

Description

Title of Invention

AZOLYLPYRIDINE PYRIDAZINONE AMIDE AS SOS1 INHIBITOR

Technical Field

The present invention relates to a novel compound having SOS1 inhibitory activity, a solvate, stereoisomer or pharmaceutically acceptable salt thereof, a pharmaceutical composition for preventing or treating a disease, comprising the same as an active ingredient, and a medicinal use thereof.

Background Art

Mutations in the RAS gene are a major oncogene with a high incidence in human cancers, and are observed in 20 to 30% of human cancers, particularly in lung cancer, colon cancer, rectal cancer, and pancreatic cancer at high rates. RAS-family proteins include KRAS, NRAS or HRAS.

RAS proteins are small GTPases that exist in cells in either a GTP-bound or GDP-bound state, and are molecular switches that cycle between an active GTP-bound state and an inactive GDP-bound state. Mutations in the RAS gene reduce the ability of the RAS, a GTPase to hydrolyze GTP, leaving this molecular switch to maintain a constitutively active GTP-bound conformation, thereby inducing oncogenic downstream signaling (for example, Raf-MEK-ERK pathway or PI3K-PDK1-AKT pathway).

Meanwhile, binding of GTPase activating protein (GAP) such as NF1 accelerates the weak intrinsic GTPase activity of RAS proteins, thereby downregulating active RAS and returning it to an inactive form. On the other hand, binding of guanine nucleotide exchange factors (GEF) such as SOS1 promotes the release of GDP from RAS proteins and increases the GTP-bound active state.

Various studies on methods for directly or indirectly inhibiting RAS have been conducted in the prior art. However, it has been found that direct inhibition of RAS is extremely difficult due to the picomolar level of affinity of GTP for the binding site, lack of other well-defined pockets, and the fact that RAS interacts with GEFs, GAPs and effectors through the wide and flat protein-protein interaction surface, which makes difficult to apply small molecule drugs, and the like. In addition, a method of indirectly inhibiting RAS by targeting farnesyl transferase has also been attempted, but an approved drug has not yet been prepared. In view of this failure to directly or indirectly inhibit RAS, it has been generally considered to be difficult to target RAS for drug development.

Under these circumstances, a method of inhibiting RAS by inhibiting the interaction between RAS and GEF to prevent the reloading of GTP has emerged.

SOS1 (Son of Sevenless 1) is a type of guanine nucleotide exchange factor (GEF), which promotes the release of GDP from RAS family proteins to allow GTP binding, thereby regulating RAS family protein signaling. Son of Sevenless (SOS) protein exists in two isoforms, SOS1 and SOS2, and only SOS1 is phosphorylated by ERK. Growth factor-induced phosphorylation of SOS1 is mostly mediated by ERK, which phosphorylates at least four serine residues in the C-terminal region of SOS1. This suggests that SOS1 plays an important role in the regulation of negative feedback of the KRAS pathway. The SOS1 protein consists of 1333 amino acids (150 kDa). SOS1 is a multi-domain protein having two tandem N-terminal histone domains (HD) followed by a Dbl homology domain (DH), a plextrin homology domain (PH), a helical linker (HL), a RAS exchange motif (REM), a CDC25 homology domain and a C-terminal proline rich domain (PR). SOS1 has two binding sites for RAS family proteins (i.e., a catalytic site that binds GDP-binding RAS family proteins and promotes exchange of guanine nucleotides, and an allosteric site that binds GTP-binding RAS family proteins and up-regulates a catalytic site activity of SOS1) (J. Med. Chem. 2021, 64, 10, 6569-6580). Selective pharmacological inhibition of catalytic site binding of SOS1 to RAS family proteins is expected to prevent SOS1-mediated activation of RAS-family proteins in a GTP-bound form.

Therefore, SOS1 inhibitor compounds are expected to inhibit signaling (for example, ERK phosphorylation) in cells downstream of RAS-family proteins, and thus novel SOS1 inhibitor compounds that bind to the SOS1 catalytic site and prevent binding and activation of RAS family proteins are being developed.

It has been reported that SOS1 is critically involved in mutant KRAS activation and oncogenic signaling in cancer (Current Opinion in Chemical Biology, 2021, 62: 109-118). Depletion of SOS1 levels reduced the survival of tumor cells with KRAS mutations, but no such effect was observed in KRAS wild-type cell lines. The SOS1 depletion effect cannot be rescued by the SOS1^{F929A} mutation in which the catalytic site is damaged or the SOS1 mutation (SOS1^{L687E/R688A}) in which the GTP-KRAS binding is defective at the allosteric site, which suggests that targeting the catalytic site or the allosteric site of SOS1 may be an effective option for the treatment of KRAS mutation cancers.

In addition, SOS1 is critically involved in the activation of RAS family protein signaling in cancer through mechanisms other than mutation of RAS family proteins. SOS1 interacts with the adapter protein Grb2 to form the SOS1/Grb2 complex. The complex binds to an activated/phosphorylated receptor tyrosine kinase (for example, EGFR, ErbB2, ErbB3, ErbB4, PDGFR-A/B, FGFR1/2/3, IGF1R, INSR, ALK, ROS, TrkA, TrkB, TrkC, RET, c-MET, VEGFR1/2/3, AXL). In addition, it has been reported that SOS1 is localized to other phosphorylated cell surface receptors such as T cell receptor (TCR), B cell receptor (BCR) and monocyte colony stimulating factor receptor, resulting in activating RAS family proteins.

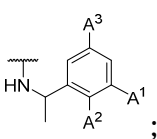
Z^1 and Z^3 are each independently N or CH;

Z^2 is N or CR^a , and Z^4 is CH; or

Z^2 is CR^a , and Z^4 is N;

R^a is H, halogen, OH, CN, substituted or unsubstituted C_1 - C_6 alkoxy, amino, substituted or unsubstituted C_1 - C_6 alkylamino, substituted or unsubstituted di(C_1 - C_6 alkyl)amino, substituted or unsubstituted C_1 - C_6 thioalkoxy, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_3 - C_7 partially unsaturated or saturated cycloalkyl, or 4- to 7-membered heterocyclyl containing 1 or 2 heteroatoms selected from N, O and S;

R^1 is H; D; halogen; OH; CN; C_1 - C_6 alkyl optionally substituted with one or more deuterium, OH, oxo (=O) or halogen; $-NR^A R^B$; $-OR^A$; partially unsaturated or saturated C_3 - C_7 cycloalkyl; optionally substituted C_6 - C_{10} aryl; optionally substituted 5- to 10-membered

heteroaryl; or  ;

R^A and R^B are each independently C_1 - C_6 alkyl optionally substituted with H or R^a ;

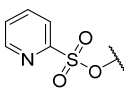
R^2 is H; C_1 - C_6 alkyl optionally substituted with one or more deuterium, OH, C_1 - C_6 alkoxy or halogen; 4- to 7-membered heterocyclyl containing 1 or 2 heteroatoms selected from N, O and S, optionally substituted with one or more R^{21a} ; or C_3 - C_7 partially unsaturated or saturated cycloalkyl optionally substituted with one or more R^{21b} ;

R^{21a} and R^{21b} are each independently C_1 - C_6 alkyl optionally substituted with one or more halogen, CN, OH, C_1 - C_6 alkoxy, carboxy or oxo; C_1 - C_6 acyl; carboxy; C_1 - C_6 alkoxy carbonyl; or C_1 - C_6 alkylsulfonyl;

R^3 is H, halogen, OH, C_1 - C_6 alkoxy, NH_2 , C_1 - C_6 alkylamino, di(C_1 - C_6 alkyl)amino, NO_2 or CN;

R^4 is H, halogen, OH, C_1 - C_6 alkoxy, NH_2 , C_1 - C_6 alkylamino, di(C_1 - C_6 alkyl)amino, NO_2 or CN;

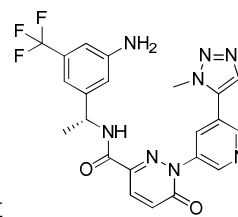
A^1 is C_1 - C_6 alkyl substituted with one or more substituents independently selected

from the group consisting of deuterium, halogen, OH, C_1 - C_3 alkoxy,  and C_1 - C_3 alkyl; or partially unsaturated or saturated C_3 - C_7 cycloalkyl; wherein the one or more substituents may be bonded to the same or different carbons, and two C_1 - C_3 alkyl groups bonded to the same carbon atom may be optionally taken together with the carbon atom to which they are attached to form a C_3 - C_4 cyclic ring;

A^2 is H, halogen, OH, CN or C_1 - C_6 alkyl;

A^3 is H, amino, C_1 - C_6 alkylamino or di(C_1 - C_6 alkyl)amino;

the carbon atoms marked with * and ** are optionally substituted with one or more



deuterium atoms, provided that; the compound of Formula I is not

In Formula I above, Z^1 is N or CH. Z^3 is N or CH. In one embodiment, Z^1 may be N, and Z^3 may be N or CH. In one embodiment, Z^1 may be CH, and Z^3 may be N or CH.

In Formula I, Z^2 is N or CR^a . Z^2 may be CR^a , and Z^4 may be CH. Z^2 may be CR^a , and Z^4 may be N. Alternatively, Z^2 may be N, and Z^4 may be CH.

Said R^a is H, halogen, OH, CN, substituted or unsubstituted C_1 - C_6 alkoxy, amino, substituted or unsubstituted C_1 - C_6 alkylamino, substituted or unsubstituted di(C_1 - C_6 alkyl)amino, substituted or unsubstituted C_1 - C_6 thioalkoxy, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_3 - C_7 partially unsaturated or saturated cycloalkyl, or 4- to 7-membered heterocyclyl containing 1 or 2 heteroatoms selected from N, O or S. In one embodiment, R^a may be H, halogen, OH, CN, C_1 - C_6 alkoxy, amino, C_1 - C_6 alkylamino, di(C_1 - C_6 alkyl)amino, or C_1 - C_6 alkyl. In one embodiment, R^a may be C_3 - C_7 partially unsaturated or saturated cycloalkyl, or 4- to 7-membered heterocyclyl containing 1 or 2 heteroatoms selected from N, O or S. For example, the 4- to 7-membered heterocyclyl may be a 4- to 6-membered heterocyclyl containing 1 or 2 heteroatoms selected from N and O. For example, the 4- to 7-membered heterocyclyl or the 4- to 6-membered heterocyclyl may be morpholinyl, piperidinyl, piperazinyl, pyrrolidinyl, azetidiny, or oxetanyl, but is not limited thereto. For example, the 4- to 7-membered heterocyclyl or the 4- to 6-membered heterocyclyl may be morpholinyl. In one

embodiment, R^a may be H, F, $-NHCH_3$, $-N(CH_3)_2$, $-OCH_3$, $-CH_3$ or .

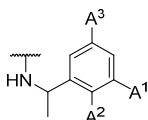
In Formula I above, R^4 is H, halogen, OH, C_1 - C_6 alkoxy, NH_2 , C_1 - C_6 alkylamino, di(C_1 - C_6 alkyl)amino, NO_2 or CN. In one embodiment, R^4 may be H or halogen. For example, R^4 may be H or F.

In one embodiment, the N-containing ring bonded to the pyridazinone/pyridinone core of Formula I may not be substituted with any substituent. In one embodiment, Z^4 may be N, and Z^2 may be CH. In addition, Z^4 may be CH, and Z^2 may be N. In one embodiment, Z^4 may be CH, Z^2 may be CR^a , and both R^a and R^4 may be H.

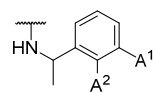
Alternatively, one or more substituents, R^a and/or R^4 may be introduced into the N-containing ring bonded to the pyridazinone/pyridinone core of Formula I. For example, R^a may be halogen, OH, CN, C_1 - C_6 alkoxy, amino, C_1 - C_6 alkylamino, di(C_1 - C_6 alkyl)amino, C_1 - C_6 alkyl, C_3 - C_7 partially unsaturated or saturated cycloalkyl, or 4- to 6-membered heterocyclyl containing 1 or 2 heteroatoms selected from N and O; and R^4 may be H or halogen. For example,

R^a may be H, and R⁴ may be halogen. In one embodiment, Z² and Z⁴ may be each CH, and R⁴ may be H or halogen.

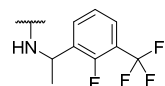
In Formula I above, R¹ is H; D; halogen; OH; CN; C₁-C₆ alkyl optionally substituted with one or more deuterium, OH, oxo (=O) or halogen; -NR^AR^B; -OR^A; partially unsaturated or saturated C₃-C₇ cycloalkyl; optionally substituted C₆-C₁₀ aryl; optionally substituted 5- to



10-membered heteroaryl; or . Said R^A and R^B are each independently C₁-C₆ alkyl optionally substituted with H or R^a. For example, R^A and R^B are each independently H or C₁-C₆ alkyl. Here, A¹, A² and A³ are each as described below. In one embodiment, R¹ may be H; D; halogen; CN; C₁-C₆ alkyl optionally substituted with one or more of deuterium, OH, oxo (=O) or halogen; partially unsaturated or saturated C₃-C₇ cycloalkyl; C₆-C₁₀ aryl; or



. For example, R¹ may be H, D, F, Br, Cl, CN, methyl, ethyl, CD₃, CF₃, -CH₂OH, -CH(OH)CH₃, -C(OH)(CH₃)₂, -C(=O)CH₃, cyclopropyl, cyclohexyl, cyclohexenyl, phenyl, or



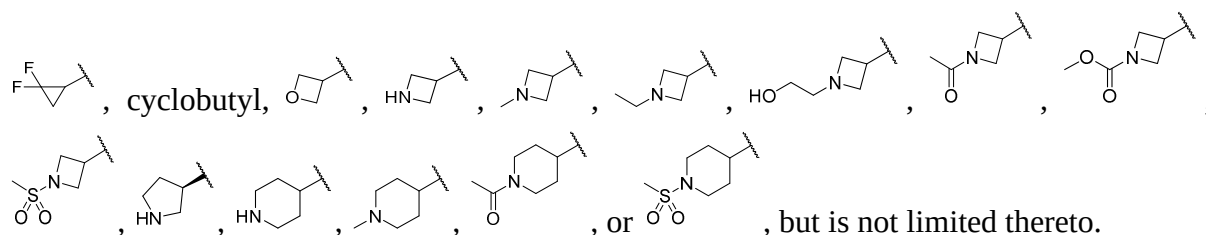
. In one embodiment, R¹ may be CN. In one embodiment, R¹ may be C₁-C₆ alkyl substituted with OH. For example, R¹ may be -CH₂OH, -CH(OH)CH₃ or -C(OH)(CH₃)₂, but is not limited thereto. In one embodiment, R¹ may be C₁-C₆ alkyl substituted with halogen. For example, R¹ may be CF₃. In one embodiment, R¹ may be C₁-C₆ alkyl substituted with oxo (=O). For example, R¹ may be -C(=O)CH₃. In one embodiment, one or more of the carbon atoms included in R¹ or the carbon atom to which R¹ is bonded may be substituted with one or more deuterium atoms. For example, R¹ may be D or CD₃, but is not limited thereto.

In Formula I above, R² is H; C₁-C₆ alkyl optionally substituted with one or more of deuterium, OH, C₁-C₆ alkoxy or halogen; 4- to 7-membered heterocyclyl containing 1 or 2 heteroatoms selected from N, O and S, optionally substituted with one or more R^{21a}; or C₃-C₇ partially unsaturated or saturated cycloalkyl, optionally substituted with one or more R^{21b}. In one embodiment, R² may be C₁-C₆ alkyl optionally substituted with one or more of deuterium, OH, C₁-C₆ alkoxy or halogen. For example, R² may be C₁-C₆ alkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy- C₁-C₆ alkyl. In this case, one or more carbon atoms included in the alkyl residue may be substituted with one or more deuterium atoms. Alternatively, R² may be 4- to 6-membered heterocyclyl containing 1 or 2 heteroatoms selected from N and O, optionally substituted with one or more R^{21a}. In addition, R² may be C₃-C₇ partially unsaturated or saturated cycloalkyl optionally substituted with one or more R^{21b}. For example, R² may be C₃-C₇ partially unsaturated or saturated cycloalkyl optionally substituted with one or more halogens (e.g., F). In one embodiment, one or more of the carbon atoms included in R² may be substituted with one or more deuterium atoms.

In the above definition of R^2 , R^{21a} and R^{21b} are each independently C_1 - C_6 alkyl optionally substituted with one or more of halogen, CN, OH, C_1 - C_6 alkoxy, carboxy or oxo; C_1 - C_6 acyl; carboxy; C_1 - C_6 alkoxy carbonyl; or C_1 - C_6 alkylsulfonyl. In one embodiment, R^{21a} is C_1 - C_4 alkyl optionally substituted with one or more of OH, C_1 - C_4 alkoxy, or oxo; C_1 - C_4 acyl; C_1 - C_4 alkoxy carbonyl; or C_1 - C_4 alkylsulfonyl. In one embodiment, R^{21b} may be halogen.

In one embodiment, R^2 may be C_1 - C_6 alkyl optionally substituted with one or more of deuterium or OH. In one embodiment, R^2 may be oxetanyl, azetidiny, pyrrolidiny, piperidiny, morpholiny or piperaziny, optionally substituted with R^{21a} . In one embodiment, R^2 may be C_3 - C_6 cycloalkyl optionally substituted with 1 to 3 halogens.

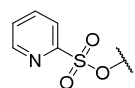
For example, R^2 may be $-CH_3$, $-CD_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2OH$, cyclopropyl,



In Formula I above, R^3 is H, halogen, OH, C_1 - C_6 alkoxy, NH_2 , C_1 - C_6 alkylamino, di(C_1 - C_6 alkyl)amino, NO_2 or CN. In one embodiment, R^3 may be H or halogen. For example, R^3 may be H or Cl.

In one embodiment, one or more substituents, R^2 and/or R^3 may be introduced into the pyrazole/triazole ring of Formula I. For example, R^2 may be C_1 - C_6 alkyl optionally substituted with one or more of deuterium, OH, C_1 - C_6 alkoxy or halogen, and R^3 may be H. For example, R^2 may be C_1 - C_6 alkyl optionally substituted with one or more of deuterium, OH, C_1 - C_6 alkoxy, or halogen, and R^3 may be halogen. For example, R^2 may be 4- to 6-membered heterocyclyl containing 1 or 2 heteroatoms selected from N and O, optionally substituted with one or more R^{21a} ; or C_3 - C_7 partially unsaturated or saturated cycloalkyl optionally substituted with one or more R^{21b} ; and R^3 may be H. For example, R^2 is 4- to 6-membered heterocyclyl containing 1 or 2 heteroatoms selected from N and O, optionally substituted with one or more R^{21a} ; or C_3 - C_7 partially unsaturated or saturated cycloalkyl optionally substituted with one or more R^{21b} ; and R^3 may be halogen. In this case, R^{21a} and R^{21b} are as described above, and particular embodiments of R^2 and R^3 described above may be applied in the same manner.

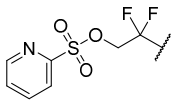
In Formula I above, A^1 is C_1 - C_6 alkyl substituted with one or more substituents independently selected from the group consisting of deuterium, halogen, OH, C_1 - C_3 alkoxy,



and C_1 - C_3 alkyl; or partially unsaturated or saturated C_3 - C_7 cycloalkyl. Said one or more substituents may be bonded to the same or different carbons. When two C_1 - C_3 alkyl groups, as the one or more substituents, are bonded to the same carbon atom, they may be optionally taken together with the carbon atom to which they are attached to form a C_3 - C_4 cyclic ring. In one embodiment, A^1 is C_1 - C_6 alkyl substituted with two or more substituents

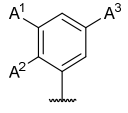
selected from deuterium, F, OH, C₁-C₃ alkoxy and C₁-C₃ alkyl, wherein two of said C₁-C₃ alkyl may be attached to the same carbon atom to form a C₃-C₄ cyclic ring. For example, A¹ may be

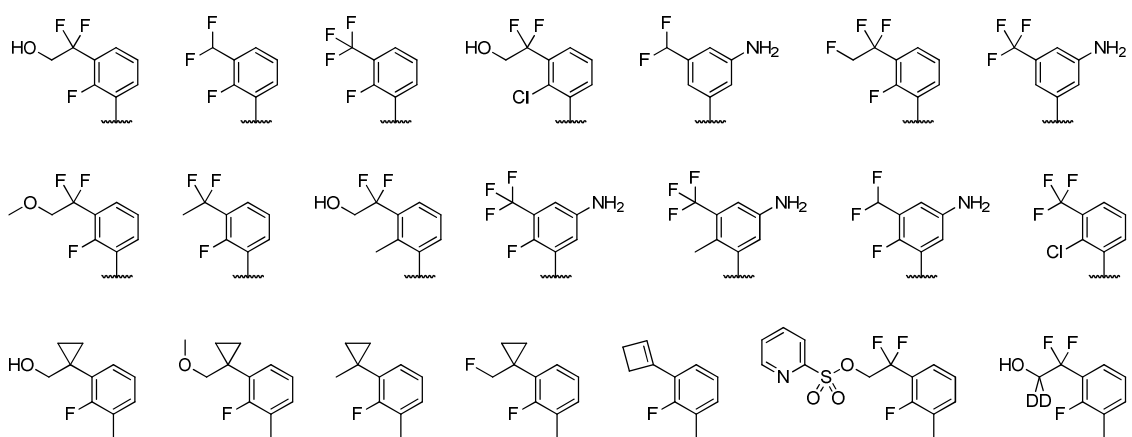
-CHF₂, -CF₃, -CF₂CH₃, -CF₂CH₂F, -CF₂CH₂OH, -CF₂CD₂OH, -CF₂CH₂OCH₃, , ,  or , but is not limited thereto. For example, A¹ may be cyclobutyl or

cyclobutenyl. For example, A¹ may be .

In Formula I above, A² is H, halogen, OH, CN or C₁-C₆ alkyl. In one embodiment, A² may be H, halogen, or C₁-C₄ alkyl. For example, A² may be H, F, Cl or -CH₃.

In Formula I above, A³ is H, amino, C₁-C₆ alkylamino or di(C₁-C₆ alkyl)amino. In one embodiment, A³ may be H or amino.

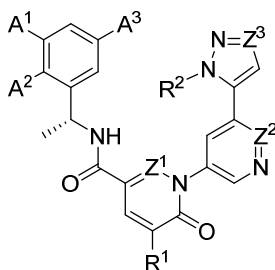
In one embodiment,  of Formula I may be selected from the following structures:



In a compound of Formula I according to the present invention, one or more carbon atoms may be substituted with one or more deuterium. R¹, R² and/or A¹ of Formula I may contain one or more deuterium atoms. In addition, one or more carbon atoms marked with * and ** in Formula I may be optionally substituted with one or more deuterium atoms. The deuterium substitution may provide therapeutic benefits resulting from higher metabolic stability, such as increased half-life in the body and/or reduced dosage. Even in the case where the term “deuterium” is not particularly described for hydrogen included in any other substituent, it is not excluded and should be construed to be within the scope of the present invention.

According to one embodiment, the compound represented by Formula I above may be a compound represented by Formula I-1 below:

[Formula I-1]



Z^1 and Z^3 are each independently N or CH;

Z^2 is N or CR^a ;

R^a is H, halogen, OH, CN, substituted or unsubstituted C_1 - C_6 alkoxy, substituted or unsubstituted C_1 - C_6 alkylamino, substituted or unsubstituted C_1 - C_6 thioalkoxy, or substituted or unsubstituted C_1 - C_6 alkyl;

R^1 is H, halogen, OH, CN, C_1 - C_6 alkyl optionally substituted with one or more deuterium or halogen, $-NR^A R^B$, $-OR^A$, C_3 - C_6 cycloalkyl, optionally substituted C_6 - C_{10} aryl, or optionally substituted 5- to 10-membered heteroaryl;

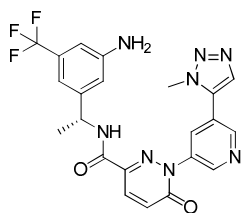
R^A and R^B are each independently C_1 - C_6 alkyl optionally substituted with R^a ;

R^2 is H, or C_1 - C_6 alkyl optionally substituted with one or more deuterium or halogen;

A^1 is C_1 - C_6 alkyl substituted with one or more substituents independently selected from the group consisting of halogen, OH, C_1 - C_3 alkoxy and C_1 - C_3 alkyl, wherein the one or more substituents may be bonded to the same or different carbons, and two C_1 - C_3 alkyls bonded to the same carbon atom may be optionally taken together with the carbon atom to which they are attached to form a C_3 - C_4 cyclic ring;

A^2 is H, halogen, OH, CN or C_1 - C_6 alkyl;

A^3 is H or amino, provided that; the compound of Formula I-1 is not



In Formula I-1, Z^1 and Z^3 are each independently N or CH.

In Formula I-1, Z^2 is N or CR^a . In this case, R^a is H, halogen, OH, CN, substituted or unsubstituted C_1 - C_6 alkoxy, substituted or unsubstituted C_1 - C_6 alkylamino, substituted or unsubstituted C_1 - C_6 thioalkoxy, or substituted or unsubstituted C_1 - C_6 alkyl. For example, R^a may be H, halogen, OH, CN, or C_1 - C_6 alkyl. For example, R^a may be H, halogen or C_1 - C_3 alkyl. For example, R^a may be H, F, $-CH_3$.

According to one embodiment, in Formula I-1 of the present invention, Z^1 may be N, Z^2 may be CR^a , and Z^3 may be N or CH. In this case, R^a is H, halogen, OH, CN, substituted or unsubstituted C_1 - C_6 alkoxy, substituted or unsubstituted C_1 - C_6 alkylamino, substituted or unsubstituted C_1 - C_6 thioalkoxy, or substituted or unsubstituted C_1 - C_6 alkyl. For example, R^a

may be H, halogen, OH, CN, or C₁-C₆ alkyl. For example, R^a may be H. For example, Z¹ may be N, Z² may be CH, and Z³ may be N. In addition, Z¹ may be N, Z² may be CH, and Z³ may be CH.

According to one embodiment, in Formula I-1 of the present invention, Z¹ may be CH, Z² may be CR^a, and Z³ may be N or CH. In this case, R^a is H, halogen, OH, CN, substituted or unsubstituted C₁-C₆ alkoxy, substituted or unsubstituted C₁-C₆ alkylamino, substituted or unsubstituted C₁-C₆ thioalkoxy, or substituted or unsubstituted C₁-C₆ alkyl. For example, R^a may be H, halogen, OH, CN, or C₁-C₆ alkyl. For example, R^a may be H. For example, Z¹ may be CH, Z² may be CH, and Z³ may be N. In addition, all of Z¹, Z² and Z³ may be CH.

According to one embodiment, in Formula I-1 of the present invention, both Z¹ and Z² may be N, and Z³ may be CH. In addition, all of Z¹, Z² and Z³ may be N.

In Formula I-1 of the present invention, R¹ is H, halogen, OH, CN, C₁-C₆ alkyl optionally substituted with one or more deuterium or halogen, -NR^AR^B, -OR^A, C₃-C₆ cycloalkyl, optionally substituted C₆-C₁₀ aryl, or optionally substituted 5- to 10-membered heteroaryl. In this case, R^A and R^B may be each independently C₁-C₆ alkyl optionally substituted with R^a, and the R^a are as described above. For example, R^a may be H, halogen, OH, CN, or C₁-C₆ alkyl.

In one embodiment, R¹ may be H, halogen, OH, CN, C₁-C₆ alkyl optionally substituted with one or more of deuterium or halogen, or C₃-C₆ cycloalkyl. In one embodiment, R¹ may be H, halogen, CN, C₁-C₃ alkyl optionally substituted with one or more of deuterium or halogen, or C₃-C₅ cycloalkyl. For example, R¹ may be H, F, Cl, Br, CN, methyl or cyclopropyl.

In Formula I-1 of the present invention, R² is H or C₁-C₆ alkyl optionally substituted with one or more deuterium. In one embodiment, R² may be C₁-C₃ alkyl optionally substituted with one or more deuterium atoms. For example, R² may be -CH₃, -CD₃ or -CH₂CH₃.

When R¹ and R² are alkyl substituted with one or more deuterium atoms, it may be preferable in terms of providing therapeutic benefits resulting from higher metabolic stability, such as increased half-life in the body and/or reduced dosage. In Formula I-1 of the present invention, even in the case where the term “deuterium” is not particularly described for hydrogen included in the substituents other than R¹ and R², it is not excluded and should be construed to be within the scope of the present invention.

In Formula I-1 of the present invention, A¹ is C₁-C₆ alkyl substituted with one or more substituents selected from the group consisting of halogen, OH and C₁-C₃ alkoxy. The number of substituents in A¹ is not limited as long as the compound is chemically stable and exhibits the desired activity. For example, C₁-C₆ alkyl may be substituted with 1, 2, 3, 4 or 5 substituents. Said one or more substituents may be different from or the same as each other. In addition, said one or more substituents may be bonded to the same or different carbons. For example, when A¹ is ethyl substituted with two F and one OH, two F may be bonded to the same carbon, and one OH may be bonded to a different carbon to form -CF₂CH₂OH. Two C₁-C₃ alkyl groups

bonded to the same carbon atom may be optionally taken together with the carbon atom to which they are attached to form a C₃-C₄ cyclic ring.

According to one embodiment, in Formula I-1 of the present invention, A¹ may be C₁-C₃ alkyl substituted with two or more substituents independently selected from the group consisting of F, OH and methoxy. For example, said C₁-C₃ alkyl may be methyl or ethyl, and may have two F substituted on the same carbon atom, and one F, OH or methoxy optionally substituted on the same or different carbon atom. For example, A¹ may be -CHF₂, -CF₃, -CF₂CH₃, -CF₂CH₂F, -CF₂CH₂OH, and -CF₂CH₂OCH₃.

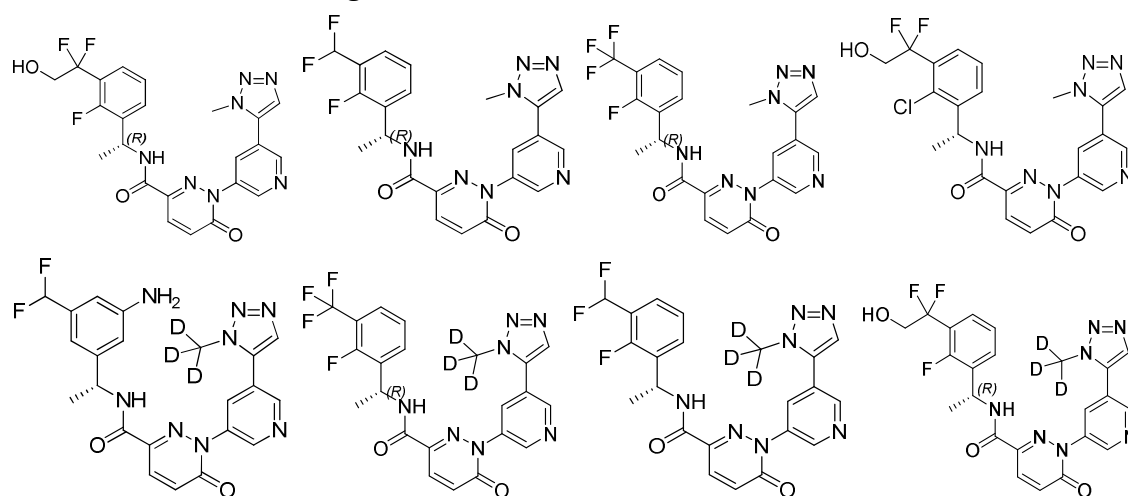
In Formula I-1 of the present invention, A² is H, halogen, OH, CN or C₁-C₆ alkyl. According to one embodiment, A² may be H, halogen, or C₁-C₃ alkyl. For example, A² may be H, F, Cl or -CH₃.

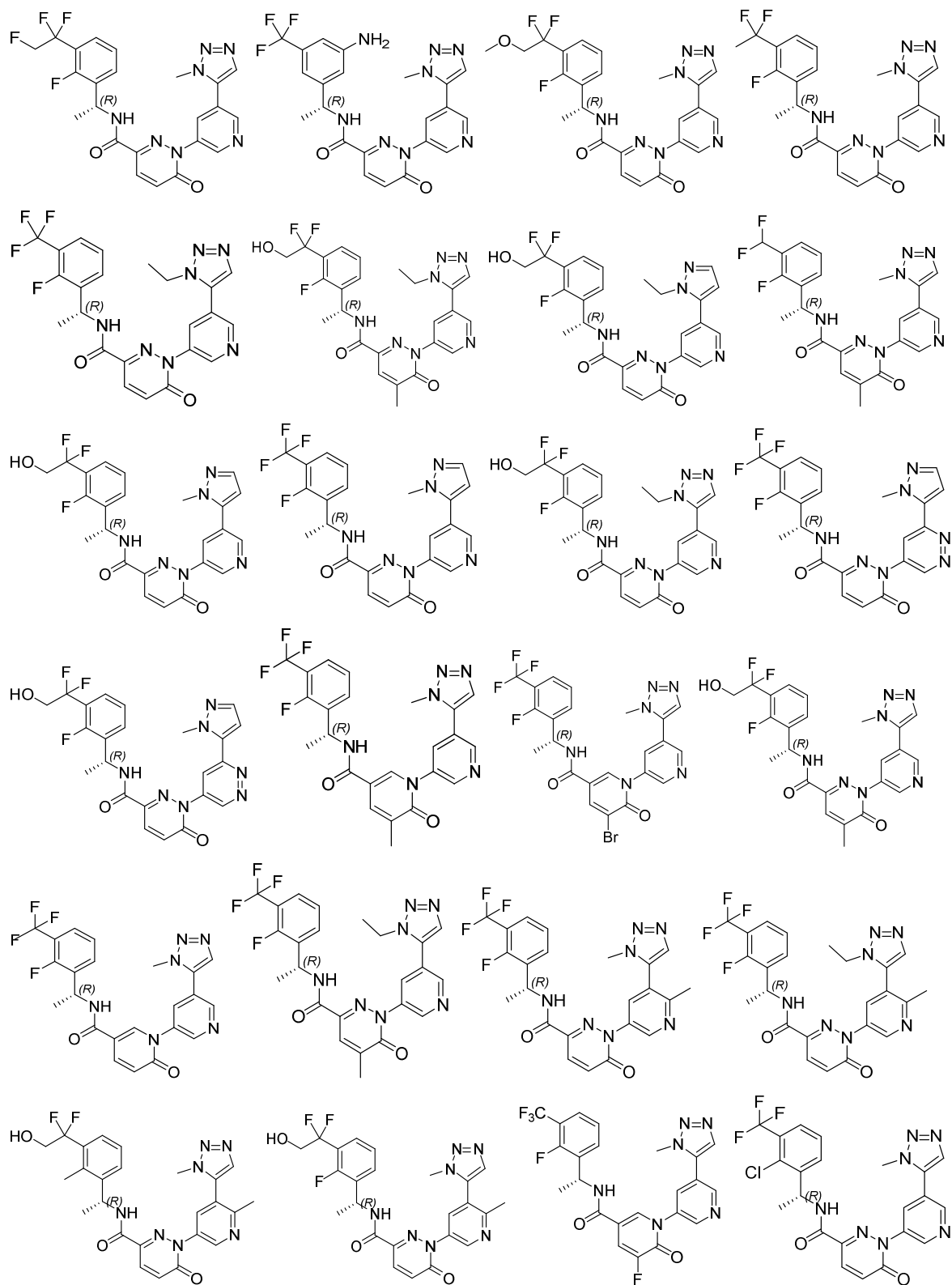
In Formula I-1 of the present invention, A³ may be H or amino. In one embodiment, A³ may be H. Alternatively, A³ may be amino.

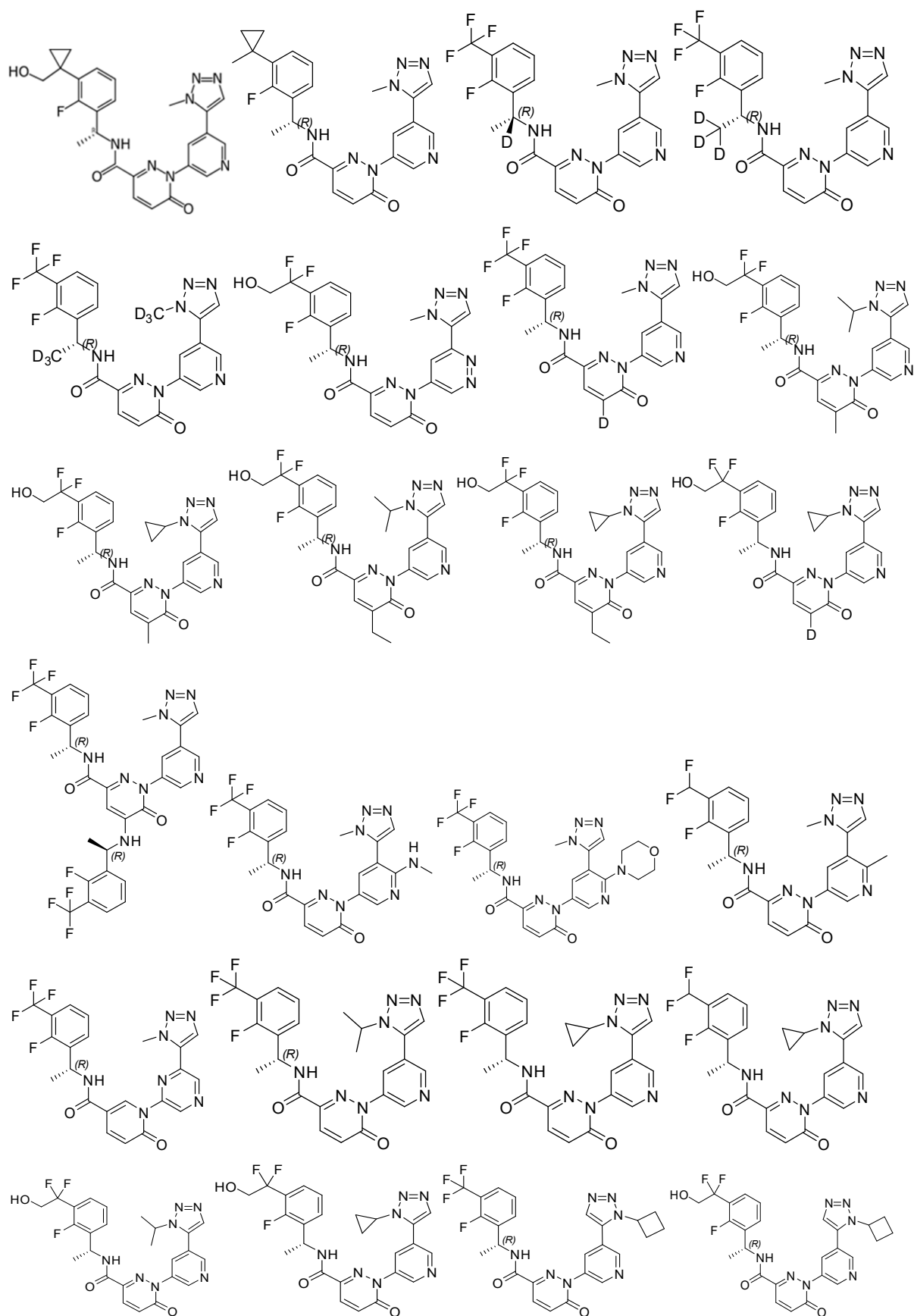
In one embodiment, in Formula I-1 of the present invention, A¹ may be C₁-C₆ alkyl substituted with one or more substituents independently selected from the group consisting of halogen, OH and C₁-C₃ alkoxy, and A² may be H, halogen, OH, CN or C₁-C₆ alkyl, and A³ may be H. In this case, A¹ may be C₁-C₃ alkyl substituted with two or more substituents independently selected from the group consisting of F, OH and methoxy. For example, A¹ may be -CHF₂, -CF₃, -CF₂CH₃, -CF₂CH₂F, -CF₂CH₂OH, and -CF₂CH₂OCH₃. In this case, A² may be H, halogen, or C₁-C₃ alkyl. For example, A² may be H, F, Cl or -CH₃.

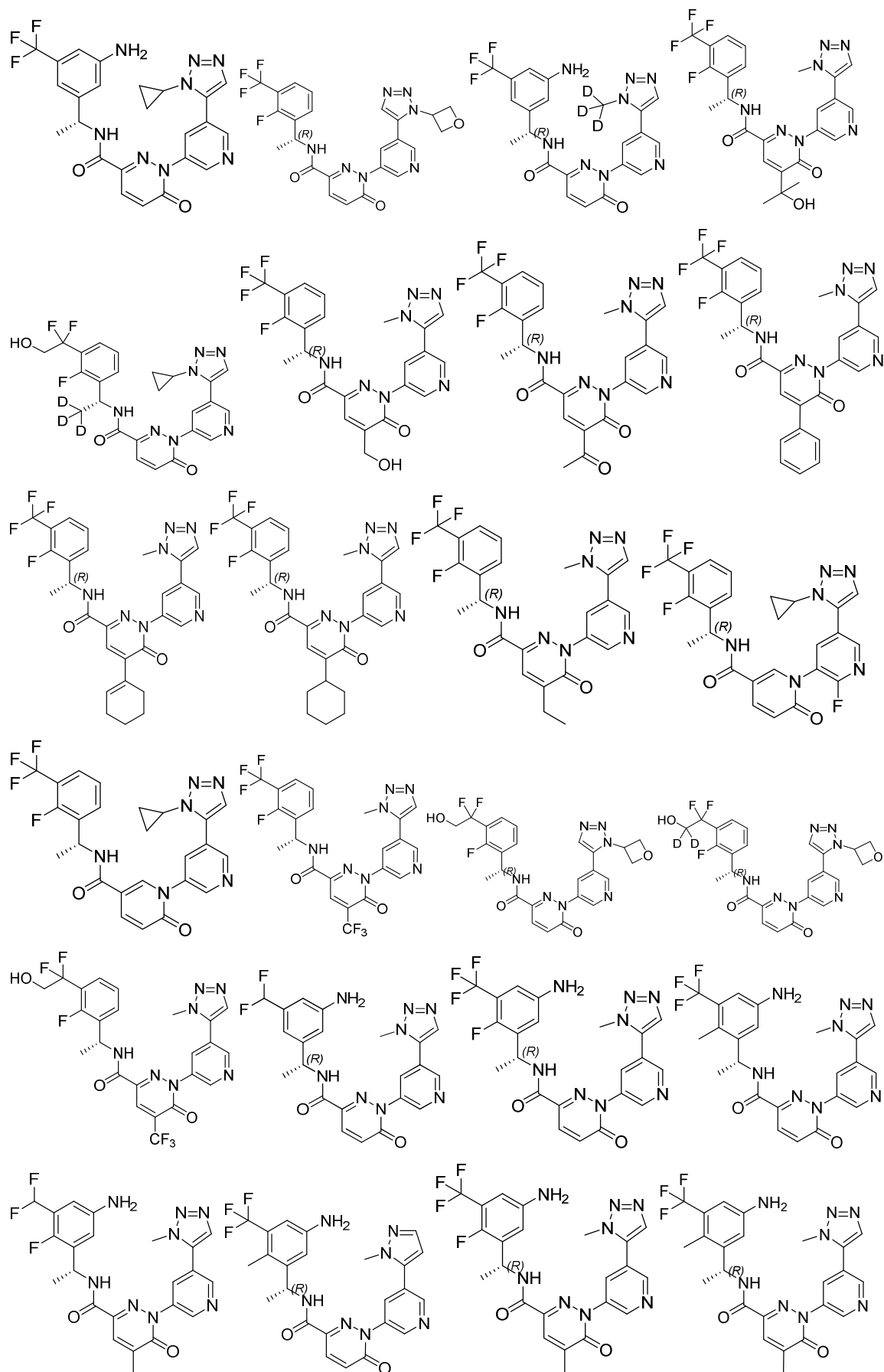
According to one embodiment, in Formula I-1 of the present invention, A¹ may be C₁-C₃ alkyl substituted with two or more F, and A² may be H, halogen or C₁-C₃ alkyl, and A³ may be amino. In this case, A¹ may be -CHF₂ or -CF₃. In addition, said A² may be H, F or -CH₃.

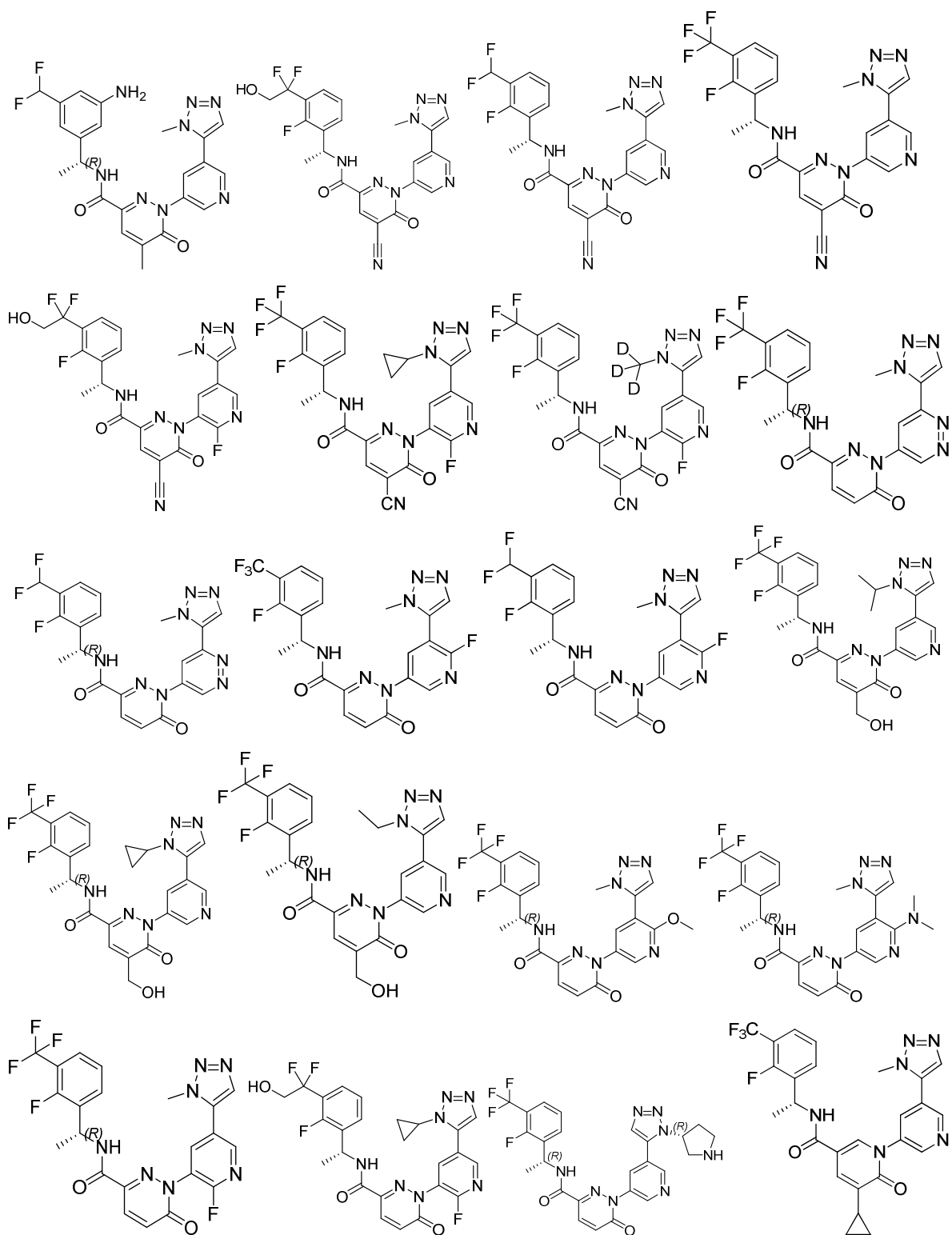
In one embodiment, the compound of Formula I or Formula I-1 may be a compound selected from the following:

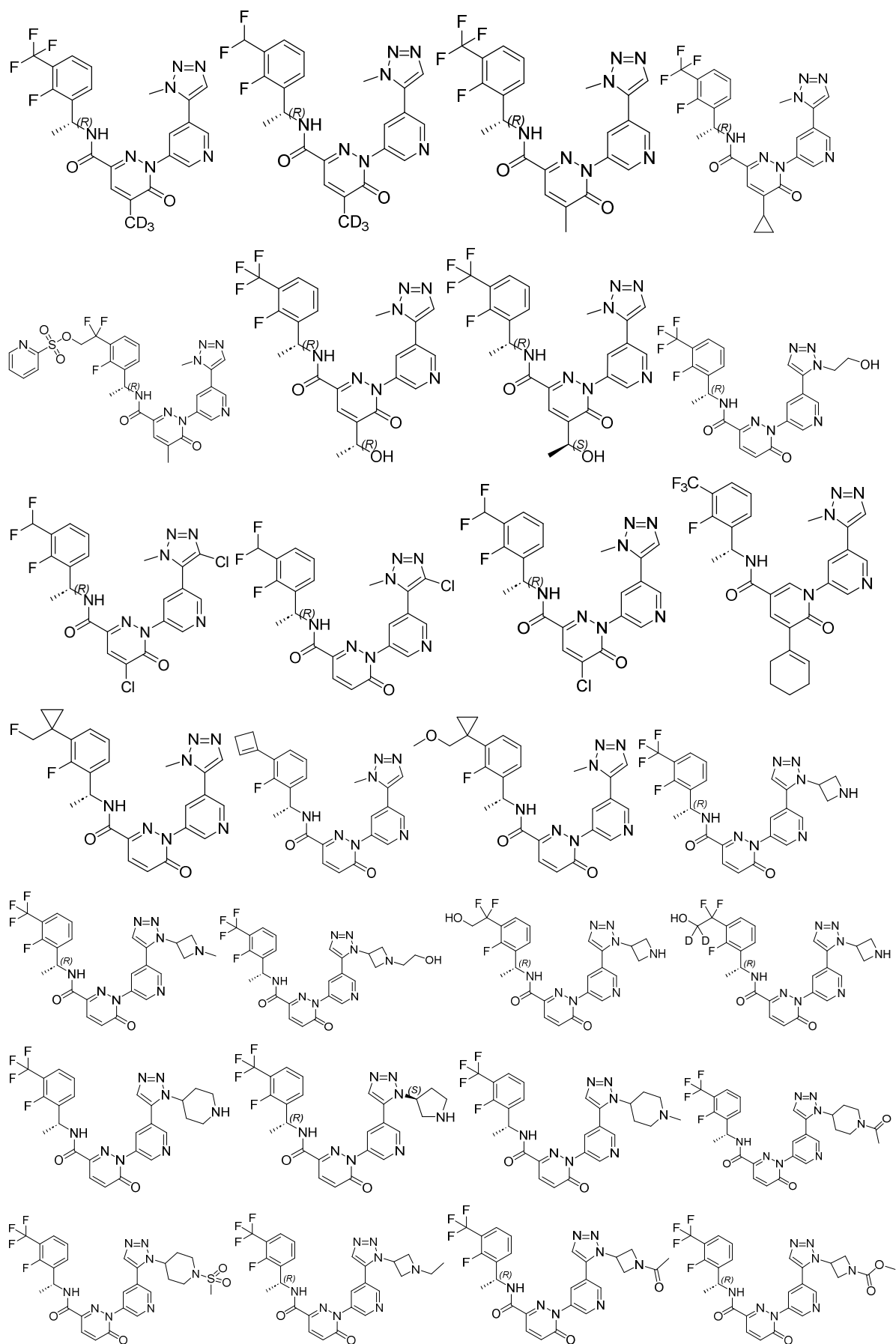


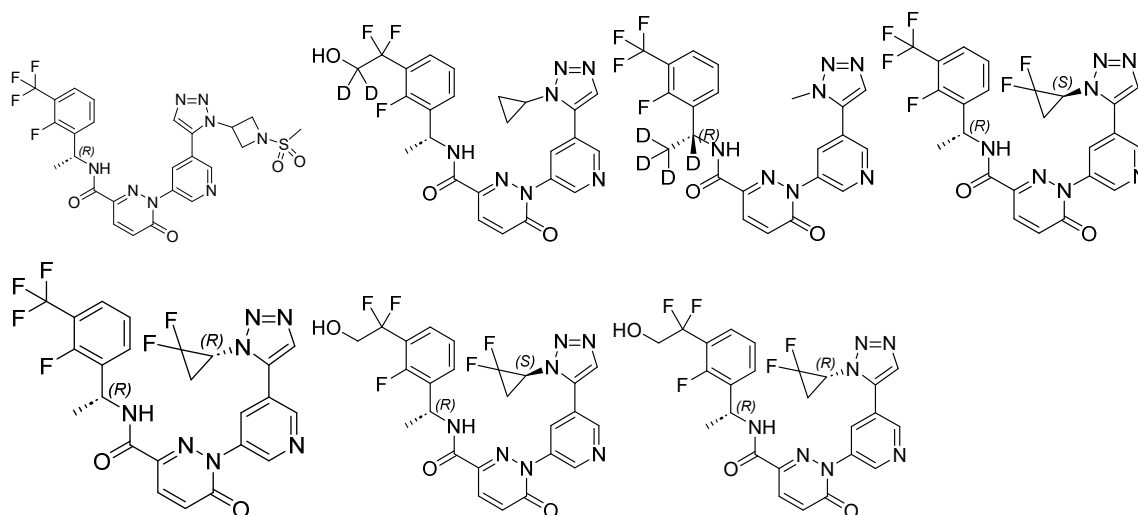












Definition

All technical and scientific terms used herein have the meanings commonly understood by one of ordinary skill in the art, and unless otherwise stated, conventional methods of measurement, methods of manufacture, conventional ingredients or substances are used based on conventional techniques such as pharmacology, pharmaceutical manufacturing chemistry, mass spectrometry, NMR, HPLC, biochemistry, and the like.

Individual features and components of each embodiment described and illustrated herein may be combined with features and components of any other embodiment without departing from the scope or spirit of the present disclosure.

Unless otherwise specified, in the present specification and the appended claims, "or" and "and" mean "and/or". The terms "include" and "included" are open-ended, and mean that a compound, composition, or method may include additional features or ingredients in addition to the listed features or ingredients. Throughout the description of the present specification and the claims, the singular encompasses the plural unless the context requires otherwise. In particular, when an indefinite article is used, the specification is to be understood as contemplating plurality as well as singularity unless the context requires otherwise.

In the present specification, the numerical range indicated using the term "to" refers to a range including the numerical values described before and after the term "to" as the lower limit and the upper limit, respectively. In the present specification, the value expressed using the term "about" may refer to a range of $\pm 20\%$ of the value, preferably $\pm 10\%$ of the value.

As used herein, the term "optional" or "optionally" is intended to include that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances where it does not. For example, the term "optionally substituted" is intended to include both unsubstituted or substituted with the specified substituent.

Compound

As used herein, the term "alkyl" refers to a fully saturated branched or unbranched (or straight chain or linear) hydrocarbon. The alkyl may be a substituted or unsubstituted alkyl group. As used herein, the term "alkyl" may refer to C₁-C₆ alkyl, C₁-C₃ alkyl, and the like. The C₁-C₆ alkyl may be a C₁ to C₆, C₁ to C₅, C₁ to C₄, C₁ to C₃, or C₁ to C₂ alkyl group. Non-limiting examples of the alkyl may be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, n-pentyl, isopentyl, neopentyl, iso-amyl, or n-hexyl.

As used herein, unless otherwise stated, the term "alkoxy" refers to a substituent in which a substituted or unsubstituted straight chain or branched chain alkyl moiety is linked to another chemical structure by oxygen. As used herein, the term "alkoxy" may refer to, for example, C₁-C₆ alkoxy, C₁-C₃ alkoxy, and the like. The alkoxy may include all possible isomers thereof such as methoxy, ethoxy, propoxy, and butoxy, or isopropoxy, isobutoxy, and t-butoxy, but is not limited thereto.

As used herein, the term "thioalkoxy" refers to a substituent in which a substituted or unsubstituted straight chain or branched chain alkyl moiety is linked to another chemical structure by sulfur.

As used herein, the term "cycloalkyl" refers to a saturated hydrocarbon ring having the specified number of carbon atoms as ring elements (that is, C₃-C₆ cycloalkyl refers to a cycloalkyl group having 3, 4, 5 or 6 carbon atoms as ring elements). As used herein, the term "cycloalkyl" may refer to, for example, C₃-C₆ cycloalkyl, C₃-C₅ cycloalkyl, or C₃-C₄ cycloalkyl. The cycloalkyl may be, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl. When the cycloalkyl contains at least one double bond, it is referred to as "partially unsaturated" cycloalkyl, but does not include an aryl ring.

As used herein, the term "halogen" refers to an atom belonging to group 17 of the periodic table. The halogen atom includes fluorine, chlorine, bromine, iodine, and the like, and may be used interchangeably with the term "halo," which means a monovalent functional group composed of halogen.

As used herein, the term "cyano" refers to -CN, which is a functional group having a triple bond between a carbon atom and a nitrogen atom.

As used herein, the term "hydroxy" refers to a -OH functional group (hydroxyl group).

As used herein, the term "oxo" refers to a double bonded oxygen substituent (=O).

As used herein, the term "acyl" refers to a substituent in which any carbon of an alkyl substituent is substituted with oxo. For example, C₁ acyl refers to formyl (-C(=O)H), and C₂ acyl refers to acetyl (-C(=O)CH₃).

As used herein, the term "carboxy" refers to -COOH.

As used herein, the term "carbonyl" refers to a divalent functional group of -C(=O)-.

As used herein, the term "alkoxycarbonyl" refers to a substituent in which either side of carbonyl is connected to alkoxy (-C(=O)-alkoxy).

As used herein, the term "amino" refers to -NH₂.

As used herein, the term "alkylamino" means that one H of -NH₂ is substituted with alkyl.

As used herein, the term "di(alkyl)amino" means that two H of -NH₂ are both substituted with alkyl. The two substituted alkyls may be the same as or different from each other.

As used herein, the term "sulfonyl" refers to a divalent functional group of -S(O)₂-.

As used herein, the term "alkylsulfonyl" refers to a monovalent substituent (-SO₂-alkyl) in which either side of sulfonyl is connected to alkyl.

As used herein, the term "aryl" refers to an aromatic hydrocarbon ring group and includes groups in which the ring is fused to one or more carbon rings. For example, aryl may be a C₆ to C₁₀ aryl group. Aryl may be phenyl, naphthyl, or tetrahydronaphthyl.

As used herein, the term "heteroaryl" refers to a heterocyclic aromatic group containing at least one heteroatom selected from B, N, O, S, P(=O), Si and P as a ring-forming atom. When the heteroaryl contains N, B or P in the ring, N, B or P of the heteroaryl may be linked to another moiety. The heteroaryl may also include a form in which two or more rings are simply attached to each other (pendant) or condensed. The heteroaryl may contain 1 to 4 heteroatoms, 1 to 3 heteroatoms, 1 or 2 heteroatoms, or 1 heteroatom selected from N, O and S. The heteroaryl may contain 5 to 10, or 5 to 6 ring atoms. Examples of monocyclic heteroaryl may include thiophenyl, furanyl, pyrrolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isooxazolyl, imidazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, and the like.

As used herein, unless otherwise stated, the term "heterocyclyl" refers to a monocyclic or polycyclic, saturated or partially unsaturated ring system containing at least one heteroatom selected from B, N, O, S, Si and P and having the specified number of ring elements (that is, 3- to 7-membered heterocyclyl refers to a heterocyclyl group having 3, 4, 5, 6 or 7 ring elements, including heteroatoms). When the heterocyclyl contains N, B or P in the ring, N, B or P of the heterocyclyl may be linked to another moiety. The polycyclic heterocyclyl may also include a form in which two or more heterocyclyl rings are simply attached to each other (pendant) or bridged or condensed or spiro bonded. The heterocyclyl may contain 1 to 4 heteroatoms, 1 to 3 heteroatoms, 1 or 2 heteroatoms, or 1 heteroatom selected from N, O and S. For example, the heteroatom may be N or O. In addition, the heterocyclyl may contain 5 to 10, 4 to 7, 5 or 6 ring atoms. For example, the heterocyclyl includes morpholinyl, oxetanyl, azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, oxany and the like, but is not limited thereto.

As used herein, the term "deuterium" is an isotope of hydrogen with a mass number of 2, which is referred to as deuterium or the abbreviation "D." The terms "deuterated" and "substituted with deuterium" refer to a moiety or compound in which all or part of the hydrogen atoms contained in the corresponding substituent are substituted with deuterium, and they are used interchangeably.

When a derivative is formed by substituting one or more hydrogen atoms in an organic compound with another atomic group, the term "substituted" in the "substituted or unsubstituted" refers to introduction of the group in place of the hydrogen atom and the term "substituent" refers to the introduced atomic group. Unless otherwise specified, substituents may be, for example, a halogen atom, a C₁-C₆ alkyl group substituted with a halogen atom (e.g. CCF₃, CHCF₂, CH₂F, CCl₃, etc.), C₁-C₆ alkoxy, C₂-C₆ alkoxyalkyl, hydroxyl, an amine group, an imine group, a nitro group, a cyano group, an amino group, an amidino group, hydrazine, hydrazone, a carboxyl group or salt thereof, a sulfonyl group, a sulfamoyl group, a sulfonic acid group or salt thereof, phosphoric acid or salt thereof, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, a C₁-C₂₀ heteroalkyl group, a C₆-C₂₀ aryl group, a C₆-C₂₀ arylalkyl group, a C₆-C₂₀ heteroaryl group, a C₇-C₂₀ heteroarylalkyl group, a C₆-C₂₀ heteroaryloxy group, a C₆-C₂₀ heteroaryloxyalkyl group, and a C₆-C₂₀ heteroarylalkyl group.

In the present specification, when a combination of substituents is mentioned as one group, for example, arylalkyl, cycloalkylalkyl, or the like, the last-mentioned group generally contains the atom attached to the end of the molecule.

In the present specification "-" is used to indicate a position at which a substituent is bonded to the remaining moiety of the compound. For example, if - is indicated at the end of a substituent, it means that the end is attached to the remaining moiety of the compound. In addition, when two or more substituents are linked by "-", it means that the substituent immediately before "-" is bonded to a substitutable atom of the substituent immediately after "-".

As used herein, the term "solvate" may refer to a compound of the present invention or a salt thereof comprising a stoichiometric or non-stoichiometric amount of a solvent bound by non-covalent intermolecular forces. Preferred solvents therefor may be solvents that are volatile, non-toxic, and/or suitable for administration to humans. The solvent may be water, in which case the "solvate" is referred to as "hydrate."

As used herein, the term "stereoisomer" may refer to a compound of the present invention or a salt thereof that has the same chemical formula or molecular formula but is optically or sterically different, and specifically, may be a diastereomer, an enantiomer or a geometric isomer.

In some embodiments, the compound of the present invention may be in the form of a racemate, a single enantiomer, a mixture of enantiomers, a single diastereomer, a mixture of diastereomers, and the like, containing one or more asymmetric centers. In one embodiment, due to the limited rotation or nature of the asymmetric center, the compound of the present invention may be in the form of an enantiomer or a diastereomer.

When two or more asymmetric centers are present in the compound of the present invention, several diastereomers and enantiomers of the chemical structures disclosed herein

may exist, and pure isomers, separated isomers, partially pure isomers, racemic mixtures or the like are all intended to fall within the scope of the present invention.

Purification of the isomers and separation of a mixture of the isomers may be achieved by standard techniques known in the art. For example, a diastereomeric mixture may be separated into its respective diastereomers by a chromatographic process or crystallization, and a racemate may be separated into its respective enantiomers by resolution or a chromatographic process on a chiral phase.

The compound of the present invention may be used in the form of a pharmaceutically acceptable salt derived from an inorganic acid or organic acid, and for example, the salt may be a salt derived from hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, acetic acid, glycolic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, malic acid, mandelic acid, tartaric acid, citric acid, ascorbic acid, palmitic acid, maleic acid, hydroxymaleic acid, benzoic acid, hydroxybenzoic acid, phenylacetic acid, cinnamic acid, salicylic acid, methanesulfonic acid, benzenesulfonic acid, toluenesulfonic acid, or the like.

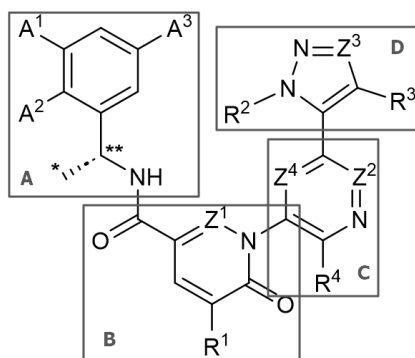
A pharmaceutically acceptable salt of the compound may be prepared by dissolving the compound of formula I in a water-miscible organic solvent, such as acetone, methanol, ethanol, acetonitrile, or the like, and adding an excess of an organic acid or adding an aqueous acid solution of an inorganic acid, and then precipitating or crystallizing. Subsequently, after evaporating the solvent or an excess of acid from this mixture, it may be prepared by drying to obtain an addition salt or by suction filtration of the precipitated salt.

General preparation method of compound

The compound according to the present invention can be prepared through chemical modifications well known to one of ordinary skill in the art of organic/pharmaceutical chemistry according to the method representatively shown below.

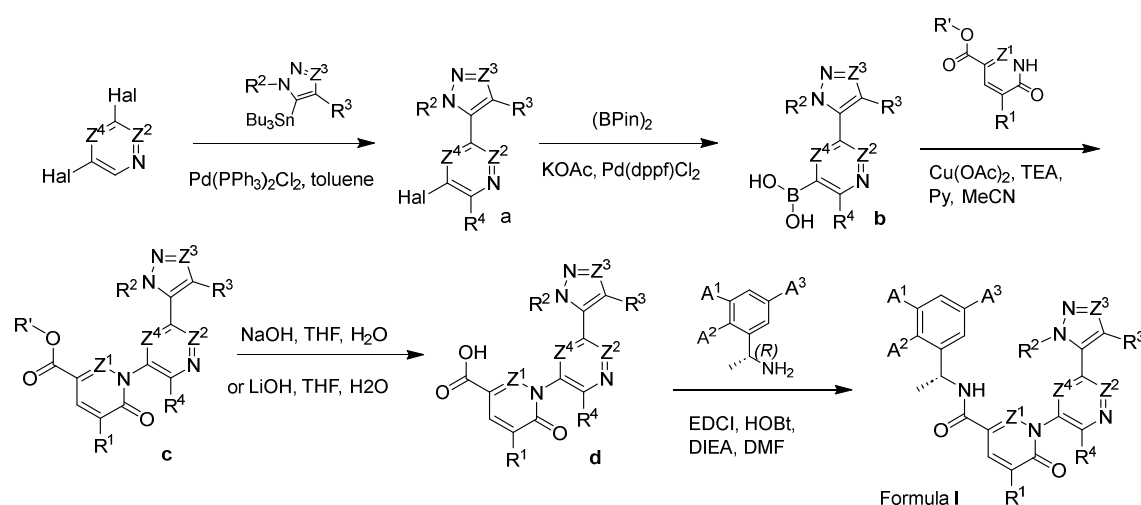
The following general reaction scheme is a general illustration of a representative preparation method of the compound of formula I. One of ordinary skill in the art will be able to easily prepare the compound of formula I by appropriately selecting a starting material, a reaction temperature, a reaction condition, a catalyst, a solvent, a treatment method, and the like suitable for the desired compound, based on the preparation methods specifically disclosed in the examples herein.

In the following reaction schemes, the designation of each substituent in a compound represented by Formula I and intermediates is the same as the substituent at the corresponding position in Formula I, unless otherwise specified. In addition, in the following reaction schemes, R' represents an alkyl group, and Hal represents a halo group (preferably Br or Cl). For convenience of explanation, each ring structure in a compound represented by Formula I is referred to separately as A-part, B-part, C-part and D-part as follows.



In one aspect, a compound of Formula I can be prepared according to the preparation method of Reaction Scheme I below.

[Reaction Scheme I]



In Reaction Scheme I above, Z^1 , Z^2 , Z^3 , Z^4 , R^1 , R^2 , R^3 , R^4 , A^1 , A^2 and A^3 are the same as in Formula I. In Reaction Scheme I, R' may be C_1 - C_6 alkyl (for example, methyl or ethyl), and Hal may be halogen (for example, Br).

In Step 1 of Reaction Scheme I above, the bis-halogenated C-part intermediate and the organotin D-part intermediate can be coupled in the presence of an appropriate solvent (for example, toluene) and a Pd catalyst to prepare Intermediate a. The reaction of Step 1 can be carried out at a temperature of about 80 °C to about 120 °C, or about 90 °C to about 100 °C, for about 10 h to about 30 h, or about 15 h to about 25 h, such as 16 h or 24 h.

In Step 2, Intermediate a can be boronated using an appropriate boronating reagent (for example, bis(pinacolato)diboron) and a catalyst (for example, a Pd catalyst) to prepare Intermediate b. The reaction of Step 2 can be carried out at a temperature of about 80 °C to about 120 °C, or about 90 °C to about 100 °C, for about 10 h to about 30 h, or about 15 h to about 25 h, such as 16 h or 24 h.

In Step 3, Intermediate b can be coupled with the A-part ester intermediate in the presence of an appropriate base (for example, pyridine) and a catalyst (for example, $Cu(OAc)_2$) to prepare Intermediate c. The reaction of Step 3 can be carried out at a temperature of about 80 °C to about 120 °C, about 90 °C to about 100 °C, or about 90 °C, for about 10 h to about 30

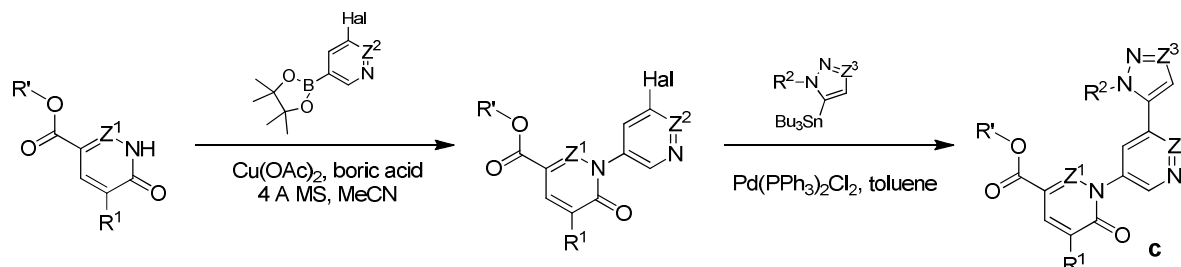
h, or about 15 h to about 25 h, such as about 16 h.

In Step 4, the ester group of Intermediate c can be hydrolyzed using an appropriate base (for example, LiOH or NaOH) to prepare Intermediate d. The reaction of Step 4 can be carried out at a temperature of about 10 °C to about 20 °C, such as about 25 °C, for about 10 h to about 30 h, or about 15 h to about 25 h, such as about 16 h.

In Step 5, a compound represented by Formula I can be prepared by amide coupling Intermediate d with the A-part intermediate. In addition to those described in Reaction Scheme I, the amide coupling reagent can be appropriately changed as needed, and accordingly, reaction conditions such as appropriate reaction time and reaction temperature can be selected. If necessary, the amide coupling reagent can be appropriately changed to, for example, HATU, TEA, DMF, DIEA, DMAP, DCM, and the like. The amide coupling reaction of Step 5 can be carried out at about 20 °C to about 30 °C for about 2 h to about 25 h. For example, the amide coupling reaction of Reaction Scheme 1 can be carried out at about 25 °C for about 2 h to about 20 h, or about 5 h to about 16 h, or about 16 h.

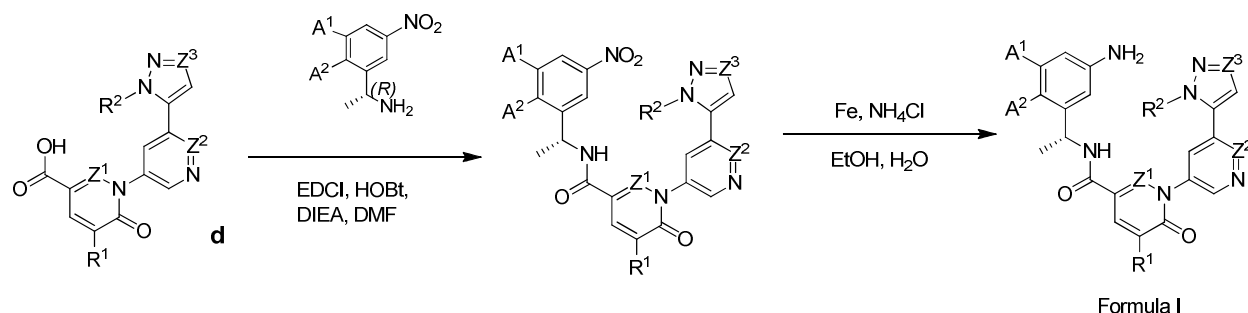
Alternatively, Intermediate c in Reaction Scheme I above can be prepared according to Reaction Scheme I-1 below. The preparation method of Reaction Scheme I-1 below has a coupling sequence different from Reaction Scheme I in that the D-part intermediate is coupled after coupling the B-part intermediate and the C-part intermediate. However, the reaction reagents and reaction conditions in each step of Reaction Scheme I-1 are the same or similar to the corresponding steps in Reaction Scheme I.

[Reaction Scheme I-1]



Alternatively, a compound represented by Formula I wherein A³ is amino can be prepared by amide coupling the intermediate having the NO₂ group and Intermediate d in the same manner as in Reaction Scheme I, followed by reduction of the NO₂ group to the NH₂ group under appropriate nitro reduction conditions (for example, Fe and NH₄Cl) (see Reaction Scheme I-2 below).

[Reaction Scheme I-2]



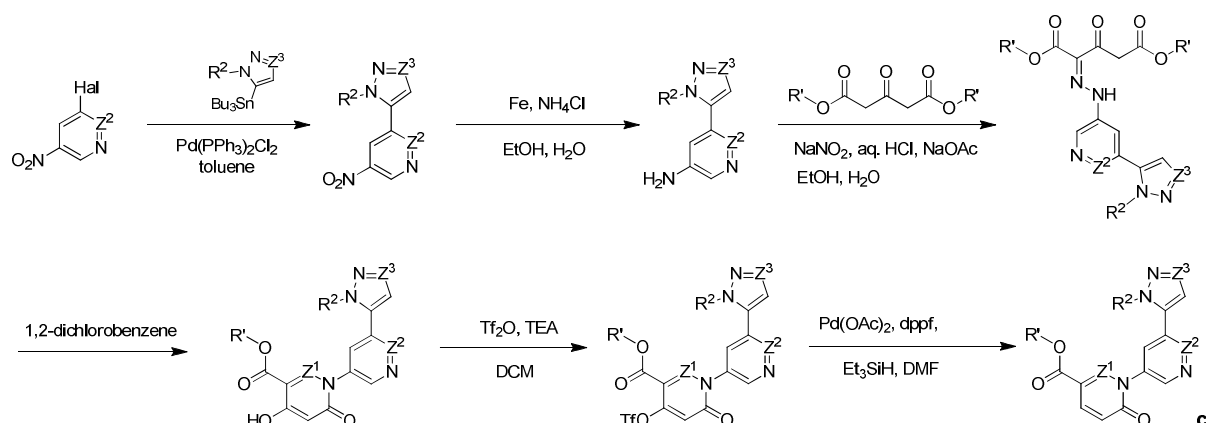
The nitro reduction reaction can be carried out at about 60 °C to about 100 °C, or about 70 °C to about 90 °C, or about 80 °C for about 5 h to about 20 h, or about 10 h to about 15 h, or about 12 h.

Alternatively, a compound represented by Formula I wherein R^1 has a substituent other than halogen (for example, CN or cyclopropyl, etc.) can be prepared by introducing the desired R^1 group into a compound represented by Formula I wherein R^1 is halogen using an appropriate cyanidation reagent (for example, CuCN and NMP) or an appropriate coupling reagent (for example, Pd(OAc)₂, PCy₃, a cycloalkylboronic acid compound)

Alternatively, a compound represented by Formula I wherein R^1 has a substituent can be prepared by using the B-part intermediate having the corresponding substituent in Reaction Scheme I, I-1 or I-2 above.

Alternatively, Intermediate c in Reaction Scheme I can be prepared according to Reaction Scheme I-3 below.

[Reaction Scheme I-3]



Step 1 of Reaction Scheme I-3 can be carried out in the same manner as in Step 1 of Reaction Scheme I except that the nitrated and halogenated C-part intermediate is used. In addition, Step 2 is a nitro reduction reaction in the same manner as in Step 2 of Reaction Scheme I-2.

In Step 3, the product of Step 2 can be reacted with 3-oxopentanedioate in the presence of an appropriate solvent and catalyst (for example, NaNO₂, NaOAc, aq. HCl, EtOH) to form a hydrazone compound. The reaction of Step 3 can be carried out at a temperature of about -

10 °C to about 30 °C, or about -5 °C to about 25 °C, or about 0 °C to about 20 °C for about 30 minutes to about 5 h, or about 1 h to about 2 h, or about 1 h.

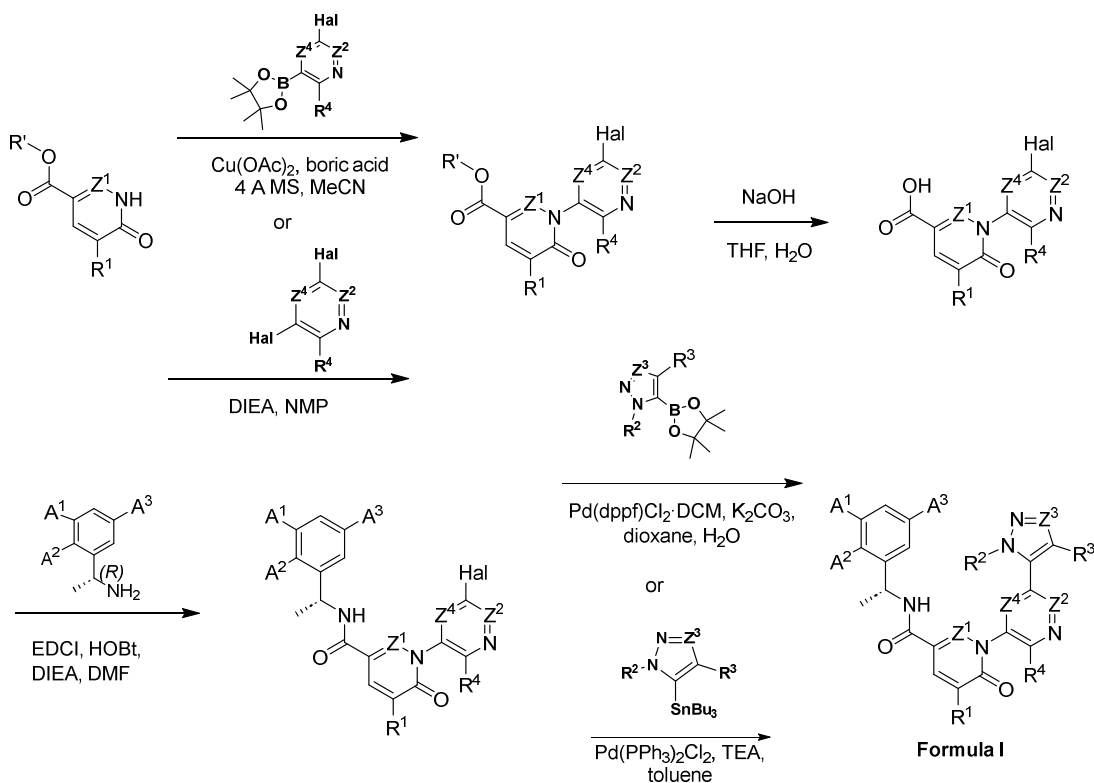
In Step 4, the product of Step 3 can be heated in the presence of an appropriate solvent (for example, 1,2-dichlorobenzene) to form a dihydropyridazinone ring. The reaction of Step 4 can be carried out at a temperature of about 120 °C to about 220 °C, or about 150 °C to about 200 °C, or about 180 °C for about 5 h to about 10 h, or about 8 h.

In Step 5, Tf₂O can be added to the product of Step 4 in an appropriate solvent (for example, TEA, DCM) to introduce a trifluoromethylsulfonyloxy group into the dihydropyridazinone ring. The reaction of Step 5 can be carried out at a temperature of about -100 °C to about 50 °C, or about -80 °C to about 30 °C, or about -70 °C to about 20 °C, for about 30 minutes to about 5 h, or about 1 h to about 3 h, or about 2 h.

In Step 6, the product of Step 5 can be reacted with DPPF and Et₃SiH in the presence of an appropriate catalyst (for example, Pd(OAc)₂) in an appropriate solvent (for example, DMF) to remove the trifluoromethylsulfonyloxy group to prepare Intermediate c. The reaction of Step 6 can be carried out at a temperature of about 50 °C to about 150 °C, or about 80 °C to about 120 °C, or about 100 °C, for about 30 minutes to about 3 h, or about 1 h to about 2 h, or about 1 h.

In one aspect, a compound represented by Formula I can be prepared as shown in Reaction Scheme IA below. The preparation method of Reaction Scheme IA below has a coupling sequence different from Reaction Scheme I and Reaction Scheme I-1 in that the A-part intermediate and the D-part intermediate are sequentially coupled after coupling the B-part intermediate and the C-part intermediate. However, the reaction reagents and reaction conditions in each step of Reaction Scheme IA are the same or similar to the corresponding steps in Reaction Scheme I or Reaction Scheme I-1.

[Reaction Scheme IA]



Medicinal use, pharmaceutical composition, and administration method

The compound of Formula I, a stereoisomer, a solvate, or a pharmaceutically acceptable salt thereof may be used for preventing or treating a SOS1 mediated disease. The compound of Formula I, a stereoisomer, a solvate, and a pharmaceutically acceptable salt thereof are as described above.

In the present specification, the term "preventing" or "prevention" refers to preventing a disease, for example, preventing a disease, condition or disorder in a subject who may be predisposed to the disease, condition or disorder but has not yet experienced or exhibited the pathology or signs of the disease.

As used herein, the term "treating" or "treatment" refers to inhibiting a disease, for example, inhibiting a disease, condition or disorder in a subject who experiences or exhibits the pathology or signs of the disease, condition or disorder, i.e., preventing recurrence of the pathology and/or signs after treatment or further development of the pathology and/or signs, or ameliorating the disease, for example, ameliorating the disease, condition or disorder in a subject who experiences or exhibits the pathology or signs of the disease, condition or disorder, i.e., reversing the pathology and/or signs, for example, reducing the severity of the disease.

The SOS1 mediated disease may include a disease that can be prevented or treated by inhibiting the interaction between SOS1 and RAS family proteins, and/or between SOS1 and RAC1. The SOS1 mediated disease may include a disease associated with the abnormal activity of SOS1 and/or RAS family proteins. The SOS1 mediated disease may be, for example, cancer. The cancer may be, for example, pancreatic cancer, lung cancer, colorectal cancer, biliary tract

cancer, multiple myeloma, melanoma, uterine cancer, cervical cancer, endometrial cancer, thyroid cancer, chronic lymphocytic leukemia, acute myeloid leukemia, bladder cancer, urothelial cancer, gastric cancer, squamous cell carcinoma of the head and neck, diffuse large B cell lymphoma, esophageal cancer, hepatocellular cancer, breast cancer, ovarian cancer, prostate cancer, glioblastoma, kidney cancer or sarcoma. In one embodiment, the cancer may be pancreatic cancer, lung cancer (for example, non-small cell lung cancer), biliary tract cancer or colorectal cancer.

The cancer may be, for example, a cancer dependent on the RAS family and the MAPK signaling pathway. The cancer may include, for example, cancer having mutation of proteins or genes, gene amplification and/or overexpression in the RAS family and MAPK signaling pathway, e.g., KRAS, NRAS, HRAS, receptor tyrosine kinases (for example, EGFR, ErbB2, ErbB3, ErbB4, PDGFR-A/B, FGFR1/2/3, IGF1R, INSR, ALK, ROS, TrkA, TrkB, TrkC, RET, c-MET, VEGFR1/2/3, AXL), GAP (for example, NF1) and SOS1 (for example, mutation, amplification or overexpression of RAF, MEK). In addition, the cancer may be a RAC1 dependent cancer.

The SOS1 mediated disease may be, for example, a disease associated with dysregulation of RAS family protein pathways, i.e., RASopathy. The RASopathy may include neurofibromatosis type 1 (NF1), Noonan syndrome, Noonan syndrome with multiple lentigines (NSML, also referred to as Leopard syndrome), capillary malformation-arteriovenous malformation syndrome (CM-AVM), Costello syndrome, CFC syndrome (Cardio-Facio-Cutaneous syndrome), Legius syndrome (also referred to as NF1-like syndrome) or hereditary gingival fibromatosis.

According to one embodiment, a compound of Formula I can be used in the treatment of a disease associated with the abnormal activity of SOS1 or RAS family proteins, or dysregulation of RAS family protein pathways by inhibiting the interaction between SOS1 and RAS family proteins, or between SOS1 and RAC1.

In one embodiment, the pharmaceutical composition may comprise conventional pharmaceutically acceptable carriers, excipients or additives. The pharmaceutical composition may be formulated according to a conventional method, and may be prepared as various oral dosage forms such as tablets, pills, powders, capsules, syrups, emulsions, microemulsions, or parenteral dosage forms such as intramuscular, intravenous or subcutaneous dosage form. The pharmaceutical composition may be a single composition or separate compositions. The pharmaceutical composition comprises the compound, stereoisomer, solvate, or pharmaceutically acceptable salt according to one aspect as an active ingredient of the pharmaceutical composition.

When the pharmaceutical composition is prepared in the form of an oral formulation, examples of additives or carriers used may include cellulose, calcium silicate, corn starch, lactose, sucrose, dextrose, calcium phosphate, stearic acid, magnesium stearate, calcium

stearate, gelatin, talc, surfactant, suspending agent, emulsifying agent, diluent, and the like. When the pharmaceutical composition of the present invention is prepared in the form of an injection, the additive or carrier may include water, saline, aqueous glucose solution, similar aqueous sugar solution, alcohol, glycol, ether (for example, polyethylene glycol 400), oil, fatty acid, fatty acid ester, glyceride, surfactant, suspending agent, emulsifying agent, and the like.

The dosage of the pharmaceutical composition is an amount effective for treatment or prevention of a subject or patient, and may be administered orally or parenterally as desired. It may be administered in one to several divided doses to be administered in an amount of 0.01 to 1000 mg, more specifically 0.1 to 300 mg per kg of body weight daily based on the active ingredient when administered orally, or in an amount of 0.01 to 100 mg, more specifically 0.1 to 50 mg per kg of body weight daily based on the active ingredient when administered parenterally. The dose to be administered to a specific subject or patient should be determined in light of several related factors such as body weight, age, sex, health condition of the patient, diet, administration time, administration method, the severity of the disease, and the like, and it should be understood that it may be appropriately increased or decreased by a specialist. The above dosage is not intended to limit the scope of the present invention in any way. A physician or veterinarian of ordinary skill in the art may readily determine and prescribe the required effective amount of the pharmaceutical composition. For example, by a physician or veterinarian, a dose of the compound of the present invention used in a pharmaceutical composition may start at a level lower than that required to achieve the desired therapeutic effect, and may gradually increase until the desired effect is achieved.

In one embodiment, the pharmaceutical composition includes within its scope a pharmaceutical composition comprising, as an active ingredient, a therapeutically effective amount of at least one of the compounds according to one embodiment, alone or in combination with a pharmaceutical carrier. The term "therapeutically effective amount" or "effective amount" refers to an amount sufficient to produce a beneficial or desired clinical result, for example, an amount sufficient to alleviate, ameliorate, stabilize, reverse, slow or delay the progression of a disease.

Meanwhile, as described below, when the compound represented by Formula I or Formula I-1 according to the present invention is administered in combination with one or more other therapeutic agents, there is provided herein a pharmaceutical composition comprising the compound according to the present invention and the other therapeutic agents. Therefore, in one embodiment, there is provided a pharmaceutical composition for preventing or treating cancer, comprising a compound represented by Formula I or Formula I-1, or a solvate, stereoisomer or pharmaceutically acceptable salt thereof; and an anticancer agent as an active ingredient. The compound represented by Formula I or Formula I-1 and the anticancer agent may be included in one pharmaceutical composition or may be formulated as individual

pharmaceutical compositions, respectively. The anticancer agent used in combination is as described below.

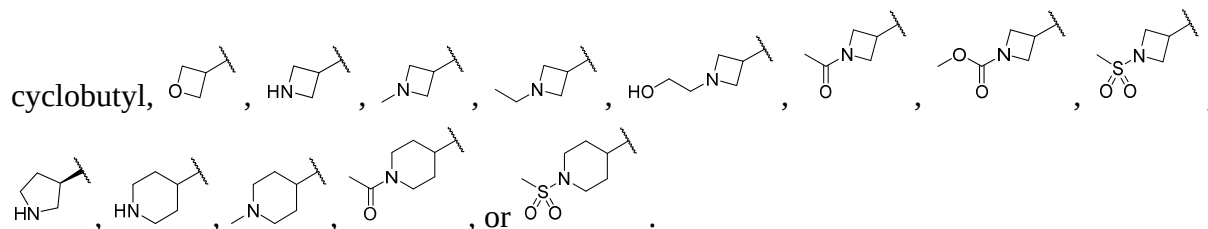
Combined administration

Optionally, the compound according to one embodiment may be administered alone, or simultaneously, separately or sequentially, in combination with the compound according to another embodiment or in combination with one or more other therapeutic agents, for example, an anticancer agent or other pharmaceutically active substances.

When used for the treatment of cancer, the compound represented by Formula I or Formula I-1 of the present invention may be administered in combination with other anticancer agents. Here, the compounds represented by Formula I and Formula I-1 are as described above.

In one embodiment, in the compound represented by Formula I according to the present invention administered in combination with the above anticancer agent, R^2 may be a 4- to 7-membered heterocyclyl containing 1 or 2 heteroatoms selected from N, O and S, optionally substituted with one or more R^{21a} ; or partially unsaturated or saturated C_3 - C_7 cycloalkyl optionally substituted with one or more R^{21b} . Here, R^{21a} and R^{21b} are each independently C_1 - C_6 alkyl optionally substituted with one or more halogen, CN, OH, C_1 - C_6 alkoxy, carboxy or oxo; C_1 - C_6 acyl; carboxy; C_1 - C_6 alkoxycarbonyl; or C_1 - C_6 alkylsulfonyl.

For example, in the compound represented by Formula I according to the present invention administered in combination with the above anticancer agent, R^2 may be a 4- to 6-membered heterocyclyl containing 1 or 2 heteroatoms selected from N and O, optionally substituted with one or more R^{21a} ; or partially unsaturated or saturated C_3 - C_7 cycloalkyl optionally substituted with one or more R^{21b} . Here, R^{21a} may be C_1 - C_4 alkyl optionally substituted with one or more OH, C_1 - C_4 alkoxy or oxo; C_1 - C_4 acyl; C_1 - C_4 alkoxycarbonyl; or C_1 - C_4 alkylsulfonyl, and R^{21b} may be halogen. For example, R^2 may be cyclopropyl, ,



In one embodiment, in the compound represented by Formula I according to the present invention administered in combination with the above anticancer agent, R^1 may be C_1 - C_6 alkyl optionally substituted with one or more deuterium, OH, oxo (=O) or halogen. For example, R^1 may be C_1 - C_6 alkyl substituted with OH. For example, R^1 may be $-CH_2OH$, $-CH(OH)CH_3$ or $-C(OH)(CH_3)_2$, but is not limited thereto. Alternatively, R^1 may be C_1 - C_6 alkyl substituted with halogen. For example, R^1 may be CF_3 . Alternatively, R^1 may be C_1 - C_6 alkyl substituted with oxo (=O). For example, R^1 may be $-C(=O)CH_3$.

The anticancer agent that can be administered in combination with the compound represented by Formula I or Formula I-1 of the present invention may be selected from the group consisting of chemical anticancer agents, targeted anticancer agents, anticancer viruses, antibody therapeutic agents, cell therapeutic agents, immune checkpoint inhibitors, and a combination thereof.

In one embodiment, the compound represented by Formula I or Formula I-1 of the present invention may be administered alone or in combination with other anticancer therapies, such as radiation therapy, taxane derivatives (for example, paclitaxel, docetaxel), platinum compounds (for example, cisplatin, carboplatin), antimetabolites (for example, 5-FU, gemcitabine, cytarabine, 6-thioguanine), CDK4/6 inhibitors (for example, abemaciclib, palbociclib), immunotherapeutic agents (for example, anti-CTLA4 antibody, anti-PD1 antibody), angiogenesis inhibitors (for example, bevacizumab, nintedanib, regorafenib), topoisomerase inhibitors (for example, irinotecan, SN-38, doxorubicin), ERK inhibitors (for example, ulixertinib, rineterkib), MDM2 inhibitors (for example, alrizomadlin), PARP inhibitors (niraparib), MCL-1 inhibitors, mTOR inhibitors (for example, rapamycin, temsirolimus, INK-128 (sapanisertib), everolimus), BET inhibitors (JQ1), CDK9 inhibitors (for example, AT-7519), IGF1/2 or IGF1-R inhibitors (NVP-ADW742), PIK inhibitors (duvelisib), EGFR inhibitors (for example, apatinib, osimertinib, cetuximab, lazertinib, gefitinib, neratinib), ErbB2 (HER2) inhibitors (for example, trastuzumab, irbinitinib, neratinib), ALK inhibitors (for example, crizotinib, alectinib), MEK inhibitors (for example, trametinib, cobimetinib), BCR-ABL inhibitors (for example, imatinib, nilotinib, dasatinib), FGFR1, FGFR2 or FGFR3 inhibitors (for example, nintedanib), ROS1 inhibitors (for example, crizotinib, entrectinib, repotrectinib), c-MET inhibitors (for example, tepotinib), AXL inhibitors (for example, bemcentinib), NTRK1 inhibitors (for example, repotrectinib), RET inhibitors (for example, pralsetinib), KRAS G12C inhibitors (for example, sotorasib, adagrasib, trametinib, JDQ443), KRAS G12D inhibitors (for example, MRTX1133), SHP2 inhibitors (for example, TNO155), mutBRAF inhibitors (for example, dabrafenib), PI3K inhibitors (for example, alpelisib, apitolisib), Aurora A inhibitors (for example, MK-5108), pan Aurora inhibitors (for example, danusertib, AMG-900, reversine), BTK inhibitors (for example, ibrutinib), Wee1 inhibitors (for example, MK-1775), DHFR inhibitors (for example, methotrexate), HSP90 inhibitors (for example, BIIB021), A3AR antagonists (for example, reversine), ubiquitin E1 enzyme inhibitors (for example, MLN-7243), Bcl-2 inhibitors (for example, ABT-737), EZH2 inhibitors (for example, GSK-343), ARID1A inhibitors (for example, GSK-343), SUMOylation inhibitors (for example, 2-D08), CHK1 inhibitors (for example, SCH-900776), HDAC inhibitors (for example, entinostat), JAK1/2 inhibitors (for example, ruxolitinib), Proteasome inhibitors (for example, carfilzomib), AKT inhibitors (for example, ipatasertib), GR inhibitors (for example, prednisolone), PLK1 inhibitors (for example, volasertib) or pan-RAF inhibitors (for example, sorafenib), etc.

The compound represented by Formula I or Formula I-1 of the present invention can be used together with other anticancer therapies described above to enhance the action of anticancer therapies, thereby significantly inhibiting the expression and activity of target proteins or genes. Specifically, the compound represented by Formula I or Formula I-1 not only has its own anticancer efficacy, but can also improve the anticancer efficacy of the targeted inhibitor. Therefore, when Formula I or Formula I-1 are used together with the above anticancer therapy, they can exhibit anticancer efficacy that is superior to the sum of the anticancer efficacy when they are used alone.

As used herein, the term "chemical anticancer agent" is also referred to as an antineoplastic agent or a cytotoxic agent. It is a general term for drugs that exhibit anticancer activity mainly by acting directly on DNA to block DNA replication, transcription, and translation processes, or by interfering with the synthesis of nucleic acid precursors in metabolic pathways and inhibiting cell division. The anti-tumor drug acts not only on tumor cells but also on normal cells and exhibits cytotoxicity. The chemical anticancer agent can be used for maintenance therapy. In addition, as used herein, the term "maintenance therapy" refers to treating cancer with drugs after initial anti-cancer treatment, and refers to a treatment method performed to prevent or delay the recurrence of cancer.

Specifically, chemical anticancer agent may be any one selected from the group consisting of alkylating agents, microtubule inhibitors, antimetabolites and topoisomerase inhibitors. The alkylating agent may be any one selected from the group consisting of Mechlorethamine, Cyclophosphamide, Ifosfamide, Melphalan, Chlorambucil, Thiotepa, Altretamine, Procarbazine, Busulfan, Streptozotocin, Carmustine, Lomustine, Dacarbazine, Cisplatin, Carboplatin and Oxaliplatin. The microtubule inhibitor may be any one selected from the group consisting of Docetaxel, Paclitaxel, Velban, Oncovin and Navelbine. The anti-metabolite may be any one selected from the group consisting of Fluorouracil, Capecitabine, Cytarabine, Gemcitabine, Fludarabine, Methotrexate, Pemetrexed, 6-thioguanine and Mercaptopurine. The topoisomerase inhibitor may be any one selected from the group consisting of Hycamtin, Camptosar, Vepesid, Blenoxane, Adriamycin, SN-38, Doxorubicin and Cerubidine.

As used herein, the term "targeted anticancer agent" is a therapeutic agent that specifically kills cancer cells by blocking signals involved in the growth and development of cancer by targeting changes in specific proteins or specific genes that frequently appear only in cancer cells. It is classified into monoclonal antibodies that react outside cells and small molecule substances that act inside cells. Monoclonal antibodies are anticancer agents that block cancer cell-inducing signals transmitted to the outside of cells, and act on initiation signals related to proliferation, death and the like, and small molecule substances act on complex signal transduction occurring inside cells.

Specifically, a protein to be targeted may be mTOR, PI3K, EGFR, VEGFR, CD20, CD38, RNAK-L, BTK, Bcr-abl, PDGFR/FGFR family, MEK, KRAS, ERK1/2, HER2/Neu, Ubiquitin, JAK, ALK, PARP, TGF β R, Proteasome, Bcl-2, C-Met, VR1, VR2, VR3, c-kit, AXL, RET, BRAF, pan-RAF, SHP2, SRC, LCK, DNMT, CDK4/6, CDK9, BET, MDM2, IGF1/2 or IGF1-R, ROS1, NTRK1, PIK, DHFR, pan-Aurora, Aurora A, WEE1, HSP90, A3AR, EZH2, ARID1A, CHK1, ATR, HDAC1/3, AKT, PLK1, SUMOylation-related proteins, STING and the like.

The targeted anticancer agent may be any one selected from the group consisting of Rapamycin, Sirolimus, Temsilorimus, Everolimus, Ridaforolimus, INK-128, Alpelisib, Cetuximab, Trastuzumab, Pertuzumab, Gefitinib, Erlotinib, Osimertinib, Lazertinib, Panitumumab, Axitinib, Lenvatinib, Bevacizumab, Ramucirumab, Aflibercept, Rituximab, Obinutuzumab, Daratumumab, Denosumab, Ibrutinib, Dasatinib, Nilotinib, Imatinib, Bosutinib, Galunisertib, Vactosertib, Futibatinib, Nintedanib, Sunitinib, Sorafenib, Cabozantinib, Regorafenib, Masitinib, Semaxanib, Tivozanib, Vandetanib, Pazopanib, Dabrafenib, Sotorasib, Adagrasib, JDQ443, MRTX1133, Ulixertinib, Afatinib, Lapatinib, Neratinib, Lenalidomide, Ixazomib, Ruxolitinib, Lestaurtinib, Pacritinib, Trametinib, Cobimetinib, Selumetinib, Binimetinib, Alectinib, Lorlatinib, Crizotinib, Venetoclax, Bemcentinib, Gilteritinib, Selpercatinib, Pralsetinib, Encorafenib, Vemurafenib, Belvarafenib, RMC-4630, Batoprotafib, WH-4-023, Olaparib, Talazoparib, Niraparib, Rucaparib, Azacitidine, Decitabine, Guadecitabine, Abemaciclib, Ribociclib, Palbociclib, CDNs, SB11285, Rineterkib, Repotrectinib, Tepotinib, Alrizomadlin, JQ1, NVP-ADW742, Duvelisib, Irbinitinib, Danusertib, MK-1775, AMG-900, BIIB021, Reversine, MLN-7243, ABT-737, MK-5108, GSK-343, 2-D08, SCH-900776, Entinostat, Carfilzomib, Apatolisib, Ipatasertib, Volasertib, AT-7519, Methotrexate, Wortmannin, ERAS-007, PYR-41, MLN4924, RO-5503781, MK-8242, SAR-405838, CGM097, DS3032b, Lactacystin, Disulfiram, Epigallocatechin-3-gallate, Marizomib, Oprozomib, Delanzomib, Epoxomicin, MG132, Beta-hydroxy beta-methylbutyrate, Bortezomib, Navitoclax, Naporafenib, PF-07284892, TNO155, Hesperadin, LY3295668, Tozasertib, Azenosertib, ZNL-02-096, RP-6306, GSK-1520489A, BIIB028, MPC-3100, PU-H71, Debio093, SNX-5422, AUY922, KF-26777, MRS-545, CAY10498, DZNep, EPZ005687, EI1, GSK126, UNC1999, Tazemetostat, Sinefungin, GSK-343, Davidiin, CID9549553, SRA737, V158411, PF-477736, AZD7762, Prexasertib, Berzosertib, Gartisertib, Ceralasertib, Panobinostat, Mocetinostat, Trichostatin A, CBUD-1001, Abexinostat, VQD-002, Perifosine, Miltefosine, MK-2206, AZD5363, Rigosertib, I-BET 151, I-BET 762, OTX-015, TEN-010, CPI-203, CPI-0610, Olinone, RVX-208, ABBV-744, LY294002, AZD5153, MT-1, MS645, Figitumumab, Mecasermin, rhIGF-1, BI 885578, Buparlisib, Copanlisib, Dactolisib, Idelalisib, Parsaclisib, Paxalisib, Taselisib, Zandelisib, Inavolisib, AZD4573, Atuveciclib, VIP152, A-1592668, JSH-150, SLS009, Roscovitine and DMXAA.

