【Description of Invention】

【Title of invention】

NOVEL COMPOUNDS AS LRRK2 PROTEIN KINASE DOMAIN INHIBITORS

【Technical Field】

The present invention relates to a novel compound that inhibits the LRRK2 (Leucine-Rich Repeat Kinase 2) protein kinase domain. The novel compound of the present invention exhibits excellent inhibitory activity against LRRK2, and has an excellent effect on the prevention or treatment of diseases mediated by or associated with LRRK2.

【Background Art】

Various genetic mutations have been studied in connection with Parkinson's disease (PD), among them, LRRK2 (Leucine-Rich Repeat Kinase 2) is known as a target for developing therapeutic agents for sporadic and familial Parkinson's disease.

The LRRK2 protein is a giant protein composed of six domains, and the enzymatic part consists of two domains including a GTPase domain and a kinase domain. The GTPase domain is subdivided into subdomains such as a Ras-like GTPase (ROC) domain and a C-terminal domain of ROC (COR). The enzymatic activity is classified into two types, which are autophosphorylation and heterologous phosphorylation of the kinase domain, and GTPase activity of the ROC domain. The other four domains constituting the LRRK2 protein are ARM, ANK, LRR, and the C-terminal WD40 domain, each of which is involved in various types of protein-protein binding.

The LRRK2 protein is the most common causative gene for autosomal dominant familial Parkinson's disease. Among the mutations, the G2019S mutation is the most common

variant and is found in both sporadic Parkinson's disease and familial Parkinson's disease. In idiopathic Parkinson's disease (iPD), oxidative stress and endoplasmic reticulum dysfunction enhance the substrate phosphorylation of the LRRK2 protein. For these reasons, overexpression of the LRRK2 protein is closely associated with Parkinson's disease.

The LRRK2 protein is mainly considered a cytosolic protein, but it is also found in the membranes of intracellular organelles such as mitochondria and lysosomes. In cells, the LRRK2 protein phosphorylates Rab GTPases, and it is known that the phosphorylated Rab proteins regulate endolysosomal membrane trafficking. In addition, the LRRK2 protein functions to maintain intracellular vesicle trafficking, including the Golgi apparatus, endosomes, and lysosomes, and also organelle homeostasis. These aforementioned activities are increased in LRRK2 protein mutations that induce Parkinson's disease. When the function of the LRRK2 protein is overactivated, symptoms of Parkinson's disease appear along with endolysosomal dysfunction, mitochondrial degradation, excessive inflammatory responses, and neuronal cell damage.

Currently, therapeutic agents for Parkinson's disease mainly consist of symptom-relieving agents. There is not yet a disease-modifying therapy that prevents Parkinson's disease or slows down its progression. Once diagnosed with Parkinson's disease, medications capable of replacing the deficient dopamine in the brain are administered, or surgery is performed.

Therefore, the present inventors have developed a novel compound that inhibits the kinase function of LRRK2, thereby completing the present invention for a novel compound capable of treating or preventing Parkinson's disease.

(Prior Art Documents)

(Non-Patent Documents)

(Non-Patent Document 1) Taymans et al. LRRK2 kinase inhibition as a therapeutic strategy for Parkinson's disease, where do we stand? Current Neuropharmacology 14(3):214-25, (2016)

(Non-Patent Document 2) Taymans, J.-M. et al. Perspective on the current state of the LRRK2 field. npj Park.'s Dis. 9, 104 (2023)

【Summary of Invention】

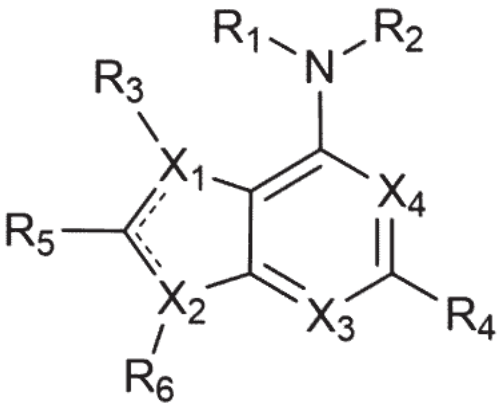
【Technical Problem】

An object of the present invention is to provide a novel compound exhibiting an effect of inhibiting the LRRK2 protein kinase domain. The compound of the present invention can inhibit the enzymatic activity of the LRRK2 protein by binding to the LRRK2 kinase domain. Another object of the present invention is to provide a method for preventing or treating Parkinson's disease using a compound that inhibits the LRRK2 kinase domain.

【Technical Solution】

The present invention relates to a compound of Formula 1 below, or a pharmaceutically acceptable salt thereof.

[Formula 1]



wherein,

----- are each independently absent or a single bond,

X_1 to X_4 are each independently C or N,

R_1 and R_2 are each independently hydrogen, alkyl, -O-alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -alkyl-cycloalkyl, -alkyl-heterocycloalkyl, -alkyl-aryl, or -alkyl-heteroaryl, or

R_1 and R_2 are heterocycloalkyl formed by linking R_1 and R_2 together,

R_3 is absent, or is hydrogen, halo, cyano, alkyl, -alkyl-O-alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl,

R_4 is hydrogen, halo, cyano, $-NH_2$, -alkyl, -alkyl-O-alkyl, -O-alkyl, $-N(R_{4A})(R_{4B})$, $-N(R_{4D})C(=O)(R_{4C})$, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl,

wherein R_{4A} to R_{4D} are each independently hydrogen, alkyl, cycloalkyl, heterocycloalkyl, -cycloalkyl-heteroaryl, heteroaryl, aryl, or -aryl-C(=O)-heterocycloalkyl,

R_5 is hydrogen, cyano, alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl,

R_6 is absent, or is hydrogen, cyano, alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl,

wherein the cycloalkyl, heterocycloalkyl, aryl, or heteroaryl may be substituted with

one or more selected from the group consisting of halo, NH_2, cyano, haloalkyl, alkyl, alkenyl, alkynyl, -alkynyl-alkyl, -O-alkyl, -alkyl-CN, -alkyl-OH, -alkyl-O-alkyl, -alkyl-NH_2, -alkyl-N(alkyl)(alkyl), -alkyl-cycloalkyl, NH_2, -N(alkyl)(alkyl), -C(=O)-NH_2, -C(=O)-heteroaryl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein the cycloalkyl, heterocycloalkyl, aryl, or heteroaryl may be unsubstituted or substituted with alkyl or -OH, wherein the alkyl may be unsubstituted or substituted with halo.

In one embodiment, in the compound of Formula 1 of the present invention,

X_1 to X_4 are each independently C or N,

R_1 and R_2 are each independently hydrogen, -C_{1-6} alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -C_{1-6} alkyl-cycloalkyl, -C_{1-6} alkyl-heterocycloalkyl, -C_{1-6} alkyl-aryl, or -C_{1-6} alkyl-heteroaryl,

or R_1 and R_2 are heterocycloalkyl formed by linking R_1 and R_2 together,

R_3 is absent, or is hydrogen, halo, cyano, -C_{1-6} alkyl, -C_{1-6} alkyl-O-C_{1-6} alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl,

R_4 is hydrogen, halo, cyano, -NH_2, -C_{1-6} alkyl, -C_{1-6} alkyl-O-C_{1-6} alkyl, -O-C_{1-6} alkyl, -N(R_{4A})(R_{4B}), -N(R_{4D})C(=O)(R_{4C}), cycloalkyl, heterocycloalkyl, aryl, or heteroaryl,

wherein R_{4A} to R_{4D} are each independently hydrogen, -C_{1-6} alkyl, cycloalkyl, heterocycloalkyl, -cycloalkyl-heteroaryl, heteroaryl, aryl, or -aryl-C(=O)-heterocycloalkyl,

R_5 is hydrogen, cyano, -C_{1-6} alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl,

R_6 is absent, or is hydrogen, cyano, -C_{1-6} alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl,

wherein the cycloalkyl, heterocycloalkyl, aryl, or heteroaryl may be substituted with one or more selected from the group consisting of halo, NH_2, cyano, cycloalkyl, haloalkyl, -C_{1-6} alkyl, -C_{2-6} alkenyl, -C_{2-6} alkynyl, -C_{2-6} alkynyl-C_{1-6} alkyl, -O-C_{1-6} alkyl, -C_{1-6} alkyl-CN, -

C_{1-6} alkyl-OH, -C_{1-6} alkyl-O-C_{1-6} alkyl, -C_{1-6} alkyl-NH_2, -C_{1-6} alkyl-N(C_{1-6} alkyl)(C_{1-6} alkyl), -C_{1-6} alkyl-cycloalkyl, -C(=O)-NH_2, -C(=O)-heteroaryl, heterocycloalkyl, and heteroaryl, wherein the heterocycloalkyl or heteroaryl may be unsubstituted or substituted with -C_{1-6} alkyl or -OH, wherein the -C_{1-6} alkyl may be unsubstituted or substituted with halo.

In one embodiment, in the compound of Formula 1 of the present invention,

X_1 to X_4 are each independently C or N,

R_1 and R_2 are each independently hydrogen or -C_{1-6} alkyl-heterocycloalkyl, wherein the heterocycloalkyl may be unsubstituted or substituted with -C_{1-6} alkyl, or

R_1 and R_2 are a 3- to 10-membered heteromonocycloalkyl or a 3- to 10-membered spiro or fused heterobicycloalkyl formed by linking R_1 and R_2 together,

wherein the 3- to 10-membered heteromonocycloalkyl or 3- to 10-membered spiro or fused heterobicycloalkyl formed by linking R_1 and R_2 together may be substituted with one or more selected from the group consisting of halo, NH_2, cyano, cycloalkyl, -C_{1-6} alkyl, -C_{2-6} alkenyl, -C_{2-6} alkynyl, -C_{2-6} alkynyl-C_{1-6} alkyl, -C_{1-6} alkyl-CN, -C_{1-6} alkyl-OH, -C_{1-6} alkyl-O-C_{1-6} alkyl, -C_{1-6} alkyl-NH_2, -C_{1-6} alkyl-N(C_{1-6} alkyl)(C_{1-6} alkyl), -C_{1-6} alkyl-cycloalkyl, -C(=O)-NH_2, -C(=O)-heteroaryl, heterocycloalkyl, and heteroaryl, wherein the heterocycloalkyl or heteroaryl may be unsubstituted or substituted with -C_{1-6} alkyl or -OH, wherein the -C_{1-6} alkyl may be unsubstituted or substituted with halo,

R_3 is absent, or is hydrogen, halo, cyano, -C_{1-6} alkyl, -C_{1-6} alkyl-O-C_{1-6} alkyl, aryl, or heteroaryl, wherein the aryl or heteroaryl may be substituted with one or more selected from the group consisting of cyano, -C_{1-6} alkyl, and heterocycloalkyl, wherein the -C_{1-6} alkyl may be unsubstituted or substituted with halo,

R_4 is hydrogen, halo, -NH_2, -C_{1-6} alkyl, -O-C_{1-6} alkyl, -N(R_{4A})(R_{4B}), or -NHC(=O)(R_{4C}),

wherein R_{4A} to R_{4C} are each independently hydrogen, -C_{1-6} alkyl, cycloalkyl, heterocycloalkyl, -cycloalkyl-heteroaryl, heteroaryl, or -aryl-C(=O)-heterocycloalkyl, wherein the aryl or heteroaryl may be unsubstituted or substituted with halo, -C_{1-6} alkyl, -O-C_{1-6} alkyl, -C_{1-6} alkyl-CN, or -C_{1-6} alkyl-OH,

R_5 is hydrogen, cyano, or -C_{1-6} alkyl,

R_6 is absent, or may be hydrogen, aryl, or heteroaryl.

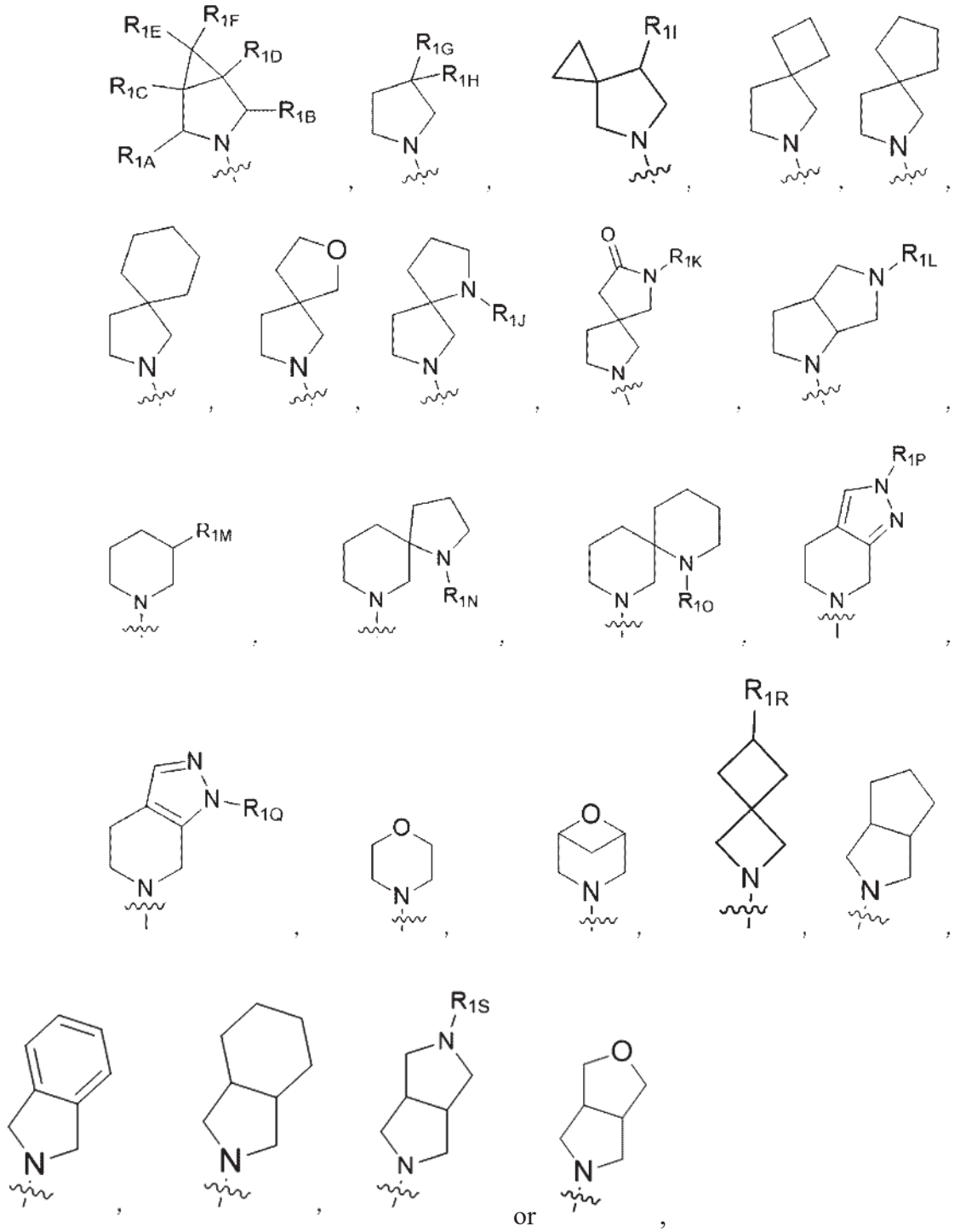
In one embodiment, in the compound of Formula 1 of the present invention,

X_1 and X_4 are each independently C or N,

X_2 and X_3 are N,

R_1 and R_2 are each independently hydrogen or -C_{1-6} alkyl-heterocycloalkyl, wherein the heterocycloalkyl may be unsubstituted or substituted with -C_{1-6} alkyl,

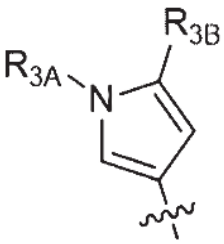
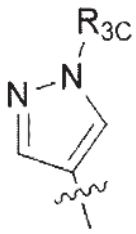
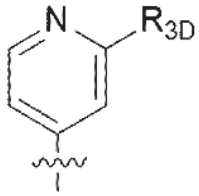
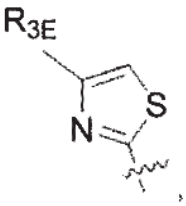
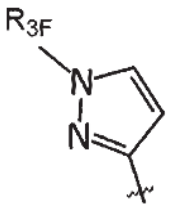
or R_1 and R_2 are a 3- to 10-membered heteromonocycloalkyl or a 3- to 10-membered spiro or fused heterobicycloalkyl formed by linking R_1 and R_2 together, wherein the 3- to 10-membered heteromonocycloalkyl or 3- to 10-membered spiro or fused heterobicycloalkyl formed by linking R_1 and R_2 together is



wherein R_{1A} to R_{1S} are each independently hydrogen, halo, NH_2, cyano, cycloalkyl, -C_{1-6} alkyl, -C_{2-6} alkenyl, -C_{2-6} alkynyl, -C_{2-6} alkynyl-C_{1-6} alkyl, -C_{1-6} alkyl-CN, -C_{1-6} alkyl-OH, -C_{1-6} alkyl-O-C_{1-6} alkyl, -C_{1-6} alkyl-NH_2, -C_{1-6} alkyl-N(C_{1-6} alkyl)(C_{1-6} alkyl), -C_{1-6} alkyl-cycloalkyl, -C(=O)-NH_2, -C(=O)-heteroaryl, heterocycloalkyl, or heteroaryl, wherein the

heterocycloalkyl or heteroaryl may be unsubstituted or substituted with -C_{1-6} alkyl or -OH, wherin the -C_{1-6} alkyl may be unsubstituted or substituted with halo,

R_3 is absent, or is hydrogen, halo, cyano, -C_{1-6} alkyl, -C_{1-6} alkyl-O-C_{1-6} alkyl, aryl,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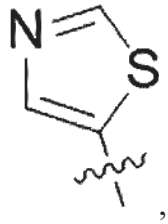

, wherein the aryl may be unsubstituted or substituted with cyano,

wherein R_{3A} to R_{3F} are each independently hydrogen, cyano, -C_{1-6} alkyl, or heterocycloalkyl, wherein the -C_{1-6} alkyl may be unsubstituted or substituted with halo,

R_4 is hydrogen, halo, -NH_2, -C_{1-6} alkyl, -O-C_{1-6} alkyl, -N(R_{4A})(R_{4B}), or -NHC(=O)(R_{4C}),

wherein R_{4A} to R_{4C} are each independently hydrogen, -C_{1-6} alkyl, cycloalkyl, heterocycloalkyl, -cycloalkyl-heteroaryl, heteroaryl, or -aryl-C(=O)-heterocycloalkyl, wherein the aryl or heteroaryl may be unsubstituted or substituted with halo, -C_{1-6} alkyl, -O-C_{1-6} alkyl, -C_{1-6} alkyl-CN, or -C_{1-6} alkyl-OH,

R_5 is hydrogen, cyano, or -C_{1-6} alkyl,

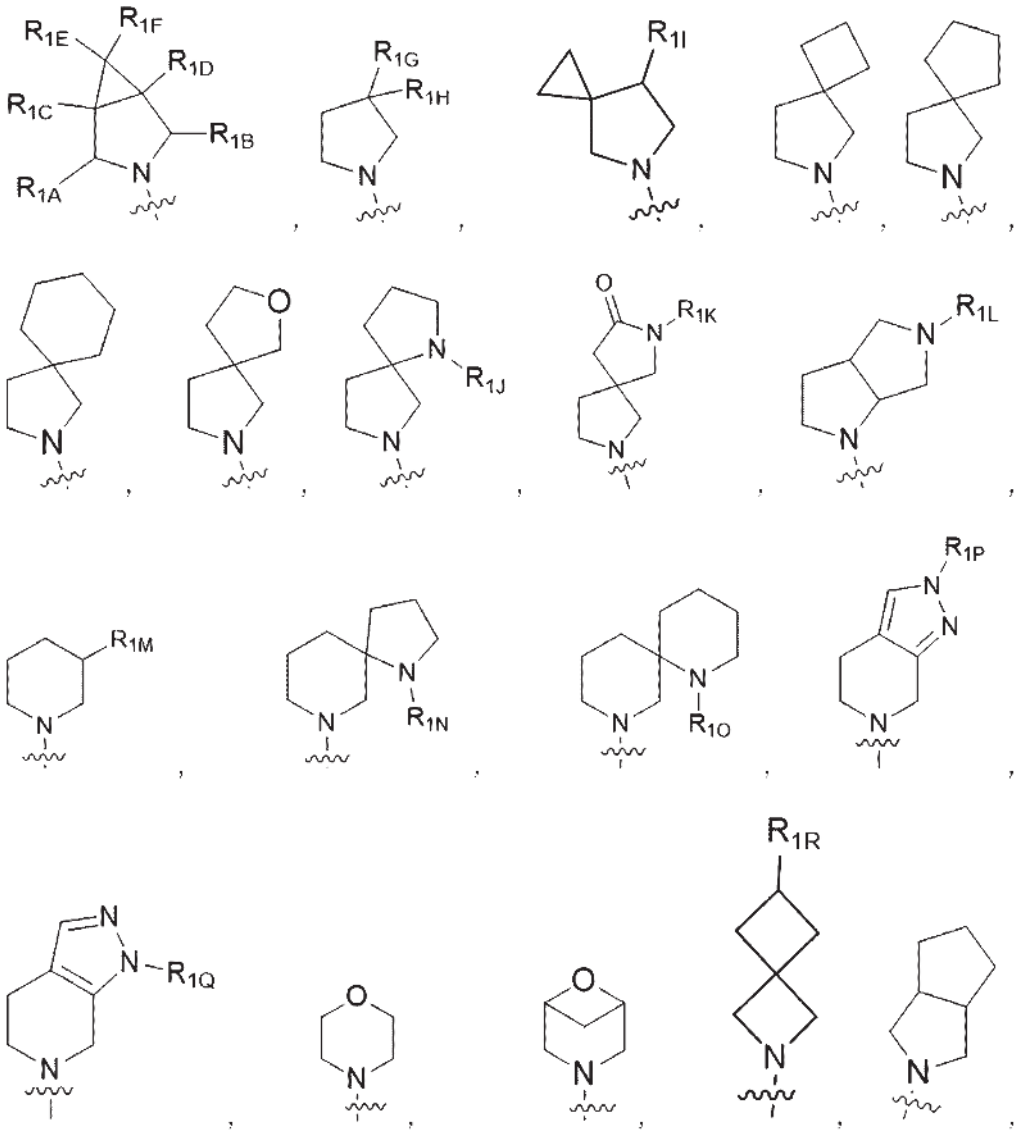
R_6 is absent, or may be hydrogen, aryl, or heteroaryl.

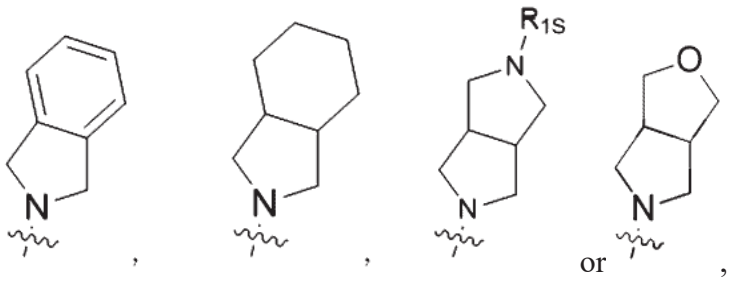
In one embodiment, in the compound of Formula 1 of the present invention,

X_1 and X_4 are each independently C or N,

X_2 and X_3 are N,

R_1 and R_2 are each independently hydrogen or -C_{1-6} alkyl-heterocycloalkyl, wherein the heterocycloalkyl may be unsubstituted or substituted with -C_{1-6} alkyl, or R_1 and R_2 are a 3- to 10-membered heteromonocycloalkyl or a 3- to 10-membered spiro or fused heterobicycloalkyl formed by linking R_1 and R_2 together, wherein the 3- to 10-membered heteromonocycloalkyl or 3- to 10-membered spiro or fused heterobicycloalkyl formed by linking R_1 and R_2 together is





wherein R_{1A} and R_{1B} are each independently hydrogen, cyano, or -C_{1-6} alkyl-OH,

R_{1C} and R_{1D} are each independently hydrogen, halo, cyano, cycloalkyl, -C_{1-6} alkyl, -C_{2-6} alkenyl, -C_{2-6} alkynyl, -C_{2-6} alkynyl-C_{1-6} alkyl, -C_{1-6} alkyl-CN, -C_{1-6} alkyl-OH, -C_{1-6} alkyl-O-C_{1-6} alkyl, -C_{1-6} alkyl-NH_2, -C_{1-6} alkyl-N(C_{1-6} alkyl)(C_{1-6} alkyl), -C_{1-6} alkyl-cycloalkyl, -C(=O)-NH_2, heterocycloalkyl, or heteroaryl, wherein the heterocycloalkyl or heteroaryl may be unsubstituted or substituted with -C_{1-6} alkyl, wherein the -C_{1-6} alkyl may be unsubstituted or substituted with halo,

R_{1E} and R_{1F} are each independently hydrogen, halo, cyano, or -C_{1-6} alkyl,

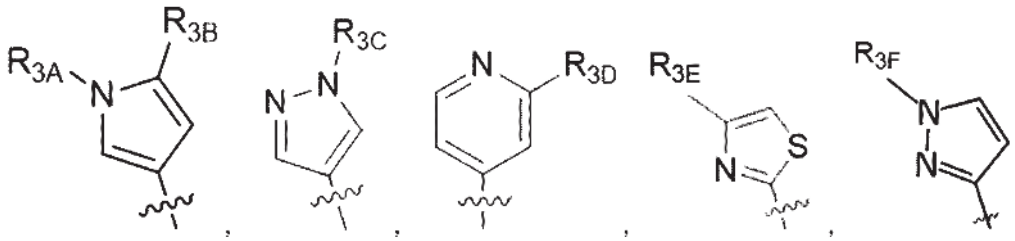
R_{1G} and R_{1H} are each independently hydrogen, -C_{1-6} alkyl, -C_{1-6} alkyl-NH_2, or -C_{1-6} alkyl-N(C_{1-6} alkyl)(C_{1-6} alkyl),

R_{1I} to R_{1L} are each independently hydrogen, halo, NH_2, or -C_{1-6} alkyl,

R_{1M} is hydrogen, -C(=O)-NH_2, or -C(=O)-heteroaryl, wherein the heteroaryl may be unsubstituted or substituted with -OH,

R_{1N} to R_{1S} are each independently hydrogen, halo, or -C_{1-6} alkyl,

R_3 is absent, or is hydrogen, halo, cyano, -C_{1-6} alkyl, -C_{1-6} alkyl-O-C_{1-6} alkyl, aryl,



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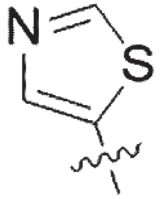


, wherein the aryl may be unsubstituted or substituted with cyano,

wherein R_{3A} to R_{3C} are each independently hydrogen, cyano, or -C_{1-6} alkyl,

R_{3D} is hydrogen, -C_{1-6} alkyl, or heterocycloalkyl, wherein the -C_{1-6} alkyl may be unsubstituted or substituted with halo,

R_{3E} and R_{3F} are each independently hydrogen or -C_{1-6} alkyl,

R_4 is hydrogen, halo, -NH_2, -C_{1-6} alkyl, -O-C_{1-6} alkyl, -N(R_{4A})(R_{4B}), or -NHC(=O)(R_{4C}),

wherein R_{4A} and R_{4B} are each independently hydrogen, -C_{1-6} alkyl, heteroaryl, or -aryl-C(=O)-heterocycloalkyl, wherein the aryl or heteroaryl may be unsubstituted or substituted with halo, -C_{1-6} alkyl, -O-C_{1-6} alkyl, -C_{1-6} alkyl-CN, or -C_{1-6} alkyl-OH,

R_{4C} is hydrogen, -C_{1-6} alkyl, cycloalkyl, heterocycloalkyl, -cycloalkyl-heteroaryl, or heteroaryl, wherein the heteroaryl may be unsubstituted or substituted with -C_{1-6} alkyl,

R_5 is hydrogen, cyano, or -C_{1-6} alkyl,

R_6 is absent, or may be hydrogen, aryl, or heteroaryl.

In one embodiment, in the compound of Formula 1 of the present invention,

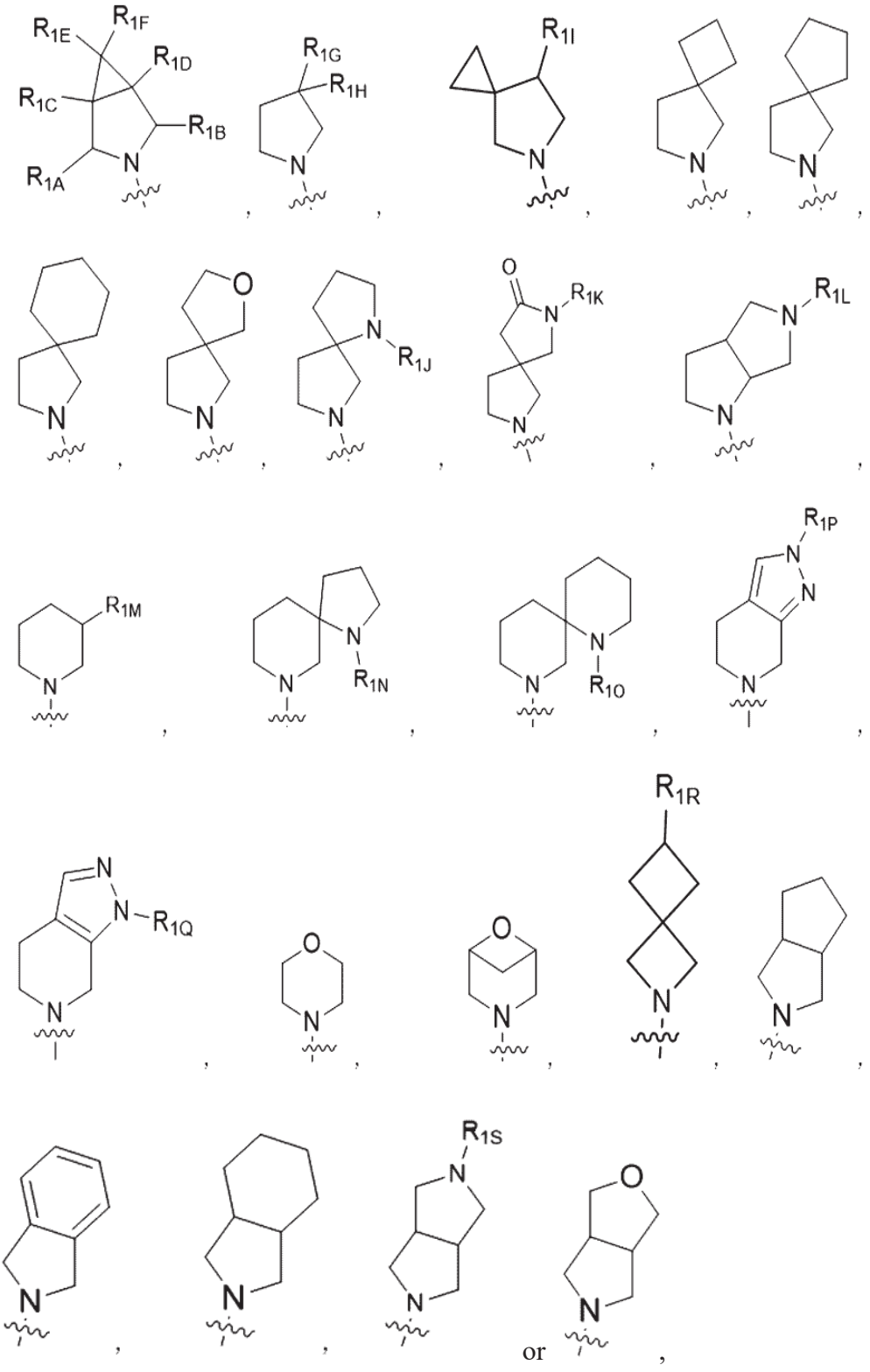
X_1 and X_4 are each independently C or N,

X_2 and X_3 are N,

R_1 and R_2 are each independently hydrogen or -C_{1-6} alkyl-piperidine, wherein the piperidine may be unsubstituted or substituted with -C_{1-6} alkyl, or

R_1 and R_2 are a 3- to 10-membered heteromonocycloalkyl or a 3- to 10-membered spiro or fused heterobicycloalkyl formed by linking R_1 and R_2 together, wherein the 3- to 10-membered heteromonocycloalkyl or 3- to 10-membered spiro or fused heterobicycloalkyl

formed by linking R_1 and R_2 together is



wherein R_{1A} and R_{1B} are each independently hydrogen, cyano, or -C_{1-6} alkyl-OH,

R_{1C} and R_{1D} are each independently hydrogen, halo, cyano, cycloalkyl, -C_{1-6} alkyl, -

C_{2-6} alkenyl, -C_{2-6} alkynyl, -C_{2-6} alkynyl-C_{1-6} alkyl, -C_{1-6} alkyl-CN, -C_{1-6} alkyl-OH, -C_{1-6} alkyl-O-C_{1-6} alkyl, -C_{1-6} alkyl-NH_2, -C_{1-6} alkyl-N(C_{1-6} alkyl)(C_{1-6} alkyl), -C_{1-6} alkyl-cycloalkyl, -C(=O)-NH_2, piperidine, or isoxazole, wherein the piperidine or isoxazole may be unsubstituted or substituted with -C_{1-6} alkyl, wherein the -C_{1-6} alkyl may be unsubstituted or substituted with halo,

R_{1E} and R_{1F} are each independently hydrogen, halo, cyano, or -C_{1-6} alkyl,

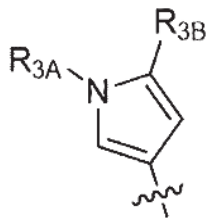
R_{1G} and R_{1H} are each independently hydrogen, -C_{1-6} alkyl, -C_{1-6} alkyl-NH_2, or -C_{1-6} alkyl-N(C_{1-6} alkyl)(C_{1-6} alkyl),

R_{1I} to R_{1L} are each independently hydrogen, halo, NH_2, or -C_{1-6} alkyl,

R_{1M} is hydrogen, -C(=O)-NH_2, or -C(=O)-pyridine, wherein the pyridine may be unsubstituted or substituted with -OH,

R_{1N} to R_{1S} are each independently hydrogen, halo, or -C_{1-6} alkyl,

R_3 is absent, or is hydrogen, halo, cyano, -C_{1-6} alkyl, -C_{1-6} alkyl-O-C_{1-6} alkyl, aryl,



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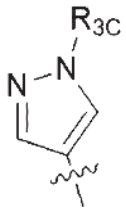

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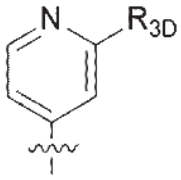

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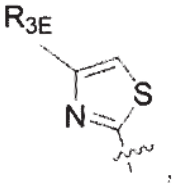

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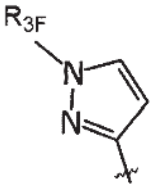

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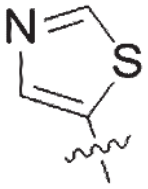


, wherein the aryl may be unsubstituted or substituted with cyano,

wherein R_{3A} to R_{3C} are each independently hydrogen, cyano, or -C_{1-6} alkyl,

R_{3D} is hydrogen, -C_{1-6} alkyl, or morpholine, wherein the -C_{1-6} alkyl may be unsubstituted or substituted with halo,

R_{3E} and R_{3F} are each independently hydrogen or -C_{1-6} alkyl,

R_4 is hydrogen, halo, -NH_2, -C_{1-6} alkyl, -O-C_{1-6} alkyl, -N(R_{4A})(R_{4B}), or -NHC(=O)(R_{4C}),

wherein R_{4A} and R_{4B} are each independently hydrogen, -C_{1-6} alkyl, pyrazole, or -aryl-C(=O)-morpholine, wherein the aryl may be unsubstituted or substituted with -O-C_{1-6} alkyl, and the pyrazole may be unsubstituted or substituted with halo, -C_{1-6} alkyl, -C_{1-6} alkyl-CN, or -C_{1-6} alkyl-OH,

R_{4C} is hydrogen, -C_{1-6} alkyl, cycloalkyl, heterocycloalkyl, -cycloalkyl-pyridine, pyrazole, or furan, wherein the pyridine, pyrazole, or furan may be unsubstituted or substituted with -C_{1-6} alkyl,

R_5 is hydrogen or -C_{1-6} alkyl,

R_6 is absent, or may be hydrogen, aryl, or heteroaryl.

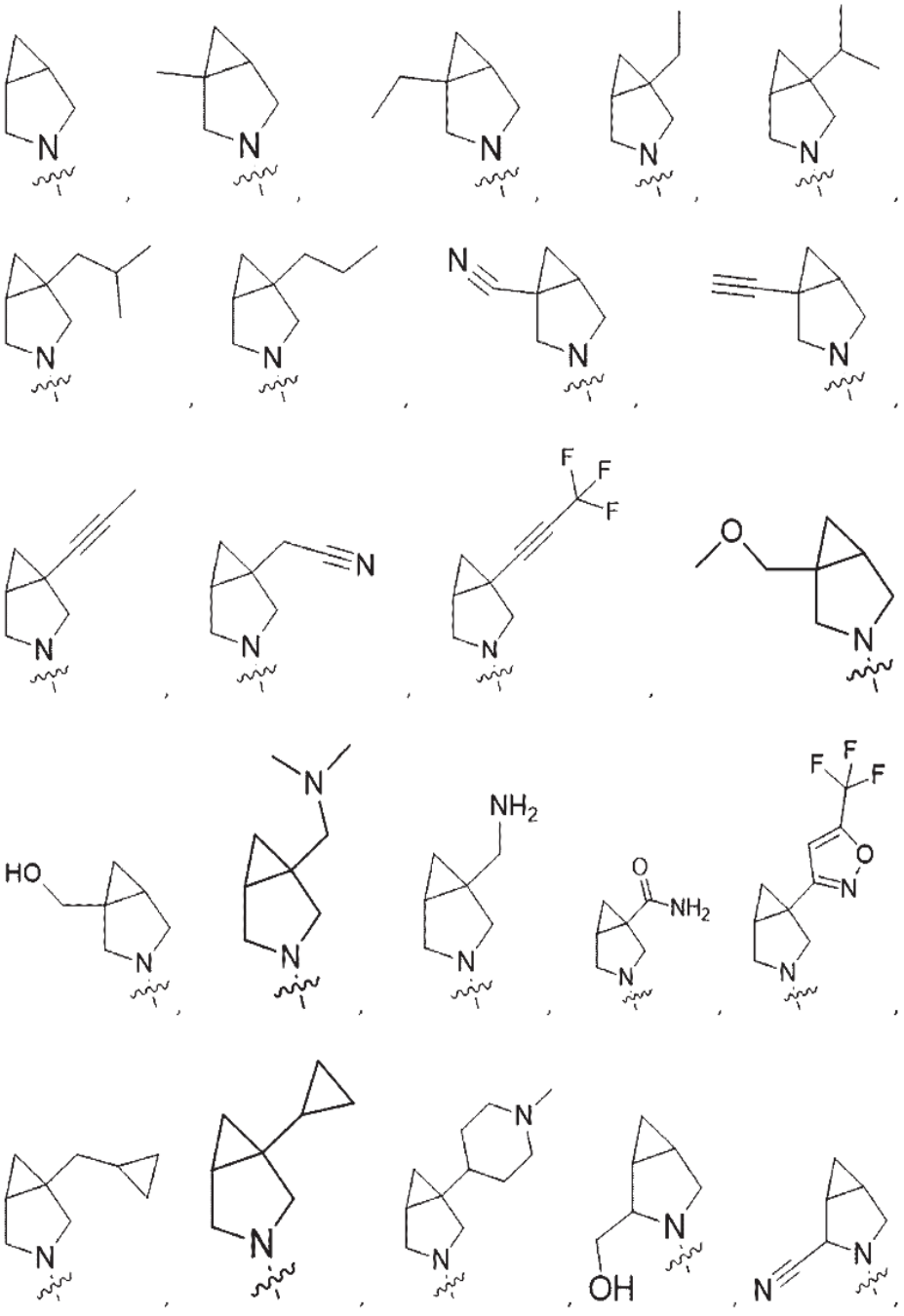
In one embodiment, in the compound of Formula 1 of the present invention,

X_1 and X_4 are each independently C or N,

X_2 and X_3 are N,

R_1 and R_2 are each independently hydrogen or -C_{1-6} alkyl-piperidine, wherein the piperidine may be unsubstituted or substituted with -C_{1-6} alkyl,

or R_1 and R_2 are a 3- to 10-membered heteromonocycloalkyl or a 3- to 10-membered spiro or fused heterobicycloalkyl formed by linking R_1 and R_2 together, wherein the 3- to 10-membered heteromonocycloalkyl or 3- to 10-membered spiro or fused heterobicycloalkyl formed by linking R_1 and R_2 together is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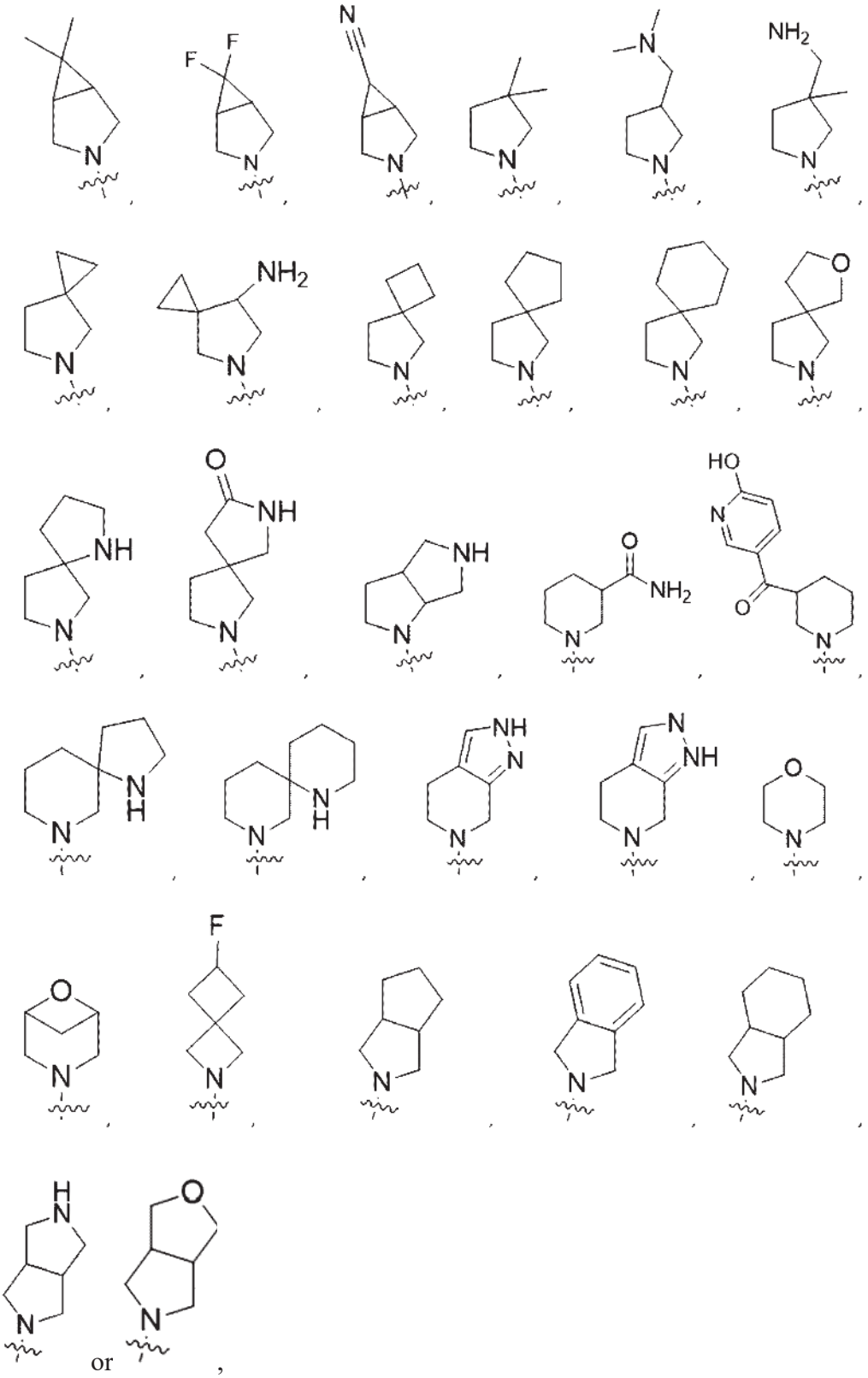
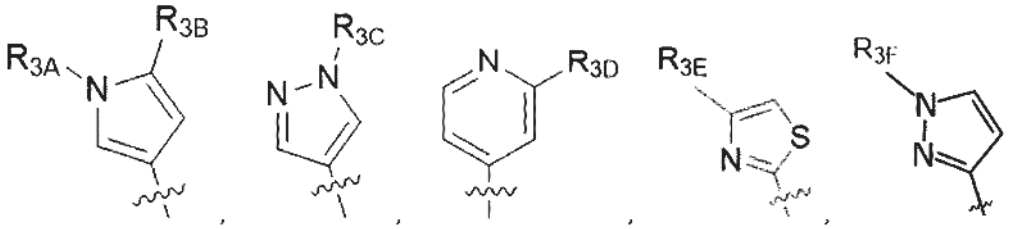
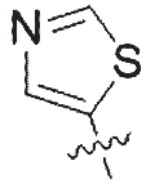


R_3 is absent, or is hydrogen, halo, cyano, -C_{1-6} alkyl, -C_{1-6} alkyl-O-C_{1-6} alkyl, aryl,



, , , , or



, wherein the aryl may be unsubstituted or substituted with cyano,

wherein R_{3A} to R_{3C} are each independently hydrogen, cyano, or -C_{1-6} alkyl,

R_{3D} is hydrogen, -C_{1-6} alkyl, or morpholine, wherein the -C_{1-6} alkyl may be unsubstituted or substituted with halo,

R_{3E} and R_{3F} are each independently hydrogen or -C_{1-6} alkyl,

R_4 is hydrogen, halo, -NH_2, -C_{1-6} alkyl, -O-C_{1-6} alkyl, -N(R_{4A})(R_{4B}), or -NHC(=O)(R_{4C}),

wherein R_{4A} and R_{4B} are each independently hydrogen, -C_{1-6} alkyl, pyrazole, or -aryl-C(=O)-morpholine, wherein the aryl may be unsubstituted or substituted with -O-C_{1-6} alkyl, and the pyrazole may be unsubstituted or substituted with halo, -C_{1-6} alkyl, -C_{1-6} alkyl-CN, or -C_{1-6} alkyl-OH,

R_{4C} is hydrogen, -C_{1-6} alkyl, cycloalkyl, heterocycloalkyl, -cycloalkyl-pyridine, pyrazole, or furan, wherein the pyridine, pyrazole, or furan may be unsubstituted or substituted with -C_{1-6} alkyl,

R_5 is hydrogen or -C_{1-6} alkyl,

R_6 is absent, or may be hydrogen, aryl, or heteroaryl.

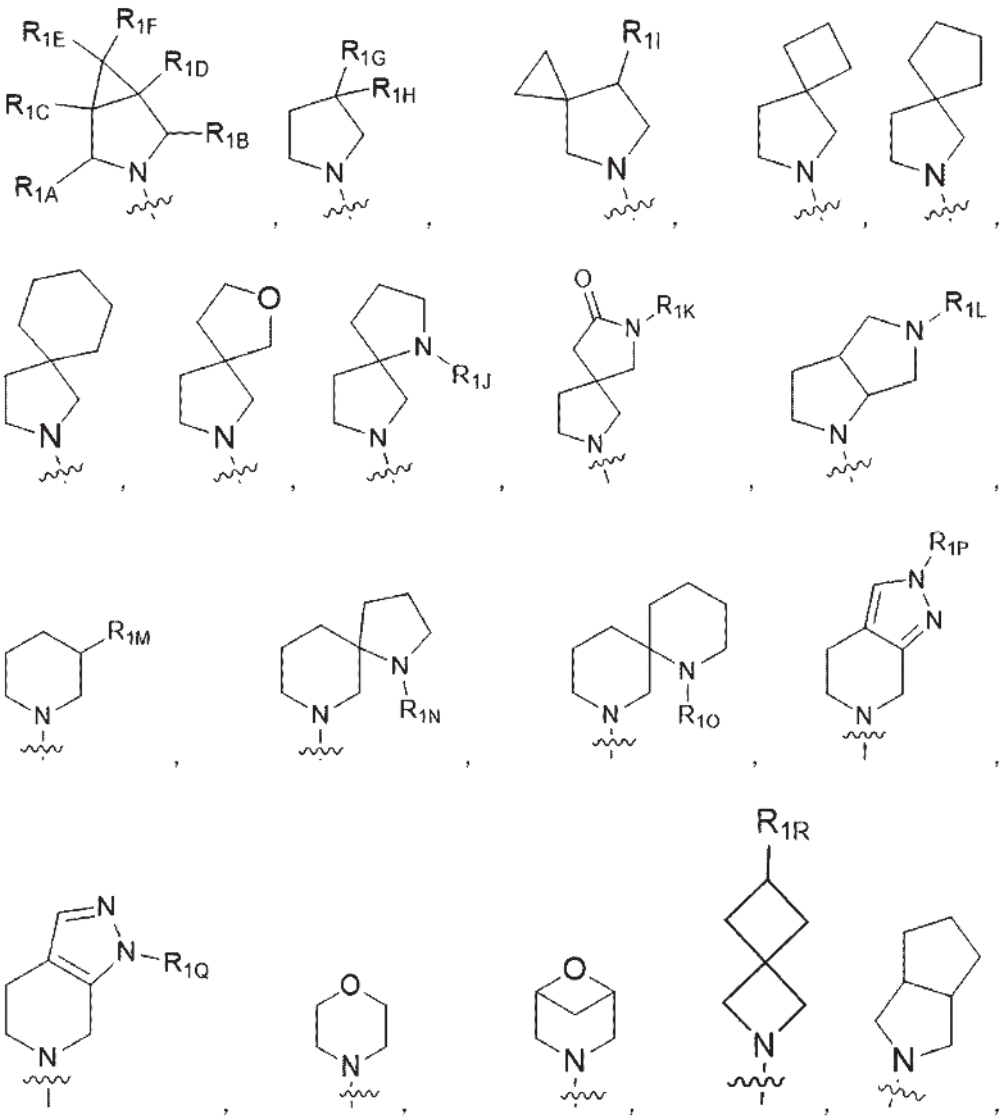
In one embodiment, in the compound of Formula 1 of the present invention,

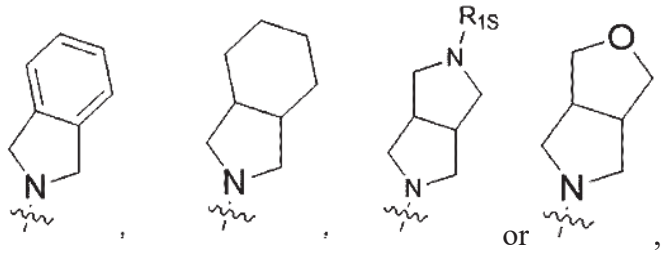
X_1 and X_4 are each independently C or N,

X_2 and X_3 are N,

R_1 and R_2 are each independently hydrogen or -C_{1-6} alkyl-piperidine, wherein the piperidine may be unsubstituted or substituted with -C_{1-6} alkyl, or

R_1 and R_2 are a 3- to 10-membered heteromonocycloalkyl or a 3- to 10-membered spiro or fused heterobicycloalkyl formed by linking R_1 and R_2 together, wherein the 3- to 10-membered heteromonocycloalkyl or 3- to 10-membered spiro or fused heterobicycloalkyl formed by linking R_1 and R_2 together is





wherein R_{1A} and R_{1B} are each independently hydrogen, cyano, or -C_{1-6} alkyl-OH,

R_{1C} and R_{1D} are each independently hydrogen, halo, cyano, cycloalkyl, -C_{1-6} alkyl, -C_{2-6} alkenyl, -C_{2-6} alkynyl, -C_{2-6} alkynyl-C_{1-6} alkyl, -C_{1-6} alkyl-CN, -C_{1-6} alkyl-OH, -C_{1-6} alkyl-O-C_{1-6} alkyl, -C_{1-6} alkyl-NH_2, -C_{1-6} alkyl-N(C_{1-6} alkyl)(C_{1-6} alkyl), -C_{1-6} alkyl-cycloalkyl, -C(=O)-NH_2, piperidine, or isoxazole, wherein the piperidine or isoxazole may be unsubstituted or substituted with -C_{1-6} alkyl, wherein the -C_{1-6} alkyl may be unsubstituted or substituted with halo,

R_{1E} and R_{1F} are each independently hydrogen, halo, cyano, or -C_{1-6} alkyl,

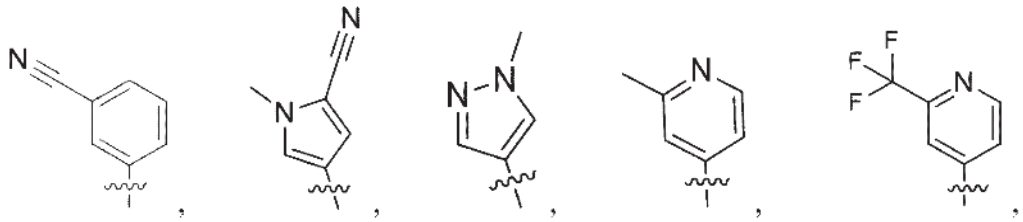
R_{1G} and R_{1H} are each independently hydrogen, -C_{1-6} alkyl, -C_{1-6} alkyl-NH_2, or -C_{1-6} alkyl-N(C_{1-6} alkyl)(C_{1-6} alkyl),

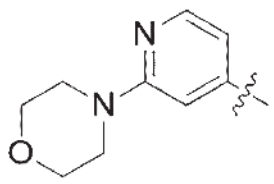
R_{1I} to R_{1L} are each independently hydrogen, halo, NH_2, or -C_{1-6} alkyl,

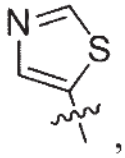
R_{1M} is hydrogen, -C(=O)-NH_2, or -C(=O)-pyridine, wherein the pyridine may be unsubstituted or substituted with -OH,

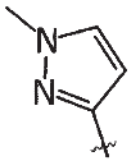
R_{1N} to R_{1S} are each independently hydrogen, halo, or -C_{1-6} alkyl,

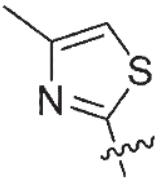
R_3 is absent, or is hydrogen, halo, cyano, -C_{1-6} alkyl, -C_{1-6} alkyl-O-C_{1-6} alkyl,





, 

, 

or 

,

R_4 is hydrogen, halo, -NH_2, -C_{1-6} alkyl, -O-C_{1-6} alkyl, -N(R_{4A})(R_{4B}), or -NHC(=O)(R_{4C}),

wherein R_{4A} and R_{4B} are each independently hydrogen, -C_{1-6} alkyl, pyrazole, or -aryl-C(=O)-morpholine, wherein the aryl may be unsubstituted or substituted with -O-C_{1-6} alkyl, and the pyrazole may be unsubstituted or substituted with halo, -C_{1-6} alkyl, -C_{1-6} alkyl-CN, or -C_{1-6} alkyl-OH,

R_{4C} is hydrogen, -C_{1-6} alkyl, cycloalkyl, heterocycloalkyl, -cycloalkyl-pyridine, pyrazole, or furan, wherein the pyridine, pyrazole, or furan may be unsubstituted or substituted with -C_{1-6} alkyl,

R_5 is hydrogen or -C_{1-6} alkyl,

R_6 is absent, or may be hydrogen, aryl, or heteroaryl.

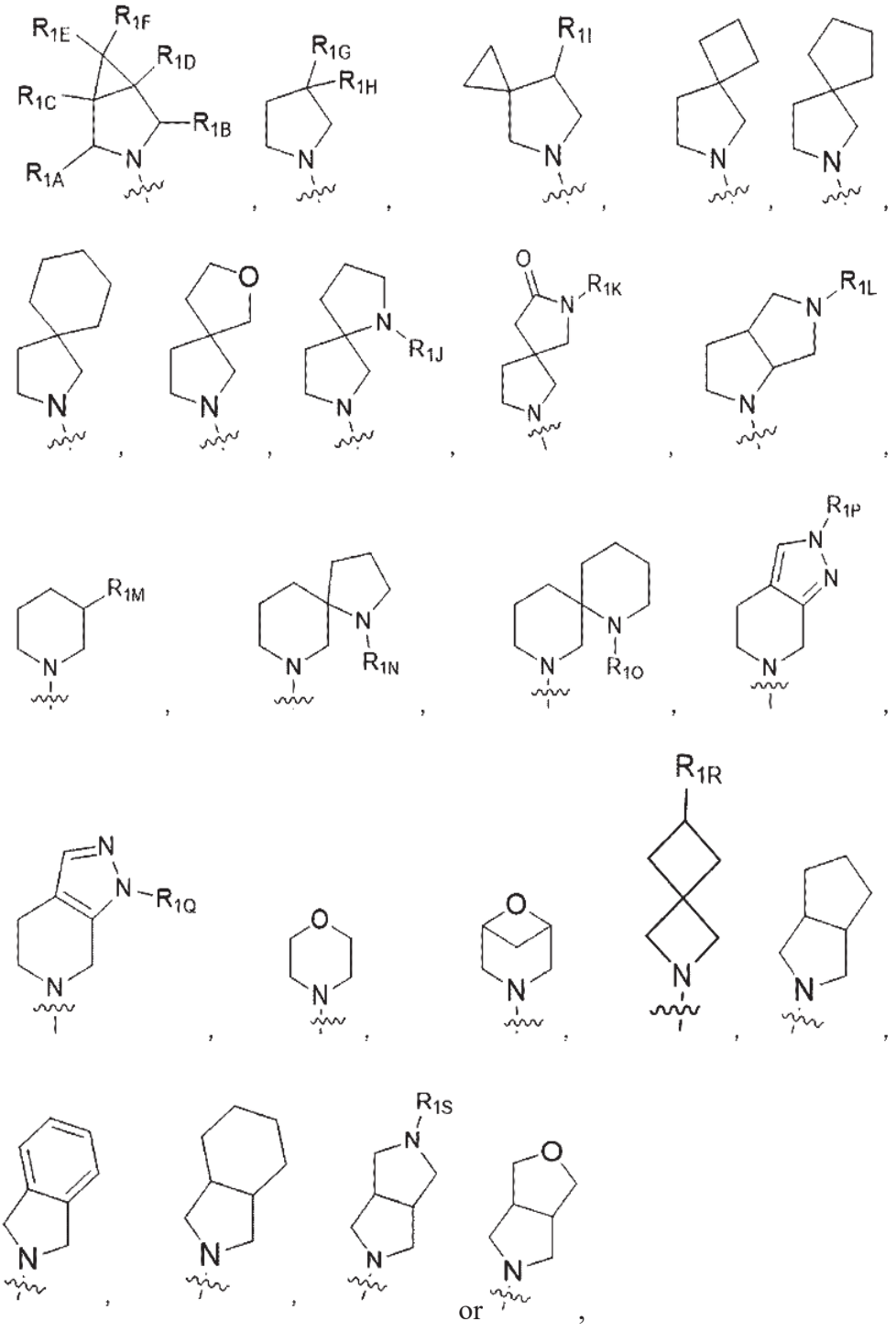
In one embodiment, in the compound of Formula 1 of the present invention,

X_1 and X_4 are each independently C or N,

X_2 and X_3 are N,

R_1 and R_2 are each independently hydrogen or -C_{1-6} alkyl-piperidine, wherein the piperidine may be unsubstituted or substituted with -C_{1-6} alkyl, or

R_1 and R_2 are a 3- to 10-membered heteromonocycloalkyl or a 3- to 10-membered spiro or fused heterobicycloalkyl formed by linking R_1 and R_2 together, wherein the 3- to 10-membered heteromonocycloalkyl or 3- to 10-membered spiro or fused heterobicycloalkyl formed by linking R_1 and R_2 together is



wherein R_{1A} and R_{1B} are each independently hydrogen, cyano, or -C_{1-6} alkyl-OH,

R_{1C} and R_{1D} are each independently hydrogen, halo, cyano, cycloalkyl, -C_{1-6} alkyl, -C_{2-6} alkenyl, -C_{2-6} alkynyl, -C_{2-6} alkynyl-C_{1-6} alkyl, -C_{1-6} alkyl-CN, -C_{1-6} alkyl-OH, -C_{1-6} alkyl-O-C_{1-6} alkyl, -C_{1-6} alkyl-NH_2, -C_{1-6} alkyl-N(C_{1-6} alkyl)(C_{1-6} alkyl), -C_{1-6} alkyl-cycloalkyl, -

C(=O)-NH_2, piperidine, or isoxazole, wherein the piperidine or isoxazole may be unsubstituted or substituted with -C_{1-6} alkyl, wherein the -C_{1-6} alkyl may be unsubstituted or substituted with halo,

R_{1E} and R_{1F} are each independently hydrogen, halo, cyano, or -C_{1-6} alkyl,

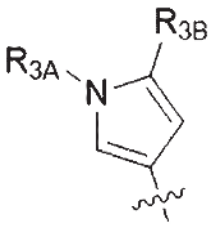
R_{1G} and R_{1H} are each independently hydrogen, -C_{1-6} alkyl, -C_{1-6} alkyl-NH_2, or -C_{1-6} alkyl-N(C_{1-6} alkyl)(C_{1-6} alkyl),

R_{1I} to R_{1L} are each independently hydrogen, halo, NH_2, or -C_{1-6} alkyl,

R_{1M} is hydrogen, -C(=O)-NH_2, or -C(=O)-pyridine, wherein the pyridine may be unsubstituted or substituted with -OH,

R_{1N} to R_{1S} are each independently hydrogen, halo, or -C_{1-6} alkyl,

R_3 is absent, or is hydrogen, halo, cyano, -C_{1-6} alkyl, -C_{1-6} alkyl-O-C_{1-6} alkyl, aryl,



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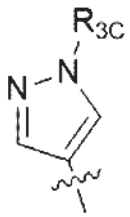

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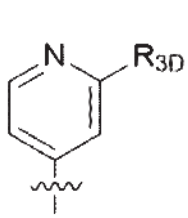

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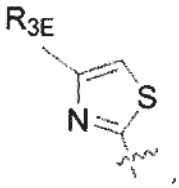

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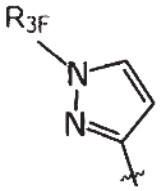
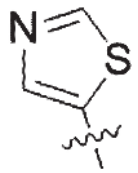


or



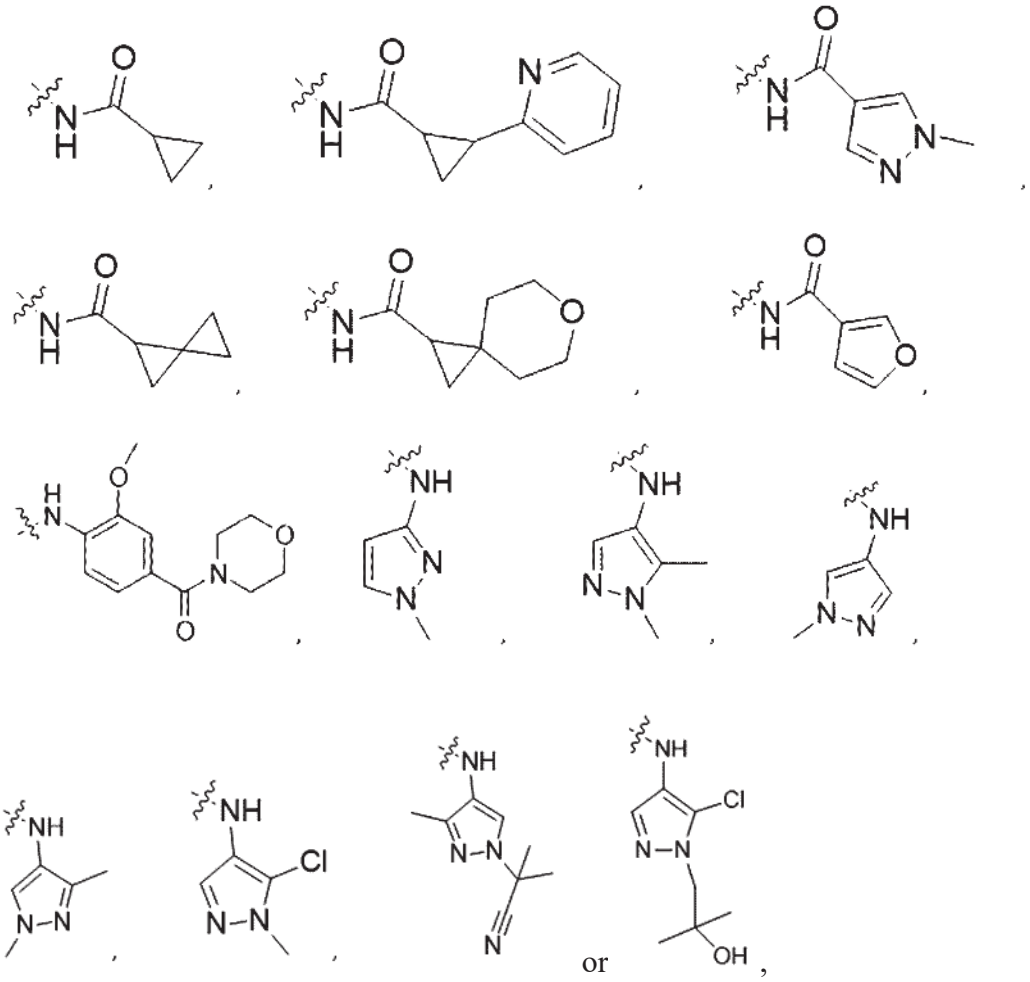
, wherein the aryl may be unsubstituted or substituted with cyano,

wherein R_{3A} to R_{3C} are each independently hydrogen, cyano, or -C_{1-6} alkyl,

R_{3D} is hydrogen, -C_{1-6} alkyl, or morpholine, wherein the -C_{1-6} alkyl may be unsubstituted or substituted with halo,

R_{3E} and R_{3F} are each independently hydrogen or -C_{1-6} alkyl,

R_4 is hydrogen, halo, -NH_2, -C_{1-6} alkyl, -O-C_{1-6} alkyl,



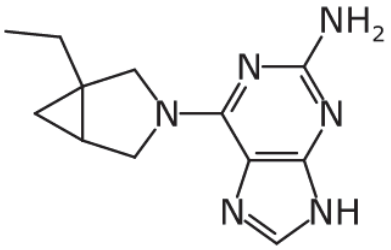
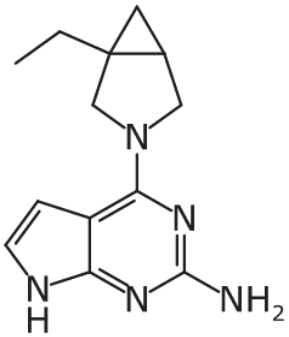
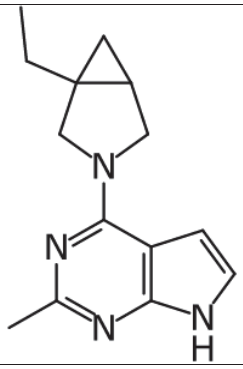
R_5 is hydrogen or -C_{1-6} alkyl,

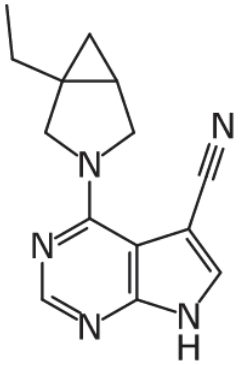
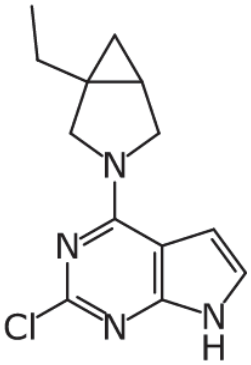
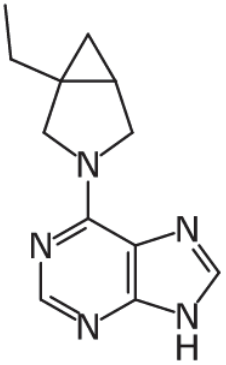
R_6 is absent, or may be hydrogen, aryl, or heteroaryl.

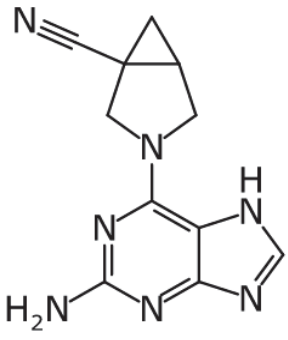
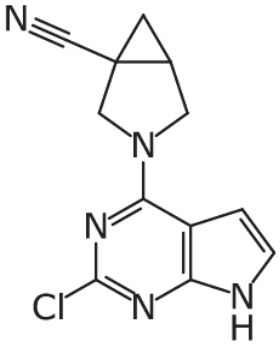
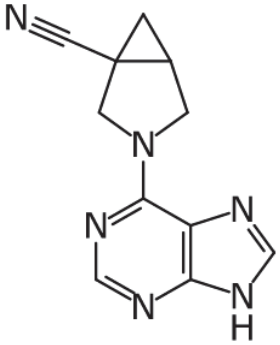
In one embodiment, the compound of the present invention may be a compound selected from the group consisting of the compounds of Table 1 below, or a pharmaceutically acceptable salt thereof.

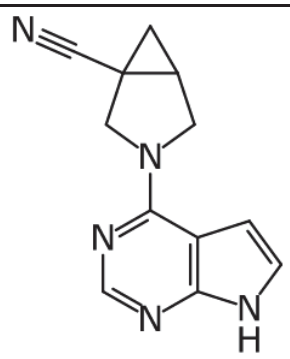
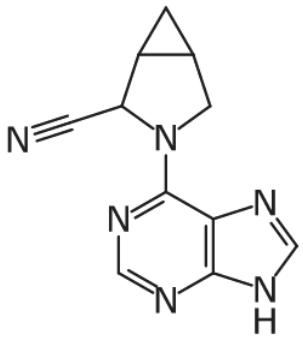
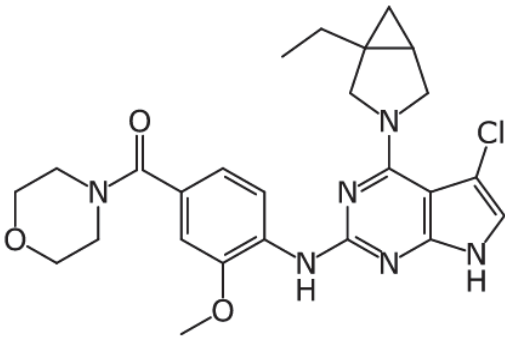
[Table 1]

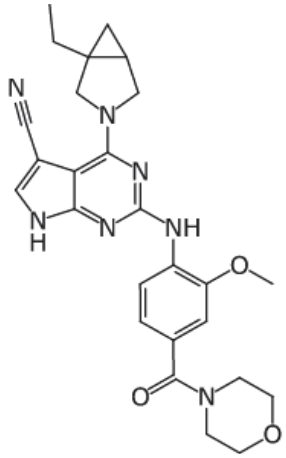
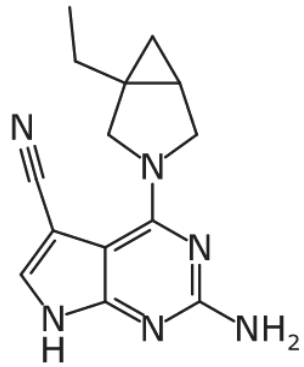
No.	Name	Formula	Compound

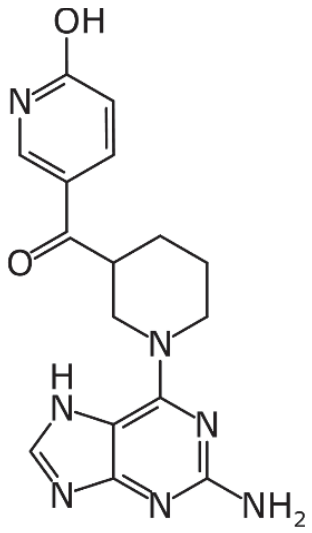
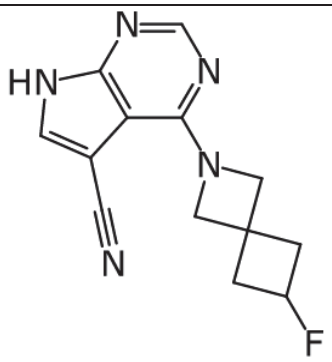
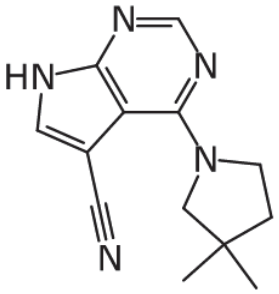
1	NRX02004		6-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-9H-purin-2-amine
2	NRX02065		4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine
3	NRX02066		4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-2-methyl-7H-pyrrolo[2,3-d]pyrimidine

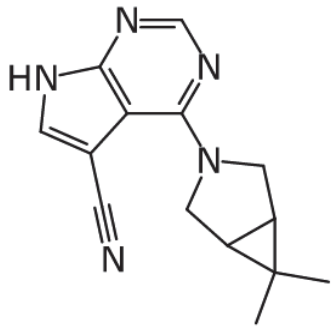
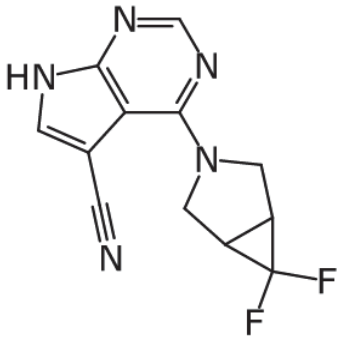
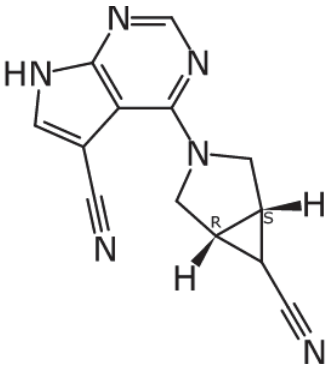
4	NRX02067		4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1,5,7-triaza-1H-indene-3-carbonitrile
5	NRX02068		2-chloro-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine
6	NRX02069		6-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-purine

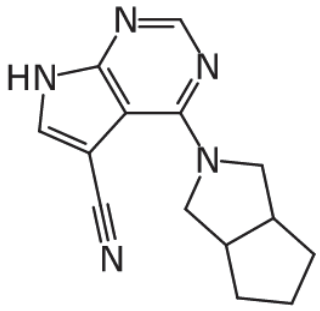
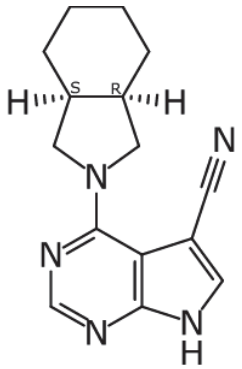
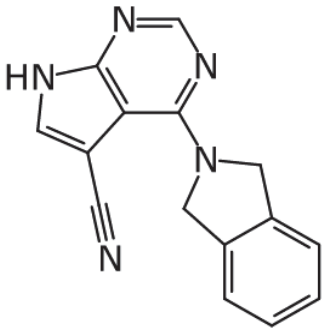
7	NRX02070		3-(2-amino-7H-purin-6-yl)-3-azabicyclo[3.1.0]hexane-1-carbonitrile
8	NRX02071		3-(2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-3-azabicyclo[3.1.0]hexane-1-carbonitrile
9	NRX02072		3-(9H-purin-6-yl)-3-azabicyclo[3.1.0]hexane-1-carbonitrile;

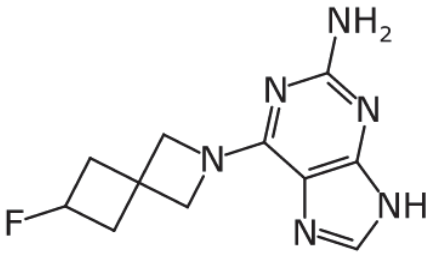
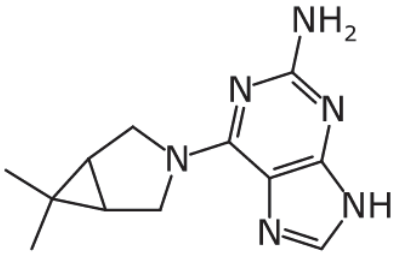
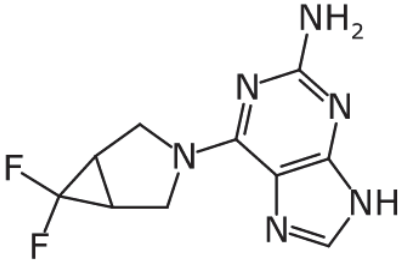
10	NRX02073		3-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-3-azabicyclo[3.1.0]hexane-1-carbonitrile
11	NRX02074		3-(9H-purin-6-yl)-3-azabicyclo[3.1.0]hexane-2-carbonitrile
12	NRX02075		(4-((5-chloro-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-methoxyphenyl)(morpholino)methanone

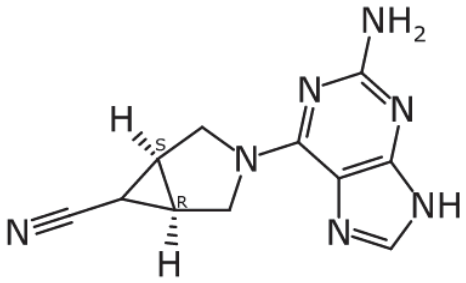
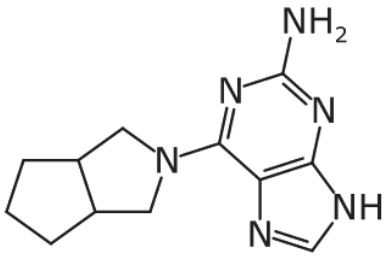
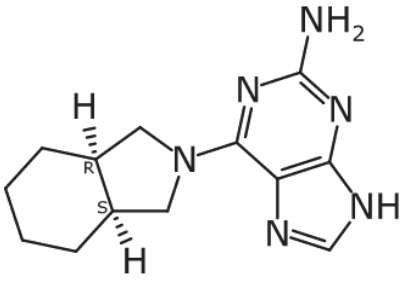
13	NRX02076		4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-2-((2-methoxy-4-(morpholine-4-carbonyl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile
14	NRX02077		2-amino-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile

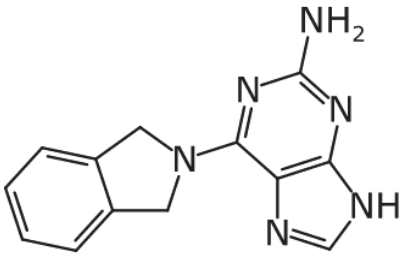
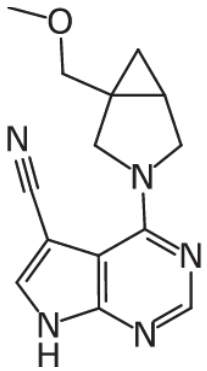
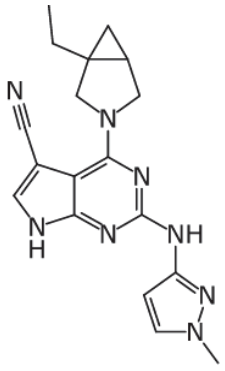
15	NRX02078		(1-(2-amino-7H-purin-6-yl)piperidin-3-yl)(6-hydroxypyridin-3-yl)methanone
16	NRX02081		4-(6-fluoro-2-azaspiro[3.3]heptan-2-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile
17	NRX02082		4-(3,3-dimethylpyrrolidin-1-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile

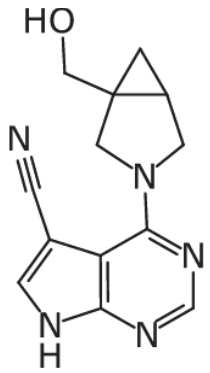
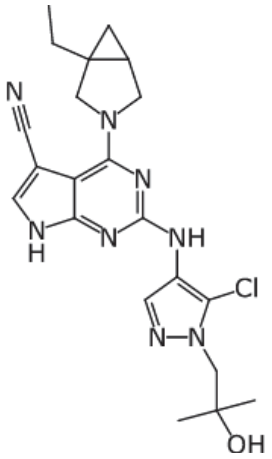
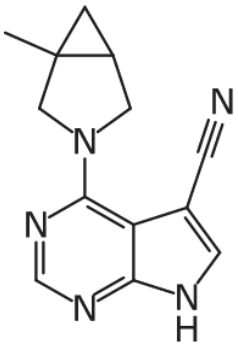
18	NRX02083		4-(6,6-dimethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile
19	NRX02084		4-(6,6-difluoro-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile
20	NRX02085		4-((1R,5S)-6-cyano-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile

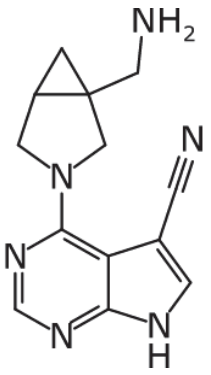
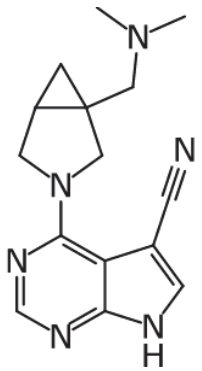
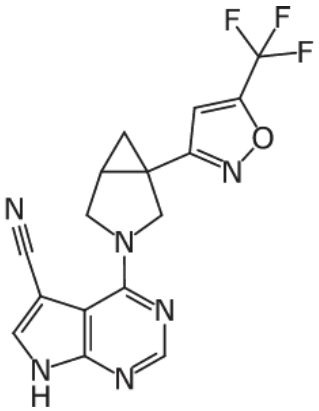
21	NRX02086		4-(hexahydrocyclopenta[c]pyrrol-2(1H)-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile
22	NRX02087		4-((3aR,7aS)-octahydro-2H-isoindol-2-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile
23	NRX02088		4-(isoindolin-2-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile

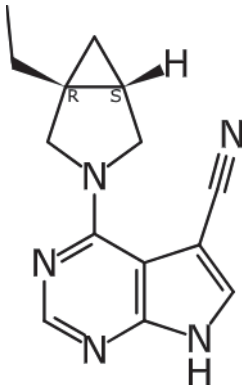
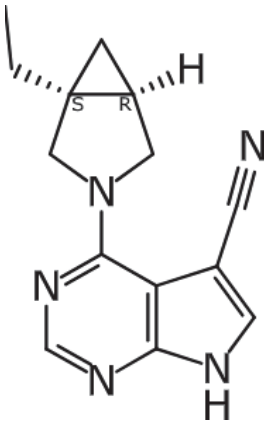
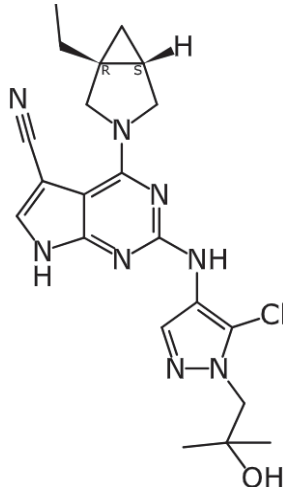
24	NRX02089		6-(6-fluoro-2-azaspiro[3.3]heptan-2-yl)-9H-purin-2-amine
25	NRX02090		6-(6,6-dimethyl-3-azabicyclo[3.1.0]hexan-3-yl)-9H-purin-2-amine
26	NRX02091		6-(6,6-difluoro-3-azabicyclo[3.1.0]hexan-3-yl)-9H-purin-2-amine

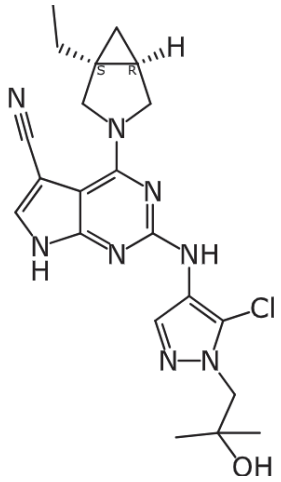
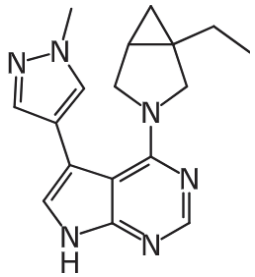
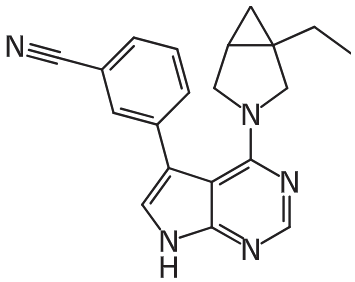
27	NRX02092		(1R,5S)-3-(2-amino-9H-purin-6-yl)-3-azabicyclo[3.1.0]hexane-6-carbonitrile
28	NRX02093		6-(hexahydrocyclopenta[c]pyrrol-2(1H)-yl)-9H-purin-2-amine
29	NRX02094		6-((3aR,7aS)-octahydro-2H-isoindol-2-yl)-9H-purin-2-amine

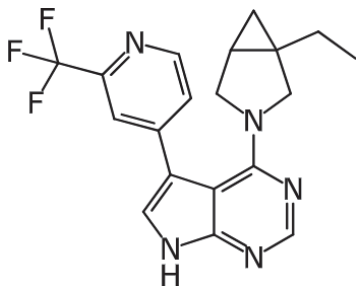
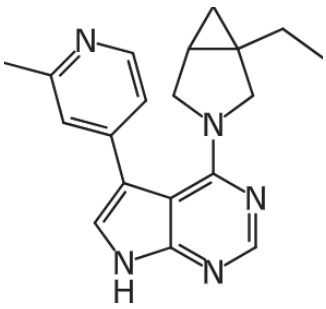
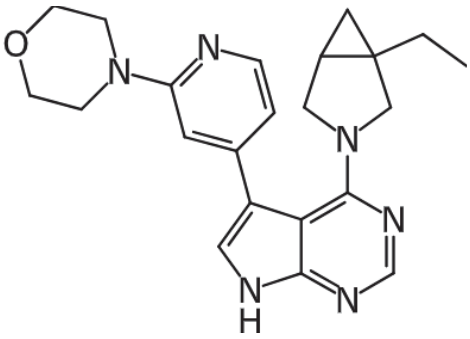
30	NRX02095		6-(isoindolin-2-yl)-9H-purin-2-amine
31	NRX02096		4-{1-(methoxymethyl)-3-azabicyclo[3.1.0]hexan-3-yl}-1H-1,5,7-triazaindene-3-carbonitrile
32	NRX02097		4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-2-((1-methyl-1H-pyrazol-3-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile

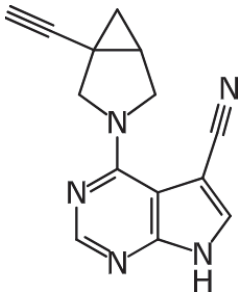
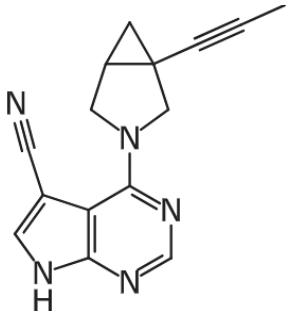
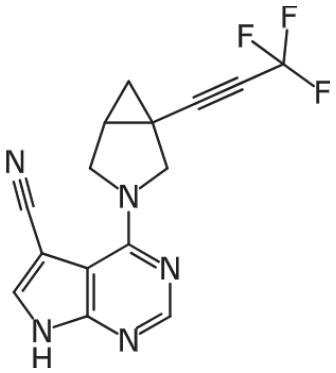
33	NRX02098		4-(1-(hydroxymethyl)-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile
34	NRX02099		2-((5-chloro-1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)amino)-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile
35	NRX02100		4-(1-methyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile

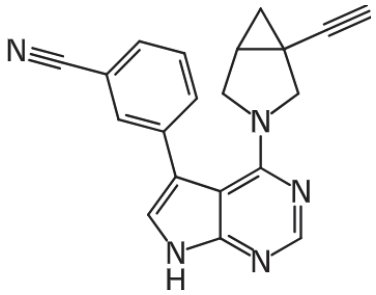
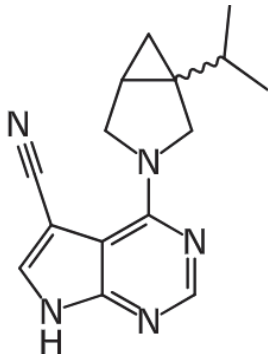
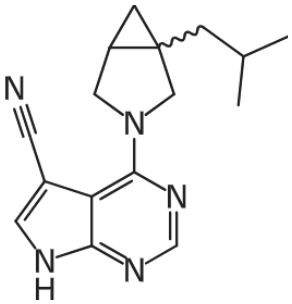
36	NRX02101		4-(1-(aminomethyl)-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile
37	NRX02102		4-(1-((dimethylamino)methyl)-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile
38	NRX02103		4-(1-(5-(trifluoromethyl)isoxazol-3-yl)-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2.3-d]pyrimidine-5-carbonitrile

