 3H), 2.84 (d, J=24.9 Hz, 2H), 2.57 (s, 3H), 1.37 (s, 3H). **MS** (ESI) m/z = 737.1 $[M+H]^+$.

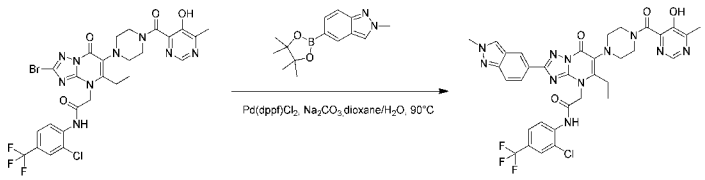
260		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(5-cyanothiophen-2-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.83 (s, 1H), 8.75 (s, 1H), 8.61 (s, 1H), 8.47 (d, J=8.7 Hz, 1H), 7.85 (d, J=3.9 Hz, 1H), 7.65 (s, 1H), 7.63 (d, J=3.9 Hz, 1H), 7.55 (d, J=8.1 Hz, 1H), 5.69 (d, J=11.0 Hz, 1H), 5.19 (s, 2H), 4.81 (d, J=11.8 Hz, 1H), 3.90-3.80 (m, 2H), 3.51 (s, 1H), 3.20 (d, J=7.1 Hz, 2H), 3.08 (s, 1H), 2.83 (dd, J=33.5, 10.3 Hz, 2H), 2.58 (s, 3H), 1.40- 1.30 (m, 3H). **MS** (ESI) m/z = 727.2 $[M+H]^+$.
261		N-[2-chloro-4-(trifluoromethyl)phenyl]-2-(5-ethyl-6-{4-[(5-hydroxy-6-methylpyrimidin-4-yl)carbonyl]piperazin-1-yl}-2-(2-methoxy-1,3-thiazol-5-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.57 (s, 1H), 8.17 (d, J=8.5 Hz, 1H), 7.84 (s, 2H), 7.63 (d, J=8.5 Hz, 1H), 5.43 (s, 2H), 4.73 (d, J=12.8 Hz, 1H), 4.12 (d, J=17.1 Hz, 4H), 3.74 (d, J=10.8 Hz, 2H), 3.46 (t, J= 11.8 Hz, 1H), 3.15 (dd, J=17.2, 10.0 Hz, 3H), 2.96 (d, J=10.7 Hz, 1H), 2.81 (d, J= 10.9 Hz, 1H), 2.54 (s, 3H), 1.33 (t, J=7.4 Hz, 3H). **MS** (ESI) m/z = 732.8 $[M+H]^+$.
262		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(7-methylpyrazolo[1,5-a]pyridin-5-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.80 (s, 1H), 9.02 (s, 1H), 8.60 (s, 1H), 8.51 (d, J = 8.7 Hz, 1H), 8.41 (s, 1H), 8.05 (d, J = 2.2 Hz, 1H), 7.60 - 7.52 (m, 3H), 6.71 (d, J = 2.2 Hz, 1H), 5.70 (d, J = 12.0 Hz, 1H), 5.20 (s, 2H), 4.82 (d, J = 10.3 Hz, 1H), 3.85 (t, J = 11.5 Hz, 2H), 3.55 - 3.47 (m, 1H), 3.25 - 3.19 (m, 2H), 3.13 - 3.06 (m, 1H), 2.93 - 2.76 (m, 5H), 2.57 (s, 3H), 1.37 (t, J = 7.5 Hz, 3H). **MS** (ESI) m/z = 749.9 $[M+H]^+$.
263		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-2-(3-oxaspiro[5.5]undec-8-en-9-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.17 (d, J = 8.6 Hz, 1H), 7.82 (s, 1H), 7.62 (d, J = 8.5 Hz, 1H), 6.97 - 6.90 (m, 1H), 5.39 (s, 2H), 4.77 - 4.65 (m, 1H), 4.17 - 4.05 (m, 1H), 3.77 - 3.66 (m, 6H), 3.51 - 3.40 (m, 1H), 3.20 – 3.04 (m, 3H), 2.94 (d, J = 10.8 Hz, 1H), 2.79 (d, J = 10.8 Hz, 1H), 2.61 - 2.55 (m, 2H), 2.53 (s, 3H), 2.23 (s, 2H), 1.70 (t, J = 6.3 Hz, 2H), 1.56 – 1.44 (m, 4H), 1.36 - 1.28 (m, 3H). **MS** (ESI) m/z = 770.0 $[M+H]^+$.
264		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2-(1H-indazol-5-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4 (7H)-yl)acetamide	**^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.12 (s, 1H), 8.73 (s, 1H), 8.64 (s, 1H), 8.51 (d, J= 8.7 Hz, 1H), 8.42 (s, 1H), 8.18 (s, 1H), 7.62–7.50 (m, 3H), 5.22 (s, 2H), 4.90-4.69 (m, 1H), 4.29-4.06 (m, 2H), 3.92–3.65 (m, 2H), 3.32–3.18 (m, 3H), 2.57 (s, 3H), 2.44–2.31 (m, 1H), 1.90-1.73 (m, 1H), 1.62–1.41 (m, 2H), 1.36 (t, J=7.4 Hz, 3H). **MS** (ESI) m/z = 761.6 $[M+H]^+$.
265		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-((1R,6R)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2-(1H-indazol-5-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.15 (s, 1H), 8.73 (s, 1H), 8.62 (s, 1H), 8.51 (d, J=8.5 Hz, 1H), 8.37 (d, J=8.8 Hz, 1H), 8.17 (s, 1H), 7.59–7.50 (m, 3H), 5.21 (s, 2H), 4.89– 4.70 (m, 1H), 4.24-4.06 (m, 2H), 3.92– 3.65 (m, 2H), 3.39-3.15 (m, 3H), 2.56 (s, 3H), 2.39-2.29 (m, 1H), 2.06–2.00 (m, 1H), 1.45-1.41 (m, 2H), 1.36 (t, J=7.2 Hz, 3H). **MS** (ESI) m/z = 761.9 $[M+H]^+$.
266		N-[2-chloro-4-(trifluoromethyl)phenyl]-2-(5-ethyl-2-{3-fluoropyrazolo[1,5-a]pyridin-5-yl}-6-{4-[(5-hydroxy-6-methylpyrimidin-4-yl)carbonyl]piperazin-1-yl}-7-oxo-[1,2,4]triazolo	**^{1}H NMR** (400 MHz,CD_3OD) δ 8.43 (s, 1H), 8.36 (d, J = 7.2 Hz, 1H), 8.29 (s, 1H), 8.05 (d, J = 8.5 Hz, 1H), 7.83 (d, J = 3.2 Hz, 1H), 7.72 (s, 1H), 7.50 (d, J = 7.4 Hz, 2H), 5.38 (s, 2H), 4.63 (d, J = 11.7 Hz, 1H), 4.49 (s, 1H), 3.65 (s, 2H), 3.37 (s, 1H), 3.05 (d, J = 7.7 Hz, 3H), 2.87 (d, J = 11.1 Hz, 1H), 2.72

		[1,5-a]pyrimidin-4-yl)acetamide	(d, J = 10.4 Hz, 1H), 2.42 (s, 3H), 1.24 (d, J = 7.5 Hz, 3H). **MS** (ESI) m/z = 753.9 $[M+H]^+$.
267		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-2-(thieno[2,3-b]pyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.80 (s, 1H), 8.98 (s, 1H), 8.64 – 8.54 (m, 2H), 8.48 (d, J = 8.6 Hz, 1H), 8.15 – 8.02 (m, 2H), 7.61 (s, 1H), 7.53 (d, J = 8.6 Hz, 1H), 7.37 - 7.30 (m, 1H), 5.69 (d, J = 13.0 Hz, 1H), 5.22 (s, 2H), 4.81 (d, J = 12.5 Hz, 1H), 3.83 (t, J = 11.3 Hz, 2H), 3.51 (t, J = 11.5 Hz, 1H), 3.22 (dd, J = 14.0, 6.7 Hz, 2H), 3.08 (t, J = 11.3 Hz, 1H), 2.88 (d, J = 10.2 Hz, 1H), 2.79 (d, J = 10.5 Hz, 1H), 2.57 (s, 3H), 1.37 (t, J = 7.4 Hz, 3H). **MS** (ESI) m/z = 753.2 $[M+H]^+$.
268		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-2-(pyrazolo[1,5-a]pyrimidin-5-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.80 (s, 1H), 9.34 (s, 1H), 8.80 (s, 1H), 8.60 (s, 1H), 8.40 (s, 1H), 8.15 (s, 1H), 8.05 (s, 1H), 7.51 (s, 1H), 7.37-7.30 (m, 1H), 6.76 (s, 1H), 5.75-7.45 (m, 3H), 4.83–4.82 (m, 1H), 3.87–3.82 (m, 2H), 3.51–3.46 (m, 1H), 3.20–2.85 (m, 3H), 2.80–2.60 (m, 2H), 2.57 (s, 3H), 1.37 (t, J = 7.4 Hz, 3H). **MS** (ESI) m/z = 737.0 $[M+H]^+$.
269		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(4-cyano-4-methylpiperidin-1-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.46 (s, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 7.75 (s, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 5.21 (s, 2H), 4.42 (d, *J* = 12 Hz, 1H), 4.15–4.10 (m, 2H), 4.05 – 4.00 (m, 1H), 3.69–3.60 (m, 2H), 3.45 – 3.40 (m, 1H), 3.25–2.95 (m, 5H), 2.85 – 2.83 (m, 1H), 2.69–2.66 (m, 1H), 2.44 (s, 3H), 1.85 (d, *J* = 13.6 Hz, 2H), 1.60-1.50 (m, 2H), 1.32 (s, 3H), 1.22–1.18 (m, 3H). **MS** (ESI) m/z = 742.0 $[M+H]^+$.
270		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(5-cyano-4-methylthiophen-2-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.53 (s, 1H), 8.13 (d, J=8.5 Hz, 1H), 7.79 (s, 1H), 7.69 (s, 1H), 7.58 (d, J=8.8 Hz, 1H), 5.41 (s, 2H), 4.69 (d, J=12.8 Hz, 1H), 4.09 (d, J=12.1 Hz, 1H), 3.71 (t, J=11.5 Hz, 2H), 3.42 (dd, J=16.1, 7.8 Hz, 1H), 3.11 (dd, J= 16.3, 9.7 Hz, 3H), 2.93 (d, J=10.9 Hz, 1H), 2.78 (d, J=10.9 Hz, 1H), 2.49 (s, 3H), 2.42 (s, 3H), 1.28 (d, J=7.5 Hz, 3H). **MS** (ESI) m/z = 740.9 $[M+H]^+$.
271		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(4-(methylsulfonyl)cyclohex-1-en-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.79 (s, 1H), 8.94 (s, 1H), 8.60 (s, 1H), 8.47 (s, 1H), 7.65 (s, 1H), 7.54 (d, J = 8.8 Hz, 1H), 7.02 (s, 1H), 5.66 (d, J = 12 Hz, 1H), 5.11 (s, 2H), 4.81 (d, J = 12 Hz, 1H), 3.85– 3.80 (m, 2H), 3.55–3.45 (m, 1H), 3.20– 3.00 (m, 5H), 2.83 (s, 3H), 2.80-2.55 (m, 4H), 2.65 (s, 3H), 2.50–2.45 (m, 1H), 2.00 –1.65 (m, 2H), 1.33 (t, J = 7.4 Hz, 3H). **MS** (ESI) m/z = 777.9 $[M+H]^+$.
272		2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-2-(pyrazolo[1,5-a]pyridin-5-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.61-8.55 (m, 2H), 8.45 (s, 1H), 8.35–8.30 (m, 1H), 7.99 (s, 1H), 7.65–7.47 (m, 3H), 6.74 (s, 1H), 5.46 (s, 2H), 4.77-4.70 (m, 1H), 4.20 – 4.15 (m, 1H), 3.80–3.71 (m, 2H), 3.55 - 3.45 (m, 1H), 3.20–3.10 (m, 3H), 3.00–2.61 (m, 2H), 2.54 (s, 3H), 1.34 (t, J=7.4 Hz, 3H). **MS** (ESI) m/z = 720.3 $[M+H]^+$.

273		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(2-methyl-2H-indazol-5-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.59 (s, 2H), 8.32 (s, 1H), 8.19 (d, J = 7.6 Hz, 1H), 8.14 (d, J = 9.0 Hz, 1H), 7.83 (s, 1H), 7.70-7.58 (m, 2H), 5.48 (s, 2H), 4.73 (d, J = 11.3 Hz, 1H), 4.23 (s, 3H), 4.14 (d, J = 12.0 Hz, 1H), 3.77 (d, J = 10.7 Hz, 2H), 3.48 (d, J = 11.4 Hz, 1H), 3.14 (s, 3H), 2.97 (d, J = 10.0 Hz, 1H), 2.82 (d, J = 9.7 Hz, 1H), 2.55 (s, 3H), 1.37-1.32 (m, 3H). **MS** (ESI) m/z = 749.9 $[M+H]^+$.
274		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl-2,2,3,3,5,5,6,6-d8)-7-oxo-2-(pyrazolo[1,5-a]pyridin-5-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.61 (d, *J* = 6.4 Hz, 1H), 8.50 – 8.45 (m, 2H), 8.18 (s, 1H), 8.02 (s, 1H), 7.85 (s, 1H), 7.64 (s, 2H), 6.75 (s, 1H), 5.50 (s, 2H), 3.17 – 3.15 (m, 2H), 2.52 (s, 3H), 1.37 -1.36 (m, 3H). **MS** (ESI) m/z = 744.2 $[M+H]^+$.

Example 273:

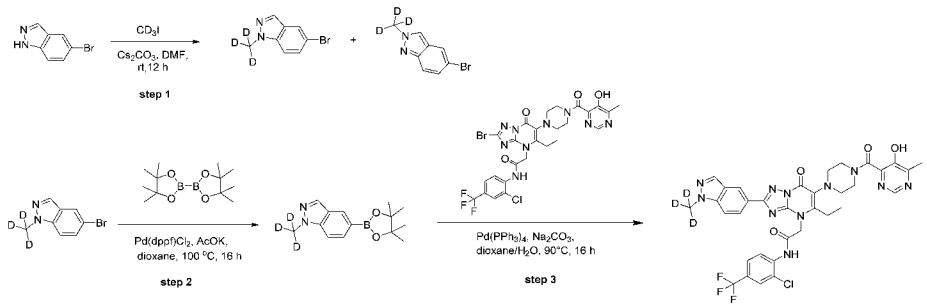
N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(2-methyl-2H-indazol-5-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide



To the solution of 2-(2-bromo-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl) piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (100 mg, 0.143 mmol), 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-indazole (48 mg, 0.186 mmol) and Na_2CO_3 (46 mg, 0.429 mmol) in dioxane/H_2O (6 mL /1 mL) was added Pd(dppf)Cl_2 (11 mg, 0.014 mmol). The reaction mixture was stirred under nitrogen at 90 °C for 2 hrs. The mixture was concentrated in *vacuo* and purified by Flash Chromatography (MeOH/DCM = 0-5%) to get the product **example 273** N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(2-methyl-2H-indazol-5-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide (18.3 mg, 0.024 mmol, 22.8 % yield) as a white solid. **^{1}H NMR** (400 MHz, DMSO) δ 10.43 (s, 1H), 10.25 (s, 1H), 8.59 (s, 1H), 8.51 (d, *J* = 7.0 Hz, 2H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.97 (d, *J* = 7.0 Hz, 2H), 7.71 (t, *J* = 8.0 Hz, 2H), 5.42 (s, 2H), 4.55 (d, *J* = 11.9 Hz, 1H), 4.20 (s, 3H), 3.62 – 3.48 (m, 3H), 3.26 (d, *J* = 12.1 Hz, 1H), 3.03 (d, *J* = 7.9 Hz, 3H), 2.85 (d, *J* = 10.4 Hz, 1H), 2.68 (d, *J* = 9.1 Hz, 1H), 2.45 (s, 3H), 1.22 (t, *J* = 7.4 Hz, 3H). **MS** (ESI) m/z = 749.9 $[M+H]^+$.

Example 275:

N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(1-(methyl-d3)-1H-indazol-5-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide



Step 1: To a mixture of 5-bromo-1*H*-indazole (5.0 g, 25.38mmol) in DMF (50 mL) was added Cesium carbonate (16.54 g, 50.76 mmol) at room temperature. After being stirred at room temperature for 30 minutes, iodomethane-d_3 (4.41g, 30.46 mmol) was added to the reaction mixture at room temperature for 12 hours. The reaction mixture was quenched by addition of H_2O (200 mL) and extracted with EtOAc (100 mL * 3). The combined organic layer was washed with brine (50 mL * 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by gel silica column chromatography (PE/EtOAc = 4:1) to give two isomers:

5-bromo-1-(methyl-d_3)-1*H*-indazole (3.3 g, 15.4 mmol, 60.7% yield) as an orange solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.04 (s, 1H), 7.99 (s, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H). **MS** (ESI, m/z): $[M+H]^+$ = 214.0, 216.0.

5-bromo-2-(methyl-d$_3$)-2*H*-indazole (1.5 g, 7.0 mmol, 27.6% yield) as a yellow solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.34 (s, 1H), 7.96 (s, 1H), 7.58 (*d*, *J* = 12.0 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H). **MS** (ESI, m/z): $[M+H]^+$ = 214.0, 216.0.

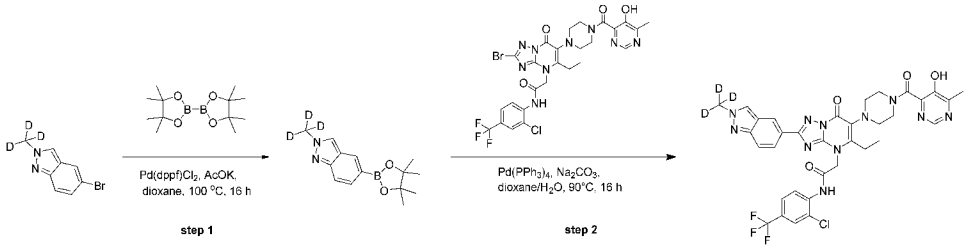
Step 2: To a mixture of 5-bromo-1-(methyl-d$_3$)-1*H*-indazole (1.0 g, 4.67 mmol) in 1,4-Dioxane (30.0 mL) was added potassium acetate (1.37 g, 14.01 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.30 g, 5.14 mmol) and Pd(dppf)Cl_2 (190 mg, 0.23 mmol) in portions at room temperature under N_2. The resulting mixture was stirred for 16 h at 100 °C for 16 hours under N_2. The solution was concentrated in vacuum and the residue was purified by gel silica column chromatography (EtOAc/PE = 1% to 10%) to give 1-(methyl-d3)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (1.1 g, 4.21 mmol, 90.1 % yield) as a yellow solid. **MS** (ESI, m/z): $[M+H]^+$ = 262.1.

Step 3: The mixture of 2-(2-bromo-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl) piperazin-1-yl)-7-oxo-4*H*,7*H*-[1,2,4]triazolo[1,5-a]pyrimidin-4-yl)-*N*-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (100 mg, 0.14 mmol), 1-(methyl-d3)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (73 mg, 0.28 mmol) , $Pd(PPh_3)_4$ (16 mg, 0.014 mmol) and sodium carbonate (45 mg, 0.42 mmol) in dioxane (12 mL) and H_2O (1 mL) was stirred at 90 °C for 16 hours under N_2. The mixture was concentrated in vacuum and purified by Prep-HPLC to give N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(1-(methyl-d3)-1H-indazol-5-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin -4(7H)-yl)acetamide (18 mg, 0.024 mmol, 16.37 % yield) as a white solid. **^{1}H NMR** (400 MHz, CD_3OD-d_4) δ 8.63 (s, 1H), 8.58 (s, 1H), 8.28 (d, J = 10.4 Hz, 1H), 8.17 (d, J = 8.4 Hz, 1H), 8.09 (s, 1H), 7.82 (s, 1H), 7.59-7.65 (m, 2 H), 5.49 (s, 2H), 4.70-4.74 (m, 1H),4.09-4.13 (m, 1 H), 3.74-3.80 (m, 2 H), 3.47-3.38(m, 1 H), 3.11 – 3.16 (m, 3H), 2.95 – 2.98 (m, 1H), 2.81-2.83 (m, 1 H), 2.53(s, 3 H), 1.35 (t, J = 7.5 Hz, 3H). **MS** (ESI, m/z): $[M+H]^+$ = 753.3.

Example 276:

N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-car

bonyl)piperazin-1-yl)-2-(2-(methyl-d3)-2H-indazol-5-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidi n-4(7H)-yl)acetamide

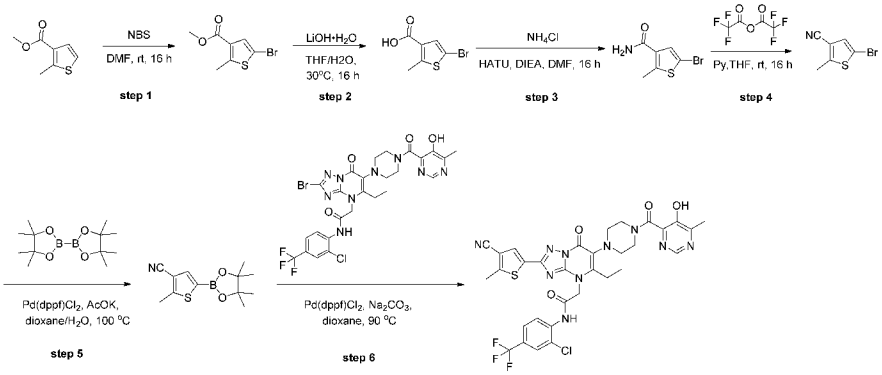


Step 1: To a mixture of 5-bromo-2-(methyl-d3)-2H-indazole (1.0 g, 4.67 mmol) in 1,4-Dioxane (30.0 mL) was added potassium acetate (1.37 g, 14.01 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.30 g, 5.14 mmol) and $Pd(dppf)Cl_2$ (190 mg, 0.23 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 hours under N_2. The mixture was concentrated in vacuum and the resulting residue was purified by silica gel column chromatography (EtOAc/PE = 1/10) to give 2-(methyl-d3)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-indazole (1.1 g, 4.21 mmol, 90 % yield) as a yellow solid. **MS** (ESI, m/z): $[M+H]^+$ = 262.1.

Step 2: The mixture of 2-(2-bromo-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl) piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(trifluoromethyl)p henyl)acetamide (100 mg, 0.14 mmol), 2-(methyl-d3)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane -2-yl)-2H-indazole (73 mg, 0.28 mmol), $Pd(PPh_3)_4$ (16 mg, 0.014 mmol) and sodium carbonate (45 mg, 0.42 mmol) in dioxane (12 mL) and H_2O (1 mL) was stirred at 90 °C for 16 hours under N_2. The mixture was concentrated in vacuum and purified by Prep-HPLC to give N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl) piperazin-1-yl)-2-(2-(methyl-d3)-2H-indazol-5-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide (33 mg, 0.044 mmol, 31.3 % yield) as a white solid. **^{1}H NMR** (400 MHz, CD_3OD-d_4) δ 8.61 (s, 1H), 8.58 (s, 1H), 8.2 (s, 1H), 8.13-8.18 (m, 2H), 7.82 (s, 1H), 7.59-7.68 (m, 2 H), 5.47 (s, 2H), 4.70-4.74 (m, 1H), 4.09-4.13 (m, 1 H), 3.74-3.80 (m, 2 H), 3.47-3.38 (m, 1 H), 3.11-3.18 (m, 3H), 2.95 - 2.98 (m, 1H), 2.81-2.83 (m, 1 H), 2.53 (s, 3 H), 1.34 (t, J = 7.5 Hz, 3H). **MS** (ESI, m/z): $[M+H]^+$ = 753.3.

Example 277:

N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(4-cyano-5-methylthiophen-2-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidi n-4(7H)-yl)acetamide



Step 1: To a solution of methyl 2-methylthiophene-3-carboxylate (5 g, 32.01 mmol) in DMF (24 mL) was added NBS (5.70 g, 32.01 mmol) at room temperature and stirred for 16 hours.

LCMS indicated completion of reaction. The reaction mixture was diluted with water (100 mL) and extracted with PE (50 mL * 3). The organic layer was washed with saturated aqueous $NaHCO_3$ and brine and dried over Na_2SO_4. After filtration, the solvent was concentrated under reduced pressure to give compound as a yellow oil afford methyl 5-bromo-2-methylthiophene-3-carboxylate (7.3 g, 31.1 mmol, 97% yield) as a yellow oil. **MS** (ESI, m/z): $[M+H]^+$ =237.0

Step 2: To a mixture of methyl 5-bromo-2-methylthiophene-3-carboxylate (7.3 g, 31.1 mmol) in THF (50 mL) and water (5 mL) was added Lithium hydroxide hydrate (2.61 g, 62.1 mmol) and stirred at room temperature for 16 hours. The mixture was quenched with aq HCl (1M) and adjusted PH=3. The mixture was diluted with EtOAc (200 mL) and extracted with water (100 mL * 3). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under vacuum to afford 5-bromo-2-methylthiophene-3-carboxylic acid (6.3 g, 28.6 mmol, 92.2% yield) as a white solid. **MS** (ESI, m/z): $[M+H]^+$ = 221.0.

Step 3: To a solution of 5-bromo-2-methylthiophene-3-carboxylic acid (6.3 g, 28.5 mmol), HATU (16.2 g, 42.8 mmol) and DIEA (7.37 g, 57 mmol) in DMF (60 mL) was added NH_4Cl (2.29 g, 42.8 mmol). The mixture was stirred at room temperature for 2 hours. LCMS indicated completion of reaction. The mixture was diluted with water (10 mL) and extracted with EtOAc (50 mL * 3). The combined organic layer was washed with brine (50 mL * 2), dried over Na_2SO_4 and concentrated in vacuum. The crude product was purified by flash silica chromatography (EtOAc/PE = 0-10%) to afford 5-bromo-2-methylthiophene-3-carboxamide (5 g, 22.7 mmol, 79.72% yield) as a white solid. **MS** (ESI, m/z): $[M+H]^+$ = 220.0.

Step 4: To a mixture of 5-bromo-2-methylthiophene-3-carboxamide (2 g, 9.09 mmol) in THF (30 mL) was added pyridine (2.75 g, 34.81 mmol) and trifluoroacetic anhydride (3.40 g, 16.18 mmol) at 0°C. The mixture was stirred at room temperature for 24 hours. The mixture was concentrated and diluted with water (100 mL) and extracted with DCM (300 mL * 3). The combined organic layer was washed with brine (50 mL * 3), dried over Na_2SO_4 and concentrated in vacuum. The crude product was purified by flash silica chromatography (EtOAc/PE = 0-10 %) to afford 5-bromo-2-methylthiophene-3-carbonitrile (1.6 g, 7.9 mmol, 87.13% yield) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.05 (s, 1H), 2.60 (s, 3H).

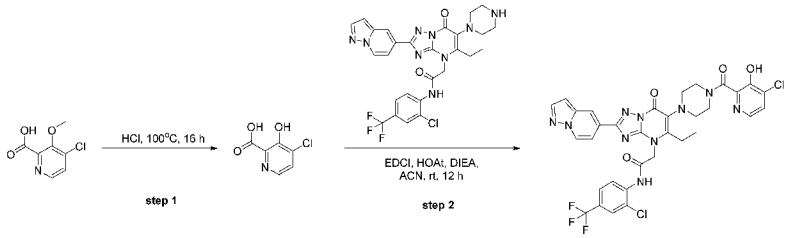
Step 5: A mixture of 5-bromo-2-methylthiophene-3-carbonitrile (500 mg, 2.47 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (820 mg, 3.21 mmol), potassium acetate (800 mg, 8.2 mmol) and $Pd(dppf)Cl_2$ (130 mg, 0.17 mmol) in anhydrous dioxane (10 mL) was stirred at 100 °C for 16 hours under N_2. The reaction mixture was concentrated in vacuum and purified by silica gel column chromatography (PE/EtOAc = 4/1) to afford 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-3-carbonitrile (410 g, 1.65 mmol, 66.5% yield) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 2.68 (s, 3H), 1.33 (s, 12H).

Step 6: The mixture of 2-(2-bromo-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl) piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(trifluoromethyl)p henyl)acetamide (100 mg, 0.14 mmol), 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2- dioxaborolan-2-yl) thiophene-3-carbonitrile (25 mg, 0.21 mmol), $Pd(dppf)Cl_2$ (14 mg, 0.014 mmol) and sodium carbonate (44.25 mg, 0.42 mmol) in dioxane (10 mL) and H_2O (1 mL) was stirred at 90°C for 16 hours under N_2. The mixture was concentrated under vacuum and purified by Prep-HPLC eluted with MeCN in H_2O (0.1% FA) to give N-(2-chloro-4-(trifluoromethyl)phenyl)-2- (2-(4-cyano-5-methylthiophen-2-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide (22.16 mg, 0.03 mmol, 20.6% yield) as a

white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.39 (s, 1H), 8.55 (s, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.97 (s, 1H), 7.91 (s, 1H), 7.71 (d, J = 8.7 Hz, 1H), 5.34 (s, 2H), 4.53 (d, J = 11.9 Hz, 1H), 3.50 (d, J = 11.1 Hz, 3H), 3.25 (s, 2H), 3.00 (s, 3H), 2.83 (d, J = 10.3 Hz, 1H), 2.68 (s, 3H), 2.44 (s, 3H), 1.19 (t, J = 7.4 Hz, 3H). **MS** (ESI, m/z): $[M+H]^+$ = 740.8.

Example 278:

2-(6-(4-(4-chloro-3-hydroxypicolinoyl)piperazin-1-yl)-5-ethyl-7-oxo-2-(pyrazolo[1,5-a]pyridin-5-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide

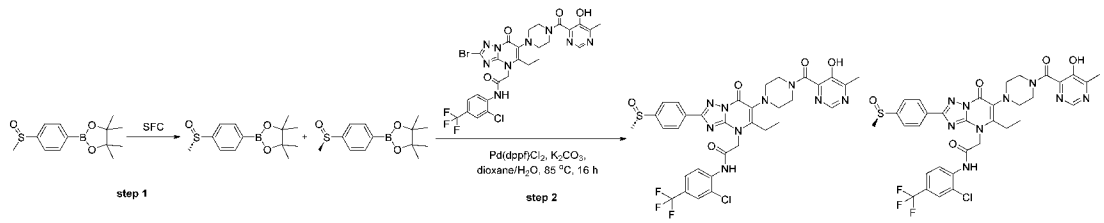


Step 1: The mixture of 4-chloro-3-methoxypyridine-2-carboxylic acid (100 mg, 0.53 mmol) and aqueous hydrogen chloride (1 mL) was stirred at 100° C for 16 hours. The resulting mixture was concentrated under vacuum to give 4-chloro-3-hydroxypicolinic acid (88 mg, 0.50 mmol, 95.6% yield) as a white solid. The crude product was used in the next step directly without further purification. **MS** (ESI, m/z): $[M+H]^+$ = 173.5

Step 2: The mixture of 4-chloro-3-hydroxypicolinic acid (88 mg, 0.51 mmol), HOAt (69 mg, 0.51 mmol) and EDCI (98 mg, 0.51 mmol) in ACN (40 mL) was stirred at room temperature for 1 hour under N_2, then N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-7-oxo-6-(piperazin-1-yl)-2-(pyrazolo[1,5-a]pyridin-5-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide (100 mg, 0.17 mmol) and DIEA (0.17 mL, 1.02 mmol) in ACN (10 mL) was added, the mixture was stirred at room temperature for 12 hours. LCMS indicated completion of reaction. The mixture was concentrated, diluted with water (10 mL), extracted with EtOAc (10 mL * 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4. The mixture was concentrated in vacuum and purified by Prep-HPLC, eluted with MeCN in H_2O (0.1% FA) to give 2-(6-(4-(4-chloro-3-hydroxypicolinoyl)piperazin-1-yl)-5-ethyl-7-oxo-2-(pyrazolo[1,5-a]pyridin-5-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (19.3 mg, 0.025 mmol, 15.3% yield) as a white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.44 (s, 1H), 8.80 (d, J = 7.3 Hz, 1H), 8.43 (s, 1H), 8.12 – 8.05 (m, 2H), 8.04 – 7.95 (m, 2H), 7.75 – 7.68 (m, 1H), 7.56 – 7.47 (m, 2H), 6.82 (d, J = 1.7 Hz, 1H), 5.42 (s, 2H), 4.57 (d, J = 11.6 Hz, 1H), 3.57 (dd, J = 30.4, 11.7 Hz, 3H), 3.28 – 3.23 (m, 1H), 3.04 (d, J = 7.5 Hz, 3H), 2.91 – 2.81 (m, 1H), 2.74 – 2.64 (m, 1H), 1.20 (dt, J = 19.3, 7.2 Hz, 4H). **MS** (ESI, m/z): $[M+H]^+$ = 755.3.

Example 279a and 279b:

(S)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(4-(methylsulfinyl)phenyl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide and (R)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(4-(methylsulfinyl)phenyl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide



Step 1: The 4,4,5,5-tetramethyl-2-(4-(methylsulfinyl)phenyl)-1,3,2-dioxaborolane (300 mg, 1.13 mmol) was separated by chiral SFC (colum: 15 10% IPA DEA C1 WHELK) to obtain (*S*)-4,4,5,5-tetramethyl-2-(4-(methylsulfinyl)phenyl)-1,3,2-dioxaborolane and (*R*)-4,4,5,5- tetramethyl -2-(4-(methylsulfinyl)phenyl)-1,3,2-dioxaborolane as a white solid.

Compound of Peak 1: (Rt = 2.204 min, 130 mg, 0.49 mmol) as the material of (*S*)-4,4,5,5-tetramethyl-2-(4-(methylsulfinyl)phenyl)-1,3,2-dioxaborolane or (*R*)-4,4,5,5-tetramethyl-2-(4-(methylsulfinyl)phenyl)-1,3,2-dioxaborolane. **MS** (ESI, m/z): $[M+H]^+$ = 267.2.

Compound of Peak 2: (Rt = 2.816 min, 130 mg, 0.49 mmol) as the material of (*R*)-4,4,5,5 -tetramethyl-2-(4-(methylsulfinyl)phenyl)-1,3,2-dioxaborolane or (*S*)-4,4,5,5-tetramethyl-2-(4-(methylsulfinyl)phenyl)-1,3,2-dioxaborolane. **MS** (ESI, m/z): $[M+H]^+$ = 267.2.

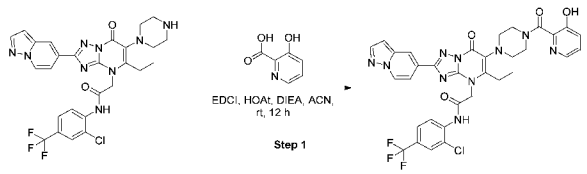
Step 2: A mixture of 2-(2-bromo-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl) piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7*H*)-yl)-*N*-(2-chloro-4-(trifluoromethyl)ph enyl)acetamide (60 mg, 0.086 mmol), (*S*)-4,4,5,5-tetramethyl-2-(4-(methylsulfinyl)phenyl) -1,3,2-dioxaborolane or (*R*)-4,4,5,5-tetramethyl-2-(4-(methylsulfinyl)phenyl)-1,3,2-dioxaborolane (23 mg, 0.086 mmol), $Pd(dppf)Cl_2$ (6 mg, 0.009 mmol) and K_2CO_3 (36 mg, 0.260 mmol) in dioxane (10 mL) and H_2O (1 mL) was stirred at 85°C for 16 hours under N_2. The mixture was filtered, concentrated in vacuum and purified by Prep-HPLC, eluted with MeCN in H_2O (0.1% FA) to obtain (*S*)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimi dine-4-carbonyl)piperazin-1-yl)-2-(4-(methylsulfinyl)phenyl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidi n-4(7H)-yl)acetamide or (R)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(4-(methylsulfinyl)phenyl)-7-oxo-[1,2,4] triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide as a white solid.

Example 279a (12.77 mg, 0.017 mmol, 19.6% yield) was synthesized from **Compound of Peak 1** using the above procedure. **^{1}H NMR** (400 MHz, MeOD-d_4) δ 8.57 (s, 1H), 8.46 – 8.37 (m, 2H), 8.16 (d, *J* = 8.5 Hz, 1H), 7.89 – 7.77 (m, 3H), 7.61 (dd, *J* = 8.6, 1.6 Hz, 1H), 5.48 (s, 2H), 4.72 (d, *J* = 12.6 Hz, 1H), 4.11 (d, *J* = 12.6 Hz, 1H), 3.75 (d, *J* = 11.5 Hz, 2H), 3.52 – 3.40 (m, 1H), 3.14 (dd, *J* = 6.8, 5.1 Hz, 3H), 2.97 (d, *J* = 11.1 Hz, 1H), 2.82 (d, *J* = 13.8 Hz, 4H), 2.53 (s, 3H), 1.34 (t, *J* = 7.5 Hz, 3H). **MS** (ESI, m/z): $[M+H]^+$ = 758.4.

Example 279b (32.39 mg, 0.043 mmol, 49.8% yield) was synthesized from **Compound of Peak 2** using the above procedure. **^{1}H NMR** (400 MHz, MeOD-d_4) δ 8.58 (s, 1H), 8.42 (d, *J* = 8.5 Hz, 2H), 8.16 (d, *J* = 8.6 Hz, 1H), 7.82 (dd, *J* = 5.2, 3.3 Hz, 3H), 7.61 (dd, *J* = 8.7, 1.6 Hz, 1H), 5.48 (s, 2H), 4.72 (d, *J* = 13.0 Hz, 1H), 4.12 (d, *J* = 12.4 Hz, 1H), 3.83 – 3.69 (m, 2H), 3.51 – 3.43 (m, 1H), 3.19 – 3.09 (m, 3H), 2.97 (d, *J* = 11.0 Hz, 1H), 2.82 (d, *J* = 13.4 Hz, 4H), 2.53 (s, 3H), 1.34 (t, *J* = 7.4 Hz, 3H). **MS** (ESI, m/z): $[M+H]^+$ = 758.4.