As used herein, the term "mTOR (mammalian target of rapamycin)" is also referred to as mechanistic target of rapamycin or FRAP1 (FK506 binding protein 12-rapamycin associated protein 1), and is a protein belonging to the PIKK (phosphatidylinositol 3-kinase-related kinase) family. mTOR is encoded by the FRAP1 gene in humans and is a serine/threonine protein kinase that regulates cell growth, cell proliferation, cell motility, cell survival, protein synthesis, and transcription. The mTOR inhibitor can inhibit tumor survival by inhibiting autophagy, lipogenesis, proliferation, and protein synthesis, etc. The mTOR inhibitor may be, for example, rapamycin, sirolimus, temsilorimus, everolimus, ridaforolimus or INK-128 (sapanisertib, MLN0128, TAK-228).

As used herein, the term "PI3K (Phosphoinositide 3-kinase)" is also referred to as phosphatidylinositol 3-kinase, and is an enzyme involved in cellular functions such as cell growth, proliferation, differentiation, motility, survival, and intracellular signal regulation, and is associated with cancer. PI3K includes subunits such as p110- $\alpha/\beta/\gamma/\delta$ (PI3K $\alpha/\beta/\gamma/\delta$). PI3K targeted anticancer agents may include alpelisib, wortmannin, LY294002, idelalisib, copanlisib, duvelisib, apitolisib (GDC-0980, RG7422, GNE 390), and the like.

As used herein, the term "epidermal growth factor receptor (EGFR)" is a cell membrane receptor that regulates cell growth, division, survival and death, and expression of EGFR is increased in tumor tissues in various cancers. Tumor tissues with increased EGFR are known to have high invasion, metastasis and resistance to anticancer agents. In one embodiment, a substance that inhibits the EGFR as an EGFR inhibitor may be cetuximab, trastuzumab, pertuzumab, gefitinib, erlotinib, osimertinib, lazertinib or panitumumab.

As used herein, the term "vascular endothelial growth factor receptor (VEGFR)" is a cell membrane receptor for vascular endothelial growth factor that induces angiogenesis, and a VEGFR inhibitor inhibits the angiogenesis to inhibit tumor growth and metastasis. In one embodiment, a VEGF inhibitor or a VEGFR inhibitor may be axitinib, lenvatinib, bevacizumab, ramucirumab or aflibercept.

As used herein, the term "CD20 (B lymphocyte antigen CD20)" is a protein expressed on the surface of B cells and is used as a target protein for treatment of B cell lymphoma. An inhibitor targeting CD20 may be rituximab or obinutuzumab.

As used herein, the term "CD38 (cluster of differentiation 38)" is a protein that regulates cell proliferation and death while acting as a signal transduction system receptor in immune cells, and an inhibitor targeting this protein may be daratumumab.

As used herein, the term "RANK-L (receptor activator of nuclear factor kappa-B ligand)" is a RANK receptor expressed on the surface of osteoclasts, and when activated by binding to the ligand, it acts to cause bone destruction. A RANK-L inhibitor is mainly used for cancer patients suffering from bone metastasis or osteoporosis, and may be specifically denosumab.

As used herein, the term "BTK (Bruton's tyrosine kinase)" is an enzyme involved in the proliferation of B cells, and when overexpressed, it can develop into hematological cancer. In one embodiment, an inhibitor targeting BTK may be ibrutinib.

As used herein, the term "Bcr-abl" is a fusion protein that is highly expressed in patients with chronic myeloid leukemia, and is known to induce abnormal proliferation of blood cells. Specifically, the inhibitor of this protein may be dasatinib, nilotinib, imatinib or bosutinib.

As used herein, the term "tumor growth factor β receptor (TGF β R)" is a cell membrane receptor for tumor growth factor, and regulates the growth, migration, differentiation and death and the like of epithelial cells and hematopoietic cells. An inhibitor targeting TGF β R may include galunisertib or vactosertib, but is not limited thereto.

As used herein, the term "PDGFR (platelet derived growth factor receptor)" is a cell membrane receptor for PDGF that is frequently expressed in cancer cells, and is known to be involved in angiogenesis to regulate cancer growth, metastasis, and drug resistance. FGFR (fibroblast growth factor receptor) is a receptor for fibroblast growth factor (FGF) and regulates various biological processes including cell growth, differentiation and migration and the like. The FGFR gene is frequently mutated, and these mutants are commonly observed in breast cancer, uterine cancer, ovarian cancer, cervical cancer, and the like. An inhibitor targeting PDGFR or FGFR may be futibatinib, nintedanib, sunitinib, imatinib, sorafenib, cabozantinib, lenvatinib, regorafenib, masitinib, semaxanib, tivozanib, vandetanib, axitinib or pazopanib.

As used herein, the term "MEK (mitogen-activated protein kinase kinase)" is a dual-specificity kinase enzyme that phosphorylates MAPK (mitogen-activated protein kinase), also referred to as MAP2K, MEK, or MAPKK. When MEK is inhibited, cell proliferation is blocked and cell death is induced. MEK targeted anticancer agents may be cobimetinib, selumetinib, trametinib or binimetinib.

As used herein, the term "KRAS (Kirsten rat sarcoma virus)" refers to a gene that produces a protein referred to as K-Ras, which is part of the RAS/MAPK pathway, and is an oncogene that instructs the growth, division, proliferation, and differentiation signals of cells. KRAS targeted anticancer agents may be sotorasib, adagrasib, JDQ443 or MRTX1133.

As used herein, the term "ERK1/2 (extracellular signal-regulated kinases 1/2)" refers to a widely expressed protein kinase intracellular signal molecule involved in functions including the regulation of meiotic, mitotic, and post-mitotic functions in cells. Disruption of the ERK pathway is commonly observed in cancer. ERK1/2 targeted anticancer agents may be rineterkib, ulixertinib (BVD-523) or ERAS-007.

As used herein, the term "HER-2/neu (human epidermal growth factor receptor 2)" regulates cell proliferation by the activation of PI3K/AKT. It is overexpressed in metastatic breast cancer and ovarian cancer and the like, and is known to induce resistance to anticancer

agents. Her2/neu targeted anticancer agents may be trastuzumab, afatinib, lapatinib, irbinitinib (tucatinib) or neratinib.

As used herein, the term "ubiquitin" maintains cellular homeostasis by binding to other proteins and inducing proteolysis by proteasome, a proteolytic enzyme (ubiquitin-proteasome system, UPS). Abnormal expression or activity of the UPS is observed in various tumors, and the inhibitor of UPS exhibits anticancer activity. For example, an inhibitor targeting ubiquitin E1 enzyme may include MLN-7243 (TAK-243), PYR-41, MLN4924, and the like, and MDM2 E3 ubiquitin ligase inhibitors may include RO-5503781 (idasanutlin), MK-8242, SAR-405838, CGM097, DS3032b, and the like.

As used herein, a "proteasome inhibitor" can treat cancer by blocking the action of the proteasome, a cellular complex that degrades proteins. The inhibition of proteasome prevents the degradation of pro-apoptotic factors such as p53 protein, thereby activating programmed cell death in tumor cells that relies on inhibition of pro-apoptotic pathways. Proteasome inhibitors may include lactacystin, disulfiram, epigallocatechin-3-gallate, marizomib (salinosporamide A), oprozomib (ONX-0912), delanzomib (CEP-18770), epoxomicin, MG132, beta-hydroxy beta-methylbutyrate, bortezomib, carfilzomib, ixazomib, and the like.

As used herein, the term "JAK (Janus kinase)" is an upstream protein to STAT, which is a transcription factor that regulates cell proliferation, cell survival, cell migration and immune response, and an inhibitor of JAK is known to reduce cell proliferation and induce cell death through inhibition of STAT activity. JAK includes JAK1, JAK2, JAK3 and TYK2 (tyrosine kinase 2). An inhibitor targeting JAK may be ruxolitinib, lestaurtinib or pacritinib.

As used herein, the term "ALK (anaplastic lymphoma kinase)" is a signal transduction mediator that promotes cell proliferation, cell migration and angiogenesis and inhibits cell death, and is overactivated in various cancer tissues. An inhibitor targeting ALK may be alectinib, lorlatinib or crizotinib.

As used herein, the term "Bcl-2" is a protein that inhibits cell death, and is overexpressed or overactivated in various cancer tissues. An inhibitor targeting Bcl-2 may include venetoclax, ABT-737, navitoclax (ABT-263), and the like.

As used herein, the term "C-Met" is a receptor for hepatocyte growth factor (HGF), and activates signal transduction related to cell growth, formation, motility, survival and angiogenesis and the like. A C-Met targeted anticancer agent may be crizotinib, tepotinib or cabozantinib.

As used herein, the term "VR (vanilloid receptor) is also known as TRPV (transient receptor potential vanilloid), and exists in the form of VR1, VR2, VR3, VR4, VR5 and VR6. VR is known to regulate proliferation, death, migration, infiltration and angiogenesis of cancer cells at each stage in the cancer progression process.

As used herein, the term "c-kit" is also known as CD117, and induces signal transduction that activates cell survival, proliferation and differentiation. c-kit is a proto-

oncogene, and overexpression or mutation of this gene is associated with cancer development. In one embodiment, a c-kit targeted anticancer agent may be imatinib, dasatinib or regorafenib.

As used herein, the term "AXL (tyrosine-protein kinase receptor UFO)" is a tyrosine kinase receptor present on the cell surface and mediates signal transduction involved in cell proliferation and survival. It is known to be involved in resistance to anticancer agents in anticancer treatment. In one embodiment, an AXL targeted anticancer agent may be bemcentinib or gilteritinib.

As used herein, the term "RET (rearranged during transfection)" is a receptor that mediates signals involved in cell proliferation, cell death and survival, and mutations in RET are known to be involved in cancer development. An inhibitor targeting RET may be selpercatinib or pralsetinib, but is not limited thereto.

As used herein, the term "BRAF" is a MAPK signal transduction mediator involved in cell proliferation, cell cycle regulation, cell survival, angiogenesis, cell migration, and the like, and genetic mutations are observed in cancer cells. An inhibitor targeting BRAF may be dabrafenib, encorafenib (LGX818) or vemurafenib.

As used herein, the term "pan-RAF" encompasses RAF family substances such as BRAF, ARAF, and CRAF. An inhibitor targeting pan-RAF may be naporafenib, belvarafenib or sorafenib.

As used herein, the term "SHP2 (Src homology region 2 domain-containing phosphatase-2)" is also referred to as tyrosine-protein phosphatase non-receptor type 11 (PTPN11) or protein-tyrosine phosphatase 1D/2C (PTP-1D/2C), and it is known to be a signal molecule that regulates various cellular processes, including cell growth, differentiation, mitotic cycle, and oncogenic transformation. Activation of SHP2 mutations is found in neuroblastoma, melanoma, acute myeloid leukemia, breast cancer, lung cancer, colorectal cancer, and the like. An inhibitor targeting SHP2 may include, for example, PF-07284892, RMC-4630 (SHP2-IN-7) or batoprotafib (TNO155).

As used herein, the term "SRC (proto-oncogene tyrosine-protein kinase)" refers to a non-receptor tyrosine kinase protein, also known as c-Src, that regulates embryonic development and cell growth, and an elevated level of its activity is known to be associated with cancer progression. The SRC inhibitor may be, for example, dasatinib or bosutinib.

As used herein, the term "LCK (lymphocyte-specific protein tyrosine kinase)" belongs to the SFK (Src kinase family) and activates T cell receptor signal transduction. Mutations and dysfunction of LCK inhibit T cell activation, and overexpression of LCK is known to be associated with cancer, asthma, type 1 diabetes mellitus, rheumatoid arthritis, psoriasis, systemic lupus erythematosus, inflammatory bowel disease (Crohn's disease and ulcerative colitis), and the like. An inhibitor targeting LCK may be, for example, WH-4-023.

As used herein, the term "PARP (poly [ADP-ribose] polymerase)" is a protein that is activated by recognition of damaged DNA in the nucleus and then activates DNA repair related

proteins. An inhibitor targeting PARP inhibits the proliferation of cancer cells by inhibiting DNA repair in cancer cells. In one embodiment, an inhibitor targeting PARP may be olaparib, talazoparib, niraparib or rucaparib.

As used herein, the term "DNA methyltransferase (DNMT)" is an enzyme that attaches a methyl group to a histone protein wrapped around DNA, and through this process, the expression of the gene is inhibited. An inhibitor targeting DNMT exhibits anticancer activity by inhibiting hypermethylation of cancer suppressor genes and inducing normal expression of cancer suppressor genes. In one embodiment, an inhibitor targeting DNMT may be azacitidine, decitabine, or guadecitabine.

As used herein, the term "CDK (cyclin dependent kinase) 4/6" is a protein that promotes cell growth by regulating the cell cycle, and is overactivated during the development and progression of various malignant tumors. An inhibitor targeting CDK4/6 exhibits anticancer activity by inhibiting the cell cycle of cancer cells, inhibiting cell proliferation and inducing cell death. An inhibitor targeting CDK4/6 may be abemaciclib (LY2835219), ribociclib or palbociclib.

As used herein, the term "Aurora kinase" is a serine/threonine kinase essential for cell proliferation and refers to a phosphotransferase enzyme that helps dividing cells distribute genetic material to daughter cells. Aurora kinase plays an important role in cell division by controlling chromatid segregation, and defects in segregation can lead to tumorigenesis. Aurora A (Aurora 2) functions during mitotic prophase and is involved in the correct replication and segregation of centrosomes (microtubule-organizing centers in eukaryotic cells). Aurora B (Aurora 1) is responsible for attaching the mitotic spindle to the centromere. Aurora C (AURKC) acts in germ cells. An inhibitor targeting Aurora A may include MK-5108, hesperadin, LY3295668, and the like. An inhibitor targeting pan-Aurora may include danusertib, AMG-900, reversine, tozasertib (VX-680), and the like.

As used herein, the term "WEE1" is a 96 kDa nuclear kinase belonging to the Ser/Thr protein kinase family, also referred to as mitosis inhibitor protein kinase Wee1. Mitosis promoting factor (MPF) regulates apoptosis caused by DNA damage, and negative regulation of MPF by WEE1 causes abnormal mitosis and resistance to apoptosis caused by DNA damage. An inhibitor targeting WEE1 can reduce the sensitivity to DNA damage-induced apoptosis in cancer cells by regulating WEE1. An inhibitor targeting WEE1 may include MK-1775 (adavosertib), azenosertib (ZN-C3), ZNL-02-096, and the like.

As used herein, the term "PKMYT1 (protein kinase, membrane-associated tyrosine/threonine 1)" belongs to the Wee1 protein kinase family, and is a regulator of CDK1 phosphorylation, and is a potent therapeutic target for the treatment of certain types of DNA damage-responsive cancers through the synthetic lethality of CCNE1 amplification. An inhibitor targeting PKMYT1 may include RP-6306, GSK-1520489A, and the like.

As used herein, the term "HSP90 (heat shock protein 90)" refers to a chaperone protein that helps other proteins fold properly, stabilizes proteins from heat stress, and assists in protein degradation. It can exhibit anticancer efficacy by stabilizing a number of proteins required for tumor growth. HSP90 inhibitors may include BIIB021, BIIB028, MPC-3100, PU-H71, Debio093, SNX-5422, AUY922, and the like.

As used herein, the term "A3AR (adenosine A3 receptor; ADORA3)" refers to a G protein-coupled receptor that binds to Gi/Gq and is involved in various intracellular signaling pathways and physiological functions, and is overexpressed in pathological human cells, and can mediate cell proliferation and cell death. A therapeutic agent targeting A3AR may include reversine, KF-26777, MRS-545, CAY10498, and the like.

As used herein, the term "EZH2 (enhancer of zeste homolog 2)" refers to a histone-lysine N-methyltransferase enzyme encoded by the EZH2 gene, which participates in histone methylation and ultimately transcriptional repression. EZH2 is an attractive target for anticancer treatment because it helps cancer cells divide and proliferate, and is found in greater amounts than in healthy cells in a wide range of cancers, including breast cancer, prostate cancer, bladder cancer, uterine cancer, kidney cancer, as well as melanoma and lymphoma. An inhibitor targeting EZH2 may include DZNep, EPZ005687, EI1, GSK126, UNC1999, tazemetostat, sinefungin, and the like.

As used herein, the term "ARID1A (AT-rich interactive domain-containing protein 1A)" is a member of the SWI/SNF family, has helicase and ATPase activities, and regulates the transcription of specific genes by altering the chromatin structure around those genes. The ARID domain is a DNA binding domain that can specifically bind to AT-rich DNA sequences known to be recognized by the SWI/SNF complex at the beta-globin locus, and the C-terminus of the protein can stimulate glucocorticoid receptor-dependent transcriptional activation. Mutations in this gene are commonly found in gastric cancer, ovarian clear cell carcinoma, and pancreatic cancer. An inhibitor targeting EZH2/ARID1A may include GSK-343, and the like.

As used herein, the term "SUMOylation" is a post-translational modification that covalently attaches a small ubiquitin-like modifier (SUMO) polypeptide to a lysine residue of a target protein. The enzymatic pathway of SUMOylation is very similar to ubiquitination and includes activating enzymes, conjugation enzymes, ligases, and deconjugation enzymes. Dysregulation of the SUMOylation pathway is observed in cancer and neurological diseases, where SUMO enzymes are upregulated in many cancers and SUMO levels are directly correlated with prognosis and disease progression. SUMOylation inhibitors may include Davidiin, CID9549553, 2-D08, and the like.

As used herein, the term "CHK1 (checkpoint kinase 1; CHEK1)" is a serine/threonine-specific protein kinase that modulates DNA damage response (DDR) and cell cycle checkpoint responses. Activation of CHK1 results in the initiation of cell cycle checkpoints, cell cycle arrest, DNA repair, and apoptosis, thereby preventing damaged cells from progressing through

the cell cycle. CHK1 is overexpressed in numerous tumors, including breast cancer, colon cancer, liver cancer, gastric cancer, and nasopharyngeal cancer, and the positive correlation between CHK1 expression and tumor grade and disease recurrence suggests that CHK1 can promote tumor growth. An inhibitor targeting CHK1 may include SCH-900776, SRA737, V158411, PF-477736, AZD7762, LY2880070 (prexasertib), and the like.

As used herein, the term "ATR (ataxia telangiectasia mutated (ATM) and RAD3-related kinase)" refers to a protein kinase implicated in cellular responses to certain forms of DNA damage (for example, double-strand breaks and replication stress). Normal cells repair damaged DNA using the ATM/ATR signal transduction system, which regulates the cellular response to double-strand DNA breaks and replication stress, referred to as the DNA damage response ("DDR"). On the other hand, many cancer cells show a high dependence on DNA repair proteins, including ATR, due to defects in ATM in the DNA repair process. An inhibitor targeting ATR may be berzosertib (VX-970), gartisertib (VX-803) or ceralasertib (AZD6738).

As used herein, the term "HDAC (histone deacetylase)" refers to an enzyme that removes the acetyl group from the ϵ -N-acetyl lysine amino acid of histone and non-histone proteins, and histones wrap DNA more tightly to regulate the expression of DNA through acetylation and deacetylation. HDAC includes subgroups such as Class I, such as HDAC1, HDAC2, and HDAC3, and Class IIA, such as HDAC4, HDAC5, and HDAC7. An HDAC inhibitor exhibits anticancer efficacy in studies on pancreatic cancer, esophageal squamous cell carcinoma (ESCC), multiple myeloma, prostate carcinoma, gastric cancer, leukemia, breast cancer, liver cancer, ovarian cancer, nasal cancer, Hodgkin's lymphoma, and neuroblastoma. An inhibitor targeting HDAC may include panobinostat (LBH589), entinostat, mocetinostat, trichostatin A, CBUD-1001, abexinostat (PCI-24781, CRA-024781), and the like.

As used herein, the term "AKT (protein kinase B: PKB)" is a set of serine/threonine-specific protein kinases that play key roles in several cellular processes such as glucose metabolism, apoptosis, cell proliferation, and transcription, and is associated with tumor cell survival, proliferation and invasiveness. Activation of AKT is commonly observed in human cancer and tumor cells, and tumor cells depend on AKT for survival. An inhibitor targeting AKT may include VQD-002, perifosine, miltefosine, MK-2206, AZD5363, ipatasertib, and the like.

As used herein, the term "PLK1 (Polo-like kinase 1)" is also referred to as serine/threonine-protein kinase 1 or serine/threonine-protein kinase 13 (STPK13), and is a 66 kDa enzyme composed of 603 amino acids. Most colorectal cancer and lung cancer are caused by K-RAS mutations and are known to depend on PLK1. When PLK1 expression is silenced by RNA interference in cell culture, K-RAS cells can be selectively killed without harming normal cells. An inhibitor targeting PLK1 may include volasertib, rigosertib, and the like.

As used herein, the term "BET (bromodomain and extraterminal domain protein)" refers to a bromodomain composed of approximately 110 amino acid proteins that recognize

acetylated lysine residues, including BRD2, BRD3, BRD4, and BRDT. It converts the signals transmitted by the acetylated lysine residues and converts them into various normal or abnormal phenotypes. Bromodomains translate the dysregulated cellular acetylome into disease phenotypes, and BETs are targets in cancer and multiple sclerosis. An inhibitor targeting BET may include JQ1, I-BET 151 (GSK1210151A), I-BET 762 (GSK525762), OTX-015, TEN-010, CPI-203, CPI-0610, Olinone, RVX-208, ABBV-744, LY294002, AZD5153, MT-1, MS645, and the like.

As used herein, the term "IGF (insulin-like growth factor)" is a protein with high sequence similarity to insulin and is involved in communication between cells and the physiological environment, and includes IGF1/2, IGF-1R, IGF-2R, and the like. IGF-1 stimulates the growth of prostate and breast cancer cells, and IGF has been found to be involved in diseases such as cancer and diabetes. An inhibitor targeting IGF1/2 or IGF-1R may include NVP-ADW742, figitumumab, mecaseimerin, rhIGF-1, BI 885578, and the like.

As used herein, the term "PIK (phosphatidylinositol kinase)" consists of phosphatidylinositol 3-kinase (PI3K) and phosphatidylinositol 4-kinase (PI4K). PI3K is involved in cell signal transduction by phosphorylating phosphoinositide on the 3-hydroxyl group of the inositol ring, and PI4K acts on phosphatidylinositol (PI) to produce the second messenger, inositol-1,4,5-trisphosphate, and their abnormalities are associated with cancer. An inhibitor targeting PIK may include duvelisib, buparlisib, copanlisib, dactolisib, idelalisib, piasclisib, paxalisib, taselisib, zandelisib, inavolisib, and the like.

As used herein, the term "CDK9 (cyclin dependent kinase 9)" is a cyclin dependent kinase associated with P-TEFb and is a cell cycle regulator. CDK9 is involved in several protein-protein interaction networks that are often involved in transcriptional deregulation in cancer. An inhibitor targeting CDK9 may include, for example, AZD4573, atueveciclib, VIP152, A-1592668, JSH-150, SLS009, AT-7519, roscovitine, and the like.

As used herein, the term "DHFR (dihydrofolate reductase)" is an enzyme that reduces dihydrofolate to tetrahydrofolate using NADPH as an electron donor, and is a component of the multiprotein complex TAK/P-TEFb, an elongation factor for transcription and function by RNA polymerase II by phosphorylating the C-terminal domain of the largest subunit of RNA polymerase II. DHFR is responsible for intracellular levels of tetrahydrofolate, and inhibiting DHFR can limit cell growth and proliferation, a hallmark of cancer and bacterial infections. An inhibitor targeting DHFR may include methotrexate, pralatrexate, pemetrexed, raltitrexed, trimetrexate, nolatrexed, piritrexim, talotrexin, and the like.

As used herein, the term "STING (stimulator of interferon genes)" is an *in vivo* sensor that recognizes DNA fragments from cancer cells, and activates immune cells in the body, such as dendritic cells, by stimulating interferon genes. A STING agonist exhibits an immune enhancing effect and cancer angiogenesis inhibitory effect. For example, a STING agonist may be CDNs, SB11285, DMXAA, and the like.

The compound represented by Formula I or Formula I-1 of the present invention can be used in combination with other targeted inhibitors described above to enhance the action of the targeted inhibitors, thereby significantly inhibiting the expression and activity of the target protein or gene. Specifically, the compound represented by Formula I or Formula I-1 not only has its own anticancer efficacy, but can also improve the anticancer efficacy of the targeted inhibitor. Therefore, when the compound represented by Formula I or Formula I-1 are used together with the targeted inhibitor, they can exhibit anticancer efficacy that is superior to the sum of the anticancer efficacy when they are used alone.

As used herein, the term "anticancer virus therapeutic agent" is a therapeutic agent that kills cancer by inserting a specific gene targeting cancer cells into a virus capable of proliferation and having infectivity. The anticancer virus therapeutic agent may be Talimogene Laherparepvec.

As used herein, the term "antibody therapeutic agent" is a therapeutic agent that exhibits an anticancer effect using an antibody that recognizes a specific protein of cancer cells as an antigen. An antibody therapeutic agent may be cetuximab, trastuzumab, emtansine, emtansine, rituximab, ibritumomab, tositumomab, brentuximab, ofatumumab, obinutuzumab, necitumumab, bevacizumab, ramucirumab, nivolumab, pembrolizumab, atezolizumab, durvalumab, ipilimumab, and the like.

As used herein, the term "immune cell therapeutic agent" is a therapeutic agent that exhibits an anticancer effect by activating an immune response in the body using immune cells such as dendritic cells, natural killer cells, T cells, and the like. An immune cell therapeutic agent is used by extracting and enhancing immune cells in the body or genetically modifying them and then injecting them back into the body. Representative immune cell therapeutic agents may include T cell receptor-modified T cells (TCR-T), chimeric antigen receptor-modified T cells (CAR-T), and the like. Specifically, it may be tisagenlecleucel or axicabtagene ciloleucel, but is not limited thereto.

As used herein, the term "immune checkpoint inhibitor" is a substance that inhibits the activity of an immune checkpoint protein, which inhibits the differentiation, proliferation, and activity of immune cells, and is known to eliminate cancer cells by preventing them from exerting functions to evade the immune system. The immune checkpoint inhibitor may be any one selected from the group consisting of an anti-CTLA-4 antibody, an anti-PD-1 antibody, an anti-PD-L1 antibody, an anti-PD-L2 antibody, an anti-B7-H4 antibody, an anti-HVEM antibody, an anti-TIM3 antibody, an anti-GAL9 antibody, an anti-LAG3 antibody, an anti-VISTA antibody, an anti-KIR antibody, an anti-BTLA antibody and an anti-TIGIT antibody. In one embodiment, the immune checkpoint inhibitor may be ipilimumab, pembrolizumab, nivolumab, cemiplimab, atezolizumab, avelumab and durvalumab and the like, but is not limited thereto.

As used herein, the term "ADC (antibody drug conjugate)" is a therapeutic agent that exhibits high anticancer effects through targeted delivery by chemical binding of an antibody and a cytotoxic drug. It may be gemtuzumab-ozogamicin, brentuximab-vedotin, trastuzumab-emtansine, inotuzumab-ozogamicin, and eribulin-mesylate, and the like.

The anticancer agent may include one or more anticancer agents. Specifically, the compound, solvate, stereoisomer or pharmaceutically acceptable salt thereof may be used together with two anticancer agents. For example, two anticancer agents may be a chemical anticancer agent and a targeted anticancer agent; a chemical anticancer agent and an anticancer virus; a targeted anticancer agent and an antibody therapeutic agent; a chemical anticancer agent and a cell therapeutic agent; and a chemical anticancer agent and an immune checkpoint inhibitor. In addition, two anticancer agents may be a targeted anticancer agent and an anticancer virus; a targeted anticancer agent and an antibody therapeutic agent; a targeted anticancer agent and a cell therapeutic agent; a targeted anticancer agent and an immune checkpoint inhibitor. In addition, two anticancer agents may be an anticancer virus and an antibody therapeutic agent; an anticancer virus and a cell therapeutic agent; and an anticancer virus and an immune checkpoint inhibitor. In addition, two anticancer agents may be an antibody therapeutic agent and a cell therapeutic agent; and an antibody therapeutic agent and an immune checkpoint inhibitor.

The compound, solvate, stereoisomer or pharmaceutically acceptable salt thereof may be used together with three anticancer agents. In addition to the two anticancer agents, a different anticancer agent may be further included and used.

The compound, solvate, stereoisomer or pharmaceutically acceptable salt thereof may be used together with four anticancer agents. In addition to the three anticancer agents, a different anticancer agent may be further included and used.

The compound, solvate, stereoisomer or pharmaceutically acceptable salt thereof may be used together with five anticancer agents. In addition to the four anticancer agents, a different anticancer agent may be further included and used.

The compound, solvate, stereoisomer or pharmaceutically acceptable salt thereof may be used together with six anticancer agents.

The compound, solvate, stereoisomer or pharmaceutically acceptable salt thereof may be used in combination with an anticancer vaccine.

As used herein, the term "anticancer vaccine" is an active immunotherapy that removes cancer cells by enhancing the immune function *in vivo* by administering a tumor-specific antigen (TSA) possessed by cancer cells to a cancer patient to activate the immune system. An anticancer vaccine may include a DNA vaccine, a peptide vaccine, a cell vaccine, and the like, depending on the type of antigen and the delivery method of antigen, and a cell vaccine and a DNA vaccine developed by introducing antigens are currently being developed representatively.

The compound, solvate, stereoisomer or pharmaceutically acceptable salt thereof may be used in combination with the anticancer agent and the anticancer vaccine. Here, the compound and the anticancer agent are the same as described above.

In another aspect, there is provided a method for preventing or treating a SOS1 mediated disease, comprising administering to a subject a compound of Formula I, a solvate, stereoisomer or pharmaceutically acceptable salt thereof, or the pharmaceutical composition comprising the same.

Among the terms or elements mentioned in the description of the method, the same as those already mentioned are the same as described above.

The administration may be oral or parenteral administration. It may be administered in one to several divided doses to be administered in an amount of 0.01 to 1000 mg, more specifically 0.1 to 300 mg per kg of body weight daily based on the active ingredient when administered orally, or in an amount of 0.01 to 100 mg, more specifically 0.1 to 50 mg per kg of body weight daily based on the active ingredient when administered parenterally. The dose to be administered to a specific subject or patient should be determined in light of several related factors such as body weight, age, sex, health condition of the patient, diet, administration time, administration method, the severity of the disease, and the like, and it may be appropriately increased or decreased by a specialist.

As used herein, the term "subject" refers to a subject in need of treatment for a disease, and more specifically means a mammal such as a human or non-human primate, a mouse, a dog, a cat, a horse, and a cow.

In another aspect, there is provided a method of inhibiting the interaction of SOS1 and RAS family proteins and/or SOS1 and RAC1 in a sample or cell, comprising administering the compound represented by Formula I, solvate, stereoisomer or pharmaceutically acceptable salt thereof to the sample or cell.

In another aspect, there is provided a medicinal use of the compound of Formula I, solvate, stereoisomer or pharmaceutically acceptable salt thereof for the prevention or treatment of a SOS1 mediated disease; or a use of the compound of Formula I, solvate, stereoisomer or pharmaceutically acceptable salt thereof for the manufacture of a medicament for the prevention or treatment of a SOS1 mediated disease.

Among the terms or elements mentioned in the description of the method or use, the same as those already mentioned are the same as described above.

Effects of Invention

The compound of Formula I, solvate, stereoisomer or pharmaceutically acceptable salt thereof has an effective inhibitory activity against SOS1, specifically, inhibits the interaction between SOS1 and RAS family proteins, or between SOS1 and RAC1, and thus, it is useful for

the prevention or treatment of a SOS1 mediated disease, specifically a disease associated with the abnormal activity of SOS1 and/or RAS family proteins.

Brief Description of Drawings

Figure 1 is a graph showing the results obtained by evaluating cell viability according to the administration of the example compounds and sotorasib alone or in combination to the lung cancer cell NCI-H358.

Figure 2 is a graph showing the results obtained by evaluating cell viability according to the administration of the example compounds and sotorasib alone or in combination to the pancreatic cancer cell MIA PaCa-2.

Figure 3 is a graph showing the results obtained by evaluating cell viability according to the administration of the example compounds and adagrasib alone or in combination to the lung cancer cell NCI-H358.

Figure 4 is a graph showing the results obtained by evaluating cell viability according to the administration of the example compounds and adagrasib alone or in combination to the pancreatic cancer cell MIA PaCa-2.

Figures 5a and 5b are graphs showing the results obtained by evaluating cell viability according to the administration of the example compounds and trametinib alone or in combination to the lung cancer cell NCI-H358.

Figures 6a and 6b are graphs showing the results obtained by evaluating cell viability according to the administration of the example compounds and trametinib alone or in combination to the gastric cancer cell SNU-1.

Figures 7a and 7b are graphs showing the results obtained by evaluating cell viability according to the administration of the example compounds and trametinib alone or in combination to the colorectal cancer cell SW480.

Figure 8 is a graph showing the results obtained by evaluating cell viability according to the administration of the example compounds and osimertinib alone or in combination to the lung cancer cell H1975.

Figure 9 is a graph showing the results obtained by evaluating cell viability according to the administration of the example compounds and osimertinib alone or in combination to the lung cancer cell HCC827.

Figure 10 is a graph showing the results obtained by evaluating cell viability according to the administration of the example compounds and lazertinib alone or in combination to the lung cancer cell H1975.

Figure 11 is a graph showing the results obtained by evaluating cell viability according to the administration of the example compounds and lazertinib alone or in combination to the lung cancer cell HCC827.

Figure 12 is a graph showing the results obtained by evaluating cell viability according to the administration of the example compounds and alpelisib alone or in combination to the PIK3CA mutant breast cancer cell MCF7.

Figure 13 is a graph showing the results obtained by evaluating cell viability according to the administration of the example compounds and JDQ443 alone or in combination to the lung cancer cell H358 having the KRAS G12C variant.

Figure 14 is a graph showing the results obtained by evaluating cell viability according to the administration of the example compounds and TNO155 alone or in combination to the lung cancer cell H358 having the KRAS G12C variant.

Figure 15 is a graph showing the results obtained by evaluating cell viability according to the administration of the example compounds and cisplatin alone or in combination to the lung cancer cell H358 having the KRAS G12C variant.

Figure 16 is a graph showing the results obtained by evaluating cell viability according to the administration of the example compounds and rineterkib alone or in combination to the lung cancer cell H358 having the KRAS G12C variant.

Figure 17 is a graph showing the results obtained by evaluating cell viability according to the administration of the example compounds and ulixertinib alone or in combination to the lung cancer cell H358 having the KRAS G12C variant.

Figure 18 is a graph showing the results obtained by evaluating cell viability according to the administration of the example compounds and pralsetinib alone or in combination to the lung cancer cell H358 having the KRAS G12C variant.

Figure 19 is a graph showing the results obtained by evaluating cell viability according to the administration of the example compounds and repotrectinib alone or in combination to the lung cancer cell H358 having the KRAS G12C variant.

Figure 20 is a graph showing the results obtained by evaluating cell viability according to the administration of the example compounds and tepotinib alone or in combination to the c-Met overexpressing gastric cancer cell SNU-5.

Figure 21 is a graph showing the results obtained by evaluating cell viability according to the administration of the example compounds and bemcentinib alone or in combination to the lung cancer cell PC-9 with high AXL expression.

Figure 22 is a graph showing the results obtained by evaluating cell viability according to the administration of the example compounds and alrizomadlin alone or in combination to the lung cancer cell A549 having the KRAS G12S variant.

Figure 23 is a graph showing the results obtained by evaluating cell viability according to the administration of the example compounds and everolimus alone or in combination to the colorectal cancer cell LoVo having the KRAS G13D variant.

Figure 24 is a graph showing the results obtained by evaluating cell viability according to the administration of the example compounds and MRTX1133 alone or in combination to the lung cancer cell AsPC-1 having the KRAS G12D variant.

Figures 25a to 25c are graph showing the results obtained by evaluating the synergy of the combined administration of the example compounds to the lung cancer cell H358 using SynergyScreen.

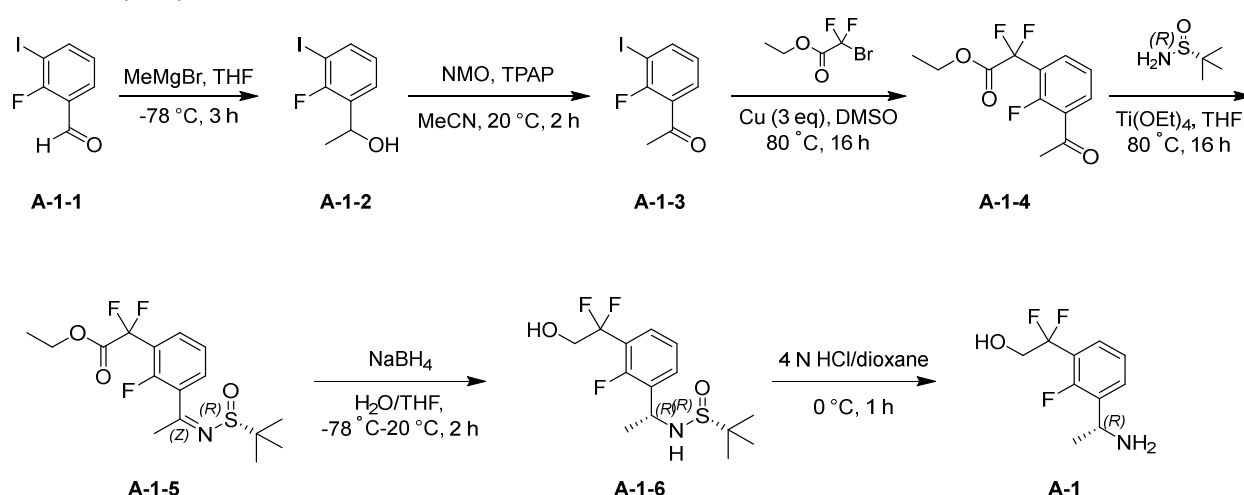
Figures 26a to 26c are graph showing the results obtained by evaluating the synergy of the combined administration of the example compounds to the lung cancer cell H358 using SynergyScreen.

Detailed Descriptions for Carrying out the Invention

Hereinafter, the present invention will be described in more detail by way of the following examples. However, the following examples are only for illustrating the present invention, and the scope of the present invention is not limited thereto.

[Preparation Examples]

Preparation Example 1: 2-[3-[(1R)-1-aminoethyl]-2-fluoro-phenyl]-2,2-difluoro-ethanol (A-1)



Step 1: Synthesis of 1-(2-fluoro-3-iodophenyl)ethanol

To a solution of 2-fluoro-3-iodo-benzaldehyde (4.0 g, 16.00 mmol) in THF (40 mL) was added dropwise MeMgBr (3 M, 8.00 mL) at -78 °C, and then the mixture was stirred for 3 h. The reaction mixture was poured into sat. aq. NH₄Cl (50 mL) and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, and then concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (7% EtOAc in petroleum ether) to give 1-(2-fluoro-3-iodo-phenyl)ethanol (4.45 g, 83.63% yield) as yellow oil. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 7.72-7.64 (m, 1H), 7.55-7.45 (m, 1H), 6.93 (t, *J* = 7.6 Hz, 1H), 5.20 (q, *J* = 6.4 Hz, 1H), 1.52 (d, *J* = 6.4 Hz, 3H).

Step 2: Synthesis of 1-(2-fluoro-3-iodophenyl)ethanone

To a solution of 1-(2-fluoro-3-iodo-phenyl)ethanol (4.45 g, 16.73 mmol) in MeCN (50 mL) was added TPAP (Tetrapropylammonium perruthenate; 587.80 mg, 1.67 mmol) and NMO (N-methyl morpholine-N-oxide; 2.94 g, 25.09 mmol), and then the mixture was stirred at 20 °C for 2 h. The mixture was filtered and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (0% EtOAc in petroleum ether) to give 1-(2-fluoro-3-iodo-phenyl)ethanone (3.8 g, 12.95 mmol, 77.44% yield, 90% purity) as a white solid. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 7.97-7.88 (m, 1H), 7.85-7.78 (dm, 1H), 7.00 (t, *J* = 7.6 Hz, 1H), 2.65 (d, *J* = 5.2 Hz, 3H).

Step 3: Synthesis of ethyl 2-(3-acetyl-2-fluoro-phenyl)-2,2-difluoro-acetate

To a solution of 1-(2-fluoro-3-iodo-phenyl)ethanone (3.0 g, 11.36 mmol) and ethyl-2-bromo-2,2-difluoro-acetate (6.92 g, 34.09 mmol, 4.38 mL) in DMSO (30 mL) was added Cu (2.17 g, 34.09 mmol), and then the mixture was stirred at 80 °C for 12 h. The reaction mixture was poured into water (50 mL) and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (5% EtOAc in petroleum ether) to give ethyl 2-(3-acetyl-2-fluoro-phenyl)-2,2-difluoro-acetate (1.8 g, 56.05% yield, 92.07% purity) as colorless oil. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 8.08-8.00 (m, 1H), 7.87-7.81 (m, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 4.42-4.37 (m, 2H), 2.66 (d, *J* = 5.2 Hz, 3H), 1.35 (t, *J* = 7.2 Hz, 3H); MS (ESI) *m/z* = 261.0 [M+H]⁺.

Step 4: Synthesis of ethyl 2-[3-[(R)-tert-butylsulfinyl]-C-methyl-carboimidoyl]-2-fluoro-phenyl]-2,2-difluoro-acetate

To a solution of ethyl 2-(3-acetyl-2-fluoro-phenyl)-2,2-difluoro-acetate (1.8 g, 6.92 mmol) and (R)-2-methylpropane-2-sulfinamide (1.26 g, 10.38 mmol) in THF (20 mL) was added Ti(OEt)₄ (4.73 g, 20.75 mmol), and then the mixture was stirred at 80 °C for 16 h. The reaction mixture was poured into water (30 mL) and EtOAc (30 mL) and filtered, and then the filtrate was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (6% EtOAc in petroleum ether) to give ethyl 2-[3-[(R)-tert-butylsulfinyl]-C-methyl-carboimidoyl]-2-fluoro-phenyl]-2,2-difluoro-acetate (1.9 g, 74.09% yield, 98.03% purity) as yellow oil. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 7.86-7.72 (m, 2H), 7.32 (t, *J* = 7.6 Hz, 1H), 4.44-4.30 (m, 2H), 2.77 (s, 3H), 1.32 (s, 9H); MS (ESI) *m/z* = 364.0 [M+H]⁺.

Step 5: Synthesis of (R)-N-[(1R)-1-[3-(1,1-difluoro-2-hydroxyethyl)-2-fluoro-phenyl]ethyl]-2-methyl-propane-2-sulfinamide

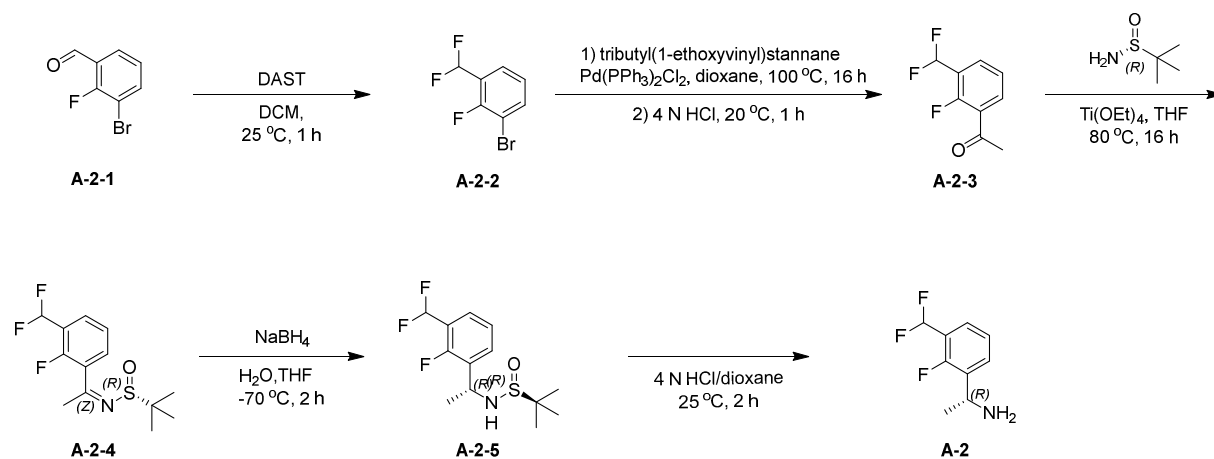
To a solution of ethyl 2-[3-[(R)-tert-butylsulfinyl]-C-methyl-carboimidoyl]-2-fluoro-phenyl]-2,2-difluoro-acetate (900 mg, 2.48 mmol) in THF (10 mL) and H₂O (0.2 mL) was added NaBH₄ (210 mg, 5.55 mmol) at -78 °C, and then the mixture was slowly warmed to 10 °C and stirred at 10 °C for 2 h. The reaction mixture was poured into ice-cold water (30 mL) and

extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure to give a crude product. Following the primary purification by silica gel column chromatography (50% EtOAc in petroleum ether), two diastereomers (about 3:1 ratio) were separated and purified by prep-HPLC (Xtimate C18 150*40 mm*10 μ m, mobile phase: [water (NH₃H₂O)-ACN]; B%: 25%-55%, 10 min). MeCN was removed under reduced pressure, and the remaining solvent was removed by lyophilization to give a main product, (R)-N-[(1R)-1-[3-(1,1-difluoro-2-hydroxyethyl)-2-fluoro-phenyl]ethyl]-2-methyl-propane-2-sulfinamide (440 mg, 50.90% yield, 92.65% purity, >99% ee) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.70 (t, *J* = 6.8 Hz, 1H), 7.48-7.39 (m, 1H), 7.35-7.25 (m, 1H), 5.87 (d, *J* = 7.6 Hz, 1H), 5.70 (t, *J* = 6.4 Hz, 1H), 4.68 (quint, *J* = 7.2 Hz, 1H), 3.90 (dt, *J* = 6.4, 14.4 Hz, 2H), 1.40 (d, *J* = 6.8 Hz, 3H), 1.10 (s, 9H); MS (ESI) *m/z* = 324.3 [M+H]⁺.

Step 6: Synthesis of 2-[3-[(1R)-1-aminoethyl]-2-fluoro-phenyl]-2,2-difluoro-ethanol

To a solution of (R)-N-[(1R)-1-[3-(1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethyl]-2-methyl-propane-2-sulfinamide (440 mg, 1.36 mmol) in dioxane (4 mL) was added 4N HCl/dioxane (2 mL) at 0 °C, and then the mixture was stirred at 0 °C for 1 h. The mixture was concentrated under reduced pressure to give **Intermediate A-1** (347 mg, 100% yield, 95% purity, HCl salt) as yellow oil. MS (ESI) *m/z* = 220.0 [M+H]⁺.

Preparation Example 2: (1R)-1-[3-(difluoromethyl)-2-fluoro-phenyl]ethanamine (A-2)



Step 1: Synthesis of 1-bromo-3-(difluoromethyl)-2-fluoro-benzene

To a solution of 3-bromo-2-fluoro-benzaldehyde (9 g, 44.33 mmol) in DCM (150 mL) was added DAST (Diethylaminosulfur trifluoride; 14.29 g, 88.67 mmol, 11.71 mL), and then the mixture was stirred at 25 °C for 1 h. After the addition of sat. NaHCO₃ (50 mL), the combined organic layers were extracted with DCM (50 mL X 3). It was washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure to give a crude product. The organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography

(100% petroleum ether) to give 1-bromo-3-(difluoromethyl)-2-fluoro-benzene (3.9 g, 39.1% yield) as colorless oil. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.98 - 7.79 (m, 1H), 7.72 - 7.57 (m, 1H), 7.37 (s, 1H), 7.31 (br t, $J = 7.8$ Hz, 1H), 7.24 (s, 1H), 7.10 (s, 1H).

Step 2: Synthesis of 1-[3-(difluoromethyl)-2-fluoro-phenyl]ethanone

A mixture of 1-bromo-3-(difluoromethyl)-2-fluoro-benzene (17 g, 75.55 mmol), tributyl(1-ethoxyvinyl)stannane (28.65 g, 79.33 mmol, 26.80 mL) and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (2.65 g, 3.78 mmol) in dioxane (300 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100°C for 16 h under N_2 atmosphere. The mixture was quenched with 4 N HCl (30 mL) and then stirred at 20°C for 1 h. The mixture was poured into water (200 mL) and extracted with EtOAc (100 mL X 3). The organic layers were washed with brine (100 mL X 3), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (2% EtOAc in petroleum ether) to give 1-[3-(difluoromethyl)-2-fluoro-phenyl]ethanone (10 g, 70.35% yield) as colorless oil. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.03-7.93 (m, 1H), 7.93-7.82 (m, 1H), 7.49-7.14 (m, 2H), 2.63-2.58 (m, 3H).

Step 3: Synthesis of (NZ,R)-N-[1-[3-(difluoromethyl)-2-fluoro-phenyl]ethylidene]-2-methyl-propane-2-sulfinamide

A mixture of 1-[3-(difluoromethyl)-2-fluoro-phenyl]ethanone (10 g, 53.15 mmol), 2-methylpropane-2-sulfinamide (6.44 g, 53.15 mmol) and $\text{Ti}(\text{OEt})_4$ (36.37 g, 159.45 mmol, 33.07 mL) in THF (80 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80°C for 16 h under N_2 atmosphere. The mixture was poured into water (100 mL) and filtered, and then the filtrate was extracted with EtOAc (100 mL X 3). The organic layers were washed with brine (50 mL X 3), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (35% EtOAc in petroleum ether) to give (NZ,R)-N-[1-[3-(difluoromethyl)-2-fluoro-phenyl]ethylidene]-2-methyl-propane-2-sulfinamide (13.0 g, 81.65% yield, 97.25% purity) as yellow oil. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.90-7.81 (m, 1H), 7.81-7.73 (m, 1H), 7.47-7.40 (m, 1H), 7.29-7.10 (m, 1H), 2.71 (br s, 3H), 1.22 (s, 9H); MS (ESI) $m/z = 292.1$ $[\text{M}+\text{H}]^+$.

Step 4: Synthesis of (R)-N-[(1R)-1-[3-(difluoromethyl)-2-fluoro-phenyl]ethyl]-2-methyl-propane-2-sulfinamide

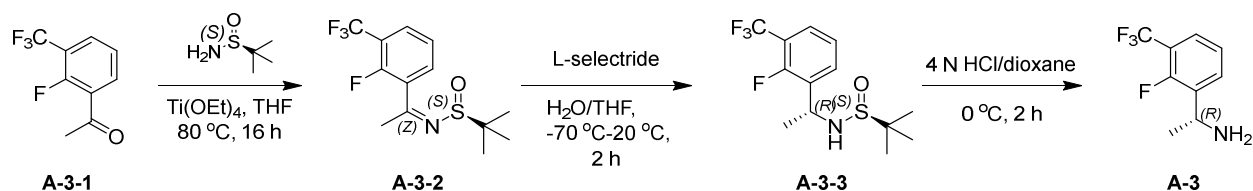
A solution of (NZ,R)-N-[1-[3-(difluoromethyl)-2-fluoro-phenyl]ethylidene]-2-methyl-propane-2-sulfinamide (13 g, 44.62 mmol) in THF (200 mL) and H_2O (5 mL) was cooled to -70°C and stirred at -70°C for 2 h under N_2 atmosphere after the addition of NaBH_4 (1.35 g, 35.70 mmol) in 3 batches. The mixture was quenched at 20°C with sat. NH_4Cl (200 mL), diluted with EtOAc (150 mL), and then extracted with EtOAc (150 mL X 3). The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (30%

EtOAc in petroleum ether) to give (R)-N-[(1R)-1-[3-(difluoromethyl)-2-fluoro-phenyl]ethyl]-2-methyl-propane-2-sulfinamide (4.4 g, 33.61% yield, 100% purity, 98.34% ee) as colorless oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.74 (t, *J* = 7.2 Hz, 1H), 7.52 (t, *J* = 6.8 Hz, 1H), 7.37-7.33 (m, 1H), 7.33-7.06 (m, 1H), 5.88 (d, *J* = 8.0 Hz, 1H), 5.75 (s, 1H), 4.69 (quint, *J* = 7.0 Hz, 1H), 1.41 (d, *J* = 6.8 Hz, 3H), 1.10 (s, 9H); MS (ESI) *m/z* = 294.1 [M+H]⁺.

Step 5: Synthesis of (1R)-1-[3-(difluoromethyl)-2-fluoro-phenyl]ethanamine

A mixture of (R)-N-[(1R)-1-[3-(difluoromethyl)-2-fluoro-phenyl]ethyl]-2-methyl-propane-2-sulfinamide (2.00 g, 6.82 mmol) in 4 N HCl/dioxane (15 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 25 °C for 2 h under N₂ atmosphere. The mixture was concentrated under reduced pressure to give **Intermediate A-2** (1.5 g, 94.02% yield, 96.43% purity, HCl salt) as a white solid. MS (ESI) *m/z* = 190.1 [M+H]⁺.

Preparation Example 3: (1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethanamine (A-3)



Step 1: Synthesis of (NZ,S)-N-[1-[2-fluoro-3-(trifluoromethyl)phenyl]ethylidene]-2-methyl-propane-2-sulfinamide

A mixture of 1-[2-fluoro-3-(trifluoromethyl)phenyl]ethanone (1.9 g, 9.22 mmol), (S)-2-methylpropane-2-sulfinamide (1.12 g, 9.22 mmol) and Ti(OEt)₄ (6.31 g, 27.65 mmol, 5.73 mL) in THF (10 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 80 °C for 16 h under N₂ atmosphere. The mixture was poured into water (30 mL) and extracted with EtOAc (30 mL X 3). The organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (24% EtOAc in petroleum ether) to give (NZ,S)-N-[1-[2-fluoro-3-(trifluoromethyl)phenyl]ethylidene]-2-methyl-propane-2-sulfinamide (2.08 g, 62.57% yield, 85.77% purity) as yellow oil. MS (ESI) *m/z* = 310.1 [M+H]⁺.

Step 2: Synthesis of (S)-N-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-2-methyl-propane-2-sulfinamide

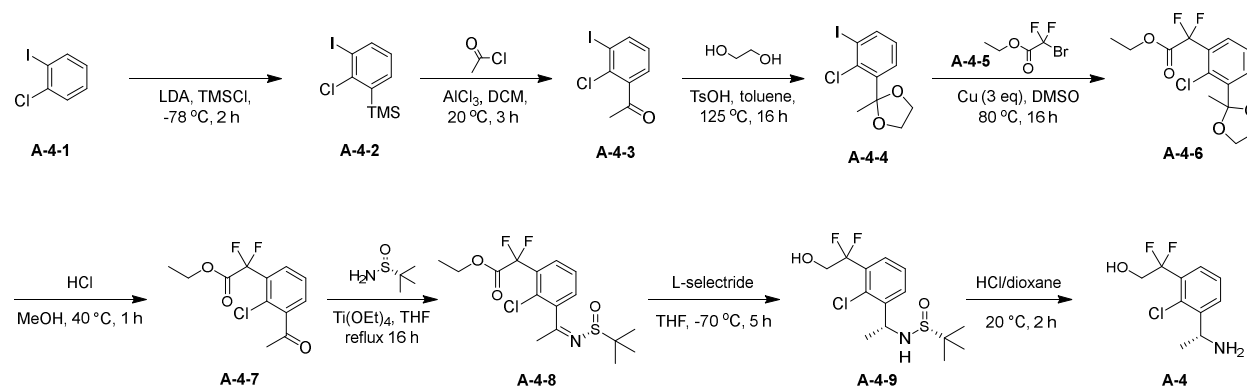
A solution of (NZ,S)-N-[1-[2-fluoro-3-(trifluoromethyl)phenyl]ethylidene]-2-methyl-propane-2-sulfinamide (2.00 g, 6.47 mmol) in THF (15 mL) was cooled to -70 °C. After the addition of L-selectride (1 M, 16.16 mL), the mixture was slowly warmed to 20 °C and stirred at 20 °C for 2 h. The reaction mixture was quenched at 20 °C with sat. aq. NH₄Cl (50 mL), diluted with EtOAc (30 mL) and extracted with EtOAc (30 mL X 3). The organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (62% EtOAc in

petroleum ether) to give a main product, (S)-N-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-2-methyl-propane-2-sulfonamide (1.23 g, 56.49% yield, 92.35% purity, 98.28% ee) as colorless oil. MS (ESI) $m/z = 312.1$ $[M+H]^+$.

Step 3: Synthesis of (1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethanamine

A mixture of (S)-N-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-2-methyl-propane-2-sulfonamide (1.1 g, 3.53 mmol) and 4 N HCl/dioxane (5 mL) in dioxane (5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 25 °C for 2 h under N_2 atmosphere. The mixture was concentrated under reduced pressure to give **Intermediate A-3** (850 mg, 96.04% yield, 97.25% purity, HCl) as a white solid. MS (ESI) $m/z = 208.0$ $[M+H]^+$.

Preparation Example 4: 2-[3-[(1R)-1-aminoethyl]-2-chloro-phenyl]-2,2-difluoroethanol (A-4)



Step 1: Synthesis of (2-chloro-3-iodo-phenyl)trimethyl-silane

A solution of 1-chloro-2-iodo-benzene (27 g, 113.23 mmol, 370.37 μ L) and TMSCl (14.76 g, 135.88 mmol, 17.24 mL) in THF (300 mL) was cooled to -78 °C and stirred at -78 °C for 2 h after the addition of LDA (2 M, 67.94 mL). The mixture was quenched with water (300 mL) and extracted with EtOAc (300 mL X 3). The organic layers were washed with brine (500 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (0% EtOAc in petroleum ether) to give (2-chloro-3-iodo-phenyl)-trimethyl-silane (32 g, 90.98% yield) as colorless oil. 1H NMR (400 MHz, $DMSO-d_6$) δ 7.99-7.94 (m, 1H), 7.47 (dd, $J = 1.2, 7.2$ Hz, 1H), 7.08-7.03 (m, 1H), 0.36-0.31 (m, 9H).

Step 2: Synthesis of 1-(2-chloro-3-iodophenyl)ethanone

Acetyl chloride (9.70 g, 123.62 mmol, 8.82 mL) was slowly added dropwise to a solution of $AlCl_3$ (16.48 g, 123.62 mmol, 6.76 mL) in DCM (200 mL) at 0 °C for 0.5 h, and (2-chloro-3-iodo-phenyl)trimethyl-silane (32 g, 103.02 mmol) in DCM (200 mL) was added. The mixture was stirred at 20 °C for 2 h and quenched with aq. Na_2CO_3 (300 mL, 10%). The reaction mixture was poured into water (200 mL) and extracted with EtOAc (300 mL X 3). The organic layers were washed with brine (200 mL X 3), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude product. The crude product was purified

by silica gel column chromatography (5% EtOAc in petroleum ether) to give 1-(2-chloro-3-iodophenyl)ethanone (13 g, 33.99% yield) as colorless oil. ^1H NMR (400 MHz, DMSO- d_6) δ 8.07 (dd, J = 1.6, 8.0 Hz, 1H), 7.61 (dd, J = 1.2, 7.6 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 2.55 (s, 3H).

Step 3: Synthesis of 2-(2-chloro-3-iodophenyl)-2-methyl-1,3-dioxolan

A mixture of toluene (200 mL), 1-(2-chloro-3-iodo-phenyl)ethanone (13 g, 46.35 mmol), ethylene glycol (8.63 g, 139.04 mmol) and TsOH (798.11 mg, 4.63 mmol) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 125 °C for 16 h under N_2 atmosphere. The mixture was poured into water (200 mL) and extracted with EtOAc (200 mL X 3). The organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (6% EtOAc in petroleum ether) to give 2-(2-chloro-3-iodophenyl)-2-methyl-1,3-dioxolan (14 g, 29.08% yield, 31.25% purity) as colorless oil. MS (ESI) m/z = 324.9 $[\text{M}+\text{H}]^+$.

Step 4: Synthesis of ethyl 2-[2-chloro-3-(2-methyl-1,3-dioxolan-2-yl)phenyl]-2,2-difluoroacetate

A mixture of 2-(2-chloro-3-iodo-phenyl)-2-methyl-1,3-dioxolan (14 g, 43.14 mmol), ethyl-2-bromo-2,2-difluoroacetate (17.51 g, 86.28 mmol, 11.08 mL), Cu (8.22 g, 129.41 mmol, 917.82 μL) in DMSO (200 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 16 h under N_2 atmosphere. The mixture was poured into water (300 mL) and extracted with EtOAc (300 mL X 3). The organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (11% EtOAc in petroleum ether) to give ethyl 2-[2-chloro-3-(2-methyl-1,3-dioxolan-2-yl)phenyl]-2,2-difluoroacetate (6 g, 23.51% yield, 54.20% purity) as colorless oil. MS (ESI) m/z = 321.0 $[\text{M}+\text{H}]^+$.

Step 5: Synthesis of ethyl 2-(3-acetyl-2-chloro-phenyl)-2,2-difluoroacetate

To a solution of ethyl 2-[2-chloro-3-(2-methyl-1,3-dioxolan-2-yl)phenyl]-2,2-difluoroacetate (6 g, 18.71 mmol) in MeOH (200 mL) was added HCl (6 M, 15 mL), and then the mixture was stirred at 40 °C for 1 h. The mixture was filtered under reduced pressure to give a residue. It was poured into water (50 mL) and extracted with EtOAc (30 mL X 3). The organic layers were washed with brine (20 mL $\times$ 3), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (8% EtOAc in petroleum ether) to give ethyl 2-(3-acetyl-2-chloro-phenyl)-2,2-difluoroacetate (6.4 g, 85.78% yield, 69.37% purity) as colorless oil. MS (ESI) m/z = 277.0 $[\text{M}+\text{H}]^+$.

Step 6: Synthesis of ethyl 2-[2-chloro-3-[(Z)-N-(1,1-dimethylethylsulfinyl)-C-methyl-carbonimidoyl]phenyl]-2,2-difluoroacetate

A mixture of ethyl 2-(3-acetyl-2-chloro-phenyl)-2,2-difluoroacetate (6 g, 21.69 mmol), 2-methylpropane-2-sulfinamide (3.94 g, 32.53 mmol) and Ti(OEt)₄ (14.84 g, 65.06 mmol, 13.49 mL) in THF (100 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 80 °C for 16 h under N₂ atmosphere. The mixture was poured into water (80 mL), filtered and then extracted with EtOAc (50 mL X 6). The organic layers were washed with brine (30 mL X 3), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (29% MTBE in petroleum ether) to give ethyl 2-[2-chloro-3-[(Z)-N-(1,1-dimethylethylsulfinyl)-C-methyl-carbonimidoyl]phenyl]-2,2-difluoroacetate (5.2 g, 51.13% yield, 81% purity) as light yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.92 - 7.76 (m, 1H), 7.74 - 7.52 (m, 2H), 4.42 - 4.27 (m, 2H), 3.34 (s, 3H), 1.24 - 1.18 (m, 9H), 1.13 (s, 3H); MS (ESI) *m/z* = 380.1 [M+H]⁺.

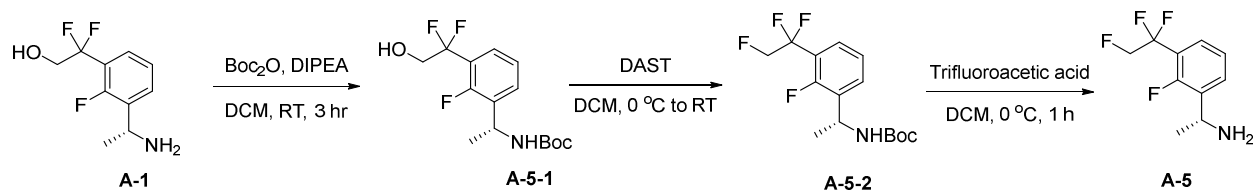
Step 7: Synthesis of (S)-N-[(1R)-1-[2-chloro-3-(1,1-difluoro-2-hydroxy-ethyl)phenyl]ethyl]-2-methyl-propane-2- sulfinamide

A mixture of ethyl 2-[2-chloro-3-[(Z)-N-(1,1-dimethylethylsulfinyl)-C-methyl-carbonimidoyl]phenyl]-2,2-difluoroacetate (2 g, 5.27 mmol) and L-selectride (1 M, 15.80 mL) in THF (50 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at -70 °C for 5 h under N₂ atmosphere. Sat. aq. NH₄Cl (100 mL) was added dropwise to the reaction mixture at -70 °C, which was then extracted with EtOAc (50 mL X 3). The organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. After the primary purification by silica gel column chromatography (5% MeOH in DCM), two diastereomers were separated and purified by prep-HPLC (Xtimate C18 150*40 mm*10 μm, mobile phase: [water (NH₃H₂O)-ACN]; B%: 10%-55%, 20 min). MeCN was removed under reduced pressure, and the remaining solvent was removed by lyophilization to give a main product, (S)-N-[(1R)-1-[2-chloro-3-(1,1-difluoro-2-hydroxy-ethyl)phenyl]ethyl]-2-methyl-propane-2- sulfinamide (1.4 g, 69.64% yield, 89% purity, 100% ee) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.72 (br d, *J* = 6.4 Hz, 1H), 7.55 - 7.41 (m, 2H), 5.70 (br t, *J* = 6.4 Hz, 1H), 5.60 (br d, *J* = 5.2 Hz, 1H), 4.91 (quint, *J* = 6.0 Hz, 1H), 4.02 (dt, *J* = 6.4, 14.4 Hz, 2H), 1.46 (br d, *J* = 6.4 Hz, 3H), 1.11 (s, 9H); MS (ESI) *m/z* = 340.1 [M+H]⁺.

Step 8: Synthesis of 2-[3-[(1R)-1-aminoethyl]-2-chloro-phenyl]-2,2-difluoroethanol

A mixture of (S)-N-[(1R)-1-[2-chloro-3-(1,1-difluoro-2-hydroxy-ethyl)phenyl]ethyl]-2-methyl-propane-2-sulfinamide (1.4 g, 4.12 mmol) and 4 N HCl/dioxane (10 mL) in dioxane (10 mL) was stirred at 20 °C for 2 h. The mixture was concentrated under reduced pressure to give **Intermediate A-4** (1.2 g, 88.77% yield, 82.93% purity, HCl salt) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.85 (br s, 3H), 7.96 (br d, *J* = 7.6 Hz, 1H), 7.68-7.62 (m, 1H), 7.62-7.55 (m, 1H), 5.75 (br s, 1H), 4.81 (br s, 1H), 4.03 (br t, *J* = 14.0 Hz, 2H), 1.53 (d, *J* = 6.8 Hz, 3H); MS (ESI) *m/z* = 236.1 [M+H]⁺.

Preparation Example 5: (R)-1-(2-fluoro-3-(1,1,2-trifluoroethyl)phenyl)ethan-1-amine (A-5)



Step 1: Synthesis of (R)-(1-(3-(1,1-difluoro-2-hydroxyethyl)-2-fluorophenyl)ethyl)carbamate

To a solution of 2-{3-[(1R)-1-aminoethyl]-2-fluorophenyl}-2,2-difluoromethan-1-ol hydrochloride (500 mg, 1.96 mmol) in DCM (3.99 mL) was added di-*tert*-butyl dicarbonate (854 mg, 3.91 mmol) and DIPEA (0.68 mL, 3.91 mmol) at 0 °C, and then the mixture was stirred at room temperature for 3 h. The mixture was added with DCM and washed with water. The organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Hex : EtOAc= 20: 1 to 10: 1) to give (R)-(1-(3-(1,1-difluoro-2-hydroxyethyl)-2-fluorophenyl)ethyl)carbamate (456 mg, 73% yield) as colorless oil. MS (ESI) *m/z* = 264.04 [M+H]⁺.

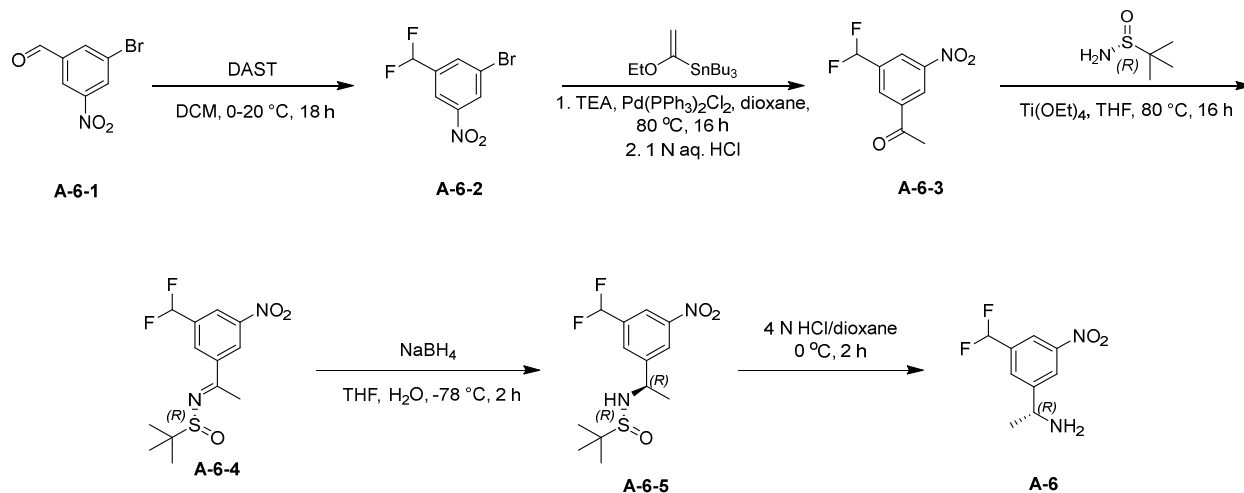
Step 2: Synthesis of tert-butyl (R)-(1-(2-fluoro-3-(1,1,2-trifluoroethyl)phenyl)ethyl)carbamate

To a solution of (R)-(1-(3-(1,1-difluoro-2-hydroxyethyl)-2-fluorophenyl)ethyl)carbamate (221 mg, 0.692 mmol) in DCM (6.92 mL) was added DAST (0.37 mL, 2.77 mmol) at 0 °C under N₂ atmosphere, and then the mixture was warmed to room temperature and stirred overnight. The mixture was quenched with sat. NaHCO₃ and extracted with DCM. The organic layers were extracted with sat. NH₄Cl and washed with brine. The organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. It was purified by silica gel column chromatography (hexane : EtOAc = 20:1 to 10:1) to give tert-butyl (R)-(1-(2-fluoro-3-(1,1,2-trifluoroethyl)phenyl)ethyl)carbamate (26 mg, 12% yield) as colorless oil. MS (ESI) *m/z* = 265.99 [M+H]⁺.

Step 3: Synthesis of (R)-1-(2-fluoro-3-(1,1,2-trifluoroethyl)phenyl)ethan-1-amine

TFA (0.15 mL) was added dropwise to a solution of tert-butyl (R)-(1-(2-fluoro-3-(1,1,2-trifluoroethyl)phenyl)ethyl)carbamate (56 mg, 0.174 mmol) in DCM (0.7 mL), and then the mixture was stirred at 0 °C for 1 h. The mixture was warmed to room temperature and quenched with sat. NaHCO₃. The organic solvent was removed by filtration under reduced pressure, and the aqueous layer was extracted with DCM. The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give **Intermediate A-5** (34.5 mg, 89% yield) as yellow oil. MS (ESI) *m/z* = 222.06 [M+H]⁺.

**Preparation Example 6: (1R)-1-[3-(difluoromethyl)-5-nitro-phenyl]ethanamine
(A-6)**



Step 1: Synthesis of 1-bromo-3-(difluoromethyl)-5-nitrobenzene

A mixed solution of 3-bromo-5-nitro-benzaldehyde (13.7 g, 59.56 mmol) and DAST (48.00 g, 297.81 mmol, 39.35 mL) in DCM (140 mL) was degassed and purged with N₂ for 3 times, and then stirred at 0 °C for 1 h. The mixture was warmed to 20 °C and stirred for 17 h under N₂ atmosphere. The reaction mixture was poured into ice-cold water and extracted with DCM (300 mL) and EtOAc (200 mL X 3). The combined organic layers were washed with brine (200mL X 2), dried over anhydrous Na₂SO₄, and then filtered under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (0~10% EtOAc/petroleum ether) to give 1-bromo-3-(difluoromethyl)-5-nitrobenzene (14.27 g, 95.07% yield) as colorless oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.57 (s, 1H), 8.40 (s, 1H), 8.29 (s, 1H), 7.34 - 7.05 (m, 1H).

Step 2: Synthesis of 1-[3-(difluoromethyl)-5-nitrophenyl]ethanone

A mixture of 1-bromo-3-(difluoromethyl)-5-nitrobenzene (12.27 g, 48.69 mmol), tributyl(1-ethoxyvinyl)stannane (19.5 g, 53.99 mmol, 18.22 mL), Pd(PPh₃)₂Cl₂ (3.42 g, 4.87 mmol) and TEA (9.85 g, 97.38 mmol, 13.55 mL) in dioxane (120 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 80 °C for 12 h under N₂ atmosphere. The mixture was quenched with 4 N HCl (24.34 mL) and then stirred at 20 °C for 1 h. The mixture was poured into water (500 mL) and extracted with EtOAc (300 mL X 3). The organic layers were washed with brine (500mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The aqueous layers were stirred while KF (2.5 g) was slowly added dropwise. The crude product was purified by silica gel column chromatography (0~10% EtOAc/petroleum ether) to give 1-[3-(difluoromethyl)-5-nitrophenyl]ethanone (8.74 g, 83.43% yield) as yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.77 (s, 1H), 8.63 (s, 1H), 8.53 (s, 1H), 7.44 - 7.14 (m, 1H), 2.73 (s, 3H).

Step 3: Synthesis of (NE,R)-N-[1-[3-(difluoromethyl)-5-nitro-phenyl]ethylidene]-2-methyl-propane-2-sulfinamide

A mixture of 1-[3-(difluoromethyl)-5-nitrophenyl]ethanone (10 g, 46.48 mmol), (R)-2-methylpropane-2-sulfinamide (8.45 g, 69.72 mmol) and Ti(OEt)₄ (31.81 g, 139.44 mmol, 28.91 mL) in THF (100 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 80 °C for 16 h under N₂ atmosphere. The mixture was poured into water (200 mL X 3), filtered and extracted with EtOAc (500 mL X 6). The organic layers were washed with brine (30 mL X 3), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (0~30% EtOAc/petroleum ether) to give (NE,R)-N-[1-[3-(difluoromethyl)-5-nitro-phenyl]ethylidene]-2-methyl-propane-2-sulfinamide (12.83 g, 82.31% yield, 94.92% purity) as yellow oil. MS (ESI) m/z = 319.1 [M+H]⁺.

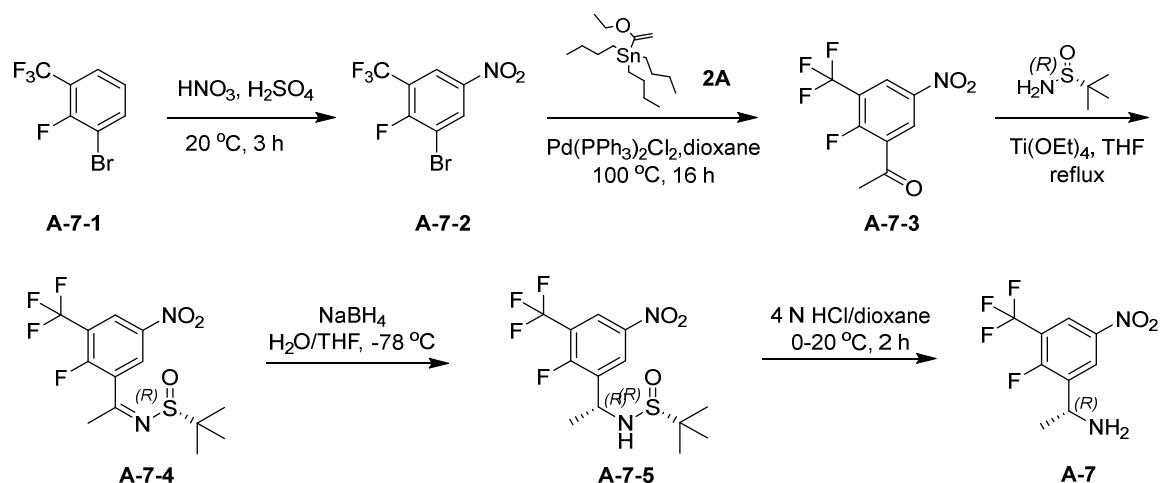
Step 4: Synthesis of (R)-N-[(1R)-1-[3-(difluoromethyl)-5-nitro-phenyl]ethyl]-2-methyl-propane-2-sulfinamide

To a solution of (NE,R)-N-[1-[3-(difluoromethyl)-5-nitro-phenyl]ethylidene]-2-methyl-propane-2-sulfinamide (4 g, 12.57 mmol) in THF (40 mL) and H₂O (0.75 mL) was added NaBH₄ (332.76 mg, 8.80 mmol) at -78 °C in 3 batches, and then the mixture was stirred at -78 °C for 2 h under N₂ atmosphere. The mixture was quenched with sat. NH₄Cl (150 mL), diluted with EtOAc (100 mL X 3), and then extracted with EtOAc (100 mL X 3). The organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (0~25% EtOAc/petroleum ether) to give (R)-N-[(1R)-1-[3-(difluoromethyl)-5-nitro-phenyl]ethyl]-2-methyl-propane-2-sulfinamide (3.21 g, 79.26% yield, 99.39% purity, 99.00% ee) as yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.51 (s, 1H), 8.30 (s, 1H), 8.11 (s, 1H), 7.37 - 7.07 (m, 1H), 6.05 (d, *J* = 8.4 Hz, 1H), 4.69 - 4.60 (m, 1H), 1.45 (d, *J* = 6.8 Hz, 3H), 1.14 (s, 9H); MS (ESI) m/z = 321.1 [M+H]⁺.

Step 5: Synthesis of (1R)-1-[3-(difluoromethyl)-5-nitro-phenyl]ethanamine

A mixture of (R)-N-[(1R)-1-[3-(difluoromethyl)-5-nitro-phenyl]ethyl]-2-methyl-propane-2-sulfinamide (532 mg, 1.66 mmol) in 4 N HCl/dioxane (30 mL) was stirred at 0 °C for 2 h. The mixture was concentrated under reduced pressure to give **Intermediate A-6** (400 mg, 98.29% yield, 88.22% purity, HCl) as a brown solid. MS (ESI) m/z = 217.0 [M+H]⁺.

Preparation Example 7: (1R)-1-[2-fluoro-5-nitro-3-(trifluoromethyl)phenyl]ethanamine (A-7)



Step 1: Synthesis of 1-bromo-2-fluoro-5-nitro-3-(trifluoromethyl)benzene

To a solution of 1-bromo-2-fluoro-3-(trifluoromethyl)benzene (10 g, 41.15 mmol) in H_2SO_4 (40 mL) was slowly added dropwise HNO_3 (25.71 g, 408.01 mmol, 18.36 mL) at 0 °C, and then the mixture was warmed to 20 °C and stirred for 3 h under N_2 atmosphere. The mixture was quenched with ice-cold water (100 mL) and extracted with EtOAc (50 mL $\times$ 3). The organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude product. The crude product was purified by silica column chromatography (2% EtOAc in petroleum ether) to give 1-bromo-2-fluoro-5-nitro-3-(trifluoromethyl)benzene (5.9 g, 49.78% yield) as colorless oil. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.95 (dd, J = 2.4, 5.2 Hz, 1H), 8.55 - 8.51 (m, 1H).

Step 2: Synthesis of 1-[2-fluoro-5-nitro-3-(trifluoromethyl)phenyl]ethanone

A mixture of 1-bromo-2-fluoro-5-nitro-3-(trifluoromethyl)benzene (5.9 g, 20.49 mmol), 1-tributyl(1-ethoxyvinyl)stannane (8.41 g, 23.29 mmol, 7.86 mL) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (1.44 g, 2.05 mmol) in dioxane (50 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 16 h under N_2 atmosphere. The mixture was cooled to 0 °C and stirred for 1 h after the addition of HCl solution (4N, 50 mL). Following the addition of water (100 mL), the reaction mixture was extracted with EtOAc (100 mL $\times$ 3). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give a residue. It was purified by silica gel column chromatography (5% EtOAc in petroleum ether) to give 1-[2-fluoro-5-nitro-3-(trifluoromethyl)phenyl]ethanone (1.6 g, 31.10% yield) as colorless oil. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.81 (dd, J = 2.8, 5.6 Hz, 1H), 8.71 (dd, J = 2.8, 5.2 Hz, 1H), 2.70 (d, J = 4.0 Hz, 3H).

Step 3: Synthesis of (NZ,R)-N-[1-[2-fluoro-5-nitro-3-(trifluoromethyl)phenyl]ethylidene]-2-methylpropane-2-sulfinamide

A mixture of 1-[2-fluoro-5-nitro-3-(trifluoromethyl)phenyl]ethanone (2.75 g, 10.95 mmol), (R)-2-methylpropane-2-sulfinamide (1.46 g, 12.05 mmol) and $\text{Ti}(\text{OEt})_4$ (7.49 g, 32.85 mmol, 6.81 mL) in THF (30 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 16 h under N_2 atmosphere. The mixture was poured into water

(50 mL) and extracted with EtOAc (50 mL X 6). The organic layers were washed with brine (50 mL X 2), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (7% EtOAc in petroleum ether) to give (NZ,R)-N-[1-[2-fluoro-5-nitro-3-(trifluoromethyl)phenyl]ethylidene]-2-methyl-1-propane-2-sulfinamide (3.43 g, 86.21% yield, 97.51% purity) as yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.80 (br d, *J* = 2.4 Hz, 1H), 8.64 - 8.52 (m, 1H), 2.78 - 2.54 (m, 3H), 1.24 (s, 6H), 1.21 - 1.11 (m, 3H); MS (ESI) *m/z* = 354.9 [M+H]⁺.

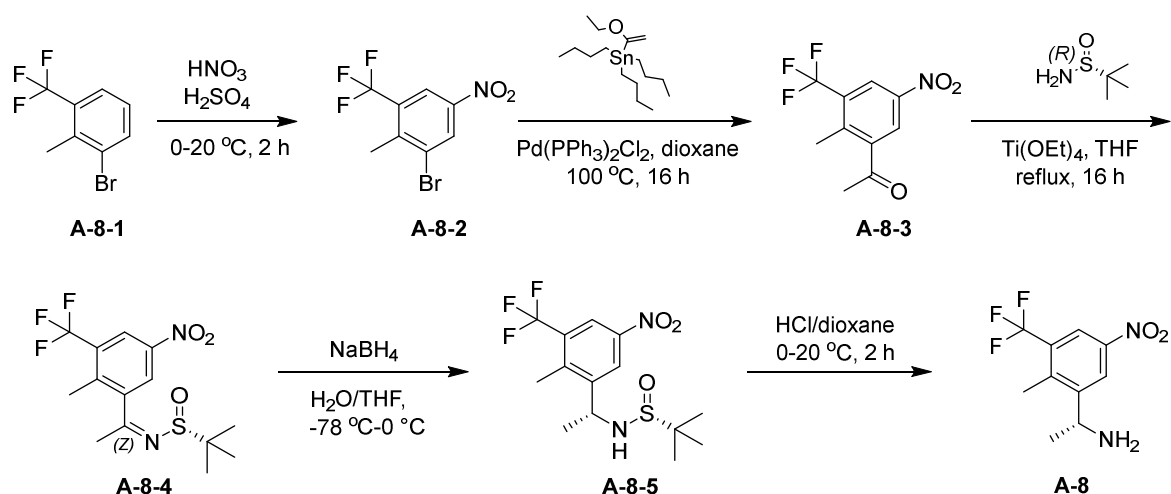
Step 4: Synthesis of (R)-N-[(1R)-1-[2-fluoro-5-nitro-3-(trifluoromethyl)phenyl]ethyl]-2-methyl-propane-2-sulfinamide

A solution of (NZ,R)-N-[1-[2-fluoro-5-nitro-3-(trifluoromethyl)phenyl]ethylidene]-2-methyl-1-propane-2-sulfinamide (3.43 g, 9.68 mmol) in THF (35 mL) and H₂O (1 mL) was degassed and purged with N₂ for 3 times. Then, NaBH₄ (230 mg, 6.08 mmol) was added at -70 °C and the mixture was stirred at -70 °C for 2 h under N₂ atmosphere. The mixture was quenched with sat. NH₄Cl (50 mL) at 20 °C, diluted with EtOAc (50 mL), and then extracted with EtOAc (50 mL X 3). The organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (20% EtOAc in petroleum ether) to give (R)-N-[(1R)-1-[2-fluoro-5-nitro-3-(trifluoromethyl)phenyl]ethyl]-2-methyl-propane-2-sulfinamide (1.72 g, 49.32% yield, 99.20% purity, 100% ee) as yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.83 (dd, *J* = 2.8, 5.6 Hz, 1H), 8.46 (dd, *J* = 2.8, 5.6 Hz, 1H), 6.14 (d, *J* = 8.8 Hz, 1H), 4.83 - 4.73 (m, 1H), 1.48 (d, *J* = 6.8 Hz, 3H), 1.13 (s, 9H); MS (ESI) *m/z* = 356.9 [M+H]⁺.

Step 5: Synthesis of (1R)-1-[2-fluoro-5-nitro-3-(trifluoromethyl)phenyl]ethanamine

To a solution of (R)-N-[(1R)-1-[2-fluoro-5-nitro-3-(trifluoromethyl)phenyl]ethyl]-2-methyl-propane-2-sulfinamide (1.5 g, 4.21 mmol) in dioxane (10 mL) was added 4 N HCl/dioxane (10 mL), and then the mixture was stirred at 20 °C for 2 h. The mixture was concentrated under reduced pressure to give **Intermediate A-7** (1.2 g, 88.77% yield, 82.93% purity, HCl) as a white solid. MS (ESI) *m/z* = 252.9 [M+H]⁺.

Preparation Example 8: (1R)-1-[2-methyl-5-nitro-3-(trifluoromethyl)phenyl]ethanamine (A-8)



Step 1: Synthesis of 1-bromo-2-methyl-5-nitro-3-(trifluoromethyl)benzene

HNO₃ (46.45 g, 737.15 mmol, 33.18 mL) was slowly added dropwise to a solution of 1-bromo-2-methyl-3-(trifluoromethyl)benzene (10 g, 41.84 mmol) in H₂SO₄ (75 mL) at 0 °C, and then the mixture was heated to 20 °C and stirred for 2 h under N₂ atmosphere. The mixture was quenched with ice-cold water (250 mL) and extracted with EtOAc (100 mL × 3). The organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica column chromatography (100% petroleum ether) to give 1-bromo-2-methyl-5-nitro-3-(trifluoromethyl)benzene (12 g, crude) as yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.71 (d, *J* = 2.0 Hz, 1H), 8.39 (d, *J* = 2.0 Hz, 1H), 2.59 (d, *J* = 1.2 Hz, 3H)

Step 2: Synthesis of 1-[2-methyl-5-nitro-3-(trifluoromethyl)phenyl]ethanone

A mixture of 1-bromo-2-methyl-5-nitro-3-(trifluoromethyl)benzene (12 g, 42.25 mmol), 1-tributyl(1-ethoxyvinyl)stannane (15.1 g, 41.81 mmol, 14.11 mL) and Pd(dppf)Cl₂ (2.97 g, 4.22 mmol) in dioxane (100 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 100 °C for 16 h under N₂ atmosphere. The mixture was cooled to 0 °C and stirred for 1 h after the addition of HCl solution (2N, 100 mL). Following the addition of water (100 mL), the reaction mixture was extracted with EtOAc (100 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to give a residue. It was purified by silica gel column chromatography (10% EtOAc in petroleum ether) to give 1-[2-methyl-5-nitro-3-(trifluoromethyl)phenyl]ethanone (5.3 g, 50.75% yield) as yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.72 (d, *J* = 2.0 Hz, 1H), 8.47 (d, *J* = 2.0 Hz, 1H), 2.66 (s, 3H), 2.50 (s, 3H).

Step 3: Synthesis of (NZ,R)-2-methyl-N-[1-[2-methyl-5-nitro-3-(trifluoromethyl)phenyl]ethylidene]propane-2-sulfinamide

A mixture of 1-[2-methyl-5-nitro-3-(trifluoromethyl)phenyl]ethanone (5.3 g, 21.44 mmol), (R)-2-methylpropane-2-sulfinamide (2.86 g, 23.58 mmol) and Ti(OEt)₄ (14.67 g, 64.32 mmol, 13.34 mL) in THF (55 mL) was degassed and purged with N₂ for 3 times, and then the

mixture was stirred at 80 °C for 16 h under N₂ atmosphere. The mixture was poured into water (100 mL) and EtOAc (100 mL) and filtered, and then the filtrate was extracted with EtOAc (50 mL X 3). The organic layers were washed with brine (50 mL X 2), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (8% EtOAc in petroleum ether) to give (NZ,R)-2-methyl-N-[1-[2-methyl-5-nitro-3-(trifluoromethyl)phenyl]ethylidene]propane-2-sulfonamide (6.7 g, 88.90% yield, 99.67% purity) as yellow oil. MS (ESI) m/z = 351.0 [M+H]⁺.

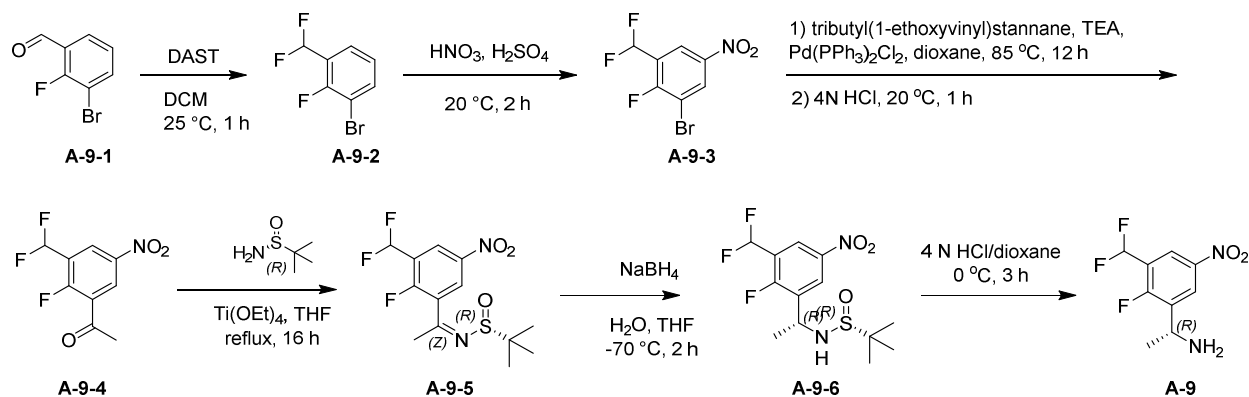
Step 4: Synthesis of (R)-2-methyl-N-[(1R)-1-[2-methyl-5-nitro-3-(trifluoromethyl)phenyl]ethyl]propane-2-sulfonamide

To a solution of (NZ,R)-2-methyl-N-[1-[2-methyl-5-nitro-3-(trifluoromethyl)phenyl]ethylidene]propane-2-sulfonamide (6.70 g, 19.12 mmol) in THF (80 mL) and H₂O (2 mL) was added NaBH₄ (230 mg, 6.08 mmol) at -78 °C in 3 batches, and then the mixture was slowly heated from -78 °C to 0 °C and stirred for 3 h under N₂ atmosphere. The mixture was quenched with sat. NH₄Cl (50 mL) at 20 °C, diluted with EtOAc (50 mL) and extracted with EtOAc (50 mL X 3). The organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (20% EtOAc/petroleum ether) to give (R)-2-methyl-N-[(1R)-1-[2-methyl-5-nitro-3-(trifluoromethyl)phenyl]ethyl]propane-2-sulfonamide (1.4 g, 19.99% yield, 96.23% purity, 99.44% ee) as yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.59 (d, *J* = 2.4 Hz, 1H), 8.31 (d, *J* = 2.4 Hz, 1H), 5.74 (d, *J* = 6.0 Hz, 1H), 4.85 (quint, *J* = 6.4 Hz, 1H), 2.54 (s, 3H), 1.51 (d, *J* = 6.4 Hz, 3H), 1.12 (s, 9H); MS (ESI) m/z = 353.0 [M+H]⁺.

Step 5: Synthesis of (1R)-1-[2-methyl-5-nitro-3-(trifluoromethyl)phenyl]ethanamine

To a solution of (R)-2-methyl-N-[(1R)-1-[2-methyl-5-nitro-3-(trifluoromethyl)phenyl]ethyl]propane-2-sulfonamide (1.40 g, 3.97 mmol) in dioxane (5 L) was added HCl/dioxane (5 mL) at 0°C, and then the mixture was stirred at 20°C for 2 h. The mixture was concentrated under reduced pressure. The residue was stirred at 20 °C for 12 h with the addition of MTBE (20 mL). The mixture was filtered to give **Intermediate A-8** (1 g, 86.11% yield, 97.39% purity, HCl) as a white solid. MS (ESI) m/z = 248.9 [M+H]⁺.

Preparation Example 9: (1R)-1-[3-(difluoromethyl)-2-fluoro-5-nitrophenyl]ethanamine (A-9)



Step 1: Synthesis of 1-bromo-3-(difluoromethyl)-2-fluoro-5-nitrobenzene

HNO₃ (14.51 g, 230.22 mmol, 10.36 mL) was slowly added dropwise to a solution of 1-bromo-3-(trifluoromethyl)-2-fluorobenzene (3.7 g, 16.44 mmol) in H₂SO₄ (30 mL) at 0 °C, and then the mixture was heated to 20 °C and stirred for 2 h. The mixture was quenched with ice-cold water (120 mL) and extracted with EtOAc (40 mL × 3). The organic layers were washed with brine (120 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica column chromatography (100% petroleum ether) to give 1-bromo-3-(difluoromethyl)-2-fluoro-5-nitrobenzene (1.8 g, 40.54% yield) as colorless oil. ¹H NMR (400 MHz, DMSO-d₆) δ 8.78 (br s, 1H), 8.47 (br d, *J* = 2.4 Hz, 1H), 7.34 (dt, *J* = 4.0, 53.4 Hz, 1H).

Step 2: Synthesis of 1-[3-(difluoromethyl)-2-fluoro-5-nitro-phenyl]ethanone

A mixture of 1-bromo-3-(difluoromethyl)-2-fluoro-5-nitrobenzene (1.8 g, 6.67 mmol), 1-tributyl(1-ethoxyvinyl)stanene (2.65 g, 7.33 mmol, 2.48 mL) and Pd(dppf)Cl₂ (233.96 mg, 333.33 μmol) in dioxane (30 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 100 °C for 16 h under N₂ atmosphere. HCl solution (4N, 30 mL) was added to the mixture, which was then stirred at 20 °C for 1 h. After water (50 mL) was added, the reaction mixture was extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine (50 mL × 3), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to give a residue. It was purified by silica gel column chromatography (2% EtOAc in petroleum ether) to give 1-[3-(difluoromethyl)-2-fluoro-5-nitro-phenyl]ethanone (1.42 g, 91.23% yield) as yellow oil. ¹H NMR (400 MHz, DMSO-d₆) δ 8.72 - 8.68 (m, 1H), 8.68 - 8.64 (m, 1H), 7.39 (t, *J* = 53.2 Hz, 1H), 2.69 (d, *J* = 4.0 Hz, 3H).

Step 3: Synthesis of (NZ,R)-N-[1-[3-(difluoromethyl)-2-fluoro-5-nitro-phenyl]ethenylidene]-2-methyl-propane-2-sulfonamide

A mixture of 1-[3-(difluoromethyl)-2-fluoro-5-nitro-phenyl]ethanone (1.4 g, 6.00 mmol), (R)-2-methylpropane-2-sulfonamide (727.80 mg, 6.00 mmol) and Ti(OEt)₄ (4.11 g, 18.01 mmol, 3.74 mL) in THF (8 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 80 °C for 16 h under N₂ atmosphere. The mixture was poured into water (50 mL) and extracted with EtOAc (50 mL × 3). The organic layers were washed with

brine (20 mL X 3), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (35% EtOAc in petroleum ether) to give (NZ,R)-N-[1-[3-(difluoromethyl)-2-fluoro-5-nitro-phenyl]ethylidene]-2-methyl-propane-2-sulfinamide (1.42 g, 70.29% yield) as yellow oil. ¹H NMR (400 MHz, DMSO-d₆) δ 8.68 - 8.64 (m, 1H), 8.56 (br s, 1H), 7.51 - 7.24 (m, 1H), 2.76 (s, 3H), 1.24 (s, 9H).

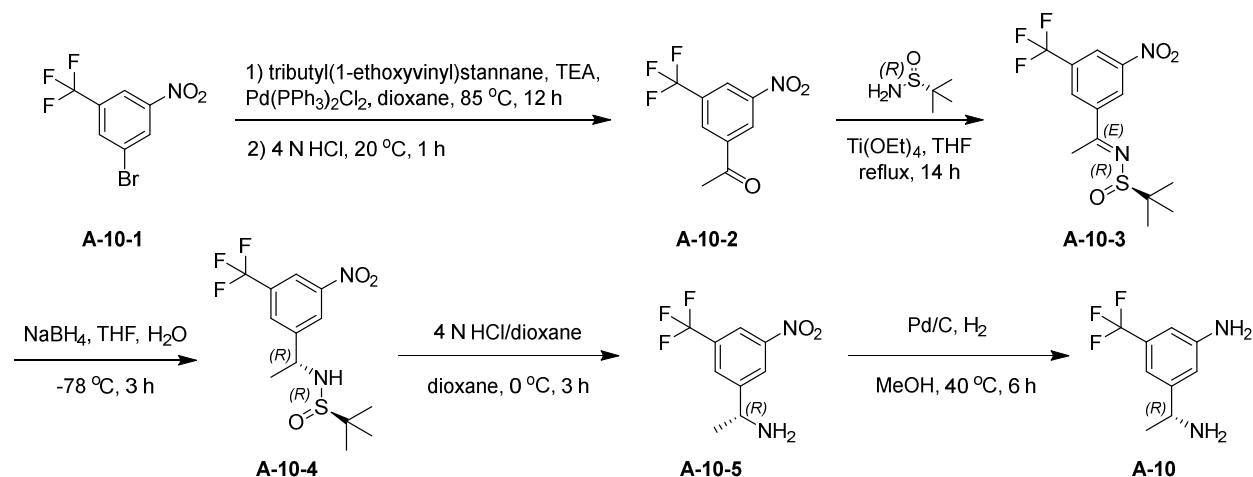
Step 4: Synthesis of (R)-N-[(1R)-1-[3-(difluoromethyl)-2-fluoro-5-nitro-phenyl]ethyl]-2-methyl-propane-2-sulfinamide

NaBH₄ (127.78 mg, 3.38 mmol) was added to a solution of (NZ,R)-N-[1-[3-(difluoromethyl)-2-fluoro-5-nitro-phenyl]ethylidene]-2-methyl-propane-2-sulfinamide (1.42 g, 4.22 mmol) in THF (20 mL) and H₂O (0.75 mL), and then the mixture was stirred at -70 °C for 2 h under N₂ atmosphere. The mixture was quenched with sat. NH₄Cl (30 mL) at 20 °C, diluted with EtOAc (30 mL) and extracted with EtOAc (30 mL X 3). The organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (100% petroleum ether) to give (R)-N-[(1R)-1-[3-(difluoromethyl)-2-fluoro-5-nitro-phenyl]ethyl]-2-methyl-propane-2-sulfinamide (902 mg, 62.04% yield, 98.25% purity, 100% ee) as colorless oil. MS (ESI) m/z = 339.1 [M+H]⁺.

Step 5: Synthesis of (1R)-1-[3-(difluoromethyl)-2-fluoro-5-nitro-phenyl]ethanamine

A mixture of (R)-N-[(1R)-1-[3-(difluoromethyl)-2-fluoro-5-nitro-phenyl]ethyl]-2-methyl-propane-2-sulfinamide (900 mg, 2.66 mmol) in 4 N HCl/dioxane (5 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 25 °C for 2 h under N₂ atmosphere. The mixture was concentrated under reduced pressure to give **Intermediate A-9** (700 mg, 96.58% yield, 99.33% purity, HCl) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 8.90 (br s, 4H), 8.52 (br d, *J* = 1.6 Hz, 1H), 7.38 (br t, *J* = 53.2 Hz, 1H), 4.77 (br s, 1H), 1.61 - 1.52 (m, 3H); MS (ESI) m/z = 235.1 [M+H]⁺.

Preparation Example 10: 3-[(1R)-1-aminoethyl]-5-(trifluoromethyl)amine (A-10)



Step 1: Synthesis of 1-[3-nitro-5-(trifluoromethyl)phenyl]ethanone

A mixture of 1-bromo-3-nitro-5-(trifluoromethyl)benzene (50 g, 185.18 mmol), 1-tributyl(1-ethoxyvinyl)stannane (70.2 g, 194.38 mmol, 65.61 mL), Pd(dppf)Cl₂ (13.00 g, 18.52 mmol) and TEA (37.48 g, 370.37 mmol, 51.55 mL) in dioxane (500 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 80 °C for 16h under N₂ atmosphere. HCl solution (4N, 200 mL) was added to the mixture, which was then stirred at 20 °C for 1 h. After water (200 mL) was added, the reaction mixture was extracted with EtOAc (150 mL X 3). The combined organic layers were washed with brine (100 mL X 3), dried over anhydrous Na₂SO₄ and then concentrated under reduced pressure to give a residue. It was purified by silica gel column chromatography (5% EtOAc in petroleum ether) to give 1-[3-nitro-5-(trifluoromethyl)phenyl]ethanone (66 g, 76.43% yield) as yellow oil. ¹H NMR (400 MHz, DMSO-d₆) δ 8.85 (s, 1H), 8.73 (s, 1H), 8.63 (s, 1H), 2.76 (s, 3H).