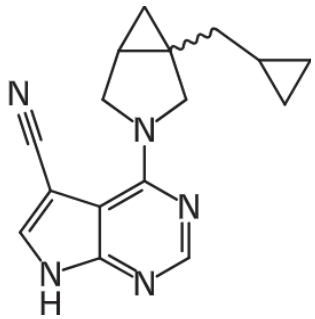
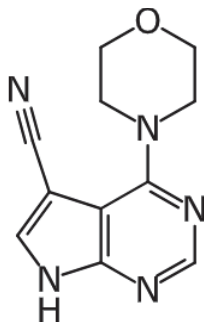
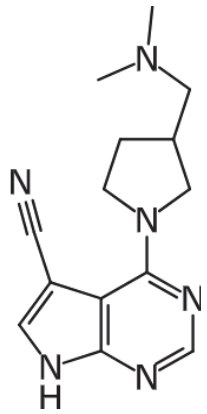
39	NRX02104		4-((1*R*,5*S*)-1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile
40	NRX02105		4-((1*S*,5*R*)-1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile
41	NRX02106		2-((5-chloro-1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)amino)-4-((1R,5S)-1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile

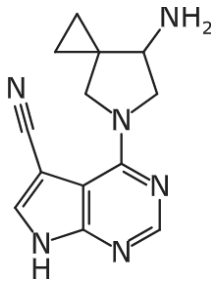
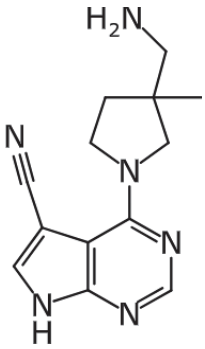
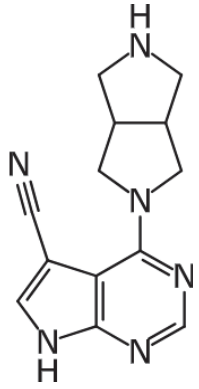
42	NRX02107		2-((5-chloro-1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)amino)-4-((1S,5R)-1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile
43	NRX02108		4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-3-(1-methyl-4-pyrazolyl)-1H-1,5,7-triazaindene
44	NRX02109		3-(4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile

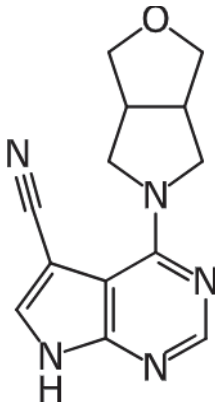
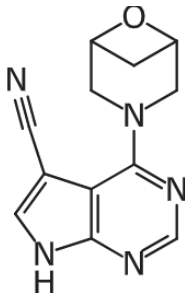
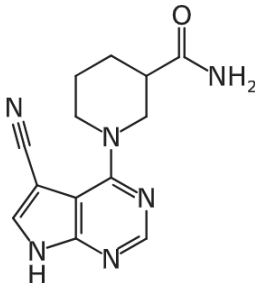
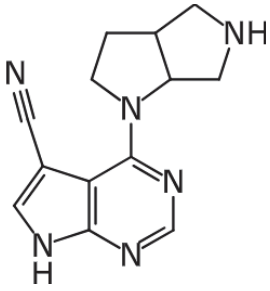
45	NRX02110		4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-5-(2-(trifluoromethyl)pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidine
46	NRX02111		4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-3-(2-methyl-4-pyridyl)-1H-1,5,7-triazaindene
47	NRX02112		4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-3-(2-morpholino-4-pyridyl)-1H-1,5,7-triazaindene

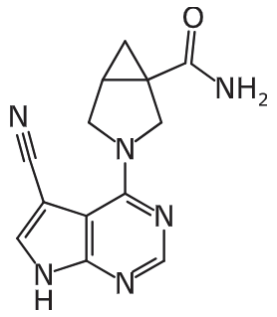
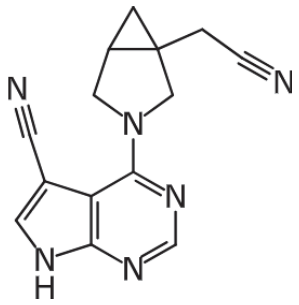
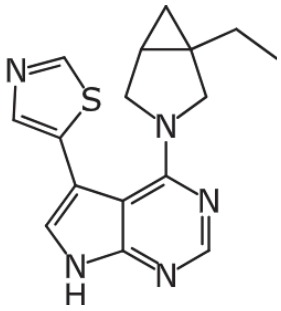
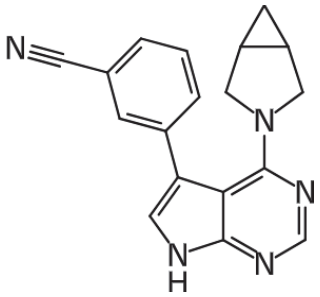
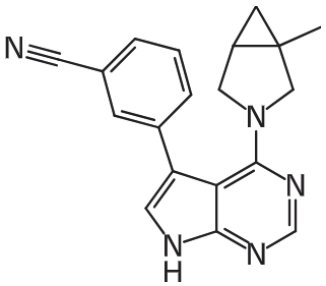
48	NRX02113		4-(1-ethynyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazaindene-3-carbonitrile
49	NRX02114		4-{1-(1-propynyl)-3-azabicyclo[3.1.0]hex-3-yl}-1H-1,5,7-triazaindene-3-carbonitrile
50	NRX02115		4-{1-(3,3,3-trifluoro-1-propynyl)-3-azabicyclo[3.1.0]hex-3-yl}-1H-1,5,7-triazaindene-3-carbonitrile

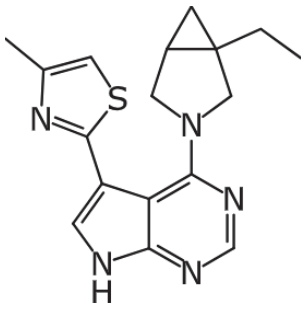
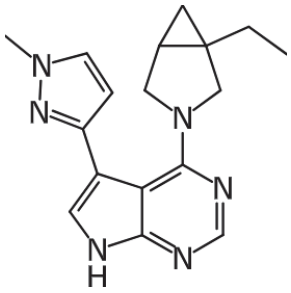
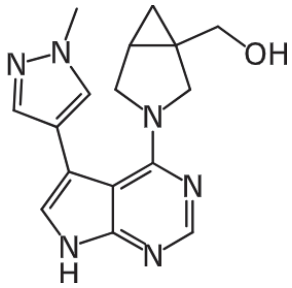
51	NRX02116		m-{4-(1-ethynyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-3-yl}benzonitrile
52	NRX02117		4-(1-isopropyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazaindene-3-carbonitrile
53	NRX02118		4-(1-isobutyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazaindene-3-carbonitrile

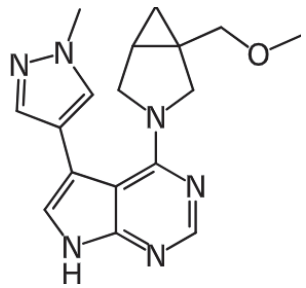
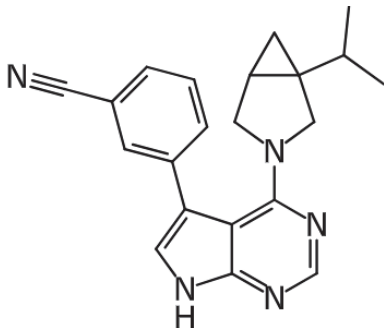
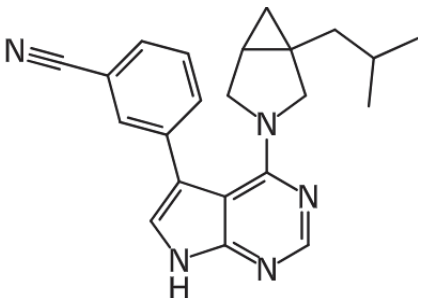
54	NRX02119		4-{1-(cyclopropylmethyl)-3-azabicyclo[3.1.0]hex-3-yl}-1H-1,5,7-triazaindene-3-carbonitrile
55	NRX02120		4-morpholino-1H-1,5,7-triazaindene-3-carbonitrile
56	NRX02121		4-{3-[(dimethylamino)methyl]-1-pyrrolidinyl}-1H-1,5,7-triazaindene-3-carbonitrile

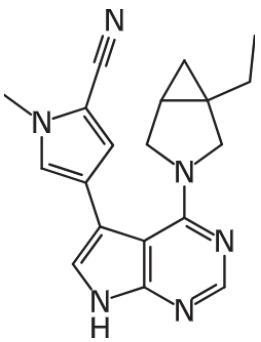
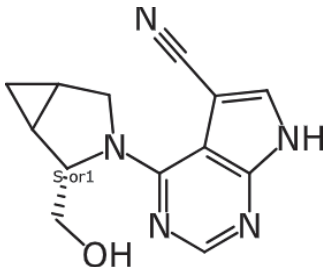
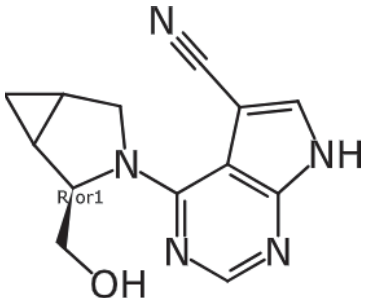
57	NRX02122		4-(7-amino-5-aza-5-spiro[2.4]heptyl)-1H-1,5,7-triazaindene-3-carbonitrile
58	NRX02123		4-[3-(aminomethyl)-3-methyl-1-pyrrolidinyl]-1H-1,5,7-triazaindene-3-carbonitrile
59	NRX02124		4-(3,7-diazabicyclo[3.3.0]oct-3-yl)-1H-1,5,7-triazaindene-3-carbonitrile

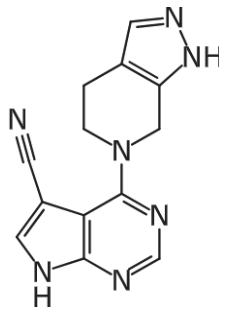
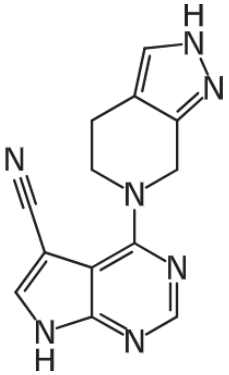
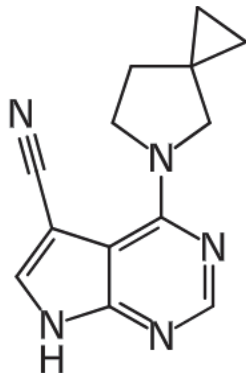
60	NRX02125		4-(3-oxa-7-azabicyclo[3.3.0]oct-7-yl)-1H-1,5,7-triazaindene-3-carbonitrile
61	NRX02126		4-(6-oxa-3-azabicyclo[3.1.1]hept-3-yl)-1H-1,5,7-triazaindene-3-carbonitrile
62	NRX02127		1-(3-cyano-1H-1,5,7-triazainden-4-yl)-3-piperidinecarboxamide
63	NRX02128		4-(2,7-diazabicyclo[3.3.0]oct-2-yl)-1H-1,5,7-triazaindene-3-carbonitrile

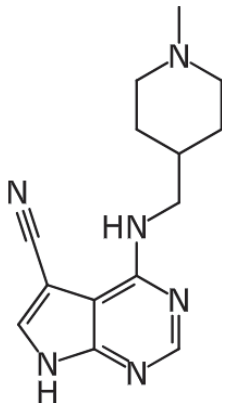
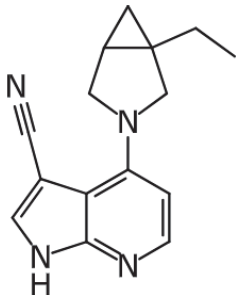
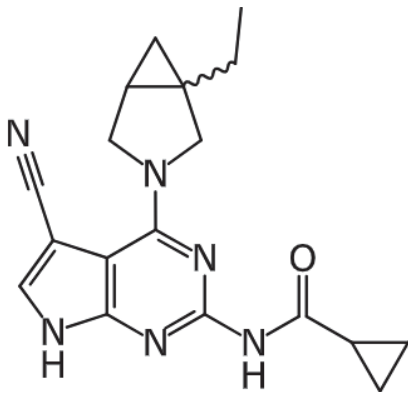
64	NRX02129		3-(3-cyano-1H-1,5,7-triazainden-4-yl)-3-azabicyclo[3.1.0]hexane-1-carboxamide
65	NRX02130		4-{1-(cyanomethyl)-3-azabicyclo[3.1.0]hex-3-yl}-1H-1,5,7-triazaindene-3-carbonitrile
66	NRX02131		5-(4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)thiazole
67	NRX02132		m-{4-(3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-3-yl}benzonitrile
68	NRX02133		m-{4-(1-methyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-3-yl}benzonitrile

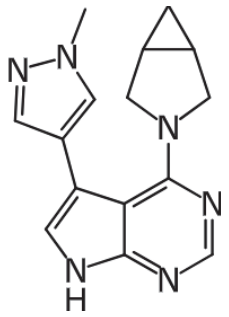
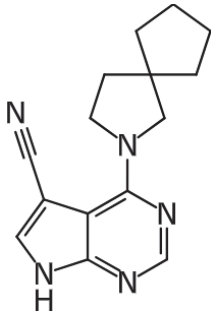
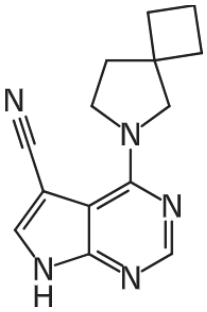
69	NRX02134		4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-3-(4-methyl-1,3-thiazol-2-yl)-1H-1,5,7-triazaindene
70	NRX02135		4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-3-(1-methyl-3-pyrazolyl)-1H-1,5,7-triazaindene
71	NRX02136		{3-[3-(1-methyl-4-pyrazolyl)-1H-1,5,7-triazainden-4-yl]-3-azabicyclo[3.1.0]hex-1-yl}methanol

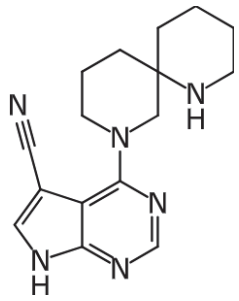
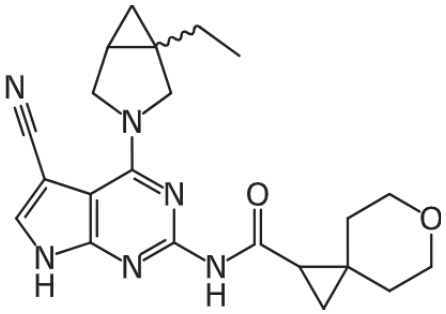
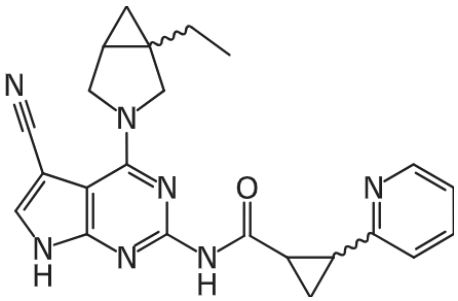
72	NRX02137		4-{1-(methoxymethyl)-3-azabicyclo[3.1.0]hex-3-yl}-3-(1-methyl-4-pyrazolyl)-1H-1,5,7-triazaindene
73	NRX02138		m-{4-(1-isopropyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-3-yl}benzonitrile
74	NRX02139		m-{4-(1-isobutyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-3-yl}benzonitrile

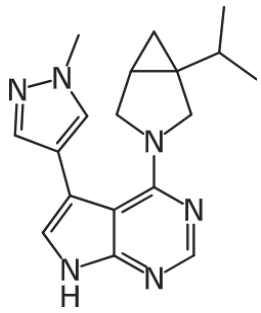
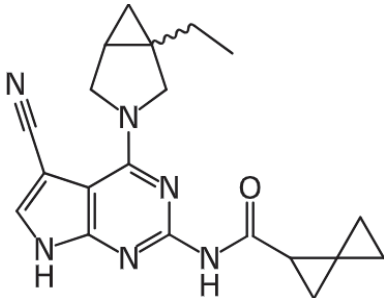
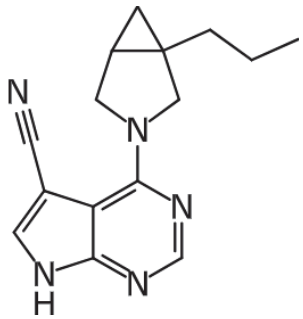
75	NRX02140		4-(4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-1-methyl-1H-pyrrole-2-carbonitrile
76	NRX02141		4-{(2S)-2-(hydroxymethyl)-3-azabicyclo[3.1.0]hex-3-yl}-1H-1,5,7-triazaindene-3-carbonitrile
77	NRX02142		4-{(2R)-2-(hydroxymethyl)-3-azabicyclo[3.1.0]hex-3-yl}-1H-1,5,7-triazaindene-3-carbonitrile

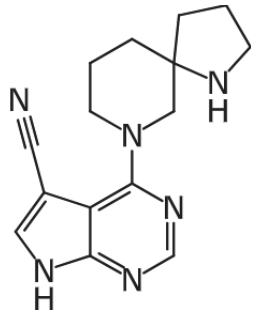
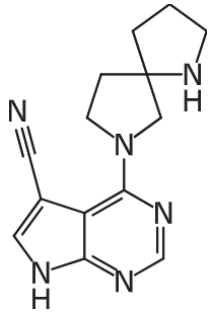
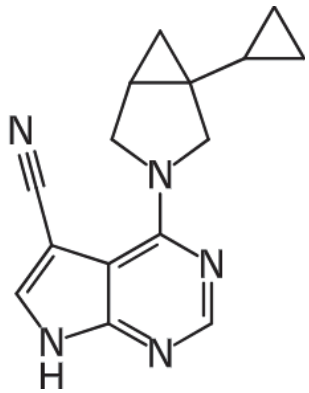
78	NRX02143		4',5',6',7'-tetrahydro-1H,3'H-1,2',3',5,5',7-hexaaza-[4,5'-biindenyl]-3-carbonitrile
79	NRX02144		4',5',6',7'-tetrahydro-1H,2'H-1,2',3',5,5',7-hexaaza-[4,5'-biindenyl]-3-carbonitrile
80	NRX02145		4-(5-aza-5-spiro[2.4]heptyl)-1H-1,5,7-triazaindene-3-carbonitrile

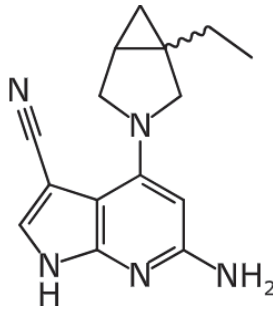
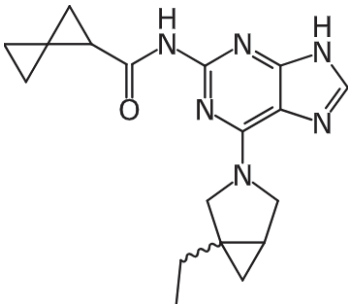
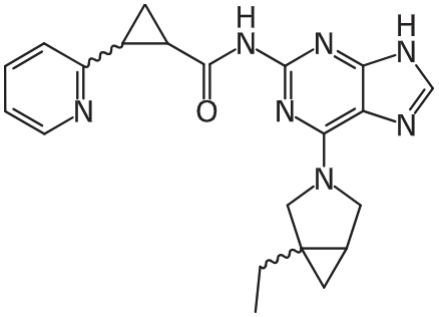
81	NRX02146		4-{[(1-methyl-4-piperidyl)methyl]amino}-1H-1,5,7-triazaindene-3-carbonitrile
82	NRX02147		4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,7-diazaindene-3-carbonitrile
83	NRX02148		N-{3-cyano-4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-6-yl}cyclopropanecarboxamide

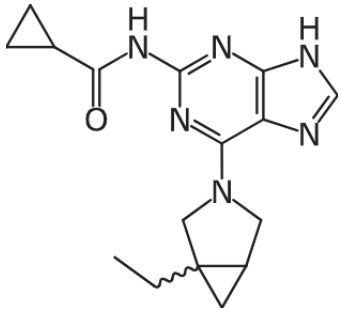
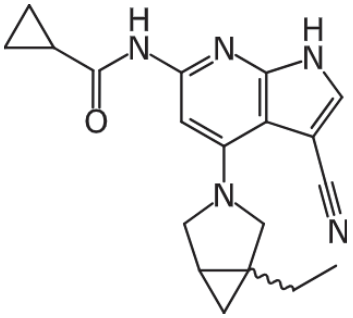
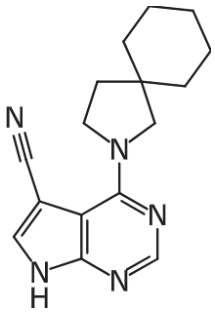
84	NRX02149		4-(3-azabicyclo[3.1.0]hex-3-yl)-3-(1-methyl-4-pyrazolyl)-1H-1,5,7-triazaindene
85	NRX02150		4-(2-aza-2-spiro[4.4]nonyl)-1H-1,5,7-triazaindene-3-carbonitrile
86	NRX02151		4-(6-aza-6-spiro[3.4]octyl)-1H-1,5,7-triazaindene-3-carbonitrile

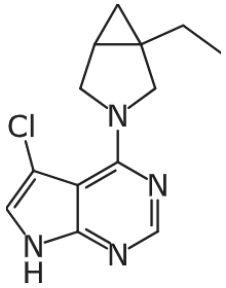
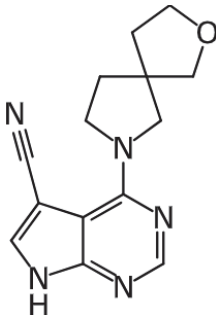
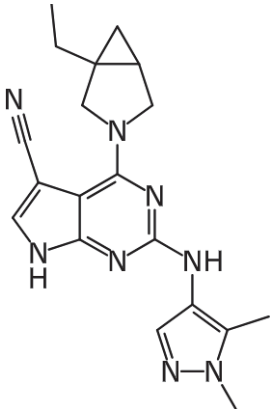
87	NRX02152		4-(1,8-diaza-8-spiro[5.5]undecyl)-1H-1,5,7-triazaindene-3-carbonitrile
88	NRX02153		N-{3-cyano-4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-6-yl}-6-oxa-1-spiro[2.5]octanecarboxamide
89	NRX02154		N-{3-cyano-4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-6-yl}-2-(2-pyridyl)cyclopropanecarboxamide

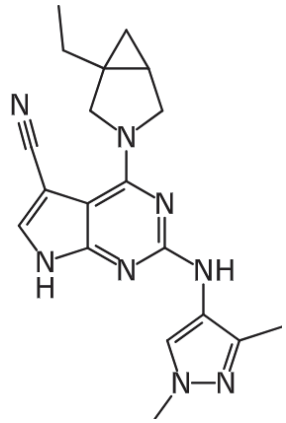
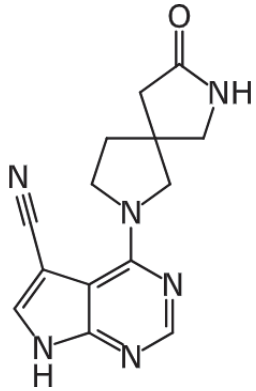
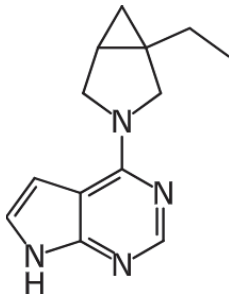
90	NRX02155		4-(1-isopropyl-3-azabicyclo[3.1.0]hex-3-yl)-3-(1-methyl-4-pyrazolyl)-1H-1,5,7-triazaindene
91	NRX02156		N-{3-cyano-4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-6-yl}-1-spiro[2.2]pentanecarboxamide
92	NRX02157		4-(1-propyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazaindene-3-carbonitrile

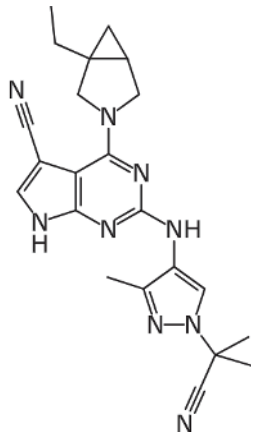
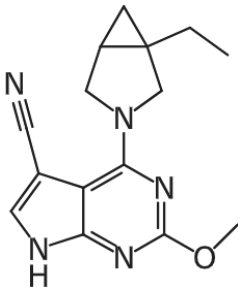
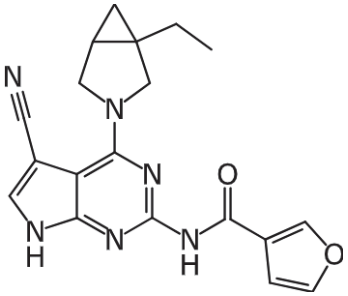
93	NRX02158		4-(1,7-diaza-7-spiro[4.5]decyl)-1H-1,5,7-triazaindene-3-carbonitrile
94	NRX02159		4-(1,7-diaza-7-spiro[4.4]nonyl)-1H-1,5,7-triazaindene-3-carbonitrile
95	NRX02160		4-(1-cyclopropyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazaindene-3-carbonitrile

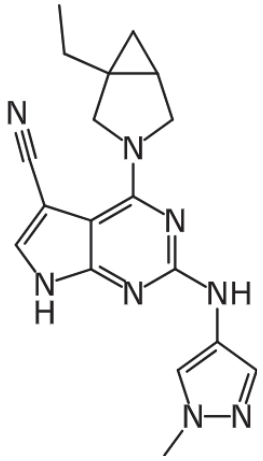
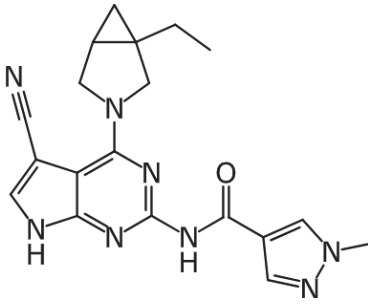
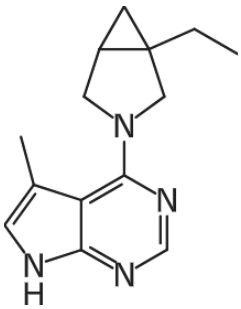
96	NRX02161		6-amino-4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,7-diazaindene-3-carbonitrile
97	NRX02162		N-{6-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-2-purinyl}-1-spiro[2.2]pentanecarboxamide
98	NRX02163		N-{6-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-2-purinyl}-2-(2-pyridyl)cyclopropanecarboxamide

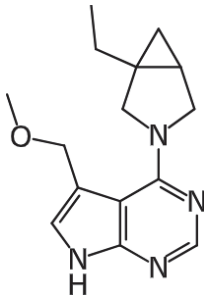
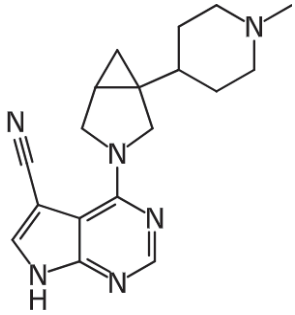
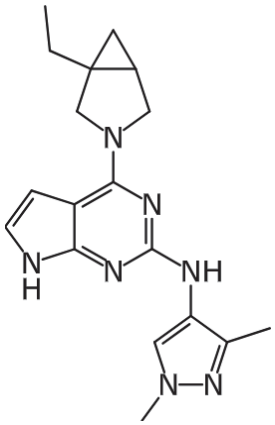
99	NRX02164		N-{6-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-2-purinyl)cyclopropanecarboxamide
100	NRX02165		N-{3-cyano-4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,7-diazainden-6-yl}cyclopropanecarboxamide
101	NRX02166		4-(2-aza-2-spiro[4.5]decyl)-1H-1,5,7-triazaindene-3-carbonitrile

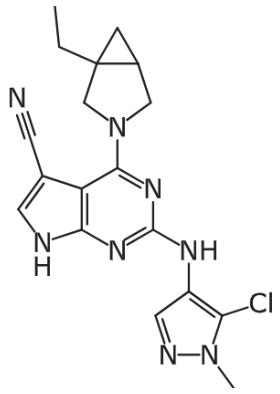
102	NRX02167		3-chloro-4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazaindene
103	NRX02168		4-(2-oxa-7-aza-7-spiro[4.4]nonyl)-1H-1,5,7-triazaindene-3-carbonitrile
104	NRX02169		4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-6-(1-methyl-5-methyl-4-pyrazolylamino)-1H-1,5,7-triazaindene-3-carbonitrile

105	NRX02170		4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-6-(1-methyl-3-methyl-4-pyrazolylamino)-1H-1,5,7-triazaindene-3-carbonitrile
106	NRX02171		4-(8-oxo-2,7-diaza-2-spiro[4.4]nonyl)-1H-1,5,7-triazaindene-3-carbonitrile
107	NRX02172		4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazaindene

108	NRX02173		2-((1-(2-cyanopropan-2-yl)-3-methyl-1*H*-pyrazol-4-yl)amino)-4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile
109	NRX02174		4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-6-methoxy-1H-1,5,7-triazaindene-3-carbonitrile
110	NRX02175		N-{3-cyano-4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-6-yl}-3-furamide

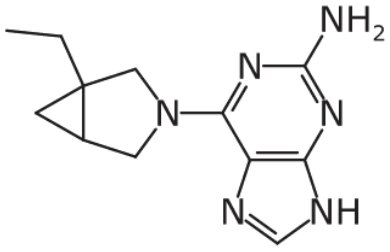
111	NRX02176		4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-6-(1-methyl-4-pyrazolylamino)-1H-1,5,7-triazaindene-3-carbonitrile
112	NRX02177		N-{3-cyano-4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-6-yl}-1-methyl-4-pyrazolecarboxamide
113	NRX02178		4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-3-methyl-1H-1,5,7-triazaindene

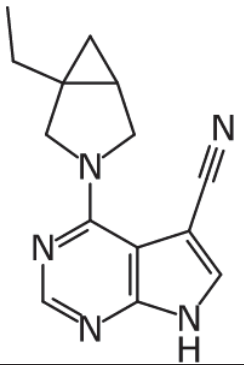
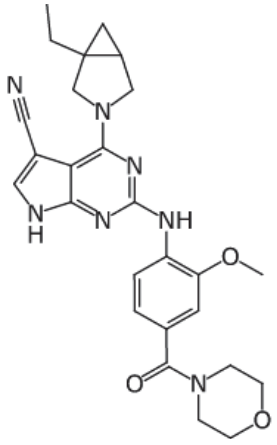
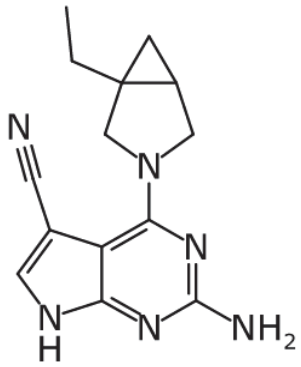
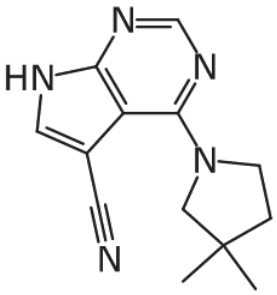
114	NRX02179		4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-5-(methoxymethyl)-7H-pyrrolo[2,3-d]pyrimidine
115	NRX02180		4-{1-(1-methyl-4-piperidyl)-3-azabicyclo[3.1.0]hex-3-yl}-1H-1,5,7-triazaindene-3-carbonitrile
116	NRX02181		1-methyl-3-methyl-4-pyrazolyl){4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-6-yl}amine

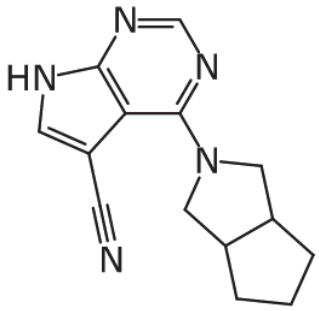
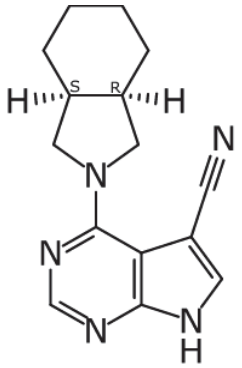
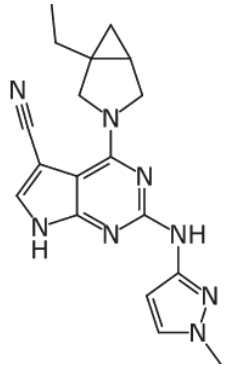
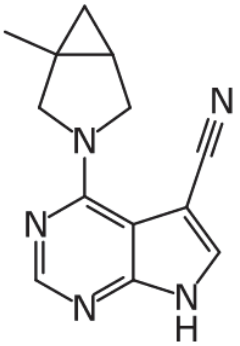
117	NRX02182		2-((5-chloro-1-methyl-1H-pyrazol-4-yl)amino)-4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile

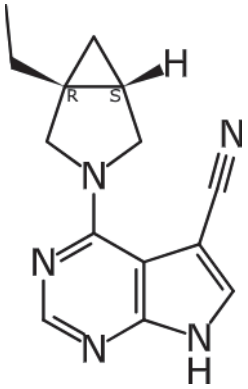
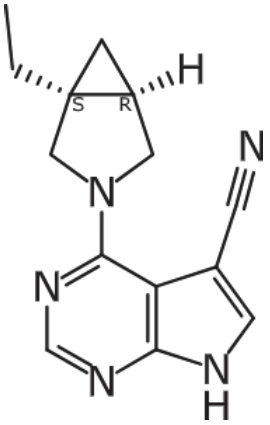
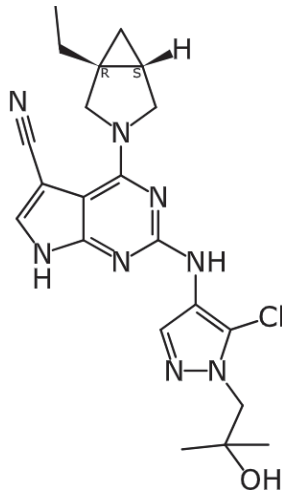
In one embodiment, the compound of the present invention may be a compound selected from the group consisting of the compounds in Table 2 below, or a pharmaceutically acceptable salt thereof.

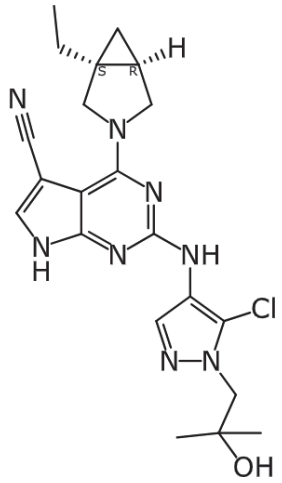
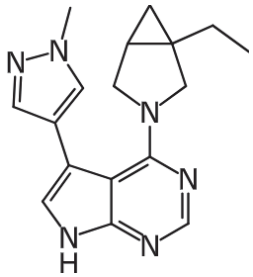
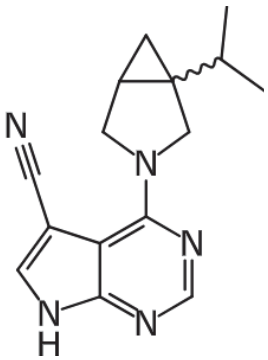
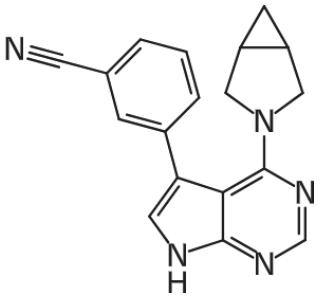
[Table 2]

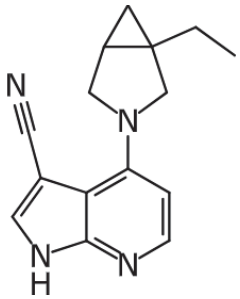
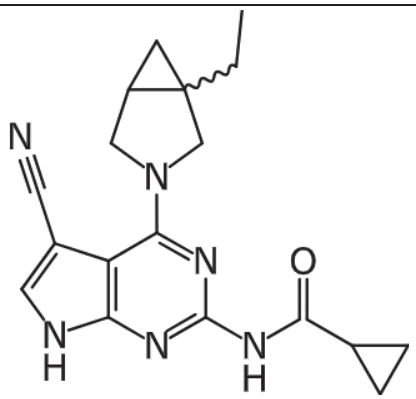
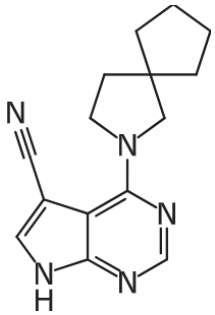
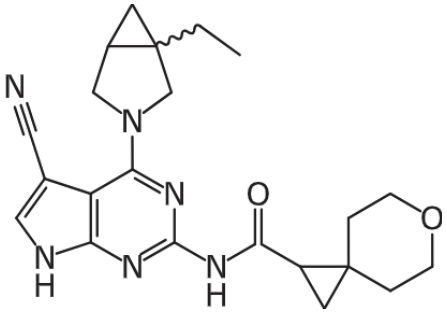
Name	Formula	Compound
NRX02004		6-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-9H-purin-2-amine

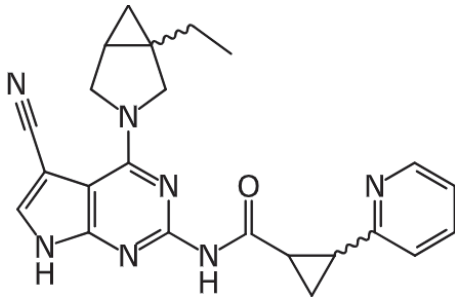
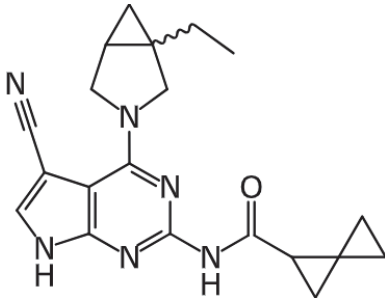
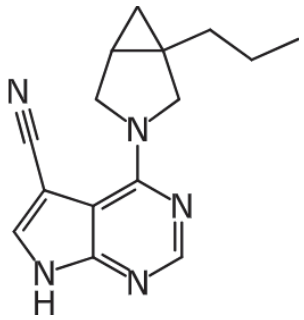
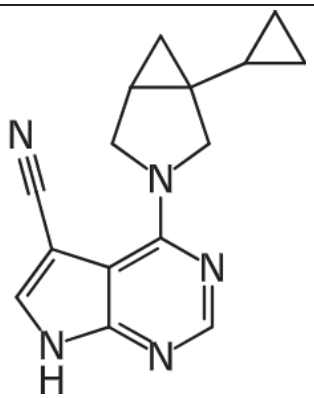
NRX02067		4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1,5,7-triaza-1H-indene-3-carbonitrile
NRX02076		4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-2-((2-methoxy-4-(morpholine-4-carbonyl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile
NRX02077		2-amino-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile
NRX02082		4-(3,3-dimethylpyrrolidin-1-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile

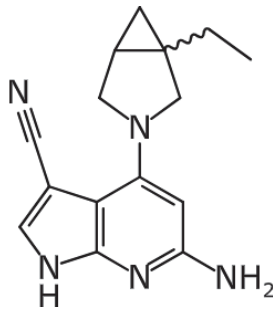
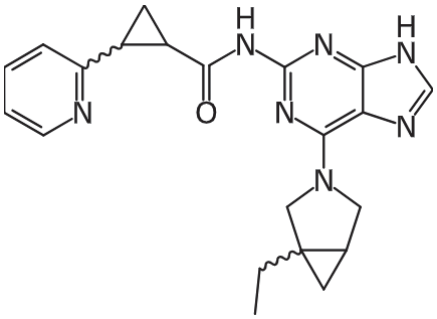
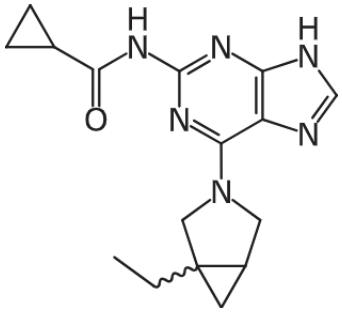
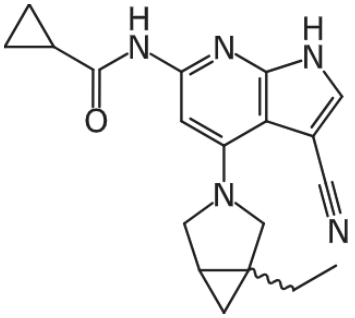
NRX02086		4-(hexahydrocyclopenta[c]pyrrol-2(1H)-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile
NRX02087		4-((3aR,7aS)-octahydro-2H-isoindol-2-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile
NRX02097		4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-2-((1-methyl-1H-pyrazol-3-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile
NRX02100		4-(1-methyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile

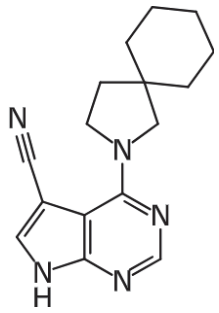
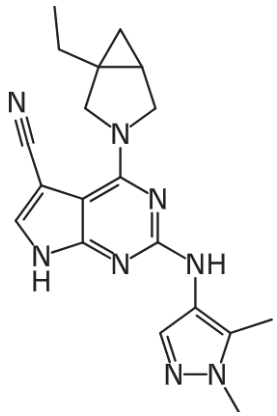
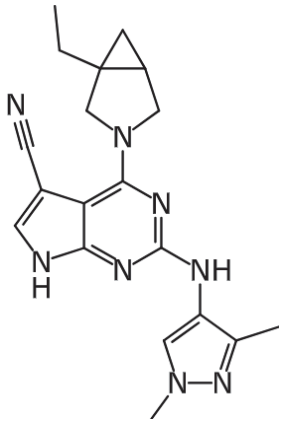
NRX02104		4-((1*R*,5*S*)-1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile
NRX02105		4-((1*S*,5*R*)-1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile
NRX02106		2-((5-chloro-1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)amino)-4-((1R,5S)-1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile

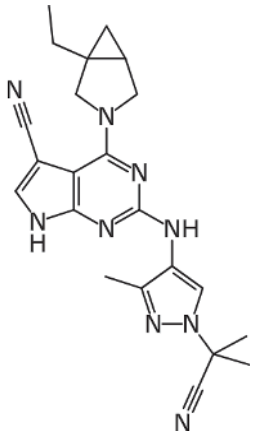
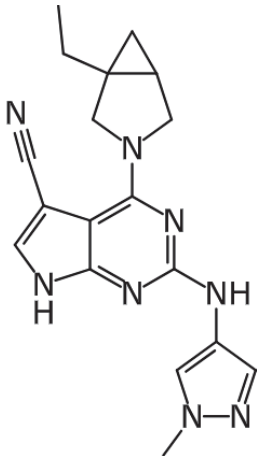
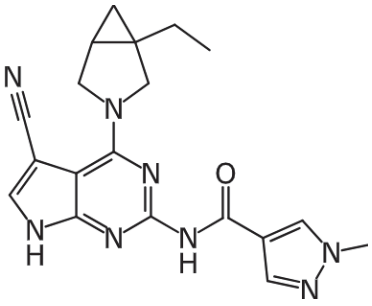
NRX02107		2-((5-chloro-1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)amino)-4-((1S,5R)-1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile
NRX02108		4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-3-(1-methyl-4-pyrazolyl)-1H-1,5,7-triazaindene
NRX02117		4-(1-isopropyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazaindene-3-carbonitrile
NRX02132		m-{4-(3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-3-yl}benzonitrile

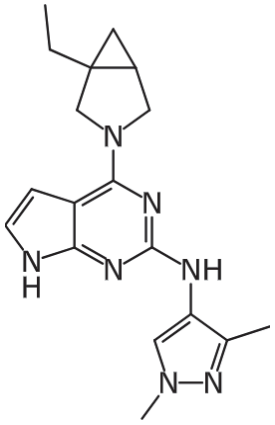
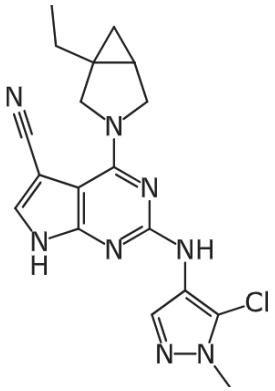
NRX02147		4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,7-diazaindene-3-carbonitrile
NRX02148		N-{3-cyano-4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-6-yl}cyclopropanecarboxamide
NRX02150		4-(2-aza-2-spiro[4.4]nonyl)-1H-1,5,7-triazaindene-3-carbonitrile
NRX02153		N-{3-cyano-4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-6-yl}-6-oxa-1-spiro[2.5]octanecarboxamide

NRX02154		N-{3-cyano-4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-6-yl}2-(2-pyridyl)cyclopropanecarboxamide
NRX02156		N-{3-cyano-4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-6-yl}-1-spiro[2.2]pentanecarboxamide
NRX02157		4-(1-propyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazaindene-3-carbonitrile
NRX02160		4-(1-cyclopropyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazaindene-3-carbonitrile

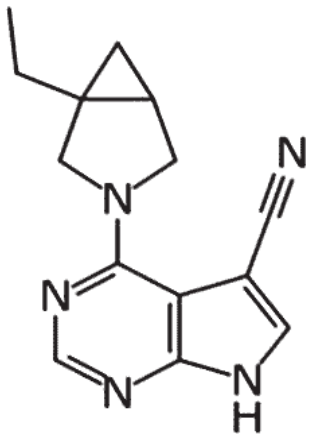
NRX02161		6-amino-4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,7-diazaindene-3-carbonitrile
NRX02163		N-{6-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-2-purinyl}2-(2-pyridyl)cyclopropanecarboxamide
NRX02164		N-{6-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-2-purinyl}cyclopropanecarboxamide
NRX02165		N-{3-cyano-4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,7-diazainden-6-yl}cyclopropanecarboxamide

NRX02166		4-(2-aza-2-spiro[4.5]decyl)-1H-1,5,7-triazaindene-3-carbonitrile
NRX02169		4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-6-(1-methyl-5-methyl-4-pyrazolylamino)-1H-1,5,7-triazaindene-3-carbonitrile
NRX02170		4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-6-(1-methyl-3-methyl-4-pyrazolylamino)-1H-1,5,7-triazaindene-3-carbonitrile

NRX02173		2-((1-(2-cyanopropan-2-yl)-3-methyl-1*H*-pyrazol-4-yl)amino)-4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile
NRX02176		4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-6-(1-methyl-4-pyrazolylamino)-1H-1,5,7-triazaindene-3-carbonitrile
NRX02177		N-{3-cyano-4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-6-yl}-1-methyl-4-pyrazolecarboxamide

NRX02181		1-methyl-3-methyl-4-pyrazolyl){4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-6-yl}amine
NRX02182		2-((5-chloro-1-methyl-1H-pyrazol-4-yl)amino)-4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile

In one embodiment, the present invention relates to the following compound (NRX02067) or a pharmaceutically acceptable salt thereof.



The compound (NRX02067) (4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1,5,7-triaza-1H-indene-3-carbonitrile) is known as

4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d] pyrimidine-5-

carbonitrile,

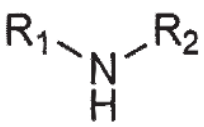
4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-1,5,7-triaza-1H-indene-3-carbonitrile,

4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazaindene-3-carbonitrile, or

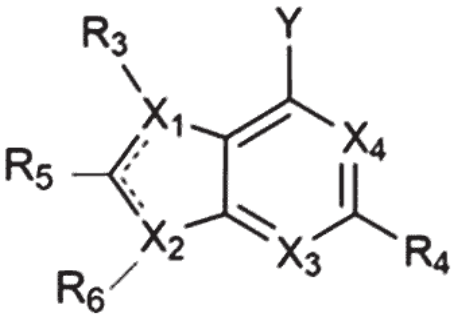
4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-1H-1,5,7-triazaindene-3-carbonitrile.

The present invention relates to a method for preparing the compound of the present invention or a pharmaceutically acceptable salt thereof, comprising the step of reacting a compound of Formula 2 below and a compound of Formula 3 below.

[Formula 2]



[Formula 3]



wherein,

····· is each independently absent or a single bond,

X_1 to X_4 are each independently C or N,

Y is halogen,

R_1 and R_2 are each independently hydrogen, alkyl, -O-alkyl, cycloalkyl,

heterocycloalkyl, aryl, heteroaryl, -alkyl-cycloalkyl, -alkyl-heterocycloalkyl, -alkyl-aryl, or -alkyl-heteroaryl,

or R_1 and R_2 are heterocycloalkyl formed by linking R_1 and R_2 together,

R_3 is absent, or is hydrogen, halo, cyano, alkyl, -alkyl-O-alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl,

R_4 is hydrogen, halo, cyano, $-NH_2$, -alkyl, -alkyl-O-alkyl, -O-alkyl, $-N(R_{4A})(R_{4B})$, $-N(R_{4D})C(=O)(R_{4C})$, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl,

wherein R_{4A} to R_{4D} are each independently hydrogen, alkyl, cycloalkyl, heterocycloalkyl, -cycloalkyl-heteroaryl, heteroaryl, aryl, or -aryl-C(=O)-heterocycloalkyl,

R_5 is hydrogen, cyano, alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl,

R_6 is absent, or is hydrogen, cyano, alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl,

wherein the cycloalkyl, heterocycloalkyl, aryl, or heteroaryl may be substituted with one or more selected from the group consisting of halo, NH_2, cyano, haloalkyl, alkyl, alkenyl, alkynyl, -alkynyl-alkyl, -O-alkyl, -alkyl-CN, -alkyl-OH, -alkyl-O-alkyl, $-alkyl-NH_2$, -alkyl-N(alkyl)(alkyl), -alkyl-cycloalkyl, NH_2, -N(alkyl)(alkyl), $-C(=O)-NH_2$, -C(=O)-heteroaryl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein the cycloalkyl, heterocycloalkyl, aryl, or heteroaryl may be unsubstituted or substituted with alkyl or -OH, wherein the alkyl may be unsubstituted or substituted with halo.

The present invention provides a pharmaceutical composition for preventing or treating a disease mediated by or associated with LRRK2, comprising the compound or a pharmaceutically acceptable salt thereof.

In one embodiment, the disease mediated by or associated with LRRK2 may be Parkinson's disease.

The present invention provides a method for preventing or treating a disease mediated by or associated with LRRK2, comprising the step of administering the compound, or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

The present invention provides a method for preventing or treating Parkinson's disease, comprising the step of administering the compound, or a pharmaceutically acceptable salt thereof, to a Parkinson's patient.

【Advantageous Effects of Invention】

The novel compound of the present invention has excellent inhibitory activity against LRRK2 protein kinase, and thus is useful for preventing or treating diseases mediated by or associated with LRRK2.

In addition, the novel compound of the present invention is useful not only for the action of disease modifying therapy, but also for symptomatic treatment of diseases related to dopamine secretion by acting as an A2AR antagonist.

Therefore, the novel compound of the present invention can be usefully used to treat or prevent Parkinson's disease.

【Brief Description of Drawings】

FIG. 1 is a result showing the degree of inhibiting the enzymatic activity of LRRK2 protein by performing an ADP-glo assay.

FIG. 2 is a result showing the degree of inhibiting the activity of LRRK2 protein by performing a NanoBRET assay in HEK 293 cells.

FIG. 3 is a result of quantitatively evaluating the level of inhibiting phosphorylation by binding to LRRK2 protein in a T-REx™ 293 LRRK2 Wild type cell line.

FIG. 4 is a Western Blot result verifying the intracellular activity of a compound against the LRRK2 kinase domain in a T-REx™ 293 LRRK2 Wild type cell line.

FIG. 5 is a result of confirming the cytotoxicity (Cell viability assay) of a compound against the LRRK2 kinase domain in a T-REx™ 293 LRRK2 Wild type cell line.

FIG. 6 is a result of analyzing by molecular calculation that a compound can act as both a type I inhibitor and a type II inhibitor against the LRRK2 kinase domain, and that a racemic mixture can bind more stably than individual structural isomers.

【Best Mode for Carrying Out the Invention】

Hereinafter, embodiments and preparation examples of the present invention will be described in detail with reference to the accompanying drawings so that those of ordinary skill in the art to which the present invention pertains can easily practice the invention. However, the present invention may be embodied in various different forms and should not be construed as being limited to the embodiments and preparation examples described herein.

Throughout the specification of the present invention, when a certain part is described as "comprising" a certain component, this means that other components are not excluded, but rather other components may be further included, unless specifically stated to the contrary.

The term "," as used in the Formulas of the present invention, means that a moiety or substituent "R" is attached to a backbone structure, in accordance with conventions used in the art.

The term "alkyl," as used herein, refers to a hydrocarbon having substituted or unsubstituted primary, secondary, tertiary, and/or quaternary carbon atoms, and includes a saturated aliphatic group comprising straight-chain, branched, cyclic forms, or combinations thereof, or stereochemical structures thereof. For example, an alkyl group may have 1 to 20

carbon atoms (i.e., C1-C20 alkyl), 1 to 10 carbon atoms (i.e., C1-C10 alkyl), or 1 to 6 carbon atoms (i.e., C1-C6 alkyl). Unless otherwise defined, in a preferred embodiment, alkyl refers to C1-C6 alkyl. Examples of suitable alkyl groups include, but are not limited to, methyl (Me, -CH3), ethyl (Et, -CH2CH3), 1-propyl (n-Pr, n-propyl, -CH2CH2CH3), 2-propyl (i-Pr, i-propyl, -CH(CH3)2), 1-butyl (n-Bu, n-butyl, -CH2CH2CH2CH3), 2-methyl-1-propyl (i-Bu, i-butyl, -CH2CH(CH3)2), 2-butyl (s-Bu, s-butyl, -CH(CH3)CH2CH3), 2-methyl-2-propyl (t-Bu, t-butyl, -C(CH3)3), 1-pentyl (n-pentyl, -CH2CH2CH2CH2CH3), 2-pentyl (-CH(CH3)CH2CH2CH3), 3-pentyl (-CH(CH2CH3)2), 2-methyl-2-butyl (-C(CH3)2CH2CH3), 3-methyl-2-butyl (-CH(CH3)CH(CH3)2), 3-methyl-1-butyl (-CH2CH2CH(CH3)2), 2-methyl-1-butyl (-CH2CH(CH3)CH2CH3), 1-hexyl (-CH2CH2CH2CH2CH2CH3), 2-hexyl (-CH(CH3)CH2CH2CH2CH3), 3-hexyl (-CH(CH2CH3)(CH2CH2CH3)), 2-methyl-2-pentyl (-C(CH3)2CH2CH2CH3), 3-methyl-2-pentyl (-CH(CH3)CH(CH3)CH2CH3), 4-methyl-2-pentyl (-CH(CH3)CH2CH(CH3)2), 3-methyl-3-pentyl (-C(CH3)(CH2CH3)2), 2-methyl-3-pentyl (-CH(CH2CH3)CH(CH3)2), 2,3-dimethyl-2-butyl (-C(CH3)2CH(CH3)2), 3,3-dimethyl-2-butyl (-CH(CH3)C(CH3)3), and octyl (-(CH2)7CH3). Furthermore, the term "alkyl" as used throughout the specification, preparation examples, and claims is intended to include both unsubstituted and substituted alkyl groups, the latter of which refers to alkyl moieties having substituents replacing one or more hydrogens on the carbons of the hydrocarbon backbone, including haloalkyl groups such as trifluoromethyl and the like.

The term "alkenyl," as used herein, refers to a hydrocarbon having primary, secondary, tertiary, and/or quaternary carbon atoms, which includes straight-chain, branched, and cyclic forms, or combinations thereof, and has one or more regions of unsaturation, i.e., a carbon-carbon sp2 double bond. For example, an alkenyl group may have 2 to 20 carbon atoms (i.e., C2-C20 alkenyl), 2 to 12 carbon atoms (i.e., C2-C12 alkenyl), 2 to 10 carbon atoms (i.e., C2-

C10 alkenyl), or 2 to 6 carbon atoms (i.e., C2-C6 alkenyl). Examples of suitable alkenyl groups include, but are not limited to, vinyl (-CH=CH2), allyl (-CH2CH=CH2), cyclopentenyl (-C5H7), and 5-hexenyl (-CH2CH2CH2CH2CH=CH2).

The term "alkynyl," as used herein, refers to a group having one or more carbon-carbon triple bonds.

The term " C_{x-y} " or " C_x-C_y," as used herein, when used in conjunction with a chemical moiety such as acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy, is understood to include groups containing x to y carbons in the chain. C_0 alkyl represents a hydrogen when the group is at a terminal position, and a bond when it is at an internal position. For example, a (C_1-C_6) alkyl group contains 1 to 6 carbon atoms in a chain.

The term "alkoxy," as used herein, refers to an alkyl group attached to the parent compound through an oxygen atom, which may be represented as -O-alkyl, wherein the alkyl group is as defined herein and may be substituted or unsubstituted. The alkyl group of the alkoxy group may have, for example, 1 to 20 carbon atoms (i.e., C1-C20 alkoxy), 1 to 12 carbon atoms (i.e., C1-C12 alkoxy), 1 to 10 carbon atoms (i.e., C1-C10 alkoxy), or 1 to 6 carbon atoms (i.e., C1-C6 alkoxy). Examples of suitable alkoxy groups may be, but are not limited to, methoxy (-O-CH3 or -OMe), ethoxy (-OCH2CH3 or -OEt), and t-butoxy (-OC(CH3)3 or -O-tBu) etc.

The term "alkoxyalkyl," as used herein, refers to an alkyl group substituted with an alkoxy group as defined herein, and may also be represented as -alkyl-O-alkyl.

The term "acyl," as used herein, refers to a -C(=O)- group.

The term "arylacyl," as used herein, refers to an acyl group, as defined herein, wherein at least one hydrogen atom is substituted with an aryl group as defined herein.

The term "-C(=O)heteroaryl," as used herein, refers to an acyl group, as defined herein,

wherein at least one hydrogen atom is substituted with a heteroaryl group as defined herein.

The terms "cycloalkyl" and "carbocyclyl," as used herein, refer to a monovalent, non-aromatic, saturated or partially unsaturated ring having 3 to 12 carbon atoms (C3-C12) as a monocyclic ring or 7 to 12 carbon atoms as a bicyclic ring. Bicyclic carbocyclyl having 7 to 12 carbon atoms may be arranged, for example, in a bicyclo[4,5], [5,5], [5,6] or [6,6] system, and bicyclic carbocyclyl having 9 to 10 ring atoms may be arranged in a bicyclo[5,6] or [6,6] system, or in a bridged system such as bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane and bicyclo[3.2.2]nonane. Examples of monocyclic carbocyclyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, cyclohexadienyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, cyclododecyl and the like.

The term "heterocycloalkyl," as used herein, refers to a substituted or unsubstituted, monovalent or divalent, saturated or partially saturated non-aromatic ring, which is monocyclic, bicyclic, or polycyclic, containing one or more heteroatoms, preferably 1 to 4 heteroatoms, and more preferably 1 to 2 heteroatoms in the ring. Furthermore, when "heterocycloalkyl" is a bicyclic or polycyclic ring system having two or more cyclic rings wherein two or more carbons are common to two adjacent rings, at least one of the rings is heterocyclic, and the other cyclic ring(s) may be, for example, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, and/or heterocycloalkyl. The bicyclic or polycyclic ring system may be a fused, bridged, or spiro ring system. Examples of "heterocycloalkyl" include, but are not limited to, piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, lactonyl, lactamyl, azetidinyl, dihydropyridinyl, dihydroindolyl, tetrahydropyridinyl(piperidinyl), tetrahydrothiophenyl, sulfur-oxidized tetrahydrothiophenyl, indolenyl, 4-piperidinyl, 2-pyrrolidonyl, tetrahydrofuranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl,

decahydroquinolinyl, octahydroisoquinolinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, pyranyl, chromenyl, xanthenyl, phenoxathiinyl, 2H-pyrrolyl, 3H-indolyl, 4H-quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4aH-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, phenanthrolinyl, phanazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, quinuclidinyl, and oxazolidinyl, piperidine, piperazine, pyrrolidine, morpholine, lactone, lactam, and the like, each of which may be substituted or unsubstituted.

The term "aryl," as used herein, includes a substituted or unsubstituted, monovalent or divalent aromatic hydrocarbon group, which is monocyclic, bicyclic, or polycyclic, wherein each of the atoms of the ring is carbon. Preferably, the aryl ring is a 6- to 20-membered ring, a 6- to 14-membered ring, a 6- to 10-membered ring, or more preferably a 6-membered ring. The aryl group may be a polycyclic ring system having two or more cyclic rings wherein two or more carbons are common to two adjacent rings, wherein at least one of the rings is aromatic, and the other cyclic ring(s) may be, for example, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, and/or heterocycloalkyl. Examples of the aryl group include benzene, naphthalene, phenanthrene, anthracene, indene, indane, phenol, aniline, and the like.

The term "heteroaryl," as used herein, refers to a substituted or unsubstituted, monovalent or divalent aromatic group, which is monocyclic, bicyclic, or polycyclic, containing one or more heteroatoms in the ring. Non-limiting examples of suitable heteroatoms that may be contained in the aromatic ring include oxygen, sulfur, and nitrogen. When "heteroaryl" is a bicyclic or polycyclic ring system having two or more cyclic rings wherein two or more carbons are common to two adjacent rings, at least one of the rings is heteroaromatic, and the other cyclic ring(s) may be, for example, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, and/or heterocyclyl. Examples of "heteroaryl" include, but are

not limited to, benzofuran, benzothiophene, pyrrole, furan, thiophene, imidazole, indole, isoindole, isoxazole, isothiazole, oxazole, thiazole, quinoline, isoquinoline, pyrazole, pyridine, pyrazine, pyridazine, pyrimidine, and the like, each of which may be substituted or unsubstituted.

The term "amino" or "amine," as used herein, refers to -NH2 wherein a hydrogen atom is unsubstituted or substituted with a substituent such as alkyl, aryl, and the like, wherein the substituent such as alkyl, aryl, and the like, substituting the hydrogen atom is as defined herein and may be substituted or unsubstituted, or may form a ring structure together with the N atom. Examples of suitable amino groups include, but are not limited to, -NH2, -N(CH3)2, -N(CH3)-CH2CH2-N(CH3)2, and the like. The term "aminealkyl," as used herein, refers to an alkyl group, as defined herein, wherein at least one hydrogen atom is substituted with an amine group as defined herein.

The terms "halo" and "halogen," as used herein, both mean halogen and include chloro, fluoro, bromo, and iodo.

The term "cyano," as used herein, refers to a -CN group.

The term "carboxyl," as used herein, refers to a -C(=O)OH group.

The term "hydroxy," as used herein, refers to an -OH group.

The term "substituted," as used herein, for example, "substituted alkyl," means that one or more hydrogen atoms of the alkyl are each independently replaced with a non-hydrogen substituent. Unless otherwise indicated, the term "substituted" may mean substituted with one or a plurality of substituents. The substituent may include, but is not limited to, any substituent described herein, for example, halogen, hydroxyl, alkyl, hydroxyalkyl, haloalkyl, cyanoalkyl, alkoxyalkyl, carbonyl (e.g., carboxyl, alkoxycarbonyl, formyl, or acyl), thiocarbonyl (e.g., thioester, thioacetate, or thioformate), alkoxyl, phosphoryl, phosphate, phosphonate,

phosphinate, amino, amido, amidine, imine, cyano, nitro, azido, sulfhydryl, alkylthio, sulfate, sulfonate, sulfamoyl, sulfonamido, sulfonyl, heterocyclyl, aralkyl, aryl, or heteroaryl. Substituted moieties on a hydrocarbon chain may themselves be substituted, as the case may be.

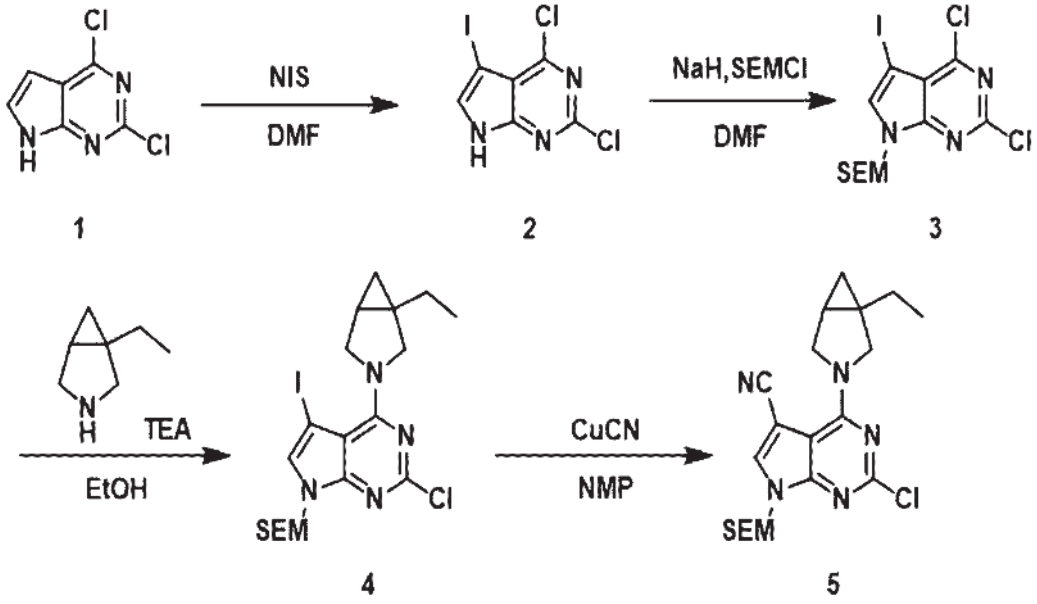
The term "pharmaceutically acceptable salt," as used herein, refers to any acid addition salt or base addition salt that is non-toxic and harmless to a patient and wherein side effects attributable to the salt do not diminish the beneficial efficacy of the compound of the present invention.

The compound according to the present invention may be converted into a pharmaceutically acceptable salt thereof by reacting with a pharmaceutically acceptable acid or base.

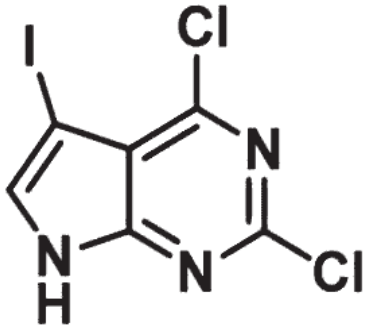
Hereinafter, the present invention will be described in further detail through preparation examples, but the following preparation examples are for illustrative purposes only and are not intended to limit the scope of the present invention.

[Preparation Example 1]

Preparation of 2-chloro-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-(trimethylsilyl)ethoxy) methyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (5)

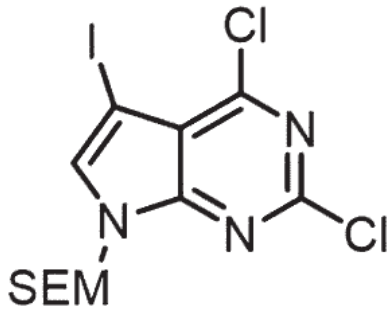


1-1. Step 1: 2,4-dichloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidine (2)



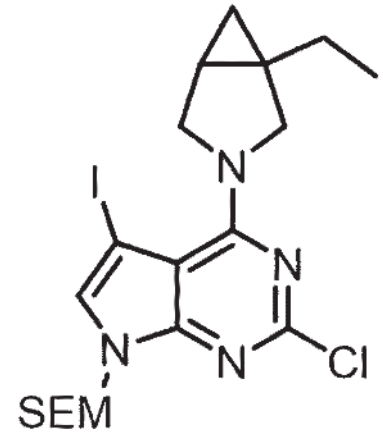
2,4-Dichloro-7H-pyrrolo[2,3-d]pyrimidine (2.66 mmol) and N-iodosuccinimide (2.93 mmol) were dissolved in dimethylformamide, and the mixture was stirred at 50°C for one hour. The solvent of the reaction mixture was concentrated under reduced pressure, and the reaction mixture was washed with ethyl acetate and brine. The reaction mixture was purified by column chromatography (SiO_2, dichloromethane : methanol = 10 : 0 to 1 : 1) to obtain the target compound (2) of Preparation Example 1 (592 mg, 1.89 mmol, 71%, m/z = 311.3, 313.8 $[M-H]^-$).

1-2. Step 2: 2,4-dichloro-5-iodo-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d] pyrimidine (3)



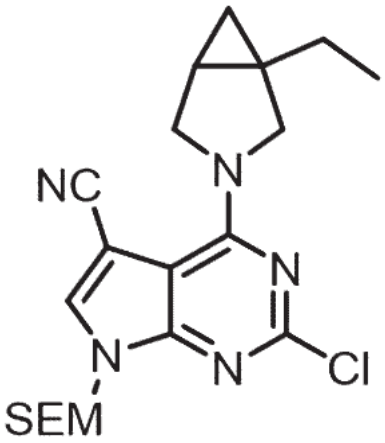
2,4-Dichloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidine (1.89 mmol) was added to dimethylformamide containing sodium hydride (1.89 mmol), and the mixture was stirred at room temperature for 30 minutes. 2-(Trimethylsilyl)ethoxymethyl chloride (2.26 mmol) was added to the reaction mixture, and the mixture was stirred at room temperature for 3 hours. The reaction mixture was washed with ethyl acetate and brine. The organic layer was dried over sodium sulfate to remove residual water, and concentrated under reduced pressure. The concentrated mixture was purified by column chromatography (SiO_2, hexane : ethyl acetate = 10 : 1 to 1 : 1) to obtain the target compound (3) of Preparation Example 1 (710 mg, 1.60 mmol, 85%).

1-3. Step 3: 2-chloro-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-5-iodo-7-((2-(trimethylsilyl) ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine (4)



2,4-Dichloro-5-iodo-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine (0.563 mmol) was added to ethanol containing 1-ethyl-3-azabicyclo[3.1.0]hexane (0.675 mmol) and triethylamine (0.844 mmol). The reaction mixture was stirred at 90°C for 2 hours. The solvent of the reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography (SiO_2, hexane : ethyl acetate = 10 : 1 to 1 : 1) to obtain the target compound (4) of Preparation Example 1 (265 mg, 0.511 mmol, 91%, m/z = 519.1 $[M^+H]^+$).

1-4. Step 4: 2-chloro-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-(trimethylsilyl)ethoxy) methyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (5)

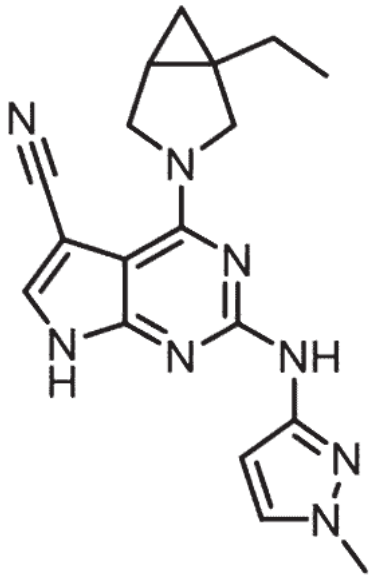


2-Chloro-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-5-iodo-7-((2-

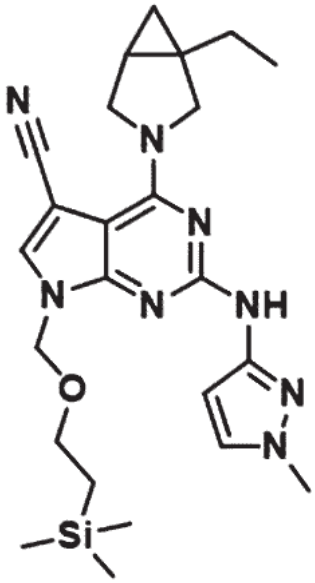
(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine (0.578 mmol) was added to 1-methyl-2-pyrrolidine containing copper cyanide (1.16 mmol). The reaction mixture was stirred at 120°C for 3 hours. After the reaction mixture was cooled to room temperature, water and ethyl acetate were added, and filtered through a Celite pad. The filtrate was extracted with ethyl acetate. The separated organic layer removed remaining water using sodium sulfate, and was concentrated under reduced pressure. The concentrated mixture was purified with (SiO_2, hexane : ethyl acetate = 10 : 1 to 1 : 1) to obtain the target compound (5) of Preparation Example 1 (210 mg, 0.502 mmol, 86.9%, m/z = 418.1 $[M^+H]^+$).

[Example 1]

Preparation of 4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-2-((1-methyl-1H-pyrazol-3-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (NRX02097)

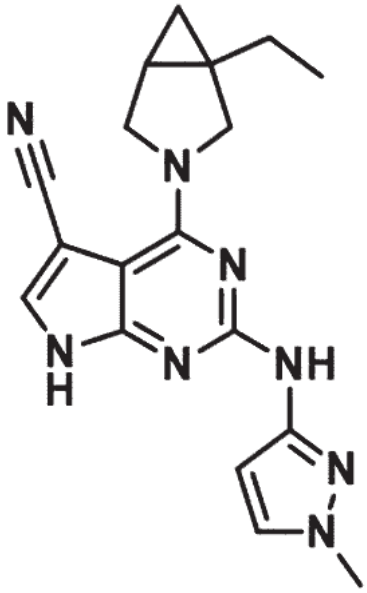


1-1. Step 1: 4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-2-((1-methyl-1H-pyrazol-3-yl)amino)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile



2-Chloro-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (0.239 mmol) was added to sec-BuOH containing 1-methyl-3-pyrazolylamine (0.311 mmol) and potassium carbonate (0.478 mmol). Degassing was performed with nitrogen gas for 5 minutes. $Pd_2(dba)_3$ (0.012 mmol) and Xphos (0.024 mmol) were added thereto. The reaction mixture was stirred at 100°C for 4 hours. The reaction mixture was filtered through a Celite pad. The filtrate was concentrated under reduced pressure, and then separated using reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the compound (25 mg, 0.052 mmol, 21.8%, m/z = 479.2 $[M^+H]^+$).

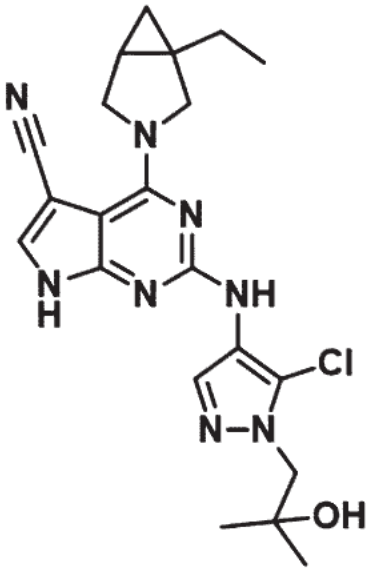
1-2. Step 2: 4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-2-((1-methyl-1H-pyrazol-3-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (NRX02097)



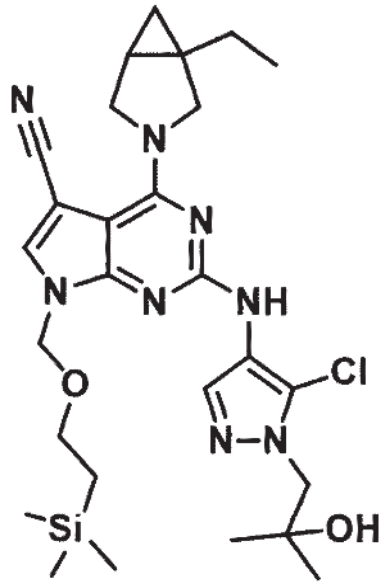
4-(1-Ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-2-((1-methyl-1H-pyrazol-3-yl)amino)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (0.094 mmol) was added to dichloromethane containing trifluoroacetic acid (4.7 mmol). The reaction mixture was stirred at 40°C for 1 hour. The reaction mixture was concentrated under reduced pressure, and separated using reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the target compound of Example 1 (0.9 mg, 2.58 μmol, 2.75%, m/z = 349.1 $[M^+H]^+$).

[Example 2]

Preparation of 2-((5-chloro-1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)amino)-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (NRX02099)



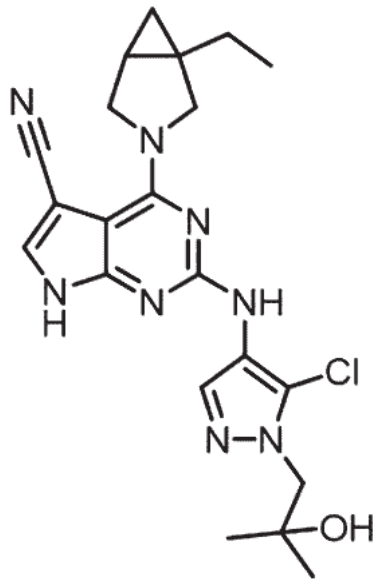
2-1. Step 1: 2-((5-chloro-1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)amino)-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d] pyrimidine-5-carbonitrile



2-Chloro-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (0.240 mmol) was added to 1,4-dioxane containing 1-(4-amino-5-chloro-1H-pyrazol-1-yl)-2-methylpropan-2-ol

(0.237 mmol) and cesium carbonate (0.712 mmol). Degassing was performed with nitrogen gas for 5 minutes. $Pd(OAc)_2$ (0.024 mmol) and BINAP (0.024 mmol) were added thereto. The reaction mixture was stirred at 100°C for 2 hours. The reaction mixture was filtered through a Celite pad. The filtrate was concentrated under reduced pressure, and then separated using reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the compound (96 mg, 0.094 mmol, 40%, m/z = 571.2 $[M^+H]^+$).

2-2. Step 2: 2-((5-chloro-1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)amino)-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (NRX02099)



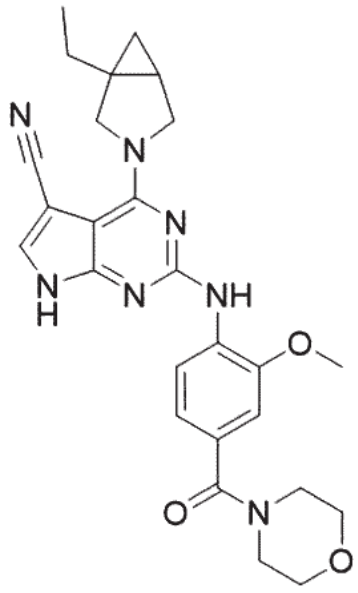
1 M tetra-n-butylammonium fluoride (0.931 mmol) was added to tetrahydrofuran containing 2-((5-chloro-1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)amino)-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (0.093 mmol). The reaction mixture was stirred at 90°C for 1 hour. The solvent of the reaction mixture was concentrated under reduced pressure, and separated using reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to

obtain the target compound of Example 2 (10 mg, 22.7 μmol, 24%, m/z = 441.1 $[M^+H]^+$).

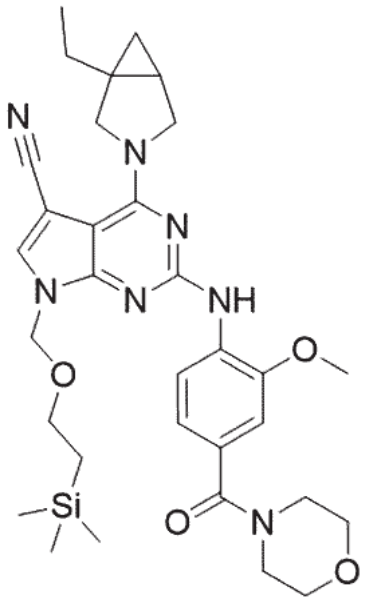
^{1}H-NMR (400 MHz, $CDCl_3$-*d*) δ 8.11 (d, *J* = 3.6 Hz, 1H), 7.39 - 7.33 (m, 1H), 6.18 (s, 1H), 4.23 (d, *J* = 10.6 Hz, 1H), 4.16 (d, *J* = 11.0 Hz, 1H), 4.07 (d, *J* = 3.8 Hz, 2H), 3.88 (d, *J* = 11.0 Hz, 1H), 3.70 (d, *J* = 10.8 Hz, 1H), 1.80 (dq, *J* = 14.6, 7.3 Hz, 2H), 1.56 - 1.38 (m, 2H), 1.21 - 1.16 (m, 6H), 1.09 - 0.94 (m, 3H), 0.73 (dd, *J* = 8.0, 4.7 Hz, 1H), 0.33 (t, *J* = 4.4 Hz, 1H), 0.09 - 0.03 (m, 2H).

[Example 3]

Preparation of 4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-2-((2-methoxy-4-(morpholine-4-carbonyl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (NRX02076)

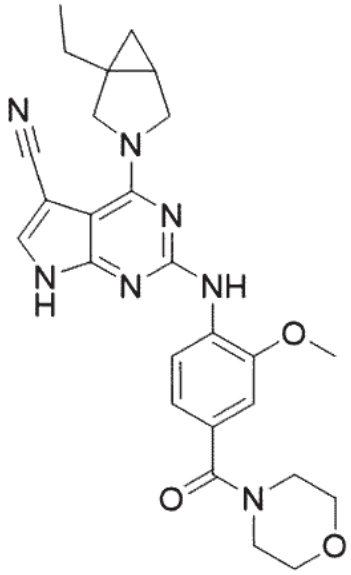


3-1. Step 1: 4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-2-((2-methoxy-4-(morpholine-4-carbonyl)phenyl)amino)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d] pyrimidine-5-carbonitrile



The compound 2-chloro-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (0.837 mmol) of Preparation Example 1 above was added to 2-butanol (8 ml) containing (4-amino-3-methoxyphenyl)morpholinomethanone (0.837 mmol) and potassium carbonate (1.67 mmol). Degassing was performed with nitrogen gas for 5 minutes. $Pd_2(dba)_3$ (0.0419 mmol) and XPhos (0.0837 mmol) were added thereto. The reaction mixture was stirred at 100°C for 2 hours. The reaction mixture was filtered through a Celite pad. The filtrate was concentrated under reduced pressure, and then separated using reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the compound (150 mg, 0.243 mmol, 29%, m/z = 618.2 $[M^+H]^+$).

3-2. Step 2: 4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-2-((2-methoxy-4-(morpholine-4-carbonyl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (NRX02076)



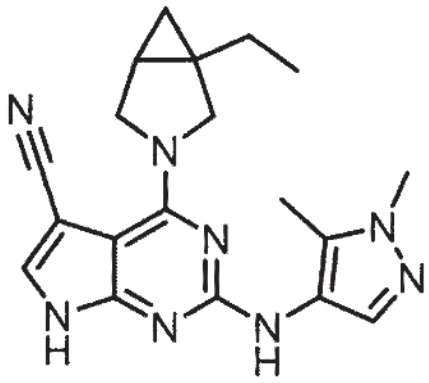
4-(1-Ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-6-(2-methoxy-4-morpholinocarbonylphenyl amino)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,5,7-triazaindene-3-carbonitrile (0.0486 mmol) was added to a dichloromethane (0.4 ml) solution. Trifluoroacetic acid (4.86 mmol) was added thereto, and the mixture was stirred at 40°C for 4 hours. The reaction mixture was concentrated under reduced pressure, and separated using reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the target compound of Example 3 (20 mg, 0.041 mmol, 84%, m/z = 488.2 $[M^+H]^+$).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.38 (s, 1H), 8.52 (d, J = 8.2 Hz, 1H), 8.02 (s, 1H), 7.49 (s, 1H),7.07 - 6.97 (m, 2H), 4.17 (d, J = 10.3 Hz, 1H), 4.08 (d, J = 10.9 Hz, 1H), 3.91 (s, 3H), 3.79 (dd, J = 10.9,4.4 Hz, 1H), 3.66 (d, J = 10.3 Hz, 1H), 3.60 (s, 3H), 3.59 (s, 1H), 3.52 (s, 4H), 2.53 (d, J = 1.0 Hz, 1H),1.80 (dd, J = 14.1, 7.2 Hz, 1H), 1.54 (dt, J = 8.3, 4.1 Hz, 1H), 1.43 (dd, J = 14.1, 7.3 Hz, 1H), 1.00 (t, J =7.4 Hz, 3H), 0.72 (dd, J = 8.0, 4.7 Hz, 1H), 0.31 (t, J = 4.2 Hz, 1H).

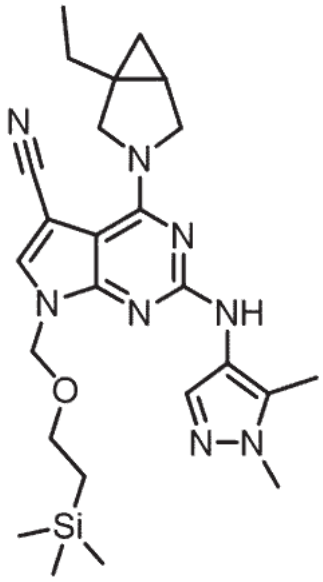
[Example 4]

Preparation of 4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-6-(1-methyl-5-methyl-4-

pyrazolylamino)-1H-1,5,7-triazaindene-3-carbonitrile (NRX02169)



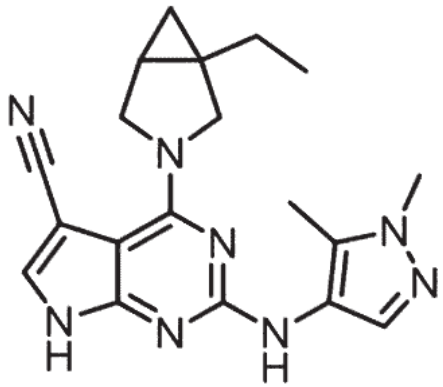
4-1 Step 1: 2-((1,5-dimethyl-1H-pyrazol-4-yl)amino)-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile



The compound (5) of Preparation Example 1 above (120 mg, 0.287 mmol), 1-methyl-5-methyl-4-pyrazolylamine (35 mg, 0.316 mmol), and cesium carbonate (281 mg, 0.861 mmol) were dissolved in 1,4-dioxane (2.8 mL). $Pd(OAc)_2$ (6.44 mg, 28.7 μmol) and BINAP (17.9 mg, 28.7 μmol) were added thereto. The reaction mixture was stirred at 100°C for 16 hours. After completion of the reaction, the reaction mixture was filtered through a Celite pad. The reaction

solvent was concentrated under reduced pressure, and then purified by column chromatography (SiO_2, hexane : ethyl acetate = 5 : 1 to 1 : 1) to obtain the desired compound (23 mg, 46.7 μmol, 16.3%, m/z = 493.1 $[M^+H]^+$).

4-2 Step 2: 4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-6-(1-methyl-5-methyl-4-pyrazolylamino)-1H-1,5,7-triazaindene-3-carbonitrile (NRX02169)

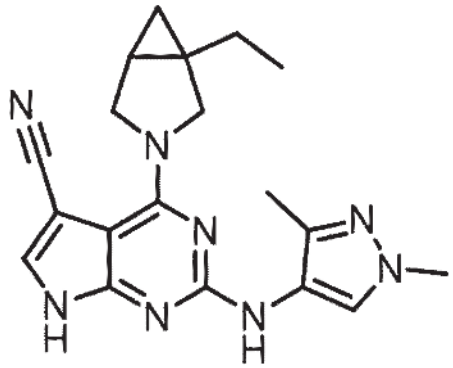


2-((1,5-Dimethyl-1H-pyrazol-4-yl)amino)-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (23 mg, 46.7 μmol) was dissolved in dichloromethane, and then trifluoroacetic acid (17.6 μL, 0.233 mmol) was added thereto. The reaction mixture was stirred at 50°C for 16 hours. The reaction solvent was concentrated under reduced pressure, and then 7 N aqueous ammonia was added thereto, followed by stirring for 30 minutes. The reaction mixture was concentrated under reduced pressure, ether was added thereto, and the solid was filtered to obtain the target compound of Example 4 (4 mg, 11 mol, 24%, m/z = 363.1 $[M^+H]^+$).