Example 280:

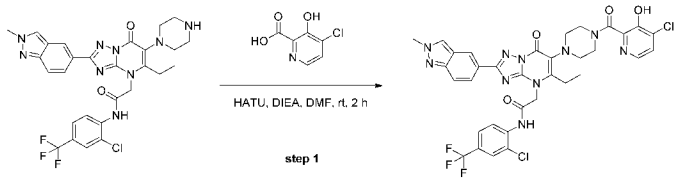
N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(3-hydroxypicolinoyl)piperazin-1-yl)-7-oxo-2-(pyrazolo[1,5-a]pyridin-5-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide



Step 1: The mixture of 3-hydroxypicolinic acid (71 mg, 0.51 mmol), HOAt (69 mg, 0.51 mmol) and EDCI (98 mg, 0.51 mmol) in ACN (40 mL) was stirred at room temperature for 1 hour under N_2, then *N*-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-7-oxo-6-(piperazin-1-yl)-2-(pyrazolo[1,5-a]pyridin-5-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7*H*)-yl)acetamide (100 mg, 0.17 mmol) and DIEA (0.17 mL, 1.02 mmol) in ACN (10 mL) was added, the mixture was stirred at room temperature for 12 hours. The mixture was then concentrated, diluted with water (10 mL), extracted with EtOAc (10 mL * 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4. The mixture was concentrated in vacuum and purified by Prep-HPLC, eluted with MeCN in H_2O (0.1% FA) to give *N*-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(3-hydroxypicolinoyl)piperazin-1-yl)-7-oxo-2-(pyrazolo[1,5-a]pyridin-5-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7*H*)-yl)acetamide (24 mg, 0.033 mmol, 19.9% yield) as a white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.41 (s, 2H), 8.80 (d, *J* = 7.3 Hz, 1H), 8.43 (s, 1H), 8.11 – 8.04 (m, 3H), 7.98 (s, 1H), 7.71 (d, *J* = 7.3 Hz, 1H), 7.50 (dd, *J* = 7.3, 1.8 Hz, 1H), 7.30 (d, *J* = 2.1 Hz, 2H), 6.82 (d, *J* = 2.1 Hz, 1H), 5.41 (s, 2H), 4.57 (d, *J* = 11.1 Hz, 1H), 3.47 (dd, *J* = 32.2, 11.4 Hz, 3H), 3.26 – 3.15 (m, 1H), 3.08 – 2.94 (m, 3H), 2.84 (d, *J* = 9.8 Hz, 1H), 2.66 (d, *J* = 10.1 Hz, 1H), 1.22 (t, *J* = 7.4 Hz, 3H). **MS** (ESI, m/z): $[M+H]^+$ = 721.4

Example 281:

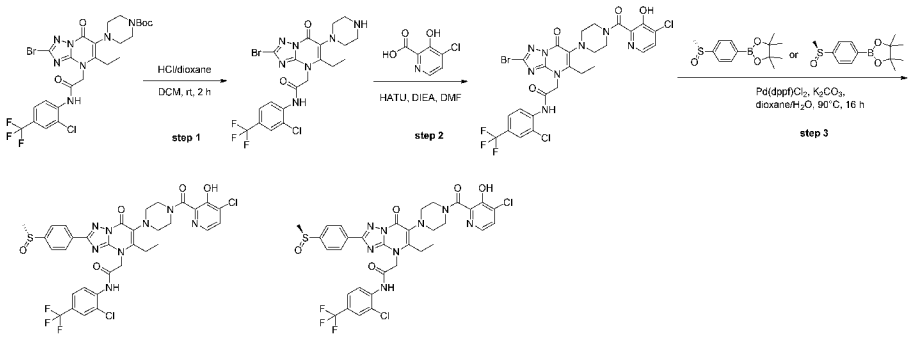
2-(6-(4-(4-chloro-3-hydroxypicolinoyl)piperazin-1-yl)-5-ethyl-2-(2-methyl-2H-indazol-5-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide



Step 1: To a mixture of 4-chloro-3-hydroxypicolinic acid (41.6 mg, 0.24 mmol) in DMF (3 mL) was added DIEA (62.04 mg, 0.48 mmol) and HATU (91.3 mg, 0.24 mmol) at room temperature. The solution was stirred at room temperature for 1 hour under N_2, then *N*-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-2-(2-methyl-2*H*-indazol-5-yl)-7-oxo-6-(piperazin-1-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7*H*)-yl)acetamide (100 mg, 0.16 mmol) was added. The mixture was stirred at room temperature for 2 hours. The mixture was purified by Prep-HPLC, eluted with MeCN in H_2O (0.1% FA) to give 2-(6-(4-(4-chloro-3-hydroxypicolinoyl)piperazin-1-yl)-5-ethyl-2-(2-methyl-2*H*-indazol-5-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7*H*)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (23.5 mg, 0.031mmol, 19.1 % yield) as a white solid. **^{1}H NMR** (400 MHz, DMSO-d6) δ 10.85 (s, 1H), 10.43 (s, 1H), 8.57 – 8.38 (m, 2H), 8.08 (d, J = 5.1 Hz, 2H), 8.01 – 7.93 (m, 2H), 7.71 (t, J = 7.7 Hz, 2H), 7.56 (d, J = 5.1 Hz, 1H), 5.42 (d, J = 10.2 Hz, 2H), 4.56 (d, J = 12.2 Hz, 1H), 4.19 (s, 3H), 3.57 (dd, J = 27.3, 11.6 Hz, 3H), 3.27 (s, 1H), 2.97 (t, J = 33.7 Hz, 4H), 2.67 (s, 1H), 1.22 (t, J = 7.3 Hz, 3H). **MS** (ESI, m/z): $[M+H]^+$ = 769.35

Example 282a and 282b:

(S)-2-(6-(4-(4-chloro-3-hydroxypicolinoyl)piperazin-1-yl)-5-ethyl-2-(4-(methylsulfinyl)phenyl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide and (R)-2-(6-(4-(4-chloro-3-hydroxypicolinoyl)piperazin-1-yl)-5-ethyl-2-(4-(methylsulfinyl)phenyl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide



Step 1: To a solution of *tert*-butyl 4-(2-bromo-4-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-5-ethyl-7-oxo-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)piperazine-1-carboxylate (300 mg, 0.45 mmol) in DCM (3 mL) was added HCl/dioxane (3 mL, 4 M) and the mixture was stirred at room temperature for 2 hours. Then the mixture was concentrated under vacuum to afford crude 2-(2-bromo-5-ethyl-7-oxo-6-(piperazin-1-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7*H*)-yl)-*N*-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (280 mg, 0.50 mmol, 109.9% yield) as hydrochloride salt. **MS** (ESI) m/z = 562.24 $[M+H]^+$

Step 2: To a solution of 2-(2-bromo-5-ethyl-7-oxo-6-(piperazin-1-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7*H*)-yl)-*N*-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (240 mg, 0.43 mmol), 4-chloro-3-hydroxypicolinic acid (90 mg, 0.52 mmol), HATU (245 mg, 0.65 mmol) in DMF (5 mL) was added DIEA (111 mg, 0.86 mmol) and the mixture was stirred at room temperature for 16 hours. Then the mixture was diluted with water (40 mL) and extracted with ethyl acetate (40 mL * 3). The organic layers were combined, washed with brine (40 mL), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The resulting residue was purified by flash chromatography (elution gradient: MeOH/DCM = 0-5%) to afford 2-(2-bromo-6-(4-(4-chloro-3-hydroxypicolinoyl)piperazin-1-yl)-5-ethyl-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7*H*)-yl)-*N*-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (180 mg, 0.25 mmol, 58.8% yield) as a brown solid. **MS** (ESI) m/z = 719.4 $[M+1+Br]^+$.

Step 3: A mixture of 2-(2-bromo-6-(4-(4-chloro-3-hydroxypicolinoyl)piperazin-1-yl)-5-ethyl-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7*H*)-yl)-*N*-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (90 mg, 0.130 mmol), (*R*)-4,4,5,5-tetramethyl-2-(4-(methylsulfinyl)phenyl)-1,3,2-dioxaborolane or (S)-4,4,5,5-tetramethyl-2-(4-(methylsulfinyl)phenyl)-1,3,2-dioxaborolane (35 mg, 0.130 mmol), $Pd(dppf)Cl_2$ (10 mg, 0.013 mmol) and K_2CO_3 (54 mg, 0.390 mmol) in dioxane (10 mL) and H_2O (1 mL) was stirred at 90°C for 16 hours under N_2. The mixture was filtered, concentrated in vacuum and purified by Prep-HPLC, eluted with MeCN in H_2O (0.1% NH_4HCO_3) to obtain (*R*)-2-(6-(4-(4-chloro-3-hydroxypicolinoyl)piperazin-1-yl)-5-ethyl-2-(4-(methylsulfinyl)phenyl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7*H*)-yl)-*N*-(2-chloro-4-(trifluoromethyl)phenyl)acetamide or (S)-2-(6-(4-(4-chloro-3-hydroxypicolinoyl)piperazin-1-yl)-5-ethyl-2-(4-(methylsulfinyl)phenyl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide as a white solid.

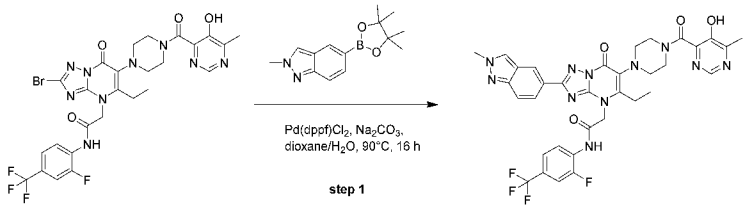
Example 282a (36.10 mg, 0.047 mmol, 37.1% yield) was synthesized from **Compound of**

Peak 1 (see the reference of **example 279a**) using the above procedure. **^{1}H NMR** (400 MHz, MeOD-d4) δ 8.40 (d, J=8.5 Hz, 2H), 8.16 (d, J=8.6 Hz, 1H), 8.00 (d, J=5.1 Hz, 1H), 7.81 (dd, J=5.5, 3.0 Hz, 3H), 7.60 (dd, J=8.7, 1.6 Hz, 1H), 7.49 (d, J=5.1 Hz, 1H), 5.48 (s, 2H), 4.72 (d, J =11.5 Hz, 1H), 3.93 – 3.65 (m, 3H), 3.46 (d, J=16.2 Hz, 1H), 3.26 – 3.06 (m, 3H), 3.02 – 2.90 (m, 1H), 2.84 (s, 3H), 2.81 – 2.73 (m, 1H), 1.33 (t, J=7.5 Hz, 3H). **MS** (ESI, m/z): $[M+H]^+$ = 777.2.

Example 282b (22.08 mg, 0.028 mmol, 22.7% yield) was synthesized from **Compound of Peak 2** (see the reference of **example 279b**) using the above procedure. **^{1}H NMR** (400 MHz, MeOD-d4) δ 8.41 (d, *J* = 8.5 Hz, 2H), 8.16 (d, 1H), 7.81 (dd, *J* = 5.3, 3.2 Hz, 3H), 7.61 (d, *J* = 8.6 Hz, 1H), 7.53 (d, *J* = 5.0 Hz, 1H), 7.27 (d, *J* = 5.0 Hz, 1H), 5.46 (s, 2H), 4.70 (d, *J* = 12.0 Hz, 1H), 3.80 – 3.56 (m, 3H), 3.52 – 3.46 (m, 1H), 3.20 – 3.10 (m, 3H), 2.92 (d, *J* = 12.1 Hz, 1H), 2.84 (s, 3H), 2.74 (d, *J* = 10.7 Hz, 1H), 1.33 (t, *J* = 7.5 Hz, 3H). **MS** (ESI, m/z): $[M+H]^+$ = 777.0.

Example 283:

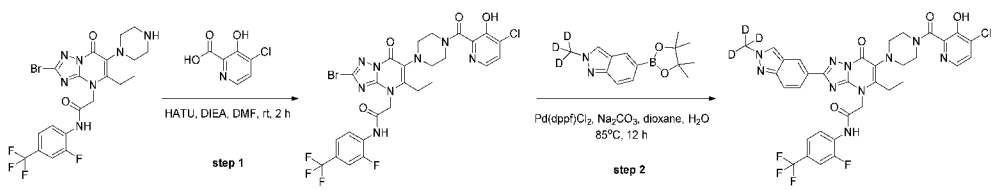
2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(2-methyl-2H-indazol-5-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide



Step 1: The mixture of 2-(2-bromo-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl) piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide (100 mg, 0.15 mmol), 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) -2H-indazole (58.08 mg, 0.22 mmol), Pd(dppf)Cl_2 (10.98 mg, 0.015mmol) and sodium carbonate (47.7 mg, 0.45 mmol) in dioxane (10 mL) and H_2O (1 mL) was stirred at 90 °C for 16 hours under N_2. Then the mixture was concentrated in vacuum and purified by Prep-HPLC to give 2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(2-methyl-2H-indazol-5-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide (23 mg, 0.031 mmol, 21.4 % yield) as a white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.74 (s, 1H), 10.24 (s, 1H), 8.59 (s, 1H), 8.49 (s, 2H), 8.24 (t, *J* = 8.2 Hz, 1H), 7.96 (dd, *J* = 9.1, 1.5 Hz, 1H), 7.81 (d, *J* = 11.2 Hz, 1H), 7.69 (d, *J* = 9.1 Hz, 1H), 7.57 (d, *J* = 8.7 Hz, 1H), 5.39 (s, 2H), 4.54 (d, *J* = 11.8 Hz, 1H), 4.19 (s, 3H), 3.53 (t, *J* = 10.7 Hz, 3H), 3.26 (d, *J* = 11.4 Hz, 1H), 3.01 (s, 3H), 2.85 (d, *J* = 10.2 Hz, 1H), 2.68 – 2.66 (m, 1H), 2.45 (s, 3H), 1.20 (t, *J* = 7.4 Hz, 3H). **MS** (ESI, m/z): $[M+H]^+$ = 734.3

Example 284:

2-(6-(4-(4-chloro-3-hydroxypicolinoyl)piperazin-1-yl)-5-ethyl-2-(2-(methyl-d3)-2H-indazol-5-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide



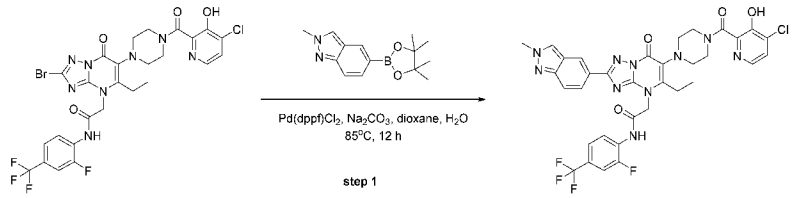
Step 1: To a mixture of 4-chloro-3-hydroxypicolinic acid (133.29 mg, 0.77 mmol) in

N,*N*-dimethylformamide (5 mL) was added DIEA (248.14 mg, 1.92 mmol) and HATU (365.02 mg, 0.96 mmol). The mixture was stirred at room temperature for 30 min followed by the addition of 2-(2-bromo-5-ethyl-7-oxo-6-(piperazin-1-yl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-4(7*H*)-yl)-*N*-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide hydrochloride (350 mg, 0.60 mmol). The mixture was stirred at room temperature for 12 hours. The mixture was diluted with water (20 mL) and extracted with EtOAc (15 mL * 3). The combined organic layer was washed with brine (15 mL * 3), dried over Na_2SO_4 and concentrated in vacuum. The resulting mixture was purified by flash silica chromatography (elution gradient: 0 to 10% MeOH in DCM, v/v) to afford 2-(2-bromo-6-(4-(4-chloro-3-hydroxypicolinoyl)piperazin-1-yl)-5-ethyl-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide (180 mg, 0.26 mmol, 43% yield) as a yellow solid. **MS** (ESI, m/z): $[M+H]^+$ = 701.0, 703.0

Step 2: To a mixture of 2-(2-bromo-6-(4-(4-chloro-3-hydroxypicolinoyl)piperazin-1-yl)-5-ethyl-7-oxo-[1,2,4]triazolo[1,5-*a*]pyrimidin-4(7H)-yl)-*N*-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide (90 mg, 0.14 mmol) in 1,4-dioxane (10 mL) and water (1 mL) was added 2-(methyl-d_3)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole (73.12 mg, 0.28 mmol), sodium carbonate (44.52 mg, 0.42 mmol) and $Pd(dppf)Cl_2$ (5.72 mg, 0.007 mmol). The mixture was degassed with N_2 and stirred at 85 °C for 12 hours. The mixture was diluted with water (20 mL) and extracted with EtOAc (15 mL * 3). The combined organic layer was washed with brine (15 mL * 3), dried over Na_2SO_4 and concentrated in vacuum. The crude product was purified by prep-HPLC (0.1% FA) to give 2-(6-(4-(4-chloro-3-hydroxypicolinoyl)piperazin-1-yl)-5-ethyl-2-(2-(methyl-d_3)-2*H*-indazol-5-yl)-7-oxo-[1,2,4]triazolo[1,5-*a*]pyrimidin-4(7*H*)-yl)-*N*-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide (20.72 mg, 0.027 mmol, 19.3% yield) as a white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.85 (s, 1H), 10.74 (s, 1H), 8.49 (s, 2H), 8.24 (t, *J* = 8.2 Hz, 1H), 8.08 (d, *J* = 5.1 Hz, 1H), 7.96 (dd, *J* = 9.0, 1.6 Hz, 1H), 7.81 (d, *J* = 9.4 Hz, 1H), 7.69 (d, *J* = 9.0 Hz, 1H), 7.56 (d, *J* = 5.1 Hz, 2H), 5.39 (s, 2H), 4.56 (d, *J* = 14.1 Hz, 1H), 3.64 – 3.48 (m, 3H), 3.29 – 3.20 (m, 1H), 3.08 – 2.92 (m, 3H), 2.85 (d, *J* = 11.8 Hz, 1H), 2.73 – 2.67 (m, 1H), 1.20 (t, *J* = 7.5 Hz, 3H). **MS** (ESI, m/z): $[M+H]^+$ = 756.2.

Example 285:

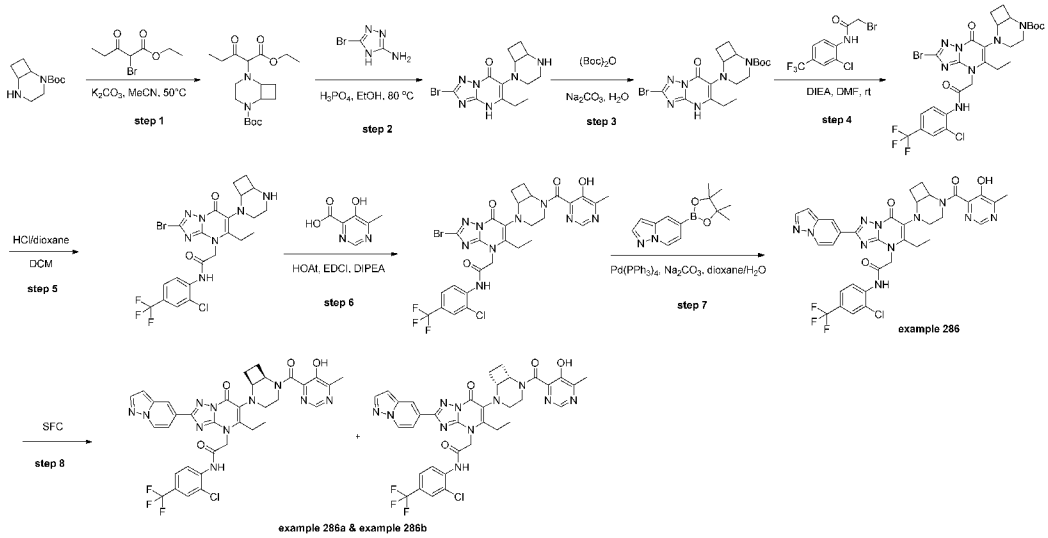
2-(6-(4-(4-chloro-3-hydroxypicolinoyl)piperazin-1-yl)-5-ethyl-2-(2-methyl-2H-indazol-5-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide



Step 1: To a mixture of 2-(2-bromo-6-(4-(4-chloro-3-hydroxypicolinoyl)piperazin-1-yl)-5-ethyl-7-oxo-[1,2,4]triazolo[1,5-*a*]pyrimidin-4(7*H*)-yl)-*N*-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide (90 mg, 0.13 mmol) in 1,4-dioxane (10 mL) and water (1 mL) was added 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole (67.11 mg, 0.26 mmol), sodium carbonate (41.34 mg, 0.39 mmol) and $Pd(dppf)Cl_2$ (5.31 mg, 0.0065 mmol). The mixture was degassed with N_2 and stirred at 85 °C for 12 hours. The mixture was diluted with water (20 mL) and extracted with EtOAc (15 mL * 3). The combined organic layer was washed with brine (15 mL * 3), dried over Na_2SO_4 and concentrated in vacuum. The crude product was purified by

prep-HPLC (0.1% FA) to give 2-(6-(4-(4-chloro-3-hydroxypicolinoyl)piperazin-1-yl)-5-ethyl-2-(2-methyl-2*H*-indazol-5-yl)-7-oxo-[1,2,4]triazolo[1,5-*a*]pyrimidin-4(7*H*)-yl)-*N*-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide (23.02 mg, 0.031 mmol, 23.8% yield) as a white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.91 – 10.74 (m, 2H), 8.49 (s, 2H), 8.24 (t, *J* = 8.2 Hz, 1H), 8.10 – 7.91 (m, 2H), 7.81 (d, *J* = 10.2 Hz, 1H), 7.69 (d, *J* = 8.9 Hz, 1H), 7.56 (d, *J* = 10.2 Hz, 2H), 5.39 (s, 2H), 4.57 (d, *J* = 11.2 Hz, 1H), 4.19 (s, 3H), 3.57 (dt, *J* = 15.9, 10.6 Hz, 3H), 3.29 – 3.22 (m, 1H), 3.09 – 2.96 (m, 3H), 2.89 – 2.81 (m, 1H), 2.73 – 2.67 (m, 1H), 1.21 (t, *J* = 7.4 Hz, 3H). **MS** (ESI, m/z): $[M+H]^+$ = 753.2.

Example 286a and 286b: N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-((1S,6R)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-7-oxo-2-(pyrazolo[1,5-a]pyridin-5-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide and N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-((1R,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-7-oxo-2-(pyrazolo[1,5-a]pyridin-5-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide



Step 1: To a mixture of cis *tert*-butyl 2,5-diazabicyclo[4.2.0]octane-2-carboxylate (1.8 g, 8.48 mmol) in acetonitrile (45 mL) was added ethyl 2-bromo-3-oxopentanoate (1.9 g, 8.48 mmol) and potassium carbonate (3.5 g, 25.44 mmol). The mixture was stirred at 50 °C for 2 hours. The mixture was filtered, the filter cake was washed with CH_3CN. The filtrate was concentrated in vacuum and purified by flash silica chromatography (elution gradient: 0 to 50% EtOAc in Hexane, v/v) to afford cis *tert*-butyl 5-(1-ethoxy-1,3-dioxopentan-2-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (1.4 g, 3.95 mmol, 46.6% yield) as yellow oil. **MS** (ESI, m/z): $[M+H]^+$ = 355.4.

Step 2 & Step 3: To a solution of cis *tert*-butyl 5-(1-ethoxy-1,3-dioxopentan-2-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (1.4 g, 3.95 mmol) in ethanol (30 mL) were added 5-bromo-4*H*-1,2,4-triazol-3-amine (965.66 mg, 5.93 mmol) and phosphoric acid (4.5 g, 39.5 mmol) . The reaction mixture was stirred at 90 °C for 48 hours under N_2. Then the mixture was added Sat.Na_2CO_3 to pH=10 with $(Boc)_2O$ (4.31 g, 19.75 mmol). The mixture was stirred at 25°C for 2 hours. The mixture was diluted with water (100 mL), extracted with EtOAc (100 mL * 3). The combined organic layers were washed with brine (80 mL) and concentrated. The residue was purified by flash silica chromatography (elution gradient: 0 to 3% MeOH in DCM, v/v) to afford cis *tert*-butyl 5-(2-bromo-5-ethyl-7-oxo-4,7- dihydro-[1,2,4]triazolo[1,5-*a*]pyrimidin-6-yl)-

2,5-diazabicyclo[4.2.0]octane-2-carboxylate (870 mg,1.9 mmol, 48.1% yield) as yellow solid. **MS** (ESI, m/z): $[M+H]^+$ = 453.1, 455.1.

Step 4: To a solution of cis *tert*-butyl 5-(2-bromo-5-ethyl-7-oxo-4,7-dihydro-[1,2,4]triazolo [1,5-*a*]pyrimidin-6-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (870 mg, 1.92 mmol) in acetonitrile (55 mL) were added 2-bromo-*N*-(2-chloro-4-(trifluoromethyl)phenyl) acetamide (668.45 mg, 2.11 mmol) and DIEA (545.91 mg, 4.22 mmol) . The mixture was stirred at 25°C for 16 hours. The mixture was concentrated in vacuum and purified by flash silica chromatography (elution gradient: 0 to 45% EtOAc in Hexane, v/v) to afford cis *tert*-butyl 5-(2-bromo-4-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-5-ethyl-7-oxo-4,7-dihydro-[1,2,4]triazolo[1,5-*a*]pyrimidin-6-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (650 mg, 0.95 mmol, 49.5% yield) as yellow solid. **MS** (ESI, m/z): $[M+H-56]^+$ = 634.1.

Step 5: To the mixture of cis *tert*-butyl 5-(2-bromo-4-(2-((2-chloro-4-(trifluoromethyl)phenyl) amino)-2-oxoethyl)-5-ethyl-7-oxo-4,7-dihydro-[1,2,4]triazolo[1,5-*a*]pyrimidin-6-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (650 mg, 0.94 mmol) in dichloromethane (20 mL) was added 4 M HCl/1,4-dioxane (10 mL). The mixture was stirred at room temperature for 2 hours. The mixture was concentrated in vacuum to give cis 2-(6-(2,5-diazabicyclo[4.2.0]octan-2-yl)-2-bromo-5-ethyl-7-oxo-[1,2,4]triazolo[1,5-*a*]pyrimidin-4(7*H*)-yl)-*N*-(2-chloro-4-(trifluoromethyl)phenyl)acetamide hydrochloride (550 mg, 0.88 mmol, 88.8% yield) as yellow solid. **MS** (ESI, m/z): $[M+H]^+$ = 588.2, 590.2.

Step 6: To a mixture of 5-hydroxy-6-methylpyrimidine-4-carboxylic acid (148 mg, 0.96 mmol) in acetonitrile (220 mL) was added HOAt (163.33 mg, 1.2 mmol) and EDCI (230.04 mg, 1.2 mmol). The mixture was stirred at room temperature for 1 hour followed by the addition of cis 2-(6-(2,5-diazabicyclo[4.2.0]octan-2-yl)-2-bromo-5-ethyl-7-oxo-[1,2,4]triazolo[1,5-*a*]pyrimidin-4(7*H*)-yl)-*N*-(2-chloro-4-(trifluoromethyl)phenyl)acetamide hydrochloride (300 mg, 0.48 mmol) and DIEA (372.21 mg, 2.88 mmol) in acetonitrile (55 mL). The mixture was stirred at 30 °C for 16 hours. The mixture was concentrated in vacuum and diluted with water (50 mL). The mixture was extracted with DCM (50 mL * 3). The combined organic layer was washed with brine (30 mL * 3), dried over Na_2SO_4 and concentrated in vacuum. The residue was purified by flash silica chromatography (elution gradient: 0 to 3% MeOH in DCM, v/v) to afford cis 2-(2-bromo-5-ethyl-6-(5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-7-oxo-[1,2,4]triazolo[1,5-*a*]pyrimidin-4(7*H*)-yl)-*N*-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (130 mg, 0.18 mmol, 18.8% yield) as yellow solid. **MS** (ESI, m/z): $[M+H]^+$ = 724.1.

Step 7: To the mixture of cis 2-(2-bromo-5-ethyl-6-(5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-7-oxo-[1,2,4]triazolo[1,5-*a*]pyrimidin-4(7*H*)-yl)-*N*-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (130 mg, 0.18 mmol) in 1,4-dioxane (10 mL) and water (1 mL) was added 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-*a*] pyridine (70.30 mg, 0.29 mmol), $Pd(PPh_3)_4$ (20.80 mg, 0.018 mmol) and sodium carbonate (57.23 mg, 0.54 mmol). The mixture was degassed with N_2 and stirred at 90°C for 12 hours. The mixture was concentrated and purified by Prep-HPLC (eluted with MeCN in H_2O, 10 mmol/L NH_4HCO_3) to give cis *N*-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-7-oxo-2-(pyrazolo[1,5-*a*]pyridin-5-yl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-4(7*H*)-yl)acetamide (**example 286**, 30 mg, 0.039 mmol, 22% yield) as white solid. **^{1}H NMR** (400 MHz, MeOD-d_4) δ 8.61 (d, *J* = 7.4 Hz, 1H), 8.58 – 8.48 (m, 2H), 8.18 (d, *J* = 8.5 Hz, 1H), 8.00 (d, *J* = 2.4 Hz, 1H), 7.83 (s, 1H), 7.63 (dd, *J* = 16.9, 9.3 Hz, 2H), 6.76 (d, *J* =

2.4 Hz, 1H), 5.64 (d, *J* = 17.7 Hz, 1H), 5.39 (d, *J* = 17.3 Hz, 1H), 4.56 – 4.37 (m, 2H), 3.82 - 3.63 (m, 3H), 3.05 - 2.84 (m, 3H), 2.52 (d, *J* = 8.9 Hz, 3H), 2.45 – 2.11 (m, 1H), 1.85 -1.55 (m, 2H), 1.43 - 1.31 (m, 4H). **MS** (ESI, m/z): $[M+H]^+$ = 762.2.

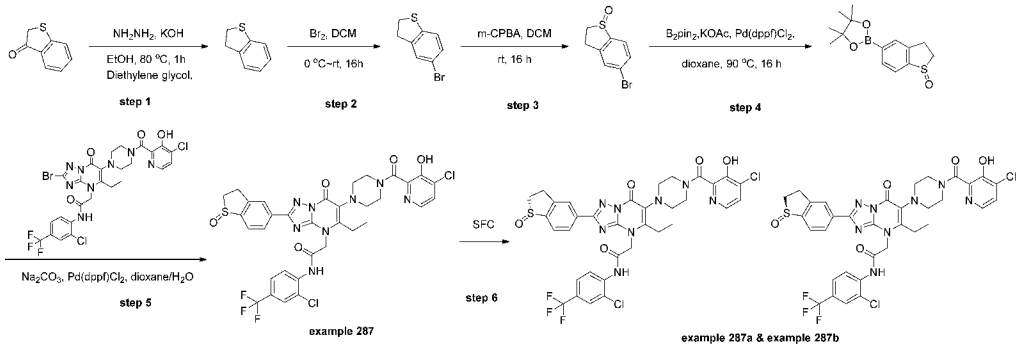
Step 8: the **example 286** was further purified by SFC to afford the **example 286a** and **example 286b** as N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-((1S,6R)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-7-oxo-2-(pyrazolo[1,5-a]pyridin-5-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide or N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-((1R,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-7-oxo-2-(pyrazolo[1,5-a]pyridin-5-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide. **MS** (ESI, m/z): $[M+H]^+$ = 762.2.

NMR of **286a**: **^{1}H NMR** (400 MHz, MeOD-d_4) δ 8.61 (d, J = 7.4 Hz, 1H), 8.58 – 8.48 (m, 2H), 8.18 (d, J = 8.5 Hz, 1H), 8.00 (d, J = 2.4 Hz, 1H), 7.82 (s, 1H), 7.63 (dd, J = 16.9, 9.3 Hz, 2H), 6.75 (d, J = 2.4 Hz, 1H), 5.63 (d, J = 17.7 Hz, 1H), 5.39 (d, J = 17.3 Hz, 1H), 4.56 – 4.36 (m, 2H), 3.80 - 3.53 (m, 3H), 3.05 - 2.80 (m, 3H), 2.51 (d, J = 8.9 Hz, 3H), 2.47 – 2.15 (m, 1H), 1.65 -1.50 (m, 2H), 1.47 - 1.30 (m, 4H).

NMR of **286b**: **^{1}H NMR** (400 MHz, MeOD-d_4) δ 8.61 (d, J = 7.4 Hz, 1H), 8.55 – 8.49 (m, 2H), 8.18 (d, J = 8.5 Hz, 1H), 8.00 (d, J = 2.4 Hz, 1H), 7.82 (s, 1H), 7.63 (dd, J = 16.9, 9.3 Hz, 2H), 6.75 (d, J = 2.4 Hz, 1H), 5.63 (d, J = 17.7 Hz, 1H), 5.39 (d, J = 17.3 Hz, 1H), 4.56 – 4.36 (m, 2H), 3.80 - 3.55 (m, 3H), 3.02 - 2.82 (m, 3H), 2.52 (d, J = 8.9 Hz, 3H), 2.47 – 2.15 (m, 1H), 1.65 -1.50 (m, 2H), 1.47 - 1.30 (m, 4H).

Example 287:

2-(6-(4-(4-chloro-3-hydroxypicolinoyl)piperazin-1-yl)-5-ethyl-2-(1-oxido-2,3-dihydrobenzo[b]thiophen-5-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide



Step 1: To a solution of benzo[b]thiophen-3(2H)-one (2.0 g, 13.3 mmol) in EtOH (10 mL) was added Hydrazinium hydroxide (10.3 g, 205.8 mmol). The solution was stirred at 80 °C for 1 hour. The solution was concentrated and the residue was added to Diethylene glycol (11.2 g, 105.49 mmol), then potassium hydroxide (2.24 g, 39.96mmol) was added. The new solution was stirred at 120 °C for 16 hours. GCMS indicated completion of reaction. EtOAc (30 mL) was added washed with brine (15 mL * 2). Concentrated and the residue was purified by gel chromatography (PE) to give 2,3-dihydrobenzo[b]thiophene (800 mg, 5.88 mmol, 44.2 % yield) as a colorless oil. **GC/MS** (ESI, m/z): $[M]^+$ = 136

Step 2: To a mixture of 2,3-dihydrobenzo[b]thiophene (830 mg, 6.09 mmol) in dichloromethane (20 mL) was added bromine (973.24 mg, 6.09 mmol) at 0 °C. The solution was stirred at room temperatures for 16 hours. Then $NaHSO_3$ (20 mL) was added, extracted with DCM

(20 mL * 2), washed with brine. Concentrated and the residue was purified by gel chromatography (PE) to give 5-bromo-2,3-dihydrobenzo[b]thiophene (900 mg, 4.18 mmol, 68.7% yield) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30 (s, 1H), 7.21 (d, *J* = 8.2 Hz, 1H), 7.06 (d, *J* = 8.2 Hz, 1H), 3.36 (d, *J* = 6.9 Hz, 2H), 3.26 (t, *J* = 7.6 Hz, 2H).

Step 3: To a solution of 5-bromo-2,3-dihydrobenzo[b]thiophene (866 mg, 4.03 mmol) in dichloromethane (20 mL) was added 3-chloroperbenzoic acid (981.82 mg, 4.84 mmol, Purity 85%) at 0 °C. The solutiion was stirred at room temperatures for 16 hours. LCMS indicated completion of reaction. NaOH (10 mL, 2N) was added. Extracted with DCM (20 mL * 3). The organic phase was washed with brine (10 mL), dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by gel chromatography PE/EtOAc (10:1 to 1:1) to give 5-bromo-2,3-dihydrobenzo[b]thiophene 1-oxide (800 mg, 3.46 mmol, 85.9 % yield) as a yellow solid. **MS** (ESI, m/z): $[M+H]^+$ = 231.0, 233.0.

Step 4: To a mixture of 5-bromo-2,3-dihydrobenzo[b]thiophene 1-oxide (120 mg, 0.52 mmol) in 1,4-Dioxane (20.0 mL) was added potassium acetate (153.1 g, 1.56 mmol), B_2pin_2 (150 mg, 0.57mmol) and $Pd(dppf)Cl_2$ (43 mg, 0.052 mmol) at room temperature under N_2. The resulting mixture was stirred at 90 °C for 16 hours under N_2. The mixture was concentrated in vacuum and the resulting residue was purified by silica gel column chromatography (EA/PE from 10% to 50%) to give 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrobenzo[b]thiophene 1-oxide (90 mg, 0.32 mmol, 62.2 % yield) as solid. **MS** (ESI, m/z): $[M+H]^+$ = 279.1, $[M+H-82]^+$ = 196.88.

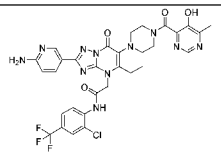
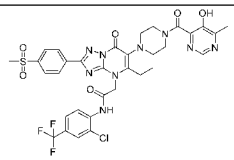
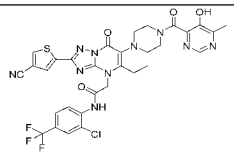
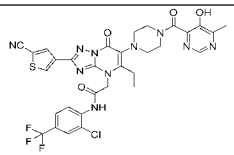
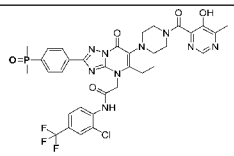
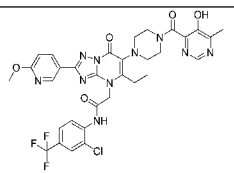
Step 5: A mixture of 2-(2-bromo-6-(4-(4-chloro-3-hydroxypicolinoyl)piperazin-1-yl)-5-ethyl-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7*H*)-yl)-*N*-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (100 mg, 0.14 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrobenzo[b] thiophene 1-oxide (47 mg, 0.17 mmol), $Pd(dppf)Cl_2$ (11 mg, 0.014 mmol) and Na_2CO_3 (45 mg, 0.42 mmol) in dioxane (10 mL) and H_2O (1 mL) was stirred at 85°C for 16 hours under N_2. The mixture was filtered, concentrated in vacuum and purified by Prep-HPLC, eluted with MeCN in H_2O (0.1% NH_4HCO_3) to obtain 2-(6-(4-(4-chloro-3-hydroxypicolinoyl)piperazin-1-yl)-5-ethyl-2-(1-oxido-2,3-dihydrobenzo[b]thiophen-5-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (**example 287**). **MS** (ESI, m/z): $[M+H]^+$ = 789.2.