Step 2: Synthesis of (NE,R)-2-methyl-N-[1-[3-nitro-5-(trifluoromethyl)phenyl]ethylidene]propane-2-sulfinamide

A mixture of 1-[3-nitro-5-(trifluoromethyl)phenyl]ethanone (66 g, 283.09 mmol), (R)-2-methylpropane-2-sulfinamide (44.60 g, 368.01 mmol) and Ti(OEt)₄ (161.44 g, 707.72 mmol, 146.76 mL) in THF (650 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 85 °C for 16 h under N₂ atmosphere. The mixture was poured into water (200 mL) and EtOAc (200 mL) and filtered, and the filtrate was extracted with EtOAc (200 mL X 3). The organic layers were washed with brine (200 mL X 2), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (12% EtOAc in petroleum ether) to give (NE,R)-2-methyl-N-[1-[3-nitro-5-(trifluoromethyl)phenyl]ethylidene]propane-2-sulfinamide (77 g, 71.07% yield, 87.88% purity) as yellow oil. ¹H NMR (400 MHz, DMSO-d₆) δ 8.84 (s, 1H), 8.65 (s, 1H), 8.54 (s, 1H), 2.86 (s, 3H), 1.25 (s, 9H); MS (ESI) m/z = 336.9 [M+H]⁺.

Step 3: Synthesis of (R)-2-methyl-N-[(1R)-1-[3-nitro-5-(trifluoromethyl)phenyl]ethyl]propane-2-sulfinamide

To a solution of (NE,R)-2-methyl-N-[1-[3-nitro-5-(trifluoromethyl)phenyl]ethylidene]propane-2-sulfinamide (38.5 g, 114.47 mmol) in THF (350 mL) and H₂O (7 mL) was added NaBH₄ (3.27 g, 86.43 mmol) at -78 °C in 3 batches, and then the mixture was stirred at -78 °C for 3 h under N₂ atmosphere. The mixture was quenched with sat. NH₄Cl (150 mL) at 20 °C, and then it was poured into water (200 mL) and extracted with EtOAc (200 mL X 3). The organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (15% EtOAc in petroleum ether) to give (R)-2-methyl-N-[(1R)-1-[3-nitro-5-(trifluoromethyl)phenyl]ethyl]propane-2-sulfinamide (30 g, 32.01% yield, 82.663% purity, 100% ee) as a green solid. ¹H NMR (400 MHz, DMSO-d₆) δ 8.63 (s, 1H), 8.38 (s, 1H), 8.29 (s, 1H), 6.07 (d, *J* = 8.8 Hz, 1H), 4.72 - 4.65 (m, 1H), 1.45 (d, *J* = 6.8 Hz, 3H), 1.14 (s, 9H); MS (ESI) m/z = 338.9 [M+H]⁺.

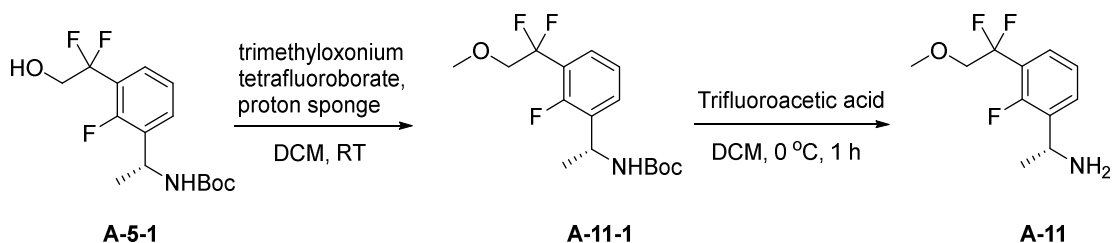
Step 4: Synthesis of (1R)-1-[3-nitro-5-(trifluoromethyl)phenyl]ethanamine

To a solution of the resulting product (R)-2-methyl-N-[(1R)-1-[3-nitro-5-(trifluoromethyl)phenyl]ethyl]propane-2-sulfonamide (30 g, 88.67 mmol) in dioxane (30 mL) was added 4 N HCl/dioxane (60 mL), and then the mixture was stirred at 20 °C for 3 h. The mixture was concentrated under reduced pressure and stirred at 20 °C for 12 h with the addition of MTBE (100 mL). It was filtered to give (1R)-1-[3-nitro-5-(trifluoromethyl)phenyl]ethanamine (23 g, 91.02% yield, 94.96% purity, HCl) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.93 - 8.61 (m, 4H), 8.51 (s, 1H), 8.45 (s, 1H), 4.74 (q, *J* = 6.8 Hz, 1H), 1.58 (d, *J* = 6.8 Hz, 3H); MS (ESI) *m/z* = 234.9 [M+H]⁺.

Step 5: Synthesis of 3-[(1R)-1-aminoethyl]-5-(trifluoromethyl)amine

A mixture of (1R)-1-[3-nitro-5-(trifluoromethyl)phenyl]ethanamine (10 g, 42.70 mmol) and Pd/C (2 g, 10% purity) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 40 °C for 6 h under H₂ atmosphere. The mixture was filtered and concentrated under reduced pressure to give **Intermediate A-10** (8.5 g, 93.87% yield, 96.29% purity) as a yellow solid. It was used in the next reaction without further purification. ¹H NMR (400 MHz, DMSO-d₆) δ 8.44 (br s, 3H), 6.97 (s, 1H), 6.84 (s, 2H), 5.75 (s, 2H), 4.30 (q, *J* = 6.8 Hz, 1H), 1.47 (d, *J* = 6.8 Hz, 3H); MS (ESI) *m/z* = 204.9 [M+H]⁺.

Preparation	Example 11:	<i>(R)</i> -1-(3-(1,1-difluoro-2-methoxyethyl)-2-fluorophenyl)ethane-1-amine (A-11)
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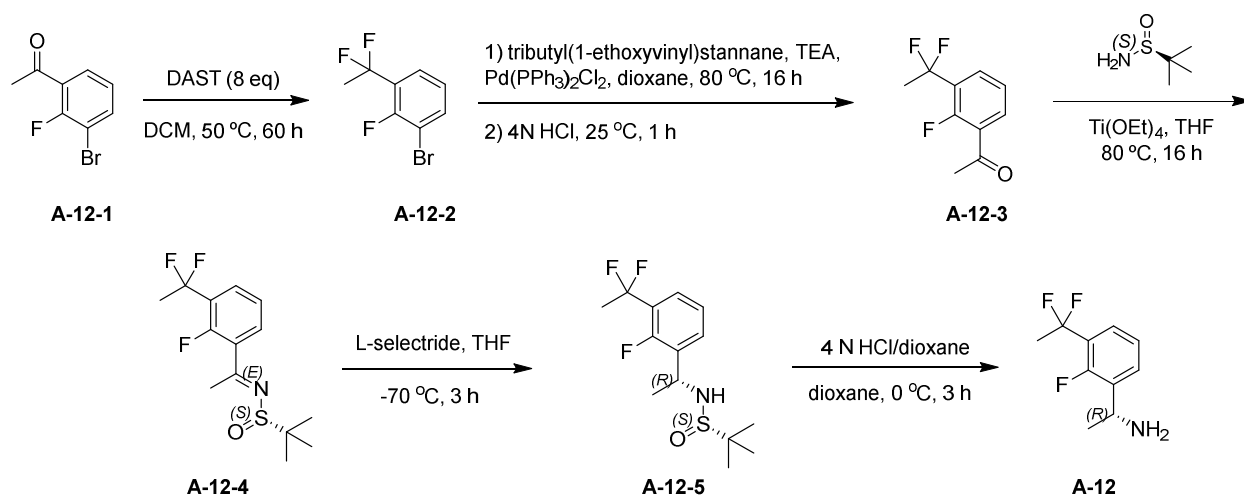
Step 1: Synthesis of tert-butyl (R)-(1-(3-(1,1-difluoro-2-methoxyethyl)-2-fluorophenyl)ethyl)carbamate

To a solution of tert-butyl (*R*)-(1-(3-(1,1-difluoro-2-hydroxyethyl)-2-fluorophenyl)ethyl)carbamate (87 mg, 0.272 mmol) in DCM (2.72 mL) was added Proton Sponge (117 mg, 0.545 mmol), trimethyloxonium tetrafluoroborate (80.6 mg, 0.545 mmol) and 4Å molecular sieve under nitrogen atmosphere, and then the mixture was stirred at 25 °C for 16 h. The reaction mixture was quenched with aq. 1 M HCl and extracted with DCM. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (25% EtOAc in hexane) to give tert-butyl (*R*)-(1-(3-(1,1-difluoro-2-methoxyethyl)-2-fluorophenyl)ethyl)carbamate (61 mg, 67% yield) as colorless oil. MS (ESI) *m/z* = 278.02 [M+H]⁺.

Step 2: Synthesis of (R)-1-(3-(1,1-difluoro-2-methoxyethyl)-2-fluorophenyl)ethan-1-
amine

To a solution of tert-butyl (*R*)-(1-(3-(1,1-difluoro-2-methoxyethyl)-2-fluorophenyl)ethyl)carbamate (61 mg, 0.183 mmol) in DCM (0.73 mL) was added trifluoroacetic acid (0.16 mL) at 0 °C. Thereafter, the mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with aq. NaHCO₃ and extracted with DCM. The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give **Intermediate A-11** (41 mg, 96% yield) as yellow oil. MS (ESI) *m/z* = 234.08 [M+H]⁺.

Preparation Example 12: (1*R*)-1-[3-(1,1-difluoroethyl)-2-fluorophenyl]ethanamine (A-12)



Step 1: Synthesis of 1-bromo-3-(1,1-difluoroethyl)-2-fluorobenzene

A mixture of 1-(3-bromo-2-fluorophenyl)ethanone (4 g, 18.43 mmol) and DAST (23.77 g, 147.44 mmol, 19.48 mL) in DCM (60 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 50 °C for 60 h under N₂ atmosphere. The reaction mixture was slowly quenched with ice-cold water (40 mL) and basified (pH = 7-8) with sat. NaHCO₃. The aqueous layers were extracted with DCM (50 mL × 3) and the organic layers were washed with brine (20 mL × 3). The organic layers were dried over anhydrous Na₂SO₄ and filtered under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (0% EA in petroleum ether) to give 1-bromo-3-(1,1-difluoroethyl)-2-fluorobenzene (3.5 g, 79.45% yield) as colorless oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.89 (br t, *J* = 7.2 Hz, 1H), 7.60 (br t, *J* = 7.2 Hz, 1H), 7.29 (t, *J* = 8.0 Hz, 1H), 2.02 (t, *J* = 19.2 Hz, 3H).

Step 2: Synthesis of 1-[3-(1,1-difluoroethyl)-2-fluorophenyl]ethanone

A mixture of 1-bromo-3-(1,1-difluoroethyl)-2-fluorobenzene (3.5 g, 14.64 mmol), 1-tributyl(1-ethoxyvinyl)stannane (5.66 g, 15.67 mmol, 5.29 mL), TEA (2.96 g, 29.28 mmol, 4.08 mL) and Pd(dppf)Cl₂ (1.03 g, 1.46 mmol) in dioxane (40 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 80 °C for 16 h under N₂ atmosphere. HCl solution (4N, 60 mL) was added to the mixture, which was then stirred at 25 °C for 1 h.

After waster (30 mL) was added, the reaction mixture was extracted with EtOAc (50 mL X 3). The organic layers were washed with brine (50 mL X 3), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a residue. It was purified by silica gel column chromatography (3% EtOAc in petroleum ether) to give 1-[3-(1,1-difluoroethyl)-2-fluoro-phenyl]ethanone (2.5 g, 84.45% yield) as colorless oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.95 (br t, *J* = 7.2 Hz, 1H), 7.82 (br t, *J* = 7.2 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 2.62 (d, *J* = 4.0 Hz, 3H), 2.05 (t, *J* = 19.2 Hz, 3H).

Step 3: Synthesis of (NE,S)-N-[1-[3-(1,1-difluoroethyl)-2-fluoro-phenyl]ethylidene]-2-methyl-propane-2-sulfinamide

A mixture of 1-[3-(1,1-difluoroethyl)-2-fluoro-phenyl]ethanone (2.7 g, 13.35 mmol), (S)-2-methylpropane-2-sulfinamide (2.43 g, 20.03 mmol) and Ti(OEt)₄ (9.14 g, 40.06 mmol, 8.31 mL) in THF (40 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 80 °C for 16 h under N₂ atmosphere. The mixture was poured into water (50 mL) and filtered, and then it was extracted with EtOAc (60 mL X 3). The organic layers were washed with brine (40 mL X 2), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (5% EtOAc in petroleum ether) to give (NE,S)-N-[1-[3-(1,1-difluoroethyl)-2-fluoro-phenyl]ethylidene]-2-methyl-propane-2-sulfinamide (3.4 g, 76.29% yield, 91.5% purity) as yellow oil. MS (ESI) *m/z* = 306.2 [M+H]⁺.

Step 4: Synthesis of (S)-N-[(1R)-1-[3-(1,1-difluoroethyl)-2-fluoro-phenyl]ethyl]-2-methylpropane-2-sulfinamide

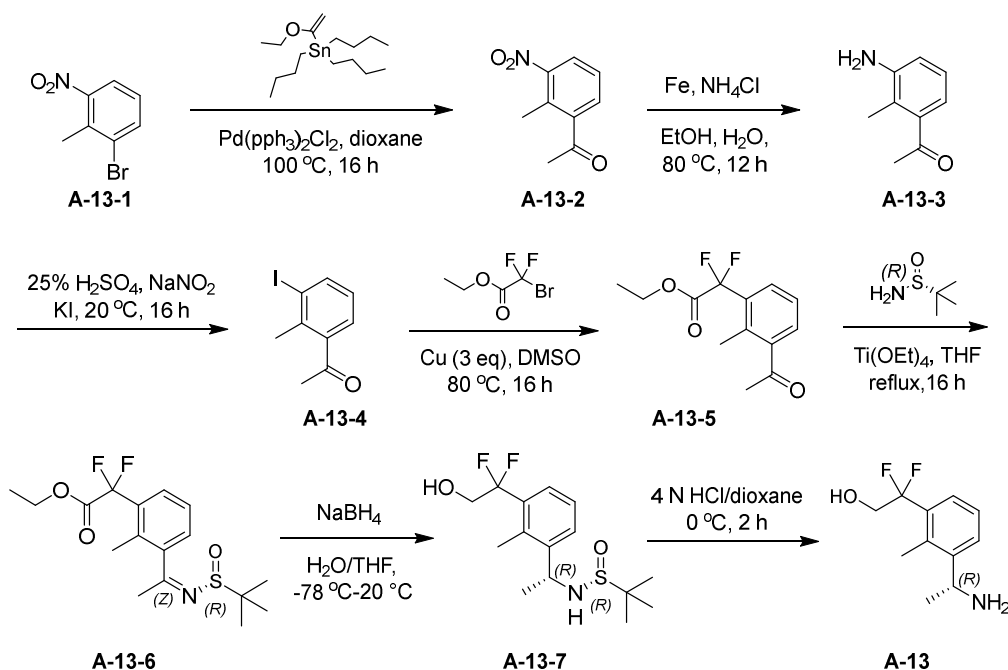
To a solution of (NE,S)-N-[1-[3-(1,1-difluoroethyl)-2-fluoro-phenyl]ethylidene]-2-methyl-propane-2-sulfinamide (3.4 g, 11.13 mmol) in THF (50 mL) was added L-selectride (1 M, 27.84 mL) at -70 °C, and then the mixture was degassed and purged with N₂ for 3 times. Thereafter, the mixture was stirred at -70 °C for 3 h under N₂ atmosphere. The reaction mixture was quenched with sat. aq. NH₄Cl (80 mL) added dropwise slowly at -70 °C, and then it was diluted with EtOAc (50 mL) and extracted with EtOAc (40 mL X 5). The organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (25% EtOAc in petroleum ether) to give a main product, (S)-N-[(1R)-1-[3-(1,1-difluoroethyl)-2-fluoro-phenyl]ethyl]-2-methylpropane-2-sulfinamide (2.3 g, 65.86% yield, 98% purity, 99.3% ee) as light yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.63 (t, *J* = 6.8 Hz, 1H), 7.51 - 7.40 (m, 1H), 7.33 - 7.26 (m, 1H), 5.54 (d, *J* = 5.6 Hz, 1H), 4.72 (quint, *J* = 6.8 Hz, 1H), 2.00 (t, *J* = 19.2 Hz, 3H), 1.49 (d, *J* = 6.8 Hz, 3H), 1.09 (s, 9H); MS (ESI) *m/z* = 308.0 [M+H]⁺.

Step 5: Synthesis of (1R)-1-[3-(1,1-difluoroethyl)-2-fluoro-phenyl]ethanamine

A mixture of (S)-N-[(1R)-1-[3-(1,1-difluoroethyl)-2-fluoro-phenyl]ethyl]-2-methylpropane-2-sulfinamide (500 mg, 1.63 mmol) and HCl/dioxane (4 N, 25 mL) in dioxane (2 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 25 °C

for 0.5 h under N₂ atmosphere. The mixture was concentrated under reduced pressure to give **Intermediate A-12** (350 mg, 89.78% yield, HCl) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.75 (br s, 3H), 7.88 (t, *J* = 7.2 Hz, 1H), 7.59 (t, *J* = 7.2 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 4.66 (br d, *J* = 5.2 Hz, 1H), 2.02 (t, *J* = 19.2 Hz, 3H), 1.56 - 1.53 (m, 3H); MS (ESI) *m/z* = 204.1 [M+H]⁺.

Preparation Example 13: 2-[3-[(1*R*)-1-aminoethyl]-2-methyl-phenyl]-2,2-difluoro-ethanol (A-13)



Step 1: Synthesis of 1-(2-methyl-3-nitro-phenyl)ethanone

A mixture of 1-bromo-methyl-3-nitro-benzene (10 g, 46.29 mmol), 1-tributyl(1-ethoxyvinyl)stannane (19.85 g, 54.96 mmol, 18.55 mL) and Pd(PPh₃)₂Cl₂ (3.25 g, 4.63 mmol) in dioxane (50 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 100 °C for 12 h under N₂ atmosphere. Following the addition of water (100 mL), the reaction mixture was extracted with EtOAc (100 mL X 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a residue. It was purified by silica gel column chromatography (20% EtOAc in petroleum ether) to give 1-(2-methyl-3-nitro-phenyl)ethanone (8.0 g, 96.46% yield) as yellow oil. The aqueous layers were adjusted to pH = 9 with aq. NaOH, and NaClO (100 mL) was slowly added under stirring. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.05 - 7.89 (m, 2H), 7.56 (t, *J* = 8.0 Hz, 1H), 2.60 (s, 3H), 2.37 (s, 3H).

Step 2: Synthesis of 1-(3-amino-2-methyl-phenyl)ethanone

To a solution of 1-(2-methyl-3-nitro-phenyl)ethanone (9.2 g, 51.35 mmol) in EtOH (100 mL) and H₂O (20 mL) was added Fe (28.67 g, 513.47 mmol) and NH₄Cl (27.47 g, 513.47 mmol). The mixture was degassed and purged with N₂ for 3 times, and then it was stirred at 80 °C for 12 h under nitrogen atmosphere. The reaction mixture was filtered, and the filtrate

was concentrated under reduced pressure. Water (100 mL) was poured into the reaction mixture, which was then extracted with EtOAc (100 mL × 3). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄ and concentrated under reduced pressure to give a crude product 1-(3-amino-2-methyl-phenyl)ethanone (6.8 g, 88.77% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 6.98 (t, *J* = 7.6 Hz, 1H), 6.84 (dd, *J* = 1.2, 7.6 Hz, 1H), 6.77 (dd, *J* = 1.2, 8.0 Hz, 1H), 5.05 (s, 2H), 2.46 (s, 3H), 2.06 (s, 3H).

Step 3: Synthesis of 1-(3-iodo-2-methyl-phenyl)ethanone

To a suspension of 1-(3-amino-2-methyl-phenyl)ethanone (6.5 g, 43.57 mmol) in H₂SO₄ (95.68 g, 975.55 mmol, 21.6 mL) was added NaNO₂ (3.01 g, 43.57 mmol) aqueous solution (220 mL) at 0 °C, and then the mixture was stirred for 1 h. The mixture was added to KI (21.70 g, 130.71 mmol) aqueous solution (220 mL) and stirred at 20 °C for 18 h. Water (100 mL) was poured into the reaction mixture, which was then extracted with EtOAc (100 mL × 3). The organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica column chromatography (6% EtOAc in petroleum ether) to give 1-(3-iodo-2-methyl-phenyl)ethanone (8.2 g, 72.37% yield) as yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.99 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 2.53 (s, 3H), 2.41 (s, 3H).

Step 4: Synthesis of ethyl 2-(3-acetyl-2-methyl-phenyl)-2,2-difluoroacetate

A mixture of 1-(3-iodo-2-methyl-phenyl)ethanone (4 g, 15.38 mmol), ethyl-2-bromo-2,2-difluoroacetate (3.43 g, 16.92 mmol, 2.17 mL) and Cu (2.93 g, 46.14 mmol, 327.24 μL) in DMSO (40 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 80 °C for 16 h under N₂ atmosphere. The mixture was poured into water (100 mL) and extracted with EtOAc (100 mL × 3). The organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (1-2% EtOAc in petroleum ether) to give ethyl 2-(3-acetyl-2-methyl-phenyl)-2,2-difluoroacetate (3.4 g, 74.11% yield, 85.91% purity) as colorless oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.86 (d, *J* = 7.6 Hz, 1H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 4.34 (q, *J* = 7.2 Hz, 2H), 2.57 (s, 3H), 2.29 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H); MS (ESI) *m/z* = 257.0 [M+H]⁺.

Step 5: Synthesis of ethyl 2-[3-[(Z)-N-[(R)-tert-butylsulfinyl]-C-methyl-carbonimidoyl]-2-methyl-phenyl)-2,2-difluoroacetate

A mixture of ethyl 2-(3-acetyl-2-methyl-phenyl)-2,2-difluoroacetate (3.4 g, 13.27 mmol), (R)-2-methylpropane-2-sulfinamide (1.77 g, 14.60 mmol) and Ti(OEt)₄ (9.08 g, 39.81 mmol, 8.25 mL) in THF (40 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 80 °C for 12 h under N₂ atmosphere. The mixture was poured into water (50 mL) and EtOAc (50 mL) and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine (50 mL × 2), dried over anhydrous Na₂SO₄ and concentrated

under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (12% EtOAc in petroleum ether) to give ethyl 2-[3-[(Z)-N-[(R)-tert-butylsulfinyl]-C-methyl-carbonimidoyl]-2-methyl-phenyl]-2,2-difluoroacetate ((2.6 g, 48.82% yield, 89.56% purity) as yellow oil. MS (ESI) m/z = 360.0 $[M+H]^+$.

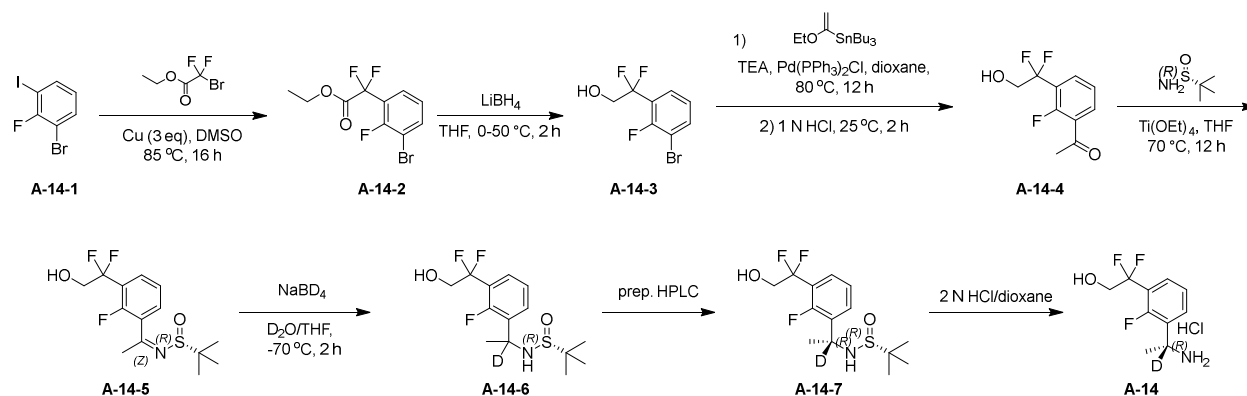
Step 6: Synthesis of (R)-N-[(1R)-1-[3-(1,1-difluoro-2-hydroxy-ethyl)-2-methyl-phenyl]ethyl]-2-methyl-propane-2-sulfinamide

A mixture of ethyl 2-[3-[(Z)-N-[(R)-tert-butylsulfinyl]-C-methyl-carbonimidoyl]-2-methyl-phenyl]-2,2-difluoroacetate (2.6 g, 7.23 mmol) and NaBH₄ (830 mg, 21.94 mmol) in THF (30 mL) and H₂O (1 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at -70 °C for 2 h under N₂ atmosphere. The mixture was quenched with sat. NH₄Cl (50 mL) at 20 °C, diluted with EtOAc (50 mL), and then extracted with EtOAc (50 mL X 3). The organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was separated and purified by prep-HPLC (YMC-Triart Prep C18 250*50 mm*10 μ m, mobile phase: [water (NH₃H₂O+NH₄HCO₃)-MeCN]; B%: 20%-50%, 20 min). MeCN was removed under reduced pressure, and the remaining solvent was removed by lyophilization to give a main product, (R)-N-[(1R)-1-[3-(1,1-difluoro-2-hydroxy-ethyl)-2-methyl-phenyl]ethyl]-2-methyl-propane-2-sulfinamide (900 mg, 38.08% yield, 97.77% purity, 100% ee) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 7.61 (d, J = 7.6 Hz, 1H), 7.39 - 7.34 (m, 1H), 7.28 (t, J = 7.2 Hz, 1H), 5.73 - 5.60 (m, 2H), 4.69 (quint, J = 6.8 Hz, 1H), 3.88 (dt, J = 6.4, 14.8 Hz, 2H), 2.37 (s, 3H), 1.37 (d, J = 6.8 Hz, 3H), 1.11 - 1.06 (m, 9H); MS (ESI) m/z = 320.0 $[M+H]^+$.

Step 7: Synthesis of 2-[3-[(1R)-1-aminoethyl]-2-methyl-phenyl]-2,2-difluoroethanol

To (R)-N-[(1R)-1-[3-(1,1-difluoro-2-hydroxy-ethyl)-2-methyl-phenyl]ethyl]-2-methyl-propane-2-sulfinamide (150 mg, 469.62 μ mol) in dioxane (2 mL) was added dropwise HCl/dioxane (4 N, 4 mL) at 0 °C, and then the mixture was stirred at 0 °C for 2 h. The mixture was concentrated under reduced pressure to give **Intermediate A-13** (115 mg, 57.48% yield, 50.52% purity) as a yellow solid. MS (ESI) m/z = 216.0 $[M+H]^+$.

Preparation Example 14: 2-[3-[(1R)-1-amino-1-deuterio-ethyl]-2-fluoro-phenyl]-2,2-difluoroethanol (A-14)



Step 1: Synthesis of ethyl 2-(3-bromo-2-fluoro-phenyl)-2,2-difluoro-acetate

To a solution of 1-bromo-2-fluoro-3-iodo-benzene (11 g, 36.56 mmol, 1 eq) in DMSO (200 mL) was added solid copper (6.97 g, 109.67 mmol, 777.82 μ L) and ethyl 2-bromo-2,2-difluoro-acetate (22.26 g, 109.67 mmol, 14.13 mL). The reaction mixture was stirred at 85 °C for 16 h under N₂ atmosphere. The reaction mixture was filtered, and then the filtrate was added with water (80 mL) and extracted with EtOAc (80 mL X 3). The organic layers were washed with brine (60 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (10 % EtOAc in petroleum ether) to give ethyl 2-(3-bromo-2-fluoro-phenyl)-2,2-difluoro-acetate (9.3 g, 77.07% yield, 90% purity) as white oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.02-7.95 (m, 1H), 7.75-7.69 (m, 1H), 7.37 (t, *J* = 8.0 Hz, 1H), 4.40-4.31 (m, 2H), 1.23 (t, *J* = 7.2 Hz, 3H).

Step 2: Synthesis of 2-(3-bromo-2-fluoro-phenyl)-2,2-difluoro-ethanol

To a solution of ethyl 2-(3-bromo-2-fluoro-phenyl)-2,2-difluoro-acetate (8.8 g, 29.62 mmol) in THF (140 mL) was slowly added LiBH₄ (2 M, 20.74 mL) at 0 °C under N₂ atmosphere. Thereafter, the reaction mixture was stirred at 50 °C for 2 h under N₂ atmosphere. Aq. NH₄Cl (80 mL) was slowly poured into the mixture, which was then extracted with EtOAc (60 mL X 3). The organic layers were washed with brine (80 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (6% EtOAc in petroleum ether) to give 2-(3-bromo-2-fluoro-phenyl)-2,2-difluoro-ethanol (7.3 g, 96.63% purity) as yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.89 (t, *J* = 7.2 Hz, 1H), 7.61-7.52 (m, 1H), 7.29 (t, *J* = 8.0 Hz, 1H), 5.76-5.70 (m, 1H), 3.96-3.88 (m, 2H).

Step 3: Synthesis of 1-[3-(1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethanone

A mixture of tributyl(1-ethoxyvinyl)stannane (8.24 g, 22.82 mmol, 7.71 mL), TEA (3.17 g, 31.37 mmol, 4.37 mL) and Pd(PPh₃)₂Cl₂ (1.10 g, 1.57 mmol) was mixed with a solution of 2-(3-bromo-2-fluoro-phenyl)-2,2-difluoro-ethanol (4 g, 15.68 mmol) in dioxane (50 mL), degassed and purged with N₂ for 3 times, and then stirred at 80 °C for 12h under N₂ atmosphere. The mixture was added with HCl solution (50 mL, 1 M) stirring at 25 °C, and then stirred at 25 °C for 1 h. Following the addition of water (30 mL), the reaction mixture was extracted with EtOAc (50 mL X 3). The combined organic layers were washed with brine (80 mL X 3), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a residue. It was purified by silica gel column chromatography (12% EtOAc in petroleum ether) to give 1-[3-(1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethanone (3.33 g, 90.43% yield, 92.93% purity) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.99-7.91 (m, 1H), 7.82-7.74 (m, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 5.73 (t, *J* = 6.8 Hz, 1H), 3.95 (dt, *J* = 6.8, 14.3 Hz, 2H), 2.60 (d, *J* = 4.4 Hz, 3H); MS (ESI) *m/z* = 218.9 [M+H]⁺.

Step 4: Synthesis of (NZ,R)-N-[1-[3-(1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethylidene]-2-methyl-propane-2-sulfinamide

To a solution of 1-[3-(1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethanone (3.33 g, 15.26 mmol) in THF (35 mL) was added (R)-2-methylpropane-2-sulfinamide (2.77 g, 22.89 mmol) and $\text{Ti}(\text{OEt})_4$ (10.44 g, 45.79 mmol, 9.50 mL), and then the mixture was stirred at 70 °C for 12 h under N_2 atmosphere. The mixture was poured into water (50 mL) and extracted with EtOAc (50 mL X 3). The organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (20% EtOAc in petroleum ether) to give (NZ, R)-N-[1-[3-(1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethylidene]-2-methyl-propane-2-sulfinamide (4.3 g, 85.90% yield, 97.99% purity) as yellow oil. ^1H NMR (400 MHz, DMSO-d_6) δ 7.79 (br t, J = 7.2 Hz, 1H), 7.68 (br t, J = 6.8 Hz, 1H), 7.41 (br t, J = 7.6 Hz, 1H), 5.75-5.71 (m, 1H), 3.93 (dt, J = 6.4, 14.0 Hz, 2H), 2.69 (br d, J = 1.6 Hz, 3H), 1.22 (s, 9H); MS (ESI) m/z = 322.1 $[\text{M}+\text{H}]^+$.

Step 5: Synthesis of (R)-N-[(1R)-1-deuterio-1-[3-(1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethyl]-2-methyl-propane-2-sulfinamide

To a solution of (NZ,R)-N-[1-[3-(1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethylidene]-2-methyl-propane-2-sulfinamide (4.3 g, 13.38 mmol) in THF (80 mL) and D_2O (1.6 mL) was added NaBD_4 (506.23 mg) at -70 °C, and then the mixture was stirred at -70 °C for 2 h under N_2 atmosphere. TLC (PE:EA = 1/1) indicated the reaction was complete. The mixture was quenched with sat. aq. NH_4Cl (50 mL) and extracted with EtOAc (50 mL X 3). The organic layers were washed with brine (80 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (20% EtOAc/petroleum ether) to give (R)-N-[(1R)-1-deuterio-1-[3-(1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethyl]-2-methyl-propane-2-sulfinamide (4.2 g, 81.28% yield, 84% purity) as yellow oil. MS (ESI) m/z = 325.0 $[\text{M}+\text{H}]^+$.

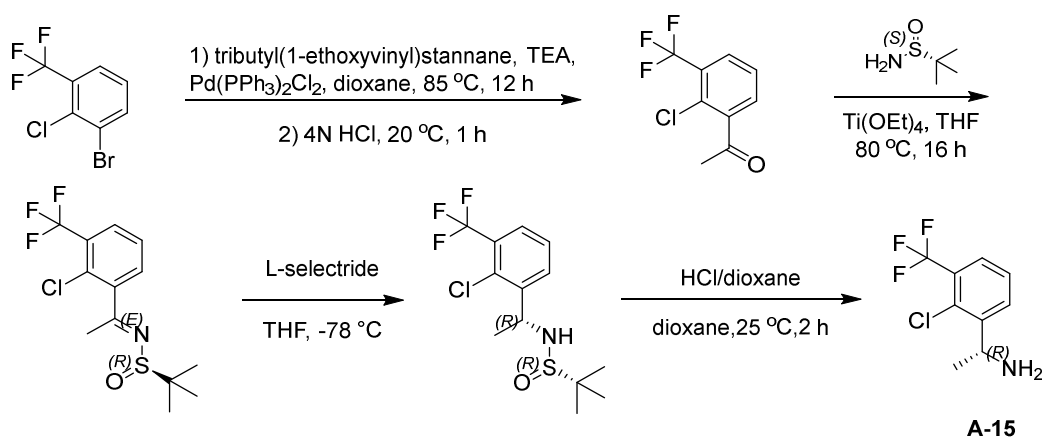
Step 6: Synthesis of (R)-N-[(1S)-1-deuterio-1-[3-(1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethyl]-2-methyl-propane-2-sulfinamide

(R)-N-[(1R)-1-deuterio-1-[3-(1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethyl]-2-methyl-propane-2-sulfinamide was purified by prep-HPLC (column: Welch Xtimate C18 250*50mm*10 μm ; mobile phase: [water ($\text{NH}_3\text{H}_2\text{O}+\text{NH}_4\text{HCO}_3$)-ACN]; 5%-55% B, 20 min). The solvent was concentrated under reduced pressure, and then the residue was lyophilized to give (R)-N-[(1S)-1-deuterio-1-[3-(1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethyl]-2-methyl-propane-2-sulfinamide (700 mg, 16.28% yield, 100% purity, peak 1) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 7.64 (t, J = 6.8 Hz, 1H), 7.48-7.39 (m, 1H), 7.33-7.26 (m, 1H), 5.70 (t, J = 6.4 Hz, 1H), 5.52 (s, 1H), 3.90 (dt, J = 6.4, 14.4 Hz, 2H), 1.48 (s, 3H), 1.09 (s, 9H); MS (ESI) m/z = 325.2 $[\text{M}+\text{H}]^+$.

Step 7: Synthesis of 2-[3-[(1R)-1-amino-1-deuterio-ethyl]-2-fluoro-phenyl]-2,2-difluoro-ethanol

To (R)-N-[(1S)-1-deuterio-1-[3-(1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethyl]-2-methyl-propane-2-sulfonamide (1.14 g, 3.51 mmol) in dioxane (5 mL) was added HCl/dioxane (20 mL) at 0 °C, and then the mixture was stirred at 20 °C for 2 h. The mixture was concentrated under reduced pressure to give **Intermediate A-14** (900 mg, 94.78% yield, 95% purity, hydrochloride salt) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 8.73 (br s, 2H), 7.87 (t, *J* = 6.8 Hz, 1H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.44-7.37 (m, 1H), 3.92 (br t, *J* = 14.2 Hz, 2H), 1.54 (s, 3H), 1.10 (s, 1H).

Preparation Example 15: (1R)-1-[2-chloro-3-(trifluoromethyl)phenyl]ethanamine (A-15)



Step 1: Synthesis of 1-[2-chloro-3-(trifluoromethyl)phenyl]ethanone

A mixture of tributyl(1-ethoxyvinyl)stannane (12.520 g, 34.67 mmol, 11.71 mL), TEA (6.24 g, 61.67 mmol, 8.58 mL) and Pd(PPh₃)₂Cl₂ (1.10 g, 1.57 mmol) was mixed with a solution of 1-bromo-2-chloro-3-(trifluoromethyl)benzene (4 g, 15.68 mmol) in dioxane (140 mL), degassed and purged with N₂ for 3 times, and then stirred at 80 °C for 16 h under N₂ atmosphere. TLC (PE:EA = 10/1) indicated that the reaction was complete. To the mixture was added HCl solution (80 mL, 1 M) under stirring at 25 °C, and then the mixture was stirred at 25 °C for 1 h. Following the addition of water (120 mL), the reaction mixture was extracted with EtOAc (150 mL X 3). The combined organic layers were washed with brine (150 mL X 3), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a residue. The aqueous layer was stirred while slowly adding sat. aq. KF (200 mL), followed by stirring at 25 °C for 1 h. It was purified by column chromatography (6% EtOAc/petroleum ether) to give 1-[2-chloro-3-(trifluoromethyl)phenyl]ethanone (4.2 g, 58.13% yield, 95% purity) as yellow oil. ¹H NMR (400 MHz, DMSO-d₆) δ 7.97 (d, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 7.6 Hz, 1H), 7.71-7.63 (m, 1H), 2.61 (s, 3H).

Step 2: Synthesis of (NE,R)-N-[1-[2-chloro-3-(trifluoromethyl)phenyl]ethylidene]-2-methyl-propane-2-sulfonamide

To a solution of 1-[2-chloro-3-(trifluoromethyl)phenyl]ethanone (4.2 g, 18.87 mmol) in THF (60 mL) was added (S)-2-methylpropane-2-sulfinamide (3.43 g, 28.30 mmol) and $\text{Ti}(\text{OEt})_4$ (12.91 g, 56.61 mmol, 11.74 mL), and then the mixture was stirred at 80 °C for 16 h under N_2 atmosphere. TLC (PE:EA = 10/1) indicated that the reaction was complete. The mixture was poured into water (40 mL) and filtered, and then the filtrate was extracted with EtOAc (60 mL X 3). The organic layers were washed with brine (80 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (6% EtOAc in petroleum ether) to give (NE,R)-N-[1-[2-chloro-3-(trifluoromethyl)phenyl]ethylidene]-2-methyl-propane-2-sulfinamide (5.15 g, 75.40% yield, 90% purity) as yellow oil. ^1H NMR (400 MHz, DMSO-d_6) δ 7.98 (br d, J = 7.6 Hz, 1H), 7.91 (br d, J = 7.6 Hz, 1H), 7.82 (br d, J = 7.6 Hz, 1H), 2.71 (s, 3H), 1.26 (s, 9H); MS (ESI) m/z = 326.0 $[\text{M}+\text{H}]^+$.

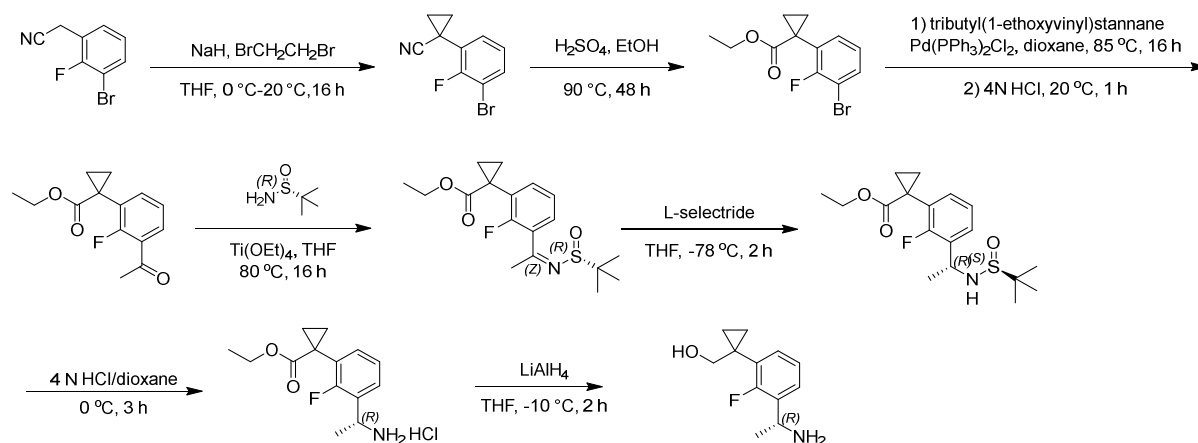
Step 3: Synthesis of N-[(1R)-1-[2-chloro-3-(trifluoromethyl)phenyl]ethyl]-2-methyl-propane-2-sulfinamide

L-selectride (1 M, 31.62 mL) was slowly added dropwise to a solution of (NE,R)-N-[1-[2-chloro-3-(trifluoromethyl)phenyl]ethylidene]-2-methyl-propane-2-sulfinamide (5.15 g, 15.81 mmol) in THF (100 mL) at -70 °C for 0.5 h, and then the mixture was stirred at -70 °C for 2 h under N_2 atmosphere. The reaction mixture was quenched with sat. aq. NH_4Cl (60 mL) added dropwise slowly at 20 °C under N_2 atmosphere, and then diluted with EtOAc (80 mL) and extracted with EtOAc (80 mL X 3). The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (13% EtOAc in petroleum ether) to give the desired peak 2 fractions, N-[(1R)-1-[2-chloro-3-(trifluoromethyl)phenyl]ethyl]-2-methyl-propane-2-sulfinamide (2 g, 78.17% yield, 89.89% purity, ee = 95.96%) as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 7.89 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 6.8 Hz, 1H), 7.63-7.54 (m, 1H), 5.66 (d, J = 5.6 Hz, 1H), 4.93 (t, J = 6.4 Hz, 1H), 1.48 (d, J = 6.8 Hz, 3H), 1.10 (s, 9H).

Step 4: Synthesis of (1R)-1-[2-chloro-3-(trifluoromethyl)phenyl]ethanamine

To a solution of N-[(1R)-1-[2-chloro-3-(trifluoromethyl)phenyl]ethyl]-2-methyl-propane-2-sulfinamide (200 mg, 610.14 μmol) in dioxane (1 mL) was added dropwise HCl /dioxane (1 mL), and then the mixture was stirred at 25 °C for 2 h. TLC (PE:EtOAc = 1:1) indicated that all starting materials were consumed and one new spot was formed. The mixture was concentrated under reduced pressure to give **Intermediate A-15** (136 mg, 99.68% yield) as a yellow solid. MS (ESI) m/z = 224.1 $[\text{M}+\text{H}]^+$.

Preparation Example 16: [1-[3-[(1R)-1-aminoethyl]-2-fluorophenyl]cyclopropyl]methanol (A-16)



A-16

Step 1: Synthesis of 1-(3-bromo-2-fluorophenyl)cyclopropanecarbonitrile

A solution of 2-(3-bromo-2-fluorophenyl)acetonitrile (4.4 g, 20.56 mmol) and 1,2-dibromoethane (5.02 g, 26.72 mmol, 2.02 mL) in THF (80 mL) was purged with N₂ for 3 times, and then NaH (1.07 g, 26.72 mmol, 60% purity) was added at 0 °C. Thereafter, the mixture was stirred at 20 °C for 16 h under N₂ atmosphere. Sat. aq. NH₄Cl was poured into the mixture, which was then extracted with EtOAc (30 mL X 3). The organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (9% EtOAc in petroleum ether) to give 1-(3-bromo-2-fluorophenyl)cyclopropanecarbonitrile (4.6 g, 75.50% yield, 81% purity) as yellow oil. ¹H NMR (400 MHz, DMSO-d₆) δ 7.74 (ddd, *J* = 1.6, 6.8, 8.0 Hz, 1H), 7.57 - 7.38 (m, 1H), 7.18 (dt, *J* = 0.8, 8.0 Hz, 1H), 1.86 - 1.60 (m, 2H), 1.57 - 1.41 (m, 2H).

Step 2: Synthesis of 1-(3-bromo-2-fluorophenyl)cyclopropanecarboxylate

A solution of 1-(3-bromo-2-fluorophenyl)cyclopropanecarbonitrile (4.69 g, 19.54 mmol) in ethanol (80 mL) and sulfuric acid (10 mL) was purged with N₂ for 3 times, and then the mixture was stirred at 90 °C for 48 h under N₂ atmosphere. TLC (PE:EA = 10:1) indicated the reaction was complete. The mixture was poured into water (20 mL) and extracted with EtOAc (20 mL X 3). The organic layers were washed with brine (100 mL X 3), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (2% EtOAc in petroleum ether) to give 1-(3-bromo-2-fluorophenyl)cyclopropanecarboxylate (3.74 g, 66.68% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ 7.63 (ddd, *J* = 1.6, 6.8, 8.0 Hz, 1H), 7.40 - 7.29 (m, 1H), 7.20 - 7.02 (m, 1H), 4.04 (q, *J* = 7.2 Hz, 2H), 1.64 - 1.47 (m, 2H), 1.29 - 1.23 (m, 2H), 1.08 (t, *J* = 7.2 Hz, 3H).

Step 3: Synthesis of ethyl 1-(3-acetyl-2-fluorophenyl)cyclopropanecarboxylate

A mixture of tributyl(1-ethoxyvinyl)stannane (9.82 g, 27.20 mmol, 9.19 mL) and Pd(PPh₃)₂Cl₂ (1.78 g, 2.54 mmol) was mixed with a solution of 1-(3-bromo-2-fluorophenyl)cyclopropanecarboxylate (3.74 g, 19.54 mmol) in THF (80 mL) and EtOAc (20 mL) and stirred at 85 °C for 16 h. The mixture was then poured into water (20 mL) and extracted with EtOAc (20 mL X 3). The organic layers were washed with brine (100 mL X 3), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (2% EtOAc in petroleum ether) to give ethyl 1-(3-acetyl-2-fluorophenyl)cyclopropanecarboxylate (3.74 g, 66.68% yield) as a yellow solid.

phenyl)cyclopropanecarboxylate (7.3 g, 25.42 mmol) in dioxane (100 mL), degassed and purged with N₂ for 3 times, and then stirred at 80 °C for 16 h under N₂ atmosphere. TLC (PE:EA = 3:1) indicated that the reaction was complete. The mixture was quenched by adding 4 N HCl solution (30 mL), and stirred at 20 °C for 1 h. TLC (PE:EA = 5:1) indicated that all intermediates were consumed and the reaction was complete. Following the addition of water (100 mL), the reaction mixture was extracted with EtOAc (100 mL X 3). The combined organic layers were washed with brine (100 mL X 3), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a residue. The aqueous layer was stirred while slowly adding sat. aq. KF (150 mL), and then stirred at 25 °C for 1h. It was purified by column chromatography (3% EtOAc in petroleum ether) to give ethyl 1-(3-acetyl-2-fluoro-phenyl)cyclopropanecarboxylate (4.6 g, 72.29% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ 7.78 - 7.68 (m, 1H), 7.65 - 7.54 (m, 1H), 7.26 (dt, *J* = 1.2, 7.6 Hz, 1H), 4.04 (dq, *J* = 1.2, 7.2 Hz, 2H), 2.58 (dd, *J* = 1.2, 4.4 Hz, 3H), 1.62 - 1.49 (m, 2H), 1.32 - 1.22 (m, 2H), 1.09 (dt, *J* = 1.2, 7.2 Hz, 3H).

Step 4: Synthesis of ethyl 1-[3-[(Z)-N-[(R)-tert-butylsulfinyl]-C-methylcarbonimidoyl]-2-fluoro-phenyl]cyclopropanecarboxylate

To a solution of ethyl-1-(3-acetyl-2-fluoro-phenyl)cyclopropanecarboxylate (2 g, 7.99 mmol) was added (R)-2-methylpropane-2-sulfinamide (968.58 mg, 7.99 mmol) and Ti(OEt)₄ (5.47 g, 23.97 mmol, 4.97 mL), and then the mixture was degassed and purged with N₂ for 3 times. Thereafter, the mixture was stirred at 80 °C for 16 h under N₂ atmosphere. The mixture was poured into water (50 mL) and was filtered, and the filtrate was extracted with EtOAc (50 mL X 3). The organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (6% EtOAc in petroleum ether) to give ethyl 1-[3-[(Z)-N-[(R)-tert-butylsulfinyl]-C-methylcarbonimidoyl]-2-fluoro-phenyl]cyclopropanecarboxylate (2.3 g, 73.28% yield, 90% purity) as yellow oil. MS (ESI) *m/z* = 354.3 [M+H]⁺.

Step 5: Synthesis of ethyl 1-[3-[(1R)-1-[(S)-tert-butylsulfinyl]amino]ethyl]-2-fluorophenyl]cyclopropanecarboxylate

L-selectride (1 M, 5.91 mL) was slowly added dropwise to a solution of ethyl 1-[3-[(Z)-N-[(R)-tert-butylsulfinyl]-C-methylcarbonimidoyl]-2-fluoro-phenyl]cyclopropanecarboxylate (1.1 g, 3.11 mmol) in THF (20 mL) at -78 °C under N₂ atmosphere, and then the mixture was stirred at -78 °C for 2 h under N₂ atmosphere. The reaction mixture was quenched with sat. aq. NH₄Cl (20 mL) added dropwise slowly at 20 °C under N₂ atmosphere, and then poured into water (20 mL) and extracted with EtOAc (20 mL X 3). The organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (19% EtOAc in petroleum ether) to give ethyl-1-[3-[(1R)-1-[(S)-tert-

butylsulfinyl]amino]ethyl]-2-fluorophenyl]cyclopropanecarboxylate (440 mg, 36.99% yield, 93% purity, ee = 95.12%) as colorless oil. ¹H NMR (400 MHz, DMSO-d₆) δ 7.46 - 7.33 (m, 1H), 7.25 - 7.17 (m, 1H), 7.15 - 7.05 (m, 1H), 5.45 (d, *J* = 6.0 Hz, 1H), 4.74 - 4.57 (m, 1H), 4.01 (dq, *J* = 2.0, 7.2 Hz, 2H), 1.51 (s, 2H), 1.47 (d, *J* = 6.8 Hz, 3H), 1.22 - 1.16 (m, 2H), 1.11 - 1.09 (m, 9H), 1.08 - 1.04 (m, 3H); MS (ESI) *m/z* = 356.1 [M+H]⁺.

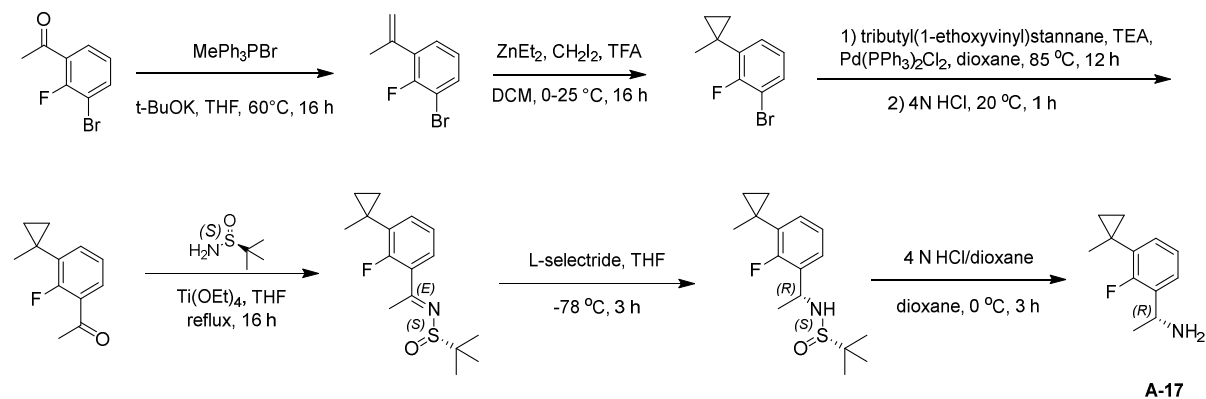
Step 6: Synthesis of ethyl-1-[3-[(1R)-1-aminoethyl]-2-fluorophenyl]cyclopropanecarboxylate

To ethyl 1-[3-[(1R)-1-[(S)-tert-butylsulfinyl]amino]ethyl]-2-fluorophenyl]cyclopropanecarboxylate (250 mg, 703.30 μmol) in dioxane (1 mL) was added dropwise HCl/dioxane (1 mL), and the mixture was degassed and purged with N₂ for 3 times. Thereafter, the mixture was stirred at 0 °C for 1 h under N₂ atmosphere. It was confirmed through LCMS that the starting materials were completely consumed. The mixture was concentrated under reduced pressure to give a crude product, ethyl-1-[3-[(1R)-1-aminoethyl]-2-fluorophenyl]cyclopropanecarboxylate (200 mg, 96.75% yield, 97.9% purity, hydrochloride salt) as a white solid, which was used in the next reaction without further purification. MS (ESI) *m/z* = 252.2 [M+H]⁺.

Step 7: Synthesis of [1-[3-[(1R)-1-aminoethyl]-2-fluorophenyl]cyclopropyl]methanol

To a solution of ethyl 1-[3-[(1R)-1-aminoethyl]-2-fluorophenyl]cyclopropanecarboxylate (200 mg, 795.87 μmol) in THF (3 mL) was added LiAlH₄ (90.62 mg, 2.39 mmol) at -10 °C, and then the mixture was stirred at -10 °C for 2 h. The mixture was quenched with aq. NaOH (15%, 0.6 mL) at 20 °C and filtered, and then the filtrate was concentrated under reduced pressure to give **Intermediate A-16** (165 mg, 74.30% yield, 75% purity) as yellow oil. ¹H NMR (400 MHz, DMSO-d₆) δ 7.47 (dt, *J* = 1.6, 7.2 Hz, 1H), 7.21 (dt, *J* = 1.6, 7.2 Hz, 1H), 7.15 - 7.08 (m, 1H), 4.68 (br t, *J* = 5.6 Hz, 1H), 4.30 (q, *J* = 6.4 Hz, 1H), 3.50 (br d, *J* = 5.6 Hz, 2H), 1.29 (d, *J* = 6.4 Hz, 3H), 0.91 - 0.85 (m, 2H), 0.73 - 0.68 (m, 2H).

Preparation Example 17: (1R)-1-[2-fluoro-3-(1-methylcyclopropyl)phenyl]ethanamine (A-17)



Step 1: Synthesis of 1-bromo-2-fluoro-3-isopropenylbenzene

A solution of t-BuOK (5.17 g, 46.08 mmol, 1 eq) and methyl (triphenyl) phosphonium; bromide (16.46 g, 46.08 mmol) in THF (100 mL) was stirred at 20 °C for 1 h. After a solution of 1-(3-bromo-2-fluoro-phenyl)ethanone (10 g, 46.08 mmol) in THF (100 mL) was added, the reaction mixture was stirred at 60 °C for 16 h under N₂ atmosphere. The mixture was poured into water (80 mL) and extracted with EtOAc (80 mL X 3). The organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (petroleum ether) to give 1-bromo-2-fluoro-3-isopropenyl-benzene (7.5 g, 68.12% yield, 90% purity) as white oil. ¹H NMR (400 MHz, DMSO-d₆) δ 7.66 - 7.49 (m, 1H), 7.36 (dt, *J* = 1.6, 7.4 Hz, 1H), 7.16 - 7.10 (m, 1H), 5.31 (d, *J* = 0.8 Hz, 1H), 5.22 (s, 1H), 2.08 (d, *J* = 0.8 Hz, 3H).

Step 2: Synthesis of 1-bromo-2-fluoro-3-(1-methylcyclopropyl)benzene

TFA (7.95 g, 69.75 mmol, 5.18 mL) was slowly added dropwise to diethylzinc (1 M, 69.75 mL) solution at 0 °C for 20 min. Thereafter, the mixture was stirred at 0 °C for 20 min, and then CH₂I₂ (18.68 g, 69.75 mmol, 5.63 mL) solution in DCM (45 mL) was added dropwise at 0 °C. The mixture was stirred at 0 °C for 20 min, and then 1-bromo-2-fluoro-3-isopropenyl-benzene (3 g, 13.95 mmol) was slowly added dropwise at 0 °C. The mixture was stirred at 25 °C for 12h. TLC (PE:EA = 10:1) indicated that the reaction was complete. The mixture was poured into water (30 mL) and extracted with DCM (30 mL X 3). The organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (petroleum ether) to give 1-bromo-2-fluoro-3-(1-methylcyclopropyl)benzene (2.7 g, 76.04% yield, 90% purity) as colorless liquid. ¹H NMR (400 MHz, DMSO-d₆) δ 7.53 (ddd, *J* = 1.6, 6.4, 8.0 Hz, 1H), 7.32 (dt, *J* = 1.6, 7.2 Hz, 1H), 7.06 (dt, *J* = 0.8, 7.8 Hz, 1H), 1.29 (s, 3H), 0.78 - 0.75 (m, 2H), 0.73 - 0.70 (m, 2H).

Step 3: Synthesis of 1-[2-fluoro-3-(1-methylcyclopropyl)phenyl]ethanone

A mixture of tributyl(1-ethoxyvinyl)stannane (6.62 g, 18.33 mmol, 6.19 mL) and Pd(PPh₃)₂Cl₂ (612.77 mg, 873.03 μmol) was mixed with a solution of 1-bromo-2-fluoro-3-(1-methylcyclopropyl)benzene (4 g, 17.46 mmol) in dioxane (60 mL), degassed and purged with N₂ for 3 times, and then stirred at 100 °C for 16 h under N₂ atmosphere. After 4 N HCl solution (10 mL) was added, the mixture was stirred at 20 °C for 1 h. Following the addition of water (50 mL), the reaction mixture was extracted with EtOAc (30 mL X 3). The combined organic layers were washed with brine (30 mL X 3), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (petroleum ether) to give 1-[2-fluoro-3-(1-methylcyclopropyl)phenyl]ethanone (2.1 g, 60.69% yield, 97% purity) as yellow oil. ¹H NMR (400 MHz, DMSO-d₆) δ 7.64 (dt, *J* = 2.0, 7.6 Hz, 1H), 7.56 (dt, *J* = 2.0, 7.2 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 2.58 (d, *J* = 4.4 Hz, 3H), 1.32 (s, 3H), 0.79 - 0.76 (m, 2H), 0.74 - 0.71 (m, 2H); MS (ESI) *m/z* = 193.0 [M+H]⁺.

Step 4: Synthesis of (NE, S)-N-[1-[2-fluoro-3-(1-methylcyclopropyl)phenyl]ethylidene]-2-methyl-propane-2-sulfinamide

To a solution of 1-[2-fluoro-3-(1-methylcyclopropyl)phenyl]ethanone (2 g, 10.40 mmol) in THF (30 mL) was added (S)-2-methylpropane-2-sulfinamide (1.51 g, 12.49 mmol) and Ti(OEt)₄ (4.75 g, 20.81 mmol, 4.32 mL), and then the mixture was purged with N₂ for 3 times. Thereafter, the mixture was stirred at 80 °C for 5 h under N₂ atmosphere. The mixture was poured into water (20 mL), and the reaction mixture was filtered and the filtrate was extracted with EtOAc (20 mL X 3). The organic layers were washed with brine (20 mL X 3), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (2% EtOAc in petroleum ether) to give (NE, S)-N-[1-[2-fluoro-3-(1-methylcyclopropyl)phenyl]ethylidene]-2-methylpropane-2-sulfinamide (2.5 g, 77.44% yield, 95.209% purity) as yellow oil. MS (ESI) m/z = 296.2 [M+H]⁺.

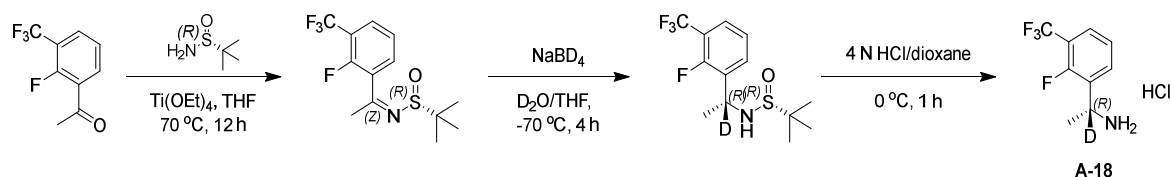
Step 5: Synthesis of (S)-N-[(1R)-1-[2-fluoro-3-(1-methylcyclopropyl)phenyl]ethyl]-2-methyl-propane-2-sulfinamide

L-selectride (1 M, 12.69 mL) was slowly added dropwise to (NE, S)-N-[1-[2-fluoro-3-(1-methylcyclopropyl)phenyl]ethylidene]-2-methyl-propane-2-sulfinamide (2.5 g, 8.46 mmol) in THF (40 mL) at -78 °C for 0.5 h under N₂ atmosphere, and then the mixture was stirred at -78 °C for 3 h under N₂ atmosphere. The reaction mixture was quenched with sat. aq. NH₄Cl (50 mL) added dropwise slowly at -78 °C under N₂ atmosphere, and then diluted with EtOAc (60 mL) and extracted with EtOAc (60 mL X 3). The organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give crude product. The crude product was purified by silica gel column chromatography (6% EtOAc in petroleum ether) to give (S)-N-[(1R)-1-[2-fluoro-3-(1-methylcyclopropyl)phenyl]ethyl]-2-methyl-propane-2-sulfinamide (2.3 g, 76.19% yield, 83.38% purity, ee = 98.7%) as yellow oil. ¹H NMR (400 MHz, DMSO-d₆) δ 7.34 - 7.25 (m, 1H), 7.19 (dt, *J* = 1.6, 7.6 Hz, 1H), 7.09 - 7.02 (m, 1H), 5.40 (d, *J* = 6.0 Hz, 1H), 4.67 (q, *J* = 6.4 Hz, 1H), 1.46 (d, *J* = 8.0 Hz, 3H), 1.28 (s, 3H), 1.09 (s, 9H), 0.74 - 0.70 (m, 2H), 0.68 (m, 2H); MS (ESI) m/z = 298.2 [M+H]⁺.

Step 6: Synthesis of (1R)-1-[2-fluoro-3-(1-methylcyclopropyl)phenyl]ethanamine

To (S)-N-[(1R)-1-[2-fluoro-3-(1-methylcyclopropyl)phenyl]ethyl]-2-methylpropane-2-sulfinamide (200 mg, 672.43 μmol) in dioxane (2 mL) was added dropwise HCl/dioxane (2 mL), and then the mixture was degassed and purged with N₂ for 3 times. Thereafter, the mixture was stirred at 25 °C for 2 h under N₂ atmosphere. The mixture was concentrated under reduced pressure to give a crude product, which was treated with MTBE (2 mL) at 25 °C for 20 min to give **Intermediate A-17** (120 mg, 73.02% yield, 94% purity, hydrochloride) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 8.53 (br s, 3H), 7.52 - 7.47 (m, 1H), 7.35 (dt, *J* = 1.6, 7.2 Hz, 1H), 7.22 - 7.17 (m, 1H), 4.61 (br s, 1H), 1.51 (d, *J* = 6.8 Hz, 3H), 1.31 (s, 3H), 0.74 (br d, *J* = 10.0 Hz, 4H); MS (ESI) m/z = 194.0 [M+H]⁺.

Preparation Example 18: (1R)-1-deuterio-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethanamine (A-18)



Step 1: Synthesis of (NZ,R)-N-[1-[2-fluoro-3-(trifluoromethyl)phenyl]ethylidene]-2-methyl-propane-2-sulfinamide

To a solution of 1-[2-fluoro-3-(trifluoromethyl)phenyl]ethanone (3 g, 14.55 mmol) in THF (50 mL) was added $\text{Ti}(\text{OEt})_4$ (9.96 g, 43.66 mmol, 9.05 mL) and (R)-2-propane-2-sulfinamide (2.65 g, 21.83 mmol), and then the mixture was stirred at 70 °C for 12 h under N_2 atmosphere. The mixture was poured into water (60 mL), and the reaction mixture was filtered and the filtrate was extracted with EtOAc (60 mL X 3). The organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (8% EtOAc in petroleum ether) to give (NZ,R)-N-[1-[2-fluoro-3-(trifluoromethyl)phenyl]ethylidene]-2-methyl-propane-2-sulfinamide (4.36 g, 90.10% yield, 93.03% purity) as yellow oil. ^1H NMR (400 MHz, DMSO-d_6) δ 7.99 (br t, $J = 7.2$ Hz, 1H), 7.92 (br t, $J = 7.2$ Hz, 1H), 7.51 (br t, $J = 8.0$ Hz, 1H), 2.72 (br d, $J = 1.2$ Hz, 3H), 1.22 (s, 9H); MS (ESI) $m/z = 310.1[\text{M}+\text{H}]^+$

Step 2: Synthesis of (R)-N-[(1R)-1-deuterio-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-2-methyl-propane-2-sulfinamide

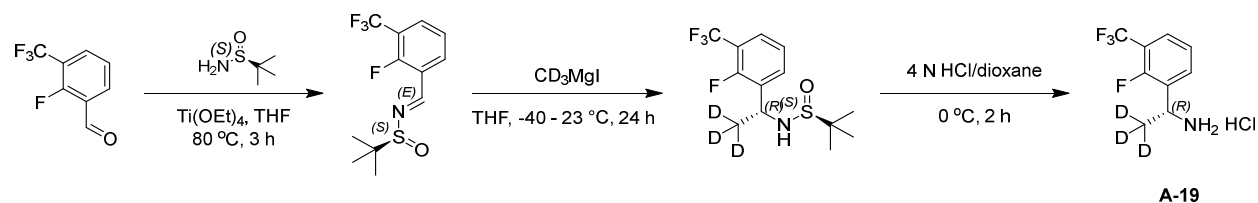
To a solution of (NZ,R)-N-[1-[2-fluoro-3-(trifluoromethyl)phenyl]ethylidene]-2-methyl-propane-2-sulfinamide (500 mg, 1.62 mmol) in THF (10 mL) and D_2O (0.2 mL) was added NaBD_4 (61.15 mg, 1.62 mmol) at -70 °C, and then the mixture was stirred at -70 °C for 4 h under N_2 atmosphere. The mixture was quenched with sat. NH_4Cl (50 mL) and poured into water (30 mL). It was extracted with EtOAc (40 mL X 3). The organic layers were washed with brine (40 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (18% EtOAc/petroleum ether) to give (R)-N-[(1R)-1-deuterio-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-2-methyl-propane-2-sulfinamide (330 mg, 48.42% yield, 74.08% purity, 98.06% ee) as yellow oil. ^1H NMR (400 MHz, DMSO-d_6) δ 7.89 (br t, $J = 7.2$ Hz, 1H), 7.70-7.62 (m, 1H), 7.42 (t, $J = 8.0$ Hz, 1H), 5.91 (s, 1H), 1.42 (s, 3H), 1.10 (s, 9H). MS (ESI) $m/z = 312.9[\text{M}+\text{H}]^+$.

Step 3: Synthesis of (1R)-1-deuterio-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethanamine

To a solution of (R)-N-[(1R)-1-deuterio-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-2-methyl-propane-2-sulfinamide (330 mg, 1.06 mmol) in dioxane (4 mL) was added 4N

HCl/dioxane (4 mL) 0 °C, and then the mixture was stirred at 0 °C for 1h. The mixture was concentrated under reduced pressure to give **Intermediate A-18** (200 mg, 90.93% yield, 90% purity) as a yellow solid. ¹H NMR (400MHz, DMSO-d₆) δ 8.80 (br s, 3H), 8.09 (t, *J* = 7.2 Hz, 1H), 7.82 (t, *J* = 7.2 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 1H), 1.56 (s, 3H); MS (ESI) *m/z* = 209.1 [M+H]⁺.

Preparation Example 19: (1R)-2,2,2-trideuterio-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethanamine (A-19)



Step 1: Synthesis of (NE, S)-N-[[2-fluoro-3-(trifluoromethyl)phenyl]methylene]-2-methyl-propane-2-sulfinamide

To a solution of 2-fluoro-3-(trifluoromethyl)benzaldehyde (5 g, 26.03 mmol, 3.59 mL) in THF (60 mL) was added (S)-2-methylpropane-2-sulfinamide (4.73 g, 39.04 mmol) and Ti(OEt)₄ (17.81 g, 78.08 mmol, 16.19 mL), and then the mixture was degassed and purged with N₂ for 3 times. Thereafter, the mixture was stirred at 80 °C for 3 h under N₂ atmosphere. The mixture was poured into water (40 mL), and the reaction mixture was filtered and extracted with EtOAc (100 mL X 3). The organic layers were washed with brine (40 mL X 3), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (5% EtOAc in petroleum ether) to give (NE, S)-N-[[2-fluoro-3-(trifluoromethyl)phenyl]methylene]-2-methyl-propane-2-sulfinamide (7.3 g, 93.75% yield, 98.7% purity) as a white solid. MS (ESI) *m/z* = 295.9 [M+H]⁺.

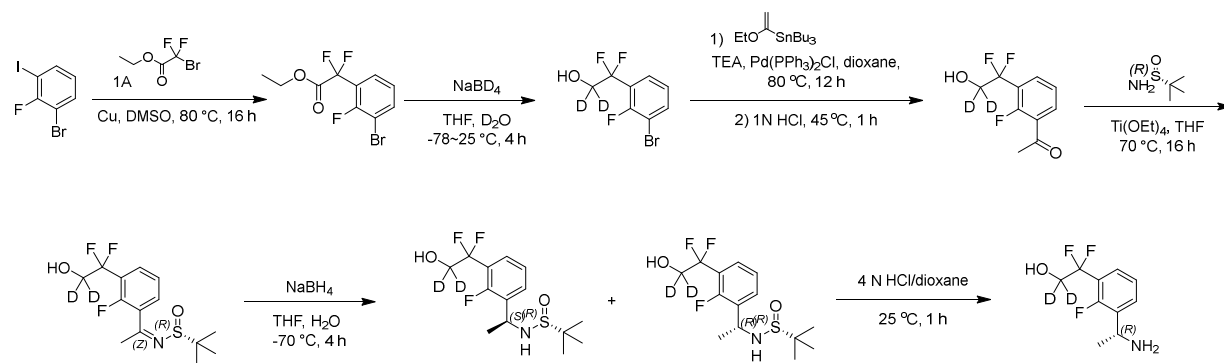
Step 2: Synthesis of (S)-2-methyl-N-[(1R)-2,2,2-trideuterio-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]propane-2-sulfinamide

To a solution of (NE, S)-N-[[2-fluoro-3-(trifluoromethyl)phenyl]methylene]-2-methyl-propane-2-sulfinamide (1.00 g, 3.39 mmol) in THF (15 mL) was slowly added dropwise iodo(trideuteriomethyl)magnesium (1 M, 5.08 mL) at -40 °C. Thereafter, the mixture was stirred at -40 °C for 6 h, and then it was warmed to 23 °C and stirred for 12 h. The mixture was quenched with sat. aq. NH₄Cl (20 mL) added dropwise slowly at 0 °C, and extracted with EtOAc (30 mL X 3). The organic layers were washed with brine (10 mL X 3), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (9% EtOAc in petroleum ether) to give (S)-2-methyl-N-[(1R)-2,2,2-trideuterio-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]propane-2-sulfinamide (65 mg, 3.69% yield, 60.5% purity, ee = 98.26%) as yellow oil. MS (ESI) *m/z* = 314.9 [M+H]⁺.

Step 3: Synthesis of (1R)-2,2,2-trideuterio-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethanamine

To a solution of (S)-2-methyl-N-[(1R)-2,2,2-trideuterio-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]propane-2-sulfonamide (65 mg, 206.77 μmol) in dioxane (1 mL) was added HCl/dioxane (4 M, 1 mL) at 0 °C, and then the mixture was degassed and purged with N₂ for 3 times. Thereafter, the mixture was stirred at 25 °C for 1 h under N₂ atmosphere. The mixture was concentrated under reduced pressure to give **Intermediate A-19** (50 mg, 78.43% yield, 80% purity, hydrochloride) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ 8.50 (br s, 3H), 7.97 (t, J = 7.2 Hz, 1H), 7.84 (t, J = 7.2 Hz, 1H), 7.54 (t, J = 8.0 Hz, 1H), 4.71 (br d, J = 5.2 Hz, 1H); MS (ESI) m/z = 314.3 [M+H]⁺.

Preparation Example 20: 2-[3-[(1R)-1-aminoethyl]-2-fluoro-phenyl]-1,1-dideuterio-2,2-difluoro-ethanol (A-20)



A-20

Step 1: Synthesis of ethyl 2-(3-bromo-2-fluoro-phenyl)-2,2-difluoroacetate

To a solution of ethyl 2-bromo-2,2-difluoroacetate (14.17 g, 69.79 mmol, 8.99 mL, 3 eq) in DMSO (200 mL) was added copper (4.43 g, 69.79 mmol, 494.98 μL , 3 eq) and 1-bromo-2-fluoro-3-iodo-benzene (7 g, 23.26 mmol, 1 eq). The reaction mixture was stirred at 85 °C for 16 h under N₂ atmosphere. TLC (PE:EA = 1:0) indicated that the reactants were completely consumed and one major spot was formed. The reaction mixture was filtered, and then the filtrate was added with water (80 mL) and extracted with EtOAc (80 mL X 3). The organic layers were washed with brine (60 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (0~10% ethyl acetate/Petroleum ether) to give ethyl 2-(3-bromo-2-fluoro-phenyl)-2,2-difluoroacetate (5.68 g, 78.08% yield, 95% purity) as colorless oil. ¹H NMR (400 MHz, DMSO-d₆) δ 7.99 (t, J = 7.2 Hz, 1H), 7.75 - 7.70 (m, 1H), 7.37 (t, J = 8.0 Hz, 1H), 4.36 (q, J = 7.2 Hz, 2H), 1.23 (t, J = 7.2 Hz, 3H).

Step 2: Synthesis of 2-(3-bromo-2-fluoro-phenyl)-1,1-dideuterio-2,2-difluoro-ethanol

To a solution of ethyl 2-(3-bromo-2-fluoro-phenyl)-2,2-difluoroacetate (3 g, 10.10 mmol) in THF (40 mL)/D₂O (0.8 mL) was added NaBD₄ (496.68 mg, 13.13 mmol) at -78 °C, and then the reaction mixture was stirred at 25 °C for 4 h under N₂ atmosphere. The mixture

was quenched with sat. aq. NH_4Cl (50 mL) added dropwise slowly at 20 °C, and extracted with EtOAc (40 mL X 3) after the addition of water (30 mL). The organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (0~11% EtOAc/PE) to give 2-(3-bromo-2-fluoro-phenyl)-1,1-dideuterio-2,2-difluoro-ethanol (2.27 g, 87.45% yield) as light gray oil. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.95 - 7.85 (m, 1H), 7.64 - 7.50 (m, 1H), 7.29 (t, J = 8.0 Hz, 1H), 5.70 (s, 1H).

Step 3: Synthesis of 1-[3-(2,2-dideuterio-1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethanone

A mixture of tributyl(1-ethoxyvinyl)stannane (4.33 g, 11.99 mmol, 4.05 mL), TEA (1.63 g, 16.11 mmol, 2.24 mL) and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (565.24 mg, 805.31 μmol) was mixed with a solution of 2-(3-bromo-2-fluoro-phenyl)-1,1-dideuterio-2,2-difluoro-ethanol (2.07 g, 8.05 mmol) in dioxane (40 mL), degassed and purged with N_2 for 3 times, and then stirred at 80 °C for 16 h under N_2 atmosphere. The mixture was added with Aq. HCl (80 mL, 1 M) under stirring at 25 °C, and then stirred at 25 °C for 1 h. Following the addition of water (40 mL), the reaction mixture was extracted with EtOAc (20 mL X 3). The combined organic layers were washed with brine (40 mL X 3), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue. Sat. aq. KF (60 mL) was slowly added, and then the mixture was stirred at 25 °C for 1 h. The residue was purified by silica gel column chromatography (0~14% EtOAc/PE) to give 1-[3-(2,2-dideuterio-1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethanone (1.6 g, 90.23% yield) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.99 - 7.90 (m, 1H), 7.83 - 7.73 (m, 1H), 7.43 (t, J = 7.6 Hz, 1H), 5.70 (s, 1H), 4.04 (s, 1H), 2.60 (d, J = 4.4 Hz, 3H); MS (ESI) m/z = 221.1 $[\text{M}+\text{H}]^+$.

Step 4: Synthesis of (NZ,R)-N-[1-[3-(2,2-dideuterio-1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethylidene]-2-methyl-propane-2-sulfinamide

To a solution of 1-[3-(2,2-dideuterio-1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethanone (230 mg, 1.04 mmol) in THF (5 mL) was added (R)-2-methylpropane-2-sulfinamide (189.91 mg, 1.57 mmol) and $\text{Ti}(\text{OEt})_4$ (714.83 mg, 3.13 mmol, 649.85 μL), and then the mixture was stirred at 70 °C for 16 h under N_2 atmosphere. The mixture was poured into water (20 mL) and extracted with EtOAc (20 mL X 3). The organic layers were washed with brine (20 mL X 2), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (0~20% EtOAc/PE) to give (NZ,R)-N-[1-[3-(2,2-dideuterio-1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethylidene]-2-methyl-propane-2-sulfinamide (250 mg, 72.31% yield, 97.7% purity) as yellow oil. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.79 (br t, J = 6.8 Hz, 1H), 7.68 (br t, J = 6.8 Hz, 1H), 7.41 (br t, J = 7.6 Hz, 1H), 5.70 (s, 1H), 2.69 (br d, J = 1.6 Hz, 3H), 1.22 (s, 9H); MS (ESI) m/z = 324.0 $[\text{M}+\text{H}]^+$.

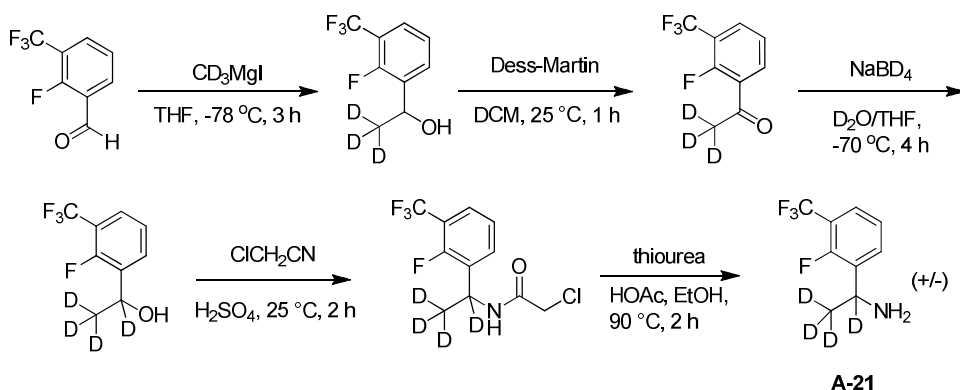
Step 5: Synthesis of (R)-N-[(1R)-1-[3-(2,2-dideuterio-1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethyl]-2-methyl-propane-2-sulfinamide

To a solution of (NZ,R)-N-[1-[3-(2,2-dideuterio-1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethylidene]-2-methyl-propane-2-sulfinamide (250 mg, 773.11 μmol) in THF (5 mL) and H₂O (0.1 mL) was added NaBH₄ (29.25 mg, 773.11 μmol) at -70 °C, and then the mixture was stirred at -70 °C for 4 h under N₂ atmosphere. The mixture was quenched with sat. aq. NH₄Cl (20 mL) at 20 °C, added with water (20 mL) and then extracted with EtOAc (20 mL X 3). The organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (0~45% EtOAc/PE) and prep-HPLC (column: Welch Xtimate C18 40*200mm 7 μm ; mobile phase: [water (NH₃H₂O + NH₄HCO₃)-ACN]; gradient:16%-56% B over 25 min). The solvent was concentrated under reduced pressure, and then the residue was lyophilized to give (R)-N-[(1S)-1-[3-(2,2-dideuterio-1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethyl]-2-methyl-propane-2-sulfinamide (30 mg, 11.93% yield, 100% purity, ee = 100 %) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 7.63 (br t, *J* = 7.2 Hz, 1H), 7.43 (t, *J* = 7.2 Hz, 1H), 7.38 - 7.22 (m, 1H), 6.04 (br d, *J* = 1.6 Hz, 1H), 5.53 (d, *J* = 5.6 Hz, 1H), 4.71 (br t, *J* = 6.4 Hz, 1H), 2.54 (s, 1H), 1.48 (d, *J* = 6.8 Hz, 3H), 1.09 (s, 9H); LC/MS (ESI) *m/z* = 326.2 [M+H]⁺. Additionally, the desired product (R)-N-[(1R)-1-[3-(2,2-dideuterio-1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethyl]-2-methyl-propane-2-sulfinamide (90 mg, 276.59 μmol , 35.78% yield, 100% purity, ee = 99.96 %) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 7.70 (t, *J* = 7.2Hz, 1H), 7.47 - 7.40 (m, 1H), 7.34 - 7.26 (m, 1H), 5.86 (d, *J* = 7.6 Hz, 1H), 4.68 (t, *J* = 7.2 Hz, 1H), 1.40 (d, *J* = 6.8 Hz, 3H), 1.10 (s, 9H); MS (ESI) *m/z* = 326.2 [M+H]⁺.

Step 6: Synthesis of 2-[3-[(1R)-1-aminoethyl]-2-fluoro-phenyl]-1,1-dideuterio-2,2-difluoro-ethanol

HCl/dioxane (4 mL) was added to (R)-N-[(1R)-1-[3-(2,2-dideuterio-1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethyl]-2-methyl-propane-2-sulfinamide (90 mg, 276.59 μmol) in dioxane (1 mL). Thereafter, the mixture was stirred at 25 °C for 2 h. LCMS confirmed the complete consumption of starting materials and the formation of the desired compound. The mixture was concentrated under reduced pressure to give **Intermediate A-20** (60 mg, 94.14% yield, 96% purity) as light gray oil. ¹H NMR (400 MHz, DMSO-d₆) δ 8.66 (br s, 2H), 7.84 (t, *J* = 7.2 Hz, 1H), 7.58 (t, *J* = 6.8 Hz, 1H), 7.46 - 7.34 (m, 1H), 4.75 - 4.56 (m, 1H), 1.54 (d, *J* = 6.4 Hz, 3H).

Preparation Example 21: (+/-)-1,2,2,2-tetradeuterio-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethanamine (A-21)



Step 1: Synthesis of 2,2,2-trideuterio-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethanol

To a solution of (2-fluoro-3-(trifluoromethyl)benzaldehyde (1 g, 5.21 mmol, 717.88 μ L) in THF (20 mL) was slowly added dropwise iodo(trideuteriomethyl)magnesium (1 M, 10.41 mL) at -78 °C under N₂ atmosphere, and then the mixture was stirred at -78 °C for 3 h. The mixture was quenched by slowly adding sat. aq. NH₄Cl (20 mL) dropwise and extracted with EtOAc (30 mL X 3). The organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (2% EtOAc in petroleum ether) to give 2,2,2-trideuterio-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethanol (900 mg, 81.88% yield, 95% purity) as yellow oil. ¹H NMR (400 MHz, DMSO-d₆) δ 7.85 (t, *J* = 7.2 Hz, 1H), 7.64 (t, *J* = 6.8 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 5.49 (d, *J* = 4.4 Hz, 1H), 5.03 (br d, *J* = 4.4 Hz, 1H).

Step 2: Synthesis of 2,2,2-trideuterio-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethanone

To a solution of 2,2,2-trideuterio-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethanol (900 mg, 4.26 mmol) in DCM (10 mL) was added (1,1-diacetoxy-3-oxo-1,2-benziodoxol-1-yl)acetate (2.17 g, 5.11 mmol, 1.58 mL) at 0 °C. Thereafter, the mixture was warmed to 25 °C and stirred at 25 °C for 1 h. The mixture was added with sat. aq. Na₂CO₃ (20 mL) and extracted with DCM (20 mL X 3). The organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (1% EtOAc in petroleum ether) to give 2,2,2-trideuterio-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethanone (630 mg, 70.67% yield, 90% purity) as white oil. ¹H NMR (400 MHz, DMSO-d₆) δ 8.13-8.05 (m, 1H), 7.85-7.77 (m, 1H), 7.35 (t, *J* = 8.0 Hz, 1H).

Step 3: Synthesis of 1,2,2,2-tetradeuterio-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethanol

To a solution of 2,2,2-trideuterio-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethanone (530 mg, 2.53 mmol) in THF (8 mL) and D₂O (0.16 mL) was added NaBD₄ (95.87 mg, 2.53 mmol) at -70 °C under N₂ atmosphere, and then the mixture was stirred at -70 °C for 4 h under N₂ atmosphere. The mixture was quenched with sat. aq. NH₄Cl (10 mL) and extracted with EtOAc (10 mL X 3). The organic layers were washed with brine (20 mL), dried over anhydrous

Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (5% EtOAc in petroleum ether) to give 1, 2, 2, 2-tetradeuterio-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethanol (430 mg, 79.98% yield, 95% purity) as white oil. ¹H NMR (400 MHz, DMSO-d₆) δ 7.85 (t, *J* = 7.2 Hz, 1H), 7.64 (t, *J* = 7.2 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 5.48 (s, 1H).

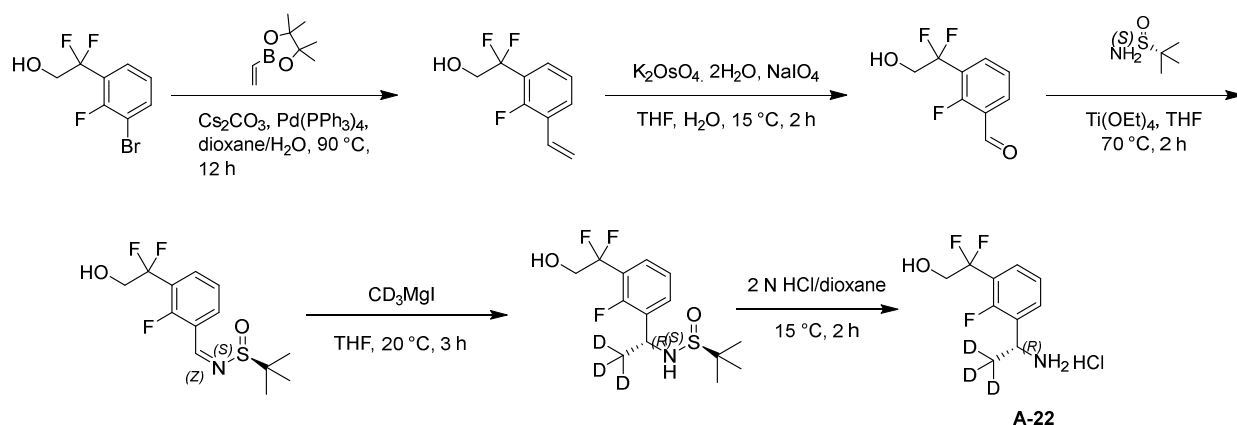
Step 4: Synthesis of 2-chloro-N-[1,2,2,2-tetradeuterio-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]acetamide

To a solution of 1,2,2,2-tetradeuterio-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethanol (400 mg, 1.89 mmol) in 2-chloroacetonitrile (2.92 g, 38.65 mmol, 2.45 mL) was slowly added sulfuric acid (2.22 g, 22.62 mmol, 1.21 mL) at 0 °C. Thereafter, the mixture was stirred at 25 °C for 2 h under N₂ atmosphere. The mixture was quenched with cold water (10 mL), adjusted to pH = 10-13 with sat. aq. NaOH, and then extracted with DCM (10 mL X 3). The organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (8% EtOAc in petroleum ether) to give 2-chloro-N-[1,2,2,2-tetradeuterio-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]acetamide (510 mg, 71.05% yield, 75.55% purity) as yellow oil. ¹H NMR (400 MHz, DMSO-d₆) δ 8.86 (s, 1H), 7.69 (td, *J* = 7.6, 15.2 Hz, 2H), 7.41 (t, *J* = 8.0 Hz, 1H), 4.09 (s, 2H); MS (ESI) *m/z* = 287.9 [M+H]⁺.

Step 5: Synthesis of (+/-)-1,2,2,2-tetradeuterio-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethanamine

To a solution of 2-chloro-N-[1,2,2,2-tetradeuterio-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]acetamide (250 mg, 869.04 μmol) in acetic acid (0.6 mL) was added thiourea (72.77 mg, 955.94 μmol) and ethanol (3 mL), and then the mixture was stirred at 90 °C for 2 h. The mixture was diluted with water (5 mL), adjusted to pH = 9-10 with sat. aq. NaOH, and then extracted with EtOAc (5 mL X 3). The organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (58% EtOAc in petroleum ether) to give **Intermediate A-21** (180 mg, 73.38% yield, 74.82% purity) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ 8.81 (br s, 1H), 8.05 (br t, *J* = 7.2 Hz, 1H), 7.76 (br t, *J* = 7.2 Hz, 1H), 7.48 (t, *J* = 8.0 Hz, 1H); MS (ESI) *m/z* = 212.0 [M+H]⁺.

Preparation Example 22: 2-[3-[(1R)-1-amino-2,2,2-trideuterio-ethyl]-2-fluoro-phenyl]-2,2-difluoro-ethanol (A-22)



Step 1: Synthesis of 2,2-difluoro-2-(2-fluoro-3-vinyl-phenyl)ethanol

To a solution of 2-(3-bromo-2-fluoro-phenyl)-2,2-difluoro-ethanol (3 g, 11.76 mmol) in dioxane (40 mL) and H₂O (5 mL) was added 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolan (4.53 g, 29.41 mmol), Cs₂CO₃ (15.33 g, 47.05 mmol) and Pd(PPh₃)₄ (2.04 g, 1.76 mmol). The mixture was degassed and substituted with nitrogen for 3 times, and then it was stirred at 90 °C for 3 h under nitrogen atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (4% EtOAc in petroleum ether) to give 2,2-difluoro-2-(2-fluoro-3-vinyl-phenyl)ethanol (1.44 g, 57.52% yield, 95% purity) as yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.81 (t, *J* = 7.2 Hz, 1H), 7.47 (t, *J* = 6.8 Hz, 1H), 7.33-7.27 (m, 1H), 6.88 (dd, *J* = 11.2, 17.6 Hz, 1H), 5.98 (d, *J* = 18.0 Hz, 1H), 5.69 (t, *J* = 6.4 Hz, 1H), 5.50 (d, *J* = 11.2 Hz, 1H), 3.97-3.87 (m, 2H).

Step 2: Synthesis of 3-(1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-benzaldehyde

To a solution of 2,2-difluoro-2-(2-fluoro-3-vinyl-phenyl)ethanol (1.44 g, 7.12 mmol) in THF (16 mL) and H₂O (4 mL) was added dipotassium;dioxido(dioxo)osmium;dihydrate (262.44 mg, 712.26 μmol) and NaIO₄ (5.94 g, 27.78 mmol) at 0 °C. Thereafter, the reaction mixture was degassed, substituted with nitrogen 3 times, and then stirred at 15 °C for 2 h under nitrogen atmosphere. The reaction mixture was filtered, and the filtrate was poured into H₂O (4 mL) and extracted with DCM (20 mL × 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (7% EtOAc in petroleum ether) to give 3-(1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-benzaldehyde (990 mg, 64.68% yield, 95% purity) as yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.26 (s, 1H), 8.03-7.95 (m, 1H), 7.88 (dt, *J* = 1.6, 7.6 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 5.83-5.71 (m, 1H), 4.09-3.81 (m, 2H).

Step 3: Synthesis of (NZ,S)-N-[[3-(1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]methylene]-2-methyl-propane-2-sulfonamide

Commercially available (S)-2-methylpropane-2-sulfonamide was used in the same manner as in Step 1 of Preparation Example 19 to give (NZ,S)-N-[[3-(1,1-difluoro-2-hydroxy-

ethyl)-2-fluoro-phenyl]methylene]-2-methyl-propane-2-sulfinamide (850 mg, 93.01% yield, 97.19% purity) as yellow oil. MS (ESI) m/z = 308.0 $[M+H]^+$.

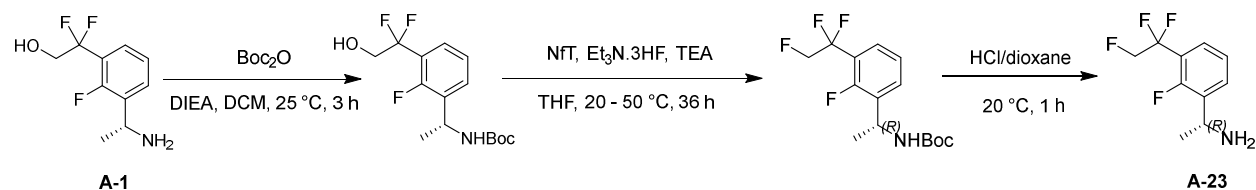
Step 4: Synthesis of (S)-2-methyl-N-[(1R)-2,2,2-trideuterio-1-[3-(1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethyl]propane-2-sulfinamide

Commercially available iodo(trideuteriomethyl)magnesium (1 M in THF) was used in the same manner as in Step 2 of Preparation Example 19 to give (S)-2-methyl-N-[(1R)-2,2,2-trideuterio-1-[3-(1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethyl]propane-2-sulfinamide (250 mg, 30.79% yield, 98.53% purity) as yellow oil. MS (ESI) m/z = 327.0 $[M+H]^+$.

Step 5: Synthesis of 2-[3-[(1R)-1-amino-2,2,2-trideuterio-ethyl]-2-fluoro-phenyl]-2,2-difluoro-ethanol

Intermediate A-22 (160 mg, 64.60% yield, 80% purity, hydrochloride) was obtained in the same manner as in Step 3 of Preparation Example 19 as yellow oil. 1H NMR (400 MHz, DMSO- d_6) δ 8.75 (br s, 3H), 7.87 (t, J = 6.8 Hz, 1H), 7.57 (t, J = 6.8 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 5.99-5.44 (m, 1H), 4.63 (br d, J = 4.0 Hz, 1H), 3.93 (br t, J = 14.4 Hz, 2H); MS (ESI) m/z = 223.1 $[M+H]^+$.

Preparation Example 22-1: (1R)-1-[2-fluoro-3-(1,1,2-trifluoroethyl)phenyl]ethanamine (A-23)



Step 1: Synthesis of tert-butyl N-[(1R)-1-[3-(1,1-difluoro-2-hydroxyethyl)-2-fluorophenyl]ethyl]carbamate

A mixture of **Intermediate A-1** (1 g, 3.91 mmol, HCl), Boc_2O (1.71 g, 7.82 mmol, 1.80 mL) and DIEA (1.01 g, 7.82 mmol, 1.36 mL) in DCM (11 mL) was degassed and purged with nitrogen for 3 times. Thereafter, the mixture was stirred at 25 °C for 3 h under nitrogen atmosphere. The mixture was concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (15% EA in PE) to give tert-butyl N-[(1R)-1-[3-(1,1-difluoro-2-hydroxyethyl)-2-fluorophenyl]ethyl]carbamate (848 mg, 59.75% yield, 88% purity) as colorless oil. 1H NMR (400 MHz, DMSO- d_6) δ 7.60 - 7.50 (m, 2H), 7.44 - 7.39 (m, 1H), 7.30 - 7.26 (m, 1H), 5.70 (t, J = 6.4 Hz, 1H), 4.92 (br t, J = 7.2 Hz, 1H), 3.91 (dt, J = 6.4, 14.4 Hz, 2H), 1.36 (s, 9H), 1.29 (d, J = 7.2 Hz, 3H); MS (ESI) m/z = 264.0 $[M+H-56]^+$.

Step 2: Synthesis of tert-butyl N-[(1R)-1-[2-fluoro-3-(1,1,2-trifluoroethyl)phenyl]ethyl]carbamate

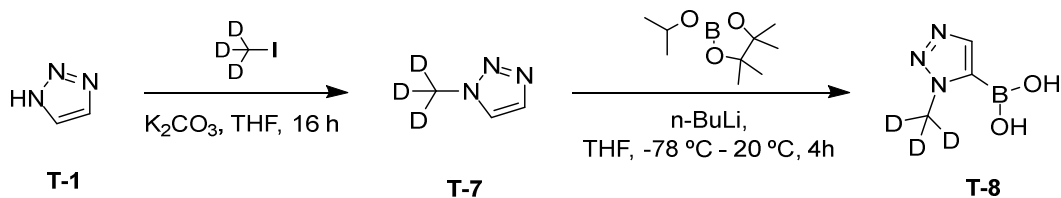
To a solution of tert-butyl N-[(1R)-1-[3-(1,1-difluoro-2-hydroxyethyl)-2-fluorophenyl]ethyl]carbamate (400 mg, 1.25 mmol), *N,N*-diethylethanamine; trihydrofluoride (605.82 mg, 3.76 mmol, 612.56 μ L) and *N,N*-diethylethanamine (760.54 mg, 7.52 mmol, 1.05

mL) in anhydrous THF (10 mL) was slowly added dropwise NfT (1.14 g, 3.76 mmol, 661.57 μ L) at 20 °C. Thereafter, the mixture was stirred at 50 °C for 36 h. The reaction mixture was concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (5% EtOAc in PE) to give tert-butyl *N*-[(1*R*)-1-[2-fluoro-3-(1,1,2-trifluoroethyl)phenyl]ethyl]carbamate (346 mg, 82.84% yield, 96.37% purity) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 7.66 - 7.54 (m, 2H), 7.51 - 7.46 (m, 1H), 7.37 - 7.32 (m, 1H), 5.03 (t, J = 13.8 Hz, 1H), 4.96 - 4.87 (m, 2H), 1.36 (s, 9H), 1.30 (d, J = 7.2 Hz, 3H); MS (ESI) m/z = 266.0 $[\text{M}+\text{H}]^+$.

Step 3: Synthesis of (1*R*)-1-[2-fluoro-3-(1,1,2-trifluoroethyl)phenyl]ethanamine

A mixture of *N*-[(1*R*)-1-[2-fluoro-3-(1,1,2-trifluoroethyl)phenyl]ethyl]carbamate (346 mg, 1.08 mmol) in HCl/dioxane (4*N*, 2 mL) and dioxane (2 mL) was degassed and purged with nitrogen for 3 times. Thereafter, the mixture was stirred at 20 °C for 1 h under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure to give Intermediate **A-23** (248 mg, 78.66% yield, 88% purity, HCl) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.66 (br s, 3H), 7.92 (t, J = 7.2 Hz, 1H), 7.66 (t, J = 6.8 Hz, 1H), 7.53 - 7.43 (m, 1H), 5.11 - 4.89 (m, 2H), 4.68 (q, J = 6.8 Hz, 1H), 1.55 (d, J = 6.8 Hz, 3H); MS (ESI) m/z = 221.9 $[\text{M}+\text{H}]^+$.

Preparation Example 23: 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)triazole (T-8)

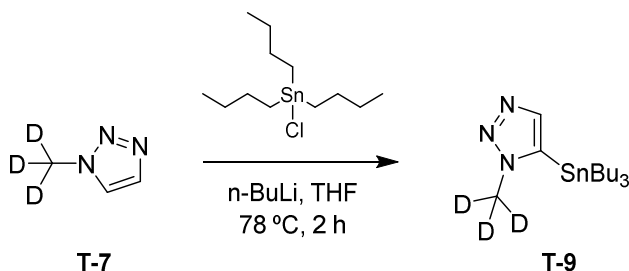


Step 1: Synthesis of 1-(trideuteriomethyl)triazole

To a solution of 1*H*-triazole (1.99 g, 28.74 mmol, 1.67 mL) in THF (25 mL) was added K_2CO_3 (7.95 g, 57.49 mmol) and trideuterio(iodo)methane (5 g, 34.49 mmol, 2.15 mL), and then the mixture was stirred at 25 °C for 12 h. The reaction mixture was poured into water (20 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (30 mL x 2), dried over Na_2SO_4 and concentrated under reduced pressure to give a crude product **Intermediate T-7** (1.18 g, 47.56% yield) as yellow oil. ^1H NMR (400 MHz, DMSO- d_6) δ 8.06 (s, 1H), 7.70 (s, 1H).