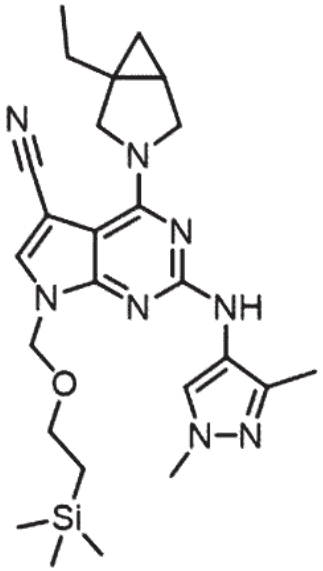
^{1}H-NMR (400 MHz, $CDCl_3$-*d*) δ 7.50 (s, 1H), 6.92 (s, 1H), 6.34 (s, 1H), 4.23 (d, *J* = 10.9 Hz, 1H), 4.15 (d, *J* = 11.1 Hz, 1H), 3.86 (d, *J* = 8.8 Hz, 1H), 3.70 (s, 4H), 3.47 (q, *J* = 7.0 Hz, 1H), 2.15 (s, 3H), 1.79 (dq, *J* = 14.6, 7.3 Hz, 1H), 1.52 - 1.43 (m, 2H), 1.20 (t, *J* = 7.0 Hz, 1H), 1.03 (t, *J* = 7.4 Hz, 3H), 0.72 (dd, *J* = 8.0, 5.1 Hz, 1H), 0.31 (t, *J* = 4.5 Hz, 1H).

[Example 5]

Preparation of 4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-6-(1-methyl-3-methyl-4-pyrazolylamino)-1H-1,5,7-triazaindene-3-carbonitrile (NRX02170)



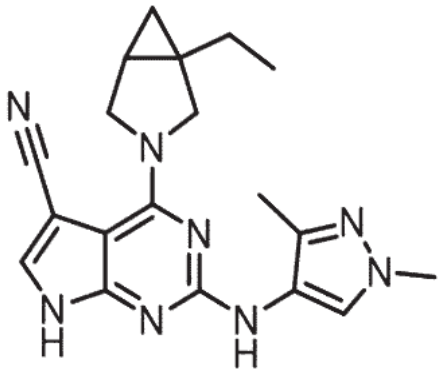
5-1 Step 1: 2-((1,3-dimethyl-1H-pyrazol-4-yl)amino)-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile



The compound (5) of Preparation Example 1 above (120 mg, 0.287 mmol), 1-methyl-3-methyl-4-pyrazolylamine (35 mg, 0.316 mmol), and potassium carbonate (119 mg, 0.861

mmol) were dissolved in 2-butanol (1.0 mL). $Pd_2(dba)_3$ (26.3 mg, 28.7 μmol) and XPhos (13.7 mg, 28.7 μmol) were added thereto. The reaction mixture was stirred at 100°C for 16 hours. After completion of the reaction, the reaction mixture was filtered through a Celite pad. The reaction solvent was concentrated under reduced pressure, and then purified by column chromatography (SiO_2, hexane : ethyl acetate = 5 : 1 to 1 : 1) to obtain the compound (120 mg, 244 μmol, 85%, m/z = 493.1 $[M^+H]^+$).

5-2 Step 2: 4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-6-(1-methyl-3-methyl-4-pyrazolylamino)-1H-1,5,7-triazaindene-3-carbonitrile (NRX02170)



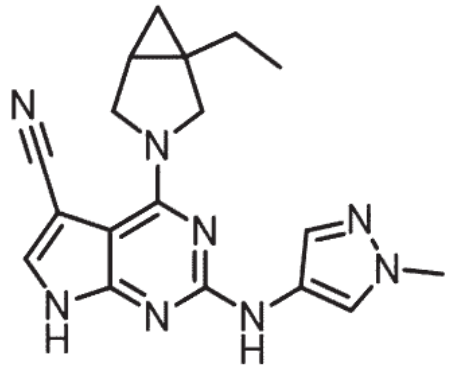
2-((1,3-Dimethyl-1H-pyrazol-4-yl)amino)-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (120 mg, 244 μmol) was dissolved in dichloromethane, and then trifluoroacetic acid (93.2 μL, 1.22 mmol) was added thereto. The reaction mixture was stirred at 50°C for 16 hours. The reaction solvent was concentrated under reduced pressure, and then 7 N aqueous ammonia was added thereto, followed by stirring for 30 minutes. The reaction solvent was concentrated under reduced pressure, and then purified by column chromatography (SiO_2, dichloromethane : methanol = 10 : 1) to obtain the target compound of Example 5 (55.4 mg, 153 μmol, 63%, m/z = 363.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, $CDCl_3$-*d*) δ 7.56 (s, 1H), 6.93 (s, 1H), 6.08 (s, 1H), 4.23 (d, *J* =

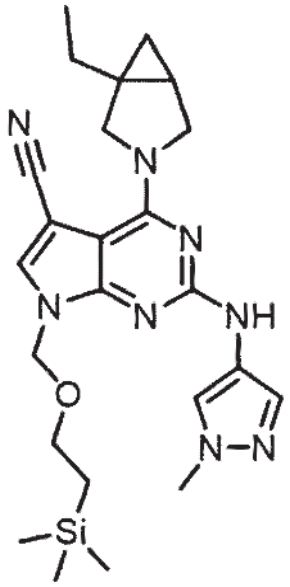
10.7 Hz, 1H), 4.16 (d, *J* = 10.9 Hz, 1H), 3.90 - 3.79 (m, 1H), 3.78 (s, 3H), 3.67 (d, *J* = 10.7 Hz, 1H), 2.19 (s, 3H), 1.81 (dq, *J* = 14.6, 7.3 Hz, 1H), 1.54 - 1.40 (m, 2H), 1.04 (t, *J* = 7.4 Hz, 3H), 0.71 (dd, *J* = 8.0, 4.9 Hz, 1H), 0.33 (t, *J* = 4.4 Hz, 1H).

[Example 6]

Preparation of 4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-6-(1-methyl-4-pyrazolylamino)-1H-1,5,7-triazaindene-3-carbonitrile (NRX02176)

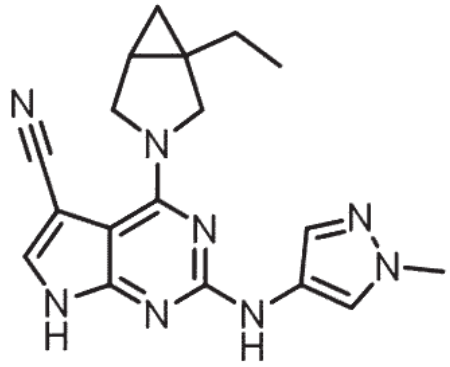


6-1 Step 1: 4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-2-((1-methyl-1H-pyrazol-4-yl)amino)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile



The compound (5) of Preparation Example 1 above (110 mg, 0.263 mmol), 1-methyl-4-pyrazolylamine (97 mg, 0.316 mmol) and potassium carbonate (109 mg, 0.789 mmol) were dissolved in 2-butanol (1.0 mL). $Pd_2(dba)_3$ (24.1 mg, 26.3 μmol) and XPhos (12.5 mg, 26.3 μmol) were added thereto. The reaction mixture was stirred at 100°C for 16 hours. After completion of the reaction, the reaction mixture was filtered through a Celite pad. The reaction solvent was concentrated under reduced pressure, and then purified by column chromatography (SiO_2, hexane : ethyl acetate = 5 : 1 to 1 : 1) to obtain the compound (51 mg, 107 μmol, 41%, m/z = 479.1 $[M^+H]^+$).

6-2 Step 2: 4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-6-(1-methyl-4-pyrazolylamino)-1H-1,5,7-triazaindene-3-carbonitrile (NRX02176)

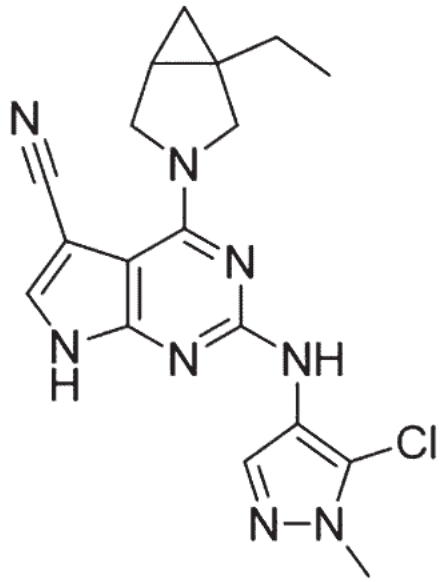


4-(1-Ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-2-((1-methyl-1H-pyrazol-4-yl)amino)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (51 mg, 107 μmol) was dissolved in tetrahydrofuran (1.0 mL), and then 1 M tetra-n-butylammonium fluoride (1.07 mL, 1.07 mmol) was added thereto. The reaction mixture was stirred at 90°C for 1 hour. The reaction mixture was concentrated under reduced pressure, and separated using reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the target compound of Example 6 (20.6 mg, 59.1 μmol, 55%, m/z = 349.1 $[M^+H]^+$).

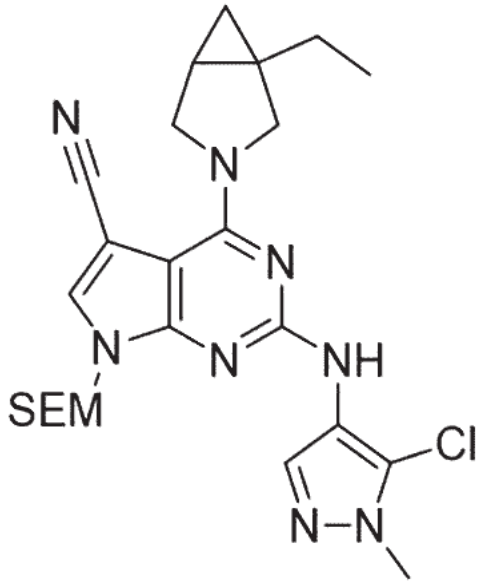
^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.08 (s, 1H), 8.68 (s, 1H), 7.89 (s, 1H), 7.78 (s, 1H), 7.49 (d, *J* = 0.7 Hz, 1H), 4.17 (d, *J* = 10.3 Hz, 1H), 4.08 (d, *J* = 10.8 Hz, 1H), 3.78 (s, 3H), 3.78 (d, *J* = 14.4 Hz, 1H), 3.63 (d, *J* = 10.3 Hz, 1H), 1.82 (dq, *J* = 14.5, 7.3 Hz, 1H), 1.53 (dt, *J* = 8.1, 4.0 Hz, 1H), 1.43 (dq, *J* = 14.7, 7.4 Hz, 1H), 1.01 (t, *J* = 7.4 Hz, 3H), 0.72 (dd, *J* = 8.0, 4.6 Hz, 1H), 0.30 (t, *J* = 4.3 Hz, 1H).

[Example 7]

Preparation of 2-((5-chloro-1-methyl-1H-pyrazol-4-yl)amino)-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (NRX02182)



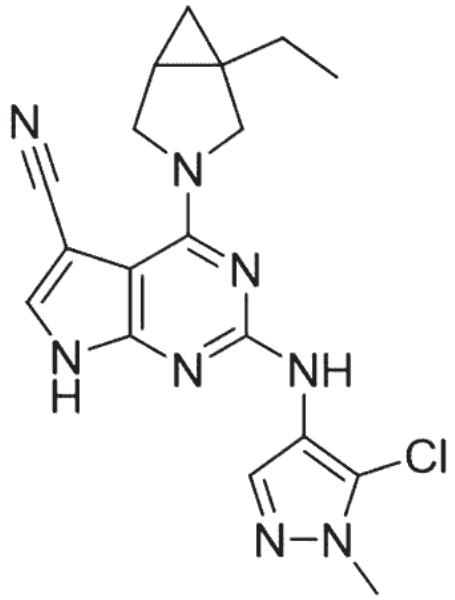
7-1 Step 1: 2-((5-chloro-1-methyl-1H-pyrazol-4-yl)amino)-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile



The compound (5) obtained in Preparation Example 1 above (120 mg, 0.29 mmol) was dissolved in dimethylformamide (1.2 mL), and then 5-chloro-1-methyl-1H-pyrazol-4-amine (57 mg, 0.44 mmol), Xphos-Pd-G2 (45 mg, 0.058 mmol), Xphos (55 mg, 0.116 mmol), and

cesium carbonate (238 mg, 0.87 mmol) were added thereto under nitrogen. The reaction mixture was stirred in a microwave reactor at 100°C for 2 hours. The reaction mixture was poured into water (30 mL) and extracted with ethyl acetate (30 mL x 3). The organic layer was washed with brine, and then remaining water was removed using sodium sulfate, followed by concentration. The concentrated reaction mixture was purified by column chromatography (SiO_2, hexane : ethyl acetate = 5 : 1 to 1 : 1) to obtain the desired compound (100 mg, 68%, m/z = 513.2 $[M^+H]^+$).

7-2 Step 2: 2-((5-chloro-1-methyl-1H-pyrazol-4-yl)amino)-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (NRX02182)



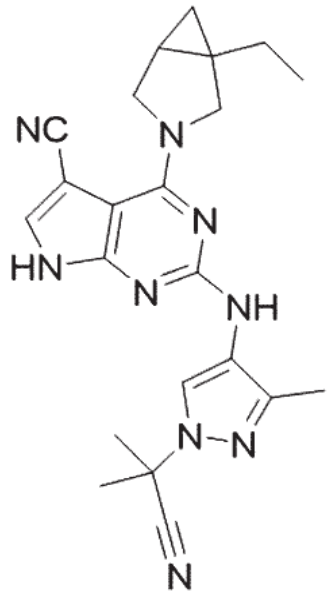
2-((5-Chloro-1-methyl-1H-pyrazol-4-yl)amino)-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (100 mg, 0.20 mmol) was dissolved in tetrahydrofuran (1 mL), and then tetra-n-butylammonium fluoride (0.2 mL, 1 N in THF) was added thereto, followed by stirring at 90°C for 4 hours. The reaction mixture was poured into water (10 mL), and the solid was filtered. The filtered solid was washed with methanol to obtain the target compound of Example 7 (15.79 mg, 21.2%, m/z

= 383.2 $[M^+H]^+$).

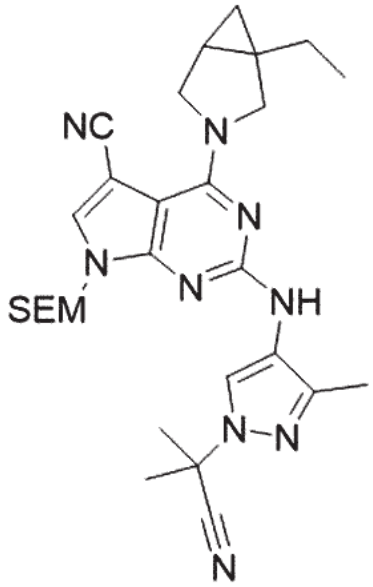
^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.09 (brs, 1H), 8.00 (s, 1H), 7.88 (s, 1H), 7.68 (s, 1H), 4.15 (d, *J* = 10.4, 1H), 4.06 (d, *J* = 10.8, 1H), 3.77 (s, 3H), 3.73 (dd, *J* = 10.8, 4.4 Hz, 1H), 3.60 (d, *J* = 10.4 Hz, 1H), 1.83 - 1.74 (m, 1H), 1.52 - 1.46 (m, 1H), 1.44 - 1.37 (m, 1H), 1.00 (t, *J* = 7.2 Hz, 3H), 0.70 - 0.67 (m, 1H), 0.28-0.25 (m, 1H).

[Example 8]

Preparation of 2-((1-(2-cyanopropan-2-yl)-3-methyl-1*H*-pyrazol-4-yl)amino)-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (NRX02173)

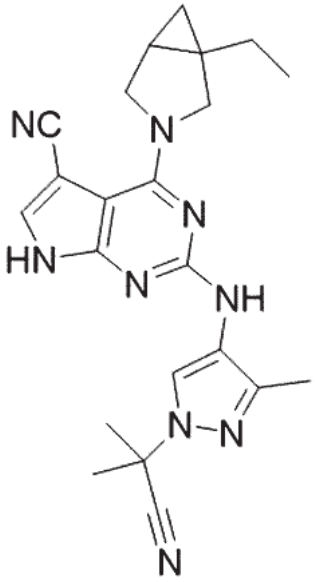


8-1 Step 1: 2-((1-(2-cyanopropan-2-yl)-3-methyl-1H-pyrazol-4-yl)amino)-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile



The compound (5) of Preparation Example 1 above (150 mg, 0.35 mmol), 2-(4-amino-3-methyl-1H-pyrazol-1-yl)-2-methylpropanenitrile (69 mg, 0.42 mmol), $Pd_2(dba)_3$ (65 mg, 0.035 mmol), Sphos (29 mg, 0.070 mmol), and cesium carbonate (228 mg, 0.70 mmol) were dissolved in 1,4-dioxane (4 mL), and then stirred at 100°C under nitrogen for 16 hours. Ammonium chloride (10 mL) was added to the reaction mixture, followed by extraction with ethyl acetate (10 mL x 3). The organic layer was washed with brine, and then remaining water was removed using sodium sulfate, followed by concentration under reduced pressure. The concentrated compound was separated using column chromatography (SiO_2, dichloromethane : methanol = 10 : 1 to 1 : 1) to obtain the desired compound (147 mg, 77.0%, m/z = 546.3 $[M^+H]^+$).

8-2 Step 2: 2-((1-(2-cyanopropan-2-yl)-3-methyl-1*H*-pyrazol-4-yl)amino)-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (NRX02173)

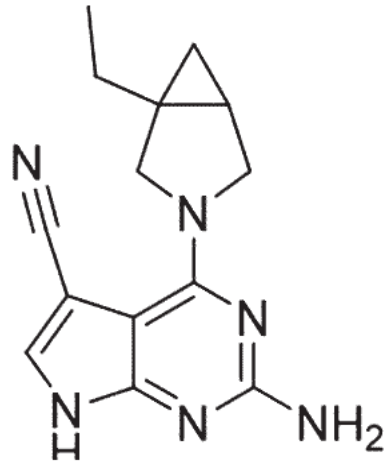


2-((1-(2-Cyanopropan-2-yl)-3-methyl-1H-pyrazol-4-yl)amino)-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (100 mg, 0.18 mmol) was dissolved in tetrahydrofuran (6 mL), and then tetra-n-butylammonium fluoride (0.2 mL, 0.20 mmol, 1 N in THF) was added thereto. The reaction mixture was stirred at 90°C for 3 hours. Water (20 mL) was added to the reaction mixture, followed by extraction with ethyl acetate (10 mL x 3). The organic layer was washed with brine, and then remaining water was removed using sodium sulfate, followed by concentration under reduced pressure. The concentrated compound was separated using column chromatography (SiO_2, dichloromethane : methanol = 10 : 1) to obtain the target compound of Example 8 (38.21 mg, 51.0%, m/z = 416.4 $[M^+H]^+$).

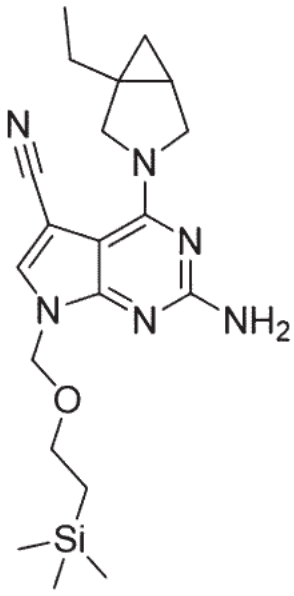
^{1}H-NMR (400 MHz, DMSO-d_6): δ 12.09 (s, 1H), 8.15 (s, 2H), 7.91 (d, J = 2.4 Hz, 1H), 4.16 (d, J = 10.4 Hz, 1H), 4.08 (d, J = 10.6 Hz, 1H), 3.79 (dd, J = 10.6, 4.2 Hz, 1H), 3.63 (d, J = 10.4 Hz, 1H), 2.17 (s, 3H), 1.94 (s, 6H), 1.78 (m, 1H), 1.52 (m, 1H), 1.43 (m, 1H), 0.99 (t, J = 7.4 Hz, 3H), 0.71 (m, 1H), 0.30 (t, J = 4.2 Hz, 1H).

[Example 9]

Preparation of 2-amino-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (NRX02077)



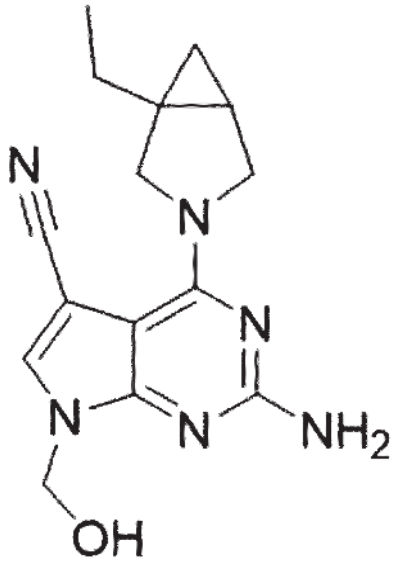
9-1. Step 1: 2-amino-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-(trimethylsilyl)ethoxy) methyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile



The compound 2-chloro-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (0.311 mmol) of Preparation Example 1 above was dissolved in ethanol (2 ml). 7 N ammonia in methanol (2 ml) was added thereto, and the mixture was reacted using a microwave reactor at 130°C for 17

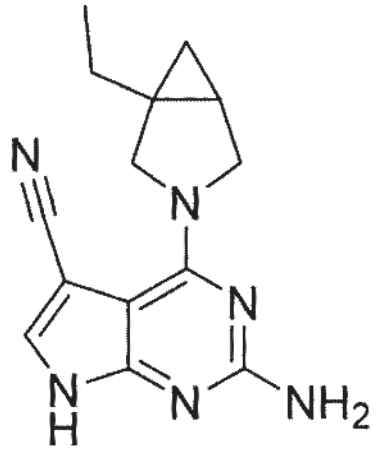
hours. The reaction mixture was concentrated under reduced pressure, and then separated using reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the compound (25 mg, 0.0627 mmol, 20%, m/z = 399.1 $[M^+H]^+$).

9-2. Step 2: 2-amino-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-(hydroxymethyl)-7H-pyrrolo [2,3-d]pyrimidine-5-carbonitrile



2-Amino-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (0.0627 mmol) was added to dichloroethane (0.6 ml). Trifluoroacetic acid (1 ml) was added thereto, and the mixture was reacted at 40°C for 16 hours. The reaction mixture was concentrated under reduced pressure, and then used in the next reaction without purification (20 mg, 0.067 mmol, 107%).

9-3. Step 3: 2-amino-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (NRX02077)

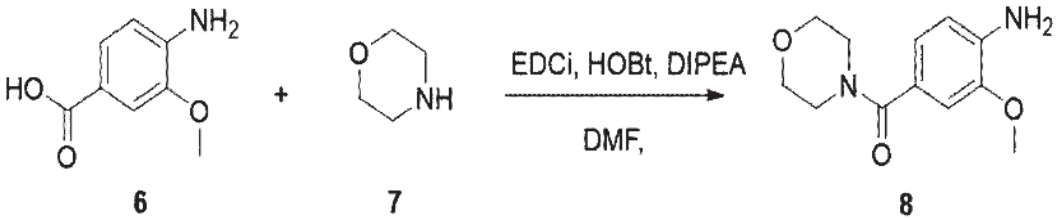


2-Amino-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-(hydroxymethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (0.067 mmol) was added to methanol (0.6 ml). Potassium carbonate (0.67 mmol) was added to the reaction mixture, followed by stirring at 40°C for 16 hours. The reaction mixture was concentrated under reduced pressure, and then separated using reverse-phase column chromatography (C18 resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the target compound of Example 9 (2.8 mg, 0.0104 mmol, 15%, m/z = 269.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.91 (s, 1H), 7.81 (s, 1H), 5.86 (s, 2H), 4.13 (d, *J* = 10.4 Hz, 1H),4.04 (d, *J* = 10.8 Hz, 1H), 3.68 (dd, *J* = 10.8, 4.3 Hz, 1H), 3.57 - 3.50 (m, 1H), 1.78 (dq, *J* = 14.6, 7.3 Hz,1H), 1.48 (dt, *J* = 8.0, 4.0 Hz, 1H), 1.41 (dq, *J* = 14.7, 7.5 Hz, 1H), 0.98 (t, *J* = 7.4 Hz, 3H), 0.67 (dd, *J* =8.0, 4.5 Hz, 1H), 0.25 (t, *J* = 4.2 Hz, 1H).

[Preparation Example 2]

Preparation of (4-amino-3-methoxyphenyl)(morpholino)methanone (8)

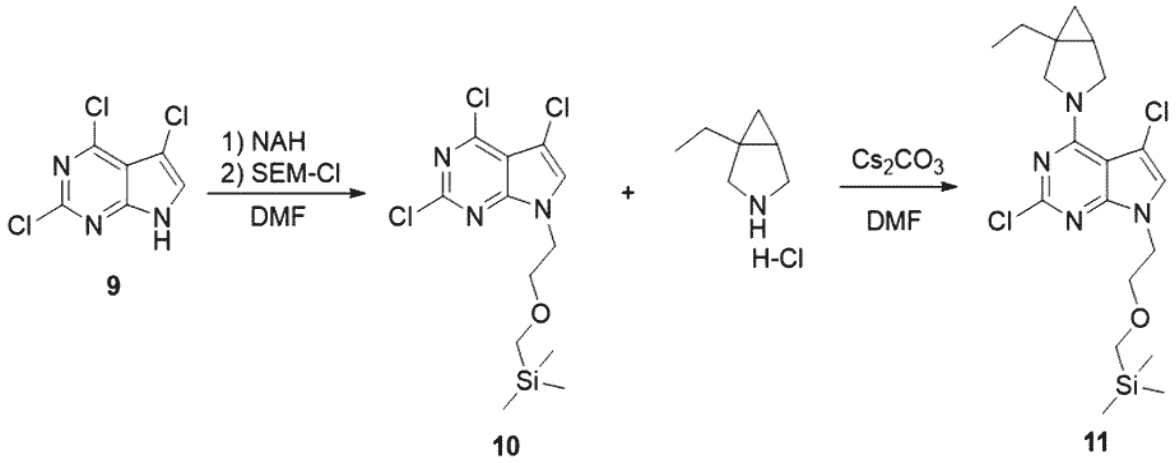


6 7 8

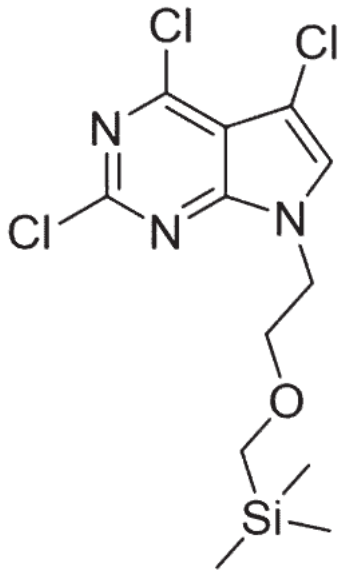
4-Amino-3-methoxybenzoic acid (6) (2 g, 12.0 mmol) was dissolved in dimethylformamide (29.9 ml), and then N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (5.73 g, 29.9 mmol) and 1-hydroxybenzotriazole hydrate (2.75 g, 17.9 mmol) were added thereto, followed by stirring at room temperature for 20 minutes. Thereafter, N,N'-diisopropylethylamine (6.25 ml, 35.9 mmol) and morpholine (7) (10.3 ml, 120 mmol) were added thereto, followed by stirring at room temperature for 21 hours. Water (30 ml) and dichloromethane (30 ml) were added to the reaction mixture, and the desired compound (8) was extracted into the dichloromethane layer. Thereafter, water (30 ml) was added to the dichloromethane layer to extract by-products into the aqueous layer, and additionally brine (30 ml) was added thereto to extract other by-products into the brine layer. Through this process, sodium sulfate was added to the dichloromethane solution in which the compound was dissolved to remove residual water, followed by concentration under reduced pressure. Thereafter, the filtrate was separated using reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the target compound (8) of Preparation Example 2 (1.47 g, 6.22 mmol, 52%, m/z = 237.3 $[M^+H]^+$).

[Preparation Example 3]

Preparation of 2,5-dichloro-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-(2-((trimethylsilyl) methoxy)ethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (11)



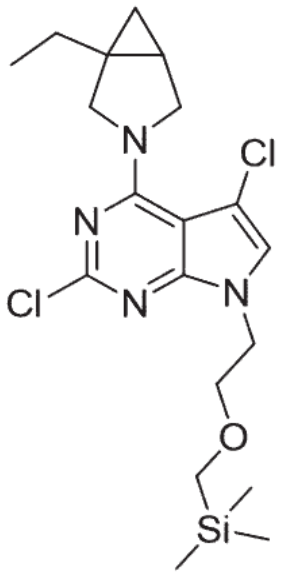
3-1. Step 1: 2,4,5-trichloro-7-(2-((trimethylsilyl)methoxy)ethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (10)



2,4,5-Trichloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (9) (170 mg, 764 μmol) was dissolved in dimethylformamide (2.6 ml), and then placed in an ice-water bath to set the solution temperature to 0°C. Sodium hydride (36.7 mg, 917 μmol) was added thereto, followed by stirring for 30 minutes. Then, [2-(chloromethoxy)ethyl]trimethylsilane (162 μl, 917 μmol) was added thereto, followed by stirring at room temperature for 3 hours. After confirming completion of the reaction, water (20 ml) and ethyl acetate (20 ml) were added to the reaction

mixture, and the desired compound was extracted into the ethyl acetate layer. The ethyl acetate layer obtained by repeating the above extraction process three times was concentrated under reduced pressure, and then the filtrate was purified by column chromatography (SiO_2, ethyl acetate : hexane = 1 : 10) to obtain the target compound (10) of Preparation Example 3, Step 1 (218 mg, 618 μmol, 80.9%, m/z = 353.7 $[M^+H]^+$).

3-2. Step 2: 2,5-dichloro-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-(2-((trimethylsilyl) methoxy)ethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (11)

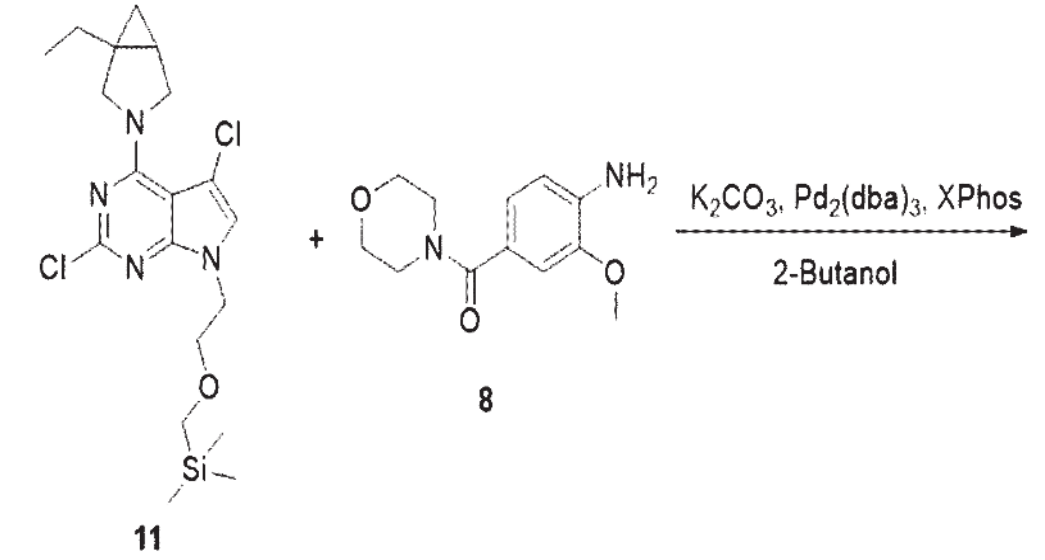


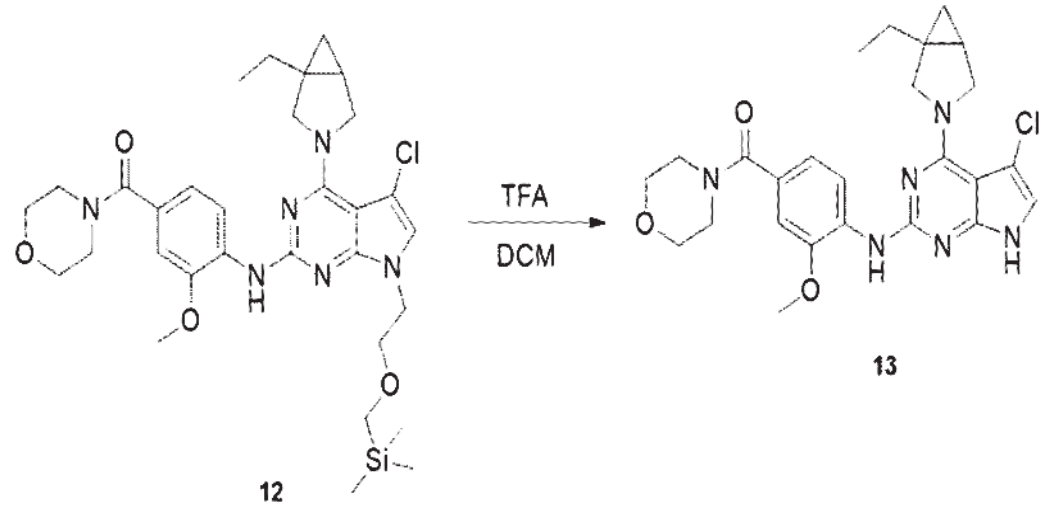
The compound (10) obtained in Step 1 of Preparation Example 3 above (180 mg, 510 μmol) was dissolved in dimethylformamide (5.1 ml), and then 1-ethyl-3-azabicyclo[3.1.0]hexane hydrochloride (82.9 mg, 561 μmol) and cesium carbonate (333 mg, 1.02 mmol) were added thereto, followed by stirring in a microwave for 1 hour. Thereafter, after confirming completion of the reaction, water (25 ml) and ethyl acetate (25 ml) were added to the reaction mixture, and the desired compound was extracted into the ethyl acetate layer. The ethyl acetate layer obtained by repeating the above extraction process three times was concentrated under reduced pressure, and then the filtrate was purified by column

chromatography (SiO_2, ethyl acetate : hexane = 1 : 10) to obtain the target compound (11) of Preparation Example 3 (190 mg, 444 μmol, 87.1%, m/z = 428.4 $[M^+H]^+$).

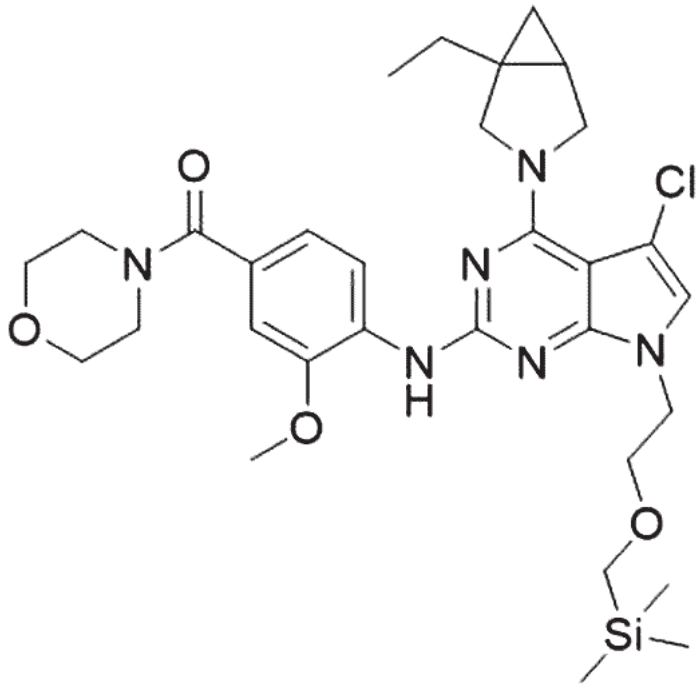
[Example 10]

Preparation of (4-((5-chloro-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-methoxyphenyl)(morpholino)methanone (NRX02075)



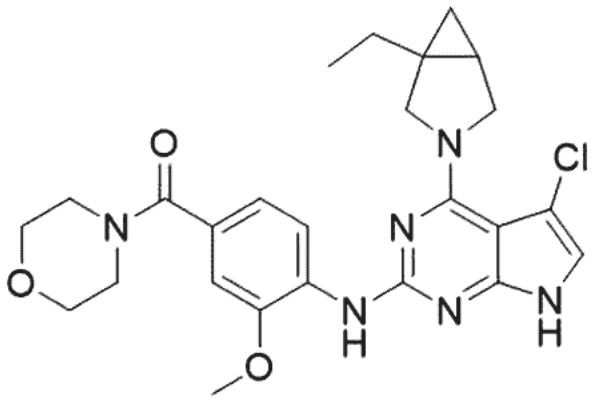


10-1. Step 1: (4-((5-chloro-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-(2-((trimethylsilyl) methoxy)ethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)amino)-3-methoxyphenyl) (morpholino)methanone (12)



The compound (11) obtained in Preparation Example 3 above (50 mg, 117 μmol) was dissolved in 2-butanol (1.2 ml), and then the compound (8) obtained in Preparation Example 2 above (34.5 mg, 146 μmol), potassium carbonate (32.3 mg, 234 μmol), tris(dibenzylideneacetone)dipalladium(0) (6.43 mg, 7.02 μmol), and dicyclohexyl[2',4',6'-tris(propan-2-yl)-[1,1'-biphenyl]-2-yl]phosphine (5.58 mg, 11.7 μmol) were added thereto, followed by stirring at 90°C for 6 hours. After confirming completion of the reaction, the mixture was filtered using a syringe filter and then concentrated under reduced pressure. Water (10 ml) and ethyl acetate (10 ml) were added to the filtrate, and the desired compound was extracted into the ethyl acetate layer. The ethyl acetate layer obtained by repeating the above extraction process three times was concentrated under reduced pressure to obtain the target compound (12) of Example 10, Step 1 (73.4 mg, 117 μmol, 100%, m/z = 628.3 $[M^+H]^+$).

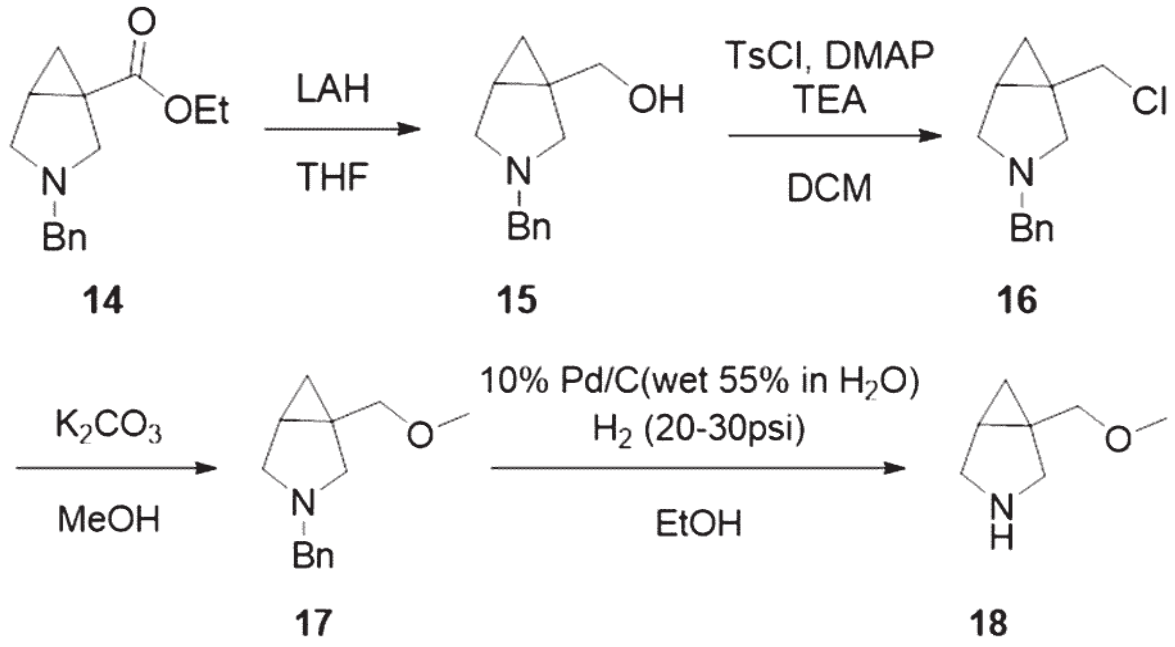
10-2. Step 2: (4-((5-chloro-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-methoxyphenyl)(morpholino)methanone (NRX02075)



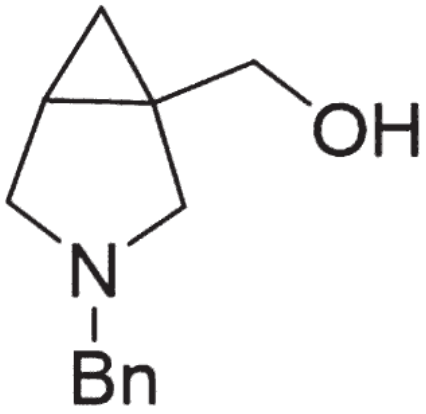
The compound (12) obtained in Step 1 of Example 10 above (73 mg, 117 μmol) was dissolved in dichloromethane (1.2 ml), and then trifluoroacetic acid (869 μl, 11.7 mmol) was added thereto, followed by stirring at 50°C for 3 hours. After confirming completion of the reaction, the mixture was concentrated under reduced pressure. The filtrate was dissolved in tetrahydrofuran (1.2 ml), and then a saturated aqueous sodium bicarbonate solution (10 ml) was added thereto, followed by stirring for 6 hours for neutralization. Thereafter, water (5 ml) and ethyl acetate (5 ml) were added to the reaction mixture, and the desired compound was extracted into the ethyl acetate layer. The ethyl acetate layer obtained by repeating the above extraction process three times was concentrated under reduced pressure, and then the compound was purified through a Prep-HPLC instrument to obtain the target compound (13) of Example 10 (12.3 mg, 24.7 μmol, 21.2%, m/z = 498.0 $[M^+H]^+$).

[Example 4]

Preparation of 1-(methoxymethyl)-3-azabicyclo[3.1.0]hexane (18)



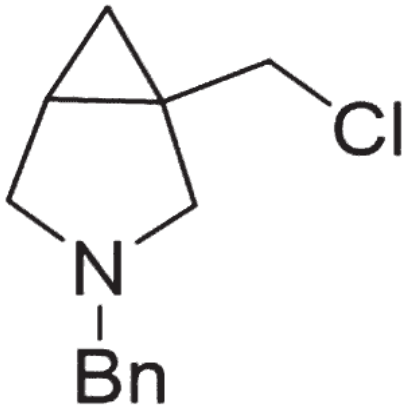
4-1. Step 1: (3-benzyl-3-azabicyclo[3.1.0]hexan-1-yl)methanol (15)



Ethyl 3-benzyl-3-azabicyclo[3.1.0]hexene-1-carboxylate (14) (0.1 g, 0.408 mmol) was added to tetrahydrofuran (2.04 mL), and the temperature was lowered to 0°C. Lithium aluminum hydride was added thereto, followed by stirring at 0°C for 30 minutes. The reaction mixture was stirred at room temperature for 1 hour. Sodium sulfate decahydrate was added to the reaction mixture, followed by stirring at room temperature for 30 minutes. Tetrahydrofuran was added to the reaction mixture, followed by filtration. The filtrate was concentrated under

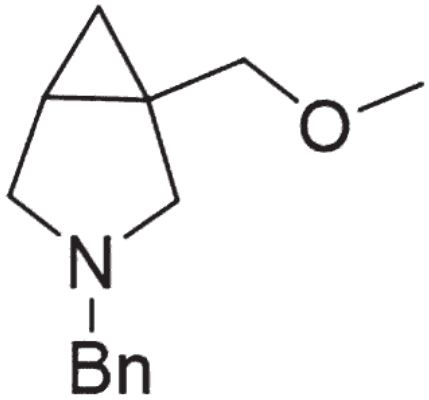
reduced pressure to obtain the compound (15) (72 mg, 0.354 mmol, 87%, m/z = 204.1 $[M^+H]^+$).

4-2. Step 2: 3-benzyl-1-(chloromethyl)-3-azabicyclo[3.1.0]hexane (16)



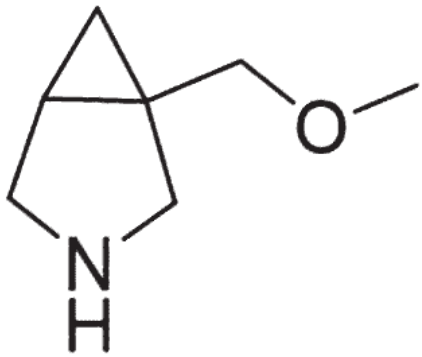
(3-Benzyl-3-azabicyclo[3.1.0]hexan-1-yl)methanol (790 mg, 3.89 mmol) was added to dichloromethane (19.4 ml), and the temperature was lowered to 0°C. Tosyl chloride (889 mg, 4.66 mmol), 4-dimethylaminopyridine (47.5 mg, 0.389 mmol), and triethylamine (865 mg, 8.55 mmol) were added thereto, followed by stirring at 0°C for 30 minutes. The reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was concentrated under reduced pressure, and water and dichloromethane were added thereto, followed by filtration. The reaction mixture was separated using column chromatography (SiO_2, ethyl acetate) to obtain the target compound (16) (598 mg, 2.7 mmol, 69%, m/z = 222.1 $[M^+H]^+$).

4-3. Step 3: 3-benzyl-1-(methoxymethyl)-3-azabicyclo[3.1.0]hexane (17)



3-Benzyl-1-(chloromethyl)-3-azabicyclo[3.1.0]hexane (20 mg, 0.090 mmol) and potassium carbonate (18.7 mg, 0.135 mmol) were added to methanol (0.45 ml), followed by stirring at 100°C for 24 hours. The reaction mixture was concentrated under reduced pressure and filtered to obtain the compound (17) (19 mg, 0.090 mmol, 100%, m/z = 218.1 $[M^+H]^+$).

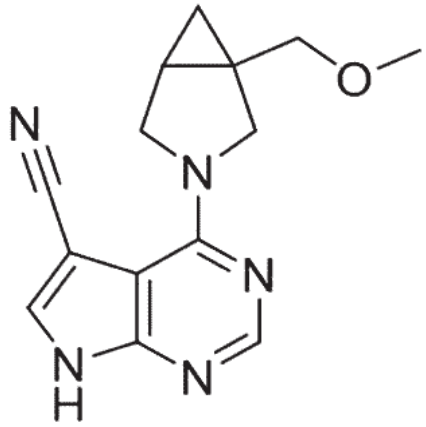
4-4. Step 4: 1-(methoxymethyl)-3-azabicyclo[3.1.0]hexane (18)



3-Benzyl-1-(methoxymethyl)-3-azabicyclo[3.1.0]hexane (93.6 mg, 0.431 mmol) was dissolved in ethanol (2.15 ml). 10% Pd/C (5 mg) was added to the reaction mixture, and then placed in a high-pressure hydrogen reactor. The reaction mixture was stirred at room temperature under 20 - 30 psi of hydrogen for 24 hours. The reaction mixture was filtered, and then the filtrate was concentrated under reduced pressure to obtain the compound (18) (47 mg, 0.37 mmol, 86%).

[Example 11]

Preparation of 4-{1-(methoxymethyl)-3-azabicyclo[3.1.0]hexan-3-yl}-1H-1,5,7-triazaindene-3-carbonitrile (NRX02096)

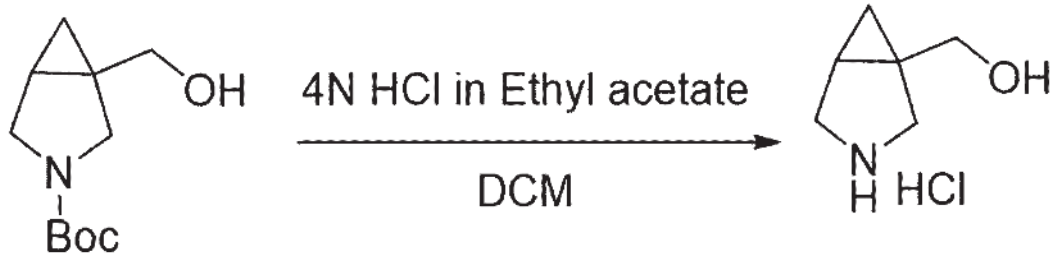


4-Chloro-1H-1,5,7-triazaindene-3-carbonitrile (44 mg, 0.246 mmol), 1-(methoxymethyl)-3-azabicyclo[3.1.0]hexane (47 mg, 0.370 mmol), triethylamine (85.8 μl, 0.62 mmol), and ethanol (1.64 ml) were mixed, followed by stirring at 85°C for 18 hours. The reaction solution was concentrated under reduced pressure, and then the filtrate was purified by reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the target compound of Example 11 (15.3 mg, 0.057 mmol, 23%, m/z = 270.1 $[M^+H]^+$).

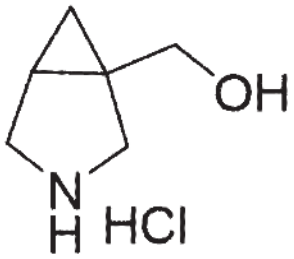
^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.25 (s, 1H), 8.20 (s, 1H), 4.16 (dd, 2H), 3.80 (m, 2H), 3.51 (m, 2H), 3.30 (s, 3H), 1.68 (dt, J = 8.4, 4.3 Hz, 1H), 0.87 (dd, J = 8.0, 4.8 Hz, 1H), 0.43 (t, J = 4.6 Hz, 1H).

[Preparation Example 5]

Preparation of (3-azabicyclo[3.1.0]hexan-1-yl)methanol (20)



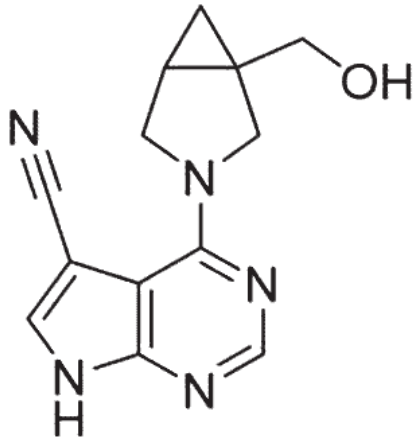
19 **20**



tert-Butyl-1-(hydroxymethyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (19) (0.1 g, 0.469 mmol) was dissolved in dichloromethane (2.34 ml), and then 1 N hydrogen chloride (ethyl acetate) was added thereto. After the reaction mixture was stirred at room temperature for 2 hours, residual solvents were concentrated under reduced pressure to obtain the target compound (20) (29.2 mg, 195 mmol, 42%).

[Example 12]

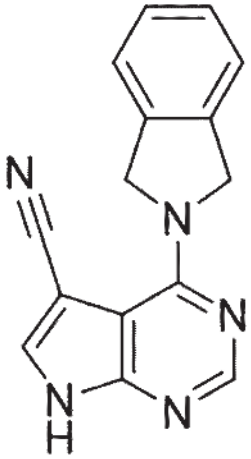
Preparation of 4-(1-(hydroxymethyl)-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (NRX02098)



4-Chloro-1H-1,5,7-triazaindene-3-carbonitrile (44 mg, 0.246 mmol), the compound (20) of Preparation Example 5 above (29.2 mg, 0.195 mmol), triethylamine (90.6 μl, 0.65 mmol), and ethanol (0.9 ml) were mixed, followed by stirring at 85°C for 18 hours. The reaction solution was concentrated under reduced pressure, and then the filtrate was purified by reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the target compound of Example 12 (1.0 mg, 0.004 mmol, 3%, m/z = 256.1 $[M^+H]^+$).

[Example 13]

Preparation of 4-(isoindolin-2-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (NRX02088)

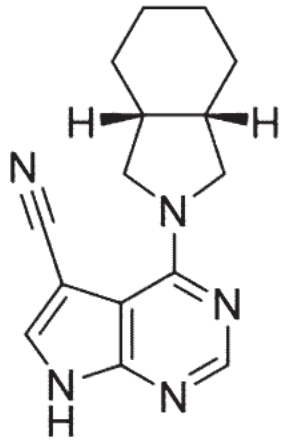


The target compound of Example 13 (21.2 mg, 0.081 mmol, 48%, m/z = 262.1 $[M^+H]^+$) was obtained by performing the same method as in Example 12 above, except for using isoindole instead of using (3-azabicyclo[3.1.0]hexan-1-yl)methanol.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.15 (s, 1H), 7.68 (s, 1H), 7.41 (dd, J = 5.4, 3.3 Hz, 2H), 7.29 (dd, J = 5.6, 3.2 Hz, 2H), 5.73 (dd, J = 7.7 Hz, 2H), 5.29 (s, 2H), 4.86 (s, 2H), 0.87 (dd, J = 8.0, 4.8 Hz, 1H), 0.43 (t, J = 4.6 Hz, 1H).

[Example 14]

Preparation of 4-((3aR,7aS)-octahydro-2H-isoindol-2-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (NRX02087)



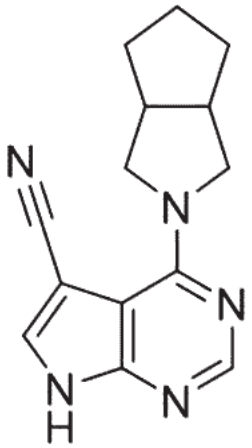
The target compound of Example 14 (20.2 mg, 0.0755 mmol, 45%, m/z = 268.1 $[M^+H]^+$) was obtained by performing the same method as in Example 12 above, except for using (3aR,7aS)-octahydro-1H-isoindole instead of using (3-azabicyclo[3.1.0]hexan-1-yl)methanol.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.05 (s, 1H), 7.68 (s, 1H), 7.41 (dd, J = 5.4, 3.3 Hz, 2H), 7.29 (dd, J = 5.6, 3.2 Hz, 2H), 5.73 (dd, J = 7.7 Hz, 2H), 5.29 (s, 2H), 4.86 (s, 2H),

0.87 (dd, *J* = 8.0, 4.8 Hz, 1H), 0.43 (t, *J* = 4.6 Hz, 1H).

[Example 15]

Preparation of 4-(hexahydrocyclopenta[c]pyrrol-2(1H)-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (NRX67086)

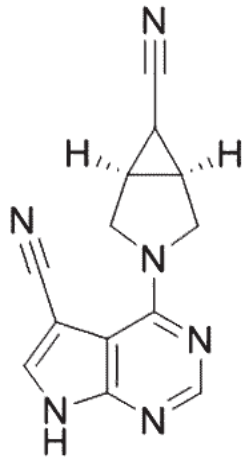


The target compound of Example 15 (14.8 mg, 0.058 mmol, 34%, m/z = 254.1 $[M^+H]^+$) was obtained by performing the same method as in Example 12 above, except for using octahydrocyclopenta[c]pyrrole instead of using (3-azabicyclo[3.1.0]hexan-1-yl)methanol.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 1H), 8.20 (s, 1H), 3.99 (dd, *J* = 11.3, 7.7 Hz, 2H), 3.61 (dd, *J* = 11.3, 3.9 Hz, 2H), 2.78 (dq, *J* = 8.0, 4.4 Hz, 2H), 1.91 - 1.80 (m, 2H), 1.82 - 1.70 (m, 1H), 1.67 - 1.56 (m, 1H), 1.54 - 1.44 (m, 2H).

[Example 16]

Preparation of 4-((1R,5S)-6-cyano-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (NRX02085)

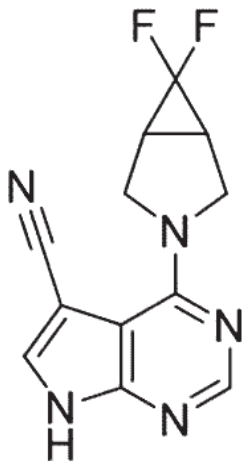


The target compound of Example 16 (8.0 mg, 0.032 mmol, 19%, m/z = 251.1 $[M^+H]^+$) was obtained by performing the same method as in Example 12 above, except for using (1R,5S)-3-azabicyclo[3.1.0]hexane-6-carbonitrile instead of using (3-azabicyclo[3.1.0]hexan-1-yl)methanol.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.82 (s, 1H), 8.26 (s, 1H), 8.20 (s, 1H), 4.23 (d, J = 11.4 Hz, 2H), 3.78 (dt, J = 11.5, 1.9 Hz, 2H), 2.55 - 2.50 (m, 2H), 1.68 (t, J = 3.5 Hz, 1H).

[Example 17]

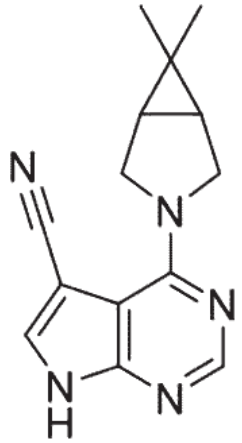
Preparation of 4-(6,6-difluoro-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (NRX02084)



The target compound of Example 17 (1.0 mg, 0.004 mmol, 2%, m/z = 262.0 $[M^+H]^+$) was obtained by performing the same method as in Example 12 above, except for using 6,6-difluoro-3-azabicyclo[3.1.0]hexane instead of using (3-azabicyclo[3.1.0]hexan-1-yl)methanol.

[Example 18]

Preparation of 4-(6,6-dimethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (NRX02083)



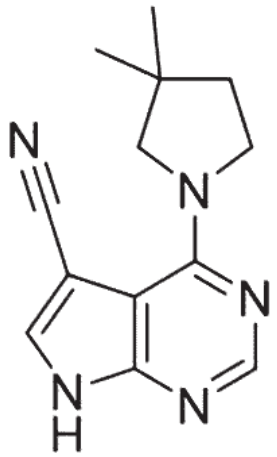
The target compound of Example 18 (19.3 mg, 0.076 mmol, 45%, m/z = 254.1 $[M^+H]^+$) was obtained by performing the same method as in Example 12 above, except for using 6,6-dimethyl-3-azabicyclo[3.1.0]hexane instead of using (3-azabicyclo[3.1.0]hexan-1-yl)methanol.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 1H), 8.20 (s, 1H), 3.92 (d, J = 11.6 Hz, 2H), 3.81 (d, J = 11.4 Hz, 2H), 1.62 (s, 2H), 1.07 (s, 3H), 0.82 (s, 3H).

[Example 19]

Preparation of 4-(3,3-dimethylpyrrolidin-1-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-

carbonitrile (NRX02082)

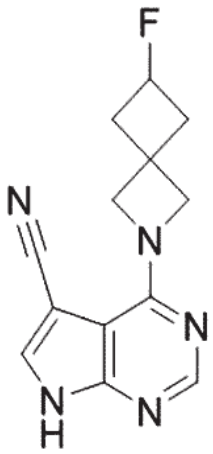


The target compound of Example 19 (9.4 mg, 0.039 mmol, 23%, m/z = 242.1 $[M^+H]^+$) was obtained by performing the same method as in Example 12 above, except for using 3,3-dimethylpyrrolidine instead of using (3-azabicyclo[3.1.0]hexan-1-yl)methanol.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.73 (s, 1H), 8.22 (s, 1H), 8.21 (s, 1H), 3.86 (t, J = 7.0 Hz, 2H), 3.55 (s, 2H), 1.82 (t, J = 7.0 Hz, 2H), 1.12 (s, 6H).

[Example 20]

Preparation of 4-(6-fluoro-2-azaspiro[3.3]heptan-2-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (NRX02081)

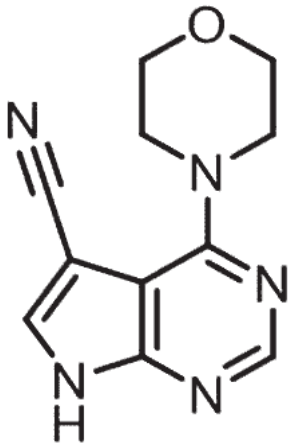


The target compound of Example 20 (16.2 mg, 0.063 mmol, 37%, m/z = 258.1 $[M^+H]^+$) was obtained by performing the same method as in Example 12 above, except for using 6-fluoro-2-azaspiro[3.3]heptene instead of using (3-azabicyclo[3.1.0]hexan-1-yl)methanol.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 1H), 8.22 (s, 1H), 5.05 (dp, J = 56.0, 6.6 Hz, 1H), 4.36 (d, J = 9.7 Hz, 4H), 2.70 (dtd, J = 13.3, 6.7, 3.2 Hz, 2H), 2.42 (dddd, J = 20.0, 13.5, 6.4, 3.2 Hz, 2H).

[Example 21]

Preparation of 4-morpholino-1H-1,5,7-triazaindene-3-carbonitrile (NRX02120)



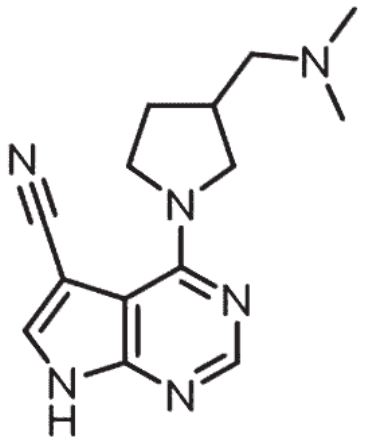
The target compound of Example 21 (44 mg, 0.192 mmol, 69%, m/z = 230.1 $[M^+H]^+$) was obtained by performing the same method as in Example 12 above, except for using morpholine (48.8 mg, 0.560 mmol) instead of using (3-azabicyclo[3.1.0]hexan-1-yl)methanol.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.34 (s, 1H), 8.31 (s, 1H), 3.73 (dd, J = 5.6, 3.4 Hz, 1H), 3.64 (dd, J = 5.5, 3.6 Hz, 1H).

[Example 22]

Preparation of 4-{3-[(dimethylamino)methyl]-1-pyrrolidinyl}-1H-1,5,7-

triazaindene-3-carbonitrile (NRX02121)

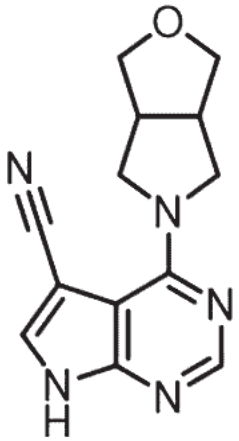


The target compound of Example 22 (62 mg, 0.229 mmol, 109%, m/z = 271.1 $[M^+H]^+$) was obtained by performing the same method as in Example 12 above, except for using N,N-dimethyl[(3-pyrrolidinyl)methyl]amine instead of using (3-azabicyclo[3.1.0]hexan-1-yl)methanol.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.22 (s, 1H), 8.19 (s, 1H), 3.98 (s, 2H), 3.64 (m, 2H), 3.52 (m, 2H), 2.50 (s, 1H), 2.43 (s, 2H), 1.35 (d, J =4 Hz, 6H), 1.32 (d, J = 4 Hz, 2H).

[Example 23]

Preparation of 4-(3-oxa-7-azabicyclo[3.3.0]oct-7-yl)-1H-1,5,7-triazaindene-3-carbonitrile (NRX02125)

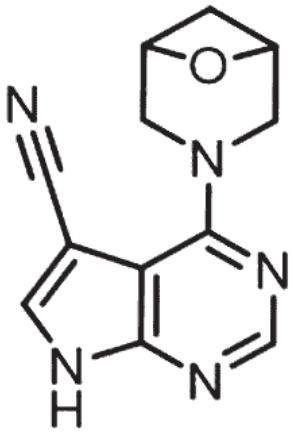


The target compound of Example 23 (61 mg, 0.237 mmol, 85%, m/z = 256.1 $[M^+H]^+$) was obtained by performing the same method as in Example 12 above, except for using 3-oxa-7-azabicyclo[3.3.0]octane instead of using (3-azabicyclo[3.1.0]hexan-1-yl)methanol.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.22 (s, 1H), 8.19 (s, 1H), 3.98 (ddt, J = 11.0, 7.5, 4.2 Hz, 2H), 3.86 - 3.77 (m, 2H), 3.81 - 3.69 (m, 2H), 3.57 (dq, J = 8.6, 3.3 Hz, 2H), 3.05 (s, 2H).

[Example 24]

Preparation of 4-(6-oxa-3-azabicyclo[3.1.1]hept-3-yl)-1H-1,5,7-triazaindene-3-carbonitrile (NRX02126)

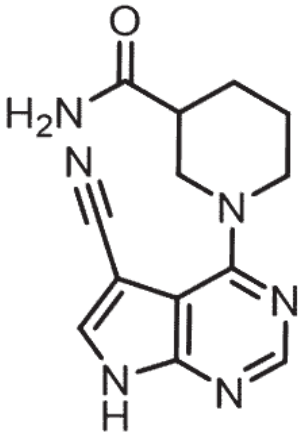


The target compound of Example 24 (31 mg, 0.126 mmol, 45%, m/z = 242.1 $[M^+H]^+$) was obtained by performing the same method as in Example 12 above, except for using 6-oxa-3-azabicyclo[3.1.1]heptane instead of using (3-azabicyclo[3.1.0]hexan-1-yl)methanol.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.33 - 8.24 (m, 2H), 4.74 (dd, J = 16.2, 6.6 Hz, 2H), 4.24 - 4.12 (m, 2H), 3.96 (s, 2H), 1.93 - 1.84 (m, 1H).

[Example 25]

Preparation of 1-(3-cyano-1H-1,5,7-triazainden-4-yl)-3-piperidinecarboxamide (NRX02127)

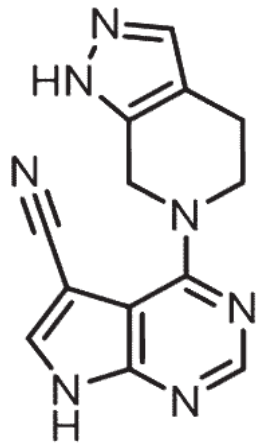


The target compound of Example 25 (62 mg, 0.230 mmol, 82%, m/z = 270.3 $[M^+H]^+$) was obtained by performing the same method as in Example 12 above, except for using 3-piperidinecarboxamide (43 mg, 0.336 mmol) instead of using (3-azabicyclo[3.1.0]hexan-1-yl)methanol.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.30 (s, 1H), 8.27 (s, 1H), 7.29 (s, 1H), 6.84 (s, 1H), 4.33 (d, J = 13.2 Hz, 1H), 4.24 (d, J = 13.1 Hz, 1H), 3.08 - 2.96 (m, 3H), 1.92 (s, 1H), 1.75 (d, J = 7.5 Hz, 1H), 1.59 (s, 2H).

[Example 26]

Preparation of 4',5',6',7'-tetrahydro-1H,3'H-1,2',3',5,5',7-hexaaza-[4,5'-biindenyl]-3-carbonitrile (NRX02143)

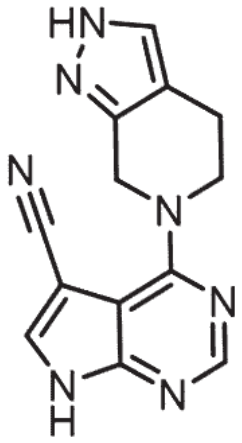


The target compound of Example 26 (37.9 mg, 0.143 mmol, 51%, m/z = 266.1 $[M^+H]^+$) was obtained by performing the same method as in Example 12 above, except for using 4,5,6,7-tetrahydro-1H-1,2,6-triazaindene (41.4 mg, 0.336 mmol) instead of using (3-azabicyclo[3.1.0]hexan-1-yl)methanol.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.90 (s, 1H), 12.53 (s, 1H), 8.33 (s, 1H), 8.31 (s, 1H), 7.48 (s, 1H), 4.75 (s, 2H), 3.93 (t, J = 5.7 Hz, 2H), 2.82 (t, J = 5.4 Hz, 2H).

[Example 27]

Preparation of 4',5',6',7'-tetrahydro-1H,2'H-1,2',3',5,5',7-hexaaza-[4,5'-biindenyl]-3-carbonitrile (NRX02144)

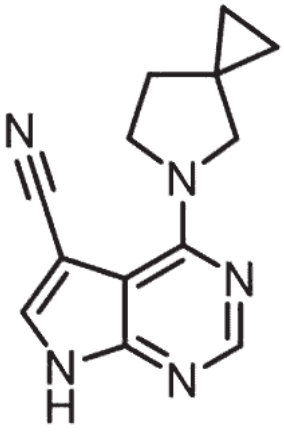


The target compound of Example 27 (38.9 mg, 0.147 mmol, 52%, m/z = 266.1 $[M^+H]^+$) was obtained by performing the same method as in Example 12 above, except for using 4,5,6,7-tetrahydro-1H-1,2,6-triazaindene (41.4 mg, 0.336 mmol) instead of using (3-azabicyclo[3.1.0]hexan-1-yl)methanol.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.90 (s, 1H), 12.53 (s, 1H), 8.33 (s, 1H), 8.31 (s, 1H), 7.48 (s, 1H), 4.75 (s, 2H), 3.93 (t, J = 5.6 Hz, 2H), 2.82 (s, 2H).

[Example 28]

Preparation of 4-(5-aza-5-spiro[2.4]heptyl)-1H-1,5,7-triazaindene-3-carbonitrile (NRX02145)

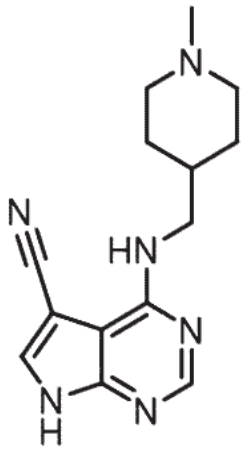


The target compound of Example 28 (47.5 mg, 0.199 mmol, 71%, m/z = 240.1 $[M^+H]^+$) was obtained by performing the same method as in Example 12 above, except for using 5-azaspiro[2.4]heptane instead of using (3-azabicyclo[3.1.0]hexan-1-yl)methanol.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.22 (s, 1H), 8.20 (s, 1H), 3.94 (t, J = 6.8 Hz, 2H), 3.67 (s, 2H), 1.94 (t, J = 6.8 Hz, 2H), 0.65 (s, 4H).

[Example 29]

Preparation of 4-{[(1-methyl-4-piperidyl)methyl]amino}-1H-1,5,7-triazaindene-3-carbonitrile (NRX02146)

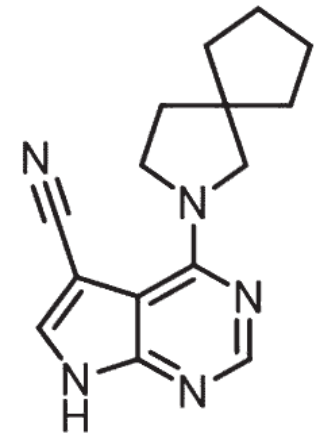


The target compound of Example 29 (12.7 mg, 0.047 mmol, 17%, m/z = 271.1 $[M^+H]^+$) was obtained by performing the same method as in Example 12 above, except for using [(1-methyl-4-piperidyl)methyl]amine instead of using (3-azabicyclo[3.1.0]hexan-1-yl)methanol.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 1H), 8.11 (s, 1H), 6.39 (t, J = 5.8 Hz, 1H), 3.43 (t, J = 6.2 Hz, 2H), 3.16 (s, 1H), 2.73 (dd, J = 11.6, 3.5 Hz, 2H), 2.12 (s, 3H), 1.79 (td, J = 11.6, 2.3 Hz, 2H), 1.62 (tq, J = 10.5, 3.0 Hz, 3H), 1.25 - 1.17 (m, 2H).

[Example 30]

Preparation of 4-(2-aza-2-spiro[4.4]nonyl)-1H-1,5,7-triazaindene-3-carbonitrile (NRX02150)

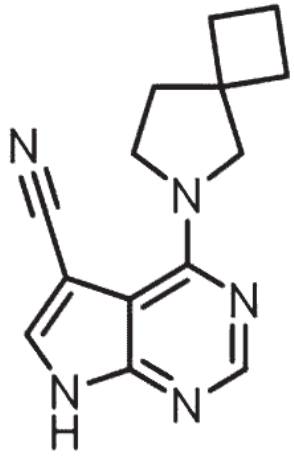


The target compound of Example 30 (55 mg, 0.206 mmol, 73%, m/z = 268.1 $[M^+H]^+$) was obtained by performing the same method as in Example 12 above, except for using 2-azaspiro[4.4]nonane instead of using (3-azabicyclo[3.1.0]hexan-1-yl)methanol.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.67 (s, 1H), 8.18 (s, 1H), 8.17 (s, 1H), 3.79 (t, J = 6.9 Hz, 2H), 3.61 (s, 2H), 1.87 (t, J = 7.0 Hz, 2H), 1.68 - 1.49 (m, 8H).

[Example 31]

Preparation of 4-(6-aza-6-spiro[3.4]octyl)-1H-1,5,7-triazaindene-3-carbonitrile (NRX02151)

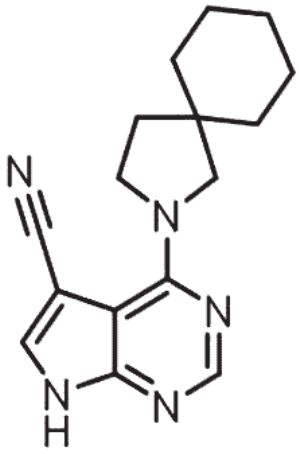


The target compound of Example 31 (55 mg, 0.217 mmol, 78%, m/z = 254.1 $[M^+H]^+$) was obtained by performing the same method as in Example 12 above, except for using 6-azaspiro[3.4]octane instead of using (3-azabicyclo[3.1.0]hexan-1-yl)methanol.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.69 (s, 1H), 8.19 (s, 1H), 8.17 (s, 1H), 3.72 (d, J = 7.0 Hz, 4H), 2.04 - 1.79 (m, 8H).

[Example 32]

Preparation of 4-(2-aza-2-spiro[4.5]decyl)-1H-1,5,7-triazaindene-3-carbonitrile (NRX02166)

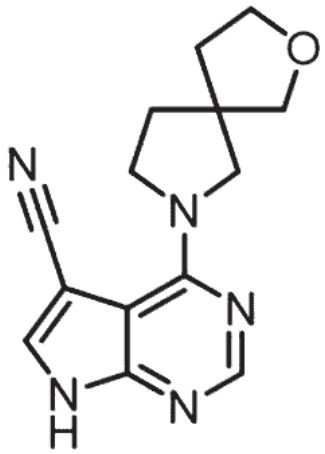


The target compound of Example 32 (19.7 mg, 0.070 mmol, 25%, m/z = 282.1 $[M^+H]^+$) was obtained by performing the same method as in Example 12 above, except for using 2-azaspiro[4.5]decane instead of using (3-azabicyclo[3.1.0]hexan-1-yl)methanol.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.70 (s, 1H), 8.19 (s, 1H), 8.17 (s, 1H), 3.77 (t, *J* = 7.1 Hz, 2H), 3.60 (s, 2H), 1.80 (t, *J* = 7.1 Hz, 2H), 1.52 - 1.35 (m, 10H).

[Example 33]

4-(2-oxa-7-aza-7-spiro[4.4]nonyl)-1H-1,5,7-triazaindene-3-carbonitrile (NRX02168)

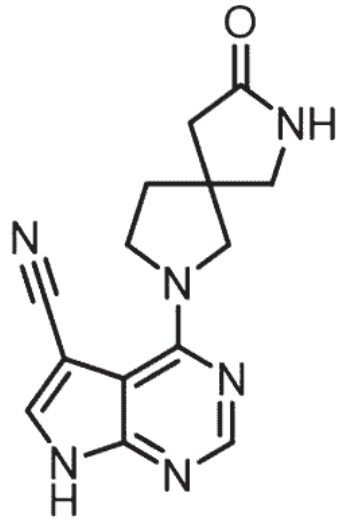


The target compound of Example 33 (48 mg, 0.178 mmol, 64%, m/z = 270.1 $[M^+H]^+$) was obtained by performing the same method as in Example 12 above, except for using 2-oxa-7-azaspiro[4.4]nonane instead of using (3-azabicyclo[3.1.0]hexan-1-yl)methanol.

^{1}H-NMR (400 MHz, $CDCl_3$-*d*) δ 8.36 (s, 1H), 7.76 (s, 1H), 4.05 (ddd, *J* = 17.3, 10.9, 7.0 Hz, 2H), 3.99 (s, 1H), 3.99 - 3.93 (m, 3H), 3.93 - 3.84 (m, 3H), 3.80 - 3.68 (m, 3H), 2.21 - 1.94 (m, 6H), 1.24 (s, 1H).

[Example 34]

Preparation of 4-(8-oxo-2,7-diaza-2-spiro[4.4]nonyl)-1H-1,5,7-triazaindene-3-carbonitrile (NRX02171)

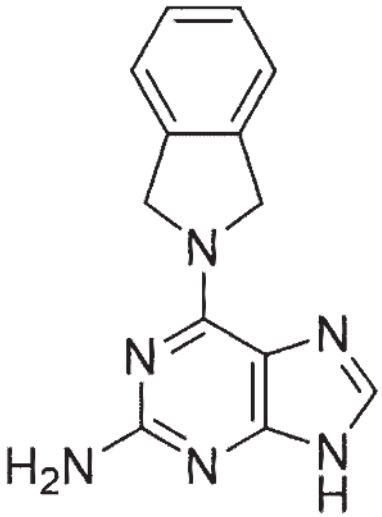


The target compound of Example 34 (35 mg, 0.124 mmol, 44%, m/z = 283.1 $[M^+H]^+$) was obtained by performing the same method as in Example 12 above, except for using 2,7-diaza-3-spiro[4.4]nonanone instead of using (3-azabicyclo[3.1.0]hexan-1-yl)methanol.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 1H), 8.22 (s, 1H), 7.66 (s, 1H), 3.88 (t, J = 7.0 Hz, 1H), 3.84 - 3.72 (m, 1H), 3.25 (d, J = 0.8 Hz, 1H), 2.26 (s, 1H), 2.06 (td, J = 6.7, 1.5 Hz, 1H), 1.30 - 1.19 (m, 1H).

[Example 35]

Preparation of 6-(isoindolin-2-yl)-9H-purin-2-amine (NRX02095)

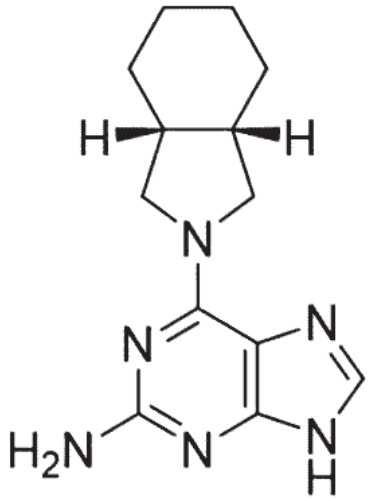


6-Chloro-9H-purin-2-amine (30 mg, 0.119 mmol), isoindole (21.3 mg, 0.178 mmol), and triethylamine (62 μl, 0.445 mmol) were added to ethanol (0.8 ml), and the mixture was stirred at 85℃ for 18 hours. The reaction solution was concentrated under reduced pressure, and then the filtrate was purified by reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the target compound of Example 35 (3.1 mg, 0.012 mmol, 10%, m/z = 253.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.15 (s, 1H), 7.68 (s, 1H), 7.41 (dd, J = 5.4, 3.3 Hz, 2H), 7.29 (dd, J = 5.6, 3.2 Hz, 2H), 5.73 (d, J = 7.7 Hz, 2H), 5.29 (s, 2H), 4.86 (s, 2H).

[Example 36]

Preparation of 6-((3aR,7aS)-octahydro-2H-isoindol-2-yl)-9H-purin-2-amine (NRX02094)

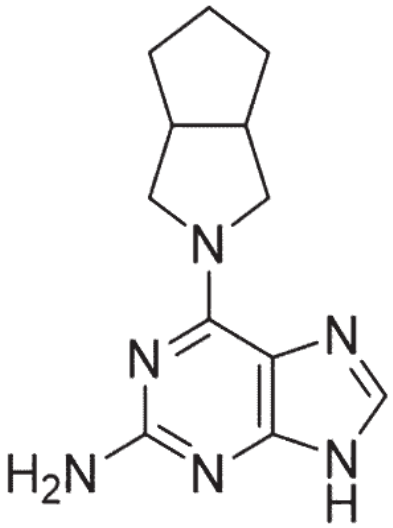


The target compound of Example 36 (29.0 mg, 0.112 mmol, 63%, m/z = 259.1 $[M^+H]^+$) was obtained by performing the same method as in Example 35 above, except for using (3aR,7aS)-octahydro-1H-isoindole instead of using isoindole.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.05 (s, 1H), 7.60 (s, 1H), 5.61 (s, 2H), 3.93 (s, 2H), 3.46 (s, 1H), 2.25 (d, J = 37.8 Hz, 3H), 1.65 - 1.26 (m, 6H).

[Example 37]

Preparation of 6-(hexahydrocyclopenta[c]pyrrol-2(1H)-yl)-9H-purin-2-amine (NRX02093)

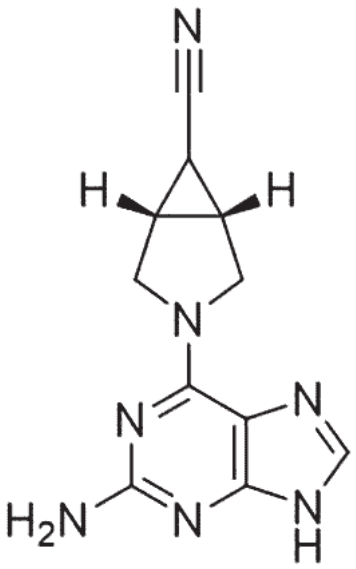


The target compound of Example 37 (27.5 mg, 0.112 mmol, 63%, m/z = 245.1 $[M^+H]^+$) was obtained by performing the same method as in Example 35 above, except for using octahydrocyclopenta[c]pyrrole instead of using isoindole.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.04 (s, 1H), 7.58 (s, 1H), 5.59 (s, 2H), 2.65 (s, 2H), 1.82 - 1.35 (m, 6H).

[Example 38]

Preparation of (1R,5S)-3-(2-amino-9H-purin-6-yl)-3-azabicyclo[3.1.0]hexane-6-carbonitrile (NRX02092)

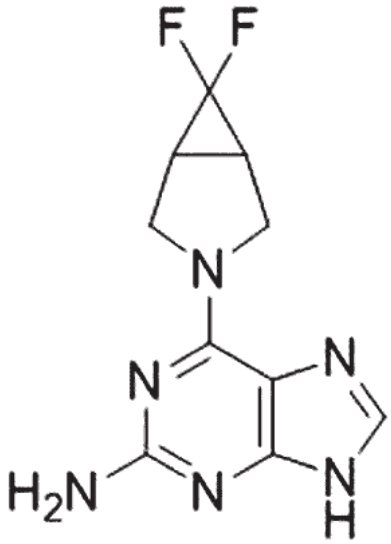


The target compound of Example 38 (27.5 mg, 0.112 mmol, 63%, m/z = 242.1 $[M^+H]^+$) was obtained by performing the same method as in Example 35 above, except for using (1R,5S)-3-azabicyclo[3.1.0]hexane-6-carbonitrile instead of using isoindole.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.10 (s, 1H), 7.63 (s, 1H), 5.72 (s, 2H), 4.07 (q, *J* = 5.3 Hz, 1H), 3.56 (s, 2H), 3.13 (d, *J* = 5.2 Hz, 1H), 2.38 (s, 2H), 1.61 (t, *J* = 3.5 Hz, 1H).

[Example 39]

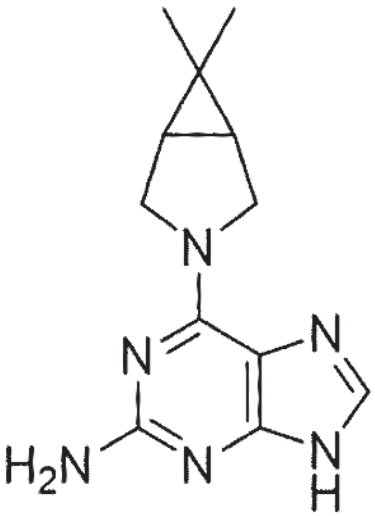
Preparation of 6-(6,6-difluoro-3-azabicyclo[3.1.0]hexan-3-yl)-9H-purin-2-amine (NRX02091)



The target compound of Example 39 (26.3 mg, 0.104 mmol, 58%, m/z = 253.1 $[M^+H]^+$) was obtained by performing the same method as in Example 35 above, except for using 6,6-difluoro-3-azabicyclo[3.1.0]hexane instead of using isoindole.

[Example 40]

Preparation of 6-(6,6-dimethyl-3-azabicyclo[3.1.0]hexan-3-yl)-9H-purin-2-amine (NRX02090)

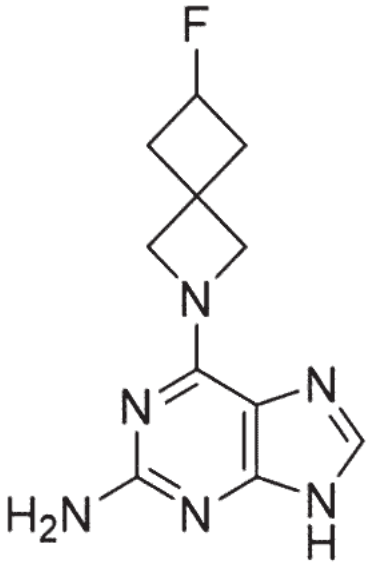


The target compound of Example 40 (23.5 mg, 0.096 mmol, 54%, m/z = 245.1 $[M^+H]^+$) was obtained by performing the same method as in Example 35 above, except for using 6,6-dimethyl-3-azabicyclo[3.1.0]hexane instead of using isoindole.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.07 (s, 1H), 7.62 (s, 1H), 5.65 (s, 2H), 4.15 (s, 1H), 3.95 (s, 1H), 3.60 (d, J = 20.2 Hz, 2H), 1.54 (s, 1H), 1.44 (s, 1H), 1.05 (s, 3H), 0.83 (s, 3H).

[Example 41]

Preparation of 6-(6-fluoro-2-azaspiro[3.3]heptan-2-yl)-9H-purin-2-amine (NRX02089)



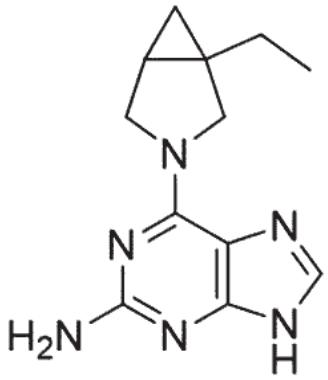
The target compound of Example 41 (15.8 mg, 0.064 mmol, 36%, m/z = 249.1 $[M^+H]^+$) was obtained by performing the same method as in Example 35 above, except for using 6-fluoro-2-azaspiro[3.3]heptene instead of using isoindole.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.23 (s, 1H), 7.67 (s, 1H), 5.98 (s, 2H), 5.02 (dp,

J = 56.0, 6.6 Hz, 1H), 4.28 (s, 4H), 2.66 (s, 2H).

[Example 42]

Preparation of 6-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-9H-purin-2-amine (NRX02004)



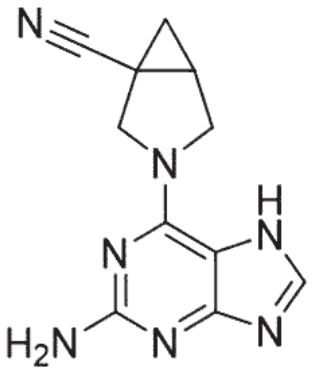
6-Bromo-9H-purin-2-amine (100 mg, 0.467 mmol), 1-ethyl-3-azabicyclo[3.1.0]hexane (62.3 mg, 0.561 mmol), and triethylamine (97.7 μl, 0.701 mmol) were added to ethanol (3.1 ml), and the mixture was stirred at 85℃ for 18 hours. The reaction solution was concentrated under reduced pressure, and then the filtrate was purified by reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the target compound of Example 42 (110 mg, 0.45 mmol, 96%, m/z = 245.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.14 (s, 1H), 7.63 (s, 1H), 5.67 (s, 2H), 1.73 (dq, *J* = 14.6, 7.4 Hz, 1H), 1.46 (dq, *J* = 15.6, 8.0 Hz, 2H), 0.95 (td, *J* = 7.4, 1.0 Hz, 3H), 0.64 (dd, *J* = 8.0, 4.5 Hz, 1H), 0.24 (t, *J* = 4.2 Hz, 1H).

[Example 43]

Preparation of 3-(2-amino-7H-purin-6-yl)-3-azabicyclo[3.1.0]hexane-1-

carbonitrile (NRX02070)

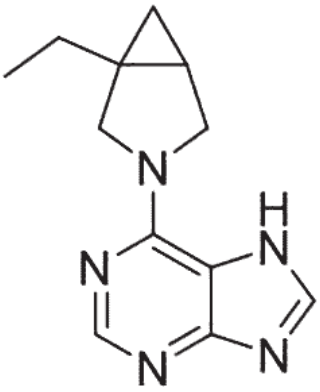


The target compound of Example 43 (6.7 mg, 0.028 mmol, 52%, m/z = 242.1 $[M^+H]^+$) was obtained by performing the same method as in Example 42 above, except for using 3-azabicyclo[3.1.0]hexane-1-carbonitrile instead of using 1-ethyl-3-azabicyclo[3.1.0]hexane.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.15 (s, 1H), 7.65 (s, 1H), 5.75 (s, 2H), 4.01 (s, 1H), 3.65 (s, 3H), 1.47 (dd, J = 8.5, 5.3 Hz, 2H), 0.95 (t, J = 5.3 Hz, 2H).