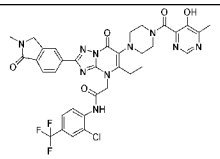
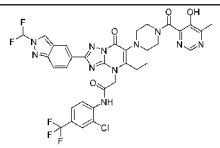
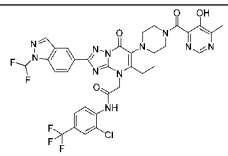
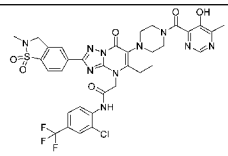
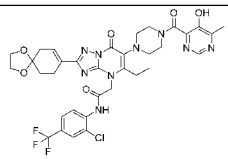
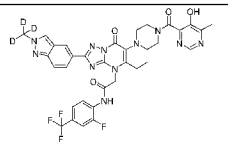
Step 6: the compound **example 287** was further purified by SFC to afford the **example 287a** and **example 287b** as (S)-2-(6-(4-(4-chloro-3-hydroxypicolinoyl)piperazin-1-yl)-5-ethyl-2-(1-oxido-2,3-dihydrobenzo[b]thiophen-5-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide or (R)-2-(6-(4-(4-chloro-3-hydroxypicolinoyl)piperazin-1-yl)-5-ethyl-2-(1-oxido-2,3-dihydrobenzo[b]thiophen-5-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide. **MS** (ESI, m/z): $[M+H]^+$ =789.2.

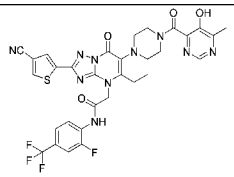
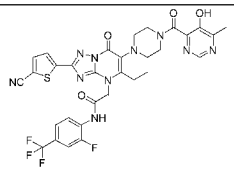
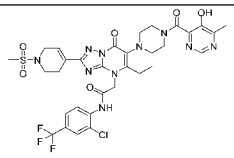
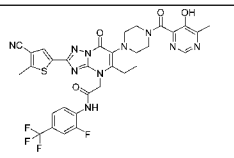
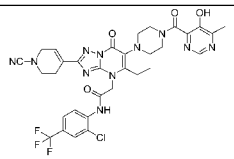
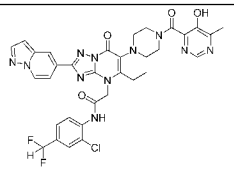
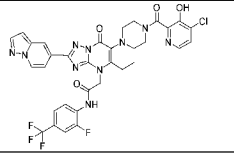
NMR of **287a**: **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.50 – 10.25 (m, 1H), 8.29 (s, 1H), 8.18 (d, J = 8.2 Hz, 1H), 8.10 – 7.90 (m, 4H), 7.72 (d, J = 8.8 Hz, 1H), 7.49 (d, J = 5.2 Hz, 1H), 5.41 (s, 2H), 4.56 (d, J = 10.1 Hz, 1H), 3.73 (dd, J = 15.4, 8.0 Hz, 1H), 3.51 – 3.30 (m, 5H), 3.27 – 3.15 (m, 2H), 3.10 – 2.91 (m, 3H), 2.84 (d, J = 11.1 Hz, 1H), 2.67 (s, 1H), 1.22 (t, J = 7.4 Hz, 3H).

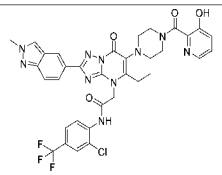
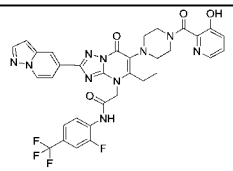
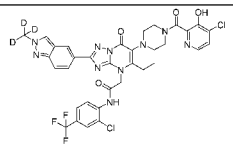
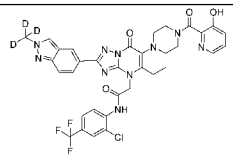
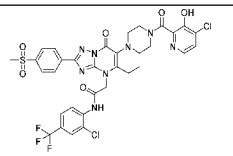
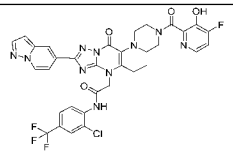
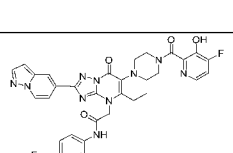
NMR of **287b**: **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.55 – 10.12 (m, 1H), 8.29 (s, 1H), 8.18 (d, J = 8.2 Hz, 1H), 8.10 – 7.90 (m, 4H), 7.72 (d, J = 8.8 Hz, 1H), 7.49 (d, J = 5.2 Hz, 1H), 5.41 (s, 2H), 4.54 - 4.45 (m, 1H), 3.73 (dd, J = 15.4, 8.0 Hz, 1H), 3.65 -3.30 (m, 5H), 3.27 – 3.15 (m, 2H), 3.03 – 2.95 (m, 3H), 2.84 (d, J = 11.1 Hz, 1H), 2.67 (s, 1H), 1.22 (t, J = 7.4 Hz, 3H).

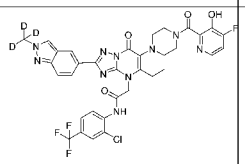
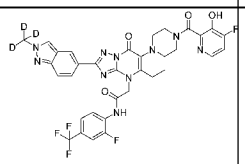
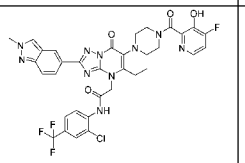
The following compounds were synthesized by using the similar methods as above procedure or reference. The start material is commercial or prepared in house.

Example number	Structure	Name of structure	Data (NMR and LCMS)
288		2-(2-(6-aminopyridin-3-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.72 (s, 1H), 8.57 (s, 1H), 8.20 - 8.16 (m, 2H), 7.84 (s, 1H), 7.63 (d, J = 8.4 Hz, 1H), 6.66 (d, J = 8.5 Hz, 1H), 5.46 (s, 2H), 4.74 (d, J = 11.7 Hz, 1H), 4.10 (d, J = 12.6 Hz, 1H), 3.79 - 3.75 (m, 2H), 3.53 – 3.41 (m, 1H), 3.22 - 3.07 (m, 3H), 2.97 (d, J = 10.3 Hz, 1H), 2.82 (d, J = 10.8 Hz, 1H), 2.54 (s, 3H), 1.35 (t, J = 7.3 Hz, 3H). **MS** (ESI) m/z = 712.0 $[M+H]^+$
290		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(4-(methylsulfonyl)phenyl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, DMSO) δ 10.44 (s, 1H), 10.25 (s, 1H), 8.59 (s, 1H), 8.36 (d, J = 8.4 Hz, 2H), 8.08 (dd, J = 15.6, 8.5 Hz, 3H), 7.98 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 5.42 (s, 2H), 4.54 (d, J = 11.7 Hz, 1H), 3.58-3.48 (m, 3H), 3.28 (s, 4H), 3.04 (d, J = 8.2 Hz, 2H), 2.86 (d, J = 10.5 Hz, 1H), 2.68 (d, J = 9.4 Hz, 1H), 2.54 (s, 1H), 2.45 (s, 3H), 1.25-1.20 (m, 3H). **MS** (ESI) m/z = 774.2 $[M+H]^+$.
291		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(4-cyanothiophen-2-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.61 (s, 1H), 8.49 (d, J = 8.8 Hz, 1H), 8.01 (d, J =5.1 Hz, 2H), 7.65 (s, 1H), 7.55 (d, J =8.8 Hz, 1H), 5.69 (d, J = 12.1 Hz, 1H), 5.17 (s, 2H), 4.81 (d, J = 12.6 Hz, 1H), 3.88-3.78 (m, 2H), 3.52 (d, J = 12.8 Hz, 1H), 3.20 (d, J =7.3 Hz, 2H), 3.08 (s, 1H), 2.83 (dd, J = 33.9, 10.8 Hz, 2H), 2.66 (s, 1H), 2.58 (s, 3H), 1.40-1.33 (m, 3H). **MS** (ESI) m/z = 727.0 $[M+H]^+$.
293		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(5-cyanothiophen-3-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.80 (s, 1H), 8.79 (s, 1H), 8.60 (s, 1H), 8.49 (d, J = 8.6 Hz, 1H), 8.35 (s, 1H), 8.27 (s, 1H), 7.65 (s, 1H), 7.55 (d, J = 8.4 Hz, 1H), 5.70 (d, J = 11.3 Hz, 1H), 5.18 (s, 2H), 4.81 (d, J = 10.7 Hz, 1H), 3.83 (s, 2H), 3.51 (s, 1H), 3.14 (d, J = 45.6 Hz, 3H), 2.83 (d, J = 26.0 Hz, 2H), 2.57 (s, 3H), 1.36 (s, 3H). **MS** (ESI) m/z = 727.0 $[M+H]^+$.
295		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(4-(dimethylphosphoryl)phenyl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, CD_3OD) δ 8.71 (s, 1H), 8.40 (d, J=6.5 Hz, 2H), 8.18 (d, J=8.6 Hz, 1H), 7.96 - 7.91 (m, 2H), 7.85 (s, 1H), 7.63 (d, J=8.8 Hz, 1H), 5.51 (s, 2H), 4.74 (d, J=12.2 Hz, 1H), 4.05 (d, J = 13.2 Hz, 1H), 3.82 - 3.73 (m, 2H), 3.48 (t, J =11.6 Hz, 1H), 3.24 – 3.12 (m, 3H), 3.00 (d, J=10.4 Hz, 1H), 2.84 (d, J=10.3 Hz, 1H), 2.61 (s, 3H), 1.85 (d, J=13.4 Hz, 6H), 1.36 (t, J=7.5 Hz, 3H). **MS** (ESI) m/z = 772.0 $[M+H]^+$.
297		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(6-methoxypyridin-3-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, MeOD-d_4) δ 8.94 (d, J =2.3 Hz, 1H), 8.58 (s, 1H), 8.41 (d, J =8.7, 2.3 Hz, 1H), 8.16 (d, J =8.6 Hz, 1H), 7.82 (s, 1H), 7.61 (d, J =8.3 Hz, 1H), 6.91 (d, J =8.7 Hz, 1H), 5.46 (s, 2H), 4.71 (d, J =12.9 Hz, 1H), 4.10 (d, J =11.8 Hz, 1H), 3.97 (s, 3H), 3.76 (s, 2H), 3.46 (d, J =11.5 Hz, 1H), 3.13 (d, J =8.0 Hz, 3H), 2.95 (s, 1H), 2.81 (d, J =11.6 Hz, 1H), 2.53 (s, 3H), 1.33 (t, J = 7.5 Hz, 3H). **MS** (ESI, m/z) = 727.1 $[M+H]^+$.

299		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(2-methyl-1-oxoisoindolin-5-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, MeOD-d_4) δ 8.58 (s, 1H), 8.41 – 8.32 (m, 2H), 8.17 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 9.4 Hz, 1H), 5.48 (s, 2H), 4.75 – 4.68 (m, 1H), 4.11 (s, 1H), 3.77 (s, 2H), 3.48 (s, 1H), 3.22 (s, 3H), 3.14 (d, J = 9.4 Hz, 4H), 3.01 – 2.92 (m, 1H), 2.83 (s, 1H), 2.53 (s, 3H), 1.35 (d, J = 7.3 Hz, 3H). **MS** (ESI, m/z) = 765.1 $[M+H]^+$.
300		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(2-(difluoromethyl)-2H-indazol-5-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.44 (s, 1H), 10.24 (s, 1H), 8.66 (s, 1H), 8.59 (s, 1H), 8.55 (s, 1H), 8.34 (dd, J = 8.8, 1.5 Hz, 1H), 8.10 – 8.05 (m, 1H), 8.00 (d, J = 9.1 Hz, 2H), 7.71 (d, J = 8.8 Hz, 1H), 5.43 (s, 2H), 4.55 (d, J = 12.4 Hz, 1H), 3.57 – 3.48 (m, 3H), 3.28 (t, J = 11.2 Hz, 1H), 3.03 (d, J = 9.6 Hz, 3H), 2.86 (d, J = 11.5 Hz, 1H), 2.68 (d, J = 9.3 Hz, 1H), 2.45 (s, 3H), 1.22 (t, J = 7.5 Hz, 3H). **MS** (ESI, m/z) = 786.3 $[M+H]^+$.
301		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(1-(difluoromethyl)-1H-indazol-5-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, MeOD-d_4) δ 8.79 (s, 1H), 8.68 (s, 1H), 8.56 (s, 1H), 8.23 (d, J = 9.1 Hz, 1H), 8.18 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 48.8, 48.2 Hz, 3H), 7.61 (d, J = 7.3 Hz, 1H), 5.48 (s, 2H), 4.72 (d, J = 13.8 Hz, 1H), 4.10 (d, J = 12.0 Hz, 1H), 3.78 (s, 2H), 3.48 (s, 1H), 3.14 (d, J = 7.4 Hz, 3H), 2.97 (d, J = 10.0 Hz, 1H), 2.83 (s, 1H), 2.53 (s, 3H), 1.34 (t, J = 7.5 Hz, 3H). **MS** (ESI, m/z) = 786.3 $[M+H]^+$.
302		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(2-methyl-1,1-dioxido-2,3-dihydrobenzo[d]isothiazol-5-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.43 (s, 1H), 8.56 (s, 1H), 8.35 – 8.27 (m, 2H), 8.09 – 7.95 (m, 3H), 7.72 (d, J = 8.7 Hz, 1H), 5.42 (s, 2H), 4.53 (d, J = 17.8 Hz, 3H), 3.52 (d, J = 9.2 Hz, 3H), 3.26 (d, J = 13.0 Hz, 2H), 3.09 – 2.96 (m, 3H), 2.85 (s, 3H), 2.68 (d, J = 8.6 Hz, 1H), 2.44 (s, 3H), 1.22 (t, J = 7.4 Hz, 3H). **MS** (ESI, m/z) = 801.2 $[M+H]^+$.
303		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-2-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, MeOD-d_4) δ 8.57 (s, 1H), 8.15 (d, J = 8.6 Hz, 1H), 7.81 (s, 1H), 7.61 (d, J = 8.7 Hz, 1H), 6.87 (s, 1H), 5.37 (s, 2H), 4.70 (d, J = 12.6 Hz, 1H), 4.08 (s, 1H), 3.98 (s, 4H), 3.73 (s, 2H), 3.47 (d, J = 11.3, 9.6 Hz, 2H), 3.16 – 3.03 (m, 3H), 2.93 (d, J = 10.3 Hz, 1H), 2.75 (s, 3H), 2.52 (s, 3H), 2.45 (s, 2H), 1.87 (t, J = 6.6 Hz, 2H), 1.30 (t, J = 7.5 Hz, 4H). **MS** (ESI, m/z) = 758.1$[M+H]^+$.
304		2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(2-(methyl-d3)-2H-indazol-5-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide	**^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.75 (s, 1H), 8.52 (d, J=28.0 Hz, 3H), 8.24 (s, 1H), 7.96 (d, J=8.8 Hz, 1H), 7.81 (d, J =10.9 Hz, 1H), 7.69 (d, J=8.2 Hz, 1H), 7.56 (d, J=8.5 Hz, 1H), 5.39 (s, 2H), 4.53 (s, 1H), 3.53 (s, 3H), 3.02 – 2.98 (m, 2H), 2.86 (s, 2H), 2.67 (s, 2H), 2.44 (s, 3H), 1.19 (d, J=6.5 Hz, 3H). **MS** (ESI, m/z) = 736.6 $[M+H]^+$.

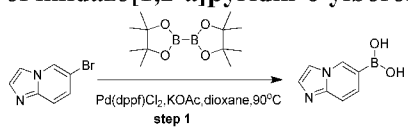
305		2-(2-(4-cyanothiophen-2-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide	**^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.74 (s, 1H), 8.73 (s, 1H), 8.56 (s, 1H), 8.23 (t, J = 8.1 Hz, 1H), 8.08 (s, 1H), 7.81 (d, J = 11.1 Hz, 1H), 7.57 (d, J = 8.6 Hz, 1H), 5.35 (s, 2H), 4.54 (d, J = 12.7 Hz, 1H), 3.49 (t, J = 11.4 Hz, 3H), 3.27 (s, 2H), 3.01 (s, 3H), 2.84 (d, J = 11.2 Hz, 1H), 2.66 (d, J = 10.3 Hz, 1H), 2.44 (s, 3H), 1.28 – 1.11 (m, 4H). **MS** (ESI, m/z) = 710.6 $[M+H]^+$
306		2-(2-(5-cyanothiophen-2-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide	**^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.72 (s, 1H), 8.53 (s, 1H), 8.22 (t, J = 8.3 Hz, 1H), 8.04 (d, J = 4.0 Hz, 1H), 7.85 (d, J = 4.0 Hz, 1H), 7.81 (d, J = 11.5 Hz, 1H), 7.57 (d, J = 8.9 Hz, 1H), 5.35 (s, 2H), 4.53 (d, J = 12.9 Hz, 1H), 3.50 (d, J = 11.1 Hz, 3H), 3.25 (s, 1H), 2.99 (s, 3H), 2.83 (d, J = 9.8 Hz, 1H), 2.66 (d, J = 9.8 Hz, 2H), 2.43 (s, 3H), 1.18 (t, J = 7.4 Hz, 3H). **MS** (ESI, m/z) = 710.6 $[M+H]^+$
307		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, MeOD-d_4) δ 8.54 (s, 1H), 8.15 (d, J = 8.7 Hz, 1H), 7.81 (s, 1H), 7.61 (d, J = 8.6 Hz, 1H), 6.95 (s, 1H), 5.39 (s, 2H), 4.70 (d, J = 12.2 Hz, 1H), 4.07 (d, J = 11.6 Hz, 1H), 3.98 (d, J = 2.7 Hz, 2H), 3.73 (s, 2H), 3.53 – 3.41 (m, 3H), 3.19 – 3.03 (m, 3H), 2.98 – 2.85 (m, 4H), 2.77 (s, 3H), 2.51 (s, 3H), 1.31 (t, J = 7.5 Hz, 3H). **MS** (ESI, m/z) = 779.4 $[M+H]^+$
308		2-(2-(4-cyano-5-methylthiophen-2-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide	**^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.02 – 10.39 (m, 1H), 8.55 (s, 1H), 8.22 (t, J=8.1 Hz, 1H), 7.91 (s, 1H), 7.80 (d, J=11.2 Hz, 1H), 7.57 (d, J=8.9 Hz, 1H), 5.33 (s, 2H), 4.53 (d, J=12.2 Hz, 1H), 3.49 (t, J=10.9 Hz, 3H), 3.26 (s, 1H), 2.99 (s, 3H), 2.83 (d, J = 10.8 Hz, 1H), 2.67 (s, 3H), 2.66 – 2.61 (m, 1H), 2.44 (s, 3H), 1.18 (t, J=7.4 Hz, 3H). **MS** (ESI, m/z) = 724.6 $[M+H]^+$
309		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(1-cyano-1,2,3,6-tetrahydropyridin-4-yl)-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.34 (s, 1H), 8.56 (s, 1H), 8.05 (d, J = 8.3 Hz, 1H), 7.96 (d, J = 1.5 Hz, 1H), 7.72 (d, J = 8.6 Hz, 1H), 6.76 (s, 1H), 5.32 (s, 2H), 4.52 (d, J = 11.6 Hz, 1H), 4.00 (d, J = 2.4 Hz, 2H), 3.55 – 3.40 (m, 5H), 3.24 (s, 1H), 2.98 (s, 3H), 2.82 (d, J = 10.4 Hz, 1H), 2.65 (s, 3H), 2.44 (s, 3H), 1.18 (t, J = 7.5 Hz, 3H). **MS** (ESI, m/z) = 726.1 $[M+H]^+$
310		N-(2-chloro-4-(difluoromethyl)phenyl)-2-(5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-2-(pyrazolo[1,5-a]pyridin-5-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.35 (s, 2H), 8.80 (d, J=7.3 Hz, 1H), 8.59 (s, 1H), 8.43 (s, 1H), 8.09 (d, J=2.2 Hz, 1H), 7.94 (d, J=8.4 Hz, 1H), 7.77 (s, 1H), 7.56 – 7.49 (m, 2H), 7.02 (t, J=55.7 Hz, 1H), 6.83 (d, J=1.8 Hz, 1H), 5.39 (s, 2H), 4.55 (d, J=12.4 Hz, 1H), 3.59 – 3.48 (m, 3H), 3.26 (d, J=12.5 Hz, 1H), 3.03 (d, J=9.0 Hz, 3H), 2.86 (d, J=11.3 Hz, 1H), 2.68 (d, J=9.6 Hz, 1H), 2.45 (s, 3H), 1.23 (t, J=7.4 Hz, 3H). **MS** (ESI, m/z) = 718.1 $[M+H]^+$
311		2-(6-(4-(4-chloro-3-hydroxypicolinoyl)piperazin-1-yl)-5-ethyl-7-oxo-2-(pyrazolo[1,5-a]pyridin-5-yl)-[1,2,4]t	**^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.76 (s, 2H), 8.79 (d, J = 7.3 Hz, 1H), 8.41 (s, 1H), 8.24 (t, J = 8.2 Hz, 1H), 8.16 – 8.03 (m, 2H), 7.82 (d, J = 11.2 Hz, 1H), 7.62 – 7.52 (m, 2H), 7.49 (dd, J = 7.3, 1.8 Hz, 1H), 6.82 (d, J = 1.7 Hz, 1H), 5.40 (s, 2H),

		riazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide	4.57 (d, J = 11.9 Hz, 1H), 3.57 (dd, J = 31.1, 11.0 Hz, 3H), 3.27 (s, 1H), 3.02 (s, 3H), 2.86 (d, J = 11.4 Hz, 1H), 2.68 (d, J = 9.2 Hz, 1H), 1.21 (t, J = 7.4 Hz, 3H). **MS** (ESI, m/z) = 739.4 $[M+H]^+$
312		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(3-hydroxypicolinoyl)piperazin-1-yl)-2-(2-methyl-2H-indazol-5-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	^{1}**H NMR** (400 MHz, DMSO-d_6) δ 10.43 (s, 2H), 8.50 (d, J = 7.3 Hz, 2H), 8.15 – 8.03 (m, 2H), 8.01 – 7.93 (m, 2H), 7.71 (t, J = 8.3 Hz, 2H), 7.36 – 7.28 (m, 2H), 5.41 (s, 2H), 4.57 (d, J = 12.2 Hz, 1H), 4.19 (s, 3H), 3.52 (d, J = 11.4 Hz, 2H), 3.24 (s, 1H), 3.01 (dd, J = 15.0, 8.2 Hz, 3H), 2.83 (d, J = 10.5 Hz, 1H), 2.66 (d, J = 11.4 Hz, 1H), 1.22 (t, J = 7.4 Hz, 3H). **MS** (ESI, m/z) = 735.41 $[M+H]^+$
313		2-(5-ethyl-6-(4-(3-hydroxypicolinoyl)piperazin-1-yl)-7-oxo-2-(pyrazolo[1,5-a]pyridin-5-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide	^{1}**H NMR** (400 MHz, DMSO-d_6) δ 10.75 (s, 1H), 10.42 (s, 1H), 8.79 (d, J=7.3 Hz, 1H), 8.41 (s, 1H), 8.24 (t, J=8.1 Hz, 1H), 8.08 (t, J=2.3 Hz, 2H), 7.82 (d, J=9.7 Hz, 1H), 7.57 (d, J=8.8 Hz, 1H), 7.49 (dd, J=7.3, 1.8 Hz, 1H), 7.36 – 7.25 (m, 2H), 6.82 (d, J=1.6 Hz, 1H), 5.40 (s, 2H), 4.57 (d, J=11.8 Hz, 1H), 3.59 – 3.42 (m, 3H), 3.25 (t, J=11.4 Hz, 1H), 3.08 – 2.92 (m, 3H), 2.84 (d, J=9.6 Hz, 1H), 2.66 (d, J=9.9 Hz, 1H), 1.20 (t, J=7.4 Hz, 4H). **MS** (ESI, m/z) = 705.5 $[M+H]^+$
314		2-(6-(4-(4-chloro-3-hydroxypicolinoyl)piperazin-1-yl)-5-ethyl-2-(2-(methyl-d3)-2H-indazol-5-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide	^{1}**H NMR** (400 MHz, DMSO-d_6) δ 10.85 (s, 1H), 10.43 (s, 1H), 8.55 – 8.47 (m, 2H), 8.08 (d, J = 5.2 Hz, 2H), 7.97 (dd, J = 8.9, 1.6 Hz, 2H), 7.71 (t, *J* = 8.6 Hz, 2H), 7.56 (d, J = 5.1 Hz, 1H), 5.41 (s, 2H), 4.57 (d, J = 11.3 Hz, 1H), 3.67 – 3.53 (m, 3H), 3.26 (d, J = 11.1 Hz, 1H), 3.03 (d, J = 7.0 Hz, 3H), 2.85 (d, J = 11.3 Hz, 1H), 2.67 (s, 1H), 1.22 (t, J = 7.4 Hz, 3H). **MS** (ESI, m/z): 772.2 $[M+H]^+$
315		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(3-hydroxypicolinoyl)piperazin-1-yl)-2-(2-(methyl-d3)-2H-indazol-5-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	^{1}**H NMR** (400 MHz, DMSO-d_6) δ 10.42 (s, 2H), 8.50 (d, J=8.6 Hz, 2H), 8.07 (d, J=5.9 Hz, 2H), 7.96 (s, 2H), 7.70 (d, J=9.1 Hz, 2H), 7.29 (d, J=3.0 Hz, 2H), 5.40 (s, 2H), 4.61 – 4.50 (m, 1H), 3.52 (s, 3H), 3.22 (s, 1H), 3.01 (d, J=23.5 Hz, 3H), 2.83 (s, 1H), 2.66 – 2.63 (m, 1H), 1.24 – 1.21 (m, 3H). **MS** (ESI, m/z): 738.3 $[M+H]^+$
316		2-(6-(4-(4-chloro-3-hydroxypicolinoyl)piperazin-1-yl)-5-ethyl-2-(4-(methylsulfonyl)phenyl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide	^{1}**H NMR** (400 MHz, DMSO-d_6) δ 10.44 (s, 1H), 8.36 (d, *J* = 8.5 Hz, 2H), 8.07 (dt, *J* = 34.6, 23.4 Hz, 5H), 7.72 (d, *J* = 8.6 Hz, 1H), 7.54 (d, *J* = 5.0 Hz, 1H), 5.42 (s, 2H), 4.56 (d, *J* = 11.1 Hz, 1H), 3.67 – 3.45 (m, 3H), 3.28 (s, 4H), 3.04 (d, *J* = 7.7 Hz, 3H), 2.85 (d, *J* = 10.5 Hz, 1H), 2.67 (s, 1H), 1.22 (t, *J* = 7.4 Hz, 4H). **MS** (ESI, m/z): 793.4 $[M+H]^+$
317		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(4-fluoro-3-hydroxypicolinoyl)piperazin-1-yl)-7-oxo-2-(pyrazolo[1,5-a]pyridin-5-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	^{1}**H NMR** (400 MHz, DMSO-d_6) δ 10.75 (s, 1H), 10.43 (s, 1H), 8.80 (d, J=7.3 Hz, 1H), 8.43 (s, 1H), 8.09 (dt, J=9.0, 6.2 Hz, 3H), 7.98 (s, 1H), 7.72 (d, J=8.6 Hz, 1H), 7.50 (dd, J=7.3, 1.8 Hz, 1H), 7.37 (dd, J=10.9, 5.3 Hz, 1H), 6.83 (d, J=2.1 Hz, 1H), 5.42 (s, 2H), 4.56 (d, J=11.8 Hz, 1H), 3.57 – 3.42 (m, 3H), 3.25 (t, J=11.2 Hz, 1H), 3.02 (d, J=5.5 Hz, 3H), 2.85 (d, J=11.1 Hz, 1H), 2.66 (d, J=9.9 Hz, 1H), 1.22 (t, J=7.4 Hz, 3H). **MS** (ESI, m/z): 739.5 $[M+H]^+$
325		2-(5-ethyl-6-(4-(4-fluoro-3-hydroxypicolinoyl)piperazin-1-yl)-7-oxo-2-(pyrazolo[1,5-a]pyridin-5-yl)-[1,2,4]t	^{1}**H NMR** (400 MHz, DMSO-d6) δ 10.74 (s, 1H), 8.79 (d, J = 7.3 Hz, 1H), 8.40 (s, 1H), 8.24 (t, J = 8.2 Hz, 1H), 7.81 (d, J = 10.7 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.49 (dd, J = 7.3, 1.7 Hz, 1H), 7.37 (dd, J = 10.9, 5.3 Hz, 1H), 6.82 (d, J = 2.2 Hz,

		riazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide	1H), 5.40 (s, 2H), 4.56 (d, J = 12.0 Hz, 1H), 3.57 – 3.38 (m, 3H), 3.26 (d, J = 12.0 Hz, 1H), 3.02 (d, J = 7.4 Hz, 3H), 2.85 (d, J = 11.6 Hz, 1H), 2.67 (s, 1H), 1.20 (t, J = 7.5 Hz, 3H). **MS** (ESI, m/z): 723.4 $[M+H]^+$
326		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(4-fluoro-3-hydroxypicolinoyl)piperazin-1-yl)-2-(2-(methyl-d3)-2H-indazol-5-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, DMSO-d_6) δ10.74 (s, 1H), 10.43 (s, 1H), 8.59 – 8.40 (m, 2H), 8.13 – 8.05 (m, 2H), 8.01 – 7.95 (m, 2H), 7.71 (t, J=7.4 Hz, 2H), 7.37 (dd, J=10.9, 5.3 Hz, 1H), 5.41 (s, 2H), 4.56 (d, J=10.7 Hz, 1H), 3.52 (d, J=9.4 Hz, 3H), 3.26 (d, J=11.9 Hz, 1H), 3.02 (d, J=7.5 Hz, 3H), 2.84 (d, J=10.3 Hz, 1H), 2.68 – 2.64 (m, 1H), 1.22 (t, J=7.5 Hz, 3H). **MS** (ESI, m/z): 756.3 $[M+H]^+$
327		2-(5-ethyl-6-(4-(4-fluoro-3-hydroxypicolinoyl)piperazin-1-yl)-2-(2-(methyl-d3)-2H-indazol-5-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide	**^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.74 (s, 1H), 8.48 (s, 2H), 8.24 (t, J=8.1 Hz, 1H), 8.12–8.06 (m, 1H), 7.96 (d, J=9.1 Hz, 1H), 7.81 (d, J=11.2 Hz, 1H), 7.69 (d, J=9.0 Hz, 1H), 7.56 (d, J=8.8 Hz, 1H), 7.37 (dd, J=10.9, 5.3 Hz, 1H), 5.39 (s, 2H), 4.56 (d, J=12.4 Hz, 1H), 3.52 (d, J=12.8 Hz, 3H), 3.26 (d, J=11.1 Hz, 1H), 3.00 (s, 3H), 2.84 (d, J=12.4 Hz, 1H), 2.67 (s, 1H), 1.20 (t, J=7.5 Hz, 3H). **MS** (ESI, m/z): 740.3 $[M+H]^+$
328		N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-6-(4-(4-fluoro-3-hydroxypicolinoyl)piperazin-1-yl)-2-(2-methyl-2H-indazol-5-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide	**^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.74 (s, 1H), 10.43 (s, 1H), 8.50 (d, J = 6.6 Hz, 2H), 8.09 (dd, J = 10.9, 7.7 Hz, 2H), 8.02 – 7.91 (m, 2H), 7.70 (t, J = 7.5 Hz, 2H), 7.37 (dd, J = 10.9, 5.3 Hz, 1H), 5.41 (s, 2H), 4.56 (d, J = 11.8 Hz, 1H), 4.19 (s, 3H), 3.52 (d, J = 10.2 Hz, 2H), 3.21 (d, J = 32.0 Hz, 2H), 3.03 (s, 3H), 2.84 (d, J = 10.3 Hz, 1H), 2.67 – 2.62 (m, 1H), 1.22 (t, J = 7.5 Hz, 4H). **MS** (ESI, m/z): 753.3 $[M+H]^+$

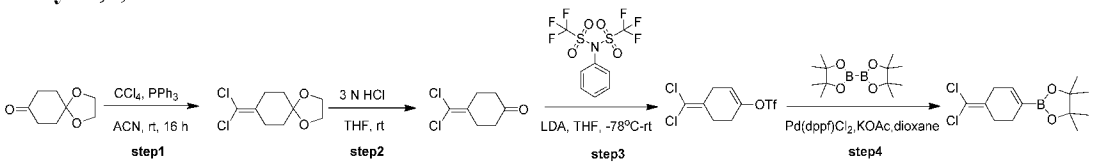
Synthesis of intermediate:

Intermediate 1: Synthesis of imidazo[1,2-a]pyridin-6-ylboronic acid



Step 1: To a solution of 6-bromoimidazo[1,2-*a*]pyridine (300 mg, 1.523 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (502 mg, 1.979 mmol) and KOAc (448 mg, 4.568 mmol) in dioxane (20 mL) stirred under nitrogen was added Pd(dppf)Cl_2 (111 mg, 0.152 mmol). The reaction mixture was stirred at 90 °C for 16 hrs. The mixture was concentrated under vacuum. Then purified by Prep-HPLC (Gemini-C18 150 * 21.2 mm 5um: MeCN--H_2O (0.1% FA): 55-85) to get the product imidazo[1,2-*a*]pyridin-6-ylboronic acid (110 mg, 0.679 mmol, yield: 44.6%) as a light yellow solid. **MS** (ESI) m/z = 163.2 $[M+H]^+$.

Intermediate 3: Synthesis of 2-(4-(dichloromethylene)cyclohex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Step 1: To a solution of PPh_3 (6.71 g, 25.6 mmol) in MeCN (10 mL) stirred under nitrogen was added dropwise the solution of 1,4-dioxaspiro[4.5]decan-8-one hydrate (1 g, 6.4 mmol) and CCl_4 (1.97 g, 12.8 mmol) in MeCN (10 mL). Following the addition, the reaction mixture was stirred at 25 °C for 16 hrs. The reaction was quenched by H_2O (30 mL), extracted with PE (30 mL), then washed by water (20 mL), brine (20 mL), dried over Na_2SO_4, concentrated and purified by flash Chromatography (EtOAc:Hexanes = 0~5%) to get product 8-(dichloromethylene)-1,4-

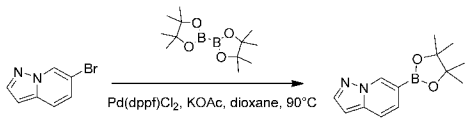
dioxaspiro[4.5]decane (1.2 g, 5.4 mmol, 84.4% yield) as a white solid. **MS** (ESI) m/z = 223.1, 225.2 $[M+H]^+$.

Step 2: To a solution of 8-(dichloromethylidene)-1,4-dioxaspiro[4.5]decane (1.2 g, 5.4 mmol) in THF (3 mL) was added a solution of 3 N HCl (3 mL). The reaction mixture was stirred at 25 °C for 16 hrs. The mixture was concentrated and purified by flash (EtOAc:Hexanes = 0~3%) to get product 4-(dichloromethylene)cyclohexan-1-one (0.7 g, 3.9 mmol, 72.2% yield) as a light yellow oil. **MS** (ESI) m/z = 179.1, 181.1 $[M+H]^+$.

Step 3: To a solution of 4-(dichloromethylene)cyclohexan-1-one (700 mg, 3.910 mmol) in THF (20 mL) was added LDA (3.9 mL, 7.819 mmol) at -78°C under N_2, the mixture was stirred at this temperature for 0.5 hr, then 1,1,1-trifluoro-*N*-phenyl-*N*-((trifluoromethyl)sulfonyl) methanesulfonamide (1396 mg, 3.910 mmol) was added. The mixture was stirred at 25°C for 16 hrs. The reaction was quenched by Sat. NH_4Cl, diluted with DCM (40 mL), then washed by water (20 mL), brine (20 mL), dried over Na_2SO_4, concentrated and purified by flash (EtOAc:Hexane = 0~10%) to get product 4-(dichloromethylene)cyclohex-1-en-1-yl trifluoromethanesulfonate (500 mg, 1.607 mmol, 41.1% yield) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.76-5.45 (m, 1H), 3.20 – 3.10 (m, 2H), 2.72 (t, *J* = 6.5 Hz, 2H), 2.50-2.46 (m, 2H).

Step 4: A mixture of 4-(dichloromethylene)cyclohex-1-en-1-yl trifluoromethanesulfonate (500 mg, 1.607 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (449 mg, 1.768 mmol), $Pd(dppf)Cl_2$ (117 mg, 0.161 mmol) and KOAc (473 mg, 4.822 mmol) in dioxane (20 mL) was stirred at 80 °C for 10 hrs. The mixture was concentrated and purified by flash (EtOAc:Hexanes = 0~5%) to get the product 2-(4-(dichloromethylene) cyclohex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (140 mg, 0.484 mmol, 30.1% yield) as a yellow solid. **^{1}HNMR** (400 MHz, $CDCl_3$) δ 6.52-6.50 (m, 1H), 3.04-3.02 (m, 2H), 2.48 (t, *J* = 6.3 Hz, 2H), 2.29-2.25 (m, 2H), 1.26 (s, 12H).