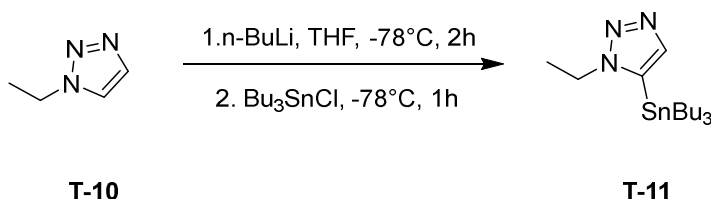
Step 2: Synthesis of [3-(trideuteriomethyl)triazol-4-yl]boronic acid

To a solution of Intermediate **T-7** (600 mg, 6.97 mmol) in THF (10 mL) was slowly added *n*-BuLi (2.5 M, 3.07 mL) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at -20 °C for 1 h and then cooled to -78 °C. To the reaction mixture was slowly added 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.56 g, 8.36 mmol, 1.71 mL) at -78 °C. After 15 min, the reaction mixture was warmed to 0 °C for 1 h. The reaction mixture was



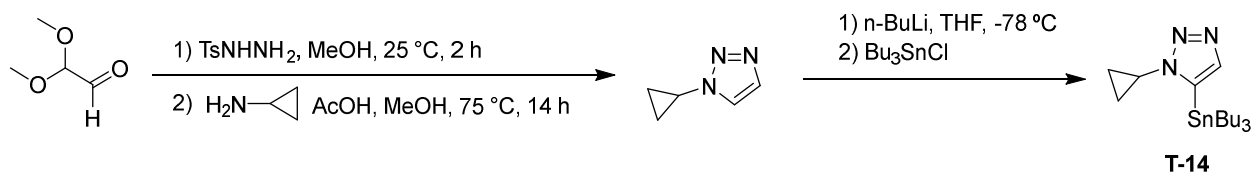
A solution of 1-(trideuteriomethyl)triazole (1 g, 11.61 mmol) in THF (20 mL) was cooled to -78 °C, and then n-BuLi (2.5 M, 5.20 mL) was slowly added, and the reaction mixture was stirred at -78 °C for 1 h. Thereafter, tributyl(chloro)stannane (5.22 g, 16.03 mmol, 4.31 mL) was slowly added, and the reaction mixture was stirred at -78 °C for 1 h under nitrogen atmosphere. The reaction mixture was quenched by slowly adding aq. NH₄Cl (20 mL) dropwise at 0 °C, and extracted with EtOAc (40 mL×3). The combined organic layers were washed with brine (20 mL x 2), dried over Na₂SO₄ and concentrated under reduced pressure to give a crude product **Intermediate T-9** (4 g, 10.66 mmol) as yellow oil. It was used in the next reaction without further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.60 (s, 1H), 1.49 (m, 4H), 1.35 - 1.21 (m, 8H), 1.19 - 1.09 (m, 6H), 0.88 - 0.83 (m, 9H).

Preparation Example 27: tributyl-(3-ethyltriazol-4-yl)stannane (T-11)



A solution of 1-ethyltriazole (500 mg, 5.15 mmol) in THF (10 mL) was cooled to -78 °C, and then n-BuLi (2.5 M, 2.31 mL) was slowly added and the reaction mixture was stirred at -78 °C for 2 h. Thereafter, tributyl(chloro)stannane (2.14 g, 6.57 mmol, 1.77 mL) was slowly added and the reaction mixture was stirred at -78 °C for 1 h under nitrogen atmosphere. The reaction mixture was quenched with aq. ammonium salt (20 mL) added slowly at 0 °C, and extracted with EtOAc (20 mL×3). The combined organic layers were washed with brine (10 mL x 2), dried over Na₂SO₄ and concentrated under reduced pressure to give **Intermediate T-11** (2.4 g, 90.54% yield, 75% purity) as light yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.58 (s, 1H), 4.33 (q, *J* = 7.2 Hz, 2H), 1.37-1.21 (m, 12H), 1.20-1.13 (m, 6H), 0.86 (d, *J* = 8.0 Hz, 12H).

Preparation Example 27-1: tributyl-(3-cyclopropyl-4-yl)stannane (T-14)



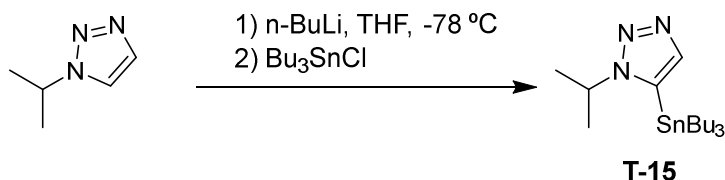
Step 1: Synthesis of 1-cyclopropyltriazole

To a solution of 4-methylbenzenesulfonohydrazide (5 g, 26.85 mmol) in methanol (50 mL) was added 2,2-dimethoxyacetaldehyde (4.89 g, 28.19 mmol, 4.25 mL). The reaction mixture was stirred at 25 °C for 2 h. Thereafter, acetic acid (1.61 g, 26.85 mmol, 1.54 mL) and cyclopropaneamine (1.53 g, 26.85 mmol, 1.86 mL) were added to the reaction mixture, which was then stirred at 75 °C for 14 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (10% EtOAc in petroleum ether) to give 1-cyclopropyltriazole (6 g, 49.15% yield, 90% purity) as yellow oil. ¹H NMR (400 MHz, DMSO-d₆) δ 8.13 (s, 1H), 7.69 (d, *J* = 0.8 Hz, 1H), 4.02 - 3.92 (m, 1H), 1.15 - 1.08 (m, 4H).

Step 2: Synthesis of tributyl-(3-cyclopropyltriazol-4-yl)stannane

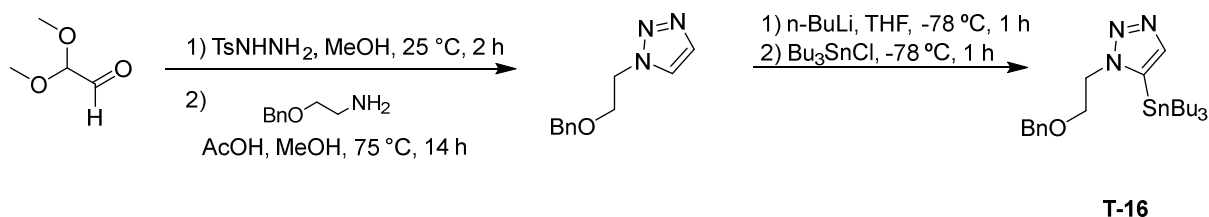
A solution of 1-cyclopropyltriazole (200 mg, 1.83 mmol) in THF (4 mL) was cooled to -78 °C, and then *n*-BuLi (2.5 M, 1.10 mL) was slowly added and the reaction mixture was stirred at -78 °C for 2 h. Thereafter, tributyl(chloro)stannane (1.14 g, 3.50 mmol, 942.15 μL) was slowly added to the reaction mixture, which was then stirred at -78 °C for 1 h under nitrogen atmosphere. The reaction mixture was quenched with aq. ammonium salt (10 mL) added slowly at 0 °C, and extracted with EtOAc (15 mL×3). The combined organic layers were washed with brine (10 mL x 2), dried over Na₂SO₄ and concentrated under reduced pressure to give **Intermediate T-14** (1 g, 95.93% yield, 70% purity) as white oil. ¹H NMR (400 MHz, DMSO-d₆) δ 7.59 (s, 1H), 3.71 (tt, *J* = 3.6, 7.2 Hz, 1H), 1.53 - 1.46 (m, 6H), 1.29 - 1.27 (m, 6H), 1.10 - 1.05 (m, 10H), 0.87 (s, 9H).

Preparation Example 27-2: tributyl-(3-isopropyltriazol-4-yl)stannane (T-15)



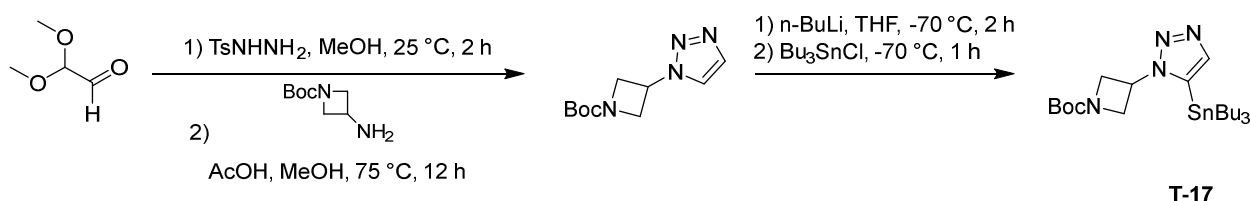
Commercially available 2,2-dimethoxyacetaldehyde and benzyloxyethanamine were used in the same manner as in Step 2 of Preparation Example 27-1 to give **Intermediate T-15** (1 g, 97.21% yield, 70% purity) as white oil. ¹H NMR (400 MHz, DMSO-d₆) δ 7.55 (s, 1H), 4.52 (td, *J* = 6.8, 13.2 Hz, 1H), 1.48 (s, 12H), 1.29 (br d, *J* = 7.6 Hz, 6H), 1.14 - 1.09 (m, 6H), 0.86 (d, *J* = 7.6 Hz, 9H).

Preparation Example 27-3: [3-(2-benzyloxyethyl)triazol-4-yl]-tributyl-stannane (T-16)



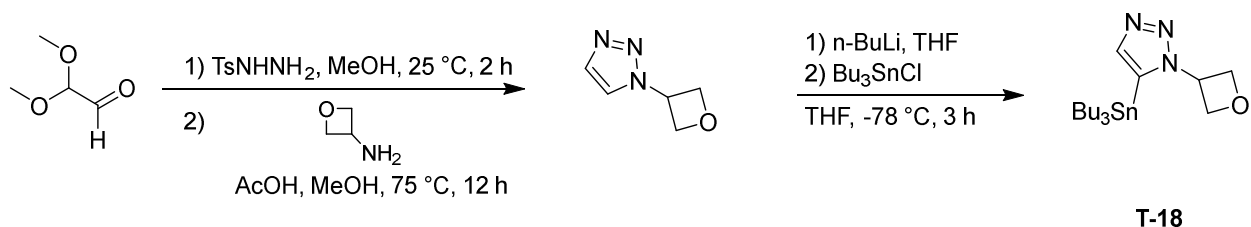
Commercially available 2,2-dimethoxyacetaldehyde and benzyloxyethanamine were used in the same manner as in Preparation Example 27-1 to give **Intermediate T-16** (720 mg, crude product) as yellow oil. It was used in the next reaction without further purification. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.82 (s, 1H), 7.40 - 7.37 (m, 3H), 7.33 (br d, $J = 6.0$ Hz, 2H), 4.71 (t, $J = 5.2$ Hz, 2H), 4.58 (s, 2H), 3.94 (t, $J = 5.2$ Hz, 2H), 1.59 - 1.55 (m, 6H), 1.37 (m, 6H), 1.19 (m, 6H), 0.96 - 0.95 (m, 6H).

Preparation Example 27-4: tert-butyl 3-(5-(tributylstanyl)-1H-1,2,3-triazol-1-yl)azetidine-1-carboxylate (T-17)



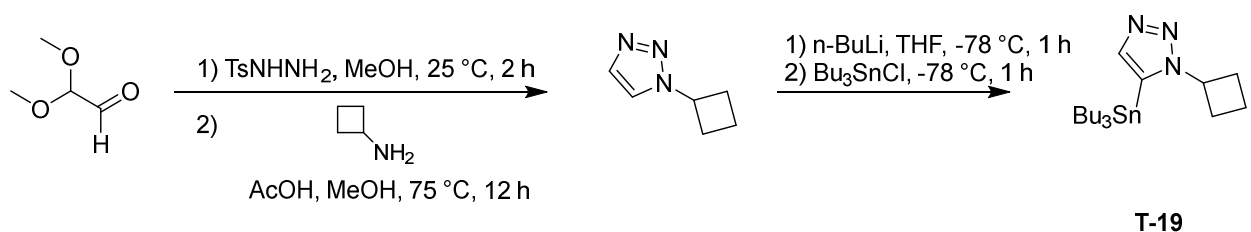
Commercially available 2,2-dimethoxyacetaldehyde and tert-butyl 3-aminoazetidine-1-carboxylate were used in the same manner as in Preparation Example 27-1 to give **Intermediate T-17** (720 mg, crude product) as yellow oil. It was used in the next reaction without further purification. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.36 (d, $J = 1.2$ Hz, 1H), 7.80 (d, $J = 0.8$ Hz, 1H), 5.50 (tt, $J = 5.2, 8.0$ Hz, 1H), 4.39 (br t, $J = 8.6$ Hz, 2H), 4.17 (br s, 2H), 1.41 (s, 9H).

Preparation Example 27-5: 1-(oxetan-3-yl)-5-(tributylstanyl)-1H-1,2,3-triazole (T-18)



Commercially available 2,2-dimethoxyacetaldehyde and 3-aminooxetane were used in the same manner as in Preparation Example 27-1 to give **Intermediate T-18** (600 mg, 1.45 mmol, 90.64% yield) as yellow oil. It was used in the next reaction without further purification. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.67 (s, 1H), 5.64 - 5.53 (m, 1H), 5.00 (d, $J = 6.8$ Hz, 4H), 1.48 - 1.42 (m, 6H), 1.28 (br d, $J = 7.6$ Hz, 6H), 1.17 - 1.11 (m, 6H), 0.87 - 0.84 (m, 9H).

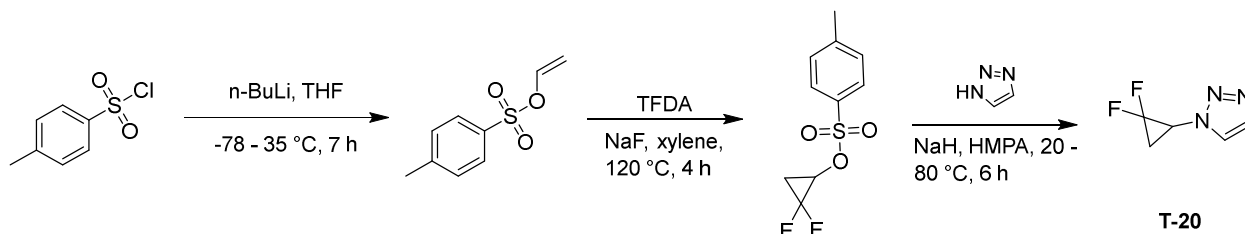
Preparation Example 27-6: tributyl-(3-cyclobutyltriazol-4-yl)stannane (T-19)



Commercially available 2,2-dimethoxyacetaldehyde and cyclobutaneamine were used

in the same manner as in Preparation Example 27-1 to give **Intermediate T-19** (1.06 g, 79.18% yield) as yellow oil. It was used in the next reaction without further purification. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.58 (s, 1H), 4.81 (quin, $J = 8.2$ Hz, 1H), 2.74 - 2.58 (m, 2H), 2.47 - 2.40 (m, 2H), 1.91 (td, $J = 4.8, 10.0$ Hz, 2H), 1.50 - 1.42 (m, 7H), 1.30 - 1.26 (m, 6H), 1.18 - 1.13 (m, 6H), 0.87 - 0.84 (m, 9H).

Preparation Example 27-7: 1-(2,2-difluorocyclopropyl)triazole (T-20)



Step 1: Synthesis of vinyl 4-methylbenzenesulfonate

$n\text{-BuLi}$ (2.5 M in hexane, 18.46 mL) was added under nitrogen atmosphere in anhydrous THF (70 mL) and the mixture was stirred at 35 °C for 4 h. After being cooled to -78 °C, a solution of 4-methylbenzenesulfonyl chloride (8 g, 41.96 mmol) in anhydrous THF (20 mL) was added dropwise for 0.5 h. The resulting mixture was stirred at -78 °C for 1 h, heated to 25 °C, and then stirred for 1 h. The reaction mixture was poured into H_2O (50 mL) and extracted with EtOAc (50 mL $\times$ 3). The combined organic layers were washed with brine (50 mL $\times$ 2), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (5% EtOAc in petroleum ether) to give vinyl 4-methylbenzenesulfonate (4.3 g, 51.69% yield) as transparent oil. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.82 (d, $J = 8.4$ Hz, 2H), 7.51 (d, $J = 8.0$ Hz, 2H), 6.73 (dd, $J = 5.6, 13.2$ Hz, 1H), 4.94 (dd, $J = 2.4, 13.2$ Hz, 1H), 4.82 (dd, $J = 2.4, 5.6$ Hz, 1H), 2.43 (s, 3H).

Step 2: Synthesis of (2,2-difluorocyclopropyl)4-methylbenzenesulfonate

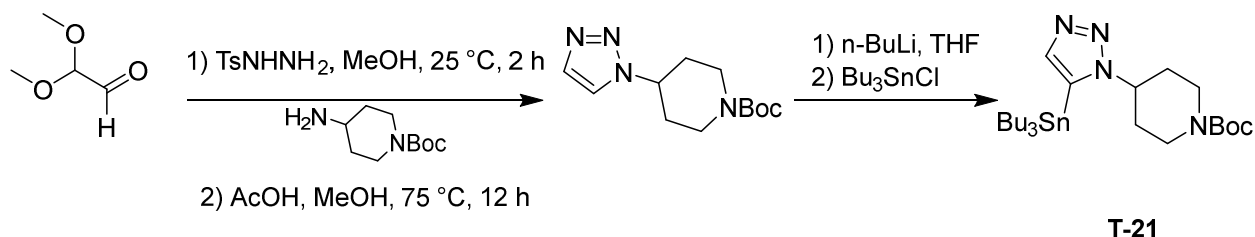
To a mixture of vinyl 4-methylbenzenesulfonate (3.5 g, 7.66 mmol) and NaF (74.13 μL , 1.77 mmol) in *o*-xylene (2 mL) was added trimethylsilyl-2,2-difluoro-2-fluorosulfonylacetate (3.5 g, 17.66 mmol) dropwise at 120 °C for 2 h. The mixture was stirred at 120 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (5% EtOAc in petroleum ether) to give (2,2-difluorocyclopropyl)4-methylbenzenesulfonate (3.77 g, 82.49% yield, 95.9% purity) as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.85 (d, $J = 8.4$ Hz, 2H), 7.53 (d, $J = 8.0$ Hz, 2H), 4.63 (ddt, $J = 2.4, 4.8, 9.2$ Hz, 1H), 2.44 (s, 3H), 2.11 - 1.93 (m, 1H), 1.83 (tdd, $J = 5.2, 10.4, 16.8$ Hz, 1H).

Step 3: Synthesis of 1-(2,2-difluorocyclopropyl)triazole

To a solution of 1H-triazole (1.63 mL, 28.20 mmol) in DMF (40 mL) was added NaH (1.13 g, 28.20 mmol, 60% purity) under nitrogen atmosphere for 3 times. The reaction mixture was stirred at 20 °C for 1 h under nitrogen atmosphere. Afterward, (2,2-difluorocyclopropyl)4-

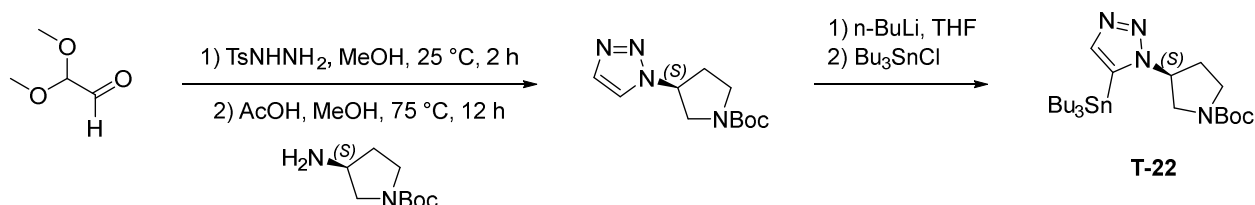
methylbenzenesulfonate (3.5 g, 14.10 mmol) in DMF (10 mL) was added dropwise for 15 min, and the mixture was stirred at 80 °C for 5 h under nitrogen conditions. The mixture was quenched with H₂O (30 mL) at 20 °C, and then extracted with EtOAc (50 mL × 4). The combined organic layers were washed with brine (20 mL × 3), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (50% DCM in PE) to give **Intermediate T-20** (400 mg, 16.8% yield, 86.02% purity) as yellow oil. MS (ESI) *m/z* = 146.1 [M+H]⁺.

Preparation Example 27-8: tert-butyl 4-(5-tributylstanyl-1H-1,2,3-triazol-1-yl)piperidine-1-carboxylate (T-21)



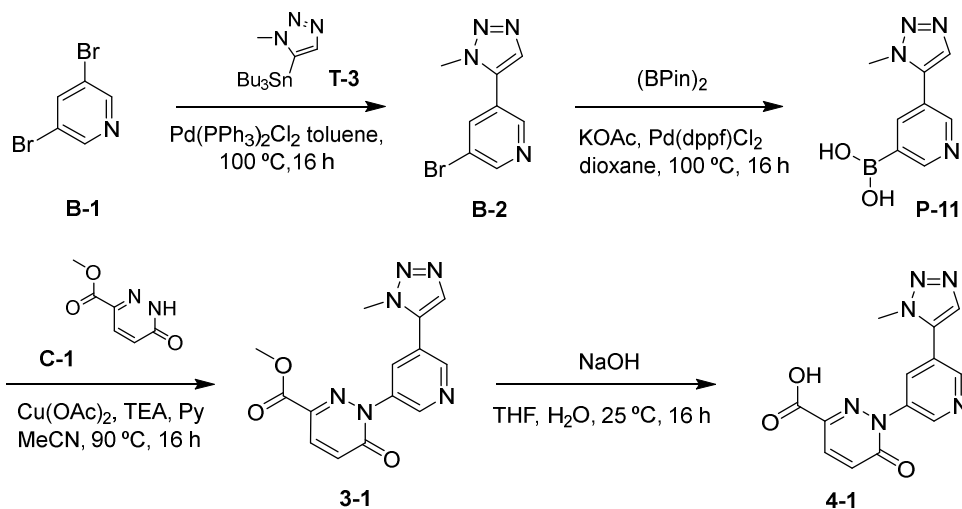
Commercially available 2,2-dimethoxyacetaldehyde and 4-methylbenzenesulfonohydrazide were used in the same manner as in Preparation Example 27-1 to give **Intermediate T-21** (3 g, 95.08% yield, 85% purity) as yellow oil. It was used in the next reaction without further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.58 (s, 1H), 4.34 (br t, *J* = 10.8 Hz, 1H), 4.14 - 4.04 (m, 2H), 2.94 (br s, 2H), 1.98 (s, 2H), 1.94 - 1.87 (m, 2H), 1.53 - 1.45 (m, 6H), 1.42 (s, 9H), 1.31 - 1.26 (m, 6H), 1.20 - 1.15 (m, 6H), 0.87 - 0.83 (m, 9H).

Preparation Example 27-9: tert-butyl (S)-3-(5-(tributylstanyl)-1H-1,2,3-triazol-1-yl)pyrrolidine-1-carboxylate (T-22)



Commercially available 2,2-dimethoxyacetaldehyde and tert-butyl (3S)-3-aminopyrrolidine-1-carboxylate were used in the same manner as in Preparation Example 27-1 to give **Intermediate T-22** (890 mg, 12.35% yield, 71% purity) as yellow oil. It was used in the next reaction without further purification. ¹H NMR (400 MHz, CDCl₃) δ 7.73 (s, 1H), 7.59 (s, 1H), 5.21 (br s, 1H), 3.91 (dd, *J* = 6.4, 12.0 Hz, 1H), 3.82 - 3.72 (m, 1H), 3.59 (br s, 2H), 2.53 - 2.40 (m, 2H), 1.46 (s, 9H); MS (ESI) *m/z* = 239.1 [M+H]⁺.

Preparation Example 28: 1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylic acid (4-1)



Step 1: Synthesis of 3-bromo-5-(3-methyltriazol-4-yl)pyridine

A solution of 3,5-dibromopyridine (10.92 g, 46.10 mmol), tributyl-(3-methyltriazol-4-yl)stannane (22.3 g, 59.92 mmol) and Pd(PPh₃)₂Cl₂ (3.24 g, 4.61 mmol) in toluene (200 mL) were substituted with nitrogen for 3 times, and then the mixture was stirred at 90 °C for 16 h under nitrogen atmosphere. The reaction mixture was poured into water (150 mL) and extracted with EtOAc (200 mL x 3). The combined organic layers were washed with brine (200 mL x 3), dried over Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (80% EA in petroleum ether) to give 3-bromo-5-(3-methyltriazol-4-yl)pyridine (4.4 g, 39.93% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.83-8.83 (m, 1H), 8.40 (t, *J* = 2.0 Hz, 1H), 8.09 (s, 1H), 7.66-7.49 (m, 1H), 4.13 (s, 3H); MS (ESI) *m/z* = 153.0 [M+H]⁺.

Step 2: Synthesis of [5-(3-methyltriazol-4-yl)-3-pyridyl]boronic acid

A solution of 3-bromo-5-(3-methyltriazol-4-yl)pyridine (6.76 g, 28.28 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxoborolan-2-yl)-1,3,2-dioxoborolan (14.36 g, 56.55 mmol), Pd(dppf)Cl₂ (2.31 g, 2.83 mmol) and KOAc (5.55 g, 56.55 mmol) in dioxane (120 mL) was substituted with nitrogen for 3 times, and then the mixture was stirred at 100 °C for 16 h under nitrogen atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (3% MeOH in DCM) to give [5-(3-methyltriazol-4-yl)-3-pyridyl]boronic acid (**Intermediate P-11**, 6.76 g, 78.52% yield, 67% purity) as a dark brown solid. MS (ESI) *m/z* = 205.1 [M+H]⁺.

Step 3: Synthesis of methyl-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate

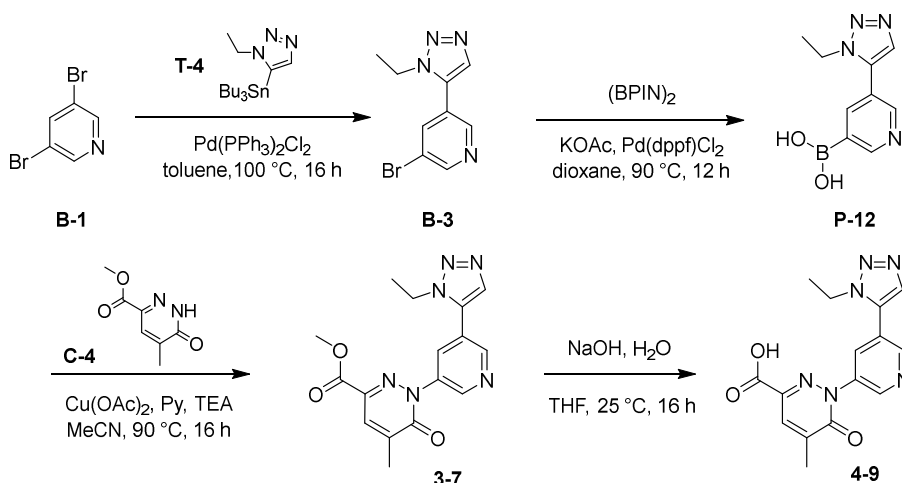
A solution of methyl-6-oxo-1H-pyridazine-3-carboxylate (3.78 g, 24.51 mmol), [5-(3-methyltriazol-4-yl)-3-pyridyl]boronic acid (5 g, 24.51 mmol), Cu(OAc)₂ (4.45 g, 24.51 mmol), TEA (4.96 g, 49.02 mmol, 6.82 mL) and pyridine (3.88 g, 49.02 mmol, 3.96 mL) in MeCN (100 mL) was substituted with oxygen for 3 times, and then the mixture was stirred at 90 °C

for 16 h under oxygen atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (3% MeOH in DCM) to give methyl-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate (1.83 g, 5.27 mmol, 21.51% yield, 89.98% purity) as a dark brown solid. MS (ESI) $m/z = 312.9$ $[M+H]^+$.

Step 4: Synthesis of 1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylic acid

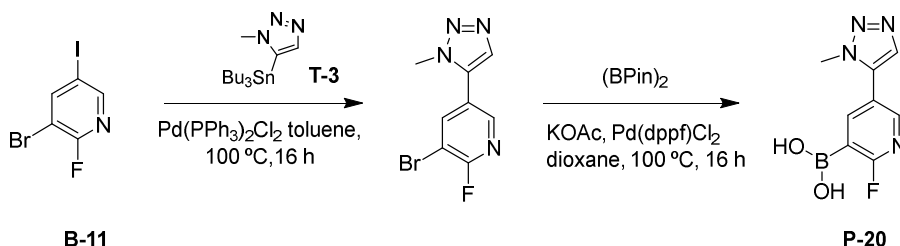
To a solution of methyl-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate (1.0 g, 3.20 mmol) in THF (4 mL), H₂O (2 mL) was added NaOH (256.16 mg, 6.40 mmol). The mixture was substituted with nitrogen for 3 times, and then stirred at 25 °C for 16 h under nitrogen atmosphere. The mixture was adjusted to pH = 2-3 with aq. 1 N HCl and then **Intermediate 4-1** (725 mg, 74.01% yield, 97.5% purity) was obtained by solid filtration as a yellow solid. MS (ESI) $m/z = 299.0$ $[M+H]^+$.

Preparation Example 28-1: 1-[5-(3-ethyltriazol-4-yl)-3-pyridyl]-5-methyl-6-oxo-pyridazine-3-carboxylic acid (4-9)



3,5-dibromopyridine and Intermediate T-4 were used in the same manner as in Preparation Example 28 to give **Intermediate 4-9** (86 mg, crude product) as a light yellow solid. MS (ESI) $m/z = 327.1$ $[M+H]^+$.

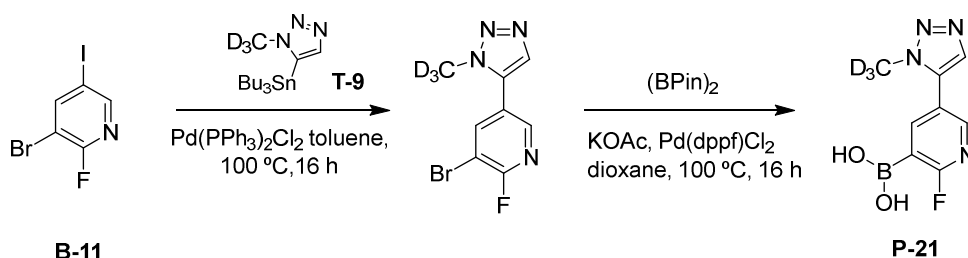
Preparation Example 28-2: (2-fluoro-5-(1-methyl-1H-1,2,3-triazol-5-yl)pyridin-3-yl)boronic acid (P-20)



3-bromo-2-fluoro-5-iodopyridine and Intermediate T-3 were used in the same manner as in Steps 1 and 2 of Preparation Example 28 to give **Intermediate P-20** as a light yellow

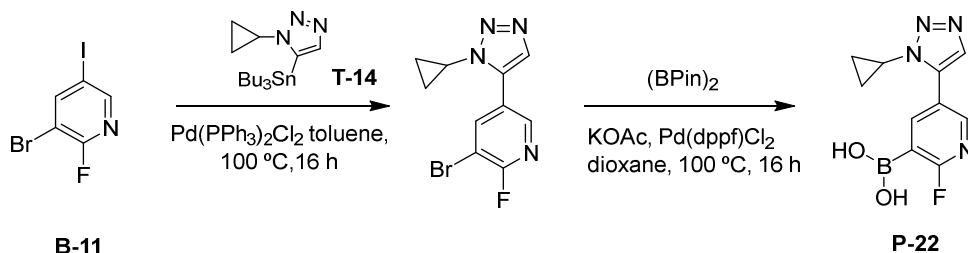
solid. MS (ESI) $m/z = 223.1$ $[M+H]^+$.

Preparation Example 28-3: (2-fluoro-5-(1-trideuteriomethyltriazol-5-yl)pyridin-3-yl]boronic acid (P-21)



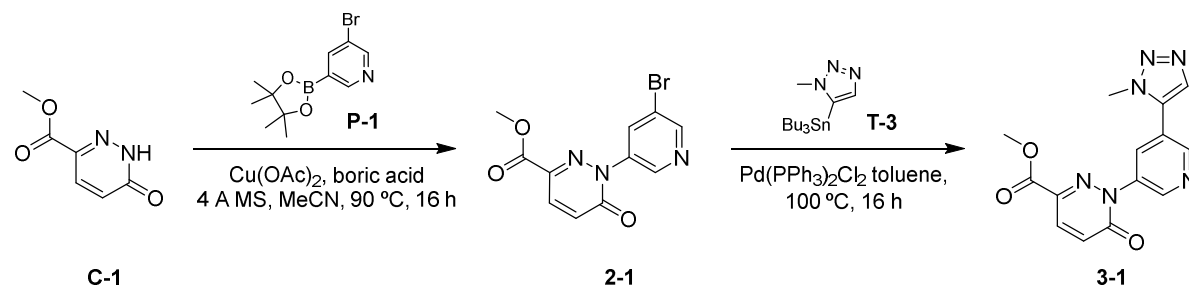
3-bromo-2-fluoro-5-iodopyridine and Intermediate T-9 were used in the same manner as in Step 1 and Step 2 of Preparation Example 28 to give **Intermediate P-21** as a light yellow solid. MS (ESI) $m/z = 226.1$ $[M+H]^+$.

Preparation Example 28-4: (2-fluoro-5-(1-cyclopropyltriazol-5-yl)pyridin-3-yl]boronic acid (P-22)



3-bromo-2-fluoro-5-iodopyridine and Intermediate T-14 were used in the same manner as in Step 1 and Step 2 of Preparation Example 28 to give **Intermediate P-22** as a light yellow solid. MS (ESI) $m/z = 249.1$ $[M+H]^+$.

Preparation Example 29: methyl-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate (3-1): Alternative method



Step 1: Synthesis of methyl 1-(5-bromo-3-pyridyl)-6-oxo-pyridazine-3-carboxylate

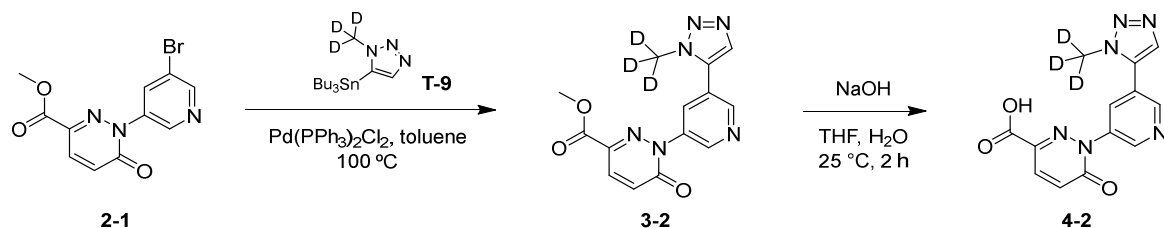
A solution of methyl 6-oxo-1H-pyridazine-3-carboxylate (5 g, 32.44 mmol), 3-bromo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (9.21 g, 32.44 mmol), $\text{Cu}(\text{OAc})_2$ (2.95 g, 16.22 mmol), boric acid (4.01 g, 64.88 mmol) and 4 Å MS (1 g) in MeCN (120 mL) was substituted with oxygen for 3 times, and then stirred at 90 °C for 16 h under oxygen atmosphere. The reaction mixture was poured into water (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4

and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (58% DCM in petroleum ether) to give methyl 1-(5-bromo-3-pyridyl)-6-oxo-pyridazine-3-carboxylate (2.2 g, 21.54% yield, 98.49% purity) as a white solid. MS (ESI) $m/z = 312.0 [M+H]^+$.

Step 2: Synthesis of methyl-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate

A solution of methyl-1-(5-bromo-3-pyridyl)-6-oxo-pyridazine-3-carboxylate (2.2 g, 7.09 mmol), tributyl-(3-methyltriazol-4-yl)stannane (7.92 g, 21.28 mmol) and $Pd(PPh_3)_2Cl_2$ (497.95 mg, 709.44 μ mol) in toluene (20 mL) was substituted with nitrogen for 3 times, and then stirred at 100 °C for 16 h under nitrogen atmosphere. The reaction mixture was filtered, and then the filtrate was extracted with EtOAc (50 mL x 3) after the addition of water (20mL). The combined organic layers were washed with brine (20 mL x 2), dried over Na_2SO_4 and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (2% MeOH in DCM) to give **Intermediate 3-1** (1.0 g, 32.50% yield, 72% purity) as a white solid. MS (ESI) $m/z = 327.1 [M+H]^+$.

Preparation Example 30: 6-oxo-1-[5-[3-(trideuteriomethyl)triazol-4-yl]-3-pyridyl]pyridazine-3-carboxylic acid (4-2)



Step 1: Synthesis of methyl 6-oxo-1-[5-[3-(trideuteriomethyl)triazol-4-yl]-3-pyridyl]pyridazine-3-carboxylate

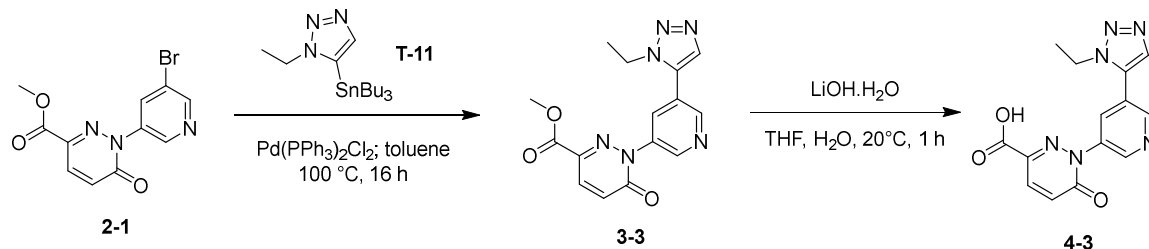
A solution of 1-(5-bromo-3-pyridyl)-6-oxo-pyridazine-3-carboxylate (1 g, 3.22 mmol), tributyl-[3-(trideuteriomethyl)triazol-4-yl]stannane (3.63 g, 9.67 mmol) and $Pd(PPh_3)_2Cl_2$ (226.34 mg, 322.47 μ mol) in toluene (10 mL) was substituted with nitrogen for 3 times, and stirred at 100°C for 16 h under nitrogen atmosphere. The reaction mixture was poured into water (20mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (20 mL x 2), dried over Na_2SO_4 and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (5% MeOH in DCM) to give methyl 6-oxo-1-[5-[3-(trideuteriomethyl)triazol-4-yl]-3-pyridyl]pyridazine-3-carboxylate (420 mg, 30.57% yield, 74% purity) as a yellow solid. MS (ESI) $m/z = 316.1 [M + H]^+$.

Step 2: Synthesis of 6-oxo-1-[5-[3-(trideuteriomethyl)triazol-4-yl]-3-pyridyl]pyridazine-3-carboxylic acid

To a solution of methyl 6-oxo-1-[5-[3-(trideuteriomethyl)triazol-4-yl]-3-pyridyl]pyridazine-3-carboxylate (420 mg, 1.33 mmol) in THF (8 mL) and H_2O (2 mL) was

added NaOH (79.92 mg, 2.00 mmol). After the nitrogen substitution for 3 times, the mixture was stirred at 25 °C for 2 h under nitrogen atmosphere. The mixture was adjusted to pH = 6-7 with aq. 1 N HCl and then concentrated under reduced pressure to give **Intermediate 4-2** (420 mg, 65.93% yield, 63% purity) as a yellow solid. MS (ESI) $m/z = 302.1 [M + H]^+$.

Preparation Example 31: 1-[5-(3-ethyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylic acid (4-3)



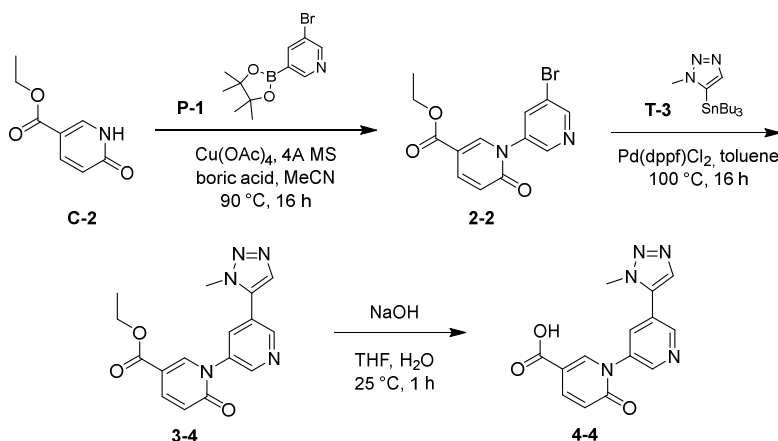
Step 1: Synthesis of 1-[5-(3-ethyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate

A solution of 1-(5-bromo-3-pyridyl)-6-oxo-pyridazine-3-carboxylate (260 mg, 838.43 μmol), tributyl-(3-ethyltriazol-4-yl)stannane (485.66 mg, 1.26 mmol) and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (58.85 mg, 83.84 μmol) in toluene (5 mL) was substituted with nitrogen for 3 times, and then stirred at 100 °C for 16 h under nitrogen atmosphere. The reaction mixture was poured into water (30 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL x 5), dried over Na_2SO_4 and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (3% MeOH in DCM) to give 1-[5-(3-ethyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate (110 mg, 13.67% yield, 34% purity) as yellow oil. MS (ESI) $m/z = 327.1 [M + H]^+$.

Step 2: Synthesis of 1-[5-(3-ethyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylic acid

To a solution of 1-[5-(3-ethyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate (110 mg, 337.10 μmol) in THF (3 mL) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (28.29 mg, 674.21 μmol) and H_2O (1 mL), and then the mixture was stirred at 20 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give a crude product. The crude product was purified by prep-HPLC (column: Welch Xtimate C18 150*30 mm*5 μm ; mobile phase: [water (HCl)-MeCN]; B%: 0%-26%, 25 min). Most of MeCN was concentrated under reduced pressure, and the remaining solvent was removed by lyophilization to give **Intermediate 4-3** (47 mg, 44.65% yield, 100% purity) as a white solid. MS (ESI) $m/z = 313.0 [M + H]^+$.

Preparation Example 32: 1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridin-3-carboxylic acid (4-4)



Step 1: Synthesis of ethyl 1-(5-bromo-3-pyridyl)-6-oxo-pyridine-3-carboxylate

A solution of ethyl 6-oxo-1H-pyridine-3-carboxylate (535.17 mg, 3.20 mmol), 3-bromo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (1 g, 3.52 mmol), $\text{Cu}(\text{OAc})_2$ (290.75 mg, 1.60 mmol), 4A MS (500 mg, 3.20 mmol) and boric acid (395.92 mg, 6.40 mmol) in MeCN (15 mL) was substituted with oxygen for 3 times, and then stirred at 90 °C for 16 h under oxygen atmosphere. The reaction mixture was filtered, and then the filtrate was concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (30% EtOAc in petroleum ether) to give ethyl 1-(5-bromo-3-pyridyl)-6-oxo-pyridine-3-carboxylate (87 mg, 7.65% yield, 90.95% purity) as a white solid. MS (ESI) $m/z = 322.9$ $[\text{M} + \text{H}]^+$.

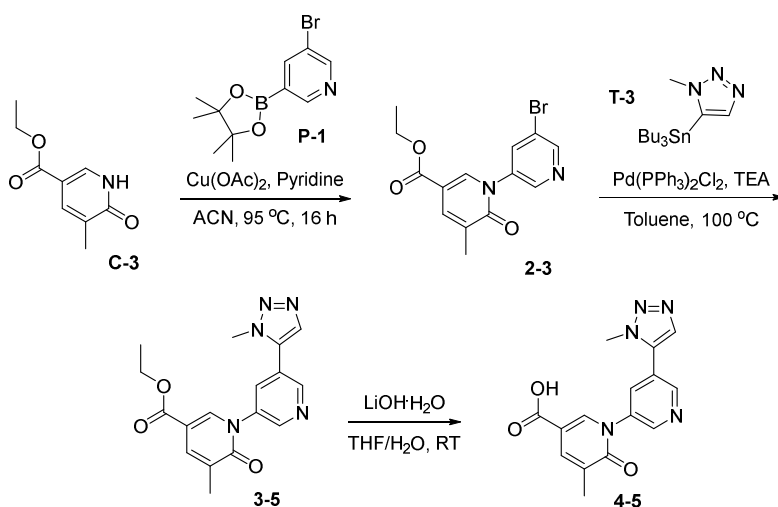
Step 2: Synthesis of ethyl 1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridine-3-carboxylate

A solution of ethyl-1-(5-bromo-3-pyridyl)-6-oxo-pyridine-3-carboxylate (87 mg, 269.23 μmol), tributyl(3-methyltriazol-4-yl)stannane (250.48 mg, 673.08 μmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (19.70 mg, 26.92 μmol) in toluene (2 mL) was substituted with nitrogen for 3 times, and then stirred at 100 °C for 16 h under nitrogen atmosphere. The reaction mixture was filtered, and then the filtrate was concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (2% MeOH in DCM) to give ethyl 1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridine-3-carboxylate (30 mg, 32.07% yield, 93.62% purity) as a white solid. MS (ESI) $m/z = 326.1$ $[\text{M} + \text{H}]^+$.

Step 3: Synthesis of 1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridine-3-carboxylic acid

To a solution of ethyl 1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridine-3-carboxylate (30 mg, 92.22 μmol) in THF (1 mL) and H₂O (0.5 mL) was added NaOH (7.38 mg, 184.43 μmol). After nitrogen substitution for 3 times, the mixture was stirred at 25 °C for 1 h under nitrogen atmosphere. The mixture was adjusted to pH = 5-6 with aq. 1 N HCl, and then the organic layers were concentrated under reduced pressure to give **Intermediate 4-4** (25 mg, crude) as yellow oil. MS (ESI) $m/z = 298.0$ $[\text{M} + \text{H}]^+$.

Preparation Example 33: 3-methyl-5'-(1-methyl-1H-1,2,3-triazol-5-yl)-2-oxo-2H-[1,3'-bipyridine]-5-carboxylic acid (4-5)



Step 1: Synthesis of ethyl 5'-bromo-3-methyl-2-oxo-2H-[1,3'-bipyridine]-5-carboxylate

To a solution of ethyl 5-methyl-6-oxo-1,6-dihydronicotinate (500 mg, 2.76 mmol) in MeCN (21.2 mL) was added 5-bromo-3-pyridineboronic acid pinacol ester (1.18 mg, 4.14 mmol), Cu(OAc)₂ (501 mg, 2.76 mmol) and pyridine (0.89 mL, 11 mmol), and then the mixture was stirred at 90 °C for 16 h. Following the addition of water, the reaction mixture was extracted with EtOAc. The combined organic layers were washed with copper sulfate(II) pentahydrate, dried over Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (50% EtOAc in hexane) to give ethyl 5'-bromo-3-methyl-2-oxo-2H-[1,3'-bipyridine]-5-carboxylate (460 mg, 49% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.77 (d, J = 2.0 Hz, 1H), 8.60 (d, J = 2.4 Hz, 1H), 8.06 (d, J = 2.4 Hz, 1H), 8.01 (t, J = 2.0 Hz, 1H), 7.84 (d, J = 0.8 Hz, 1H), 4.34 (q, J = 7.0 Hz, 2H), 2.22 (s, 3H), 1.37 (t, J = 7.2 Hz, 3H); MS (ESI) m/z = 336.95, 338.95 [M+H]⁺.

Step 2: Synthesis of ethyl 3-methyl-5'-(1-methyl-1H-1,2,3-triazol-5-yl)-2-oxo-2H-[1,3'-bipyridine]-5-carboxylate

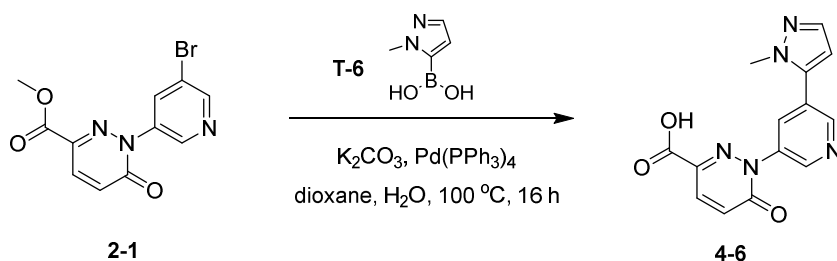
A solution of ethyl 5'-bromo-3-methyl-2-oxo-2H-[1,3'-bipyridine]-5-carboxylate (300 mg, 0.890 mmol), tributyl(1-methyl-1H-1,2,3-triazol-5-yl)stannane (993 mg, 2.67 mmol), TEA (124 μL, 0.890 mmol) and Pd(PPh₃)₂Cl₂ (62.6 mg, 0.089 mmol) in toluene (8.9 mL) was substituted with nitrogen for 3 times, and then stirred at 100 °C for 17h under nitrogen atmosphere. The reaction mixture was poured into water (30 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL x 5), dried over Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (17% EtOAc in hexane) to give ethyl 3-methyl-5'-(1-methyl-1H-1,2,3-triazol-5-yl)-2-oxo-2H-[1,3'-bipyridine]-5-carboxylate (81 mg,

27% yield) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 8.79 (d, J = 2.0 Hz, 1H), 8.74 (d, J = 2.4 Hz, 1H), 8.16 (d, J = 2.0 Hz, 1H), 7.97 (t, J = 2.2 Hz, 1H), 7.87-7.86 (m, 2H), 4.36 (q, J = 7.2 Hz, 2H), 4.18 (s, 3H), 2.24 (s, 3H), 1.37 (t, J = 7.2 Hz, 3H); MS (ESI) m/z = 340.07 $[\text{M}+\text{H}]^+$.

Step 3: Synthesis of 3-methyl-5'-(1-methyl-1H-1,2,3-triazol-5-yl)-2-oxo-2H-[1,3'-bipyridine]-5-carboxylic acid

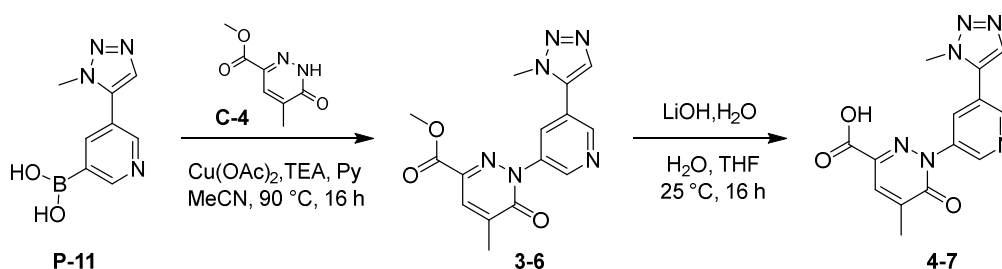
To a solution of ethyl 3-methyl-5'-(1-methyl-1H-1,2,3-triazol-5-yl)-2-oxo-2H-[1,3'-bipyridine]-5-carboxylate (81 mg, 0.239 mmol) in THF (2.39 mL) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (30 mg, 0.716 mmol) and H_2O (1.19 mL), and then the mixture was stirred at 25 °C for 1 h. The reaction mixture was poured into water and adjusted to pH = 1 with aq. 1 N HCl, and then **Intermediate 4-5** (73 mg, 98% yield) was obtained by solid filtration as a white solid. MS (ESI) m/z = 312.04 $[\text{M}+\text{H}]^+$.

Preparation Example 34: 1-[5-(2-methylpyrazol-3-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylic acid (4-6)



A solution of methyl 1-(5-bromo-3-pyridyl)-6-oxo-pyridazine-3-carboxylate (500 mg, 1.61 mmol), (2-methylpyrazol-3-yl)boronic acid (406.06 mg, 3.22 mmol), K_2CO_3 (557.09 mg, 4.03 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (186.32 mg, 161.24 μmol) in dioxane (5 mL) and H_2O (0.5 mL) was substituted with nitrogen for 3 times, and then stirred at 100 °C for 16 h under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure to remove the solvent, and then diluted with water (10 mL). With the addition of aq. 1 N HCl, the reaction mixture was adjusted to pH = 3-4, and then extracted with EtOAc (20 mL $\times$ 3). The organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give a crude product, **Intermediate 4-6** (835 mg, crude) as a brown solid. MS (ESI) m/z = 298.1 $[\text{M}+\text{H}]^+$.

Preparation Example 35: 5-methyl-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylic acid (4-7)



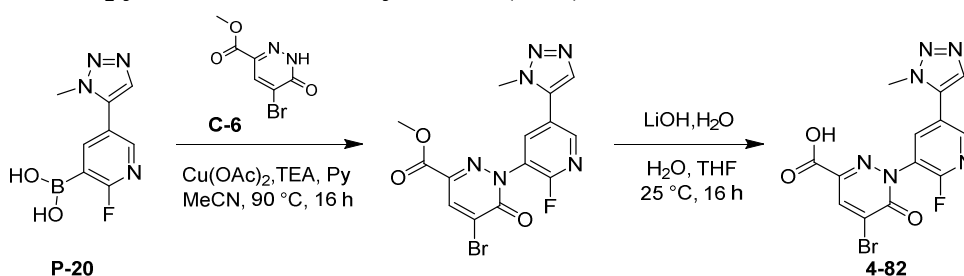
Step 1: Synthesis of methyl 5-methyl-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate

A solution of methyl 5-methyl-6-oxo-1H-pyridazine-3-carboxylate (200 mg, 1.19 mmol), [5-(3-methyltriazol-4-yl)-3-pyridyl]boronic acid (242.63 mg, 1.19 mmol), Cu(OAc)₂ (216.03 mg, 1.19 mmol), TEA (240.71 mg, 2.38 mmol, 331.11 μ L) and pyridine (188.17 mg, 2.38 mmol, 192.01 μ L) in MeCN (5 mL) was substituted with nitrogen for 3 times, and then stirred at 90 °C for 16 h under nitrogen atmosphere. After the addition of water (30 mL), the reaction mixture was extracted with EtOAc (30 mL $\times$ 3). The organic layers were washed with brine (50 mL), dried over Na₂SO₄, and then concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (1% MeOH in DCM) to give methyl 5-methyl-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate (305 mg, 69.15% yield, 88% purity) as a yellow solid. MS (ESI) m/z = 327.1 [M+H]⁺.

Step 2: Synthesis of 5-methyl-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylic acid

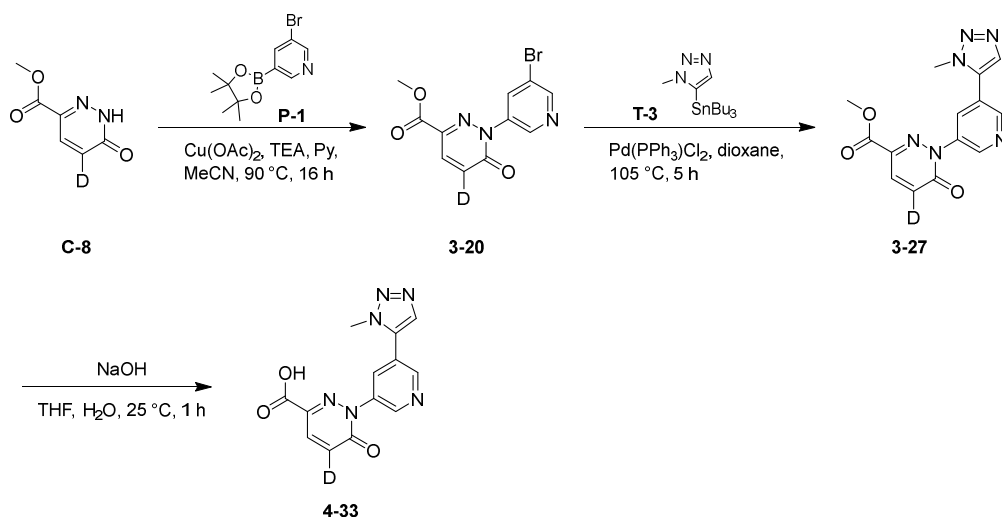
LiOH·H₂O (117.67 mg, 2.80 mmol) and H₂O (2 mL) were added to a solution of methyl 5-methyl-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate (305 mg, 934.70 μ mol) in THF (4 mL), and then stirred at 25 °C for 16 h. The reaction mixture was concentrated under reduced pressure to remove solvent, and then diluted with water (10 mL). The reaction mixture was adjusted to pH = 3-4 with aq. 1 N HCl, and then extracted with EtOAc (20 mL $\times$ 3). The organic layers were washed with brine (30 mL), dried over Na₂SO₄, and then concentrated under reduced pressure to give **Intermediate 4-7** (63 mg, 20.29% yield, 94% purity) as a white solid. MS (ESI) m/z = 313.1 [M+H]⁺.

Preparation Example 35-1: 5-methyl-1-[5-(3-methyltriazol-4-yl)-2-fluoro-3-pyridyl]-6-oxo-pyridazine-3-carboxylic acid (4-82)



Intermediate **P-20** and methyl 5-bromo-6-oxo-1,6-dihydropyridazine-3-carboxylate (**C-6**) were used in the same manner as in Preparation Example 35 to give **Intermediate 4-82** as a yellow solid. MS (ESI) m/z = 395.1 [M+H]⁺.

Preparation Example 36: 5-deuterio-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate (4-33)



Step 1: Synthesis of methyl 1-(5-bromo-3-pyridyl)-5-deuterio-6-oxo-pyridazine-3-carboxylate

A solution of methyl 5-deuterio-6-oxo-1H-pyridazine-3-carboxylate (95 mg, 612.39 μmol), 3-bromo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**P-1**, 521.68 mg, 1.84 mmol), $\text{Cu}(\text{OAc})_2$ (111.23 mg, 612.39 μmol), TEA (185.90 mg, 1.84 mmol, 255.71 μL) and pyridine (145.32 mg, 1.84 mmol, 148.29 μL) in MeCN (4 mL) was substituted with oxygen for 3 times, and then stirred at 90 °C for 16 h under oxygen atmosphere. The reaction mixture was filtered, and then the filtrate was concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (30% EtOAc in petroleum ether) to give methyl 1-(5-bromo-3-pyridyl)-5-deuterio-6-oxo-pyridazine-3-carboxylate (105 mg, 43.54% yield, 79% purity) as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.84 (d, $J = 2.0$ Hz, 2H), 8.39 (t, $J = 2.0$ Hz, 1H), 7.95 - 7.91 (s, 1H), 3.88 (s, 3H); MS (ESI) $m/z = 312.8$ $[\text{M}+\text{H}]^+$.

Step 2: Synthesis of methyl 5-deuterio-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate

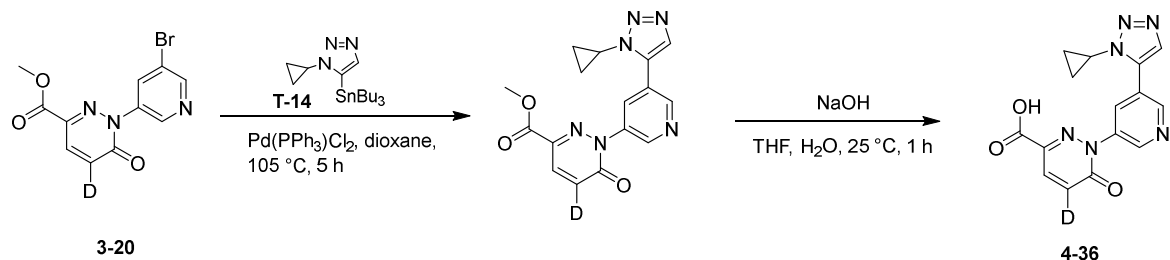
A solution of methyl 1-(5-bromo-3-pyridyl)-5-deuterio-6-oxo-pyridazine-3-carboxylate (105 mg, 337.50 μmol), tributyl(3-methyltriazol-4-yl)stannane (220.00 mg, 591.18 μmol) and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (23.69 mg, 33.75 μmol) in dioxane (3 mL) was substituted with nitrogen for 3 times, and then stirred at 105 °C for 5 h under nitrogen atmosphere. The reaction mixture was filtered, and then the filtrate was concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (2% MeOH in PE) to give methyl 5-deuterio-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate (100 mg, 53.62% yield, 56.7% purity) as a yellow solid. MS (ESI) $m/z = 314.3$ $[\text{M}+\text{H}]^+$.

Step 3: Synthesis of 5-deuterio-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylic acid

A solution of methyl 5-deuterio-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-

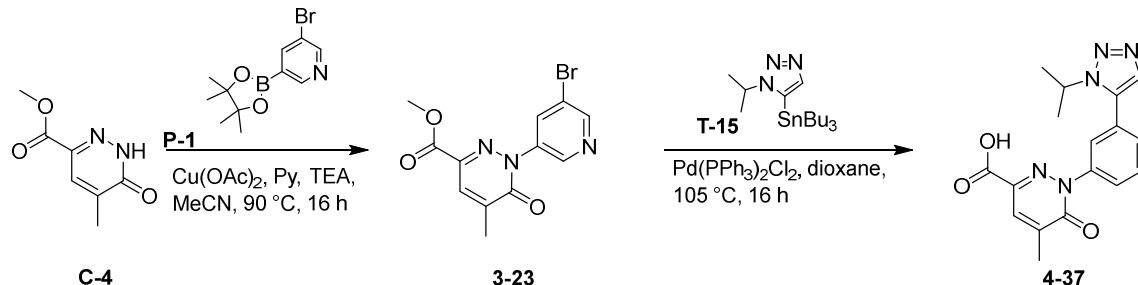
pyridazine-3-carboxylate (50 mg, 159.60 μmol , 1 eq) and NaOH (12.77 mg, 319.19 μmol , 2 eq) in THF (1 mL) and H₂O (0.5 mL) was substituted with nitrogen for 3 times, and then stirred at 25 °C for 1 h under nitrogen atmosphere. The reaction mixture was adjusted to pH = 5-6 with aq. 1 N HCl, and then concentrated under reduced pressure to give **Intermediate 4-33** (40 mg, 57.45% yield, 68.6% purity) as a yellow solid. It was used in the next reaction without further purification. MS (ESI) m/z = 299.9 [M+H]⁺.

Preparation Example 36-1: 1-[5-(3-cyclopropyltriazol-4-yl)-3-pyridyl]-5-deuterio-6-oxo-pyridazine-3-carboxylic acid (4-36)



Intermediate 3-20 and intermediate T-14 were used in the same manner as in Steps 2 and 3 of Preparation Example 36 to give **Intermediate 4-36** (20 mg, 79.12% yield, 98.6% purity) as a yellow solid. MS (ESI) m/z = 326.1 [M+H]⁺.

Preparation Example 36-2: 1-[3-(3-isopropyltriazol-4-yl)phenyl]-5-methyl-6-oxo-pyridazine-3-carboxylic acid (4-37)



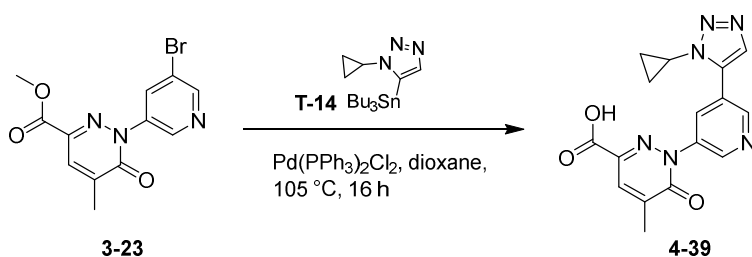
Step 1: Synthesis of methyl 1-(5-bromo-3-pyridyl)-5-methyl-6-oxo-pyridazine-3-carboxylate

A solution of methyl 5-methyl-6-oxo-1H-pyridazine-3-carboxylate (600 mg, 3.57 mmol), 3-bromo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (1.01 g, 3.57 mmol), Cu(OAc)₂ (1.30 g, 7.14 mmol), TEA (722.14 mg, 7.14 mmol, 993.31 μL) and pyridine (564.50 mg, 7.14 mmol, 576.02 μL) in MeCN (15 mL) was substituted with oxygen for 3 times, and then stirred at 90 °C for 16 h under oxygen atmosphere. The reaction mixture was filtered, and then the filtrate was concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (80% EtOAc in petroleum ether) to give methyl 1-(5-bromo-3-pyridyl)-5-methyl-6-oxo-pyridazine-3-carboxylate (Intermediate 3-23, 200 mg, 13.83% yield, 80% purity) as a yellow solid. MS (ESI) m/z = 325.9 [M+H]⁺.

Step 2: Synthesis of 1-[3-(3-isopropyltriazol-4-yl)phenyl]-5-methyl-6-oxo-pyridazine-3-carboxylic acid

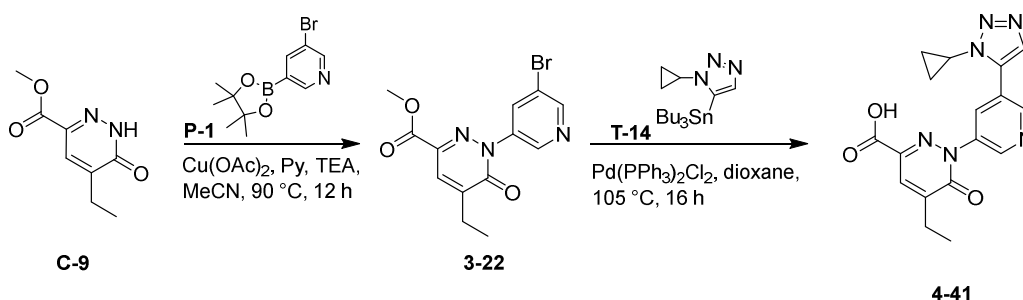
A solution of methyl 1-(5-bromo-3-pyridyl)-5-methyl-6-oxo-pyridazine-3-carboxylate (200 mg, 617.04 μmol), tributyl-(3-isopropyltriazol-4-yl)stannane (600 mg, 1.50 mmol) and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (86.62 mg, 123.41 μmol) in dioxane (5 mL) was substituted with nitrogen for 3 times, and then stirred at 105 °C for 16 h under nitrogen atmosphere. The reaction mixture was filtered, and then the filtrate was concentrated under reduced pressure to give a crude product. The crude product was purified by prep-HPLC (Column: Welch Xtimate C18 40*200 mm 7 μm ; mobile phase: [water (hydrochloride)-ACN]; 0%-38% B, 20.5 minute). The acetonitrile was concentrated under reduced pressure, and the remaining solvent was removed by lyophilization to give **Intermediate 4-37** (30 mg, 13.63% yield, 95.15% purity) as a yellow solid. MS (ESI) $m/z = 341.0$ $[\text{M}+\text{H}]^+$.

Preparation Example 36-3: 1-[5-(3-cyclopropyltriazol-4-yl)-3-pyridyl]-5-methyl-6-oxo-pyridazine-3-carboxylic acid (4-39)



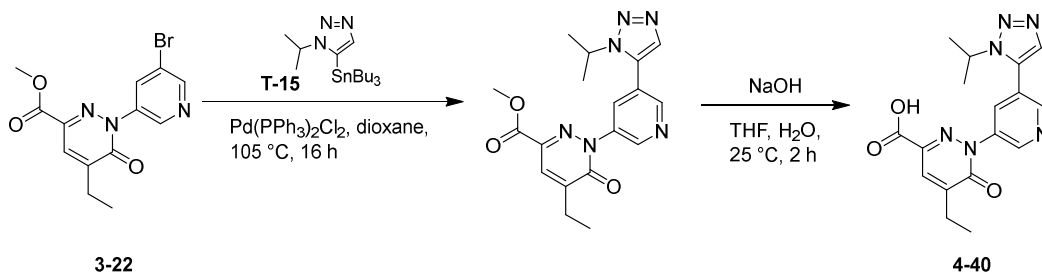
Intermediates 3-23 and T-14 were used in the same manner as in Step 2 of Preparation Example 36-2 to give **Intermediate 4-39** (40 mg, 25.04% yield, 98% purity) as a dark brown solid. MS (ESI) $m/z = 339.1$ $[\text{M}+\text{H}]^+$.

Preparation Example 36-4: 1-[5-(3-cyclopropyltriazol-4-yl)-3-pyridyl]-5-ethyl-6-oxo-pyridazine-3-carboxylic acid (4-41)



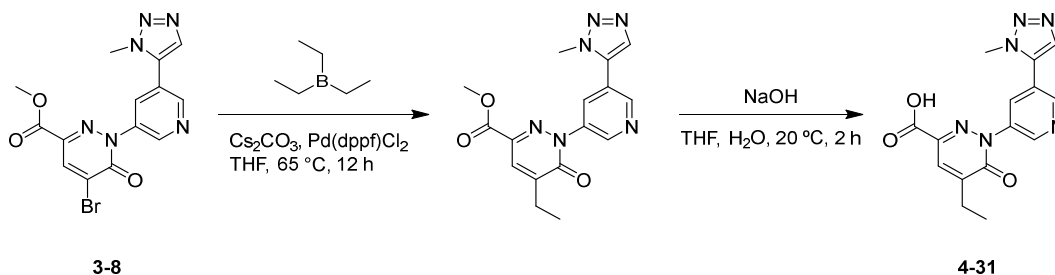
Intermediates C-9 and P-1 were used in the same manner as in Preparation Example 36-2 to give **Intermediate 4-41** (90 mg, 38.44% yield, 89% purity) as yellow oil. MS (ESI) $m/z = 353.0$ $[\text{M}+\text{H}]^+$.

Preparation Example 36-5: 1-[5-(3-isopropyltriazol-4-yl)-3-pyridyl]-5-ethyl-6-oxo-pyridazine-3-carboxylic acid (4-40)



Intermediate 3-22 (the product obtained in Step 1 of Preparation Example 36-5) and Intermediate T-15 were used in the same manner as in Preparation Example 36-1 to give **Intermediate 4-40** (90 mg, 74.48% yield, 79.6% purity) as yellow oil. MS (ESI) m/z = 355.1 $[M+H]^+$.

Preparation Example 36-6: 5-ethyl-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylic acid (4-31)



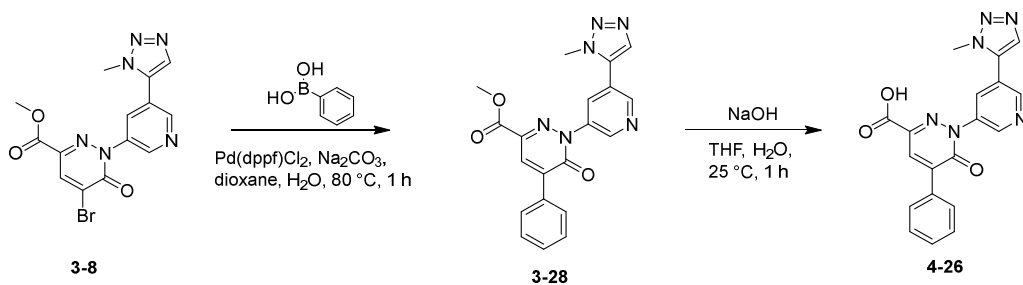
Step 1: Synthesis of methyl 5-ethyl-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate

A solution of 5-bromo-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate (46 mg, 117.59 μmol), Cs_2CO_3 (76.63 mg, 235.19 μmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (3.44 mg, 4.70 μmol) and triethyl borate (1 M in THF, 470.37 μL) in THF (3 mL) was substituted with nitrogen for 3 times, and then stirred at 70 °C for 12 h under nitrogen atmosphere. The reaction mixture was filtered, and then the filtrate was concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (3% DCM in MeOH) to give methyl 5-ethyl-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate (26 mg, 32.48% yield, 50% purity) as a white solid. MS (ESI) m/z = 340.6 $[M+H]^+$.

Step 2: Synthesis of 5-ethyl-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylic acid

The intermediate, methyl 5-ethyl-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate was used in the same manner as in Step 3 of Preparation Example 36 to give **Intermediate 4-31** (20 mg, 48.14% yield, 60% purity) as a yellow solid. MS (ESI) m/z = 326.9 $[M+H]^+$.

Preparation Example 36-7: 1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-5-phenyl-pyridazine-3-carboxylic acid (4-26)



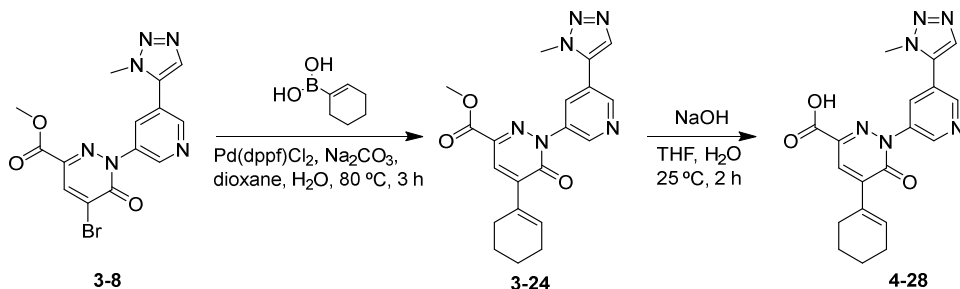
Step 1: Synthesis of methyl 1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-5-phenylpyridazine-3-carboxylate

A solution of 5-bromo-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate (**Intermediate 3-8**, 30 mg, 76.69 μmol), phenylboronic acid (28.05 mg, 230.07 μmol), Pd(dppf)Cl₂ (5.61 mg, 7.67 μmol), Na₂CO₃ (16.26 mg, 153.38 μmol) and H₂O (0.4 mL) in dioxane (4 mL) was degassed and purged with nitrogen for 3 times. Then the mixture was stirred at 80 °C for 1 h under nitrogen atmosphere. The mixture was purified by silica column chromatography (7% MeOH in DCM) to give methyl-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-5-phenyl-pyridazine-3-carboxylate (**Intermediate 3-28**, 58 mg, 97.36% yield, 100% purity) as a yellow solid. MS (ESI) m/z = 389.1[M+H]⁺.

Step 2: Synthesis of 1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-5-phenylpyridazine-3-carboxylic acid

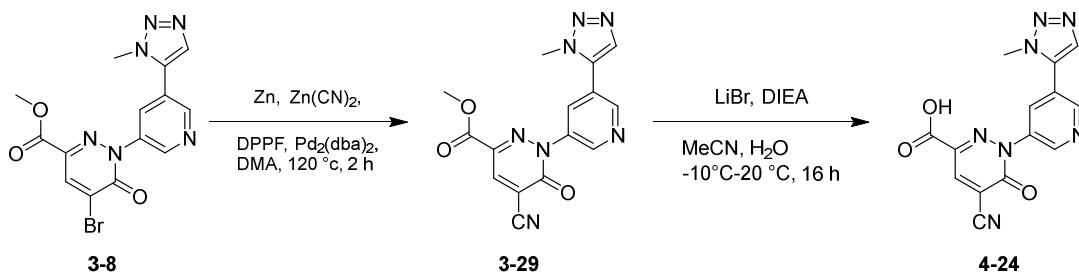
Intermediate 3-28 was used in the same manner as in Step 2 of Preparation Example 36-1 to give **Intermediate 4-26** (55 mg, 98.38% yield, 62% purity) as a yellow solid. MS (ESI) $m/z = 375.1 [M+H]^+$.

Preparation Example 36-8: 5-(cyclohexen-1-yl)-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylic acid (4-28)



Intermediate 3-8 and (cyclohexen-1-yl)boronic acid (which is commercially available) were used in the same manner as in Preparation Example 36-7 to give **Intermediate 4-28** (56 mg, 75.46% yield, 76.66% purity) as a yellow solid. MS (ESI) m/z = 379.2 $[M+H]^+$.

Preparation Example 36-9: 5-cyano-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylic acid (4-24)



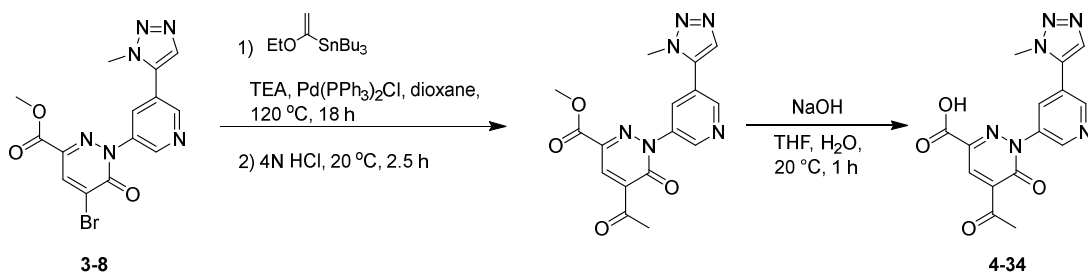
Step 1: Synthesis of methyl 5-cyano-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate

Zn(CN)₂ (70 mg, 596 μmol) and Zn (40 mg, 611 μmol) were added to a solution of methyl 5-bromo-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate (200 mg, 511 μmol), DPPF (56.69 mg, 102 μmol) and Pd₂(dba)₃ (46.82 mg, 51.1 μmol) in DMA (3 mL). Then the mixture was substituted with nitrogen for 3 times, and stirred at 120 °C for 2 h under nitrogen atmosphere. The reaction mixture was filtered, the filtrate was poured into water (20 mL), and then extracted with EtOAc (15 mL x 4). The combined organic layers were washed with brine (10 mL x 3), dried over Na₂SO₄, and then concentrated under reduced pressure to give a crude product. The aq. layers were quenched with aq. 1N HCl (5 mL) and stirred overnight. The residue was purified by silica gel column chromatography (0~100% ethyl acetate/Petroleum ether) to give methyl 5-cyano-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate (73 mg, 25.23% yield, 59.6% purity) as dark brown oil. MS (ESI) *m/z* = 338.1 [M+H]⁺.

Step 2: Synthesis of 5-cyano-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylic acid

LiBr (29.89 mg, 344 μmol) was added to a solution of H₂O (1 mL) in MeCN (1 mL) at -10 °C for more than 1 minute. Then the mixture was stirred at -10 °C for 1 h to give solution A. Methyl 5-cyano-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate (43 mg, 127 μmol) and DIEA (39.97 μL, 229 μmol) were added dropwise to the solution A at -10 °C, and then it was stirred at 20 °C for 1 h. The reaction mixture was poured into water (5 mL), adjusted to pH = 4 with aq. 1 N HCl, and then extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (5 mL x 2), dried over Na₂SO₄, and then concentrated under reduced pressure to give **Intermediate 4-24** (25 mg, 60.06% yield, 99% purity) as brown oil. MS (ESI) *m/z* = 323.9 [M+H]⁺.

Preparation Example 36-10: 5-acetyl-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylic acid (4-34)



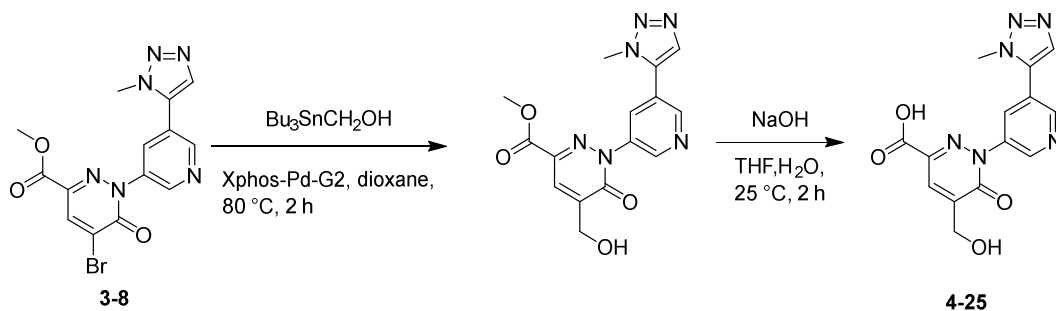
Step 1: Synthesis of methyl 5-acetyl-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate

Tributyl(1-ethoxyvinyl)stannane (454.23 mg, 1.26 mmol, 424.91 μL), TEA (212.12 mg, 2.10 mmol, 291.77 μL) and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (73.57 mg, 104.81 μmol) were added to a solution of methyl 5-bromo-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate (410 mg, 1.05 mmol) in dioxane (6 mL). Then the mixture was stirred at 120°C for 18 h under N_2 atmosphere. To the mixture was added HCl solution (50 mL, 1 M) under stirring at 20°C , and then the mixture was stirred at 20°C for 2.5 h. After the addition of water (10 mL), the reaction mixture was extracted with EtOAc (20 mL $\times$ 3). The combined organic layers were washed with brine (10 mL $\times$ 3), dried over anhydrous Na_2SO_4 , and then concentrated under reduced pressure to give a residue. Sat. aq. KF (15 mL) was slowly added to the aqueous layer under stirring, and then the mixture was stirred at 25°C for 1 h. The product was purified by silica gel column chromatography (2% MeOH in DCM) to give methyl 5-acetyl-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate (200 mg, 21.54% yield, 40% purity) as a yellow solid. MS (ESI) $m/z = 355.1$ $[\text{M}+\text{H}]^+$.

Step 2: Synthesis of 5-acetyl-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylic acid

Methyl 5-acetyl-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate was used in the same manner as in Step 3 of Preparation Example 36 to give **Intermediate 4-34** (80 mg, 41.57% yield, 99.8% purity) as a yellow solid. MS (ESI) $m/z = 340.9$ $[\text{M}+\text{H}]^+$.

Preparation Example 36-11: 5-(hydroxymethyl)-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylic acid (4-25)



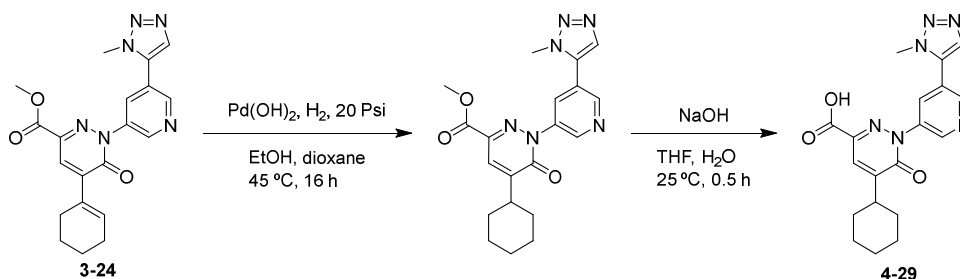
Step 1: Synthesis of methyl 5-(hydroxymethyl)-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate

Xphos-Pd-G2 (10.06 mg, 12.78 μmol), tributylstanylmethanol (123.12 mg, 383.46 μmol) was added to a solution of methyl 5-bromo-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate (50 mg, 127.82 μmol) in dioxane (3 mL). Then the mixture was stirred at 80 $^{\circ}\text{C}$ for 2 h. The mixture was purified by silica gel column chromatography (5% MeOH in DCM) to give methyl 5-(hydroxymethyl)-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate (21 mg, 44.03% yield, 91.74% purity) as yellow oil. MS (ESI) $m/z = 343.0$ $[\text{M}+\text{H}]^{+}$.

Step 2: Synthesis of 5-(hydroxymethyl)-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylic acid

Methyl-5-(hydroxymethyl)-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate was used in the same manner as in Step 3 of Preparation Example 36 to give **Intermediate 4-25** (20 mg, 99.31% yield, 96% purity) as a yellow solid. MS (ESI) $m/z = 329.0$ $[\text{M}+\text{H}]^{+}$.

Preparation Example 36-12: 5-cyclohexyl-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylic acid (4-29)



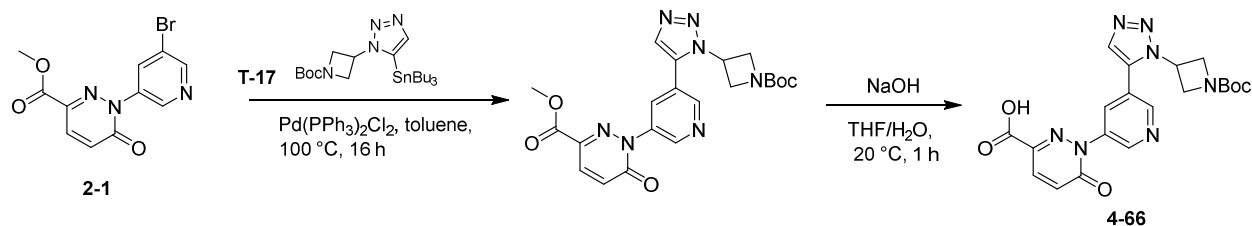
Step 1: Synthesis of methyl 5-cyclohexyl-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate

$\text{Pd}(\text{OH})_2$ (13.96 mg, 19.88 μmol , 20% purity) was added to a solution of Intermediate 3-24 (26 mg, 66.26 μmol) in dioxane (4 mL) and ethanol (4 mL) under nitrogen atmosphere. Hydrogen was purged several times under reduced pressure. Then the mixture was stirred at 45 $^{\circ}\text{C}$ for 16 h under hydrogen atmosphere (20 Psi). The reaction mixture was filtered, and then the filtrate was concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (3% DCM in MeOH) to give methyl 5-cyclohexyl-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate (30 mg, 98.56% yield, 85.860% purity) as a white solid. MS (ESI) $m/z = 395.0$ $[\text{M}+\text{H}]^{+}$.

Step 2: Synthesis of 5-cyclohexyl-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylic acid

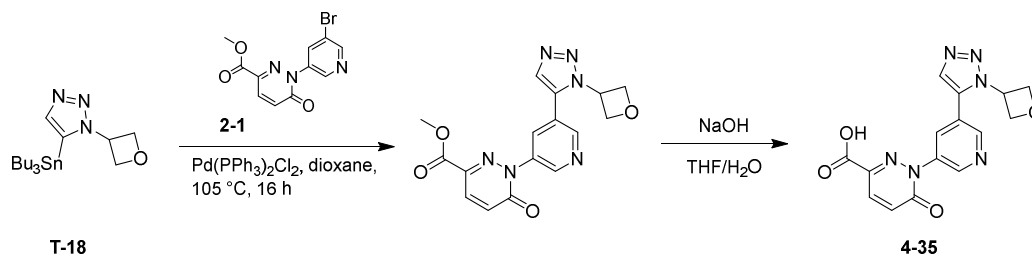
Methyl 5-cyclohexyl-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate was used in the same manner as in Step 3 of Preparation Example 36 to give **Intermediate 4-29** (30 mg, 93.19% yield, 89.880% purity) as a yellow solid. MS (ESI) $m/z = 380.7$ $[\text{M}+\text{H}]^{+}$.

Preparation Example 36-13: 1-[5-[3-(1-tert-butoxycarbonylazetidin-3-yl)triazol-4-yl]-3-pyridyl]-6-oxo-pyridazine-3-carboxylic acid (4-66)



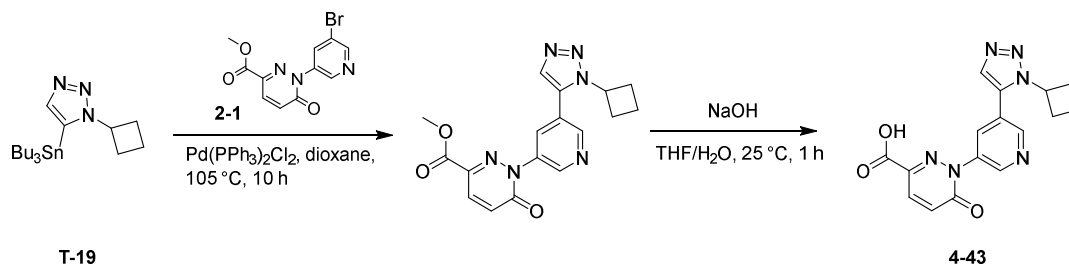
Methyl 1-(5-bromopyridin-3-yl)-6-oxo-1,6-dihydropyridazine-3-carboxylate (**2-1**) and Intermediate T-17 were used in the same manner as in Preparation Example 36-1 to give **Intermediate 4-66** (380 mg, 69.96% purity, 71.36% yield) as yellow oil. MS (ESI) $m/z = 340.0$ $[M+H]^+$.

Preparation Example 36-14: 1-[5-[3-(oxetan-3-yl)triazol-4-yl]-3-pyridyl]-6-oxo-pyridazine-3-carboxylic acid (4-35)



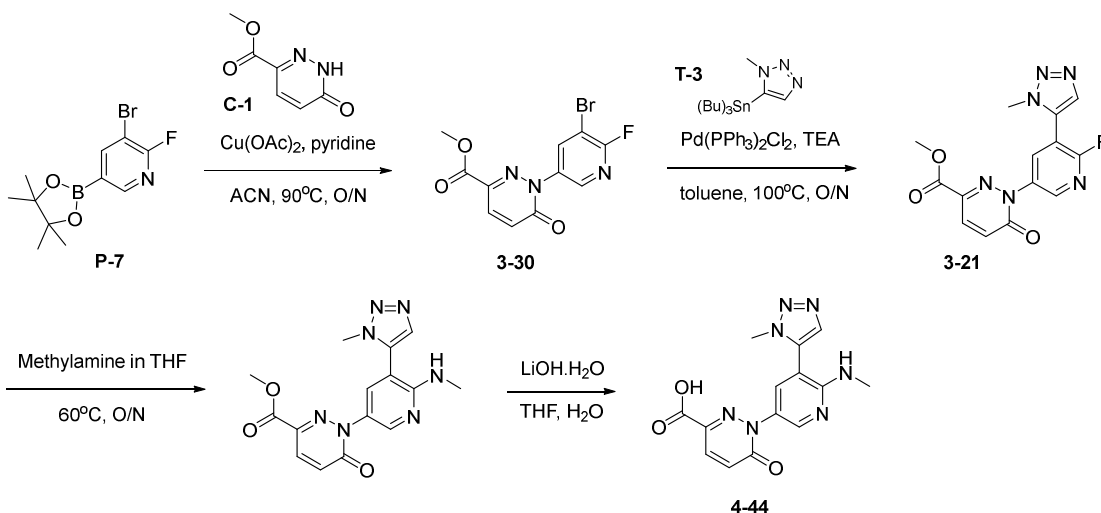
Intermediates 2-1 and T-18 were used in the same manner as in Preparation Example 36-1 to give **Intermediate 4-35** (27 mg, 32.53 μ mol, 38.42 yield, 41% purity) as a light yellow solid. MS (ESI) $m/z = 341.0$ $[M+H]^+$.

Preparation Example 36-15: 1-[5-(3-cyclobutyl-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylic acid (4-43)



Intermediates 2-1 and T-19 were used in the same manner as in Preparation Example 36-1 to give **Intermediate 4-43** (50 mg, 81.13% yield, 93.48% purity) as a yellow solid. MS (ESI) $m/z = 339.0$ $[M+H]^+$.

Preparation Example 37: 1-[6-(methylamino)-5-(1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxylic acid (4-44)



Step 1: Synthesis of methyl 1-(5-bromo-6-fluoro-3-pyridyl)-6-oxo-1,6-dihydropyridazine-3-carboxylate

Methyl 6-oxo-1,6-dihydropyridazine-3-carboxylate (**C-1**) and Intermediate P-7 were used in the same manner as in Step 1 of Preparation Example 33 to give **Intermediate 3-30** (213 mg, 100%) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 8.54 (dd, $J = 2.4, 1.2$ Hz, 1H), 8.37 (dd, $J = 7.6, 2.4$ Hz, 1H), 7.95 (d, $J = 9.6$ Hz, 1H), 7.12 (d, $J = 10.0$ Hz, 1H), 3.40 (s, 3H); MS (ESI) $m/z = 327.9$ $[\text{M}+\text{H}]^+$, 329.9 $[\text{M}+3\text{H}]^+$.

Step 2: Synthesis of methyl 1-[6-fluoro-5-(1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxylate

Intermediates 3-30 and T-3 were used in the same manner as in Step 2 of Preparation Example 33 to give **Intermediate 3-21** (145 mg, 67%) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 8.73 (q, $J = 7.3$ Hz, 1H), 8.24 (dd, $J = 8.0, 2.8$ Hz, 1H), 7.99 (d, $J = 9.6$ Hz, 1H), 7.89 (s, 1H), 7.15 (d, $J = 9.6$ Hz, 1H), 4.13 (d, $J = 1.2$ Hz, 3H), 4.00 (s, 3H); MS (ESI) $m/z = 331.0$ $[\text{M}+\text{H}]^+$.

Step 3: Synthesis of methyl 1-[6-(methylamino)-5-(1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxylate

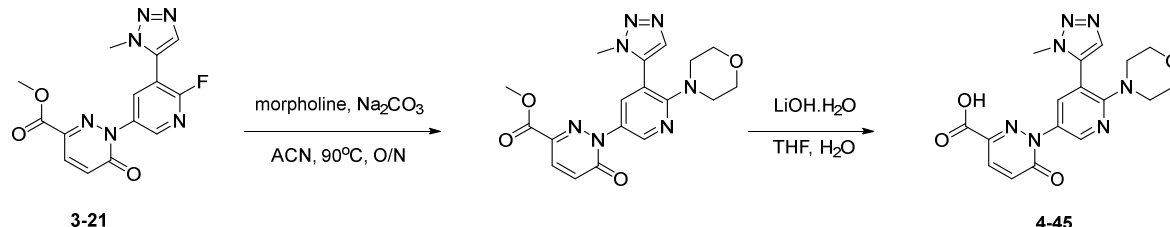
A solution of Intermediate 3-21 (70 mg, 0.212 mmol) in methylamine (1M in THF, 1.1 mL) was stirred at 60°C for 16 h under N_2 atmosphere. Methylamine (1M in THF, 1.1 mL) was further added to the reaction mixture and stirred at 60°C for 2 h. Then the reaction mixture was concentrated under reduced pressure, crystallized by DCM and hexane to give methyl 1-[6-(methylamino)-5-(1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxylate (63mg, 87%) as a yellow solid. It was used in the next reaction without further purification. MS (ESI) $m/z = 342.0$ $[\text{M}+\text{H}]^+$.

Step 4: Synthesis of 1-[6-(methylamino)-5-(1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxylic acid

The intermediate, methyl 1-[6-(methylamino)-5-(1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxylate was used in the same manner as in Step 3

of Preparation Example 33 to give **Intermediate 4-44** (25 mg, 41%) as a yellow solid. MS (ESI) $m/z = 328.0$ $[M+H]^+$.

Preparation Example 38: 1-[5-(1-methyl-1H-1,2,3-triazol-5-yl)-6-morpholino-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxylic acid (4-45)



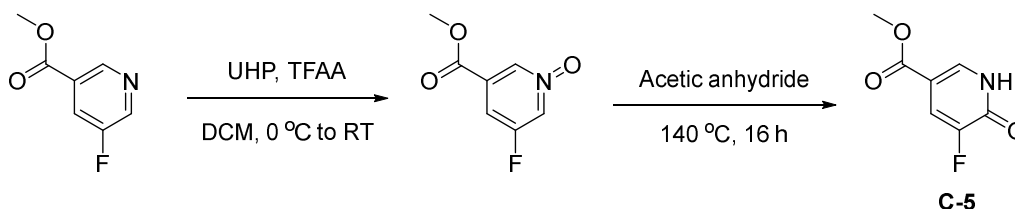
Step 1: Synthesis of methyl 1-[5-(1-methyl-1H-1,2,3-triazol-5-yl)-6-morpholino-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxylate

Intermediate 3-21 (65 mg, 0.197 mmol), morpholine (25.5 μ L, 0.295 mmol) and Na_2CO_3 (42 mg, 0.394 mmol) in MeCN (0.5 mL) were placed in a microwave vial and stirred at 90°C for 17.5 h. Then the mixture was cooled to room temperature and diluted with EtOAc. The solid was filtered with celite pad, washed with EtOAc. The filtrate was concentrated under reduced pressure. The product was purified by silica gel column chromatography to give methyl 1-[5-(1-methyl-1H-1,2,3-triazol-5-yl)-6-morpholino-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxylate (54 mg, 69%) as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 8.67 (d, $J = 2.8$ Hz, 1H), 7.95 (d, $J = 9.6$ Hz, 1H), 7.81 (s, 1H), 7.79 (d, $J = 2.8$ Hz, 1H), 7.11 (d, $J = 10.0$ Hz, 1H), 4.04 (s, 3H), 3.99 (s, 3H), 3.66 (t, $J = 4.6$ Hz, 4H), 3.14 (t, $J = 4.8$ Hz, 4H); MS (ESI) $m/z = 398.1$ $[M+H]^+$.

Step 2: Synthesis of 1-[5-(1-methyl-1H-1,2,3-triazol-5-yl)-6-morpholino-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxylic acid

The intermediate, methyl 1-[5-(1-methyl-1H-1,2,3-triazol-5-yl)-6-morpholino-3-pyridyl]-6-oxo-1,6-dihydro-pyridazine-3-carboxylate was used in the same manner as in Step 3 of Preparation Example 33 to give **Intermediate 4-45** (33 mg, 63%) as a yellow solid. MS (ESI) $m/z = 384.1$ $[M+H]^+$.

Preparation Example 39: methyl 5-fluoro-6-oxo-1,6-dihydropyridin-3-carboxylate (C-5)



Step 1: Synthesis of 3-fluoro-5-(methoxycarbonyl)pyridine-1-oxide

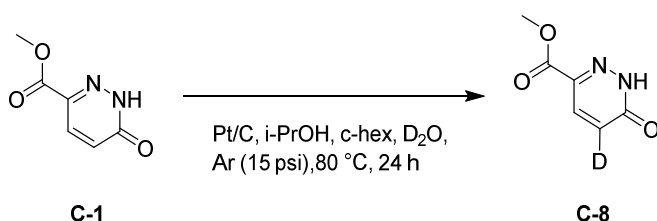
Urea hydrogen peroxide (1.27 g, 13.5 mmol) and trifluoroacetic acid anhydride (4.66 mL, 33.5 mmol) were added to a solution of methyl-5-fluoronicotinate (1 g, 6.45 mmol) in DCM (14.3 mL) under nitrogen atmosphere at 0 °C. Then the reaction mixture was stirred at 25 °C

for 17 h. The reaction mixture was cooled to 0 °C, added with aq. NaHCO₃, and then extracted with DCM. The combined organic layers were washed with aq. sodium bisulfate, dried over Na₂SO₄, and then concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (5% MeOH in DCM) to give 3-fluoro-5-(methoxycarbonyl)pyridine-1-oxide (245 mg, 22% yield) as a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 9.07 (s, 1H), 8.67 (s, 1H), 8.01 (ddd, *J* = 8.6, 2.8, 1.6 Hz, 1H), 3.99 (s, 3H); MS (ESI) *m/z* = 171.95 [M+H]⁺.

Step 2: Synthesis of methyl 5-fluoro-6-oxo-1,6-dihydropyridine-3-carboxylate

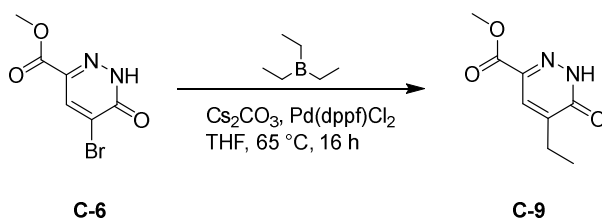
A solution of 3-fluoro-5-(methoxycarbonyl)pyridine-1-oxide (394 mg, 2.30 mmol) in acetic anhydride (11.3 mL) was stirred at 140 °C for 17 h under nitrogen atmosphere. The reaction mixture was quenched with aq. NaHCO₃ and extracted with EtOAc. The combined organic layers were dried over Na₂SO₄, and then concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (5% MeOH in DCM) to give **Intermediate C-5** (129 mg, 33% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 12.81 (brs, 1H), 8.07-8.08 (m, 1H), 7.77 (dd, *J* = 10.4, 2.2 Hz, 1H), 3.89 (s, 3H).

Preparation Example 40: methyl 5-deuterio-6-oxo-1H-pyridazine-3-carboxylate (C-8)



A solution of methyl 6-oxo-1H-pyridazine-3-carboxylate (200 mg, 1.30 mmol), Pt/C (163.59 mg, 38.93 μmol, 5% purity) in D₂O (4 mL), isopropanol (0.2 mL) and cyclohexane (1.8 mL) was degassed and purged with argon for 3 times. Then the mixture was stirred at 90 °C for 24 h under argon atmosphere in 50 mL autoclave. The reaction mixture was diluted with DCM (20 mL), filtered, and the filter cake was washed with DCM (20 mL x 2), concentrated under reduced pressure to give **Intermediate C-8** (100 mg, 49.68% yield) as a brown solid. ¹H NMR (400 MHz, DMSO-d₆) δ 7.89 (s, 1H), 3.91 (s, 3H); MS (ESI) *m/z* = 155.9 [M+H]⁺.

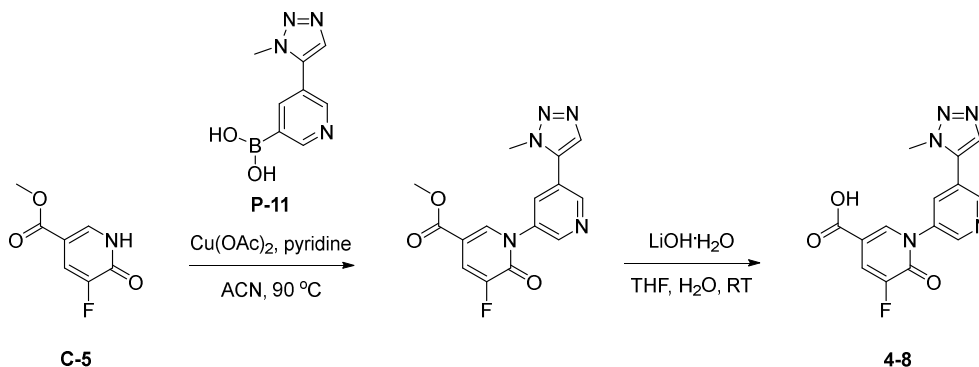
Preparation Example 41: methyl 5-ethyl-6-oxo-1H-pyridazine-3-carboxylate (C-9)



A solution of methyl 5-bromo-6-oxo-1H-pyridazine-3-carboxylate (46 mg, 117.59

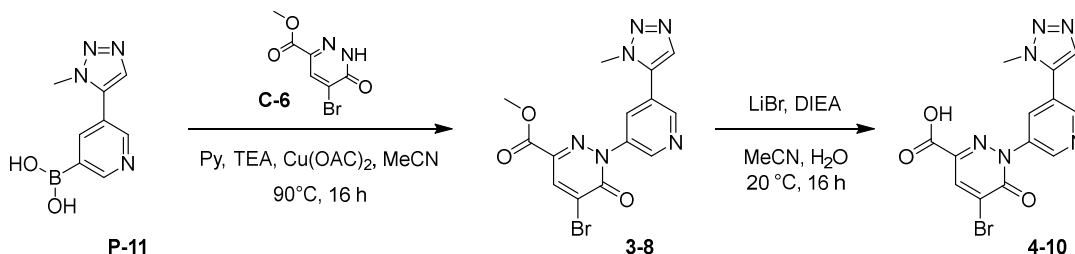
μmol), Cs_2CO_3 (6.99 g, 21.46 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (3.14 g, 4.29 mmol) and triethyl borate (1 M, 107.29 mL) in THF (60 mL) was substituted with nitrogen for 3 times, and then stirred at 65 °C for 16 h under nitrogen atmosphere. The reaction mixture was filtered, and then the filtrate was concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (1% DCM in MeOH) to give **Intermediate C-9** (930 mg, 42.82% yield, 90% purity) as a dark brown solid. MS (ESI) $m/z = 183.1$ $[\text{M}+\text{H}]^+$.