[Example 44]

Preparation of 6-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-purine (NRX02069)



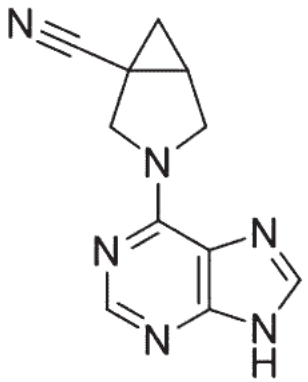
6-Bromo-7H-purine (10 mg, 0.05 mmol), 1-ethyl-3-azabicyclo[3.1.0]hexane (6.7 mg,

0.06 mmol), and triethylamine (10.5 μl, 0.075 mmol) were added to ethanol (0.5 ml), and the mixture was stirred at 85℃ for 18 hours. The reaction solution was concentrated under reduced pressure, and then the filtrate was purified by reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the target compound of Example 44 (15.9 mg, 0.069 mmol, 138%, m/z = 230.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.11 (s, 1H), 8.03 (s, 1H), 4.07 - 3.45 (m, 3H), 1.71 (dq, J = 14.7, 7.4 Hz, 1H), 1.45 (dq, J = 14.5, 7.4 Hz, 1H).

[Example 45]

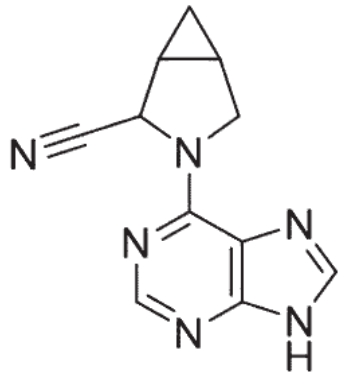
Preparation of 3-(9H-purin-6-yl)-3-azabicyclo[3.1.0]hexane-1-carbonitrile (NRX02072)



The target compound of Example 45 (22.4 mg, 0.099 mmol, 187%, m/z = 227.1 $[M^+H]^+$) was obtained by performing the same method as in Example 44 above, except for using 3-azabicyclo[3.1.0]hexane-1-carbonitrile instead of using 1-ethyl-3-azabicyclo[3.1.0]hexane.

[Example 46]

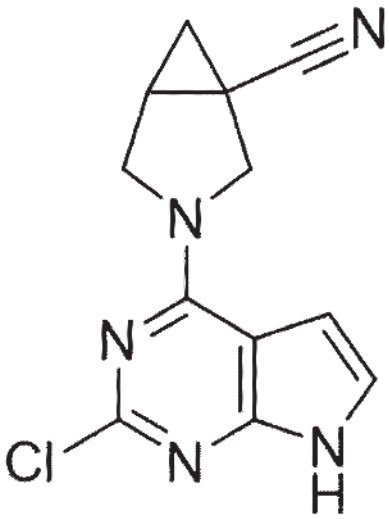
Preparation of 3-(9H-purin-6-yl)-3-azabicyclo[3.1.0]hexane-2-carbonitrile (NRX02074)



The target compound of Example 46 (6.3 mg, 0.028 mmol, 30%, m/z = 227.1 $[M^+H]^+$) was obtained by performing the same method as in Example 44 above, except for using 3-azabicyclo[3.1.0]hexane-2-carbonitrile instead of using 1-ethyl-3-azabicyclo[3.1.0]hexane.

[Example 47]

Preparation of 3-(2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-3-azabicyclo[3.1.0]hexane-1-carbonitrile (NRX02071)

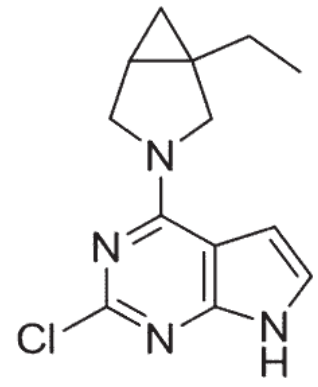


2,4-Dichloro-7H-pyrrolo[2,3-*d*]pyridine (7.96 mg, 0.042 mmol), 3-azabicyclo[3.1.0]hexane-2-carbonitrile hydrobromide (10 mg, 0.053 mmol), and triethylamine (11.1 μl, 0.079 mmol) were added to ethanol (0.53 ml), and the mixture was stirred at 85℃ for 18 hours. The reaction solution was concentrated under reduced pressure, and then the filtrate was purified by reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the target compound of Example 47 (6 mg, 0.023 mmol, 44%, m/z = 260.0 $[M^+H]^+$).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.84 (s, 1H), 7.15 (dd, *J* = 3.6, 2.3 Hz, 1H), 6.59 (d, *J* = 3.3 Hz, 1H), 4.26 (d, *J* = 10.6 Hz, 1H), 4.01 (d, *J* = 10.3 Hz, 1H), 3.82 (s, 2H), 2.53 (s, 1H), 1.55 (dd, *J* = 8.6, 5.4 Hz, 1H), 1.05 (t, *J* = 5.5 Hz, 1H).

[Example 48]

Preparation of 2-chloro-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine (NRX02068)

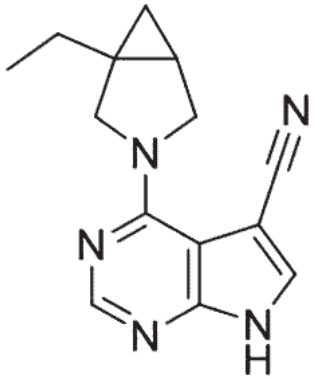


The target compound of Example 48 (6 mg, 0.023 mmol, 44%, m/z = 263.1 $[M^+H]^+$) was obtained by performing the same method as in Example 47 above, except for using 1-ethyl-3-azabicyclo[3.1.0]hexane instead of using 3-azabicyclo[3.1.0]hexane-2-carbonitrile

hydrobromide.

[Example 49]

Preparation of 4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1,5,7-triaza-1H-indene-3-carbonitrile (NRX02067)

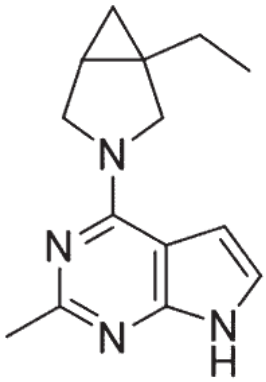


4-Chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (28.9 mg, 0.162 mmol), 1-ethyl-3-azabicyclo[3.1.0]hexane (20 mg, 0.18 mmol), and triethylamine (62.7 μl, 0.450 mmol) were added to ethanol (0.9 ml), and the mixture was stirred at 85℃ for 18 hours. The reaction solution was concentrated under reduced pressure, and then the filtrate was purified by reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the target compound of Example 49 (25.9 mg, 0.102 mmol, 56%, m/z = 254.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.25 (s, 1H), 8.19 (s, 1H), 4.17 (d, J = 10.4 Hz, 1H), 4.08 (d, J = 11.0 Hz, 1H), 3.77 (dd, J = 10.9, 4.4 Hz, 1H), 3.64 (d, J = 10.5 Hz, 1H), 1.80 (dd, J = 14.0, 7.2 Hz, 1H), 1.53 (dt, J = 8.1, 4.1 Hz, 1H), 1.42 (dq, J = 14.9, 7.5 Hz, 1H), 0.99 (t, J = 7.4 Hz, 3H), 0.71 (dd, J = 8.0, 4.6 Hz, 1H), 0.71 (dd, J = 8.0, 4.6 Hz, 1H).

[Example 50]

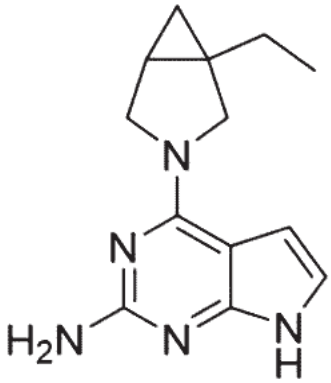
Preparation of 4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-2-methyl-7H-pyrrolo[2,3-d]pyrimidine (NRX02066)



4-Chloro-2-methyl-7H-pyrrolo[2,3-d]pyrimidine (10 mg, 0.060 mmol), 1-ethyl-3-azabicyclo[3.1.0]hexane (7.96 mg, 0.072 mmol), and triethylamine (12.5 μl, 0.089 mmol) were added to ethanol (0.6 ml), and the mixture was stirred at 85℃ for 18 hours. The reaction solution was concentrated under reduced pressure, and then the filtrate was purified by reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the target compound of Example 50 (24.2 mg, 0.10 mmol, 166%, m/z = 243.1 $[M^+H]^+$).

[Example 51]

Preparation of 4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine (NRX02065)

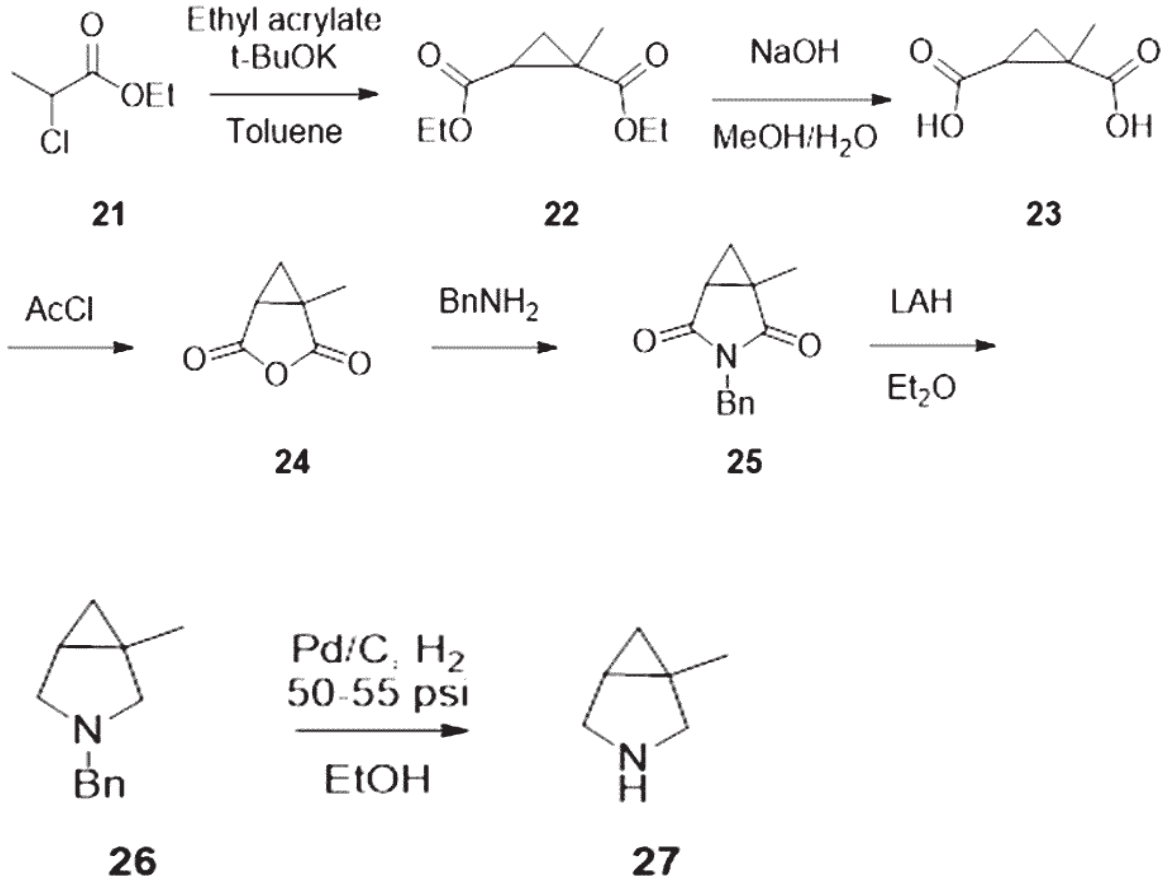


4-Chloro-7H-pyrrolo[2,3-d]pyrimidin-2-amine (27.3 mg, 0.162 mmol), 1-ethyl-3-azabicyclo[3.1.0]hexane (20 mg, 0.18 mmol), and triethylamine (62.7 μl, 0.45 mmol) were added to ethanol (1.6 ml), and the mixture was stirred at 85℃ for 18 hours. The reaction solution was concentrated under reduced pressure, and then the filtrate was purified by reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the target compound of Example 51 (16.1 mg, 0.066 mmol, 37%, m/z = 244.2 $[M^+H]^+$).

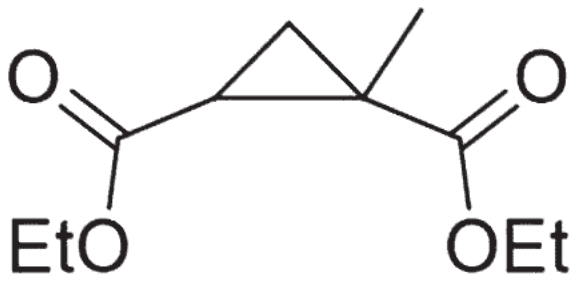
^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.73 (s, 1H), 8.13 (s, 1H), 6.66 (dd, *J* = 3.6, 2.1 Hz, 1H), 6.30 (dd, *J* = 3.7, 1.7 Hz, 1H), 5.43 (s, 2H), 3.92 (dd, *J* = 25.6, 10.4 Hz, 2H), 1.71 (dd, *J* = 14.1, 7.2 Hz, 1H), 1.53 - 1.40 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H), 0.67 (dd, *J* = 8.0, 4.4 Hz, 1H), 0.67 (dd, *J* = 8.0, 4.4 Hz, 1H).

[Preparation Example 6]

Preparation of 1-methyl-3-azabicyclo[3.1.0]hexane (27)



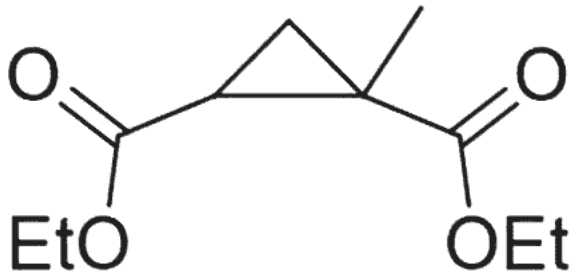
6-1. Step 1: diethyl 1-methylcyclopropane-1,2-dicarboxylate (22)



Ethyl-2-chloropropanoate (21) (5 g, 36.6 mmol) and ethyl acrylate (3.98 ml, 36.6 mmol) were added to toluene (26.1 ml), and the temperature was lowered to 0℃. tert-Butoxide (tetrahydrofuran) was added dropwise to the reaction solution, and the mixture was stirred at 0℃ for 1 hour. The reaction solution was concentrated under reduced pressure, and water and

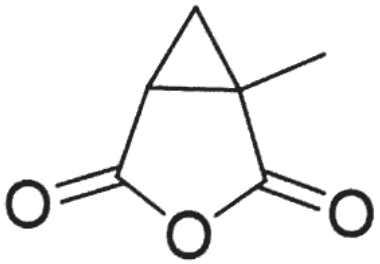
ethyl acetate were added thereto, followed by filtration to obtain compound (22) (7.3 g, 36.4 mmol, 99%).

6-2. Step 2: 1-methylcyclopropane-1,2-dicarboxylic acid (23)



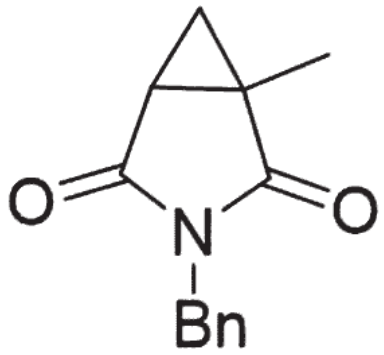
Diethyl 1-methylcyclopropane-1,2-dicarboxylic acid (22) (7.33 g, 36.6 mmol) and sodium hydroxide (4.39 g, 110 mmol) were added to methanol (36.6 ml) and water (36.6 ml), and the mixture was stirred at room temperature for 14 hours. The reaction solution was concentrated under reduced pressure, and water and ethyl acetate were added thereto, followed by filtration to obtain compound (23) (5.35 g, 37.1 mmol, 101%).

6-3. Step 3: 1-methyl-3-oxabicyclo[3.1.0]hexane-2,4-dione (24)



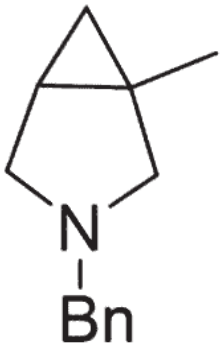
1-Methylcyclopropane-1,2-dicarboxylate (23) (787 mg, 4.98 mmol) was added to acetyl chloride (3.18 ml, 44.8 mmol), and the mixture was stirred under reflux for 1 hour. The reaction solution was concentrated under reduced pressure to obtain compound (24) (798 g, 5.69 mmol, 114%).

6-4. Step 4: 3-benzyl-1-methyl-3-azabicyclo[3.1.0]hexane-2,4-dione (25)



1-Methyl-3-oxabicyclo[3.1.0]hexane-2,4,-dione (24) (697 mg, 4.97 mmol) was added to benzylamine (0.54 ml, 4.97 mmol), and the mixture was stirred at 190℃ for 7 hours. The reaction solution was concentrated under reduced pressure, and isopropyl alcohol, ethyl acetate, and hexane were added thereto, followed by filtration to obtain compound (25) (559 mg, 2.44 mmol, 49%, m/z = 216.1 $[M^{+}H]^{+}$).

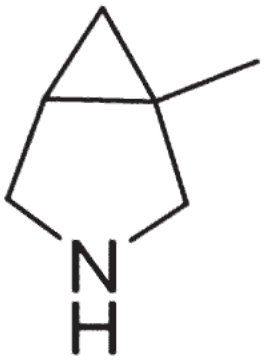
6-5. Step 5: 3-benzyl-1-methyl-3-azabicyclo[3.1.0]hexane (26)



3-Benzyl-1-methyl-3-azabicyclo[3.1.0]hexane-2,4-dione (25) (4.35 g, 20.2 mmol) was added to diethyl ether (57.7 ml), and the temperature was lowered to 0℃. Sodium bis-(2-methoxyethoxy)-aluminum dihydride (18.6 g, 91.9 mmol) was added to the reaction solution, and the mixture was stirred at 0℃ for 30 minutes, and then stirred at room temperature for 16

hours. The reaction solution was concentrated under reduced pressure, and water and diethyl ether were added thereto, followed by filtration to obtain compound (26) (2.25 g, 12 mmol, 60%, m/z = 188.2 $[M^+H]^+$).

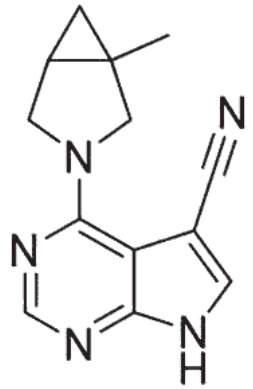
6-6. Step 6: 1-methyl-3-azabicyclo[3.1.0]hexane (27)



3-Benzyl-1-methyl-3-azabicyclo[3.1.0]hexane (26) (250 mg, 1.33 mmol) was added to ethanol (3.34 ml). 10% Pd/C (17.5 mg) was added to the reaction solution, and then the mixture was placed in a high-pressure hydrogen reactor and stirred at room temperature for 22 hours under 50 - 55 psi of hydrogen. The reaction solution was concentrated under reduced pressure, and isopropyl alcohol, ethyl acetate, and hexane were added thereto, followed by filtration to obtain compound (27) (100 mg, 1.03 mmol, 77%).

[Example 52]

Preparation of 4-(1-methyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (NRX02100)

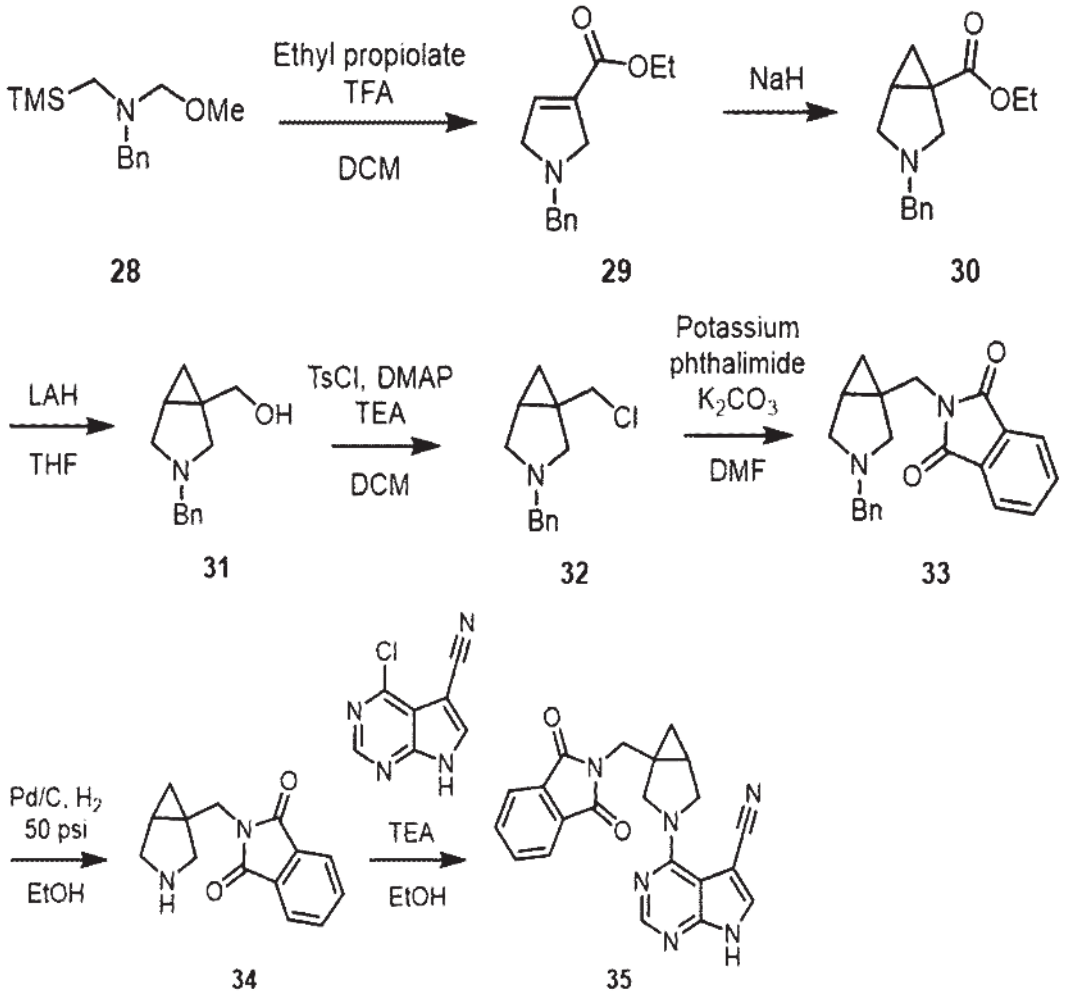


4-Chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (50 mg, 0.28 mmol), the compound (27) of Preparation Example 6 above (45.3 mg, 0.467 mmol), and triethylamine (108 μl, 0.778 mmol) were added to ethanol (1.56 ml), and the mixture was stirred at 85℃ for 18 hours. The reaction solution was concentrated under reduced pressure, and then the filtrate was purified by reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the target compound of Example 52 (25.4 mg, 0.106 mmol, 34%, m/z = 240.1 $[M^+H]^+$).

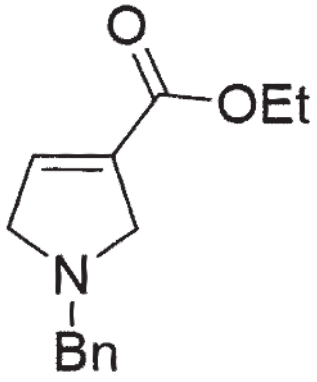
^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.27 - 8.22 (m, 1H), 8.21 - 8.14 (m, 1H), 4.19 (dd, *J* = 10.7, 3.4 Hz, 1H), 4.09 (dd, *J* = 10.8, 3.3 Hz, 1H), 3.58 (dd, *J* = 10.7, 3.3 Hz, 1H), 1.50 (dd, *J* = 8.4, 4.4 Hz, 1H), 1.35 - 1.28 (m, 3H), 0.68 (dt, *J* = 12.7, 6.0 Hz, 1H), 0.31 (q, *J* = 4.4 Hz, 1H).

[Preparation Example 7]

Preparation of 4-(1-((1,3-dioxoisoindolin-2-yl)methyl)-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (35)



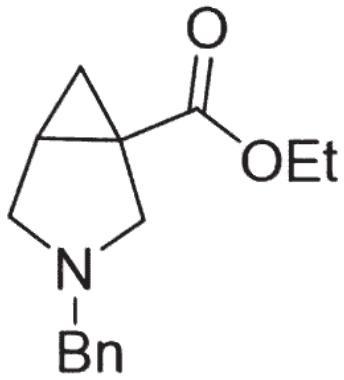
7-1. Step 1: ethyl 1-benzyl-2,5-dihydro-1H-pyrrole-3-carboxylate (29)



N-Benzyl-1-methoxy-N-((trimethylsilyl)methyl)methanamine (28) (24.3 g, 102 mmol) and ethyl propiolate (7.42 ml, 73.2 mmol) were added to dichloromethane (293 ml),

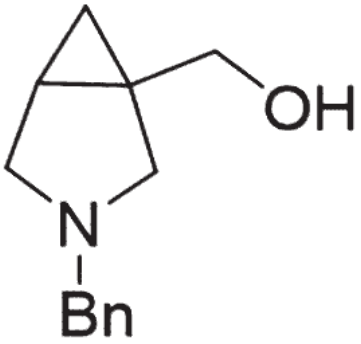
and the temperature was lowered to 0℃. Trifluoroacetic acid was added dropwise to the reaction solution, and the mixture was stirred at room temperature for 4 hours. A saturated sodium bicarbonate aqueous solution was added to the reaction solution for neutralization. Water and dichloromethane were added to the reaction solution, followed by filtration. The reaction solution was separated using column chromatography (SiO_2, ethyl acetate) to obtain the target compound (29) (13.3 g, 57.4 mmol, 78.45%, m/z = 232.1 $[M^+H]^+$).

7-2. Step 2: ethyl 3-benzyl-3-azabicyclo[3.1.0]hexane-1-carboxylate (30)



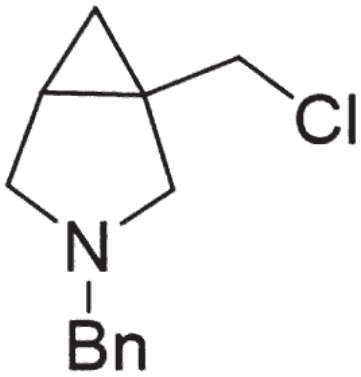
It was added to dimethyl sulfoxide (135 ml), and the temperature was lowered to 0℃. Sodium hydride (2.94 g, 73.5 mmol) was added to dimethyl sulfoxide (135 ml), and the temperature was lowered to 0℃. Trimethylsulfoxonium iodide was added dropwise to the reaction solution, and the mixture was stirred at room temperature for 1 hour. Ethyl 1-benzyl-2,5-dihydro-1H-pyrrole-3-carboxylate (29) (13.1 g, 56.6 mmol) was added to the reaction solution, and the mixture was stirred at room temperature for 1 hour. A saturated ammonium chloride aqueous solution was added for neutralization. Water and ethyl acetate were added to the reaction solution, followed by filtration. The reaction solution was separated using column chromatography (SiO_2, ethyl acetate) to obtain the target compound (30) (3.1 g, 12.6 mmol, 22.35%, m/z = 246.1 $[M^+H]^+$).

7-3. Step 3: (3-benzyl-3-azabicyclo[3.1.0]hexan-1-yl)methanol (31)



Ethyl-3-benzyl-3-azabicyclo[3.1.0]hexene-1-carboxylate (30) (0.1 g, 0.408 mmol) was added to tetrahydrofuran (2.04 ml), and the temperature was lowered to 0℃. Lithium aluminum hydride was added thereto, and the mixture was stirred at 0℃ for 30 minutes. The reaction solution was stirred at room temperature for 1 hour. Sodium sulfate decahydrate was added thereto, and the mixture was stirred at room temperature for 30 minutes. Tetrahydrofuran was added to the reaction solution, followed by filtration. The filtrate was concentrated under reduced pressure to obtain the target compound (31) (72 mg, 0.354 mmol, 87%, m/z = 204.1 $[M^+H]^+$).

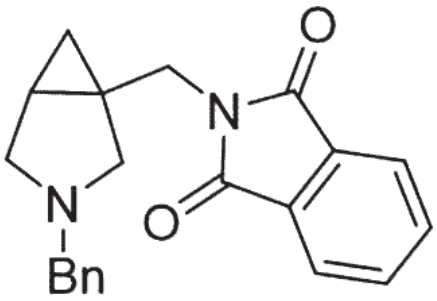
7-4. Step 4: 3-benzyl-1-(chloromethyl)-3-azabicyclo[3.1.0]hexane (32)



(3-Benzyl-3-azabicyclo[3.1.0]hexan-1-yl)methanol (790 mg, 3.89 mmol) was added

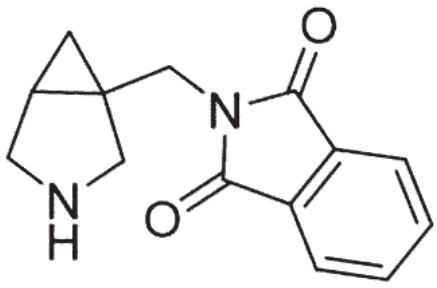
to dichloromethane (19.4 ml), and the temperature was lowered to 0℃. Tosyl chloride (889 mg, 4.66 mmol), 4-dimethylaminopyridine (47.5 mg, 0.389 mmol), and triethylamine (865 mg, 8.55 mmol) were added thereto, and the mixture was stirred at 0℃ for 30 minutes. The reaction solution was stirred at room temperature for 24 hours. The reaction solution was concentrated under reduced pressure, and water and dichloromethane were added thereto, followed by filtration to obtain the target compound (32) (598 mg, 2.7 mmol, 69%, m/z = 222.1 $[M^+H]^+$).

7-5. Step 5: 2-((3-benzyl-3-azabicyclo[3.1.0]hexan-1-yl)methyl)isoindoline-1,3-dione (33)



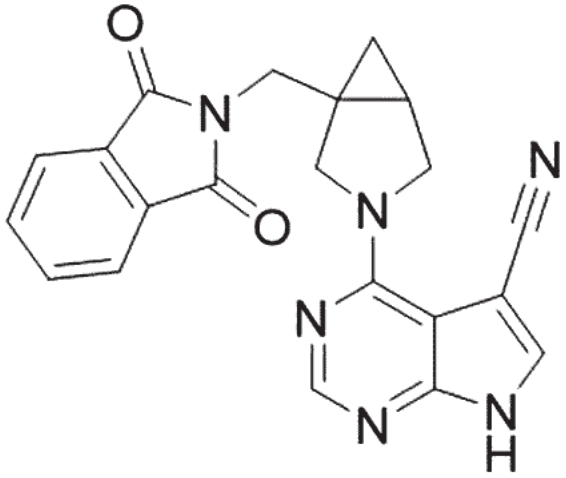
3-Benzyl-1-(chloromethyl)-3-azabicyclo[3.1.0]hexane (398 mg, 1.79 mmol) was added to dimethylformamide (3.59 ml). Potassium phthalimide (349 mg, 1.88 mmol) and potassium carbonate (397 mg, 2.87 mmol) were added to the reaction solution, and the mixture was stirred under reflux for 20 hours. The reaction solution was stirred at room temperature for 24 hours. The reaction solution was concentrated under reduced pressure, and water and dichloromethane were added thereto, followed by filtration to obtain the target compound (33) (515 mg, 1.55 mmol, 86%, m/z = 333.1 $[M^+H]^+$).

7-6. Step 6: 2-((3-azabicyclo[3.1.0]hexan-1-yl)methyl)isoindoline-1,3-dione (34)



2-((3-Benzyl-3-azabicyclo[3.1.0]hexan-1-yl)methyl)isoindoline-1,3-dione (515 mg, 1.55 mmol) was added to ethanol (5.16 ml). 10% Pd/C (36 mg) was added to the reaction solution, and then the mixture was placed in a high-pressure hydrogen reactor. The reaction solution was stirred at room temperature for 20 hours under 50 psi of hydrogen. After filtering the reaction solution, the filtrate was concentrated under reduced pressure to obtain the target compound (34) (324 mg, 1.34 mmol, 86%, m/z = 243.1 $[M^+H]^+$).

7-7. Step 7: 4-(1-((1,3-dioxoisoindolin-2-yl)methyl)-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (35)

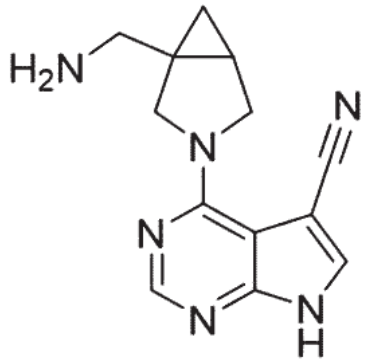


4-Chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (100 mg, 0.560 mmol), 2-((3-azabicyclo[3.1.0]hexan-1-yl)methyl)isoindoline-1,3-dione (187 mg, 0.672 mmol), and triethylamine (197 μl, 1.4 mmol) were added to ethanol (2.8 ml), and the mixture was stirred

at 85℃ for 18 hours. The reaction solution was concentrated under reduced pressure, and then the filtrate was purified by reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the target compound (35) (160 mg, 0.416 mmol, 74%, m/z = 385.1 $[M^+H]^+$).

[Example 53]

Preparation of 4-(1-(aminomethyl)-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (NRX02101)

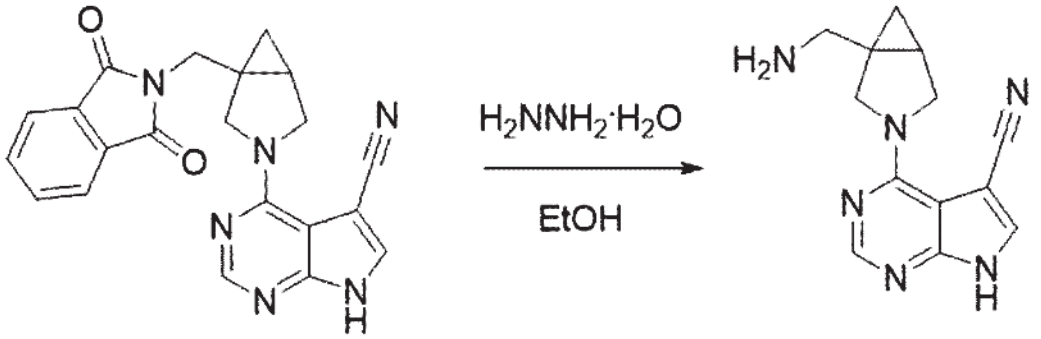


4-(1-((1,3-Dioxoisoindolin-2-yl)methyl)-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (160 mg, 0.416 mmol) and hydrazine monohydrate (278 mg, 1.66 mmol) were added to ethanol (4.16 ml), and the mixture was stirred at 80℃ for 18 hours. The reaction solution was concentrated under reduced pressure, and water and dichloromethane were added thereto, followed by filtration. The filtrate was purified by reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the target compound of Example 53 (3.4 mg, 0.21 mmol, 50%, m/z = 255.1 $[M^+H]^+$).

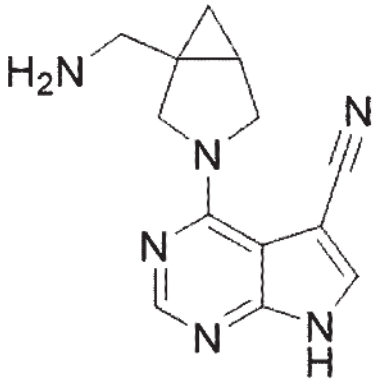
^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.98 (s, 1H), 8.94 (s, 1H), 4.93 (d, J = 10.8 Hz, 1H), 4.84 (d, J = 10.6 Hz, 1H), 4.59 (dd, J = 10.6, 4.4 Hz, 1H), 4.51 (d, J = 10.8 Hz, 1H), 3.55 (s, 2H), 2.45 - 2.35 (m, 1H), 1.60 (dd, J = 8.0, 4.5 Hz, 1H), 1.07 (t, J = 4.3 Hz, 1H).

[Preparation Example 8]

Preparation of 4-(1-(aminomethyl)-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d] pyrimidine-5-carbonitrile (36)



35 36

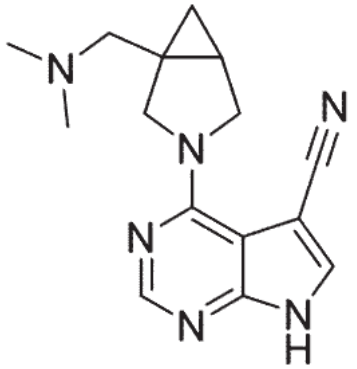


4-(1-((1,3-Dioxoisoindolin-2-yl)methyl)-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (160 mg, 0.416 mmol) and hydrazine monohydrate (278 mg, 1.66 mmol) were added to ethanol (4.16 ml), and the mixture was stirred at 80℃ for 18 hours. The reaction solution was concentrated under reduced pressure, and water and dichloromethane were added thereto, followed by filtration. The filtrate was purified by reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the target compound (36) of Preparation Example 8 (3.4 mg, 0.21 mmol, 50%, m/z = 255.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.98 (s, 1H), 8.94 (s, 1H), 4.93 (d, J = 10.8 Hz, 1H), 4.84 (d, J = 10.6 Hz, 1H), 4.59 (dd, J = 10.6, 4.4 Hz, 1H), 4.51 (d, J = 10.8 Hz, 1H), 3.55 (s, 2H), 2.45 - 2.35 (m, 1H), 1.60 (dd, J = 8.0, 4.5 Hz, 1H), 1.07 (t, J = 4.3 Hz, 1H).

[Example 54]

Preparation of 4-(1-((dimethylamino)methyl)-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (NRX02102)

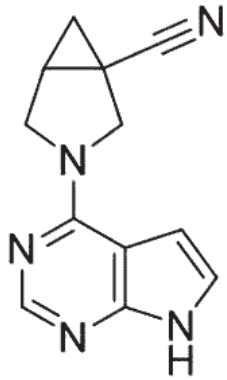


The compound (36) of Preparation Example 8 above (50 mg, 0.197 mmol), sodium cyanoborohydride (18.5 mg, 0.295 mmol), and formaldehyde (8.86 mg, 0.295 mmol) were stirred at room temperature for 18 hours. The reaction solution was concentrated under reduced pressure and purified by reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the target compound of Example 54 (5.4 mg, 0.019 mmol, 9%, m/z = 283.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.20 (s, 1H), 8.16 (s, 1H), 4.10 (dd, J = 13.1, 10.9 Hz, 2H), 3.82 (dd, J = 10.7, 4.4 Hz, 1H), 3.70 (d, J = 11.0 Hz, 1H), 2.50 (s, 1H), 2.31 (d, J = 12.6 Hz, 1H), 2.17 (s, 6H), 1.52 (dt, J = 8.3, 4.2 Hz, 1H), 0.72 (dd, J = 8.1, 4.8 Hz, 1H), 0.39 (t, J = 4.5 Hz, 1H).

[Example 55]

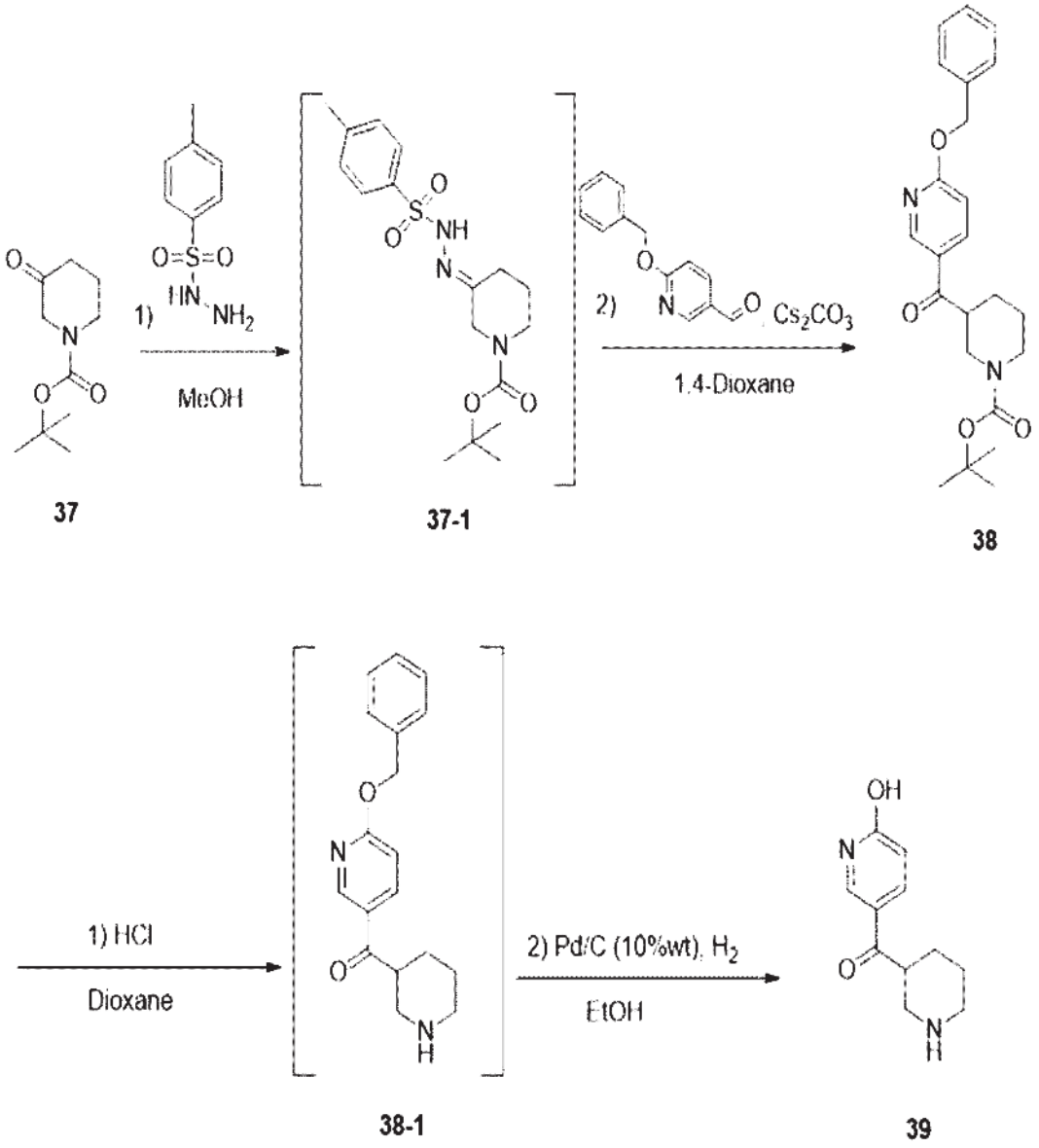
Preparation of 3-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-3-azabicyclo[3.1.0]hexane-1-carbonitrile (NRX02073)



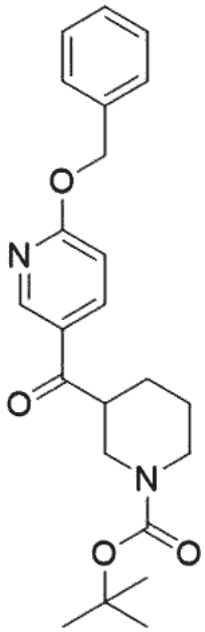
4-Chloro-7H-pyrrolo[2,3-d]pyrimidine (6.5 mg, 0.042 mmol) and 3-azabicyclo[3.1.0]hexane-1-carbonitrile hydrobromide (10 mg, 0.053 mmol) were added to ethanol (0.53 ml), and the mixture was stirred at 80°C for 18 hours. The reaction solution was concentrated under reduced pressure, and then the filtrate was purified by reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the target compound of Example 55 (4.1 mg, 0.018 mmol, 34%, m/z = 226.1 $[M^+H]^+$).

[Preparation Example 9]

Preparation of (6-hydroxypyridin-3-yl)(piperidin-3-yl)methanone (39)

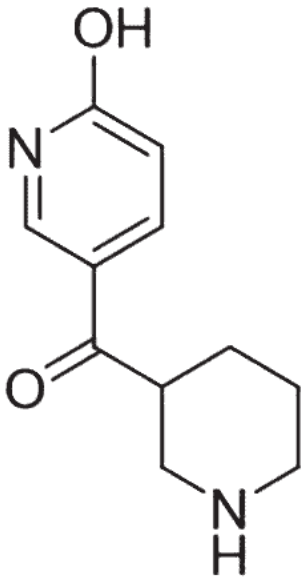


9-1. Step 1: *tert*-butyl 3-(6-(benzyloxy)nicotinoyl)piperidine-1-carboxylate (38)



tert-Butyl 3-oxopiperidine-1-carboxylate (37) (100 mg, 502 μmol) was dissolved in methanol (2.5 ml), and then 4-methylbenzenesulfonohydrazide (93.5 mg, 502 μmol) was added thereto, followed by stirring at room temperature for 3 hours, and the formation of tert-butyl (E)-3-(2-tosylhydrazinylidene)piperidine-1-carboxylate intermediate (37-1) was confirmed using an LC/MS instrument. The reaction solution was concentrated under reduced pressure and then dissolved in 1,4-dioxane (2.5 ml), and 6-(benzyloxy)nicotinaldehyde (107 mg, 502 μmol) and cesium carbonate (245 mg, 753 μmol) were added thereto, followed by stirring at 100℃ for 18 hours. After confirming the completion of the reaction, the reaction solution was concentrated under reduced pressure. Thereafter, the filtrate was purified using reverse-phase column chromatography (C18 resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the compound (38) of Step 1 of Preparation Example 9 above (61 mg, 154 μmol, 30.7%, m/z = 397.7 $[M^+H]^+$).

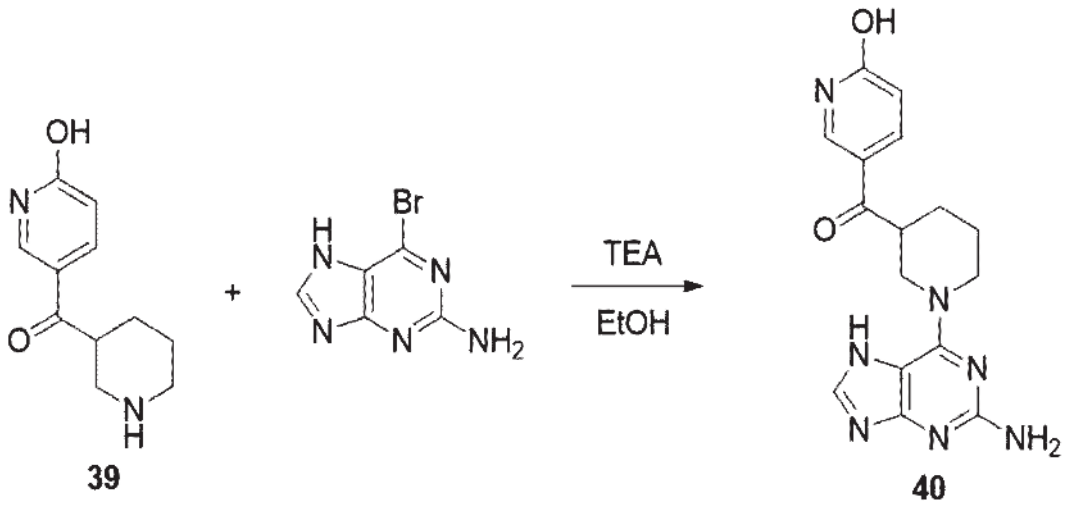
9-2. Step 2: (6-hydroxypyridin-3-yl)(piperidin-3-yl)methanone (39)



The compound (38) obtained in Step 1 of Preparation Example 9 above (61 mg, 154 μmol) was dissolved in 1,4-dioxane (1.0 ml), and then 4 N hydrochloric acid (515 μl, 15.4 mmol) dissolved in dioxane was added thereto, followed by stirring at room temperature for 19 hours, and the formation of (6-(benzyloxy)pyridin-3-yl)(piperidin-3-yl)methanone intermediate (38-1) was confirmed using an LC/MS instrument. The reaction solution was concentrated under reduced pressure, and then dissolved in ethanol (513 μl), and palladium charcoal (6 mg) was added thereto, and the flask was sealed using a septum. Thereafter, a hydrogen balloon was inserted therein, followed by stirring at room temperature for 3 hours to confirm the completion of the reaction. Thereafter, the reaction solution was filtered to remove palladium and other by-products using a syringe filter, and the filtrate was concentrated under reduced pressure to obtain the target compound (39) of Preparation Example 9 (47.7 mg, 154 μmol, 99%, m/z = 207.2 $[M^+H]^+$).

[Example 56]

Preparation of (1-(2-amino-7*H*-purin-6-yl)piperidin-3-yl)(6-hydroxypyridin-3-yl)methanone (NRX02078)

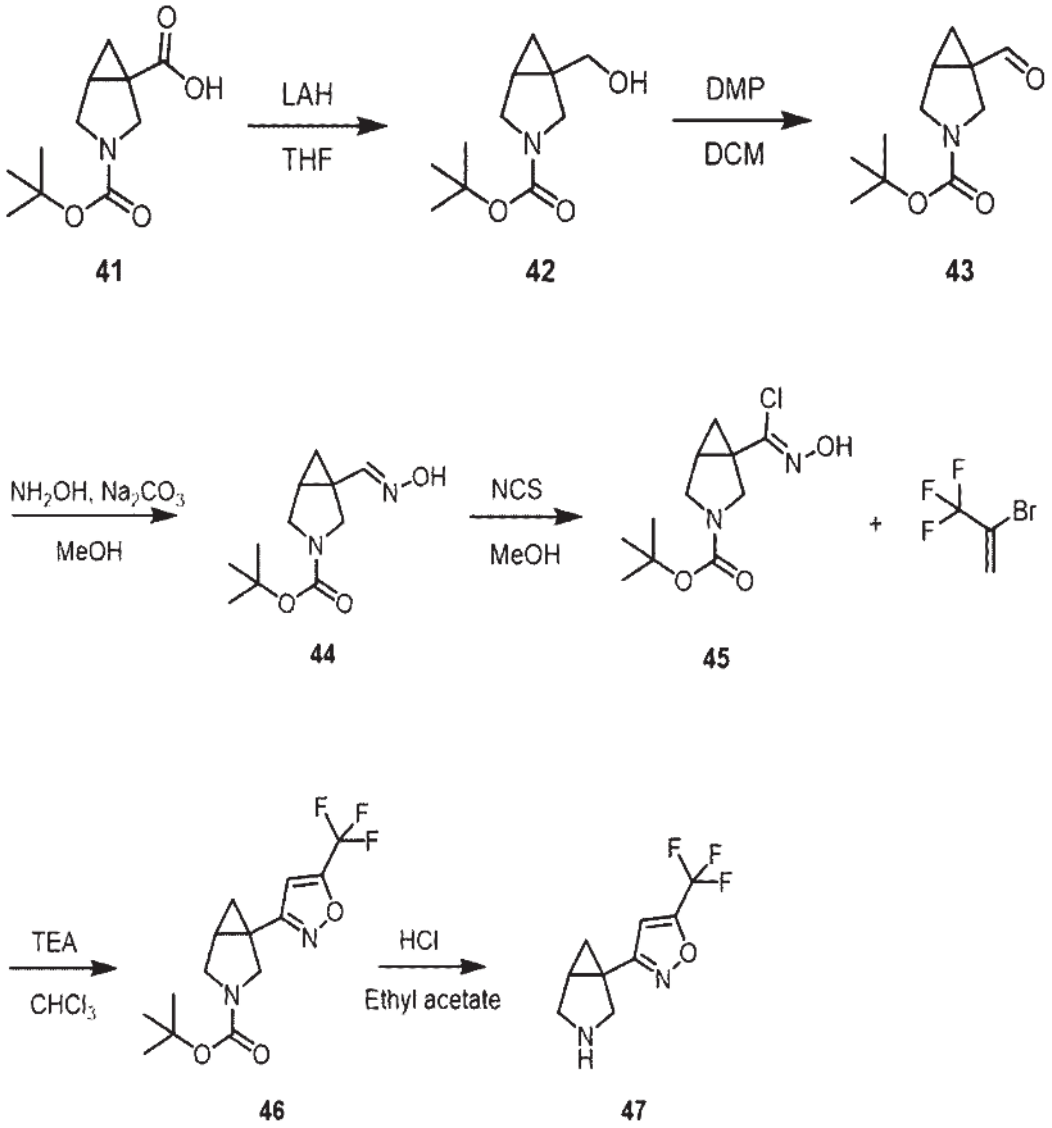


The compound (39) obtained in Preparation Example 9 above (47.4 mg, 231 μmol) was dissolved in ethanol (2.31 ml), and then 6-bromo-*7H*-purin-2-amine (44.5 mg, 208 μmol) and triethylamine (80.6 μl, 578 μmol) were added thereto, followed by stirring at 80℃ for 18 hours. After confirming the completion of the reaction, the reaction solution was concentrated under reduced pressure, and then purified using reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the target compound (40) of Example 56 (13.5 mg, 39.8 μmol, 17.2%, m/z = 340.4 $[M^+H]^+$).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.24 (s, 1H), 8.45 (d, 1H), 8.11 (s, 1H), 7.86 (dd, 1H), 7.67 (s, 1H), 6.36 (d, 1H), 5.72 (s, 2H), 3.13 (s, 1H), 2.90 (s, 2H), 2.65 (s, 1H), 1.82-1.87 (m, 1H), 1.66-1.75 (m, 2H), 1.52-1.56 (m, 1H).

[Preparation Example 10]

Preparation of 3-(3-azabicyclo[3.1.0]hexan-1-yl)-5-(trifluoromethyl)isoxazole (47)



10-1. Step 1: *tert*-butyl 1-(hydroxymethyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (42)

3-(*tert*-Butoxycarbonyl)-3-azabicyclo[3.1.0]hexane-1-carboxylic acid (41) (315 mg, 1.39 mmol) was dissolved in tetrahydrofuran (6.93 ml), and then placed in an ice bath to cool to 0℃. Thereafter, lithium aluminum hydride (105 mg, 2.77 mmol) was slowly added thereto in portions, followed by stirring slowly for 10 minutes. After 10 minutes, the ice bath was removed, and the mixture was stirred at room temperature for 1 hour to confirm the completion

of the reaction. Water and 1 M sodium hydroxide were added thereto in an amount of 100 μl each, and additionally 300 μl of water was added thereto, followed by stirring for 15 minutes to terminate the reactivity of the reaction solution. Thereafter, an excess amount of anhydrous sodium sulfate was added to the filtrate to remove moisture, followed by filtration using Celite. The filtered filtrate was concentrated under reduced pressure to obtain the compound (42) of Step 1 of Preparation Example 10 (272 mg, 1.27 mmol, 91.9%, m/z = 214.3 $[M^+H]^+$).

10-2. Step 2: *tert*-butyl 1-formyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (43)

The material (42) obtained in Step 1 of Preparation Example 10 above (300 mg, 1.41 mmol) was dissolved in dichloromethane (7.0 ml), and then placed in an ice bath to cool to 0°C. Thereafter, Dess-Martin periodinane (795 mg, 1.69 mmol) was slowly added thereto, and the ice bath was removed, followed by stirring at room temperature for 3 hours. After confirming the completion of the reaction, a saturated sodium bicarbonate solution (2 ml) and a solution prepared by dissolving thiosulfate (2 g) in water (5 ml) were added thereto, followed by stirring for 30 minutes, and then dichloromethane (30 ml) and water (30 ml) were added thereto, and the desired compound was extracted into a dichloromethane layer using a separatory funnel. The above process was repeated three times, and anhydrous sodium sulfate was added to the collected dichloromethane layers to remove residual moisture, followed by filtration. The filtrate was concentrated under reduced pressure to obtain the compound (43) of Step 2 (297 mg, 1.41 mmol, 99.9%, m/z = 212.3 $[M^+H]^+$).

10-3. Step 3: *tert*-butyl (E)-1-((hydroxyimino)methyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (44)

The material (43) obtained in Step 2 of Preparation Example 10 above (297 mg, 1.41

mmol) was dissolved in methanol (14.1 ml), and then hydroxylamine hydrochloride (195 mg, 2.81 mmol) and sodium carbonate (224 mg, 2.11 mmol) were added thereto, followed by stirring at room temperature for 19 hours. After confirming the completion of the reaction, ethyl acetate (40 ml) and water (40 ml) were added thereto, and the desired compound was extracted into an ethyl acetate layer using a separatory funnel. The above process was repeated three times, and the collected ethyl acetate layers were concentrated under reduced pressure, and the filtrate was purified using column chromatography (SiO_2, ethyl acetate : hexane = 1 : 3) to obtain the compound (44) of Step 3 (82.0 mg, 362 μmol, 25.8%, m/z = 227.3 $[M^+H]^+$).

10-4. Step 4: *tert*-butyl (Z)-1-(chloro(hydroxyimino)methyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (45)

The material (44) obtained in Step 3 of Preparation Example 10 above (82 mg, 362 μmol) was dissolved in dimethylformamide (1.81 ml), placed in an ice bath to cool to 0℃, and then N-chlorosuccinimide (194 mg, 1.45 mmol) was added thereto, followed by stirring at room temperature for 19 hours. After confirming the completion of the reaction, ethyl acetate (20 ml) and water (20 ml) were added thereto, and the desired compound was extracted into an ethyl acetate layer using a separatory funnel. The above process was repeated three times, anhydrous sodium sulfate was added to the collected ethyl acetate layers to remove residual moisture, followed by filtration through a filter. The filtrate was concentrated under reduced pressure to obtain the compound (45) of Step 4 (83.0 mg, 318 μmol, 87.9%, m/z = 261.7 $[M^+H]^+$).

10-5. Step 5: *tert*-butyl -1-(5-(trifluoromethyl)isoxazole-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (46)

The material (45) obtained in Step 4 of Preparation Example 10 above (83 mg, 318 μmol) was dissolved in chloroform (3.2 ml) and placed in an ice bath to cool to 0℃. Thereafter, 2-bromo-3,3,3-trifluoropropene (139 mg, 796 μmol) and triethylamine (65.1 μl, 478 μmol) were slowly added thereto, followed by stirring at room temperature for 3 hours. After confirming the completion of the reaction, ethyl acetate (15 ml) and water (15 ml) were added thereto, and the desired compound was extracted into an ethyl acetate layer using a separatory funnel. The above process was repeated three times, and the collected ethyl acetate layers were concentrated under reduced pressure, and the filtrate was purified using column chromatography (SiO_2, ethyl acetate : hexane = 1 : 5 to 1 : 3) to obtain the compound (46) of Step 5 (22.0 mg, 69.1 μmol, 21.7%, m/z = 319.3 $[M^+H]^+$).

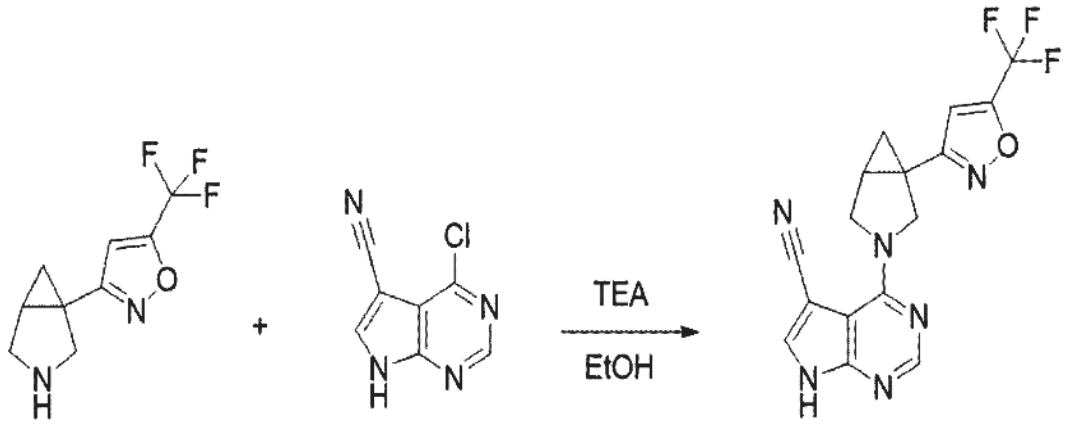
^{19}F-NMR (400 MHz, DMSO-d_6) δ -63.12 (d, J = 11.8 Hz, 3F).

10-6. Step 6: 3-(3-azabicyclo[3.1.0]hexan-1-yl)-5-(trifluoromethyl)isoxazole (47)

The material (46) obtained in Step 5 of Preparation Example 10 above (22 mg, 69.1 μmol) was dissolved in ethyl acetate (138 μl), and then 2 M hydrochloric acid (11.2 μl, 276 μmol) dissolved in ethyl acetate was added thereto, followed by stirring at room temperature for 3 hours. After confirming the completion of the reaction, the reaction solution was concentrated under reduced pressure. The filtrate was purified using a Prep-HPLC instrument to obtain the target compound (47) of Preparation Example 10 above (10.7 mg, 42.0 μmol, 60.8%, m/z = 219.2 $[M^+H]^+$).

[Example 57]

Preparation of 4-(1-(5-(trifluoromethyl)isoxazole-3-yl)-3-azabicyclo[3.1.0]hexan-3-yl)-7*H*-pyrrolo[2.3-*d*]pyrimidine-5-carbonitrile (NRX02103)

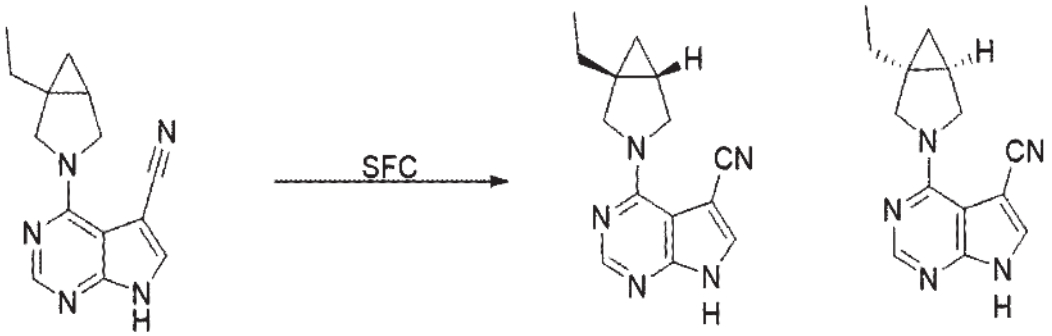


47 48

The compound (47) obtained in Preparation Example 10 above (10.7 mg, 42.0 μmol) was dissolved in ethanol (210 μl), and then 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (6.75 mg, 37.8 μmol) and triethylamine (14.6 μl, 105 μmol) were added thereto, followed by stirring at 80°C for 13 hours. After confirming the completion of the reaction, the reaction solution was concentrated under reduced pressure. The filtrate was purified using reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the target compound (48) of Example 57 (10.4 mg, 28.9 μmol, 68.7%, m/z = 361.3 $[M^+H]^+$).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.28-8.20 (m, 2H), 7.44 (q, *J*=1.0Hz, 1H), 4.50 (d, *J*=11.0Hz, 1H), 4.27 (d, *J*=10.6Hz, 1H), 4.19 (d, *J*=11.0Hz, 1H), 3.92 (dd, *J*=10.5, 4.3Hz, 1H), 2.45 (s, 1H), 2.34 (dt, *J*=8.8, 4.7Hz, 1H), 1.50 (dd, *J*=8.4, 5.2Hz, 1H), 1.19 (s, 1H), 1.08 (t, *J*=5.1Hz, 1H).

[Preparation Example 11]

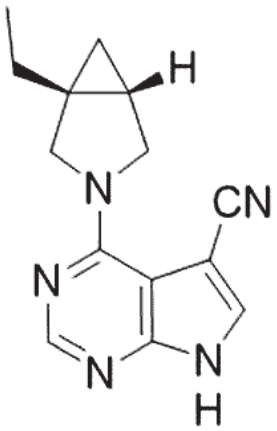


49 50

4-(1-Ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (Example 30) was separated by SFC (Daicel AD (25*250 mm, 10 μm), CO_2 / MeOH[0.2% NH_3 (7 M in MeOH)] = 80 / 20) to obtain the desired target compounds (49 : 594.40 mg, e.e. 97.32%, and 50 : 590.00 mg, 99.83% purity, e.e. 100.00%), respectively.

[Example 58]

Preparation of 4-((1*R*,5*S*)-1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (NRX02104)



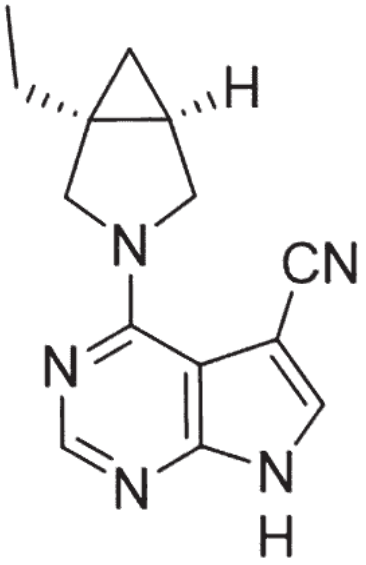
4-(1-Ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (Example 30) was separated by SFC (Daicel AD (25*250 mm, 10 μm), CO_2 / MeOH[0.2% NH_3 (7 M in MeOH)] = 80 / 20) to obtain the target compound (594.40 mg, e.e.

97.32%).

^{1}H-NMR (400 MHz, $CDCl_3$-*d*): δ 8.33 (s, 1H), 7.76 (s, 1H), 4.32 (d, *J* = 10.8 Hz, 1H), 4.25 (d, *J* = 11.0 Hz, 1H), 3.98 (dd, *J* = 10.8, 3.8 Hz, 1H), 3.77 (d, *J* = 10.8 Hz, 1H), 1.84 (m, 1H), 1.57 - 1.45 (m, 2H), 1.06 (t, *J* = 7.6 Hz, 3H), 0.77 (dd, *J* = 8.0, 5.2 Hz, 1H), 0.36 (t, *J* = 4.6 Hz, 1H).

[Example 59]

Preparation of 4-((1*S*,5*R*)-1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (NRX02105)

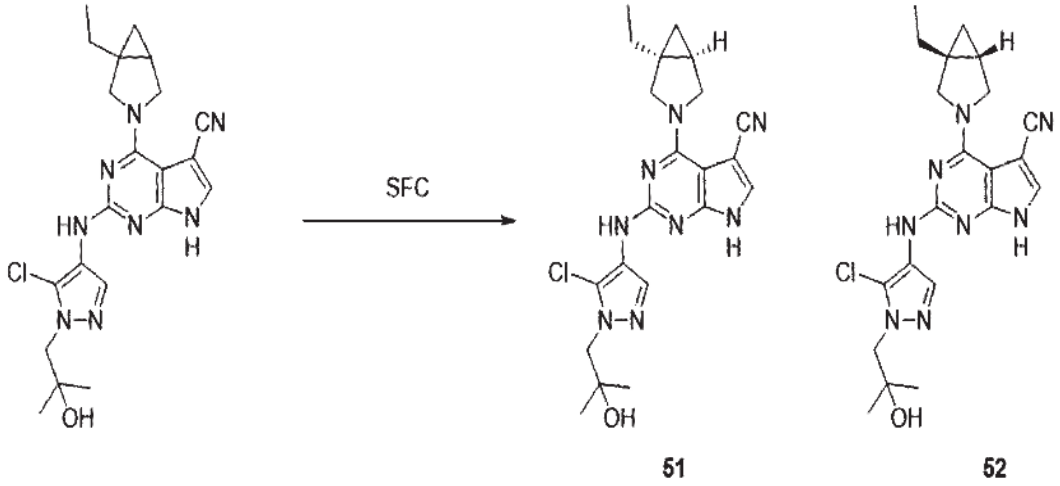


4-(1-Ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (Example 30) was separated by SFC (Daicel AD (25*250 mm, 10 μm), CO_2 / MeOH[0.2% NH_3 (7 M in MeOH)] = 80 / 20) to obtain the target compound (590.00 mg, 99.83% purity, e.e. 100.00%).

^{1}H-NMR (400 MHz, $CDCl_3$-*d*): δ 8.33 (s, 1H), 7.76 (s, 1H), 4.32 (d, *J* = 10.8 Hz, 1H), 4.24 (d, *J* = 11.0 Hz, 1H), 3.98 (dd, *J* = 10.6, 3.6 Hz, 1H), 3.77 (d, *J* = 10.8 Hz, 1H), 1.84 (m, 1H), 1.57 - 1.45 (m, 2H), 1.07 (t, *J* = 7.4 Hz, 3H), 0.77 (dd, *J* = 7.8, 5.2 Hz, 1H), 0.36 (t, *J* =

4.4 Hz, 1H).

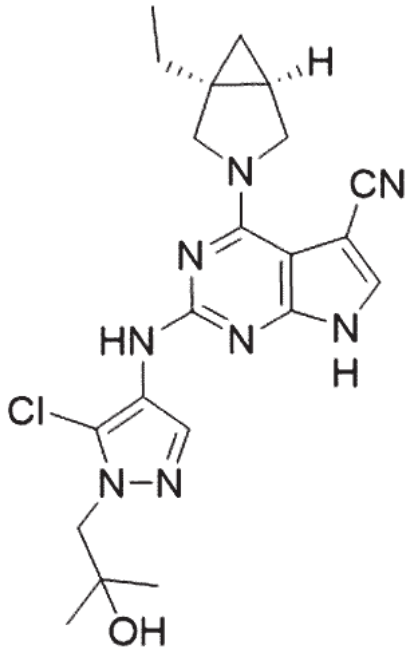
[Preparation Example 12]



2-((5-Chloro-1-(2-hydrox-2-methylpropyl)-1H-pyrazol-4-yl)amino)-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (Example 2) was separated by SFC (Daicel AD-3 (4.6*100 mm, 3 μm), CO_2 / EtOH[0.2% NH_3 (7 M in MeOH)] = 65 / 35) to obtain the target compounds (51 : 603.4 mg, e.e 99.27%, m/z = 441.4 $[M^+H]^+$, and 52 : 632.3 mg, e.e 97.9%, m/z = 414.4 $[M^+H]^+$), respectively.

[Example 60]

Preparation of 2-((5-chloro-1-(2-hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)amino)-4-((1*R*,5*S*)-1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (NRX02106)

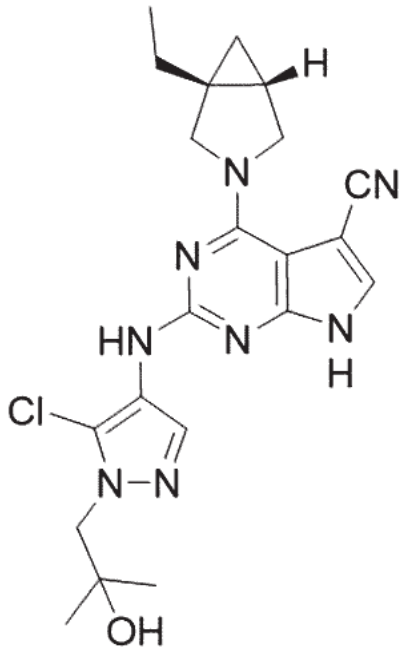


2-((5-Chloro-1-(2-hydrox-2-methylpropyl)-1H-pyrazol-4-yl)amino)-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (Example 2) was separated by SFC (Daicel AD-3 (4.6*100 mm, 3 μm), CO_2 / EtOH[0.2% NH_3 (7 M in MeOH)] = 65 / 35) to obtain the target compound (603.4 mg, e.e 99.27%, m/z = 441.4 $[M^+H]^+$).

^{1}H-NMR (400 MHz, DMSO-d_6): δ 12.14 (s, 1H), 7.98 (s, 1H), 7.88 (d, *J* = 3.0 Hz, 1H), 7.74 (s, 1H), 4.72 (s, 1H), 4.12 (d, *J* = 10.4 Hz, 1H), 4.03 (d, *J* = 11.0 Hz, 1H), 3.99 (s, 2H), 3.70 (dd, *J* = 11.0, 4.2 Hz, 1H), 3.57 (d, *J* = 10.4 Hz, 1H), 1.77 (m, 1H), 1.48 (m, 1H), 1.40 (m, 1H), 1.13 (s, 6H), 0.98 (t, *J* = 7.4 Hz, 3H), 0.68 (dd, *J* = 7.8, 4.6 Hz, 1H), 0.26 (t, *J* = 4.2 Hz, 1H).

[Example 61]

Preparation of 2-((5-chloro-1-(2-hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)amino)-4-((1*S*,5*R*)-1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (NRX02107)

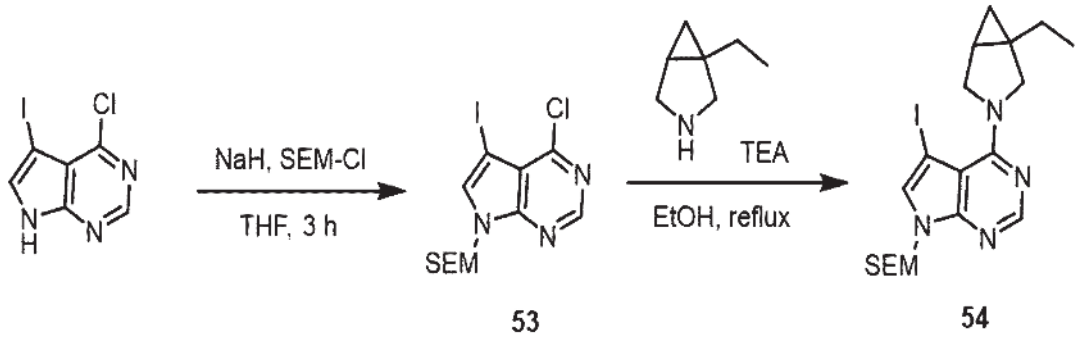


2-((5-Chloro-1-(2-hydrox-2-methylpropyl)-1H-pyrazol-4-yl)amino)-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (Example 2) was separated by SFC (Daicel AD-3 (4.6*100 mm, 3 μm), CO_2 / EtOH[0.2% NH_3 (7 M in MeOH)] = 65 / 35) to obtain the target compound (632.3 mg, e.e 97.9%, m/z = 414.4 $[M^+H]^+$).

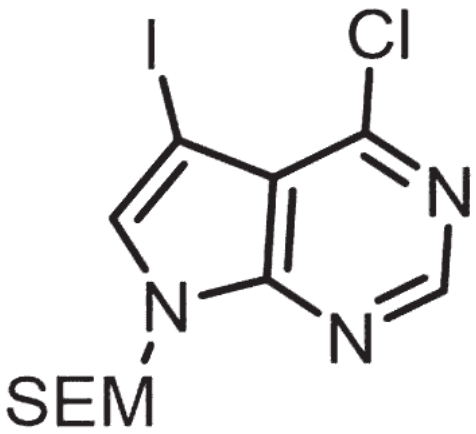
^{1}H-NMR (400 MHz, DMSO-d_6): δ 12.14 (s, 1H), 7.98 (s, 1H), 7.88 (d, *J* = 2.8 Hz, 1H), 7.74 (s, 1H), 4.72 (s, 1H), 4.12 (d, *J* = 10.4 Hz, 1H), 4.03 (d, *J* = 11.0 Hz, 1H), 3.99 (s, 2H), 3.70 (dd, *J* = 11.0, 4.2 Hz, 1H), 3.57 (d, *J* = 10.4 Hz, 1H), 1.77 (m, 1H), 1.48 (m, 1H), 1.45 - 1.32 (m, 1H), 1.13 (s, 6H), 0.98 (t, *J* = 7.4 Hz, 3H), 0.68 (dd, *J* = 7.8, 4.6 Hz, 1H), 0.26 (t, *J* = 4.2 Hz, 1H).

[Preparation Example 13]

Preparation of 4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-5-iodo-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine (54)

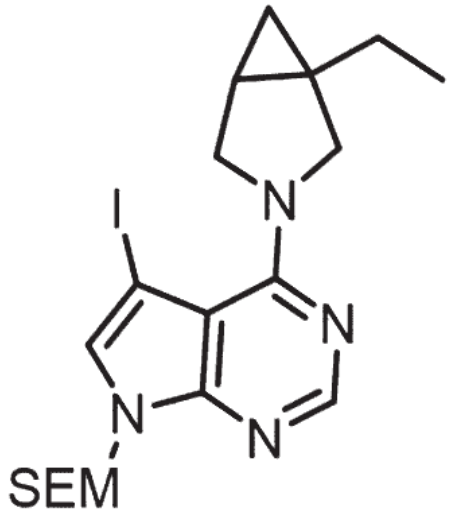


13-1. Step 1: 4-chloro-5-iodo-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine (53)



2,4-Dichloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidine (17.9 mmol) was added to tetrahydrofuran containing sodium hydride (17.9 mmol), followed by stirring at room temperature for 30 minutes. 2-(Trimethylsilyl)ethoxymethyl chloride (19.3 mmol) was added to the reaction solution, followed by stirring at room temperature for 3 hours. The reaction solution was washed using ethyl acetate and brine. The organic layer was treated with sodium sulfate to remove remaining water, and concentrated under reduced pressure. The concentrated mixture was separated using column chromatography (SiO_2, hexane : ethyl acetate = 10 : 1 to 1 : 1) to obtain the target compound (5.48 mg, 13.4 mmol, 75%).

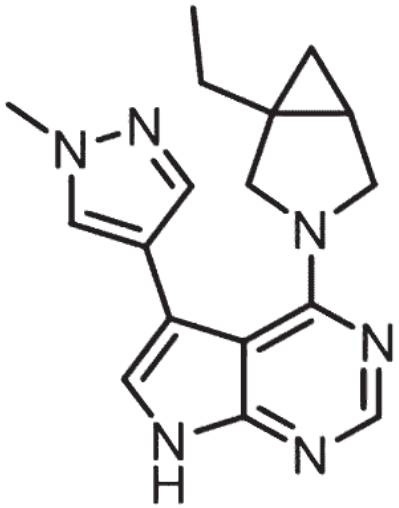
13-2 Step 2: 4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-5-iodo-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine (54)



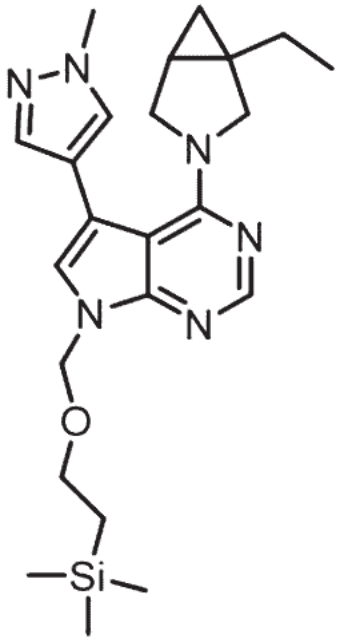
4-Chloro-5-iodo-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3]pyrimidine (4.88 mmol) was added to *n*-butanol containing 1-ethyl-3-azabicyclo[3.1.0]hexane (5.37 mmol) and triethylamine (14.6 mmol). The reaction solution was stirred at 120℃ for 16 hours. The solvent of the reaction solution was concentrated under reduced pressure, and separated using column chromatography (SiO_2, hexane : ethyl acetate = 10 : 1 to 1 : 1) to obtain the target compound (54) of Preparation Example 13 (2.06 g, 4.25 mmol, 87%, m/z = 485.1 $[M^+H]^+$).

[Example 62]

Preparation of 4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-3-(1-methyl-4-pyrazolyl)-1H-1,5,7-triazaindene (NRX02108)



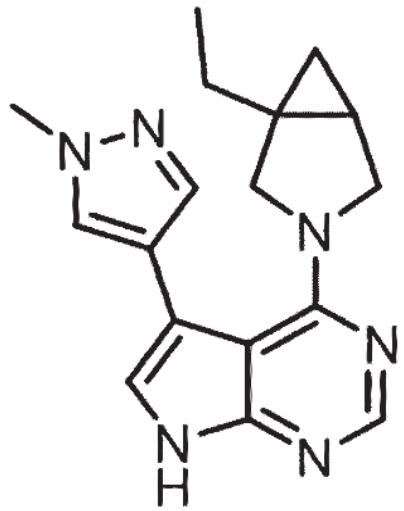
62-1. Step 1: 4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine



The compound (54) obtained in Preparation Example 13 above (0.239 mmol) was added to 1,4-dioxane/water containing (1-methyl-1H-pyrazo-4-yl-)boronic acid (0.206 mmol) and potassium carbonate (0.619 mmol). Degassing was performed for 5 minutes with nitrogen gas. $Pd(dppf)Cl_2$ (0.010 mmol) was added thereto. The reaction solution was stirred at 100℃

for 2 hours. The reaction solution was filtered through a Celite pad. The filtrate was concentrated under reduced pressure, and then separated using column chromatography (SiO_2, hexane : ethyl acetate = 5 : 1 to 1 : 1) to obtain the compound (28 mg, 0.064 mmol, 31%, m/z = 439.1 $[M^+H]^+$).

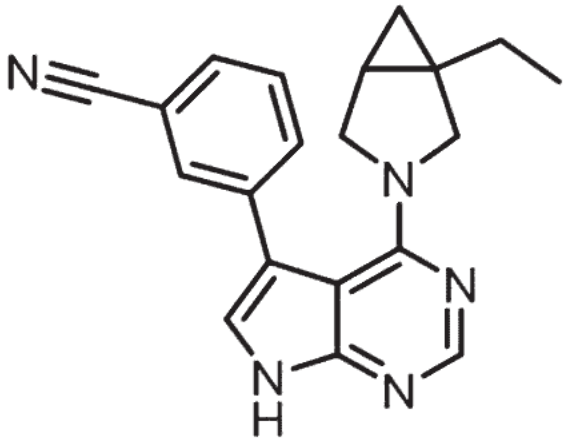
62-2. Step 2: 4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-3-(1-methyl-4-pyrazolyl)-1H-1,5,7-triazaindene (NRX02108)



4-(1-Ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-5-((1-methyl-1H-pyrazol-4-yl)amino)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine (0.064 mmol) was added to dichloromethane containing trifluoroacetic acid (1.91 mmol). The reaction solution was stirred at 40℃ for 1 hour. The reaction solution was concentrated under reduced pressure, dissolved in dichloromethane, and then potassium carbonate (0.32 mmol) was added thereto. The reaction solution was stirred at 50℃ for 1 hour. The reaction solution was concentrated under reduced pressure, and then separated using reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the target compound of Example 62 above (7 mg, 22.7 μmol, 36%, m/z = 349.1 $[M^+H]^+$).

[Example 63]

Preparation of 3-(4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile (NRX02109)



63-1. Step 1: 3-(4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile

The target compound of Step 1 of Example 63 (10 mg, 0.022 mmol, 21%, m/z = 460.1 $[M^+H]^+$) was obtained by performing the same method as in Step 1 of Example 62 above, except for using (3-cyanophenyl)boronic acid instead of using (1-methyl-1H-pyrazo-4-yl-)boronic acid.

63-2 Step 2: 3-(4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile (NRX02109)

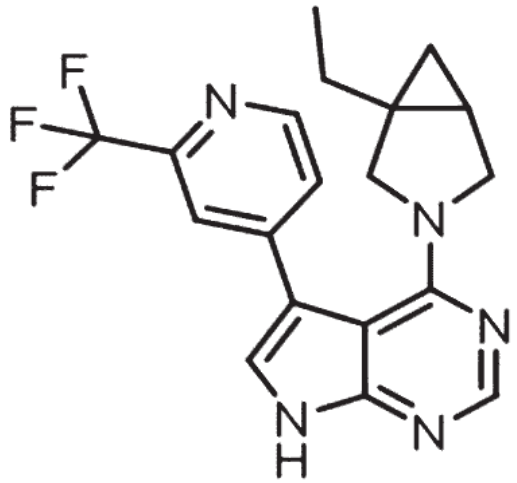
The target compound of Example 63 (16 mg, 0.049 mmol, 35%, m/z = 330.1 $[M^+H]^+$) was obtained by performing the same method as in Step 2 of Example 62 above.

^{1}H-NMR (400 MHz, $CDCl_3$-*d*) δ 8.33 (s, 1H), 7.74 - 7.58 (m, 3H), 7.51 (td, *J* = 7.7, 0.7 Hz, 1H), 7.25 (s, 1H), 7.08 (d, *J* = 5.0 Hz, 1H), 3.78 (d, *J* = 10.6 Hz, 1H), 3.69 (d, *J* = 10.8 Hz, 1H), 3.18 (dd, *J* = 10.7, 3.8 Hz, 1H), 2.99 (d, *J* = 10.5 Hz, 1H), 1.60 - 1.50 (m, 1H), 1.31 -

1.18 (m, 1H), 1.08 (dt, *J* = 7.7, 3.7 Hz, 1H), 0.76 (t, *J* = 7.5 Hz, 3H), 0.42 (dd, *J* = 7.8, 5.0 Hz, 1H), 0.26 - 0.16 (m, 1H).

[Example 64]

Preparation of 4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-5-(2-(trifluoromethyl)pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidine (NRX02110)



64-1 Step 1: 4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-5-(2-(trifluoromethyl)pyridin-4-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine

The desired compound (67 mg, 0.206 mmol, 39%, m/z = 504.1 $[M^+H]^+$) was obtained by performing in the same method as in Step 1 of Example 62 above, except for using (2-(trifluoromethyl)pyridin-4-yl)boronic acid instead of using (1-methyl-1H-pyrazo-4-yl-)boronic acid.

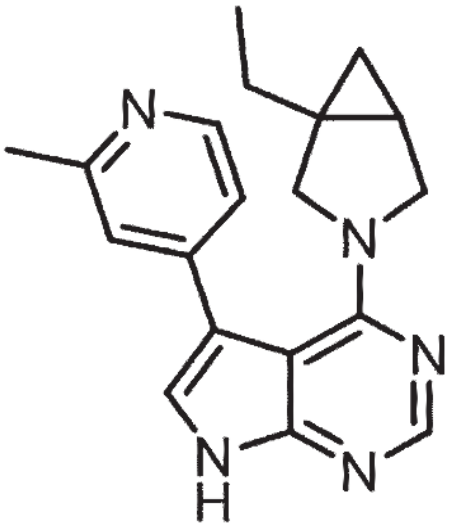
64-2 Step 2: 4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-5-(2-(trifluoromethyl)pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidine (NRX02110)

The target compound of Example 64 (25.6 mg, 0.069 mmol, 52%, m/z = 374.1 $[M^+H]^+$) was obtained by performing in the same method as in Step 2 of Example 62 above.

^{1}H-NMR (400 MHz, $CDCl_3$-*d*) δ 10.58 (s, 1H), 8.73 (d, *J* = 5.1 Hz, 1H), 8.38 (s, 1H), 7.75 (s, 1H), 7.56 (d, *J* = 5.4 Hz, 1H), 7.26 (dd, *J* = 2.5, 1.2 Hz, 5H), 7.24 (s, 3H), 3.87 (d, *J* = 10.4 Hz, 1H), 3.75 (d, *J* = 10.6 Hz, 1H), 3.25 (dd, *J* = 10.8, 3.9 Hz, 1H), 3.08 (d, *J* = 10.5 Hz, 1H), 1.59 (s, 8H), 1.34 - 1.24 (m, 1H), 1.25 (s, 2H), 1.10 (s, 1H), 0.83 - 0.75 (m, 1H), 0.78 (s, 3H), 0.46 - 0.38 (m, 1H), 0.25 (t, *J* = 4.4 Hz, 1H).

[Example 65]

Preparation of 4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-3-(2-methyl-4-pyridyl)-1H-1,5,7-triazaindene (NRX02111)



65-1 Step 1: 4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-5-(2-methylpyridin-4-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine

The target compound of Step 1 of Example 65 (47 mg, 0.106 mmol, 35%, m/z = 450.1 $[M^+H]^+$) was obtained by performing in the same method as in Step 1 of Example 62 above, except for using (2-methyl-pyridin-4-yl)boronic acid instead of using (1-methyl-1H-pyrazo-4-

yl-)boronic acid.