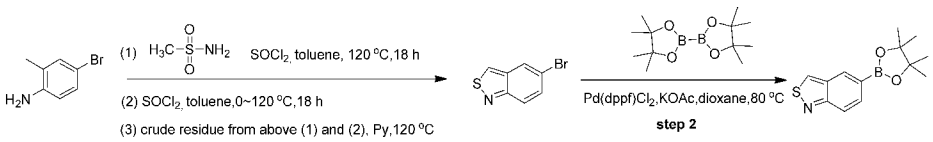
Intermediate 5: Synthesis of 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo [1,5-a]pyridine



Step 1

Step 1: To a solution of 6-bromopyrazolo[1,5-a]pyridine (150 mg, 0.76 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (251 mg, 0.989 mmol) and KOAc (149 mg, 1.52 mmol) in dioxane (3 mL) was added $Pd(dppf)Cl_2$ (55 mg, 0.076 mmol). The reaction mixture was stirred under nitrogen at 80°C for 16 hrs. The mixture was concentrated under vacuum. Then purified by Flash Chromatography (EtOAc/hexanes =0-3%) to get the product 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine (70 mg, 0.286 mmol, yield: 37.7 %) as a colorless oil. **MS** (ESI) m/z = 260.0 $[M+H]^+$.

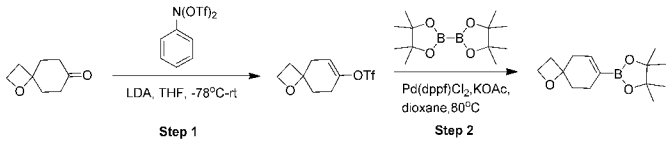
Intermediate 7: Synthesis of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[c] isothiazole



Step 1: A mixture of methanesulfonamide (7.2 g, 75.6 mmol) and $SOCl_2$ (13.09 g, 110 mmol) in toluene (10 mL) was stirred at 120 °C for 18 hrs under nitrogen. After cooling to the room temperature, toluene was removed under reduced pressure and the residue was used directly in the next step. To a solution of 4-bromo-2-methylaniline (2.0 g, 10.7 mmol) in toluene (40 mL) was added $SOCl_2$ (1.41 g, 11.8 mmol) dropwise at 0°C. After the addition was complete, the reaction mixture was heated at 120°C for 18 hrs. Pyridine (0.97 g, 12.3 mmol) and the crude residue from the above reactions were added to the mixture. The resulted solution was then stirred at 120°C for 18 hrs. The reaction mixture was concentrated under reduced pressure, dissolved in EtOAc (100 mL) and washed with H_2O (2*100 mL). The organic layer was washed with brine (100 mL), dried with Na_2SO_4 and concentrated in vacuum to give the crude product which was purified by Flash Chromatography (EtOAc/hexanes = 0-10%) to get the product 5-bromobenzo[c]isothiazole (1.5 g, 0.007 mol, yield: 65.4%) as a yellow solid. **MS** (ESI) m/z = 214.0, 216.0 $[M+H]^+$.

Step 2: To a solution of 5-bromobenzo[c]isothiazole (800 mg, 3.737 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1043 mg, 4.111 mmol) and KOAc (733 mg, 7.474 mmol) in dioxane (15 mL) was added $Pd(dppf)Cl_2$ (273 mg, 0.374 mmol). The reaction mixture was stirred at 80 °C for 10 hrs under nitrogen. The mixture was concentrated under vacuum. Then purified by Flash Chromatography (EtOAc/hexanes = 0-3%) to get the product 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) benzo[c]isothiazole (600 mg, 2.298 mmol, yield: 61.5%) as a green solid. **^{1}H NMR** (400 MHz, CD_3OD) δ 9.68 (s, 1H), 8.36 (s, 1H), 7.76 (d, J = 0.6 Hz, 2H), 1.40 (s, 12H). **MS** (ESI) m/z = 262.2 $[M+H]^+$.

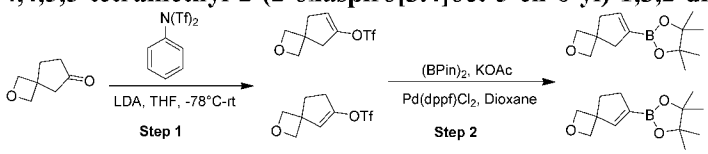
Intermediate 9: Synthesis of 4,4,5,5-tetramethyl-2-(1-oxaspiro[3.5]non-6-en-7-yl)-1,3,2-dioxaborolane



Step 1: To a solution of 1-oxaspiro[3.5]nonan-7-one (200 mg, 1.4 mmol) in THF (8 mL) was added LDA (1.1 mL, 2.2 mmol, 2 M in THF) at -78°C under N_2. The mixture was stirred at this temp for 0.5 hrs. Then 1,1,1-trifluoro-*N*-phenyl-*N*-((trifluoromethyl)sulfonyl) methanesulfonamide (611 mg, 1.6 mmol) was added. The mixture was stirred at 25°C for 16 hrs. The reaction was quenched by Sat. NH_4Cl, diluted with DCM (40 mL), then washed by water (20 mL), brine (20 mL), dried over Na_2SO_4, concentrated and purified by flash (EtOAc:Hexane = 0~5%) to get product 1-oxaspiro [3.5]non-6-en-7-yl trifluoromethanesulfonate (190 mg, 0.7 mmol, 48.9% yield) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.66-5.56 (m, 1H), 4.62–4.50 (m, 2H), 2.66-2.50 (m, 3H), 2.46 (t, J=7.7 Hz, 2H), 2.42–2.31 (m, 1H), 2.22-2.09 (m, 1H), 2.05–1.94 (m, 1H).

Step 2: A mixture of 1-oxaspiro[3.5]non-6-en-7-yl trifluoromethanesulfonate (170 mg, 0.70 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)- 1,3,2-dioxaborolane (213 mg, 0.84 mmol), $Pd(dppf)Cl_2$ (51 mg, 0.07 mmol) and Potassium acetate (137 mg, 1.40 mmol) in dioxane (8 mL) was stirred at 80 °C overnight. The mixture was concentrated and purified by flash (EtOAc:Hexanes = 0~6%) to get the product 4,4,5,5-tetramethyl-2-(1-oxaspiro [3.5]non-6-en-7-yl)-1,3,2-dioxaborolanelane (160 mg, 0.34 mmol, 39.8% yield) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.44 – 6.37 (m, 1H), 4.58 – 4.48 (m, 2H), 2.53 – 2.47 (m, 2H), 2.44 – 2.31 (m, 3H), 2.24 - 2.14 (m, 1H), 2.00 - 1.80 (m, 2H), 1.25 (s, 12H).

Intermediate 10: Synthesis of 4,4,5,5-tetramethyl-2-(2-oxaspiro[3.4]oct-6-en-6-yl)-1,3,2-dioxaborolane and 4,4,5,5-tetramethyl-2-(2-oxaspiro[3.4]oct-5-en-6-yl)-1,3,2-dioxaborolane

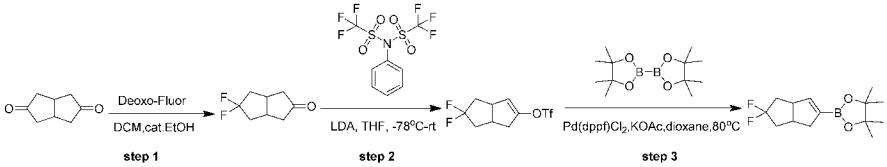


Step 1: To a solution of 2-oxaspiro [3.4]octan-6-one (200 mg, 1.6 mmol) in THF (5 mL) was added LDA (1.19 mL, 2.4 mmol) at -78°C under N_2, the mixture was stirred at this temperature for 0.5 hr, then 1,1,1-trifluoro-*N*-phenyl-*N*-((trifluoromethyl)sulfonyl)methanesulfonamide (740 mg, 1.9 mmol) was added. The mixture was stirred at 25°C for 16 hrs. The reaction was quenched by Sat. NH_4Cl, diluted with DCM (40 mL), then washed by water (20 mL), brine (20 mL), dried over Na_2SO_4, concentrated and purified by flash (EtOAc:Hexane = 0~10%) to get the mixture of 2-oxaspiro[3.4]oct-6-en-6-yl trifluoromethanesulfonate and 2-oxaspiro[3.4]oct-5-en-6-yl trifluoro methanesulfonate (220 mg, 0.77 mmol, 48.4% yield) as a colorless oil. **^{1}HNMR** (400 MHz, $CDCl_3$) δ 5.96 - 5.55 (m, 1H), 4.73 – 4.61 (m, 4H), 2.96 - 2.36 (m, 4H).

Step 2: A mixture of 2-oxaspiro [3.4] oct-6-en-6-yl trifluoromethanesulfonate and 2-oxaspiro [3.4]oct-5-en-6-yl trifluoromethanesulfonate (220 mg, 0.85 mmol), 4,4,5,5-tetramethyl -2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (238 mg, 0.94 mmol), $Pd(dppf)Cl_2$ (62 mg, 0.085 mmol) and KOAc (167 mg, 1.70 mmol) in dioxane (6 mL) was stirred at 80 °C for 3 hrs. The mixture was concentrated and purified by flash (EtOAc:Hexanes = 0~8%) to get the product 4,4,5,5-tetramethyl-2-(2-oxaspiro[3.4]oct-6-en-6-yl)-1,3,2-dioxaborolane and 4,4,5,5-tetramethyl-2-(2-oxaspiro[3.4]oct-5-en-6-yl)-1,3,2-dioxaborolane (160 mg, 0.34 mmol, 39.8% yield) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.68 - 6.39 (m, 1H), 4.73 – 4.59 (m, 4H), 2.46 - 2.19 (m, 4H), 1.26 (s, 12H).

Intermediate 12: Synthesis of 2-(5,5-difluoro-1,3a,4,5,6,6a-hexahydropentalen-2-yl)

-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

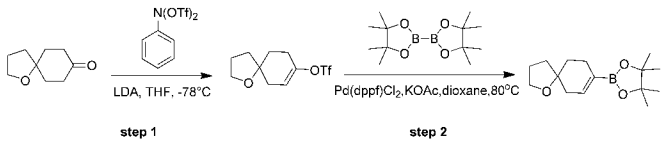


Step 1: A solution of Deoxo-Fluor (16 g, 72.4 mmol) in DCM (100 mL) was added to a cold (0 °C) solution of hexahydropentalene-2,5-dione (5 g, 36.2 mmol) in DCM (250 mL) followed by addition of a catalytic amount of EtOH (0.50 g, 10.8 mmol). The reaction mixture was stirred at the room temperature for 16 hrs. The reaction was quenched by Sat. $NaHCO_3$, diluted with DCM (300 mL), then washed by water (200 mL), brine (200 mL), dried over Na_2SO_4, concentrated and purified by flash (EtOAc:Hexane = 0~10%) to get product 5,5-difluorohexahydropentalen-2(1*H*)-one (600 mg, 3.7 mmol, 10.2% yield) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.96 - 2.92 (m, 2H), 2.59 - 2.49 (m, 4H), 2.20 (dd, J = 19.3, 4.3 Hz, 2H), 2.10 – 1.85 (m, 2H).

Step 2: To a solution of 5,5-difluoro-hexahydropentalen-2-one (400 mg, 2.498 mmol) in THF (20 mL) was added LDA (2.5 mL, 4.995 mmol) at -78°C under N_2, the mixture was stirred at this temperature for 0.5 hr, then 1,1,1-trifluoro-*N*-phenyl-*N*-((trifluoromethyl)sulfonyl)methane sulfonamide (892.23 mg, 2.4975 mmol) was added. The mixture was stirred at 25°C for 16 hrs. The reaction was quenched by Sat. NH_4Cl, diluted with DCM (40 mL), then washed by water (20 mL), brine (20 mL), dried over Na_2SO_4, concentrated and purified by flash (EtOAc:Hexane = 0~30%) to get 5,5-difluoro-1,3a,4,5,6,6a-hexahydropentalen-2-yl trifluoromethane sulfonate (300 mg, 0.72 mmol, 28.8% yield) as a light yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.60 (d, *J* = 1.8 Hz, 1H), 3.44 – 3.30 (m, 1H), 2.99-2.89 (m, 2H), 2.46 – 2.27 (m, 3H), 2.02 – 1.87 (m, 2H).

Step 3: A mixture of 5,5-difluoro-1,3a,4,5,6,6a-hexahydropentalen-2-yl trifluoromethane sulfonate (300 mg, 1.027 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (286.76 mg, 1.129 mmol), $Pd(dppf)Cl_2$ (75.12 mg, 0.103 mmol) and KOAc (302.26 mg, 3.080 mmol) in dioxane(20 mL) was stirred at 80 °C for 10 hrs. The mixture was concentrated and purified by flash (EtOAc:Hexanes = 0~5%) to get the product 2-(5,5-difluoro-1,3a,4,5,6,6a-hexahydropentalen-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (130 mg, 0.48 mmol, 46.9% yield) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.33 (dd, *J* = 4.1, 2.0 Hz, 1H), 3.38 – 3.30 (m, 1H), 2.92 – 2.82 (m, 1H), 2.76 – 2.68 (m, 1H), 2.36 – 2.20 (m, 3H), 1.98 – 1.75 (m, 2H), 1.27 (d, *J* = 8.2 Hz, 12H).

Intermediate 13: Synthesis of 4,4,5,5-tetramethyl-2-(1-oxaspiro[4.5]dec-7-en-8-yl)-1,3,2-dioxaborolane

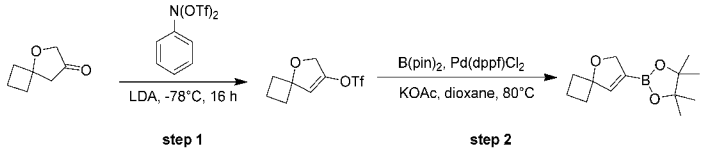


Step 1: To a solution of 1-oxaspiro[4.5]decan-8-one (200 mg, 1.3 mmol) in THF (5 mL) was added LDA (1.5 mL, 2.6 mmol) at -78°C under N_2, the mixture was stirred at this temperature for 0.5 hr, then 1,1,1-trifluoro-*N*-phenyl-*N*-((trifluoromethyl)sulfonyl)methanesulfonamide (505 mg, 1.3 mmol) was added. The mixture was stirred at 25°C for 16 hrs. The reaction was quenched by Sat. NH_4Cl, diluted with DCM (40 mL), then washed by water (20 mL), brine (20 mL), dried over Na_2SO_4, concentrated and purified by flash (EtOAc:Hexane = 0~10%) to get product 1-oxaspiro[4.5]dec-7-en-8-yl trifluoromethanesulfonate (150 mg, 0.52 mmol, yield: 40.3 %) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.75-5.65 (m, 1H), 3.95-3.80 (m, 2H), 2.65-2.55 (m, 1H), 2.40-2.20 (m, 3H), 2.05-1.85 (m, 3H), 1.80-1.70 (m, 3H).

Step 2: A mixture of 1-oxaspiro[4.5]dec-7-en-8-yl trifluoromethanesulfonate (150 mg, 0.52 mmol) , 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (146 mg, 0.57 mmol), $Pd(dppf)Cl_2$ (38 mg, 0.05 mmol) and KOAc (103 mg, 1.04 mmol) in dioxane(5 mL) was stirred at 80 °C for 3 hrs. The mixture was concentrated and purified by flash (EtOAc:Hexanes = 0~10%) to get the product 4,4,5,5-tetramethyl-2-{1-oxaspiro[4.5] dec-7-en-8-yl}-1,3,2-dioxaborolane (80 mg, 0.3 mmol, yield: 58.2%) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.50-6.45 (m, 1H), 3.95-3.80 (m, 2H), 2.40-2.15 (m, 4H), 1.95-1.85 (m, 2H), 1.75-1.55 (m, 4H), 1.25 (s, 12H).

Intermediate 14: Synthesis of 4,4,5,5-tetramethyl-2-(5-oxaspiro[3.4]oct-7-en-7-yl)-1,3,2-

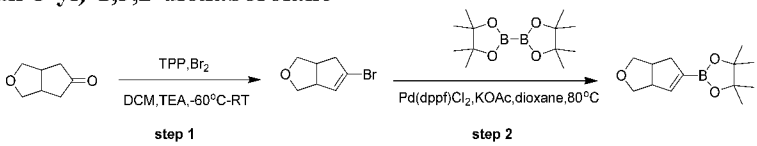
dioxaborolane



Step 1: To a solution of 5-oxaspiro[3.4]octan-7-one (300 mg, 2.38 mmol) in THF (5 mL) was added LDA (2.5 mL, 4.75 mmol) at -78°C under N_2, the mixture was stirred at this temperature for 0.5 hr, then 1,1,1-trifluoro-*N*-phenyl-*N*-((trifluoromethyl)sulfonyl)methane sulfonamide (926 mg, 2.38 mmol) was added. The mixture was stirred at 25°C for 16 hrs. The reaction was quenched by Sat. NH_4Cl, diluted with DCM (40 mL), then washed by water (20 mL), brine (20 mL), dried over Na_2SO_4, concentrated and purified by flash (EtOAc:Hexane = 0~10%) to get product 5-oxaspiro[3.4]oct-7-en-7-yl trifluoromethanesulfonate (150 mg, 0.58 mmol, yield: 24.4 %) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.05-6.02 (m, 1H), 4.20-4.10 (m, 1H), 3.96 (s, 1H), 2.45-2.15 (m, 6H).

Step 2: A mixture of 5-oxaspiro[3.4]oct-7-en-7-yl trifluoromethanesulfonate (100 mg, 0.38 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (108 mg, 0.42 mmol), Pd(dppf)Cl_2 (28 mg, 0.038 mmol) and KOAc (76 mg, 0.77 mmol) in dioxane(5 mL) was stirred at 80 °C for 3 hrs. The mixture was concentrated and purified by flash (EtOAc:Hexanes = 0~10%) to get the product 4,4,5,5-tetramethyl-2-{5-oxaspiro[3.4]oct-7-en-7-yl}-1,3,2-dioxaborolane (25 mg, 0.1 mmol, yield: 27.8%) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75-7.70 (m, 1H), 4.68 (dd, J = 13.2, 2.0 Hz, 2H), 2.35-2.30 (m, 2H), 2.20-2.05 (m, 2H), 1.65-1.55 (m, 2H), 1.19 (s, 12H).

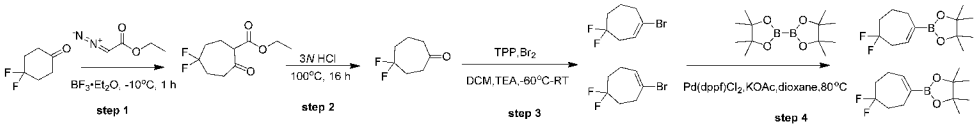
Intermediate 15 : Synthesis of 4,4,5,5-tetramethyl-2-(3,3a,4,6a-tetrahydro-1H-cyclopenta[c]furan-5-yl)-1,3,2-dioxaborolane



Step 1: To a solution of Triphenyl phosphite (737.88 mg, 2.378 mmol) in DCM (15 mL) stirred under nitrogen at -60 °C was added Br_2 (329.37 mg, 2.061 mmol). The reaction mixture was stirred at -60 °C for 30 minutes. Then added TEA (320.85 mg, 3.171 mmol) and stirred at -60 °C for 30 minutes. Then added tetrahydro-1*H*-cyclopenta[*c*]furan-5(3*H*)-one (200 mg, 1.585 mmol). The reaction mixture was stirred at the room temperature for 16 hrs. The reaction mixture was quenched with water (20 mL). The crude mixture was extracted with DCM (50 mL*3), and the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated in vacuo, then purified by Flash Chromatography (EtOAc/hexanes = 0-10%) to get the product 5-bromo-3,3a,4,6a-tetrahydro-1*H*-cyclopenta[*c*]furan (143 mg, 0.756 mmol, yield: 47.7%) as a pale yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.72 (dd, *J* = 4.3, 2.1 Hz, 1H), 3.89 – 3.53 (m, 4H), 3.39 – 3.28 (m, 1H), 3.10 – 2.84 (m, 2H), 2.48 – 2.26 (m, 1H).

Step 2: To a solution of 5-bromo-3,3a,4,6a-tetrahydro-1*H*-cyclopenta[*c*]furan (143 mg, 0.756 mmol) , 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (211.29 mg, 0.832 mmol) and KOAc (148.47 mg, 1.513 mmol) in dioxane (15 mL) was added Pd(dppf)Cl_2 (54.89 mg, 0.0756 mmol). The reaction mixture was stirred under nitrogen at 80 °C for 3 hrs. The mixture was concentrated under vacuum. Then purified by Flash Chromatography (EtOAc/hexanes = 0-3%) to get the product 4,4,5,5-tetramethyl-2-(3,3a,4,6a-tetrahydro-1*H*-cyclopenta[*c*]furan-5-yl)-1,3,2-dioxaborolane (37 mg, 0.157 mmol, yield: 20.7%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.29–6.27 (m, 1H), 3.86–3.72 (m, 2H), 3.75–3.67 (m, 1H), 3.54–3.41 (m, 2H), 2.70–2.66 (m, 1H), 2.34–2.30 (m, 1H), 2.06–2.00 (m, 1H), 1.26 (s, 12H).

Intermediate 16: Synthesis of 2-(4,4-difluorocyclohept-1-en-1-yl)-4,4,5,5- tetramethyl -1,3,2-dioxaborolane and 2-(5,5-difluorocyclohept-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Step 1: A solution of 4,4-difluorocyclohexan-1-one (1000 mg, 7.456 mmol), ethyl 2-diazo

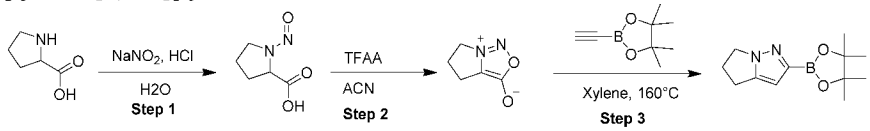
acetate (1106 mg, 9.693 mmol) and $BF_3{\cdot}Et_2O$ (1376 mg, 9.693 mmol) in DCM (20 mL) was stirred at -10 °C for 2 hrs. The mixture was concentrated and purified by Flash Chromatography (EtOAc/hexanes = 0-10%) to get the product ethyl 5,5-difluoro-2-oxocyclo heptane-1-carboxylate (500 mg, 1.930 mmol, yield: 25.9%) as oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.26 – 4.19 (m, 2H), 2.81 – 2.52 (m, 1H), 2.49 – 2.44 (m, 2.5H), 2.38 – 1.85 (m, 5.5H), 1.34 – 1.26 (m, 3H).

Step 2: ethyl 5,5-difluoro-2-oxocycloheptane-1-carboxylate (5.6 g, 25.4 mmol) in 3 M aqueous HCl (13.5 mL) was stirred at 100 °C for 16 hrs. The reaction mixture was added to water (50 mL) and extracted with EA (50 mL * 3), and the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated in vacuo, then purified by Flash Chromatography (EtOAc/hexanes = 0-10%) to get the product 4,4-difluorocycloheptan-1-one (2.3 g, 0.016 mmol, yield: 61.0%) as a pale colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.63 – 2.52 (m, 4H), 2.26 – 2.07 (m, 4H), 1.92 – 1.84 (m, 2H).

Step 3: To a solution of Triphenyl phosphite (1256.63 mg, 4.05 mmol) in DCM (15 mL) stirred under nitrogen at -60°C was added Br_2 (560.93 mg, 3.51 mmol). The reaction mixture was stirred at -60°C for 30 minutes. Then added TEA (546.43 mg, 5.4 mmol) and stirred at -60°C for 30 minutes. Then added 4,4-difluorocycloheptan-1-one (400 mg, 2.7 mmol). The reaction mixture was stirred at the room temperature for 16 hrs. The reaction mixture was quenched with water (20 mL). The crude mixture was extracted with DCM (50 mL * 3), and the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated in vacuo, then purified by Flash Chromatography (EtOAc/hexanes = 0-3%) to get the mixture of 1-bromo-4,4 -difluorocyclohept-1-ene and 1-bromo-5,5-difluorocyclohept-1-ene (320 mg, 1.516 mmol, yield: 56.2%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.27 – 5.95 (m, 1H), 2.90 – 2.55 (m, 2.5H), 2.24 – 1.62 (m, 5.5H).

Step 4: To a solution of the mixture of 1-bromo-4,4-difluorocyclohept-1-ene and 1-bromo-5,5-difluorocyclohept-1-ene (320 mg, 1.516 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (423.52 mg, 1.668 mmol) and KOAc (297.61 mg, 3.032 mmol) in dioxane (10 mL) was added $Pd(dppf)Cl_2$ (110.02 mg, 0.152 mmol). The reaction mixture was stirred under nitrogen at 80 °C for 10 hrs. The mixture was concentrated under vacuum. Then purified by Flash Chromatography (EtOAc/hexanes = 0-1%) to get the mixture of 2-(4,4-difluorocyclohept-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and 2-(5,5-difluorocyclohept-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (110 mg, 0.426 mmol, yield: 28.1%) as colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.84 – 6.37 (m, 1H), 2.30 – 2.25 (m, 4H), 1.97 – 1.85 (m, 4H), 1.31 – 1.22 (m, 12H).

Intermediate 19 : Synthesis of 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole



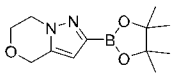
Step 1: To a solution of pyrrolidine-2-carboxylic acid (250 mg, 2.17 mmol), $NaNO_2$ (210 mg, 3.04 mmol) in H_2O (1 mL) was added con. HCl (0.5 mL) at 0°C. The mixture was stirred at 25°C for 6 hrs. The mixture was diluted with H_2O (10 mL), extracted with DCM (15 mL * 8). The combined organic was dried over Na_2SO_4, filtered, then concentrated to get the product nitrosoproline (140 mg, 0.87 mmol, 40.3% yield) as a white solid.

Step 2: To a solution of 1-nitrosopyrrolidine-2-carboxylic acid (1.6 g, 11.1 mmol) in MeCN (20 mL) was added TFAA (4.66g, 22.2 mmol) at 0°C. The mixture was stirred at 25°C for 2 hrs. Then K_2CO_3 (3.07 g, 22.2 mmol) was added, the mixture was further stirred at 25°C for 1 hr. The mixture was filtered and the filtrate was concentrated and purified by flash (MeOHDCM = 0~10%) to get the product 5,6-dihydro-4*H*-pyrrolo[1,2-*c*][1,2,3]oxadiazol-7-ium-3-olate (0.82 g, 5.9 mmol, 53.1% yield) as a yellow oil. **MS** (ESI) m/z = 253.1 $[M+H]^+$.

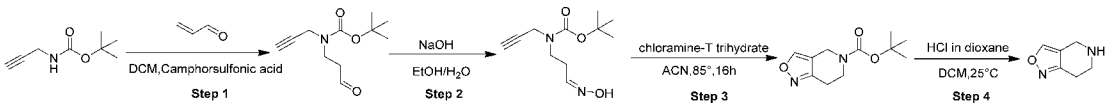
Step 3: A mixture of 5,6-dihydro-4*H*-pyrrolo[1,2-*c*] [1,2,3] oxadiazol-7-ium-3-olate (820 mg, 6.5 mmol), 2-ethynyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.98 g, 13.0 mmol) in Xylene (15 mL) was stirred at 160 °C for 20 hrs. The mixture was concentrated and purified by Prep-HPLC (Gemini-C18 150 * 21.2 mm, 5um: MeCN-H_2O (0.1%TFA): 5-40) to get the product 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole (180 mg, 0.61 mmol, 9.5% yield) as oil. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 6.21 (s, 1H), 4.07 – 4.03 (m, 2H), 2.82 –

2.77 (m, 2H), 2.57 – 2.52 (m, 2H), 1.25 (s, 12H).

The following compound was synthesized using the above method:

Intermediate 19B 	2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazine	**^{1}HNMR** (400 MHz, DMSO-d_6) δ (400 MHz, DMSO) δ 6.30 (s, 1H), 4.78 (s, 2H), 4.13 (t, J = 5.4 Hz, 2H), 4.05 - 4.03 (m, 2H), 1.26 (s, 12H).

Intermediate 20: Synthesis of 4,5,6,7-tetrahydroisoxazolo[4,3-c]pyridine hydrogen chloride



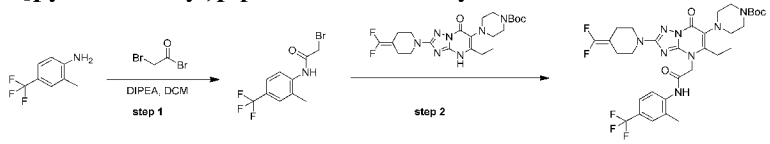
Step 1: Add prop-2-enal (3.2 g, 20.6 mmol) and camphorsulfonic acid (0.96 g, 4 mmol) to a cooled ice water bath solution of tert-butyl N-(prop-2-yn-1-yl)carbamate (11.5 g, 206 mmol) in DCM (60 mL), stirring the resulting mixture at 0 °C for 15 minutes, then stirring the resulting mixture for 4 hours at room temperature. The mixture was diluted with water (50 mL), extracted with DCM (50 mL * 3). The combined organic layers were washed with brine (100 mL) and dried over Na_2SO_4, then concentrated under vacuum, purified by Flash Chromatography (EtOAc/Hexanes = 0-10%) to give the product tert-butyl N-(3-oxopropyl)-N-(prop-2-yn-1-yl) carbamate (1.7 g, 8 mmol, yield: 38 %) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.81 (t, *J* = 1.4 Hz, 1H), 4.07 (d, *J* = 17.2 Hz, 2H), 3.64 (t, *J* = 6.6 Hz, 2H), 2.79 (t, *J* = 6.4 Hz, 2H), 2.23 (t, *J* = 2.4 Hz, 1H), 1.53 – 1.41 (m, 9H).

Step 2: Add hydroxylamine hydrochloride (615 mg, 8.85 mmol) to cooled ice water bath suspension of tert-butyl N-(3-oxopropyl)-N-(prop-2-yn-1-yl)carbamate (1.7 g, 8 mmol) in H_2O/EtOH (30 mL/10 mL), then a solution of NaOH (708 mg, 17.7 mmol) dissolved in EtOH /H_2O (5 mL/10 mL) was added to the mixture dropwise over 15 minutes. The resulting mixture was stirred for 3 hours at room temperature. Then concentrated in vacuo, the mixture was diluted with water (50 mL), extracted with MTBE (50 mL * 3). The combined organic layers were washed with brine (100 mL) and dried over Na_2SO_4, then concentrated under vacuum, purified by Flash Chromatography (EtOAc/Hexanes = 0-30%) to give the product tert-butyl N-[(3E) -3-(hydroxyimino)propyl]-N-(prop-2-yn-1-yl)carbamate (1.5 g, 6.6 mmol, yield: 82%) as a yellow oil. **MS** (ESI) m/z = 249.1 $[M+Na]^+$.

Step 3: To a solution of tert-butyl N-[(3Z)-3-(hydroxyimino)propyl]-N-(prop-2-yn-1-yl) carbamate (1500 mg, 6.63 mmol) in MeCN (15 mL) was added a suspension of chloramine-T trihydrate (1640 mg, 6.63 mmol). The reaction mixture was stirred at 85°C for 6 hrs. The mixture was diluted with water (30 mL), extracted with MTBE (30 mL * 3). The combined organic layers were washed with brine (30 mL) and dried over Na_2SO_4, then concentrated under vacuum and purified by Flash Chromatography (EtOAc/Hexanes = 0-50%) and to get the product tert-butyl 6,7-dihydroisoxazolo[4,3-c]pyridine-5(4H)-carboxylate (650 mg, 2.90 mmol, 43.8 % yield) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 4.53 (s, 2H), 3.70 (t, *J* = 5.6 Hz, 2H), 2.87 (t, *J* = 5.9 Hz, 2H), 1.49 (s, 9H).

Step 4: To a solution of tert-butyl 6,7-dihydroisoxazolo[4,3-c]pyridine-5(4H)-carboxylate (650 mg, 2.90 mmol) in DCM (3 mL) was added HCl in dioxane (1 mL, 4M). The reaction mixture was stirred at the room temperature for 2 hrs. Then concentrated in vacuo to get the crude product 4,5,6,7-tetrahydroisoxazolo[4,3-c]pyridine hydrogen chloride (300 mg, 2.41 mmol, yield: 83%) as a yellow solid. **MS** (ESI) m/z =125.1 $[M+H]^+$.

Intermediate 22: Synthesis of tert-butyl 4-(2-(4-(difluoromethylene)piperidin-1-yl) -5-ethyl-4-(2-((2-methyl-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-7-oxo-4,7-dihydro-[1, 2,4]triazolo[1,5-a]pyrimidin-6-yl)piperazine-1-carboxylate

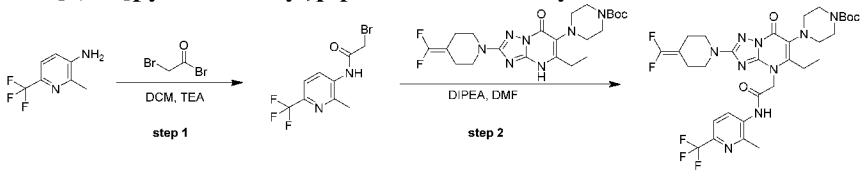


Step 1: To a solution of 2-methyl-4-(trifluoromethyl) aniline (175 mg, 1 mmol) in DCM (10 mL) were added DIPEA (387 mg, 3 mmol) and 2-bromoacetyl bromide (605 mg, 3 mmol) at 0°C.

The mixture was stirred at room temperature for 16 hrs. The mixture was diluted with water (20 mL), extracted with DCM (20 mL*3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, concentrated under vacuum and purified by Flash Chromatography (EtOAc/Hexanes = 0-13%) to give the product 2-bromo-N-(2-methyl-4-(trifluoromethyl)phenyl) acetamide (181 mg, 0.61 mmol, 61% yield) as white solid. **MS** (ESI) m/z = 295.9, 297.9 $[M+H]^+$.

Step 2: To a solution of tert-butyl 4-{2-[4-(difluoromethylidene)piperidin-1-yl]-5-ethyl-7-oxo-4H-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl}piperazine-1-carboxylate (80 mg, 0.1668 mmol) in DMF (10 mL) were added 2-bromo-N-[2-methyl-4-(trifluoromethyl)phenyl]acetamide (74.08 mg, 0.25 mmol) and DIPEA (64.67 mg, 0.5 mmol). The mixture was stirred at room temperature for 16 hrs. The mixture was diluted with water (20 mL), extracted with EtOAc (20 mL * 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4,concentrated under vacuum and purified by Flash Chromatography (EtOAc/Hexanes = 0-70%) to give the product tert-butyl 4-(2-(4-(difluoromethylene)piperidin-1-yl)-5-ethyl-4-(2-((2-methyl-4-(trifluoro methyl)phenyl)amio)-2-oxoethyl)-7-oxo-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)piperazi ne-1-carboxylate (100 mg, 0.14 mmol, 87% yield) as white solid. **MS** (ESI) m/z = 695.2 $[M+H]^+$.

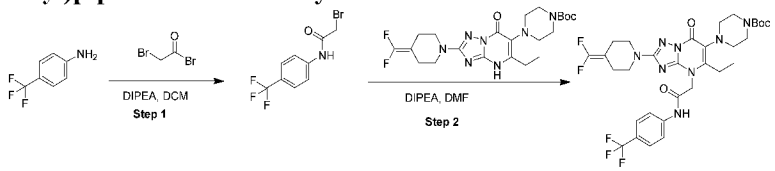
Intermediate 23: Synthesis of tert-butyl 4-(2-(4-(difluoromethylene)piperidin-1-yl) -5-ethyl-4-(2-((2-methyl-6-(trifluoromethyl)pyridin-3-yl)amino)-2-oxoethyl)-7-oxo-4,7-dihydr o-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)piperazine-1-carboxylate



Step 1: To a solution of 2-methyl-6-(trifluoromethyl)pyridin-3-amine (150 mg, 0.85 mmol) in DCM (10 mL) were added TEA (257 mg, 2.55 mmol) and 2-bromoacetyl bromide (515 mg, 2.55 mmol).The reaction mixture was stirred at room temperature for 5 hrs. The mixture was diluted with water (10 mL), extracted with DCM (10 mL * 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, concentrated under vacuum and purified by Flash Chromatography (EtOAc/hexanes = 0-25%) to give the product 2-bromo-N-[2-methyl-6-(trifluoromethyl)pyridin-3-yl] acetamide (200 mg, 0.67 mmol, 79% yield) as white solid. **MS** (ESI) m/z = 297.0, 298.9 $[M+H]^+$.

Step 2: To a solution of tert-butyl 4-{2-[4-(difluoromethylidene)piperidin-1-yl]-5-ethyl-7-oxo-4H-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl}piperazine-1-carboxylate(50 mg, 0.1 mmol) in DMF (5 mL) were added 2-bromo-N-[2-methyl-6-(trifluoromethyl)pyridin-3-yl]acetamide (46.48 mg, 0.15 mmol) and DIPEA (40.44 mg, 3 mmol). The mixture was stirred at room temperature for 16 hrs. The mixture was diluted with water (20 mL), extracted with EtOAc (20 mL * 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4,concentrated under vacuum and purified by Flash Chromatography (EtOAc-Hexanes = 0-70%) to give the product tert-butyl 4-(2-(4-(difluoromethylene)piperidin-1-yl)-5-ethyl-4-(2-((2-methyl-6- (trifluoro methyl)pyridin-3-yl)amino)-2-oxoethyl)-7-oxo-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)pi perazine-1-carboxylate (62 mg, 0.089 mmol, 85% yield) as a colorless oil. **MS** (ESI) m/z = 640.2 $[M+H-56]^+$.