Preparation Example 42: 3-fluoro-5'-(1-methyl-1H-1,2,3-triazol-5-yl)-2-oxo-2H-[1,3'-bipyridine]-5-carboxylic acid (4-8)



Intermediate C-5 of Preparation Example 39 was used in the same manner as in Steps 1 and 3 of Preparation Example 33 to give **Intermediate 4-8** (12.8 mg, 58% yield). MS (ESI) $m/z = 316.06$ $[\text{M}+\text{H}]^+$.

Preparation Example 42-1: 5-bromo-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylic acid (4-10)



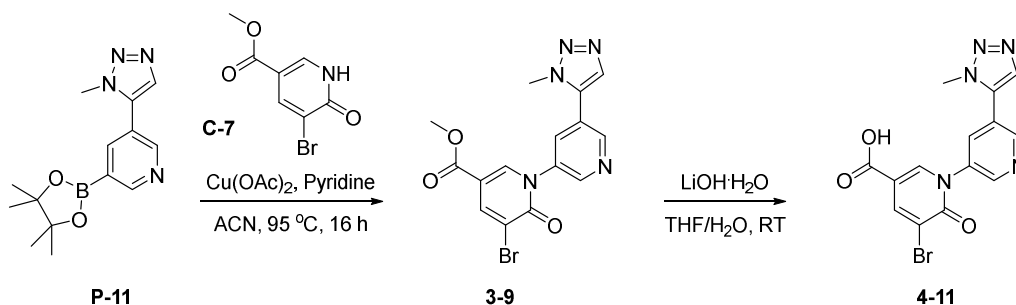
Step 1: Synthesis of methyl 5-bromo-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate

Intermediates C-6 and P-11 were used in the same manner as in Step 1 of Preparation Example 36-2 to give **Intermediate 3-8** (137 mg, 13.78% yield, 93% purity) as a yellow solid. MS (ESI) $m/z = 391.0$, 392.9 $[\text{M}+\text{H}]^+$.

Step 2: Synthesis of 5-bromo-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylic acid

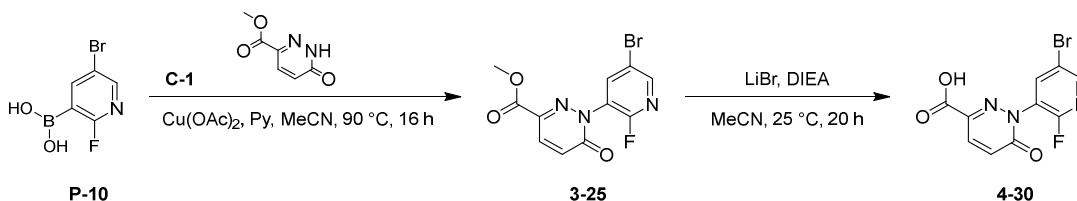
Intermediate 3-8 was used in the same manner as in Step 2 of Preparation Example 36-9 **Intermediate 4-10** (90 mg, crude product) as a brown solid. MS (ESI) $m/z = 376.9$, 379.0 $[\text{M}+\text{H}]^+$.

Preparation Example 42-2: 3-bromo-5'-(1-methyl-1H-1,2,3-triazol-5-yl)-2-oxo-2H-[1,3'-bipyridine]-5-carboxylic acid (4-11)



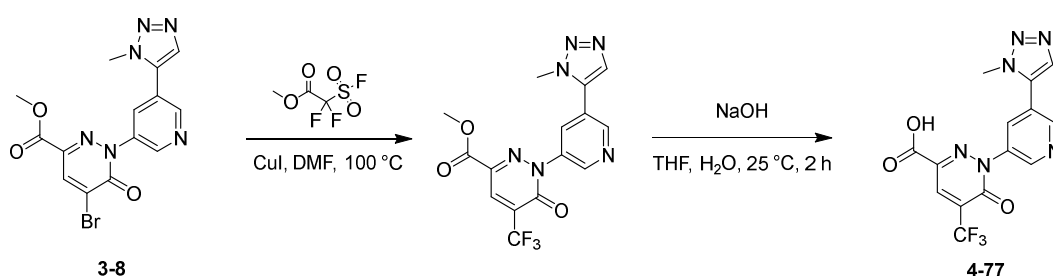
Intermediates P-11 and C-7 were used in the same manner as in Preparation Example 35 to give **Intermediate 4-11** (52 mg, 71% yield) as a light yellow solid. MS (ESI) m/z = 375.98, 377.97 $[\text{M}+\text{H}]^+$.

Preparation Example 42-3: 1-(5-bromo-2-fluoro-3-pyridyl)-6-oxo-pyridazine-3-carboxylic acid (4-30)



Commercially available (5-bromo-2-fluoropyridin-3-yl)boronic acid (**P-10**) and Intermediate C-1 were used in the same manner as in Preparation Example 42-1 to give **Intermediate 4-30** (45 mg, 78.85% yield, 93.6% purity, hydrochloride) as a yellow solid. MS (ESI) m/z = 313.8 $[\text{M}+\text{H}]^+$.

Preparation Example 42-4: 1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-5-(trifluoromethyl)pyridazine-3-carboxylic acid (4-77)



Step 1: Synthesis of methyl 1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-5-(trifluoromethyl)pyridazine-3-carboxylate

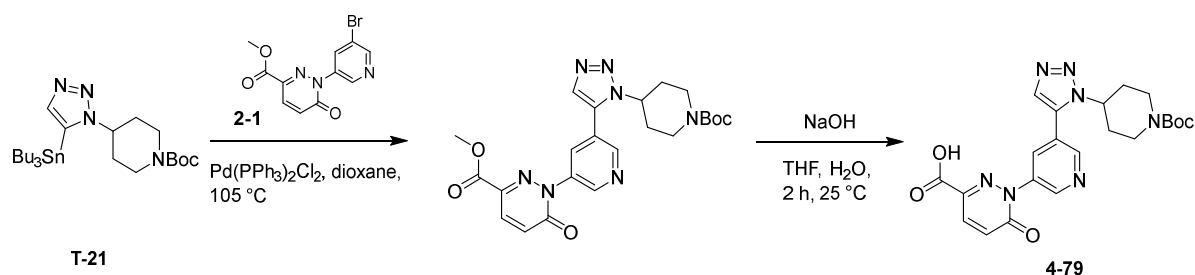
CuI (14.61 mg, 76.69 μmol) and methyl 2,2-difluoro-2-fluorosulfonylacetate (736.67 mg, 3.83 mmol, 487.86 μL) were added to a solution of Intermediate 3-8 (300 mg, 766.91 μmol) in DMF (5 mL). The mixture was stirred at 80 °C for 3 h. The reaction mixture was concentrated under reduced pressure to give a crude product. The crude product was diluted with EtOAc (30 mL) and washed with brine (15 mL $\times$ 3). The organic layers were dried over anhydrous Na_2SO_4 , and then concentrated under reduced pressure to give a crude product. The crude product was

purified by silica gel column chromatography (1% MeOH in DCM) to give methyl 1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-5-(trifluoromethyl)pyridazine-3-carboxylate (40 mg, 9.59% yield, 69.9% purity) as yellow oil. MS (ESI) $m/z = 380.9 [M+H]^+$.

Step 2: Synthesis of 1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-5-(trifluoromethyl)pyridazine-3-carboxylic acid

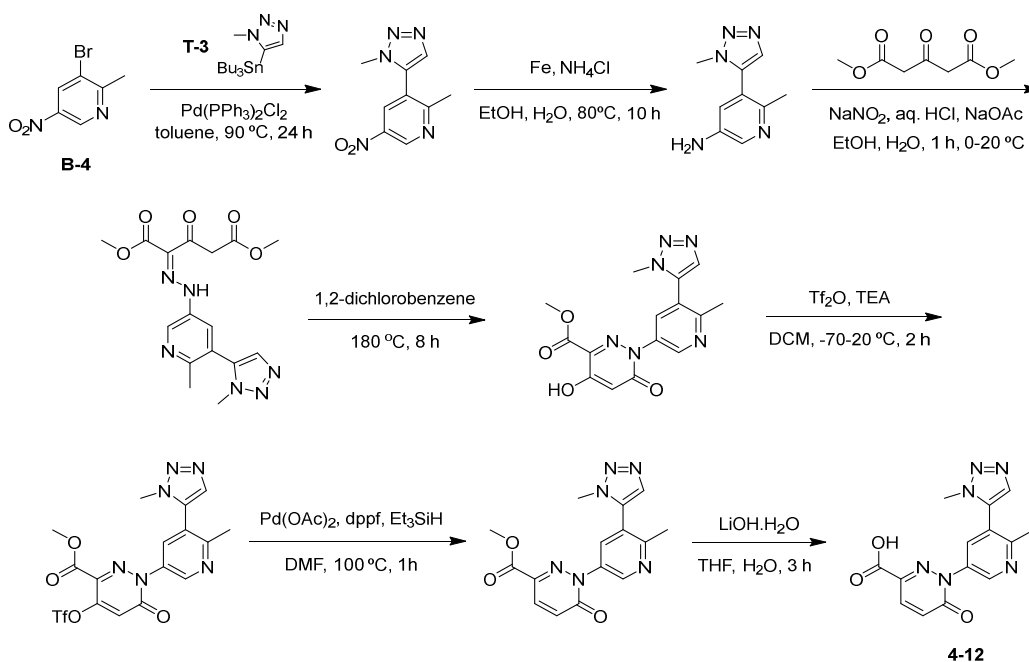
The intermediate, methyl 1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-5-(trifluoromethyl)pyridazine-3-carboxylate was used in the same manner as in Step 2 of Preparation Example 35 to give **Intermediate 4-77** (30 mg, 27.26% yield, 35% purity) as a yellow solid. MS (ESI) $m/z = 366.9 [M+H]^+$.

Preparation Example 42-5: 1-[5-[3-(1-tert-butoxycarbonyl-4-piperidyl)triazol-4-yl]-3-pyridyl]-6-oxo-pyridazine-3-carboxylic acid (4-79)



Intermediates T-21 and 2-1 were used in a similar manner as in Preparation Example 31 to give **Intermediate 4-79** (450 mg, 81.58% yield, 88% purity) as a yellow solid. MS (ESI) $m/z = 468.1 [M+H]^+$.

Preparation Example 43: 1-(6-methyl-5-(1-methyl-1H-1,2,3-triazol-5-yl)pyridin-3-yl)-6-oxo-1,6-dihydropyridazine-3-carboxylic acid (4-12)



Step 1: Synthesis of 2-methyl-3-(3-methyltriazol-4-yl)-5-nitro-pyridine

A solution of 3-bromo-2-methyl-5-nitro-pyridine (10 g, 46.08 mmol), tributyl-(3-methyltriazol-4-yl)stannane (17.15 g, 46.08 mmol) and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (1.62 g, 2.30 mmol) in toluene (100 mL) was substituted with nitrogen for 3 times, and then stirred at 100 °C for 16 h under nitrogen atmosphere. The reaction mixture was filtered, and then the filtrate was concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (50% EtOAc in petroleum ether) to give 2-methyl-3-(3-methyltriazol-4-yl)-5-nitro-pyridine (7.7 g, 58.00% yield, 76.08% purity) as a yellow solid. MS (ESI) $m/z = 220.1$ $[\text{M}+\text{H}]^+$.

Step 2: Synthesis of 6-methyl-5-(3-methyltriazol-4-yl)pyridine-3-amine

Fe (9.81 g, 175.64 mmol) and NH_4Cl (18.79 g, 351.28 mmol) were added to a solution of 2-methyl-3-(3-methyltriazol-4-yl)-5-nitro-pyridine (7.7 g, 35.13 mmol) in EtOH (150 mL) and H_2O (50 mL), and then the mixture was stirred at 80 °C for 3 h under nitrogen atmosphere. The reaction mixture was filtered, and then the filtrate was concentrated under reduced pressure. After the addition of water (15 mL), the reaction mixture was extracted with EtOAc (60 mL $\times$ 3). The combined organic layers were washed with brine (20 mL $\times$ 2), dried over Na_2SO_4 , and then concentrated under reduced pressure to give a crude product, 6-methyl-5-(3-methyltriazol-4-yl)pyridine-3-amine (5.86 g, 84.62% yield, 95.98% purity) as a yellow solid. MS (ESI) $m/z = 190.1$ $[\text{M}+\text{H}]^+$.

Step 3: Synthesis of dimethyl (2E)-2-[[6-methyl-5-(3-methyltriazol-4-yl)-3-pyridyl]hydrazono]-3-oxo-pentanedioate

A solution of NaNO_2 (1.38 g, 19.98 mmol) in H_2O (15 mL) was added to HCl (12 M, 8.39 mL) and 6-methyl-5-(3-methyltriazol-4-yl)pyridine-3-amine (3.78 g, 19.98 mmol) in H_2O (20 mL) at 0 °C. Then dimethyl 3-oxopentanedioate (3.48 g, 19.98 mmol, 2.88 mL) in EtOH (12 mL) and NaOAc (12.00 g, 146.27 mmol) in H_2O (40 mL) were added to the reaction mixture. The reaction mixture was stirred at 20 °C for 1 h. The reaction mixture was concentrated under reduced pressure, then extracted with EtOAc (30 mL $\times$ 3). The combined organic layers were washed with brine (20 mL $\times$ 2), dried over Na_2SO_4 , and then concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (5% MeOH in DCM) to give dimethyl (2E)-2-[[6-methyl-5-(3-methyltriazol-4-yl)-3-pyridyl]hydrazono]-3-oxo-pentanedioate (6.1 g, 70.10% yield, 85.96% purity) as yellow oil. MS (ESI) $m/z = 375.1$ $[\text{M}+\text{H}]^+$.

Step 4: Synthesis of methyl 4-hydroxy-1-[6-methyl-5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate

A mixture of dimethyl (2E)-2-[[6-methyl-5-(3-methyltriazol-4-yl)-3-pyridyl]hydrazono]-3-oxo-pentanedioate (6.1 g) in 1,2-dichlorobenzene (80 mL) was stirred at 180 °C for 8 h. The reaction mixture was filtered, and then the filtrate was concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (4% MeOH in DCM) to give methyl 4-hydroxy-1-[6-methyl-5-(3-

methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate (1.18 g, 15.65% yield, 74% purity) as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 12.22 (br s, 1H), 8.75 (d, J = 2.4 Hz, 1H), 8.04 (d, J = 2.4 Hz, 1H), 7.98 (s, 1H), 6.23 (s, 1H), 3.90 (s, 3H), 3.84 (s, 3H), 2.42 (s, 3H); MS (ESI) m/z = 343.0 $[\text{M}+\text{H}]^+$.

Step 5: Synthesis of methyl 1-[6-methyl-5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-4-(trifluoromethylsulfonyloxy)pyridazine-3-carboxylate

TEA (869.09 mg, 8.59 mmol, 1.20 mL) and trifluoromethylsulfonyl trifluoromethanesulfonate (1.62 g, 5.73 mmol, 944.72 μL) in DCM (5 mL) were slowly added to a mixture of methyl 4-hydroxy-1-[6-methyl-5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate (0.98 g, 2.86 mmol) in DCM (15 mL) at -70°C , and then the mixture was stirred at 20°C for 2 h. After the addition of water (15 mL), the reaction mixture was extracted with DCM (30 mL X 3). The combined organic layers were washed with brine (10 mL x 2), dried over Na_2SO_4 , and then concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (50% EtOH in petroleum ether) to give methyl 1-[6-methyl-5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-4-(trifluoromethylsulfonyloxy)pyridazine-3-carboxylate (939 mg, 47.85% yield, 69.21% purity) as a yellow solid. MS (ESI) m/z = 475.1 $[\text{M}+\text{H}]^+$.

Step 6: Synthesis of methyl 1-[6-methyl-5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxopyridazine-3-carboxylate

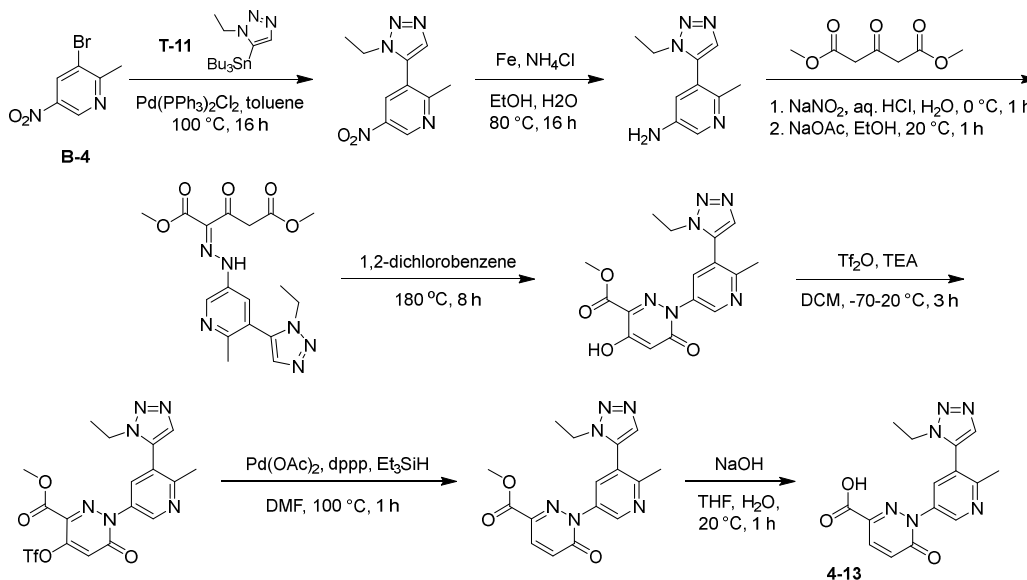
A solution of methyl 1-[6-methyl-5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-4-(trifluoromethylsulfonyloxy)pyridazine-3-carboxylate (939 mg, 1.98 mmol), $\text{Pd}(\text{OAc})_2$ (66.66 mg, 296.92 μmol), Dppp (244.92 mg, 593.84 μmol) and Et_3SiH (299.22 mg, 2.57 mmol, 411.01 μL) in DMF (10 mL) was substituted with nitrogen for 3 times, and then stirred at 100°C for 1 h under nitrogen atmosphere. After the addition of water (15 mL), the reaction mixture was extracted with EtOAc (40 mL X 3). The combined organic layers were washed with brine (20 mL x 2), dried over Na_2SO_4 , and then concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (3% MeOH in DCM) to give methyl 1-[6-methyl-5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxopyridazine-3-carboxylate (850 mg, 1.56 mmol, 78.96% yield, 60% purity) as a yellow solid. MS (ESI) m/z = 327.1 $[\text{M}+\text{H}]^+$.

Step 7: Synthesis of 1-[6-methyl-5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxopyridazine-3-carboxylic acid

$\text{LiOH}\cdot\text{H}_2\text{O}$ (173.61 mg, 4.14 mmol) was added to a solution of methyl 1-[6-methyl-5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxopyridazine-3-carboxylate (450 mg, 1.38 mmol) in THF (4 mL) and H_2O (2 mL). Then the mixture was stirred at 25°C for 1 h. After the addition of water (10 mL), the reaction mixture was extracted with EtOAc (20 mL X 3), and then the organic layers were removed. The mixture was adjusted to pH = 2-3 with aq. 1 N HCl, and then extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine

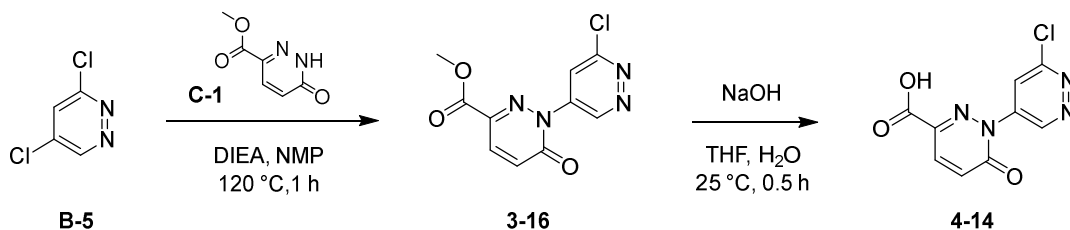
(10 mL x 2), dried over Na₂SO₄, and then concentrated under reduced pressure to give **Intermediate 4-12** (287 mg, 48.83% yield, 73.27% purity) as a yellow solid. MS (ESI) m/z = 313.0 [M+H]⁺.

Preparation Example 43-1: 1-[5-(3-ethyltriazol-4-yl)-6-methyl-3-pyridyl]-6-oxo-pyridazine-3-carboxylic acid (4-13)



Intermediate T-11 was concentrated in the same manner as in Preparation Example 43 to give **Intermediate 4-13** (55 mg, 55.45% yield, 67.66% purity) as a white solid. MS (ESI) m/z = 327.0 [M+H]⁺.

Preparation Example 44: 1-(6-chloropyridazin-4-yl)-6-oxo-pyridazine-3-carboxylic acid (4-14)



Step 1: Synthesis of methyl 1-(6-chloropyridazin-4-yl)-6-oxo-pyridazine-3-carboxylate

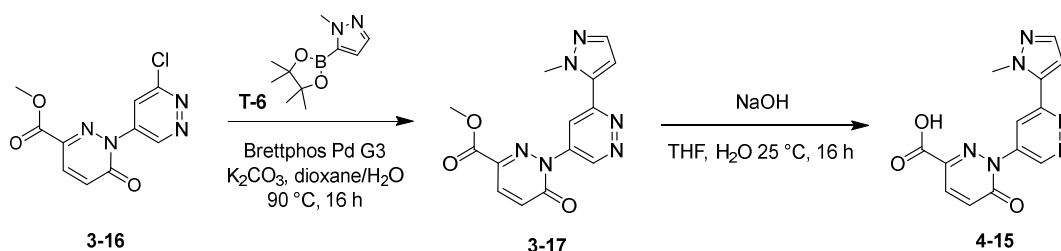
A solution of 3,5-dichloropyridazine (5 g, 33.56 mmol), methyl 6-oxo-1H-pyridazine-3-carboxylate (5.17 g, 33.56 mmol) and DIEA (21.69 g, 167.81 mmol, 29.23 mL) in NMP (5 mL) was stirred in microwave at 120 °C for 1 h. After the addition of water (100 mL), the reaction mixture was extracted with EtOAc (100 mL X 3). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, and then concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (30% EtOAc in petroleum ether) to give methyl 1-(6-chloropyridazin-4-yl)-6-oxo-pyridazine-3-carboxylate (**Intermediate 3-16**; 1.92 g, 19.95% yield, 93% purity) as a yellow solid. ¹H

NMR (400 MHz, DMSO- d_6) δ 9.67 (d, J = 2.0 Hz, 1H), 8.32 (d, J = 2.0 Hz, 1H), 7.97 (d, J = 10.0 Hz, 1H), 7.28 (d, J = 10.0 Hz, 1H), 3.92 (s, 3H); MS (ESI) m/z = 266.9 $[M+H]^+$.

Step 2: Synthesis of 1-(6-chloropyridazin-4-yl)-6-oxo-pyridazine-3-carboxylic acid

NaOH (174.00 mg, 4.35 mmol) was added to a solution of methyl 1-(6-chloropyridazin-4-yl)-6-oxo-pyridazine-3-carboxylate (580 mg, 2.18 mmol) in THF (6 mL), H₂O (2 mL). Then the mixture was stirred at 20 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure to give **Intermediate 4-14** (540 mg, 84.42% yield, 85.90% purity) as a yellow solid. MS (ESI) m/z = 253.1 $[M+H]^+$.

Preparation Example 45: 1-[6-(2-methylpyrazol-3-yl)pyridazin-4-yl]-6-oxo-pyridazine-3-carboxylic acid (4-15)



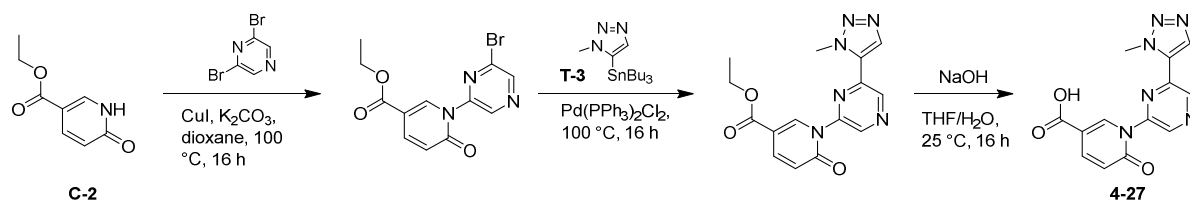
Step 1: Synthesis of methyl 1-[6-(2-methylpyrazol-3-yl)pyridazin-4-yl]-6-oxo-pyridazine-3-carboxylate

A solution of Intermediate 3-16 (300 mg, 1.13 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (351.14 mg, 1.69 mmol), BrettPhos Pd G3 (101.99 mg, 112.51 μ mol) and K₂CO₃ (310.99 mg, 2.25 mmol) in dioxane (5 mL) and H₂O (0.5 mL) was substituted with nitrogen for 3 times, and then it was stirred at 90 °C for 3 h under nitrogen atmosphere. After the addition of water (30 mL), the reaction mixture was extracted with EtOAc (30 mL X 3). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, and then concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (30% EtOAc in petroleum ether) to give methyl 1-[6-(2-methylpyrazol-3-yl)pyridazin-4-yl]-6-oxo-pyridazine-3-carboxylate (67 mg, 17.77% yield, 93.2% purity) as a yellow solid. MS (ESI) m/z = 313.1 $[M+H]^+$.

Step 2: Synthesis of 1-[6-(2-methylpyrazol-3-yl)pyridazin-4-yl]-6-oxo-pyridazine-3-carboxylic acid

NaOH (17.16 mg, 429.10 μ mol) and H₂O (1 mL) were added to a solution of methyl 1-[6-(2-methylpyrazol-3-yl)pyridazin-4-yl]-6-oxo-pyridazine-3-carboxylate (67 mg, 214.55 μ mol) in THF (2 mL). Then the mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give **Intermediate 4-15** (60 mg, 45.76% yield, 48.8% purity) as a white solid. MS (ESI) m/z = 299.0 $[M+H]^+$.

Preparation Example 46: 1-[6-(3-methyltriazol-4-yl)pyrazin-2-yl]-6-oxo-pyridine-3-carboxylic acid (4-27)



Step 1: Synthesis of ethyl 1-(6-bromopyrazin-2-yl)-6-oxo-pyridine-3-carboxylate

A solution of ethyl 6-oxo-1H-pyridine-3-carboxylate (5.46 g, 32.65 mmol), 2,6-dibromopyrazine (9.32 g, 39.18 mmol), CuI (1.24 g, 6.53 mmol), Cs₂CO₃ (10.64 g, 32.65 mmol) and 2-(dimethylamino)acetic acid (3.37 g, 32.65 mmol) in dioxane (80 mL) was degassed and purged with N₂ for 3 times. The mixture was stirred at 100 °C for 16 h under N₂ atmosphere. The reaction mixture was diluted with water and extracted with EtOAc (50 mL X 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, and then concentrated under reduced pressure to give a crude product. The crude product was purified by silica column chromatography (20% EtOAc in PE) to give ethyl 1-(6-bromopyrazin-2-yl)-6-oxo-pyridine-3-carboxylate (237 mg, 2.13% yield, 95.32% purity) as a yellow solid. ¹H NMR (400MHz, DMSO-*d*₆) δ 9.12 (s, 1H), 9.01 (s, 1H), 8.61 (d, *J* = 2.4 Hz, 1H), 7.94 (dd, *J* = 2.4, 9.6 Hz, 1H), 6.64 (d, *J* = 10.0 Hz, 1H), 4.29 (q, *J* = 7.2 Hz, 2H), 1.29 (t, *J* = 7.2 Hz, 3H); MS (ESI) *m/z* = 323.9 [M+H]⁺.

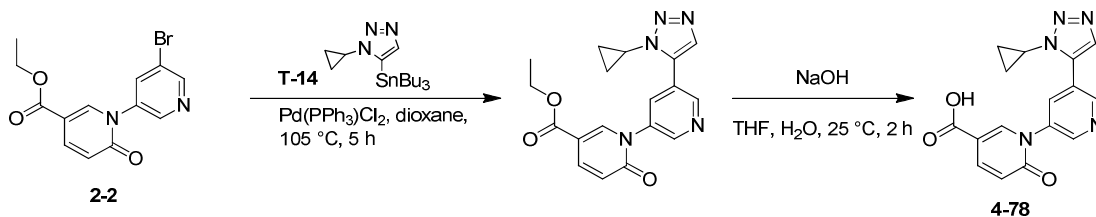
Step 2: Synthesis of ethyl 1-[6-(3-methyltriazol-4-yl)pyrazin-2-yl]-6-oxo-pyridine-3-carboxylate

A solution of ethyl 1-(6-bromopyrazin-2-yl)-6-oxo-pyridine-3-carboxylate (150 mg, 462.78 μmol), tributyl 3-methyl-1H-1,2,4-triazol-4-ylstannane (223.88 mg, 601.61 μmol) and Pd(PPh₃)₂Cl₂ (32.48 mg, 46.28 μmol) in dioxane (4 mL) was degassed and substituted with nitrogen for 3 times, and then it was stirred at 100 °C for 16 h under nitrogen atmosphere. The reaction mixture was filtered, and then the filtrate was concentrated under reduced pressure to give ethyl 1-[6-(3-methyltriazol-4-yl)pyrazin-2-yl]-6-oxo-pyridine-3-carboxylate (104 mg, 68.87% yield, 100% purity) as a yellow solid. ¹H NMR (400MHz, DMSO-*d*₆) δ 9.29 (s, 1H), 9.15 (s, 1H), 8.79 (d, *J* = 2.6 Hz, 1H), 8.56 (s, 1H), 7.95 (dd, *J* = 2.6, 9.6 Hz, 1H), 6.67 (d, *J* = 9.6 Hz, 1H), 4.34 (s, 3H), 4.28 (q, *J* = 7.2 Hz, 2H), 1.31 - 1.28 (m, 3H); MS (ESI) *m/z* = 327.0 [M+H]⁺.

Step 3: Synthesis of 1-[6-(3-methyltriazol-4-yl)pyrazin-2-yl]-6-oxo-pyridine-3-carboxylic acid

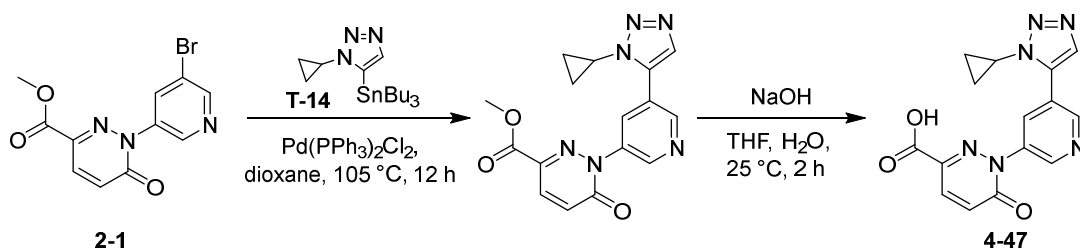
Ethyl 1-[6-(3-methyltriazol-4-yl)pyrazin-2-yl]-6-oxo-pyridine-3-carboxylate was used in the same manner as in Step 3 of Preparation Example 36 to give **Intermediate 4-27** (45 mg, 96.55% yield, 98.06% purity) as a yellow solid. MS (ESI) *m/z* = 299.1 [M+H]⁺.

Preparation Example 46-1: 1-[5-(3-cyclopropyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridine-3-carboxylic acid (4-78)



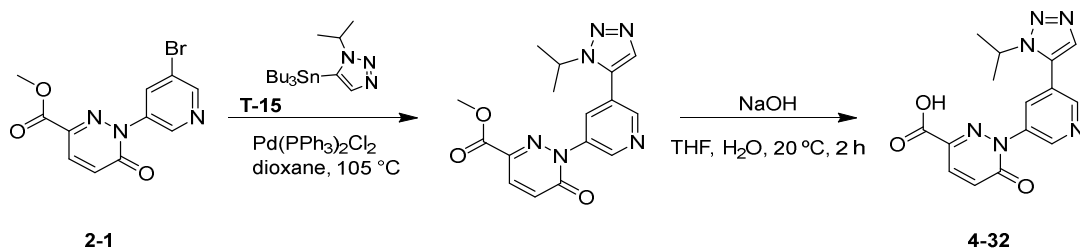
Intermediates 2-2 and T-14 were used in the same manner as in Steps 2 and 3 of Preparation Example 36 to give **Intermediate 4-78** (120 mg, 93.23% yield, 96.8% purity) as a yellow solid. MS (ESI) $m/z = 323.9 [M+H]^+$.

Preparation Example 47: 1-[5-(3-cyclopropyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylic acid (4-47)



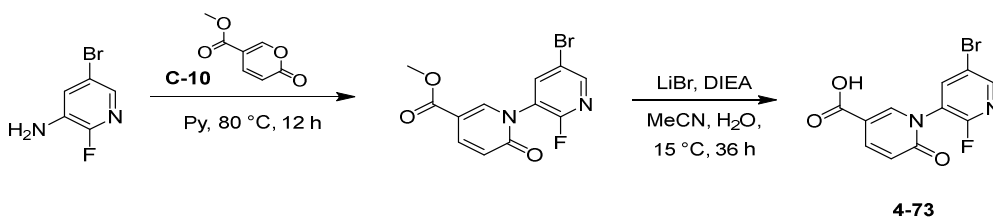
Intermediates 2-1 and T-14 were used in the same manner as in Steps 2 and 3 of Preparation Example 36 to give **Intermediate 4-47** (35 mg, 88.82% yield, 97.3% purity) as a yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ 9.03 (d, $J = 2.0$ Hz, 1H), 8.95 (d, $J = 2.4$ Hz, 1H), 8.56 (t, $J = 2.0$ Hz, 1H), 8.17 (s, 1H), 7.96 (d, $J = 9.6$ Hz, 1H), 7.22 (d, $J = 9.6$ Hz, 1H), 4.01 (td, $J = 3.6, 7.3$ Hz, 2H), 1.20 - 1.15 (m, 2H), 1.12 (br d, $J = 2.8$ Hz, 2H); MS (ESI) $m/z = 324.9 [M+H]^+$.

Preparation Example 47-1: 1-[5-(3-isopropyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylic acid (4-32)



Intermediates 2-1 and T-15 were used in the same manner as in Steps 2 and 3 of Preparation Example 36 to give **Intermediate 4-32** (55 mg, 93.99% yield, 98.31% purity) as a yellow solid. MS (ESI) $m/z = 326.6 [M+H]^+$.

Preparation Example 48: 1-(5-bromo-2-fluoro-3-pyridyl)-6-oxo-pyridine-3-carboxylic acid (4-73)



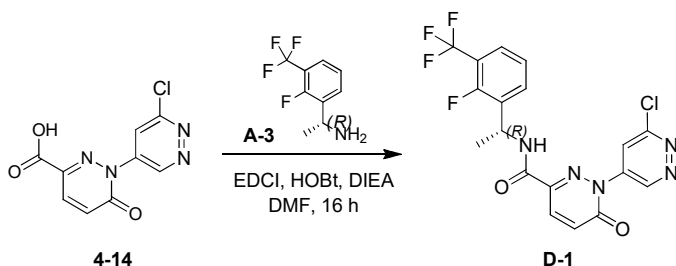
Step 1: Synthesis of methyl 1-(5-bromo-2-fluoro-3-pyridyl)-6-oxo-pyridine-3-carboxylate

5-bromo-2-fluoro-pyridine-3-amine (5 g, 26.18 mmol) was added to a solution of methyl 6-oxopyran-3-carboxylate (**C-10**; 8.07 g, 52.36 mmol) in pyridine (100 mL). The mixture was stirred at 80 °C for 12 h under nitrogen atmosphere. The reaction mixture was filtered, and then the filtrate was concentrated under reduced pressure to give a crude product. The crude product was purified by silica column chromatography (12% EtOAc in PE) to give a residue. The residue was dissolved in MeOH (5 mL) and purified by prep-HPLC (column: Welch Xtimate C18 250*50mm*10μm; mobile phase: [water(NH₄HCO₃)-MeCN]; 5%-55% B, 20 minutes). Most of MeCN was removed under reduced pressure, and the remaining solvent was removed by lyophilization to give methyl 1-(5-bromo-2-fluoro-3-pyridyl)-6-oxo-pyridine-3-carboxylate (360 mg, 4.12% yield, 98.08% purity) as a yellow-white solid. MS (ESI) m/z = 326.8 [M+H]⁺.

Step 2: Synthesis of 1-(5-bromo-2-fluoro-3-pyridyl)-6-oxo-pyridine-3-carboxylic acid

The intermediate, methyl 1-(5-bromo-2-fluoro-3-pyridyl)-6-oxo-pyridine-3-carboxylate was used in the same manner as in Step 2 of Preparation Example 36-9 to give **Intermediate 4-73** (60 mg, 60.43% yield, 96.39% purity) as a white solid. MS (ESI) m/z = 313.0 [M+H]⁺.

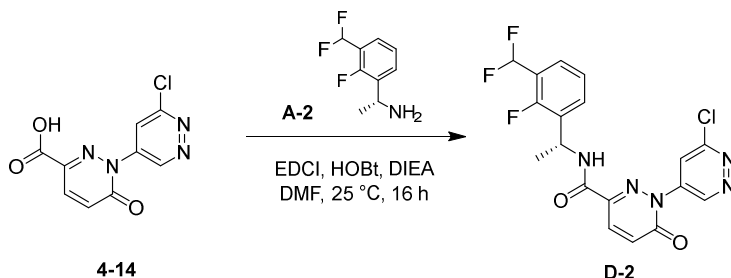
Preparation Example 49: 1-(6-chloropyridazin-4-yl)-N-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-6-oxo-pyridazine-3-carboxamide (D-1)



DIEA (752.07 mg, 5.82 mmol, 1.01 mL), HOBT (393.14 mg, 2.91 mmol) and EDCI (557.77 mg, 2.91 mmol) were added to a solution of 1-(6-chloropyridazin-4-yl)-6-oxo-pyridazine-3-carboxylic acid (490 mg, 1.94 mmol) and Intermediate A-3 (378.06 mg, 1.55 mmol, HCl salt) in DMF (6 mL). The mixture was degassed and purged with N₂ for 3 times, and then stirred at 25 °C for 5 h under N₂ atmosphere. After the addition of water (8 mL), the reaction mixture was extracted with EtOAc (20 mL X 3). The combined organic layers were washed with brine (10 mL x 2), dried over anhydrous Na₂SO₄, and then concentrated under

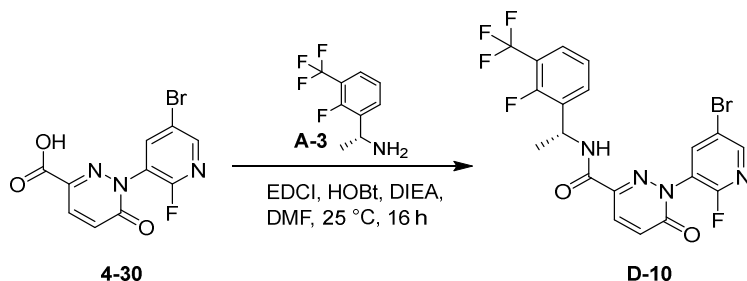
reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (3% MeOH in DCM) to give **Intermediate D-1** (140 mg, 11.33% yield, 69.37% purity) as brown oil. MS (ESI) $m/z = 442.1$ $[M+H]^+$.

Preparation Example 49-1: 1-(6-chloropyridazin-4-yl)-N-[(1R)-1-[2-fluoro-3-(difluoromethyl)phenyl]ethyl]-6-oxo-pyridazine-3-carboxamide (D-2)



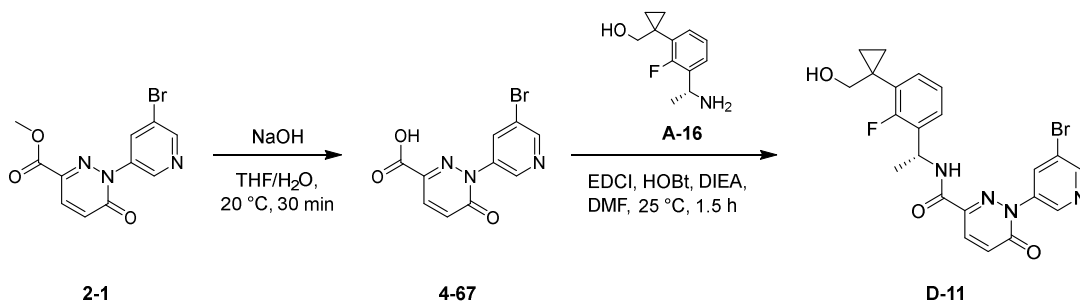
Intermediate A-2 was used in the same manner as in Preparation Example 49 to give **Intermediate D-2** (37.0 mg, 30.83% yield) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.97 (d, $J = 2.0$ Hz, 1H), 9.21 (d, $J = 8.0$ Hz, 1H), 8.75 (d, $J = 2.0$ Hz, 1H), 8.46 (s, 1H), 7.94 (d, $J = 10.0$ Hz, 1H), 7.72 (br t, $J = 7.2$ Hz, 1H), 7.57 - 7.51 (m, 1H), 7.35 (d, $J = 8.0$ Hz, 1H), 7.28 (d, $J = 10.0$ Hz, 1H), 7.22 (t, $J = 7.2$ Hz, 1H), 5.44 (quint, $J = 7.2$ Hz, 1H), 4.43 (s, 3H), 1.55 (d, $J = 7.2$ Hz, 3H); MS (ESI) $m/z = 471.2$ $[M+H]^+$.

Preparation Example 49-2: 1-(5-bromo-2-fluoro-3-pyridyl)-N-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-6-oxo-pyridazine-3-carboxamide (D-10)



Intermediates A-3 and 4-30 were used in the same manner as in Preparation Example 49 to give **Intermediate D-10** (30 mg, 55.80% yield, 93.46% purity) as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 8.42 (s, 1H), 8.10 (dd, $J = 2.4, 7.6$ Hz, 1H), 8.05 (m, 1H), 7.54 (t, $J = 7.2$ Hz, 2H), 7.35 (m, 1H), 7.26 - 7.20 (m, 1H), 7.12 (dd, $J = 1.2, 9.6$ Hz, 1H), 5.43 (m, 1H), 1.62 (d, $J = 7.2$ Hz, 3H); MS (ESI) $m/z = 504.9$ $[M+H]^+$.

Preparation Example 49-3: 1-(5-bromo-3-pyridyl)-N-[(1R)-1-[2-fluoro-3-[1-(hydroxymethyl)cyclopropyl]phenyl]ethyl]-6-oxo-pyridazine-3-carboxamide (D-11)



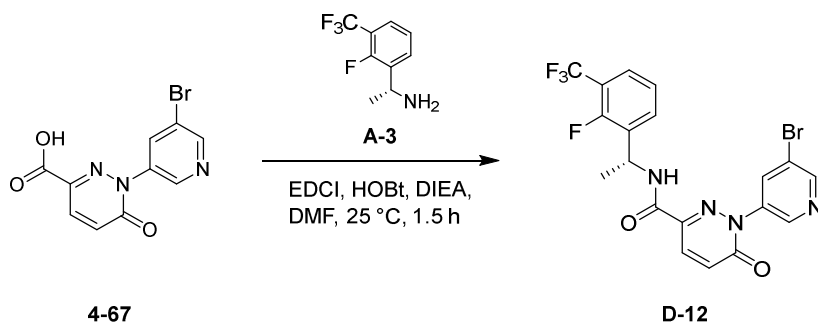
Step 1: Synthesis of 1-(5-bromo-3-pyridyl)-6-oxo-pyridazine-3-carboxylic acid

Intermediate **2-1** was used in the same manner as in Step 2 of Preparation Example 30 to give **Intermediate 4-67** (1.85 g, 92.04% yield, 95% purity) as a light yellow solid. MS (ESI) $m/z = 295.9 [M+H]^+$.

Step 2: Synthesis of 1-(5-bromo-3-pyridyl)-N-[(1R)-1-[2-fluoro-3-[(1-hydroxymethyl)cyclopropyl]phenyl]ethyl]-6-oxo-pyridazine-3-carboxamide

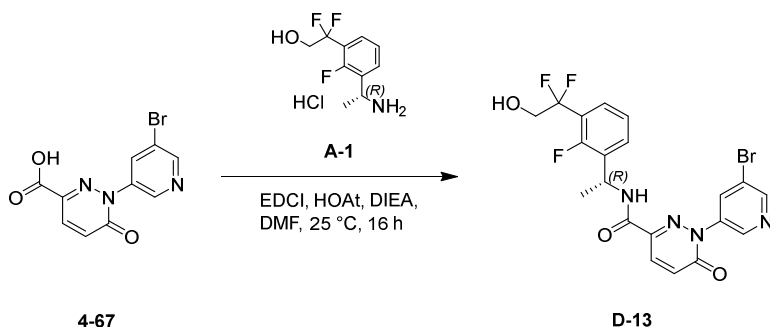
Intermediates **4-67** and **A-16** were used in the same manner as in Preparation Example 49 to give **intermediate D-11** (240 mg, 30.80% yield, 89.82% purity) as a yellow solid. MS (ESI) $m/z = 489.0 [M+H]^+$.

Preparation Example 49-4: 1-(5-bromo-3-pyridyl)-N-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-6-oxo-pyridazine-3-carboxamide (D-12)



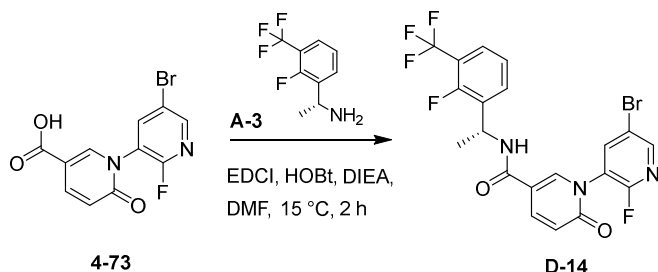
Intermediates **4-67** and **A-3** were used in the same manner as in Preparation Example 49 to give **Intermediate D-12** (34.3 g, 71.01% yield, 95% purity) as a light yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.14 (d, $J = 7.6$ Hz, 1H), 9.01 (d, $J = 2.0$ Hz, 1H), 8.83 (d, $J = 2.0$ Hz, 1H), 8.54 (t, $J = 2.0$ Hz, 1H), 7.90 (d, $J = 9.6$ Hz, 1H), 7.83 (t, $J = 7.2$ Hz, 1H), 7.68 (t, $J = 6.8$ Hz, 1H), 7.41 (t, $J = 7.6$ Hz, 1H), 7.20 (d, $J = 9.6$ Hz, 1H), 5.43 (quin, $J = 7.2$ Hz, 1H), 1.52 (d, $J = 7.2$ Hz, 3H); MS (ESI) $m/z = 486.8 [M+H]^+$.

Preparation Example 49-5: 1-(5-bromo-3-pyridyl)-N-[(1R)-1-[3-(1,1-difluoro-2-hydroxy-ethyl)-2-fluorophenyl]ethyl]-6-oxo-pyridazine-3-carboxamide (D-13)



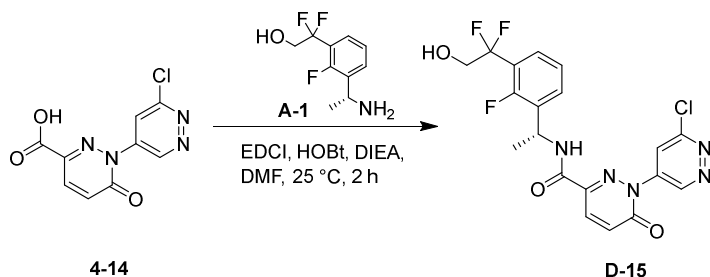
Intermediates A-1 and 4-67 were used in the same manner as in Preparation Example 49 to give **Intermediate D-13** (280 mg, 49.57% yield, 89.2% purity) as a white solid. MS (ESI) $m/z = 498.8 [M+H]^+$.

Preparation Example 49-6: 1-(5-bromo-2-fluoro-3-pyridyl)-N-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-6-oxo-pyridine-3-carboxamide (D-14)



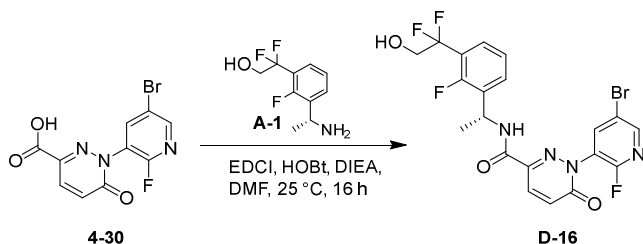
Intermediates A-3 and 4-73 were used in the same manner as in Preparation Example 49 to give **Intermediate D-14** (30 mg, 55.80% yield, 93.46% purity) as a yellow solid.

Preparation Example 49-7: 1-(6-chloropyridazin-4-yl)-N-[(1R)-1-[3-(1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethyl]-6-oxo-pyridazine-3-carboxamide (D-15)



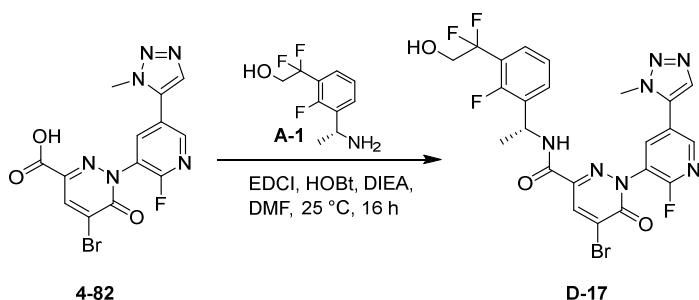
Intermediates A-1 and 4-14 were used in the same manner as in Preparation Example 49 to give **Intermediate D-15** (66 mg, 13.65% yield, 26% purity) as a yellow solid.

Preparation Example 49-8: 1-(5-bromo-2-fluoropyridin-3-yl)-N-[(1R)-1-[3-(1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethyl]-6-oxo-pyridazine-3-carboxamide (D-16)



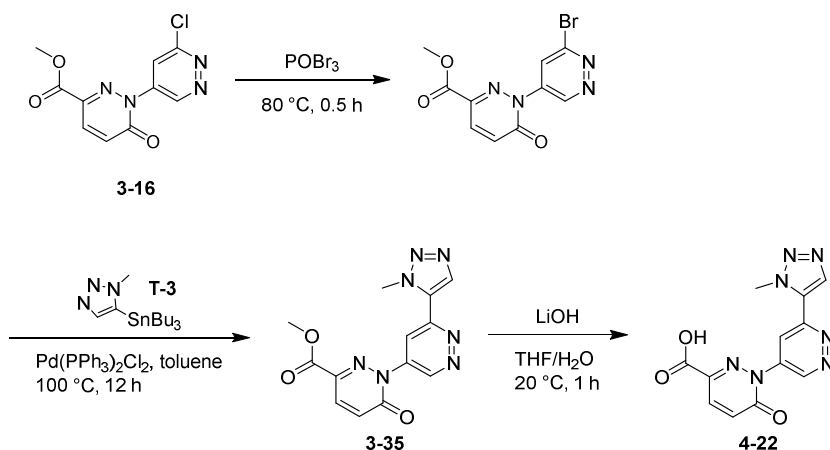
Intermediates A-1 and 4-30 were used in the same manner as in Preparation Example 49 to give **Intermediate D-16** (10 mg, 21.30% yield, 90.84% purity) as colorless oil. ^1H NMR (400 MHz, MeOD) δ 8.48 (t, J = 2.8 Hz, 2H), 8.01 (d, J = 10.0 Hz, 1H), 7.55 (br t, J = 7.2 Hz, 1H), 7.48 (br t, J = 6.8 Hz, 1H), 7.23 (t, J = 7.6 Hz, 1H), 7.18 (d, J = 10.0 Hz, 1H), 5.48 (q, J = 7.2 Hz, 1H), 4.00 (t, J = 13.6 Hz, 2H), 1.55 (d, J = 7.2 Hz, 3H); MS (ESI) m/z = 516.8 $[\text{M}+\text{H}+1]^+$.

Preparation Example 49-9: N-{(R)-1-[3-(1,1-difluoro-2-hydroxyethyl)-2-fluorophenyl]ethyl}-5-bromo-1-[5-(1-methyl-1H-1,2,3-triazol-5-yl)-2-fluoropyridin-3-yl]-6-oxo-1,6-dihydropyridazine-3-carboxamide (D-17)



Intermediates A-1 and 4-82 were used in the same manner as in Preparation Example 49 to give **Intermediate D-17** (45 mg, 55.80% yield, 93.46% purity) as a yellow solid. MS (ESI) m/z = 596.1 $[\text{M}+\text{H}]^+$.

Preparation Example 50: 1-[6-(3-methyltriazol-4-yl)pyridazin-4-yl]-6-oxo-pyridazine-3-carboxylic acid (4-22)



Step 1: Synthesis of methyl 1-(6-bromopyridazin-4-yl)-6-oxo-pyridazine-3-carboxylate

A solution of methyl 1-(6-chloropyridazin-4-yl)-6-oxo-pyridazine-3-carboxylic acid (250 mg, 937.59 μmol) in phosphoryl bromide (709.22 μL , 6.98 mmol) was stirred at 80 °C for 0.5 h. After the addition of water (10 mL) slowly, the reaction mixture was extracted with EtOAc (20 mL X 3). The combined organic layers were washed with brine (10 mL x 2), dried over Na_2SO_4 , and then concentrated under reduced pressure to give methyl 1-[6-(3-methyltriazol-4-yl)pyridazin-4-yl]-6-oxo-pyridazine-3-carboxylate (145 mg, 42.75% yield, 86%

purity) as black oil. MS (ESI) $m/z = 311.0$ $[M+H]^+$.

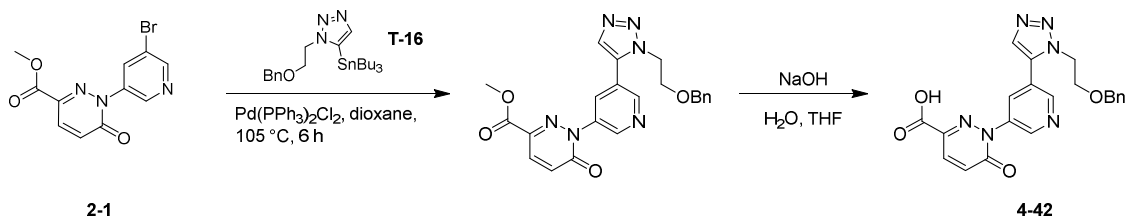
Step 2: Synthesis of methyl 1-[6-(3-methyltriazol-4-yl)pyridazin-4-yl]-6-oxo-pyridazine-3-carboxylate

A solution of methyl 1-(6-bromopyridazin-4-yl)-6-oxo-pyridazine-3-carboxylate (145 mg, 466.10 μmol), tributyl-3-methyltriazol-4-ylstannane (346.91 mg, 932.20 μmol) and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (65.43 mg, 93.22 μmol) in toluene (4 mL) was degassed and substituted with nitrogen for 3 times, and then stirred at 100 °C for 12 h under nitrogen atmosphere. The reaction mixture was filtered, and then the filtrate was concentrated under reduced pressure to give methyl 1-[6-(3-methyltriazol-4-yl)pyridazin-4-yl]-6-oxo-pyridazine-3-carboxylate (146 mg, crude product) as black oil. MS (ESI) $m/z = 314.1$ $[M+H]^+$.

Step 3: Synthesis of 1-[6-(3-methyltriazol-4-yl)pyridazin-4-yl]-6-oxo-pyridazine-3-carboxylic acid

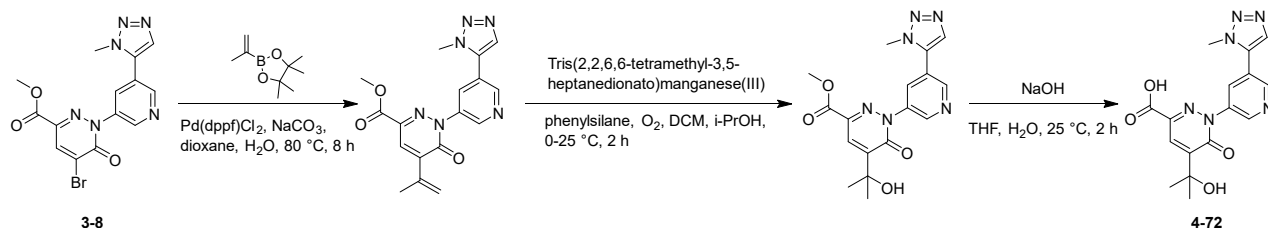
$\text{LiOH}\cdot\text{H}_2\text{O}$ (19.56 mg, 466.05 μmol) and H_2O (1 mL) were added to a solution of methyl 1-[6-(3-methyltriazol-4-yl)pyridazin-4-yl]-6-oxo-pyridazine-3-carboxylate (146 mg, 466.05 μmol) in THF (2 mL), and then the mixture was stirred at 20 °C for 1 h. The reaction mixture was adjusted to pH = 3-4 with aq. 1 N HCl, and extracted with EtOAc (20 mL $\times$ 3). The combined organic layers were washed with H_2O (20 mL) and brine (10 mL $\times$ 3), dried over anhydrous Na_2SO_4 , and then concentrated under reduced pressure to give **Intermediate 4-22** (130 mg, 57.79% yield, 62% purity) as black oil. MS (ESI) $m/z = 300.1$ $[M+H]^+$.

Preparation Example 51: 1-[5-[3-(2-benzyloxyethyl)triazol-4-yl]-3-pyridyl]-6-oxo-pyridazine-3-carboxylic acid (4-42)



Intermediates 2-1 and T-16 were used in the same manner as in Preparation Example 30 to give **Intermediate 4-42** (70 mg, 34.36% yield, 38% purity) as a brown solid. MS (ESI) $m/z = 419.2$ $[M+H]^+$.

Preparation Example 52: methyl 5-isopropenyl-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate (4-72)



Step 1: Synthesis of methyl 5-isopropenyl-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate

Pd(dppf)Cl₂ (18.71 mg, 25.56 μ mol), Na₂CO₃ (54.19 mg, 511.27 μ mol) and 2-isopropenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (128.87 mg, 766.91 μ mol) were added to a solution of 5-bromo-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate (100 mg, 255.64 μ mol) in dioxane (5 mL) and water (0.5 mL). The mixture was stirred at 80 °C for 3 h under nitrogen atmosphere. The reaction mixture was filtered, and then the filtrate was concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (1% MeOH in DCM) to give methyl 5-isopropenyl-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate (90 mg, 71.40% yield, 71.46% purity) as a yellow solid. MS (ESI) m/z = 353.0 [M+H]⁺.

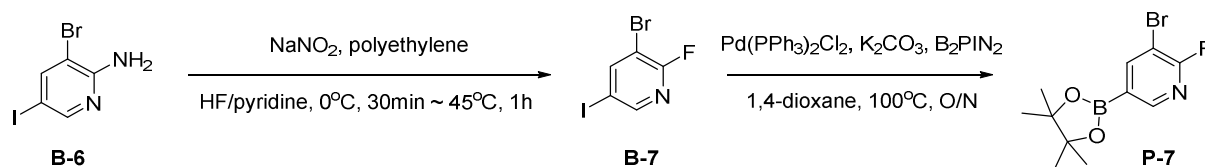
Step 2: Synthesis of methyl 5-(1-hydroxy-1-methyl-ethyl)-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate

Phenylsilane (55.28 mg, 510.86 μ mol, 63.04 μ L) and tris[(Z)-1-tert-butyl-4,4-dimethyl-3-oxo-pent-1-en-1-yl]manganese (15.45 mg, 25.54 μ mol) were added to a solution of methyl 5-isopropenyl-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate (90 mg, 255.43 μ mol) in DCM (1 mL) and *i*-PrOH (4 mL). The mixture was stirred at 0 °C for 5 h under oxygen atmosphere. The reaction mixture was filtered, and then the filtrate was concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (1% MeOH in DCM) to give methyl 5-(1-hydroxy-1-methyl-ethyl)-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate (60 mg, 55.26% yield, 87.14% purity) as a yellow solid. MS (ESI) m/z = 370.9 [M+H]⁺.

Step 3: Synthesis of methyl 5-isopropenyl-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate

The intermediate, methyl 5-(1-hydroxy-1-methyl-ethyl)-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxylate was used in the same manner as in Step 4 of Preparation Example 28 to give **Intermediate 4-72** (50 mg, 81.01% yield, 93.528% purity) as a yellow solid. MS (ESI) m/z = 356.9 [M+H]⁺.

Preparation Example 53: 3-bromo-2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (P-7)



Step 1: Synthesis of 3-bromo-2-fluoro-5-iodopyridine

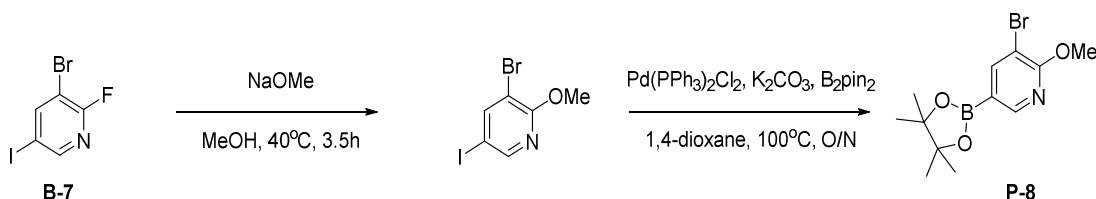
Sodium nitrite (402 mg, 5.82 mmol) was added dropwise to 3-bromo-5-iodopyridine-2-amine (1.5 g, 5.02 mmol) in HF/pyridine mixture (21 mL) at 0 °C in a polyethylene reaction vessel. The reaction mixture was stirred at 0 °C for 0.5 h, and then it was warmed to 45 °C and stirred for 1 h. After the addition of ice, the reaction mixture was adjusted to pH = 5 with aq. NaHCO₃, and then extracted with ether. The combined organic layers were washed with water,

dried over Na₂SO₄, and then concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography to give 3-bromo-2-fluoro-5-iodopyridine (1.32 g, 87%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.34-8.33 (m, 1H), 8.25 (dd, *J* = 8.0, 2.0 Hz, 1H).

Step 2: Synthesis of 3-bromo-2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine

Bis(pinacolato)diboron (1.22 g, 4.82 mmol) and K_2CO_3 (1.21 g, 8.76 mmol) were added to a solution of 3-bromo-2-fluoro-5-iodopyridine (1.32 g, 4.38 mmol) in dioxane (10 mL), and then the mixture was substituted with nitrogen for 3 times. Bis(triphenylphosphine)palladium(II) dichloride (154 mg, 0.219 mmol) was added and stirred at 100 °C for 18 h under nitrogen atmosphere. The reaction mixture was diluted with EtOAc, and then the combined organic layers were washed with aq. NH_4Cl , water and brine, dried over Na_2SO_4 , and then concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography to give **Intermediate P-7** (1.04 g, 79%) as a white solid. 1H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.32 (d, J = 9.2 Hz, 1H), 1.35 (s, 12H). MS (ESI) m/z = 302.0, 304.0 $[M+H]^+$.

Preparation Example 53-1: 3-bromo-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (P-8)



Step 1: Synthesis of 3-bromo-5-iodo-2-methoxypyridine

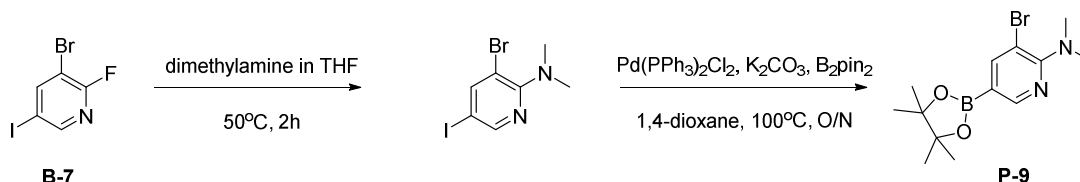
NaOMe (43 mg) was added to a solution of 3-bromo-2-fluoro-5-iodopyridine (200 mg, 0.663 mmol) in methanol (2.2 mL) in portions. Then the mixture was stirred at room temperature for 3.5 h. The reaction mixture was concentrated under reduced pressure. The crude product was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and then concentrated under reduced pressure to give 3-bromo-5-iodo-2-methoxypyridine (200 mg, 96%) as a gray solid. ¹H NMR (400 MHz, CDCl₃) δ 8.26 (d, *J* = 2.0 Hz, 1H), 8.05 (d, *J* = 2.0 Hz, 1H), 3.98 (s, 3H).

Step 2: Synthesis of 3-bromo-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine

Bis(pinacolato)diboron (178 mg, 0.701 mmol) and potassium carbonate (176 mg, 1.27 mmol) were added to a solution of 3-bromo-5-iodo-2-methoxypyridine (200 mg, 0.637 mmol) in dioxane (2 mL). The mixture was degassed and purged with nitrogen. The mixture was added with bis(triphenylphosphine)palladium(II)dichloride (22 mg, 0.0319 mmol), and stirred at 100 °C for 16.5 h under nitrogen atmosphere. The mixture was cooled to room temperature and diluted

with EtOAc. The mixture was washed with sat. aq. NH_4Cl , water and brine. The organic layers were dried over anhydrous Na_2SO_4 , and then concentrated under reduced pressure. It was purified by silica column chromatography to give **Intermediate P-8** (90 mg, 45%) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 8.44 (d, J = 1.6 Hz, 1H), 8.15 (d, J = 1.6 Hz, 1H), 4.04 (s, 3H), 1.33 (s, 12H); MS (ESI) m/z = 314.0 $[\text{M}+\text{H}]^+$.

Preparation Example 53-2: *N,N*-dimethyl-[3-bromo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]amine (P-9)



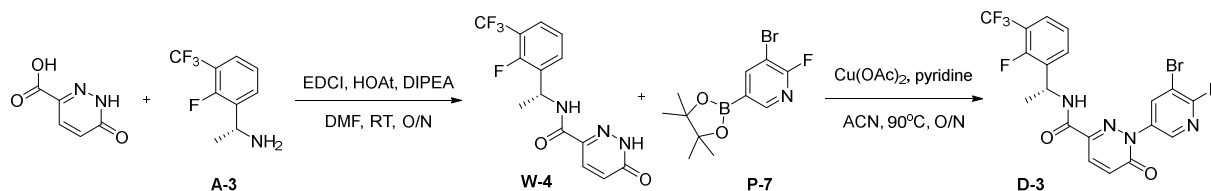
Step 1: Synthesis of *N,N*-dimethyl(3-bromo-5-iodo-2-pyridyl)amine

3-bromo-2-fluoro-5-iodopyridine (100 mg, 0.331 mmol) was added to a solution of dimethylamine (2M in THF, 0.83 mL), and the mixture was stirred at 50 °C for 2 h under nitrogen atmosphere. The resultant was cooled to room temperature, and then extracted with EtOAc and water. The organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 , and then concentrated under reduced pressure to give *N,N*-dimethyl-(3-bromo-5-iodo-2-pyridyl)amine (108 mg, 100%) as a yellow solid. It was used in the next reaction without further purification. ^1H NMR (400 MHz, CDCl_3) δ 8.30 (d, J = 2.0 Hz, 1H), 7.98 (d, J = 2.0 Hz, 1H), 2.98 (s, 6H); MS (ESI) m/z = 326.7 $[\text{M}+\text{H}]^+$, 328.7 $[\text{M}+3\text{H}]^+$.

Step 2: Synthesis of *N,N*-dimethyl-[3-bromo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]amine

The intermediate, *N,N*-dimethyl-(3-bromo-5-iodo-2-pyridyl)amine (108 mg, 0.330 mmol) was used in the same manner as in Step 2 of Preparation Example 53 to give **Intermediate P-9** (57 mg, 53%) as a brown solid. MS (ESI) m/z = 327.0 $[\text{M}+\text{H}]^+$, 329.0 $[\text{M}+3\text{H}]^+$.

Preparation Example 54: (R)-1-(5-bromo-6-fluoropyridin-3-yl)-*N*-(1-(2-fluoro-3-trifluoromethyl)phenyl)ethyl)-6-oxo-1,6-dihydropyridazine-3-carboxamide (D-3)



Step 1: Synthesis of (R)-*N*-(1-(2-fluoro-3-trifluoromethyl)phenyl)ethyl)-6-oxo-1,6-dihydropyridazine-3-carboxamide

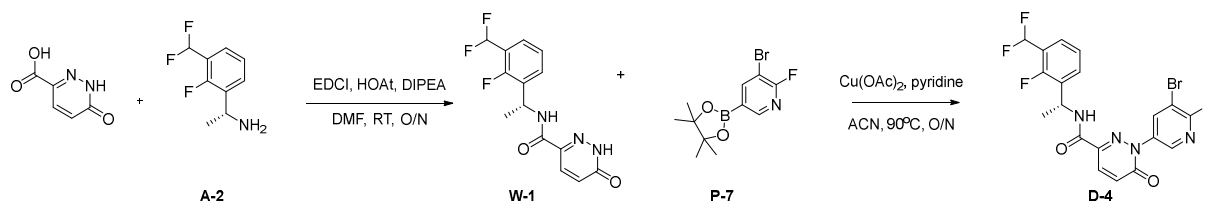
EDCI (205 mg, 1.07 mmol), HOAt (146 mg, 1.07 mmol) and DIEA (0.37 mL, 2.14 mmol) were added to a solution of 6-oxo-1,6-dihydropyridazine-3-carboxylic acid (100 mg, 0.714 mmol) and Intermediate A-3 (174 mg, 0.714 mmol, HCl) in DMF (3 mL). The mixture was degassed and purged with N_2 for 3 times, and then stirred at 25 °C for 18 h under N_2 .

atmosphere. The reaction mixture was poured into water and extracted with EtOAc. The combined organic layers were washed with brine for 5 times, dried over anhydrous Na₂SO₄, and then concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography to give a main product, (R)-N-(1-(2-fluoro-3-trifluoromethyl)phenyl)ethyl)-6-oxo-1,6-dihydropyridazine-3-carboxamide (164 mg, 70% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 12.39 (br, 1H), 8.04 (d, *J* = 10.0 Hz, 1H), 7.56-7.52 (m, 3H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.06 (d, *J* = 10.0 Hz, 1H), 5.44 (quint, *J* = 7.3, 14.7 Hz, 1H), 1.63 (d, *J* = 7.2 Hz, 3H); MS (ESI) *m/z* = 330.1 [M+H]⁺.

Step 2: Synthesis of (R)-1-(5-bromo-6-fluoropyridin-3-yl)-N-(1-(2-fluoro-3-trifluoromethyl)phenyl)ethyl)-6-oxo-1,6-dihydropyridazine-3-carboxamide

To a solution of (R)-N-(1-(2-fluoro-3-trifluoromethyl)phenyl)ethyl)-6-oxo-1,6-dihydropyridazine-3-carboxamide (164 mg, 0.498 mmol) in MeCN (8 mL) was added 3-bromo-2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaboron-2-yl)pyridine (301 mg, 0.996 mmol), Cu(OAc)₂ (91 mg, 0.498 mmol) and pyridine (0.16 mL, 1.99 mmol), and the mixture was stirred at 90 °C for 19 h. After the addition of water, the reaction mixture was extracted with EtOAc. The combined organic layers were washed with copper sulfate(II) pentahydrate, dried over Na₂SO₄, and then concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography to give **Intermediate D-3** (219 mg, 87% yield, 99.3% purity) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.46-8.45 (m, 1H), 8.37 (dd, *J* = 7.4, 2.6 Hz, 1H), 8.04 (d, *J* = 9.6 Hz, 1H), 7.55 (t, *J* = 7.4 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.24-7.22 (m, 1H), 7.13 (d, *J* = 9.6 Hz, 1H), 5.43 (quint, *J* = 7.3, 14.7 Hz, 1H), 1.64 (d, *J* = 7.2 Hz, 3H); MS (ESI) *m/z* = 503.0 [M+H]⁺, 505.0 [M+3H]⁺.

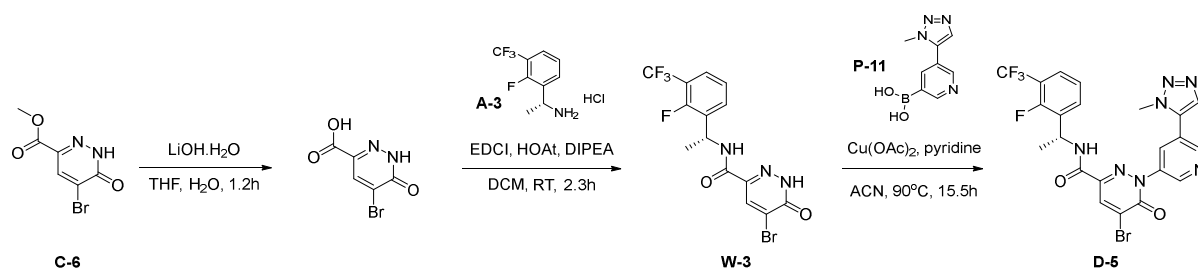
Preparation Example 54-1: (R)-1-(5-bromo-6-fluoropyridin-3-yl)-N-(1-(3-difluoromethyl)-2-fluorophenyl)ethyl)-6-oxo-1,6-dihydropyridazine-3-carboxamide (D-4)



Commercially available 6-oxo-1,6-dihydropyridazine-3-carboxylic acid and Intermediate A-2 were used in the same manner as in Preparation Example 54 to give **Intermediate D-4** (87 mg, 37% 2Step yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.46-8.45 (m, 1H), 8.37 (dd, *J* = 7.6, 2.4 Hz, 1H), 8.05 (d, *J* = 10.0 Hz, 1H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.46 (t, *J* = 7.2 Hz, 1H), 7.26-7.22 (m, 1H), 7.13 (d, *J* = 9.6 Hz, 1H), 6.90 (t, *J* = 55.0 Hz, 1H), 5.43 (quint, *J* = 7.4, 15.1 Hz, 1H), 1.63 (d, *J* = 7.2 Hz, 3H); MS (ESI) *m/z* = 484.9 [M+H]⁺, 487.0 [M+3H]⁺.

Preparation Example 54-2: N-{(R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl}-5-bromo-1-[5-(1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-

3-carboxamide (D-5)



Step 1: Synthesis of 5-bromo-6-oxo-1,6-dihydro-3-pyridazinecarboxylic acid

LiOH·H₂O (94 mg, 2.23 mmol) was added to a solution of methyl 5-bromo-6-oxo-1,6-dihydro-3-pyridazinecarboxylate (**C-6**, 260 mg, 1.12 mmol) in THF (11.2 mL) and H₂O (5.6 mL), and the mixture was stirred at 25 °C for 1.2 h. The reaction mixture was poured into water, and the aqueous layer was adjusted to pH = 4 with 1N-HCl, and then extracted with EtOAc for 3 times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and then concentrated under reduced pressure to give 5-bromo-6-oxo-1,6-dihydro-3-pyridazinecarboxylic acid (215 mg, 88%) as a yellow solid. MS (ESI) *m/z* = 218.9 [M+H]⁺, 220.9 [M+3H]⁺.

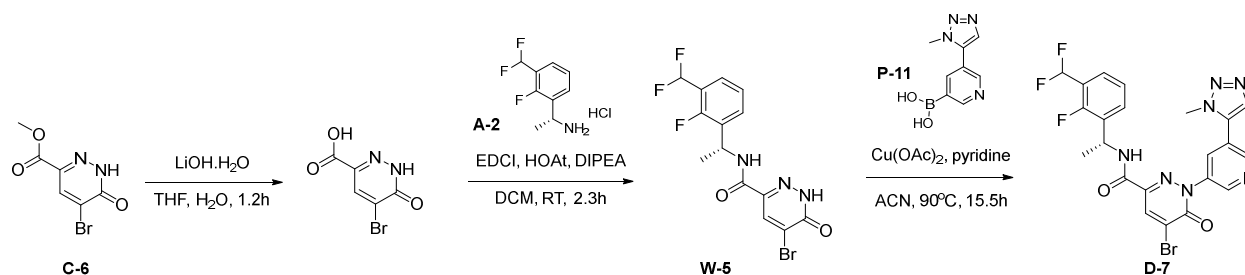
Step 2: Synthesis of *N*-{(R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl}-5-bromo-6-oxo-1,6-dihydropyridazine-3-carboxamide

Intermediate A-3 was used in the same manner as in Step 1 of Preparation Example 54 to give **Intermediate W-3** (120 mg, 30%) as a yellow solid. MS (ESI) *m/z* = 408.0 [M+H]⁺, 409.9 [M+3H]⁺.

Step 3: *N*-{(R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl}-5-bromo-1-[5-(1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide

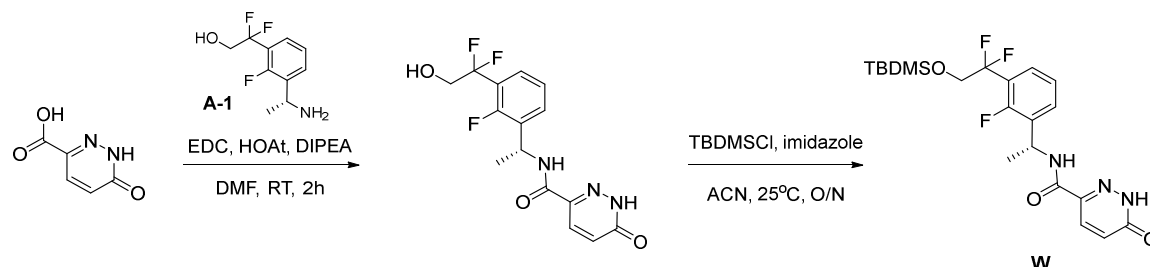
Intermediates W-3 and P-11 were used in the same manner as in Step 2 of Preparation Example 54 to give **Intermediate D-5** (101 mg, 61%) as a light pink solid. ¹H NMR (400 MHz, CDCl₃) δ 8.96 (s, 1H), 8.81 (s, 1H), 8.48 (s, 1H), 8.20 (t, *J* = 2.2 Hz, 1H), 7.89 (s, 1H), 7.57-7.53 (m, 2H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.24-7.22 (m, 1H), 5.43 (quin, *J* = 7.4, 14.9 Hz, 1H), 4.19 (s, 3H), 1.66 (d, *J* = 6.4 Hz, 3H); MS (ESI) *m/z* = 566.2 [M+H]⁺, 569.2 [M+3H]⁺.

Preparation Example 54-3: *N*-{(R)-1-[3-(difluoromethyl)-2-fluorophenyl]ethyl}-5-bromo-1-[5-(1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide (D-7)



Intermediate C-6 was used in the same manner as in Preparation Example 54-2 to give **Intermediate D-7** (80 mg, 36%) as a brown solid. MS (ESI) m/z = 548.1 $[M+H]^+$, 550.1 $[M+3H]^+$.

Preparation Example 54-4: (R)-N-(1-(3-(2-((tert-butyldimethylsilyl)oxy)-1,1-difluoroethyl)-2-fluorophenyl)ethyl)-6-oxo-1,6-dihydropyridazine-3-carboxamide (W)



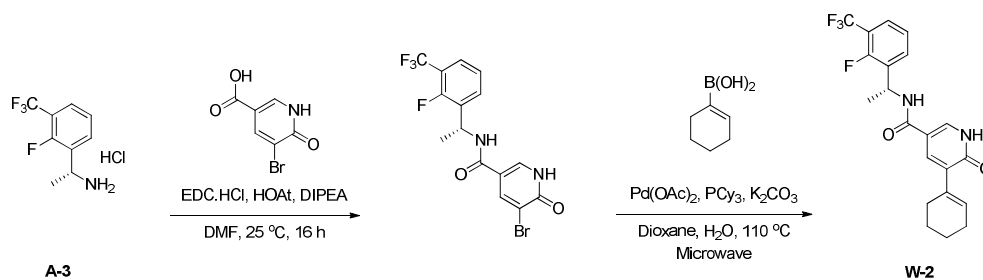
Step 1: Synthesis of N-[(1R)-1-[3-(1,1-difluoro-2-hydroxyethyl)-2-fluorophenyl]ethyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide

Commercially available 6-oxo-1,6-dihydropyridazine-3-carboxylic acid and Intermediate A-1 were used in the same manner as in Step 1 of Preparation Example 54 to give the intermediate, N-[(1R)-1-[3-(1,1-difluoro-2-hydroxyethyl)-2-fluorophenyl]ethyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide (281 mg, 58% yield) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 13.44 (br, 1H), 8.98 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 10.0 Hz, 1H), 7.65 (t, J = 7.0 Hz, 1H), 7.43 (t, J = 6.8 Hz, 1H), 7.28 (t, J = 7.8 Hz, 1H), 6.95 (d, J = 9.6 Hz, 1H), 5.72 (t, J = 6.4 Hz, 1H), 5.38 (quin, J = 7.1, 14.5 Hz, 1H), 3.91 (td, J = 14.4, 6.4 Hz, 2H), 1.48 (d, J = 7.2 Hz, 3); MS (ESI) m/z = 342.01 $[M+H]^+$.

Step 2: Synthesis of (R)-N-(1-(3-(2-((tert-butyldimethylsilyl)oxy)-1,1-difluoroethyl)-2-fluorophenyl)ethyl)-6-oxo-1,6-dihydropyridazine-3-carboxamide

TBDMSCl (149 mg, 0.988 mmol) and imidazole (84 mg, 1.24 mmol) were added to a solution of N-[(1R)-1-[3-(1,1-difluoro-2-hydroxyethyl)-2-fluorophenyl]ethyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide (281 mg, 0.823 mmol) in MeCN (9 mL) at room temperature, and the mixture was stirred for 14 h. The mixture was diluted with EtOAc, quenched with 10% aq. NaHCO_3 , and then extracted. The organic layers were dried over anhydrous Na_2SO_4 , filtered, and then concentrated under reduced pressure. The crude product was purified by silica column chromatography to give **Intermediate W** (300 mg, 80% yield) as a yellow-white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 13.41 (br, 1H), 8.94 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 9.6 Hz, 1H), 7.66 (t, J = 7.0 Hz, 1H), 7.42 (t, J = 6.8 Hz, 1H), 6.93 (d, J = 9.6 Hz, 1H), 5.37 (quin, J = 7.2, 16.9 Hz, 1H), 4.12 (t, J = 13.4 Hz, 2H), 1.47 (d, J = 7.2 Hz, 3H), 0.73 (s, 9H), -0.05 (d, J = 2.8 Hz, 6H); MS (ESI) m/z = 456.07 $[M+H]^+$.

Preparation Example 54-5: (R)-5-(cyclohex-1-en-1-yl)-N-(1-(2-fluoro-3-(trifluoromethyl)phenyl)ethyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (W-2)



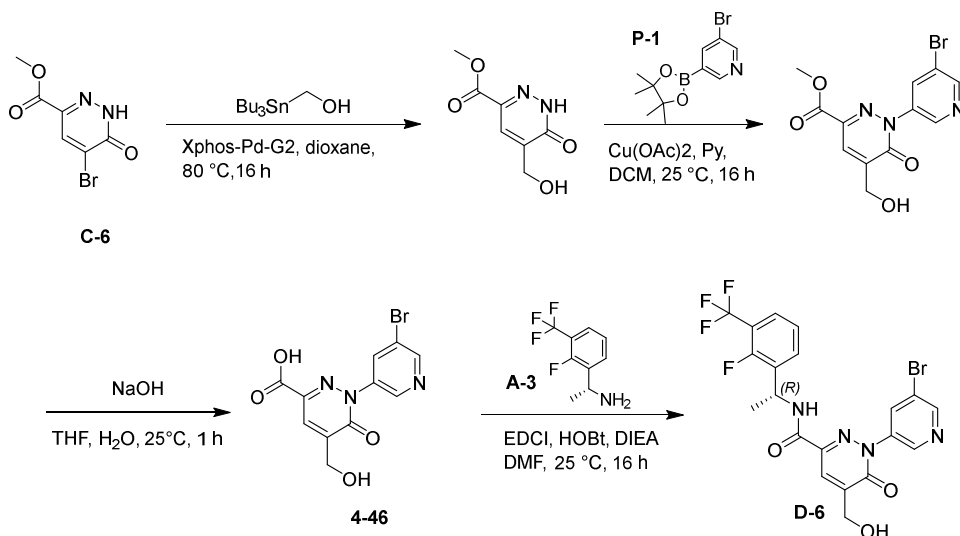
Step 1: Synthesis of (R)-5-bromo-N-(1-(2-fluoro-3-(trifluoromethyl)phenyl)ethyl)-6-oxo-1,6-dihydropyridine-3-carboxamide

Commercially available 5-bromo-6-oxo-1,6-dihydropyridine-3-carboxylic acid and Intermediate A-3 were used in the same manner as in Step 1 of Preparation Example 54 to give the intermediate, (R)-5-bromo-N-(1-(2-fluoro-3-(trifluoromethyl)phenyl)ethyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (250 mg, 75 % yield) as a yellow-white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.79 (d, J = 7.2 Hz, 1H), 8.38 (d, J = 2.4 Hz, 1H), 8.12 (d, J = 2.4 Hz, 1H), 7.76 (t, J = 6.8 Hz, 1H), 7.66 (t, J = 7.2 Hz, 1H), 7.39 (t, J = 7.8 Hz, 1H), 5.33 (quin, J = 7.0 Hz, 1H), 1.46 (d, J = 6.8 Hz, 3H); MS (ESI) m/z = 407.01 $[\text{M}+\text{H}]^+$, 4.8.99 $[\text{M}+3\text{H}]^+$.

Step 2: Synthesis of (R)-5-(cyclohex-1-en-1-yl)-N-(1-(2-fluoro-3-(trifluoromethyl)phenyl)ethyl)-6-oxo-1,6-dihydropyridine-3-carboxamide

K_2CO_3 (64.1 mg, 0.463 mmol), $\text{Pd}(\text{OAc})_2$ (5.3 mg, 0.0232 mmol) and PCy_3 (13 mg, 0.00463 mmol) were added to a solution of (R)-5-bromo-N-(1-(2-fluoro-3-(trifluoromethyl)phenyl)ethyl)-6-oxo-1,6-dihydropyridine-3-carboxamide and (1-cyclohexen-1-yl)boronic acid (88 mg, 0.695 mmol) in dioxane (1.2 mL) and H_2O (0.23 mL), and the mixture was stirred at 110 °C for 1 h using microwave. The reaction mixture was poured into water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 , and then concentrated under reduced pressure to give a crude product. The crude product was filtered by silica column chromatography (DCM: MeOH = 20: 1 to 10: 1) to give **Intermediate W-2** (64 mg, 49% yield) as an ivory solid. MS (ESI) m/z = 567.32 $[\text{M}+\text{H}]^+$.

Preparation Example 54-6: N-{(R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl}-5-bromo-1-[5-(1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide (D-6)



Step 1: Synthesis of methyl 5-(hydroxymethyl)-6-oxo-1H-pyridazine-3-carboxylate

A solution of methyl 5-bromo-6-oxo-1H-pyridazine-3-carboxylate (10 g, 42.91 mmol), tributylstannylmethanol (27.56 g, 85.83 mmol), [2-(2-aminophenyl)phenyl]-chloro-palladium;dicyclohexyl-[3-(2,4,6-triisopropylphenyl)phenyl]phosphan (3.38 g, 4.29 mmol) in dioxane (150 mL) was substituted with nitrogen for 3 times, and then stirred at 80 °C for 16 h under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (2% MeOH in DCM) to give methyl 5-(hydroxymethyl)-6-oxo-1H-pyridazine-3-carboxylate (3.4 g, 40.44% yield, 94% purity) as a brown solid. MS (ESI) m/z = 184.9 $[M+H]^+$.

Step 2: Synthesis of methyl 1-(5-bromo-3-pyridyl)-5-(hydroxymethyl)-6-oxo-pyridazine-3-carboxylate

A solution of methyl 5-(hydroxymethyl)-6-oxo-1H-pyridazine-3-carboxylate (1.2 g, 6.52 mmol), 3-bromo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (2.22 g, 7.82 mmol), Cu(OAc)₂ (1.18 g, 6.52 mmol) and pyridine (1.58 mL, 19.55 mmol) in DCM (30 mL) was stirred at 25 °C for 16 h under oxygen atmosphere. The reaction mixture was filtered, and then the filtrate was concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel chromatography (2% MeOH in DCM) to give methyl 1-(5-bromo-3-pyridyl)-5-(hydroxymethyl)-6-oxo-pyridazine-3-carboxylate (220 mg, 8.39% yield, 84.5% purity) as a white solid. MS (ESI) m/z = 341.8 $[M+H]^+$.

Step 3: Synthesis of 1-(5-(4-(2,4,6-trifluorophenyl)phenyl)-3-pyridyl)-5-(hydroxymethyl)-6-oxo-pyridazine-3-carboxylic acid

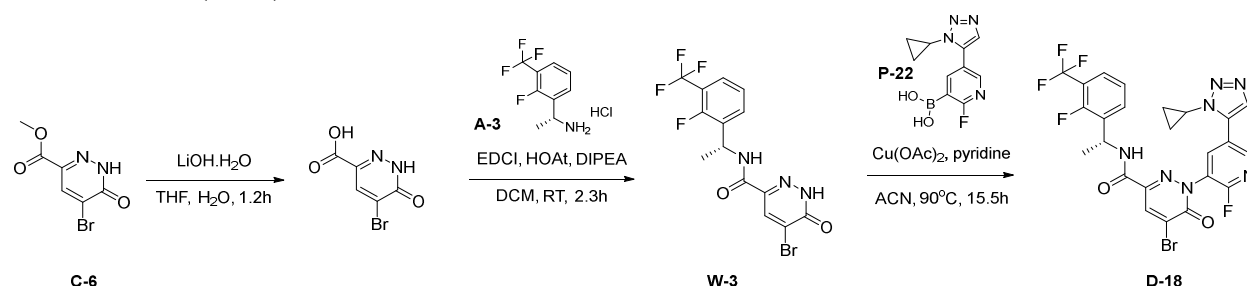
NaOH (38.81 mg, 970.22 μ mol) was added to a solution of methyl 1-(5-bromo-3-pyridyl)-5-(hydroxymethyl)-6-oxo-pyridazine-3-carboxylate (220 mg, 646.81 μ mol) in THF (4 mL) and H₂O (0.5 mL). The reaction mixture was stirred at 20 °C for 1 h. The mixture was adjusted to pH = 6-7 with aq. 1N HCl and concentrated under reduced pressure to give **Intermediate 4-46** (200 mg, 65.90% yield, 69.5% purity) as a yellow solid. MS (ESI) m/z =

327.9 [M+H]⁺.

Step 4: Synthesis of 1-(5-bromo-3-pyridyl)-5-(hydroxymethyl)-6-oxo-N-[rac-(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]pyridazine-3-carboxamide

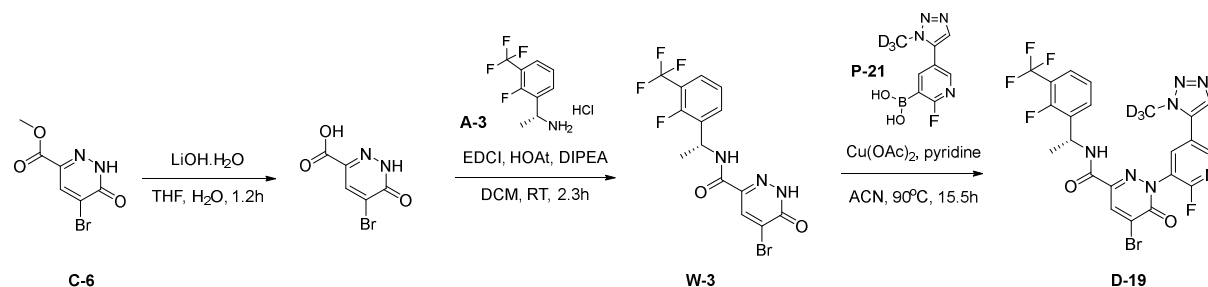
Intermediates 4-46 and A-3 were used in the same manner as in Preparation Example 36 to give **Intermediate D-6** (200 mg, 349.26 μmol, 56.95% yield, 89.98% purity) as a yellow solid. MS (ESI) m/z = 516.9 [M+H]⁺.

Preparation Example 54-7: N-{(R)-1-[3-(trifluoromethyl)-2-fluorophenyl]ethyl}-5-bromo-1-[5-(1-cyclopropyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide (D-18)



Intermediates C-6 and P-22 were used in the same manner as in Preparation Example 54-2 to give **Intermediate D-18** (80 mg, 36%) as a brown solid. MS (ESI) m/z = 584.1 [M+H]⁺, 586.3 [M+3H]⁺.

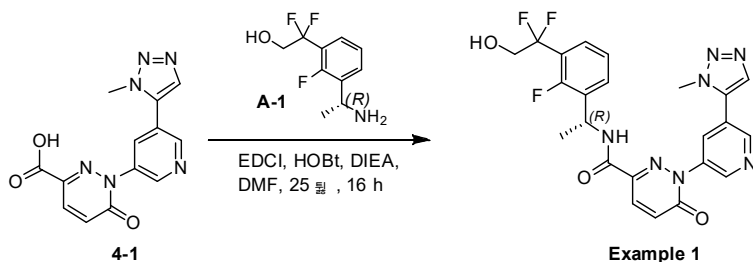
Preparation Example 54-8: N-{(R)-1-[3-(trifluoromethyl)-2-fluorophenyl]ethyl}-5-bromo-1-[5-(1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide (D-19)



Intermediates C-6 and P-21 were used in the same manner as in Preparation Example 54-2 to give **Intermediate D-19** (80 mg, 36%) as a brown solid. MS (ESI) m/z = 584.1 [M+H]⁺, 586.3 [M+3H]⁺.

[Examples]

Example 1: N-[(1R)-1-[3-(1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethyl]-1-[5-(3-methyl-1H-1,2,3-triazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide

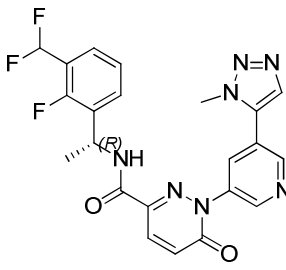


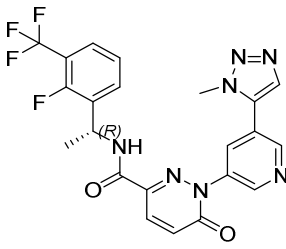
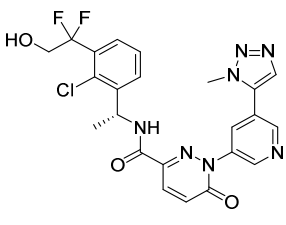
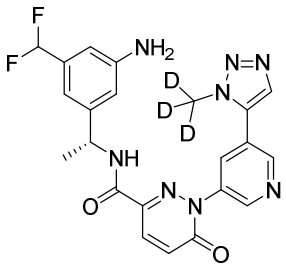
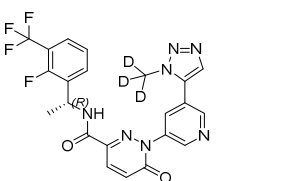
To a solution of Intermediate 4-1 (725 mg, 2.43 mmol) and Intermediate A-1 (497.17 mg, 1.94 mmol, HCl salt) in DMF (8 mL), HOBT (492.69 mg, 3.65 mmol), DIEA (942.49 mg, 7.29 mmol, 1.27 mL) and EDCI (698.98 mg, 3.65 mmol) were added. The mixture was degassed and purged with N₂ for 3 times, and then stirred at 25 °C for 16 h under N₂ atmosphere. The reaction mixture was poured into water (10 mL) and extracted with EtOAc (30 mL×3). The combined organic layers were washed with brine (10 mL×3), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (2% MeOH in DCM) to give **a compound of Example 1** (1074.1 mg, 89.30% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.13 (d, *J* = 2.4 Hz, 1H), 9.08 (d, *J* = 8.0 Hz, 1H), 8.93 (d, *J* = 2.0 Hz, 1H), 8.52 (t, *J* = 2.0 Hz, 1H), 8.14 (s, 1H), 7.93 (d, *J* = 9.6 Hz, 1H), 7.65 (t, *J* = 7.2 Hz, 1H), 7.47 - 7.41 (m, 1H), 7.31 - 7.26 (m, 1H), 7.23 (d, *J* = 9.6 Hz, 1H), 5.72 (t, *J* = 6.4 Hz, 1H), 5.42 (quint, *J* = 7.2 Hz, 1H), 4.17 (s, 3H), 3.91 (dt, *J* = 6.4, 14.4 Hz, 2H), 1.49 (d, *J* = 7.2 Hz, 3H); MS (ESI) *m/z* = 500.1 [M+H]⁺.

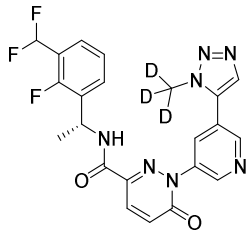
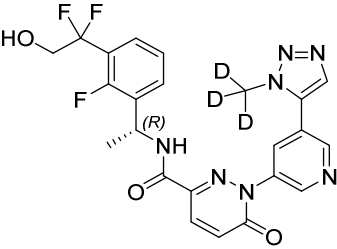
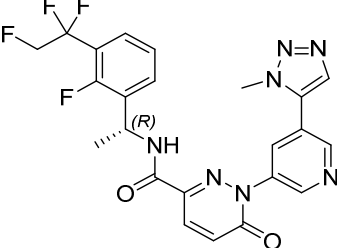
Examples 1-1 to 1-72

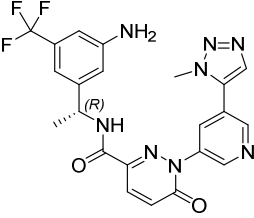
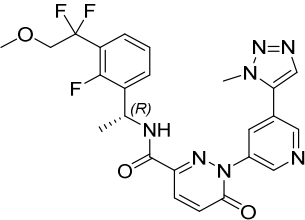
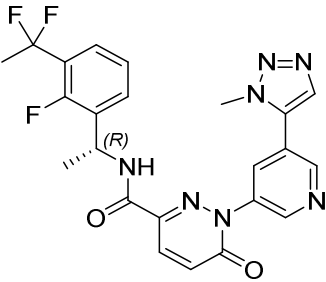
The compounds in Table 1 below were prepared in the same manner as in Example 1 through one-step amide coupling using the corresponding intermediates described in the Preparation Examples.

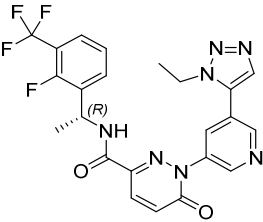
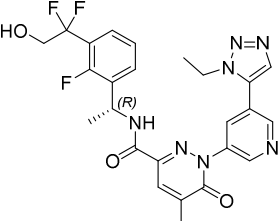
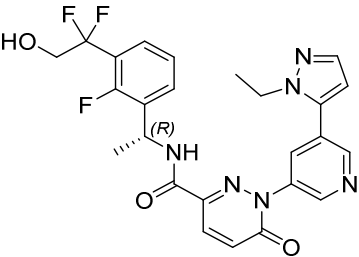
[Table 1]

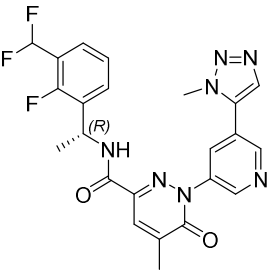
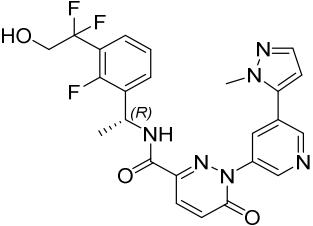
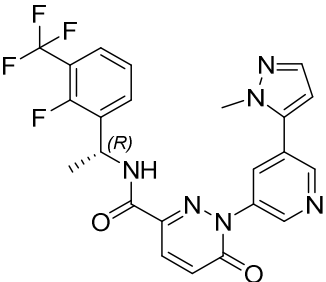
No.	Chemical Name/Structure	Spectra (LCMS / ¹ H NMR)
1-1	N-[(1R)-1-[3-(difluoromethyl)-2-fluorophenyl]ethyl]-1-[5-(3-methyl-1H-1,2,4-triazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide 	LCMS: <i>t</i> _R = 0.540 min, MS (ESI) <i>m/z</i> = 470.2 [M+H] ⁺ . ¹H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 9.12 (d, <i>J</i> = 2.4 Hz, 1H), 9.08 (d, <i>J</i> = 8.0 Hz, 1H), 8.92 (d, <i>J</i> = 2.0 Hz, 1H), 8.51 (t, <i>J</i> = 2.0 Hz, 1H), 8.13 (s, 1H), 7.92 (d, <i>J</i> = 10.0 Hz, 1H), 7.69 (t, <i>J</i> = 7.2 Hz, 1H), 7.53 (t, <i>J</i> = 6.8 Hz, 1H), 7.36 - 7.32 (m, 1H), 7.24 - 7.08 (m, 2H), 5.42 (t, <i>J</i> = 7.2 Hz, 1H), 4.17 (s, 3H), 1.50 (d, <i>J</i> = 7.2 Hz, 3H).
1-2	N-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-1-[5-(3-	LCMS: <i>t</i> _R = 2.105 min, MS (ESI) <i>m/z</i> = 488.1 [M+H] ⁺ .