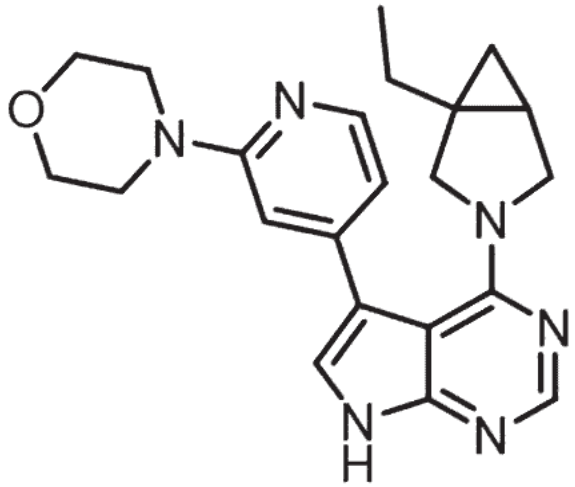
65-2 Step 2: 4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-3-(2-methyl-4-pyridyl)-1H-1,5,7-triazaindene (NRX02111)

The target compound of Example 65 (37.1 mg, 0.116 mmol, 40%, m/z = 321.1 $[M^+H]^+$) was obtained by performing in the same method as in Step 2 of Example 62 above.

^{1}H-NMR (400 MHz, $CDCl_3$-*d*) δ 11.10 (s, 1H), 8.50 (d, *J* = 5.1 Hz, 1H), 8.36 (d, *J* = 2.7 Hz, 1H), 7.33 - 7.15 (m, 3H), 3.88 (d, *J* = 10.4 Hz, 1H), 3.76 (d, *J* = 10.7 Hz, 1H), 3.26 (dd, *J* = 10.9, 3.8 Hz, 1H), 3.10 (d, *J* = 10.7 Hz, 1H), 1.59 (dd, *J* = 14.3, 7.3 Hz, 1H), 1.33 - 1.23 (m, 3H), 1.11 (dt, *J* = 7.6, 3.8 Hz, 1H), 0.80 (td, *J* = 7.5, 3.1 Hz, 3H), 0.46 - 0.38 (m, 1H), 0.27 (t, *J* = 4.3 Hz, 1H).

[Example 66]

Preparation of 4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-3-(2-morpholino-4-pyridyl)-1H-1,5,7-triazaindene (NRX02112)



66-1 Step 1: 4-(4-(4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-

(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)pyridin-2-yl)morpholine

The compound of Step 1 of Example 66 (58 mg, 0.111 mmol, 54%, m/z = 521.1 $[M^+H]^+$) was obtained by performing in the same method as in Step 1 of Example 62 above, except for using 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl) instead of using (1-methyl-1H-pyrazo-4-yl-)boronic acid.

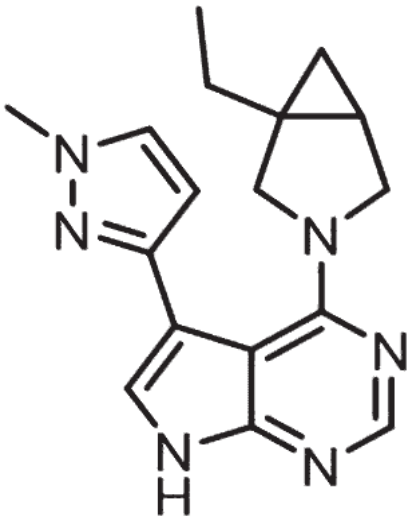
66-2 Step 2: 4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-3-(2-morpholino-4-pyridyl)-1H-1,5,7-triazaindene (NRX02112)

The target compound of Example 66 (52.7 mg, 0.135 mmol, 52%, m/z = 391.1 $[M^+H]^+$) was obtained by performing in the same method as in Step 2 of Example 62 above.

^{1}H-NMR (400 MHz, $CDCl_3$-*d*) δ 10.32 (s, 1H), 8.21 (s, 1H), 7.31 - 7.24 (m, 1H), 7.25 (s, 1H), 7.13 (s, 1H), 6.70 (s, 1H), 3.86 (s, 4H), 3.56 (s, 4H), 3.30 (s, 1H), 3.12 (s, 1H), 1.63 (s, 1H), 1.27 (s, 1H), 1.12 (s, 1H), 0.82 (s, 3H), 0.41 (s, 1H), 0.20 (s, 1H).

[Example 67]

Preparation of 4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-3-(1-methyl-3-pyrazolyl)-1H-1,5,7-triazaindene (NRX02135)



67-1 Step 1: 4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-5-(1-methyl-1H-pyrazol-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine

The target compound of Step 1 of Example 67 (37 mg, 0.084 mmol, 41%, m/z = 439.1 $[M^+H]^+$) was obtained by performing in the same method as in Step 1 of Example 62 above, except for using 4,4,5,5-tetramethyl-2-(1-methyl-3-pyrazolyl)-1,3,2-dioxaborolane (0.1 g, 0.206 mmol) instead of using (1-methyl-1H-pyrazo-4-yl-)boronic acid.

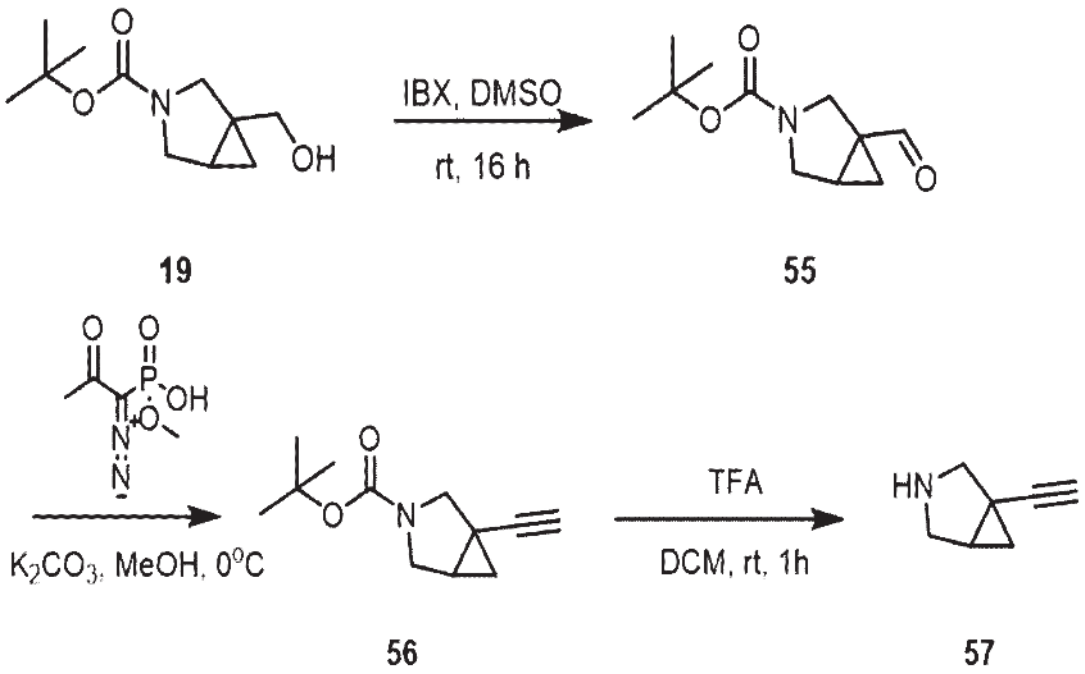
67-2 Step 2: 4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-3-(1-methyl-3-pyrazolyl)-1H-1,5,7-triazaindene (NRX02135)

The target compound of Example 8 (11.1 mg, 0.036 mmol, 43%, m/z = 309.1 $[M^+H]^+$) was obtained by performing in the same method as in Step 2 of Example 67 above.

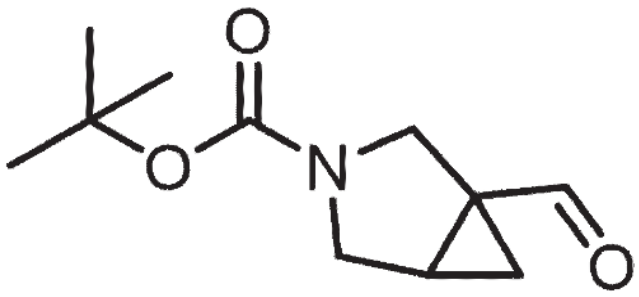
^{1}H-NMR (400 MHz, $CDCl_3$-*d*) δ 10.99 (s, 1H), 8.23 (s, 1H), 7.39 (d, *J* = 2.1 Hz, 1H), 7.10 (s, 1H), 6.29 (d, *J* = 2.2 Hz, 1H), 3.95 (s, 3H), 3.82 (dd, *J* = 21.9, 11.1 Hz, 2H), 3.71 (s, 3H), 3.37 (dd, *J* = 11.2, 4.1 Hz, 1H), 3.12 (dd, *J* = 11.0, 1.2 Hz, 1H), 1.60 (dq, *J* = 14.5, 7.3 Hz, 1H), 1.34 - 1.20 (m, 2H), 1.14 (dt, *J* = 7.9, 3.9 Hz, 1H), 0.82 (t, *J* = 7.4 Hz, 3H), 0.44 (ddt, *J* = 7.9, 4.8, 1.1 Hz, 1H), 0.28 - 0.19 (m, 1H)

[Preparation Example 14]

Preparation of 1-ethynyl-3-azabicyclo[3.1.0]hexane (57)



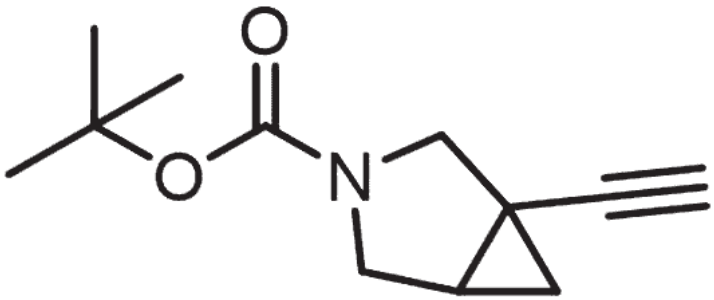
14-1 Step 1: tert-butyl 1-formyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (55)



IBX (2.95 g, 10.5 mmol) was added to dimethyl sulfoxide (24 mL) containing tert-butyl 1-(hydroxymethyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (19) (1.5 g, 7.03 mmol), followed by stirring at room temperature for 16 hours. Ethyl acetate was added to the reaction solution, and filtered through a Celite Pad. The filtrate was washed using sodium bicarbonate,

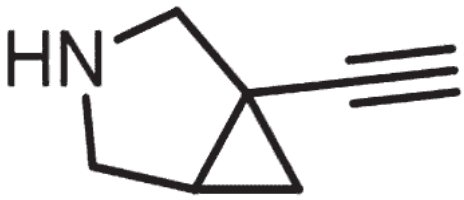
and the organic layer was treated with sodium sulfate to remove remaining water, and concentrated under reduced pressure to obtain the compound (55) of Preparation Example 14. It was used in the next reaction without purification.

14-2 Step 2: tert-butyl 1-ethynyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (56)



Bestmann-Ohira reagent (2.46 g, 12.8 mmol) was added to methanol (28 mL) at 0℃ containing tert-butyl 1-formyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (55) (1.5 g, 7.1 mmol) and potassium carbonate (6.78 g, 21.3 mmol), followed by stirring at room temperature for 16 hours. The reaction solution was washed using water and ethyl acetate. The organic layer was treated with sodium sulfate to remove remaining water. The concentrated mixture was separated using column chromatography (SiO2, hexane : ethyl acetate = 1 : 1) to obtain the compound (56) of Preparation Example 14 (977 mg, 4.71 mmol, 66%).

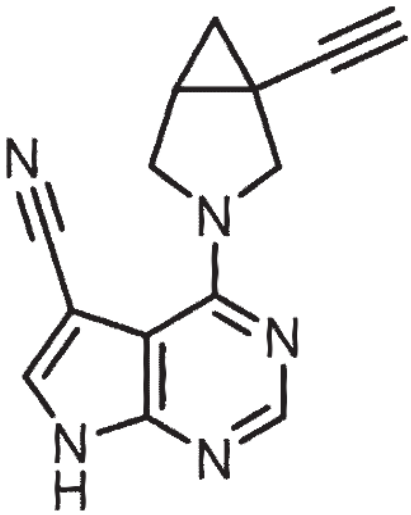
14-3 Step 3: 1-ethynyl-3-azabicyclo[3.1.0]hexane (57)



tert-Butyl 1-ethynyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (56) (94 mg, 0.454 mmol) was added to dichloromethane containing trifluoroacetic acid (4.54 mmol). The reaction solution was stirred at room temperature for 1 hour. The reaction solution was concentrated under reduced pressure, and ethanol and basic resin were added thereto to adjust the pH to 8, followed by filtration to obtain the compound (57) of Preparation Example 14. It was directly used in the next reaction without purification.

[Example 68]

Preparation of 4-(1-ethynyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazaindene-3-carbonitrile (NRX02113)



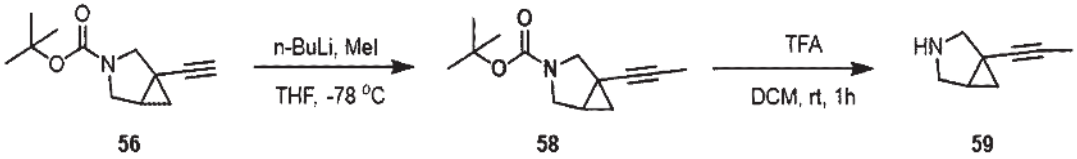
4-Chloro-1H-1,5,7-triazaindene-3-carbonitrile (50 mg, 0.28 mmol) and the compound (57) of Preparation Example 14 above (36 mg, 0.336 mmol), triethylamine (142 mg, 1.4 mmol) were added to ethanol (1.5 mL), followed by stirring at 80°C for 12 hours. The reaction solution was concentrated under reduced pressure, and then separated using column chromatography (SiO_2, dichloromethane : methanol = 10 : 1) to obtain the target compound (19.1 mg, 27%, m/z = 250.1 $[M^+H]^+$).

1H-NMR (400 MHz, DMSO-d_6) δ 8.29 (s, 1H), 8.23 (s, 1H), 4.36 (d, J = 10.6 Hz, 1H),

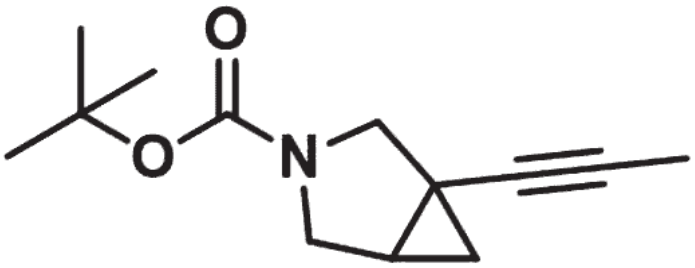
4.20 (d, *J* = 10.8 Hz, 1H), 3.85 (dd, *J* = 10.8, 4.2 Hz, 1H), 3.78 (d, *J* = 10.6 Hz, 1H), 3.08 (s, 1H), 2.13 (dt, *J* = 8.7, 4.7 Hz, 1H), 1.24 (s, 1H), 1.18 (dd, *J* = 8.2, 4.8 Hz, 1H), 0.76 (t, *J* = 4.9 Hz, 1H).

[Preparation Example 15]

Preparation of 1-(prop-1-yn-1-yl)-3-azabicyclo[3.1.0]hexane (59)



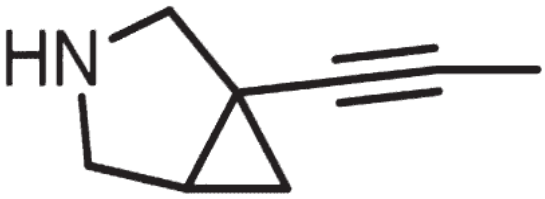
15-1 Step 1: tert-butyl 1-(prop-1-yn-1-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (58)



2.5 M *n*-butyllithium (0.580 μL, 1.45 mmol) was added dropwise to anhydrous tetrahydrofuran (2.4 mL) containing the compound (56) of Preparation Example 14 above (100 mg, 0.482 mmol) at -78℃. The reaction solution was stirred at the same temperature for 1 hour. Iodomethane (342 mg, 2.41 mmol) was added thereto, and the reaction solution was stirred at room temperature for 16 hours. Water and ether were added to the reaction solution, followed by washing several times with ether. The organic layer was treated with magnesium sulfate to remove remaining water, and concentrated under reduced pressure to obtain the compound (58)

of Preparation Example 15. It was used in the next reaction without purification.

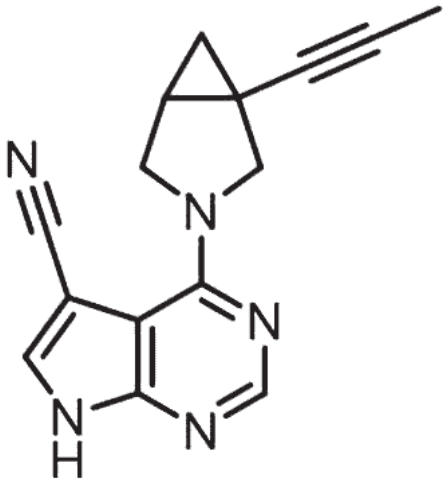
15-2 Step 2: 1-(prop-1-yn-1-yl)-3-azabicyclo[3.1.0]hexane (59)



tert-Butyl 1-(prop-1-yn-1-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (58) (107 mg, 0.484 mmol) was added to dichloromethane containing trifluoroacetic acid (9.67 mmol). The reaction solution was stirred at room temperature for 1 hour. The reaction solution was concentrated under reduced pressure, and ethanol and basic resin were added thereto to adjust the pH to 8, followed by filtration to obtain the compound (59) of Preparation Example 15. It was directly used in the next reaction without purification.

[Example 69]

Preparation of 4-{1-(1-propynyl)-3-azabicyclo[3.1.0]hex-3-yl}-1H-1,5,7-triazaindene-3-carbonitrile (NRX02114)

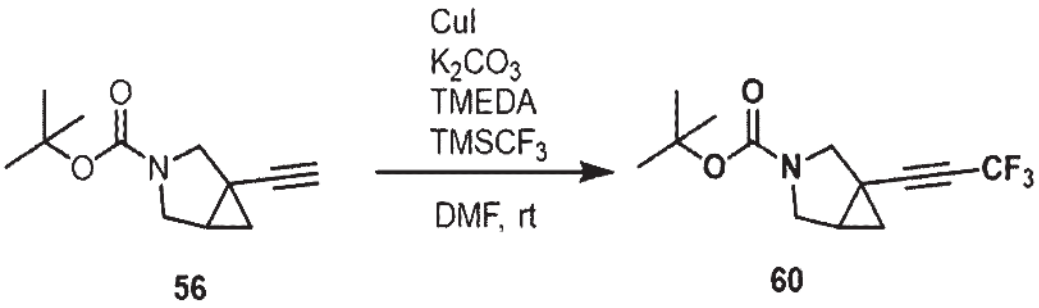


4-Chloro-1H-1,5,7-triazaindene-3-carbonitrile (80 mg, 0.448 mmol) and the compound (59) of Preparation Example 15 above (54 mg, 0.448 mmol), triethylamine (227 mg, 2.24 mmol) were added to ethanol (2.2 mL), followed by stirring at 80°Cfor 12 hours. The reaction solution was concentrated under reduced pressure, and then separated using column chromatography (SiO_2, dichloromethane : methanol = 10 : 1) to obtain the target compound (87 mg, 74%, m/z = 264.1 $[M^+H]^+$).

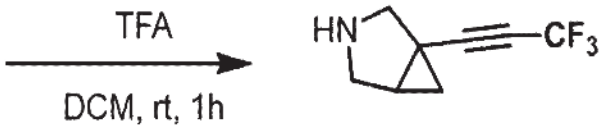
^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 1H), 8.18 (s, 1H), 4.29 (d, J = 10.5 Hz, 1H), 4.13 (d, J = 10.8 Hz, 1H), 3.78 (dd, J = 10.9, 4.1 Hz, 1H), 3.69 (d, J = 10.6 Hz, 1H), 1.98 (dt, J = 8.4, 4.5 Hz, 1H), 1.76 (s, 3H),1.07 (s, 1H), 0.63 (s, 1H).

[Preparation Example 16]

Preparation of 1-(3,3,3-trifluoroprop-1-yn-1-yl)-3-azabicyclo[3.1.0]hexane (61)

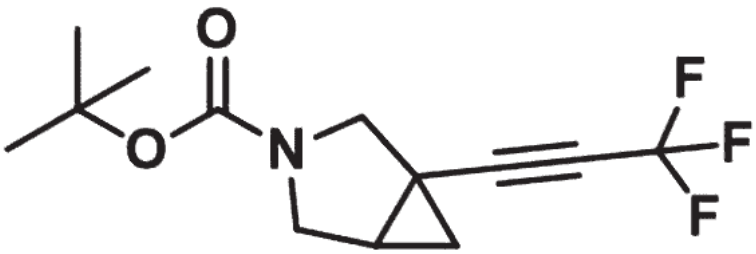


56 60



61

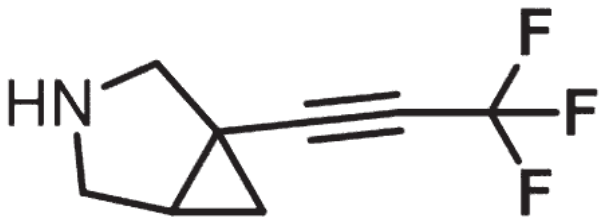
16-1 Step 1: tert-butyl 1-(3,3,3-trifluoroprop-1-yn-1-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (60)



CuI (138 mg, 0.724 mmol), potassium carbonate (200 mg, 1.45 mmol), TMEDA (84 mg, 0.724 mmol), and dimethylformamide (5 mL) were added to a 50 mL flask, followed by stirring for 15 minutes. Additionally, $TMSCF_3$ (0.12 uL, 0.95 mmol) was added thereto, and the reaction solution was cooled to 0°C. The compound (56) of Preparation Example 14 above (100 mg, 0.482 mmol) and $TMSCF_3$ (0.12 μL, 0.95 mmol) were added thereto, and the reaction solution was stirred at room temperature for 24 hours. Water and ether were added to the

reaction solution, followed by washing several times with ether. The organic layer was treated with magnesium sulfate to remove remaining water, and concentrated under reduced pressure to obtain the target compound (60) of Preparation Example 16. It was used in the next reaction without purification.

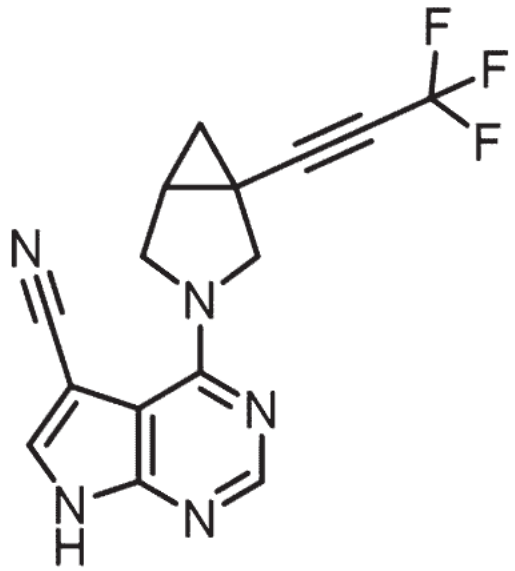
16-2 Step 2 1-(3,3,3-trifluoroprop-1-yn-1-yl)-3-azabicyclo[3.1.0]hexane (61)



tert-butyl 1-(3,3,3-trifluoroprop-1-yn-1-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (60) (133 mg, 0.484 mmol) was added to dichloromethane containing trifluoroacetic acid (9.67 mmol). The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, and ethanol and a basic resin were added thereto to adjust the pH to 8, followed by filtration to obtain the target compound (61) of Preparation Example 16. It was directly used in the next reaction without purification.

[Example 70]

Preparation of 4-{1-(3,3,3-trifluoro-1-propynyl)-3-azabicyclo[3.1.0]hex-3-yl}-1H-1,5,7-triazaindene-3-carbonitrile (NRX02115)

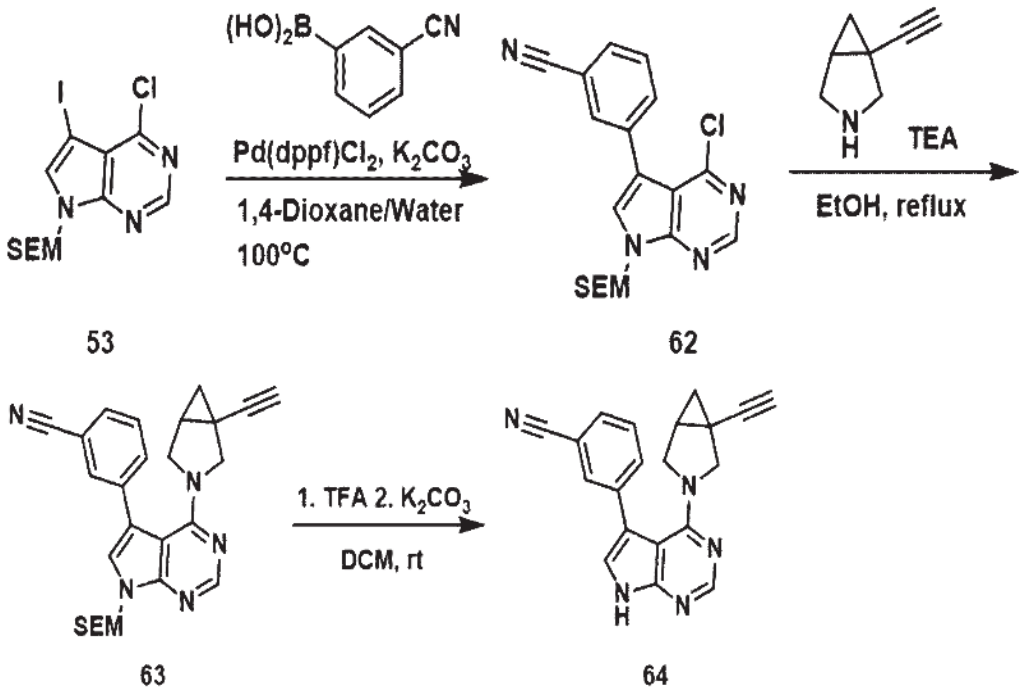


4-Chloro-1H-1,5,7-triazaindene-3-carbonitrile (80 mg, 0.448 mmol), the compound (61) of Preparation Example 16 (54 mg, 0.448 mmol), triethylamine (227 mg, 2.24 mmol), and ethanol (2.2 ml) were mixed and stirred at 80°C for 12 hours. After the reaction solution was concentrated under reduced pressure, the reaction mixture was separated using column chromatography (SiO_2, dichloromethane : methanol = 10 : 1) to obtain the target compound (87 mg, 74%, m/z = 264.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.26 (s, 1H), 8.21 (s, 1H), 4.42 (d, J = 10.5 Hz, 1H), 4.22 (d, J = 10.8 Hz, 1H), 3.90 - 3.80 (m, 2H), 3.13 (d, J = 5.2 Hz, 1H), 1.43 (dd, J = 8.4, 5.1 Hz, 1H), 0.98 (t, J = 5.3 Hz, 1H).

[Example 71]

Preparation of m-{4-(1-ethynyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-3-yl}benzonitrile (NRX02116)



71-1 Step 1: 3-(4-chloro-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile (62)

After the compound (53) (1.0 g, 2.44 mmol) obtained in Preparation Example 13 was dissolved in 1,4-dioxane/water, (3-cyanophenyl)boronic acid (394 mg, 2.68 mmol), potassium carbonate (2.33 g, 7.32 mmol), and $Pd(dppf)_2Cl_2$ (110 mg, 0.122 mmol) were added thereto, followed by stirring at 100°C for 2 hours. The reaction mixture was filtered through a Celite pad and then concentrated under reduced pressure. The reaction mixture was separated using column chromatography (SiO_2, hexane : ethyl acetate = 5 : 1) to obtain the target compound (62) (796 mg, 85%, m/z = 385.1 $[M^+H]^+$).

71-2 Step 2: 3-(4-(1-ethynyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile (63)

The compound (62) (100 mg, 0.260 mmol) obtained in Example 71 was added to the

compound (57) of Preparation Example 14 (33 mg, 0.312 mmol), N-ethylbis(isopropyl)amine (101 mg, 0.779 mmol), and ethanol (1.3 ml), followed by stirring at 80°C for 16 hours. After the reaction solution was concentrated under reduced pressure, the reaction mixture was separated using column chromatography (SiO_2, hexane : ethyl acetate = 10 : 1) to obtain the target compound (63) (83 mg, 70%, m/z = 456.1 $[M^+H]^+$).

71-3 Step 3: m-{4-(1-ethynyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-3-yl}benzonitrile (NRX02116)

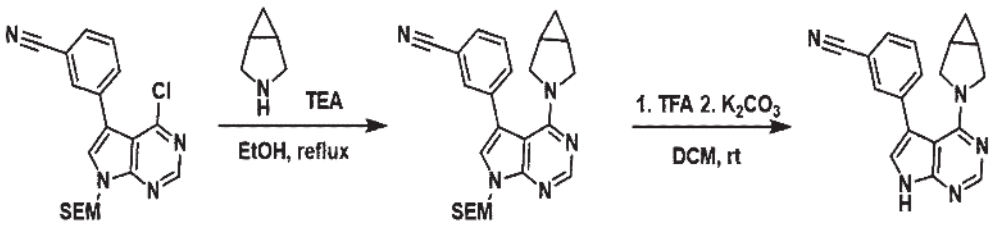
The compound (63) (80 mg, 0.176 mmol) obtained in Example 71 was added to dichloromethane containing trifluoroacetic acid (1.76 mmol). The reaction mixture was stirred at 50°C for 2 hours. The reaction mixture was concentrated under reduced pressure, dissolved in dichloromethane, and then potassium carbonate (0.88 mmol) was added thereto. The reaction mixture was stirred at 50°C for 1 hour. After the reaction mixture was concentrated under reduced pressure, it was separated using column chromatography (SiO_2, hexane : ethyl acetate = 10 : 1) to obtain the target compound (64) of Example 71 (14 mg, 43.6 μmol, 25%, m/z = 326.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, $CDCl_3$-*d*) δ 10.16 (s, 1H), 8.36 (d, *J* = 1.0 Hz, 1H), 7.72 (tt, *J* = 1.6, 0.8 Hz, 1H), 7.64 (dddd, *J* = 13.2, 8.9, 2.2, 1.2 Hz, 2H), 7.57 - 7.48 (m, 1H), 7.16 - 7.11 (m, 1H), 4.14 - 4.02 (m, 1H), 3.79 (d, *J* = 11.0 Hz, 1H), 3.20 (d, *J* = 10.9 Hz, 2H), 1.93 (d, *J* = 0.9 Hz, 1H), 1.66 (dt, *J* = 8.3, 4.3 Hz, 1H), 0.95 (dd, *J* = 8.0, 5.1 Hz, 1H), 0.59 (t, *J* = 4.9 Hz, 1H).

[Example 72]

Preparation of m-{4-(3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-3-

yl}benzonitrile (NRX02132)



62 65 66

72-1 Step 1: 3-(4-chloro-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile (65)

The compound (62) (120 mg, 0.312 mmol) obtained in Example 71 was added to 3-azabicyclo[3.1.0]hexane (41 mg, 0.343 mmol), N-ethylbis(isopropyl)amine (121 mg, 0.935 mmol), and ethanol (1.6 ml), followed by stirring at 80°C for 16 hours. After the reaction solution was concentrated under reduced pressure, the reaction mixture was separated using column chromatography (SiO_2, hexane : ethyl acetate = 10 : 1) to obtain the compound (80 mg, 0.186 mmol, 60%, m/z = 432.1 $[M^+H]^+$).

72-2 Step 2: m-{4-(3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-3-yl}benzonitrile (NRX02132)

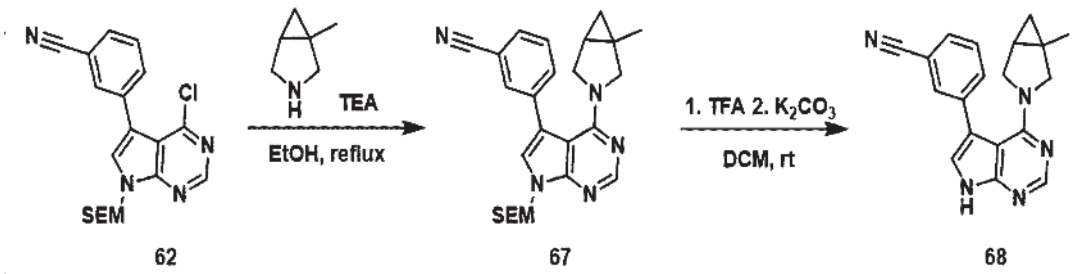
The compound (65) (80 mg, 0.186 mmol) obtained in Example 72 was added to dichloromethane containing trifluoroacetic acid (3.72 mmol). The reaction mixture was stirred at 50°C for 2 hours. The reaction mixture was concentrated under reduced pressure, dissolved in dichloromethane, and then potassium carbonate (0.88 mmol) was added thereto. The reaction mixture was stirred at 50°C for 1 hour. After the reaction mixture was concentrated under reduced pressure, it was separated using column chromatography (SiO2, dichloromethane : methanol = 10 : 1) to obtain the target compound (66) of Example 72 (35 mg, 117 μmol, 63%,

m/z = 302.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, $CDCl_3$- *d*) δ 9.56 (s, 1H), 8.33 (d, *J* = 1.4 Hz, 1H), 7.72 (td, *J* = 1.8, 0.6 Hz, 1H), 7.68 - 7.57 (m, 2H), 7.50 (td, *J* = 7.7, 0.6 Hz, 1H), 7.11 - 7.04 (m, 1H), 3.80 (d, *J* = 10.9 Hz, 2H), 3.14 (d, *J* = 10.8 Hz, 2H), 1.33 (dddd, *J* = 7.7, 3.8, 2.4, 1.2 Hz, 2H), 0.48 (td, *J* = 7.7, 5.1 Hz, 1H), 0.09 - 0.03 (m, 1H)

[Example 73]

m-{4-(1-methyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-3-yl}benzonitrile (NRX02133)



73-1 Step 1: 3-(4-(1-methyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile (67)

The target compound (67) (121 mg, 0.272 mmol, 80%, m/z = 446.1 $[M^+H]^+$) was obtained in the same manner as in Step 1 of Example 72, except that 1-methyl-3-azabicyclo[3.1.0]hexane (27) (39.4 mg, 0.405 mmol) was used instead of 3-azabicyclo[3.1.0]hexane in Example 72.

73-2 Step 2: m-{4-(1-methyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-3-yl}benzonitrile (NRX02133)

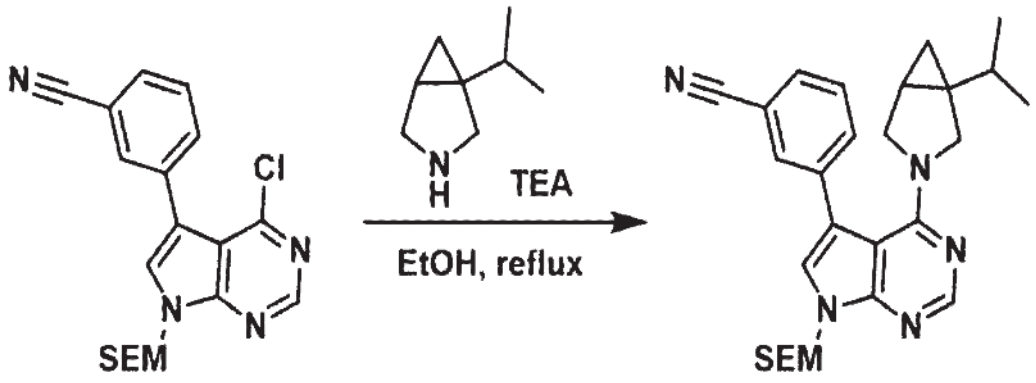
The target compound (68) (29.3 mg, 0.093 mmol, 35%, m/z = 316.1 $[M^+H]^+$) was

obtained in the same manner as in Step 2 of Example 72.

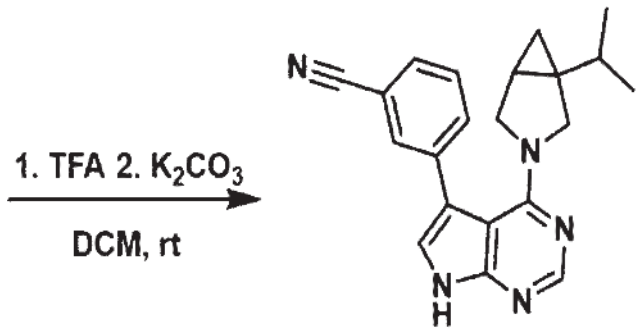
^{1}H-NMR (400 MHz, $CDCl_3$- *d*) δ 10.46 (s, 1H), 8.34 (d, *J* = 0.9 Hz, 1H), 7.75 - 7.57 (m, 2H), 7.50 (t, *J* = 7.7 Hz, 1H), 7.10 (s, 1H), 3.86 (d, *J* = 10.7 Hz, 1H), 3.65 (d, *J* = 10.7 Hz, 1H), 3.16 (dd, *J* = 10.8, 3.8 Hz, 1H), 2.99 (d, *J* = 10.7 Hz, 1H), 1.12 (d, *J* = 2.9 Hz, 3H), 1.03 (dt, *J* = 7.7, 3.9 Hz, 1H), 0.39 (dd, *J* = 7.7, 5.0 Hz, 1H), 0.24 (t, *J* = 4.4 Hz, 1H).

[Example 74]

Preparation of m-{4-(1-isopropyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-3-yl}benzonitrile (NRX02138)



62 69



70

74-1 Step 1: 3-(4-(1-methyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-

(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile (69)

The target compound (69) (164 mg, 0.346 mmol, 89%, m/z = 474.1 $[M^+H]^+$) was obtained in the same manner as in Step 1 of Example 72, except that 1-isopropyl-3-azabicyclo[3.1.0]hexane hydrochloride (75.6 mg, 0.468 mmol) was used instead of 3-azabicyclo[3.1.0]hexane in Example 72.

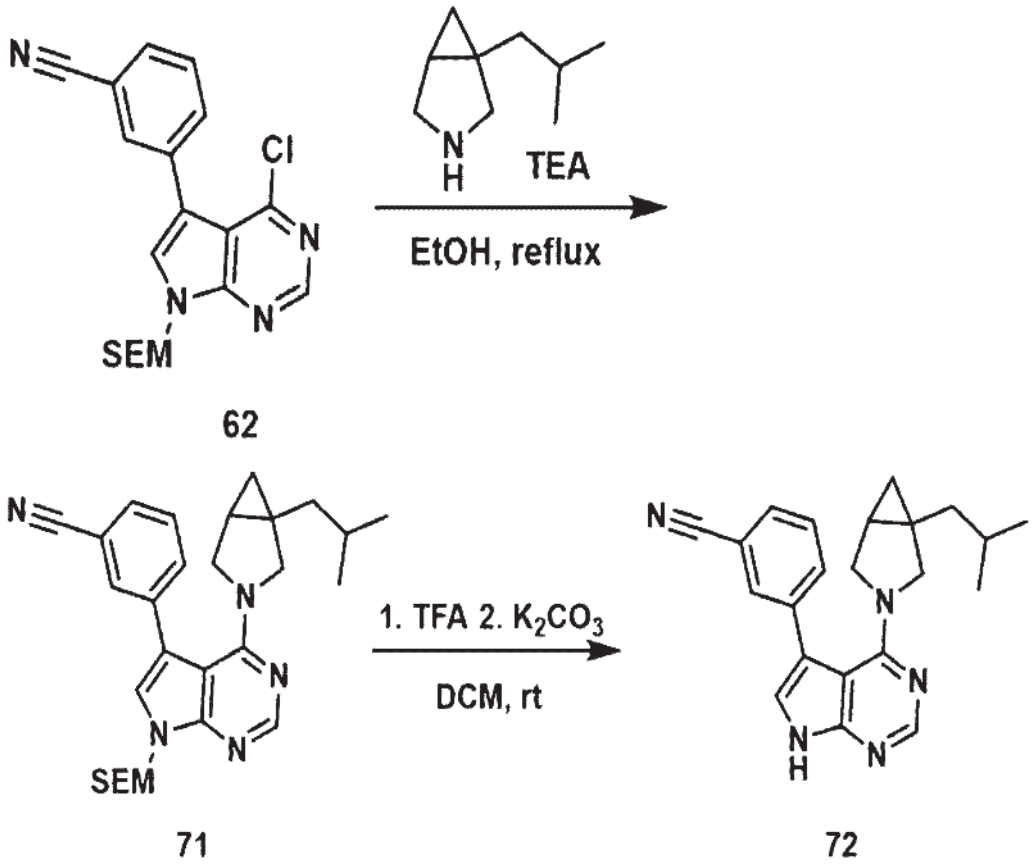
74-2 Step 2: m-{4-(1-isopropyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-3-yl}benzonitrile (NRX02138)

The target compound (70) (31.6 mg, 0.092 mmol, 27%, m/z = 344.1 $[M^+H]^+$) was obtained in the same manner as in Step 2 of Example 72.

^{1}H-NMR (400 MHz, $CDCl_3$-*d*) δ 10.20 (s, 1H), 8.35 (s, 1H), 7.75 - 7.59 (m, 3H), 7.52 (td, *J* = 7.7, 0.6 Hz, 1H), 7.08 (d, *J* = 3.4 Hz, 1H), 3.77 (d, *J* = 10.8 Hz, 1H), 3.63 (d, *J* = 10.5 Hz, 1H), 3.22 (dd, *J* = 10.9, 3.8 Hz, 1H), 3.07 - 2.98 (m, 1H), 1.45 (dq, *J* = 13.0, 6.5 Hz, 1H), 1.14 (dt, *J* = 7.8, 3.8 Hz, 1H), 0.82 (d, *J* = 6.8 Hz, 3H), 0.71 (d, *J* = 6.9 Hz, 3H), 0.46 (dd, *J* = 7.9, 4.9 Hz, 1H), 0.24 - 0.17 (m, 1H).

[Example 75]

Preparation of m-{4-(1-isobutyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-3-yl}benzonitrile (NRX02139)



75-1 Step 1: 3-(4-(1-isobutyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile (71)

The target compound (71) (166 mg, 0.340 mmol, 83%, m/z = 489.1 $[M^+H]^+$) was obtained in the same manner as in Step 1 of Example 72, except that 1-isobutyl-3-azabicyclo[3.1.0]hexane hydrochloride (86.5 mg, 0.493 mmol) was used instead of 3-azabicyclo[3.1.0]hexane in Example 72.

75-2 Step 2: m-{4-(1-isobutyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-3-yl}benzonitrile (NRX02139)

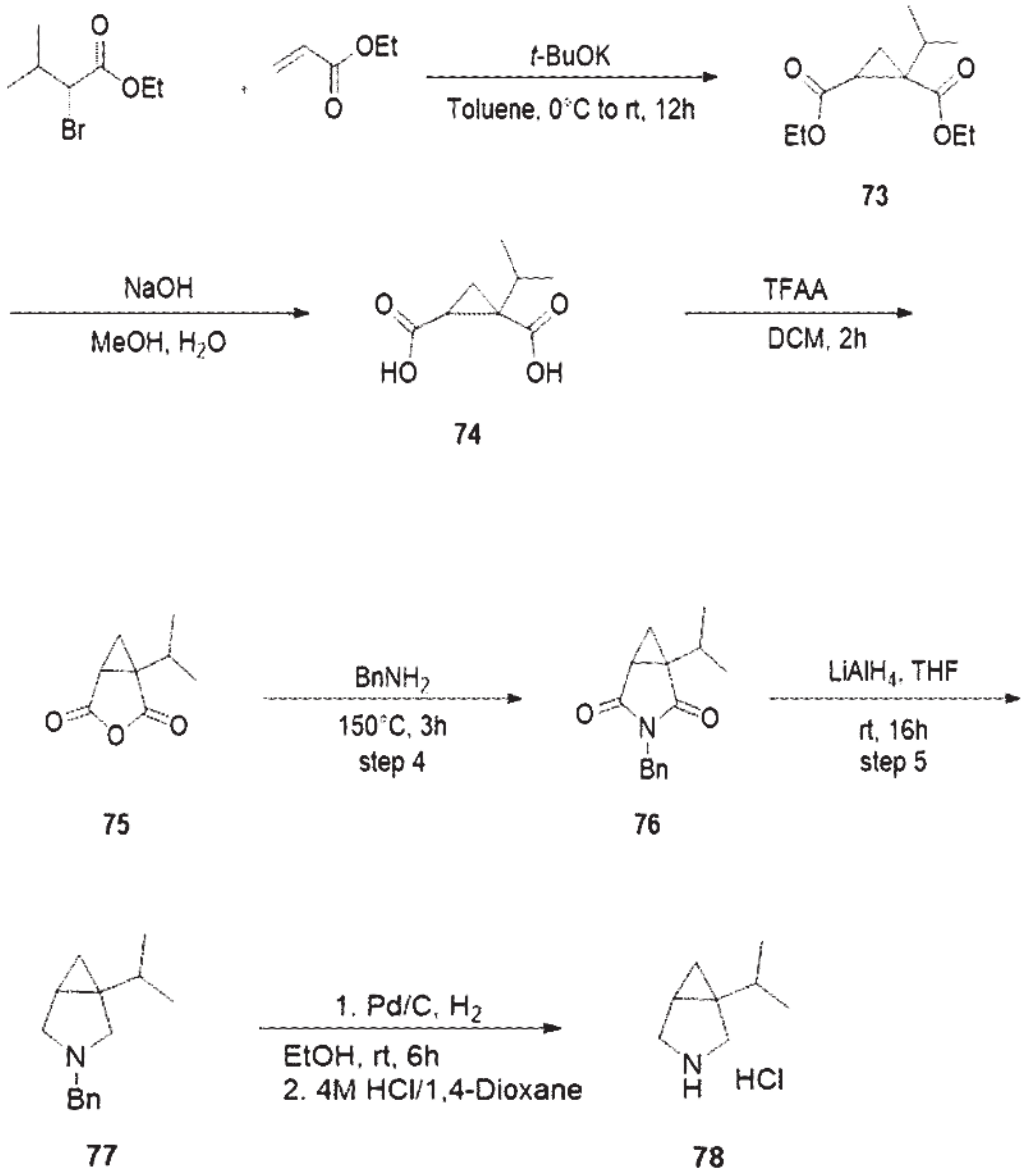
The target compound (72) (53.2 mg, 0.149 mmol, 44%, m/z = 358.1 $[M^+H]^+$) was

obtained in the same manner as in Step 2 of Example 72.

^{1}H-NMR (400 MHz, $CDCl_3$-*d*) δ 10.67 (s, 1H), 8.36 (s, 1H), 7.75 - 7.58 (m, 3H), 7.51 (td, *J* = 7.7, 0.6 Hz, 1H), 7.10 (s, 1H), 3.74 (dd, *J* = 13.2, 10.7 Hz, 2H), 3.28 (dd, *J* = 10.8, 3.9 Hz, 1H), 2.97 (d, *J* = 10.5 Hz, 1H), 1.56 (ddd, *J* = 13.8, 6.2, 1.1 Hz, 1H), 1.41 (ddt, *J* = 14.5, 12.9, 6.6 Hz, 1H), 1.03 (dt, *J* = 7.8, 3.9 Hz, 1H), 0.98 (dd, *J* = 13.9, 8.2 Hz, 1H), 0.79 (dd, *J* = 10.0, 6.6 Hz, 6H), 0.47 (dd, *J* = 7.7, 5.0 Hz, 1H), 0.38 - 0.31 (m, 1H).

[Preparation Example 17]

Preparation of 1-isopropyl-3-azabicyclo[3.1.0]hexane hydrochloride (78)



17-1 Step 1: diethyl 1-isopropylcyclopropane-1,2-dicarboxylate (73)

After ethyl 2-bromo-3-methylbutanoate (10 g, 47.82 mmol) was dissolved in toluene (50 mL), ethyl acrylate (4837 mg, 47.82 mmol) and tert-butoxide (5903 mg, 52.61 mmol) were added thereto at 0°C. The reaction mixture was stirred at room temperature for 12 hours. After the reaction was quenched with ammonium chloride (150 mL), extraction was performed with ethyl acetate (250 mL x 3). The organic layer was washed with brine, and then the remaining water was removed using sodium sulfate, followed by concentration under reduced pressure to

obtain the desired compound (73) (9.8 g, crude, m/z = 229.3 $[M^+H]^+$).

17-2 Step 2: 1-isopropylcyclopropane-1,2-dicarboxylic acid (74)

After the compound (73) (9.8 g, 38.54 mmol) obtained in Preparation Example 17 was dissolved in methanol (40 mL), sodium hydroxide (9.3 g, 231.34 mmol) dissolved in water (20 mL) was added thereto. The reaction mixture was stirred at 90°C for 12 hours. After the reaction mixture was concentrated under reduced pressure, water (100 mL) was added thereto, followed by washing with ethyl acetate (50 mL). The aqueous layer was adjusted to pH 1 by adding 3 M hydrochloric acid thereto, and then extracted with ethyl acetate (200 mL x 3). The organic layer was washed with brine, and then the remaining water was removed using sodium sulfate, followed by concentration under reduced pressure to obtain the desired compound (74) (6.9 g, crude, m/z = 171.0 $[M^-H]^-$).

17-3 Step 3: 1-isopropyl-3-oxabicyclo[3.1.0]hexane-2,4-dione (75)

After the compound (74) (6.9 g, 38.54 mmol) obtained in Preparation Example 17 was dissolved in dichloromethane (55 mL), TFAA (12.1 g, 57.81 mmol) was added thereto at 0°C. The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure to obtain the desired compound (75) (6.4 g, crude, m/z = 187.2 $[M^+MeOH]^+$).

17-4 Step 4: 3-benzyl-1-isopropyl-3-azabicyclo[3.1.0]hexane-2,4-dione (76)

The compound (75) (6.4 g, 38.54 mmol) obtained in Preparation Example 17 and benzylamine (4129 mg, 38.54 mmol) were stirred at 150°C for 3 hours. The reaction mixture was separated using column chromatography (SiO_2, hexane : ethyl acetate = 5 : 1 to 1 : 1) to

obtain the compound (76) (3.2 g, 34.1%, m/z = 244.3 $[M^+H]^+$).

17-5 Step 5: 3-benzyl-1-isopropyl-3-azabicyclo[3.1.0]hexane (77)

After the compound (76) (3.2 g, 13.16 mmol) obtained in Preparation Example 17 was dissolved in THF (20 mL), lithium aluminum hydride (999 mg, 26.33 mmol) was added thereto at 0°C. After the reaction mixture was stirred at room temperature for 16 hours, the reaction was quenched with ammonium chloride (150 mL), followed by filtration through a Celite pad. The filtrate was extracted with ethyl acetate (200 mL x 3), washed with brine, and then the remaining water was removed using sodium sulfate, followed by concentration under reduced pressure. The reaction mixture was separated using column chromatography (SiO_2, hexane : ethyl acetate = 5 : 1 to 1 : 1) to obtain the compound (77) (1.64 g, 57.8%, m/z = 230.3 $[M^+H]^+$).

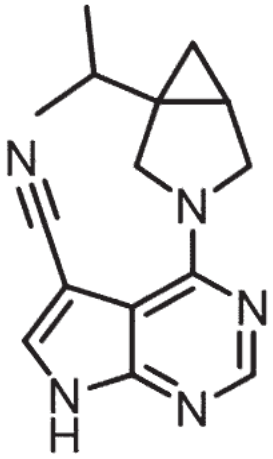
17-6 Step 6: 1-isopropyl-3-azabicyclo[3.1.0]hexane hydrochloride (78)

After the compound (77) (1.64 g, 7.61 mmol) obtained in Preparation Example 17 was dissolved in ethanol (10 mL), 10% Pd/C (50% wt. H_2O) (300 mg) was added thereto. The reaction mixture was stirred under hydrogen at room temperature for 6 hours. After 4 M hydrochloric acid (4 mL) was added thereto, the mixture was further stirred for 30 minutes. The reaction mixture was filtered through a celite pad, and the filtrate was concentrated under reduced pressure to obtain the desired compound (78) (1.306 g, crude, m/z = 126.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.92 (s, 1H), 9.44 (s, 1H), 3.49 - 3.31 (m, 3H), 3.26 (m, 1H), 1.66 (m, 1H), 1.44 (m, 1H), 0.99 (dd, *J* = 9.8, 5.6 Hz, 4H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.75 (t, *J* = 7.4 Hz, 1H).

[Example 76]

Preparation of 4-(1-isopropyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazaindene-3-carbonitrile (NRX02117)

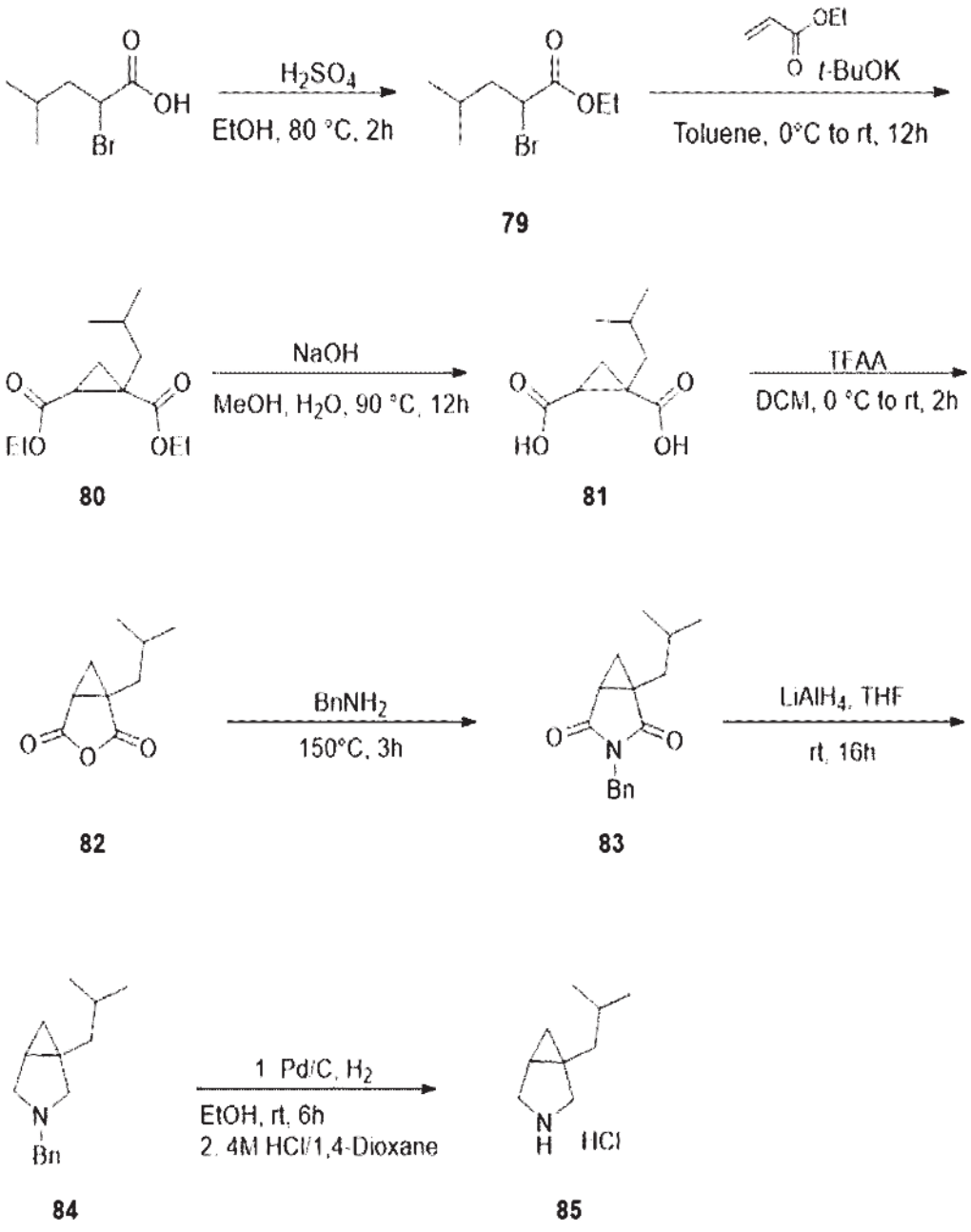


4-Chloro-1H-1,5,7-triazaindene-3-carbonitrile (150 mg, 0.84 mmol), the compound (78) of Preparation Example 17 (149 mg, 0.92 mmol), and triethylamine (254 mg, 2.52 mmol) were added to ethanol (3.0 ml), and stirred at 50°C for 12 hours. After the reaction solution was concentrated under reduced pressure, the filtrate was purified by prep-HPLC (acetonitrile/water/10 mM ammonium carbonate) to obtain the target compound of Example 76 (76.85 mg, 34.2%, m/z = 268.4 $[M^+H]^+$).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.74 (s, 1H), 8.25 (s, 1H), 8.20 (s, 1H), 4.10 (d, *J* = 4.0 Hz, 1H), 4.07 (d, *J* = 3.2 Hz, 1H), 3.80 - 3.68 (m, 2H), 1.75 - 1.63 (m, 1H), 1.57 (m, 1H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.76 (dd, *J* = 7.8, 4.8 Hz, 1H), 0.26 (t, *J* = 4.4 Hz, 1H).

[Preparation Example 18]

Preparation of 1-isobutyl-3-azabicyclo[3.1.0]hexane hydrochloride (85)



18-1 Step 1: ethyl 2-bromo-4-methylpentanoate (79)

After 2-bromo-4-methylpentanoic acid (10 g, 51.26 mmol) was dissolved in ethanol (60 mL), sulfuric acid (0.3 mL) was added thereto. The reaction mixture was stirred at 80°C for 2 hours. After the reaction, the reaction mixture was concentrated under reduced pressure, water (100 mL) was added thereto, and extraction was performed with ethyl acetate (150 mL

x 3). The organic layer was washed with brine, and then the remaining water was removed using sodium sulfate, followed by concentration under reduced pressure to obtain the desired target compound (79) (9.8 g, crude).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.30 - 4.16 (m, 3H), 1.96 - 1.86 (m, 2H), 1.83 - 1.71 (m, 1H), 1.30 (t, *J* = 7.2 Hz, 3H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H).

18-2 Step 2: diethyl 1-isobutylcyclopropane-1,2-dicarboxylate (80)

After the compound (79) (9.8 g, 43.92 mmol) obtained in Preparation Example 18 was dissolved in toluene (50 mL), ethyl acrylate (4398 mg, 43.92 mmol) and tert-butoxide (5421 mg, 48.31 mmol) were added thereto at 0°C under nitrogen. The reaction mixture was stirred at room temperature for 12 hours. After the reaction was quenched with ammonium chloride (150 mL), extraction was performed with ethyl acetate. The organic layer was washed with brine, and then the remaining water was removed using sodium sulfate, followed by concentration under reduced pressure to obtain the desired target compound (10.6 g, crude, m/z = 243.3 $[M^+H]^+$).

18-3 Step 3: 1-isobutylcyclopropane-1,2-dicarboxylic acid (81)

After the compound (80) (10.6 g, 43.74 mmol) obtained in Preparation Example 18 was dissolved in methanol (50 mL), sodium hydroxide (10.5 g, 262.44 mmol) dissolved in water (20 mL) was added thereto. The reaction mixture was stirred at 90°C for 12 hours. After the reaction solvent was concentrated under reduced pressure, water (100 mL) was added thereto, followed by washing with ethyl acetate (50 mL). The aqueous layer was adjusted to pH 1 with 3 M hydrochloric acid and extracted with ethyl acetate (200 mL x 3). The organic layer was washed with brine, and then the remaining water was removed using sodium sulfate,

followed by concentration under reduced pressure to obtain the desired target compound (81) (9.8 g, crude, m/z = 187.2 $[M^+H]^+$).

18-4 Step 4:1-isobutyl-3-oxabicyclo[3.1.0]hexane-2,4-dione (82)

After the compound (81) (9.8 g, 43.74 mmol) obtained in Preparation Example 18 was dissolved in dichloromethane (50 mL), trifluoroacetic anhydride (13.7 g, 65.61 mmol) was added thereto at 0°C under nitrogen. The reaction mixture was stirred at room temperature for 2 hours. After the reaction, the reaction mixture was concentrated under reduced pressure to obtain the desired compound (82) (9.8 g, crude, m/z = 169.2 $[M^+MeOH]^+$).

18-5 Step 5: 3-benzyl-1-isobutyl-3-azabicyclo[3.1.0]hexane-2,4-dione (83)

The compound (82) (9.8 g, 43.74 mmol) obtained in Preparation Example 18 and benzylamine (4686 mg, 43.74 mmol) were stirred at 150°C for 3 hours. The reaction mixture was separated using column chromatography (SiO_2, hexane : ethyl acetate = 5 : 1 to 1 : 1) to obtain the target compound (83) (6.0 g, 45.4%, m/z = 258.3 $[M^+H]^+$).

18-6 Step 6: 3-benzyl-1-isobutyl-3-azabicyclo[3.1.0]hexane (84)

After the compound (83) (6.0 g, 23.31 mmol) obtained in Preparation Example 18 was dissolved in tetrahydrofuran (25 mL), LAH (1769 mg, 46.63 mmol) was added thereto at 0°C under nitrogen. The reaction mixture was stirred at room temperature for 16 hours. The reaction was quenched with ammonium chloride (150 mL) and filtered through a Celite Pad. The filtrate was extracted with ethyl acetate (200 mL x 3), washed with brine, and then the remaining water was removed using sodium sulfate, followed by concentration under reduced pressure. The reaction mixture was separated using column chromatography (SiO_2, hexane : ethyl acetate =

5 : 1 to 1 : 1) to obtain the compound (84) (3.2 g, 59.8%, m/z = 230.3 $[M^+H]^+$).

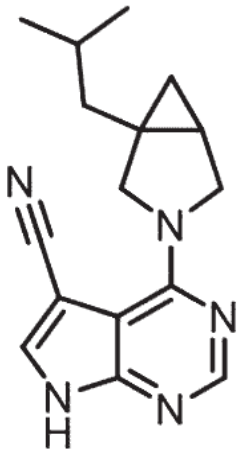
18-7 Step 7: Preparation of 1-isobutyl-3-azabicyclo[3.1.0]hexane hydrochloride (85)

After the compound (84) (1.9 g, 8.28 mmol) obtained in Preparation Example 18 was dissolved in ethanol (10 mL), 10% Pd/C (50% wt. H_2O) (350 mg) was added thereto. The reaction mixture was stirred under hydrogen at room temperature for 6 hours. 4 M hydrochloric acid was added thereto, followed by further stirring for 30 minutes. The reaction mixture was filtered through a Celite Pad and concentrated under reduced pressure to obtain the desired compound (85) (1.3 g, crude, m/z = 140.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.94 (s, 1H), 9.44 (s, 1H), 3.42 (m, 3H), 3.21 (m, 1H), 1.73 - 1.61 (m, 2H), 1.36 (d, *J* = 3.4 Hz, 1H), 1.22 (m, 1H), 1.11 - 1.04 (m, 1H), 1.00 - 0.84 (m, 6H), 0.74 (t, *J* = 7.0 Hz, 1H).

[Example 77]

Preparation of 4-(1-isobutyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazaindene-3-carbonitrile (NRX02118)



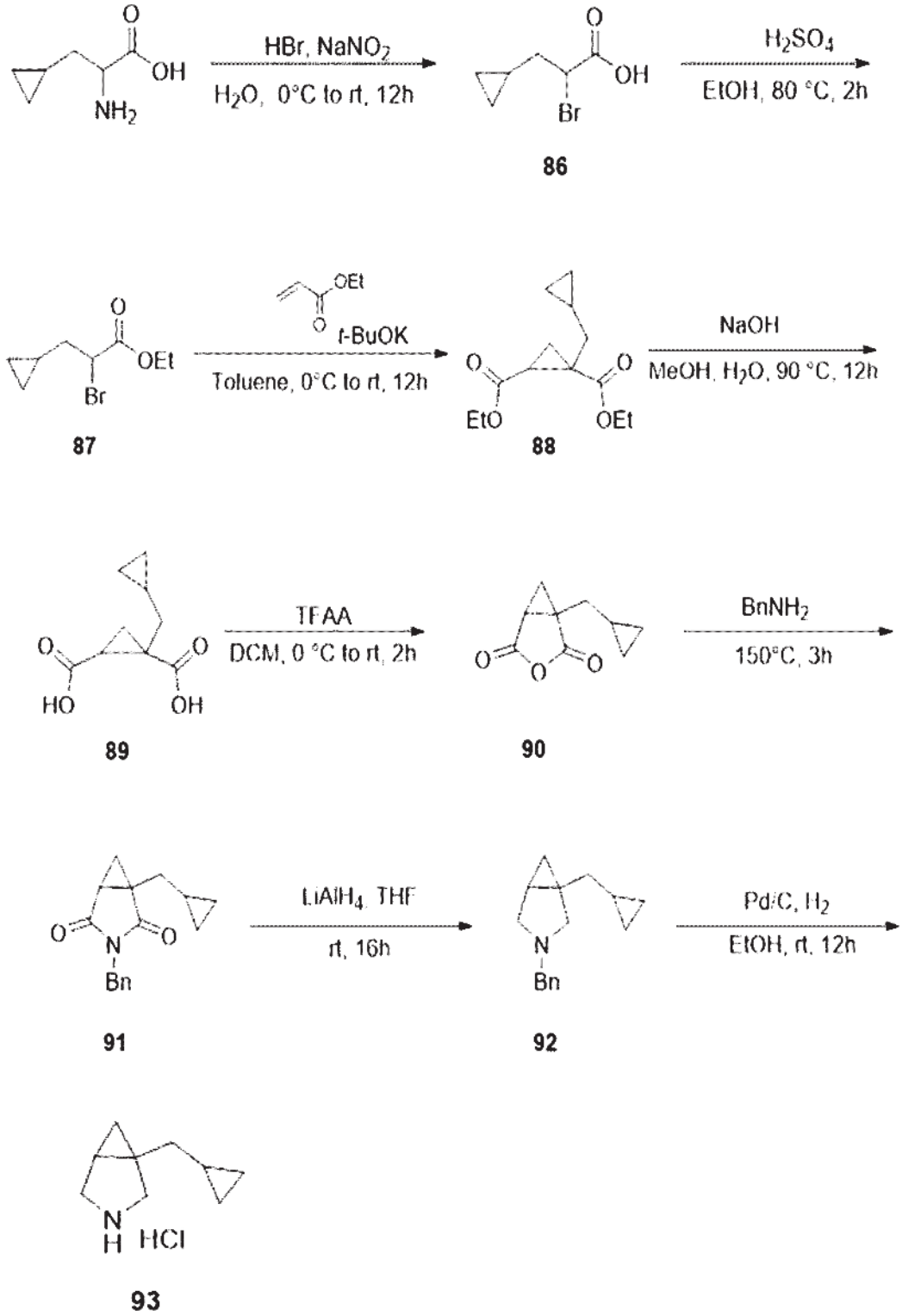
4-Chloro-1H-1,5,7-triazaindene-3-carbonitrile (100 mg, 0.57 mmol), the compound

(85) of Preparation Example 18 (112 mg, 0.63 mmol), and triethylamine (176 mg, 1.74 mmol) were added to ethanol (3.0 ml) and stirred at 50°C for 12 hours. After the reaction solution was concentrated under reduced pressure, the filtrate was purified by prep-HPLC (acetonitrile/water/10 mM ammonium carbonate) to obtain the target compound of Example 18 (36.61 mg, 24.0%, m/z = 282.3 $[M^+H]^+$).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.78 (s, 1H), 8.25 (s, 1H), 8.20 (s, 1H), 4.18 (d, *J* = 10.6 Hz, 1H), 4.10 (d, *J* = 11.0 Hz, 1H), 3.78 (dd, *J* = 11.0, 4.4 Hz, 1H), 3.66 (d, *J* = 10.6 Hz, 1H), 1.87 - 1.74 (m, 2H), 1.45 (m, 1H), 1.25 - 1.13 (m, 1H), 0.96 (dd, *J* = 9.6, 6.4 Hz, 6H), 0.74 (dd, *J* = 7.8, 4.8 Hz, 1H), 0.37 (t, *J* = 4.4 Hz, 1H).

[Preparation Example 19]

Preparation of 4-(1-(cyclopropylmethyl)-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (93)



19-1 Step 1: 2-bromo-3-cyclopropylpropanoic acid (86)

After 2-amino-3-cyclopropylpropanoic acid (1 g, 7.74 mmol) was dissolved in water

(9 mL), 40% hydrobromic acid (12 mL) was added thereto. The reaction mixture was stirred at 0°C for 10 minutes, and sodium nitrite (801 mg, 11.61 mmol) dissolved in water (3 mL) was added thereto. The reaction mixture was stirred at room temperature for 12 hours. Water (100 mL) was added to the reaction mixture, followed by extraction with ethyl acetate (150 mL x 3). The organic layer was washed with brine, and then the remaining water was removed using sodium sulfate, followed by concentration under reduced pressure to obtain the desired compound (86) (1.52 g, crude, m/z = 190.9 $[M^-H]^-$).

19-2 Step 2: ethyl 2-bromo-3-cyclopropylpropanoate (87)

After the compound (86) (1.52 g, 7.74 mmol) obtained in Preparation Example 19 was dissolved in ethanol (8 mL), sulfuric acid (0.3 mL) was added thereto. The reaction mixture was stirred at 80°C for 2 hours. After the reaction mixture was concentrated under reduced pressure, water (100 mL) was added thereto, followed by extraction with ethyl acetate (150 mL x 3). The organic layer was washed with brine, and then the remaining water was removed using sodium sulfate, followed by concentration under reduced pressure to obtain the desired compound (87) (1.70 g, crude, m/z = 221.1 $[M^+H]^+$).

19-3 Step 3: diethyl 1-(cyclopropylmethyl)cyclopropane-1,2-dicarboxylate (88)

After the compound (87) (1.70 g, 7.74 mmol) obtained in Preparation Example 19 was dissolved in toluene (10 mL), ethyl acrylate (738 mg, 7.37 mmol) and tert-butoxide (910 mg, 8.11 mmol) were added thereto at 0°C under nitrogen. The reaction mixture was stirred at room temperature for 12 hours. After the reaction was quenched with ammonium chloride (150 mL), extraction was performed with ethyl acetate (250 mL x 3). The organic layer was washed with brine, and then the remaining water was removed using sodium sulfate, followed by

concentration under reduced pressure to obtain the desired target compound (88) (1.72 g, crude, m/z = 241.3 $[M^+H]^+$).

19-4 Step 4: 1-(cyclopropylmethyl)cyclopropane-1,2-dicarboxylic acid (89)

After the compound (88) (1.72 g, 7.15 mmol) obtained in Preparation Example 19 was dissolved in methanol (25 mL), sodium hydroxide (1.71 g, 42.90 mmol) dissolved in water (25 mL) was added thereto. The reaction mixture was stirred at 90°C for 12 hours. After the reaction, the reaction solvent was concentrated under reduced pressure, water (100 mL) was added thereto, and extraction was performed with ethyl acetate (50 mL). The aqueous layer was adjusted to pH 1 with 3 M hydrochloric acid and extracted with ethyl acetate (150 mL x 3). The organic layer was washed with brine, and then the remaining water was removed using sodium sulfate, followed by concentration under reduced pressure to obtain the desired target compound (89) (1.56 g, crude, m/z = 185.2 $[M^+H]^+$).

19-5 Step 5: 1-(cyclopropylmethyl)-3-oxabicyclo[3.1.0]hexane-2,4-dione (90)

After the company (89) (1.56 g, 7.15 mmol) obtained in Preparation Example 19 was dissolved in tetrahydrofuran (25 mL), trifluoroacetic anhydride (3.00 g, 14.30 mmol) was added thereto at 0°C under nitrogen. The reaction mixture was stirred at room temperature for 2 hours. After the reaction, the reaction solvent was concentrated under reduced pressure to obtain the desired compound (90) (1.56 g, crude, m/z = 199.2 $[M^+MeOH]^+$).

19-6 Step 6: 1-(cyclopropylmethyl)-3-oxabicyclo[3.1.0]hexane-2,4-dione (91)

The compound (90) (1.56 g, 7.15 mmol) obtained in Preparation Example 19 and benzylamine (766 mg, 7.15 mmol) were stirred at 150°C for 3 hours. The reaction mixture was

separated using column chromatography (SiO_2, hexane : ethyl acetate = 5 : 1 to 1 : 1) to obtain the desired compound (91) (363 mg, 18.9%, m/z = 256.3 $[M^+H]^+$).

19-7 Step 7: 3-benzyl-1-(cyclopropylmethyl)-3-azabicyclo[3.1.0]hexane (92)

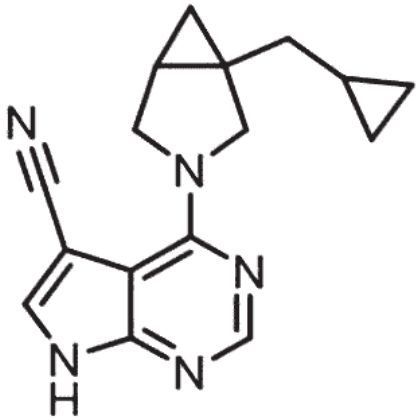
After the compound (91) (363 mg, 1.42 mmol) obtained in Preparation Example 19 was dissolved in tetrahydrofuran (6 mL), LAH (142 mg, 3.55 mmol) was added thereto at 0°C under nitrogen. The reaction mixture was stirred at room temperature for 16 hours. After the reaction was quenched with ammonium chloride (150 mL), the mixture was filtered through a Celite Pad, and the filtrate was extracted with ethyl acetate (200 mL x 3). The organic layer was washed with brine, and then the remaining water was removed using sodium sulfate, followed by concentration under reduced pressure. The mixture was separated using column chromatography (SiO_2, hexane : ethyl acetate = 10 : 1 to 1 : 1) to obtain the desired compound (92) (184 mg, 57.0%, m/z = 228.3 $[M^+H]^+$).

19-8 Step 8: 1-(cyclopropylmethyl)-3-azabicyclo[3.1.0]hexane hydrochloride (93)

After the compound (92) (184 mg, 0.81 mmol) obtained in Preparation Example 19 was dissolved in ethanol (4 mL), 10% Pd/C (50% wt. H_2O) (40 mg) was added thereto. The reaction mixture was stirred at room temperature for 12 hours. After the reaction, 4 M hydrochloric acid/1,4-dioxane (1 mL) was added thereto, followed by further stirring for 0.5 hours. The catalyst was removed by filtration through a Celite Pad, and the filtrate was concentrated under reduced pressure to obtain the desired compound (93) (120 mg, crude, m/z = 138.2 $[M^+H]^+$).

[Example 78]

Preparation of 4-{1-(cyclopropylmethyl)-3-azabicyclo[3.1.0]hex-3-yl}-1H-1,5,7-triazaindene-3-carbonitrile (NRX02119)

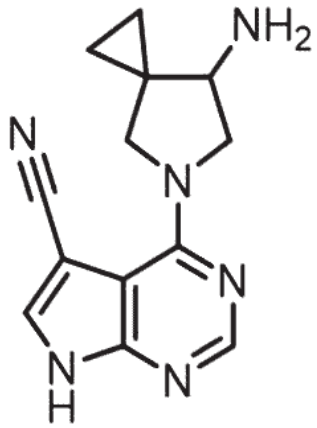


4-Chloro-1H-1,5,7-triazaindene-3-carbonitrile (118 mg, 0.66 mmol), the compound (93) of Preparation Example 19 (120 mg, 0.72 mmol), and triethylamine (201 mg, 1.98 mmol) were added to ethanol (4.0 ml) and stirred at 80°C for 4 hours. After the reaction solution was concentrated under reduced pressure, the reaction mixture was separated using column chromatography (SiO_2, dichloromethane : methanol = 10 : 1) to obtain the target compound of Example 78 (170 mg, 0.608 mol, 92%, m/z = 280.8 $[M^+H]^+$).

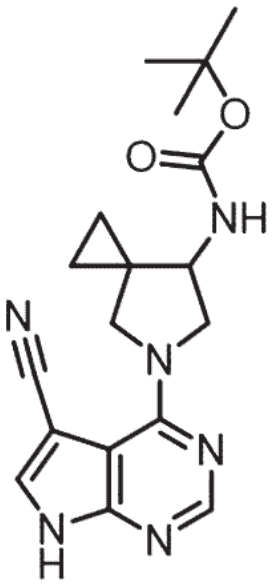
^{1}H-NMR (400 MHz, DMSO-d_6): δ 12.79 (s, 1H), 8.25 (s, 1H), 8.21 (s, 1H), 4.25 (d, *J* = 10.6 Hz, 1H), 4.12 (d, *J* = 11.0 Hz, 1H), 3.82 - 3.73 (m, 2H), 1.63 (dd, *J* = 14.2, 7.0 Hz, 1H), 1.56 (m, 1H), 1.41 (dd, *J* = 14.2, 6.8 Hz, 1H), 0.86 - 0.74 (m, 2H), 0.47 - 0.42 (m, 2H), 0.32 (t, *J* = 4.4 Hz, 1H), 0.17 - 0.08 (m, 2H).

[Example 79]

Preparation of 4-(7-amino-5-aza-5-spiro[2.4]heptyl)-1H-1,5,7-triazaindene-3-carbonitrile (NRX02122)

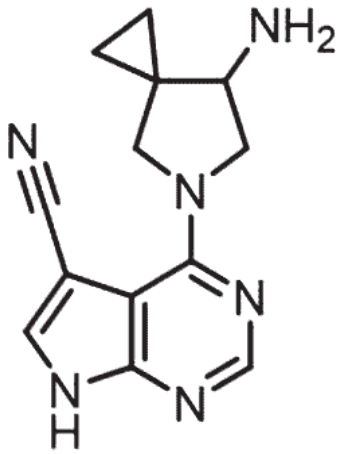


79-1. Step 1: tert-butyl (5-(5-cyano-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-azaspiro[2.4]heptan-7-yl)carbamate



4-Chloro-1H-1,5,7-triazaindene-3-carbonitrile (50 mg, 0.280 mmol), tert-butyl 5-aza-7-spiro[2.4]heptylcarbamate (89.2 mg, 0.420 mmol), and triethylamine (195 μl, 1.40 mmol) were added to ethanol (1.5 ml) and stirred at 80°C for 18 hours. After the reaction solution was concentrated under reduced pressure, the reaction mixture was separated using column chromatography (SiO_2, dichloromethane : methanol = 10 : 1) to obtain the target compound (50 mg, 0.135 mmol, 48%, m/z = 355.1 $[M^+H]^+$).

79-2. Step 2: 4-(7-amino-5-aza-5-spiro[2.4]heptyl)-1H-1,5,7-triazaindene-3-carbonitrile (NRX02122)

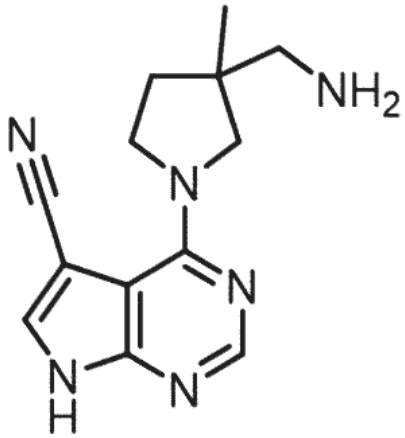


4 M hydrochloric acid was added to 1,4-dioxane containing tert-butyl (5-(5-cyano-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-azaspiro[2.4]heptan-7-yl)carbamate. The reaction mixture was stirred at 70°C for 16 hours. The solid in the reaction mixture was filtered to obtain the target compound of Example 79 (15.5 mg, 0.141 mmol, 43%, m/z = 255.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, DMSO- d_6) δ 8.29 (s, 2H), 8.27 (s, 2H), 8.25 (s, 1H), 4.33 (d, J = 10.7 Hz, 2H), 4.14 (s, 1H), 3.53 (d, J = 4.9 Hz, 2H), 3.50 (s, 2H), 1.22 - 1.11 (m, 2H), 0.94 - 0.87 (m, 2H), 0.77 - 0.74 (m, 3H).

[Example 80]

Preparation of 4-[3-(aminomethyl)-3-methyl-1-pyrrolidinyl]-1H-1,5,7-triazaindene-3-carbonitrile (NRX02123)



80-1 Step 1: tert-butyl ((1-(5-cyano-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-3-methylpyrrolidin-3-yl)methyl)carbamate

4-Chloro-1H-1,5,7-triazaindene-3-carbonitrile (50 mg, 0.280 mmol), tert-butyl ((3-methylpyrrolidin-3-yl)methyl)carbamate (90 mg, 0.420 mmol), and triethylamine (195 μl, 1.40 mmol) were added to ethanol (1.5 ml) and stirred at 80°C for 18 hours. After the reaction solution was concentrated under reduced pressure, the reaction mixture was separated using column chromatography (SiO_2, dichloromethane : methanol = 10 : 1) to obtain the target compound (99.8 mg, 0.280 mmol, 100%, m/z = 357.1 $[M^+H]^+$).

80-2 Step 2: 4-[3-(aminomethyl)-3-methyl-1-pyrrolidinyl]-1H-1,5,7-triazaindene-3-carbonitrile (NRX02123)

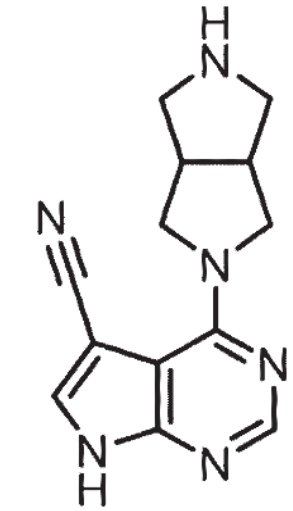
4 M hydrochloric acid (1.4 mL) was added to 1,4-dioxane containing tert-butyl ((1-(5-cyano-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-3-methylpyrrolidin-3-yl)methyl)carbamate (99.8 mg, 0.280 mmol). The reaction mixture was stirred at 70°C for 16 hours. The solid in the reaction mixture was filtered to obtain the target compound of Example 80 (61 mg, 0.280 mmol, 85%, m/z = 257.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.31 (s, 1H), 8.26 (s, 1H), 8.03 (s, 2H), 3.92 (q, J =

8.8 Hz, 2H), 3.75 (d, *J* = 11.5 Hz, 2H), 2.89 (d, *J* = 6.6 Hz, 2H), 2.11 - 2.03 (m, 1H), 1.88 (dd, *J* = 13.4, 7.6 Hz, 1H), 1.21 - 1.13 (m, 3H).

[Example 81]

Preparation of 4-(3,7-diazabicyclo[3.3.0]oct-3-yl)-1H-1,5,7-triazaindene-3-carbonitrile (NRX02124)



81-1 Step 1: tert-butyl ((1-(5-cyano-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-3-methylpyrrolidin-3-yl)methyl)carbamate

4-Chloro-1H-1,5,7-triazaindene-3-carbonitrile (37.5 mg, 0.210 mmol), tert-butyl hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (67 mg, 0.315 mmol), and triethylamine (146 μl, 1.40 mmol) were added to ethanol (1.0 ml) and stirred at 80°C for 18 hours. After the reaction solution was concentrated under reduced pressure, the reaction mixture was separated using column chromatography (SiO_2, dichloromethane : methanol = 10 : 1) to obtain the compound (99.8 mg, 0.280 mmol, 100%, m/z = 355.1 $[M^+H]^+$).

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81-2 Step 2: 4-(3,7-diazabicyclo[3.3.0]oct-3-yl)-1H-1,5,7-triazaindene-3-

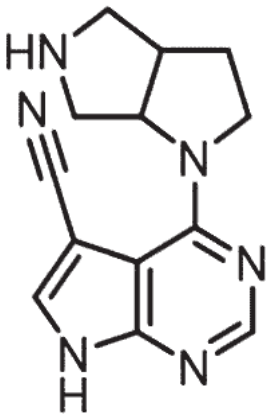
carbonitrile (NRX02124)

4 M hydrochloric acid (1.4 mL) was added to 1,4-dioxane containing tert-butyl ((1-(5-cyano-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-3-methylpyrrolidin-3-yl)methyl)carbamate (99.8 mg, 0.280 mmol). The reaction mixture was stirred at 70°C for 16 hours. The solid in the reaction mixture was filtered to obtain the target compound of Example 81 (36 mg, 0.142 mmol, 51%, m/z = 255.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, DMSO-d6) δ 10.15 (s, 1H), 8.31 (s, 1H), 8.27 (s, 1H), 4.05 (d, J = 10.7 Hz, 1H), 3.97 - 3.87 (m, 1H), 3.80 (d, J = 9.3 Hz, 1H), 2.31 - 2.24 (m, 2H), 1.91 - 1.80 (m, 1H).

[Example 82]

Preparation of 4-(2,7-diazabicyclo[3.3.0]oct-2-yl)-1H-1,5,7-triazaindene-3-carbonitrile (NRX02128)



82-1 Step 1: Preparation of tert-butyl 1-(5-cyano-7H-pyrrolo[2,3-d]pyrimidin-4-yl)hexahydropyrrolo[3,4-b]pyrrole-5(1H)-carboxylate

4-Chloro-1H-1,5,7-triazaindene-3-carbonitrile (50.0 mg, 0.280 mmol), tert-butyl 2,7-diazabicyclo[3.3.0]octane-7-carboxylate (71 mg, 0.336 mmol), and triethylamine (195 μl, 1.40

mmol) were added to ethanol (1.4 ml) and stirred at 80°C for 18 hours. After the reaction solution was concentrated under reduced pressure, the reaction mixture was separated using column chromatography (SiO_2, dichloromethane : methanol = 10 : 1) to obtain the compound (99.8 mg, 0.280 mmol, 100%, m/z = 355.1 $[M^+H]^+$).

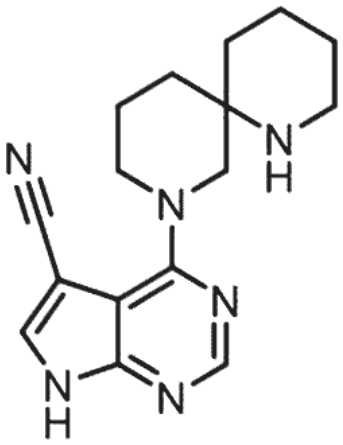
82-2 Step 2: 4-(2,7-diazabicyclo[3.3.0]oct-2-yl)-1H-1,5,7-triazaindene-3-carbonitrile (NRX02128)

4 M hydrochloric acid (1.4 mL) was added to 1,4-dioxane containing tert-butyl ((1-(5-cyano-7H-pyrrolo[2,3-d]pyrimidin-4-yl)hexahydropyrrolo[3,4-b]pyrrole-5(1H)-carboxylate (99.8 mg, 0.280 mmol). The reaction mixture was stirred at 70°C for 16 hours. The solid in the reaction mixture was filtered to obtain the target compound of Example 82 (70 mg, 0.276 mmol, 98%, m/z = 255.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.28 (s, 1H), 9.12 (s, 1H), 8.29 (s, 1H), 8.25 (s, 1H), 4.85 (d, J = 3.9 Hz, 1H), 4.12 (dt, J = 15.1, 9.0 Hz, 1H), 3.98 (tt, J = 9.3, 3.9 Hz, 1H), 3.36 (s, 4H), 3.17 - 3.09 (m, 3H), 2.20 - 2.06 (m, 2H).

[Example 83]

Preparation of 4-(1,8-diaza-8-spiro[5.5]undecyl)-1H-1,5,7-triazaindene-3-carbonitrile (NRX02152)



83-1 Step 1: tert-butyl 8-(5-cyano-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1,8-diazaspiro[5.5]undecane-1-carboxylate

4-Chloro-1H-1,5,7-triazaindene-3-carbonitrile (50.0 mg, 0.280 mmol), tert-butyl 1,8-diazaspiro[5.5]undecanecarboxylate (85.5 mg, 0.336 mmol), and triethylamine (195 μl, 1.40 mmol) were added to ethanol (1.4 ml) and stirred at 80°C for 18 hours. After the reaction solution was concentrated under reduced pressure, the reaction mixture was separated using column chromatography (SiO_2, dichloromethane : methanol = 10 : 1) to obtain the target compound (75 mg, 0.189 mmol, 68%, m/z = 397.1 $[M^+H]^+$).