Intermediate 24: Synthesis of tert-butyl 4-(2-(4-(difluoromethylene)piperidin-1-yl)-5-ethyl-7-oxo-4-(2-oxo-2-((4-(trifluoromethyl)phenyl)amino)ethyl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)piperazine-1-carboxylate

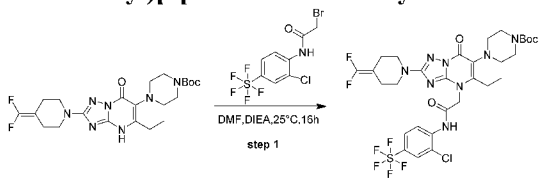


Step 1: To a solution of 4-(trifluoromethyl)aniline (322 mg,2 mmol) in DCM (20 mL) were added TEA (606 mg, 6 mmol) and 2-bromoacetyl bromide (1.21 g, 6 mmol).The reaction mixture was stirred at room temperature for 16 hrs. The mixture was diluted with water (20 mL), extracted with DCM (20 mL * 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, concentrated under vacuum and purified by Flash Chromatography (EtOAc/hexanes = 0-8%) to give the product 2-bromo-N-(4-(trifluoromethyl)phenyl) acetamide. (350 mg, 1.24mmol,

62% yield) as a yellow solid. **MS** (ESI) m/z = 281.9, 283.9 $[M+H]^+$.

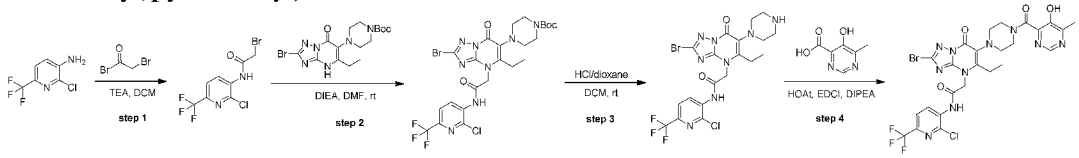
Step 2: To a solution of tert-butyl 4-{2-[4-(difluoromethylidene)piperidin-1-yl]-5-ethyl-7-oxo-4H-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl}piperazine-1-carboxylate (80 mg, 0.17 mmol) in DMF (5 mL) were added 2-bromo-N-[4-(trifluoromethyl)phenyl]acetamide (70 mg, 0.25 mmol) and DIPEA (65 mg, 0.5 mmol). The mixture was stirred at room temperature for 16 hrs. The mixture was diluted with water (20 mL), extracted with EtOAc (20 mL * 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, concentrated under vacuum and purified by Flash Chromatography (EtOAc-Hexanes = 0-50%) to give the tert-butyl 4-(2-(4-(difluoromethylene)piperidin-1-yl)-5-ethyl-7-oxo-4-(2-oxo-2-((4-(trifluoromethyl) phenyl) amino) ethyl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)piperazine-1-carboxylate (110 mg, 0.16 mmol, 96% yield) as yellow solid. **MS** (ESI) m/z = 681.3 $[M+H]^+$.

Intermediate 26: Synthesis of tert-butyl 4-(4-(2-((2-chloro-4- (pentafluoro-λ⁶-sulfaneyl) phenyl)amino)-2-oxoethyl)-2-(4-(difluoromethylene)piperidin-1-yl)-5-ethyl-7-oxo-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)piperazine-1-carboxylate



Step 1: To a solution of tert-butyl 4-{2-[4-(difluoromethylidene)piperidin-1-yl]-5-ethyl-7-oxo-4H-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl}piperazine-1-carboxylate (100 mg, 0.21 mmol) in DMF (10 mL) were added 2-bromo-N-[2-chloro-4-(pentafluoro-λ⁶-sulfanyl)phenyl]acetamide (117 mg, 0.31 mmol) and DIPEA (81 mg, 0.63 mmol). The mixture was stirred at room temperature for 16 hrs. The mixture was diluted with water (20 mL), extracted with EtOAc (20 mL * 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4,concentrated under vacuum and purified by Flash Chromatography (EtOAc/Hexanes = 0-70%) to give the product tert-butyl 4-(4-(2-((2-chloro-4-(pentafluoro-λ⁶-sulfaneyl)phenyl)amino) -2-oxoethyl)-2-(4-(difluoromethylene)piperidin-1-yl)-5-ethyl-7-oxo-4,7-dihydro-[1,2,4]triazolo[1, 5-a]pyrimidin-6-yl)piperazine-1-carboxylate (80 mg, 0.10 mmol, 49 % yield) as solid. **MS** (ESI) m/z = 716.8 $[M+H-56]^+$.

Intermediate 27: Synthesis of 2-(2-bromo-5-ethyl-6-(4-(5-hydroxy-6- methylpyrimidine -4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-6-(trifluoromethyl)pyridin-3-yl)acetamide



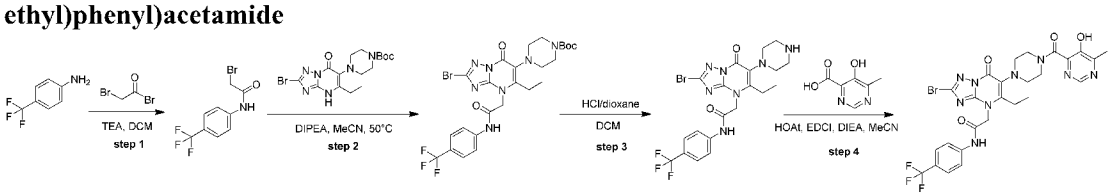
Step 1: To a solution of 2-chloro-6-(trifluoromethyl)pyridin-3-amine (500 mg, 2.54 mmol) and TEA (772 mg) in DCM (5 mL) was added 2-bromoacetyl bromide (1.54 g, 7.63 mmol) at 0°C, the mixture was stirred at room temperature for 16 hrs. The mixture was purified by flash (EtOAc: hexanes = 0~30%) to get 2-bromo-N-[2-chloro-6-(trifluoromethyl)pyridin-3-yl]acetamide (600 mg, 1.89 mmol, yield: 74.4%) as a yellow solid. **MS** (ESI) m/z = 318.9 $[M+H]^+$.

Step 2: A mixture of tert-butyl 4-{2-bromo-5-ethyl-7-oxo-4H-[1,2,4]triazolo[1,5-a] pyrimidin-6-yl}piperazine-1-carboxylate (100 mg, 0.23 mmol), 2-bromo-N-[2-chloro-6- (trifluoro methyl)pyridin-3-yl]acetamide (89 mg, 0.28 mmol) and DIEA (90 mg, 0.7 mmol) in DMF (3 mL) was stirred at room temperature for 6 hrs. The mixture was purified by flash (MeOH: DCM = 0~10%) to get the product tert-butyl 4-[2-bromo-4-({[2-chloro-6-(trifluoromethyl) pyridin-3-yl] carbamoyl}methyl)-5-ethyl-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl]piperazine-1-carboxylate (100 mg, 0.15 mmol, yield: 65.4%) as a grey solid. **MS** (ESI) m/z = 609.1 $[M+H-56]^+$.

Step 3: To a solution of tert-butyl 4-(2-bromo-4-(2-((2-chloro-6-(trifluoromethyl)pyridin-3-yl) amino)-2-oxoethyl)-5-ethyl-7-oxo-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)piperazine-1-carboxylate (100 mg, 0.15 mmol) in DCM (2 mL) was added HCl/dioxane (1 mL, 4M), the mixture was stirred at room temperature for 1 hr. The mixture was concentrated to get the product 2-(2-bromo-5-ethyl-7-oxo-6-(piperazin-1-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-6-(trifluoromethyl)pyridin-3-yl)acetamide (90 mg, 0.16 mmol, yield: 106.3%) as a white solid. **MS** (ESI) m/z = 565.1 $[M+H]^+$.

Step 4: A mixture of 5-hydroxy-6-methylpyrimidine-4-carboxylic acid (49 mg, 0.32 mmol), HOAt (54 mg, 0.39 mmol) and EDCI (76 mg, 0.39 mmol) in MeCN (6 mL) was stirred at room temperature for 1 hr under nitrogen atmosphere, then 2-(2-bromo-5-ethyl-7-oxo-6- (piperazin-1-yl) -[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-6-(trifluoromethyl)pyridin-3-yl)acetamide (90 mg, 0.16 mmol) and DIPEA (103 mg, 0.79 mmol) in MeCN (3 mL) was added, the mixture was stirred at room temperature for 1 hr. The mixture was purified by flash (MeOH:DCM = 0~10%) to get the product 2-(2-bromo-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4- carbonyl) piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-6-(trifluoromethyl)p yridin-3-yl)acetamide (70 mg, 0.1 mmol, yield: 62.5%) as a yellow solid. **MS** (ESI) m/z = 701.0 $[M+H]^+$.

Intermediate 28: Synthesis of 2-(2-bromo-5-ethyl-6-(4-(5-hydroxy-6- methylpyrimidine -4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(4-(trifluorom ethyl)phenyl)acetamide



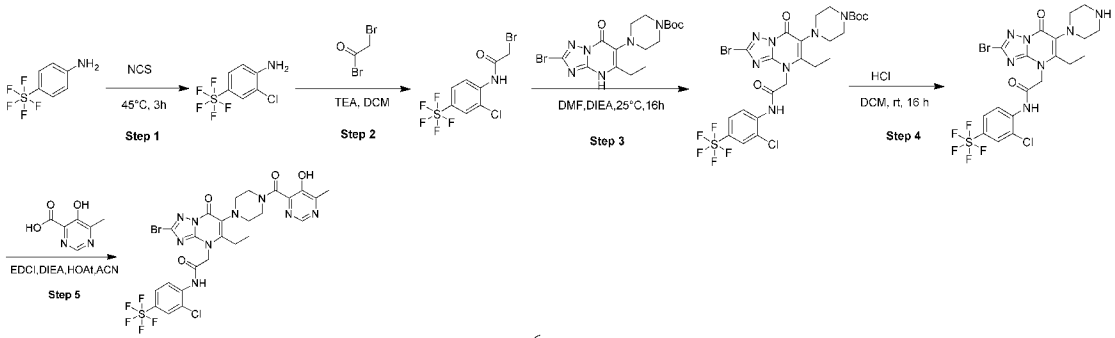
Step 1: To a solution of 4-(trifluoromethyl)aniline (1 g, 6.2 mmol) in DCM (20 mL) were added TEA (1.87 g, 18.6 mmol) and 2-bromoacetyl bromide (3.75 g, 18.6 mmol) at 0°C. The reaction mixture was stirred at room temperature for 16 hrs. The mixture was diluted with water (20 mL), extracted with DCM (20 mL * 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, concentrated under vacuum and purified by Flash Chromatography (EtOAc/hexanes = 0-8%) to give the product 2-bromo-N-(4-(trifluoromethyl) phenyl) acetamide (1.4 g, 5 mmol, 80% yield) as a yellow solid. **MS** (ESI) m/z = 282.0, 284.0 $[M+H]^+$.

Step 2: To a solution of tert-butyl 4-{2-bromo-5-ethyl-7-oxo-4H-[1,2,4]triazolo[1,5-a] pyrimidin-6-yl}piperazine-1-carboxylate (1.5 g, 3.5 mmol) in MeCN (20 mL) were added 2-bromo-N-[4-(trifluoromethyl)phenyl]acetamide (1.48 g, 5.2 mmol) and DIPEA (1.36 g, 10.5 mmol). The mixture was stirred at 50°C for 16 hrs. The mixture was concentrated under vacuum and purified by Flash Chromatography (EtOAc/Hexanes = 0-50%) to give the product tert-butyl 4-(2-bromo-5-ethyl-7-oxo-4-(2-oxo-2-((4-(trifluoromethyl)phenyl)amino)ethyl)-4,7-dihydro-[1,2, 4]triazolo[1,5-a]pyrimidin-6-yl)piperazine-1-carboxylate (335 mg, 0.5 mmol, 14% yield) as a white solid. **MS** (ESI) m/z = 572.0, 574.0 $[M+H-56]^+$.

Step 3: To a solution of tert-butyl 4-[2-bromo-5-ethyl-7-oxo-4-({[4-(trifluoromethyl) phenyl] carbamoyl}methyl)-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl]piperazine-1-carboxylate (335 mg, 0.53 mmol) in DCM (5 mL) was added HCl in dioxane (5 mL，4M). The mixture was stirred at room temperature for 2 hrs. The mixture was concentrated under vacuum to give the crude product 2-(2-bromo-5-ethyl-7-oxo-6-(piperazin-1-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(4-(trifluoromethyl)phenyl)acetamide (300 mg, 0.56 mmol, 100% yield) as white solid. **MS** (ESI) m/z = 528.0. 530.0 $[M+H]^+$.

Step 4: The mixture of 5-hydroxy-6-methylpyrimidine-4-carboxylic acid (164 mg, 1.06 mmol), HOAt (181 mg, 1.32 mmol) and EDCI (254 mg, 1.3 mmol) in MeCN (25 mL) was stirred at room temperature for 1 hr under argon, then 2-[2-bromo-5-ethyl-7-oxo-6-(piperazin-1-yl)-[1,2,4] triazolo [1,5-a]pyrimidin-4-yl]-N-[4-(trifluoromethyl)phenyl]acetamide (300 mg, 0.53 mmol) and DIEA (412 mg, 3.18 mmol) in MeCN (5 mL) was added, the mixture was stirred at room temperature for 1 hr. The mixture was diluted with water (30 mL), extracted with EtOAc (30 mL * 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, concentrated under vacuum and purified by Flash Chromatography (MeOH:DCM = 0-5%) to give 2-(2-bromo-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(4-(trifluoromethyl)phenyl)acetamide (152 mg, 0.228 mmol, 43% yield) as a white solid. **MS** (ESI) m/z = 664.0, 665.9 $[M+H]^+$

Intermediate 29: Synthesis of tert-butyl 4-(2-bromo-4-(2-((2-chloro-4-(pentafluoro-λ^6-sulfaneyl)phenyl)amino)-2-oxoethyl)-5-ethyl-7-oxo-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidi n-6-yl)piperazine-1-carboxylate



Step 1: To a solution of 4-(pentafluoro-λ^6-sulfanyl)aniline (1700 mg, 7.75 mmol) in MeCN (20mL) were added NCS (1035 mg, 7.75 mmol) , the mixture was stirred at 45°C for 16 hrs. The mixture was diluted with water (20 mL), extracted with DCM (20 mL * 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, concentrated under vacuum and purified by Flash Chromatography (EtOAc/Hexanes = 0-20%) to give the product 2-chloro-4-(pentafluoro-λ^6-sulfanyl)aniline (1500 mg, 5.91 mmol, 76 % yield) as a yellow oil. **MS** (ESI) m/z = 253.9 $[M+H]^+$.

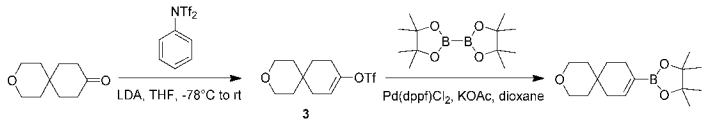
Step 2: To a solution of 2-chloro-4-(pentafluoro-λ^6-sulfanyl)aniline (1500 mg, 5.91 mmol) in DCM (15 mL) were added 2-bromoacetyl bromide (3581 mg, 17.74 mmol) and TEA (1795 mg, 17.74 mmol). The mixture was stirred at room temperature for 1 hr. The mixture was diluted with water (20 mL), extracted with DCM (20 mL * 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, concentrated under vacuum and purified by Flash Chromatography (EtOAc/Hexanes = 0-30%) to give the product 2-bromo-N-[2-chloro-4-(pentafluoro-λ^6-sulfanyl)phenyl]acetamide (900 mg, 2.40 mmol, 40.6 % yield) as a white solid. **MS** (ESI) m/z = 375.7$[M+H]^+$.

Step 3: To a solution of tert-butyl 4-{2-[4-(difluoromethylidene)piperidin-1-yl]-5-ethyl-7-oxo-4H-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl}piperazine-1-carboxylate (450 mg, 1.053 mmol) in DMF (10 mL) were added 2-bromo-N-[2-chloro-4-(pentafluoro-λ^6-sulfanyl)phenyl]acetamide (512 mg, 1.37 mmol) and DIPEA (408 mg, 3.16 mmol). The mixture was stirred at room temperature for 16 hrs. The mixture was diluted with water (20 mL), extracted with EtOAc (20 mL * 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, concentrated under vacuum and purified by Flash Chromatography (EtOAc-Hexanes = 0-70%) to give the product tert-butyl 4-(2-bromo-4-(2-((2-chloro-4-(pentafluoro-λ^6-sulfaneyl) phenyl)amino) -2-oxoethyl)-5-ethyl-7-oxo-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)piperazine-1-carboxylate (280 mg, 0.38 mmol, 36 % yield) as a yellow solid. **MS** (ESI) m/z = 663.7 $[M+H]^+$

Step 4: To a solution of tert-butyl 4-(2-bromo-4-(2-((2-chloro-4-(pentafluoro-λ^6-sulfaneyl) phenyl)amino)-2-oxoethyl)-5-ethyl-7-oxo-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)piperazine-1-carboxylate (100 mg, 0.138 mmol) in DCM (5 mL) was added HCl in dioxane (3 mL, 4M). The mixture was stirred at room temperature for 2 hrs. The mixture was concentrated under vacuum to give the crude product 2-[2-bromo-5-ethyl-7-oxo-6-(piperazin-1-yl)-[1,2,4]triazolo [1,5-a]pyrimidin-4-yl]-N-[2-chloro-4-(pentafluoro-λ^6-sulfanyl)phenyl]acetamide (80 mg, 0.13 mmol, 93% yield) as a white solid. **MS** (ESI) m/z = 619.8 $[M+H]^+$

Step 5: The mixture of 5-hydroxy-6-methylpyrimidine-4-carboxylic acid (60 mg, 0.387 mmol), HOAt (43 mg, 0.32 mmol) and EDCI (62 mg, 0.32 mmol) in MeCN (15 mL) was stirred at room temperature for 1 hr under argon, then 2-(2-bromo-5-ethyl-7-oxo-6-(piperazin-1-yl) -[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(pentafluoro-λ^6-sulfaneyl)phenyl)acetamide (80 mg, 0.13 mmol) and DIEA (83 mg, 0.64 mmol) in MeCN (5 mL) was added, the mixture was stirred at room temperature for 1 hr. The mixture was diluted with water (20 mL), extracted with EtOAc (20 mL * 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, concentrated under vacuum and purified by Flash Chromatography (MeOH/DCM = 0-5%) to give the product 2-(2-bromo-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl) piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(pentafluoro-λ^6-sulfaneyl)phenyl)acetamide (40 mg, 0.052 mmol, 40.7 % yield) as yellow solid. **MS** (ESI) m/z = 755.7 $[M+H]^+$.

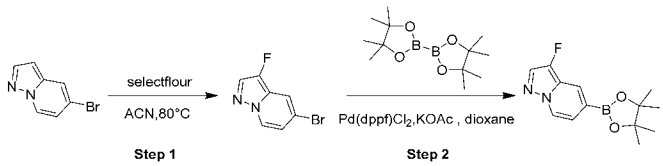
Intermediate 30: Synthesis of 4,4,5,5-tetramethyl-2-(3-oxaspiro[5.5]undec-8-en-9-yl)-1,3,2-dioxaborolane



Step 1: To a solution of 3-oxaspiro[5.5]undecan-9-one (250 mg, 1.49 mmol) in THF (8 mL) was added LDA (1.2 mL, 2.40 mmol, 2 M in THF) at -78°C under N_2. The mixture was stirred at this temperature for 0.5 hr. Then 1,1,1-trifluoro-*N*-phenyl-*N*-((trifluoromethyl)sulfonyl) methanesulfonamide (637 mg, 1.78 mmol) was added. The mixture was stirred at 25°C for 16 hrs. The reaction was quenched by Sat. NH_4Cl and diluted with ethyl acetate (40 mL). Then it was washed by water (20 mL), brine (20 mL). The organic layer was dried over Na_2SO_4, concentrated and purified by flash (ethyl acetate:Hexane = 0~5%) to get product 3-oxaspiro[5.5]undec-8-en-9-yl trifluoromethanesulfonate (310 mg, 1.03 mmol, 69.5% yield) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.69 (t, *J* = 4.1 Hz, 1H), 3.77 – 3.62 (m, 4H), 2.38 - 2.31 (m, 2H), 2.14 (dd, *J* = 6.2, 2.6 Hz, 2H), 1.71 (t, *J* = 6.5 Hz, 2H), 1.54 - 1.46 (m, 4H).

Step 2: A mixture of 3-oxaspiro[5.5]undec-8-en-9-yl trifluoromethanesulfonate (310 mg, 1.03 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaboro lane (315 mg, 1.24 mmol), $Pd(dppf)Cl_2$ (75 mg, 0.10 mmol) and Potassium acetate (203 mg, 2.06 mmol) in dioxane (8 mL) was stirred at 80 °C overnight under N_2. The mixture was concentrated and purified by flash (ethyl acetate:Hexanes = 0~6%) to get the product 4,4,5,5-tetramethyl-2-(3-oxaspiro[5.5]undec-8-en- 9-yl)-1,3,2-dioxaborolane (200 mg, 0.72 mmol, 69.6% yield) as a colorless oil. **^{1}HNMR** (400 MHz, $CDCl_3$) δ 6.49 – 6.44 (m, 1H), 3.71 – 3.60 (m, 4H), 2.15 - 2.09 (m, 2H), 2.04 - 2.01 (m, 2H), 1.48 (t, *J* = 6.4 Hz, 2H), 1.44 – 1.39 (m, 4H), 1.24 (s, 12H).

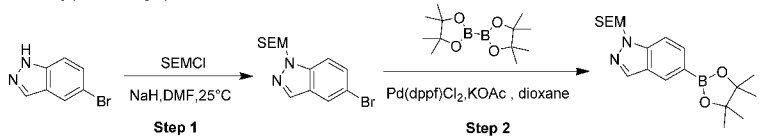
Intermediate 31: Synthesis of 3-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) pyrazolo[1,5-a]pyridine



Step 1: To a solution of 5-bromopyrazolo[1,5-a]pyridine (500 mg, 2.537 mmol) in MeCN (10 mL) was added selectfluor (988 mg, 2.7191 mmol). The reaction mixture was stirred at 80°C for 16 hrs. The mixture was concentrated under vacuum. Then purified by Flash Chromatography (EtOAc/hexanes = 0-5%) to get the product 5-bromo-3-fluoropyrazolo[1,5-a]pyridine (220 mg, 1.023 mmol, yield: 40.3%) as a yellow solid. **MS** (ESI) m/z = 214.9 $[M+H]^+$.

Step 2: To a solution of 5-bromo-3-fluoropyrazolo[1,5-a]pyridine (100 mg, 0.465 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (130 mg, 0.5116 mmol) and KOAc (91 mg, 0.930 mmol) in dioxane (3 mL) was added $Pd(dppf)Cl_2$ (34 mg, 0.046 mmol). The reaction mixture was stirred under nitrogen at 80°C for 16 hrs. The mixture was concentrated under vacuum to get 3-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) pyrazolo[1,5-a]pyridine (50 mg, 0.19 mmol, yield: 41%) as brown oil. **MS** (ESI) m/z = 263.1 $[M+H]^+$.

Intermediate 32 : Synthesis of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole



Step 1: To a solution of 5-bromo-1H-indazole (1000 mg, 5.075 mmol) in DMF (10 mL) was added NaH (304 mg, 7.613 mmol). The reaction mixture was stirred at 0°C for 30 min. Then SEMCl (1269 mg, 7.613 mmol) was added, the reaction mixture was stirred at 25°C for 16 hrs. The mixture was concentrated under vacuum. Then purified by Flash Chromatography (EtOAc/ hexanes = 0-5%) to get the product 5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole (1500 mg, 4.573 mmol, yield: 90.1%) as yellow solid. **MS** (ESI) m/z = 327.0 $[M+H]^+$.

Step 2: To a solution of 5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole (500 mg, 1.523 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (425 mg, 1.675 mmol) and KOAc (299 mg, 3.046 mmol) in dioxane (3 mL) was

added $Pd(dppf)Cl_2$ (110 mg, 0.152 mmol). The reaction mixture was stirred under nitrogen at 80 °C for 16 hrs under N_2. The mixture was concentrated under vacuum and purified by Flash Chromatography (EtOAc/hexanes = 0-5%) to get 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) -1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole (250 mg, 0.66 mmol, yield: 43.7%) as a colorless oil. **MS** (ESI) m/z = 375.1 $[M+H]^+$.

Intermediate 33: Synthesis of 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) pyrazolo[1,5-a]pyridine

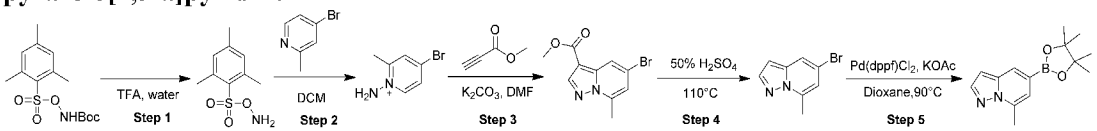


Step 1: To a solution of 4-bromo-2-methylpyridine (2 g, 11.6 mmol) in THF (20 mL) was added LDA (11.5 mL, 23.2 mmol) at -78°C under N_2, the mixture was stirred at this temperature for 0.5 hr, then N-methoxy-N-methylacetamide (1.2 g, 11.6 mmol) was added. The mixture was stirred at 25°C for 16 hrs. The reaction was quenched by Sat. NH_4Cl, diluted with EtOAc (50 mL), washed by water (20 mL), brine (20 mL), dried over Na_2SO_4, concentrated and purified by flash (EtOAc:Hexane = 0~10%) to get product 1-(4-bromopyridin-2-yl)propan-2-one (800 mg, 3.74 mmol, yield: 32.2%) as yellow oil. **MS** (ESI) m/z = 214.0, 216.0 $[M+H]^+$.

Step 2: To a solution of Ethyl O-mesitylsulfonylacetohydroxamate (2 g, 7 mmol) in dioxane (3 mL) was added $HClO_4$ (0.8 mL) at 0°C, the mixture was stirred at 25°C for 0.5 hr, ice water was added to the mixture then filtered. The filter cake collected was dissolved in DCM (3 mL), 1-(4-bromopyridin-2-yl)propan-2-one (800 mg, 3.74 mmol) was added, the mixture was stirred at 25°C for 1 hr. The mixture was concentrated in *vacuo*, dissolved in DMF (3 mL), K_2CO_3 (1.55 g, 11.2 mmol) was added to the mixture and the mixture was stirred at 25°C for 4 hrs. The reaction was diluted with water, extracted with EtOAc. The combined organic layers were washed by water (20 mL), brine (20 mL), dried over Na_2SO_4, concentrated and purified by flash (EtOAc:Hexane = 0~10%) to get product 5-bromo-2-methylpyrazolo[1,5-a]pyridine (110 mg, 0.52 mmol, yield: 13.9%) as a yellow oil. **MS** (ESI) m/z = 213.1 $[M+H]^+$.

Step 3: A mixture of 5-bromo-2-methylpyrazolo[1,5-a]pyridine (110 mg, 0.52 mmol) , 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (147 mg, 0.58 mmol), $Pd(dppf)Cl_2$ (37 mg, 0.052 mmol) and KOAc (154 mg, 1.57 mmol) in dioxane(5 mL) was stirred at 90 °C for 16 hrs under Ar atmosphere. The mixture was concentrated and the residue was purified by combiflash (EtOAc: Hexanes = 0~10%) to get the product 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine (50 mg, 0.19 mmol, yield: 37.2%) as a colorless oil. **MS** (ESI) m/z = 259.3 $[M+H]^+$.

Intermediate 34: Synthesis of 7-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) pyrazolo[1,5-a]pyridine



Step 1: To a solvent of TFA (10 mL) was added tert-butyl N-{[(2,4,6-trimethylbenzene) sulfonyl] oxy} carbamate (2 g, 6.3 mmol) at 0°C. The mixture was stirred at this temp for 2 hrs. The mixture was added ice water at 0°C, then filtered. The filter cake was concentrated to get the product amino 2,4,6-trimethylbenzenesulfonate (1.3 g, 4.8 mmol, 76.2% yield) as white solid. **MS** (ESI) m/z = 216.1 $[M+H]^+$.

Step 2: A mixture of amino 2,4,6-trimethylbenzenesulfonate (1.3 g, 6.0 mmol), 4-bromo-2-methylpyridine (0.83 g, 4.8 mmol) in DCM (20 mL) was stirred at 25°C for 16 hrs. The mixture was concentrated and triturated by chloroform, filtered. The filtrate was added Et_2O, filtered. The filter cake was concentrated to get the product 1-amino-4-bromo-2-methylpyridine -1-ium (1.2 g, 3.8 mmol, 64.4% yield) as white solid. **MS** (ESI) m/z = 187.0 $[M]^+$.

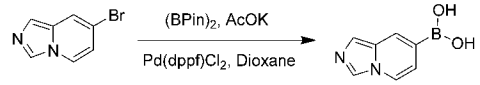
Step 3: A mixture of 1-amino-4-bromo-2-methylpyridin-1-ium (1 g, 5.3 mmol), methyl prop-2-ynoate (0.45 g, 5.3 mmol), K_2CO_3 (1.47 g, 10.6 mmol) in DMF (15 mL) was stirred at 25°C for 16 hrs. The mixture was diluted with EtOAc (100 mL), washed by water (30 mL * 2), brine (30 mL), dried over Na_2SO_4, concentrated and purified by flash (DCM: Hexanes = 0~40%) to get the product methyl 5-bromo-7-methylpyrazolo[1,5-a]pyridine-3-carboxylate (0.29 g, 1.1

mmol, 18.8% yield) as white solid. **MS** (ESI) m/z = 269.0 $[M+H]^+$.

Step 4: A mixture of methyl 5-bromo-7-methylpyrazolo[1,5-a]pyridine-3-carboxylate (290 mg, 1.08 mmol) in 50% H_2SO_4 (8 mL) was stirred at 110°C for 20 hrs. The mixture was neutralized by Sat. NaOH, then extracted with EtOAc (50 mL * 2). The combined organic layer was washed by water (30 mL * 2), brine (20 mL), dried over Na_2SO_4. concentrated, and purified by flash (DCM: Hexanes = 0~30%) to get the product 5-bromo-7-methylpyrazolo[1,5-a]pyridine (190 mg, 0.85 mmol, 79.3% yield) as colorless oil. **MS** (ESI) m/z = 211.0; 213.0 $[M+H]^+$.

Step 5: A mixture of 5-bromo-7-methylpyrazolo[1,5-a]pyridine (190 mg, 0.9 mmol) , 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (251 mg, 1.0 mmol), $Pd(dppf)Cl_2$ (65 mg, 0.09 mmol) and KOAc (177 mg, 1.8 mmol) in dioxane (6 mL) was stirred at 90 °C for 6 hrs. The mixture was concentrated to get the product 7-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) pyrazolo[1,5-a]pyridine (190 mg, crude) as black oil. **MS** (ESI) m/z = 259.0 $[M+H]^+$.

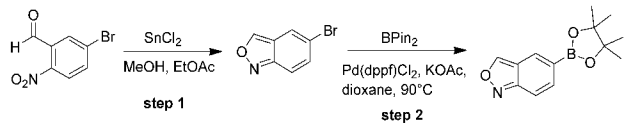
Intermediate 35: Synthesis of imidazo[1,5-a]pyridin-7-ylboronic acid



Step 1

Step 1: A mixture of 7-bromoimidazo[1,5-a]pyridine (100 mg, 0.51 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (142 mg, 0.56 mmol), $Pd(dppf)Cl_2$ (37 mg, 0.051 mmol) and KOAc (100 mg, 1.01 mmol) in dioxane (6 mL) was stirred at 80°C for 16 hrs under N_2. The mixture was filtered, then concentrated and purified by Prep-HPLC (Gemini-C18 150 * 21.2 mm, 5um:ACN--H_2O (0.1% FA): 0-10) to get the product imidazo[1,5-a]pyridin-7-ylboronic acid (70 mg, 0.039 mmol, 76.6% yield) as brown solid. **MS** (ESI) m/z = 163.1 $[M+H]^+$.

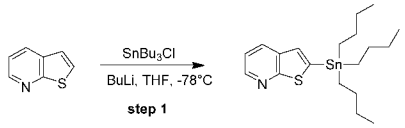
Intermediate 35: Synthesis of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[c] isoxazole



Step 1: To a solution of 5-bromo-2-nitrobenzaldehyde (690 mg, 3 mmol) in MeOH-EtOAc (1:1, 20 mL) was added $SnCl_2 \cdot 2H_2O$ (2.03 g, 9 mmol). The mixture was stirred at room temperature for 24 hrs. The reaction was quenched by saturated $NaHCO_3$ (20 mL) and filtered. The aqueous phase was extracted with EA (20 mL * 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, concentrated under vacuum, purified by Flash Chromatography (PE/EtOAc = 0-5%) to give the product 5-bromobenzo[c]isoxazole (517 mg, 2.6 mmol, 87% yeild) as a white solid. ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 9.11 (d, J = 0.8 Hz, 1H), 7.78 (s, 1H), 7.55 (d, J = 9.4 Hz, 1H), 7.36 (dd, J = 9.4, 1.6 Hz, 1H).

Step 2: The mixture of 5-bromobenzo[c]isoxazole (417 mg, 2.1 mmol), $(BPin)_2$ (641.73 mg, 2.52 mmol), KOAc (620.02 mg, 6.3 mmol) and $Pd(dppf)Cl_2$ (154.09 mg. 0.21 mmol) in dioxane (20 mL) was stirred at 90°C for 1 hr under N_2 atmosphere. The mixture was concentrated under vacuum and purified by Flash Chromatography (EtOAc-hexanes = 0-5%) to give the product 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[c]isoxazole (110 mg, 0.44 mmol, 21% yield) as a yellow solid. **MS** (ESI) m/z = 246.1 $[M+H]^+$.

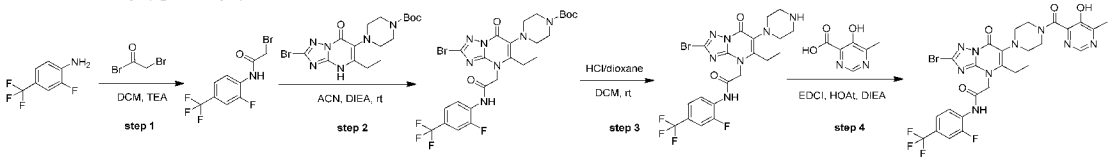
Intermediate 36: Synthesis of 2-(tributylstannyl)thieno[2,3-b]pyridine



Step 1: To a cold (-78°C) solution of thieno[2,3-b]pyridine (135 mg, 1 mmol) in anhydrous THF (20 mL) was added n-butyllithium (0.4 mL, 1.1 mmol) dropwise. The reaction mixture was stirred for 60 minutes at -78°C under N_2. A solution of Bu_3SnCl (357.5 mg, 1.1 mmol) in anhydrous THF (5 mL) was added and the reaction mixture was stirred for 30 minutes at -78°C. The solution was allowed to warm to room temperature over a period of 2 hours. The mixture was quenched with NH_4Cl solution (20 mL), extracted with EA (20 mL * 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, concentrated under vacuum,

purified by Flash Chromatography (EtOAc-hexanes = 0-3%) to give the product 2-(tributylstannyl) thieno[2,3-b]pyridine (275 mg, 0.64 mmol, 64% yeild) as colorless oil. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.46 (dd, J = 4.5, 1.4 Hz, 1H), 8.21 (dd, J = 8.0, 1.5 Hz, 1H), 7.47 (s, 1H), 7.34 (dd, J = 8.0, 4.5 Hz, 1H), 1.52 (dt, J = 8.1, 7.1 Hz, 6H), 1.28 (dd, J = 14.7, 7.3 Hz, 6H), 1.17 – 1.09 (m, 6H), 0.83 (dd, J = 9.3, 5.3 Hz, 9H). **MS** (ESI) m/z = 426.1 $[M+H]^+$.

Intermediate 37: Synthesis of 2-(2-bromo-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide



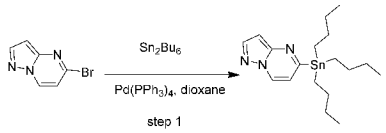
Step 1: A mixture of 2-fluoro-4-(trifluoromethyl)aniline (500 mg, 2.8 mmol) and TEA (850 mg, 8.4 mmol) in DCM (5 mL) was added 2-bromoacetyl bromide (1.7 g, 8.4 mmol) dropwise at 0 °C. The mixture was warmed up to room temperature and stirred at this temperature for 16 hrs. The mixture was concentrated and purified by flash (EtOAc: Hexanes = 0~10%) to get the product 2-bromo-N-[2-fluoro-4-(trifluoromethyl)phenyl]acetamide (600 mg, 2 mmol, yield: 71.4%) as a yellow solid. **MS** (ESI) m/z = 300.0 $[M+H]^+$.

Step 2: A mixture of 2-bromo-N-[2-fluoro-4-(trifluoromethyl)phenyl]acetamide (300 mg, 1 mmol), tert-butyl 4-(2-bromo-5-ethyl-7-oxo-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl) piperazine-1-carboxylate (428 mg, 1 mmol), DIPEA (388 mg, 3 mmol) in ACN (5 mL) was stirred at 25°C for 16 hrs. The mixture was concentrated and purified by combi-flash (MeOH : DCM = 0~10%) to get the tert-butyl 4-(2-bromo-5-ethyl-4-(2-((2-fluoro-4-(trifluoromethyl)phenyl) amino) -2-oxoethyl)-7-oxo-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)piperazine-1-carboxylate (320 mg, 0.49 mmol, yield: 49.4%) as a pale yellow solid. **MS** (ESI) m/z = 592.1 $[M+H-56]^+$.

Step 3: To a solution of tert-butyl 4-(2-bromo-5-ethyl-4-(2-((2-fluoro-4-(trifluoromethyl) phenyl)amino)-2-oxoethyl)-7-oxo-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)piperazine-1-carboxylate (320 mg, 0.49 mmol) in DCM (3 mL) was added HCl/Dioxane (1 mL, 4M), then stir the mixture at 25°C for 1 hr. The mixture was concentrated to get the crude product 2-[2-bromo-5-ethyl-7-oxo-6-(piperazin-1-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4-yl]-N-[2-fluoro-4-(trifluoromethyl)phenyl]acetamide (250 mg, 0.46 mmol) as a white solid. **MS** (ESI) m/z = 546.2 $[M+H]^+$.