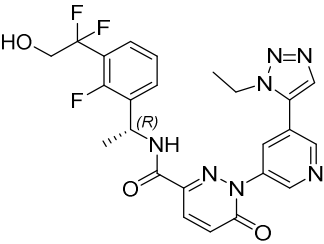
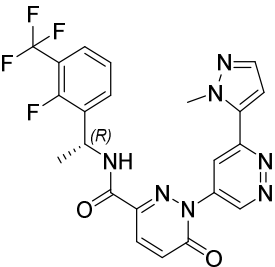
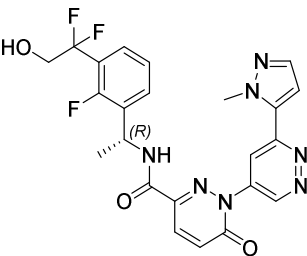
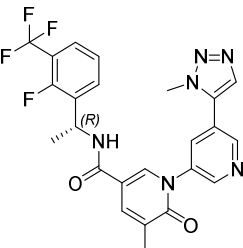
	methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide 	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ = 9.16-9.10 (m, 2H), 8.92 (d, <i>J</i> = 2.0 Hz, 1H), 8.51 (t, <i>J</i> = 2.0 Hz, 1H), 8.13 (s, 1H), 7.92 (d, <i>J</i> = 9.6 Hz, 1H), 7.83 (br t, <i>J</i> = 7.2 Hz, 1H), 7.68 (br t, <i>J</i> = 7.2 Hz, 1H), 7.40 (t, <i>J</i> = 7.6 Hz, 1H), 7.22 (d, <i>J</i> = 9.6 Hz, 1H), 5.46 - 5.39 (m, 1H), 4.17 (s, 3H), 1.51 (d, <i>J</i> = 7.2 Hz, 3H).
1-3	N-[(1R)-1-[2-chloro-3-(1,1-difluoro-2-hydroxy-ethyl)phenyl]ethyl]-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide 	LCMS: <i>t</i>_R = 0.515 min, MS (ESI) <i>m/z</i> = 516.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ = 9.19 - 9.13 (m, 2H), 8.93 (d, <i>J</i> = 2.0 Hz, 1H), 8.53 (t, <i>J</i> = 2.0 Hz, 1H), 8.14 (s, 1H), 7.91 (d, <i>J</i> = 9.6 Hz, 1H), 7.70 (d, <i>J</i> = 7.6 Hz, 1H), 7.54 - 7.50 (m, 1H), 7.47 - 7.42 (m, 1H), 7.23 (d, <i>J</i> = 9.6 Hz, 1H), 5.70 (t, <i>J</i> = 6.4 Hz, 1H), 5.58 - 5.51 (m, 1H), 4.18 (s, 3H), 4.03 (dt, <i>J</i> = 6.4, 14.4 Hz, 2H), 1.47 (d, <i>J</i> = 7.2 Hz, 3H).
1-4	N-[(1R)-1-[3-amino-5-(difluoromethyl)phenyl]ethyl]-6-oxo-1-[5-[3-(trideuteriomethyl)triazol-4-yl]-3-pyridyl]pyridazine-3-carboxamide 	LCMS : <i>t</i>_R = 0.433 min, MS (ESI) <i>m/z</i> = 470.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ = 9.12 (d, <i>J</i> = 2.0 Hz, 1H), 8.94-8.90 (m, 2H), 8.50 (s, 1H), 8.12 (s, 1H), 7.95 (d, <i>J</i> = 9.6 Hz, 1H), 7.23 (d, <i>J</i> = 9.6 Hz, 1H), 6.94 (s, 1H), 6.80 (s, 1H), 6.69 (br s, 2H), 6.66 (br s, 1H), 6.58 (s, 1H), 5.36 (s, 2H), 5.07-5.02 (m, 1H), 1.45 (br d, <i>J</i> = 7.2 Hz, 3H).
1-5	N-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-6-oxo-1-[5-[3-(trideuteriomethyl)triazol-4-yl]-3-pyridyl]pyridazine-3-carboxamide 	LCMS : <i>t</i>_R = 0.560 min, MS (ESI) <i>m/z</i> = 491.3 [M+H]⁺. ¹H NMR (400 MHz, METHANOL-<i>d</i>₄) δ = 9.10 (d, <i>J</i> = 2.4 Hz, 1H), 8.87 (d, <i>J</i> = 1.6 Hz, 1H), 8.50 (t, <i>J</i> = 2.0 Hz, 1H), 8.04 - 8.00 (m, 2H), 7.72 (br t, <i>J</i> = 7.2 Hz, 1H), 7.59 (br t, <i>J</i> = 7.2 Hz, 1H), 7.31 (t, <i>J</i> = 7.6 Hz, 1H), 7.21 (d, <i>J</i>

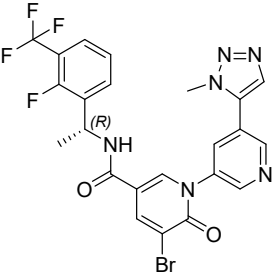
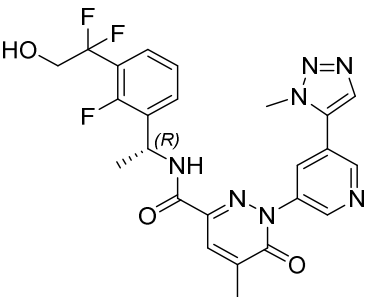
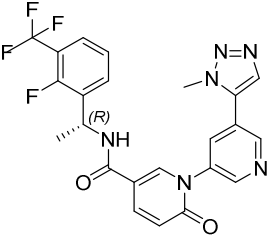
		= 9.6 Hz, 1H), 5.53 - 5.48 (m, 1H), 1.59 (d, $J = 7.2$ Hz, 3H).
1-6	N-[(1R)-1-[3-(difluoromethyl)-2-fluorophenyl]ethyl]-6-oxo-1-[5-[3-(trideuteriomethyl)triazol-4-yl]-3-pyridyl]pyridazine-3-carboxamide 	LCMS : $t_R = 0.531$ min, MS (ESI) $m/z = 473.3$ $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) $\delta = 9.14$-9.08 (m, 2H), 8.93 (d, $J = 2.0$ Hz, 1H), 8.52 (t, $J = 2.0$ Hz, 1H), 8.14 (s, 1H), 7.93 (d, $J = 9.6$ Hz, 1H), 7.69 (br t, $J = 7.0$ Hz, 1H), 7.53 (br t, $J = 6.4$ Hz, 1H), 7.37-7.33 (m, 1H), 7.24 (s, 1H), 7.23-7.21 (m, 1H), 5.42 (br t, $J = 7.6$ Hz, 1H), 1.50 (d, $J = 7.2$ Hz, 3H).
1-7	N-[(1R)-1-[3-(1,1-difluoro-2-hydroxyethyl)-2-fluorophenyl]ethyl]-6-oxo-1-[5-[3-(trideuteriomethyl)triazol-4-yl]-3-pyridyl]pyridazine-3-carboxamide 	LCMS : $t_R = 0.512$ min, MS (ESI) $m/z = 503.3$ $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) $\delta = 9.13$ (d, $J = 2.4$ Hz, 1H), 9.08 (d, $J = 8.4$ Hz, 1H), 8.93 (d, $J = 2.0$ Hz, 1H), 8.52 (t, $J = 2.0$ Hz, 1H), 8.14 (s, 1H), 7.93 (d, $J = 9.6$ Hz, 1H), 7.65 (t, $J = 7.2$ Hz, 1H), 7.44 (t, $J = 6.8$ Hz, 1H), 7.31 - 7.26 (m, 1H), 7.23 (d, $J = 9.86$ Hz, 1H), 5.72 (t, $J = 6.4$ Hz, 1H), 5.42 (quint, $J = 7.2$ Hz, 1H), 3.91 (dt, $J = 6.4, 14.4$ Hz, 2H), 1.49 (d, $J = 7.2$ Hz, 3H).
1-8	(R)-N-(1-(2-fluoro-3-(1,1,2-trifluoroethyl)phenyl)ethyl)-1-(5-(1-methyl-1H-1,2,3-triazol-5-yl)pyridin-3-yl)-6-oxo-1,6-dihydropyridazine-3-carboxamide 	LCMS : $t_R = 2.542$ min, MS (ESI) $m/z = 502.18$ $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) $\delta = 9.13$-9.11 (m, 1H), 8.93 (d, $J = 2.0$ Hz, 1H), 8.52 (t, $J = 2.0$ Hz, 1H), 8.14 (s, 1H), 7.93 (d, $J = 9.6$ Hz, 1H), 7.72 (t, $J = 7.2$ Hz, 1H), 7.52 (t, $J = 6.8$ Hz, 1H), 7.35 (t, $J = 7.8$ Hz, 1H), 7.23 (d, $J = 10$ Hz, 1H), 5.42 (quint, $J = 7.3$ Hz, 1H), 5.05 (t, $J = 13.8$ Hz, 1H), 4.94 (t, $J = 13.8$ Hz, 1H), 4.18 (s, 3H), 1.50 (d, $J = 7.2$ Hz, 3H).
1-9	N-[(1R)-1-[3-amino-5-	LCMS : $t_R = 1.375$ min, MS (ESI) m/z

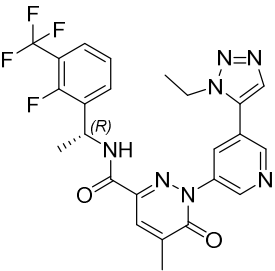
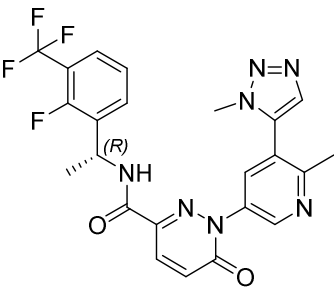
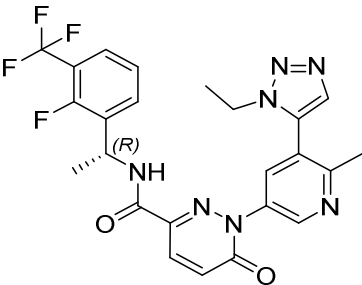
	(trifluoromethyl)phenyl]ethyl]-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide 	= 485.4 [M+H]⁺. ¹H NMR (400 MHz, METHANOL-<i>d</i>₄): δ = 9.09 (d, <i>J</i> = 2.4 Hz, 1H), 8.85 (d, <i>J</i> = 2.0 Hz, 1H), 8.48 (t, <i>J</i> = 2.4 Hz, 1H), 8.05 - 8.02 (m, 2H), 7.21 (d, <i>J</i> = 9.6 Hz, 1H), 6.90 (br d, <i>J</i> = 6.0 Hz, 2H), 6.81 (s, 1H), 5.15 (q, <i>J</i> = 7.2 Hz, 1H), 4.19 (s, 3H), 1.54 (d, <i>J</i> = 7.2 Hz, 3H).
1-10	(<i>R</i>)-N-(1-(3-(1,1-difluoro-2-methoxyethyl)-2-fluorophenyl)ethyl)-1-(5-(1-methyl-1H-1,2,3-triazol-5-yl)pyridin-3-yl)-6-oxo-1,6-dihydropyridazine-3-carboxamide 	LCMS : <i>t</i>_R = 2.543 min, MS (ESI) <i>m/z</i> = 514.19 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ = 9.13-9.11 (m, 2H), 8.93 (d, <i>J</i> = 2.0 Hz, 1H), 8.52 (t, <i>J</i> = 2.2 Hz, 1H), 8.14 (s, 1H), 7.93 (d, <i>J</i> = 10 Hz, 1H), 7.67 (t, <i>J</i> = 7.2 Hz, 1H), 7.46 (t, <i>J</i> = 6.8 Hz, 1H), 7.30 (t, <i>J</i> = 7.8 Hz, 1H), 7.23 (d, <i>J</i> = 9.6 Hz, 1H), 5.42 (quint, <i>J</i> = 7.2 Hz, 1H), 4.18 (s, 3H), 3.96 (t, <i>J</i> = 14 Hz, 1H), 3.33 (s, 3H), 1.49 (d, <i>J</i> = 8.0 Hz, 3H).
1-11	N-[(1<i>R</i>)-1-[3-(1,1-difluoroethyl)-2-fluorophenyl]ethyl]-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide 	LCMS : <i>t</i>_R = 2.471 min, MS (ESI) <i>m/z</i> = 484.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ = 9.13 (d, <i>J</i> = 2.4 Hz, 1H), 9.07 (d, <i>J</i> = 8.0 Hz, 1H), 8.92 (d, <i>J</i> = 2.0 Hz, 1H), 8.52 (t, <i>J</i> = 2.0 Hz, 1H), 8.13 (s, 1H), 7.92 (d, <i>J</i> = 10.0 Hz, 1H), 7.64 (t, <i>J</i> = 7.2 Hz, 1H), 7.46 (t, <i>J</i> = 7.2 Hz, 1H), 7.28 (t, <i>J</i> = 7.6 Hz, 1H), 7.22 (d, <i>J</i> = 10.0 Hz, 1H), 5.43 (quint, <i>J</i> = 7.2 Hz, 1H), 4.17 (s, 3H), 2.01 (t, <i>J</i> = 19.2 Hz, 3H), 1.50 (d, <i>J</i> = 7.2 Hz, 3H).
1-12	N-[(1<i>R</i>)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-1-[5-(3-ethyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide	LCMS : <i>t</i>_R = 2.651 min, MS (ESI) <i>m/z</i> = 502.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ = 9.19-9.11 (m, 2H), 8.87 (d, <i>J</i> = 2.0 Hz, 1H), 8.47 (t, <i>J</i> = 2.0 Hz, 1H), 8.10 (s, 1H), 7.92 (d, <i>J</i> = 9.6 Hz, 1H), 7.83 (br

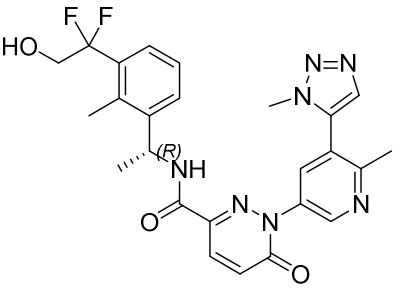
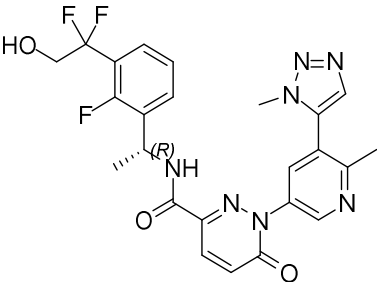
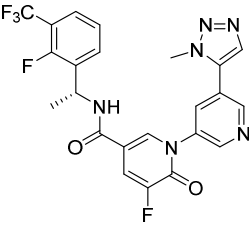
		t, $J = 7.2$ Hz, 1H), 7.68 (br t, $J = 7.2$ Hz, 1H), 7.40 (t, $J = 7.6$ Hz, 1H), 7.22 (d, $J = 9.6$ Hz, 1H), 5.43 (quint, $J = 7.2$ Hz, 1H), 4.50 (q, $J = 7.2$ Hz, 2H), 1.52 (d, $J = 7.2$ Hz, 3H), 1.40 (t, $J = 7.2$ Hz, 3H).
1-13	N-[(1R)-1-[3-(1,1-difluoro-2-hydroxyethyl)-2-fluoro-phenyl]ethyl]-1-[5-(3-ethyl-1,2,4-triazol-4-yl)-3-pyridyl]-5-methyl-6-oxo-pyridazine-3-carboxamide 	LCMS : $t_R = 1.844$ min, MS (ESI) $m/z = 528.2$ $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) $\delta = 9.14$ (d, $J = 2.4$ Hz, 1H), 9.04 (d, $J = 8.4$ Hz, 1H), 8.85 (d, $J = 2.0$ Hz, 1H), 8.47 (t, $J = 2.0$ Hz, 1H), 8.09 (s, 1H), 7.85 (d, $J = 1.6$ Hz, 1H), 7.63 (t, $J = 6.8$ Hz, 1H), 7.44 (t, $J = 6.8$ Hz, 1H), 7.28 (t, $J = 7.6$ Hz, 1H), 5.72 (t, $J = 6.4$ Hz, 1H), 5.42 (t, $J = 7.6$ Hz, 1H), 4.50 (q, $J = 7.6$ Hz, 2H), 3.96-3.87 (m, 2H), 2.21 (d, $J = 1.2$ Hz, 3H), 1.49 (d, $J = 7.2$ Hz, 3H), 1.40 (t, $J = 7.2$ Hz, 3H).
1-14	N-[(1R)-1-[3-(1,1-difluoro-2-hydroxyethyl)-2-fluoro-phenyl]ethyl]-1-[5-(2-ethylpyrazol-3-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide 	LCMS : $t_R = 1.830$ min, MS (ESI) $m/z = 513.2$ $[M+H]^+$. 1H NMR (400 MHz, METHANOL-d_4) $\delta = 9.05$ (d, $J = 2.4$ Hz, 1H), 8.75 (d, $J = 2.0$ Hz, 1H), 8.38 (t, $J = 2.4$ Hz, 1H), 8.01 (d, $J = 9.6$ Hz, 1H), 7.62 (d, $J = 2.0$ Hz, 1H), 7.57 (t, $J = 6.8$ Hz, 1H), 7.51-7.46 (m, 1H), 7.25-7.19 (m, 2H), 6.56 (d, $J = 2.0$ Hz, 1H), 5.50 (q, $J = 6.8$ Hz, 1H), 4.60 (br s, 2H), 4.27 (q, $J = 7.2$ Hz, 2H), 3.99 (t, $J = 13.6$ Hz, 2H), 1.57 (d, $J = 7.2$ Hz, 3H), 1.41 (t, $J = 7.2$ Hz, 3H).
1-15	N-[(1R)-1-[3-(difluoromethyl)-2-fluoro-phenyl]ethyl]-5-methyl-1-[5-(3-methyl-1,2,4-triazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide	LCMS : $t_R = 2.279$ min, MS (ESI) $m/z = 484.2$ $[M+H]^+$. 1H NMR (400MHz, DMSO-d_6) $\delta = 9.12$ (d, $J = 2.4$ Hz, 1H), 9.03 (d, $J = 8.0$ Hz, 1H), 8.91 (d, $J = 2.0$ Hz, 1H), 8.51 (t, $J = 2.0$ Hz, 1H), 8.13 (s, 1H),

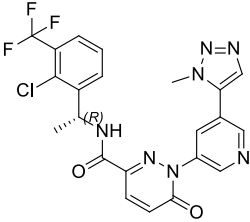
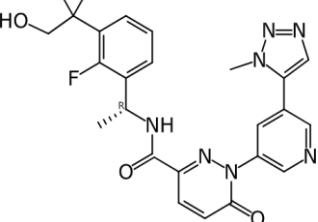
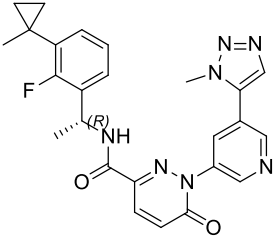
		7.85 (d, $J = 1.2$ Hz, 1H), 7.68 (br t, $J = 7.6$ Hz, 1H), 7.52 (s, 1H), 7.36 - 7.29 (m, 1H), 7.22 (s, 1H), 7.08 (s, 1H), 5.41 (br t, $J = 7.6$ Hz, 1H), 4.17 (s, 3H), 2.21 (s, 3H), 1.50 (d, $J = 7.2$ Hz, 3H)
1-16	N-[(1R)-1-[3-(1,1-difluoro-2-hydroxyethyl)-2-fluoro-phenyl]ethyl]-1-[5-(2-methylpyrazol-3-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide 	LCMS : $t_R = 0.514$ min, MS (ESI) $m/z = 341.0$ $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) $\delta = 9.14$-9.03 (m, 2H), 8.86 (d, $J = 2.0$ Hz, 1H), 8.42 (t, $J = 2.0$ Hz, 1H), 7.92 (d, $J = 9.6$ Hz, 1H), 7.65 (t, $J = 6.6$ Hz, 1H), 7.57 (d, $J = 2.0$ Hz, 1H), 7.47-7.41 (m, 1H), 7.32-7.25 (m, 1H), 7.22 (d, $J = 9.6$ Hz, 1H), 6.64 (d, $J = 2.0$ Hz, 1H), 5.72 (t, $J = 6.4$ Hz, 1H), 5.43 (t, $J = 7.6$ Hz, 1H), 3.95 (s, 3H), 3.94-3.83 (m, 2H), 1.49 (d, $J = 7.2$ Hz, 3H).
1-17	N-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-1-[5-(2-methylpyrazol-3-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide 	LCMS : $t_R = 2.270$ min, MS (ESI) $m/z = 487.1$ $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) $\delta = 9.15$ (d, $J = 7.6$ Hz, 1H), 9.05 (d, $J = 2.4$ Hz, 1H), 8.86 (d, $J = 2.0$ Hz, 1H), 8.42 (t, $J = 2.0$ Hz, 1H), 7.92 (d, $J = 9.6$ Hz, 1H), 7.83 (t, $J = 7.2$ Hz, 1H), 7.68 (t, $J = 6.8$ Hz, 1H), 7.57 (d, $J = 2.0$ Hz, 1H), 7.40 (t, $J = 8.0$ Hz, 1H), 7.22 (d, $J = 9.6$ Hz, 1H), 6.64 (d, $J = 2.0$ Hz, 1H), 5.46 - 5.40 (m, 1H), 3.95 (s, 3H), 1.51 (d, $J = 7.2$ Hz, 3H).
1-18	N-[(1R)-1-[3-(1,1-difluoro-2-hydroxyethyl)-2-fluoro-phenyl]ethyl]-1-[5-(3-ethyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide	LCMS : $t_R = 1.617$ min, MS (ESI) $m/z = 514.2$ $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) $\delta = 9.17$-9.06 (m, 2H), 8.87 (d, $J = 2.0$ Hz, 1H), 8.48 (t, $J = 2.0$ Hz, 1H), 8.10 (s, 1H), 7.93 (d, $J = 9.6$ Hz, 1H), 7.65 (t, $J = 7.2$ Hz, 1H), 7.44 (t, $J = 6.8$ Hz, 1H), 7.31-7.26 (m, 1H), 7.23 (d, $J = 9.6$ Hz,

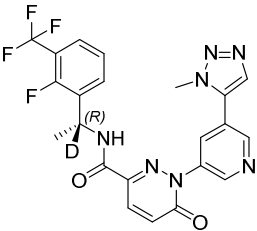
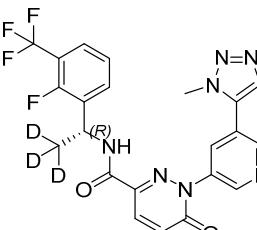
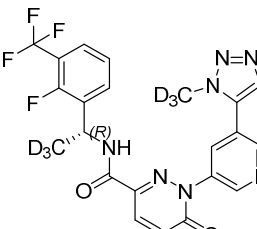
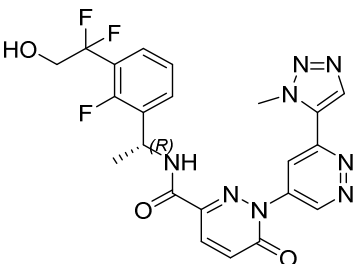
		1H), 7.04-7.03 (m, 1H), 5.72 (t, $J = 6.4$ Hz, 1H), 5.48-5.37 (m, 1H), 4.51 (q, $J = 7.2$ Hz, 2H), 3.95-3.83 (m, 2H), 1.50 (d, $J = 7.2$ Hz, 3H), 1.41 (t, $J = 7.2$ Hz, 3H).
1-19	N-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-1-[6-(2-methylpyrazol-3-yl)pyridazin-4-yl]-6-oxo-pyridazine-3-carboxamide 	LCMS : $t_R = 2.350$ min, MS (ESI) $m/z = 488.1$ $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) $\delta = 9.89$ (d, $J = 2.4$ Hz, 1H), 9.26 (d, $J = 7.6$ Hz, 1H), 8.62 (d, $J = 2.4$ Hz, 1H), 7.94 (d, $J = 9.6$ Hz, 1H), 7.87 (t, $J = 7.2$ Hz, 1H), 7.70 (t, $J = 7.2$ Hz, 1H), 7.64 (d, $J = 2.0$ Hz, 1H), 7.43 (t, $J = 7.6$ Hz, 1H), 7.27 (d, $J = 9.6$ Hz, 1H), 6.98 (d, $J = 2.0$ Hz, 1H), 5.46 (t, $J = 7.2$ Hz, 1H), 4.24 (s, 3H), 1.56 (d, $J = 7.2$ Hz, 3H).
1-20	N-[(1R)-1-[3-(1,1-difluoro-2-hydroxyethyl)-2-fluoro-phenyl]ethyl]-1-[6-(2-methylpyrazol-3-yl)pyridazin-4-yl]-6-oxo-pyridazine-3-carboxamide 	LCMS : $t_R = 2.705$ min, MS (ESI) $m/z = 500.1$ $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) $\delta = 9.82$ (d, $J = 2.4$ Hz, 1H), 8.63 (d, $J = 2.4$ Hz, 1H), 8.00 (d, $J = 10.0$ Hz, 1H), 7.64 - 7.58 (m, 2H), 7.50 (t, $J = 6.8$ Hz, 1H), 7.28 - 7.25 (m, 1H), 7.27 - 7.21 (m, 1H), 6.95 (d, $J = 2.0$ Hz, 1H), 5.51 (q, $J = 6.8$ Hz, 1H), 4.29 (s, 3H), 4.00 (t, $J = 13.6$ Hz, 2H), 1.61 (d, $J = 7.2$ Hz, 3H)
1-21	(R)-N-(1-(2-fluoro-3-(trifluoromethyl)phenyl)ethyl)-3-methyl-5'-(1-methyl-1H-1,2,3-triazol-5-yl)-2-oxo-2H-[1,3'-bipyridine]-5-carboxamide 	LCMS : $t_R = 2.696$ min, MS (ESI) $m/z = 501.14$ $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) $\delta = 8.95$ (d, $J = 2.0$ Hz, 2H), 8.86 (d, $J = 2.0$ Hz, 1H), 8.73 (d, $J = 6.8$ Hz, 1H), 8.39 (d, $J = 2.4$ Hz, 1H), 8.36 (t, $J = 2.2$ Hz, 1H), 8.13 (s, 1H), 7.91-7.90 (m, 1H), 7.77 (t, $J = 7.0$ Hz, 1H), 7.67 (t, $J = 6.8$ Hz, 1H), 7.40 (t, $J = 7.8$ Hz, 1H),

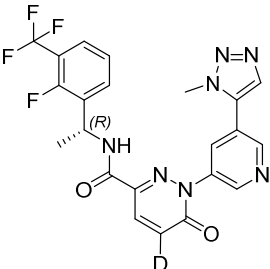
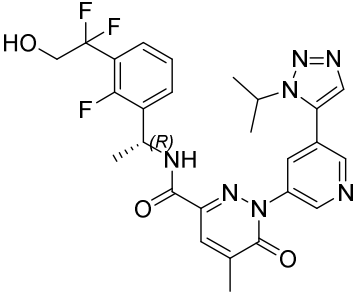
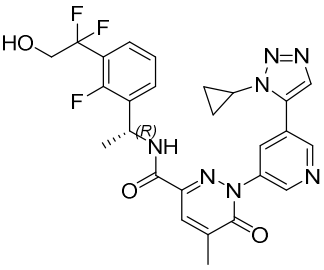
		5.36 (quint, $J = 7.0$ Hz, 1H), 4.16 (s, 3H), 2.11 (s, 3H), 1.47 (d, $J = 7.2$ Hz, 3H).
1-22	(R)-3-bromo-N-(1-(2-fluoro-3-(trifluoromethyl)phenyl)ethyl)-5'-(1-methyl-1H-1,2,3-triazol-5-yl)-2-oxo-2H-[1,3'-bipyridine]-5-carboxamide 	LCMS : $t_R = 2.542$ min, MS (ESI) $m/z = 502.18$ $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) $\delta = 9.13-9.11$ (m, 1H), 8.93 (d, $J = 2.0$ Hz, 1H), 8.52 (t, $J = 2.0$ Hz, 1H), 8.14 (s, 1H), 7.93 (d, $J = 9.6$ Hz, 1H), 7.72 (t, $J = 7.2$ Hz, 1H), 7.52 (t, $J = 6.8$ Hz, 1H), 7.35 (t, $J = 7.8$ Hz, 1H), 7.23 (d, $J = 10$ Hz, 1H), 5.42 (quint, $J = 7.3$ Hz, 1H), 5.05 (t, $J = 13.8$ Hz, 1H), 4.94 (t, $J = 13.8$ Hz, 1H), 4.18 (s, 3H), 1.50 (d, $J = 7.2$ Hz, 3H).
1-23	N-[(1R)-1-[3-(1,1-difluoro-2-hydroxyethyl)-2-fluoro-phenyl]ethyl]-5-methyl-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide 	LCMS : $t_R = 1.701$ min, MS (ESI) $m/z = 514.2$ $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) $\delta = 9.12$ (d, $J = 2.4$ Hz, 1H), 9.03 (d, $J = 8.0$ Hz, 1H), 8.91 (d, $J = 2.0$ Hz, 1H), 8.51 (t, $J = 2.0$ Hz, 1H), 8.13 (s, 1H), 7.86 (d, $J = 1.2$ Hz, 1H), 7.64 (br t, $J = 7.2$ Hz, 1H), 7.46-7.42 (m, 1H), 7.30-7.26 (m, 1H), 5.72 (t, $J = 6.4$ Hz, 1H), 5.42 (t, $J = 7.2$ Hz, 1H), 4.17 (s, 3H), 3.91 (br d, $J = 6.0$ Hz, 2H), 2.21 (d, $J = 1.2$ Hz, 3H), 1.49 (d, $J = 7.2$ Hz, 3H).
1-24	N-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridine-3-carboxamide 	LCMS : $t_R = 1.748$ min, MS (ESI) $m/z = 487.1$ $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) $\delta = 8.95$ (d, $J = 2.0$ Hz, 1H), 8.87 (d, $J = 2.4$ Hz, 1H), 8.75 (d, $J = 7.2$ Hz, 1H), 8.51 (d, $J = 2.4$ Hz, 1H), 8.37 (t, $J = 2.0$ Hz, 1H), 8.13 (s, 1H), 7.99 (dd, $J = 2.4$, 9.6 Hz, 1H), 7.77 (t, $J = 7.2$ Hz, 1H), 7.67 (t, $J = 6.8$ Hz, 1H), 7.40 (t, $J = 8.0$ Hz, 1H), 6.61 (d, $J = 9.6$ Hz, 1H), 5.40-

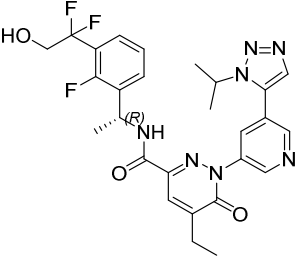
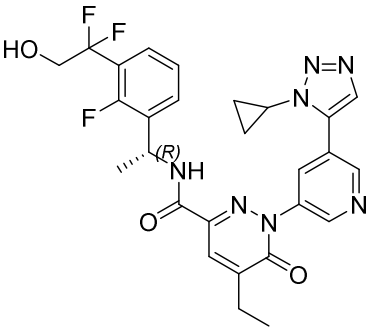
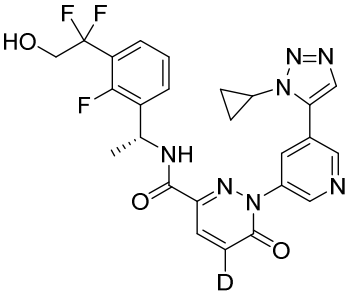
		5.32 (m, 1H), 4.16 (s, 3H), 1.47 (d, $J = 7.2$ Hz, 3H).
1-25	1-[5-(3-ethyltriazol-4-yl)-3-pyridyl]-N-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-5-methyl-6-oxo-pyridazine-3-carboxamide 	LCMS : $t_R = 2.373$ min, MS (ESI) $m/z = 516.2$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) $\delta = 9.13$ (d, $J = 2.4$ Hz, 1H), 9.09 (d, $J = 8.0$ Hz, 1H), 8.85 (d, $J = 2.0$ Hz, 1H), 8.46 (t, $J = 2.0$ Hz, 1H), 8.09 (s, 1H), 7.86 - 7.80 (m, 2H), 7.68 (t, $J = 7.2$ Hz, 1H), 7.39 (t, $J = 7.6$ Hz, 1H), 5.42 (quint, $J = 7.2$ Hz, 1H), 4.50 (q, $J = 7.2$ Hz, 2H), 2.20 (s, 3H), 1.51 (d, $J = 7.2$ Hz, 3H), 1.40 (t, $J = 7.2$ Hz, 3H).
1-26	N-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-1-[6-methyl-5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide 	LCMS : $t_R = 2.207$ min, MS (ESI) $m/z = 502.2$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) $\delta = 9.03$ (d, $J = 2.4$ Hz, 1H), 8.82 (br d, $J = 8.0$ Hz, 1H), 8.25 (d, $J = 2.4$ Hz, 1H), 7.94 (s, 1H), 7.88 (s, 1H), 7.91 (s, 1H), 7.84 (t, $J = 7.6$ Hz, 1H), 7.66 (t, $J = 7.2$ Hz, 1H), 7.39 (t, $J = 7.6$ Hz, 1H), 7.17 (d, $J = 9.6$ Hz, 1H), 5.44 (t, $J = 7.2$ Hz, 1H), 3.95 (s, 3H), 2.47 (s, 3H), 1.56 (d, $J = 7.2$ Hz, 3H).
1-27	1-[5-(3-ethyltriazol-4-yl)-6-methyl-3-pyridyl]-N-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-6-oxo-pyridazine-3-carboxamide 	LCMS : $t_R = 2.237$ min, MS (ESI) $m/z = 516.2$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) $\delta = 9.09$ (d, $J = 8.0$ Hz, 1H), 9.03 (d, $J = 2.4$ Hz, 1H), 8.25 (d, $J = 2.4$ Hz, 1H), 7.99 (s, 1H), 7.88 (d, $J = 9.6$ Hz, 1H), 7.82 (t, $J = 7.6$ Hz, 1H), 7.68 (t, $J = 6.8$ Hz, 1H), 7.40 (t, $J = 7.6$ Hz, 1H), 7.19 (d, $J = 9.6$ Hz, 1H), 5.41 (quint, $J = 7.2$ Hz, 1H), 4.27 (q, $J = 7.2$ Hz, 2H), 2.42 (s, 3H), 1.51 (d, $J = 7.2$ Hz, 3H), 1.31 (t, $J = 7.2$ Hz, 3H).
1-28	N-[(1R)-1-[3-(1,1-difluoro-2-hydroxyethyl)-2-methyl-phenyl]ethyl]-1-[6-methyl-	LCMS : $t_R = 1.617$ min, MS (ESI) $m/z = 510.2$ $[M+H]^+$.

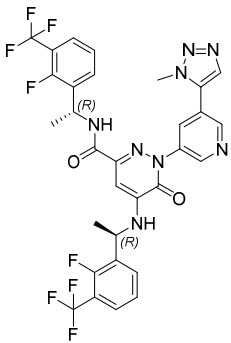
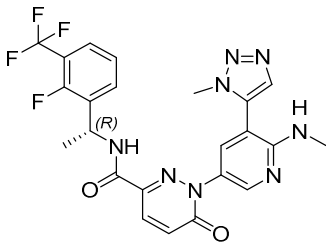
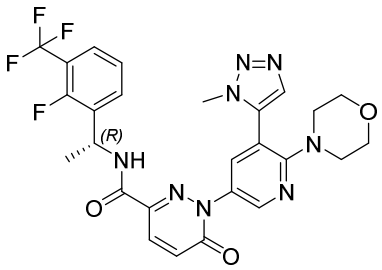
	5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide 	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ = 9.06-8.97 (m, 1H), 8.31 (d, <i>J</i> = 2.4 Hz, 1H), 8.01 (s, 1H), 7.87 (d, <i>J</i> = 9.6 Hz, 1H), 7.57 (d, <i>J</i> = 7.6 Hz, 1H), 7.35 (d, <i>J</i> = 7.6 Hz, 1H), 7.29-7.22 (m, 1H), 7.18 (d, <i>J</i> = 9.6 Hz, 1H), 5.41-5.32 (m, 1H), 3.92 (s, 3H), 3.90-3.82 (m, 2H), 2.46 (s, 3H), 2.43-2.43 (m, 1H), 2.41 (s, 2H), 1.43 (br d, <i>J</i> = 6.8 Hz, 3H).
1-29	(N-[(1R)-1-[3-(1,1-difluoro-2-hydroxyethyl)-2-fluoro-phenyl]ethyl]-1-[6-methyl-5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide 	LCMS : <i>t</i>_R = 1.519 min, MS (ESI) <i>m/z</i> = 514.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ = 9.23-9.12 (m, 2H), 8.54 (d, <i>J</i> = 2.0 Hz, 1H), 8.07 (s, 1H), 7.90 (d, <i>J</i> = 9.6 Hz, 1H), 7.67 (br t, <i>J</i> = 6.8 Hz, 1H), 7.44 (br t, <i>J</i> = 6.8 Hz, 1H), 7.27 (t, <i>J</i> = 7.6 Hz, 1H), 7.21 (d, <i>J</i> = 9.6 Hz, 1H), 5.48 - 5.44 (m, 1H), 3.97 (s, 3H), 3.91 (br t, <i>J</i> = 14.4 Hz, 2H), 2.54 (s, 3H), 1.50 (br d, <i>J</i> = 6.8 Hz, 3H).
1-30	(R)-3-fluoro-N-(1-(2-fluoro-3-(trifluoromethyl)phenyl)ethyl)-5'-(1-methyl-1H-1,2,3-triazol-5-yl)-2-oxo-2H-[1,3'-bipyridine]-5-carboxamide 	LCMS : <i>t</i>_R = 2.937 min, MS (ESI) <i>m/z</i> = 505.16 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ = 9.14 (d, <i>J</i> = 6.8 Hz, 1H), 8.76 (d, <i>J</i> = 1.6 Hz, 1H), 8.70 (d, <i>J</i> = 2.4 Hz, 1H), 8.46 (d, <i>J</i> = 2.0 Hz, 1H), 8.36 (dd, <i>J</i> = 10.8, 2.0 Hz, 1H), 8.15 (t, <i>J</i> = 2.2 Hz, 1H), 8.10 (s, 1H), 7.80 (t, <i>J</i> = 7.0 Hz, 1H), 7.68 (d, <i>J</i> = 7.2 Hz, 1H), 5.20 (q, <i>J</i> = 6.4 Hz, 1H).
1-31	N-[(1R)-1-[2-chloro-3-(trifluoromethyl)phenyl]ethyl]-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide	LCMS : <i>t</i>_R = 2.062 min, MS (ESI) <i>m/z</i> = 504.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ = 9.13 (d, <i>J</i> = 8.0 Hz, 1H), 8.60 (s, 1H), 8.35 (s, 1H), 8.20 (s, 1H), 7.66 (s, 2H), 7.43 - 7.29 (m, 4H), 7.28 - 7.20 (m, 1H), 5.14 (t, <i>J</i> = 7.2 Hz, 1H), 3.15 - 3.08 (m, 2H), 3.08 - 2.98 (m, 2H), 2.91

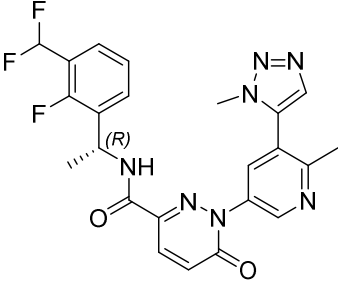
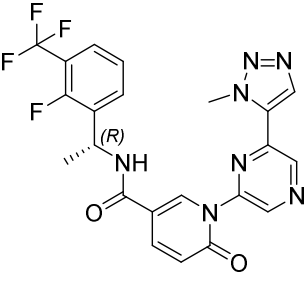
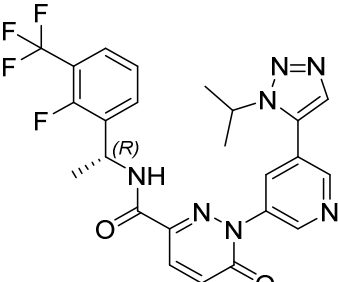
		- 2.85 (m, 1H), 2.02 - 1.93 (m, 1H), 1.92 - 1.81 (m, 2H), 1.57 (dd, $J = 3.6$, 8.8 Hz, 1H), 1.50 (d, $J = 7.2$ Hz, 3H), 0.96 (d, $J = 6.8$ Hz, 3H).
1-32	N-[(1R)-1-[2-fluoro-3-[1-(hydroxymethyl)cyclopropyl]phenyl]ethyl]-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide 	LCMS : $t_R = 2.643$ min, MS (ESI) $m/z = 488.1$ $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) $\delta = 9.13$ (d, $J = 2.0$ Hz, 1H), 8.98 (br d, $J = 8.4$ Hz, 1H), 8.92 (d, $J = 1.6$ Hz, 1H), 8.52 (d, $J = 2.0$ Hz, 1H), 8.13 (s, 1H), 7.93 (d, $J = 9.6$ Hz, 1H), 7.34 (br t, $J = 7.2$ Hz, 1H), 7.25 - 7.17 (m, 2H), 7.06 (t, $J = 7.6$ Hz, 1H), 5.40 (quin, $J = 7.2$ Hz, 1H), 4.65 (t, $J = 5.6$ Hz, 1H), 4.17 (s, 3H), 3.43 (br d, $J = 6.0$ Hz, 2H), 1.46 (br d, $J = 7.2$ Hz, 3H), 0.82 (m, 2H), 0.65 (m, 2H).
1-33	N-[(1R)-1-[2-fluoro-3-(1-methylcyclopropyl)phenyl]ethyl]-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide 	LCMS : $t_R = 2.072$ min, MS (ESI) $m/z = 474.2$ $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) $\delta = 9.13$ (d, $J = 2.4$ Hz, 1H), 8.96 (d, $J = 8.4$ Hz, 1H), 8.92 (d, $J = 2.0$ Hz, 1H), 8.51 (t, $J = 2.4$ Hz, 1H), 8.13 (s, 1H), 7.92 (d, $J = 9.6$ Hz, 1H), 7.32 (t, $J = 7.6$ Hz, 1H), 7.22 (d, $J = 9.6$ Hz, 2H), 7.08 - 7.04 (m, 1H), 5.42 - 5.37 (m, 1H), 4.17 (s, 3H), 1.47 (d, $J = 7.2$ Hz, 3H), 1.29 (s, 3H), 0.73 (d, $J = 2.0$ Hz, 2H), 0.69 (d, $J = 2.4$ Hz, 2H).
1-34	N-[(1R)-1-deuterio-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide	LCMS : $t_R = 2.018$ min, MS (ESI) $m/z = 489.2$ $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) $\delta = 9.15$-9.10 (m, 2H), 8.93 (d, $J = 2.0$ Hz, 1H), 8.51 (t, $J = 2.4$ Hz, 1H), 8.13 (s, 1H), 7.92 (d, $J = 10.0$ Hz, 1H), 7.84 (br t, $J = 7.2$ Hz, 1H), 7.68 (br t, $J = 7.2$ Hz, 1H), 7.40 (t, $J = 8.0$ Hz, 1H), 7.22

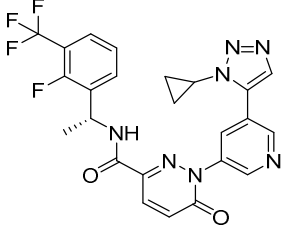
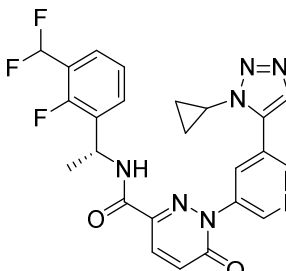
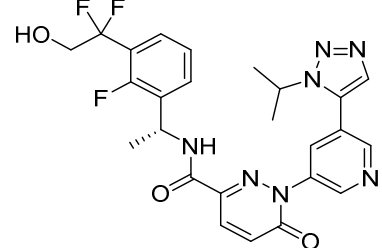
		(d, $J = 10.0$ Hz, 1H), 4.17 (s, 3H), 1.51 (s, 3H).
1-35	N-((R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]-ethyl-(2,2,2-trideuterio))-1-[5-(1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide 	LCMS : $t_R = 1.278$ min, MS (ESI) $m/z = 491.1$ $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) $\delta = 9.17 - 9.09$ (m, 2H), 8.93 (d, $J = 2.0$ Hz, 1H), 8.52 (t, $J = 2.0$ Hz, 1H), 8.14 (s, 1H), 7.93 (d, $J = 10.0$ Hz, 1H), 7.83 (t, $J = 7.2$ Hz, 1H), 7.69 (t, $J = 7.2$ Hz, 1H), 7.41 (t, $J = 7.8$ Hz, 1H), 7.23 (d, $J = 10.0$ Hz, 1H), 5.42 (d, $J = 8.0$ Hz, 1H), 4.18 (s, 3H).
1-36	N-((R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]-ethyl-(2,2,2-trideuterio))-1-(5-{1-[trideuteriomethyl]-1H-1,2,3-triazol-5-yl}-3-pyridyl)-6-oxo-1,6-dihydropyridazine-3-carboxamide 	LCMS : $t_R = 0.621$ min, MS (ESI) $m/z = 494.3$ $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) $\delta = 9.14 - 9.09$ (m, 2H), 8.93 (d, $J = 2.0$ Hz, 1H), 8.51 (t, $J = 2.0$ Hz, 1H), 8.13 (s, 1H), 7.92 (d, $J = 9.6$ Hz, 1H), 7.83 (t, $J = 7.2$ Hz, 1H), 7.68 (t, $J = 6.8$ Hz, 1H), 7.40 (t, $J = 7.6$ Hz, 1H), 7.22 (d, $J = 9.6$ Hz, 1H), 5.41 (d, $J = 7.6$ Hz, 1H).
1-37	N-((1R)-1-[3-(1,1-difluoro-2-hydroxyethyl)-2-fluoro-phenyl]ethyl)-6'-(1-methyl-1H-1,2,3-triazol-5-yl)-6-oxo-6H-[1,4'-bipyridazine]-1,6-dihydro-3-carboxamide 	LCMS : $t_R = 0.556$ min, MS (ESI) $m/z = 501.2$ $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) $\delta = 9.97$ (d, $J = 2.4$ Hz, 1H), 9.20 (d, $J = 8.0$ Hz, 1H), 8.75 (d, $J = 2.4$ Hz, 1H), 8.46 (s, 1H), 7.94 (d, $J = 10.0$ Hz, 1H), 7.68 (br t, $J = 7.2$ Hz, 1H), 7.45 (br t, $J = 6.8$ Hz, 1H), 7.33 - 7.25 (m, 2H), 5.72 (br s, 1H), 5.44 (quin, $J = 7.2$ Hz, 1H), 4.43 (s, 3H), 3.92 (br t, $J = 14.2$ Hz, 2H), 1.53 (d, $J = 7.2$ Hz, 3H).
1-38	N-((R)-1-[2-fluoro-3-	LCMS : $t_R = 1.871$ min, MS (ESI) m/z

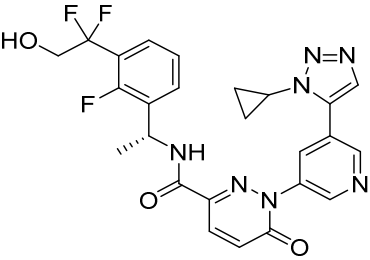
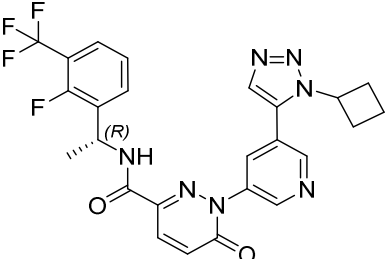
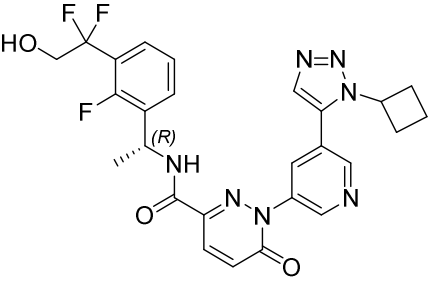
	(trifluoromethyl)phenyl]ethyl}-1-[5-(1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-5-deuterio-3-carboxamide 	= 489.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ = 9.14 - 9.11 (m, 2H), 8.93 (d, <i>J</i> = 2.0 Hz, 1H), 8.52 (t, <i>J</i> = 2.0 Hz, 1H), 8.13 (s, 1H), 7.95 - 7.90 (m, 1H), 7.84 (t, <i>J</i> = 7.2 Hz, 1H), 7.69 (t, <i>J</i> = 6.8 Hz, 1H), 7.41 (t, <i>J</i> = 7.6 Hz, 1H), 5.44 (t, <i>J</i> = 7.2 Hz, 1H), 4.17 (s, 3H), 1.52 (d, <i>J</i> = 7.2 Hz, 3H).
1-39	N-{(R)-1-[3-(1,1-difluoro-2-hydroxyethyl)-2-fluorophenyl]ethyl}-1-[5-(1-isopropyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-5-methyl-6-oxo-1,6-dihydropyridazine-3-carboxamide 	LCMS : t_R = 1.258 min, MS (ESI) m/z = 542.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ = 9.12 (t, <i>J</i> = 2.4 Hz, 1H), 8.69 (t, <i>J</i> = 2.0 Hz, 1H), 8.20 - 8.15 (m, 1H), 7.92 (d, <i>J</i> = 1.2 Hz, 1H), 7.86 (d, <i>J</i> = 2.4 Hz, 1H), 7.60 (br d, <i>J</i> = 8.4 Hz, 1H), 7.53 (br t, <i>J</i> = 7.6 Hz, 1H), 7.45 (br t, <i>J</i> = 6.8 Hz, 1H), 7.25 - 7.19 (m, 1H), 5.42 (br t, <i>J</i> = 7.2 Hz, 1H), 4.18 - 3.98 (m, 2H), 2.34 (s, 3H), 1.68 (ddd, <i>J</i> = 2.0, 6.8, 11.2 Hz, 6H), 1.63 - 1.60 (m, 3H).
1-40	N-{(R)-1-[3-(1,1-difluoro-2-hydroxyethyl)-2-fluorophenyl]ethyl}-1-[5-(1-cyclopropyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-5-methyl-6-oxo-1,6-dihydropyridazine-3-carboxamide 	LCMS : t_R = 1.225 min, MS (ESI) m/z = 540.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ = 9.11 (d, <i>J</i> = 2.4 Hz, 1H), 9.03 - 8.98 (m, 2H), 8.63 (t, <i>J</i> = 2.0 Hz, 1H), 8.16 (s, 1H), 7.85 (d, <i>J</i> = 1.2 Hz, 1H), 7.63 (br t, <i>J</i> = 6.8 Hz, 1H), 7.44 (br t, <i>J</i> = 6.8 Hz, 1H), 7.27 (t, <i>J</i> = 7.6 Hz, 1H), 5.72 (t, <i>J</i> = 6.4 Hz, 1H), 5.41 (quin, <i>J</i> = 7.2 Hz, 1H), 4.07 - 3.99 (m, 1H), 3.91 (dt, <i>J</i> = 6.4, 14.3 Hz, 2H), 2.21 (d, <i>J</i> = 0.8 Hz, 3H), 1.48 (d, <i>J</i> = 7.2 Hz, 3H), 1.19 - 1.11 (m, 4H).
1-41	N-{(R)-1-[3-(1,1-difluoro-2-hydroxyethyl)-2-fluorophenyl]ethyl}-5-ethyl-1-[5-(1-	LCMS : t_R = 1.225 min, MS (ESI) m/z = 556.2 [M+H]⁺.

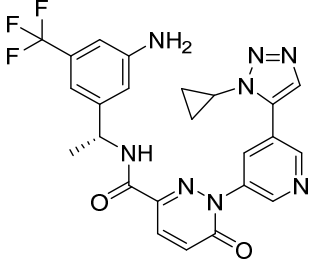
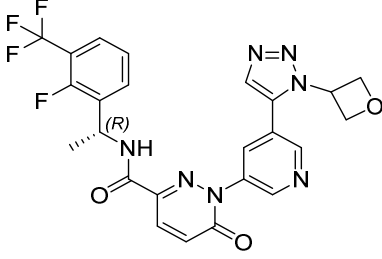
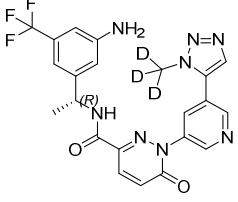
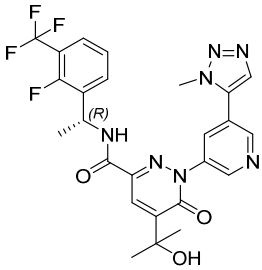
	isopropyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide 	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ = 9.16 (d, <i>J</i> = 2.0 Hz, 1H), 9.05 (br d, <i>J</i> = 8.0 Hz, 1H), 8.79 (d, <i>J</i> = 1.6 Hz, 1H), 8.41 (s, 1H), 8.03 (s, 1H), 8.07 - 7.97 (m, 1H), 7.76 (s, 1H), 7.64 (br t, <i>J</i> = 6.8 Hz, 1H), 7.44 (br t, <i>J</i> = 6.8 Hz, 1H), 7.30 - 7.24 (m, 1H), 5.71 (br s, 1H), 5.42 (br t, <i>J</i> = 7.6 Hz, 1H), 4.78 (td, <i>J</i> = 6.8, 13.2 Hz, 1H), 3.91 (br t, <i>J</i> = 13.2 Hz, 2H), 2.60 (q, <i>J</i> = 7.2 Hz, 2H), 1.53 (s, 6H), 1.49 (br d, <i>J</i> = 7.2 Hz, 3H), 1.18 (t, <i>J</i> = 7.6 Hz, 3H).
1-42	N-{(R)-1-[3-(1,1-difluoro-2-hydroxyethyl)-2-fluorophenyl]ethyl}-1-[5-(1-cyclopropyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-5-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxamide 	LCMS : <i>t</i>_R = 1.185 min, MS (ESI) <i>m/z</i> = 554.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ = 9.11 (d, <i>J</i> = 2.0 Hz, 1H), 9.04 - 8.99 (m, 2H), 8.63 (s, 1H), 8.16 (s, 1H), 7.76 (s, 1H), 7.64 (br t, <i>J</i> = 7.2 Hz, 1H), 7.44 (br t, <i>J</i> = 7.2 Hz, 1H), 7.31 - 7.23 (m, 1H), 5.71 (t, <i>J</i> = 6.4 Hz, 1H), 5.42 (quin, <i>J</i> = 7.2 Hz, 1H), 4.06 - 4.00 (m, 1H), 3.92 (dt, <i>J</i> = 6.0, 14.4 Hz, 2H), 2.60 (q, <i>J</i> = 7.2 Hz, 2H), 1.49 (d, <i>J</i> = 7.2 Hz, 3H), 1.21 - 1.13 (m, 7H).
1-43	N-[(1R)-1-[3-(1,1-difluoro-2-hydroxyethyl)-2-fluoro-phenyl]ethyl]-6-oxo-1,6-dihydropyridazine-5-deuterio-3-carboxamide 	LCMS : <i>t</i>_R = 1.144 min, MS (ESI) <i>m/z</i> = 527.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ = 9.12 (d, <i>J</i> = 2.4 Hz, 1H), 9.07 (d, <i>J</i> = 8.0 Hz, 1H), 9.02 (d, <i>J</i> = 2.0 Hz, 1H), 8.65 (t, <i>J</i> = 2.0 Hz, 1H), 8.17 (s, 1H), 7.92 (s, 1H), 7.64 (br t, <i>J</i> = 7.2 Hz, 1H), 7.44 (br t, <i>J</i> = 6.8 Hz, 1H), 7.31 - 7.24 (m, 1H), 5.71 (br s, 1H), 5.49 - 5.35 (m, 1H), 4.08 - 3.99 (m, 1H), 3.96 - 3.87 (m, 2H), 1.49 (d, <i>J</i> = 7.2 Hz, 3H), 1.19 - 1.13 (m, 4H).
1-44	N-{(R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl}-5-{(R)-1-[2-	LCMS : <i>t</i>_R = 2.780 min, MS (ESI) <i>m/z</i> = 693.2 [M+H]⁺.

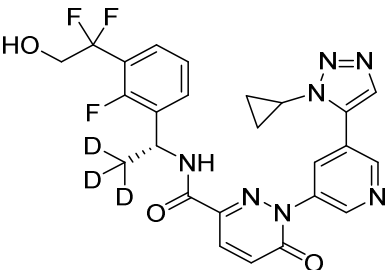
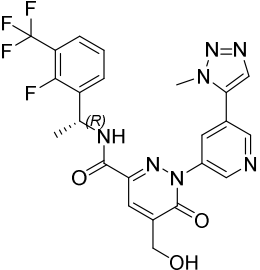
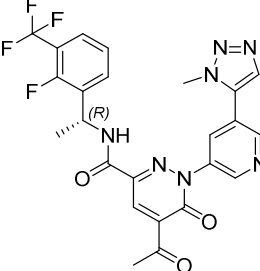
	fluoro-3-(trifluoromethyl)phenyl]ethylamino}-1-[5-(1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide 	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ = 9.38 (d, <i>J</i> = 7.2 Hz, 1H), 9.12 (d, <i>J</i> = 8.4 Hz, 1H), 8.88 (d, <i>J</i> = 2.0 Hz, 1H), 8.83 (d, <i>J</i> = 2.4 Hz, 1H), 8.25 (t, <i>J</i> = 2.2 Hz, 1H), 8.06 (s, 1H), 7.85-7.77 (m, 2H), 7.70-7.64 (m, 3H), 7.42-7.35 (m, 2H), 5.48 (quin, <i>J</i> = 7.3, 14.7 Hz, 1H), 5.26 (quin, <i>J</i> = 7.0, 14.0 Hz, 1H), 4.01 (s, 3H), 1.51 (d, <i>J</i> = 7.2 Hz, 3H), 1.48 (d, <i>J</i> = 7.2 Hz, 3H).
1-45	N-{(R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl}-1-[6-(methylamino)-5-(1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide 	LCMS : <i>t</i>_R = 2.710 min, MS (ESI) <i>m/z</i> = 517.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ = 9.06 (d, <i>J</i> = 8.0 Hz, 1H), 8.52 (d, <i>J</i> = 2.4 Hz, 1H), 7.88-7.84 (m, 3H), 7.80 (d, <i>J</i> = 2.4 Hz, 1H), 7.68 (t, <i>J</i> = 7.2 Hz, 1H), 7.40 (t, <i>J</i> = 7.4 Hz, 1H), 7.11 (d, <i>J</i> = 9.6 Hz, 1H), 6.44-6.42 (m, 1H), 5.41 (quin, <i>J</i> = 7.4, 14.5 Hz, 1H), 3.90 (s, 3H), 2.84 (d, <i>J</i> = 4.8 Hz, 3H), 1.51 (d, <i>J</i> = 6.8 Hz, 3H).
1-46	N-{(R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl}-1-[5-(1-methyl-1H-1,2,3-triazol-5-yl)-6-morpholino-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide 	LCMS : <i>t</i>_R = 2.874 min, MS (ESI) <i>m/z</i> = 572.3 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ = 9.11 (d, <i>J</i> = 8.0 Hz, 1H), 8.77 (d, <i>J</i> = 2.4 Hz, 1H), 8.09 (d, <i>J</i> = 2.8 Hz, 1H), 7.97 (s, 1H), 7.88 (d, <i>J</i> = 9.6 Hz, 1H), 7.83 (t, <i>J</i> = 7.2 Hz, 1H), 7.69 (t, <i>J</i> = 7.0 Hz, 1H), 7.40 (t, <i>J</i> = 7.8 Hz, 1H), 7.17 (d, <i>J</i> = 10.0 Hz, 1H), 5.42 (quin, <i>J</i> = 7.1, 14.3 Hz, 1H), 4.02 (s, 3H), 3.58 (t, <i>J</i> = 4.6 Hz, 4H), 3.03 (t, <i>J</i> = 4.6 Hz, 4H), 1.51 (d, <i>J</i> = 6.8 Hz, 3H).
1-47	N-{(R)-1-[3-(difluoromethyl)-2-fluorophenyl]ethyl}-1-[6-methyl-5-(1-	LCMS : <i>t</i>_R = 0.531 min, MS (ESI) <i>m/z</i> = 484.1 [M+H]⁺.

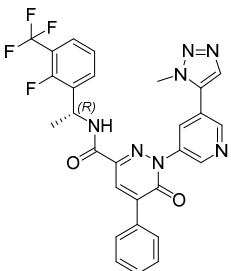
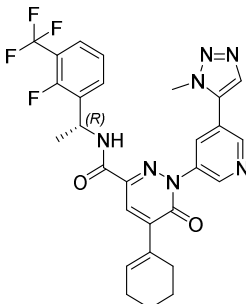
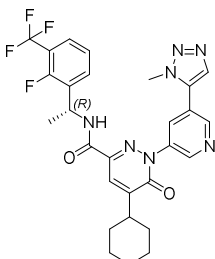
	methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide 	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ = 9.05 (d, <i>J</i> = 8.0 Hz, 1H), 9.01 (d, <i>J</i> = 2.4 Hz, 1H), 8.27 (d, <i>J</i> = 2.4 Hz, 1H), 8.03 (s, 1H), 7.89 (d, <i>J</i> = 10.0 Hz, 1H), 7.67 (t, <i>J</i> = 7.2 Hz, 1H), 7.53 (t, <i>J</i> = 6.8 Hz, 1H), 7.32 (t, <i>J</i> = 7.6 Hz, 1H), 7.22 (t, <i>J</i> = 54.4 Hz, 1H), 7.19 (d, <i>J</i> = 10.0 Hz, 1H), 5.40 (quin, <i>J</i> = 7.2 Hz, 1H), 3.95 (s, 3H), 2.47 (s, 3H), 1.49 (d, <i>J</i> = 7.2 Hz, 3H).
1-48	N-[(R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-1-[6-(1-methyl-1H-1,2,3-triazol-5-yl)pyrazin-2-yl]-6-oxo-1,6-dihydropyridine-3-carboxamide 	LCMS : <i>t</i>_R = 0.632 min, MS (ESI) <i>m/z</i> = 488.1 [M+H]⁺. ¹H NMR (400 MHz, MeOD) δ = 9.18 (d, <i>J</i> = 3.6 Hz, 2H), 8.69 (d, <i>J</i> = 2.4 Hz, 1H), 8.44 (s, 1H), 8.10 (dd, <i>J</i> = 2.8, 10.0 Hz, 1H), 7.74-7.66 (m, 1H), 7.63-7.56 (m, 1H), 7.33 (t, <i>J</i> = 8.0 Hz, 1H), 6.72 (d, <i>J</i> = 9.6 Hz, 1H), 5.46 (q, <i>J</i> = 7.2 Hz, 1H), 4.41 (s, 3H), 1.59 (d, <i>J</i> = 7.2 Hz, 3H).
1-49	N-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-1-[5-(3-isopropyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide 	LCMS : <i>t</i>_R = 2.261 min, MS (ESI) <i>m/z</i> = 514.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ = 9.16 (d, <i>J</i> = 2.0 Hz, 1H), 9.13 (d, <i>J</i> = 8.0 Hz, 1H), 8.80 (d, <i>J</i> = 2.0 Hz, 1H), 8.41 (t, <i>J</i> = 2.0 Hz, 1H), 8.03 (s, 1H), 7.92 (d, <i>J</i> = 9.6 Hz, 1H), 7.83 (t, <i>J</i> = 7.2 Hz, 1H), 7.68 (t, <i>J</i> = 7.2 Hz, 1H), 7.40 (t, <i>J</i> = 7.6 Hz, 1H), 7.22 (d, <i>J</i> = 9.6 Hz, 1H), 5.43 (quin, <i>J</i> = 7.2 Hz, 1H), 4.78 (quin, <i>J</i> = 6.8 Hz, 1H), 1.54 - 1.51 (m, 9H).
1-50	N-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-1-[5-(1-cyclopropyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide	LCMS : <i>t</i>_R = 2.179 min, MS (ESI) <i>m/z</i> = 514.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ = 9.14 - 9.09 (m, 2H), 9.02 (d, <i>J</i> = 2.0 Hz, 1H), 8.64 (t, <i>J</i> = 2.0 Hz, 1H), 8.16 (s,

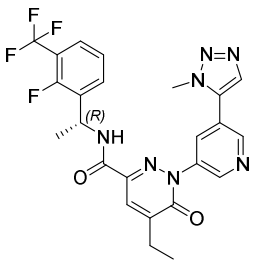
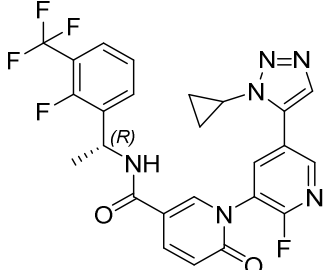
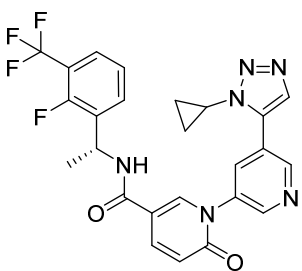
		1H), 7.92 (d, J = 9.6 Hz, 1H), 7.82 (t, J = 7.2 Hz, 1H), 7.68 (t, J = 7.2 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H), 7.22 (d, J = 9.6 Hz, 1H), 5.42 (t, J = 7.2 Hz, 1H), 4.06 - 3.99 (m, 1H), 1.51 (d, J = 7.2 Hz, 3H), 1.18 - 1.12 (m, 4H).
1-51	N-[(1R)-1-[3-(difluoromethyl)-2-fluorophenyl]ethyl]-1-[5-(1-cyclopropyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide 	LCMS : t_R = 1.959 min, MS (ESI) m/z = 496.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ = 9.12 (d, J = 2.4 Hz, 1H), 9.07 (d, J = 8.0 Hz, 1H), 9.02 (d, J = 2.0 Hz, 1H), 8.65 (t, J = 2.0 Hz, 1H), 8.17 (s, 1H), 7.92 (d, J = 9.6 Hz, 1H), 7.68 (br t, J = 7.2 Hz, 1H), 7.53 (br t, J = 7.2 Hz, 1H), 7.35 - 7.29 (m, 1H), 7.24 - 7.20 (m, 2H), 7.08 (s, 1H), 5.42 (quin, J = 7.2 Hz, 1H), 4.06 - 4.00 (m, 1H), 1.50 (d, J = 7.2 Hz, 3H), 1.18 - 1.12 (m, 4H).
1-52	N-[(1R)-1-[3-(1,1-difluoro-2-hydroxyethyl)-2-fluorophenyl]ethyl]-1-[5-(1-isopropyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide 	LCMS : t_R = 1.683 min, MS (ESI) m/z = 528.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ = 9.16 (d, J = 2.4 Hz, 1H), 9.08 (d, J = 8.2 Hz, 1H), 8.80 (d, J = 2.0 Hz, 1H), 8.41 (t, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.92 (d, J = 9.6 Hz, 1H), 7.64 (br t, J = 7.2 Hz, 1H), 7.48 - 7.41 (m, 1H), 7.27 (t, J = 7.6 Hz, 1H), 7.22 (d, J = 9.6 Hz, 1H), 5.72 (t, J = 6.4 Hz, 1H), 5.46 - 5.37 (m, 1H), 4.78 (quin, J = 6.4 Hz, 1H), 3.96 - 3.86 (m, 2H), 1.52 (d, J = 6.4 Hz, 6H), 1.49 (d, J = 7.2 Hz, 3H).
1-53	N-[(1R)-1-[3-(1,1-difluoro-2-hydroxyethyl)-2-fluorophenyl]ethyl]-1-[5-(1-cyclopropyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide	LCMS : t_R = 1.614 min, MS (ESI) m/z = 526.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ = 9.12 (d, J = 2.4 Hz, 1H), 9.07 (d, J = 8.0 Hz, 1H), 9.02 (d, J = 2.0 Hz, 1H), 8.65 (t, J = 2.4 Hz, 1H), 8.17 (s, 1H), 7.93 (d, J = 9.6 Hz, 1H), 7.64 (br t, J =

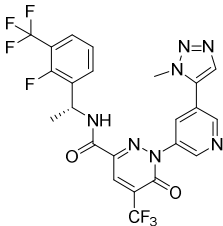
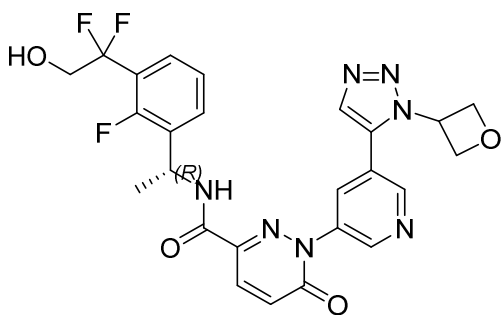
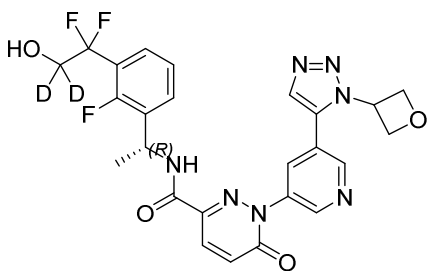
		6.8 Hz, 1H), 7.44 (br t, J = 6.8 Hz, 1H), 7.30 - 7.25 (m, 1H), 7.23 (d, J = 9.6 Hz, 1H), 5.71 (t, J = 6.4 Hz, 1H), 5.47 - 5.37 (m, 1H), 4.08 - 3.99 (m, 1H), 3.91 (dt, J = 6.4, 14.4 Hz, 2H), 1.49 (d, J = 7.2 Hz, 3H), 1.19 - 1.13 (m, 4H).
1-54	N-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-1-[5-(1-cyclobutyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide 	LCMS : t_R = 2.334 min, MS (ESI) m/z = 528.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ = 8.98 (d, J = 2.4 Hz, 1H), 8.69 (d, J = 1.6 Hz, 1H), 8.13 (t, J = 2.4 Hz, 1H), 8.07 (d, J = 9.6 Hz, 1H), 7.84 (s, 1H), 7.55 (t, J = 7.2 Hz, 2H), 7.44 - 7.39 (m, 1H), 7.25 - 7.21 (m, 1H), 7.15 (d, J = 9.6 Hz, 1H), 5.47 - 5.41 (m, 1H), 4.94 - 4.86 (m, 1H), 2.99 - 2.89 (m, 2H), 2.58 - 2.51 (m, 2H), 2.07 - 1.90 (m, 2H), 1.64 (d, J = 7.2 Hz, 3H).
1-55	1-[5-(1-cyclobutyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-N-[(1R)-1-[3-(1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethyl]-6-oxo-pyridazine-3-carboxamide 	LCMS : t_R = 1.769 min, MS (ESI) m/z = 540.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ = 9.10 (d, J = 2.4 Hz, 1H), 8.68 (d, J = 2.0 Hz, 1H), 8.17 (t, J = 2.0 Hz, 1H), 8.07 (d, J = 9.6 Hz, 1H), 7.88 (s, 1H), 7.59 (br d, J = 8.4 Hz, 1H), 7.56 - 7.51 (m, 1H), 7.45 (t, J = 6.8 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 7.16 (d, J = 9.6 Hz, 1H), 5.47 - 5.39 (m, 1H), 4.92 (quin, J = 8.4 Hz, 1H), 4.20 - 4.02 (m, 2H), 3.59 (br t, J = 6.4 Hz, 1H), 2.94 (quin, J = 10.0 Hz, 2H), 2.60 - 2.51 (m, 2H), 2.08 - 1.91 (m, 2H), 1.62 (d, J = 7.2 Hz, 3H).
1-56	1-[5-(1-cyclopropyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-N-[(1R)-1-[3-amino-5-(trifluoromethyl)phenyl]ethyl]pyridazine-3-carboxamide	LCMS : t_R = 1.735 min, MS (ESI) m/z = 511.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ = 9.11 (d, J = 2.4 Hz, 1H), 9.01 (d, J = 2.0 Hz, 1H), 8.97 (d, J = 8.4 Hz, 1H),

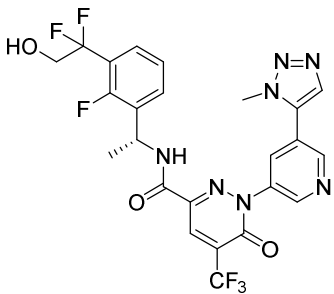
		8.64 (t, $J = 2.4$ Hz, 1H), 8.15 (s, 1H), 7.94 (d, $J = 9.6$ Hz, 1H), 7.23 (d, $J = 9.6$ Hz, 1H), 6.80 (br d, $J = 11.2$ Hz, 2H), 6.71 (s, 1H), 5.55 (s, 2H), 5.06 (quin, $J = 7.2$ Hz, 1H), 4.09 - 3.95 (m, 1H), 1.45 (d, $J = 7.2$ Hz, 3H), 1.18 - 1.11 (m, 4H).
1-57	1-[5-[1-(oxetan-3-yl)triazol-5-yl]-3-pyridyl]-6-oxo-N-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]pyridazine-3-carboxamide 	LCMS : $t_R = 2.019$ min, MS (ESI) $m/z = 530.1$ $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) $\delta = 9.18 - 9.10$ (m, 2H), 8.80 (d, $J = 2.0$ Hz, 1H), 8.34 (t, $J = 2.0$ Hz, 1H), 8.19 (s, 1H), 7.93 (d, $J = 9.6$ Hz, 1H), 7.84 (t, $J = 7.6$ Hz, 1H), 7.69 (t, $J = 7.2$ Hz, 1H), 7.41 (t, $J = 8.0$ Hz, 1H), 7.24 (d, $J = 9.6$ Hz, 1H), 5.93 - 5.82 (m, 1H), 5.48 - 5.40 (m, 1H), 5.08 - 5.03 (m, 2H), 5.01 - 4.97 (m, 2H), 1.53 (d, $J = 7.2$ Hz, 3H).
1-58	N-[(1R)-1-amino-5-(trifluoromethyl)phenyl]ethyl]-6-oxo-1-[5-[1-(trideuteriomethyl)triazol-5-yl]-3-pyridyl]pyridazine-3-carboxamide 	LCMS : $t_R = 1.695$ min, MS (ESI) $m/z = 488.2$ $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) $\delta = 9.17 - 9.08$ (m, 2H), 8.93 (d, $J = 2.0$ Hz, 1H), 8.54 (t, $J = 2.0$ Hz, 1H), 8.14 (s, 1H), 7.94 (d, $J = 9.6$ Hz, 1H), 7.41 - 7.28 (m, 2H), 7.25 - 7.20 (m, 2H), 5.21 - 5.11 (m, 3H), 1.50 (d, $J = 7.2$ Hz, 3H).
1-59	(R)-N-(1-(2-fluoro-3-(trifluoromethyl)phenyl)ethyl)-5-(2-hydroxypropane-2-yl)-1-(5-(1-methyl-1H-1,2,3-triazol-5-yl)pyridin-3-yl)-6-oxo-1,6-dihydropyridazine-3-carboxamide 	LCMS : $t_R = 1.833$ min, MS (ESI) $m/z = 546.0$ $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) $\delta = 9.14 - 9.04$ (m, 2H), 8.92 (d, $J = 1.6$ Hz, 1H), 8.48 (s, 1H), 8.17 - 8.02 (m, 2H), 7.82 (br t, $J = 7.2$ Hz, 1H), 7.68 (br t, $J = 7.2$ Hz, 1H), 7.40 (t, $J = 7.6$ Hz, 1H), 5.51 (s, 1H), 5.43 (quin, $J = 7.2$ Hz, 1H), 4.17 (s, 3H), 1.53 - 1.47 (m, 9H).

1-60	1-[5-(1-cyclopropyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-N-[(1R)-2,2,2-trideuterio-1-[3-(1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethyl]pyridazine-3-carboxamide 	LCMS : t_R = 1.588 min, MS (ESI) m/z = 529.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ = 9.12 (d, J = 2.4 Hz, 1H), 9.06 (d, J = 8.0 Hz, 1H), 9.02 (d, J = 2.0 Hz, 1H), 8.65 (t, J = 2.0 Hz, 1H), 8.17 (s, 1H), 7.93 (d, J = 10.0 Hz, 1H), 7.64 (t, J = 6.8 Hz, 1H), 7.44 (t, J = 6.8 Hz, 1H), 7.28 (t, J = 7.6 Hz, 1H), 7.23 (d, J = 10.0 Hz, 1H), 5.71 (br s, 1H), 5.40 (d, J = 8.0 Hz, 1H), 4.07 - 4.00 (m, 1H), 3.91 (dt, J = 3.5, 14.0 Hz, 2H), 1.19 - 1.13 (m, 4H).
1-61	N-[(R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-5-(hydroxymethyl)-1-[5-(1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide 	LCMS: MS (ESI) m/z = 518.1 $[M+H]^+$. 1H NMR (400MHz, DMSO-d_6) δ = 9.15-9.09 (m, 2H), 8.92 (d, J = 2.0 Hz, 1H), 8.51 (t, J = 2.0 Hz, 1H), 8.13 (s, 1H), 7.91 (s, 1H), 7.83 (t, J = 7.2 Hz, 1H), 7.68 (t, J = 7.2 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 5.64 (t, J = 5.6 Hz, 1H), 5.44 (t, J = 7.2 Hz, 1H), 4.47 (br d, J = 4.4 Hz, 2H), 4.17 (s, 3H), 1.52 (d, J = 7.2 Hz, 3H).
1-62	N-[(R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-5-acetyl-1-[5-(1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide 	LCMS : t_R = 1.295 min, MS (ESI) m/z = 530.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ = 9.20 (br d, J = 7.6 Hz, 1H), 9.11 (d, J = 2.0 Hz, 1H), 8.96 (d, J = 1.6 Hz, 1H), 8.51 (s, 1H), 8.13 (d, J = 1.6 Hz, 2H), 7.82 (br t, J = 7.2 Hz, 1H), 7.68 (br t, J = 7.2 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 5.44 (quin, J = 7.2 Hz, 1H), 4.17 (s, 3H), 2.60 (s, 3H), 1.52 (br d, J = 7.2 Hz, 3H).
1-63	N-[(R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-1-[5-(1-	LCMS : t_R = 0.722 min, MS (ESI) m/z = 564.2 $[M+H]^+$.

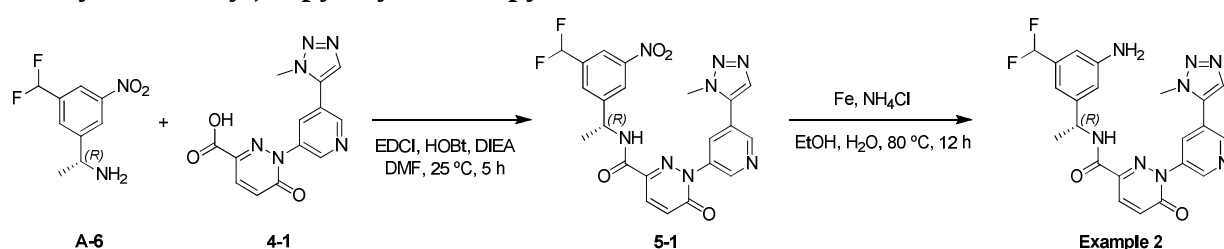
	methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-5-phenyl-1,6-dihydropyridazine-3-carboxamide 	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ = 9.21-9.12 (m, 2H), 8.94 (d, <i>J</i> = 2.0 Hz, 1H), 8.56 (t, <i>J</i> = 2.0 Hz, 1H), 8.14 (s, 1H), 8.01 (s, 1H), 7.91-7.83 (m, 3H), 7.69 (t, <i>J</i> = 7.2 Hz, 1H), 7.52-7.47 (m, 3H), 7.42 (t, <i>J</i> = 8.0 Hz, 1H), 5.46 (quin, <i>J</i> = 7.2 Hz, 1H), 4.18 (s, 3H), 1.53 (d, <i>J</i> = 7.2 Hz, 3H).
1-64	N-{(R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl}-5-(1-cyclohexen-1-yl)-1-[5-(1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide 	LCMS : <i>t</i>_R = 0.732 min, MS (ESI) <i>m/z</i> = 568.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ = 9.13 - 9.03 (m, 2H), 8.91 (d, <i>J</i> = 1.6 Hz, 1H), 8.48 (s, 1H), 8.13 (s, 1H), 7.82 (br t, <i>J</i> = 7.2 Hz, 1H), 7.70 - 7.65 (m, 2H), 7.40 (t, <i>J</i> = 7.6 Hz, 1H), 7.16 (br s, 1H), 5.43 (br t, <i>J</i> = 7.2 Hz, 1H), 4.16 (s, 3H), 2.34 (br s, 2H), 2.23 (br d, <i>J</i> = 2.4 Hz, 2H), 1.69 (br d, <i>J</i> = 4.8 Hz, 2H), 1.59 (br d, <i>J</i> = 5.6 Hz, 2H), 1.51 (br d, <i>J</i> = 7.2 Hz, 3H).
1-65	N-{(R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl}-5-cyclohexyl-1-[5-(1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide 	LCMS : <i>t</i>_R = 1.859 min, MS (ESI) <i>m/z</i> = 569.9 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ = 9.11 (d, <i>J</i> = 2.4 Hz, 1H), 9.08 (d, <i>J</i> = 7.6 Hz, 1H), 8.91 (d, <i>J</i> = 2.0 Hz, 1H), 8.50 (t, <i>J</i> = 2.0 Hz, 1H), 8.13 (s, 1H), 7.83 (t, <i>J</i> = 7.6 Hz, 1H), 7.71 - 7.65 (m, 2H), 7.40 (t, <i>J</i> = 7.6 Hz, 1H), 5.42 (t, <i>J</i> = 7.6 Hz, 1H), 4.17 (s, 3H), 2.87 - 2.74 (m, 1H), 1.92 - 1.59 (m, 6H), 1.51 (d, <i>J</i> = 7.2 Hz, 3H), 1.39 - 1.30 (m, 4H).

1-66	N-{(R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl}-5-ethyl-1-[5-(1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide 	LCMS : t_R = 0.720 min, MS (ESI) m/z = 516.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ = 9.00 (d, J = 2.4 Hz, 1H), 8.77 (d, J = 2.0 Hz, 1H), 8.22 (t, J = 2.0 Hz, 1H), 7.92 (s, 1H), 7.88 (s, 1H), 7.59 - 7.53 (m, 2H), 7.45 (br d, J = 8.0 Hz, 1H), 7.26 - 7.22 (m, 1H), 5.45 (quin, J = 7.2 Hz, 1H), 4.19 (s, 3H), 2.71 (q, J = 7.6 Hz, 2H), 1.65 (d, J = 7.2 Hz, 3H), 1.29 (t, J = 7.6 Hz, 3H).
1-67	(R)-5'-(1-cyclopropyl-1H-1,2,3-triazol-5-yl)-2'-fluoro-N-(1-(2-fluoro-3-(trifluoromethyl)phenyl)ethyl)-2-oxo-2H-[1,3'-bipyridine]-5-carboxamide 	LCMS : t_R = 0.563 min, MS (ESI) m/z = 531.3 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ = 8.78-8.74 (m, 2H), 8.68 (dd, J = 2.4, 8.8 Hz, 1H), 8.47 (d, J = 2.4 Hz, 1H), 8.13 (s, 1H), 8.05 (dd, J = 2.8, 10.0 Hz, 1H), 7.77 (t, J = 7.2 Hz, 1H), 7.67 (t, J = 7.2 Hz, 1H), 7.39 (t, J = 8.0 Hz, 1H), 6.64 (d, J = 9.6 Hz, 1H), 5.36 (quin, J = 7.2 Hz, 1H), 4.08-4.00 (m, 1H), 1.47 (d, J = 7.2 Hz, 3H), 1.16-1.08 (m, 4H).
1-68	1-[5-(1-cyclopropyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-N-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-2-oxo-2H-[1,3'-bipyridine]-5-carboxamide 	LCMS : t_R = 1.357 min, MS (ESI) m/z = 513.0 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ = 9.05 (d, J = 1.2 Hz, 1H), 8.87 (d, J = 2.0 Hz, 1H), 8.75 (br d, J = 6.8 Hz, 1H), 8.51 (d, J = 2.4 Hz, 1H), 8.46 (s, 1H), 8.15 (s, 1H), 7.99 (dd, J = 2.4, 9.6 Hz, 1H), 7.77 (br t, J = 7.2 Hz, 1H), 7.67 (br t, J = 7.2 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H), 6.61 (d, J = 9.6 Hz, 1H), 5.36 (quin, J = 7.2 Hz, 1H), 4.05 (tt, J = 3.6, 7.2 Hz, 1H), 1.47 (d, J = 7.0 Hz, 3H), 1.18 - 1.09 (m, 4H).
1-69	N-[(R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-1-[5-(1-methyl-1 H-1,2,3-triazol-5-yl)-3-pyridyl]-6-	LCMS : t_R = 1.919 min, MS (ESI) m/z = 555.9 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ =

	oxo-5-(trifluoromethyl)-pyridazine-3-carboxamide 	9.29 (br d, $J = 7.2$ Hz, 1H), 9.09 (br s, 1H), 8.97 (br s, 1H), 8.50 (br s, 1H), 8.25 (br s, 1H), 8.14 (s, 1H), 7.83 (br s, 1H), 7.69 (br s, 1H), 7.41 (br t, $J = 7.2$ Hz, 1H), 5.50 - 5.39 (m, 1H), 4.16 (s, 3H), 1.53 (br d, $J = 6.4$ Hz, 3H).
1-70	(<i>R</i>)-N-(1-(3-(1,1-difluoro-2-hydroxyethyl)-2-fluorophenyl)ethyl)-1-(5-(1-(oxetan-3-yl)-1H-1,2,3-triazol-5-yl)pyridin-3-yl)-6-oxo-1,6-dihydropyridazine-3-carboxamide 	LCMS : $t_R = 0.788$ min, MS (ESI) $m/z = 542.0$ $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) $\delta =$ 9.15 (d, $J = 2.4$ Hz, 1H), 9.09 (d, $J = 8.0$ Hz, 1H), 8.79 (d, $J = 2.0$ Hz, 1H), 8.34 (t, $J = 2.0$ Hz, 1H), 8.19 (s, 1H), 7.93 (d, $J = 9.6$ Hz, 1H), 7.65 (br t, $J = 7.2$ Hz, 1H), 7.44 (br t, $J = 6.8$ Hz, 1H), 7.28 (t, $J = 7.6$ Hz, 1H), 7.24 (d, $J = 9.6$ Hz, 1H), 5.90 - 5.83 (m, 1H), 5.71 (t, $J = 6.4$ Hz, 1H), 5.43 (t, $J = 7.2$ Hz, 1H), 5.05 (dt, $J = 3.6, 6.4$ Hz, 2H), 5.01 - 4.97 (m, 2H), 3.96 - 3.87 (m, 2H), 1.50 (d, $J = 7.2$ Hz, 3H).
1-71	(<i>R</i>)-N-(1-(3-(1,1-difluoro-2-hydroxyethyl)-2,2-dideuterio)-2-fluorophenyl)ethyl)-1-(5-(1-(oxetan-3-yl)-1H-1,2,3-triazol-5-yl)pyridin-3-yl)-6-oxo-1,6-dihydropyridazine-3-carboxamide 	LCMS : $t_R = 1.444$ min, MS (ESI) $m/z = 544.2$ $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) $\delta =$ 9.15 (s, 1H), 9.08 (br d, $J = 8.4$ Hz, 1H), 8.79 (s, 1H), 8.34 (s, 1H), 8.18 (s, 1H), 7.93 (d, $J = 9.6$ Hz, 1H), 7.65 (br t, $J = 7.2$ Hz, 1H), 7.44 (br t, $J = 6.8$ Hz, 1H), 7.28 (t, $J = 7.6$ Hz, 1H), 7.23 (d, $J = 10.0$ Hz, 1H), 5.91 - 5.82 (m, 1H), 5.67 (s, 1H), 5.48 - 5.38 (m, 1H), 5.07 - 5.03 (m, 2H), 5.01 - 4.96 (m, 2H), 1.50 (br d, $J = 7.2$ Hz, 3H). Deuterated ratio: 98.85%.

1-72	(R)-N-(1-(3-(1,1-difluoro-2-hydroxyethyl)-2-fluorophenyl)ethyl)-1-(5-(1-methyl-1H-1,2,3-triazol-5-yl)pyridin-3-yl)-6-oxo-5-(trifluoromethyl)-1,6-dihydropyridazine-3-carboxamide 	LCMS : t_R = 0.940 min, MS (ESI) m/z = 567.9 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ = 9.23 (d, J = 8.4 Hz, 1H), 9.10 (d, J = 2.4 Hz, 1H), 8.97 (d, J = 2.0 Hz, 1H), 8.50 (t, J = 2.0 Hz, 1H), 8.26 (s, 1H), 8.14 (s, 1H), 7.69 - 7.62 (m, 1H), 7.45 (br t, J = 6.8 Hz, 1H), 7.32 - 7.25 (m, 1H), 5.71 (t, J = 6.4 Hz, 1H), 5.44 (quin, J = 7.2 Hz, 1H), 4.17 (s, 3H), 3.91 (dt, J = 6.4, 14.4 Hz, 2H), 1.50 (d, J = 7.2 Hz, 3H).
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Example 2: N-[(1R)-1-[3-amino-5-(difluoromethyl)phenyl]ethyl]-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide



Step 1: Synthesis of N-[(1R)-1-[3-(difluoromethyl)-5-nitro-phenyl]ethyl]-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide

To a solution of **Intermediate 4-1** (88 mg, 295.05 μ mol) and **Intermediate A-6** (52.18 mg, 206.53 μ mol, HCl) in DMF (2 mL) was added HOBt (59.80 mg, 442.57 μ mol), EDCI (84.84 mg, 442.57 μ mol) and DIEA (114.40 mg, 885.14 μ mol, 154.18 μ L). The mixture was degassed and purged with N_2 for 3 times, and then stirred at 30 °C for 5 h under N_2 atmosphere. The reaction mixture was poured into water (10 mL) and extracted with EtOAc (30 mL $\times$ 3). The combined organic layers were washed with brine (10 mL $\times$ 3), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (2% MeOH in DCM) to give N-[(1R)-1-[3-(difluoromethyl)-5-nitro-phenyl]ethyl]-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide (66 mg, 33.34% yield, 74% purity) as brown oil. MS (ESI) m/z = 497.1 $[M+H]^+$.

Step 2: Synthesis of N-[(1R)-1-[3-amino-5-(difluoromethyl)phenyl]ethyl]-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide

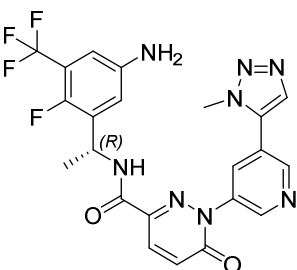
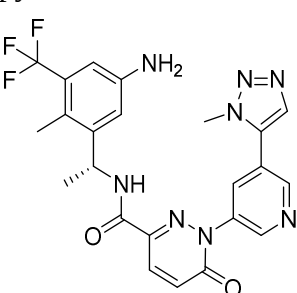
To a solution of N-[(1R)-1-[3-(difluoromethyl)-5-nitro-phenyl]ethyl]-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide (62 mg, 124.89 μ mol) in EtOH (3 mL) and H_2O (1 mL) was added Fe (34.87 mg, 624.46 μ mol) and NH_4Cl (66.81 mg, 1.25 mmol). The mixture was degassed and purged with N_2 for 3 times, and then stirred at 80 °C

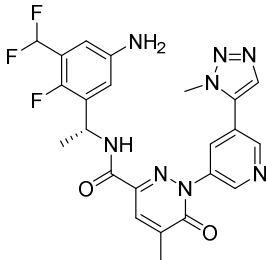
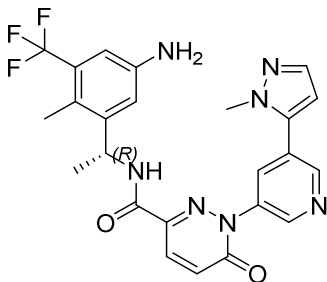
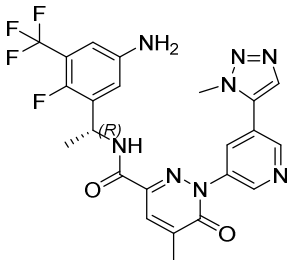
for 12 h under N₂ atmosphere. The reaction mixture was concentrated by filtration under reduced pressure, and then poured into water (10 mL) and extracted with EtOAc (10 mL×3). The combined organic layers were washed with brine (10 mL×3), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by prep-HPLC (Welch Xtimate C18 150*30 mm*5 μm; mobile phase: [water(NH₃H₂O+ NH₄HCO₃)-MeCN]; B%: 8%-48%, 28 min). The remaining solvent was removed by lyophilization to give **a compound of Example 2** (11.9 mg, 20.24% yield, 99.08% purity) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.12 (d, *J* = 2.4 Hz, 1H), 8.95 - 8.90 (m, 2H), 8.51 (t, *J* = 2.4 Hz, 1H), 8.12 (s, 1H), 7.95 (d, *J* = 10.0 Hz, 1H), 7.23 (d, *J* = 10.0 Hz, 1H), 6.95 (s, 1H), 6.81 (s, 1H), 6.69 (s, 2H), 6.67 (s, 1H), 6.59 (s, 1H), 5.37 (s, 2H), 5.08 - 5.01 (m, 1H), 4.16 (s, 3H), 1.46 (d, *J* = 7.2 Hz, 3H); MS (ESI) *m/z* = 467.2 [M+H]⁺.

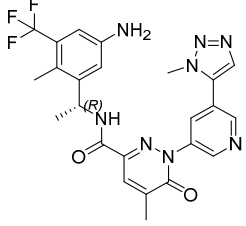
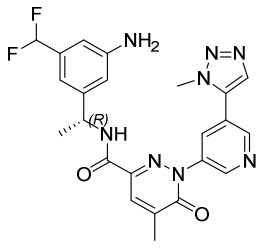
Examples 2-1 to 2-7

The compounds in Table 2 below were prepared in the same manner as in Example 2 through a two-step method of amide coupling followed by reducing a nitro group, using the corresponding intermediates described in the Preparation Examples.

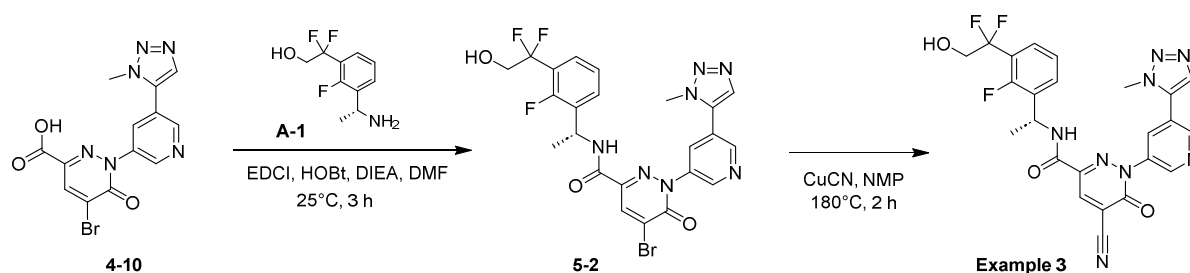
[Table 2]

No.	Chemical Name/Structure	Spectra (LCMS / ¹ H NMR)
2-1	N-[(1R)-1-[5-amino-2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide 	LCMS : <i>t_R</i> = 1.724 min, MS (ESI) <i>m/z</i> = 503.2 [M+H] ⁺ . ¹H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 9.14 (d, <i>J</i> = 2.4 Hz, 1H), 9.02 (d, <i>J</i> = 7.6 Hz, 1H), 8.93 (d, <i>J</i> = 2.0 Hz, 1H), 8.52 (t, <i>J</i> = 2.0 Hz, 1H), 8.13 (s, 1H), 7.94 (d, <i>J</i> = 9.6 Hz, 1H), 7.24 (d, <i>J</i> = 9.6 Hz, 1H), 6.84 (dd, <i>J</i> = 2.4, 6.0 Hz, 1H), 6.73 (dd, <i>J</i> = 2.8, 5.6 Hz, 1H), 5.40 (s, 2H), 5.30-5.23 (m, 1H), 4.17 (s, 3H), 1.46 (d, <i>J</i> = 7.2 Hz, 3H).
2-2	N-[(1R)-1-[5-amino-2-methyl-3-(trifluoromethyl)phenyl]ethyl]-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide 	LCMS : <i>t_R</i> = 1.691 min, MS (ESI) <i>m/z</i> = 499.4 [M+H] ⁺ . ¹H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 9.33 (d, <i>J</i> = 7.2 Hz, 1H), 9.16 (d, <i>J</i> = 2.4 Hz, 1H), 8.94 (d, <i>J</i> = 2.0 Hz, 1H), 8.62 (t, <i>J</i> = 2.0 Hz, 1H), 8.16 (s, 1H), 7.91 (d, <i>J</i> = 10.0 Hz, 1H), 7.73 (s, 1H), 7.61 (d, <i>J</i> = 1.6 Hz, 1H), 7.23 (d, <i>J</i> = 10.0 Hz, 1H), 5.39-5.23 (m, 3H), 4.18 (s, 3H), 2.51-2.49 (m, 3H), 2.47 (s, 3H), 1.48 (d, <i>J</i> = 6.8 Hz, 3H).

2-3	N-[(1R)-1-[5-amino-3-(difluoromethyl)-2-fluoro-phenyl]ethyl]-5-methyl-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide 	LCMS : t_R = 2.242 min, MS (ESI) m/z = 467.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ = 9.13 (d, J = 2.4 Hz, 1H), 8.93-8.89 (m, 2H), 8.52 (t, J = 2.4 Hz, 1H), 8.13 (s, 1H), 7.87 (d, J = 1.2 Hz, 1H), 7.19 (s, 1H), 7.05 (s, 1H), 6.91 (s, 1H), 6.74-6.70 (m, 1H), 6.62 (dd, J = 2.8, 5.2 Hz, 1H), 5.27-5.21 (m, 3H), 4.16 (s, 3H), 2.22 (d, J = 1.2 Hz, 3H), 1.44 (d, J = 7.2 Hz, 3H).
2-4	N-[(1R)-1-[5-amino-2-methyl-3-(trifluoromethyl)phenyl]ethyl]-1-[5-(2-methylpyrazol-3-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide 	LCMS : t_R = 1.876 min, MS (ESI) m/z = 498.2 $[M+H]^+$. 1H NMR (400MHz, DMSO-d_6) δ = 9.07 (d, J = 2.0 Hz, 1H), 8.95 (d, J = 7.6 Hz, 1H), 8.84 (d, J = 2.0 Hz, 1H), 8.42 (t, J = 2.0 Hz, 1H), 7.92 (d, J = 10.0 Hz, 1H), 7.56 (d, J = 2.0 Hz, 1H), 7.22 (d, J = 10.0 Hz, 1H), 6.86 (s, 1H), 6.79 (d, J = 2.0 Hz, 1H), 6.63 (d, J = 2.0 Hz, 1H), 5.33 - 5.22 (m, 3H), 3.93 (s, 3H), 2.24 (s, 3H), 1.41 (d, J = 6.8 Hz, 3H).
2-5	N-[(1R)-1-[5-amino-2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-5-methyl-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide 	LCMS : t_R = 1.929 min, MS (ESI) m/z = 517.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ = 9.22 (d, J = 2.4 Hz, 1H), 9.05 (d, J = 8.0 Hz, 1H), 8.99 (d, J = 2.0 Hz, 1H), 8.60 (t, J = 2.0 Hz, 1H), 8.21 (s, 1H), 7.96 (d, J = 1.2 Hz, 1H), 6.91 (dd, J = 2.4, 5.6 Hz, 1H), 6.81 (dd, J = 2.8, 5.2 Hz, 1H), 5.49 (s, 2H), 5.37-5.31 (m, 1H), 4.25 (s, 3H), 2.30 (d, J = 1.2 Hz, 3H), 1.51 (d, J = 7.2 Hz, 3H).
2-6	N-[(1R)-1-[5-amino-2-methyl-3-(trifluoromethyl)phenyl]ethyl]-5-methyl-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide	LCMS : t_R = 1.929 min, MS (ESI) m/z = 513.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ = 9.12 (d, J = 2.4 Hz, 1H), 8.91-8.86 (m, 2H), 8.50 (t, J = 2.0 Hz, 1H), 8.12 (s, 1H), 7.86 (s, 1H), 6.86 (d, J = 1.6 Hz, 1H), 6.79 (d,

		$J = 2.0 \text{ Hz, 1H), 5.28 (s, 2H), 5.25 (br d, } J = 7.6 \text{ Hz, 1H), 4.15 (s, 3H), 2.23 (s, 3H), 2.21 (s, 3H), 1.41 (d, } J = 6.8 \text{ Hz, 3H).$
2-7	N-[(1R)-1-[3-amino-5-(difluoromethyl)phenyl]ethyl]-5-methyl-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide 	LCMS : $t_R = 1.463 \text{ min}$, MS (ESI) $m/z = 481.1 [M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) $\delta = 9.11$ (d, $J = 2.4 \text{ Hz, 1H)$, 8.90 - 8.86 (m, 2H), 8.50 (t, $J = 2.0 \text{ Hz, 1H)$, 8.12 (s, 1H), 7.88 (d, $J = 1.2 \text{ Hz, 1H)$, 6.94 (s, 1H), 6.80 (s, 1H), 6.69 (br s, 2H), 6.66 (s, 1H), 6.58 (s, 1H), 5.36 (s, 2H), 5.06 - 5.02 (m, 1H), 4.15 (s, 3H), 2.22 (s, 3H), 1.45 (d, $J = 7.2 \text{ Hz, 3H)$

Example 3: 5-cyano-N-[(1R)-1-[3-(1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethyl]-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide



Step 1: Synthesis of 5-bromo-N-[(1R)-1-[3-(1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethyl]-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide

To a solution of Intermediate 4-10 (80 mg, 212.12 μmol) and Intermediate A-1 (54.23 mg, 212.12 μmol , HCl) in DMF (4 mL) was added EDCI (81.33 mg, 424.23 μmol), HOBT (57.32 mg, 424.23 μmol) and DIEA (82.24 mg, 636.35 μmol , 110.84 μL). The mixture was degassed and purged with N_2 for 3 times, and then stirred at 30 $^\circ\text{C}$ for 5 h under N_2 atmosphere. The reaction mixture was poured into water (10 mL) and extracted with EtOAc (30 mL $\times$ 3). The combined organic layers were washed with brine (10 mL $\times$ 3), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (2% MeOH in DCM) to give 5-bromo-N-[(1R)-1-[3-(1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethyl]-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide (85 mg, 69.29% yield) as a yellow solid. MS (ESI) $m/z = 580.1 [M+H]^+$.