83-2 Step 2: 4-(1,8-diaza-8-spiro[5.5]undecyl)-1H-1,5,7-triazaindene-3-carbonitrile (NRX02152)

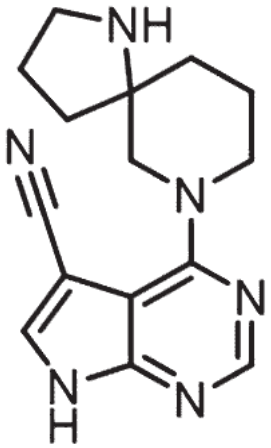
4 M hydrochloric acid (1.4 mL) was added to 1,4-dioxane containing tert-butyl 8-(5-cyano-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1,8-diazospiro[5.5]undecane-1-carboxylate (75 mg, 0.189 mmol). The reaction mixture was stirred at 50°C for 16 hours. After the reaction mixture was concentrated under reduced pressure, it was basified with 6 N sodium hydroxide and extracted with ethyl acetate. The organic layer was washed using sodium sulfate to remove the remaining water, followed by concentration under reduced pressure. The concentrated mixture

was separated using reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the target compound of Example 83 (30 mg, 101 μmol, 54%, m/z = 297.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, DMSO- d_6) δ 8.33 - 8.24 (m, 3H), 5.75 (s, 1H), 3.97 (d, J = 13.2 Hz, 1H), 3.82 (s, 1H), 3.76 - 3.61 (m, 2H), 2.76 (d, J = 5.4 Hz, 2H), 1.88 - 1.63 (m, 4H), 1.52 - 1.34 (m, 6H).

[Example 84]

Preparation of 4-(1,7-diaza-7-spiro[4.5]decyl)-1H-1,5,7-triazaindene-3-carbonitrile (NRX02158)



84-1 Step 1: tert-butyl 7-(5-cyano-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1,7-diazaspiro[4.5]decane-1-carboxylate

4-Chloro-1H-1,5,7-triazaindene-3-carbonitrile (50.0 mg, 0.280 mmol), tert-butyl 1,7-diaza-1-spiro[4.5]decanecarboxylate (80.8 mg, 0.336 mmol), and triethylamine (195 μl, 1.40 mmol) were added to ethanol (1.4 ml) and stirred at 80°C for 2 hours. After the reaction solution was concentrated under reduced pressure, the reaction mixture was separated using column chromatography (SiO_2, hexane : ethyl acetate = 5 : 1) to obtain the compound (85.6 mg, 0.224

mmol, 80%, m/z = 383.1 $[M^+H]^+$).

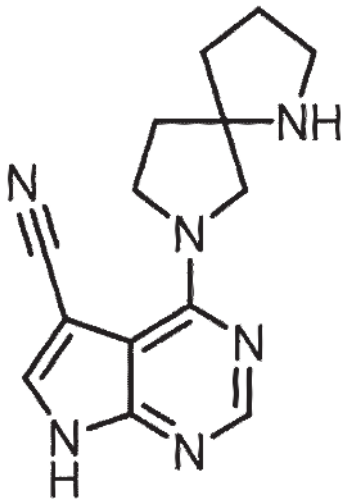
84-2 Step 2: 4-(1,7-diaza-7-spiro[4.5]decyl)-1H-1,5,7-triazaindene-3-carbonitrile(NRX02158)

4 M hydrochloric acid (1.4 mL) was added to 1,4-dioxane containing tert-butyl 7-(5-cyano-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1,7-diazospiro[4.5]decane-1-carboxylate (86 mg, 0.224 mmol). The reaction mixture was stirred at 50°C for 16 hours. After the reaction mixture was concentrated under reduced pressure, it was basified with 6 N sodium hydroxide and extracted with ethyl acetate. The organic layer was washed using sodium sulfate to remove the remaining water, followed by concentration under reduced pressure. The concentrated mixture was separated using reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the target compound of Example 84 (18 mg, 83.4 μmol, 28%, m/z = 283.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 1H), 8.22 (s, 1H), 8.21 (s, 1H), 3.89 (t, *J* = 10.8 Hz, 2H), 3.81 (td, *J* = 9.6, 4.2 Hz, 1H), 3.65 (d, *J* = 11.2 Hz, 1H), 2.82 (dt, *J* = 12.8, 4.7 Hz, 1H), 2.72 (ddd, *J* = 12.5, 7.7, 4.0 Hz, 1H), 2.07 (dt, *J* = 11.4, 6.9 Hz, 1H), 1.90 (dt, *J* = 12.4, 8.3 Hz, 1H), 1.67 - 1.51 (m, 3H), 1.46 (s, 3H).

[Example 85]

Preparation of 4-(1,7-diaza-7-spiro[4.4]nonyl)-1H-1,5,7-triazaindene-3-carbonitrile (NRX02159)



85-1 Step 1: Preparation of tert-butyl 7-(5-cyano-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1,7-diazaspiro[4.4]nonane-1-carboxylate

4-Chloro-1H-1,5,7-triazaindene-3-carbonitrile (50.0 mg, 0.280 mmol), tert-butyl 1,7-diaza-1-spiro[4.4]nonanecarboxylate (76 mg, 0.336 mmol), and triethylamine (195 μl, 1.40 mmol) were added to ethanol (1.4 ml) and stirred at 80°C for 2 hours. After the reaction solution was concentrated under reduced pressure, the reaction mixture was separated using column chromatography (SiO_2, hexane : ethyl acetate = 5 : 1) to obtain the target compound (85 mg, 0.231 mmol, 82%, m/z = 369.1 $[M^+H]^+$).

85-2 Step 2: 4-(1,7-diaza-7-spiro[4.4]nonyl)-1H-1,5,7-triazaindene-3-carbonitrile (NRX02159)

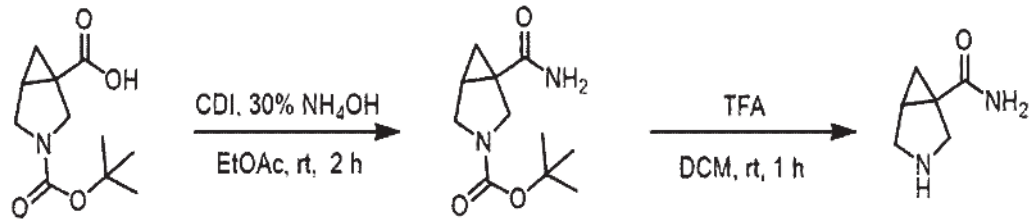
4 M hydrochloric acid (1.4 mL) was added to 1,4-dioxane containing tert-butyl 7-(5-cyano-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1,7-diazospiro[4.4]nonane-1-carboxylate (85 mg, 0.231 mmol). The reaction mixture was stirred at 50°C for 16 hours. After the reaction mixture was concentrated under reduced pressure, it was basified with 6 N sodium hydroxide and extracted with ethyl acetate. The organic layer was washed using sodium sulfate to remove the

remaining water, followed by concentration under reduced pressure. The concentrated mixture was separated using reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the target compound of Example 85 (45 mg, 170 μmol, 74%, m/z = 269.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.11 (s, 1H), 8.04 (s, 1H), 3.91 - 3.75 (m, 2H), 3.65 (s, 2H), 2.94 - 2.77 (m, 2H), 1.96 - 1.89 (m, 2H), 1.74 (s, 3H), 1.77 - 1.69 (m, 2H), 1.24 (s, 1H).

[Preparation Example 20]

Preparation of 3-azabicyclo[3.1.0]hexane-1-carboxamide (95)



94 95

20-1 Step 1: tert-butyl 1-carbamoyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (94)

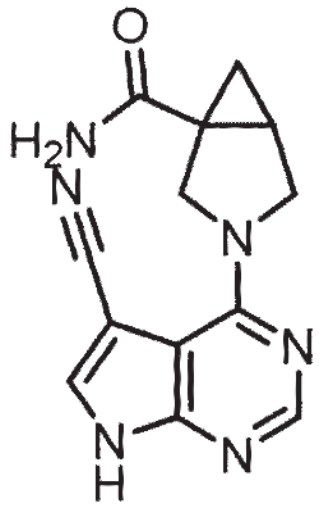
3-tert-Butoxycarbonyl-3-azabicyclo[3.1.0]hexane-1-carboxylic acid (0.2 g, 0.880 mmol) was dissolved in ethyl acetate (1.3 mL), and then CDI (214 mg, 1.32 mmol) and 30% ammonium hydroxide (0.5 mL) were added. The reaction mixture was stirred at 45°C for 2 hours. Ethyl acetate (50 mL) was added to the reaction mixture, and washed several times with water (50 mL), citric acid (50 mL), and an aqueous sodium carbonate solution in that order. The organic layer was washed using sodium sulfate to remove the remaining water, and concentrated under reduced pressure to obtain the compound (94) of Preparation Example 20.

20-2 Step 2: 3-azabicyclo[3.1.0]hexane-1-carboxamide (95)

The compound (94) of the Preparation Example (199 mg, 0.879 mmol) was dissolved in dichloromethane, and then trifluoroacetic acid (17.6 mmol) was added. The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, and ethanol and basic resin were added to adjust the pH to 8, followed by filtration to obtain the desired compound (95) of Preparation Example 20.

[Example 86]

Preparation of 3-(3-cyano-1H-1,5,7-triazainden-4-yl)-3-azabicyclo[3.1.0]hexane-1-carboxamide (NRX02129)



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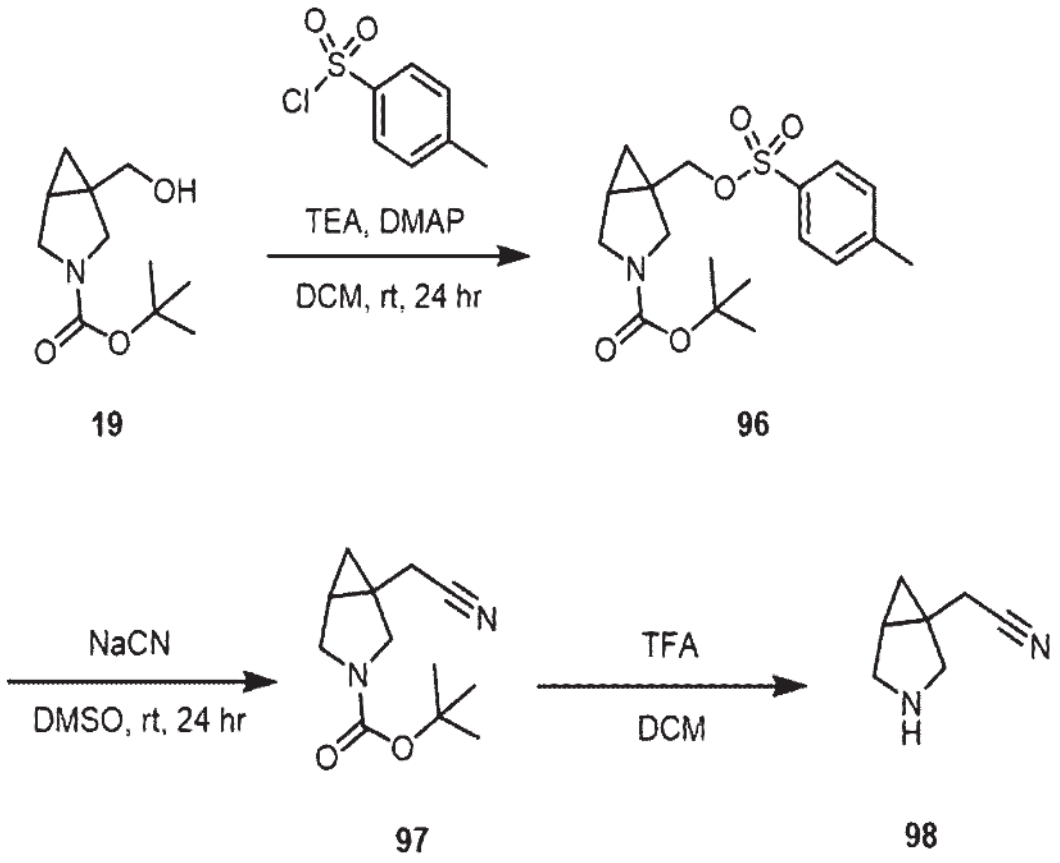
4-Chloro-1H-1,5,7-triazaindene-3-carbonitrile (50.0 mg, 0.280 mmol), the compound (95) obtained in Preparation Example 20 (42 mg, 0.336 mmol), and triethylamine (195 μl, 1.40 mmol) were added to ethanol (1.4 ml) and stirred at 80°C for 18 hours. After the reaction solution was concentrated under reduced pressure, the reaction mixture was separated using column chromatography (SiO_2, dichloromethane : methanol = 10 : 1) to obtain the target compound of Example 86 (6.7 mg, 0.025 mmol, 9%, m/z = 269.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.21 (dt, J = 21.2, 7.1 Hz, 1H), 7.15 (s, 1H), 7.05 (s, 1H), 4.28 - 4.17 (m, 1H), 4.12 (dd, J = 11.3, 4.6 Hz, 1H), 4.06 - 3.97 (m, 1H), 3.86 (s, 1H),

2.11 (s, 1H), 1.44 - 1.36 (m, 1H), 0.66 (s, 1H).

[Preparation Example 21]

Preparation of 3-azabicyclo[3.1.0]hexane-1-carboxamide (98)



21-1 Step 1: tert-butyl 1-((tosyloxy)methyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (96)

tert-Butyl 1-(hydroxymethyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (19) (200 mg, 0.938 mmol) was dissolved in dichloromethane (5 mL). Triethylamine (285 mg, 2.81 mmol), dimethylaminopyridine (11.5 mg, 0.094 mmol), and *p*-(chlorosulfonyl)toluene (268 mg, 1.41 mmol) were added to the reaction mixture. The reaction mixture was stirred at 4°C for 18 hours. After the reaction, the reaction mixture was concentrated under reduced pressure, and ethyl

acetate and an aqueous sodium carbonate solution were added thereto. The organic layer was washed several times with 0.1 M hydrochloric acid and water, and then the remaining water was removed using sodium sulfate, followed by concentration under reduced pressure to obtain the target compound (96) of Preparation Example 21 (275 mg, 0.748 mmol, 80%).

21-2 Step 2: tert-butyl 1-(cyanomethyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (97)

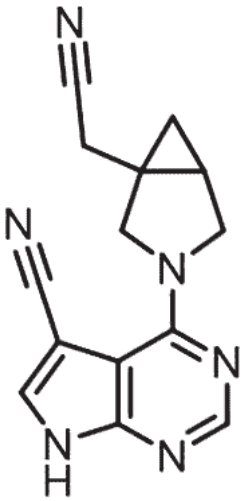
Sodium cyanide (183 mg, 3.74 mmol) was added to dimethyl sulfoxide (30 mL) in which the compound (96) (275 mg, 0.748 mmol) obtained in Preparation Example 21 was dissolved. The reaction mixture was stirred at room temperature for 24 hours. After the reaction, water was added to the reaction mixture, and extracted with dichloromethane. The organic layer was washed several times with 0.1 M hydrochloric acid and water, and then the remaining water was removed using sodium sulfate, followed by concentration under reduced pressure to obtain the compound (97) of Preparation Example 21.

21-3 Step 3: 3-azabicyclo[3.1.0]hexane-1-carboxamide (98)

The compound (97) of Preparation Example 21 (166 mg, 0.747 mmol) was dissolved in dichloromethane, and then trifluoroacetic acid (14.9 mmol) was added. The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, and ethanol and basic resin were added to adjust the pH to 8, followed by filtration to obtain the compound (98), which was used directly in the next reaction without purification.

[Example 87]

Preparation of 4-{1-(cyanomethyl)-3-azabicyclo[3.1.0]hex-3-yl}-1H-1,5,7-triazaindene-3-carbonitrile (NRX02130)

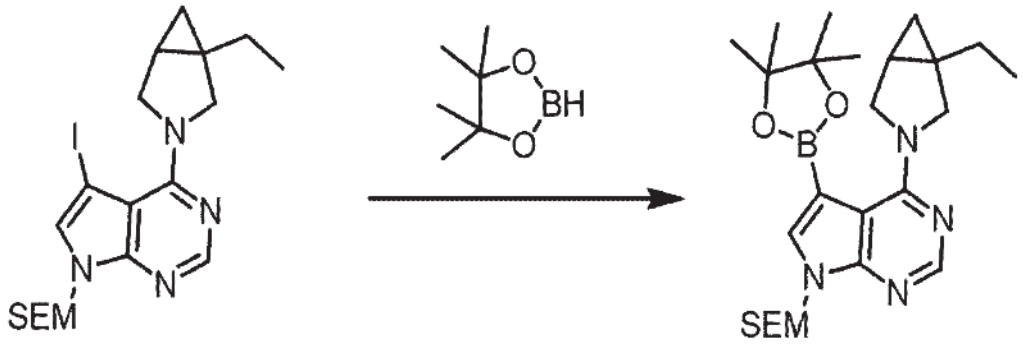


4-Chloro-1H-1,5,7-triazaindene-3-carbonitrile (50.0 mg, 0.280 mmol), the compound (98) of Preparation Example 21 (51 mg, 0.420 mmol), and triethylamine (195 μl, 1.40 mmol) were added to ethanol (1.4 ml) and stirred at 80°C for 18 hours. After the reaction solution was concentrated under reduced pressure, the reaction mixture was separated using column chromatography (SiO_2, dichloromethane : methanol = 10 : 1) to obtain the target compound (43 mg, 0.163 mmol, 58%, m/z = 265.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 1H), 8.19 (s, 1H), 4.25 (d, J = 10.8 Hz, 1H), 4.11 (d, J = 10.7 Hz, 1H), 3.82 (dd, J = 10.7, 4.2 Hz, 1H), 3.67 (d, J = 10.9 Hz, 1H), 3.01 - 2.87 (m, 2H), 1.74 (dt, J = 8.2, 4.2 Hz, 1H), 0.91 (dd, J = 8.2, 5.0 Hz, 1H), 0.48 (t, J = 4.6 Hz, 1H).

[Preparation Example 22]

Preparation of 4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine (99)

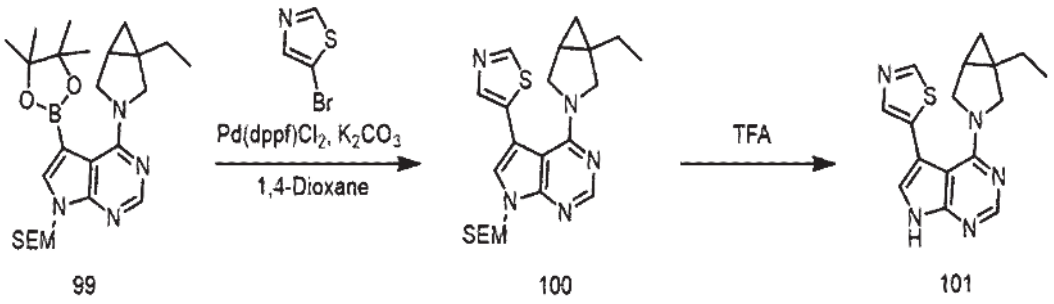


54 **99**

The compound (54) of Preparation Example 13 (695 mg, 1.43 mmol) was dissolved in 1,4-dioxane (14 mL), and then 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (734 mg, 5.74 mmol), triethylamine (581 mg, 5.74 mmol), Pd2(dba)3 (131 mg, 0.143 mmol), and XPhos (68.4 mg, 0.143 mmol) were added in that order. The reaction mixture was stirred at 95°C for 18 hours. After cooling the reaction mixture to room temperature, water was added to the reaction mixture, and extracted with ethyl acetate. The organic layer was washed using sodium sulfate to remove the remaining water, followed by concentration under reduced pressure. The concentrated mixture was separated using column chromatography (SiO_2, hexane : ethyl acetate = 5 : 1 to 1 : 1) to obtain the compound (99) of Preparation Example 22 (500 mg, 1.03 mmol, 85%).

[Example 88]

Preparation of 5-(4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)thiazole (NRX02131)



88-1 Step 1: 5-(4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)thiazole (100)

The compound (99) of Preparation Example 22 (130 mg, 0.268 mmol), 5-bromo-1,3-thiazole (48.4 mg, 0.295 mmol), and potassium carbonate (256 mg, 0.805 mmol) were dissolved in 1,4-dioxane (1.1 mL). Then, Pd(pddf)Cl_2 (9.8 mg, 0.013 mmol) was added to the reaction mixture. The reaction mixture was stirred at 100°C for 16 hours. After the reaction, the mixture was filtered through a Celite Pad and concentrated under reduced pressure. The concentrated mixture was separated using column chromatography (SiO_2, hexane : ethyl acetate = 1 : 1) to obtain the target compound (100) (105 mg, 0.238 mmol, 89%).

88-2 Step 2: 5-(4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)thiazole (NRX02131)

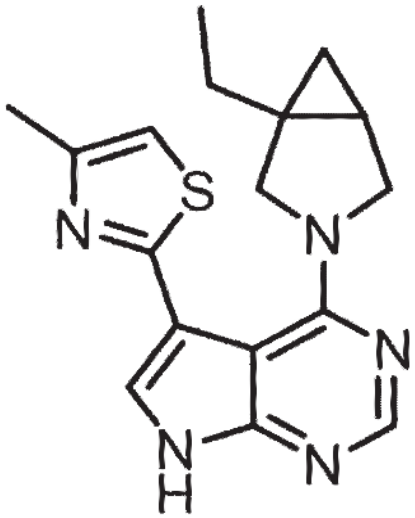
The compound (100) (105 mg, 0.238 mmol) obtained in Example 88 was added to dichloromethane containing trifluoroacetic acid (3.72 mmol). The reaction mixture was stirred at 50°C for 2 hours. The reaction mixture was concentrated under reduced pressure, dissolved in dichloromethane, and then potassium carbonate (0.88 mmol) was added thereto. The reaction mixture was stirred at 50°C for 1 hour. After the reaction mixture was concentrated under reduced pressure, it was separated using column chromatography (SiO_2, dichloromethane :

methanol = 10 : 1) to obtain the target compound (101) (35.8 mg, 115 μmol, 48%, m/z = 312.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, $CDCl_3$-*d*) δ 8.82 (d, *J* = 0.8 Hz, 1H), 8.32 - 8.27 (m, 1H), 7.80 (dd, *J* = 3.8, 0.7 Hz, 1H), 7.14 (d, *J* = 4.2 Hz, 1H), 3.84 (ddd, *J* = 21.5, 10.8, 5.0 Hz, 2H), 3.28 (dd, *J* = 10.9, 4.0 Hz, H), 3.11 - 3.01 (m, 1H), 1.34 - 1.21 (m, 1H), 1.12 (td, *J* = 7.3, 3.4 Hz, 1H), 1.02 (td, *J* = 7.5, 1.7 Hz, 1H), 0.81 (td, *J* = 7.5, 2.6 Hz, 3H), 0.47 - 0.36 (m, 1H), 0.19 (t, *J* = 4.3 Hz, 1H).

[Example 89]

Preparation of 4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-3-(4-methyl-1,3-thiazol-2-yl)-1H-1,5,7-triazaindene (NRX02134)



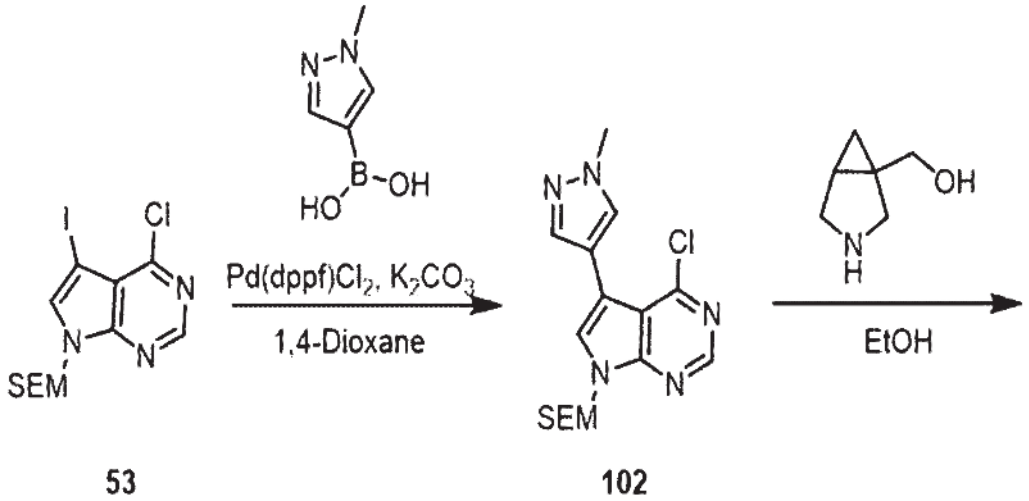
The reaction was performed in the same manner as in Example 88, except for using 2-bromo-4-methyl-1,3-thiazole instead of using 5-bromo-1,3-thiazole, to obtain the target compound of Example 89 (11 mg, 0.036 mmol, 44%, m/z = 326.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, $CDCl_3$-*d*) δ 10.39 (s, 1H), 8.29 (s, 1H), 7.26 (s, 1H), 6.90 (q, *J* = 1.0 Hz, 1H), 3.86 (d, *J* = 11.0 Hz, 1H), 3.78 (d, *J* = 10.6 Hz, 1H), 3.40 (dd, *J* = 11.0, 4.0 Hz, 1H), 3.20 - 3.12 (m, 1H), 2.57 - 2.48 (m, 3H), 1.65 - 1.53 (m, 2H), 1.34 - 1.21 (m, 2H), 1.19 -

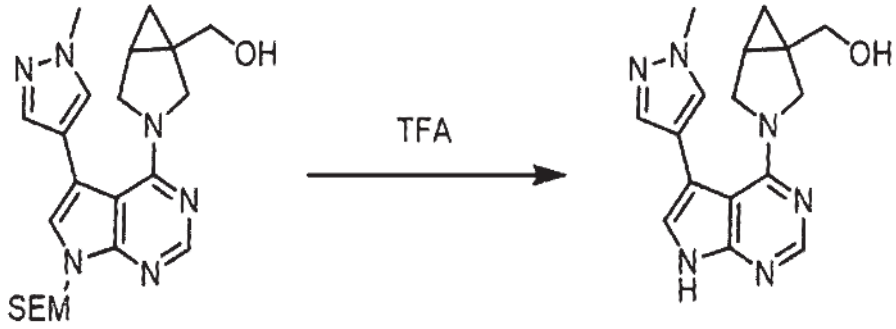
1.08 (m, 1H), 0.82 (t, *J* = 7.4 Hz, 3H), 0.44 (dd, *J* = 7.8, 4.8 Hz, 1H), 0.32 - 0.21 (m, 1H).

[Example 90]

Preparation of {3-[3-(1-methyl-4-pyrazolyl)-1H-1,5,7-triazainden-4-yl]-3-azabicyclo[3.1.0]hex-1-yl}methanol (NRX02136)



53 102



103 104

90-1 Step 1: 4-chloro-5-(1-methyl-1H-pyrazol-4-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine (102)

The compound (53) (200 mg, 0.488 mmol) obtained in Preparation Example 13, (1-methyl-4-pyrazolyl)boranediol (73.8 mg, 0.586 mmol), and potassium carbonate (466 mg, 1.46 mmol) were dissolved in 1,4-dioxane/water (1.1 mL). Then, Pd(pddf)Cl_2 (22 mg, 0.024 mmol) was added to the reaction mixture. The reaction mixture was stirred at 100°C for 2 hours. After the reaction, the mixture was filtered through a Celite Pad and concentrated under reduced pressure. The concentrated mixture was separated using column chromatography (SiO_2, hexane : ethyl acetate = 1 : 1) to obtain the compound (102) (110 mg, 0.302 mmol, 62%).

90-2 Step 2: (3-(5-(1-methyl-1H-pyrazol-4-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-3-azabicyclo[3.1.0]hexan-1-yl)methanol (103)

The compound (102) (50 mg, 0.137 mmol) obtained in the Example, the compound (20) (46.6 mg, 0.412 mmol) obtained in Preparation Example 5, and triethylamine (95.8 μl, 687 mmol) were added to ethanol (1.4 ml) and stirred at 80°C for 18 hours. After the reaction solution was concentrated under reduced pressure, the reaction mixture was separated using column chromatography (SiO_2, dichloromethane : methanol = 10 : 1) to obtain the target compound (103) (27 mg, 0.062 mmol, 45%, m/z = 441.1 $[M^+H]^+$).

90-3 Step 3: (3-(5-(1-methyl-1H-pyrazol-4-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-3-azabicyclo[3.1.0]hexan-1-yl)methanol (NRX02136)

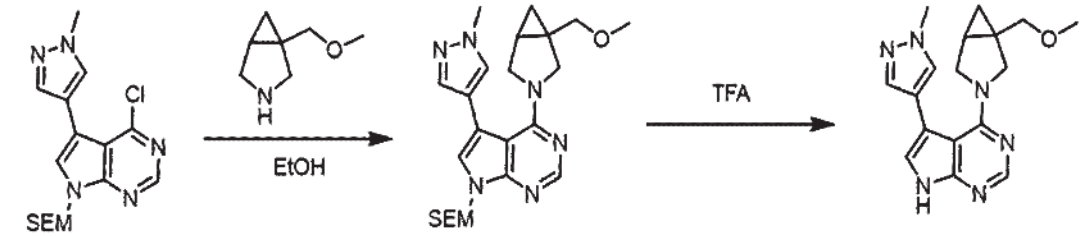
The compound (103) (27 mg, 0.062 mmol) obtained in the Example was added to dichloromethane containing trifluoroacetic acid (0.617 mmol). The reaction mixture was stirred at 50°C for 2 hours. The reaction mixture was concentrated under reduced pressure,

dissolved in dichloromethane, and then potassium carbonate (0.309 mmol) was added thereto. The reaction mixture was stirred at room temperature for 30 minutes. After the reaction mixture was concentrated under reduced pressure, it was separated using column chromatography (SiO_2, dichloromethane : methanol = 10 : 1) to obtain the target compound (6.8 mg, 21.9 μmol, 35%, m/z = 311.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, $CDCl_3$-*d*) δ 9.60 (s, 1H), 8.28 (s, 1H), 7.50 (s, 1H), 7.38 (s, 1H), 6.95 (s, 1H), 4.05 (d, *J* = 11.0 Hz, 1H), 3.96 (s, 3H), 3.83 (d, *J* = 11.1 Hz, 1H), 3.68 (d, *J* = 11.6 Hz, 1H), 3.61 (d, *J* = 11.5 Hz, 1H), 3.36 - 3.26 (m, 2H), 0.88 (d, *J* = 6.2 Hz, 1H), 0.64 (dd, *J* = 8.0, 5.0 Hz, 1H), 0.39 (t, *J* = 4.5 Hz, 1H).

[Example 91]

Preparation of 4-{1-(methoxymethyl)-3-azabicyclo[3.1.0]hex-3-yl}-3-(1-methyl-4-pyrazolyl)-1H-1,5,7-triazaindene (NRX02137)



102 105 106

91-1 Step 1: 4-(1-(methoxymethyl)-3-azabicyclo[3.1.0]hexan-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine (105)

The reaction was performed in the same manner as in Step 2 of Example 90, except for using the compound (18) of Preparation Example 4 (52.4 mg, 0.412 mmol) instead of the

compound (20) obtained in Preparation Example 5, to obtain the target compound (105) (51.7 mg, 114 μmol, 83%, m/z = 455.1 $[M^+H]^+$).

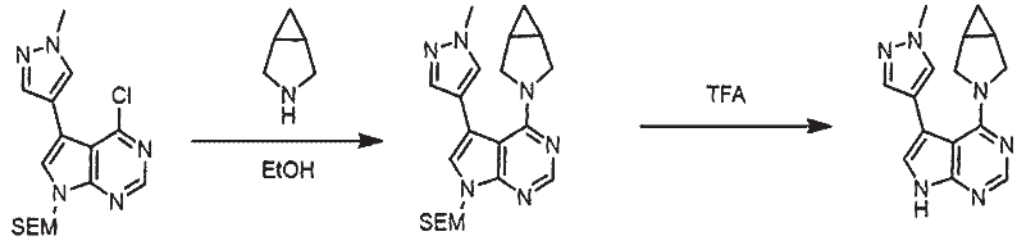
91-2 Step 2: 4-{1-(methoxymethyl)-3-azabicyclo[3.1.0]hex-3-yl}-3-(1-methyl-4-pyrazolyl)-1H-1,5,7-triazaindene (NRX02137)

The reaction was performed in the same manner as in Step 3 of Example 90 to obtain the target compound (106) (28.6 mg, 88.2 μmol, 78%, m/z = 325.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, $CDCl_3$-*d*) δ 10.25 (s, 1H), 8.26 (s, 1H), 7.49 (s, 1H), 7.37 (s, 1H), 6.95 (s, 1H), 4.02 (d, *J* = 11.0 Hz, 1H), 3.96 (s, 2H), 3.83 (d, *J* = 11.1 Hz, 1H), 3.43 (d, *J* = 10.5 Hz, 1H), 3.37 (d, *J* = 10.4 Hz, 1H), 3.34 - 3.31 (m, 1H), 3.30 (s, 3H), 1.30 (dt, *J* = 8.0, 4.0 Hz, 1H), 0.64 (ddt, *J* = 8.1, 5.1, 1.0 Hz, 1H), 0.38 (t, *J* = 4.6 Hz, 1H).

[Example 92]

Preparation of 4-(3-azabicyclo[3.1.0]hex-3-yl)-3-(1-methyl-4-pyrazolyl)-1H-1,5,7-triazaindene (NRX02149)



102 107 108

92-1 Step 1: 4-(3-azabicyclo[3.1.0]hexan-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine (107)

The reaction was performed in the same manner as in Step 2 of Example 90, except

for using 3-azabicyclo[3.1.0]hexane (43.4 mg, 0.363 mmol) instead of the compound (20) from Preparation Example 5, to obtain the target compound (107) (88 mg, 214 μmol, 71%, m/z = 411.1 $[M^+H]^+$).

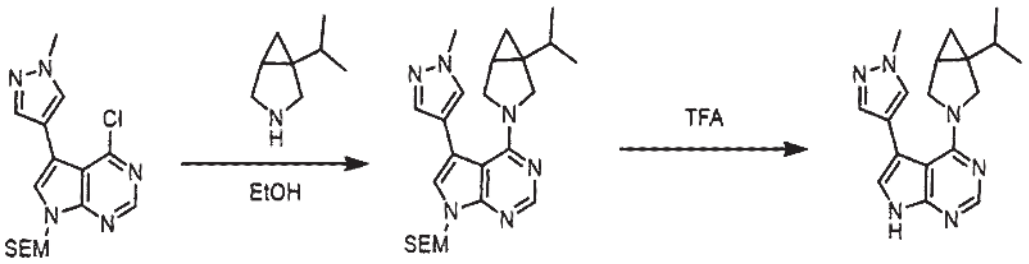
92-2 Step 2: 4-(3-azabicyclo[3.1.0]hex-3-yl)-3-(1-methyl-4-pyrazolyl)-1H-1,5,7-triazaindene (NRX02149)

The reaction was performed in the same manner as in Step 3 of Example 90 to obtain the target compound (108) (21 mg, 59.9 μmol, 28%, m/z = 281.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.76 (s, 2H), 8.12 (s, 1H), 7.74 - 7.67 (m, 2H), 7.45 - 7.39 (m, 2H), 7.10 (d, *J* = 2.4 Hz, 2H), 5.50 (d, *J* = 7.3 Hz, 1H), 3.88 (s, 1H), 3.87 (s, 5H), 3.78 (dd, *J* = 10.9, 4.5 Hz, 4H), 3.14 (dt, *J* = 11.0, 1.7 Hz, 4H), 1.40 (dddd, *J* = 7.3, 3.5, 2.2, 1.1 Hz, 3H), 0.45 (td, *J* = 7.6, 4.6 Hz, 2H), 0.06 (d, *J* = 4.1 Hz, 1H).

[Example 93]

Preparation of 4-(1-isopropyl-3-azabicyclo[3.1.0]hex-3-yl)-3-(1-methyl-4-pyrazolyl)-1H-1,5,7-triazaindene (NRX02155)



93-1 Step 1: 4-(1-isopropyl-3-azabicyclo[3.1.0]hexan-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine (109)

The reaction was performed in the same manner as in Step 2 of Example 90, except for using the compound (78) from Preparation Example 17 (55.7 mg, 0.345 mmol) instead of the compound (20) from Preparation Example 5, to obtain the target compound (109) (94 mg, 208 μmol, 72%, m/z = 453.1 $[M^+H]^+$).

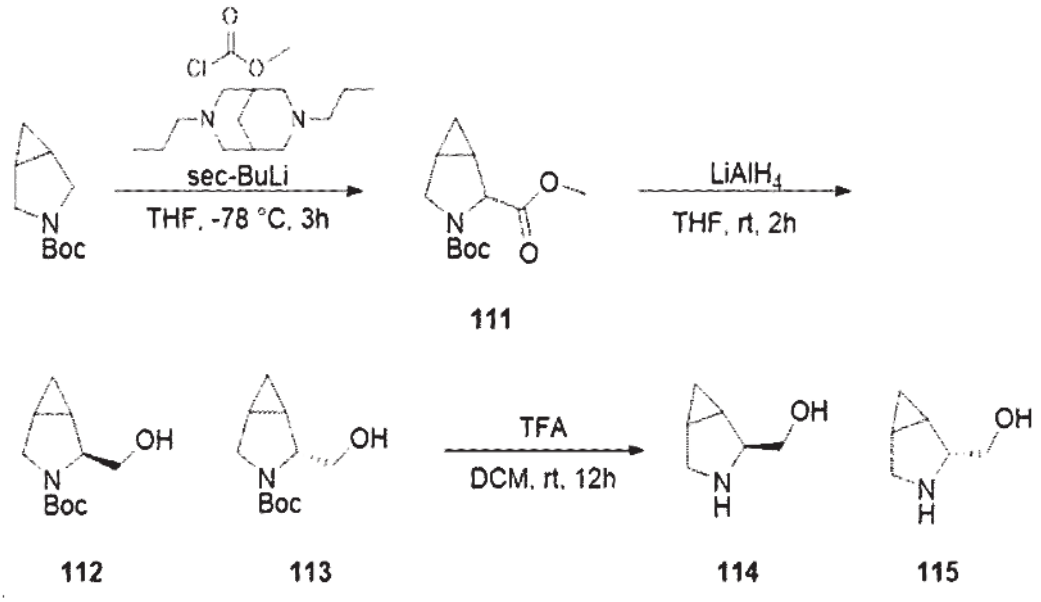
93-2 Step 2: 4-(1-isopropyl-3-azabicyclo[3.1.0]hex-3-yl)-3-(1-methyl-4-pyrazolyl)-1H-1,5,7-triazaindene (NRX02155)

The reaction was performed in the same manner as in Step 3 of Example 90 to obtain the target compound (110) (34 mg, 105 μmol, 59%, m/z = 323.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, $CDCl_3$-*d*) δ 10.92 (s, 1H), 8.27 (s, 1H), 7.49 (t, *J* = 1.0 Hz, 1H), 7.37 (t, *J* = 1.0 Hz, 1H), 7.25 (d, *J* = 2.4 Hz, 1H), 6.98 - 6.93 (m, 1H), 3.96 (t, *J* = 1.3 Hz, 3H), 3.91 - 3.84 (m, 1H), 3.74 (d, *J* = 10.8 Hz, 1H), 3.33 (dd, *J* = 11.1, 3.9 Hz, 1H), 3.13 (d, *J* = 10.8 Hz, 1H), 1.55 - 1.42 (m, 1H), 1.26 - 1.16 (m, 1H), 0.88 (dt, *J* = 6.9, 1.3 Hz, 3H), 0.78 (dt, *J* = 6.9, 1.3 Hz, 3H), 0.49 (dd, *J* = 8.0, 4.9 Hz, 1H), 0.20 - 0.13 (m, 1H).

[Preparation Example 23]

Preparation of ((2*S*)-3-azabicyclo[3.1.0]hexan-2-yl)methanol (115) 와 ((2*R*)-3-azabicyclo[3.1.0]hexan-2-yl)methanol (116)



23-1 Step 1: 3-(*tert*-butyl) 2-methyl 3-azabicyclo[3.1.0]hexane-2,3-dicarboxylate (111)

tert-Butyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (4300 mg, 23.46 mmol) and 3,7-dipropyl-3,7-diazabicyclo[3.3.1]nonane (6416 mg, 30.49 mmol) were dissolved in anhydrous tetrahydrofuran (40 mL), and then sec-butyllithium (27 mL) was added at -78°C under nitrogen. The reaction mixture was stirred at -78°C for 1 hour, and then methyl carbonochloridate (2660 mg, 28.15 mmol) dissolved in anhydrous tetrahydrofuran (30 mL) was added. The reaction mixture was stirred at -78°C for 3 hours. After the reaction was quenched with ammonium chloride (150 mL), extraction was performed with ethyl acetate (250 mL x 3). The organic layer was washed with brine, and then the remaining water was removed using sodium sulfate, followed by concentration under reduced pressure. The reaction mixture concentrated under reduced pressure was separated using column chromatography (SiO_2, hexane : ethyl acetate = 10 : 1 to 1 : 1) to obtain the target compound (111) (1.60 g, 28.2%, m/z = 242.2 $[M^+H]^+$).

23-2 Step 2: *tert*-butyl (2*S*)-2-(hydroxymethyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (112) and *tert*-butyl (2*R*)-2-(hydroxymethyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (113)

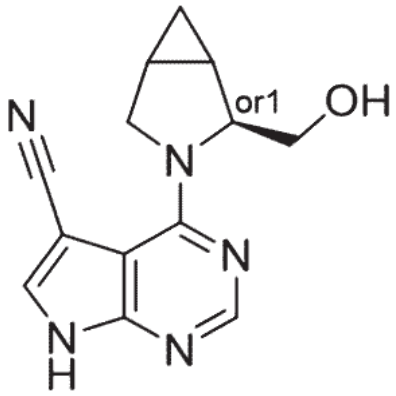
The compound (111) from Preparation Example 23 (1.00 g, 4.14 mmol) was dissolved in tetrahydrofuran (8 mL), and then lithium aluminum hydride (173 mg, 4.56 mmol) was added at 0°C. The reaction mixture was stirred at room temperature for 2 hours. After the reaction was quenched with ammonium chloride (150 mL), the mixture was filtered through a Celite Pad. The filtrate was extracted with ethyl acetate (250 mL x 3). The organic layer was washed with brine, and then the remaining water was removed using sodium sulfate, followed by concentration under reduced pressure. The reaction mixture concentrated under reduced pressure was separated using column chromatography (SiO_2, hexane : ethyl acetate = 10 : 1 to 1 : 1) to obtain the desired target compounds (112: 435 mg, 49.2%, m/z = 158.2 $[M^+H]^+$, 113: 87 mg, 9.85%, m/z = 158.2 $[M^+H]^+$), respectively.

23-3 Step 3: ((2*S*)-3-azabicyclo[3.1.0]hexan-2-yl)methanol (114) and ((2*R*)-3-azabicyclo[3.1.0]hexan-2-yl)methanol (115)

The compound (112 or 113) from Preparation Example 23 (50 mg, 0.23 mmol) was dissolved in dichloromethane (2 mL), and then trifluoroacetic acid (0.2 mL) was added. The reaction mixture was stirred at room temperature for 12 hours. Upon completion of the reaction, the reaction mixture was concentrated under reduced pressure to obtain the desired target compound (114 or 115), which was used in the next reaction without purification (50 mg, crude, m/z = 114.1 $[M^+H]^+$).

[Example 94]

Preparation of 4-{(2S)-2-(hydroxymethyl)-3-azabicyclo[3.1.0]hex-3-yl}-1H-1,5,7-triazaindene-3-carbonitrile (NRX02141)



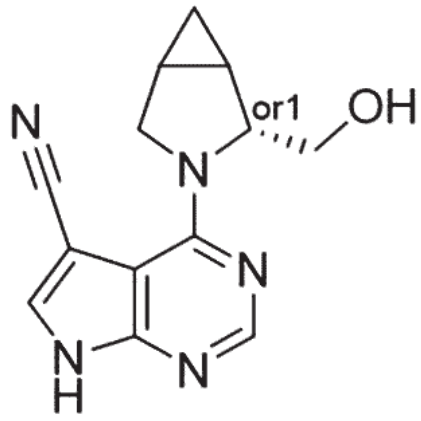
The compound (114) from Preparation Example 23 (50 mg, 0.23 mmol) was dissolved in ethanol (3 mL). Triethylamine (64 mg, 0.69 mmol) and 4-chloro-1H-1,5,7-triazaindene-3-carbonitrile (38 mg, 0.21 mmol) were added thereto. The reaction mixture was stirred at 100°C for 12 hours. After the reaction mixture was concentrated under reduced pressure, water was added, and extraction was performed with ethyl acetate. The organic layer was washed with brine, and then the remaining water was removed using sodium sulfate, followed by concentration. The concentrate was purified via prep-HPLC (acetonitrile/water/10 mM ammonium carbonate) to obtain the desired target compound (22.78 mg, 38.8%, m/z = 256.2 $[M^+H]^+$).

^{1}H-NMR (400 MHz, DMSO-d_6) : δ 12.88 (s, 1H), 8.30 (s, 1H), 8.29 (s, 1H), 5.03 (s, 1H), 4.52 - 4.46 (m, 1H), 4.32 (d, J = 9.4 Hz, 1H), 4.04 (dd, J = 9.8, 4.2 Hz, 1H), 3.76 (dd, J = 9.4, 5.2 Hz, 1H), 3.24 (dd, J = 9.8, 8.2 Hz, 1H), 1.94 (m, 1H), 1.90 - 1.82 (m, 1H), 0.75 (m, 1H), 0.61 (m, 1H).

[Example 95]

Preparation of 4-{(2R)-2-(hydroxymethyl)-3-azabicyclo[3.1.0]hex-3-yl}-1H-1,5,7-

triazaindene-3-carbonitrile (NRX02142)

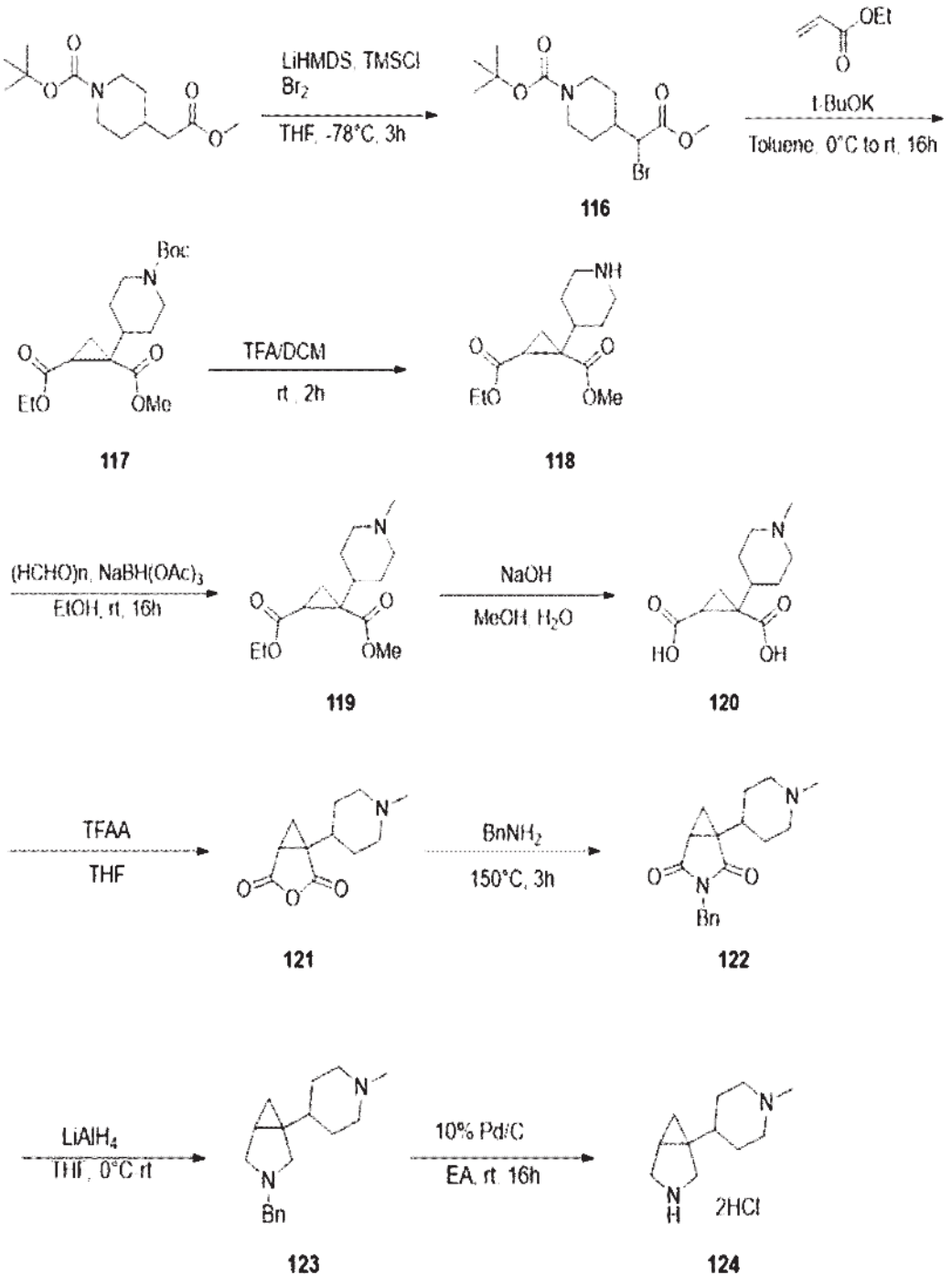


The compound (115) from Preparation Example 23 (50 mg, 0.23 mmol) was dissolved in ethanol (3 mL). Triethylamine (64 mg, 0.69 mmol) and 4-chloro-1H-1,5,7-triazaindene-3-carbonitrile (38 mg, 0.21 mmol) were added thereto. The reaction mixture was stirred at 100°C for 12 hours. After the reaction mixture was concentrated under reduced pressure, water was added, and extraction was performed with ethyl acetate. The organic layer was washed with brine, and then the remaining water was removed using sodium sulfate, followed by concentration. The concentrated reaction mixture was purified via prep-HPLC (acetonitrile/water/10 mM ammonium carbonate) to obtain the desired target compound (17.04 mg, 31.8%, m/z = 256.2 $[M^+H]^+$).

^{1}H-NMR (400 MHz, DMSO-d_6) : δ 12.77 (s, 1H), 8.25 (s, 1H), 8.18 (s, 1H), 4.89 - 4.78 (m, 2H), 4.03 (dd, *J* = 10.0, 4.0 Hz, 1H), 3.91 (d, *J* = 10.0 Hz, 1H), 3.66 - 3.57 (m, 1H), 3.57 - 3.47 (m, 1H), 1.73 (m, 1H), 1.67 (m, 1H), 0.70 (m, 1H), 0.05 - 0.01 (m, 1H).

[Preparation Example 24]

Preparation of 4-(3-azabicyclo[3.1.0]hex-1-yl)-1-methylpiperidine (124)



24-1 Step 1: tert-butyl 4-(1-bromo-2-methoxy-2-oxoethyl)piperidine-1-carboxylate (116)

tert-Butyl 4-(2-methoxy-2-oxoethyl)piperidine-1-carboxylate (10.0 g, 38.86 mmol)

was introduced into anhydrous tetrahydrofuran (50 mL) and cooled to -78°C, and then LiHMDS (1 M, 70 mL) was added thereto, followed by stirring at the same temperature for 1 hour. TMSCl (7.6 g, 69.95 mmol) was slowly added to the reaction mixture, and the mixture was further stirred at -40°C for 1 hour. Additionally, bromine (7.4 g, 46.63 mmol) was added thereto, and the mixture was stirred for an additional 20 minutes. The reaction mixture was poured into saturated aqueous sodium bicarbonate solution (300 mL) and extracted with ethyl acetate (200 mL x 3). The organic layer was washed with brine, and the remaining water was removed using sodium sulfate, followed by concentration. The concentrated reaction mixture was separated using column chromatography (SiO_2, hexane : ethyl acetate = 10 : 1 to 1 : 1) to obtain the compound (116) of Preparation Example 24 (10.2 g, 78%, m/z = 280.1/282.1 [M-t-Bu-1/M-t-Bu^+1]$^+$).

24-2 Step 2: 2-ethyl 1-methyl 1-(1-(tert-butoxycarbonyl)piperidin-4-yl)cyclopropane-1,2-dicarboxylate (117)

The compound (116) obtained in Preparation Example 24 (10.2 g, 30.34 mmol) was dissolved in toluene (150 mL), and then ethyl acrylate (2.7 g, 27.30 mmol) was added thereto, followed by cooling to -20°C. tert-Butoxide (3.7 g, 33.37 mmol) was slowly added thereto, and the mixture was stirred at room temperature for 2 hours. After the reaction was quenched with ammonium chloride (500 mL), extraction was performed with ethyl acetate (200 mL x 3). The organic layer was washed with brine, and then the remaining water was removed using sodium sulfate, followed by concentration under reduced pressure. The mixed solution was separated using column chromatography (SiO_2, hexane : ethyl acetate = 10 : 1 to 1 : 1) to obtain the desired compound (117) (5.3 g, 49.15%, m/z = 300.2/301.2 [M-t-Bu/M-t-Bu^+H]$^+$).

24-3 Step 3: 2-ethyl 1-methyl 1-(piperidin-4-yl)cyclopropane-1,2-dicarboxylate (118)

The compound (117) from Preparation Example 24 (5.3 g, 1.51 mmol) was dissolved in dichloromethane (10 mL), and then trifluoroacetic acid (5 mL) was added thereto. The reaction mixture was stirred at room temperature for 2 hours. After the reaction, the mixture was concentrated under reduced pressure to obtain the desired compound (118) (6 g, crude, m/z = 256.2 $[M^+H]^+$).

24-4 Step 4: 2-ethyl 1-methyl 1-(1-methylpiperidin-4-yl)cyclopropane-1,2-dicarboxylate (119)

The compound (118) from Preparation Example 24 (6 g, 23.05 mmol) was dissolved in methanol (20 mL), and then $(CH_2O)_n$ (7.1 g, 235.01 mmol) was added thereto. After the reaction mixture was stirred for 0.5 hours, sodium cyanoborohydride (4.4 g, 70.50 mmol) was added thereto. The reaction mixture was stirred at 50°C for 4 hours. The reaction mixture was filtered and then concentrated under reduced pressure to obtain the desired compound (119) (6 g, crude, m/z = 270.3 $[M^+H]^+$).

24-5 Step 5: 1-(1-methylpiperidin-4-yl)cyclopropane-1,2-dicarboxylic acid (120)

The compound (119) from Preparation Example 24 (6 g, 22.28 mmol) was dissolved in methanol (30 mL), and then sodium hydroxide (10.7 g, 267.32 mmol, in 8 mL H_2O) was added thereto, followed by stirring at 50°C for 16 hours. After the reaction solvent was concentrated under reduced pressure, hydrochloric acid (4 M, 67 mL) was added thereto to obtain the desired compound (120) (15 g, crude, m/z = 228.2 $[M^+H]^+$).

24-6 Step 6: 1-(1-methylpiperidin-4-yl)-3-oxabicyclo[3.1.0]hexane-2,4-dione (121)

The compound (120) from Preparation Example 24 (15 g, crude) was dissolved in tetrahydrofuran (80 mL), and then trifluoroacetic anhydride (20 mL) was added thereto, followed by stirring at room temperature for 16 hours. After the reaction solvent was concentrated under reduced pressure, the desired compound (121) was obtained (18 g, crude).

24-7 Step 7: 3-benzyl-1-(1-methylpiperidin-4-yl)-3-azabicyclo[3.1.0]hexane-2,4-dione (121)

The compound (122) from Preparation Example 24 (18 g, 86.02 mmol) and benzylamine (18.4 g, 172.04 mmol) were stirred at 150°C for 3 hours. Water (500 mL) was added to the reaction mixture, and extraction was performed with ethyl acetate (200 mL x 3). The organic layer was washed with brine, and then the remaining water was removed using sodium sulfate, followed by concentration. The concentrated reaction mixture was purified via column chromatography (SiO_2, dichloromethane : methanol = 10 : 1 (10% ammonium hydroxide)) to obtain the desired compound (122) (2 g, 42.2% over 5 steps, m/z = 299.3 $[M^+H]^+$).

24-8 Step 8: 3-benzyl-1-(1-methylpiperidin-4-yl)-3-azabicyclo[3.1.0]hexane (123)

The compound (122) from Preparation Example 24 (2 g, 6.70 mmol) was dissolved in tetrahydrofuran (30 mL), and then LAH (1.5 g, 40.22 mmol) was slowly added thereto, followed by stirring at 50°C for 16 hours. Sodium sulfate decahydrate (2 g) and ethyl acetate (200 mL) were added to the reaction mixture, and the mixture was filtered. The filtrate was concentrated under reduced pressure and then separated via prep-HPLC (acetonitrile/water/10 mM ammonium carbonate) to obtain the desired compound (123) (700 mg, 38.62%, m/z =

271.3 $[M^+H]^+$).

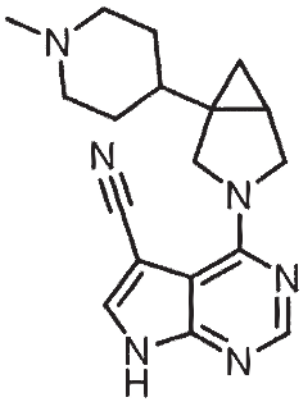
24-9 Step 9: 1-(1-methylpiperidin-4-yl)-3-azabicyclo[3.1.0]hexane dihydrochloride (123)

The compound (123) from Preparation Example 24 (700 mg, 0.11 mmol) was dissolved in ethyl acetate (25 mL), and then Pd/C (850 mg, 10% Pd/C) was added thereto, followed by stirring at room temperature under hydrogen for 16 hours. The reaction mixture was filtered through a celite pad, and the filtrate was concentrated under reduced pressure to obtain the desired compound (124) (562.98 mg, 85.89%, m/z 181.3 $[M^+H]^+$).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.62 (s, 2H), 3.26 - 3.14 (m, 6H), 3.09 (d, J = 11.2 Hz, 1H), 2.72 - 2.54 (m, 5H), 1.79 - 1.35 (m, 6H), 0.77 (t, J = 5.0 Hz, 1H), 0.71 - 0.61 (m, 1H).

[Example 96]

Preparation of 4-{1-(1-methyl-4-piperidyl)-3-azabicyclo[3.1.0]hex-3-yl}-1H-1,5,7-triazaindene-3-carbonitrile (NRX02180)



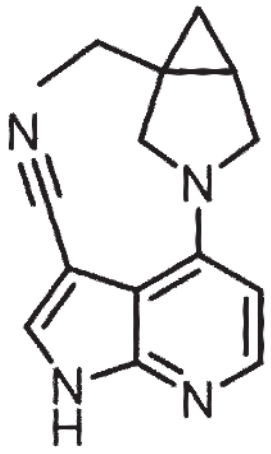
The compound (124) from Preparation Example 24 (72.8 mg, 0.336 mmol) was dissolved in ethanol (1.5 mL). Triethylamine (142 mg, 1.40 mmol) and 4-chloro-1H-1,5,7-triazaindene-3-carbonitrile (50 mg, 0.280 mmol) were added thereto. The reaction mixture was

stirred at 80°C for 12 hours. After the reaction mixture was concentrated under reduced pressure, water was added, and extraction was performed with ethyl acetate. The organic layer was washed with brine, and then the remaining water was removed using sodium sulfate, followed by concentration. The concentrated reaction mixture was purified via column chromatography (SiO_2, dichloromethane : methanol = 10 : 1) to obtain the target compound of Example 96 (40 mg, 0.124 mmol, 44%, m/z = 323.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, $CDCl_3$-*d*) δ 8.43 (s, 1H), 8.26 (d, *J* = 1.2 Hz, 1H), 7.71 (d, *J* = 1.0 Hz, 1H), 4.24 (t, *J* = 10.3 Hz, 2H), 3.88 (dd, *J* = 11.0, 4.3 Hz, 1H), 3.76 (d, *J* = 10.8 Hz, 1H), 3.42 (d, *J* = 11.8 Hz, 3H), 2.61 (t, *J* = 1.2 Hz, 3H), 2.56 - 2.46 (m, 3H), 2.08 - 1.93 (m, 1H), 1.88 (d, *J* = 13.8 Hz, 1H), 1.82 - 1.73 (m, 2H), 1.62 (dq, *J* = 8.4, 4.7 Hz, 3H), 0.87 (dd, *J* = 8.8, 4.9 Hz, 1H), 0.36 (t, *J* = 4.8 Hz, 1H).

[Example 97]

Preparation of 4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,7-diazaindene-3-carbonitrile (NRX02147)



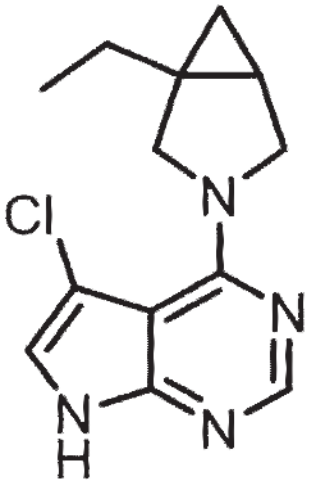
4-Chloro-1H-1,7-triazaindene-3-carbonitrile (100 mg, 0.563 mmol), 1-ethyl-3-azabicyclo[3.1.0]hexane (166 mg, 1.13 mmol), and triethylamine (235 μl, 1.69 mmol) were introduced into N-methyl-2-pyrrolidone (2.8 ml) and stirred at 160°C for 18 hours. After the

reaction solution was concentrated under reduced pressure, the reaction mixture was separated using column chromatography (SiO_2, dichloromethane : methanol = 10 : 1) to obtain the target compound of Example 97 (20 mg, 0.079 mmol, 14%, m/z = 253.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.48 (s, 1H), 8.22 (s, 1H), 7.94 (d, *J* = 5.6 Hz, 1H), 6.35 (d, *J* = 5.8 Hz, 1H), 3.99 (d, *J* = 9.5 Hz, 1H), 3.84 (d, *J* = 9.7 Hz, 1H), 3.59 (dd, *J* = 9.7, 4.2 Hz, 1H), 3.48 (dd, *J* = 9.4, 1.0 Hz, 1H), 1.79 (dq, *J* = 14.5, 7.3 Hz, 1H), 1.53 (dt, *J* = 8.0, 4.0 Hz, 1H), 1.44 (dt, *J* = 14.8, 7.4 Hz, 1H), 1.00 (t, *J* = 7.4 Hz, 3H), 0.69 (dd, *J* = 7.9, 4.5 Hz, 1H), 0.44 (t, *J* = 4.3 Hz, 1H).

[Example 98]

Preparation of 3-chloro-4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazaindene (NRX02167)



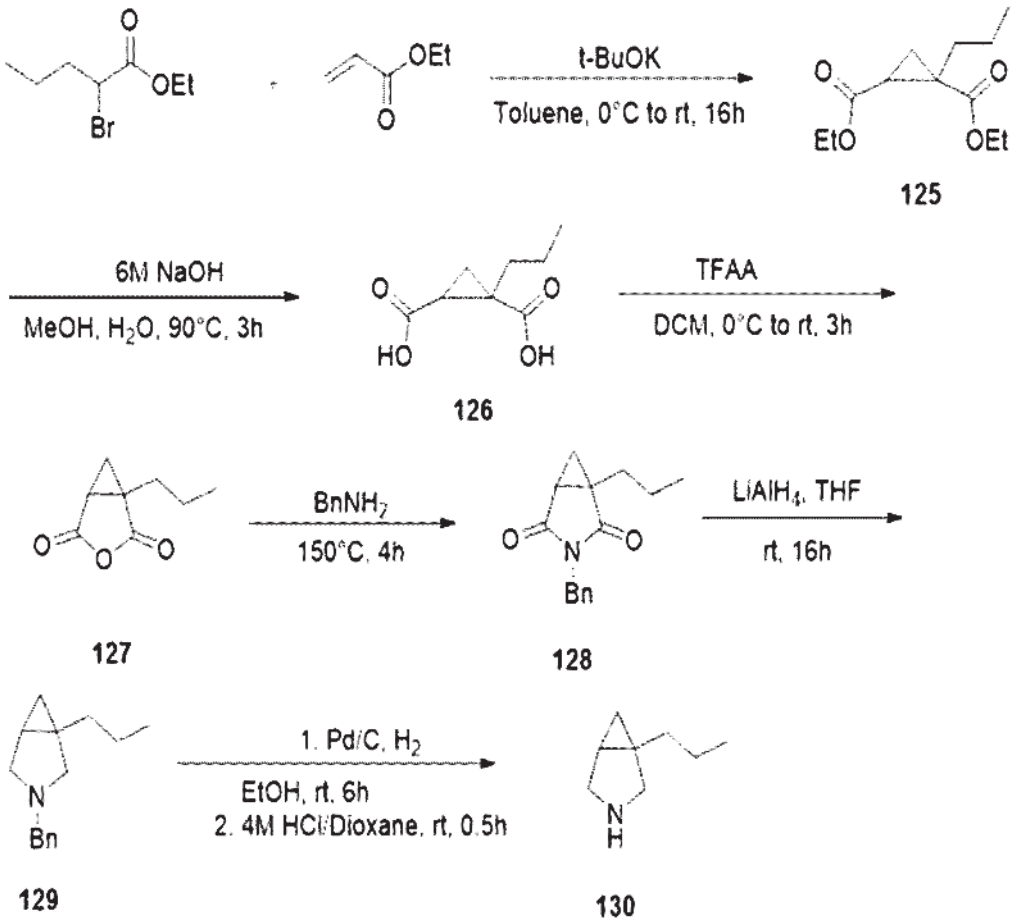
3,4-Dichloro-1H-1,5,7-triazaindene (50 mg, 0.266 mmol), 1-ethyl-3-azabicyclo[3.1.0]hexane (43 mg, 0.293 mmol), and triethylamine (135 mg, 1.33 mmol) were dissolved in ethanol (1.3 mL). The reaction mixture was stirred at 80°C for 18 hours. After the reaction solvent was concentrated under reduced pressure, the mixture was separated using column chromatography (SiO_2, dichloromethane : methanol = 10 : 1) to obtain the target

compound of Example 98 (16 mg, 0.060 mmol, 22%, m/z = 263.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, $CDCl_3$-*d*) δ 10.47 (s, 1H), 8.23 (s, 1H), 7.07 (s, 1H), 4.34 (d, *J* = 11.1 Hz, 1H), 4.27 (d, *J* = 11.1 Hz, 1H), 3.86 (dd, *J* = 11.1, 4.3 Hz, 1H), 3.64 (dt, *J* = 11.0, 0.8 Hz, 1H), 1.79 (dq, *J* = 14.6, 7.4 Hz, 1H), 1.50 (dt, *J* = 14.1, 7.4 Hz, 1H), 1.42 (dt, *J* = 8.1, 4.1 Hz, 1H), 1.02 (t, *J* = 7.5 Hz, 3H), 0.65 (ddt, *J* = 7.0, 4.9, 1.2 Hz, 1H), 0.29 (t, *J* = 4.4 Hz, 1H).

[Preparation Example 25]

Preparation of 1-propyl-3-azabicyclo[3.1.0]hexane (130)



25-1 Step 1: diethyl 1-propylcyclopropane-1,2-dicarboxylate (125)

Ethyl 2-bromopentanoate (5 g, 23.91 mmol) and ethyl acrylate (2.42 g, 23.91 mmol)

were dissolved in toluene (30 mL), and then tert-butoxide (2951 mg, 26.30 mmol) was added thereto at 0°C under nitrogen. The reaction mixture was stirred at room temperature for 16 hours. After the reaction was quenched by adding ammonium chloride (300 mL) thereto, extraction was performed with ethyl acetate (150 mL x 3). The organic layer was washed with brine, and then the remaining water was removed using sodium sulfate, followed by concentration to obtain the target compound (5.4 g, crude, m/z = 229.3 $[M^+H]^+$).

25-2 Step 2: 1-propylcyclopropane-1,2-dicarboxylic acid (126)

The compound (125) from Preparation Example 25 (5.4 g, 23.65 mmol) was dissolved in methanol (25 mL), and then 6 M sodium hydroxide (25 mL) was added thereto, followed by stirring at 90°C for 3 hours. After the reaction solvent was concentrated under reduced pressure, water (300 mL) was added, and the mixture was washed with ethyl acetate (100 mL). The aqueous layer was adjusted to pH 1 with 3 M hydrochloric acid and extracted with ethyl acetate (200 mL x 3). The organic layer was washed with brine, and then the remaining water was removed using sodium sulfate, followed by concentration to obtain the target compound (4.5 g, crude, m/z = 173.2 $[M^+H]^+$).

25-3 Step 3: 1-propyl-3-oxabicyclo[3.1.0]hexane-2,4-dione (127)

The compound (126) obtained in Preparation Example 25 (4.5 g, 23.65 mmol) was dissolved in methanol (30 mL), and then trifluoroacetic anhydride (7460 mg, 35.47 mmol) was added dropwise thereto at 0°C. The reaction mixture was stirred at room temperature for 3 hours, and then the reaction solvent was concentrated under reduced pressure to obtain the desired target compound (4.5 g, crude, m/z = 169.0 $[M^+MeOH\text{-}OH]^+$).

25-4 Step 4: 3-benzyl-1-propyl-3-azabicyclo[3.1.0]hexane-2,4-dione (128)

The compound (127) obtained in Preparation Example 25 (4.5 g, 23.65 mmol) and benzylamine (2799 mg, 23.65 mmol) were stirred at 150°C for 4 hours. The reaction mixture was separated using column chromatography (SiO_2, hexane : ethyl acetate = 10 : 1) to obtain the target compound (2.67 g, 45.8% yield in 4 steps, m/z 244.1 $[M^+H]^+$).

25-5 Step 5: 3-benzyl-1-propyl-3-azabicyclo[3.1.0]hexane (129)

The compound (128) obtained in Preparation Example 25 (2.67 g, 10.97 mmol) was dissolved in tetrahydrofuran (24 mL), and then LAH (834 mg, 21.94 mmol) was slowly added thereto at 0°C under nitrogen. The reaction mixture was stirred at room temperature for 16 hours. After the reaction was quenched by adding ammonium chloride (300 mL) thereto, extraction was performed with ethyl acetate (150 mL x 3). The organic layer was washed with brine, and then the remaining water was removed using sodium sulfate, followed by concentration. After concentration, the mixture was separated using column chromatography (SiO_2, hexane : ethyl acetate = 10 : 1) to obtain the target compound (1.14 g, 48.3%, m/z = 216.1 $[M^+H]^+$).

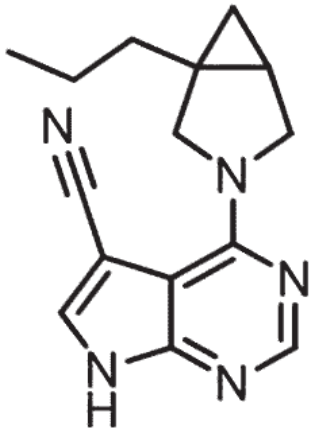
25-6 Step 6: 1-propyl-3-azabicyclo[3.1.0]hexane (130)

The compound (129) obtained in Preparation Example 25 (1.14 g, 5.29 mmol) was dissolved in ethanol (8 mL), and then 10% Pd/C (50% wt. H_2O) (300 mg) was added thereto, followed by stirring at room temperature under hydrogen for 6 hours. 4 N Hydrochloric acid (1,4-dioxane, 5 mL) was added thereto, and the mixture was further stirred for 0.5 hours. Pd/C was filtered through a Celite pad, and the filtrate was concentrated under reduced pressure to obtain the target compound (720.08 mg, crude, 1 eq. HCl salt, m/z = 126.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, $CDCl_3$-*d*) : δ 9.95 (s, 1H), 9.45 (s, 1H), 3.42 (m, 3H), 3.21 (dd, *J* = 16.2, 8.6 Hz, 1H), 1.73 - 1.60 (m, 1H), 1.45 - 1.27 (m, 4H), 1.04 (dd, *J* = 6.2, 4.6 Hz, 1H), 0.96 - 0.88 (m, 3H), 0.72 (t, *J* = 7.4 Hz, 1H).

[Example 99]

Preparation of 4-(1-propyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazaindene-3-carbonitrile (NRX02157)

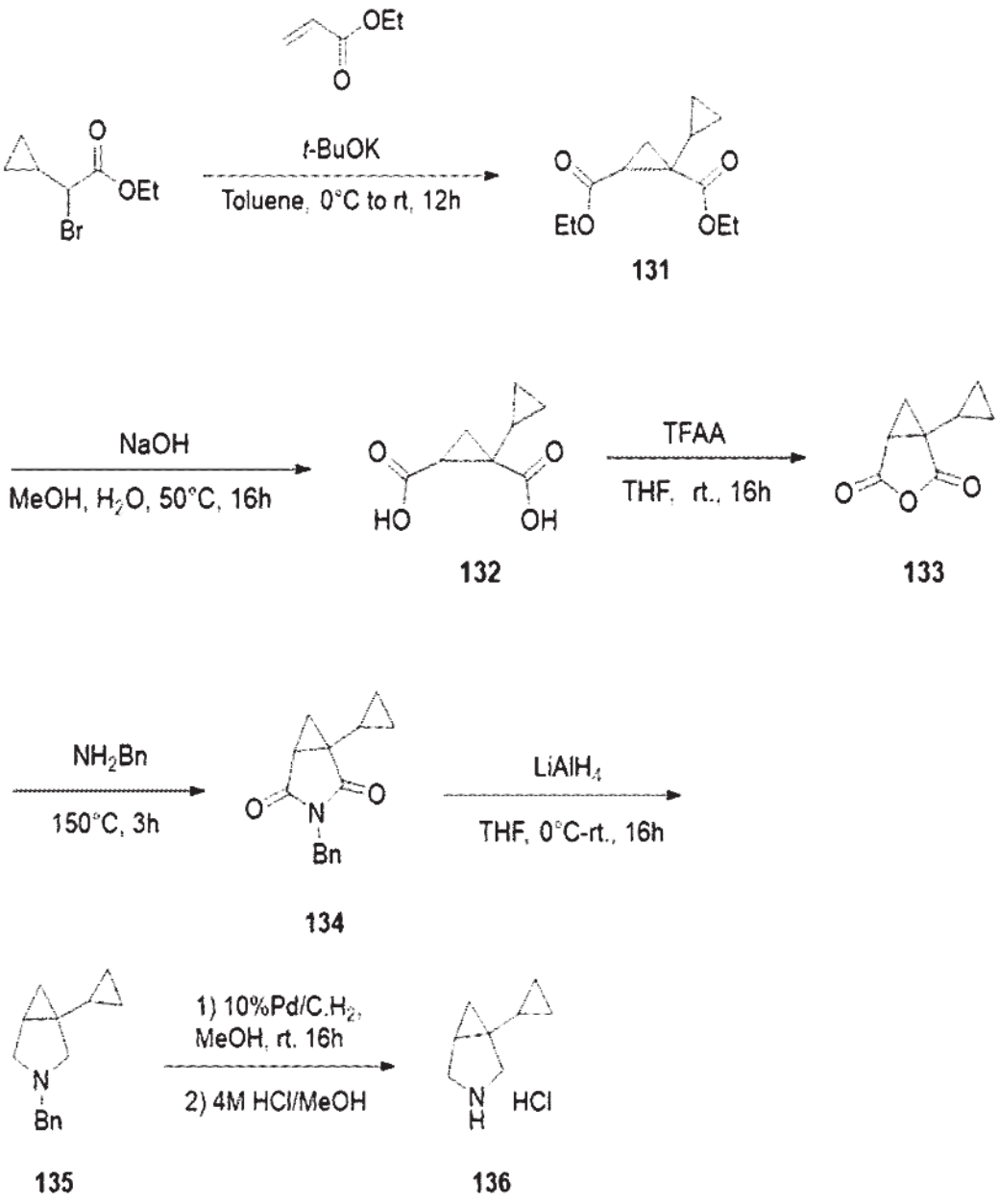


4-Chloro-1H-1,5,7-triazaindene-3-carbonitrile (50 mg, 0.280 mmol), the compound (130) from Preparation Example 25 (54.2 mg, 0.336 mmol), and triethylamine (195 μl, 1.40 mmol) were added to ethanol (1.5 ml) and stirred at 80°C for 2 hours. After the reaction solution was concentrated under reduced pressure, the reaction mixture was separated using column chromatography (SiO_2, dichloromethane : methanol = 10 : 1) to obtain the target compound of Example 99 (28 mg, 0.105 mmol, 37%, m/z = 268.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 1H), 8.19 (s, 1H), 4.17 (d, *J* = 10.4 Hz, 1H), 4.09 (d, *J* = 11.0 Hz, 1H), 3.77 (dd, *J* = 10.9, 4.4 Hz, 1H), 3.64 (d, *J* = 10.4 Hz, 1H), 1.84 - 1.73 (m, 1H), 1.54 - 1.39 (m, 3H), 1.34 (ddd, *J* = 13.2, 9.2, 6.5 Hz, 1H), 0.94 (t, *J* = 7.3 Hz, 3H), 0.71 (dd, *J* = 8.0, 4.6 Hz, 1H), 0.30 (t, *J* = 4.3 Hz, 1H).

[Preparation Example 26]

Preparation of 1-cyclopropyl-3-azabicyclo[3.1.0]hexane hydrochloride (136)



26-1 Step 1: diethyl [1,1'-bi(cyclopropane)]-1,2-dicarboxylate (131)

Ethyl 2-bromo-2-cyclopropylacetate (10.0 g, 48.29 mmol) was dissolved in toluene (100 mL), and then ethyl acrylate (4.8 g, 48.29 mmol) was added thereto. The reaction mixture

was stirred at 0°C for 5 minutes, and then tert-butoxide (6.0 g, 53.12 mmol) was slowly added thereto, followed by stirring at room temperature for 12 hours. The reaction was quenched by adding saturated aqueous ammonium chloride solution (200 mL), and then extraction was performed with ethyl acetate (120 mL x 3). The organic layer was washed with brine, and the remaining water was removed using sodium sulfate, followed by concentration under reduced pressure to obtain the desired compound (9.5 g, crude, m/z = 227.3 $[M^+H]^+$).

26-2 Step 2: [1,1'-bi(cyclopropane)]-1,2-dicarboxylic acid (132)

The compound (131) from Preparation Example 26 (9.5 g, 41.99 mmol) was dissolved in methanol (50 mL), and then sodium hydroxide (10.1 g in 50 mL water, 251.91 mmol) was added thereto. The reaction mixture was stirred at 50°C for 16 hours. After the reaction mixture was concentrated under reduced pressure, water (100 mL) was added, and 6 N hydrochloric acid was added thereto to adjust the pH < 1. The reaction mixture was extracted with ethyl acetate (100 mL x 3). The organic layer was washed with brine, and the remaining water was removed using sodium sulfate, followed by concentration under reduced pressure to obtain the desired compound (132) (9.3 g, crude, m/z = 171.2 $[M^+H]^+$).

26-3 Step 3: 1-cyclopropyl-3-oxabicyclo[3.1.0]hexane-2,4-dione (133)

The compound (132) from Preparation Example 26 (9.3 g, 54.65 mmol) was dissolved in tetrahydrofuran (15 mL), and then trifluoroacetic anhydride (5 mL) was added thereto at 0°C, followed by stirring at room temperature for 16 hours. Upon completion of the reaction, the reaction mixture was concentrated under reduced pressure to obtain the desired compound (9.1 g, crude, m/z = 153.1 $[M^+H]^+$).

26-4 Step 4: 3-benzyl-1-cyclopropyl-3-azabicyclo[3.1.0]hexane-2,4-dione (134)

The compound (133) from Preparation Example 26 (9.1 g, 59.81 mmol) and benzylamine (9.6 g, 89.71 mmol) were added and stirred at 150°C for 3 hours. After the reaction mixture was concentrated under reduced pressure, the mixture was separated using column chromatography (SiO_2, hexane : ethyl acetate = 10 : 1) to obtain the desired compound (5.3 g, 45.6% over 4 steps, m/z = 242.2 $[M^+H]^+$).

26-5 Step 5: 3-benzyl-1-cyclopropyl-3-azabicyclo[3.1.0]hexane (135)

The compound (134) from Preparation Example 26 (5.3 g, 21.97 mmol) was dissolved in tetrahydrofuran (50 mL), and then LAH (1.7 g, 43.93 mmol) was slowly added thereto at 0°C under nitrogen. The reaction mixture was stirred at room temperature for 16 hours. After the reaction was quenched by adding ammonium chloride (200 mL) thereto, extraction was performed with ethyl acetate (110 mL x 3). The organic layer was washed with brine, and then the remaining water was removed using sodium sulfate, followed by concentration. After concentration, the mixture was separated using column chromatography (SiO_2, hexane : ethyl acetate = 10 : 1) to obtain the target compound (2.2 g, 46.95%, m/z = 214.1 $[M^+H]^+$).

26-6 Step 6: 1-cyclopropyl-3-azabicyclo[3.1.0]hexane hydrochloride (136)

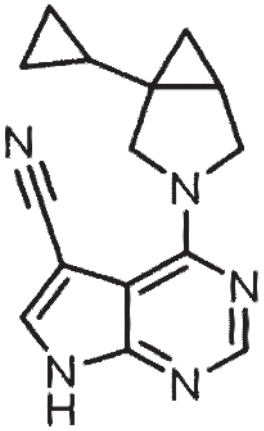
The compound (135) from Preparation Example 26 (1.2 g, 5.63 mmol) was dissolved in methanol (10 mL), and then 10% Pd/C (300 mg) was added thereto, followed by stirring at room temperature under hydrogen for 16 hours. 4 N Hydrochloric acid (in MeOH, 6 mL) was added to the reaction mixture, and the mixture was concentrated under reduced pressure to obtain the desired compound (818.56 mg, 91.1%, m/z = 124.2 $[M^+H]^+$).

^{1}H-NMR (400 MHz, $CDCl_3$-*d*) δ 9.64 (s, 1H), 9.18 (s, 1H), 3.61 - 3.24 (m, 4H), 1.37

- 1.23 (m, 1H), 1.12 (s, 1H), 0.95 (s, 1H), 0.67 (s, 1H), 0.49 (d, *J* = 7.2 Hz, 2H), 0.08 (d, *J* = 13.8 Hz, 2H).

[Example 100]

Preparation of 4-(1-cyclopropyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazaindene-3-carbonitrile (NRX02160)

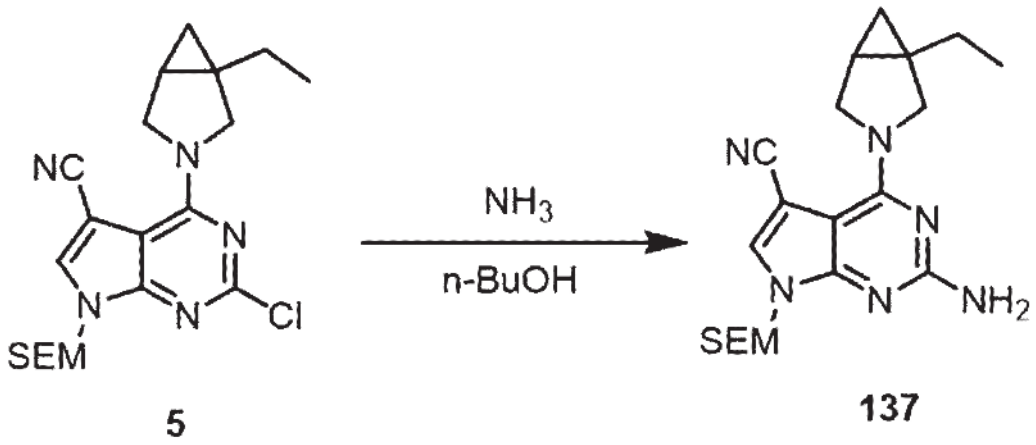


4-Chloro-1H-1,5,7-triazaindene-3-carbonitrile (50 mg, 0.280 mmol), the target compound (136) from Preparation Example 26 (53.6 mg, 0.336 mmol), and triethylamine (195 μl, 1.40 mmol) were added to ethanol (1.5 ml) and stirred at 80°C for 2 hours. After the reaction solution was concentrated under reduced pressure, the reaction mixture was separated using column chromatography (SiO_2, dichloromethane : methanol = 10 : 1) to obtain the target compound of Example 100 (25.7 mg, 96.9 μmol, 35%, m/z = 266.1 $[M^+H]^+$).

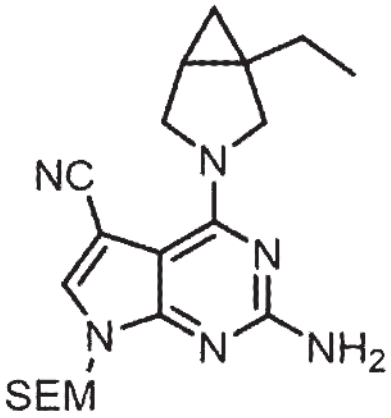
^{1}H-NMR (400 MHz, $CDCl_3$-*d*) δ 8.32 (s, 1H), 7.74 (s, 1H), 4.38 (d, *J* = 10.9 Hz, 1H), 4.21 (d, *J* = 10.9 Hz, 1H), 3.92 (dd, *J* = 10.9, 4.4 Hz, 1H), 3.85 (d, *J* = 10.9 Hz, 1H), 1.42 (dt, *J* = 8.4, 4.2 Hz, 1H), 1.23 (tt, *J* = 8.2, 4.1 Hz, 2H), 0.76 - 0.68 (m, 1H), 0.56 - 0.42 (m, 2H), 0.30 (t, *J* = 4.6 Hz, 1H), 0.23 - 0.07 (m, 2H).

[Preparation Example 27]

Preparation of 2-amino-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (137)



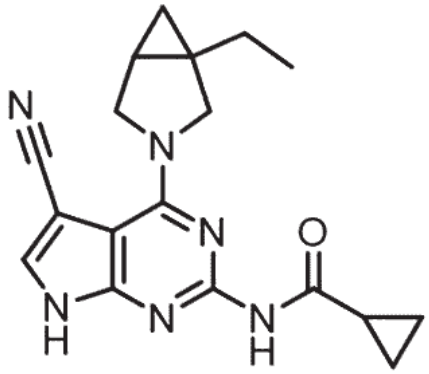
5 137



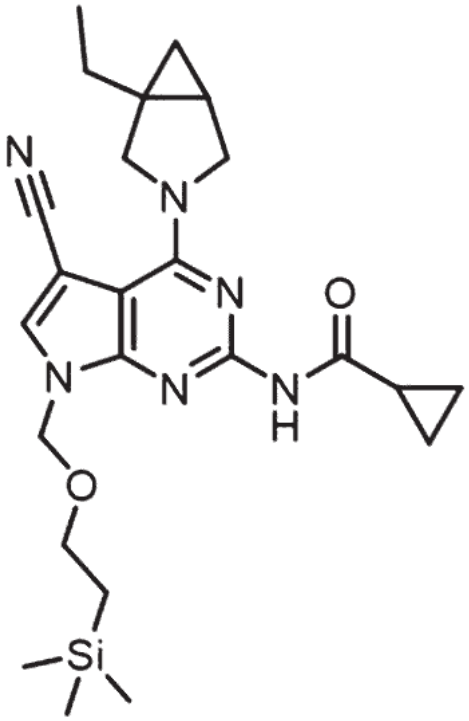
2-Chloro-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (0.311 mmol) was dissolved in *n*-butanol, and then aqueous ammonia (31.1 mmol) was added thereto. The reaction mixture was stirred in a microwave reactor at 140°C for 16 hours. After the reaction mixture was concentrated under reduced pressure, the mixture was separated via reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the target compound (137) of Preparation Example 27 (32 mg, 80.3 μmol, 26%, m/z = 399.1 $[M^+H]^+$).

[Example 101]

Preparation of N-{3-cyano-4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-6-yl}cyclo propanecarboxamide (NRX02148)



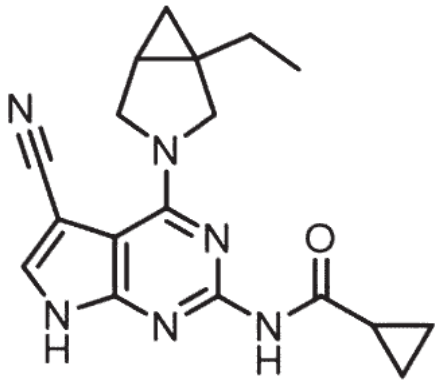
101-1 Step 1: N-(5-cyano-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-(trimethyl lsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl)cyclo propane carboxamide



The compound (137) obtained in Preparation Example 27 (32 mg, 0.080 mmol) was dissolved in pyridine (1 mL), and then cyclopropanecarbonyl chloride (42 mg, 0.401 mmol)

was added thereto. The reaction mixture was stirred at 120°C for 1 hour. After the reaction mixture was concentrated under reduced pressure, the mixture was separated using column chromatography (SiO_2, hexane : ethyl acetate = 10 : 1 to 1 : 1) to obtain the compound (17 mg, 0.036 mmol, 45%, m/z = 467.1 $[M^+H]^+$).