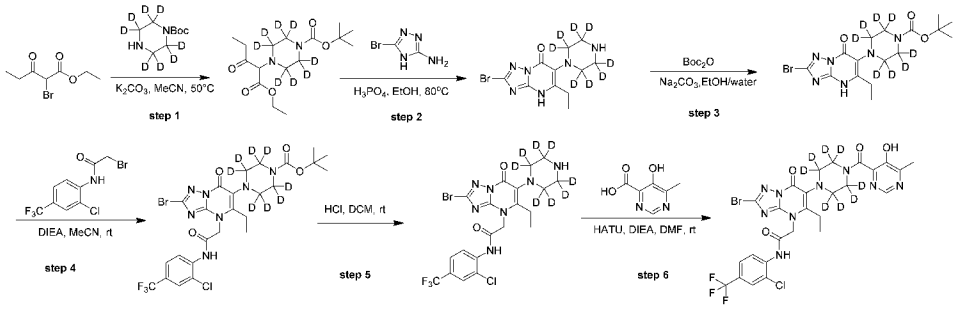
Step 4: The mixture of 5-hydroxy-6-methylpyrimidine-4-carboxylic acid (141 mg, 0.91 mmol), HOAt (156 mg, 1.14 mmol) and EDCI (219 mg, 1.14 mmol) was stirred in ACN (20 mL) at 25°C for 1h under N_2, then 2-[2-bromo-5-ethyl-7-oxo-6-(piperazin-1-yl)-[1,2,4]triazolo [1,5-a]pyrimidin-4-yl]-N-[2-fluoro-4-(trifluoromethyl)phenyl]acetamide (250 mg, 0.46 mmol) and DIPEA (296 mg, 2.3 mmol) in MeCN (5 mL) was added and further stirred for 1 h. The mixture was concentrated and purified by flash (MeOH:DCM = 0~10%) to get 2-(2-bromo-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide (100 mg, 0.15 mmol, yield: 31.8%) as yellow solid. **MS** (ESI) m/z = 682.2 $[M+H]^+$.

Intermediate 38: Synthesis of 5-(tributylstannyl)pyrazolo[1,5-a]pyrimidine



Step 1: To a solution of 5-bromopyrazolo[1,5-a]pyrimidine (200 mg, 1 mmol) and $Pd(PPh_3)_4$ (116.71 mg, 0.1 mmol) in dioxane (10 mL) was added 1,1,1,2,2,2-hexabutyldistannane (1171.81 mg, 2 mmol). The mixture was stirred at 100°C for 16 hrs under Ar atmosphere. The mixture was concentrated under vacuum, purified by Flash Chromatography (PE/EtOAc = 0-5%) to give the product 5-(tributylstannyl)pyrazolo[1,5-a]pyrimidine. (275 mg, 0.64 mmol, 64% yeild) as a colorless oil. **MS** (ESI) m/z = 410.1 $[M+H]^+$.

Intermediate 40: Synthesis of 2-(2-bromo-5-ethyl-6-(4-(5-hydroxy-6- methylpyrimidine-4-carbonyl)piperazin-1-yl-2,2,3,3,5,5,6,6-d_8)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide



Step 1: The mixture of ethyl 2-bromo-3-oxopentanoate (574 mg, 2.57 mmol), tert-butyl piperazine-1-carboxylate-2,2,3,3,5,5,6,6-d_8 (500 mg, 2.57 mmol) and K_2CO_3 (1.06 g,7.71 mmol) in ACN (10 mL) was stirred at 50°C for 2 hrs. The mixture was filtered, the cake was washed with ACN. The filtrate was concentrated under vacuum and purified by Flash Chromatography (EtOAc/hexanes = 0-12%) to give the product tert-butyl 4-(1-ethoxy-1,3-dioxopentan-2-yl) piperazine-1-carboxylate-2,2,3,3,5,5,6,6-d_8 (454 mg, 1.34 mmol, 60% yield) as a yellow oil. **MS** (ESI) m/z = 337.2 $[M+H]^+$.

Step 2& Step 3: To a solution of tert-butyl 4-(1-ethoxy-1,3-dioxopentan-2-yl) piperazine-1-carboxylate-2,2,3,3,5,5,6,6-d_8 (454 mg, 1.35 mmol) in EtOH (10 mL) were added 5-bromo-4H-1,2,4-triazol-3-amine (329.88 mg, 2.02 mmol) and H_3PO_4 (1.32 g, 13.5 mmol). The reaction mixture was stirred at 85°C for 48 hrs under N_2. Then the mixture was basified with Sat.Na_2CO_3 to pH=10 and treated with Boc_2O (1.76 g, 8.09 mmol). The mixture was stirred at 25°C for 2 hrs. The mixture was diluted with water (20 mL), extracted with EtOAc (20 mL * 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, concentrated under vacuum and purified by Flash Chromatography (MeOH/DCM = 0-3%) to give the product tert-butyl 4-(2-bromo-5-ethyl-7-oxo-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl) piperazine-1-carboxylate-2,2,3,3,5,5,6,6-d_8 (93 mg, 0.15 mmol, 11% yield) as a colorless oil. **MS** (ESI) m/z = 435.1, 437.1 $[M+H]^+$.

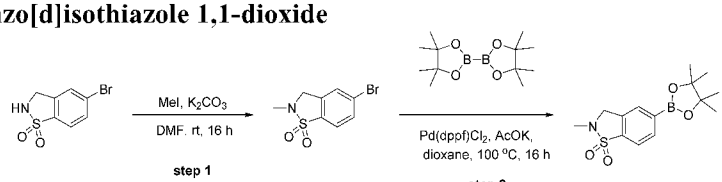
Step 4: To a solution of tert-butyl 4-(2-bromo-5-ethyl-7-oxo-4,7-dihydro-[1,2,4] triazolo[1, 5-a]pyrimidin-6-yl)piperazine-1-carboxylate-2,2,3,3,5,5,6,6-d_8 (93 mg, 0.15 mmol) in ACN (10 mL) were added 2-bromo-N-[2-chloro-4-(trifluoromethyl)phenyl]acetamide (33.23 mg, 0.1 mmol) and DIPEA (57.96 mg, 0.44 mmol). The mixture was stirred at 25°C for 16 hrs. The mixture was concentrated under vacuum and purified by Flash Chromatography (EtOAc/hexanes = 0-55%) to give tert-butyl 4-(2-bromo-4-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-5-ethyl-7-oxo-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)piperazine-1-carboxylate-2,2,3,3,5,5,6, 6-d_8 (47 mg, 0.07 mmol, 46% yield) as a yellow oil. **MS** (ESI) m/z = 614.0, 616.0 $[M+H-56]^+$.

Step 5: To a solution of tert-butyl 4-(2-bromo-4-(2-((2-chloro-4-(trifluoromethyl) phenyl) amino)-2-oxoethyl)-5-ethyl-7-oxo-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)piperazine-1-carboxylate-2,2,3,3,5,5,6,6-d_8 (47 mg, 0.07 mmol) in DCM (5 mL) was added HCl in dioxane (2 mL). The mixture was stirred at room temperature for 1 hr. The mixture was concentrated under vacuum to give the crude product 2-(2-bromo-5-ethyl-7-oxo-6-(piperazin-1-yl- 2,2,3,3,5,5,6,6-d_8) -[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (40 mg, 0.07 mmol, 100% yield) as a white solid. **MS** (ESI) m/z = 570.1, 572.1 $[M+H]^+$.

Step 6: The mixture of 5-hydroxy-6-methylpyrimidine-4-carboxylic acid (21.58 mg, 0.14 mmol), HOAt (23.82 mg, 0.17 mmol) and EDCI (33.55 mg,0.17 mmol) in ACN (25 mL) was stirred at 25^{0}C for 1 hr under argon, then 2-(2-bromo-5-ethyl-7-oxo-6-(piperazin-1-yl-2,2,3,3,5,

5,6,6-d_8)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl) acetamide (40 mg, 0.07 mmol) and DIEA (45.23 mg, 0.35 mmol) in ACN (5 mL) was added, the mixture was stirred at room temperature for 1 hr. The mixture was concentrated to remove ACN, diluted with water (20 mL), extracted with EtOAc (20 mL * 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, concentrated under vacuum and purified by Flash Chromatography (MeOH/DCM = 0-3%) to give 2-(2-bromo-5-ethyl-6-(4- (5-hydroxy-6-methyl pyrimidine-4-carbonyl)piperazin-1-yl-2,2,3,3,5,5,6,6-d_8)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (25 mg, 0.03 mmol, 50% yield) as a yellow oil. **MS** (ESI) m/z = 706.1, 708.1 $[M+H]^+$

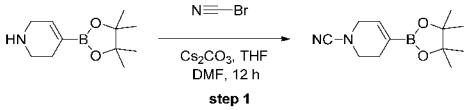
Intermediate 42: Synthesis of 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) -2,3-dihydrobenzo[d]isothiazole 1,1-dioxide



Step 1: To a suspension of 5-bromo-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide (400 mg, 1.61 mmol) and Potassium carbonate (222.52 mg, 1.61 mmol) in DMF (4 mL) was added MeI (799.83 mg, 5.64 mmol). The reaction mixture was stirred at room temperature for 16 hours. The reaction was cooled and concentrated in vacuum. The solution was diluted with DCM (20 mL * 2), washed with water (20 mL * 2), dried over Na_2SO_4 and concentrated in vacuum to afford 5-bromo-2-methyl-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide (350 mg, 1.34 mmol, 82.8% yield) as a white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.95 (d, J = 11.3 Hz, 1H), 7.85 – 7.61 (m, 2H), 7.50 (d, J = 7.8, 2.9 Hz, 1H), 1.68 (d, J = 13.5 Hz, 6H). **MS** (ESI, m/z) = 262.12 $[M+H]^+$.

Step 2: The mixture of 5-bromo-2-methyl-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide (200 mg, 0.76 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (324 mg, 1.28 mmol), potassium acetate (209 mg, 2.13 mmol) and Pd(dppf)Cl_2 (8.7 mg, 0.011 mmol) in 1,4-Dioxane (5 mL) was heated at 100° C under N_2 for 16 hrs. The reaction mixture was concentrated in vacuum and purified by silica gel column chromatography (PE/EtOAc = 10/1) to afford 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide (104 mg, 0.37 mmol, 44.3% yield) as a white solid. **MS** (ESI, m/z) = 309.1$[M+H]^+$.

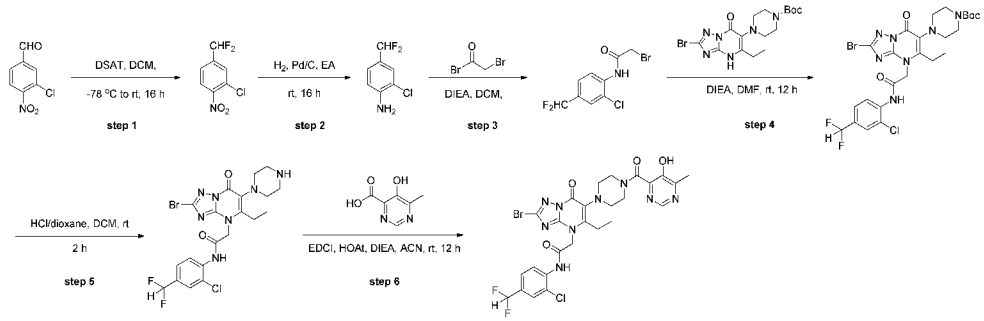
Intermediate 43: Synthesis of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carbonitrile



Step 1: To a solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine hydrochloride (0.5 g, 2.04 mmol) in DMF was added cesium carbonate (1.10 g, 3.39 mmol) at 0° C. The mixture was stirred for 15 min at 0°C and cyanogen bromide solution (0.22 g, 2.04 mmol) in THF (1 mL) was added dropwise. The mixture was stirred for 16 hours. LCMS indicated completion of reaction. The reaction mixture was quenched with ice water and diluted with DCM. The aqueous layer was separated and extracted with DCM (10 mL * 2). The combined organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated to afford 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carbonitrile (140 mg, 0.60 mmol, 29.4% yield) as yellow solid. **MS** (ESI, m/z) = 235.2 $[M+H]^+$.

Intermediate 44: Synthesis of 2-(2-bromo-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine

-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(difluoromethyl)phenyl)acetamide



Step 1: To a mixture of 3-chloro-4-nitrobenzaldehyde (1900 mg, 10.24 mmol) in DCM (20 mL) was added diethylaminosulfur trifluoride (1980 mg, 12.29 mmol) at -78°C. The mixture was stirred at the same temperature for 10 min. The cooling bath was removed, and the mixture was stirred overnight. Concentrated aqueous $NaHCO_3$ solution was added slowly to the mixture and the mixture was extracted with DCM (50 mL * 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by column chromatography (PE) to give 2-chloro-4-(difluoromethyl)-1-nitrobenzene (1800 mg, 8.6 mmol, 84.7% yield) as a yellow oil. **MS** (ESI, m/z) = 207.5 $[M+H]^+$

Step 2: A mixture of 2-chloro-4-(difluoromethyl)-1-nitrobenzene (4.1 g, 21.4 mmol) and Pd/C (0.23 g, 2.15 mmol) in ethyl acetate (250 mL) was stirred for 16 hours at 25°C under H_2. The reaction mixture was filtered by celite, concentrated to obtain 2-chloro-4-(difluoromethyl) aniline (3.0 g, 16.9 mmol, 78.7% yield) as a yellow oil. **MS** (ESI, m/z) = 178.2 $[M+H]^+$

Step 3: To the mixture of 2-chloro-4-(difluoromethyl)aniline (3.89 g, 21.91 mmol) and ethyldiisopropylamine (8.5 g, 65.73 mmol) in dichloromethane (50 mL) was added 2-bromoacetyl bromide (13.2 g, 65.73 mmol) dropwise at 0°C under N_2. The resulting mixture was stirred at room temperature for 16 hours under N_2. The mixture was diluted with water (50 mL), extracted with DCM (50 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, concentrated under vacuum and purified by Flash Chromatography (EtOAc/Hexane = 0-20%) to give 2-bromo-N-(2-chloro-4-(difluoromethyl) phenyl)acetamide (3.1 g, 10.4 mmol, 45.04%) as a yellow solid. **MS** (ESI, m/z) = 298.5 $[M+H]^+$

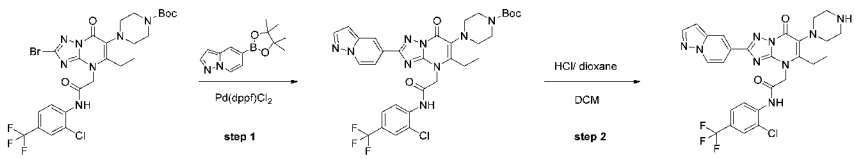
Step 4: To the mixture of tert-butyl 4-(2-bromo-5-ethyl-7-oxo-4,7- dihydro-[1,2,4]triazolo [1,5-a]pyrimidin-6-yl)piperazine-1-carboxylate (500 mg, 1.17 mmol) in DMF (8 mL) was added 2-bromo-N-(2-chloro-4-(difluoromethyl)phenyl)acetamide (349 mg, 1.17 mmol) and ethyldiisopropylamine (453 mg, 3.51 mmol). The mixture was stirred at room temperature for 12 hours under N_2. LCMS indicated completion of reaction. The mixture was diluted with water (50 mL) and extracted with EtOAc (50 mL * 3). The combined organic layer was washed with brine (50 mL * 3), dried over Na_2SO_4 and concentrated in vacuum. The crude product was purified by flash silica chromatography (elution gradient: 30 to 70% EtOAc in Hexane) to afford tert-butyl 4-(2-bromo-4-(2-((2-chloro-4-(difluoromethyl)phenyl)amino)-2-oxo ethyl)-5-ethyl-7-oxo-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)piperazine-1-carboxylate (384 mg, 0.59 mmol, 50.89%) as yellow solid. **MS** (ESI, m/z) = 588.1 $[M+H-56]^+$

Step 5: To the mixture of tert-butyl 4-(2-bromo-4-(2-((2-chloro-4-(difluoromethyl)phenyl) amino)-2-oxoethyl)-5-ethyl-7-oxo-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)piperazine-1-carboxylate (384 mg, 0.59 mmol) in dichloromethane (5 mL) was added 4 M HCl/dioxane (5 mL). The mixture was stirred at room temperature for 2 hours. The resulting mixture was concentrated

under vacuum to give 2-(2-bromo-5-ethyl-7-oxo-6-(piperazin-1-yl)-[1,2,4]triazolo[1,5-a] pyrimidin-4(7*H*)-yl)-*N*-(2-chloro-4-(difluoromethyl)phenyl)acetamide (300 mg, 0.55 mmol, 92.6%) as a yellow solid. **MS** (ESI, m/z) = 544.2 $[M+H]^+$

Step 6: The mixture of 5-hydroxy-6-methylpyrimidine-4-carboxylic acid (254 mg, 1.65 mmol), 1-Hydroxy-7-azabenzotriazole (224 mg, 1.65 mmol) and 3-(ethyliminomethylideneamino) -*N*,*N*-dimethylpropan-1-amine (316 mg, 1.65mmol) in acetonitrile (40 mL) was stirred at room temperature for 1 hour under N_2, then 2-(2-bromo-5-ethyl-7-oxo-6-(piperazin-1-yl)-[1,2,4] triazolo[1,5-a]pyrimidin-4(7*H*)-yl)-*N*-(2-chloro-4-(difluoromethyl)phenyl)acetamide (300 mg, 0.55 mmol) and ethyldiisopropylamine (0.55 mL, 3.30 mmol) in acetonitrile (10 mL) was added. The mixture was stirred at room temperature for 16 hours. The mixture was concentrated to remove MeCN, diluted with water (20 mL), extracted with EtOAc (20 mL * 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, concentrated under vacuum. The residue was purified by C18 column chromatography eluted with MeCN in H_2O (0.1% FA) to afford 2-(2-bromo-5-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-oxo-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-chloro-4-(difluoromethyl)phenyl)acetamide (100 mg, 0.14 mmol, 18.2%) as a yellow solid. **MS** (ESI, m/z) = 680.1 $[M+H]^+$

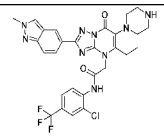
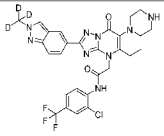
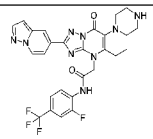
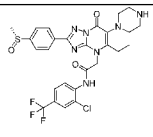
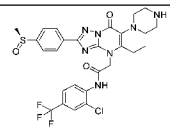
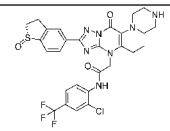
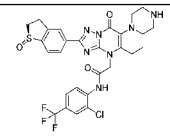
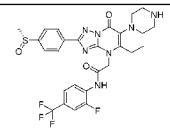
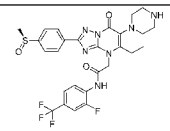
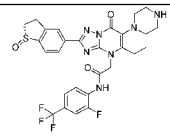
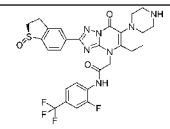
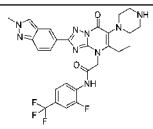
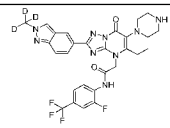
Intermediate 45: Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-7-oxo-6-(piperazin-1-yl)-2-(pyrazolo[1,5-a]pyridin-5-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide



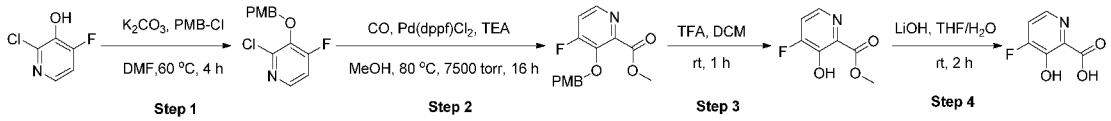
Step 1: To the mixture of tert-butyl 4-(2-bromo-4-(2-((2-chloro-4-(trifluoromethyl) phenyl)amino)-2-oxoethyl)-5-ethyl-7-oxo-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)pipera zine-1-carboxylate (1000 mg, 1.51 mmol) in 1,4-Dioxane (20 mL) and water (2 mL) was added 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine (552 mg, 2.27 mmol), sodium carbonate (480 mg, 4.53 mmol) and $Pd(dppf)Cl_2$ (110 mg, 0.15 mmol). The mixture was stirred at 85°C for 12 hours under N_2. The reaction mixture was quenched by addition of H_2O and extracted with EtOAc (100 mL * 3). The combined organic layers were washed with brine (100 mL * 3), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The mixture was purified by silica gel column chromatography (PE/EtOAc = 1/2) to afford tert-butyl 4-(4-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-5-ethyl-7-oxo-2-(pyrazolo[1,5-a] pyridin-5-yl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)piperazine-1-carboxylate (689 mg, 0.98 mmol, 65.2% yield) as yellow solid. **MS** (ESI, m/z) = 700.4 $[M+H]^+$

Step 2: To a solution of *tert*-butyl 4-(4-(2-((2-chloro-4-(trifluoromethyl)phenyl) amino)-2-oxoethyl)-5-ethyl-7-oxo-2-(pyrazolo[1,5-a]pyridin-5-yl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimid in-6-yl)piperazine-1-carboxylate (689 mg, 0.98 mmol) in DCM (10 mL) was added hydrogen chloride (7 mL, 4M in dioxane). The mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated in vacuum to afford *N*-(2-chloro-4- (trifluoromethyl)phenyl)- 2-(5-ethyl-7-oxo-6-(piperazin-1-yl)-2-(pyrazolo[1,5-a]pyridin-5-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7*H*)-yl)acetamide (540 mg, 0.9 mmol, 92.8% yield) as white solid. **MS** (ESI, m/z) = 600.2 $[M+H]^+$

The following **Intermediates** was synthesized using the same procedure as **Intermediate 45**:

Intermediate 46 N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-2-(2-methyl-2H-indazol-5-yl)-7-oxo-6-(piperazin-1-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide		**MS** (ESI, m/z) = 614.2 $[M+H]^+$
Intermediate 47 N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-2-(2-(methyl-d3)-2H-indazol-5-yl)-7-oxo-6-(piperazin-1-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide		**MS** (ESI, m/z) = 617.2 $[M+H]^+$
Intermediate 48 2-(5-ethyl-7-oxo-6-(piperazin-1-yl)-2-(pyrazolo[1,5-a]pyridin-5-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide		**MS** (ESI, m/z) = 584.2 $[M+H]^+$
Intermediate 49 (R)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-2-(4-(methylsulfinyl)phenyl)-7-oxo-6-(piperazin-1-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide		**MS** (ESI, m/z) = 622.1 $[M+H]^+$
Intermediate 50 (S)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-2-(4-(methylsulfinyl)phenyl)-7-oxo-6-(piperazin-1-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide		**MS** (ESI, m/z) = 622.1 $[M+H]^+$
Intermediate 51 (R)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-2-(1-oxido-2,3-dihydrobenzo[b]thiophen-5-yl)-7-oxo-6-(piperazin-1-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide		**MS** (ESI, m/z) =634.1 $[M+H]^+$
Intermediate 52 (S)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(5-ethyl-2-(1-oxido-2,3-dihydrobenzo[b]thiophen-5-yl)-7-oxo-6-(piperazin-1-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)acetamide		**MS** (ESI, m/z) = 634.1 $[M+H]^+$
Intermediate 53 (R)-2-(5-ethyl-2-(4-(methylsulfinyl)phenyl)-7-oxo-6-(piperazin-1-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide		**MS** (ESI, m/z) =606.2 $[M+H]^+$
Intermediate 54 (S)-2-(5-ethyl-2-(4-(methylsulfinyl)phenyl)-7-oxo-6-(piperazin-1-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide		**MS** (ESI, m/z) = 606.2 $[M+H]^+$
Intermediate 55 (R)-2-(5-ethyl-2-(1-oxido-2,3-dihydrobenzo[b]thiophen-5-yl)-7-oxo-6-(piperazin-1-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide		**MS** (ESI, m/z) = 618.2 $[M+H]^+$
Intermediate 56 (S)-2-(5-ethyl-2-(1-oxido-2,3-dihydrobenzo[b]thiophen-5-yl)-7-oxo-6-(piperazin-1-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide		**MS** (ESI, m/z) = 618.2 $[M+H]^+$
Intermediate 57 2-(5-ethyl-2-(2-methyl-2H-indazol-5-yl)-7-oxo-6-(piperazin-1-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide		**MS** (ESI, m/z) = 598.2 $[M+H]^+$
Intermediate 58 2-(5-ethyl-2-(2-(methyl-d3)-2H-indazol-5-yl)-7-oxo-6-(piperazin-1-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-4(7H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide		**MS** (ESI, m/z) = 601.2 $[M+H]^+$

Intermediate 59: Synthesis of 4-fluoro-3-hydroxypicolinic acid



Step 1: A mixture of 2-chloro-4-fluoropyridin-3-ol (600 mg, 4.07 mmol) and potassium carbonate (843 mg, 6.11 mmol) in DMF (10 mL). The reaction mixture was flushed with N_2, then 4-methoxybenzylchloride (701 mg, 4.48 mmol) was added. The mixture was stirred at 60°C for 4 hours. LCMS indicated completion of reaction. EtOAc (10 mL) was added and was washed with water (2 * 10 mL) and brine (10 mL), dried over Na_2SO_4, filtered and evaporated. The crude product was purified by column chromatography (PE/EA = 5:1). The product containing fractions were combined, concentrated under reduced pressure to give 2-chloro-4-fluoro-3-[(4-methoxy phenyl)methoxy]pyridine (800 mg, 3.0 mmol, 73.5% yield) as a yellow oil. **MS** (ESI, m/z): $[M+H]^+ = 268.0$

Step 2: To a solution of 2-chloro-4-fluoro-3-[(4-methoxyphenyl)methoxy]pyridine (1200 mg, 4.48 mmol) in TEA (1360 mg, 13.44 mmol) and methanol (10 mL) was added [1,1'-Bis (diphenyl phosphino)ferrocene]dichloropalladium(II),complex with dichloromethane (365 mg, 0.45 mmol). The mixture was stirred at 80°C for 16 hours under 10 bars of CO. The reaction mixture was filtered through celite and concentrated under reduced pressure. The crude product was purified by column chromatography (PE/EA = 1:1) to give methyl 4-fluoro-3-((4-methoxybenzyl)oxy) picolinate (460 mg, 1.58 mmol, 35.2% yield) as dark green solid. **MS** (ESI, m/z): $[M+H]^+ =292.1$

Step 3: To a solution of methyl 4-fluoro-3-((4-methoxybenzyl)oxy)picolinate (200 mg, 0.69 mmol) in DCM (4 mL) at room temperature was added trifluoroacetic acid (786 mg, 6.90 mmol) . The solution was stirred at room temperature for 1 hour. The resulting mixture was concentrated under vacuum to afford methyl 4-fluoro-3-hydroxypicolinate (277 mg, 1.62 mmol, 235.7%) as a yellow solid. **MS** (ESI, m/z): $[M+H]^+ = 171.9$

Step 4: To a solution of methyl 4-fluoro-3-hydroxypyridine-2-carboxylate (200 mg, 1.17 mmol) in THF: H_2O (2:1) was added Lithium Hydroxide (140 mg, 5.85 mmol) at 0°C. The solution was stirred at room temperature for 2 hours. The residue was purified by C18 column chromatography eluted with MeCN in 0.1% FA/water to afford 4-fluoro-3-hydroxypicolinic acid (120 mg, 0.76 mmol, 65.4%) as a white solid. **MS** (ESI, m/z): $[M+H]^+ =158$.

Detection method for cell proliferation:

The CellTiter-Glo® 2.0 Assay provides a homogeneous method for quantifying the number of viable cells in culture by measuring the metabolite ATP.

SW-48, a human colon cancer cell line used in this study, has the microsatellite instability-high (MSI-H) phenotype, and was obtained from Roche. SW-48 cells were cultured in 1640 basal media (BasalMedia, L210KJ) supplemented with 10% fetal bovine serum (Gibco, 10091-148) and 1% penicillin-streptomycin (Solarbio, P1400) at 37°C in a 5% CO_2 incubator.

Experimental procedure:

Cells were detached using 0.25% trypsin-EDTA (Solarbio, T1300) for a few minutes and then neutralized with culture medium. After centrifugation at 300 g for 5 min, the supernatant was discarded, and the cells were resuspended in culture medium and counted using a CountStar (IC1000). The SW-48 cells were diluted in culture medium to the desired density, and 40μL of cell suspension (at a final density of 1500 cells/well) was added to the black-bottomed 384-well plate (Corning, 3764). An additional plate was prepared and labeled as Day0 to quantify the baseline level of viable cells before adding compounds. The 384-well plate was then incubated overnight in a 5% CO_2 incubator at 37°C.

After overnight incubation, compounds were added to the 384-well plate using an Echo 650 (Beckman, Echo 650) in triplicate, with a 3-fold, 10-point dilution series, and the final DMSO concentration was 0.1%. Each compound was treated twice, and on the day of dosing, the Day0

plate was also measured using CTG (Promega, G9243). After 96 hours of compound treatment, 30μL of CTG reagent was added to each well and incubated at room temperature for 30 minutes, followed by measurement using an enzyme reader (TECAN, Spark) for 300ms read time.

Data analysis:

The Z' factor was used to measure the success of the experiment, with a value greater than 0.7 indicating reliable experimental results.

Z' = 1-3*(High_SD+Low_SD)/(High-Low)

The data were analyzed based on the GI50 values:

Curve fitting was performed based on the concentration of the samples and the percentage of growth (%G), calculated using the following formula:

When Sample<Day0, %G = (Sample-Day0)/Day0*100; when Sample≥Day0, %G = (Sample-Day0)/(High-Day0)*100. Here, Day0 represents the initial cell viability level when the compounds were added, High and Sample represent the cell viability levels of the solvent control group (0.1% DMSO) and the compound treatment group, respectively, at the end of the compound incubation period, and Low represents the cell-free PBS group. Percentages of 100%, 0%, and -100% represent no growth inhibition, growth arrest, and complete cell killing, respectively.

In this study, the four-parameter curve fitting method (XLfit, equation 201) was used.

The Biology data shown below in Table 1:

Table 1: Biology data

Compound Number	CTG-cell Proliferation GI_{50} (uM)	Compound Number	CTG-cell Proliferation GI_{50} (uM)
Example 1	A	**Example 25**	A
Example 7	A	**Example 26**	A
Example 8	A	**Example 41**	A
Example 9	A	**Example 76**	A
Example 10	A	**Example 79**	A
Example 11	A	**Example 89**	A
Example 12	A		

A: <0.5 uM; B: 0.5 uM-1 uM; C: 1 μM<C≤5 μM; D:> 5 μM.

Table 1-1: Biology data

Compound Number	CTG-cell Proliferation GI_{50} (uM)	Compound Number	CTG-cell Proliferation GI_{50} (uM)
Example 37	A	**Example 222**	A
Example 43	A	**Example 223**	A
Example 45	A	**Example 224**	A
Example 46	A	**Example 225**	A
Example 51	C	**Example 227**	C
Example 52	C	**Example 228**	A
Example 57	A	**Example 229**	A
Example 58	A	**Example 230**	A
Example 63	A	**Example 231**	A
Example 73	A	**Example 232**	A
Example 77	A	**Example 234**	A
Example 78	A	**Example 235**	A
Example 95	A	**Example 236**	B
Example 97	A	**Example 238**	A
Example 107	A	**Example 240**	A

Example 108	A	**Example 241**	A
Example 126	A	**Example 243**	A
Example 127	A	**Example 244**	A
Example 133	A	**Example 245**	A
Example 134	A	**Example 246**	A
Example 136	A	**Example 247**	A
Example 148	A	**Example 248**	A
Example 149	A	**Example 250**	A
Example 181	A	**Example 253**	A
Example 184	A	**Example 254**	A
Example 185	A	**Example 255**	A
Example 200	A	**Example 256**	A
Example 201	A	**Example 257**	A
Example 202	B	**Example 259**	A
Example 208	A	**Example 260**	A
Example 211	A	**Example 261**	A
Example 212	A	**Example 262**	A
Example 214	A	**Example 263**	A
Example 215	A	**Example 264**	A
Example 216	A	**Example 265**	C
Example 219	A	**Example 266**	A
Example 220	A	**Example 267**	A
Example 221	A		

A：<0.5 uM; B: 0.5 uM-1 uM; C: 1 μM<C≤5 μM; D:> 5 μM.

Table 1-2: Biology data

Compound Number	CTG-cell Proliferation GI_{50} (uM)	Compound Number	CTG-cell Proliferation GI_{50} (uM)
Example 45	0.020	**Example 293**	0.080
Example 46	0.019	**Example 295**	0.258
Example 78	0.033	**Example 297**	0.118
Example 200	0.014	**Example 299**	0.106
Example 201	0.005	**Example 300**	0.046
Example 224	0.037	**Example 301**	0.021
Example 270	0.030	**Example 302**	0.020
Example 271	0.148	**Example 303**	0.062
Example 272	0.032	**Example 304**	0.054
Example 273	0.018	**Example 305**	0.098
Example 274	0.029	**Example 306**	0.196
Example 275	0.083	**Example 307**	0.063
Example 276	0.018	**Example 308**	0.062
Example 277	0.030	**Example 309**	0.169
Example 278	0.045	**Example 310**	0.041

Example 279a	0.025	**Example 311**	0.036
Example 279b	0.026	**Example 312**	0.032
Example 280	0.074	**Example 313**	0.123
Example 281	0.035	**Example 314**	0.049
Example 282a	0.013	**Example 315**	0.053
Example 282b	0.022	**Example 316**	0.010
Example 283	0.038	**Example 317**	0.015
Example 284	0.041	**Example 325**	0.054
Example 285	0.039	**Example 326**	0.009
Example 286a	0.038	**Example 327**	0.022
Example 286b	0.116	**Example 328**	0.011
Example 287a	0.073		
Example 287b	0.019		
Example 288	0.051		
Example 290	0.014		
Example 291	0.036		

ADP-Glo assay for WRN ATPase activity:

WRN is an ATP-dependent helicase that can bind and hydrolyze ATP during the unwinding process, producing ADP, which provides energy to unwind double-stranded DNA. Therefore, we can use the ADP-Glo method to determine the inhibitory effect of compounds on the WRN helicase by detecting the amount of ADP produced.

The WRN (500-946) protein was purchased from ICE (S2201T-H03H). The double-stranded DNA substrate was obtained by annealing equal amounts of primers SEQ ID No: 1(TTTTTTTTTTTTTTTTTTTTTTTTTTTTTCGTACCCGATGTGTTCGTTC) and SEQ ID No: 2 (GAACGAACACATCGGGTACG-TTTTTTTTTTTTTTTTTTTTTTTTTTTTT) in 2× Phanta Max buffer (Vazyme, P505-d1-AB) (95 °C for 5 minutes, 55 °C for 30 seconds), with the primers synthesized by Xianghongbio (Beijing). The amount of ADP produced was measured using the ADP-Glo assay kit (Promega, V9101).

Before the formal experiment, a preliminary experiment was performed to determine the optimal enzyme assay conditions (including buffer, reaction time, and the concentration of the protein, ATP, and DNA substrate). The final reaction system consisted of 10 nM WRN protein, 0.2 nM DNA substrate, and 300 μM ATP. The buffer of the reaction system was prepared with deionized water to a final concentration of 30 mM Tris (pH 7.5), 2 mM $MgCl_2$, 0.02% BSA, 50 mM NaCl, and 0.10% Pluronic F-68.

To determine the inhibitory effect of compounds, a gradient dilution of the compounds was first performed using DMSO (10-point 3-fold dilution). The diluted compounds (with a starting concentration of 10 mM) were transferred to a 384-well plate (PerkinElmer, 6007290) in 5 nL using an Echo (Beckman, Echo 650). Each compound was tested in duplicate, and 2.5 μL of buffer containing 2X ATP (600 μM) and 2X WRN (20 nM) was added, followed by preincubation at room temperature for 3 hours. The positive control (high control) was a DMSO group without compound treatment but containing WRN (no inhibitory effect), and the negative control (low control) was a DMSO group without WRN (maximum inhibitory effect). Subsequently, 2.5μL of buffer containing 2X DNA (0.4 nM) was added to start the reaction, followed by incubation at room temperature for 30 minutes. Afterwards, 5μL of ADP-Glo reagent was added and incubated at room temperature for 40 minutes to terminate the enzyme reaction and consume excess ATP. Finally, 10μL of ATP detection reagent was added to convert ADP to ATP, and the newly formed ATP was detected by a luciferase reaction using a plate reader (TECAN, Spark) with a detection time of 300 ms.

Data analysis:

The Z' factor was used to measure the success of the experiment, with a value greater than

0.6 indicating reliable experimental results.

Z' = 1-3*(HC_SD+LC_SD)/(HC-LC)

IC50 calculation:

Curve fitting was performed based on the concentration of the samples and the percentage of inhibition (% Inhibition), calculated using the following formula:

%Inhibition = 100 x (Readout_HC – Readout_Sample) / (Readout_HC – Readout_LC)

Here, HC represents the positive control (high control), which is a DMSO group without compound treatment but containing WRN (no inhibitory effect); LC represents the negative control (low control), which is a DMSO group without WRN (maximum inhibitory effect).

In this study, the four-parameter curve fitting method (XLfit, equation 205) was used to calculate the absolute IC50 (AbIC50), which is the concentration point at which the inhibition is 50%.