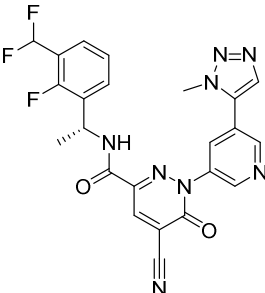
Step 2: Synthesis of 5-cyano-N-[(1R)-1-[3-(1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethyl]-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide

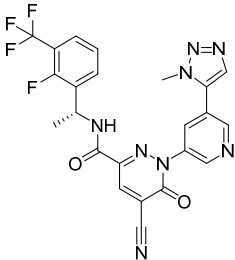
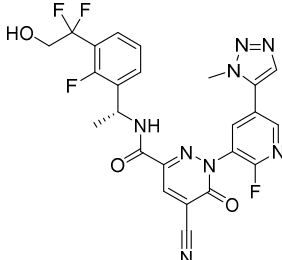
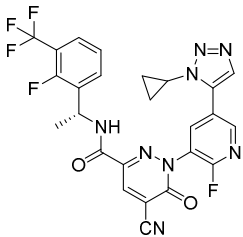
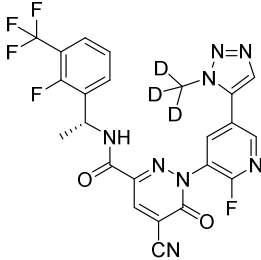
To a solution of 5-bromo-N-[(1R)-1-[3-(1,1-difluoro-2-hydroxy-ethyl)-2-fluorophenyl]ethyl]-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide (85 mg, 146.97 μmol) in NMP (3 mL) was added CuCN (131.63 mg, 1.47 mmol, 321.06 μL). The reaction mixture was heated in the microwave at 180 $^{\circ}\text{C}$ for 2 h. The reaction mixture was poured into water (30 mL), and extracted with EtOAc (10 mL $\times$ 3). The combined organic layers were washed with brine (20 mL $\times$ 3), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude product. The crude product was purified by prep-HPLC (column: Xtimate C18 150*40 mm*10 μm ; mobile phase: [water (NH_4HCO_3)-MeCN]; gradient:12%-52% B over 36 min). MeCN was removed under reduced pressure, and the remaining solvent was removed by lyophilization to give **a compound of Example 3** (2.4 mg, 2.69% yield) as a white solid. ^1H NMR (400 MHz, METHANOL- d_4) δ = 9.09 (br s, 1H), 8.90 (br s, 1H), 8.52 (s, 1H), 8.48 (t, J = 2.0 Hz, 1H), 8.04 (s, 1H), 7.55 (br t, J = 6.8 Hz, 1H), 7.48 (br t, J = 6.8 Hz, 1H), 7.22 (t, J = 8.0 Hz, 1H), 5.49 (q, J = 7.2 Hz, 1H), 4.19 (s, 3H), 3.98 (t, J = 13.6 Hz, 2H), 1.56 (d, J = 7.2 Hz, 3H); MS (ESI) m/z = 525.3 $[\text{M}+\text{H}]^+$.

Examples 3-1 to 3-5

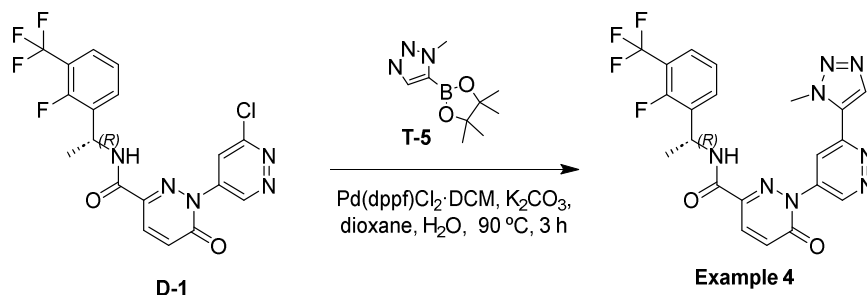
The compounds in Table 3 below were prepared in the same manner as in Example 3 through a two-step method of amide coupling followed by substitution with a cyano group, using the corresponding intermediates described in the Preparation Examples.

[Table 3]

No.	Chemical Name/Structure	Spectra (LCMS / ^1H NMR)
3-1	5-cyano-N-[(1R)-1-[3-(difluoromethyl)-2-fluorophenyl]ethyl]-1-[5-(1-methyl-1H-1,2,3-triazol-5-yl)pyridin-3-yl]-6-oxo-1,6-dihydropyridazine-3-carboxamide 	LCMS: t_R = 1.850 min, MS (ESI) m/z = 495.2 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, METHANOL- d_4) δ = 9.09 (br s, 1H), 8.90 (br s, 1H), 8.51 (s, 1H), 8.48 (t, J = 2.0 Hz, 1H), 8.04 (s, 1H), 7.55 (br t, J = 6.8 Hz, 1H), 7.48 (br t, J = 6.8 Hz, 1H), 7.22 (t, J = 8.0 Hz, 1H), 7.15-7.08 (m, 1H), 5.49 (q, J = 7.2 Hz, 1H), 4.20 (s, 3H), 1.56 (d, J = 7.2 Hz, 3H).
3-2	5-cyano-N-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-1-[5-(1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide	LCMS : t_R = 0.565 min, MS (ESI) m/z = 513.0 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ = 9.27 (d, J = 7.6 Hz, 1H), 9.09 (d, J = 2.4 Hz, 1H), 8.98 (d, J = 2.0 Hz, 1H), 8.66 (s, 1H), 8.49 (t, J = 2.4 Hz, 1H), 8.14 (s, 1H), 7.82 (t, J = 7.2 Hz, 1H), 7.69 (t, J =

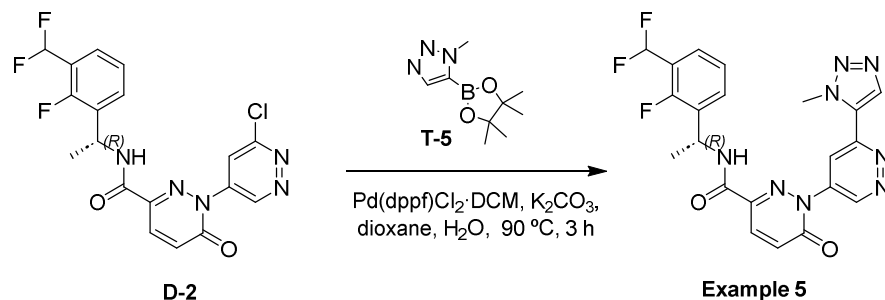
		7.2 Hz, 1H), 7.41 (t, $J = 8.0$ Hz, 1H), 5.43 (quin, $J = 7.2$ Hz, 1H), 4.16 (s, 3H), 1.52 (d, $J = 7.2$ Hz, 3H).
3-3	5-cyano-N-[(1R)-1-[2-fluoro-3-(1,1-difluoro-2-hydroxy-ethyl)-2-fluorophenyl]-1-(5-(1-methyl-1H-1,2,3-triazol-5-yl)-2-fluoropyridin-3-yl)-6-oxo-1,6-dihydropyridazine-3-carboxamide 	LCMS : $t_R = 0.545$ min, MS (ESI) $m/z = 543.1$ $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) $\delta = 9.03$ (d, $J = 8$ Hz, 1H), 8.82 - 8.73 (m, 2H), 8.67 (s, 1H), 8.15 (s, 1H), 7.59 (br t, $J = 6.8$ Hz, 1H), 7.42 (br t, $J = 6.8$ Hz, 1H), 7.31 - 7.25 (m, 1H), 5.70 (br s, 1H), 5.40 (br t, $J = 7.2$ Hz, 1H), 4.15 (s, 3H), 3.91 (br t, $J = 14.2$ Hz, 2H), 1.45 (d, $J = 7.2$ Hz, 3H).
3-4	5-cyano-N-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-1-(5-(1-cyclopropyl-1H-1,2,3-triazol-5-yl)-2-fluoropyridin-3-yl)-6-oxo-1,6-dihydropyridazine-3-carboxamide 	LCMS : $t_R = 0.555$ min, MS (ESI) $m/z = 557.1$ $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) $\delta = 9.25$ (d, $J = 7.6$ Hz, 1H), 8.76 - 8.63 (m, 3H), 8.14 (s, 1H), 7.80 (t, $J = 7.2$ Hz, 1H), 7.67 (t, $J = 7.2$ Hz, 1H), 7.39 (t, $J = 7.6$ Hz, 1H), 5.41 (quin, $J = 7.2$ Hz, 1H), 4.07 - 3.98 (m, 1H), 1.50 (d, $J = 7.2$ Hz, 3H), 1.18 - 1.12 (m, 4H).
3-5	5-cyano-N-[(1R)-1-(2-fluoro-3-(trifluoromethyl)phenyl)ethyl]-1-[2-fluoro-5-(1-(methyl-trideuterio)-1H-1,2,3-triazol-5-yl)pyridin-3-yl]-6-oxo-1,6-dihydropyridazine-3-carboxamide 	LCMS : $t_R = 0.560$ min, MS (ESI) $m/z = 534.1$ $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) $\delta = 9.27$ (d, $J = 7.6$ Hz, 1H), 8.76 - 8.63 (m, 3H), 8.14 (s, 1H), 7.82 (t, $J = 7.2$ Hz, 1H), 7.69 (t, $J = 7.2$ Hz, 1H), 7.41 (t, $J = 8.0$ Hz, 1H), 5.43 (quin, $J = 7.2$ Hz, 1H), 1.52 (d, $J = 7.2$ Hz, 3H).

Example 4: N-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-1-[6-(3-methyltriazol-4-yl)pyridazin-4-yl]-6-oxo-pyridazine-3-carboxamide



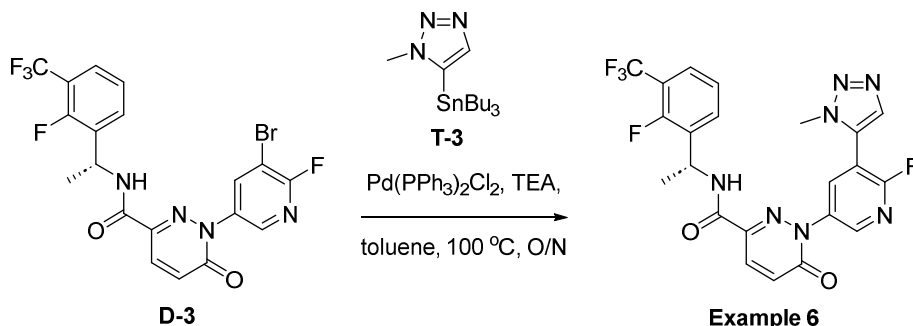
A mixture of **Intermediate D-1** (65 mg, 147.14 μmol), **Intermediate T-5** (461.39 mg, 2.21 mmol), K_2CO_3 (40.67 mg, 294.27 μmol) and $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ (12.02 mg, 14.71 μmol) in dioxane (3 mL) and H_2O (0.3 mL) was degassed and purged with N_2 for 3 times, and then stirred at 90 °C for 3 h under N_2 atmosphere. The reaction mixture was poured into water (8 mL) and extracted with EtOAc (20 mL $\times$ 3). The combined organic layers were washed with brine (10 mL $\times$ 2), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, and purified by silica gel column chromatography (3% MeOH in DCM) to give a crude product. The crude product was purified by prep-HPLC (column: Welch Xtimate C18 150 $\times$ 30 mm $\times$ 5 μm ; mobile phase: [water (HCl)-MeCN]; gradient: 20%-60% B over 25 min). MeCN was removed under reduced pressure, and the remaining solvent was removed by lyophilization to give a **compound of Example 4** (4.1 mg, 5.31% yield) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 9.99-9.91 (m, 1H), 8.86-8.75 (m, 1H), 8.51-8.42 (m, 1H), 8.01 (d, J = 9.6 Hz, 1H), 7.77 (br t, J = 7.1 Hz, 1H), 7.61 (br t, J = 7.2 Hz, 1H), 7.34 (t, J = 7.6 Hz, 1H), 7.23 (d, J = 10.0 Hz, 1H), 5.53 (q, J = 7.2 Hz, 1H), 4.54 (s, 3H), 1.64 (d, J = 7.2 Hz, 3H); MS (ESI) m/z = 489.1 $[\text{M}+\text{H}]^+$.

Example 5: N-[(1R)-1-[2-fluoro-3-(difluoromethyl)phenyl]ethyl]-1-[6-(3-methyltriazol-4-yl)pyridazin-4-yl]-6-oxo-pyridazine-3-carboxamide



The compound of Example 5 was obtained as a while solid in the same manner as in Example 4 using **Intermediate D-2** (37.0 mg, 30.83% yield, 100% purity). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 9.97 (d, J = 2.0 Hz, 1H), 9.21 (d, J = 8.0 Hz, 1H), 8.75 (d, J = 2.0 Hz, 1H), 8.46 (s, 1H), 7.94 (d, J = 10.0 Hz, 1H), 7.72 (br t, J = 7.2 Hz, 1H), 7.57 - 7.51 (m, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.28 (d, J = 10.0 Hz, 1H), 7.22 (t, J = 7.2 Hz, 1 H), 5.44 (quin, J = 7.2 Hz, 1H), 4.43 (s, 3H), 1.55 (d, J = 7.2 Hz, 3H); MS (ESI) m/z = 471.0 $[\text{M}+\text{H}]^+$.

Example 6: (R)-N-(1-(2-fluoro-3-(trifluoromethyl)phenyl)ethyl)-1-(6-fluoro-5-(1-methyl-1H-1,2,3-triazol-5-yl)pyridin-3-yl)-6-oxo-1,6-dihydropyridazine-3-carboxamide

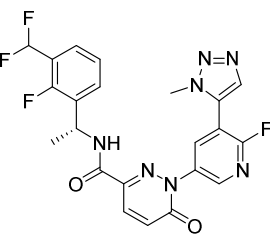


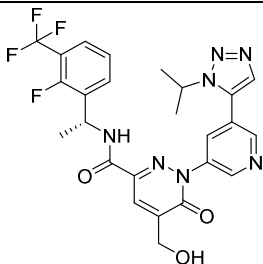
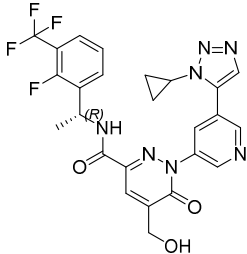
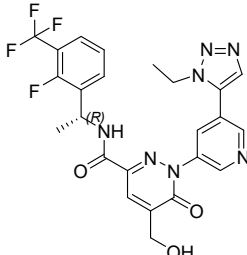
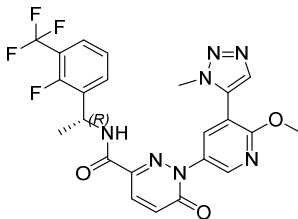
The compound of **Example 6** was obtained as a white solid in the same manner as in Step 2 of Preparation Example 33 using **Intermediate D-3** and **Intermediate T-3** (34 mg, 28% yield, 97.5% purity) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ = 9.12 (d, J = 8.0 Hz, 1H), 8.86 (s, 1H), 8.68 (dd, J = 8.4, 2.4 Hz, 1H), 8.08 (s, 1H), 7.92 (d, J = 9.6 Hz, 1H), 7.82 (t, J = 7.0 Hz, 1H), 7.69 (t, J = 7.2 Hz, 1H), 7.23 (d, J = 9.6 Hz, 1H), 5.42 (quin, J = 7.2, 14.4 Hz, 1H), 4.10 (s, 3H), 1.51 (d, J = 6.8 Hz, 3H); MS (ESI) m/z = 506.1 $[\text{M}+\text{H}]^+$.

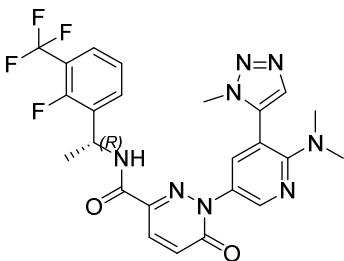
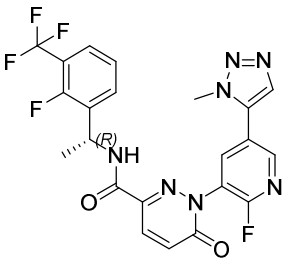
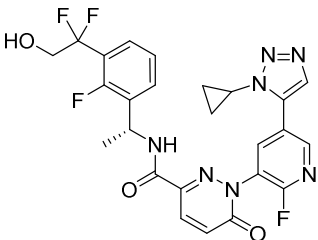
Examples 6-1 to 6-9

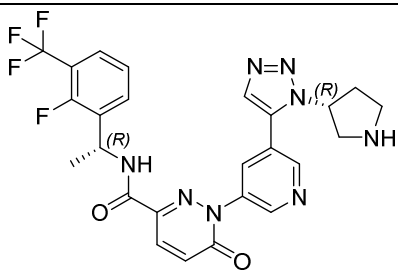
The compounds in Table 4 below were prepared in the same manner as in Example 6 through one-step stille coupling, using the corresponding intermediates described in the Preparation Examples.

[Table 4]

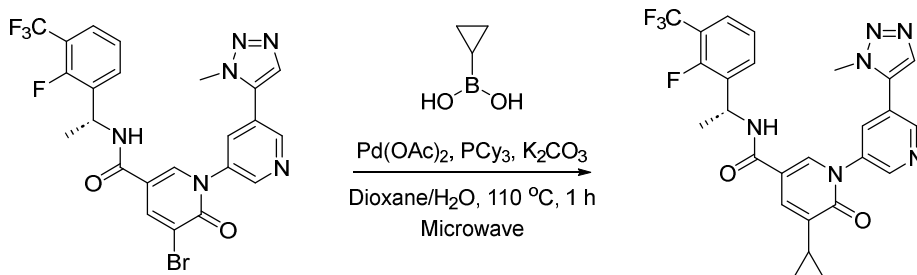
No.	Chemical Name/Structure	Spectra (LCMS / ^1H NMR)
6-1	<i>N</i> -{(1R)-1-(3-(difluoromethyl)-2-fluorophenyl)ethyl}-1-(6-fluoro-5-(1-methyl-1H-1,2,3-triazol-5-yl)pyridin-3-yl)-6-oxo-1,6-dihydropyridazine-3-carboxamide 	LCMS : t_R = 2.663 min, MS (ESI) m/z = 488.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ = 9.09 (d, J = 8.0 Hz, 1H), 8.87-8.86 (m, 1H), 8.69 (dd, J = 8.4, 2.4 Hz, 1H), 8.09 (d, J = 1.2 Hz, 1H), 7.92 (d, J = 9.6 Hz, 1H), 7.68 (t, J = 7.0 Hz, 1H), 7.53 (t, J = 7.0 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.23 (t, J = 54.4 Hz, 1H), 7.23 (d, J = 9.6 Hz, 1H), 5.41 (quin, J = 7.3, 14.7 Hz, 1H), 4.10 (s, 3H), 1.50 (d, J = 7.2 Hz, 1H).
6-2	<i>N</i> -{(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl}-1-[5-(1-isopropyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-5-(hydroxymethyl)-6-oxo-1,6-dihydropyridazine-3-carboxamide	LCMS : t_R = 1.928 min, MS (ESI) m/z = 546.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ = 9.16 (d, J = 2.4 Hz, 1H), 9.12 (d, J = 8.0 Hz, 1H), 8.80 (d, J = 2.0 Hz, 1H), 8.41 (t, J = 2.0 Hz,

		1H), 8.02 (s, 1H), 7.90 (s, 1H), 7.82 (br t, J = 7.2 Hz, 1H), 7.68 (br t, J = 7.2 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H), 5.64 (t, J = 5.6 Hz, 1H), 5.44 (quin, J = 7.2 Hz, 1H), 4.77 (td, J = 6.8, 13.2 Hz, 1H), 4.46 (br d, J = 4.4 Hz, 2H), 1.52 (d, J = 6.4 Hz, 9H).
6-3	N-((R)-1-[2-fluoro-3-(fluoromethyl)phenyl]ethyl)-1-[5-(1-cyclopropyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-5-(hydroxymethyl)-6-oxo-1,6-dihydropyridazine-3-carboxamide 	LCMS : t_R = 1.372 min, MS (ESI) m/z = 544.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ = 9.11 (br s, 2H), 9.01 (br s, 1H), 8.64 (br s, 1H), 8.16 (s, 1H), 7.90 (br s, 1H), 7.82 (br t, J = 6.8 Hz, 1H), 7.68 (br t, J = 6.0 Hz, 1H), 7.40 (br t, J = 7.6 Hz, 1H), 5.65 (br s, 1H), 5.44 (br t, J = 7.2 Hz, 1H), 4.47 (br d, J = 4.0 Hz, 2H), 4.02 (br s, 1H), 1.51 (br d, J = 6.8 Hz, 3H), 1.14 (br d, J = 8.4 Hz, 4H).
6-4	N-((R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl)-1-[5-(1-ethyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-5-(hydroxymethyl)-6-oxo-1,6-dihydropyridazine-3-carboxamide 	LCMS : t_R = 1.344 min, MS (ESI) m/z = 532.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ = 9.14 (d, J = 2.0 Hz, 1H), 9.11 (br d, J = 8.0 Hz, 1H), 8.86 (d, J = 1.6 Hz, 1H), 8.47 (s, 1H), 8.08 (s, 1H), 7.90 (s, 1H), 7.83 (br t, J = 7.6 Hz, 1H), 7.68 (br t, J = 7.2 Hz, 1H), 7.40 (br t, J = 7.6 Hz, 1H), 5.68 - 5.59 (m, 1H), 5.44 (br t, J = 7.6 Hz, 1H), 4.53 - 4.45 (m, 4H), 1.52 (br d, J = 7.2 Hz, 3H), 1.40 (t, J = 7.2 Hz, 3H).
6-5	N-((R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl)-1-[6-methoxy-5-(1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide 	LCMS : t_R = 1.850 min, MS (ESI) m/z = 518.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ = 9.08 (d, J = 7.6 Hz, 1H), 8.75 (d, J = 2.4 Hz, 1H), 8.29 (d, J = 2.4 Hz, 1H), 7.92 (s, 1H), 7.90 (d, J = 9.6 Hz, 1H), 7.83 (t, J = 7.4 Hz, 1H), 7.69 (t, J = 7.2 Hz, 1H), 7.41 (t, J = 7.8 Hz, 2H), 7.19 (d, J = 9.6 Hz, 1H), 5.43 (quin, J = 7.2, 14.5 Hz, 1H), 4.01 (s, 3H), 4.00 (s, 3H), 1.52 (d, J = 7.2 Hz, 3H).

6-6	N-{(R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl}-1-[6-(dimethylamino)-5-(1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide 	LCMS : t_R = 1.615 min, MS (ESI) m/z = 531.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ = 9.08 (d, J = 8.0 Hz, 1H), 8.66 (d, J = 2.4 Hz, 1H), 7.98 (d, J = 2.4 Hz, 1H), 7.89-7.82 (m, 3H), 7.69 (t, J = 7.2 Hz, 1H), 7.40 (t, J = 7.8 Hz, 1H), 7.15 (d, J = 10.0 Hz, 1H), 5.42 (quin, J = 7.3, 14.8 Hz, 1H), 3.92 (s, 3H), 2.72 (s, 6H), 1.51 (d, J = 6.8 Hz, 3H).
6-7	N-{(R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl}-1-[2-fluoro-5-(1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide 	LCMS : t_R = 2.018 min, MS (ESI) m/z = 506.0 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ = 9.11 (d, J = 7.6 Hz, 1H), 8.76 - 8.63 (m, 2H), 8.12 (s, 1H), 7.96 (d, J = 9.6 Hz, 1H), 7.79 (t, J = 7.2 Hz, 1H), 7.67 (t, J = 7.2 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H), 7.26 (d, J = 10.0 Hz, 1H), 5.41 (quin, J = 7.2 Hz, 1H), 4.17 (s, 3H), 1.48 (d, J = 7.2 Hz, 3H).
6-8	N-{(R)-1-[2-fluoro-3-(1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethyl}-1-[2-fluoro-5-(1-cyclopropyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide 	LCMS : t_R = 0.880 min, MS (ESI) m/z = 544.0 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ = 9.04 (d, J = 8.0 Hz, 1H), 8.83 - 8.74 (m, 2H), 8.16 (s, 1H), 7.97 (d, J = 10.0 Hz, 1H), 7.60 (br t, J = 6.8 Hz, 1H), 7.43 (br t, J = 6.8 Hz, 1H), 7.31 - 7.20 (m, 2H), 5.70 (br s, 1H), 5.40 (br t, J = 7.2 Hz, 1H), 4.06 - 3.98 (m, 1H), 3.91 (br t, J = 14.2 Hz, 2H), 1.45 (d, J = 7.2 Hz, 3H), 1.17 - 1.10 (m, 4H).
6-9	N-{(R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl}-6-oxo-1-(5-(1-((R)-pyrrolidin-3-yl)-1H-1,2,3-triazol-5-yl)pyridin-3-yl)-1,6-dihydropyridazine-3-carboxamide	LCMS : t_R = 0.451 min, MS (ESI) m/z = 543.3 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ = 9.17 (d, J = 2.0 Hz, 1H), 9.14 (br d, J = 7.6 Hz, 1H), 8.82 (d, J = 1.6 Hz, 1H), 8.45 - 8.40 (m, 1H), 8.07 (s, 1H), 7.92 (d, J = 9.6 Hz,

	1H), 7.83 (br t, $J = 7.2$ Hz, 1H), 7.68 (br t, $J = 7.2$ Hz, 1H), 7.40 (t, $J = 7.6$ Hz, 1H), 7.22 (d, $J = 9.6$ Hz, 1H), 5.43 (br t, $J = 7.2$ Hz, 1H), 5.09 - 4.93 (m, 1H), 3.28 - 3.22 (m, 1H), 3.20 (d, $J = 6.8$ Hz, 1H), 3.13 (br d, $J = 4.4$ Hz, 1H), 3.10 (br s, 1H), 2.89 (ddd, $J = 5.6, 7.6, 11.2$ Hz, 1H), 2.27 - 2.14 (m, 2H), 1.52 (d, $J = 7.2$ Hz, 3H).
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Example 7: (R)-3-cyclopropyl-N-(1-(2-fluoro-3-(trifluoromethyl)phenyl)ethyl)-5'-(1-methyl-1H-1,2,3-triazol-5-yl)-2-oxo-2H-[1,3'-bipyridine]-5-carboxamide



Example 1-22

Example 7

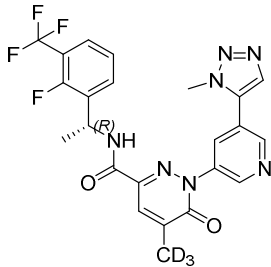
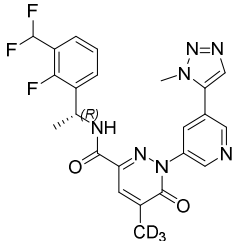
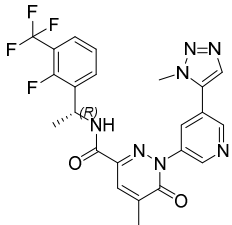
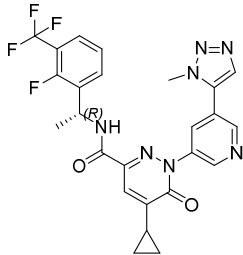
The compound of **Example 7** was obtained as a white solid by reacting the compound of **Example 1-22** in a similar manner to Example 4 (4.0 mg, 21% yield). ^1H NMR (400 MHz, DMSO- d_6) δ = 8.95 (d, $J = 2.0$ Hz, 1H), 8.86 (d, $J = 2.4$ Hz, 1H), 8.73 (d, $J = 7.2$ Hz, 1H), 8.37 (t, $J = 2.2$ Hz, 1H), 8.33 (d, $J = 2.4$ Hz, 1H), 8.13 (s, 1H), 7.75 (t, $J = 7.0$ Hz, 1H), 7.67 (t, $J = 7.2$ Hz, 1H), 7.50 (d, $J = 2.0$ Hz, 1H), 7.40 (t, $J = 8.0$ Hz, 1H), 5.35 (quin, $J = 6.9$ Hz, 1H), 4.16 (s, 3H), 2.08-2.03 (m, 1H), 1.47 (d, $J = 6.8$ Hz, 3H), 0.93 (dd, $J = 8.4, 2.0$ Hz, 1H), 0.75-0.72 (m, 2H); MS (ESI) m/z = 527.21 $[\text{M}+\text{H}]^+$.

Examples 7-1 to 7-4

The compounds in Table 5 below were prepared in the same manner as in Example 7 through one-step Suzuki coupling, using the corresponding intermediates described in the Preparation Examples.

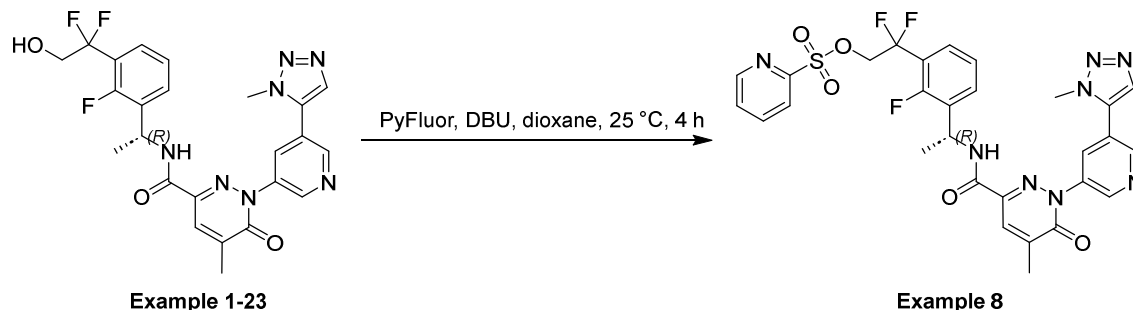
[Table 5]

No.	Chemical Name/Structure	Spectra (LCMS / ^1H NMR)
7-1	N-{(R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl}-5-[methyl-trideuterio]-1-[5-(1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide	LCMS : t_R = 1.771 min, MS (ESI) m/z = 505.2 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ = 9.12 (d, $J = 2.4$ Hz, 1H), 9.09 (d, $J = 7.6$ Hz, 1H), 8.92 (d, $J = 2.0$ Hz, 1H), 8.51 (t, $J = 2.2$ Hz, 1H), 8.13 (s, 1H), 7.86 (s, 1H), 7.82 (t, $J = 7.2$ Hz, 1H), 7.68 (t, $J =$

		7.2 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 5.45-5.41 (m, 1H), 4.17 (s, 3H), 1.51 (d, J = 6.8 Hz, 3H).
7-2	N-{(R)-1-[3-(difluoromethyl)-2-fluorophenyl]ethyl}-5-[methyl-trideuterio]-1-[5-(1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide 	LCMS : t_R = 1.698 min, MS (ESI) m/z = 487.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ = 9.12 (d, J = 2.4 Hz, 1H), 9.06 (d, J = 8.4 Hz, 1H), 8.92 (d, J = 2.0 Hz, 1H), 8.14 (s, 1H), 7.86 (s, 1H), 7.68 (t, J = 7.2 Hz, 1H), 7.53 (t, J = 6.8 Hz, 1H), 7.32 (t, J = 7.6 Hz, 1H), 7.23 (t, J = 54.2 Hz, 1H), 5.43-5.40 (m, 1H), 4.17 (s, 3H), 1.49 (d, J = 6.8 Hz, 3H).
7-3	N-{(R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl}-5-methyl-1-[5-(1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide 	LCMS : t_R = 1.797 min, MS (ESI) m/z = 502.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ = 9.12-9.09 (m, 2H), 8.92 (d, J = 1.6 Hz, 1H), 8.51 (t, J = 2.0 Hz, 1H), 8.14 (s, 1H), 7.86 (d, J = 1.2 Hz, 1H), 7.82 (t, J = 7.6 Hz, 1H), 7.69 (t, J = 6.8 Hz, 1H), 7.41 (t, J = 7.8 Hz, 1H), 5.45-5.41 (m, 1H), 4.17 (s, 3H), 2.21 (s, 3H), 1.51 (d, J = 6.8 Hz, 3H).
7-4	N-{(R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl}-5-cyclopropyl-1-[5-(1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide 	LCMS : t_R = 3.022 min, MS (ESI) m/z = 528.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ = 9.11 (d, J = 2.0 Hz, 1H), 9.08 (d, J = 8.0 Hz, 1H), 8.92 (d, J = 2.0 Hz, 1H), 8.52 (t, J = 2.0 Hz, 1H), 8.14 (s, 1H), 7.82 (t, J = 7.4 Hz, 1H), 7.68 (t, J = 6.8 Hz, 1H), 7.40 (t, J = 7.8 Hz, 1H), 7.37 (s, 1H), 5.41 (quin, J = 7.3, 14.7 Hz, 1H), 4.18 (s, 3H), 2.25-2.20 (m, 1H), 1.50 (d, J = 7.2 Hz, 3H), 1.11 (dd, J = 8.2, 2.2 Hz,

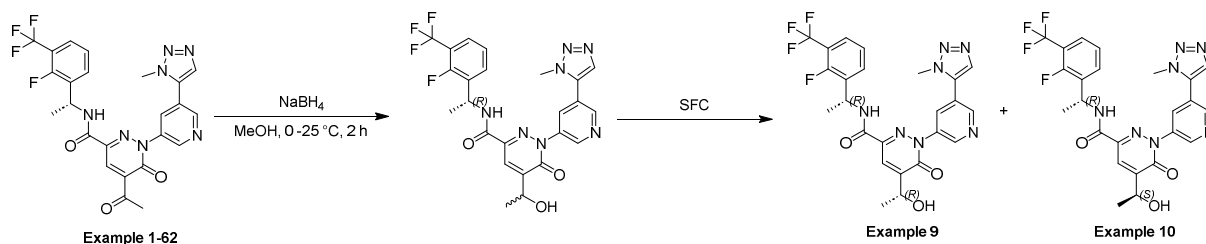
	2H), 0.97-0.95 (m, 2H).
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Example 8: N-[(R)-1-{3-[1,1-difluoro-2-(2-pyridylsulfonyloxy)ethyl]-2-fluorophenyl}ethyl]-5-methyl-1-[5-(1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide



A mixture of N-[(1R)-1-[3-(1,1-difluoro-2-hydroxyethyl)-2-fluorophenyl]ethyl]-5-methyl-1-[5-(3-methyl-1H-1,2,3-triazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide (20 mg, 38.95 μ mol), pyridine-2-sulfonyl fluoride (18.83 mg, 116.85 μ mol), DBU (35.58 mg, 233.70 μ mol, 35.23 μ L) in dioxane (2 mL) was degassed and purged with N₂ for 3 times, and then stirred at 25 °C for 4 h under N₂ atmosphere. The reaction mixture was concentrated under reduced pressure and diluted with EtOAc (5 mL). Then it was washed with brine (5 mL $\times$ 3), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a residue. The crude product was purified by prep-HPLC (column: Welch Xtimate C18 40 $\times$ 200 mm 7 μ m; mobile phase: [water (NH₃H₂O+NH₄HCO₃)-MeCN]; 22%-62% B over 25 min), and most of MeCN was removed under reduced pressure. The remaining solvent was removed by lyophilization to give **a compound of Example 8** (6.3 mg, 24.68% yield, 99.88% purity) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.11 (br s, 1H), 9.03 (br d, *J* = 7.6 Hz, 1H), 8.91 (s, 1H), 8.79 (br d, *J* = 3.6 Hz, 1H), 8.50 (br s, 1H), 8.20 - 8.10 (m, 2H), 8.07 (br d, *J* = 7.6 Hz, 1H), 7.86 (s, 1H), 7.83 - 7.78 (m, 1H), 7.72 - 7.65 (m, 1H), 7.42 (br d, *J* = 6.4 Hz, 1H), 7.34 - 7.25 (m, 1H), 5.39 (br t, *J* = 7.2 Hz, 1H), 4.94 (br t, *J* = 13.2 Hz, 2H), 4.16 (s, 3H), 2.21 (s, 3H), 1.47 (br d, *J* = 6.8 Hz, 3H); MS (ESI) *m/z* = 654.9 [M+H]⁺.

Examples 9 and 10: N-[(R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-5-[(R)-1-hydroxyethyl]-1-[5-(1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide and N-[(R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-5-[(S)-1-hydroxyethyl]-1-[5-(1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide



Step 1: Synthesis of N-((R)-1-(2-fluoro-3-(trifluoromethyl)phenyl)ethyl)-5-(1-hydroxyethyl)-1-(5-(1-methyl-1H-1,2,3-triazol-5-yl)pyridin-3-yl)-6-oxo-1,6-dihydropyridazine-3-carboxamide

A compound of Example 1-62 (80 mg, 151.10 μ mol) in MeOH (3 mL) MeOH (3 mL) was cooled to 0 °C, NaBH₄ (11.43 mg, 302.20 μ mol) was added dropwise under N₂ atmosphere, then the mixture was stirred at 0 °C for 2 h under N₂ atmosphere. The reaction mixture was quenched with aq. NH₄Cl (4 mL) added dropwise slowly at 0 °C and extracted with DCM (10 mL $\times$ 3). The combined organic layers were washed with brine (5 mL $\times$ 2), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (2% MeOH in DCM) to give a crude product as a yellow solid. The crude product was dissolved in DMF (5 mL) and then purified by prep-HPLC (column: Welch Xtimate C18 40*200mm 7 μ m; mobile phase: [water (NH₃H₂O + NH₄HCO₃)-MeOH]; 38%-78% B over 25 min). Most of MeCN was removed under reduced pressure, and the remaining solvent was removed by lyophilization to give N-((R)-1-(2-fluoro-3-(trifluoromethyl)phenyl)ethyl)-5-(1-hydroxyethyl)-1-(5-(1-methyl-1H-1,2,3-triazol-5-yl)pyridin-3-yl)-6-oxo-1,6-dihydropyridazine-3-carboxamide (15 mg, 15.84% yield, 84.8% purity, 0.8% ee) as a white solid. MS (ESI) m/z = 532.1 [M+H]⁺.

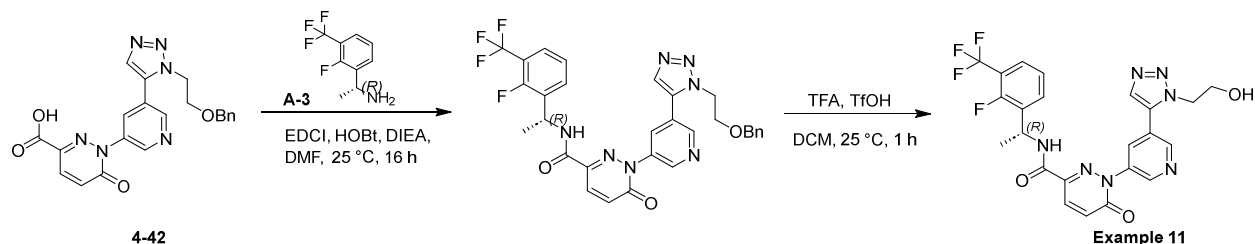
Step 2: Synthesis of N-{(R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl}-5-[(R)-1-hydroxyethyl]-1-[5-(1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide and N-{(R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl}-5-[(S)-1-hydroxyethyl]-1-[5-(1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide

N-((R)-1-(2-fluoro-3-(trifluoromethyl)phenyl)ethyl)-5-(1-hydroxyethyl)-1-(5-(1-methyl-1H-1,2,3-triazol-5-yl)pyridin-3-yl)-6-oxo-1,6-dihydropyridazine-3-carboxamide (10 mg, 18.82 μ mol) was further purified by SFC separation (column: DAICEL CHIRALCEL OD (250mm*30mm,10 μ m); mobile phase: [CO₂- EtOH (0.1% NH₃H₂O)]; B%: 40%, isocratic elution mode). Two peaks were confirmed by SFC analysis. The compound confirmed in the first peak (R_t = 1.339 min) was concentrated under reduced pressure. Then MeCN (5 mL) and H₂O (25 mL) were added, and the solvent was removed by lyophilization to give **a compound of Example 9** (4 mg, 31.17% yield, 77.92% purity, 99.84% ee) as a white solid. The compound confirmed in the second peak (R_t = 1.558 min) were concentrated under reduced pressure. Then MeCN (5 mL) and H₂O (25 mL) were added, and the solvent was removed by lyophilization to give **a compound of Example 10** (4.2 mg, 39.07% yield, 93.03% purity, 99.42 ee) as a white solid.

Compound of Example 9: ¹H NMR (400 MHz, CD₃OD) δ = 9.10 (d, *J* = 2.0 Hz, 1H), 8.86 (s, 1H), 8.50 (s, 1H), 8.11 (s, 1H), 8.03 (s, 1H), 7.74 - 7.70 (m, 1H), 7.59 (br t, *J* = 6.8 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 1H), 5.51 (q, *J* = 6.8 Hz, 1H), 4.97 (m, 1H), 4.21 (s, 3H), 1.59 (d, *J* = 7.0 Hz, 3H), 1.46 (d, *J* = 6.4 Hz, 3H); MS (ESI) m/z = 532.1 [M+H]⁺.

Compound of Example 10: ^1H NMR (400 MHz, CD_3OD) δ = 9.10 (d, J = 1.6 Hz, 1H), 8.86 (s, 1H), 8.50 (s, 1H), 8.11 (s, 1H), 8.03 (s, 1H), 7.71 (br t, J = 7.2 Hz, 1H), 7.59 (br t, J = 7.2 Hz, 1H), 7.32 (br d, J = 7.6 Hz, 1H), 5.51 (q, J = 6.8 Hz, 1H), 4.96 (br s, 1H), 4.21 (s, 3H), 1.59 (d, J = 7.2 Hz, 4H), 1.47 (d, J = 6.4 Hz, 3H); MS (ESI) m/z = 530.2 $[\text{M}+\text{H}]^+$.

Example 11: N-{(R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl}-1-{5-[1-(2-hydroxyethyl)-1H-1,2,3-triazol-5-yl]-3-pyridyl}-6-oxo-1,6-dihydropyridazine-3-carboxamide



Step 1: Synthesis of 1-[5-[3-(2-benzyloxyethyl)triazol-4-yl]-3-pyridyl]-N-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-6-oxo-pyridazine-3-carboxamide

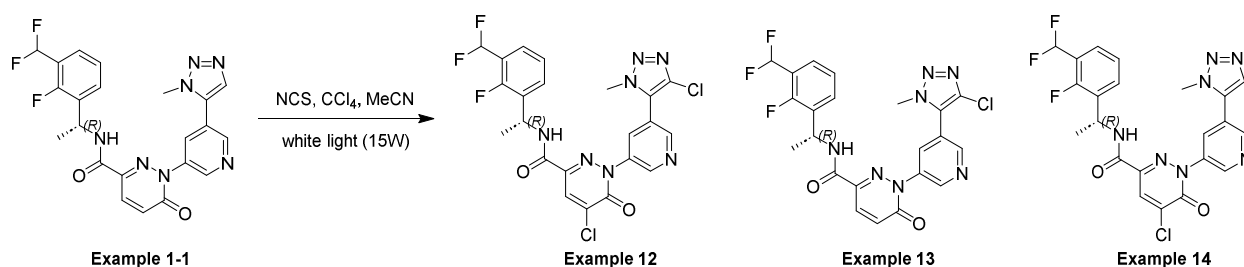
To a mixture of Intermediate 4-42 (70 mg, 167.30 μmol) and Intermediate A-3 (40.76 mg, 167.30 μmol , HCl) in DMF (4mL), EDCI (64.14 mg, 334.60 μmol), HOBT (45.21 mg, 334.60 μmol) and DIEA (64.87 mg, 501.91 μmol , 87.42 μL) was added, and the mixture was degassed and purged with N_2 for 3 times, and was stirred at 25 $^\circ\text{C}$ for 16 h under N_2 atmosphere. The reaction mixture was poured into water (10 mL) and extracted with EtOAc (15 mL $\times$ 3). The combined organic layers were washed with brine (5 mL $\times$ 3), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (1% MeOH in DCM) to give 1-[5-[3-(2-benzyloxyethyl)triazol-4-yl]-3-pyridyl]-N-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-6-oxo-pyridazine-3-carboxamide (20 mg, 16.33% yield, 83% purity) as a yellow solid. ^1H NMR (400 MHz, CD_3OD) δ = 9.02 (d, J = 2.4 Hz, 1H), 8.77 (d, J = 2.0 Hz, 1H), 8.50 (t, J = 2.0 Hz, 1H), 8.00 - 7.97 (m, 1H), 7.97 - 7.96 (m, 1H), 7.71 (br t, J = 6.8 Hz, 1H), 7.58 (t, J = 6.8 Hz, 1H), 7.29 (t, J = 7.6 Hz, 1H), 7.17 - 7.10 (m, 4H), 7.06 - 7.00 (m, 2H), 5.48 (s, 1H), 4.66 (t, J = 4.8 Hz, 2H), 4.36 (s, 2H), 3.94 (t, J = 4.8 Hz, 2H), 1.56 (d, J = 7.2 Hz, 3H); MS (ESI) m/z = 608.3 $[\text{M}+\text{H}]^+$.

Step 2: Synthesis of N-{(R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl}-1-{5-[1-(2-hydroxyethyl)-1H-1,2,3-triazol-5-yl]-3-pyridyl}-6-oxo-1,6-dihydropyridazine-3-carboxamide

A mixture of 1-[5-[3-(2-benzyloxyethyl)triazol-4-yl]-3-pyridyl]-N-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-6-oxo-pyridazine-3-carboxamide (19 mg, 31.27 μmol), trifluoromethanesulfonic acid (211.20 mg, 1.41 mmol, 124.53 μL) and TFA (42.79 mg, 375.27 μmol , 27.88 μL) in DCM (1.5 mL) was degassed and purged with N_2 for 3 times, and stirred at 20 $^\circ\text{C}$ for 1 h under N_2 atmosphere. The mixture was concentrated under reduced pressure to give a crude product. The crude product was dissolved in DMF (5 mL) and purified by prep-HPLC (column: Welch Xtimate C18 40*200mm 7 μm ; mobile phase: [water($\text{NH}_3\text{H}_2\text{O}+\text{NH}_4\text{HCO}_3$)-MeCN]; 16%-56% B, 25 min) to give a compound of Example

11 (6.8 mg, 41.80% yield, 99.47% purity) as a white solid. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ = 9.17 - 9.07 (m, 2H), 8.91 (d, J = 2.0 Hz, 1H), 8.55 (t, J = 2.0 Hz, 1H), 8.08 (s, 1H), 7.92 (d, J = 9.6 Hz, 1H), 7.83 (br t, J = 7.2 Hz, 1H), 7.68 (t, J = 7.2 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.22 (d, J = 9.6 Hz, 1H), 5.42 (quin, J = 7.2 Hz, 1H), 5.13 (t, J = 5.2 Hz, 1H), 4.48 (t, J = 5.2 Hz, 2H), 3.84 (q, J = 5.2 Hz, 2H), 1.51 (d, J = 7.2 Hz, 3H); MS (ESI) m/z = 518.1 $[\text{M}+\text{H}]^+$.

Examples 12, 13 and 14: N-{(R)-1-[3-(difluoromethyl)-2-fluorophenyl]ethyl}-5-chloro-1-[5-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide, N-{(R)-1-[3-(difluoromethyl)-2-fluorophenyl]ethyl}-1-[5-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide and N-{(R)-1-[3-(difluoromethyl)-2-fluorophenyl]ethyl}-5-chloro-1-[5-(1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide



A mixture of the compound of Example 1-1 (100 mg, 213.03 μmol) and NCS (42.67 mg, 319.54 μmol) in CCl_4 (1 mL) and MeCN (0.5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 25 $^\circ\text{C}$ for 24 h under white light (15 W). The mixture was filtrated, and filtrate was poured into water (10 mL) and extracted with EtOAc (20 mL $\times$ 3). The combined organic layers were washed with H_2O , dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude product. The crude product was dissolved in DMF (5 mL) and was purified by prep-HPLC (column: Welch Xtimate C18 40*200mm 7 μm ; mobile phase: [water ($\text{NH}_3\text{H}_2\text{O}$ + NH_4HCO_3)-ACN]; 22%-62% B over 25 min) to afford three products respectively. The first one: **Compound of Example 12** (6.2 mg, 5.41% yield, 100% purity) as a white solid. The second one: **Compound of Example 13** (10.8 mg, 9.89% yield, 98.3% purity) as a white solid. The third one: **Compound of Example 14** (5.6 mg, 4.38% yield, 83.95% purity) as a white solid.

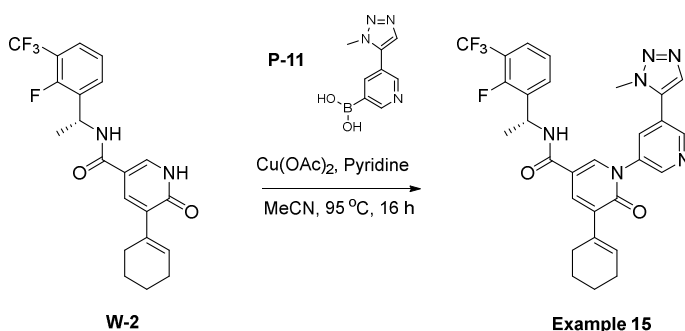
Compound of Example 12: ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ = 9.18 (d, J = 2.4 Hz, 1H), 9.14 (d, J = 8.0 Hz, 1H), 8.90 (d, J = 2.0 Hz, 1H), 8.52 (t, J = 2.0 Hz, 1H), 8.19 (s, 1H), 7.68 (br t, J = 7.6 Hz, 1H), 7.53 (br t, J = 6.8 Hz, 1H), 7.36 - 7.30 (m, 1H), 7.21 (s, 1H), 7.08 (s, 1H), 5.41 (quin, J = 7.2 Hz, 1H), 4.11 (s, 3H), 1.50 (d, J = 7.2 Hz, 3H); MS (ESI) m/z = 537.9 $[\text{M}+\text{H}]^+$.

Compound of Example 13: ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ = 9.21 (d, J = 2.4 Hz, 1H), 9.08 (d, J = 8.0 Hz, 1H), 8.88 (d, J = 2.0 Hz, 1H), 8.54 (t, J = 2.0 Hz, 1H), 7.92 (d, J = 9.6 Hz, 1H), 7.69 (br t, J = 7.2 Hz, 1H), 7.54 (br t, J = 6.8 Hz, 1H), 7.37 - 7.30 (m, 1H), 7.26 - 7.20

(m, 2H), 7.09 (s, 1H), 5.46 - 5.37 (m, 1H), 4.12 (s, 3H), 1.51 (d, $J = 7.2$ Hz, 3H); MS (ESI) $m/z = 504.0$ $[M+H]^+$.

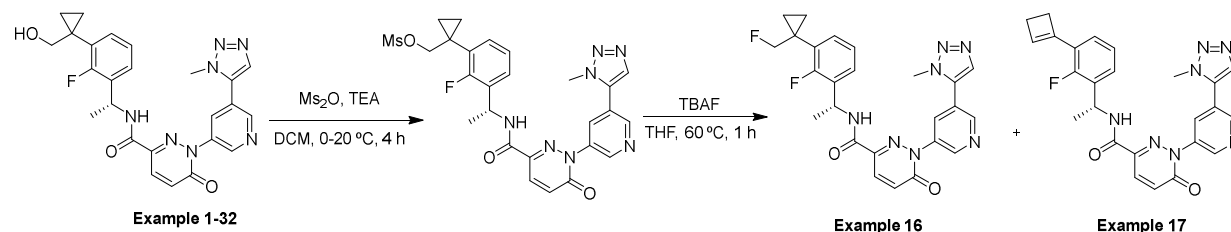
Compound of Example 14: ^1H NMR (400 MHz, DMSO- d_6) $\delta = 9.15$ (d, $J = 8.0$ Hz, 1H), 9.10 (d, $J = 2.0$ Hz, 1H), 8.95 (d, $J = 2.0$ Hz, 1H), 8.52 - 8.48 (m, 1H), 8.20 (s, 1H), 8.13 (s, 1H), 7.70 - 7.66 (m, 1H), 7.53 (br t, $J = 6.8$ Hz, 1H), 7.35 - 7.31 (m, 1H), 7.21 (s, 1H), 7.08 (s, 1H), 5.41 (t, $J = 7.6$ Hz, 1H), 4.16 (s, 3H), 1.50 (d, $J = 7.2$ Hz, 3H); MS (ESI) $m/z = 504.0$ $[M+H]^+$.

Example 15: N-{(R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl}-5-(1-cyclohexen-1-yl)-5'-(1-methyl-1H-1,2,3-triazol-5-yl)-6-oxo-1H-[1,3'-bipyridyl]-3-carboxamide



Intermediate W-2 and Intermediate P-11 were reacted in the same manner as in Step 3 of Preparation Example 28 to obtain **a compound of Example 15** (27.3 mg, 31% yield) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) $\delta = 8.94$ (d, $J = 2.0$ Hz, 1H), 8.85 (d, $J = 2.4$ Hz, 1H), 8.80 (d, $J = 7.2$ Hz, 1H), 8.41 (d, $J = 2.4$ Hz, 1H), 8.35 (t, $J = 2.2$ Hz, 1H), 8.13 (s, 1H), 7.87 (d, $J = 2.8$ Hz, 1H), 7.77 (t, $J = 7.4$ Hz, 1H), 7.68 (t, $J = 6.8$ Hz, 1H), 7.40 (t, $J = 7.6$ Hz, 1H), 6.41 (m, 1H), 5.37 (quin, $J = 7.0$ Hz, 1H), 4.18 (s, 3H), 2.34-2.33 (m, 2H), 2.16-2.15 (m, 2H), 1.69-1.65 (m, 2H), 1.61-1.57 (m, 2H), 1.48 (d, $J = 7.2$ Hz, 3H); MS (ESI) $m/z = 567.31$ $(M + H)^+$.

Examples 16 and 17: N-[(R)-1-{2-fluoro-3-[1-(fluoromethyl)cyclopropyl]phenyl}ethyl]-1-[5-(1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide and N-[(R)-1-{3-(1-cyclobuten-1-yl)-2-fluorophenyl}ethyl]-1-[5-(1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide



Step 1: Synthesis of [1-[2-fluoro-3-[(1R)-1-[1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carbonyl]amino]ethyl]phenyl]cyclopropyl]methyl methanesulfonate

A mixture of the compound of Example 1-32 (100 mg, 204.29 μmol) and TEA (26.87

mg, 265.58 μ mol, 36.96 μ L) in DCM (5 mL) was degassed and purged with N₂ for 3 times, and then methylsulfonyl methanesulfonate (71.17 mg, 408.58 μ mol) was added dropwise to the mixture at 0 °C, and then the mixture was stirred at 0 °C for 1 h under N₂ atmosphere. Thereafter, the mixture was allowed to warm to 20 °C, and then was stirred at 20 °C for 2 h. The reaction mixture was poured into water (10 mL) and extracted with DCM (15 mL $\times$ 3). The combined organic layers were washed with brine (10 mL $\times$ 3), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (1% MeOH in DCM) to give product [1-[2-fluoro-3-[(1R)-1-[[1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carbonyl]amino]ethyl]phenyl]cyclopropyl]-methyl methanesulfonate (60 mg, 27.94% yield, 54% purity) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.12 (d, *J* = 2.0 Hz, 1H), 9.00 (br d, *J* = 8.0 Hz, 1H), 8.92 (d, *J* = 1.6 Hz, 1H), 8.51 (s, 1H), 8.13 (s, 1H), 7.92 (d, *J* = 9.6 Hz, 1H), 7.42 - 7.36 (m, 1H), 7.26 - 7.19 (m, 2H), 7.16 - 7.08 (m, 1H), 5.40 (quin, *J* = 6.8 Hz, 1H), 4.17 (s, 3H), 2.97 (s, 2H), 1.47 (br d, *J* = 6.8 Hz, 3H), 1.03 (m, 2H), 0.92 (m, 2H); MS (ESI) *m/z* = 568.2 [M+H]⁺.

Step 2: Synthesis of N-[(R)-1-{2-fluoro-3-[1-(fluoromethyl)cyclopropyl]phenyl}ethyl]-1-[5-(1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide, N-{(R)-1-[3-(1-cyclobuten-1-yl)-2-fluorophenyl]ethyl}-1-[5-(1-methyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide

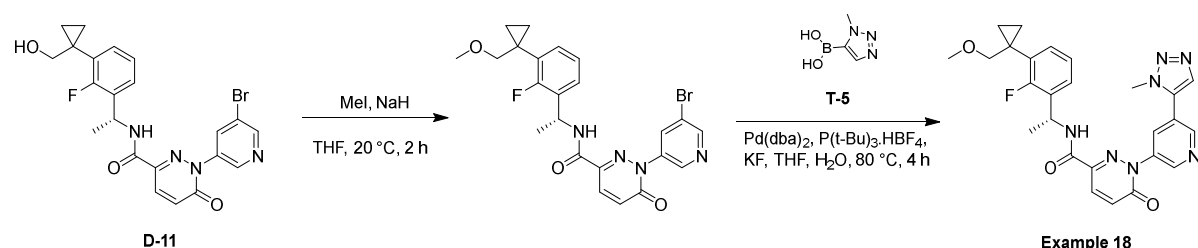
A mixture of [1-[2-fluoro-3-[(1R)-1-[[1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carbonyl]amino]ethyl]phenyl]cyclopropyl]methyl methanesulfonate (60 mg, 105.71 μ mol) and TBAF (1 M in THF, 158.56 μ L) in THF (2 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 60 °C for 1h under N₂ atmosphere. The reaction mixture was poured into water (10 mL) and extracted with EtOAc (10 mL $\times$ 3). The combined organic layers were washed with brine (5 mL $\times$ 3), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (1% MeOH in DCM) to give a crude product as a yellow solid. Thereafter, the crude product was further purified by prep-HPLC (column: Xtimate C18 150*40mm*10 μ m; mobile phase: [water (NH₃H₂O+NH₄HCO₃)-MeCN]; 18%-58% B over 32 min) to afford two peaks. The compound obtained in peak 1 was concentrated under reduced pressure to remove most of MeCN. The remaining solvent was removed by lyophilization to give **a compound of Example 16** (7.1 mg, 13.67% yield, 100% purity) as a white solid. The compound obtained in peak 2 was concentrated under reduced pressure to remove most of MeCN. The remaining solvent was removed by lyophilization to give **a compound of Example 17** (3.6 mg, 7.20% yield, 99.7% purity) as a white solid.

Compound of Example 16: ¹H NMR (400 MHz, DMSO- *d*₆) δ = 9.13 (d, *J* = 2.4 Hz, 1H), 9.00 (d, *J* = 8.4 Hz, 1H), 8.92 (d, *J* = 2.0 Hz, 1H), 8.52 (t, *J* = 2.0 Hz, 1H), 8.13 (s, 1H),

7.93 (d, $J = 9.6$ Hz, 1H), 7.39 (dt, $J = 1.2, 7.2$ Hz, 1H), 7.27 - 7.21 (m, 2H), 7.13 - 7.08 (m, 1H), 5.41 (quin, $J = 7.2$ Hz, 1H), 4.47 - 4.27 (m, 2H), 4.17 (s, 3H), 1.47 (d, $J = 7.2$ Hz, 3H), 0.97 (m, 2H), 0.90 - 0.85 (m, 2H); MS (ESI) $m/z = 490.0$ $[M+H]^+$.

Compound of Example 17: ^1H NMR (400 MHz, DMSO- d_6) $\delta = 9.13$ (d, $J = 2.4$ Hz, 1H), 9.02 (d, $J = 8.0$ Hz, 1H), 8.93 (d, $J = 2.0$ Hz, 1H), 8.52 (t, $J = 2.0$ Hz, 1H), 8.14 (s, 1H), 7.93 (d, $J = 9.6$ Hz, 1H), 7.44 - 7.34 (m, 1H), 7.25 - 7.18 (m, 2H), 7.18 - 7.13 (m, 1H), 6.38 (d, $J = 2.8$ Hz, 1H), 5.41 (quin, $J = 7.2$ Hz, 1H), 4.17 (s, 3H), 2.84 - 2.79 (m, 2H), 2.55 (m, 2H), 1.49 (d, $J = 7.2$ Hz, 3H); MS (ESI) $m/z = 472.2$ $[M+H]^+$.

Example 18: N-[(1R)-1-[2-fluoro-3-[1-(methoxymethyl)cyclopropyl]phenyl]ethyl]-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide



Step 1: Synthesis of 1-(5-bromo-3-pyridyl)-N-[(1R)-1-[2-fluoro-3-[1-(methoxymethyl)cyclopropyl]phenyl]ethyl]-6-oxo-pyridazine-3-carboxamide

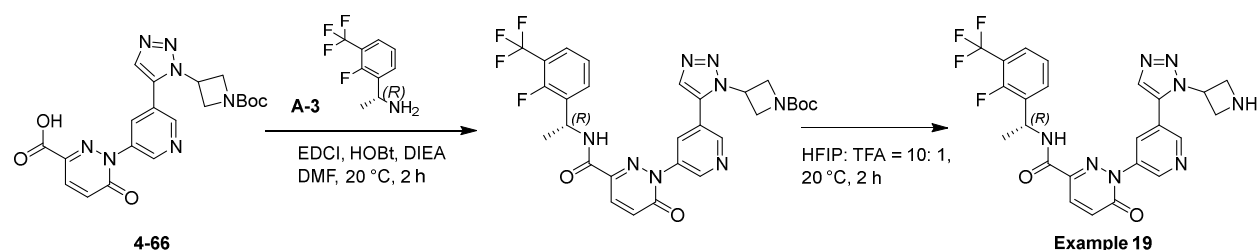
To a mixture of Intermediate D-11 (100 mg, 205.20 μmol) in THF (3 mL) was added NaH (24.62 mg, 615.61 μmol , 60% purity) at 50 °C. The resulting mixture was stirred at 20 °C for 15 minutes. Iodomethane (58.25 mg, 410.41 μmol , 25.55 μL) was added to the reaction mixture, and the mixture was stirred at 20 °C for 2 h. The reaction mixture was quenched with ice-cold water (10 mL) and extracted with EtOAc (30 mL $\times$ 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (32% EtOAc in PE) to give 1-(5-bromo-3-pyridyl)-N-[(1R)-1-[2-fluoro-3-[1-(methoxymethyl)cyclopropyl]phenyl]ethyl]-6-oxo-pyridazine-3-carboxamide (46 mg, 29.27% yield, 65.47% purity) as yellow oil. MS (ESI) $m/z = 502.9$ $[M+H]^+$.

Step 2: Synthesis of N-[(1R)-1-[2-fluoro-3-[1-(methoxymethyl)cyclopropyl]phenyl]ethyl]-1-[5-(3-methyltriazol-4-yl)-3-pyridyl]-6-oxo-pyridazine-3-carboxamide

A mixture of 1-(5-bromo-3-pyridyl)-N-[(1R)-1-[2-fluoro-3-[1-(methoxymethyl)cyclopropyl]phenyl]ethyl]-6-oxo-pyridazine-3-carboxamide (46 mg, 91.75 μmol), (3-methyltriazol-4-yl)boronic acid (34.93 mg, 275.26 μmol), KF (10.66 mg, 183.51 μmol , 4.30 μL), $\text{Pd}(\text{dba})_2$ (5.28 mg, 9.18 μmol) and tri-tert-butylphosphonium;tetrafluoroborate (2.66 mg, 9.18 μmol) in THF (2 mL)/ H_2O (0.4 mL) was degassed and purged with N_2 for 3 times, and then was stirred at 80 °C for 4 h. Concentrated $\text{NH}_3 \cdot \text{H}_2\text{O}$ (51.45 mg, 367.04 μmol , 56.54 μL , 25% purity) was added, and the mixture was

stirred at 20 °C for 24 h under N₂ atmosphere. The reaction mixture was filtrated, and the filtrate was concentrated under reduced pressure to give a crude product. The crude product was purified by prep-HPLC (column: Xtimate C18 150*40mm*10µm;mobile phase: [water(NH₃H₂O+NH₄HCO₃)-ACN];18%-58% B over 32 min), and the remaining solvent was removed by lyophilization to give **a compound of Example 18** (6.5 mg, 13.44% yield, 95.53% purity) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.13 (d, *J* = 2.4 Hz, 1H), 8.98 (d, *J* = 8.4 Hz, 1H), 8.92 (d, *J* = 2.0 Hz, 1H), 8.52 (t, *J* = 2.0 Hz, 1H), 8.13 (s, 1H), 7.93 (d, *J* = 10.0 Hz, 1H), 7.35 (t, *J* = 6.8 Hz, 1H), 7.25-7.18 (m, 2H), 7.09-7.03 (m, 1H), 5.40 (q, *J* = 7.6 Hz, 1H), 4.17 (s, 3H), 3.41-3.35 (m, 2H), 3.16 (s, 3H), 1.47 (d, *J* = 7.2 Hz, 3H), 0.86-0.81 (m, 2H), 0.78-0.72 (m, 2H); MS (ESI) *m/z* = 504.2 [M+H]⁺.

Example 19: N-{(R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl}-1-{5-[1-(1-methyl-3-azetidiny)-1H-1,2,3-triazol-5-yl]-3-pyridyl}-6-oxo-1,6-dihydropyridazine-3-carboxamide



Step 1: Synthesis of tert-butyl 3-[5-[5-[3-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]carbamoyl]-6-oxo-pyridazin-1-yl]-3-pyridyl]triazol-1-yl]azetidine-1-carboxylate

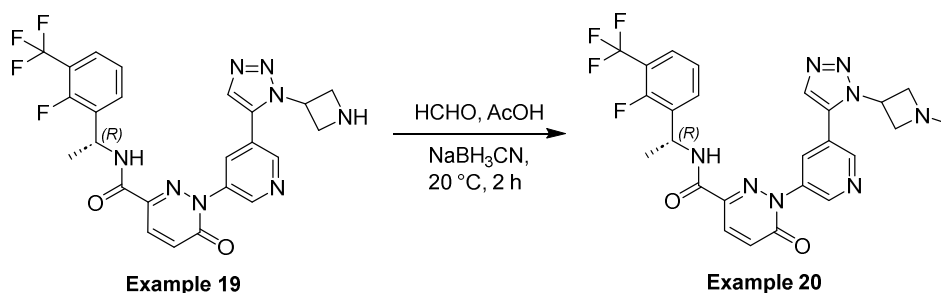
Intermediate 4-66 and Intermediate A-3 were used for synthesis in the same manner as in Example 1 to give tert-butyl 3-[5-[5-[3-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]carbamoyl]-6-oxo-pyridazin-1-yl]-3-pyridyl]triazol-1-yl]azetidine-1-carboxylate (270 mg , 45.46% yield, 91.53% purity) as a yellow solid. MS (ESI) *m/z* = 629.4 [M+H]⁺.

Step 2: Synthesis of N-{(R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl}-1-{5-[1-(1-methyl-3-azetidiny)-1H-1,2,3-triazol-5-yl]-3-pyridyl}-6-oxo-1,6-dihydropyridazine-3-carboxamide

To a mixture of tert-butyl 3-[5-[5-[3-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]carbamoyl]-6-oxo-pyridazin-1-yl]-3-pyridyl]triazol-1-yl]azetidine-1-carboxylate (250 mg, 397.72 µmol) in HFIP (2 mL) was added TFA (0.2 mL), and the mixture was degassed and purged with N₂ for 3 times. Then the mixture was stirred at 20 °C for 2 h under N₂ atmosphere. The mixture was concentrated under reduced pressure to give a crude product. The crude product was purified by prep-TLC (SiO₂, DCM: MeOH = 5:1) to give a compound as white oil. It was further purified by prep-HPLC (column: Welch Xtimate C18 40*200mm 7µm; mobile phase: [water(NH₄HCO₃)-MeCN]; 12%-52% B over 25 min) to

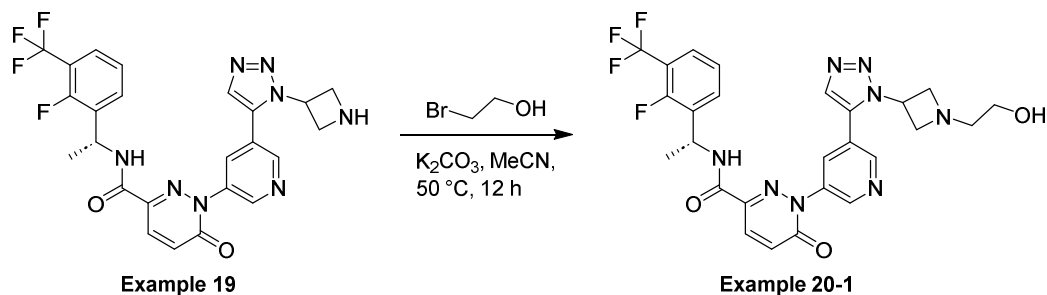
give a compound of **Example 19** (7.4 mg, 24.49% yield, 99.27% purity) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 9.17-9.09 (m, 2H), 8.80 (d, J = 2.0 Hz, 1H), 8.36 (t, J = 2.0 Hz, 1H), 8.14 (s, 1H), 7.92 (d, J = 10.0 Hz, 1H), 7.84 (br t, J = 7.2 Hz, 1H), 7.67 (t, J = 6.8 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.22 (d, J = 10.0 Hz, 1H), 5.45 (quind, J = 7.6, 15.2 Hz, 2H), 4.06 (dt, J = 4.0, 7.6 Hz, 2H), 3.79 (br t, J = 8.0 Hz, 2H), 1.52 (d, J = 7.2 Hz, 3H); MS (ESI) m/z = 529.2 $[\text{M}+\text{H}]^+$.

Example 20: **N-{(R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl}-1-{5-[1-(1-methyl-3-azetidiny)-1H-1,2,3-triazol-5-yl]-3-pyridyl}-6-oxo-1,6-dihydropyridazine-3-carboxamide**



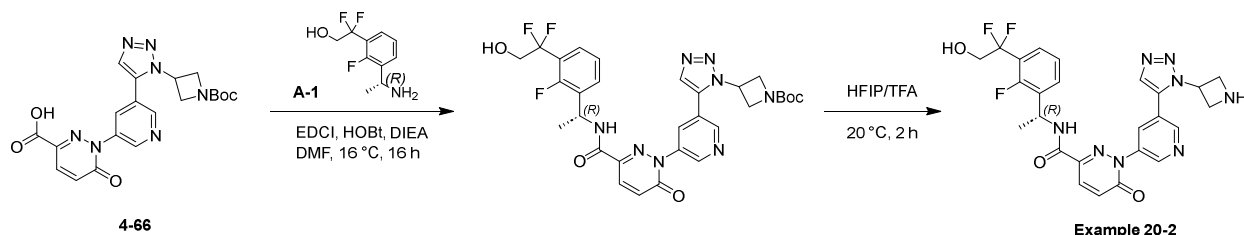
To a compound of Example 19 (50 mg, 94.61 μmol) in MeOH (1 mL) were added AcOH (11.36 mg, 189.23 μmol , 10.83 μL), NaBH_3CN (23.78 mg, 378.46 μmol) and HCHO (15.36 mg, 189.23 μmol , 14.09 μL) in MeOH (1 mL). The mixture was degassed and purged with N_2 for 3 times, and then stirred at 20 $^\circ\text{C}$ for 2 h under N_2 atmosphere. The mixture was concentrated under reduced pressure to give a crude product. The crude product was dissolved in MeOH (5 mL) and purified by prep-HPLC (column: Welch Xtimate C18 40*200mm 7 μm ; mobile phase: [water($\text{NH}_3\text{H}_2\text{O}+\text{NH}_4\text{HCO}_3$)-MeCN]; 20%-60% B over 25 min) to give a compound of **Example 20** (9.5 mg, 18.51% yield, 100% purity) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 9.16-9.08 (m, 2H), 8.82 (d, J = 2.0 Hz, 1H), 8.39 (t, J = 2.0 Hz, 1H), 8.14 (s, 1H), 7.92 (d, J = 10.0 Hz, 1H), 7.83 (t, J = 7.2 Hz, 1H), 7.68 (t, J = 7.2 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.23 (d, J = 10.0 Hz, 1H), 5.43 (quin, J = 7.2 Hz, 1H), 5.24 (quin, J = 6.8 Hz, 1H), 3.83-3.77 (m, 2H), 3.45 (t, J = 6.8 Hz, 2H), 2.29 (s, 3H), 1.52 (d, J = 7.2 Hz, 3H); MS (ESI) m/z = 543.2 $[\text{M}+\text{H}]^+$.

Example 20-1: **(R)-N-(1-(2-fluoro-3-(trifluoromethyl)phenyl)ethyl)-1-(5-(1-(2-hydroxyethyl)azetidiny)-1H-1,2,3-triazol-5-yl)pyridin-3-yl)-6-oxo-1,6-dihydropyridazine-3-carboxamide**



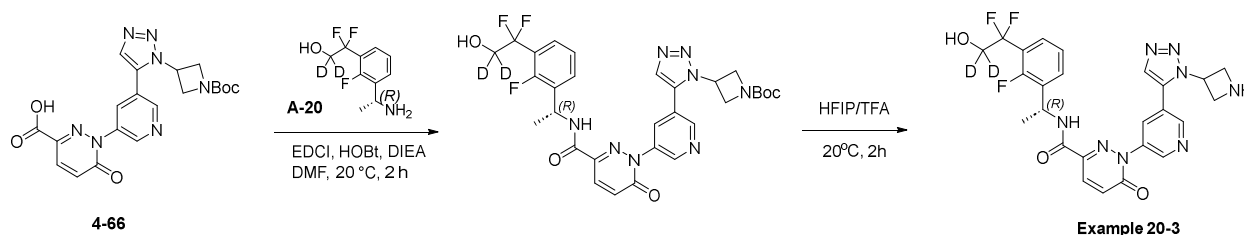
A mixture of the compound of Example 19 (60 mg, 113.54 μmol), 2-bromoethanol (14.19 mg, 113.54 μmol , 8.05 μL) and K_2CO_3 (47.07 mg, 340.61 μmol) in MeCN (2 mL) was stirred at 50 $^\circ\text{C}$ for 12 h, and then concentrated under reduced pressure to give a crude product. The crude product was purified by prep-TLC (SiO_2 , $\text{DCM}:\text{MeOH} = 10:1$) to give a residue. The resulting product was dissolved in MeOH (5 mL) and purified by prep-HPLC (column: F-Prepulisite XP tC 18 40*200mm*7 μm ; mobile phase: $[\text{water}(\text{NH}_3\text{H}_2\text{O}+\text{NH}_4\text{HCO}_3)-\text{ACN}]$; gradient: 16%-56% B over 20 min). Most of MeCN was concentrated under reduced pressure and the remaining solvent was removed by lyophilization to give **a compound of Example 20-1** (10.4 mg, 15.94% yield, 99.64% purity) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) $\delta = 9.16\text{--}9.09$ (m, 2H), 8.82 (d, $J = 1.6$ Hz, 1H), 8.39 (s, 1H), 8.14 (s, 1H), 7.92 (d, $J = 10.0$ Hz, 1H), 7.83 (br t, $J = 7.2$ Hz, 1H), 7.67 (br t, $J = 7.2$ Hz, 1H), 7.40 (t, $J = 8.0$ Hz, 1H), 7.23 (d, $J = 10.0$ Hz, 1H), 5.43 (quin, $J = 7.2$ Hz, 1H), 5.28 (quin, $J = 6.8$ Hz, 1H), 4.46–4.38 (m, 1H), 3.82 (br t, $J = 7.6$ Hz, 2H), 3.52 (br t, $J = 7.2$ Hz, 2H), 3.37 (br s, 2H), 2.54 (br t, $J = 6.0$ Hz, 2H), 1.52 (br d, $J = 7.2$ Hz, 3H); MS (ESI) $m/z = 573.2$ $[\text{M}+\text{H}]^+$.

Example 20-2: (R)-1-(5-(1-(azetidin-3-yl)-1H-1,2,3-triazol-5-yl)pyridin-3-yl)-N-(1-(3-(1,1-difluoro-2-hydroxyethyl)-2-fluorophenyl)ethyl)-6-oxo-1,6-dihydropyridazine-3-carboxamide



Intermediate 4-66 and Intermediate A-1 were used for synthesis in the same manner as in Example 19 to give **a compound of Example 20-2** (13 mg, 34.15% yield, 99.73% purity) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) $\delta = 9.14$ (d, $J = 2.4$ Hz, 1H), 9.07 (d, $J = 8.0$ Hz, 1H), 8.80 (d, $J = 2.0$ Hz, 1H), 8.37 (t, $J = 2.0$ Hz, 1H), 8.14 (s, 1H), 7.93 (d, $J = 10.0$ Hz, 1H), 7.65 (br t, $J = 7.2$ Hz, 1H), 7.43 (br t, $J = 6.8$ Hz, 1H), 7.28 (t, $J = 7.6$ Hz, 1H), 7.23 (d, $J = 10.0$ Hz, 1H), 5.73 (br t, $J = 5.6$ Hz, 1H), 5.51–5.37 (m, 2H), 4.10–4.01 (m, 2H), 3.97–3.85 (m, 2H), 3.79 (br t, $J = 8.0$ Hz, 2H), 1.50 (d, $J = 7.2$ Hz, 3H); MS (ESI) $m/z = 541.2$ $[\text{M}+\text{H}]^+$.

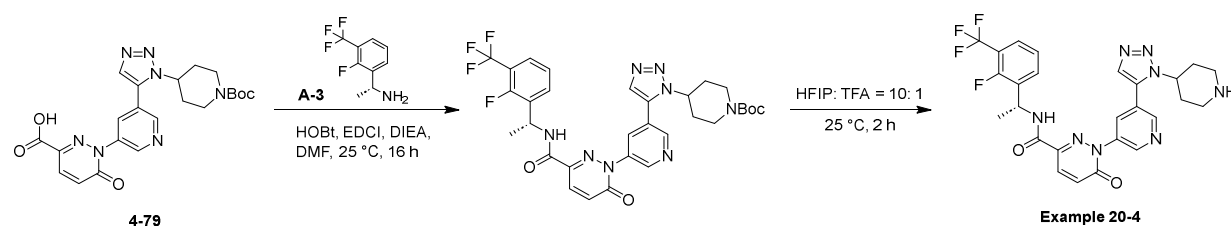
Example 20-3: (R)-1-(5-(1-(azetidin-3-yl)-1H-1,2,3-triazol-5-yl)pyridin-3-yl)-N-(1-(3-(1,1-difluoro-2-hydroxyethyl)-2,2-dideuterio)-2-fluorophenyl)ethyl)-6-oxo-1,6-dihydropyridazine-3-carboxamide



Intermediate 4-66 and Intermediate A-20 were used for synthesis in the same manner

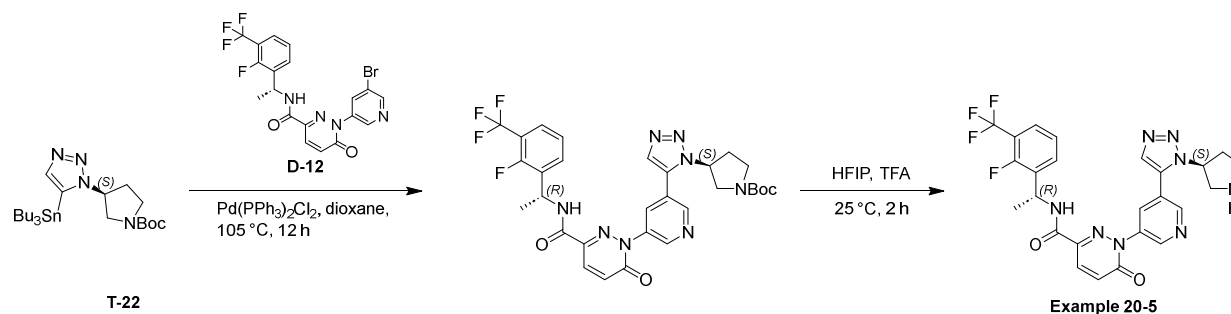
as in Example 19 to give **a compound of Example 20-3** (15.2 mg, 36.01% yield, 100% purity, deuterated ratio: 98.97%) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ = 9.15 (d, J = 2.0 Hz, 1H), 9.08 (br d, J = 8.0 Hz, 1H), 8.80 (d, J = 2.0 Hz, 1H), 8.37 (t, J = 2.0 Hz, 1H), 8.14 (s, 1H), 7.93 (d, J = 10.0 Hz, 1H), 7.65 (br t, J = 6.8 Hz, 1H), 7.44 (t, J = 6.8 Hz, 1H), 7.28 (t, J = 7.6 Hz, 1H), 7.23 (d, J = 10.0 Hz, 1H), 5.68 (br s, 1H), 5.45 (td, J = 7.6, 20.0 Hz, 2H), 4.46-4.26 (m, 1H), 4.09 (br d, J = 3.2 Hz, 2H), 3.85 (br s, 2H), 1.50 (d, J = 7.2 Hz, 3H); MS (ESI) m/z = 543.2 $[\text{M}+\text{H}]^+$.

Example 20-4: N-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-6-oxo-1-[5-[3-(4-piperidyl)triazol-4-yl]-3-pyridyl]pyridazine-3-carboxamide



Intermediate 4-79 and Intermediate A-3 were used for synthesis in the same manner as in Example 19 to give **a compound of Example 20-4** (14.2 mg, 23.70% yield, 99.037% purity) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ = 9.17 - 9.12 (m, 2H), 8.81 (d, J = 2.0 Hz, 1H), 8.42 (t, J = 2.0 Hz, 1H), 8.04 (s, 1H), 7.92 (d, J = 10.0 Hz, 1H), 7.83 (t, J = 7.2 Hz, 1H), 7.68 (t, J = 7.2 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.23 (d, J = 10.0 Hz, 1H), 5.43 (quin, J = 7.2 Hz, 1H), 4.53 - 4.42 (m, 1H), 3.02 (br d, J = 12.8 Hz, 2H), 2.59 - 2.53 (m, 2H), 2.04 - 1.93 (m, 4H), 1.52 (d, J = 7.2 Hz, 3H); MS (ESI) m/z = 557.2 $[\text{M}+\text{H}]^+$.

Example 20-5: N-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-6-oxo-1-[5-[3-[(3S)-pyrrolidin-3-yl]triazol-4-yl]-3-pyridyl]pyridazine-3-carboxamide



Step 1: Synthesis of tert-butyl (3S)-3-[5-[5-[3-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]carbamoyl]-6-oxo-pyridazin-1-yl]-3-pyridyl]triazol-1-yl]pyrrolidine-1-carboxylate

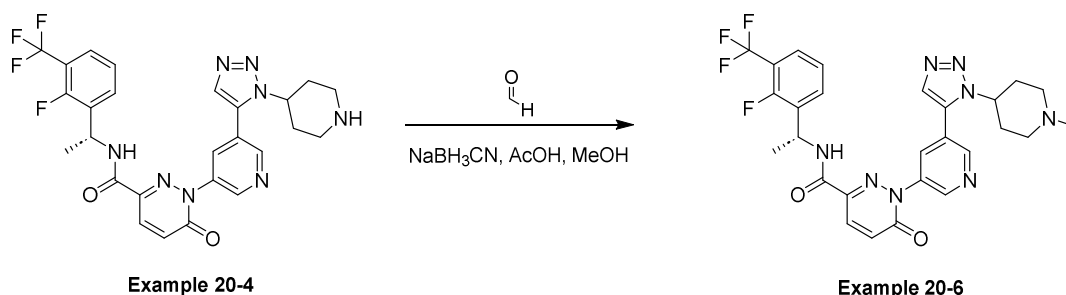
A mixture of Intermediate T-22 (330 mg, 625.79 μmol), Intermediate D-12 (151.83 mg, 312.90 μmol) and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (21.96 mg, 31.29 μmol) in dioxane (4 mL) was degassed and purged with nitrogen for 3 times, and then stirred at 105 °C for 12 h under N_2 atmosphere. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure and purified by column chromatography (0~2% MeOH/DCM) to give tert-butyl (3S)-3-[5-[5-[3-

[[[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]carbamoyl]-6-oxo-pyridazin-1-yl]-3-pyridyl]triazol-1-yl]pyrrolidin-1-carboxylate (170 mg, 76.94% yield, 91% purity) as a yellow solid. MS (ESI) m/z = 643.2 $[M+H]^+$.

Step 2: Synthesis of N-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-6-oxo-1-[5-[3-[(3S)-pyrrolidin-3-yl]triazol-4-yl]-3-pyridyl]pyridazine-3-carboxamide

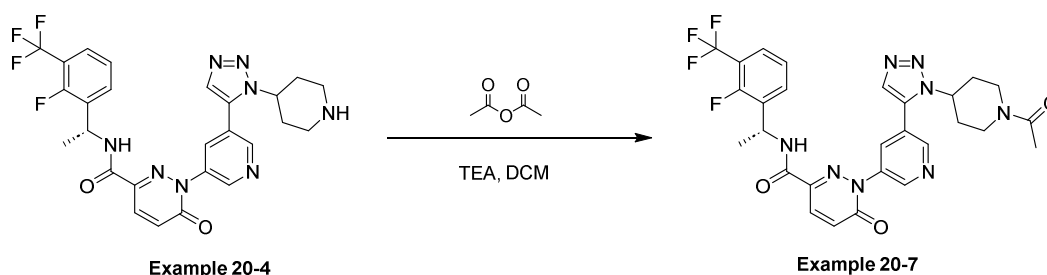
The compound of Example 20-5 (23.9 mg, 16.65% yield, 100% purity) was obtained as a white solid in the same manner as in Step 2 of Example 19. ^1H NMR (400 MHz, DMSO- d_6) δ = 9.16 (s, 1H), 9.15 - 9.11 (m, 1H), 8.82 (s, 1H), 8.43 (s, 1H), 8.07 (s, 1H), 7.92 (d, J = 9.6 Hz, 1H), 7.83 (br t, J = 7.2 Hz, 1H), 7.68 (br t, J = 7.2 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.22 (d, J = 9.6 Hz, 1H), 5.43 (br t, J = 7.2 Hz, 1H), 5.01 (br s, 1H), 3.21 (br dd, J = 6.8, 11.6 Hz, 2H), 3.13 - 3.07 (m, 2H), 2.92 - 2.84 (m, 1H), 2.25 - 2.14 (m, 2H), 1.52 (br d, J = 7.2 Hz, 3H); MS (ESI) m/z = 543.2 $[M+H]^+$.

Example 20-6: (R)-N-(1-(2-fluoro-3-(trifluoromethyl)phenyl)ethyl)-1-(5-(1-(1-methylpiperidin-4-yl)-1H-1,2,3-triazol-5-yl)pyridin-3-yl)-6-oxo-1,6-dihydropyridazine-3-carboxamide



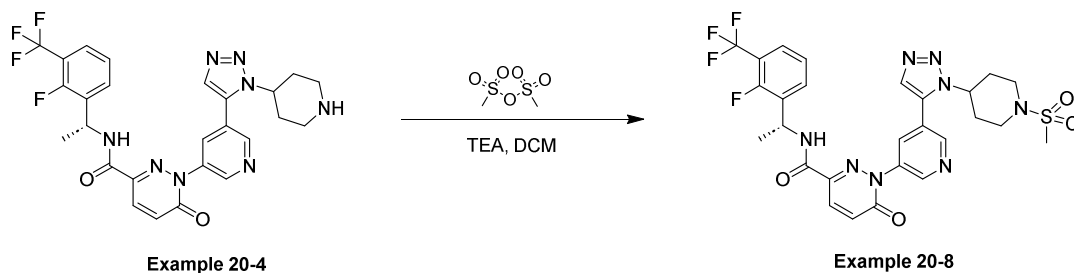
Example 20-4 was reacted in the same manner as in Example 30 to obtain **a compound of Example 20-6** (23.9 mg, 38.85% yield, 100% purity) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ = 9.16 (d, J = 2.4 Hz, 1H), 9.14 (d, J = 8.0 Hz, 1H), 8.81 (d, J = 2.0 Hz, 1H), 8.44 (t, J = 2.0 Hz, 1H), 8.05 (s, 1H), 7.91 (d, J = 10.0 Hz, 1H), 7.83 (t, J = 7.2 Hz, 1H), 7.68 (t, J = 7.2 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.24 (d, J = 10.0 Hz, 1H), 5.43 (quin, J = 7.2 Hz, 1H), 4.38 (ddd, J = 4.0, 7.2, 11.2 Hz, 1H), 2.90 - 2.80 (m, 2H), 2.20 (br d, J = 4.0 Hz, 1H), 2.18 (s, 3H), 2.14 (br s, 1H), 2.05 - 1.97 (m, 4H), 1.53 (d, J = 7.2 Hz, 3H); MS (ESI) m/z = 571.0 $[M+H]^+$.

Example 20-7: (R)-1-(5-(1-(1-acetylpiperidin-4-yl)-1H-1,2,3-triazol-5-yl)pyridin-3-yl)-N-(1-(2-fluoro-3-(trifluoromethyl)phenyl)ethyl)-6-oxo-1,6-dihydropyridazine-3-carboxamide



To a mixture of N-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-6-oxo-1-[5-[3-(4-piperidyl)triazol-4-yl]-3-pyridyl]pyridazine-3-carboxamide (**Example 20-4**, 50.00 mg, 89.85 μmol) in DCM (2 mL) was added TEA (13.64 mg, 134.77 μmol , 18.76 μL) and acetic anhydride (11.01 mg, 107.81 μmol , 10.13 μL). The mixture was stirred at 25 °C for 2 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to give a crude product. The crude product was purified by prep-HPLC (column: F-Prepulis XP tC 18 40*200mm*7 μm ; mobile phase: [water(NH₃H₂O+NH₄HCO₃)-ACN]; 22%-62% B, 20 min), and then most of ACN was removed under reduced pressure. The remaining solvent was removed by lyophilization to give **a compound of Example 20-7** (27.9 mg, 51.88% yield, 100% purity) as a white solid. ¹H NMR (400 MHz, CD₃OD) δ = 9.13 (d, J = 2.0 Hz, 1H), 8.80 (d, J = 1.6 Hz, 1H), 8.51 - 8.44 (m, 1H), 8.02 (d, J = 10.0 Hz, 1H), 8.00 (s, 1H), 7.73 (t, J = 6.8 Hz, 1H), 7.60 (t, J = 7.2 Hz, 1H), 7.32 (t, J = 8.0 Hz, 1H), 7.22 (d, J = 9.6 Hz, 1H), 5.51 (q, J = 7.2 Hz, 1H), 4.82 - 4.73 (m, 2H), 4.72 - 4.48 (m, 2H), 4.08 (br d, J = 13.2 Hz, 1H), 2.95 - 2.73 (m, 1H), 2.36 - 2.25 (m, 1H), 2.19 (br d, J = 2.4 Hz, 1H), 2.15 (s, 4H), 1.60 (d, J = 7.2 Hz, 3H); ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.17 (d, J = 2.4 Hz, 1H), 9.15 (d, J = 8.0 Hz, 1H), 8.84 (d, J = 2.0 Hz, 1H), 8.46 (t, J = 2.0 Hz, 1H), 8.07 (s, 1H), 7.93 (d, J = 10.0 Hz, 1H), 7.83 (t, J = 7.2 Hz, 1H), 7.68 (t, J = 7.2 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.24 (d, J = 10.0 Hz, 1H), 5.52 - 5.34 (m, 1H), 4.79 - 4.63 (m, 1H), 4.46 (br d, J = 14.0 Hz, 1H), 3.93 (br d, J = 13.6 Hz, 1H), 3.25 - 3.13 (m, 1H), 2.75 - 2.65 (m, 1H), 2.11 (br d, J = 8.8 Hz, 2H), 2.09 - 2.06 (m, 1H), 2.04 (s, 3H), 2.00 - 1.86 (m, 1H), 1.52 (d, J = 7.2 Hz, 3H); MS (ESI) m/z = 599.2 [M+H]⁺.

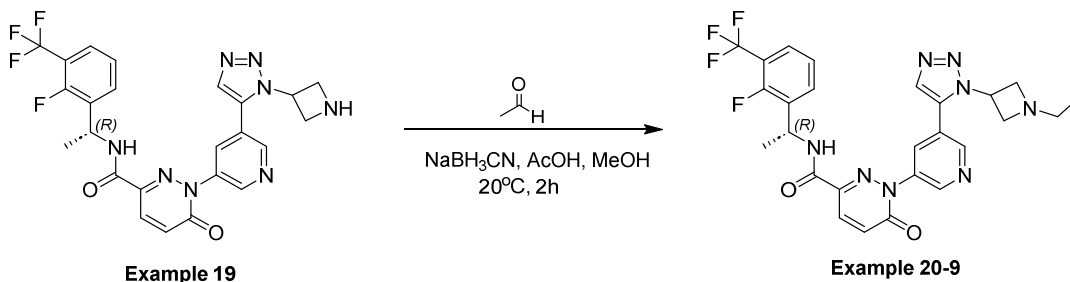
Example 20-8: (R)-N-(1-(2-fluoro-3-(trifluoromethyl)phenyl)ethyl)-1-(5-(1-(1-(methylsulfonyl)piperidine-4-yl)-1H-1,2,3-triazol-5-yl)pyridin-3-yl)-6-oxo-1,6-dihydropyridazine-3-carboxamide



The compound of Example 20-4 and commercially available methanesulfonic acid anhydride were used for synthesis in the same manner as in Example 20-7 to give **a compound of Example 20-8** (41.8 mg, 73.31% yield, 100% purity) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.19 (d, J = 2.4 Hz, 1H), 9.14 (d, J = 8.0 Hz, 1H), 8.83 (d, J = 2.0 Hz, 1H), 8.46 (t, J = 2.0 Hz, 1H), 8.07 (s, 1H), 7.92 (d, J = 10.0 Hz, 1H), 7.83 (br t, J = 7.2 Hz, 1H), 7.68 (t, J = 7.2 Hz, 1H), 7.44 - 7.37 (m, 1H), 7.24 (d, J = 10.0 Hz, 1H), 5.43 (quin, J = 7.2 Hz, 1H), 4.66 - 4.56 (m, 1H), 3.68 (br d, J = 12.0 Hz, 2H), 2.99 - 2.93 (m, 2H), 2.91 (s, 3H), 2.19 (br s, 4H), 1.53 (d, J = 7.2 Hz, 3H); MS (ESI) m/z = 635.5 [M+H]⁺.

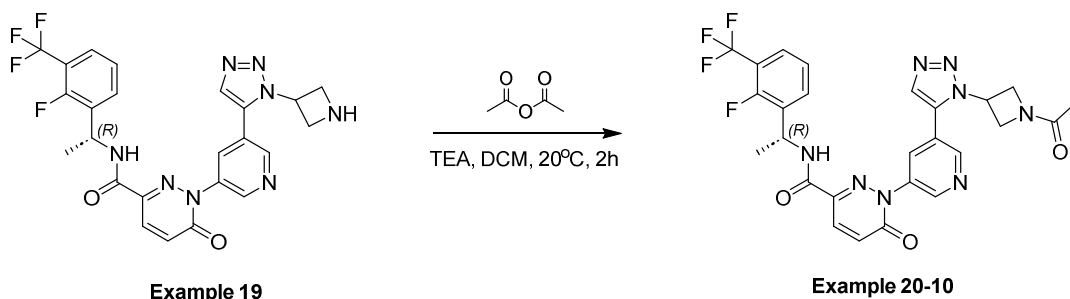
Example 20-9: (R)-1-(5-(1-(1-ethylazetidin-3-yl)-1H-1,2,3-triazol-5-yl)pyridin-3-

yl)-N-(1-(2-fluoro-3-(trifluoromethyl)phenyl)ethyl)-6-oxo-1,6-dihydropyridazine-3-carboxamide



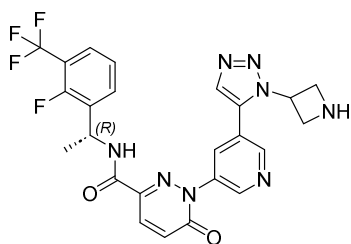
The compound of Example 19 was reacted in the same manner as in Example 30 to obtain **a compound of Example 20-9** (35.3 mg, 55.87% yield, 100% purity) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 9.13 (d, J = 2.4 Hz, 1H), 9.11 (d, J = 8.0 Hz, 1H), 8.82 (d, J = 2.0 Hz, 1H), 8.40 (t, J = 2.0 Hz, 1H), 8.14 (s, 1H), 7.92 (d, J = 10.0 Hz, 1H), 7.83 (t, J = 7.2 Hz, 1H), 7.68 (t, J = 7.2 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.23 (d, J = 10.0 Hz, 1H), 5.42 (quin, J = 7.2 Hz, 1H), 5.26 (quin, J = 6.8 Hz, 1H), 3.78 (t, J = 7.2 Hz, 2H), 3.44-3.40 (m, 2H), 2.48-2.43 (m, 2H), 1.53 (d, J = 7.2 Hz, 3H), 0.87 (t, J = 7.2 Hz, 3H); MS (ESI) m/z = 557.4 $[\text{M}+\text{H}]^+$.

Example 20-10: (R)-1-(5-(1-(1-acetylazetidin-3-yl)-1H-1,2,3-triazol-5-yl)pyridin-3-yl)-N-(1-(2-fluoro-3-(trifluoromethyl)phenyl)ethyl)-6-oxo-1,6-dihydropyridazine-3-carboxamide

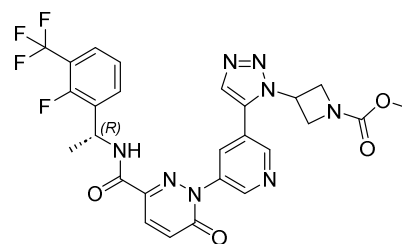
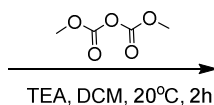


The compound of Example 19 was reacted in the same manner as in Example 20-7 to obtain **a compound of Example 20-10** (24.1 mg, 44.65% yield, 100% purity) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 9.20-9.07 (m, 2H), 8.82 (s, 1H), 8.38 (br s, 1H), 8.18 (s, 1H), 7.93 (d, J = 9.6 Hz, 1H), 7.83 (br t, J = 7.2 Hz, 1H), 7.68 (br t, J = 7.2 Hz, 1H), 7.45-7.35 (m, 1H), 7.24 (d, J = 10.0 Hz, 1H), 5.56-5.47 (m, 1H), 5.46-5.38 (m, 1H), 4.68-4.60 (m, 2H), 4.43-4.34 (m, 1H), 4.32-4.24 (m, 1H), 1.80 (s, 3H), 1.52 (br d, J = 7.2 Hz, 3H); MS (ESI) m/z = 571.2 $[\text{M}+\text{H}]^+$.

Example 20-11: methyl (R)-3-(5-(5-(3-((1-(2-fluoro-3-(trifluoromethyl)phenyl)ethyl)carbamoyl)-6-oxopyridazin-1(6H)-yl)pyridin-3-yl)-1H-1,2,3-triazol-1-yl)azetidine-1-carboxylate



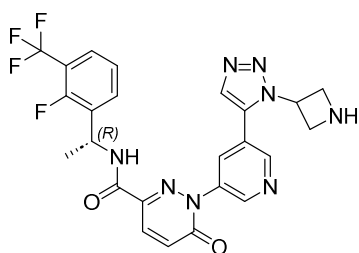
Example 19



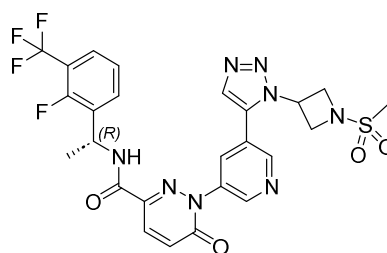
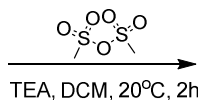
Example 20-11

The compound of Example 19 and commercially available dimethyl dicarbonate were reacted in the same manner as in Example 20-7 to obtain **a compound of Example 20-11** (30.3 mg, 54.54% yield, 99.88% purity) as a white solid. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ = 9.16 (d, J = 2.0 Hz, 1H), 9.13 (br d, J = 8.0 Hz, 1H), 8.81 (d, J = 1.6 Hz, 1H), 8.36 (s, 1H), 8.17 (s, 1H), 7.93 (d, J = 9.6 Hz, 1H), 7.83 (br t, J = 7.2 Hz, 1H), 7.68 (br t, J = 7.2 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.24 (d, J = 10.0 Hz, 1H), 5.55-5.47 (m, 1H), 5.43 (br t, J = 7.2 Hz, 1H), 4.49-4.37 (m, 4H), 3.59 (s, 3H), 1.52 (br d, J = 7.2 Hz, 3H); MS (ESI) m/z = 587.0 $[\text{M}+\text{H}]^+$.