101-2 Step 2: N-{3-cyano-4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-6-yl}cyclopropanecarboxamide (NRX02148)



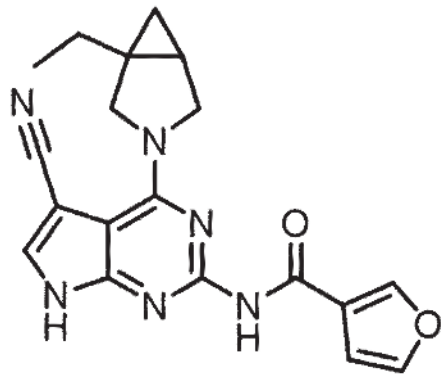
N-(5-Cyano-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl)cyclopropanecarboxamide (17 mg, 0.036 mmol) was introduced into dichloromethane containing trifluoroacetic acid (1.91 mmol). The reaction mixture was stirred at 40°C for 3 hours. After the reaction mixture was concentrated under reduced pressure, the mixture was separated via reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the target compound of Example 101 (8.2 mg, 24.4 μmol, 67%, m/z = 337.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.55 (s, 1H), 10.08 (s, 1H), 8.06 (s, 1H), 4.15 (d, J = 10.5 Hz, 1H), 4.07 (d, J = 11.0 Hz, 1H), 3.72 (dd, J = 11.0, 4.3 Hz, 1H), 3.58 (d, J = 10.5 Hz, 1H), 1.75 (dq, J = 14.5, 7.3 Hz, 1H), 1.48 (dt, J = 8.1, 4.1 Hz, 1H), 1.39 (dq, J = 14.7, 7.5 Hz, 1H), 1.19 (s, 1H), 0.95 (t, J = 7.4 Hz, 3H), 0.74 (tt, J = 7.9, 3.0 Hz, 4H), 0.66 (dd, J = 8.0,

4.6 Hz, 1H), 0.24 (t, *J* = 4.3 Hz, 1H).

[Example 102]

N-{3-cyano-4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-6-yl}-3-furamide (NRX02175)



102-1 Step 1: N-(5-cyano-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl)furan-3-carboxamide

The desired compound (43 mg, 87.3 μmol, 72%, m/z = 493.1 $[M^+H]^+$) was obtained in the same manner as in Step 1 of Example 101, except for using 3-furoyl chloride instead of cyclopropanecarbonyl chloride.

102-2 Step 2: N-{3-cyano-4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazaind en-6-yl}-3-furamide (NRX02175)

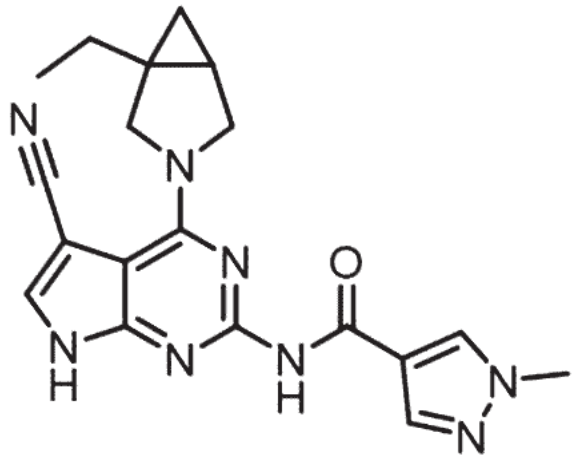
Cyano-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl)furan-3-carboxamide (43 mg, 0.087 mmol) was dissolved in tetrahydrofuran (1.0 mL), and then 1 M tetra-*n*-butylammonium fluoride (0.873 mL, 0.873 mmol) was added thereto. The reaction mixture

was stirred at 90°C for 1 hour. After the reaction mixture was concentrated under reduced pressure, the mixture was separated via reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the target compound of Example 102 (12 mg, 33.1 μmol, 38%, m/z = 363.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.08 (s, 1H), 8.44 (dd, *J* = 1.6, 0.8 Hz, 1H), 8.16 (d, *J* = 1.4 Hz, 1H), 7.77 (t, *J* = 1.7 Hz, 1H), 6.97 (dd, *J* = 1.9, 0.8 Hz, 1H), 4.19 (dd, *J* = 25.8, 10.8 Hz, 2H), 3.78 (dd, *J* = 11.0, 4.3 Hz, 1H), 3.64 (d, *J* = 10.6 Hz, 1H), 1.80 (dq, *J* = 14.7, 7.4 Hz, 1H), 1.58 - 1.38 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H), 0.72 (dd, *J* = 8.0, 4.7 Hz, 1H), 0.29 (t, *J* = 4.3 Hz, 1H).

[Example 103]

Preparation of N-{3-cyano-4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-6-yl}-1-methyl-4-pyrazolecarboxamide (NRX02177)



103-1 Step 1: N-(5-cyano-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl)-1-methyl-1H-pyrazole-4-carboxamide

The desired compound (60 mg, 118 μmol, 94%, m/z = 507.1 $[M^+H]^+$) was obtained in the same manner as in Step 1 of Example 101, except for using 1-methyl-4-pyrazolecarbonyl chloride instead of cyclopropanecarbonyl chloride.

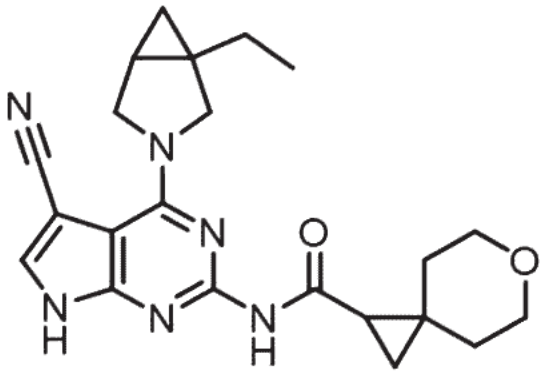
103-2 Step 2: N-{3-cyano-4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-6-yl}-1-methyl-4-pyrazolecarboxamide (NRX02177)

The desired target compound (6.3 mg, 16.7 μmol, 14%, m/z = 377.1 $[M^+H]^+$) was obtained in the same manner as in Step 2 of Example 101.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.35 (s, 1H), 8.15 (s, 1H), 8.02 (d, J = 0.7 Hz, 1H), 4.22 (d, J = 10.6 Hz, 1H), 4.16 (d, J = 11.0 Hz, 1H), 3.88 (s, 3H), 3.78 (dd, J = 11.0, 4.3 Hz, 1H), 3.64 (d, J = 10.6 Hz, 1H), 1.80 (dq, J = 14.5, 7.3 Hz, 1H), 1.58 - 1.38 (m, 2H), 1.00 (t, J = 7.4 Hz, 3H), 0.71 (dd, J = 8.0, 4.7 Hz, 1H), 0.29 (t, J = 4.3 Hz, 1H).

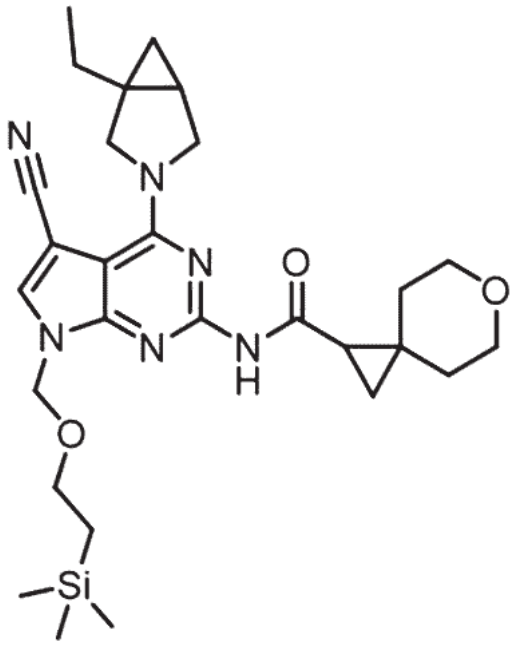
[Example 104]

Preparation of N-{3-cyano-4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-6-yl}-6-oxa-1-spiro[2.5]octanecarboxamide (NRX02153)



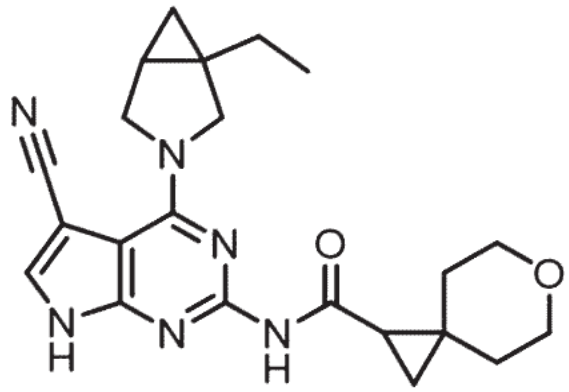
104-1 Step 1: N-(5-cyano-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-

(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl)-6-oxaspiro[2.5]octane-1-carboxamide



The compound (137) obtained in Preparation Example 27 (50 mg, 0.125 mmol) was dissolved in dimethylformamide (0.6 mL), and then 6-oxa-1-spiro[2.5]octanecarboxylic acid (58.8 mg, 0.376 mmol), HATU (143 mg, 0.376 mmol), and triethylamine (63.5 mg, 627 mmol) were added thereto. The reaction mixture was stirred at 100°C for 16 hours. After the reaction mixture was concentrated under reduced pressure, the mixture was separated via reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the compound (21 mg, 39.1 μmol, 31%, m/z = 537.1 $[M^+H]^+$).

104-2 Step 2: N-{3-cyano-4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-6-yl}-6-oxa-1-spiro[2.5]octanecarboxamide (NRX02153)

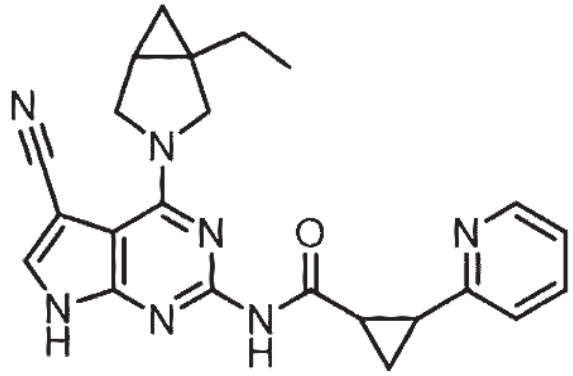


N-(5-Cyano-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl)-6-oxaspiro[2.5]octane-1-carboxamide (21 mg, 0.039 mmol) was introduced into dichloromethane containing trifluoroacetic acid (1.0 mL). The reaction mixture was stirred at 40°C for 3 hours. After the reaction mixture was concentrated under reduced pressure, acetonitrile and potassium carbonate (0.391 mmol) were added thereto, followed by stirring for an additional 1 hour. After the reaction mixture was concentrated under reduced pressure, the mixture was separated via reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the target compound of Example 104 (14.7 mg, 36.2 μmol, 92%, m/z = 407.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.55 (s, 1H), 10.03 (s, 1H), 8.07 (s, 1H), 4.14 (d, J = 10.5 Hz, 1H), 4.07 (dd, J = 11.1, 2.0 Hz, 1H), 3.72 (dt, J = 9.7, 4.5 Hz, 1H), 3.64 - 3.49 (m, 4H), 3.38 (t, J = 7.8 Hz, 1H), 2.23 (s, 1H), 1.81 - 1.70 (m, 1H), 1.67 - 1.34 (m, 6H), 1.03 (dd, J = 5.4, 3.9 Hz, 1H), 0.95 (t, J = 7.4 Hz, 3H), 0.81 (dd, J = 7.8, 3.9 Hz, 1H), 0.66 (dd, J = 7.9, 4.7 Hz, 1H), 0.24 (t, J = 4.3 Hz, 1H).

[Example 105]

Preparation of N-{3-cyano-4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-6-yl}2-(2-pyridyl)cyclopropanecarboxamide (NRX02154)



105-1 Step 1: N-(5-cyano-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl)-2-(pyridin-2-yl)cyclopropane-1-carboxamide

The target compound (30 mg, 55.2 μmol, 44%) was obtained in the same manner as in Step 1 of Example 104, except for using 2-(2-pyridyl)cyclopropanecarboxylic acid instead of 6-oxa-1-spiro[2.5]octanecarboxylic acid.

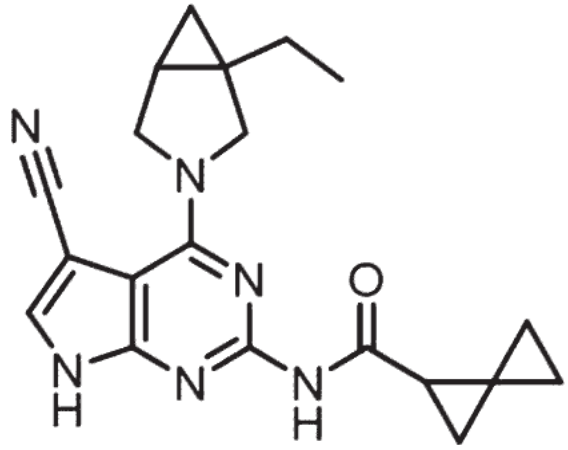
105-2 Step 2: N-{3-cyano-4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-6-yl}2-(2-pyridyl)cyclopropanecarboxamide (NRX02154)

The target compound of Example 105 (18.5 mg, 44.7 μmol, 81%) was obtained in the same manner as in Step 2 of Example 104.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.57 (s, 1H), 10.16 (s, 1H), 8.44 - 8.38 (m, 1H), 8.06 (d, J = 2.0 Hz, 1H), 7.64 (td, J = 7.7, 1.8 Hz, 1H), 7.38 (dq, J = 7.8, 1.1 Hz, 1H), 7.15 (ddd, J = 7.5, 4.8, 1.2 Hz, 1H), 4.10 (t, J = 10.4 Hz, 1H), 3.97 (d, J = 11.1 Hz, 1H), 3.68 - 3.59 (m, 1H), 3.56 (d, J = 10.5 Hz, 1H), 2.54 - 2.49 (m, 1H), 1.73 (dq, J = 14.6, 7.3 Hz, 1H), 1.51 - 1.30 (m, 4H), 0.94 (t, J = 7.4 Hz, 3H), 0.65 (dt, J = 7.9, 4.1 Hz, 1H), 0.20 (q, J = 4.7 Hz, 1H).

[Example 106]

Preparation of N-{3-cyano-4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-6-yl}-1-spiro[2.2]pentanecarboxamide (NRX02156)



106-1 Step 1: N-(5-cyano-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl)spiro[2.2]pentane-1-carboxamide

The compound (27 mg, 55.2 μmol, 44%) was obtained by carrying out in the same manner as Step 1 of Example 104, except for using 1-spiro[2.2]pentenecarboxylic acid instead of 6-oxa-1-spiro[2.5]octanecarboxylic acid.

106-2 Step 2: N-{3-cyano-4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-6-yl}-1-spiro[2.2]pentanecarboxamide (NRX02156)

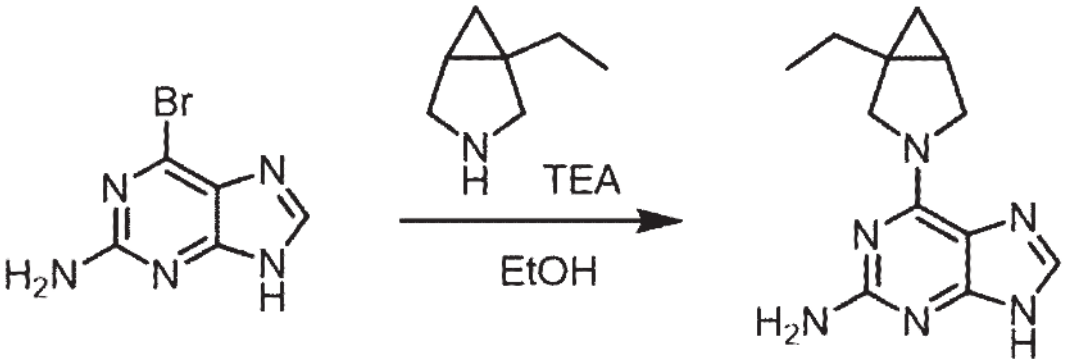
The target compound of Example 106 (14.4 mg, 39.7 μmol, 72%) was obtained by carrying out in the same manner as Step 2 of Example 104.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.54 (s, 1H), 9.89 (s, 1H), 8.06 (s, 1H), 4.14 (d, J = 10.5 Hz, 1H), 4.06 (dd, J = 11.1, 1.7 Hz, 1H), 3.71 (dt, J = 10.9, 4.0 Hz, 1H), 3.61 - 3.53 (m, 1H), 2.59 (s, 1H), 1.75 (dq, J = 14.6, 7.3 Hz, 1H), 1.48 (dt, J = 8.0, 4.0 Hz, 1H), 1.44 - 1.31

(m, 2H), 1.24 (dd, *J* = 7.5, 3.2 Hz, 1H), 0.95 (t, *J* = 7.4 Hz, 3H), 0.89 - 0.74 (m, 3H), 0.73 - 0.62 (m, 2H), 0.23 (t, *J* = 4.3 Hz, 1H).

[Preparation Example 28]

Preparation of 6-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-9H-purin-2-amine (138)



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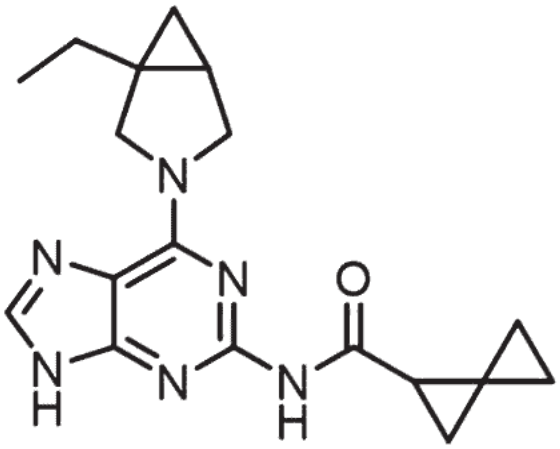
6-bromo-7H-purin-2-amine (500 mg, 2.34 mmol) was added to 1-ethyl-3-azabicyclo[3.1.0]hexane (379 mg, 2.57 mmol), triethylamine (488 μl, 3.5 mmol), and ethanol (11.5 ml), and stirred at 80°C for 4 hours. After the reaction solution was concentrated under reduced pressure, the mixture was separated using reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the target compound (138) of Preparation Example 28 (527 mg, 2.16 mmol, 92%, m/z = 245.1 $[M^+H]^+$).

[Example 107]

Preparation of N-{6-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-2-purinyl}-1-spiro[2.2]pentanecarboxamide (NRX02162)

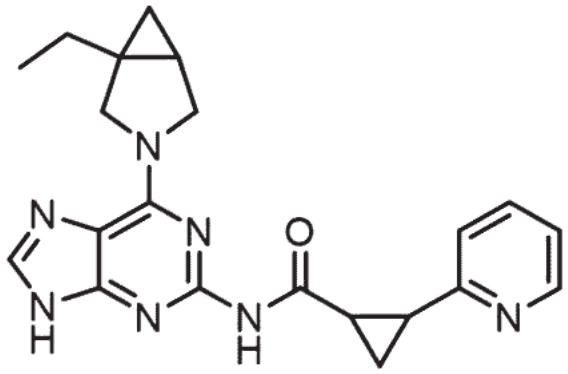


After the compound (138) obtained in Preparation Example 28 (50.0 mg, 0.205 mmol) was dissolved in dimethylformamide (0.6 mL), 1-spiro[2.2]pentanecarboxylic acid (60.0 mg, 0.535 mmol), HATU (233 mg, 0.614 mmol), and triethylamine (104 mg, 1.02 mmol) were added. The reaction solution was stirred at 80°C for 2 hours. After the reaction solution was concentrated under reduced pressure, it was separated using reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the target compound of Example 107 (15.6 mg, 46.1 μmol, 22.5%, m/z = 339.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.71 (s, 1H), 9.79 (s, 1H), 7.89 (s, 1H), 4.54 (s, 1H), 4.02 (s, 1H), 3.85 - 3.38 (m, 1H), 2.61 (s, 1H), 1.71 (dq, *J* = 14.6, 7.3 Hz, 1H), 1.45 (dd, *J* = 14.8, 8.0 Hz, 2H), 1.34 (t, *J* = 3.8 Hz, 1H), 1.22 (dd, *J* = 7.5, 3.3 Hz, 1H), 0.93 (t, *J* = 7.4 Hz, 3H), 0.88 - 0.73 (m, 4H), 0.72 - 0.66 (m, 1H), 0.63 (dd, *J* = 8.0, 4.6 Hz, 1H), 0.23 (t, *J* = 4.3 Hz, 1H).

[Example 108]

N-{6-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-2-purinyl}2-(2-pyridyl) cyclopropane carboxamide (NRX02163)

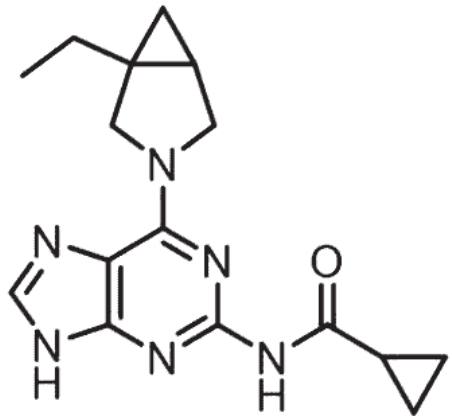


The desired target compound (11 mg, 28.2 μmol, 14%) was obtained by carrying out in the same manner as Example 107, except for using 2-(2-pyridyl)cyclopropanecarboxylic acid instead of 1-spiro[2.2]pentanecarboxylic acid.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.74 (s, 1H), 10.06 (s, 1H), 8.41 (d, J = 4.5 Hz, 1H), 7.90 (s, 1H), 7.64 (td, J = 7.6, 1.8 Hz, 1H), 7.41 - 7.34 (m, 1H), 7.15 (ddd, J = 7.5, 4.8, 1.1 Hz, 1H), 4.57 (s, 1H), 3.96 (s, 1H), 3.78 (s, 1H), 3.59 (s, 1H), 1.68 (s, 1H), 1.48 - 1.40 (m, 4H), 0.91 (t, J = 7.3 Hz, 3H), 0.62 (dd, J = 7.9, 4.6 Hz, 1H), 0.19 (s, 1H).

[Example 109]

N-{6-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-2-purinyl}cyclopropanecarboxamide (NRX02164)



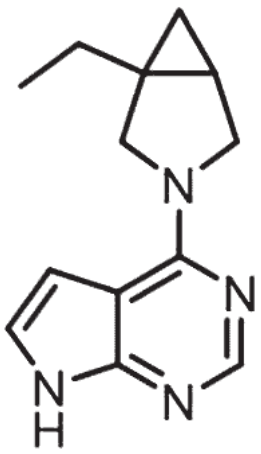
To the target compound (138) obtained in Preparation Example 28 (50 mg, 0.205

mmol) and pyridine (1.0 mL), cyclopropanecarbonyl chloride (23.5 mg, 225 μmol) was added. The reaction solution was stirred at 60°C for 16 hours. After the reaction solution was concentrated under reduced pressure, it was separated using reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the target compound of Example 109 (14.1 mg, 45.1 μmol, 22%, m/z = 313.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.72 (s, 1H), 9.98 (s, 1H), 7.90 (s, 1H), 4.59 (s, 1H), 4.03 (s, 1H), 3.55 (d, *J* = 55.5 Hz, 1H), 2.22 (s, 1H), 1.71 (dq, *J* = 14.6, 7.3 Hz, 1H), 1.45 (dd, *J* = 14.1, 7.3 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3H), 0.79 - 0.67 (m, 4H), 0.71 - 0.59 (m, 1H), 0.23 (t, *J* = 4.4 Hz, 1H).

[Example 110]

Preparation of 4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazaindene (NRX02172)



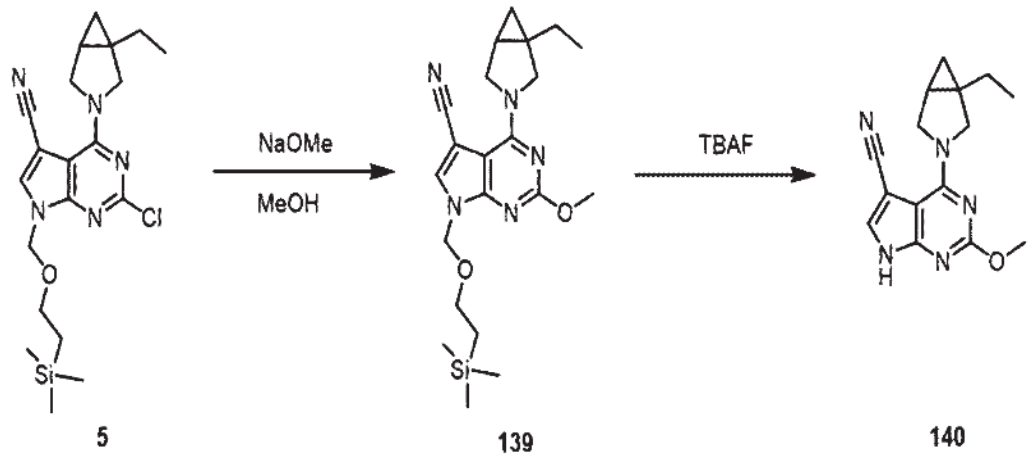
4-chloro-1H-1,5,7-triazaindene (20 mg, 0.130 mmol), 1-ethyl-3-azabicyclo[3.1.0]hexane (23.1 mg, 0.156 mmol), and potassium carbonate (124 mg, 0.391 mmol) were dissolved in 1,4-dioxane (0.651 mL). The reaction solution was stirred at 100°C for 16 hours. After the reaction solution was concentrated under reduced pressure, it was separated using column chromatography (SiO_2, dichloromethane : methanol = 10 : 1) to obtain

the target compound of Example 110 (20.5 mg, 89.8 μmol, 69%, m/z = 229.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, $CDCl_3$-*d*) δ 9.60 (s, 1H), 8.27 (s, 1H), 6.99 (dd, *J* = 3.8, 1.7 Hz, 1H), 6.54 (dd, *J* = 3.7, 1.4 Hz, 1H), 4.10 (dd, *J* = 20.6, 10.3 Hz, 2H), 3.85 (s, 1H), 3.64 (s, 1H), 1.77 (dq, *J* = 14.6, 7.4 Hz, 1H), 1.55 - 1.42 (m, 2H), 1.02 (t, *J* = 7.5 Hz, 3H), 0.73 (ddt, *J* = 8.1, 4.8, 1.0 Hz, 1H), 0.41 (t, *J* = 4.4 Hz, 1H).

[Example 111]

Preparation of 4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-6-methoxy-1H-1,5,7-triazaindene-3-carbonitrile (NRX02174)



111-1 Step 1: 4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-2-methoxy-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile

The compound (5) obtained in Preparation Example 1 (50 mg, 0.120 mmol) and 25% w/w sodium methoxide (1.2 mL, 5.98 mmol) were stirred at 70°C for 16 hours. After the reaction was terminated with ammonium chloride (30 mL), extraction was performed with ethyl acetate (250 mL x 3). The organic layer was washed with brine, and then remaining water was removed using sodium sulfate, and concentrated under reduced pressure to obtain the

desired target compound (44.5 mg, crude, m/z = 414.1 $[M^+H]^+$).

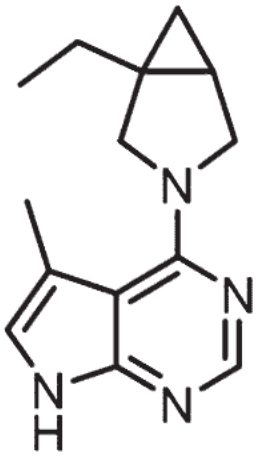
111-2 Step 2: 4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-6-methoxy-1H-1,5,7-triazaindene-3-carbonitrile (NRX02174)

After 4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-2-methoxy-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (44.5 mg, 0.108 mmol) was dissolved in tetrahydrofuran (1.0 mL), 1 M tetra-*n*-butylammonium fluoride (1.08 mL, 1.08 mmol) was added. The reaction solution was stirred at 90°C for 16 hours. After the reaction solution was concentrated under reduced pressure, it was separated using reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the target compound of Example 111 (26.8 mg, 94.6 μmol, 88%, m/z = 284.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, $CDCl_3$-*d*) δ 11.18 (s, 1H), 7.54 (s, 1H), 4.27 (d, *J* = 10.8 Hz, 1H), 4.21 (d, *J* = 11.0 Hz, 1H), 3.95 (s, 2H), 3.72 (d, *J* = 10.9 Hz, 1H), 1.80 (dq, *J* = 14.6, 7.4 Hz, 1H), 1.56 - 1.42 (m, 2H), 0.74 (dd, *J* = 8.0, 5.0 Hz, 1H), 0.34 (t, *J* = 4.4 Hz, 1H).

[Example 112]

Preparation of 4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-3-methyl-1H-1,5,7-triazaindene (NRX02178)

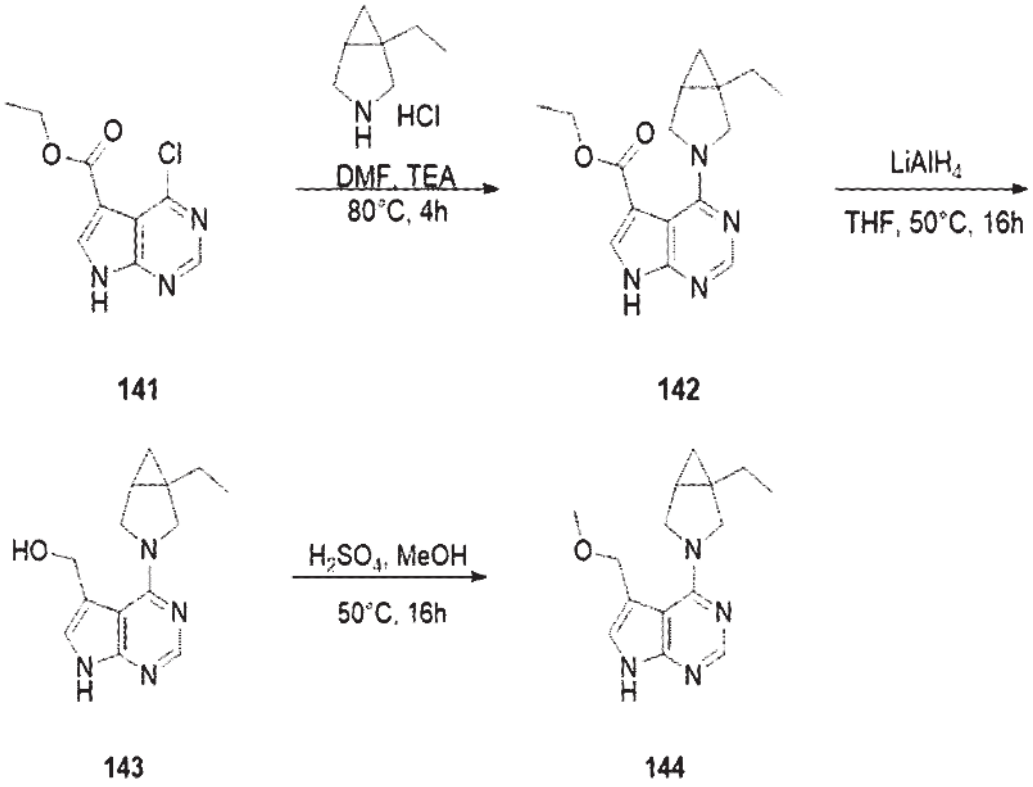


4-chloro-3-methyl-1H-1,5,7-triazaindene (50 mg, 0.298 mmol) was added to 1-ethyl-3-azabicyclo[3.1.0]hexane (52.9 mg, 0.358 mmol), triethylamine (195 μl, 1.40 mmol), and ethanol (1.5 ml), and stirred at 80°C for 18 hours. After the reaction solution was concentrated under reduced pressure, the reaction solution was separated using column chromatography (SiO_2, dichloromethane : methanol = 10 : 1) to obtain the target compound of Example 112 (34.4 mg, 0.142 mmol, 48%, m/z = 243.1 $[M^+H]^+$).

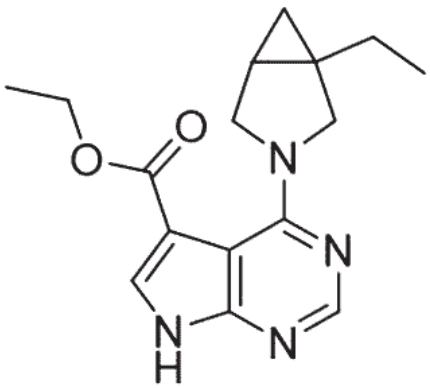
^{1}H-NMR (400 MHz, $CDCl_3$-*d*) δ 9.48 (s, 1H), 8.23 (s, 1H), 6.84 (d, *J* = 1.9 Hz, 1H), 4.22 (d, *J* = 10.4 Hz, 1H), 4.12 (d, *J* = 10.5 Hz, 1H), 3.74 (dd, *J* = 10.5, 4.2 Hz, 1H), 3.53 (dd, *J* = 10.5, 1.2 Hz, 1H), 2.40 (d, *J* = 1.1 Hz, 3H), 1.79 (dq, *J* = 14.6, 7.4 Hz, 1H), 1.49 (dq, *J* = 14.7, 7.5 Hz, 1H), 1.40 (dt, *J* = 8.0, 4.0 Hz, 1H), 1.01 (t, *J* = 7.5 Hz, 3H), 0.63 (ddt, *J* = 8.0, 4.8, 1.0 Hz, 1H), 0.31 (t, *J* = 4.3 Hz, 1H).

[Example 113]

Preparation of 4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-5-(methoxymethyl)-7H-pyrrolo[2,3-d]pyrimidine (NRX02179)



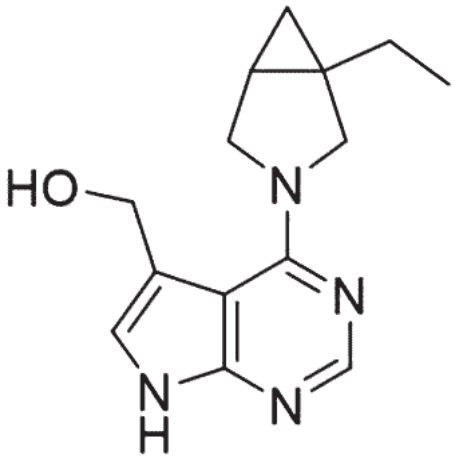
113-1 Step 1: ethyl 4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carboxylate (142)



After 1-ethyl-3-azabicyclo[3.1.0]hexane hydrochloride (654 mg, 4.43 mmol) was dissolved in dimethylformamide (10 mL), triethylamine (1.1 g, 11.08 mmol) and ethyl 4-

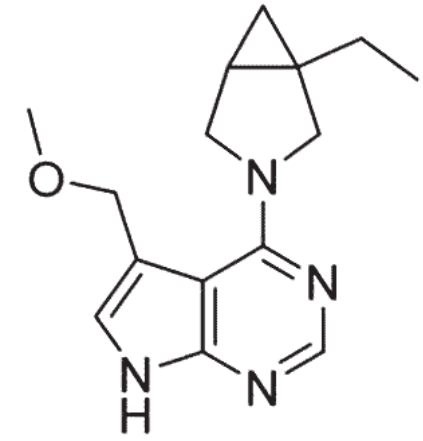
chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carboxylate (1.0 g, 4.43 mmol) were added. The reaction solution was stirred at 80°C for 16 hours. After the reaction, the reaction solution was added to water (120 mL) and extracted with ethyl acetate (60 mL x 3). The organic layer was washed with brine, and remaining water was removed with sodium sulfate, and concentrated under reduced pressure. The concentrated compound was purified by column chromatography (SiO_2, dichloromethane : methanol = 10 : 1) to obtain the desired compound (900 mg, 67.61%, m/z 301.2 $[M^+H]^+$).

113-2 Step 2: (4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanol (143)



After ethyl 4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carboxylate (115 mg, 0.38 mmol) was dissolved in tetrahydrofuran (4 mL), LAH (44 mg, 1.15 mmol) was added. The reaction solution was stirred at 50°C, and LAH (130 mg, 3.4 mmol) was added in three portions over 16 hours. The reaction was terminated by adding sodium sulfate decahydrate (200 mg), and after filtration, the filtrate was concentrated. The concentrate was purified by column chromatography (SiO_2, dichloromethane : methanol = 10 : 1) to obtain the desired compound (45 mg, 45.5%, m/z = 259.1 $[M^+H]^+$).

113-3 Step 3: 4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-5-(methoxymethyl)-7H-pyrrolo[2,3-d]pyrimidine (NRX02179)

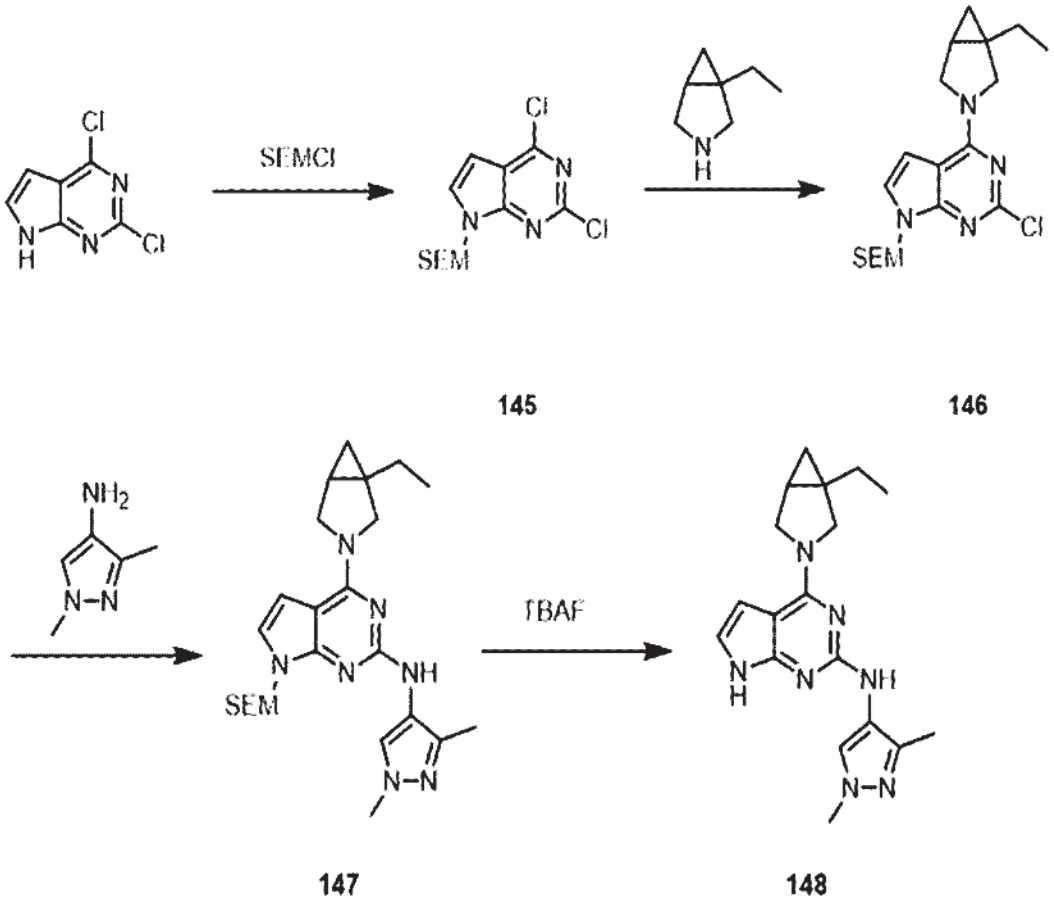


After (4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanol (30 mg, 0.12 mmol) was dissolved in methanol (4 mL), sulfuric acid (50 μL, 98% wt.) was added at 0°C. The reaction solution was stirred at 50°C for 16 hours. The reaction solution cooled to room temperature was added to ice water (10 mL) and extracted with ethyl acetate (15 mL x 3). The organic layer was washed with brine, and remaining water was removed with sodium sulfate, and concentrated under reduced pressure. The concentrated mixture was purified by prep-HPLC (40% ACN in H_2O (0.1% NH_4HCO_3)) to obtain the desired target compound of Example 113 (15.58 mg, 32.84%, m/z = 273.3 $[M^+H]^+$).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.62 (brs, 1H), 8.05 (s, 1H), 7.23 (s, 1H), 4.57 - 4.37 (m, 2H), 4.26 (d, J = 10.6 Hz, 1H), 4.17 (d, J = 10.8 Hz, 1H), 3.69 (dd, J = 10.9, 4.0 Hz, 1H), 3.53 (d, J = 10.7 Hz, 1H), 3.22 (s, 3H), 1.76 - 1.72 (m, 1H), 1.54 - 1.38 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H), 0.70 - 0.55 (m, 1H), 0.18 - 0.17 (m, 1H).

[Example 114]

(1-methyl-3-methyl-4-pyrazolyl){4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-6-yl}amine (NRX02181)



114-1 Step 1: 2,4-dichloro-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine (145)

4,6-dichloro-1H-1,5,7-triazaindene (5.32 mmol) was added to dimethylformamide containing sodium hydride (5.85 mmol) and stirred at room temperature for 30 minutes. 2-(trimethylsilyl)ethoxymethyl chloride (5.74 mmol) was added to the reaction solution and stirred at room temperature for 3 hours. The reaction solution was washed using ethyl acetate and brine. The organic layer was freed of remaining water using sodium sulfate, and concentrated under reduced pressure. The concentrated mixture was separated using column chromatography (SiO_2, hexane : ethyl acetate = 10 : 1 to 1 : 1) to obtain the desired compound

(1.5 g, 4.71 mmol, 89%).

114-2 Step 2: 2-chloro-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine (146)

2,4-dichloro-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine (0.314 mmol) was added to ethanol containing 1-ethyl-3-azabicyclo[3.1.0]hexane (0.377 mmol) and triethylamine (0.943 mmol). The reaction solution was stirred at 90°C for 2 hours. The solvent of the reaction solution was concentrated under reduced pressure and separated using column chromatography (SiO_2, hexane : ethyl acetate = 10 : 1 to 1 : 1) to obtain the desired compound (85 mg, 0.216 mmol, 69%, m/z = 394.1 $[M^+H]^+$).

114-3 Step 3: N-(1,3-dimethyl-1H-pyrazol-4-yl)-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine (147)

2-chloro-4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine (0.216 mmol), 1-methyl-3-methyl-4-pyrazolylamine (0.324 mmol), and potassium carbonate (0.649 mmol) were dissolved in 2-butanol (1.0 mL). $Pd_2(dba)_3$ (21.6 μmol) and XPhos (21.6 μmol) were added. The reaction solution was stirred at 100°C for 16 hours. After termination of the reaction, the reaction solution was filtered through a Celite Pad. The reaction solvent was concentrated under reduced pressure and then purified by column chromatography (SiO_2, hexane : ethyl acetate = 5 : 1 to 1 : 1) to obtain the desired compound (47 mg, 100 μmol, 46%, m/z = 468.1 $[M^+H]^+$).

114-4 Step 4: (1-methyl-3-methyl-4-pyrazolyl){4-(1-ethyl-3-azabicyclo[3.1.0]hex-

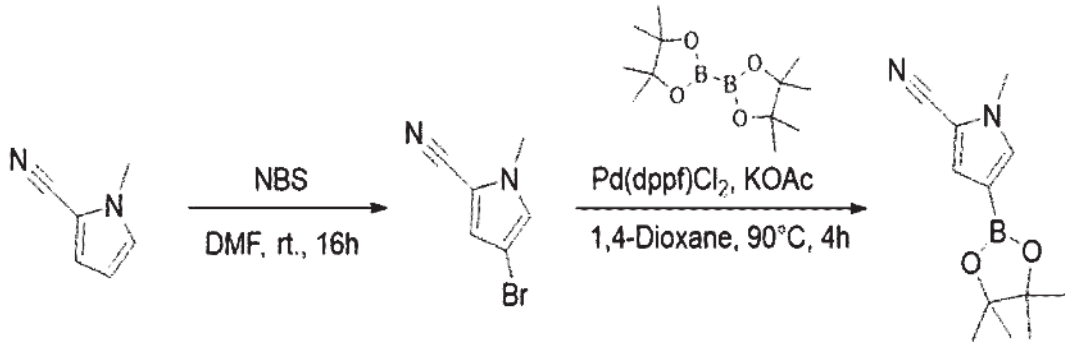
3-yl)-1H-1,5,7-triazainden-6-yl}amine (NRX02181)

After (1-methyl-3-methyl-4-pyrazolyl){4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,5,7-triazainden-6-yl}amine (47 mg, 100 μmol) was dissolved in tetrahydrofuran (1.0 mL), 1 M tetra-n-butylammonium fluoride (2.01 mL, 2.01 mmol) was added. The reaction solution was stirred at 90°C for 16 hours. After the reaction solution was concentrated under reduced pressure, it was separated using reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the target compound of Example 114 (15.0 mg, 44.5 μmol, 44%, m/z = 338.1 $[M^+H]^+$).

^{1}H-NMR (400 MHz, $CDCl_3$-*d*) δ 8.48 (s, 1H), 7.69 (s, 1H), 6.74 (d, *J* = 3.6 Hz, 1H), 6.40 (d, *J* = 3.5 Hz, 1H), 4.06 (dd, *J* = 20.0, 10.7 Hz, 2H), 3.82 (s, 3H), 2.25 (s, 3H), 1.77 (dq, *J* = 14.6, 7.4 Hz, 1H), 1.57 - 1.47 (m, 2H), 1.24 (s, 1H), 1.01 (t, *J* = 7.4 Hz, 3H), 0.76 (dd, *J* = 8.1, 4.9 Hz, 1H), 0.39 (t, *J* = 4.5 Hz, 1H).

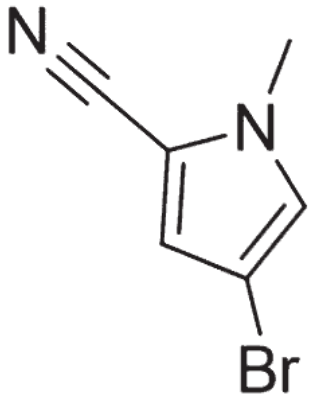
[Preparation Example 29]

Preparation of 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-2-carbonitrile (150)



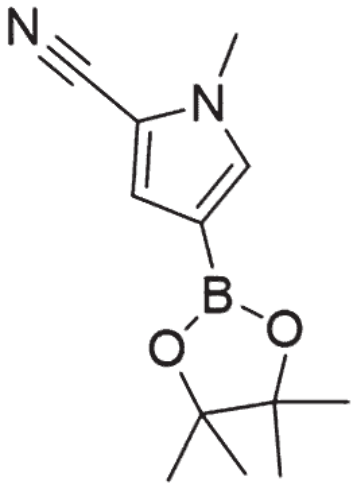
149 150

29-1 Step 1: 4-bromo-1-methyl-1H-pyrrole-2-carbonitrile (149)



After 1-methyl-1H-pyrrole-2-carbonitrile (800 mg, 7.54 mmol) was dissolved in dimethylformamide (20 mL), *N*-bromosuccinimide (1.3 g, 7.54 mmol) was added and stirred at room temperature for 16 hours. The reaction solution was added to water (80 mL) and extracted with ethyl acetate (50 mL x 3). The organic layer was washed using brine, and remaining water was removed using sodium sulfate, and concentrated under reduced pressure. The concentrated mixture was separated using column chromatography (SiO_2, hexane : ethyl acetate = 10 : 1 to 1 : 1) to obtain the desired compound (149) (1.2 g, 86.04%, m/z = 185.0 $[M^+]^+$).

29-2 Step 2: 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-2-carbonitrile (150)

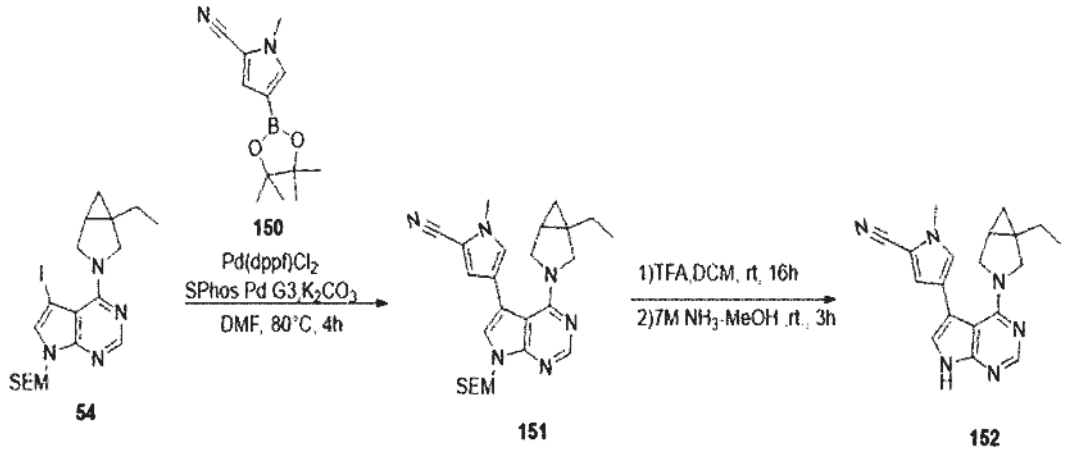


After the compound (149) obtained in Preparation Example 29 (1.2 g, 6.49 mmol) was dissolved in anhydrous 1,4-dioxane (20 mL), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (3.3 g, 12.97 mmol), potassium acetate (1.6 g, 16.21 mmol), and Pd(dppf)Cl_2 (712 mg, 0.97 mmol) were added. The reaction solution was stirred at 90°C for 4 hours. The reaction solution was added to water (100 mL) and extracted with ethyl acetate (80 mL x 3). The organic layer was washed using brine, and remaining water was removed using sodium sulfate, and concentrated under reduced pressure. The concentrated mixture was separated using column chromatography (SiO_2, hexane : ethyl acetate = 10 : 1) to obtain the target compound (150) of Preparation Example 29 (1.2 g, 79.72%).

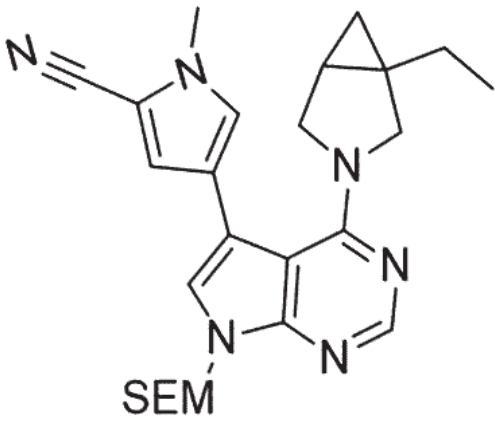
^{1}H-NMR (400 MHz, $CDCl_3$-*d*) δ 7.18 (d, *J* = 1.4 Hz, 1H), 7.09 (d, *J* = 1.6 Hz, 1H), 3.77 (s, 3H), 1.30 (s, 12H).

[Example 115]

Preparation of 4-(4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-1-methyl-1H-pyrrole-2-carbonitrile (NRX02140)



115-1 Step 1: 4-(4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-1-methyl-1H-pyrrole-2-carbonitrile (151)

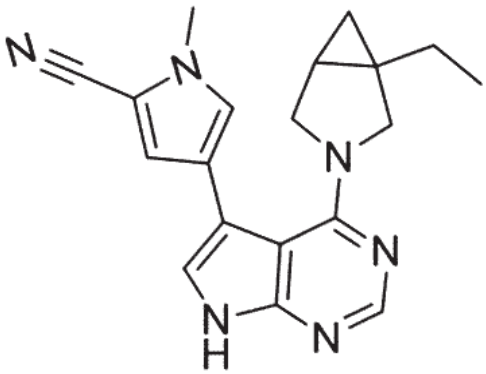


After the compound (150) of Preparation Example 29 (335 mg, 1.44 mmol) was dissolved in dimethylformamide (5 mL), the compound (54) of Preparation Example 13 (699 mg, 1.44 mmol), potassium carbonate (399 mg, 2.89 mmol), SPhos Pd G3 (225 mg, 0.20 mmol), and $Pd(dppf)Cl_2$ (211 mg, 0.20 mmol) were added. The reaction solution was stirred at 80°C for 4 hours. The reaction solution was added to water (60 mL) and extracted with ethyl acetate (40 mL x 3). The organic layer was washed with brine, and after remaining water was

removed with sodium sulfate, concentrated under reduced pressure. The concentrated compound was separated using column chromatography (SiO_2, hexane : ethyl acetate = 10 : 1 to 1 : 1) and prep-HPLC (acetonitrile/water/10mM ammonium carbonate) to obtain the desired compound (151) (120 mg, 18%).

^{1}H-NMR (400 MHz, $CDCl_3$-*d*) δ 8.42 (s, 1H), 7.05 (d, *J* = 5.0 Hz, 1H), 6.87 (d, *J* = 14.0 Hz, 2H), 5.62 (s, 2H), 3.89 (s, 5H), 3.66 - 3.54 (m, 2H), 3.41 (s, 1H), 3.18 (s, 1H), 1.79 - 1.68 (m, 1H), 1.39 - 1.29 (m, 2H), 1.00 - 0.94 (m, 2H), 0.92 - 0.88 (m, 3H), 0.55 (s, 1H), 0.28 (s, 1H), 0.01 (s, 9H).

115-2 Step 2: 4-(4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-1-methyl-1H-pyrrole-2-carbonitrile (NRX02140)



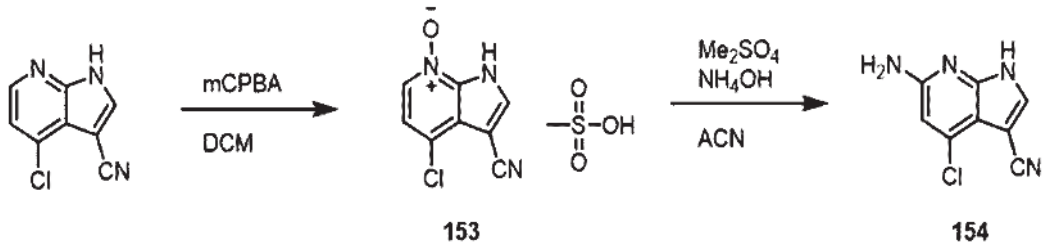
After 4-(4-(1-ethyl-3-azabicyclo[3.1.0]hexan-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-1-methyl-1H-pyrrole-2-carbonitrile (120 mg, 0.26 mmol) was dissolved in dichloromethane (2 mL), trifluoroacetic acid (1 mL) was added and stirred at room temperature for 16 hours. After the reaction solution was concentrated, ammonia/methanol (7 M, 3 mL) was added and additionally stirred for 3 hours. The reaction solution was added to water (80 mL) and extracted with ethyl acetate (50 mL x 3). The organic layer was washed using brine, and remaining water was removed using

sodium sulfate, and concentrated under reduced pressure. The concentrated compound was separated using prep-HPLC (acetonitrile/water/10 mM ammonium carbonate) to obtain the target compound of Example 115 (43.9 mg, 51%, m/z = 333.2 $[M^+H]^+$).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.80 (s, 1H), 8.12 (s, 1H), 7.22 (d, J = 1.6 Hz, 1H), 7.11 (d, J = 2.4 Hz, 1H), 6.95 (d, J = 1.6 Hz, 1H), 3.79 (s, 3H), 3.71 (dd, J = 10.6, 3.7 Hz, 2H), 3.24 (dd, J = 10.8, 3.8 Hz, 1H), 2.96 (d, J = 10.4 Hz, 1H), 1.66 - 1.54 (m, 1H), 1.31 - 1.17 (m, 2H), 0.79 (t, J = 7.4 Hz, 3H), 0.45 - 0.38 (m, 1H), 0.25 (t, J = 4.0 Hz, 1H).

[Preparation Example 30]

Preparation of 6-amino-4-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (154)



30-1 Step 1: 4-chloro-3-cyano-1H-pyrrolo[2,3-b]pyridine 7-oxide, methanesulfonic acid (153)

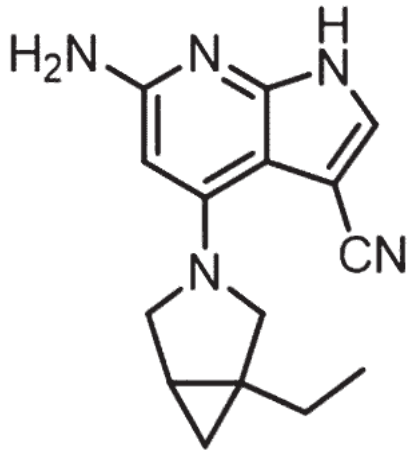
After 4-chloro-1H-1,7-diazaindene-3-carbonitrile (1.0 g, 5.63 mmol) was dissolved in dichloromethane (56 mL), meta-chloroperoxybenzoic acid (2.78 g, 11.3 mmol, purity 70%) was added at 0°C. After stirring at room temperature for 16 hours, methanesulfonic acid (812 mg, 8.45 mmol) was added, and then additionally stirred for 15 minutes. Diethyl ether was added and the solid was filtered to obtain the desired compound (153) (1.8 g, 6.21 mmol, 110%).

30-2 Step 2: 6-amino-4-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (154)

After the compound (153) obtained in Preparation Example 30 (1.5 g, 5.18 mmol) was dissolved in acetonitrile (11.3 mL), dimethyl sulfate (718 mg, 5.7 mmol) was added and stirred at 60°C for 16 hours. After the reaction solution was cooled to room temperature, it was subdivided into three 15 mL vials. Ammonia (7 N in methanol, 5 mL) was added to each vial, and then stirred at 70°C for 48 hours. After the reaction was completed, the reaction solution was concentrated under reduced pressure and then separated using column chromatography (SiO_2, hexane : ethyl acetate = 1 : 1) to obtain the desired compound (154) (31.7 mg, 0.165 mmol, 3%).

[Example 116]

Preparation of 6-amino-4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,7-diazaindene-3-carbonitrile (NRX02161)

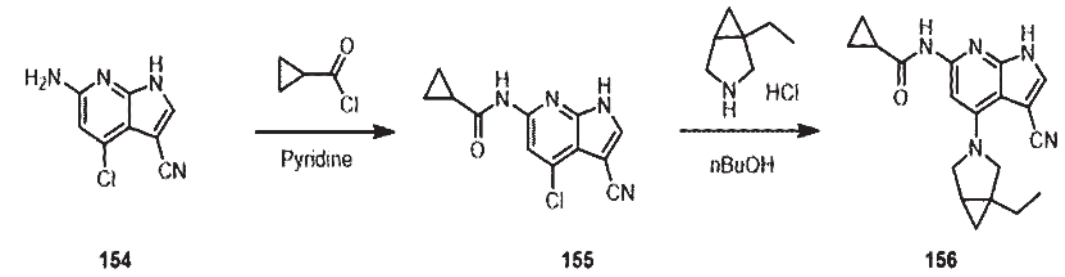


After the compound (154) obtained in Preparation Example 30 (28 mg, 0.145 mmol), 1-ethyl-3-azabicyclo[3.1.0]hexane (64.4 mg, 0.436 mmol), and triethylamine (0.101 mL, 0.727 mmol) were dissolved in *n*-butanol (0.485 mL), the mixture was stirred in a microwave reactor at 140°C for 4 hours. After the reaction, it was concentrated under reduced pressure and separated using reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to

1 : 9) to obtain the target compound of Example 116 (2 mg, 7.48 μmol, 5%).

[Example 117]

Preparation of N-{3-cyano-4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,7-diazainden-6-yl}cyclopro panecarboxamide (NRX02165)



154 155 156

117-1 Step 1: N-(4-chloro-3-cyano-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (155)

After the compound (154) obtained in Preparation Example 30 (20 mg, 0.104 mmol) was dissolved in anhydrous pyridine (0.5 mL), cyclopropanecarbonyl chloride (11.9 mg, 0.114 mmol) was added and stirred at room temperature for 2 hours. After the reaction solvent was concentrated under reduced pressure, methanol was added, the reaction solution was cooled, and 10% ammonium hydroxide was added. After the reaction solution was concentrated under reduced pressure, it was separated using reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the desired compound (8 mg, 30.7 μmol, 30%).

117-2 Step 2: N-{3-cyano-4-(1-ethyl-3-azabicyclo[3.1.0]hex-3-yl)-1H-1,7-diazainden-6-yl}cyclopro panecarboxamide (NRX02165)

After N-(4-chloro-3-cyano-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (8 mg, 30.7 μmol) was dissolved in *n*-butanol (0.5 mL), 1-ethyl-3-azabicyclo[3.1.0]hexane

(22.7 mg, 0.153 mmol) and triethylamine (31.1 mg, 0.307 mmol) were added and stirred at 140°C for 16 hours. After the reaction solution was concentrated under reduced pressure, it was separated using reverse-phase column chromatography (C_{18} resin, water : acetonitrile = 9 : 1 to 1 : 9) to obtain the target compound of Example 117 (4 mg, 11.9 μmol, 39%).

[Test Example 1]

Compound Screening against LRRK2 Kinase Domain (ADP-glo)

The degree of activity by which the compounds of the present invention according to the above Examples inhibit LRRK2 kinase reaction was quantitatively evaluated using the ADP-Glo™ Kinase Assay (Promega) method. In the above method, the degree of conversion of adenosine triphosphate (ATP) to adenosine diphosphate (ADP) according to the enzymatic reaction was measured as a luminescence value to analyze kinase activity. An increase in the luminescence signal means an increase in the amount of ADP produced by the kinase reaction.

For the LRRK2 protein, two types of purified human LRRK2 (WT) (SignalChem, #L10-11G) and LRRK2 (G2019S) (SignalChem, #L10-12GG) were used, and LRRKtide (SignalChem, #L10-58) was used as a substrate for phosphorylation. Ultra-Pure ATP (Promega, #V916A) was used as ATP, which is a mediator of the kinase reaction. ADP-Glo™ Reagent (Promega, #V912B), which terminates the enzymatic reaction and at the same time destroys the remaining ATP, was used, and Kinase Detection Buffer (Promega, #V913B) and Kinase Detection Substrate (Promega, #V914B), which convert ADP back into ATP and induce a luciferase/luciferin reaction, were used as a mixture.

The LRRK2 kinase reaction inhibitory ability of the compounds of the present invention was conducted by the following method. The composition of the Assay buffer is 50

mM Tris pH 7.4, 10 mM $MgCl_2$, 1 mM EGTA, 0.01% Brij-35, 2.5 mM DTT, and the reaction of all reagents between experiments was conducted in the assay buffer. In the kinase reaction and the entire assay, each reagent was executed in a volume ratio of compound : enzyme : substrate/ATP = 2 : 1 : 2, and enzyme reaction solution : ADP-GloTM Reagent : Kinase Detection Solution = 2 : 2 : 1, respectively. The compounds were first analyzed for activity at two final concentrations of 100 and 10 nM by serial dilution from a 0.5 mM DMSO Stock, and among them, substances superior to the Reference compound were selected, and the degree of enzyme reaction inhibition was measured at ten final concentrations of 10,000, 2,000, 400, 80, 16, 3.2, 0.640, 0.128, 0.0256, and 0.00512 nM.

During the experiment, the compound was first reacted with each human LRRK2, LRRK2 (22.2 nM) and LRRK2 (G2019S) (15 nM) at room temperature for 20 minutes, and then according to the LRRK2 type, the substrate (200,000, 150,000 nM) and each ATP (12.5, 35 μM) were mixed and added, and reacted for 2 hours for the wild type and 1 hour for the mutant type. For the detection reaction, after treating with ADP-Glo^{TM} Reagent, it was waited for 40 minutes, and then Kinase Detection Solution was added and allowed to stand for 30 minutes.

After the completion of all Assay reactions, the degree of LRRK2 kinase reaction inhibitory efficacy of the compounds was obtained as a Luminescence (Gain: 150, Integration Time: 1 sec, Read Height: 1 mm) value using a Synergy NEO2 Multi-mode Reader (BioTek). From the Luminescence values measured at 10 concentrations of the substances showing higher activity at 2 concentrations compared to the Reference compound, IC_{50} (nM) values that inhibit enzyme activity by 50% were derived using GraphPad Prism (ver. 9.0) software. As shown in Table 3, it was confirmed that the compounds of the present invention can excellently inhibit LRRK2 kinase reaction.

[Table 3]

Compound	ADP-glo IC_{50} (WT) (IC_{50} < 50 nM: ++++ 50 nM ≤ IC_{50} < 500 nM: +++ 500 nM ≤ IC_{50} < 5000 nM: ++ IC_{50} ≥ 5000 nM: +)	ADP-glo IC_{50} (G2019S) (IC_{50} < 50 nM: ++++ 50 nM ≤ IC_{50} < 500 nM: +++ 500 nM ≤ IC_{50} < 5000 nM: ++ IC_{50} ≥ 5000 nM: +)
NRX02004	++++	++++
NRX02065	++	++
NRX02066	++	++
NRX02067	++++	++++
NRX02068	+	+
NRX02069	++	++
NRX02070	++	++
NRX02071	++	++
NRX02072	++	++
NRX02073	++	++
NRX02074	++	++
NRX02075	++	++
NRX02076	++++	++++
NRX02077	++++	++++
NRX02078	++	++
NRX02081	+++	+++
NRX02082	++++	++++
NRX02083	+++	++
NRX02084	+++	+++
NRX02085	+++	+++
NRX02086	++++	+++
NRX02087	++++	++++
NRX02088	++	+++
NRX02089	++	++
NRX02090	++	++
NRX02091	++	+++
NRX02092	++	++
NRX02093	++	++
NRX02094	++	++
NRX02095	++	++
NRX02096	+++	+++

NRX02097	++++	++++
NRX02098	+++	+++
NRX02099	+++	+++
NRX02100	++++	++++
NRX02101	++	++
NRX02102	+	++
NRX02103	+	++
NRX02104	++++	++++
NRX02105	+++	++++
NRX02106	++++	++++
NRX02107	++++	++++
NRX02108	+++	++++
NRX02109	++	++
NRX02110	+	+
NRX02111	+++	+++
NRX02112	++	++
NRX02113	+++	+++
NRX02114	++	+++
NRX02115	++	++
NRX02116	+++	++
NRX02117	++++	++++
NRX02118	+++	+++
NRX02119	+++	+++
NRX02120	++	++
NRX02121	++	+
NRX02122	++	++
NRX02123	+++	+++
NRX02124	++	++
NRX02125	++	++
NRX02126	++	+++
NRX02127	+++	+++
NRX02128	++	++
NRX02129	++	++
NRX02130	+++	+++
NRX02131	++	++
NRX02132	++++	+++
NRX02133	+++	++
NRX02134	++	+++
NRX02135	++	++
NRX02136	++	++
NRX02137	++	++

NRX02138	+	++
NRX02139	+	+
NRX02140	++	++
NRX02141	++	++
NRX02142	++	++
NRX02143	++	+++
NRX02144	++	+++
NRX02145	+++	+++
NRX02146	+	++
NRX02147	++++	++++
NRX02148	++++	++++
NRX02149	+++	+++
NRX02150	++++	++++
NRX02151	+++	+++
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NRX02159	+++	+
NRX02160	++++	++++
NRX02161	++++	++++
NRX02162	+++	++
NRX02163	++++	++
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NRX02167	+++	+++
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NRX02171	++	++
NRX02172	++	++
NRX02173	++++	++++
NRX02174	++	++
NRX02175	++	+++
NRX02176	++++	++++
NRX02177	++++	+++
NRX02178	++	+++

NRX02179	++	+++
NRX02180	++	+++
NRX02181	++++	++++
NRX02182	++++	++++

[Test Example 2]

IntraCellular Activity Verification of Compounds against LRRK2 Kinase Domain (NanoBRET)

To quantitatively measure the interaction with LRRK2 protein in living cells, NanoBRET assay (Promega) was performed. After transducing the LRRK2 target kinase fused to NanoLuc luciferase protein into cells, the binding affinity of the test compound with the selected kinase protein by competitive displacement with a fluorescent NanoBRET kinase-ligand tracer was measured by NanoBRET^{TM} energy.

After transfecting HEK 293 cells using a plasmid expressing NanoLuc-LRRK2 fusion protein, the cells were seeded into a 96-well plate at 20,000 cells/well and cultured in a humidified incubator at 37°C, 5% CO_2. After 24 hours, they were treated with a NanoBRET tracer (0.0083 μM). Thereafter, the compounds of the present invention as competitive inhibitor against the tracer were treated with increasing doses (from 1 nM to 10 μM) for 2 hours. Subsequently, 50 μl of a 3x substrate + inhibitor solution was added. Thereafter, the plates were analyzed with a Biotek Synergy NEO2 plate reader equipped with NanoBRET filters (donor emission wavelength 450 nm and acceptor emission wavelength 600 nm). The BRET ratio was calculated as the ratio of the donor emission wavelength to the acceptor emission wavelength, and based on the value expressed in milliBRET units (mBU) by multiplying the BRET ratio by 1,000, the degree to which the compounds of the present invention inhibit the interaction between the intracellular wild-type LRRK2 protein and G2019S mutant LRRK2 protein and

the tracer using GraphPad Prism (ver. 9.0) software is shown in Fig. 1 and Fig. 2.

The IC_{50} (nM) that inhibits the interaction between LRRK2 protein and the tracer by 50% was derived and is shown in Table 4 below.

The IC_{50} (nM) was calculated for experimental values that were confirmed at 1 point (10 μM) or 2 points (0.1, 10 μM or 1, 10 μM) by initial screening and had a binding affinity similar to or an activity equal to or higher than the reference substance.

[Table 4]

Compound	NanoBRET IC_{50} (WT)	NanoBRET IC_{50} (G2019S)
NRX02067	500 nM	1500 nM
NRX02099	1.35 nM	0.55 nM
NRX02104	1061 nM	2301 nM
NRX02105	137 nM	8078 nM
NRX02106	2.33 nM	905.70 nM
NRX02107	27.98 nM	0.80 nM
NRX02147	325.40 nM	166.10 nM
NRX02148	174.50 nM	227.40 nM
NRX02150	114.10 nM	412.20 nM
NRX02153	139.80 nM	331.30 nM
NRX02154	94.23 nM	209.40 nM
NRX02156	277.80 nM	299.40 nM
NRX02157	305.70 nM	342.70 nM
NRX02160	325.40 nM	379 nM
NRX02161	182.70 nM	255.80 nM
NRX02165	6.39 nM	17.14 nM
NRX02166	98.91 nM	401.30 nM
NRX02169	3.08 nM	4.93 nM
NRX02170	0.93 nM	0.62 nM
NRX02173	2.34 nM	1.12 nM
NRX02174	2.22 nM	0.80 nM

As shown in Table 4 above, it was confirmed that the compounds of the present invention excellently inhibit the activities of intracellular wild-type LRRK2 protein and

G2019S mutant LRRK2 protein.

[Test Example 3]

IntraCellular Activity Verification of Compounds against LRRK2 Kinase Domain (AlphaLISA)

The degree to which the compounds of the present invention bind to LRRK2 protein and inhibit phosphorylation in T-REx™ 293 LRRK2 wild type and G2019S cell lines and HEK293 cell lines overexpressing LRRK2 wild type and G2019S was quantitatively evaluated. It was conducted using AlphaScreen (Amplified Luminescent Proximity Homogeneous Assay Screen), which is an immunoassay method using Luminescent Oxygen Radical.

LRRK2 protein was used as a substrate for the reaction with the compound (LRRK2 inhibitor), and receptor beads bound with an antibody capable of recognizing and reacting with the phosphate group of the substrate were used.

Donor beads coated with streptavidin were used to bind with the LRRK2 substrate.

AlphaLISA® SureFire® Ultra™ was purchased from PerkinElmer, and quantitative analysis was conducted through the following process using a bright white 384-well proxiplate (#6008280; Perkin Elmer).

T-REx™ 293 LRRK2 wild type and G2019S cells were seeded into a 96-well plate at 20,000 cells/well and cultured overnight in a humidified incubator at 37°C, 5% CO_2. The next day, the growth medium was removed, and 100 μl of fresh DMEM medium containing 1 μg/ml of Tetracycline was added. HEK293 cell lines overexpressing LRRK2 wild type and G2019S were also experimented under the same conditions, but 100 μl of fresh DMEM containing 1 μg/ml of Tetracycline was not added. After 48 hours, they were treated with increasing doses

of the compounds of the present invention. The cells were incubated in an incubator for 2 hours. The cells were harvested, lysed, and then transferred to a 10 μl 384-well plate.

After 5 μl of biotinylated receptor beads were added, it was allowed to stand at room temperature for 1 hour. After the reaction of the above process was completed, 5 μl of donor beads were added and allowed to stand at room temperature for 1 hour. Since donor beads are very sensitive to light, this process was conducted in a dark state.

After all reactions were completed, the LRRK2 phosphorylation inhibitory efficacy of the compounds was detected and analyzed for AlphaScreen signals (Excitation 680 nm, Emission 615 nm) using a Synergy NEO2 Multi-mode Plate Reader (BioTek), and the obtained results were nonlinearly regression fitted as shown in Fig. 3 using GraphPad Prism (Ver. 9.0), and IC_{50} values were derived and are shown in Table 5 below.

[Table 5]

Compound	AlphaLISA IC_{50} (WT)	AlphaLISA IC_{50} (G2019S)
NRX02004	6189 nM	269 nM
NRX02053	17703 nM	2331 nM
NRX02067	40.26 nM	14.52 nM
NRX02076	251.20 nM	168.80 nM
NRX02077	67.73 nM	88.11 nM
NRX02097	1.92 nM	35.67 nM
NRX02099	0.76 nM	1.30 nM
NRX02104	71.49 nM	13.99 nM
NRX02105	706 nM	74.61 nM
NRX02106	0.26 nM	0.05 nM
NRX02107	1.79 nM	5.04 nM
NRX02108	590.30 nM	1707 nM
NRX02109	121.70 nM	> 10000 nM
NRX02111	256.60 nM	> 10000 nM
NRX02147	183 nM	276.90 nM
NRX02148	410.70 nM	690.30 nM
NRX02150	319.30 nM	548.90 nM
NRX02153	201.40 nM	102.10 nM

NRX02154	172.80 nM	568.90 nM
NRX02156	309.30 nM	999.40 nM
NRX02157	353.40 nM	966.20 nM
NRX02161	244.10 nM	679.10 nM
NRX02165	19.91 nM	30.86 nM
NRX02166	672.80 nM	254.90 nM
NRX02169	5.87 nM	11.95 nM
NRX02170	2.66E-07 nM	19.04 nM
NRX02172	11410 nM	10290 nM
NRX02173	2.08E-08 nM	42.33 nM
NRX02174	11610 nM	12.34 nM
NRX02175	2450 nM	922.40 nM
NRX02176	3.24E-06 nM	0.80 nM

As shown in Table 5 above, it was confirmed that the compounds of the present invention bind to intracellular wild-type LRRK2 protein and G2019S mutant LRRK2 protein to excellently inhibit phosphorylation.

[Test Example 4]

IntraCellular Activity Verification of Compounds against LRRK2 Kinase Domain (Western Blot)

T-REx™ 293 LRRK2 wild type cells were seeded into a 96-well plate at 20,000 cells/well and cultured overnight in a humidified incubator at 37°C, 5% CO_2. The next day, the growth medium was removed, and 100 μl of fresh DMEM medium containing 1 μg/ml of tetracycline was added. After 48 hours, they were treated with 100 μl of the compounds of the present invention. The cells (final concentrations of 0.1 μM and 10 μM) were incubated in an incubator for 2 hours. After the cells were harvested and lysed, the same amount of protein (20 μg) was subjected to 8 - 12% SDS PAGE to separate proteins by size. Then, after being transferred to a PVDF membrane, it was blocked with 10% SKIM MILK for 1 hour. Primary

antibodies [p-LRRK2, ab133450, Abcam, LRRK2, ab133474, Abcam, p-Rab10, ab230261, Abcam, Rab10, ab237703, Abcam] were diluted in a 5% BSA solution at a ratio of 1:1,000 and reacted at 4°C for 16 hours. The membrane was washed with Tris-buffered saline (TBS) buffer containing 0.1% Tween 20, (TBS-T). This was repeated three times. After the membrane was reacted with a horseradish peroxidase-labeled secondary antibody at room temperature for 1 hour, washing was repeated. An ECL kit (1705062, Bio-rad) was used. It was visualized as shown in Fig. 4.

As shown in Fig. 4, it was confirmed that the compounds of the present invention inhibit the phosphorylation of LRRK2 and the phosphorylation of Rab10 protein, which is a substrate of LRRK2, better in a dose-dependent manner compared to the comparison groups GNE-0877 (DNL-201) and PF-06447475.

[Test Example 5]

Cytotoxicity Verification of Compounds against LRRK2 Kinase Domain (Cell viability assay)

To verify the cytotoxicity of the compounds, T-Rex^{TM} 293 LRRK2 wild type cells were seeded into a 96-well plate at 20,000 cells/well and cultured overnight in a humidified incubator at 37°C, 5% CO_2. The next day, the growth medium was removed, and 100 μl of fresh DMEM medium containing 1 μg/ml of tetracycline was added. After 24 hours, they were treated with the compounds of the present invention at different concentrations (from 1 nM to 10 μM). After 24 hours, after treating with 100 μl of CellTiter-Glo (G9241, Promega), luminescence values were measured using a Synergy NEO2 Multi-mode Plate Reader (BioTek). From the obtained results, the % cell viability was derived using GraphPad Prism (Ver. 9.0).

As shown in Fig. 5, it was confirmed that the LRRK2 inhibitors of the present invention did not inhibit cell survival. The same results were confirmed in U2OS, a cell line with low expression of LRRK2.

[Test Example 6]

Antagonist Binding Verification against A2AR GPCR (G-protein coupled receptor) Protein (Cell viability assay)

To verify the antagonist binding of the compounds to Adenosine A2A receptor (A2AR), three types of experiments were requested to Eurofins (https://www.eurofinsdiscovery.com/), and the results regarding whether binding occurred were secured as shown in Table 6 below.

[Table 6]

Compound	*in vitro* pharmacology : binding assays	*in vitro* pharmacology: Adenosine Binding Assays	gpcrSCAN
NRX02067	84.2 % inhibition	1.1E-07 M (IC_{50})	Agonist (max response) : 0 Antagonist (max response) : 29.751

In the service name *in vitro* pharmacology : binding assay experiment, the compounds were tested at a concentration of 1.0E-06 M. Whether competitive binding occurred with a ligand known as a radioisotope was measured, and compound binding was calculated as % inhibition on the binding of the ligand specific to each target. In the service name *in vitro* pharmacology: Adenosine Binding Assays, whether binding occurred was measured for various concentrations of the compounds to confirm IC_{50} using a radioisotope. In the service

name gpcrSCAN, whether the compounds bind as an agonist or an antagonist was verified by an assay method that monitors GPCR activity through secondary messenger signaling in real time.

As shown in Table 6, it was confirmed that the novel LRRK2 inhibitors of the present invention bind as an antagonist to A2AR GPCR.

[Test Example 7]

Molecular Calculations Analysis on Kinase Type I Inhibition and Type II Inhibition of Structural Isomers

For Protein model building, the three-dimensional structure of LRRK2 protein was generated from the cryo-electron microscopy (cryo-EM) resolution structures of 8FO7 and 8U8A reported in the Protein Data Bank (PDB). Two protein dimensional structures were used as templates, and the missing loop regions among the three-dimensional structures were modeled using the entire FASTA sequence of the corresponding protein. By utilizing homology modeling, an accurate protein three-dimensional structure model was built based on the target-template alignment. The resulting protein three-dimensional structure model reflected the coordinates of the template and the compounds binding thereto, and the optimal protein three-dimensional structure was secured by repeating the insertion and deletion of additional protein residues and modeling using a fragment library. In addition, the process of reconstructing side chains was repeated to ensure accuracy.

For Molecular docking calculations, the initial protein-ligand structure was generated using Schrodinger's Glide docking software. The docking grid included the space occupied by the compounds binding within the two proteins and a 10Å buffer zone in each dimension.

Atomic charges were scaled by 0.8, and charges below a threshold of 0.15 were blocked. As for the docking settings, extra precision was used, planarity of conjugated ð-bonds was enforced, and hydrogen bond interactions were considered. The final docking score included a strain correction term, and molecular docking between the protein and the compounds was repeatedly performed without additional structural constraints.

For Molecular dynamics simulations, parameters including protein geometry and interaction information were used, and the site of the protein for analysis and the GTP ligand existing in other regions were excluded. After building the system and parameters, the protein and the ligand were solvated with TIP3P water and placed in a cubic box with a 10 Å padding, and the system was equilibrated with counter ions to correct charges. Thereafter, geometry optimization was performed using a conjugate gradient algorithm of 20,000 cycles (20 ps). Then, using the Particle Mesh Ewald (PME) method, unconstrained equilibration was performed for 80 ps under constant temperature and volume (NVT ensemble) conditions under periodic boundary conditions, and the PME cutoff distance was 10 Å. In addition, simulation in an unconstrained NPT ensemble for 20 ns, a rigid body TIP3P water model was used. All molecular dynamics simulations were performed with the SHAKE algorithm using a particle mesh Ewald grid spacing of 1.0. Temperature and pressure were controlled by Lansgevin dynamics parameters and a modified Nose-Hoover method. All simulations were performed at 300 K and 1 bar. When reasonable root-mean-square deviation (RMSD) convergence was not observed within the 20 ns run, an additional 50 ns run was performed. For a free ligand in water, a 5 ns NPT simulation was performed instead of the standard 20 ns simulation. From the simulation trajectory, the pair interaction energy between the ligand and the surrounding environment was extracted. For the average van der Waals (vdW) and electrical interaction energies, the approximate Gibbs ligand binding energy was derived using a linear interaction

energy formalism. For the approximate Gibbs energy, the electrical interaction energy scaling factor β was set to 0.43. Post-analysis of the simulation trajectory was performed using the MDAnalysis package.

$$\Delta G_{bind} = \alpha\left(\overline{E}^{vdW}_{bound} - \overline{E}^{vdW}_{free}\right) + \beta\left(\overline{E}^{ele}_{bound} - \overline{E}^{elec}_{free}\right) \quad Eq.\,1$$

$$\overline{E} - Average\ Energy$$

Based on the results of molecular docking and molecular dynamics simulation calculations, it was predicted that the two ligands are highly likely to enter the binding pocket of LRRK2 protein (PDB ID: 8U8A). When both NRX02104 and NRX02105 enter the binding pocket, the binding affinities were calculated as -13.79 kcal/mol and -12.63 kcal/mol, respectively. On the other hand, under the pure structural isomer condition, two NRX02104 or two NRX02105 ligands bound to the protein and showed affinities of -12.63 and -10.94 kcal/mol, respectively.

Molecular docking and molecular dynamics simulations were performed under various ligand binding conditions. Specifically, cases where a single ligand occupies the binding pocket and cases where two ligands representing structural isomer pure or racemic conditions are in the binding pocket were analyzed. Thereafter, a Gibbs free energy profile was constructed using the linear interaction energy approximation method. The results predicted that NRX02104 would bind to a preferred site and release a free energy of -8.66 kcal/mol. As shown in the contact profile, it was confirmed that binding at this site is mainly determined by hydrogen bond interaction with Lys1906 residue and hydrophobic interaction with Phe1890 residue. Thereafter, another NRX02104 bound to the adjacent empty space and additionally released -4.07 kcal/mol, bringing the system to State A of Fig. 6, which takes the system to -12.73 kcal/mol from the initial condition. However, the binding of NRX02105 is stronger in the

adjacent empty space than that of NRX02104, and the former moves the system to -13.79 kcal/mol from the initial condition, which was predicted as State B of Fig. 6. Therefore, it was predicted that the equilibrium would highly likely be dominated by the form in which both ligands bind to the protein in this structure, more specifically, by state B. On the other hand, under the NRX02104 pure structural isomer condition, the equilibrium was predicted to be in a form such as State A of Fig. 6. Similarly, under the NRX02105 pure structural isomer condition, it was predicted to become State C of Fig. 6 with an energy value of -10.94 kcal/mol. Lastly, under the racemic condition, some forms such as State D of Fig. 6 may appear, and the Gibbs energy was predicted to be larger by 1 kcal/mol or more compared to B.

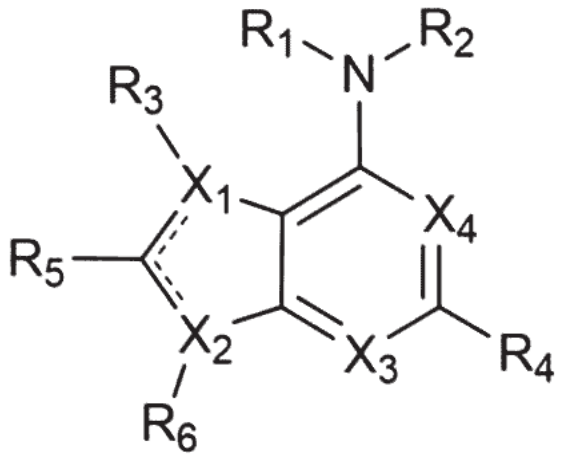
These calculation results were consistent with experimental data showing that a racemic mixture of NRX02104 and NRX02105 exhibits higher affinity for the protein than individual structural isomer forms. In addition, it was predicted that the racemic mixture would highly likely act as a Type II kinase inhibitor as well as a Type I kinase inhibitor, compared to the individual structural isomers.

【Claims】

【Claim 1】

A compound of Formula 1 below, or a pharmaceutically acceptable salt thereof:

[Formula 1]



wherein,

····· is each independently absent or a single bond,

X_1 to X_4 are each independently C or N,

R_1 and R_2 are each independently hydrogen, alkyl, -O-alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -alkyl-cycloalkyl, -alkyl-heterocycloalkyl, -alkyl-aryl, or -alkyl-heteroaryl, or

R_1 and R_2 are heterocycloalkyl formed by linking R_1 and R_2 together,

R_3 is absent, or is hydrogen, halo, cyano, alkyl, -alkyl-O-alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl,

R_4 is hydrogen, halo, cyano, $-NH_2$, -alkyl, -alkyl-O-alkyl, -O-alkyl, $N(R_{4A})(R_{4B})$, $-N(R_{4D})C(=O)(R_{4C})$, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl,

wherein R_{4A} to R_{4D} are each independently hydrogen, alkyl, cycloalkyl, heterocycloalkyl, -cycloalkyl-heteroaryl, heteroaryl, aryl, or -aryl-C(=O)-heterocycloalkyl,

R_5 is hydrogen, cyano, alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl,

R_6 is absent, or is hydrogen, cyano, alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl,

wherein the cycloalkyl, heterocycloalkyl, aryl, or heteroaryl may be substituted with one or more selected from the group consisting of halo, NH_2, cyano, haloalkyl, alkyl, alkenyl, alkynyl, -alkynyl-alkyl, -O-alkyl, -alkyl-CN, -alkyl-OH, -alkyl-O-alkyl, -alkyl- NH_2, -alkyl-N(alkyl)(alkyl), -alkyl-cycloalkyl, NH_2, -N(alkyl)(alkyl), -C(=O)-NH_2, -C(=O)-heteroaryl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein the cycloalkyl, heterocycloalkyl, aryl, or heteroaryl may be unsubstituted or substituted with alkyl or -OH, wherein the alkyl may be unsubstituted or substituted with halo.

【Claim 2】

The compound of Formula 1, or a pharmaceutically acceptable salt thereof, according to claim 1,

wherein X_1 to X_4 are each independently C or N,

R_1 and R_2 are each independently hydrogen, -C_{1-6}alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -C_{1-6}alkyl-cycloalkyl, -C_{1-6}alkyl-heterocycloalkyl, -C_{1-6}alkyl-aryl or -C_{1-6}alkyl-heteroaryl, or

R_1 and R_2 are heterocycloalkyl formed by linking R_1 and R_2 together,

R_3 is absent, or is hydrogen, halo, cyano, -C_{1-6}alkyl, -C_{1-6}alkyl-O-C_{1-6}alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl,

R_4 is hydrogen, halo, cyano, -NH_2, -C_{1-6}alkyl, -C_{1-6}alkyl-O-C_{1-6}alkyl, -O-C_{1-6}alkyl, -N(R_{4A})(R_{4B}), -N(R_{4D})C(=O)(R_{4C}), cycloalkyl, heterocycloalkyl, aryl or heteroaryl,

wherein R_{4A} to R_{4D} are each independently hydrogen, -C_{1-6}alkyl, cycloalkyl, heterocycloalkyl, -cycloalkyl-heteroaryl, heteroaryl, aryl or -aryl-C(=O)-heterocycloalkyl,

R_5 is hydrogen, cyano, -C_{1-6}alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl,

R_6 is absent, or is hydrogen, cyano, -C_{1-6}alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl,

wherein the cycloalkyl, heterocycloalkyl, aryl or heteroaryl may be substituted with one or more selected from the group consisting of halo, NH_2, cyano, cycloalkyl, haloalkyl, -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{2-6}alkynyl-C_{1-6}alkyl, -O-C_{1-6}alkyl, -C_{1-6}alkyl-CN, -C_{1-6}alkyl-OH, -C_{1-6}alkyl-O-C_{1-6}alkyl, -C_{1-6}alkyl-NH_2, -C_{1-6}alkyl-N(C_{1-6}alkyl)(C_{1-6}alkyl), -C_{1-6}alkyl-cycloalkyl, -C(=O)-NH_2, -C(=O)-heteroaryl, heterocycloalkyl, and heteroaryl, wherein the heterocycloalkyl or heteroaryl may be unsubstituted or substituted with -C_{1-6}alkyl or -OH, wherein the -C_{1-6}alkyl may be unsubstituted or substituted with halo.