The Biology data shown below in Table 2:

Table 2: Biology data

Compound Number	ATPase activity IC_{50}(μM)	Compound Number	ATPase activity IC_{50}(μM)
Example 1	A	**Example 6**	A
Example 7	A	**Example 8**	A
Example 9	A	**Example 10**	A
Example 11	A	**Example 12**	A
Example 14	A	**Example 25**	A
Example 26	A	**Example 34**	A
Example 41	A	**Example 76**	A
Example 79	A	**Example 89**	A

A：<0.5 uM; B: 0.5 uM-1 uM; C: 1 μM<C≤5 μM; D:> 5 μM.

Table 2-1: Biology data

Compound Number	ATPase activity IC_{50}(μM)	Compound Number	ATPase activity IC_{50}(μM)
Example 37	A	**Example 224**	A
Example 43	A	**Example 225**	A
Example 45	A	**Example 227**	A
Example 46	A	**Example 228**	A
Example 51	A	**Example 229**	A
Example 52	A	**Example 230**	A
Example 57	A	**Example 231**	A
Example 58	A	**Example 232**	A
Example 63	A	**Example 234**	A
Example 73	A	**Example 235**	A
Example 77	A	**Example 236**	A
Example 78	A	**Example 238**	A
Example 95	A	**Example 240**	A
Example 97	A	**Example 241**	A
Example 107	A	**Example 243**	A
Example 108	A	**Example 244**	A
Example 126	A	**Example 245**	A
Example 127	A	**Example 246**	A
Example 133	A	**Example 247**	A
Example 134	A	**Example 248**	A
Example 136	A	**Example 250**	A
Example 148	A	**Example 253**	A
Example 149	A	**Example 254**	A
Example 181	A	**Example 255**	A
Example 184	A	**Example 256**	A
Example 185	A	**Example 257**	A
Example 200	A	**Example 259**	A

Example 201	A	**Example 260**	A
Example 202	A	**Example 261**	A
Example 208	A	**Example 262**	A
Example 211	A	**Example 263**	A
Example 212	A	**Example 264**	A
Example 214	A	**Example 265**	A
Example 215	A	**Example 266**	A
Example 216	A	**Example 267**	A
Example 219	A	**Example 268**	A
Example 220	A	**Example 269**	A
Example 221	A	**Example 270**	A
Example 222	A	**Example 271**	A
Example 223	A	**Example 272**	A

A：<0.5 uM; B: 0.5 uM-1 uM; C: 1 μM<C≤5 μM; D:> 5 μM.

Table 2-2: Biology data

Compound Number	ATPase activity IC_{50}(μM)	Compound Number	ATPase activity IC_{50}(μM)
Example 45	0.027	**Example 293**	0.045
Example 46	0.020	**Example 295**	0.020
Example 78	0.022	**Example 297**	0.045
Example 200	0.021	**Example 299**	0.041
Example 201	0.016	**Example 300**	0.024
Example 224	0.020	**Example 301**	0.025
Example 270	0.042	**Example 302**	0.016
Example 271	0.051	**Example 303**	0.037
Example 272	0.022	**Example 304**	0.026
Example 273	0.010	**Example 305**	0.034
Example 274	0.014	**Example 306**	0.061
Example 275	0.031	**Example 307**	0.017
Example 276	0.013	**Example 308**	0.015
Example 277	0.026	**Example 309**	0.009
Example 278	0.020	**Example 310**	0.010
Example 279a	0.011	**Example 311**	0.017
Example 279b	0.008	**Example 312**	0.014
Example 280	0.055	**Example 313**	0.055
Example 281	0.018	**Example 314**	0.017
Example 282a	0.007	**Example 315**	0.035
Example 282b	0.010	**Example 316**	0.011
Example 283	0.019	**Example 317**	0.020
Example 284	0.019	**Example 325**	0.047
Example 285	0.014	**Example 326**	0.016
Example 286a	0.020		
Example 286b	0.213		
Example 287a	0.011		
Example 287b	0.011		
Example 288	0.019		
Example 290	0.010		
Example 291	0.022		

Measurement of WRN helicase unwinding activity

Fluorescence quantification is used to measure the helicase activity of WRN, where DNA single strands are labeled with fluorescence and quenching groups, annealed and then unwound by WRN at specific sites, exposing the labeled fluorescence group and producing fluorescence. The fluorescence intensity of different compounds treated is measured to determine their inhibitory effect on WRN helicase. The WRN (500-946) protein is purchased from ICE (S2201T-H03H). The fluorescence-labeled double-stranded DNA substrate is annealed by equal amounts of BHQ2 and TAMRA in 2×Phanta Max Buffer, and the primers are synthesized by Xianghongbio. Pre-experiments were conducted to determine optimal enzyme assay conditions, including buffer, reaction time, and protein, ATP, and DNA substrate concentrations. The final reaction system

includes 20 nM WRN protein, 200 nM DNA substrate, and 1 mM ATP in a buffer composed of 25 mM Tris (pH 7.5), 2 mM $MgCl_2$, 1 mM DTT, 50 mM NaCl, and 0.01% Tween-20. To determine the inhibitory effect of compounds, compounds were first gradient-diluted with DMSO (3-fold dilution, 10 points). The diluted compounds (initial concentration point 10 mM) were transferred to a 384-well plate (Greiner, 781090) using the Echo liquid handler (Beckman, Echo 650) at 50 nL per well. Each compound was treated in duplicate, and the high control was treated with WRN-conjugated DMSO without any inhibitor, and the low control was treated with DMSO without WRN (maximum inhibition effect). After adding 22.5 μL buffer containing DNA double-stranded substrate and WRN, the plate was incubated at room temperature for 15 minutes. Then, after adding 2.5 μL buffer containing 10X ATP (10 mM), the plate was incubated for 1 hour at room temperature. Finally, the fluorescence intensity was measured using a plate reader (TECAN, Spark) with an excitation filter of 535±25 nm and an emission filter of 595±35 nm.

Data analysis:

The Z' factor was used to measure whether the experiment was successful. If Z' > 0.7, the experiment result is considered reliable. The Z' factor is calculated as follows:

Z' = 1-3*(HC_SD + LC_SD)/(HC-LC)

where HC stands for high control, which is the WRN-conjugated DMSO without any inhibitor, and LC stands for low control, which is the DMSO without WRN (maximum inhibition effect).

IC50 calculation:

To obtain the IC50 value, a curve-fitting equation is used to fit the concentration of samples with the % Inhibition of the compounds. The % Inhibition is calculated using the following formula:

%Inhibition = 100 x (Readout_HC - Readout_Sample) / (Readout_HC - Readout_LC)

where Readout_HC is the fluorescence intensity of high control, Readout_Sample is the fluorescence intensity of the sample well, and Readout_LC is the fluorescence intensity of low control. In this experiment, the four-parameter curve fitting method (XLfit, equation 205) was used to calculate the absolute IC50 (AbIC50), which is the concentration where the inhibition rate reaches 50%.

The Biology data shown below in Table 3:

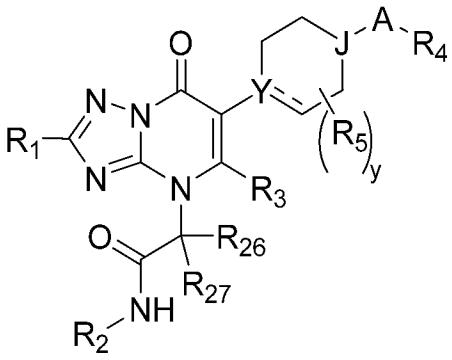
Table 3: Biology data

Compound Number	**Fork helicase assay IC_{50}(uM)**	**Compound Number**	**Fork helicase assay IC_{50}(uM)**
Example 1	A	**Example 6**	A
Example 7	A	**Example 8**	A
Example 9	A	**Example 10**	A
Example 12	A	**Example 25**	A
Example 34	A	**Example 41**	A
Example 76	A	**Example 79**	A
Example 89	A		

A: <0.5 uM; B: 0.5 uM-1 uM; C: 1 μM<C≤5 μM; D:> 5 μM.

CLAIMS

1. A compound of formula (I), or a pharmaceutically acceptable salt, a hydrate, a solvate, a prodrug, a stereoisomer, a deuterated product or a tautomer thereof:



(I)

wherein

A is a linker selected from -C(O)-, -S(O)-, -$S(O)_2$-, and  ;

Y is N, C, or CH;

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

Y=== means Y is linked via a single bond to the adjacent carbon atom when Y is CH, or Y is linked via a double bond to the adjacent atom when Y is C, and when Y=== is a single bond, Y is carbon unsubstituted or substituted by OH or F;

when Y is N, Y=== is a single bond;

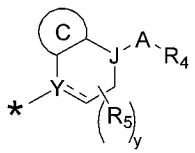
J is N or CH;

when J is N, and A is a linker selected from -C(O)-, -S(O)-, -$S(O)_2$-, and  ;

when J is CH, and A is a linker selected from-S(O)-, -$S(O)_2$-, and  ;

R_5 is independently selected from:

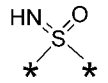
- H,
- -(C_1-C_4)alkyl,
- -(C_3-C_5)cycloalkyl,
- or two R_5 substituents on the same ring carbon atom may join, together with the carbon atom to which they are attached, to form a (C_3-C_4)cycloalkyl spiro ring or a 3 or 4-membered heterocyclyl spiro ring, wherein said heterocyclyl spiro ring contains ring carbon ring atoms and one ring heteroatom selected from O, N and S,
- when J is N, a R_5 substituent form ring C:



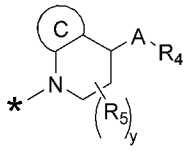
wherein ring C is a fused (C_3-C_6)cycloalkyl ring, a fused (C_3-C_6)heterocyclyl ring or a

fused phenyl ring, wherein said fused (C_3-C_6)heterocyclyl ring contains ring carbon atoms and one ring heteroatom selected from O, N and S,

- when J is CH, Y is N, ═══ is a single bond, and



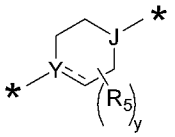
A is a linker selected from -S(O)-, -S(O)$_2$-, and , a R_5 substituent form ring C:



,

- when J is N, two R_5 substituents may join to form a (C_1-C_3)alkylene bridge or a heteroalkylene bridge, wherein said heteroalkylene bridge is one heteroatom selected from N and O, or is -CH_2-O-CH_2-;

and wherein one or more H atoms on the ring:



may be replaced by deuterium;

R_1 is:

(C_3-C_4)cycloalkyl

- (C_3-C_4)cycloalkyl is unsubstituted or substituted by 1 or 2 R_{33}, wherein R_{33} is halo, and wherein said (C_3-C_4)cycloalkyl or halo-substituted (C_3-C_4)cycloalkyl is substituted by 0, 1 or 2 R_{15} substituents,
- (C_3-C_4)cycloalkyl has 2 substituents at the same ring carbon atom which join to form a (C_3-C_6)cycloalkyl spiro ring, or 3, 4, 5, or 6 membered heterocyclyl spiro ring contains ring carbon atoms and 1 or 2 ring heteroatom selected from O, N and S, and wherein said cycloalkyl or heterocyclyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23},
- (C_3-C_4)cycloalkyl is fused to (C_3-C_6)cycloalkyl ring, or 3, 4, 5, or 6 membered heterocyclyl ring contains ring carbon atoms and 1-4 ring heteroatom selected from O, N and S, and wherein said cycloalkyl or heterocyclyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23},
- For C_4 cycloalkyl, it can be bridged by 1 or 2 carbon atoms, and wherein said bridged C_4 cycloalkyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23};

or cycloalkenyl

- a partially unsaturated monocyclic ring containing 5 or 6 ring carbon atoms containing 0, 1 or 2 R_{33}, wherein R_{33} is halo, and the cycloalkenyl
  - ✧ contains one =CF_2 substituent and 0, 1 or 2 R_{15} substituents,
  - ✧ contains one substituent selected from =CCl_2, -S(O)C_{1-4}alkyl, -S(O)$_2$(C_{1-4}alkyl), and CN, and contains 0, 1 or 2 R_{15} substituents which is not =CCl_2, -S(O)C_{1-4}alkyl, -S(O)$_2$(C_{1-4}alkyl), or CN,
  - ✧ has 2 substituents at the same ring carbon atom which join to form a (C_3-C_6)

cycloalkyl spiro ring, or 3, 4, 5, or 6 membered heterocyclyl spiro ring containing ring carbon atoms and 1 or 2 ring heteroatom selected from O, N and S, and wherein said cycloalkyl or heterocyclyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23},

- ✧ is fused to (C_3-C_6)cycloalkyl ring, or 3, 4, 5, or 6 membered heterocyclyl ring containing ring carbon atoms and 1-4 ring heteroatom selected from O, N and S, and wherein said cycloalkyl or heterocyclyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23},
- ✧ is bridged, and said bridge contains 1 or 2 carbon atoms, and substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23};

- a partially unsaturated monocyclic ring containing 7 ring carbon atoms is substituted by 0, 1 or 2 R_{15} substituents;
  - ✧ contains 0 or 1 $=CF_2$ substituent,
  - ✧ has 2 substitutents at the same ring carbon atom which join to form a (C_3-C_6)cycloalkyl spiro ring, or 3, 4, 5, or 6 membered heterocyclyl spiro ring contains ring carbon atoms and 1 or 2 ring heteroatoms selected from O, N and S, and wherein said cycloalkyl or heterocyclyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23},
  - ✧ is fused to (C_3-C_6)cycloalkyl ring, or 3, 4, 5, or 6 membered heterocyclyl ring contains ring carbon atoms and 1-4 ring heteroatoms selected from O, N and S, and wherein said cycloalkyl or heterocyclyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23};

or heterocyclyl

- heterocyclyl is a 4 or 7 membered fully saturated or partially unsaturated group comprising ring carbon atoms and 1 or 2 ring heteroatoms independently selected from N, O and S, wherein said heterocyclyl is unsubstituted or substituted by 1, 2, 3 or 4, preferably 1 or 2, R_{33}, wherein R_{33} is halo, wherein said heterocyclyl or halo-substituted heterocyclyl
  - ✧ contains 0, 1 or 2 R_{15} substituents and 0 or 1 $=CF_2$ substituent,
  - ✧ contains one substituent selected from CN, -S(O)C_{1-4}alkyl, and -S(O)$_2C_{1-4}$ alkyl, and contains 0, 1 or 2 substituents selected from halogen, C_{1-4}alkyl, C_{1-4} haloalkyl and C_{3-4} cycloalkyl,
  - ✧ has 2 substitutents at the same ring carbon atom which join to form a (C_3-C_6)cycloalkyl spiro ring, or 3, 4, 5, or 6 membered heterocyclyl spiro ring contains ring carbon atoms and 1 or 2 ring heteroatoms selected from O, N and S, and wherein said cycloalkyl or heterocyclyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23},
  - ✧ is fused to (C_3-C_6)cycloalkyl ring, or 3, 4, 5, or 6 membered heterocyclyl ring contains ring carbon atoms and 1-4 ring heteroatoms selected from O, N and S, and wherein said cycloalkyl or heterocyclyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23};
  - ✧ is fused to phenyl, wherein said phenyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23};
- heterocyclyl is a 5 or 6 membered fully saturated or partially unsaturated group comprising ring carbon atoms and 1 or 2 ring heteroatoms independently selected from

N, O and S, wherein said heterocyclyl is unsubstituted or substituted by 1, 2, 3 or 4, preferably 1 or 2 R_{33}, wherein R_{33} is halo, wherein said heterocyclyl or halo-substituted heterocyclyl

- ✧ contains one $=CF_2$ substituent and 0, 1 or 2 R_{15} substituents,
- ✧ contains one substituent selected from $=CCl_2$, CN, and $-S(O)_2C_{1-4}$ alkyl, and contains 0, 1 or 2 R_{15} substituents which is not $=CCl_2$, CN, or $-S(O)_2C_{1-4}$ alkyl,
- ✧ has 2 substituents at the same ring carbon atom which join to form a (C_4-C_7)cycloalkyl spiro ring, or 4, 5, 6, or 7 membered heterocyclyl spiro ring containing ring carbon atoms and 1 or 2 ring heteroatoms selected from O, N and S, and wherein said cycloalkyl or heterocyclyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23},
- ✧ is fused to (C_4-C_6)cycloalkyl ring, or 4, 5, or 6 membered heterocyclyl ring containing ring carbon atoms and 1-3 ring heteroatoms selected from N and S, or 5-6 membered heteroaryl ring containing ring carbon atoms and 1-3 ring heteroatoms selected from N and S, or 1 ring O atom and 1 or 2 ring heteroatoms selected from N and S; and wherein said cycloalkyl, heterocyclyl or heteroaryl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23};
- ✧ is fused to phenyl, wherein said phenyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23};

or heteroaryl, wherein said heteroaryl is a 5 or 6 membered fully unsaturated monocyclic group comprising ring carbon atoms and 1, 2, 3 or 4 ring heteroatoms independently selected from N, O and S, preferably 1 or 2 ring heteratoms, wherein the total number of ring S atoms does not exceed 1, and the total number of ring O atoms does not exceed 1, the heteroaryl is substituted by one or more substituents selected from CN, $-S(O)C_{1-4}$alkyl, $-S(O)_2C_{1-4}$ alkyl, $R_{25}(R_{24})N-$ and C_{1-4}alkoxy and contains 0, 1 or 2 R_{15} substituents which is not CN, or $-S(O)C_{1-4}$alkyl, or $-S(O)_2C_{1-4}$ alkyl, or $R_{25}(R_{24})N-$ or C_{1-4}alkoxy;

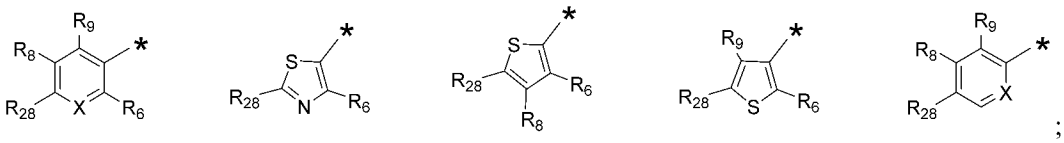
or wherein said heteroaryl is a 5 or 6 membered fully unsaturated monocyclic group comprising ring carbon atoms and 1, 2, 3 or 4 ring heteroatoms independently selected from N, O and S, preferably 1 or 2 ring heteratoms, wherein the total number of ring S atoms does not exceed 1, and the total number of ring O atoms does not exceed 1; said heteroaryl contains 0, 1 or 2 R_{15} substituents and is fused to 4, 5 or 6 membered heterocyclyl or 5-6 membered heteroaryl, wherein the heterocyclyl ring contains ring carbon atoms and 1-4 ring heteroatom selected from N, O and S and the heteroaryl ring contains ring carbon atoms and 1, 2, 3 or 4 ring heteroatoms independently selected from N, O and S, and wherein the heterocyclyl and heteroaryl are substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23};

or phenyl, wherein said phenyl is unsubstituted or substituted by 1, 2, 3 or 4, preferably 1 or 2, R_{33}, wherein R_{33} is halo, and wherein said phenyl or halo-substituted phenyl contains 1 or 2 substituents selected from CN, $-S(O)C_{1-4}$alkyl, $-S(O)C_{3-6}$cycloalkyl, $-S(O)_2C_{1-4}$alkyl, halogenated $-S(O)C_{1-4}$alkyl, halogenated $-S(O)_2C_{1-4}$alkyl, and $-PO(C_{1-4}alkyl)_2$,
or wherein said phenyl is unsubstituted or substituted by 1, 2, 3 or 4 R_{15}, and is fused to 4, 5 or 6 membered monocyclic ring or 6, 7, 8, 9 or 10 membered di-cyclic ring, wherein said 4, 5 or 6 membered monocyclic ring or 6, 7, 8, 9 or 10 membered di-cyclic ring contains ring carbon atoms

and 0-3 ring heteroatoms selected from N, O and S and is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23};
wherein, the 4, 5 or 6 membered ring or 6, 7, 8, 9 or 10 membered di-cyclic ring is saturated, partially saturated or unsaturated heterocycle or carbocycle,
each R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23} is independently selected from:

- halo,
- CN,
- $-S(O)_2C_{1-4}$alkyl, unsubstituted or substituted by 1,2 or 3 halo,
- $-PO(C_{1-4}$ alkyl$)_2$,
- (C_1-C_4)alkyl-O- unsubstituted or substituted by 1,2 or 3 halo,
- (C_1-C_4)alkyl unsubstituted or substituted by deuterium, OH, -O-(C_1-C_2)alkyl or 1,2 or 3 halo,
- (C_3-C_4)cycloalkyl unsubstituted or substituted by deuterium, OH, -O-(C_1-C_2)alkyl or 1,2 or 3 halo,
- $HOC(O)-(CH_2)_n-$,
- $H_3C-C(O)(CH_2)_n-$,
- (C_1-C_4)alkyl-O-$C(O)(CH_2)_n$,
- =O,
- azetidinyl or pyrrolidinyl, wherein said azetidinyl and pyrrolidinyl are linked to the rest of the molecule via the N atom, and are each unsubstituted or substituted by 1 or 2 F,
- $R_{25}(R_{24})N-$, wherein R_{24} is H or (C_1-C_4)alkyl unsubstituted or substituted by 1, 2 or 3 halo, R_{25} is H or (C_1-C_4)alkyl unsubstituted or substituted by 1,2 or 3 halo,
- $=CF_2$,
- $=CCl_2$,
- $-S(O)C_{1-4}$alkyl, unsubstituted or substituted by 1,2 or 3 halo,
- $-S(O)C_{3-6}$cycloalkyl,
- $-S(O)_2C_{3-6}$cycloalkyl,

wherein n is 0, 1 or 2,
R_{26} is CH_3, H, halogen or deuterium;
R_{27} is CH_3, H, halogen or deuterium;
or R_{26} and R_{27} join, together with the carbon atom to which they are attached, to form a cyclopropyl ring;
R_2 is the moiety selected from:



;

R_6 is selected from:

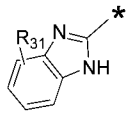
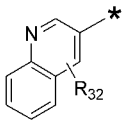
- H,
- halo,

- $(C_1$-$C_4)$alkyl unsubstituted or substituted by 1, 2 or 3 halo,
- $(C_3$-$C_5)$cycloalkyl unsubstituted or substituted by 1, 2 or 3 halo,
- -O-$(C_1$-$C_4)$alkyl unsubstituted or substituted by 1, 2 or 3 halo,
- OH, and
- CN;

R_8 is selected from H, halo, and $(C_1$-$C_4)$alkyl unsubstituted or substituted by 1,2 or 3 halo;
R_9 is selected from H, O-CH_3, OH, CN, CH_3 and halo;
R_{28} is selected from:

- SF_5,
- Deuterium,
- H,
- -C(O)H,
- halo,
- $(C_1$-$C_4)$alkyl unsubstituted or substituted by 1, 2 or 3 halo or deuterium,
- $(C_2$-$C_4)$alkynyl,
- $(C_2$-$C_4)$alkenyl,
- $(C_3$-$C_5)$cycloalkyl unsubstituted or substituted by 1, 2 or 3 halo or deuterium,
- OCF_3;

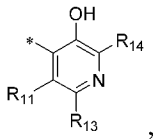
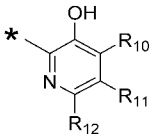
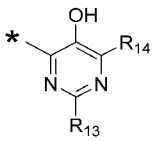
X is selected from C-R_7 and N, wherein R_7 is H or halo, or R_7 can join, together with R_{28} or R_6, and the atoms to which they are attached, to form a fused $(C_4$-$C_6)$cycloalkyl ring, wherein said fused $(C_4$-$C_6)$cycloalkyl ring is unsubstituted or substituted by 1, 2 or 3 halo,
or
R_2 is selected from:


and


wherein
R_{31} is selected from H, halo and CH_3,
R_{32} is selected from H, halo and CH_3,
R_3 is:

- O-CH_3,
- $N(CH_3)_2$,
- S-CH_3,
- $(C_1$-$C_4)$alkyl unsubstituted or substituted by 1, 2 or 3 substituents independently selected from halo and OH;

R_4 is selected from:


,

and


wherein

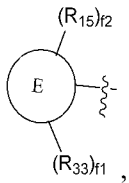
R_{10}, R_{11}, R_{12}, R_{13} and R_{14} are each independently selected from:

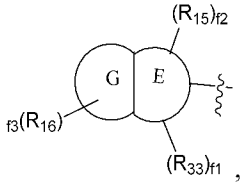
- H,
- Deuterium,
- halo,
- $(C_1$-$C_4)$alkyl unsubstituted or substituted by 1, 2 or 3 halo or deuterium substituents,
- $(C_1$-$C_2)$alkyl substituted by -O-(C_1-$C_2)$alkyl or OH,
- -S-$(C_1$-$C_3)$alkyl,
- -O-$(C_1$-$C_4)$alkyl unsubstituted or substituted by 1,2 or 3 halo or deuterium substituents,
- OH,
- $(C_3$-$C_5)$cycloalkyl, wherein said $(C_3$-$C_5)$Cycloalkyl is unsubstituted or substituted by 1 or 2 halo or deuterium,
- -O-$(C_3$-$C_5)$cycloalkyl,
- -$NR_{34}R_{35}$, wherein R_{34} and R_{35} are each independently selected from:
  - ✧ H,
  - ✧ Deuterium,
  - ✧ $(C_1$-$C_4)$alkyl, wherein said $(C_1$-$C_4)$alkyl is unsubstituted or substituted by OH or -O$(C_1$-$C_2)$alkyl,

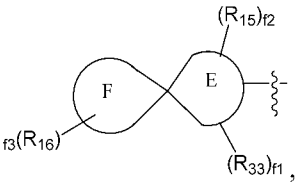
  or R_{34} and R_{35} can join, together with the atom to which they are attached, to form an azetidinyl, pyrrolidinyl or piperidinyl ring, wherein said azetidinyl, pyrrolidinyl and piperidinyl are unsubstituted or substituted with CH_3;
- CN,
- -$(C_2$-$C_4)$alkenyl,
- -$(C_2$-$C_4)$alkynyl,
- -C(O)H, and
- -C(O)$(C_1$-$C_4)$alkyl;

and

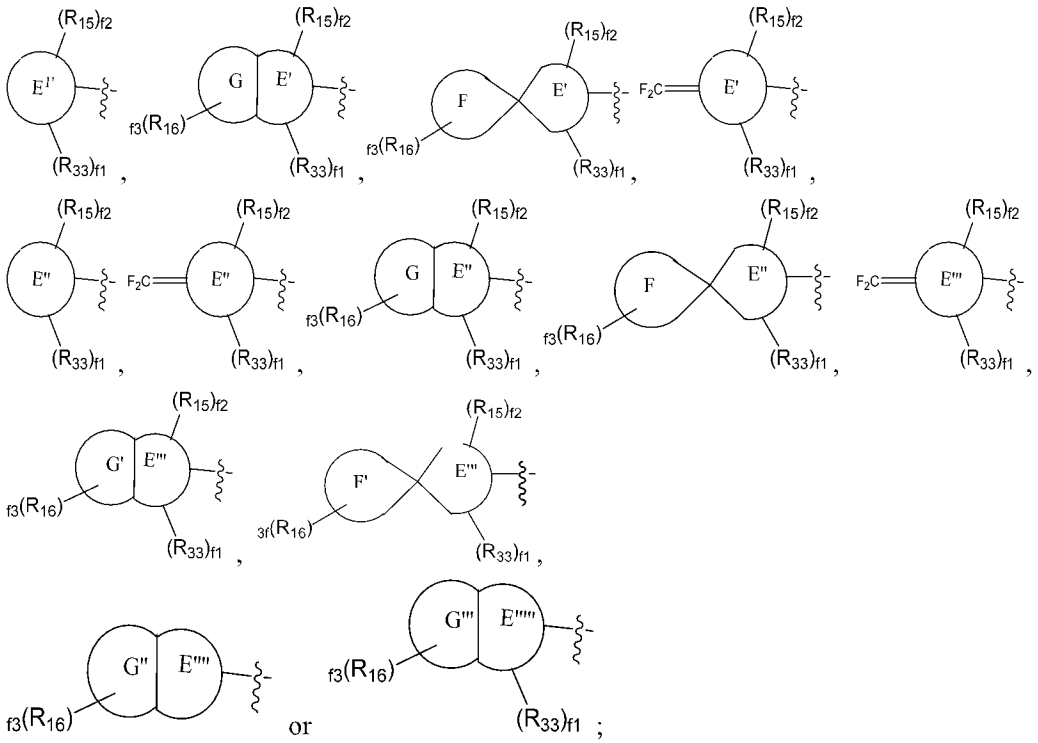
* indicates a point of attachment.

2. The compound of claim 1, or a pharmaceutically acceptable salt, a hydrate, a solvate, a prodrug, a stereoisomer, a deuterated product or a tautomer thereof, wherein R_1 is 

, 

, 

,



wherein, ring E is (C_3-C_4)cycloalkyl which contains 0, 1, or 2 R_{15} substituents;

or E is a substituted 5-6-membered cycloalkenyl, or a substituted 5-6-membered heterocyclyl, which is substituted by 1 or 2 substituents selected from $=CF_2$, CN, $-S(O)_2C_{1-4}$alkyl, and $=CCl_2$, and 0, 1, or 2 R_{15} substituents which are not $=CF_2$, CN, $-S(O)_2C_{1-4}$alkyl, or $=CCl_2$;

or E is a phenyl substituted by 1 or 2 substituents selected from CN, $-S(O)_2C_{1-4}$alkyl, $-S(O)C_{1-4}$alkyl, $-S(O)C_{3-6}$cycloalkyl, halogenated $-S(O)C_{1-4}$alkyl, halogenated $-S(O)_2C_{1-4}$alkyl and $-PO(C_{1-4}alkyl)_2$ and 0, 1, or 2 R_{15} substituents which are not CN, $-S(O)_2C_{1-4}$alkyl, $-S(O)C_{1-4}$alkyl, $-S(O)C_{3-6}$cycloalkyl, halogenated $-S(O)C_{1-4}$alkyl, halogenated $-S(O)_2C_{1-4}$alkyl or $-PO(C_{1-4}alkyl)_2$;

or E is a 5-6-membered heteroaryl substituted by 1 or 2 substituents selected from CN, $R_{25}(R_{24})N$- and $-OC_{1-4}$alkyl and 0, 1, or 2 R_{15} substituents which are not CN, or $R_{25}(R_{24})N$- or $-OC_{1-4}$alkyl;

ring E' is independently selected from partially unsaturated monocyclic ring C5-C7 cycloalkenyl;

ring $E^{1'}$ is independently selected from partially unsaturated monocyclic ring C7 cycloalkenyl;

ring E" is independently selected from 4 or 7 membered fully saturated or partially unsaturated heterocyclyl comprising ring carbon atoms and 1 or 2 ring heteroatoms independently selected from N, O and S;

ring E''' is independently selected from 5 or 6 membered fully saturated or partially unsaturated heterocyclyl;

ring E'''' is independently selected from 5-6 membered heteroaryl comprising ring carbon atoms and 1, 2, 3 or 4 ring heteroatoms independently selected from N, O and S, preferably 1 or 2 ring heteraoms, wherein the total number of ring S atoms does not exceed 1, and the total number of ring O atoms does not exceed 1;

ring E''''' is independently selected from phenyl;

ring F is independently selected from (C_3-C_6)cycloalkyl or 3, 4, 5, or 6 membered heterocyclyl comprising ring carbon atoms and 1 or 2 ring heteroatom selected from O, N and S;

ring F' is independently selected from (C_4-C_5)cycloalkyl, or 4, 5, 6 or 7 membered

heterocyclyl comprising ring carbon atoms and 1 or 2 ring heteroatoms selected from O, N and S;

ring G is independently selected from (C_3-C_6)cycloalkyl, or 3, 4, 5, or 6 membered heterocyclyl comprising ring carbon atoms and 1-4 ring heteroatom selected from O, N and S;

ring G' is independently selected from (C_4-C_6)cycloalkyl, or 4, 5, or 6 membered heterocyclyl comprising ring carbon atoms and 1-3 ring heteroatom selected from N and S, or 5-6 membered heteroaryl comprising ring carbon atoms and 1-3 ring heteroatom selected from N and S, or 1 ring O atom and 1 or 2 ring heteroatoms selected from N and S;

ring G" is independently selected from 4, 5 or 6 membered heterocyclyl or 5-6 membered heteroaryl, wherein the heterocyclyl ring contains ring carbon atoms and 1-4 ring heteroatoms selected from N, O and S and the heteroaryl ring contains ring carbon atoms and 1, 2, 3 or 4 ring heteroatoms independently selected from N, O and S;

ring G"' is independently selected from 4, 5 or 6 membered ring contains ring carbon atoms and 0-3 ring heteroatoms selected from N, O and S; preferably G"' is independently selected from (C_4-C_6)cycloalkyl, 4, 5, or 6 membered heterocyclyl comprising ring carbon atoms and 1-3 ring heteroatom selected from N and S, or 1 ring O atom and 1 or 2 ring heteroatoms selected from N and S or 5-6 membered heteroaryl comprising ring carbon atoms and 1-3 ring heteroatoms selected from N and S, or 1 ring O atom and 1 or 2 ring heteroatoms selected from N and S;

R_{33} is halo;

each R_{15} and R_{16} is independently selected from:

- halo,
- CN,
- -S(O)$_2$C$_{1-4}$alkyl, unsubstituted or substituted by 1,2 or 3 halo,
- -PO(C_{1-4} alkyl)$_2$,
- (C_1-C_4)alkyl-O- unsubstituted or substituted by 1,2 or 3 halo,
- (C_1-C_4)alkyl unsubstituted or substituted by deuterium, OH, -O-(C_1-C_2)alkyl or 1,2 or 3 halo,
- HOC(O)-(CH_2)$_n$-,
- H_3C-C(O)(CH_2)$_n$-,
- (C_1-C_4)alkyl-O-C(O)(CH_2)$_n$,
- =O,
- azetidinyl or pyrrolidinyl, wherein said azetidinyl and pyrrolidinyl are linked to the rest of the molecule via the N atom, and are each unsubstituted or substituted by 1 or 2 F,
- $R_{25}(R_{24})N$-, wherein R_{24} is H or (C_1-C_4)alkyl unsubstituted or substituted by 1, 2 or 3 halo, R_{25} is H or (C_1-C_4)alkyl unsubstituted or substituted by 1,2 or 3 halo,
- =CF_2,
- =CCl_2,
- -S(O)C$_{1-4}$alkyl, unsubstituted or substituted by 1,2 or 3 halo,
- -S(O)C$_{3-6}$cycloalkyl,
- -S(O)$_2$C$_{3-6}$cycloalkyl,

wherein n is 0, 1 or 2,

f1 is 0, 1 or 2,

f2 is 0, 1 or 2,
f3 is 0, 1 or 2.