Example 20-12: (R)-N-(1-(2-fluoro-3-(trifluoromethyl)phenyl)ethyl)-1-(5-(1-(1-methylsulfonyl)azetidin-3-yl)-1H-1,2,3-triazol-5-yl)pyridin-3-yl)-6-oxo-1,6-dihydropyridazine-3-carboxamide



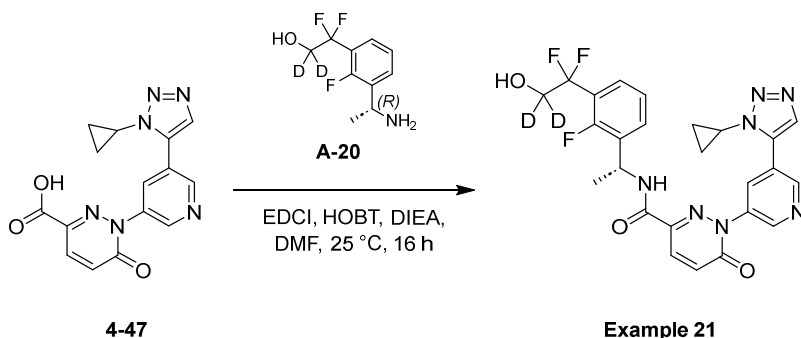
Example 19



Example 20-12

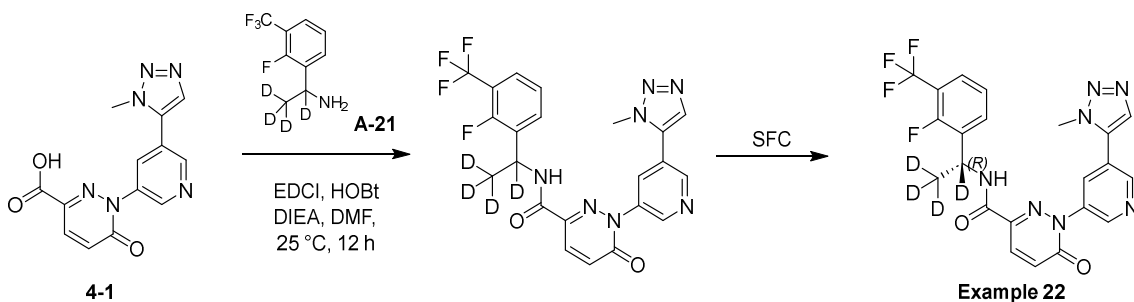
The compound of Example 19 and commercially available methanesulfonic anhydride were reacted in the same manner as in Example 20-7 to give **a compound of Example 20-12** (10.9 mg, 18.97% yield, 99.86% purity) as a white solid. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ = 9.22-9.06 (m, 2H), 8.82 (br s, 1H), 8.45-8.32 (m, 1H), 8.19 (s, 1H), 7.93 (br d, J = 9.6 Hz, 1H), 7.83 (br t, J = 6.4 Hz, 1H), 7.72-7.63 (m, 1H), 7.45-7.36 (m, 1H), 7.24 (br d, J = 10.0 Hz, 1H), 5.59-5.48 (m, 1H), 5.43 (br t, J = 6.8 Hz, 1H), 4.48 (br s, 2H), 4.42-4.35 (m, 2H), 3.12 (s, 3H), 1.53 (br d, J = 6.8 Hz, 3H); MS (ESI) m/z = 606.9 $[\text{M}+\text{H}]^+$.

Example 21: N-[(R)-1-{3-[1,1-difluoro-2-hydroxyethyl-2,2-dideuterio]-2-fluorophenyl}ethyl]-1-[5-(1-cyclopropyl-1H-1,2,3-triazol-5-yl)-3-pyridyl]-6-oxo-1,6-dihydropyridazine-3-carboxamide



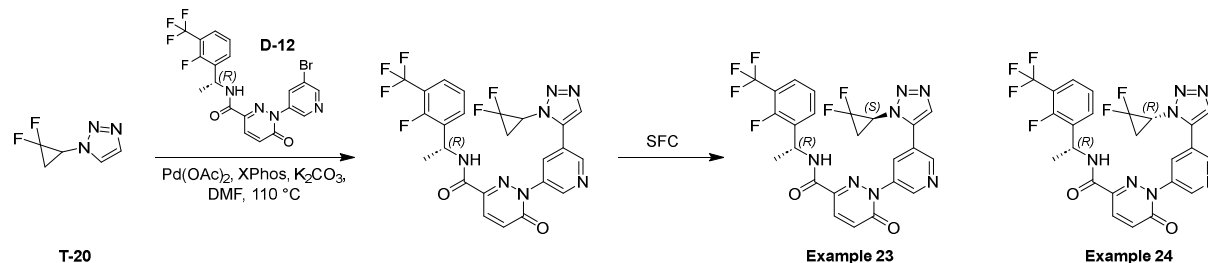
Intermediate 4-47 and Intermediate A-20 were used for synthesis in the same manner as in Example 1 to give **a compound of Example 21** (40.6 mg, 28.38% yield, 100% purity, deuterated ratio: 99.00%) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 9.12 (d, J = 2.4 Hz, 1H), 9.07 (d, J = 8.0 Hz, 1H), 9.02 (d, J = 2.0 Hz, 1H), 8.65 (t, J = 2.0 Hz, 1H), 8.17 (s, 1H), 7.93 (d, J = 9.6 Hz, 1H), 7.64 (t, J = 6.8 Hz, 1H), 7.44 (t, J = 6.8 Hz, 1H), 7.28 (t, J = 7.6 Hz, 1H), 7.22 (d, J = 9.6 Hz, 1H), 5.68 (br s, 1H), 5.42 (quin, J = 7.2 Hz, 1H), 4.06 - 4.00 (m, 1H), 1.49 (d, J = 7.2 Hz, 3H), 1.19 - 1.13 (m, 4H); MS (ESI) m/z = 528.3 $[\text{M}+\text{H}]^+$.

Example 22: (R)-N-(1-(2-fluoro-3-(trifluoromethyl)phenyl)ethyl-1,2,2,2-tetradeuterio)-1-(5-(1-methyl-1H-1,2,3-triazol-5-yl)pyridin-3-yl)-6-oxo-1,6-dihydropyridazine-3-carboxamide



Intermediate 4-1 and Intermediate A-21 were used for synthesis in the same manner as in Example 1 to give (+/-) N-(1-(2-fluoro-3-(trifluoromethyl)phenyl)ethyl-1,2,2,2-tetradeuterio)-1-(5-(1-methyl-1H-1,2,3-triazol-5-yl)pyridin-3-yl)-6-oxo-1,6-dihydropyridazine-3-carboxamide (50 mg, 40.47% yield, 94.18% purity) as yellow oil. It was further purified by SFC separation (column: REGIS (s,s) WHELK-O1 (250mm*30mm,5um); mobile phase: $[\text{CO}_2\text{-MeOH}(0.1\%\text{NH}_3\text{H}_2\text{O})]$; B%:50%, isocratic elution mode). The resulting compound was added with MeCN (5 mL) and H_2O (25 mL) and dried by lyophilization to obtain a white solid. It was dissolved in MeOH (5 mL) and purified by prep-HPLC (column: Welch Xtimate C18 40*200mm 7 μm ; mobile phase: $[\text{water}(\text{NH}_3\text{H}_2\text{O}+\text{NH}_4\text{HCO}_3)\text{-MeCN}]$; 18%-58% B over 25 min) to give **a compound of Example 22** (7.3 mg, 14.48% yield, 99.18% purity, 100 % ee, deuterated ratio: 99.609 %) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 9.12 (d, J = 2.4 Hz, 2H), 8.92 (d, J = 2.0 Hz, 1H), 8.51 (t, J = 2.4 Hz, 1H), 8.13 (s, 1H), 7.92 (d, J = 10.0 Hz, 1H), 7.83 (t, J = 7.2 Hz, 1H), 7.68 (t, J = 6.8 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.22 (d, J = 10.0 Hz, 1H), 4.17 (s, 3H); MS (ESI) m/z = 492.1 $[\text{M}+\text{H}]^+$.

Examples 23 and 24: 1-[5-[3-[(1S)-2,2-difluorocyclopropyl]triazol-4-yl]-3-pyridyl]-N-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-6-oxo-pyridazine-3-carboxamide and 1-[5-[3-[(1R)-2,2-difluorocyclopropyl]triazol-4-yl]-3-pyridyl]-N-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-6-oxo-pyridazine-3-carboxamide



Step 1: Synthesis of 1-[5-[3-(2,2-difluorocyclopropyl)triazol-4-yl]-3-pyridyl]-N-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-6-oxo-pyridazine-3-carboxamide

A mixture of Intermediate D-12 (100 mg, 206.09 μmol) and Intermediate T-20 (89.72 mg, 618.26 μmol), Pd(OAc)₂ (9.25 mg, 41.22 μmol), K₂CO₃ (56.97 mg, 412.18 μmol) and XPhos (39.30 mg, 82.44 μmol) in DMF (4 mL) was degassed and purged with N₂ for 3 times, and then stirred at 110 °C for 16 h under N₂ atmosphere. The reaction mixture was filtered, and the filtrate was diluted with water (5 mL) and then extracted with EtOAc (15 mL $\times$ 3). The combined organic layers were washed with brine (5 mL $\times$ 3), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (2% MeOH in DCM) to give 1-[5-[3-(2,2-difluorocyclopropyl)triazol-4-yl]-3-pyridyl]-N-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-6-oxo-pyridazine-3-carboxamide (35 mg, 27.72% yield, 89.69% purity) as a yellow solid. MS (ESI) m/z = 550.0 [M+H]⁺.

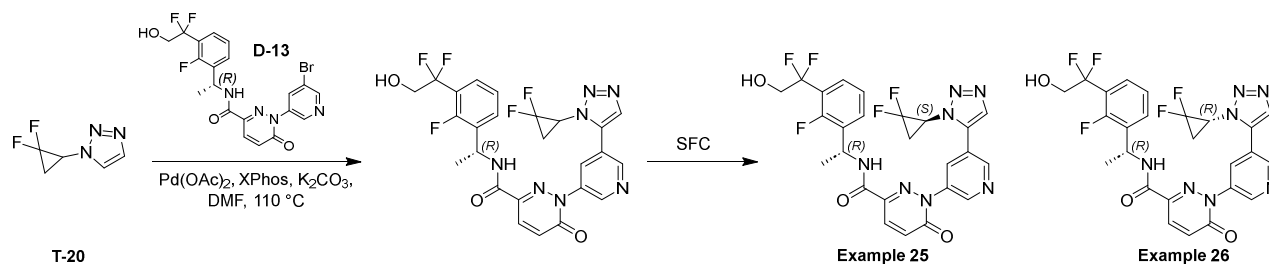
Step 2: Synthesis of 1-[5-[3-[(1S)-2,2-difluorocyclopropyl]triazol-4-yl]-3-pyridyl]-N-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-6-oxo-pyridazine-3-carboxamide, 1-[5-[3-[(1R)-2,2-difluorocyclopropyl]triazol-4-yl]-3-pyridyl]-N-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-6-oxo-pyridazine-3-carboxamide

1-[5-[3-(2,2-difluorocyclopropyl)triazol-4-yl]-3-pyridyl]-N-[(1R)-1-[2-fluoro-3-(trifluoromethyl)phenyl]ethyl]-6-oxo-pyridazine-3-carboxamide (35 mg, 63.70 μmol) was further purified by SFC separation (column: DAICEL CHIRALCEL OD (250mm $\times$ 30mm,10 μm); mobile phase: [CO₂- EtOH (0.1% NH₃H₂O)]; B%: 40%, isocratic elution mode). Two peaks were confirmed by SFC analysis. The compound confirmed in the first peak (R_t = 0.838 min) was concentrated under reduced pressure, MeCN (5 mL) and H₂O (10 mL) were added, and the solvent was removed by lyophilization to obtain **a compound of Example 23** (10.4 mg, 28.81% yield, 96.96% purity) as a light yellow solid. The compound confirmed in the second peak (R_t = 1.146 min) was concentrated under reduced pressure, MeCN (5 mL) and H₂O (10 mL) were added, and the solvent was removed by lyophilization to give **a compound of Example 24** (14 mg, 39.80% yield, 99.50% purity) as a white solid.

Compound of Example 23: ^1H NMR (400 MHz, DMSO- d_6) δ = 9.15 (d, J = 2.0 Hz, 1H), 9.08 (br d, J = 7.6 Hz, 1H), 9.00 (d, J = 1.6 Hz, 1H), 8.58 (s, 1H), 8.26 (s, 1H), 7.92 (d, J = 9.6 Hz, 1H), 7.82 (br t, J = 7.2 Hz, 1H), 7.68 (br t, J = 6.8 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H), 7.23 (d, J = 9.6 Hz, 1H), 5.42 (quin, J = 7.2 Hz, 1H), 5.15 - 5.06 (m, 1H), 2.66 - 2.56 (m, 1H), 2.47 - 2.39 (m, 1H), 1.51 (br d, J = 7.2 Hz, 3H); MS (ESI) m/z = 550.2 $[\text{M}+\text{H}]^+$.

Compound of Example 24: ^1H NMR (400 MHz, DMSO- d_6) δ = 9.15 (d, J = 2.0 Hz, 1H), 9.08 (br d, J = 7.6 Hz, 1H), 8.99 (s, 1H), 8.58 (s, 1H), 8.26 (s, 1H), 7.92 (d, J = 9.6 Hz, 1H), 7.83 (br t, J = 7.2 Hz, 1H), 7.68 (br t, J = 6.8 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.23 (d, J = 9.6 Hz, 1H), 5.42 (br t, J = 7.2 Hz, 1H), 5.15 - 5.05 (m, 1H), 2.64 - 2.56 (m, 1H), 2.45 - 2.36 (m, 1H), 1.51 (br d, J = 7.2 Hz, 3H); MS (ESI) m/z = 550.2 $[\text{M}+\text{H}]^+$.

Examples 25 and 26: 1-[5-[3-[(1S)-2,2-difluorocyclopropyl]triazol-4-yl]-3-pyridyl]-N-[(1R)-1-[3-(1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethyl]-6-oxo-pyridazine-3-carboxamide and 1-[5-[3-[(1R)-2,2-difluorocyclopropyl]triazol-4-yl]-3-pyridyl]-N-[(1R)-1-[3-(1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethyl]-6-oxo-pyridazine-3-carboxamide



Step 1: Synthesis of 1-[5-[3-(2,2-difluorocyclopropyl)triazol-4-yl]-3-pyridyl]-N-[(1R)-1-[3-(1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethyl]-6-oxo-pyridazine-3-carboxamide

Intermediates T-20 and D-13 were used for synthesis in the same manner as in Step 1 of Example 33 to give 1-[5-[3-(2,2-difluorocyclopropyl)triazol-4-yl]-3-pyridyl]-N-[(1R)-1-[3-(1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethyl]-6-oxo-pyridazine-3-carboxamide (32 mg, 12.32% yield, 100% purity) as a white solid. MS (ESI) m/z = 562.2 $[\text{M}+\text{H}]^+$.

Step 2: Synthesis of 1-[5-[3-[(1S)-2,2-difluorocyclopropyl]triazol-4-yl]-3-pyridyl]-N-[(1R)-1-[3-(1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethyl]-6-oxo-pyridazine-3-carboxamide and 1-[5-[3-[(1R)-2,2-difluorocyclopropyl]triazol-4-yl]-3-pyridyl]-N-[(1R)-1-[3-(1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethyl]-6-oxo-pyridazine-3-carboxamide

1-[5-[3-(2,2-difluorocyclopropyl)triazol-4-yl]-3-pyridyl]-N-[(1R)-1-[3-(1,1-difluoro-2-hydroxy-ethyl)-2-fluoro-phenyl]ethyl]-6-oxo-pyridazine-3-carboxamide (32 mg, 56.99 μmol) was further purified by SFC separation (column: DAICEL CHIRALCEL OD (250mm*30mm,10 μm); mobile phase: $[\text{CO}_2$ - EtOH (0.1% $\text{NH}_3\text{H}_2\text{O}$)]); B%: 40%, isocratic elution mode). Two peaks were confirmed by SFC analysis. The compound confirmed in the first peak (R_t = 1.545 min) was concentrated under reduced pressure, MeCN (5 mL) and H_2O

(10 mL) were added, and the solvent was removed by lyophilization to obtain **a compound of Example 25** (9.9 mg, 30.94% yield, 100% purity) as a white solid. The compound confirmed in the second peak ($R_t = 1.717$ min) was concentrated under reduced pressure, MeCN (5 mL) and H₂O (10 mL) were added, and the solvent was removed by lyophilization to obtain **a compound of Example 26** (11.2 mg, 35.00% yield, 100% purity) as a white solid. The absolute stereochemical configurations, S and R, of the difluorocyclopropyl triazole of the compounds of Examples 25 and 26 were arbitrarily indicated.

Compound of Example 25: ¹H NMR (400 MHz, DMSO-d₆) δ = 9.21 (d, J = 2.4 Hz, 1H), 9.08 (d, J = 8.0 Hz, 1H), 9.06 (d, J = 2.0 Hz, 1H), 8.65 (t, J = 2.0 Hz, 1H), 8.32 (s, 1H), 7.99 (d, J = 9.6 Hz, 1H), 7.70 (t, J = 7.2 Hz, 1H), 7.50 (t, J = 6.8 Hz, 1H), 7.34 (t, J = 7.6 Hz, 1H), 7.30 (d, J = 9.6 Hz, 1H), 5.77 (t, J = 6.4 Hz, 1H), 5.48 (t, J = 7.2 Hz, 1H), 5.21 - 5.10 (m, 1H), 3.98 (dt, J = 6.4, 14.4 Hz, 2H), 2.70 - 2.61 (m, 1H), 2.52 - 2.43 (m, 1H), 1.55 (d, J = 7.2 Hz, 3H); MS (ESI) m/z = 562.2 [M+H]⁺.

Compound of Example 26: ¹H NMR (400 MHz, DMSO-d₆) δ = 9.15 (d, J = 2.4 Hz, 1H), 9.02 (d, J = 8.0 Hz, 1H), 8.99 (d, J = 2.0 Hz, 1H), 8.59 (t, J = 2.0 Hz, 1H), 8.26 (s, 1H), 7.93 (d, J = 10.0 Hz, 1H), 7.64 (t, J = 6.8 Hz, 1H), 7.44 (t, J = 6.8 Hz, 1H), 7.28 (t, J = 7.6 Hz, 1H), 7.23 (d, J = 9.6 Hz, 1H), 5.71 (t, J = 6.4 Hz, 1H), 5.42 (quin, J = 7.2 Hz, 1H), 5.16 - 5.05 (m, 1H), 3.91 (dt, J = 6.4, 14.4 Hz, 2H), 2.64 - 2.55 (m, 1H), 2.42 (dt, J = 4.8, 10.0 Hz, 1H), 1.49 (d, J = 7.2 Hz, 3H); MS (ESI) m/z = 562.2 [M+H]⁺.

[Experimental Example]

Experimental Example 1: SOS-catalyzed nucleotide exchange assay

SOS1 activity was measured by SOS1-mediated GTP loading quantification of KRAS^{G12D}. GTP loaded KRAS^{G12D} was detected by HTRF (Homogeneous Time Resolved Fluorescence) using anti-GST terbium (Cisbio, France) as a donor and a fluorescence GTP analogue (EDA-GTP-DY-647P1, [DY-647P1 labeled 2'/3'-O-(2-aminoethyl-carbamoyl)guanosine-5'-triphosphate (Jena bioscience, Germany)]) as an acceptor.

Assay buffer was composed of 10 mM HEPES pH 7.4, 150 mM NaCl, 5 mM MgCl₂, 1 mM DTT, 0.05% BSA Fraction V pH 7.0 (Sigma) and 0.0025% (v/v) Igepal (Sigma). KRAS^{G12D} working solution was prepared by adding equal amounts of GST-KRAS^{G12D} (100 nM) and anti-GST-terbium (2 nM; Cisbio, France) to the assay buffer and culturing on ice for 10 minutes. SOS1_{cat} working solution was prepared by adding equal amounts of HIS-SOS1_{cat} (160 nM; Cytoskeleton, US) and EDA-GTP-DY-647P1 (200 nM; Jena bioscience, Germany) to the assay buffer. Control solution was prepared by adding equal volumes of EDA-GTP-DY-647P1 and the assay buffer for normalization control to exclude GEF-independent GTP loading and background signals. In order to induce a reaction, 5 μ L of the SOS1_{cat} working solution or the control solution was injected into each well. 5 μ L of a compound having various

concentrations from 128 pM to 10 μ M was added to wells containing the SOS1_{cat} working solution and incubated at room temperature for 10 minutes to bind to SOS1.

10 uL of the KRAS^{G12D} solution was added to each well and incubated for 30 minutes at room temperature while shaking. HTRF was measured using a Thermo Varioskan (excitation 334 nm, emission 665 nm). The IC₅₀ of each inhibitor was analyzed using Graphad Prism.

The SOS1 inhibitory activity of the Example compounds measured by the above method was evaluated based on the following criteria, and the results are shown in Table 6.

IC ₅₀ range	< 50 nM	50 nM $\leq$ IC ₅₀ < 150 nM	$\geq$ 150 nM
Class	A	B	C

NA = Not Applied

As shown in Table 6 below, the Example compounds herein exhibited excellent SOS1 inhibitory activity.

[Table 6]

Example No.	SOS-catalyzed exchange assay	nucleotide	Example No.	SOS-catalyzed exchange assay	nucleotide
1	A		1-68	A	
1-1	B		1-69	B	
1-2	B		1-70	A	
1-3	B		1-71	A	
1-4	B		1-72	A	
1-5	B		2	B	
1-6	B		2-1	A	
1-7	A		2-2	A	
1-8	A		2-3	A	
1-9	A		2-4	A	
1-10	A		2-5	A	
1-11	B		2-6	A	
1-12	A		2-7	A	
1-13	A		3	C	
1-14	C		3-1	B	
1-15	A		3-2	B	
1-16	B		3-3	A	
1-17	B		3-4	B	
1-18	A		3-5	B	
1-19	C		4	C	
1-20	B		5	C	
1-21	A		6	B	
1-22	C		6-1	B	
1-23	A		6-2	A	
1-24	A		6-3	A	
1-25	A		6-4	A	

1-26	B	6-5	NA
1-27	B	6-6	NA
1-28	NA	6-7	A
1-29	B	6-8	A
1-30	C	6-9	A
1-31	NA	7	A
1-32	NA	7-1	B
1-33	NA	7-2	B
1-34	B	7-3	B
1-35	B	7-4	A
1-36	A	8	A
1-37	B	9	A
1-38	B	10	B
1-39	A	11	A
1-40	A	12	B
1-41	A	13	B
1-42	A	14	A
1-43	A	15	A
1-44	NA	16	NA
1-45	NA	17	NA
1-46	B	18	NA
1-47	NA	19	A
1-48	C	20	A
1-49	B	20-1	A
1-50	A	20-2	A
1-51	A	20-3	A
1-52	A	20-4	A
1-53	A	20-5	B
1-54	A	20-6	A
1-55	A	20-7	A
1-56	A	20-8	A
1-57	A	20-9	A
1-58	A	20-10	A
1-59	A	20-11	A
1-60	A	20-12	A
1-61	B	21	A
1-62	B	22	A
1-63	B	23	B
1-64	C	24	B
1-65	C	25	A
1-66	B	26	A
1-67	A		

Experimental Example 2: KRAS^{G12C}::SOS1 protein-protein interaction (PPI) inhibition assay

Protein-protein interaction between SOS1 and KRAS^{G12C} was detected using KRAS G12C/SOS1 binding kit from CISBIO (64KRASG12PEH, CISBIO, FRANCE) according to the manufacturer's assay method. Briefly, the maximum concentration of an inhibitor sample was set to be 3 μ M, and the inhibitor sample was diluted 7 times by 1/3, and samples having a total of 8 concentrations were prepared. In HTRF (Homogeneous Time-Resolved Fluorescence) exclusive 96-well low-volume white plate (66PL96005, CISBIO, FRANCE), 2 μ L of an inhibitor sample prepared for each concentration, 5 μ L of a mixed solution of Tag1 labeled KRAS^{G12C} protein and GTP diluted with the dilution solution provided by the manufacturer, and 5 μ L of Tag2 labeled SOS1 protein were mixed, and added with 8 μ L of a diluted solution where anti-Tag1 KRAS^{G12C} XL665 (HTRF acceptor) labeled antibody and anti-Tag2 SOS1 Terbium cryptate (HTRF donor) labeled antibody were mixed in an equal ratio and cultured at room temperature for 2 h. Thereafter, the HTRF signal generated by the antibody was measured using a Thermo Varioskan multi-purpose plate signal detector, and the result value was calculated as the ratio of the signals emitted at 665 nm and 620 nm as shown below.

$$\text{Result value} = 10^4 \times 665 \text{ nm signal} / 620 \text{ nm signal}$$

The IC₅₀ value of each inhibitor was analyzed with the result values of three replicates by using the Graphad Prism 9.0 software.

The degree of inhibition of the Example compounds on SOS1 and KRAS^{G12C} interaction measured by the above method was evaluated based on the following criteria, and the results are shown in Table 7.

IC ₅₀ range	< 50 nM	50 nM $\leq$ IC ₅₀ < 150 nM	$\geq$ 150 nM
Class	A	B	C

NA = Not Applied

[Table 7]

Example No.	KRAS G12C::SOS1 PPI	Example No.	KRAS G12C::SOS1 PPI
1	A	1-68	A
1-1	A	1-69	A
1-2	B	1-70	NA
1-3	B	1-71	NA
1-4	A	1-72	NA
1-5	B	2	B
1-6	A	2-1	A
1-7	A	2-2	A
1-8	B	2-3	A
1-9	A	2-4	A
1-10	B	2-5	A
1-11	B	2-6	A

1-12	B	2-7	A
1-13	A	3	C
1-14	C	3-1	C
1-15	A	3-2	B
1-16	B	3-3	A
1-17	C	3-4	B
1-18	A	3-5	B
1-19	C	4	C
1-20	C	5	C
1-21	A	6	B
1-22	B	6-1	C
1-23	A	6-2	B
1-24	A	6-3	A
1-25	B	6-4	B
1-26	B	6-5	B
1-27	B	6-6	B
1-28	C	6-7	A
1-29	A	6-8	A
1-30	C	6-9	A
1-31	B	7	A
1-32	C	7-1	B
1-33	C	7-2	A
1-34	A	7-3	A
1-35	B	7-4	A
1-36	B	8	A
1-37	B	9	B
1-38	A	10	B
1-39	A	11	B
1-40	A	12	C
1-41	A	13	C
1-42	A	14	B
1-43	A	15	A
1-44	C	16	C
1-45	B	17	C
1-46	B	18	C
1-47	C	19	A
1-48	C	20	A
1-49	A	20-1	B
1-50	A	20-2	A
1-51	B	20-3	A
1-52	B	20-4	B
1-53	A	20-5	B
1-54	B	20-6	A
1-55	A	20-7	A

1-56	A	20-8	A
1-57	B	20-9	A
1-58	A	20-10	A
1-59	B	20-11	A
1-60	A	20-12	A
1-61	A	21	A
1-62	A	22	A
1-63	B	23	B
1-64	C	24	C
1-65	B	25	A
1-66	A	26	A
1-67	B		

Experimental Example 3: Evaluation of cancer cell growth inhibition

The lung cancer cell line NCI-H358 having the KRAS G12C variant was dispensed into 100 μ l of cell culture solution (RPMI1640 with L-glutamine (300mg/L), 10% fetal bovine serum (FBS), 1% P/S) per well of a 96-well cell culture plate (U-shape clear bottom plate, SPL 34896) to contain approximately 2000 cells, centrifuged at 1300 RPM for 3 minutes, and then cultured for 72 h under conditions of 37 °C and 5% carbon dioxide. When three-dimensional cell spheroids were formed, the cells were treated with each compound to final concentrations of 0.002 μ M, 0.005 μ M, 0.014 μ M, 0.041 μ M, 0.12 μ M, 0.37 μ M, 1.11 μ M, 3.33 μ M and 10 μ M per well, and cultured under conditions of 37 °C and 5% carbon dioxide for 5 days. Thereafter, the plate with the cells cultured was adapted to room temperature for 10 minutes, and then 50 μ L of CellTiter-Glo® 3D Cell Viability Assay (PROMEGA, G9683) solution was dispensed, and reacted on a horizontal stirrer at a speed of 300 RPM for 30 minutes to induce the cell lysis. 150 μ L of each stirred solution was taken and transferred to a new white 96-well cell culture plate (Nunc™ MicroWell™ 96-Well, Nunclon Delta-Treated, Flat-Bottom Microplate, 136101), and the luminescence intensity was measured using a Varioskan™ LUX microplate reader. Thereafter, based on the measured values, the degree of cell growth in the well treated with each compound was calculated when the final cell density value of the well not treated with the test substance was set to 100%.

The cancer cell growth inhibition ability of the example compounds measured by the above method was evaluated based on the following criteria, and the results are shown in Table 8.

IC ₅₀ range	$\leq 1 \mu\text{M}$	$1 \mu\text{M} < \text{IC}_{50} \leq 3 \mu\text{M}$	$> 3 \mu\text{M}$
Class	A	B	C

NA = Not Applied

[Table 8]

Example No.	H358 cell viability	Example No.	H358 cell viability
-------------	---------------------	-------------	---------------------

1	A	1-68	NA
1-1	A	1-69	NA
1-2	A	1-70	NA
1-3	NA	1-71	NA
1-4	C	1-72	NA
1-5	A	2	A
1-6	C	2-1	A
1-7	A	2-2	NA
1-8	NA	2-3	A
1-9	A	2-4	A
1-10	NA	2-5	A
1-11	A	2-6	A
1-12	A	2-7	C
1-13	NA	3	NA
1-14	NA	3-1	NA
1-15	A	3-2	A
1-16	A	3-3	NA
1-17	A	3-4	NA
1-18	NA	3-5	NA
1-19	NA	4	C
1-20	C	5	NA
1-21	NA	6	A
1-22	A	6-1	NA
1-23	A	6-2	A
1-24	A	6-3	A
1-25	A	6-4	A
1-26	A	6-5	NA
1-27	NA	6-6	NA
1-28	NA	6-7	A
1-29	A	6-8	NA
1-30	NA	6-9	NA
1-31	NA	7	A
1-32	NA	7-1	A
1-33	C	7-2	A
1-34	NA	7-3	A
1-35	NA	7-4	A
1-36	NA	8	NA
1-37	C	9	NA
1-38	NA	10	NA
1-39	A	11	NA
1-40	A	12	NA
1-41	NA	13	NA
1-42	A	14	B
1-43	NA	15	A
1-44	NA	16	NA
1-45	NA	17	NA
1-46	A	18	NA

1-47	NA	19	NA
1-48	NA	20	NA
1-49	NA	20-1	NA
1-50	A	20-2	NA
1-51	NA	20-3	NA
1-52	A	20-4	NA
1-53	A	20-5	NA
1-54	A	20-6	NA
1-55	NA	20-7	NA
1-56	NA	20-8	NA
1-57	NA	20-9	NA
1-58	A	20-10	NA
1-59	NA	20-11	NA
1-60	NA	20-12	NA
1-61	A	21	NA
1-62	A	22	A
1-63	A	23	NA
1-64	B	24	NA
1-65	NA	25	NA
1-66	NA	26	NA
1-67	A		

Experimental Example 4: Evaluation of cancer cell growth inhibition according to combined administration

When the example compound was used in combination with an anticancer agent, the effect on the growth ability of cancer cells expressing KRAS variant or EGFR variant was confirmed. In order to confirm the effect of the example compound in combination with a MEK inhibitor or a KRAS G12C inhibitor in the cell line having the KRAS variant, the cell growth inhibitory effect by the treatment of the example compound in combination with a MEK inhibitor or a KRAS G12C inhibitor was confirmed in the gastric cancer cell line SNU-1 and the pancreatic cancer cell line KP4 having the KRAS G12D variant, the lung cancer cell line NCI-H358 and the pancreatic cancer cell line MIA PaCa-2 having the KRAS G12C variant, the colorectal cancer cell line SW480 having the KRAS G12V variant, the lung cancer cell line A549 having the KRAS G12S variant, the colorectal cancer cell line LoVo having the KRAS G13D variant. In addition, in order to confirm the effect of the example compound in combination with an EGFR inhibitor in the cell line having the EGFR variant, the cell growth inhibitory effect by the treatment of the example compound in combination with an EGFR inhibitor was confirmed in the lung cancer cell line H1975 having the EGFR L858R/T790M variant and the lung cancer cell line HCC827 having the EGFR Del19 variant.

Experimental Example 4.1: Cell dispensing well plate and test solution preparation

The cell line stored in the liquid nitrogen tank was taken out, quickly thawed at 37 °C, then diluted with 10 times the volume of cell culture medium, and centrifuged to remove the frozen storage medium. The recovered cell pellet was mixed well with the culture medium, placed in a culture flask, and cultured under conditions of 37 °C and 5% carbon dioxide to stabilize the cells. Each cell was cultured in RPMI 1640 Medium (1x) or Dulbecco Modified Eagle Medium (DMEM, 1x) medium containing 10% (v/v) FBS and 1% (v/v) penicillin/streptomycin. Thereafter, the cells were obtained from the flask and centrifuged to remove the culture medium, and washed with PBS (Phosphate Buffered Saline), and then centrifuged again to remove the PBS. The cells were diluted with culture medium to 1.25×10^4 cells/mL and dispensed at 40 μ L per well in a 384-well plate. In addition, the cells were diluted with medium to 5×10^4 cells/mL and dispensed at 100 μ L per well in a 96-well plate. Thereafter, the plate onto which the cells were dispensed was cultured for 24 h under conditions of 37 °C and 5% carbon dioxide.

Example 1-2, Example 1-1, Example 2-5, Example 2-4, Example 2-7, Example 1-24, Example 1-8, Example 1-21, Example 1-5, Example 20, Example 21, Example 1-51, Example 6-3, Example 9, Example 1-69 and Example 1-68, and a MEK inhibitor, a KRAS G12C inhibitor and an EGFR inhibitor (INK-128, sotorasib, adagrasib, trametinib, osimertinib, lazertinib, etc.) were each dissolved in 99.5% (v/v) dimethyl sulfoxide (hereinafter, DMSO) to a concentration of 10 mM.

Experimental Example 4.2: Evaluation of cell viability of lung cancer cell NCI-H358 according to combined administration with sotorasib

A well plate in which the lung cancer cell line NCI-H358 having the KRAS G12C variant was dispensed was treated with a test solution of sotorasib and the example compounds.

The cells were treated by adding 10 μ L of a test solution of sotorasib, Example 1-2, Example 1-1 and Example 2-5, respectively, alone or sotorasib in combination with one of Example 1-2, Example 1-1 and Example 2-5 (Combi.) to a 384-well plate so that the final concentration of each substance was 100 nM to 97.7 pM in 50 μ L of the solution per well. In a 96-well plate, the cells were treated by diluting each substance in medium at 3 times the treatment concentration and adding 50 μ L per well so that the final concentration of each substance was 120 nM to 2 nM in 150 μ L of a solution.

The cells treated with the test solution were evaluated in the same manner as in Experimental Example 4.1 to obtain the graph in Figure 1.

Referring to Figure 1, it was confirmed that the cell viability of the lung cancer cell NCI-H358 was decreased when treated with sotorasib and the example compound in combination compared to when treated with sotorasib and the example compound, respectively, alone.

Experimental Example 4.3: Evaluation of cell viability of pancreatic cancer cell MIA PaCa-2 according to combined administration with sotorasib

A well plate in which the pancreatic cancer cell line MIA PaCa-2 having the KRAS G12C variant was dispensed was treated with a test solution of sotorasib and the example compounds.

The cells were treated by adding 10 μ L of a test solution of sotorasib, Example 1-2, Example 1-1 and Example 2-5, respectively, alone or sotorasib in combination with one of Example 1-2, Example 1-1 and Example 2-5 (Combi.) to a 384-well plate so that the final concentration of each substance was 100 nM to 97.7 pM in 50 μ L of the solution per well. In a 96-well plate, the cells were treated by diluting each substance in medium at 3 times the treatment concentration and adding 50 μ L per well so that the final concentration of each substance was 120 nM to 2 nM in 150 μ L of a solution.

The cells treated with the test solution were evaluated in the same manner as in Experimental Example 4.1 to obtain the graph in Figure 2.

Referring to Figure 2, it was confirmed that the cell viability of the pancreatic cancer cell MIA PaCa-2 was decreased when treated with sotorasib and the example compound in combination compared to when treated with sotorasib and the example compound, respectively, alone.

Experimental Example 4.4: Evaluation of cell viability of lung cancer cell NCI-H358 according to combined administration with adagrasib

A well plate in which the lung cancer cell line NCI-H358 having the KRAS G12C variant was dispensed was treated with a test solution of adagrasib and the example compounds.

The cells were treated by adding 10 μ L of a test solution of adagrasib, Example 1-2, Example 1-1 and Example 2-5, respectively, alone or adagrasib in combination with one of Example 1-2, Example 1-1 and Example 2-5 (Combi.) to a 384-well plate so that the final concentration of each substance was 100 nM to 97.7 pM in 50 μ L of the solution per well. In a 96-well plate, the cells were treated by diluting each substance in medium at 3 times the treatment concentration and adding 50 μ L per well so that the final concentration of each substance was 120 nM to 2 nM in 150 μ L of a solution.

The cells treated with the test solution were evaluated in the same manner as in Experimental Example 4.1 to obtain the graph in Figure 3.

Referring to Figure 3, it was confirmed that the cell viability of the lung cancer cell NCI-H358 was decreased when treated with adagrasib and the example compound in combination compared to when treated with adagrasib and the example compound, respectively, alone.

Experimental Example 4.5: Evaluation of cell viability of pancreatic cancer cell MIA PaCa-2 according to combined administration with adagrasib

A well plate in which the pancreatic cancer cell line MIA PaCa-2 having the KRAS G12C variant was dispensed was treated with a test solution of adagrasib and the example compounds.

The cells were treated by adding 10 μ L of a test solution of adagrasib, Example 1-2, Example 1-1 and Example 2-5, respectively, alone or adagrasib in combination with one of Example 1-2, Example 1-1 and Example 2-5 (Combi.) to a 384-well plate so that the final concentration of each substance was 100 nM to 97.7 pM in 50 μ L of the solution per well. In a 96-well plate, the cells were treated by diluting each substance in medium at 3 times the treatment concentration and adding 50 μ L per well so that the final concentration of each substance was 120 nM to 2 nM in 150 μ L of a solution.

The cells treated with the test solution were evaluated in the same manner as in Experimental Example 4.1 to obtain the graph in Figure 4.

Referring to Figure 4, it was confirmed that the cell viability of the pancreatic cancer cell MIA PaCa-2 was decreased when treated with adagrasib and the example compound in combination compared to when treated with adagrasib and the example compound, respectively, alone.

Experimental Example 4.6: Evaluation of cell viability of lung cancer cell NCI-H358 according to combined administration with trametinib

A well plate in which the lung cancer cell line NCI-H358 having the KRAS G12C variant was dispensed was treated with a test solution of trametinib and the example compounds.

The cells were treated by adding 10 μ L of a test solution of trametinib, Example 1-2, Example 1-1, Example 2-5, Example 2-4 and Example 2-7, respectively, alone or trametinib in combination with one of Example 1-2, Example 1-1, Example 2-5, Example 2-4 and Example 2-7 (Combi.) to a 384-well plate so that the final concentration of each substance was 100 nM to 97.7 pM in 50 μ L of the solution per well. In a 96-well plate, the cells were treated by diluting each substance in medium at 3 times the treatment concentration and adding 50 μ L per well so that the final concentration of each substance was 120 nM to 2 nM in 150 μ L of a solution.

The cells treated with the test solution were evaluated in the same manner as in Experimental Example 4.1 to obtain the graphs in Figures 5a and 5b.

Referring to Figures 5a and 5b, it was confirmed that the cell viability of the lung cancer cell NCI-H358 was decreased when treated with trametinib and the example compound in combination compared to when treated with trametinib and the example compound, respectively, alone.

Experimental Example 4.7: Evaluation of cell viability of gastric cancer cell SNU-1 according to combined administration with trametinib

A well plate in which the gastric cancer cell line SNU-1 having the KRAS G12D variant was dispensed was treated with a test solution of trametinib and the example compounds.

The cells were treated by adding 10 μ L of a test solution of trametinib, Example 1-2, Example 1-1, Example 2-5, Example 2-4 and Example 2-7, respectively, alone or trametinib in

combination with one of Example 1-2, Example 1-1, Example 2-5, Example 2-4 and Example 2-7 (Combi.) to a 384-well plate so that the final concentration of each substance was 100 nM to 97.7 pM in 50 μ L of the solution per well. In a 96-well plate, the cells were treated by diluting each substance in medium at 3 times the treatment concentration and adding 50 μ L per well so that the final concentration of each substance was 120 nM to 2 nM in 150 μ L of a solution.

The cells treated with the test solution were evaluated in the same manner as in Experimental Example 4.1 to obtain the graphs in Figures 6a and 6b.

Referring to Figures 6a and 6b, it was confirmed that the cell viability of the gastric cancer cell SNU-1 was decreased when treated with trametinib and the example compound in combination compared to when treated with trametinib and the example compound, respectively, alone.

Experimental Example 4.8: Evaluation of cell viability of colorectal cancer cell SW480 according to combined administration with trametinib

A well plate in which the colorectal cancer cell line SW480 having the KRAS G12V variant was dispensed was treated with a test solution of trametinib and the example compounds.

The cells were treated by adding 10 μ L of a test solution of trametinib, Example 1-2, Example 1-1, Example 2-5, Example 2-4 and Example 2-7, respectively, alone or trametinib in combination with one of Example 1-2, Example 1-1, Example 2-5, Example 2-4 and Example 2-7 (Combi.) to a 384-well plate so that the final concentration of each substance was 100 nM to 97.7 pM in 50 μ L of the solution per well. In a 96-well plate, the cells were treated by diluting each substance in medium at 3 times the treatment concentration and adding 50 μ L per well so that the final concentration of each substance was 120 nM to 2 nM in 150 μ L of a solution.

The cells treated with the test solution were evaluated in the same manner as in Experimental Example 4.1 to obtain the graphs in Figures 7a and 7b.

Referring to Figures 7a and 7b, it was confirmed that the cell viability of the colorectal cancer cell SW480 was decreased when treated with trametinib and the example compound in combination compared to when treated with trametinib and the example compound, respectively, alone.

Experimental Example 4.9: Evaluation of cell viability of lung cancer cell H1975 according to combined administration with osimertinib

A well plate in which the lung cancer cell line H1975 having the EGFR L858R/T790M variant was dispensed was treated with a test solution of osimertinib and the example compounds.

The cells were treated by adding 10 μ L of a test solution of osimertinib, Example 1-2, Example 1-1 and Example 2-5, respectively, alone or osimertinib in combination with one of Example 1-2, Example 1-1 and Example 2-5 (Combi.) to a 384-well plate so that the final concentration of each substance was 100 nM to 97.7 pM in 50 μ L of the solution per well. In a

96-well plate, the cells were treated by diluting each substance in medium at 3 times the treatment concentration and adding 50 μ L per well so that the final concentration of each substance was 120 nM to 2 nM in 150 μ L of a solution.

The cells treated with the test solution were evaluated in the same manner as in Experimental Example 4.1 to obtain the graph in Figure 8.

Referring to Figure 8, it was confirmed that the cell viability of the lung cancer cell H1975 was decreased when treated with osimertinib and the example compound in combination compared to when treated with osimertinib and the example compound, respectively, alone.

Experimental Example 4.10: Evaluation of cell viability of lung cancer cell HCC827 according to combined administration with osimertinib

A well plate in which the lung cancer cell line HCC827 having the EGFR Del19 variant was dispensed was treated with a test solution of osimertinib and the example compounds.

The cells were treated by adding 10 μ L of a test solution of osimertinib, Example 1-2, Example 1-1 and Example 2-5, respectively, alone or osimertinib in combination with one of Example 1-2, Example 1-1 and Example 2-5 (Combi.) to a 384-well plate so that the final concentration of each substance was 100 nM to 97.7 pM in 50 μ L of the solution per well. In a 96-well plate, the cells were treated by diluting each substance in medium at 3 times the treatment concentration and adding 50 μ L per well so that the final concentration of each substance was 120 nM to 2 nM in 150 μ L of a solution.

The cells treated with the test solution were evaluated in the same manner as in Experimental Example 4.1 to obtain the graph in Figure 9.

Referring to Figure 9, it was confirmed that the cell viability of the lung cancer cell HCC827 was decreased when treated with osimertinib and the example compound in combination compared to when treated with osimertinib and the example compound, respectively, alone.

Experimental Example 4.11: Evaluation of cell viability of lung cancer cell H1975 according to combined administration with lazertinib

A well plate in which the lung cancer cell line H1975 having the EGFR L858R/T790M variant was dispensed was treated with a test solution of lazertinib and the example compounds.

The cells were treated by adding 10 μ L of a test solution of lazertinib, Example 1-2, Example 1-1 and Example 2-5, respectively, alone or lazertinib in combination with one of Example 1-2, Example 1-1 and Example 2-5 (Combi.) to a 384-well plate so that the final concentration of each substance was 100 nM to 97.7 pM in 50 μ L of the solution per well. In a 96-well plate, the cells were treated by diluting each substance in medium at 3 times the treatment concentration and adding 50 μ L per well so that the final concentration of each substance was 120 nM to 2 nM in 150 μ L of a solution.

The cells treated with the test solution were evaluated in the same manner as in Experimental Example 4.1 to obtain the graph in Figure 10.

Referring to Figure 10, it was confirmed that the cell viability of the lung cancer cell H1975 was decreased when treated with lazertinib and the example compound in combination compared to when treated with lazertinib and the example compound, respectively, alone.

Experimental Example 4.12: Evaluation of cell viability of lung cancer cell HCC827 according to combined administration with lazertinib

A well plate in which the lung cancer cell line HCC827 having the EGFR Del19 variant was dispensed was treated with a test solution of lazertinib and the example compounds.

The cells were treated by adding 10 μ L of a test solution of lazertinib, Example 1-2, Example 1-1 and Example 2-5, respectively, alone or lazertinib in combination with one of Example 1-2, Example 1-1 and Example 2-5 (Combi.) to a 384-well plate so that the final concentration of each substance was 100 nM to 97.7 pM in 50 μ L of the solution per well. In a 96-well plate, the cells were treated by diluting each substance in medium at 3 times the treatment concentration and adding 50 μ L per well so that the final concentration of each substance was 120 nM to 2 nM in 150 μ L of a solution.

The cells treated with the test solution were evaluated in the same manner as in Experimental Example 4.1 to obtain the graph in Figure 11.

Referring to Figure 11, it was confirmed that the cell viability of the lung cancer cell HCC827 was decreased when treated with lazertinib and the example compound in combination compared to when treated with lazertinib and the example compound, respectively, alone.

Experimental Example 4.13: Evaluation of cell viability of breast cancer cell MCF7 according to combined administration with alpelisib

A well plate in which PIK3CA mutant breast cancer cell line MCF7 was dispensed was treated with a test solution of alpelisib and the example compounds.

The cells were treated by adding 10 μ L of a test solution of alpelisib, Example 1-2, Example 2-5, Example 1-24, Example 1-8 and Example 1-21, respectively, alone or alpelisib in combination with one of Example 1-2, Example 2-5, Example 1-24, Example 1-8 and Example 1-21 (Combi.) to a 384-well plate so that the final concentration of each substance was 100 nM to 97.7 pM in 50 μ L of the solution per well.

The cells treated with the test solution were cultured under conditions of 37 °C and 5% carbon dioxide for 72 h. Thereafter, the plate with the cells cultured was adapted to room temperature for 30 minutes. Then, in order to quantify cytotoxicity, 50 μ L of Cell Titer-Glo Reagent (CTG, Promega), which measures the amount of ATP, was dispensed per well into a 384-well plate. Cell lysis was induced by mixing the contents for 2 minutes, the luminescence signal was stabilized for 10 minutes, and then the luminescence intensity was measured using a Varioskan™ LUX microplate reader. The cell viability in the well treated with each

compound was calculated when the final value of the well not treated with the test substance was set to 100%.

Referring to Figure 12, it was confirmed that the cell viability of the breast cancer cell MCF7 was decreased when treated with alpelisib and the example compound in combination compared to when treated with alpelisib and the example compound, respectively, alone.

Experimental Example 4.14: Evaluation of cell viability of lung cancer cell H358 according to combined administration with JDQ443

A well plate in which the lung cancer cell line H358 having the KRAS G12C variant was dispensed was treated with a test solution of JDQ443 and the example compounds.

The cells were treated by adding 10 μ L of a test solution of JDQ443 and Example 1-2, respectively, alone or JDQ443 in combination with Example 1-2 (Combi.) to a 384-well plate so that the final concentration of JDQ443 was 100 nM to 6.1 pM and the final concentration of Example 1-2 was 30 μ M to 13.7 nM in 50 μ L of the solution per well.

The cells treated with the test solution were evaluated in the same manner as in Experimental Example 4.13 to obtain the graph in Figure 13.

Referring to Figure 13, it was confirmed that the cell viability of the lung cancer cell H358 was decreased when treated with JDQ443 and the example compound in combination compared to when treated with JDQ443 and the example compound, respectively, alone.

Experimental Example 4.15: Evaluation of cell viability of lung cancer cell H358 according to combined administration with TNO155

A well plate in which the lung cancer cell line H358 having the KRAS G12C variant was dispensed was treated with a test solution of TNO155 and the example compounds.

The cells were treated by adding 10 μ L of a test solution of TNO155, Example 1-2 and Example 1-5, respectively, alone or TNO155 in combination with one of Example 1-2 and Example 1-5 (Combi.) to a 384-well plate so that the final concentration of each substance was 10 μ M to 41.1 nM in 50 μ L of the solution per well.

The cells treated with the test solution were evaluated in the same manner as in Experimental Example 4.13 to obtain the graph in Figure 14.

Referring to Figure 14, it was confirmed that the cell viability of the lung cancer cell H358 was decreased when treated with TNO155 and the example compound in combination compared to when treated with TNO155 and the example compound, respectively, alone.

Experimental Example 4.16: Evaluation of cell viability of lung cancer cell H358 according to combined administration with cisplatin

A well plate in which the lung cancer cell line H358 having the KRAS G12C variant was dispensed was treated with a test solution of cisplatin and the example compounds.

The cells were treated by adding 10 μ L of a test solution of cisplatin, Example 1-2 and Example 1-5, respectively, alone or cisplatin in combination with one of Example 1-2 and

Example 1-5 (Combi.) to a 384-well plate so that the final concentration of each substance was 5 μ M to 156 nM in 50 μ L of the solution per well.

The cells treated with the test solution were evaluated in the same manner as in Experimental Example 4.13 to obtain the graph in Figure 15.

Referring to Figure 15, it was confirmed that the cell viability of the lung cancer cell H358 was decreased when treated with cisplatin and the example compound in combination compared to when treated with cisplatin and the example compound, respectively, alone.

Experimental Example 4.17: Evaluation of cell viability of lung cancer cell H358 according to combined administration with rineterkib

A well plate in which the lung cancer cell line H358 having the KRAS G12C variant was dispensed was treated with a test solution of rineterkib and the example compounds.

The cells were treated by adding 10 μ L of a test solution of rineterkib, Example 1-2 and Example 1-5, respectively, alone or rineterkib in combination with one of Example 1-2 and Example 1-5 (Combi.) to a 384-well plate so that the final concentration of each substance was 1 μ M to 31.3 nM in 50 μ L of the solution per well.

The cells treated with the test solution were evaluated in the same manner as in Experimental Example 4.13 to obtain the graph in Figure 16.

Referring to Figure 16, it was confirmed that the cell viability of the lung cancer cell H358 was decreased when treated with rineterkib and the example compound in combination compared to when treated with rineterkib and the example compound, respectively, alone.

Experimental Example 4.18: Evaluation of cell viability of lung cancer cell H358 according to combined administration with ulixertinib

A well plate in which the lung cancer cell line H358 having the KRAS G12C variant was dispensed was treated with a test solution of ulixertinib and the example compounds.

The cells were treated by adding 10 μ L of a test solution of ulixertinib, Example 1-2 and Example 1-5, respectively, alone or ulixertinib in combination with one of Example 1-2 and Example 1-5 (Combi.) to a 384-well plate so that the final concentration of each substance was 1 μ M to 31.3 nM in 50 μ L of the solution per well.

The cells treated with the test solution were evaluated in the same manner as in Experimental Example 4.13 to obtain the graph in Figure 17.

Referring to Figure 17, it was confirmed that the cell viability of the lung cancer cell H358 was decreased when treated with ulixertinib and the example compound in combination compared to when treated with ulixertinib and the example compound, respectively, alone.

Experimental Example 4.19: Evaluation of cell viability of lung cancer cell H358 according to combined administration with pralsetinib

A well plate in which the lung cancer cell line H358 having the KRAS G12C variant was dispensed was treated with a test solution of pralsetinib and the example compounds.

The cells were treated by adding 10 μ L of a test solution of pralsetinib, Example 1-2 and Example 1-5, respectively, alone or pralsetinib in combination with one of Example 1-2 and Example 1-5 (Combi.) to a 384-well plate so that the final concentration of each substance was 1 μ M to 31.3 nM in 50 μ L of the solution per well.

The cells treated with the test solution were evaluated in the same manner as in Experimental Example 4.13 to obtain the graph in Figure 18.

Referring to Figure 18, it was confirmed that the cell viability of the lung cancer cell H358 was decreased when treated with pralsetinib and the example compound in combination compared to when treated with pralsetinib and the example compound, respectively, alone.

Experimental Example 4.20: Evaluation of cell viability of lung cancer cell H358 according to combined administration with repotrectinib

A well plate in which the lung cancer cell line H358 having the KRAS G12C variant was dispensed was treated with a test solution of repotrectinib and the example compounds.

The cells were treated by adding 10 μ L of a test solution of repotrectinib, Example 1-2 and Example 1-5, respectively, alone or repotrectinib in combination with one of Example 1-2 and Example 1-5 (Combi.) to a 384-well plate so that the final concentration of each substance was 1 μ M to 31.3 nM in 50 μ L of the solution per well.

The cells treated with the test solution were evaluated in the same manner as in Experimental Example 4.13 to obtain the graph in Figure 19.

Referring to Figure 19, it was confirmed that the cell viability of the lung cancer cell H358 was decreased when treated with repotrectinib and the example compound in combination compared to when treated with repotrectinib and the example compound, respectively, alone.

Experimental Example 4.21: Evaluation of cell viability of gastric cancer cell SNU-5 according to combined administration with tepotinib

A well plate in which the c-Met overexpressing gastric cancer cell line SNU-5 was dispensed was treated with a test solution of tepotinib and the example compounds.

The cells were treated by adding 10 μ L of a test solution of tepotinib and Example 1-2, respectively, alone or tepotinib in combination with Example 1-2 (Combi.) to a 384-well plate so that the final concentration of each substance was 10 μ M to 9.77 nM in 50 μ L of the solution per well.

The cells treated with the test solution were evaluated in the same manner as in Experimental Example 4.13 to obtain the graph in Figure 20.

Referring to Figure 20, it was confirmed that the cell viability of the gastric cancer cell SNU-5 was decreased when treated with tepotinib and the example compound in combination compared to when treated with tepotinib and the example compound, respectively, alone.

Experimental Example 4.22: Evaluation of cell viability of lung cancer cell PC-9 according to combined administration with bemcentinib

A well plate in which the lung cancer cell line PC-9 with high AXL expression was dispensed was treated with a test solution of bemcentinib and the example compounds.

The cells were treated by adding 10 μ L of a test solution of bemcentinib and Example 1-2, respectively, alone or bemcentinib in combination with Example 1-2 (Combi.) to a 384-well plate so that the final concentration of each substance was 10 μ M to 9.77 nM in 50 μ L of the solution per well.

The cells treated with the test solution were evaluated in the same manner as in Experimental Example 4.13 to obtain the graph in Figure 21.

Referring to Figure 21, it was confirmed that the cell viability of the lung cancer cell PC-9 was decreased when treated with bemcentinib and the example compound in combination compared to when treated with bemcentinib and the example compound, respectively, alone.

Experimental Example 4.23: Evaluation of cell viability of lung cancer cell A549 according to combined administration with alrizomadlin

A well plate in which the lung cancer cell line A549 having the KRAS G12S variant was dispensed was treated with a test solution of alrizomadlin and the example compounds.

The cells were treated by adding 10 μ L of a test solution of alrizomadlin and Example 1-2, respectively, alone or alrizomadlin in combination with Example 1-2 (Combi.) to a 384-well plate so that the final concentration of each substance was 10 μ M to 9.77 nM in 50 μ L of the solution per well.

The cells treated with the test solution were evaluated in the same manner as in Experimental Example 4.13 to obtain the graph in Figure 22.

Referring to Figure 22, it was confirmed that the cell viability of the lung cancer cell A549 was decreased when treated with alrizomadlin and the example compound in combination compared to when treated with alrizomadlin and the example compound, respectively, alone.

Experimental Example 4.24: Evaluation of cell viability of colorectal cancer cell LoVo according to combined administration with everolimus

A well plate in which the colorectal cancer cell line LoVo having the KRAS G13D variant was dispensed was treated with a test solution of everolimus and the example compounds.

The cells were treated by adding 10 μ L of a test solution of everolimus and Example 1-2, respectively, alone or everolimus in combination with Example 1-2 (Combi.) to a 384-well plate so that the final concentration of each substance was 10 μ M to 9.77 nM in 50 μ L of the solution per well.

The cells treated with the test solution were evaluated in the same manner as in Experimental Example 4.13 to obtain the graph in Figure 23.

Referring to Figure 23, it was confirmed that the cell viability of the colorectal cancer cell LoVo was decreased when treated with everolimus and the example compound in

combination compared to when treated with everolimus and the example compound, respectively, alone.

Experimental Example 4.25: Evaluation of cell viability of lung cancer cell AsPC-1 according to combined administration with MRTX1133

A well plate in which the lung cancer cell line AsPC-1 having the KRAS G12D variant was dispensed was treated with a test solution of MRTX1133 and the example compounds.

The cells were treated by adding 50 μ L of a test solution of MRTX1133, Example 1-2 and Example 1-5, respectively, alone or MRTX1133 in combination with one of Example 1-2 and Example 1-5 (Combi.) to a 96-well plate so that the final concentration of MRTX1133 was 100 nM to 20 nM and the final concentration of the example compound was 5 μ M in 150 μ L of the solution per well.

The cells treated with the test solution were evaluated and the cell viability of a well treated with test solution alone or in combination was evaluated in the same manner as in Experimental Example 4.1 to obtain the graph in Figure 24.

Referring to Figure 24, it was confirmed that the cell viability of the lung cancer cell AsPC-1 was decreased when treated with MRTX1133 and the example compound in combination compared to when treated with MRTX1133 and the example compound, respectively, alone.

Experimental Example 5.1: Determination of combination concentration by SynergyScreen™

The cells were treated by adding 5 μ L of a test solution of Example 1-2 per well to a 384 well plate in which the lung cancer cell line H358 having the KRAS G12S variant was dispensed so that the final concentration of the substance was 31.6 μ M to 0.00316 μ M in 50 μ L of the solution per well. The cells treated with Example 1-2 were cultured under conditions of 37 °C and 5% carbon dioxide for 72 h or 120 h. In order to measure cell viability, each well was treated with 24 μ L of ATPlite 1Step™ (PerkinElmer) solution, then mixed for 2 minutes, and reacted by blocking light for 5 minutes, and then the luminescence signal was measured using an Envision multilabel reader (PerkinElmer). The cell viability was determined according to the formula below, and the concentration (EFFECT₂₀) of Example 1-2 that induces 20% cell death was calculated using IDBS XLfit 5. The EFFECT₂₀ concentration of Example 1-2 determined through the experiment was applied as the final treatment concentration of Example 1-2 during the combination effect experiment.

% growth= 100% x (luminescence treated wells, t=end / luminescence of untreated wells, t=end).

Experimental Example 5.2: Evaluation of combination efficacy by SynergyScreen™

In order to confirm the effect of Example 1-2 in combination with various anticancer agents, a total of 42 anticancer agents, including cytotoxic anticancer agents and targeted anticancer agents, were used for evaluation (Table 9). A 384 well plate in which the lung cancer cell line H358 having the KRAS G12S variant was dispensed was treated with Example 1-2 at a final concentration of 1854 nM when the culture time was 72 h and was treated with Example 1-2 at a final concentration of 652 nM when the culture time was 120 h, respectively. After treatment of Example 1-2, the plate was treated with the combined anticancer agent so that the final concentration of each substance was 31.6 μ M to 0.00316 μ M in 50 μ L of the solution per well. The cells treated with the test solution were cultured under conditions of 37 °C and 5% carbon dioxide for the culture time indicated in Table 9. In order to measure cell viability, each well was treated with 24 μ L of ATPlite 1Step™ (PerkinElmer) solution, then mixed for 2 minutes, and reacted by blocking light for 5 minutes, and then the luminescence signal was measured using an Envision multilabel reader (PerkinElmer). The cell viability was determined in the same manner as in Experimental Example 4.1, and the effect of the combination treatment was evaluated by comparing the cell viability of the group treated with the combined anticancer agent or Example 1-2 alone with the cell viability of the combined treatment.

Synergy 1 (Equation 1) was determined from the decrease in cell viability (%) (increase in cell death) when used in combination with Example 1-2 compared to the cell viability (%) when the combined anticancer agent was used alone, and Synergy 2 (Equation 2) was determined to be the difference between Synergy 1 and cell death rate (%) when Example 1-2 was used alone.

[Equation 1]

Synergy 1 (%) = cell viability (%) when the combined anticancer agent is used alone - cell viability (%) when used in combination with the example compound

[Equation 2]

Synergy 2 (%) = Synergy 1 (%) - cell death rate (%) when the example compound is used alone

If the synergy by treatment with Example 1-2 in combination compared to the combined anticancer agent alone is 50% or more, it is indicated as "++++", if it is less than 50% and more than 30%, it is indicated as "+++", if it is less than 30% and more than 10%, it is indicated as "++", and if it is less than 10%, it is indicated as "+". The results are shown in Figures 25a to 26c.

[Table 9]

No	Anticancer agent	Target/ Mechanism	Culture time (h)	Concentration (log M)		Synergy 1	Synergy 2
				Anticancer agent	Ex. 1-2		

1	Paclitaxel	Taxane derivatives	72	-9.0	-5.9	++	++
2	Cytarabine	Antimetabolite	72	-8.5	-5.9	++	-
3	Palbociclib	CDK4/6 inhibition	72	-8.5	-5.9	++	-
4	Nintedanib	Inhibition of angiogenesis or FGFR1/FGFR2/FGFR3 inhibition	72	-6.0	-5.9	++	++
5	Regorafenib	Inhibition of angiogenesis	72	-8.5	-5.9	++	+
6	SN-38	TOP1 inhibition	72	-10.5	-5.9	++	-
7	Doxorubicin	TOP2 inhibition	72	-9.0	-5.9	++++	++
8	Niraparib	PARP inhibition	72	-8.5	-5.9	++	-
9	JQ1	BET inhibition	120	-8.5	-6.3	++	-
10	NVP-ADW742	IGF1/2 or IGF1-R inhibition	72	-8.5	-5.9	++	-
11	duvelisib	PIK inhibition	72	-7.0	-5.9	++	+
12	Gefitinib	EGFR inhibition	72	-7.0	-5.9	+++	++
13	Irbinitinib (tucatinib)	ErbB2(HER2) inhibition	72	-6.5	-5.9	++	++
14	Neratinib	HER2, EGFR inhibition	72	-9.0	-5.9	+++	++
15	Alectinib	ALK inhibition	72	-6.0	-5.9	++	-
16	Cobimetinib	MEK inhibition	72	-8.0	-5.9	+++	++
17	Imatinib	BCR-ABL inhibition	72	-8.5	-5.9	++	+
18	Dasatinib		72	-8.0	-5.9	+++	++
19	Dabrafenib	mutBRAF inhibition	72	-8.5	-5.9	++	+
20	Sorafenib	pan-RAF	72	-8.5	-5.9	++	+

21	AT-7519	CDK9 inhibition	72	-8.5	-5.9	++	-
22	danusertib	pan Aurora	72	-7.0	-5.9	+++	+
23	ibrutinib	BTK	72	-8.0	-5.9	+++	+
24	MK-1775	WEE1	72	-7.0	-5.9	++	++
25	methotrexate	DHFR	72	-7.5	-5.9	++	+++
26	AMG-900	pan Aurora	72	-8.0	-5.9	+++	++
27	BIIB021	HSP90	72	-9.5	-5.9	+++	+
28	6-thioguanine	purine antimetabolite	72	-7.0	-5.9	+++	+
29	reversine	A3AR antagonism, pan-aurora inhibition	120	-8.0	-6.3	++	+
30	MLN-7243	ubiquitin E1 enzyme	120	-7.5	-6.3	++	+
31	ABT-737	Bcl-2	72	-7.0	-5.9	+++	++
32	MK-5108	Aurora A	72	-7.5	-5.9	++	++
33	GSK-343	EZH2/ARID1A	120	-8.5	-6.3	++	-
34	2-D08	SUMOylation	120	-6.0	-6.3	+++	+
35	SCH-900776	CHK1	72	-7.5	-5.9	++	+
36	entinostat	HDAC1, HDAC3	72	-7.5	-5.9	++	-
37	ruxolitinib	JAK1/2	72	-6.0	-5.9	++	+
38	carfilzomib	proteasome	72	-9.0	-5.9	++	-
39	apitolisib	PI3K $\alpha/\beta/\delta/\gamma$	72	-8.5	-5.9	+++	+
40	ipatasertib	AKT	72	-8.0	-5.9	++	+
41	prednisolone	GR	72	No Concentration-dependent change	-5.9	NA	NA
42	volasertib	PLK1	72	-8.0	-5.9	++	-

Referring to Table 9 and Figures 25a to 26c, when the conventional anticancer agent and the example compound were used in combination, the cell death rate was higher than the simple sum of the cell death rates when the conventional anticancer agent and the example compound were used alone. That is, the example compound can exhibit synergistic anticancer activity when used in combination with an anticancer agent.

It should be understood that any feature, property, compound, compound moiety, or number described in connection with a particular aspect, embodiment, or example of the present invention is applicable to any other aspect, embodiment, or example described herein, as appropriate. All features, or individual steps of a method or process disclosed herein can be arbitrarily combined, except where such features and/or steps constitute a mutually exclusive combination.

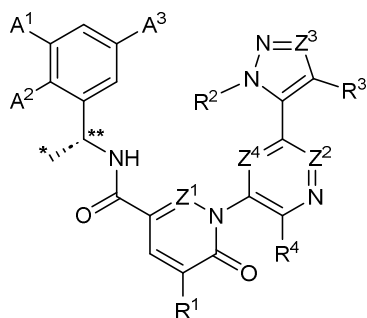
Although specific embodiments of the present invention have been described herein, the present invention is not limited to the described embodiments, and it should be understood that it is intended to cover any equivalents, modifications or uses of known or customary techniques by those skilled in the art based on the disclosure herein.

Claims

[Claim 1]

A compound represented by Formula I below, or a solvate, stereoisomer or pharmaceutically acceptable salt thereof:

[Formula I]



in Formula I,

Z¹ and Z³ are each independently N or CH;

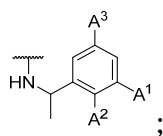
Z² is N or CR^a, and Z⁴ is CH; or

Z² is CR^a, and Z⁴ is N; and

R^a is H, halogen, OH, CN, substituted or unsubstituted C₁-C₆ alkoxy, amino, substituted or unsubstituted C₁-C₆ alkylamino, substituted or unsubstituted di(C₁-C₆ alkyl)amino, substituted or unsubstituted C₁-C₆ thioalkoxy, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted partially unsaturated or saturated C₃-C₇ cycloalkyl, or a 4- to 7-membered heterocyclyl containing 1 or 2 heteroatoms selected from N, O and S;

R¹ is H; D; halogen; OH; CN; C₁-C₆ alkyl optionally substituted with one or more of deuterium, OH, oxo (=O) or halogen; -NR^AR^B; -OR^A; partially unsaturated or saturated C₃-C₇ cycloalkyl; optionally substituted C₆-C₁₀ aryl; optionally substituted 5- to 10-membered

heteroaryl; or



R^A and R^B are each independently H or C₁-C₆ alkyl optionally substituted with R^a;

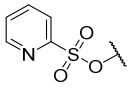
R² is H; C₁-C₆ alkyl optionally substituted with one or more of deuterium, OH, C₁-C₆ alkoxy or halogen; a 4- to 7-membered heterocyclyl containing 1 or 2 heteroatoms selected from N, O and S, optionally substituted with one or more R^{21a}; or partially unsaturated or saturated C₃-C₇ cycloalkyl optionally substituted with one or more R^{21b};

R^{21a} and R^{21b} are each independently C₁-C₆ alkyl optionally substituted with one or more of halogen, CN, OH, C₁-C₆ alkoxy, carboxy or oxo; C₁-C₆ acyl; carboxy; C₁-C₆ alkoxycarbonyl; or C₁-C₆ alkylsulfonyl;

R³ is H, halogen, OH, C₁-C₆ alkoxy, NH₂, C₁-C₆ alkylamino, di(C₁-C₆ alkyl)amino, NO₂ or CN;

R⁴ is H, halogen, OH, C₁-C₆ alkoxy, NH₂, C₁-C₆ alkylamino, di(C₁-C₆ alkyl)amino, NO₂ or CN;

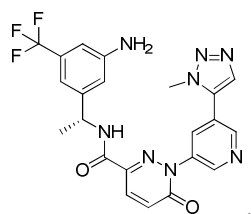
A¹ is C₁-C₆ alkyl substituted with one or more substituents independently selected

from the group consisting of deuterium, halogen, OH, C₁-C₃ alkoxy,  and C₁-C₃ alkyl; or partially unsaturated or saturated C₃-C₇ cycloalkyl; wherein said one or more substituents may be bonded to the same or different carbons, and two C₁-C₃ alkyl groups bonded to the same carbon atom may be optionally taken together with the carbon atom to which they are attached to form a C₃-C₄ cyclic ring;

A² is H, halogen, OH, CN or C₁-C₆ alkyl;

A³ is H, amino, C₁-C₆ alkylamino or di(C₁-C₆ alkyl)amino; and

the carbon atoms marked with * and ** are optionally substituted with one or more deuterium atoms; with the proviso that the compound represented by Formula I is not



[Claim 2]

The compound, or solvate, stereoisomer or pharmaceutically acceptable salt thereof according to claim 1, wherein

one or more of R¹, R² and A¹ comprise deuterium; and/or

one or more of the carbon atoms marked with * and ** are substituted with deuterium.

[Claim 3]

The compound, or solvate, stereoisomer or pharmaceutically acceptable salt thereof according to claim 1, wherein Z⁴ is CH.

[Claim 4]

The compound, or solvate, stereoisomer or pharmaceutically acceptable salt thereof according to claim 3, wherein

Z² is CR^a, and

R^a and R⁴ are both H; or

R^a is halogen, OH, CN, C₁-C₆ alkoxy, amino, C₁-C₆ alkylamino, di(C₁-C₆ alkyl)amino, C₁-C₆ alkyl, partially unsaturated or saturated C₃-C₇ cycloalkyl, or a 4- to 6-membered heterocyclyl containing 1 or 2 heteroatoms selected from N and O, and R⁴ is H or halogen; or

R^a is H, and R⁴ is halogen.

[Claim 5]

The compound, or solvate, stereoisomer or pharmaceutically acceptable salt thereof according to claim 4, wherein

R^a is H, F, $-NHCH_3$, $-N(CH_3)_2$, $-OCH_3$, $-CH_3$ or , and R^4 is H or F.

[Claim 6]

The compound, or solvate, stereoisomer or pharmaceutically acceptable salt thereof according to claim 1, wherein

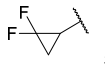
R^2 is a 4- to 6-membered heterocyclyl containing 1 or 2 heteroatoms selected from N and O, optionally substituted with one or more R^{21a} ; or partially unsaturated or saturated C_3 - C_7 cycloalkyl optionally substituted with one or more R^{21b} ; and/or

R^3 is halogen, and

R^{21a} is C_1 - C_4 alkyl optionally substituted with one or more of OH, C_1 - C_4 alkoxy or oxo; C_1 - C_4 acyl; C_1 - C_4 alkoxycarbonyl; or C_1 - C_4 alkylsulfonyl, and R^{21b} is halogen.

[Claim 7]

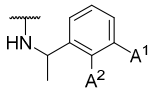
The compound, or solvate, stereoisomer or pharmaceutically acceptable salt thereof according to claim 1, wherein

R^2 is $-CH_3$, $-CD_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2OH$, cyclopropyl, , cyclobutyl, , , , , , , , , , , , , , , , or , and R^3 is H or Cl.

[Claim 8]

The compound, or solvate, stereoisomer or pharmaceutically acceptable salt thereof according to claim 1, wherein

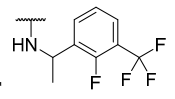
R^1 is H; D; halogen; CN; C_1 - C_6 alkyl optionally substituted with one or more of deuterium, OH, oxo ($=O$) or halogen; partially unsaturated or saturated C_3 - C_7 cycloalkyl; C_6 -

C_{10} aryl; or .

[Claim 9]

The compound, or solvate, stereoisomer or pharmaceutically acceptable salt thereof according to claim 8, wherein

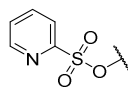
R^1 is H, D, F, Br, Cl, CN, methyl, ethyl, CD_3 , CF_3 , $-CH_2OH$, $-CH(OH)CH_3$, $-C(OH)(CH_3)_2$, $-C(=O)CH_3$, cyclopropyl, cyclohexyl, cyclohexenyl, phenyl, or



[Claim 10]

The compound, or solvate, stereoisomer or pharmaceutically acceptable salt thereof according to claim 1, wherein

A^1 is C_1 - C_6 alkyl substituted with two or more substituents independently selected

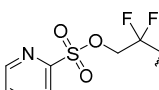
from the group consisting of deuterium, halogen, OH, C_1 - C_3 alkoxy,  and C_1 - C_3 alkyl; or partially unsaturated or saturated C_3 - C_7 cycloalkyl; wherein said two C_1 - C_3 alkyl groups, when bonded to the same carbon atom, are taken together with the carbon atom to which they are attached to form a C_3 - C_4 cyclic ring,

A^2 is H, halogen or C_1 - C_4 alkyl, and

A^3 is H or amino.

[Claim 11]

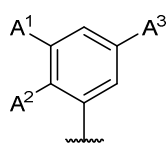
The compound, or solvate, stereoisomer or pharmaceutically acceptable salt thereof according to claim 10, wherein

A^1 is selected from the group consisting of $-CHF_2$, $-CF_3$, $-CF_2CH_3$, $-CF_2CH_2F$, $-CF_2CH_2OH$, $-CF_2CD_2OH$, $-CF_2CH_2OCH_3$, , , , ,  and cyclobutenyl; and

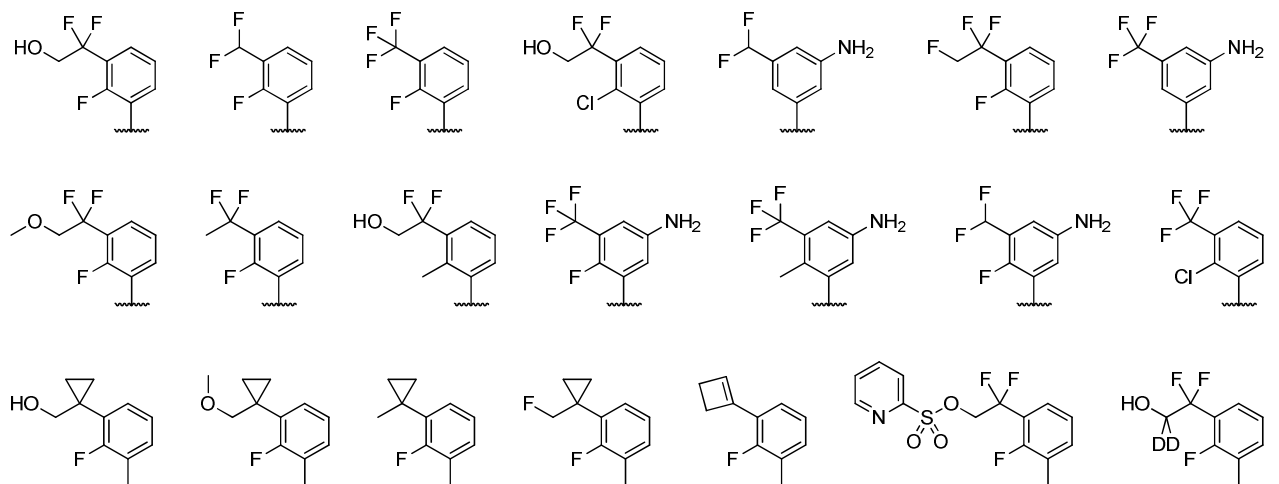
A^2 is H, F, Cl or $-CH_3$.

[Claim 12]

The compound, or solvate, stereoisomer or pharmaceutically acceptable salt thereof according to claim 1, wherein



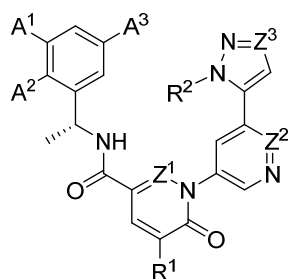
of Formula I is selected from the following structures:



[Claim 13]

The compound, or solvate, stereoisomer or pharmaceutically acceptable salt thereof according to claim 1, wherein the compound is a compound represented by Formula I-1 below:

[Formula I-1]



in Formula I-1,

Z^1 and Z^3 are each independently N or CH;

Z^2 is N or CR^a ;

R^a is H, halogen, OH, CN, substituted or unsubstituted C_1 - C_6 alkoxy, substituted or unsubstituted C_1 - C_6 alkylamino, substituted or unsubstituted C_1 - C_6 thioalkoxy, or substituted or unsubstituted C_1 - C_6 alkyl;

R^1 is H, halogen, OH, CN, C_1 - C_6 alkyl optionally substituted with one or more deuterium or halogen, $-NR^A R^B$, $-OR^A$, C_3 - C_6 cycloalkyl, optionally substituted C_6 - C_{10} aryl, or optionally substituted 5- to 10-membered heteroaryl;

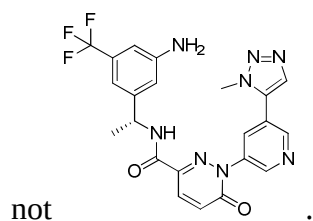
R^A and R^B are each independently C_1 - C_6 alkyl optionally substituted with R^a ;

R^2 is H, or C_1 - C_6 alkyl optionally substituted with one or more of deuterium or halogen;

A^1 is C_1 - C_6 alkyl substituted with one or more substituents independently selected from the group consisting of halogen, OH, C_1 - C_3 alkoxy and C_1 - C_3 alkyl, wherein said one or more substituents may be bonded to the same or different carbons, and two C_1 - C_3 alkyl groups bonded to the same carbon atom may be optionally taken together with the carbon atom to which they are attached to form a C_3 - C_4 cyclic ring;

A^2 is H, halogen, OH, CN or C_1 - C_6 alkyl; and

A³ is H or amino, with the proviso that the compound represented by Formula I-1 is



[Claim 14]

The compound, or solvate, stereoisomer or pharmaceutically acceptable salt thereof according to claim 13, wherein

Z¹ is N, and Z² is CH, and Z³ is N or CH; or

Z¹ and Z² are both CH, and Z³ is N; or

Z¹ and Z² are both N, and Z³ is N or CH.

[Claim 15]

The compound, or solvate, stereoisomer or pharmaceutically acceptable salt thereof according to claim 13, wherein

R¹ is H, halogen, CN, C₁-C₃ alkyl or C₃-C₅ cycloalkyl; and

R² is C₁-C₃ alkyl optionally substituted with one or more deuterium.

[Claim 16]

The compound, or solvate, stereoisomer or pharmaceutically acceptable salt thereof according to claim 13, wherein

A¹ is C₁-C₃ alkyl substituted with two or more substituents independently selected from the group consisting of F, OH and methoxy;

A² is H, halogen or C₁-C₃ alkyl, and

A³ is H.

[Claim 17]

The compound, or solvate, stereoisomer or pharmaceutically acceptable salt thereof according to claim 13, wherein

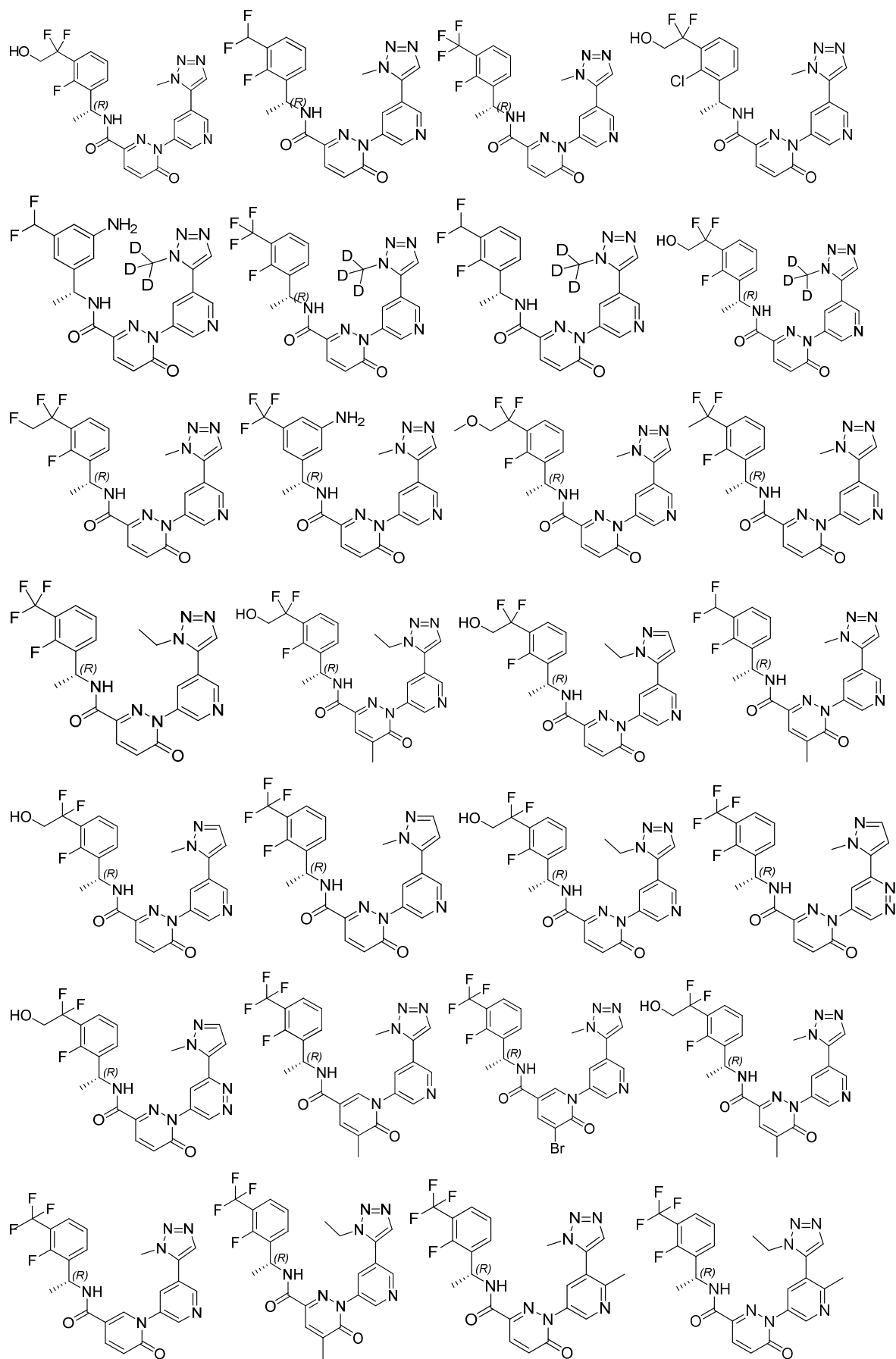
A¹ is C₁-C₃ alkyl substituted with two or more F,

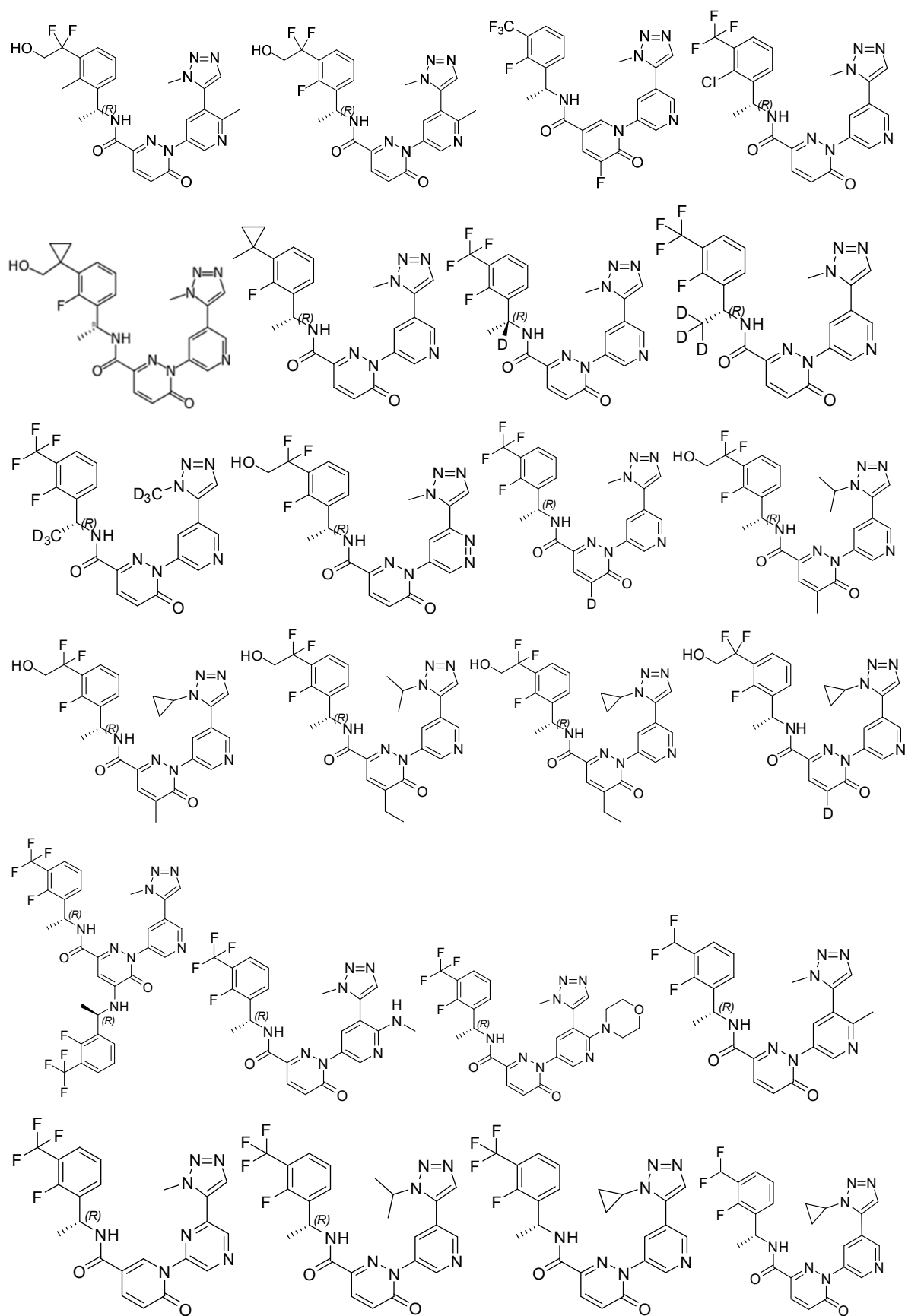
A² is H, halogen or C₁-C₃ alkyl, and

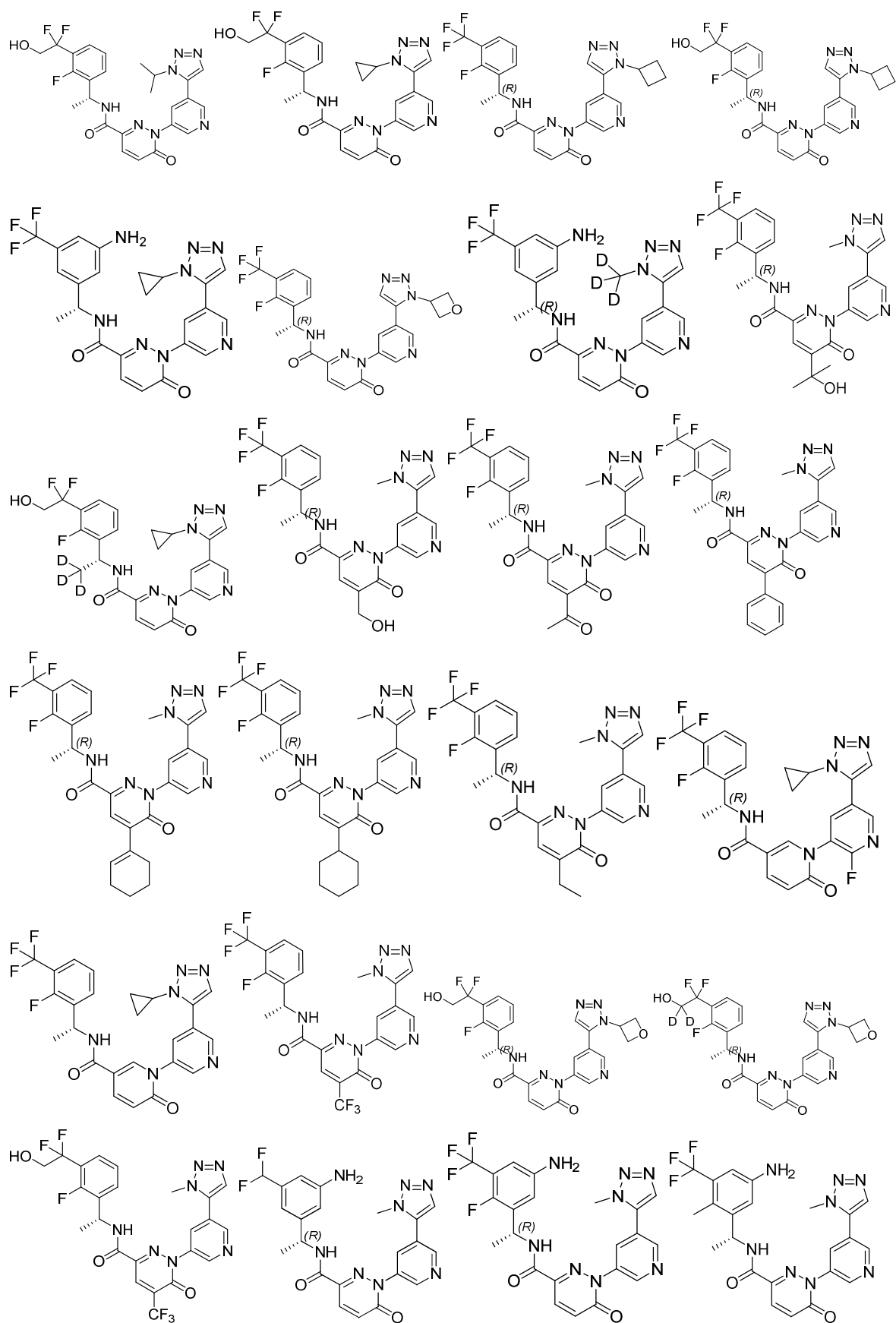
A³ is amino.

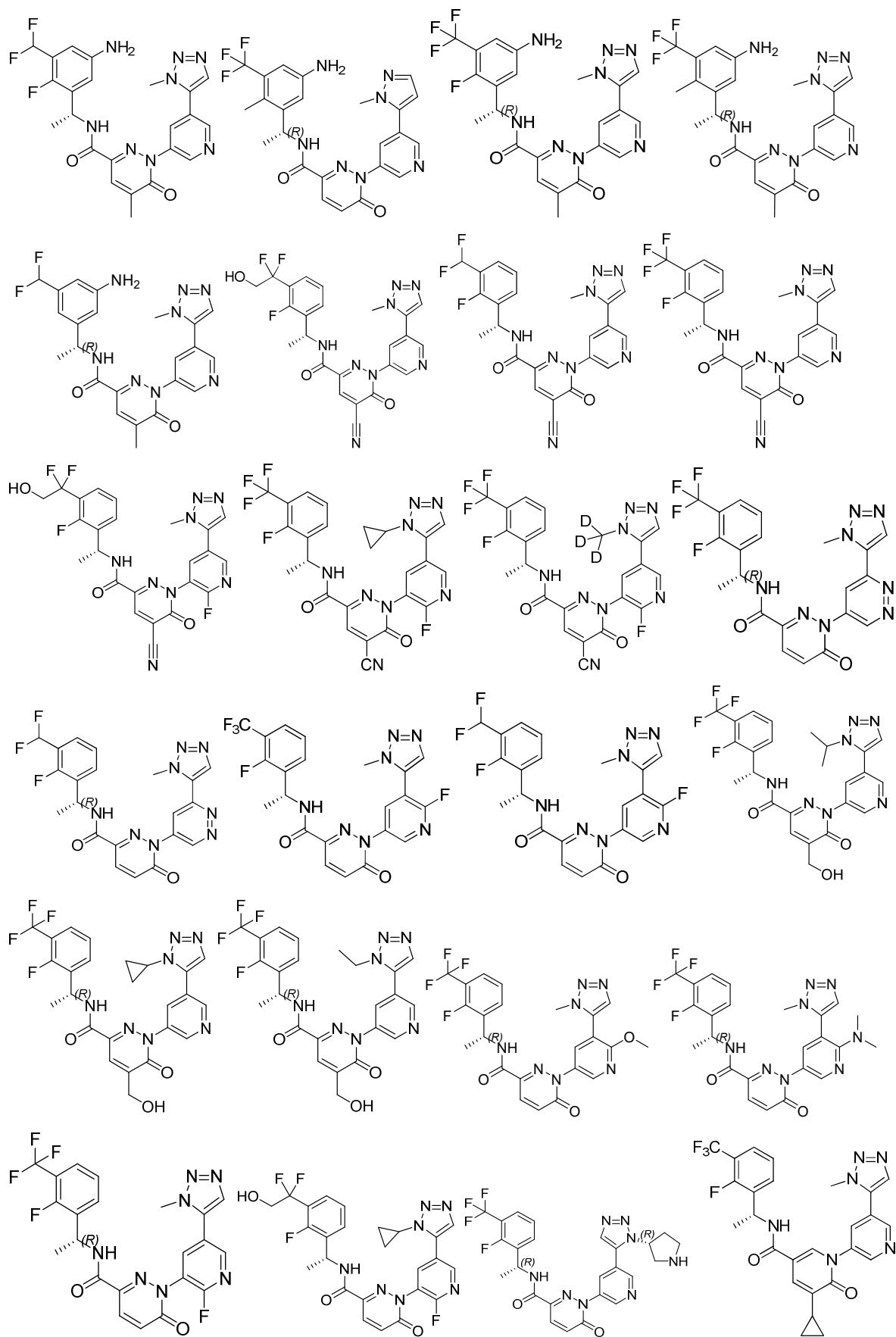
[Claim 18]

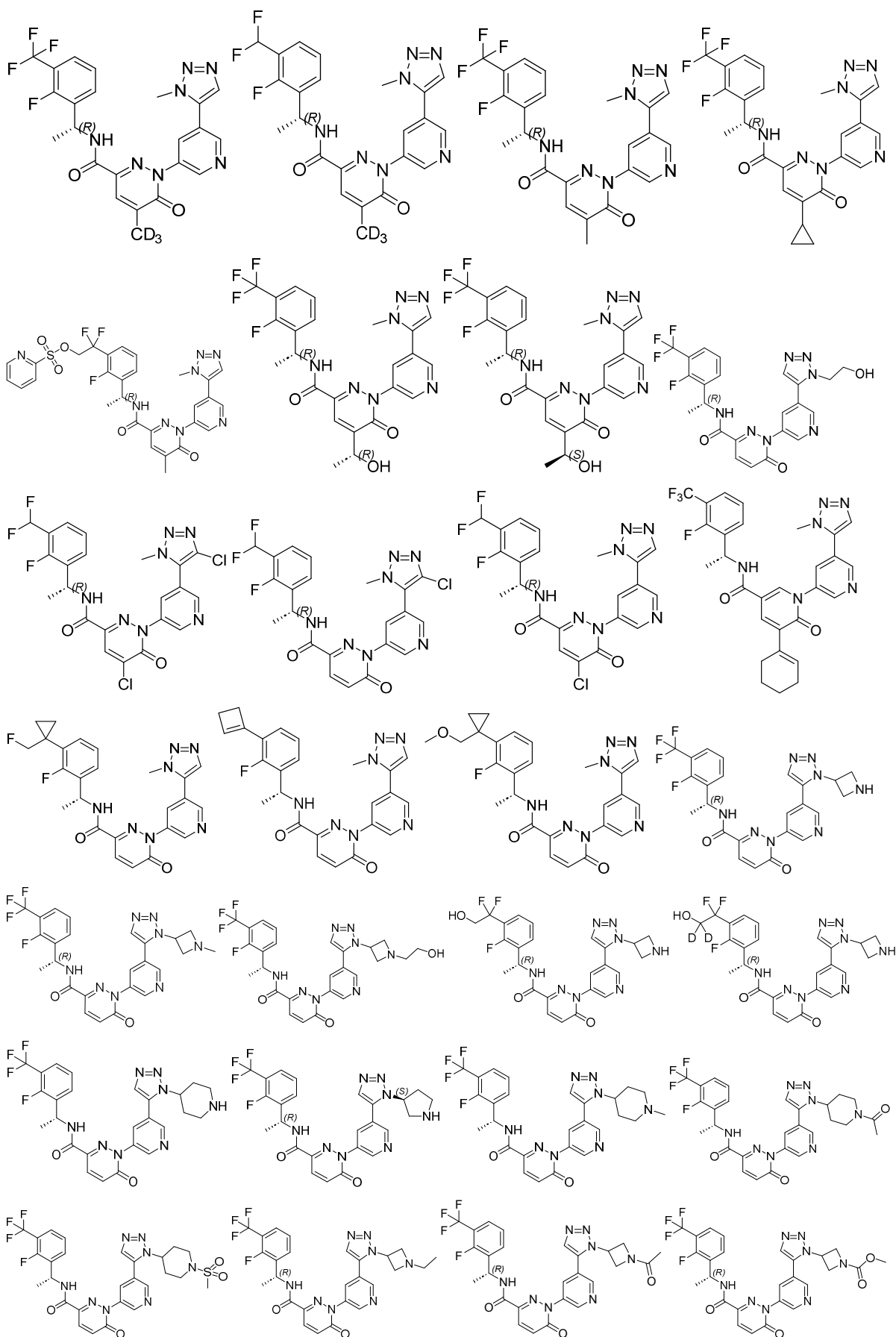
The compound, or solvate, stereoisomer or pharmaceutically acceptable salt thereof according to claim 1, characterized in that the compound is selected from:

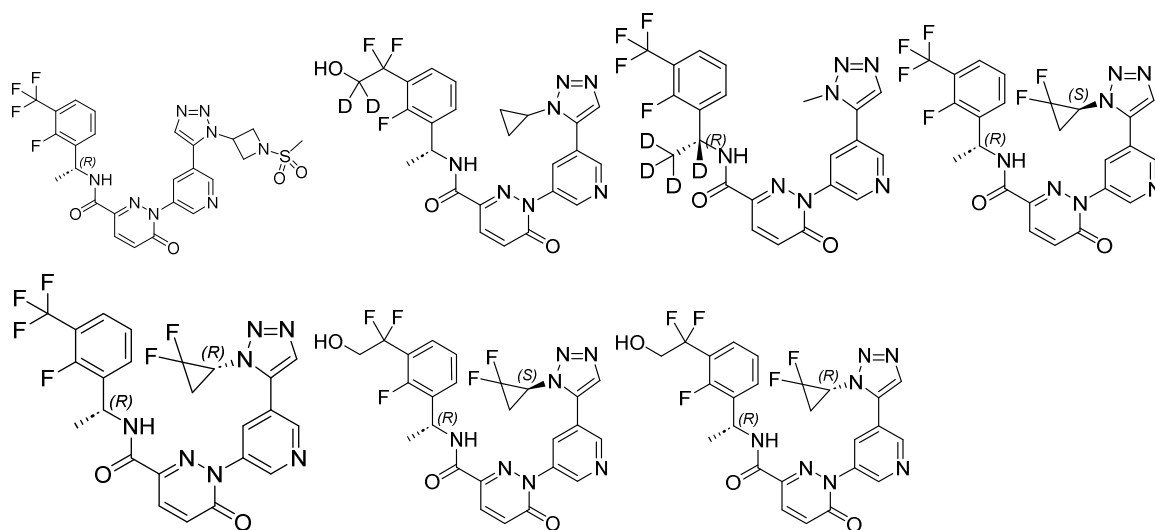












[Claim 19]

A pharmaceutical composition comprising the compound, or solvate, stereoisomer or pharmaceutically acceptable salt thereof according to any one of claims 1 to 18 as an active ingredient.

[Claim 20]

The pharmaceutical composition according to claim 19, characterized in that the pharmaceutical composition is for the prevention or treatment of a SOS1 mediated disease.

[Claim 21]

The pharmaceutical composition according to claim 20, characterized in that the SOS1 mediated disease is cancer or RASopathy.

[Claim 22]

The pharmaceutical composition according to claim 21, characterized in that the cancer is selected from the group consisting of pancreatic cancer, lung cancer, colorectal cancer, biliary tract cancer, multiple myeloma, melanoma, uterine cancer, cervical cancer, endometrial cancer, thyroid cancer, chronic lymphocytic leukemia, acute myeloid leukemia, bladder cancer, urothelial cancer, gastric cancer, squamous cell carcinoma of the head and neck, diffuse large B cell lymphoma, esophageal cancer, hepatocellular cancer, breast cancer, ovarian cancer, prostate cancer, glioblastoma, kidney cancer and sarcoma.

[Claim 23]

The pharmaceutical composition according to claim 21, characterized in that the RASopathy is selected from the group consisting of neurofibromatosis type 1, Noonan syndrome, Leopard syndrome, capillary malformation-arteriovenous malformation syndrome,

Costello syndrome, CFC syndrome (Cardio-Facio-Cutaneous syndrome), Legius syndrome, and hereditary gingival fibromatosis.

[Claim 24]

A method for preventing or treating a SOS1 mediated disease, comprising administering to a subject the compound, or solvate, stereoisomer or pharmaceutically acceptable salt thereof according to any one of claims 1 to 18.

[Claim 25]

Use of the compound, or solvate, stereoisomer or pharmaceutically acceptable salt thereof according to any one of claims 1 to 18 for use in the prevention or treatment of a SOS1 mediated disease.

[Claim 26]

Use of the compound, or solvate, stereoisomer or pharmaceutically acceptable salt thereof according to any one of claims 1 to 18 for the manufacture of a medicament for the prevention or treatment of a SOS1 mediated disease.