3. The compound of claim 1 or claim 2, or a pharmaceutically acceptable salt, a hydrate, a solvate, a prodrug, a stereoisomer, a deuterated product or a tautomer thereof, wherein R_1 is:

cycloalkenyl

- a partially unsaturated monocyclic ring containing 5 or 6 ring carbon atoms containing 0, 1 or 2 R_{33}, wherein R_{33} is halo, and the cycloalkenyl
  - ✧ contains one $=CF_2$ substituent and 0, 1 or 2 R_{15} substituents,
  - ✧ contains one substituent selected from $=CCl_2$, $-S(O)C_{1-4}$alkyl, $-S(O)_2(C_{1-4}$alkyl), and CN, and contains 0, 1 or 2 R_{15} substituents which are not $=CCl_2$, $-S(O)C_{1-4}$alkyl, $-S(O)_2(C_{1-4}$alkyl), or CN,
  - ✧ has 2 substituents at the same ring carbon atom which join to form a $(C_3$-$C_6)$ cycloalkyl spiro ring, or 3, 4, 5, or 6 membered heterocyclyl spiro ring containing ring carbon atoms and 1 or 2 ring heteroatom selected from O, N and S, and wherein said cycloalkyl or heterocyclyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23},
  - ✧ is fused to $(C_3$-$C_6)$cycloalkyl ring, or 3, 4, 5, or 6 membered heterocyclyl ring contains ring carbon atoms and 1-4 ring heteroatom selected from O, N and S, and wherein said cycloalkyl or heterocyclyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23},
  - ✧ is bridged, and said bridge contains 1 or 2 carbon atoms, and substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23};
- a partially unsaturated monocyclic ring containing 7 ring carbon atoms is substituted by 0, 1 or 2 R_{15} substituents;
  - ✧ contains 0 or 1 $=CF_2$ substituent,
  - ✧ has 2 substitutents at the same ring carbon atom which join to form a $(C_3$-$C_6)$cycloalkyl spiro ring, or 3, 4, 5, or 6 membered heterocyclyl spiro ring contains ring carbon atoms and 1 or 2 ring heteroatoms selected from O, N and S, and wherein said cycloalkyl or heterocyclyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23},
  - ✧ is fused to $(C_3$-$C_6)$cycloalkyl ring, or 3, 4, 5, or 6 membered heterocyclyl ring contains ring carbon atoms and 1-4 ring heteroatoms selected from O, N and S, and wherein said cycloalkyl or heterocyclyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23};

or heterocyclyl

- heterocyclyl is a 4 or 7 membered fully saturated or partially unsaturated group comprising ring carbon atoms and 1 or 2 ring heteroatoms independently selected from N, O and S, wherein said heterocyclyl is unsubstituted or substituted by 1, 2, 3 or 4, preferably 1 or 2, R_{33}, wherein R_{33} is halo, wherein said heterocyclyl or halo-substituted heterocyclyl
  - ✧ contains 0, 1 or 2 R_{15} substituents and 0 or 1 $=CF_2$ substituent,
  - ✧ contains one substituent selected from CN, $-S(O)C_{1-4}$alkyl, and $-S(O)_2C_{1-4}$ alkyl, and contains 0, 1 or 2 substituents selected from halogen, C_{1-4}alkyl, C_{1-4} haloalkyl and C_{3-4} cycloalkyl,

- ✧ has 2 substitutents at the same ring carbon atom which join to form a (C_3-C_6)cycloalkyl spiro ring, or 3, 4, 5, or 6 membered heterocyclyl spiro ring contains ring carbon atoms and 1 or 2 ring heteroatoms selected from O, N and S, and wherein said cycloalkyl or heterocyclyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23},
- ✧ is fused to (C_3-C_6)cycloalkyl ring, or 3, 4, 5, or 6 membered heterocyclyl ring contains ring carbon atoms and 1-4 ring heteroatoms selected from O, N and S, and wherein said cycloalkyl or heterocyclyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23};
- ✧ is fused to phenyl, wherein said phenyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23};

- heterocyclyl is a 5 or 6 membered fully saturated or partially unsaturated group comprising ring carbon atoms and 1 or 2 ring heteroatoms independently selected from N, O and S, wherein said heterocyclyl is unsubstituted or substituted by 1, 2, 3 or 4, preferably 1 or 2 R_{33}, wherein R_{33} is halo, wherein said heterocyclyl or halo-substituted heterocyclyl
  - ✧ contains one $=CF_2$ substituent and 0, 1 or 2 R_{15} substituents,
  - ✧ contains one substituent selected from $=CCl_2$, CN, and $-S(O)_2C_{1-4}$ alkyl, and contains 0, 1 or 2 R_{15} substituents which is not $=CCl_2$, CN, or $-S(O)_2C_{1-4}$ alkyl,
  - ✧ has 2 substituents at the same ring carbon atom which join to form a (C_4-C_7)cycloalkyl spiro ring, or 4, 5, 6 or 7 membered heterocyclyl spiro ring contains ring carbon atoms and 1 or 2 ring heteroatoms selected from O, N and S, and wherein said cycloalkyl or heterocyclyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23},
  - ✧ is fused to (C_4-C_6)cycloalkyl ring, 4, 5, or 6 membered heterocyclyl ring containing ring carbon atoms and 1-3 ring heteroatoms selected from N and S, or 5-6 membered heteroaryl ring containing ring carbon atoms and 1-3 ring heteroatoms selected from N and S, or 1 ring O atom and 1 or 2 ring heteroatoms selected from N and S; and wherein said cycloalkyl, heterocyclyl or heteroaryl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23};
  - ✧ is fused to phenyl, wherein said phenyl is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23};

or heteroaryl, wherein said heteroaryl is a 5 or 6 membered fully unsaturated monocyclic group comprising ring carbon atoms and 1, 2, 3 or 4 ring heteroatoms independently selected from N, O and S, preferably 1 or 2 ring heteratoms, wherein the total number of ring S atoms does not exceed 1, and the total number of ring O atoms does not exceed 1, the heteroaryl is substituted by one or more substituents selected from CN, $-S(O)C_{1-4}$alkyl, $-S(O)_2C_{1-4}$ alkyl, $R_{25}(R_{24})N$- and C_{1-4}alkoxy and contains 0, 1 or 2 R_{15} substituents which is not CN, $-S(O)C_{1-4}$alkyl, or $-S(O)_2C_{1-4}$ alkyl, or $R_{25}(R_{24})N$- or C_{1-4}alkoxy;
or wherein said heteroaryl is a 5 or 6 membered fully unsaturated monocyclic group comprising ring carbon atoms and 1, 2, 3 or 4 ring heteroatoms independently selected from N, O and S, preferably 1 or 2 ring heteratoms, wherein the total number of ring S atoms does not exceed 1, and the total number of ring O atoms does not exceed 1; said heteroaryl contains 0, 1 or 2 R_{15} substituents and is fused to 4, 5 or 6 membered heterocyclyl or 5-6 membered heteroaryl, wherein

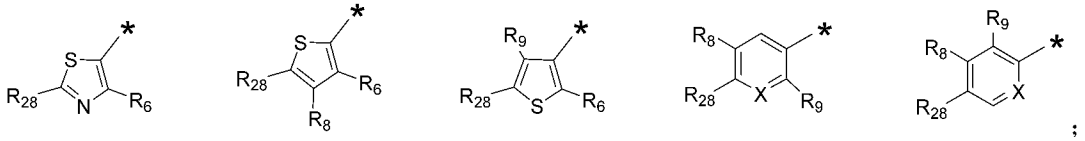
the heterocyclyl ring contains ring carbon atoms and 1-4 ring heteroatom selected from N, O and S and the heteroaryl ring contains ring carbon atoms and 1, 2, 3 or 4 ring heteroatoms independently selected from N, O and S, and wherein the heterocyclyl and heteroaryl are substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23};

or phenyl, wherein said phenyl is unsubstituted or substituted by 1, 2, 3 or 4, preferably 1 or 2, R_{33}, wherein R_{33} is halo, and wherein said phenyl or halo-substituted phenyl contains 1 or 2 substituents selected from CN, -S(O)C_{1-4}alkyl, -S(O)C_{3-6}cycloalkyl, -$S(O)_2C_{1-4}$alkyl, and -$PO(C_{1-4}alkyl)_2$,
or wherein said phenyl is unsubstituted or substituted by 1, 2, 3 or 4 R_{15}, and is fused to 4, 5 or 6 membered monocyclic ring or 6, 7, 8, 9 or 10 membered di-cyclic ring, wherein said 4, 5 or 6 membered monocyclic ring or 6, 7, 8, 9 or 10 membered di-cyclic ring contains ring carbon atoms and 0-3 ring heteroatoms selected from N, O and S, and is substituted by 0, 1 or 2 substituents independently selected from R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23};
wherein, the 4, 5 or 6 membered ring or 6, 7, 8, 9 or 10 membered di-cyclic ring is saturated, partially saturated or unsaturated heterocycle or carbocycle,
each R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{22} and R_{23} is independently selected from:

- halo,
- CN,
- -$S(O)_2C_{1-4}$alkyl, unsubstituted or substituted by 1,2 or 3 halo,
- -$PO(C_{1-4}$ alkyl$)_2$,
- (C_1-C_4)alkyl-O- unsubstituted or substituted by 1,2 or 3 halo,
- (C_1-C_4)alkyl unsubstituted or substituted by deuterium, OH, -O-(C_1-C_2)alkyl or 1,2 or 3 halo,
- (C_3-C_4)cycloalkyl unsubstituted or substituted by deuterium, OH, -O-(C_1-C_2)alkyl or 1,2 or 3 halo,
- HOC(O)-$(CH_2)_n$-,
- H_3C-C(O)$(CH_2)_n$-,
- (C_1-C_4)alkyl-O-C(O)$(CH_2)_n$,
- =O,
- azetidinyl or pyrrolidinyl, wherein said azetidinyl and pyrrolidinyl are linked to the rest of the molecule via the N atom, and are each unsubstituted or substituted by 1 or 2 F,
- $R_{25}(R_{24})$N-, wherein R_{24} is H or (C_1-C_4)alkyl unsubstituted or substituted by 1, 2 or 3 halo, R_{25} is H or (C_1-C_4)alkyl unsubstituted or substituted by 1,2 or 3 halo,
- =CF_2,
- =CCl_2,
- -S(O)C_{1-4}alkyl, unsubstituted or substituted by 1,2 or 3 halo,
- -S(O)C_{3-6}cycloalkyl,
- -$S(O)_2C_{3-6}$cycloalkyl,

wherein n is 0, 1 or 2.

4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, a hydrate, a solvate, a prodrug, a stereoisomer, a deuterated product or a tautomer thereof, wherein R_2 is selected from:


;

X is selected form: N, or CH;

R_6 is selected from:

- H,
- halo,
- (C_1-C_4)alkyl unsubstituted or substituted by 1, 2 or 3 halo,
- (C_3-C_5)cycloalkyl unsubstituted or substituted by 1, 2 or 3 halo,
- -O-(C_1-C_4)alkyl unsubstituted or substituted by 1, 2 or 3 halo,
- OH, and
- CN;

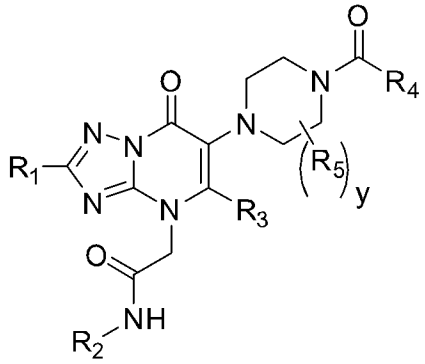
R_8 is selected from H, halo, and (C_1-C_4)alkyl unsubstituted or substituted by 1,2 or 3 halo;

R_9 is selected from H, O-CH_3, OH, CN, CH_3 and halo;

R_{28} is selected from:

- SF_5,
- Deuterium,
- H,
- -C(O)H,
- halo,
- (C_1-C_4)alkyl unsubstituted or substituted by 1, 2 or 3 halo or deuterium,
- (C_2-C_4)alkynyl,
- (C_2-C_4)alkenyl,
- (C_3-C_5)cycloalkyl unsubstituted or substituted by 1, 2 or 3 halo or deuterium,
- OCF_3.

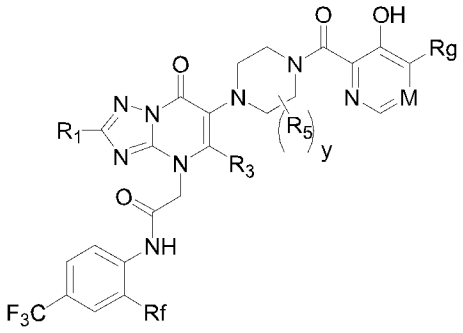
5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt, a hydrate, a solvate, a prodrug, a stereoisomer, a deuterated product or a tautomer thereof, wherein the compound has a structure of formula (II)



(II)

wherein, R_1, R_2, R_3, R_4, R_5 and y is defined as claim 1.

6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt, a hydrate, a solvate, a prodrug, a stereoisomer, a deuterated product or a tautomer thereof, wherein the compound has a structure of formula (III):



(III)

wherein

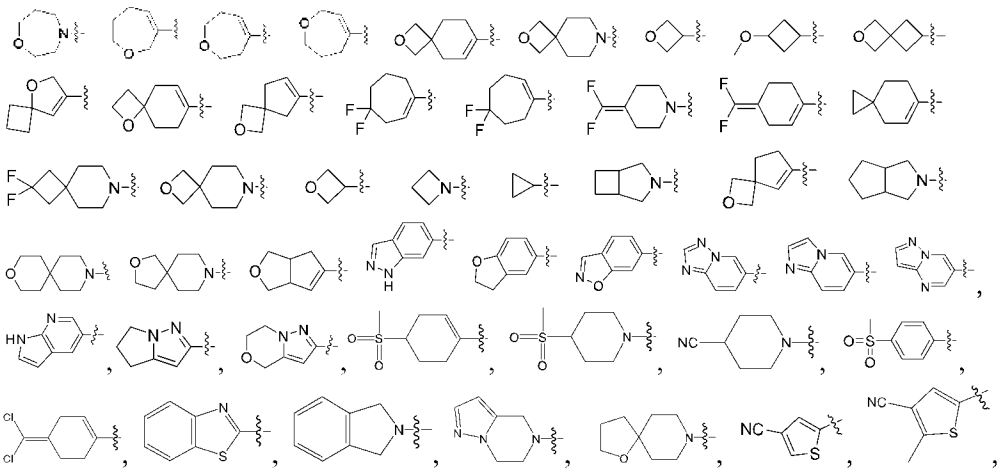
M is N or CH;

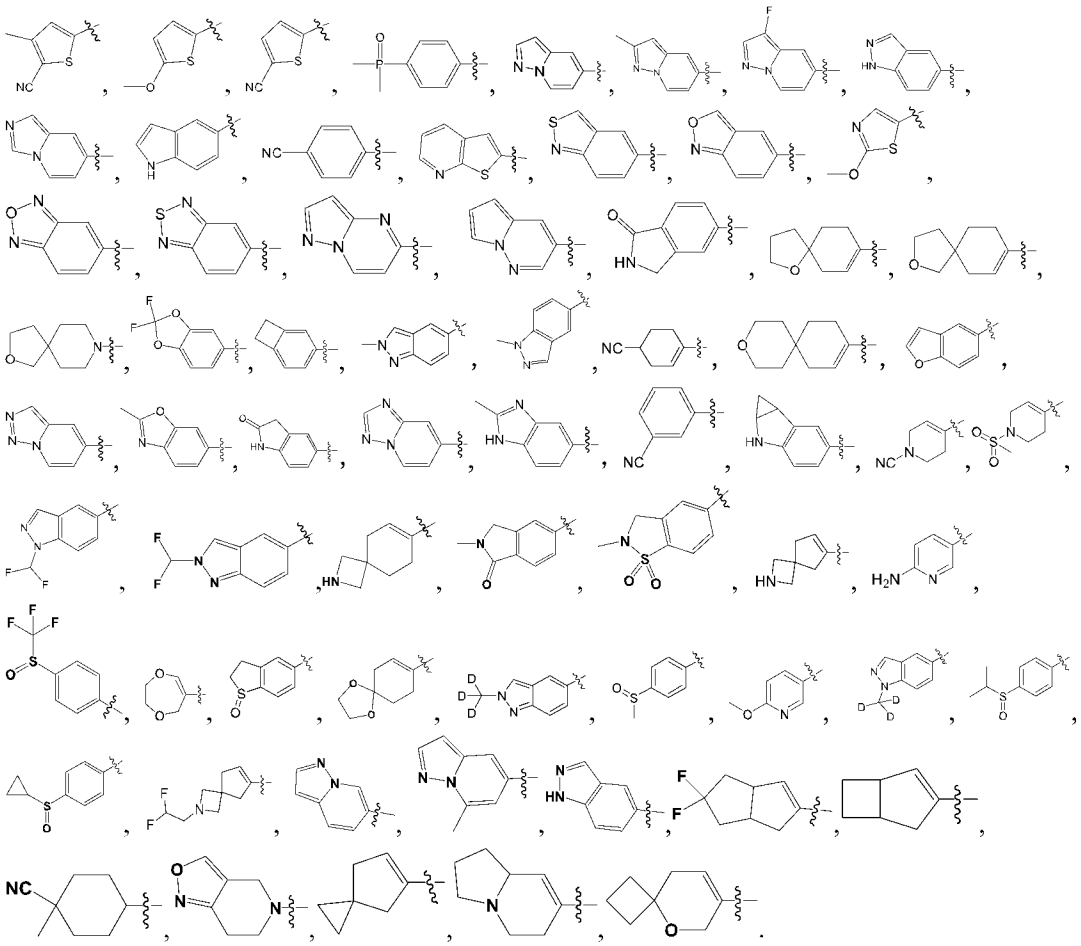
Rf is selected from H, halogen, C_{1-6} alkyl, and halogenated C_{1-6} alkyl; preferably Rf is halogen;

Rg is selected from H, halogen, C_{1-6} alkyl, and halogenated C_{1-6} alkyl;

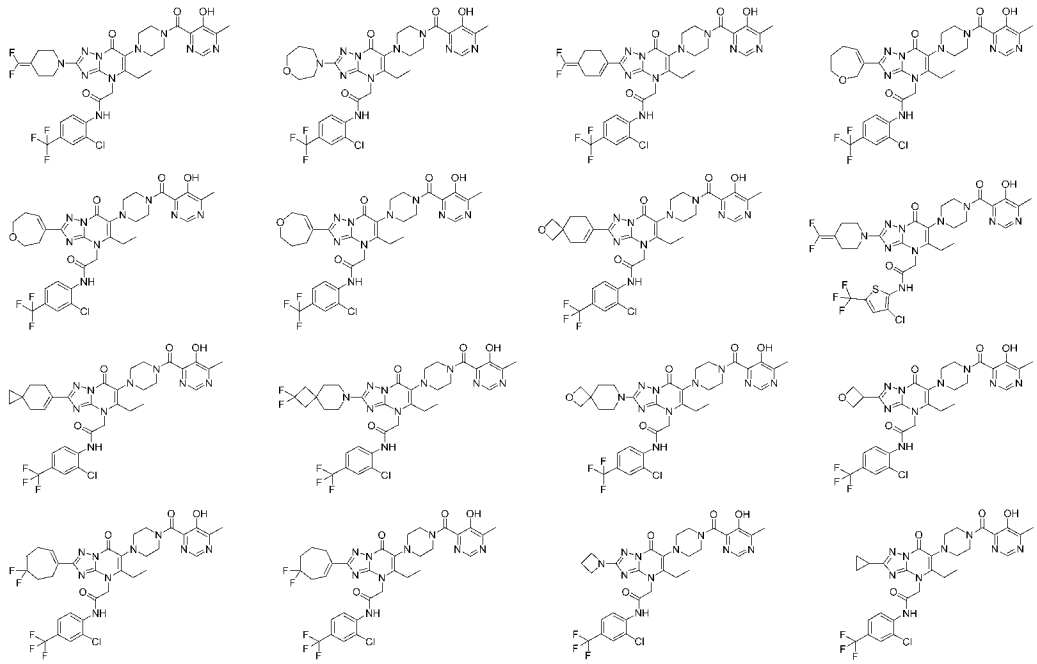
and R_1, R_3, R_5 and y are defined as above.

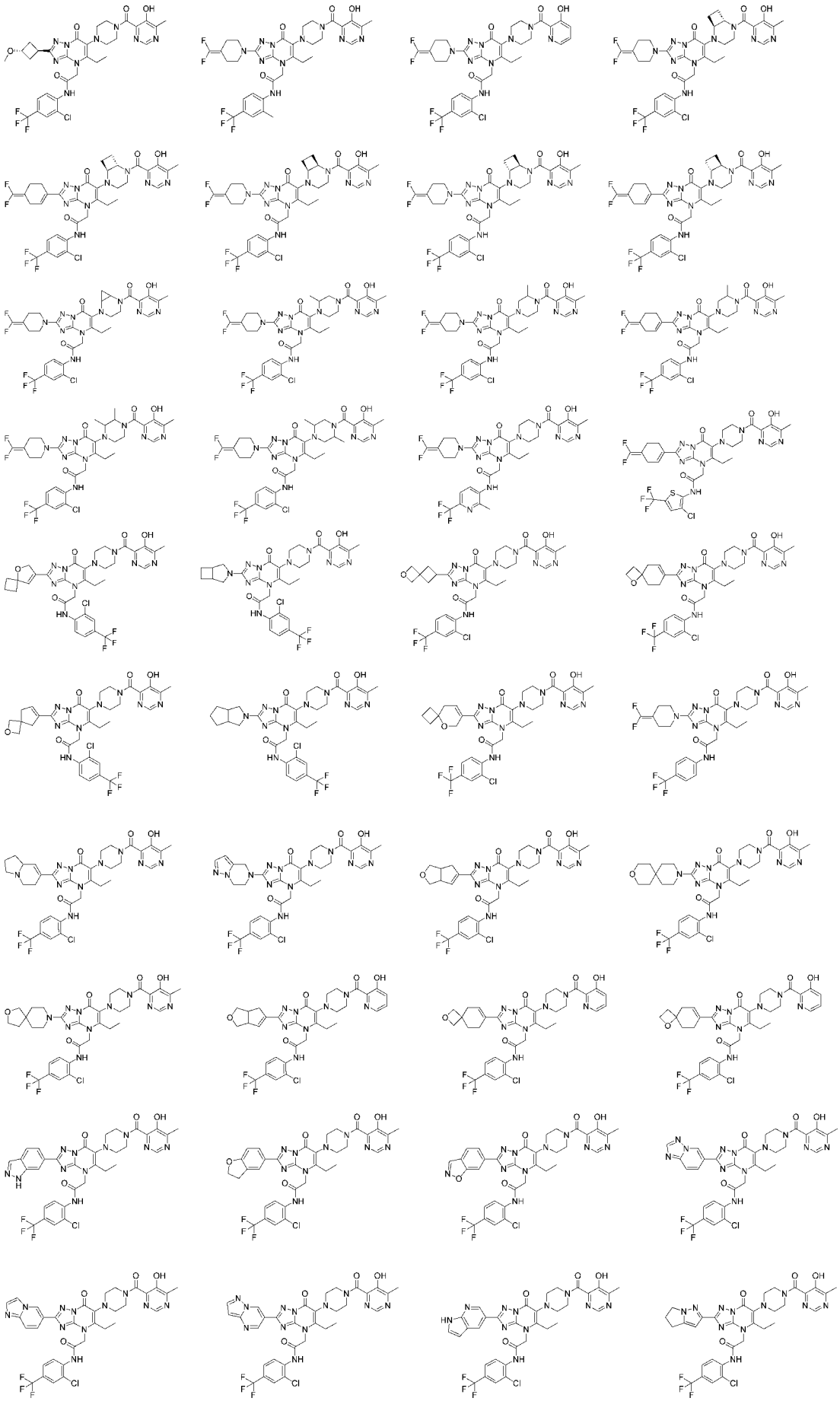
7. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt, a hydrate, a solvate, a prodrug, a stereoisomer, a deuterated product or a tautomer thereof, wherein R_1 is independently selected from:

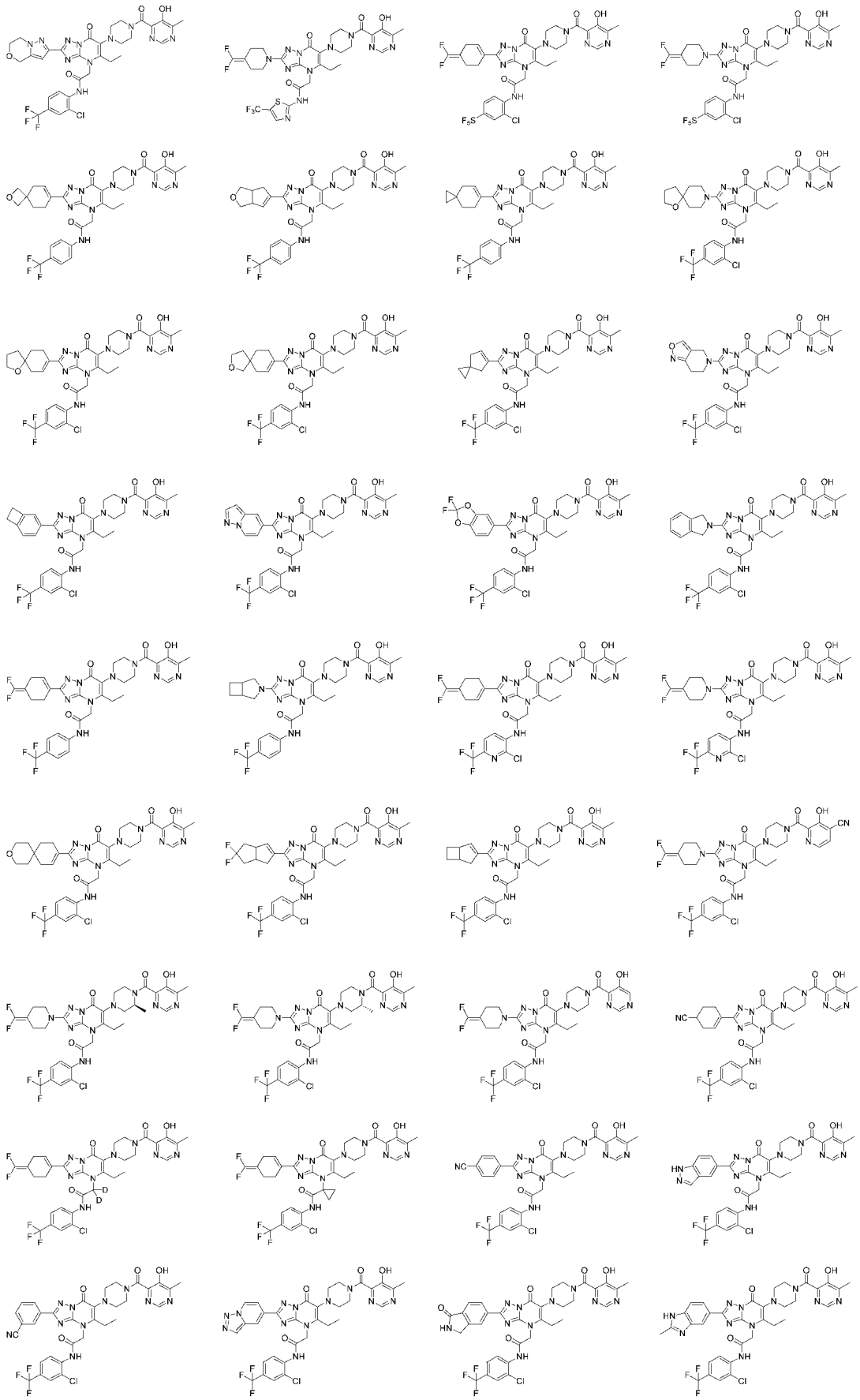


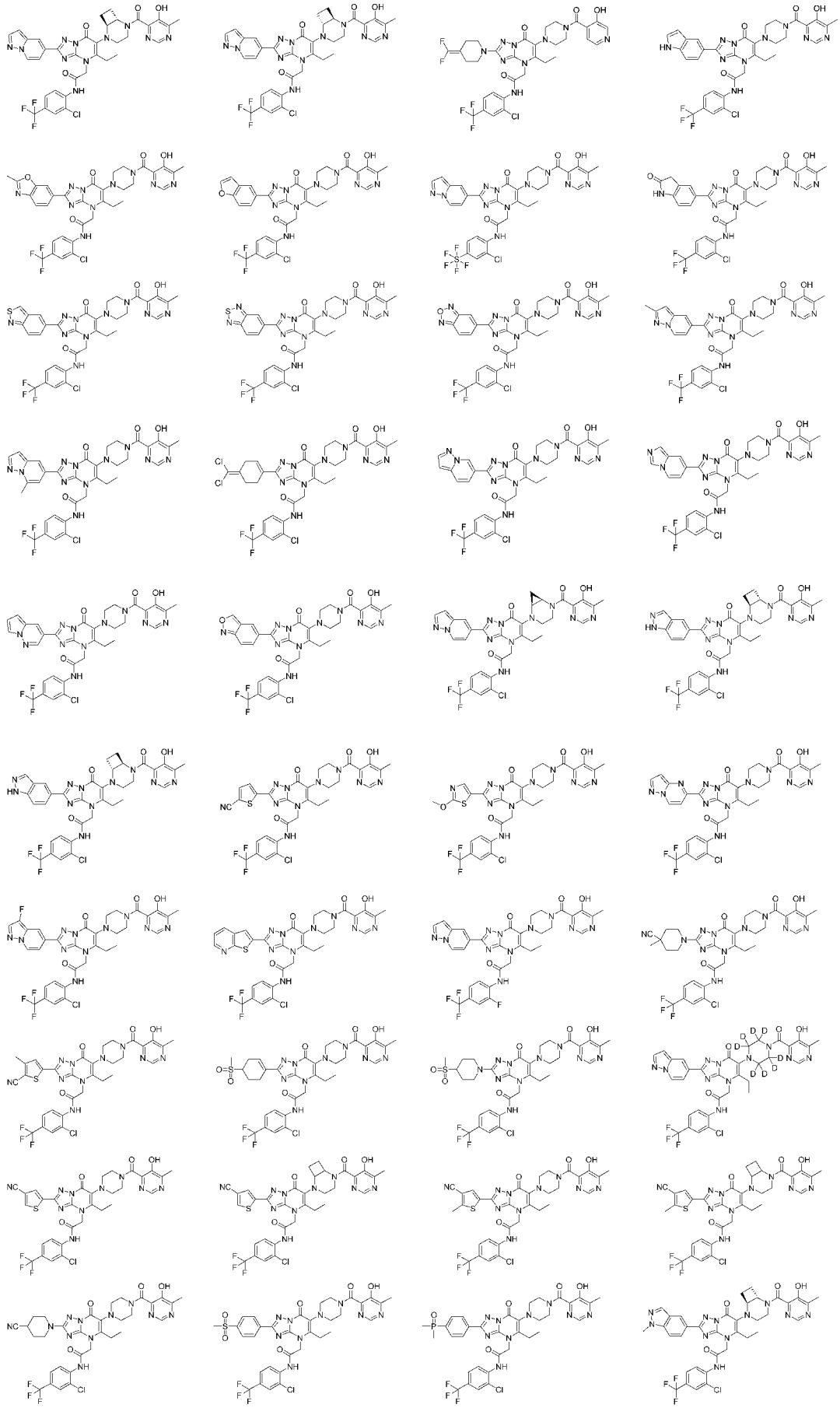


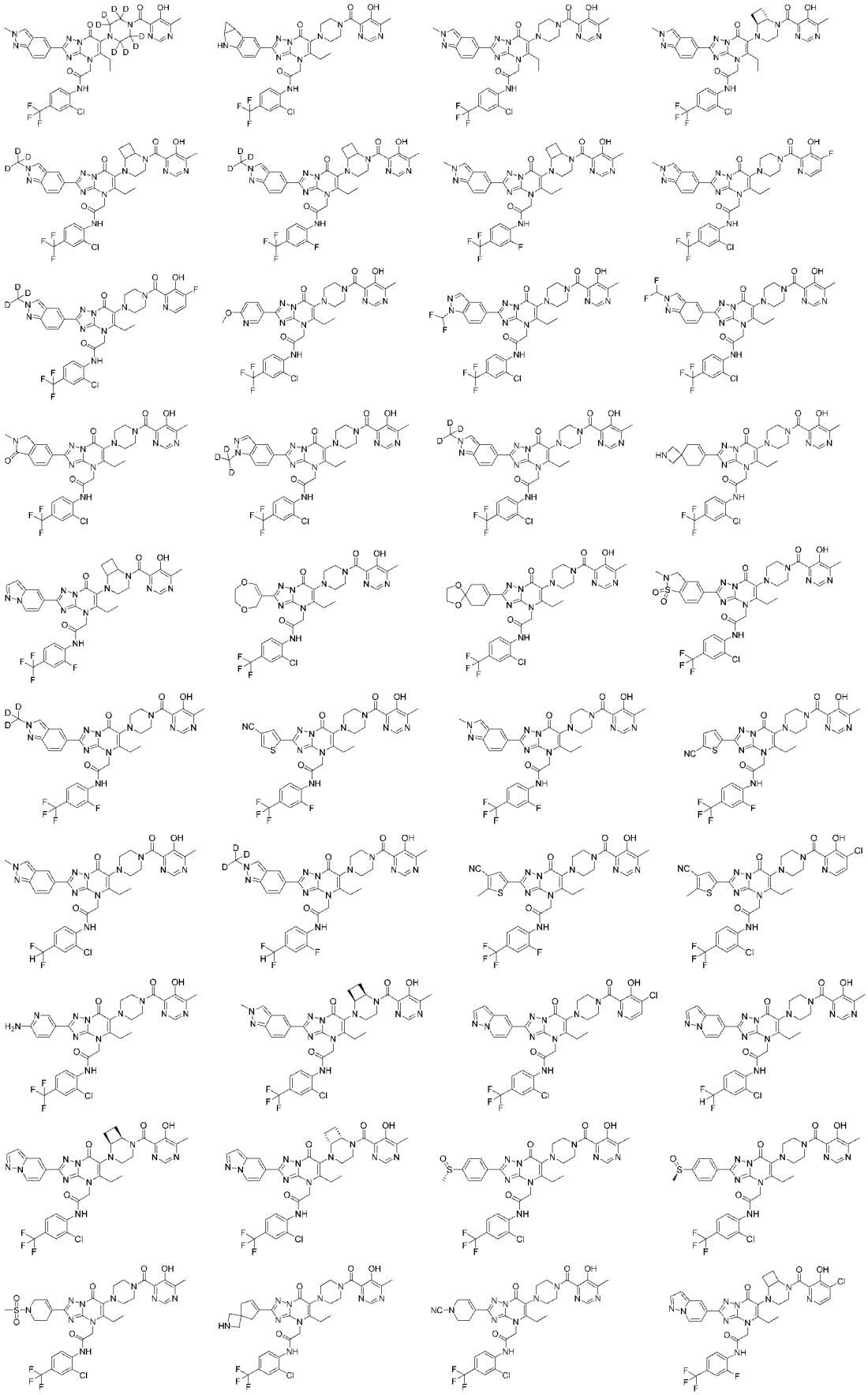
8. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt, a hydrate, a solvate, a prodrug, a stereoisomer, a deuterated product or a tautomer thereof, wherein the compound is selected from:

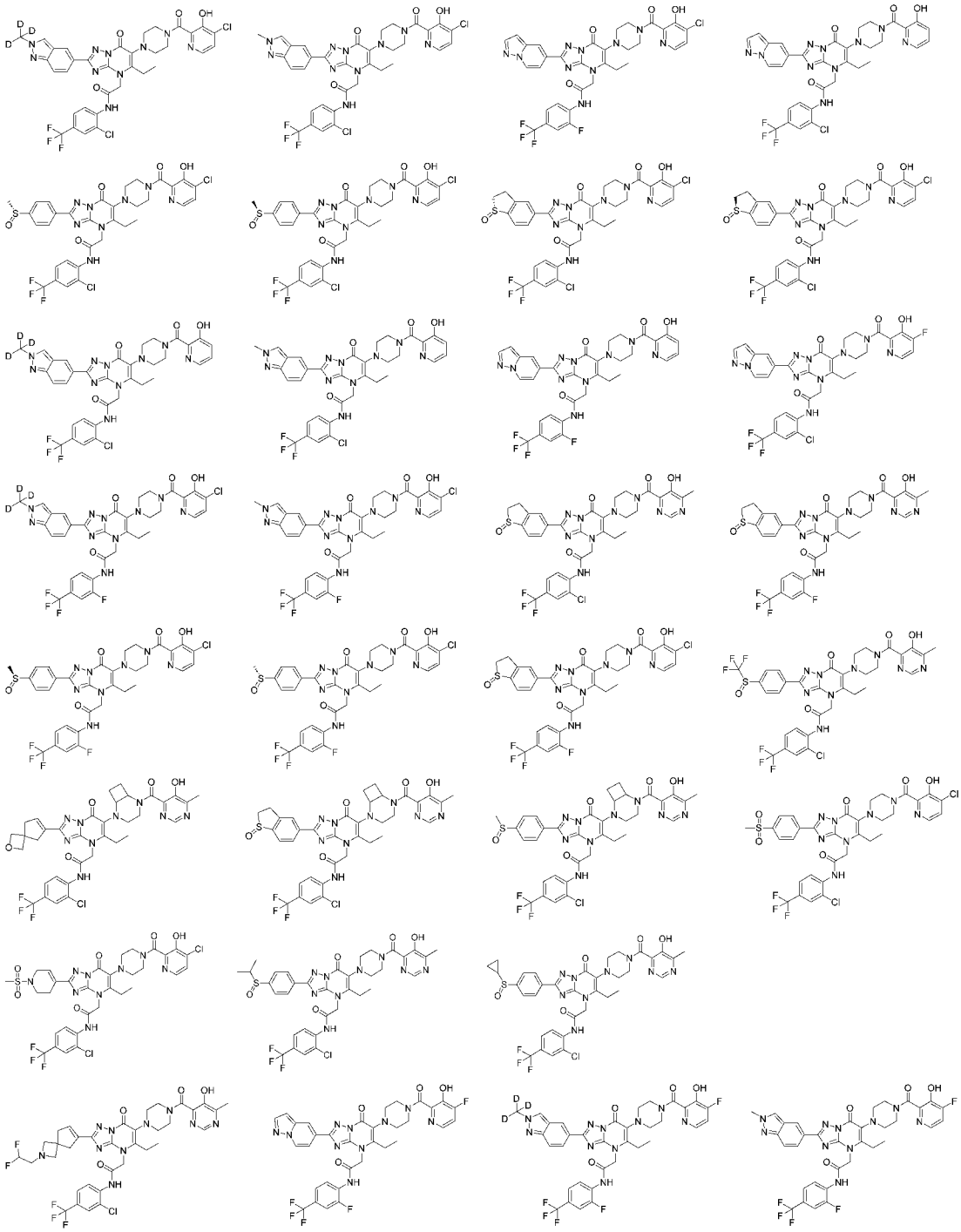












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9. A pharmaceutical composition comprising a compound of any one of claims 1-8, or a pharmaceutically acceptable salt, a hydrate, a solvate, a prodrug, a stereoisomer, a deuterated product or a tautomer thereof and one or more pharmaceutically acceptable carriers or excipients.

10. A use of a compound of any one of claims 1-8, or a pharmaceutically acceptable salt, a hydrate, a solvate, a prodrug, a stereoisomer, a deuterated product or a tautomer thereof in the manufacture of a medicament for the treatment of a disorder or disease which can be treated by WRN inhibition.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2024/098708

A. CLASSIFICATION OF SUBJECT MATTER

C07D487/04(2006.01)i; A61K31/519(2006.01)i; A61P35/00(2006.01)i

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)

IPC: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)

CNTXT,DWPI,ENTXT,ENTXTC,REGISTRY(STN),CAPLUS(STN),MARPAT(STN),Web of science,BAIDU,CNKI,WRN, werner,helicase,tumor,tumour,structure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PX	WO 2024105610 A1 (NOVARTIS AG) 23 May 2024 (2024-05-23) abstract,claims 1-8, description pages 28-43	1-10
PX	WO 2024105553 A1 (NOVARTIS AG) 23 May 2024 (2024-05-23) abstract,description pages 2-13,132,139,141-142,145,148-150	1-10
X	WO 2022249060 A1 (NOVARTIS AG) 01 December 2022 (2022-12-01) abstract, claims 1-35,description pages 2-11	1-10
A	WO 2018229683 A1 (NOVARTIS AG) 20 December 2018 (2018-12-20) abstract, claims 1-20	1-10
A	CN 102439011 A (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 02 May 2012 (2012-05-02) abstract, claims 1-34	1-10

☐ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
03 September 2024	**13 September 2024**

Name and mailing address of the ISA/CN	Authorized officer
CHINA NATIONAL INTELLECTUAL PROPERTY ADMINISTRATION **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088, China**	**LI,QingFang** Telephone No. **(+86) 010-53966126**

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2024/098708

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WO 2024105610 A1	23 May 2024	US 2024197715 A1	20 June 2024
WO 2024105553 A1	23 May 2024	None	
WO 2022249060 A1	01 December 2022	None	
WO 2018229683 A1	20 December 2018	None	
CN 102439011 A	02 May 2012	ZA 201106268 B	27 February 2013
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