【Claim 3】

The compound of Formula 1, or a pharmaceutically acceptable salt thereof, according to claim 1,

wherein X_1 to X_4 are each independently C or N,

R_1 and R_2 are each independently hydrogen or -C_{1-6}alkyl-heterocycloalkyl, wherein the heterocycloalkyl may be unsubstituted or substituted with -C_{1-6}alkyl, or

R_1 and R_2 are 3- to 10-membered heteromonocycloalkyl or 3- to 10-membered spiro or fused heterobicycloalkyl formed by linking R_1 and R_2 together,

wherein the 3- to 10-membered heteromonocycloalkyl or 3- to 10-membered spiro or fused heterobicycloalkyl formed by linking R_1 and R_2 together may be substituted with one or more selected from the group consisting of halo, NH_2, cyano, cycloalkyl, -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{2-6}alkynyl-C_{1-6}alkyl, -C_{1-6}alkyl-CN, -C_{1-6}alkyl-OH, -C_{1-6}alkyl-O-C_{1-6}alkyl, -C_{1-6}alkyl-NH_2, -C_{1-6}alkyl-N(C_{1-6}alkyl)(C_{1-6}alkyl), -C_{1-6}alkyl-cycloalkyl, -C(=O)-NH_2, -C(=O)-heteroaryl, heterocycloalkyl, and heteroaryl, wherein the heterocycloalkyl or

heteroaryl may be unsubstituted or substituted with -C_{1-6}alkyl or -OH, wherein the -C_{1-6}alkyl may be unsubstituted or substituted with halo,

R_3 is absent, or is hydrogen, halo, cyano, -C_{1-6}alkyl, -C_{1-6}alkyl-O-C_{1-6}alkyl, aryl or heteroaryl, wherein the aryl or heteroaryl may be substituted with one or more selected from the group consisting of cyano, -C_{1-6}alkyl, and heterocycloalkyl, wherein the -C_{1-6}alkyl may be unsubstituted or substituted with halo,

R_4 is hydrogen, halo, -NH_2, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -N(R_{4A})(R_{4B}), or -NHC(=O)(R_{4C}),

wherein R_{4A} to R_{4C} are each independently hydrogen, -C_{1-6}alkyl, cycloalkyl, heterocycloalkyl, -cycloalkyl-heteroaryl, heteroaryl or -aryl-C(=O)-heterocycloalkyl, wherein the aryl or heteroaryl may be unsubstituted or substituted with halo, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -C_{1-6}alkyl-CN, or -C_{1-6}alkyl-OH,

R_5 is hydrogen, cyano, or-C_{1-6}alkyl,

R_6 is absent, or is hydrogen, aryl or heteroaryl.

【Claim 4】

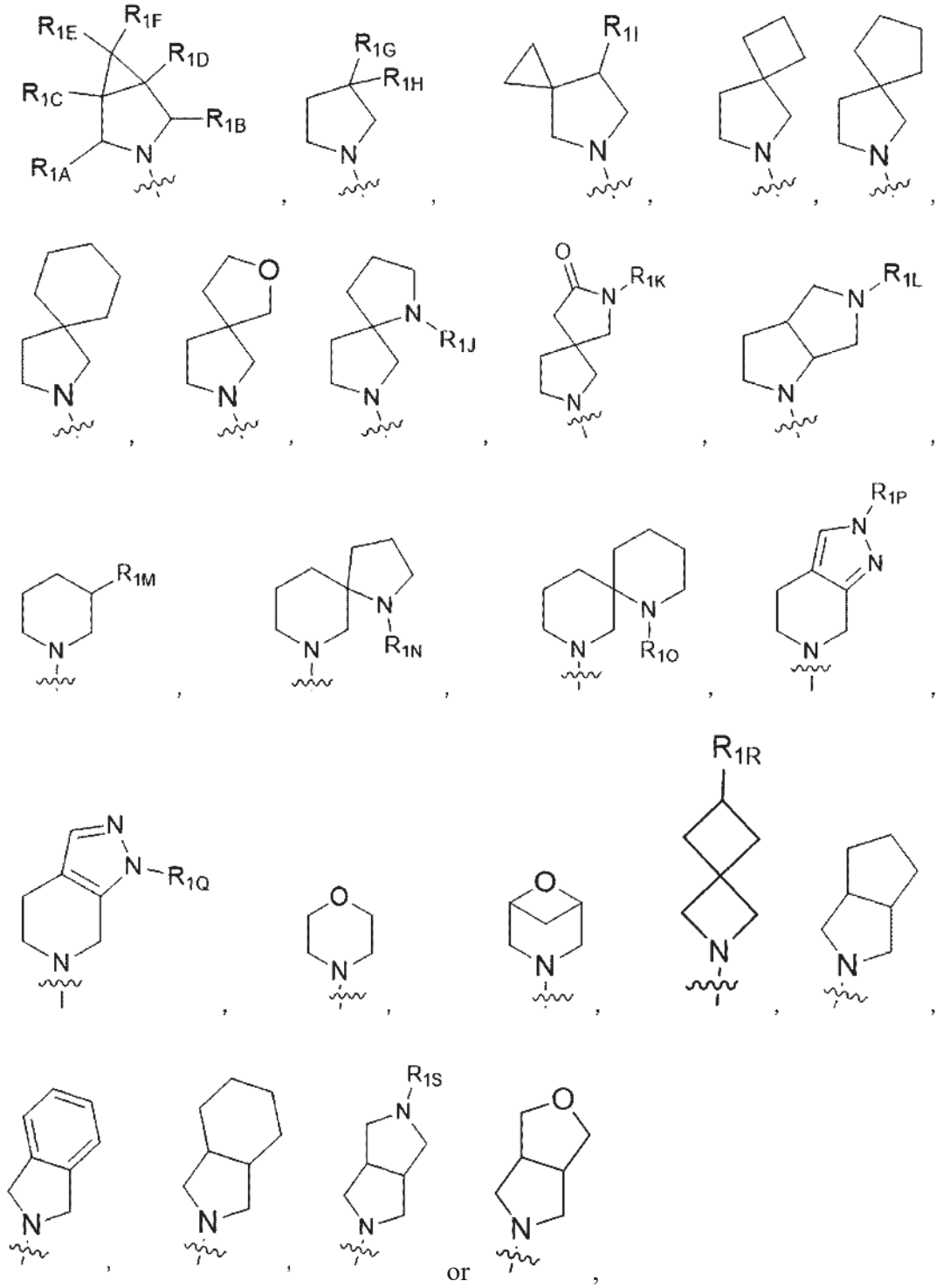
The compound of Formula 1, or a pharmaceutically acceptable salt thereof, according to claim 1,

wherein X_1 and X_4 are each independently C or N,

X_2 and X_3 are N,

R_1 and R_2 are each independently hydrogen or -C_{1-6}alkyl-heterocycloalkyl, wherein the heterocycloalkyl may be unsubstituted or substituted with -C_{1-6}alkyl, or

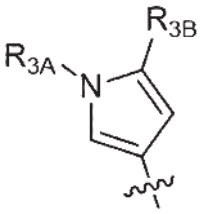
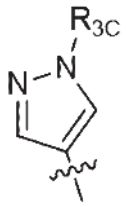
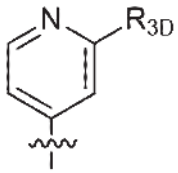
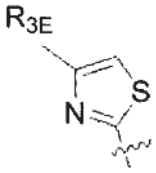
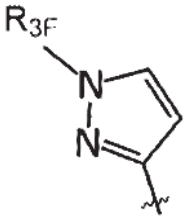
R_1 and R_2 are 3- to 10-membered heteromonocycloalkyl or 3- to 10-membered spiro or fused heterobicycloalkyl formed by linking R_1 and R_2 together, wherein the 3- to 10-membered heteromonocycloalkyl or 3- to 10-membered spiro or fused heterobicycloalkyl formed by linking R_1 and R_2 together is



wherein R_{1A} to R_{1S} are each independently hydrogen, halo, NH_2, cyano, cycloalkyl, -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{2-6}alkynyl-C_{1-6}alkyl, -C_{1-6}alkyl-CN, -C_{1-6}alkyl-OH, -C_{1-6}alkyl-O-C_{1-6}alkyl, -C_{1-6}alkyl-NH_2, -C_{1-6}alkyl-N(C_{1-6}alkyl)(C_{1-6}alkyl), -C_{1-6}alkyl-cycloalkyl, -C(=O)-NH_2, -C(=O)-heteroaryl, heterocycloalkyl, or heteroaryl, wherein the heterocycloalkyl

or heteroaryl may be unsubstituted or substituted with -C_{1-6}alkyl or -OH, wherein the -C_{1-6}alkyl may be unsubstituted or substituted with halo,

R_3 is absent, or is hydrogen, halo, cyano, -C_{1-6}alkyl, -C_{1-6}alkyl-O-C_{1-6}alkyl, aryl,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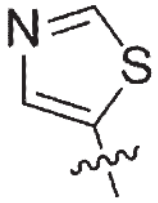

, wherein the aryl may be unsubstituted or substituted with cyano,

wherein R_{3A} to R_{3F} are each independently hydrogen, cyano, -C_{1-6}alkyl or heterocycloalkyl, wherein -C_{1-6}alkyl may be unsubstituted or substituted with halo,

R_4 is hydrogen, halo, -NH_2, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -N(R_{4A})(R_{4B}), or -NHC(=O)(R_{4C}),

wherein R_{4A} to R_{4C} are each independently hydrogen, -C_{1-6}alkyl, cycloalkyl, heterocycloalkyl, -cycloalkyl-heteroaryl, heteroaryl or -aryl-C(=O)-heterocycloalkyl, wherein the aryl or heteroaryl may be unsubstituted or substituted with halo, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -C_{1-6}alkyl-CN, or -C_{1-6}alkyl-OH,

R_5 is hydrogen, cyano, or -C_{1-6}alkyl,

R_6 is absent, or is hydrogen, aryl or heteroaryl.

【Claim 5】

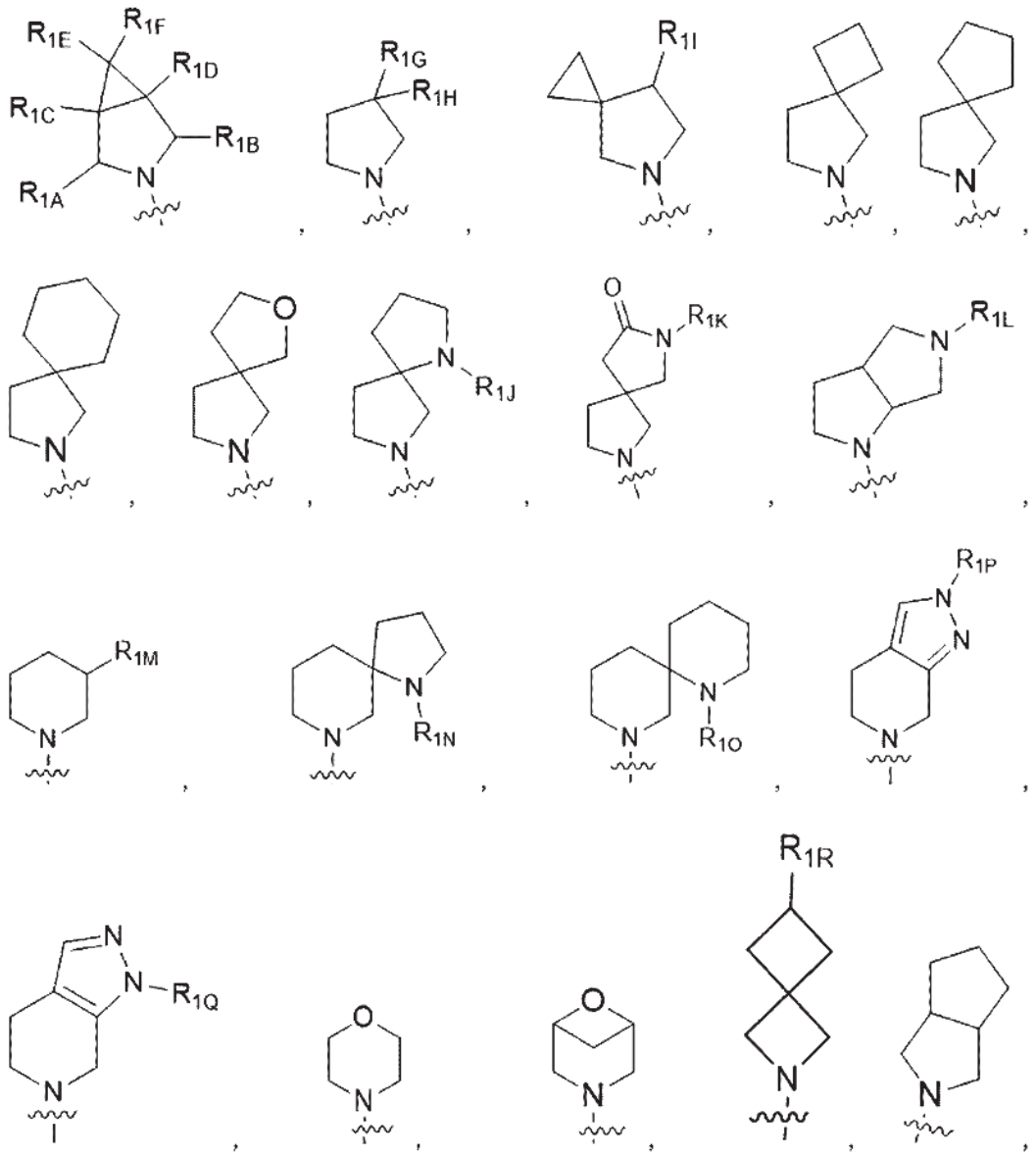
The compound of Formula 1, or a pharmaceutically acceptable salt thereof, according to claim 1,

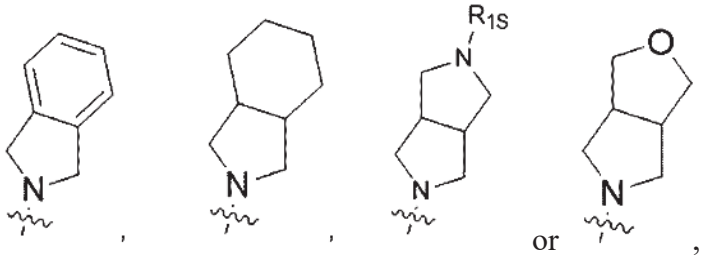
wherein X_1 and X_4 are each independently C or N,

X_2 and X_3 are N,

R_1 and R_2 are each independently hydrogen or -C_{1-6}alkyl-heterocycloalkyl, wherein the heterocycloalkyl may be unsubstituted or substituted with -C_{1-6}alkyl, or

R_1 and R_2 are 3- to 10-membered heteromonocycloalkyl or 3- to 10-membered spiro or fused heterobicycloalkyl formed by linking R_1 and R_2 together, wherein the 3- to 10-membered heteromonocycloalkyl or 3- to 10-membered spiro or fused heterobicycloalkyl formed by linking R_1 and R_2 together is





, , or ,

wherein R_{1A} and R_{1B} are each independently hydrogen, cyano, or -C_{1-6}alkyl-OH,

R_{1C} and R_{1D} are each independently hydrogen, halo, cyano, cycloalkyl, -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{2-6}alkynyl-C_{1-6}alkyl, -C_{1-6}alkyl-CN, -C_{1-6}alkyl-OH, -C_{1-6}alkyl-O-C_{1-6}alkyl, -C_{1-6}alkyl-NH_2, -C_{1-6}alkyl-N(C_{1-6}alkyl)(C_{1-6}alkyl), -C_{1-6}alkyl-cycloalkyl, -C(=O)-NH_2, heterocycloalkyl, or heteroaryl, wherein the heterocycloalkyl or heteroaryl may be unsubstituted or substituted with -C_{1-6}alkyl, wherein the -C_{1-6}alkyl may be unsubstituted or substituted with halo,

R_{1E} and R_{1F} are each independently hydrogen, halo, cyano, or -C_{1-6}alkyl,

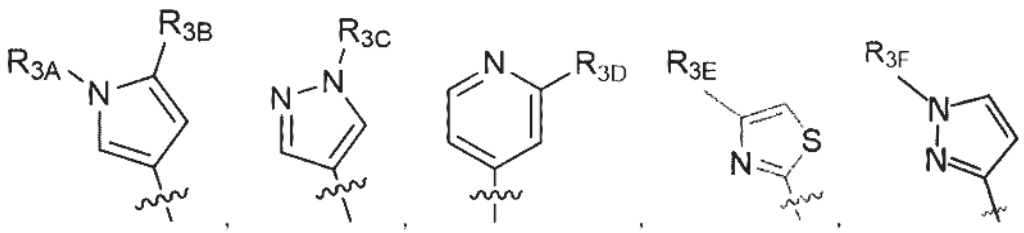
R_{1G} and R_{1H} are each independently hydrogen, -C_{1-6}alkyl, -C_{1-6}alkyl-NH_2, or -C_{1-6}alkyl-N(C_{1-6}alkyl)(C_{1-6}alkyl),

R_{1I} to R_{1L} are each independently hydrogen, halo, NH_2 or -C_{1-6}alkyl,

R_{1M} is hydrogen, -C(=O)-NH_2, or -C(=O)-heteroaryl, wherein the heteroaryl may be unsubstituted or substituted with -OH,

R_{1N} to R_{1S} are each independently hydrogen, halo, or -C_{1-6}alkyl,

R_3 is absent, or is hydrogen, halo, cyano, -C_{1-6}alkyl, -C_{1-6}alkyl-O-C_{1-6}alkyl, aryl,



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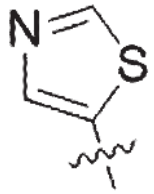


, wherein the aryl may be unsubstituted or substituted with cyano,

wherein R_{3A} to R_{3C} are each independently hydrogen, cyano or -C_{1-6}alkyl,

R_{3D} is hydrogen, -C_{1-6}alkyl or heterocycloalkyl, wherein -C_{1-6}alkyl may be unsubstituted or substituted with halo,

R_{3E} and R_{3F} are each independently hydrogen or -C_{1-6}alkyl,

R_4 is hydrogen, halo, -NH_2, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -N(R_{4A})(R_{4B}), or -NHC(=O)(R_{4C}),

wherein R_{4A} and R_{4B} are each independently hydrogen, -C_{1-6}alkyl, heteroaryl or -aryl-C(=O)-heterocycloalkyl, wherein the aryl or heteroaryl may be unsubstituted or substituted with halo, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -C_{1-6}alkyl-CN, or -C_{1-6}alkyl-OH,

R_{4C} is hydrogen, -C_{1-6}alkyl, cycloalkyl, heterocycloalkyl, -cycloalkyl-heteroaryl or heteroaryl, wherein the heteroaryl may be unsubstituted or substituted with -C_{1-6}alkyl,

R_5 is hydrogen, cyano, or -C_{1-6}alkyl,

R_6 is absent, or is hydrogen, aryl or heteroaryl.

【Claim 6】

The compound of Formula 1, or a pharmaceutically acceptable salt thereof, according to claim 1,

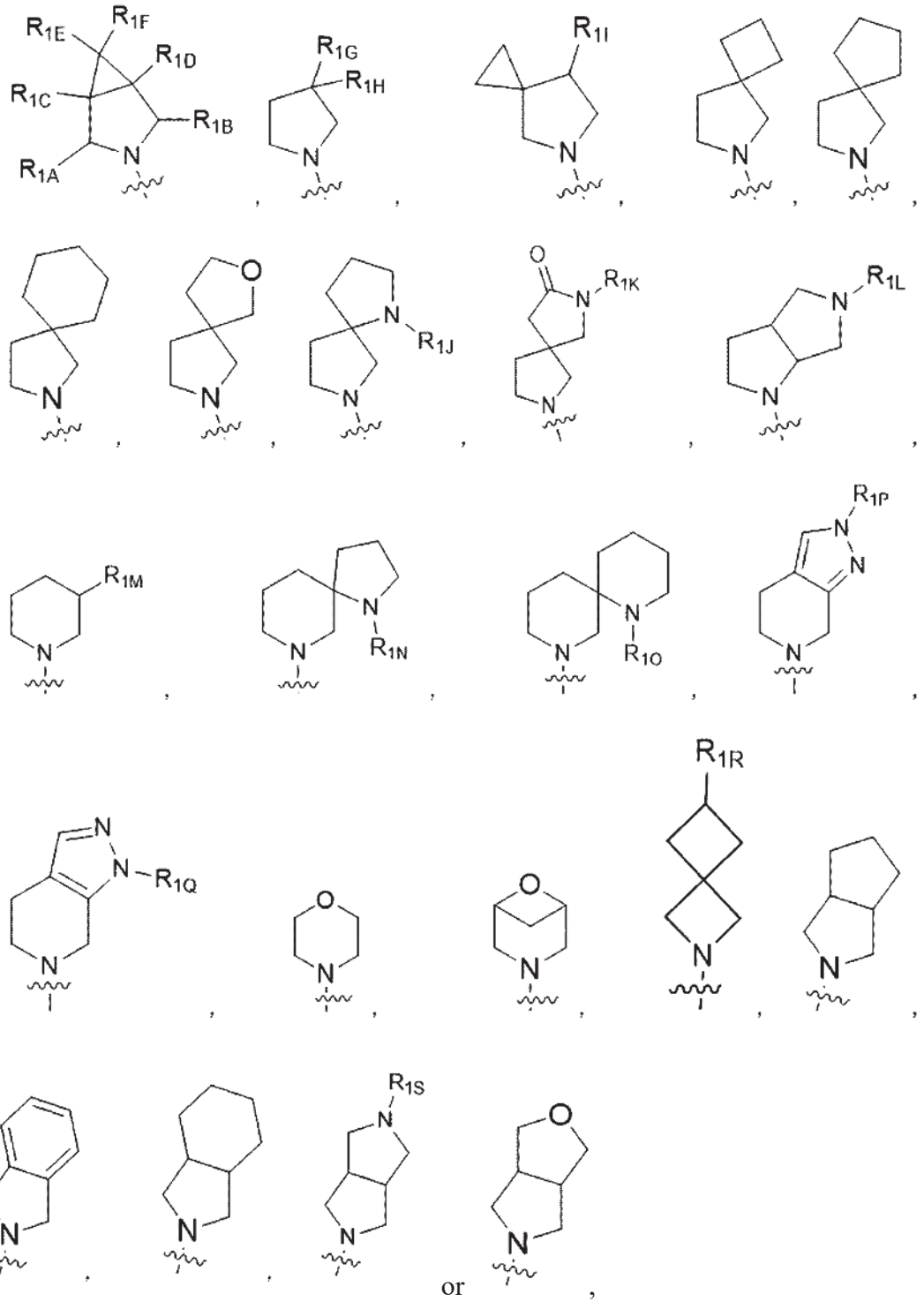
wherein X_1 and X_4 are each independently C or N,

X_2 and X_3 are N,

R_1 and R_2 are each independently hydrogen or -C_{1-6}alkyl-piperidine, wherein the piperidine may be unsubstituted or substituted with -C_{1-6}alkyl, or

R_1 and R_2 are 3- to 10-membered heteromonocycloalkyl or 3- to 10-membered spiro or fused heterobicycloalkyl formed by linking R_1 and R_2 together, wherein the 3- to 10-

membered heteromonocycloalkyl or 3- to 10-membered spiro or fused heterobicycloalkyl formed by linking R_1 and R_2 together is



wherein R_{1A} and R_{1B} are each independently hydrogen, cyano, or -C_{1-6}alkyl-OH,

R_{1C} and R_{1D} are each independently hydrogen, halo, cyano, cycloalkyl, -C_{1-6}alkyl, -C_{2-}

$_{6}$alkenyl, -C_{2-6}alkynyl, -C_{2-6}alkynyl-C_{1-6}alkyl, -C_{1-6}alkyl-CN, -C_{1-6}alkyl-OH, -C_{1-6}alkyl-O-C_{1-6}alkyl, -C_{1-6}alkyl-NH_2, -C_{1-6}alkyl-N(C_{1-6}alkyl)(C_{1-6}alkyl), -C_{1-6}alkyl-cycloalkyl, -C(=O)-NH_2, piperidine or isoxazole, wherein the piperidine or isoxazole may be unsubstituted or substituted with -C_{1-6}alkyl, wherein the -C_{1-6}alkyl may be unsubstituted or substituted with halo,

R_{1E} and R_{1F} are each independently hydrogen, halo, cyano, or -C_{1-6}alkyl,

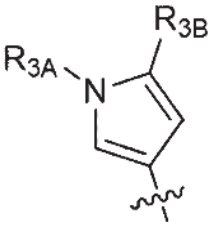
R_{1G} and R_{1H} are each independently hydrogen, -C_{1-6}alkyl, -C_{1-6}alkyl-NH_2, or -C_{1-6}alkyl-N(C_{1-6}alkyl)(C_{1-6}alkyl),

R_{1I} to R_{1L} are each independently hydrogen, halo, NH_2 or -C_{1-6}alkyl,

R_{1M} is hydrogen, -C(=O)-NH_2, or -C(=O)-pyridine, wherein the pyridine may be unsubstituted or substituted with -OH,

R_{1N} to R_{1S} are each independently hydrogen, halo, or -C_{1-6}alkyl,

R_3 is absent, or is hydrogen, halo, cyano, -C_{1-6}alkyl, -C_{1-6}alkyl-O-C_{1-6}alkyl, aryl,



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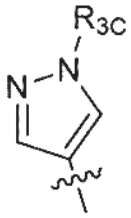

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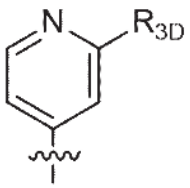

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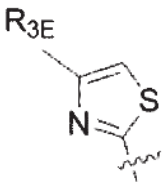

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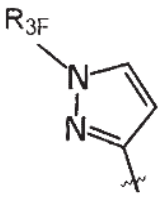

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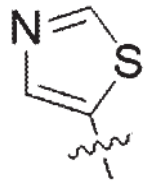


, wherein the aryl may be unsubstituted or substituted with cyano,

wherein R_{3A} to R_{3C} are each independently hydrogen, cyano or -C_{1-6}alkyl,

R_{3D} is hydrogen, -C_{1-6}alkyl or morpholine, wherein -C_{1-6}alkyl may be unsubstituted or substituted with halo,

R_{3E} and R_{3F} are each independently hydrogen or -C_{1-6}alkyl,

R_4 is hydrogen, halo, -NH_2, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -N(R_{4A})(R_{4B}), or -NHC(=O)(R_{4C}),

wherein R_{4A} and R_{4B} are each independently hydrogen, -C_{1-6}alkyl, pyrazole or -aryl-C(=O)-morpholine, wherein the aryl may be unsubstituted or substituted with -O-C_{1-6}alkyl, wherein the pyrazole may be unsubstituted or substituted with halo, -C_{1-6}alkyl, -C_{1-6}alkyl-CN, or -C_{1-6}alkyl-OH,

R_{4C} is hydrogen, -C_{1-6}alkyl, cycloalkyl, heterocycloalkyl, -cycloalkyl-pyridine, pyrazole or furan, wherein the pyridine, pyrazole or furan may be unsubstituted or substituted with -C_{1-6}alkyl,

R_5 is hydrogen or -C_{1-6}alkyl,

R_6 is absent, or is hydrogen, aryl or heteroaryl.

【Claim 7】

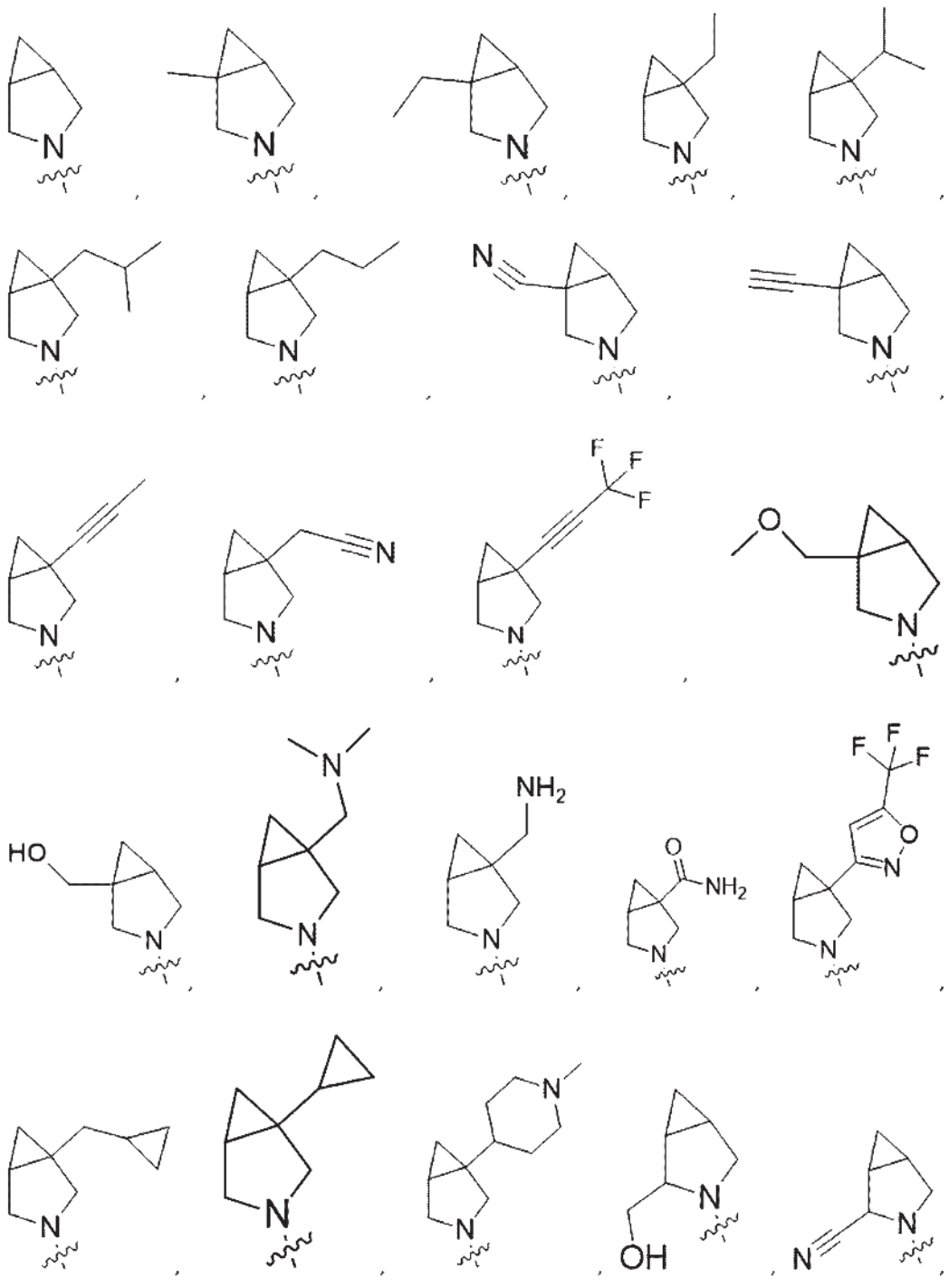
The compound of Formula 1, or a pharmaceutically acceptable salt thereof, according to claim 1,

wherein X_1 and X_4 are each independently C or N,

X_2 and X_3 are N,

R_1 and R_2 are each independently hydrogen or -C_{1-6}alkyl-piperidine, wherein the piperidine may be unsubstituted or substituted with -C_{1-6}alkyl, or

R_1 and R_2 are 3- to 10-membered heteromonocycloalkyl or 3- to 10-membered spiro or fused heterobicycloalkyl formed by linking R_1 and R_2 together, wherein the 3- to 10-membered heteromonocycloalkyl or 3- to 10-membered spiro or fused heterobicycloalkyl formed by linking R_1 and R_2 together is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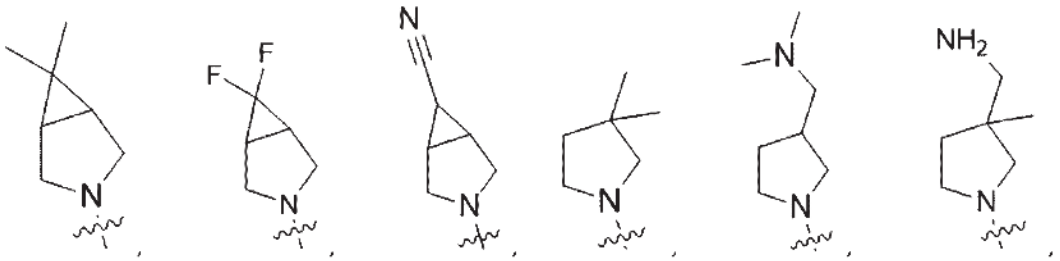
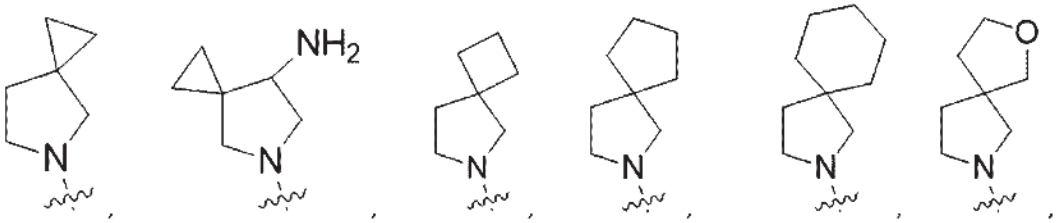
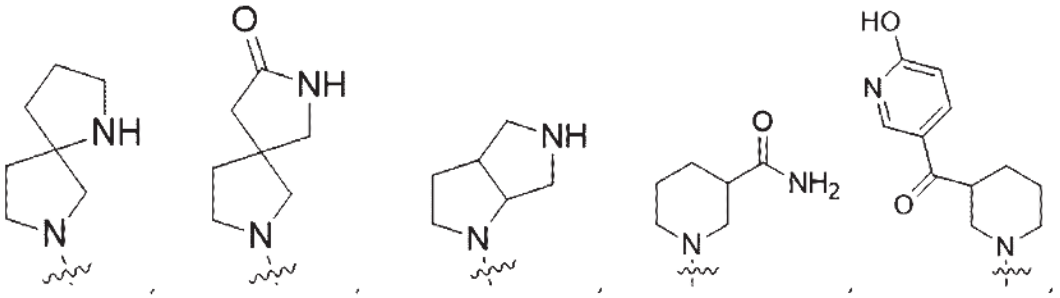
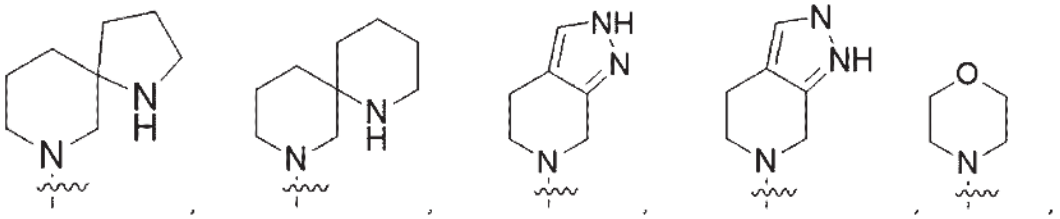
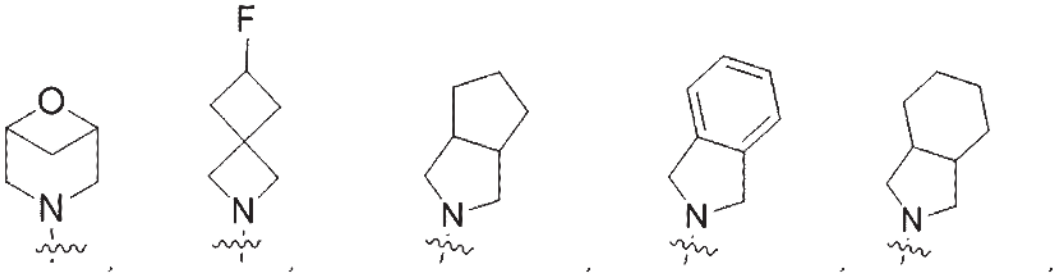
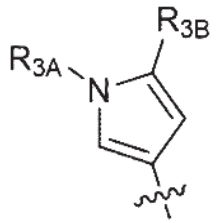
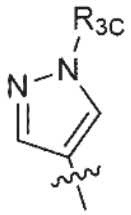
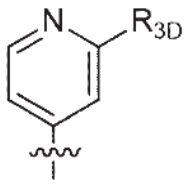
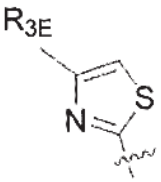
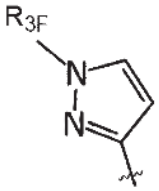
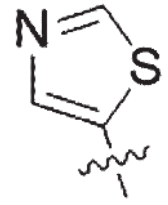






or ,

R_3 is absent, or is hydrogen, halo, cyano, -C_{1-6}alkyl, -C_{1-6}alkyl-O-C_{1-6}alkyl, aryl, , , , ,  or , wherein the aryl may be unsubstituted or substituted with cyano,

wherein R_{3A} to R_{3C} are each independently hydrogen, cyano or -C_{1-6}alkyl,

R_{3D} is hydrogen, -C_{1-6}alkyl or morpholine, wherein -C_{1-6}alkyl may be unsubstituted or substituted with halo,

R_{3E} and R_{3F} are each independently hydrogen or -C_{1-6}alkyl,

R_4 is hydrogen, halo, -NH_2, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -N(R_{4A})(R_{4B}), or -NHC(=O)(R_{4C}),

wherein R_{4A} and R_{4B} are each independently hydrogen, -C_{1-6}alkyl, pyrazole or -aryl-C(=O)-morpholine, wherein the aryl may be unsubstituted or substituted with -O-C_{1-6}alkyl, the pyrazole may be unsubstituted or substituted with halo, -C_{1-6}alkyl, -C_{1-6}alkyl-CN, or -C_{1-6}alkyl-OH,

R_{4C} is hydrogen, -C_{1-6}alkyl, cycloalkyl, heterocycloalkyl, -cycloalkyl-pyridine, pyrazole or furan, wherein the pyridine, pyrazole or furan may be unsubstituted or substituted with -C_{1-6}alkyl,

R_5 is hydrogen or -C_{1-6}alkyl,

R_6 is absent, or is hydrogen, aryl or heteroaryl.

【Claim 8】

The compound of Formula 1, or a pharmaceutically acceptable salt thereof, according

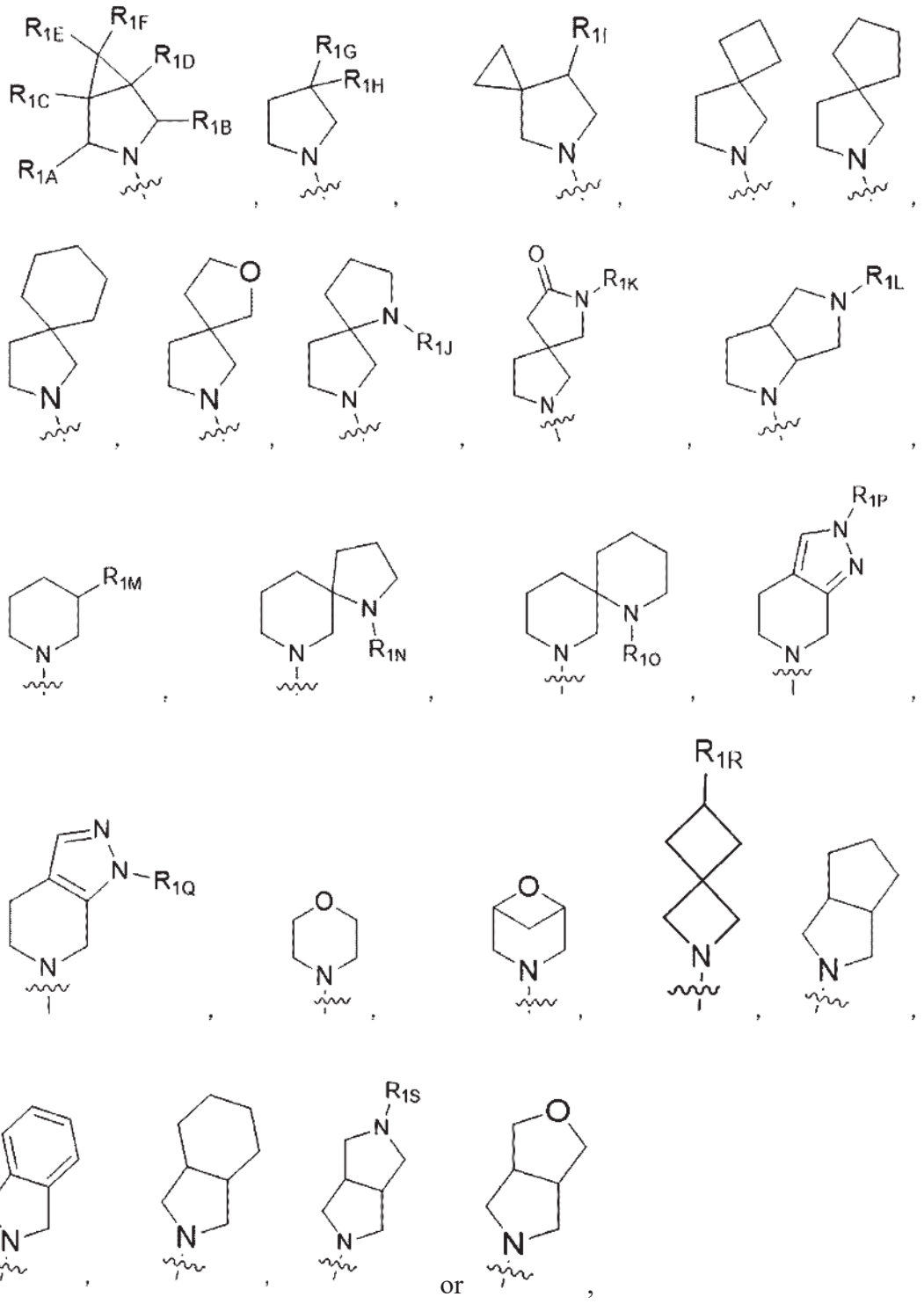
to claim 1,

wherein X_1 and X_4 are each independently C or N,

X_2 and X_3 are N,

R_1 and R_2 are each independently hydrogen or -C_{1-6}alkyl-piperidine, wherein the piperidine may be unsubstituted or substituted with -C_{1-6}alkyl,

or R_1 and R_2 are 3- to 10-membered heteromonocycloalkyl or 3- to 10-membered spiro or fused heterobicycloalkyl formed by linking R_1 and R_2 together, wherein the 3- to 10-membered heteromonocycloalkyl or 3- to 10-membered spiro or fused heterobicycloalkyl formed by linking R_1 and R_2 together is



wherein R_{1A} and R_{1B} are each independently hydrogen, cyano, or -C_{1-6}alkyl-OH,

R_{1C} and R_{1D} are each independently hydrogen, halo, cyano, cycloalkyl, -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{2-6}alkynyl-C_{1-6}alkyl, -C_{1-6}alkyl-CN, -C_{1-6}alkyl-OH, -C_{1-6}alkyl-O-C_{1-6}alkyl, -C_{1-6}alkyl-NH_2, -C_{1-6}alkyl-N(C_{1-6}alkyl)(C_{1-6}alkyl), -C_{1-6}alkyl-cycloalkyl, -C(=O)-NH_2,

piperidine or isoxazole, wherein the piperidine or isoxazole may be unsubstituted or substituted with -C_{1-6}alkyl, wherein the -C_{1-6}alkyl may be unsubstituted or substituted with halo,

R_{1E} and R_{1F} are each independently hydrogen, halo, cyano, or -C_{1-6}alkyl,

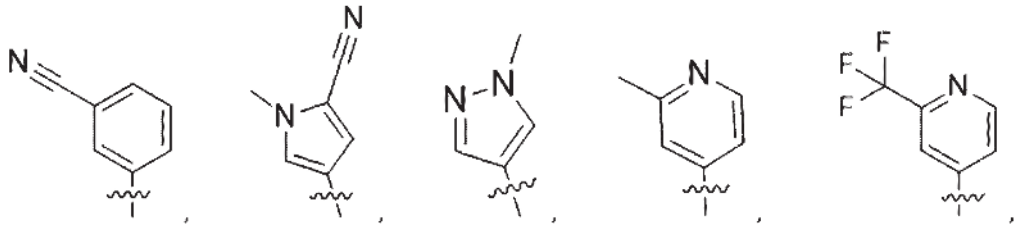
R_{1G} and R_{1H} are each independently hydrogen, -C_{1-6}alkyl, -C_{1-6}alkyl-NH_2, or -C_{1-6}alkyl-N(C_{1-6}alkyl)(C_{1-6}alkyl),

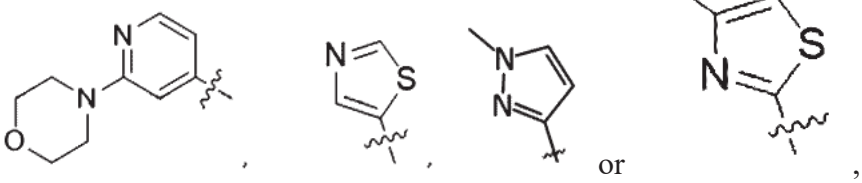
R_{1I} to R_{1L} are each independently hydrogen, halo, NH_2 or -C_{1-6}alkyl,

R_{1M} is hydrogen, -C(=O)-NH_2, or -C(=O)-pyridine, wherein the pyridine may be unsubstituted or substituted with -OH,

R_{1N} to R_{1S} are each independently hydrogen, halo, or -C_{1-6}alkyl,

R_3 is absent, or is hydrogen, halo, cyano, -C_{1-6}alkyl, -C_{1-6}alkyl-O-C_{1-6}alkyl,





R_4 is hydrogen, halo, -NH_2, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -N(R_{4A})(R_{4B}), or -NHC(=O)(R_{4C}),

wherein R_{4A} and R_{4B} are each independently hydrogen, -C_{1-6}alkyl, pyrazole or -aryl-C(=O)-morpholine, wherein the aryl may be unsubstituted or substituted with -O-C_{1-6}alkyl, the pyrazole may be unsubstituted or substituted with halo, -C_{1-6}alkyl, -C_{1-6}alkyl-CN, or -C_{1-6}alkyl-OH,

R_{4C} is hydrogen, -C_{1-6}alkyl, cycloalkyl, heterocycloalkyl, -cycloalkyl-pyridine, pyrazole or furan, wherein the pyridine, pyrazole or furan may be unsubstituted or substituted

with -C_{1-6}alkyl,

R_5 is hydrogen or -C_{1-6}alkyl,

R_6 is absent, or is hydrogen, aryl or heteroaryl.

【Claim 9】

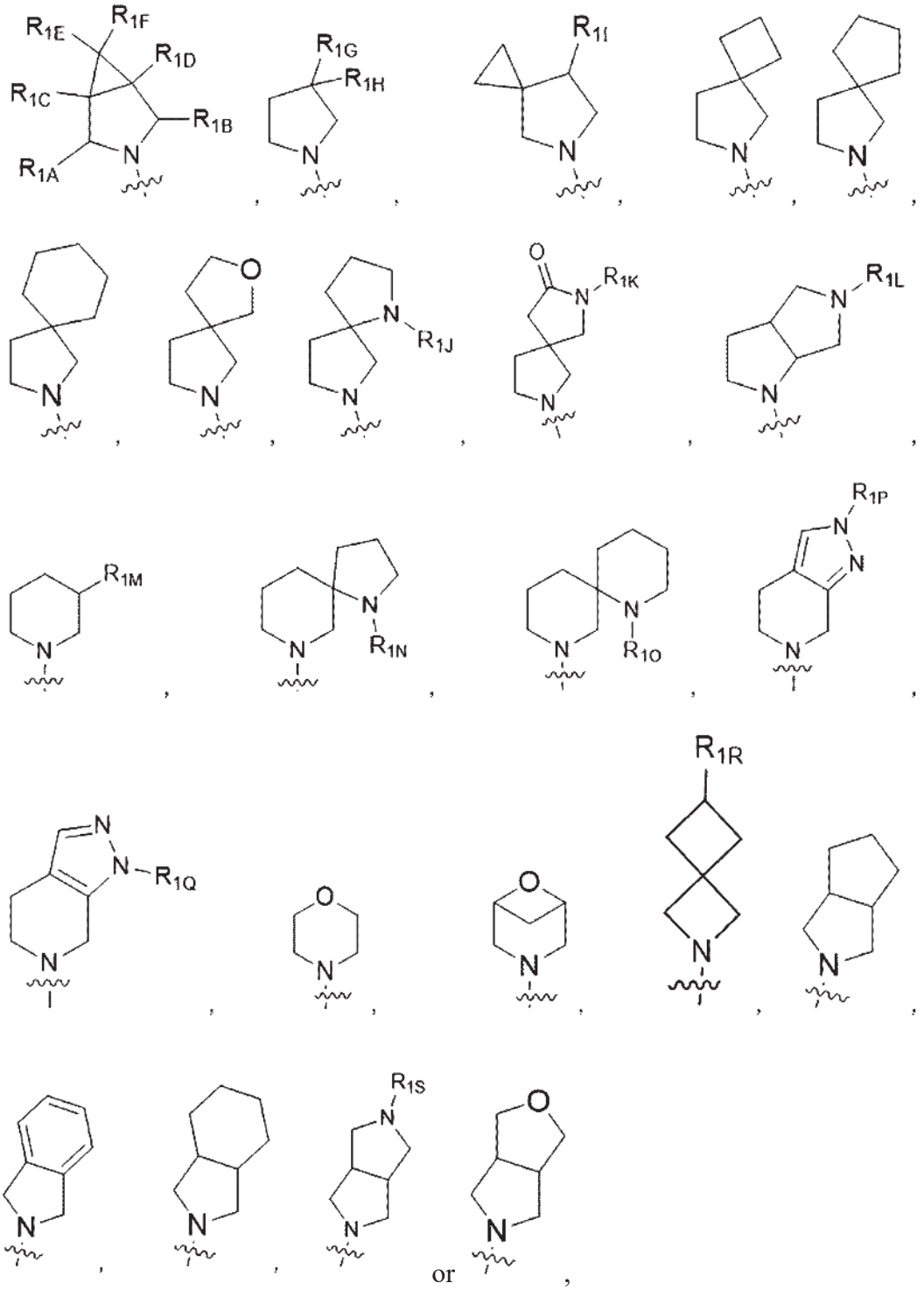
The compound of Formula 1, or a pharmaceutically acceptable salt thereof, according to claim 1,

wherein X_1 and X_4 are each independently C or N,

X_2 and X_3 are N,

R_1 and R_2 are each independently hydrogen or -C_{1-6}alkyl-piperidine, wherein the piperidine may be unsubstituted or substituted with -C_{1-6}alkyl, or

R_1 and R_2 are 3- to 10-membered heteromonocycloalkyl or 3- to 10-membered spiro or fused heterobicycloalkyl formed by linking R_1 and R_2 together, wherein the 3- to 10-membered heteromonocycloalkyl or 3- to 10-membered spiro or fused heterobicycloalkyl formed by linking R_1 and R_2 together is



wherein R_{1A} and R_{1B} are each independently hydrogen, cyano, or -C_{1-6}alkyl-OH,

R_{1C} and R_{1D} are each independently hydrogen, halo, cyano, cycloalkyl, -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{2-6}alkynyl-C_{1-6}alkyl, -C_{1-6}alkyl-CN, -C_{1-6}alkyl-OH, -C_{1-6}alkyl-O-C_{1-6}alkyl, -C_{1-6}alkyl-NH_2, -C_{1-6}alkyl-N(C_{1-6}alkyl)(C_{1-6}alkyl), -C_{1-6}alkyl-cycloalkyl, -C(=O)-NH_2,

piperidine or isoxazole, wherein the piperidine or isoxazole may be unsubstituted or substituted with C_{1-6}alkyl, wherein the C_{1-6}alkyl may be unsubstituted or substituted with halo,

R_{1E} and R_{1F} are each independently hydrogen, halo, cyano, or -C_{1-6}alkyl,

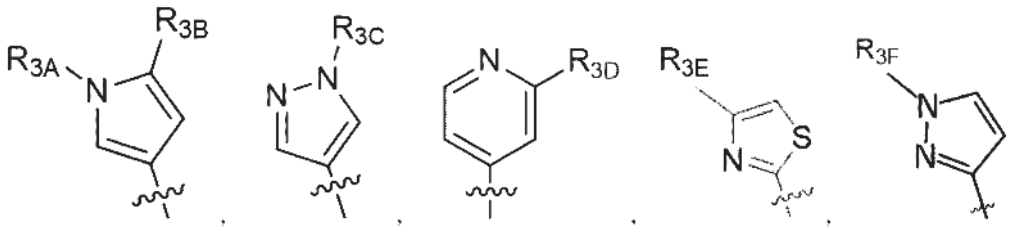
R_{1G} and R_{1H} are each independently hydrogen, -C_{1-6}alkyl, -C_{1-6}alkyl-NH_2, or -C_{1-6}alkyl-N(C_{1-6}alkyl)(C_{1-6}alkyl),

R_{1I} to R_{1L} are each independently hydrogen, halo, NH_2 or -C_{1-6}alkyl,

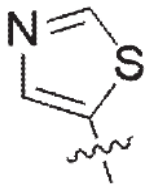
R_{1M} is hydrogen, -C(=O)-NH_2, or -C(=O)-pyridine, wherein the pyridine may be unsubstituted or substituted with -OH,

R_{1N} to R_{1S} are each independently hydrogen, halo, or -C_{1-6}alkyl,

R_3 is absent, or is hydrogen, halo, cyano, -C_{1-6}alkyl, -C_{1-6}alkyl-O-C_{1-6}alkyl, aryl,



or

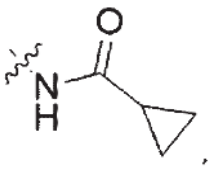


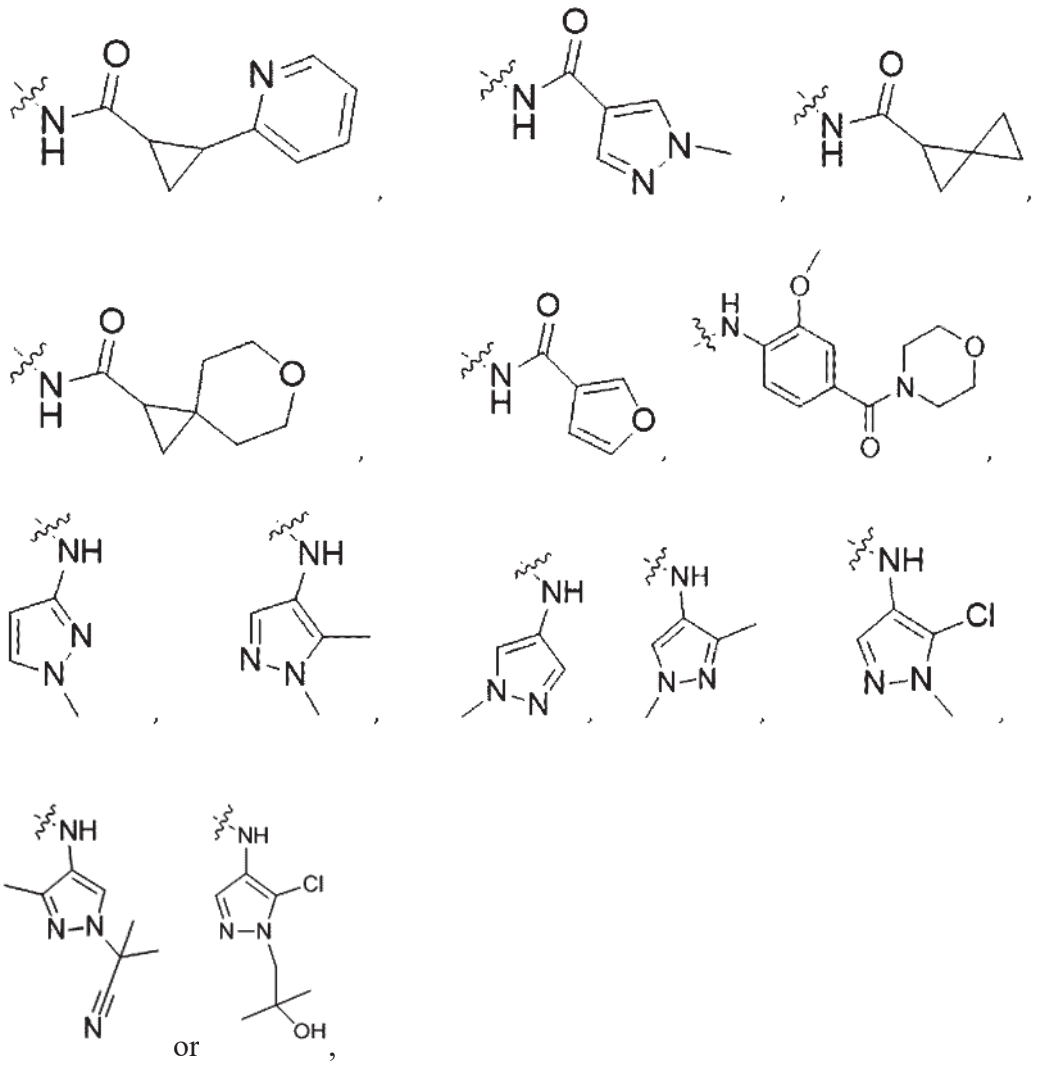
, wherein the aryl may be unsubstituted or substituted with cyano,

wherein R_{3A} to R_{3C} are each independently hydrogen, cyano or -C_{1-6}alkyl,

R_{3D} is hydrogen, -C_{1-6}alkyl or morpholine, wherein -C_{1-6}alkyl may be unsubstituted or substituted with halo,

R_{3E} and R_{3F} are each independently hydrogen or -C_{1-6}alkyl,

R_4 is hydrogen, halo, -NH_2, -C_{1-6}alkyl, -O-C_{1-6}alkyl 

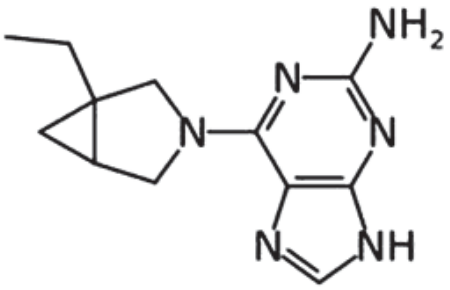
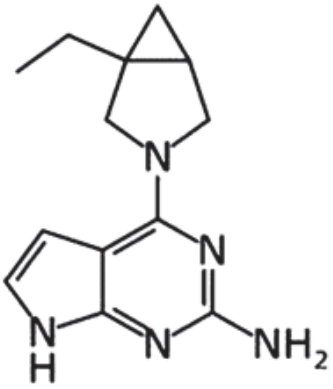


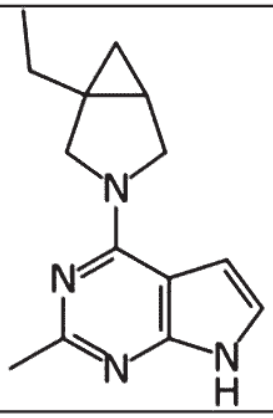
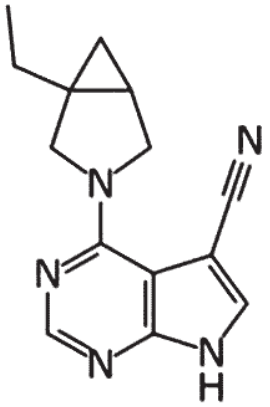
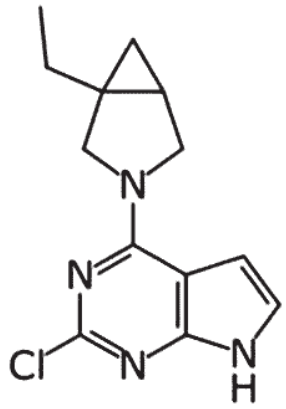
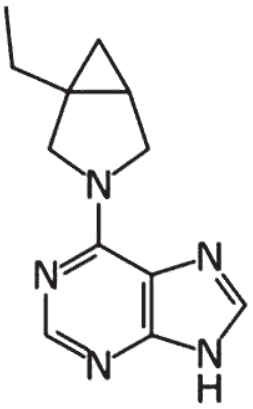
R_5 is hydrogen or -$C_{1\text{-}6}$alkyl,

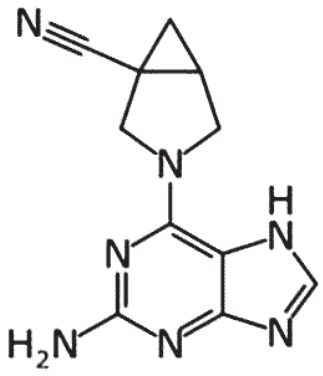
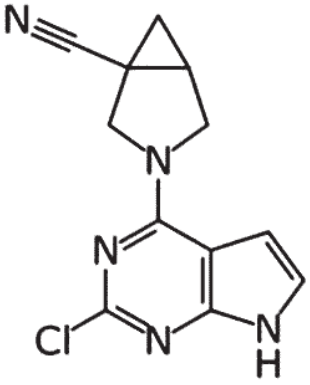
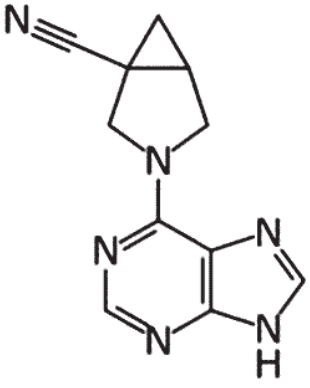
R_6 is absent, or is hydrogen, aryl or heteroaryl.

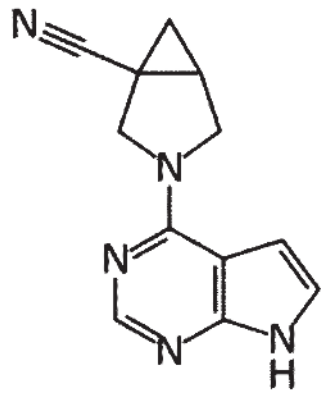
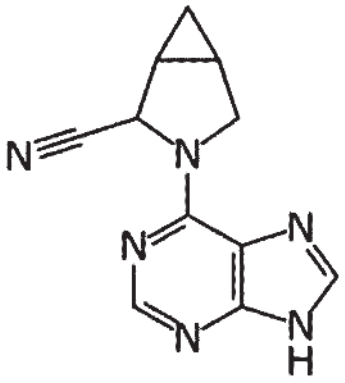
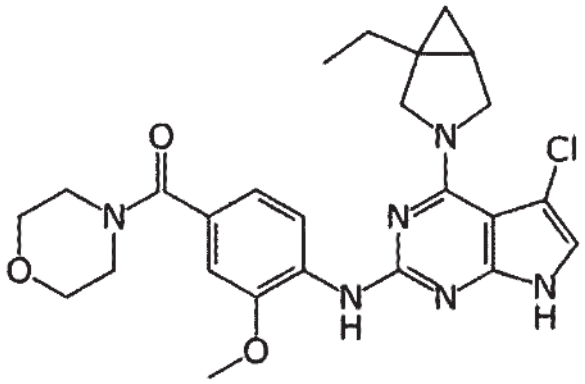
【Claim 10】

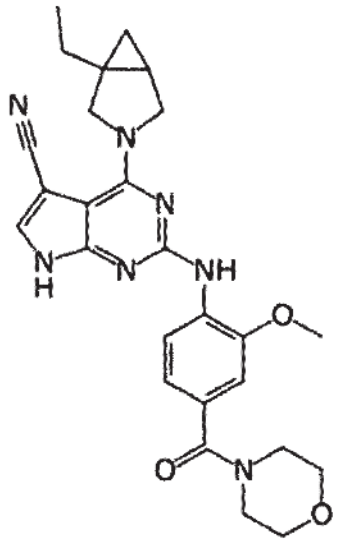
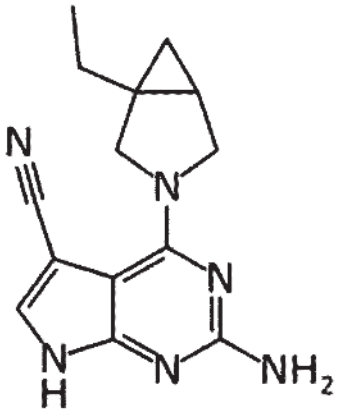
The compound selected from the group consisting of the following compounds, or a pharmaceutically acceptable salt thereof, according to claim 1:

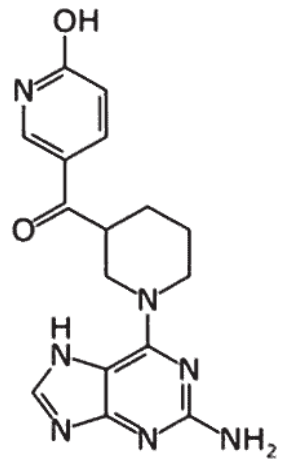
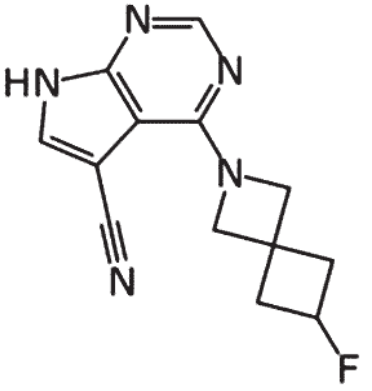
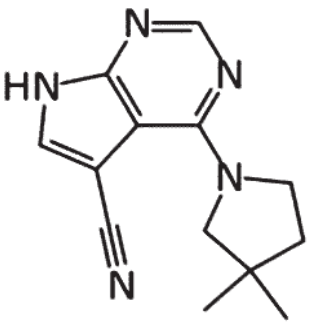
Compound No.	Formula
1	
2	

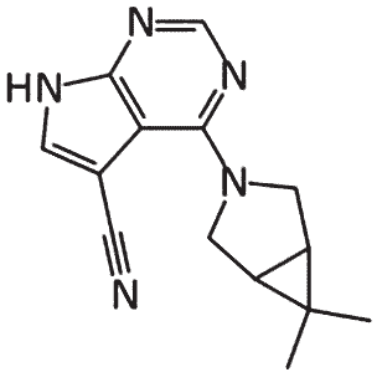
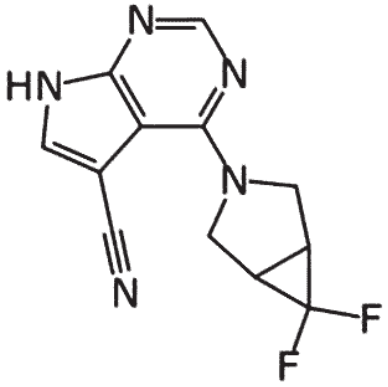
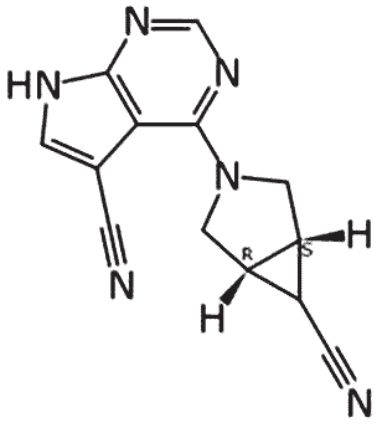
3	
4	
5	
6	

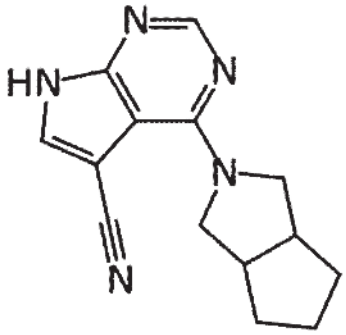
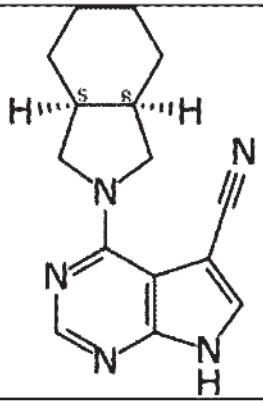
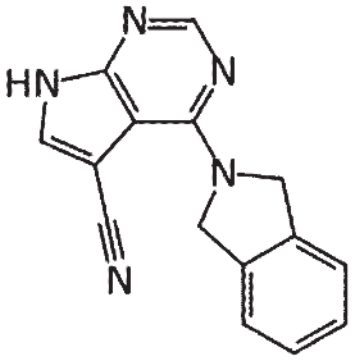
7	
8	
9	

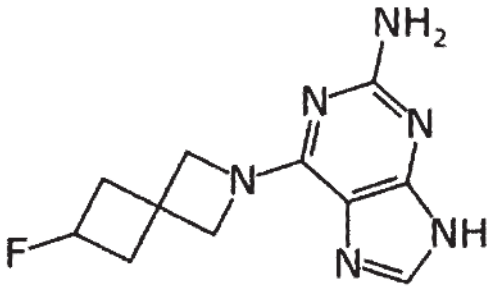
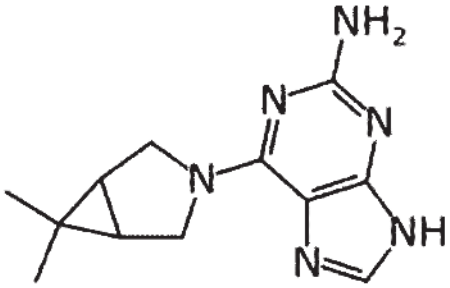
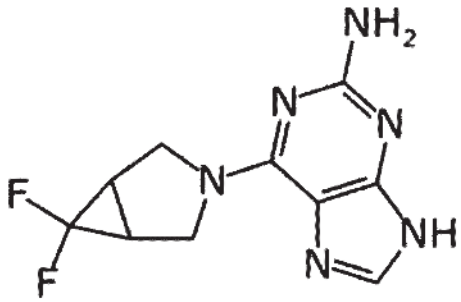
10	
11	
12	

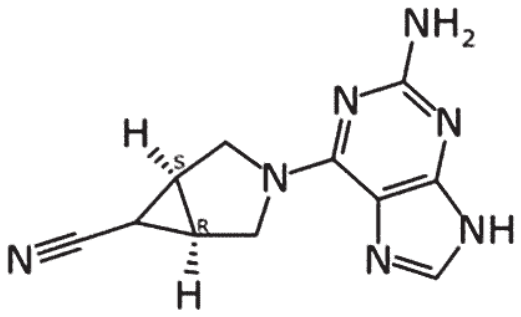
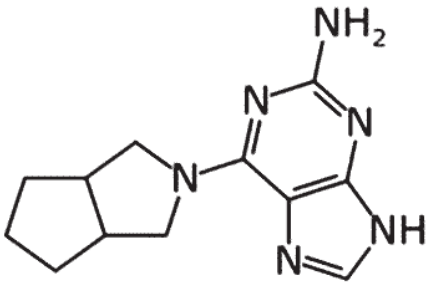
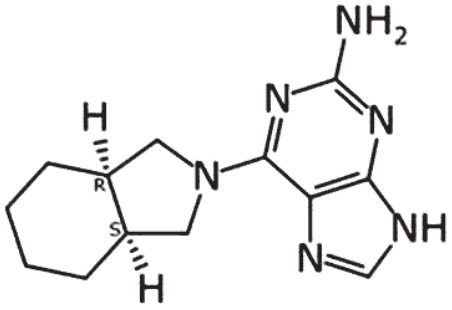
13	
14	

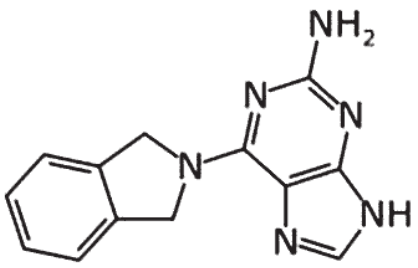
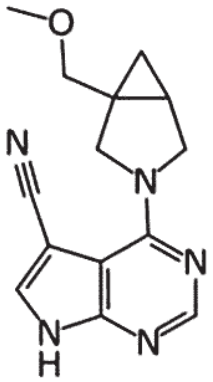
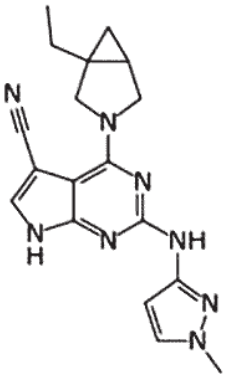
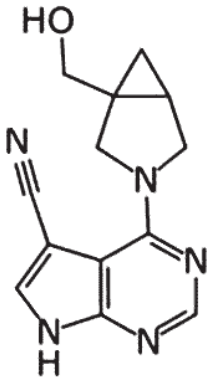
15	
16	
17	

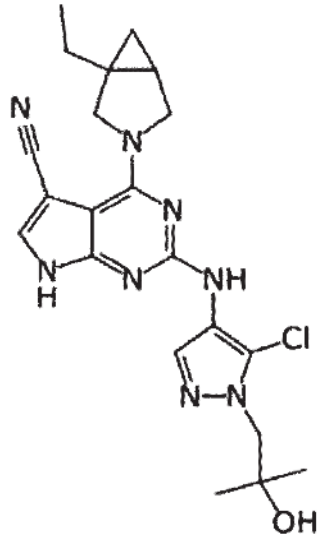
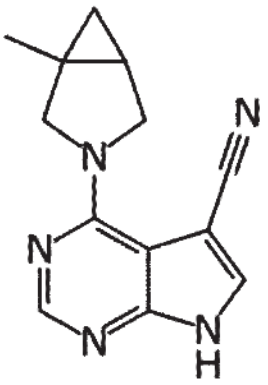
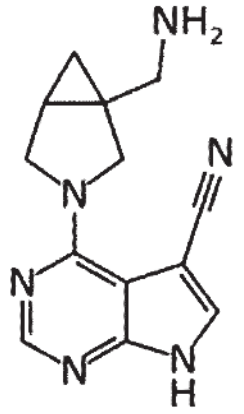
18	
19	
20	

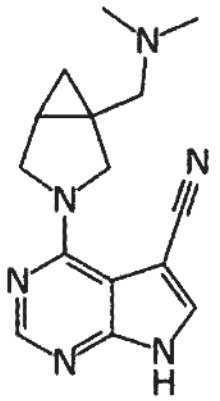
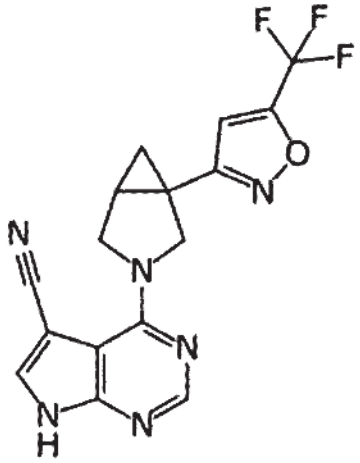
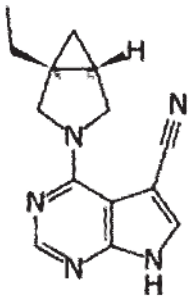
21	
22	
23	

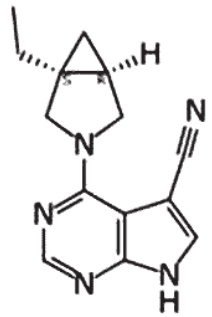
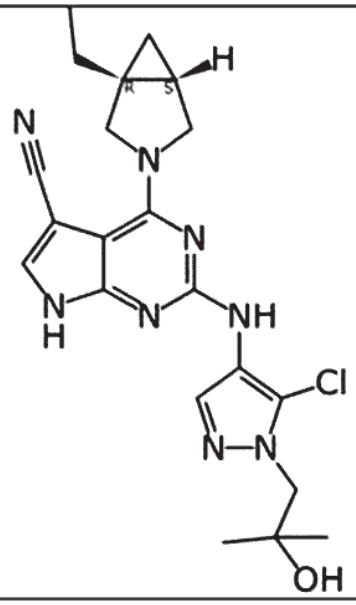
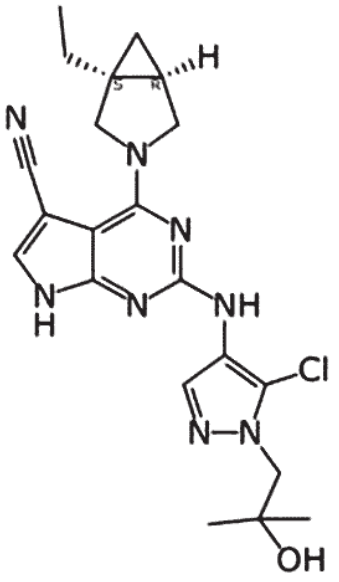
24	
25	
26	

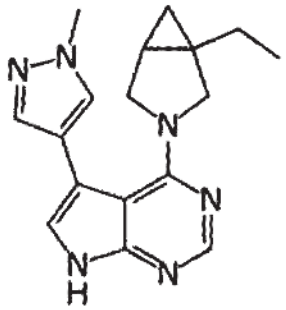
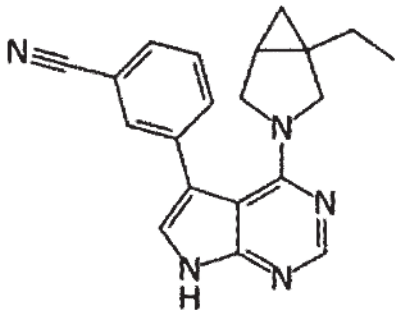
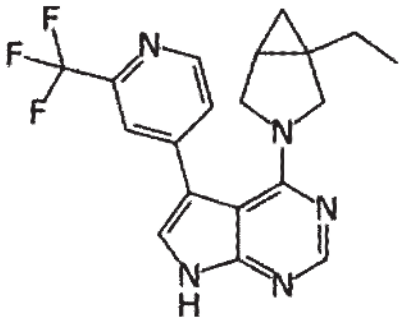
27	
28	
29	

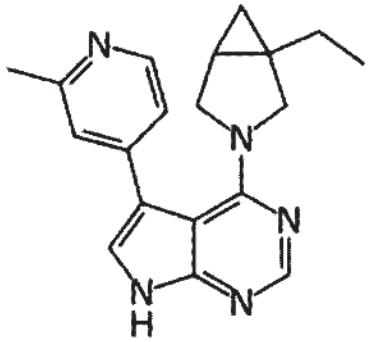
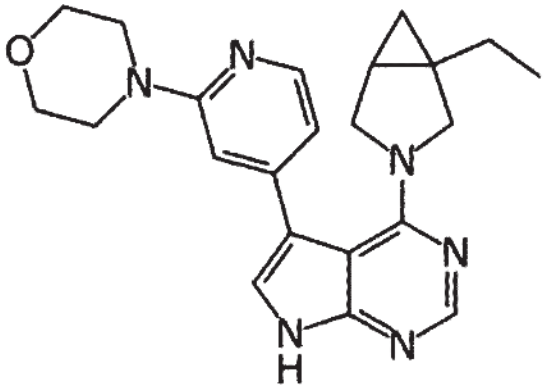
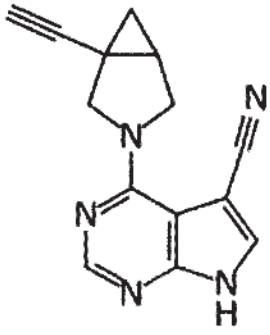
30	
31	
32	
33	

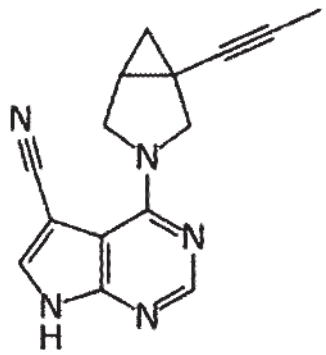
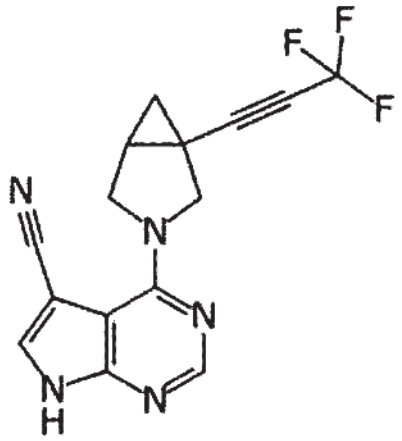
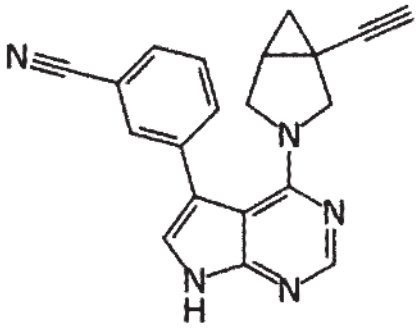
34	
35	
36	

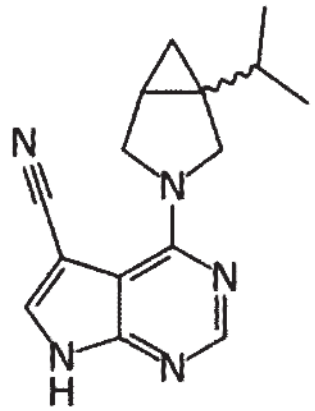
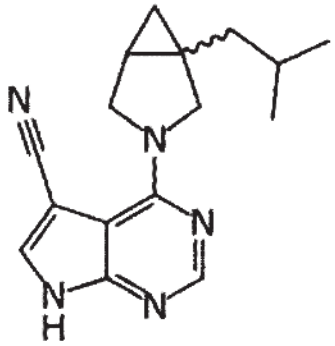
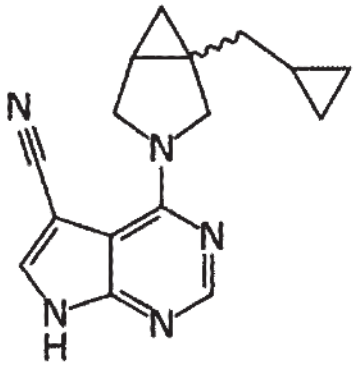
37	
38	
39	

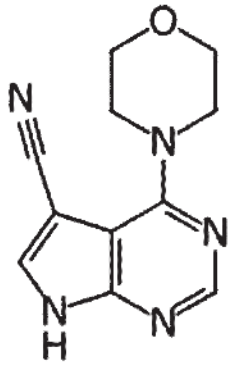
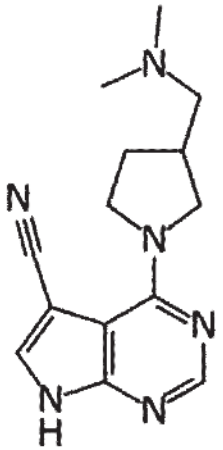
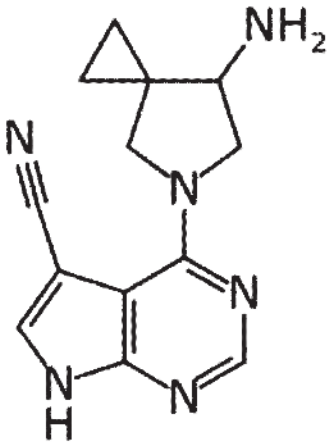
40	
41	
42	

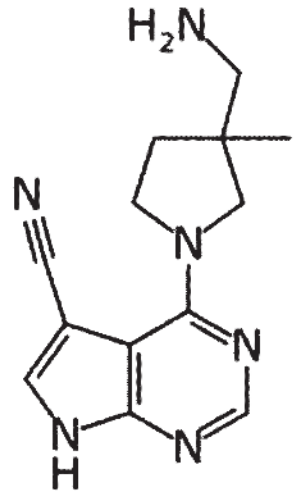
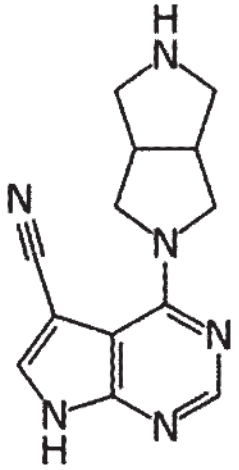
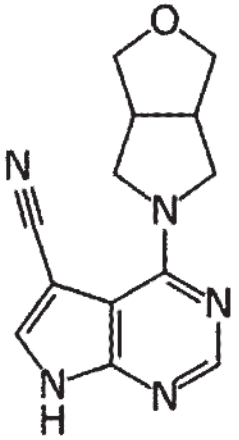
43	
44	
45	

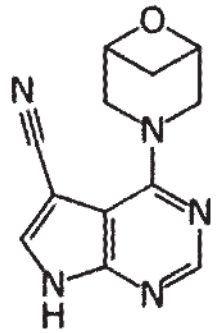
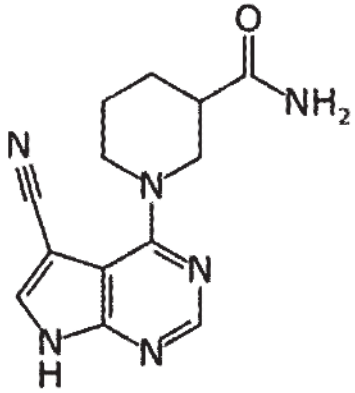
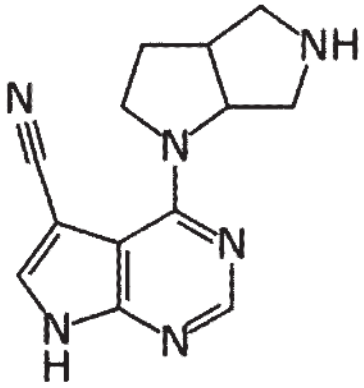
46	
47	
48	

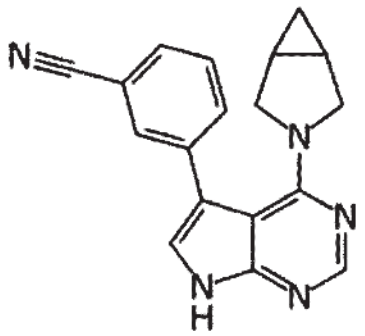
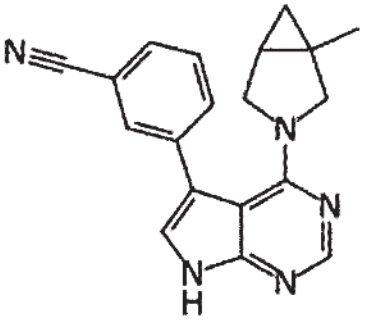
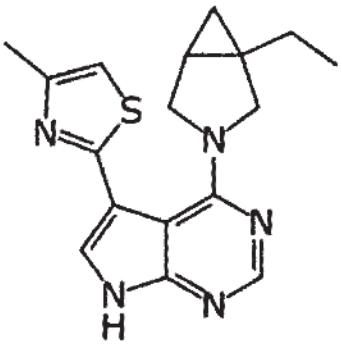
49	
50	
51	

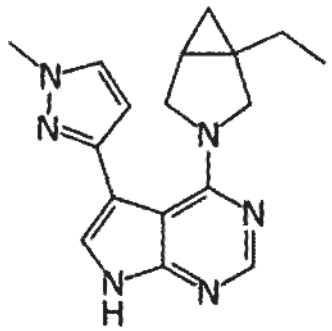
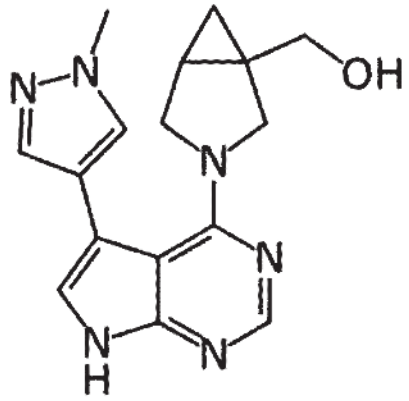
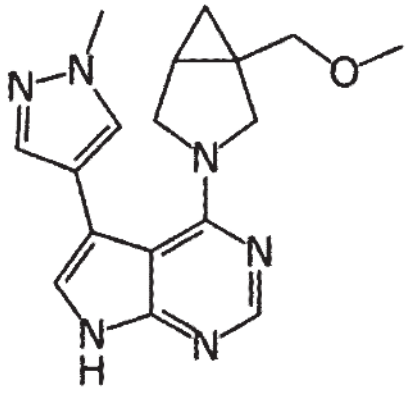
52	
53	
54	

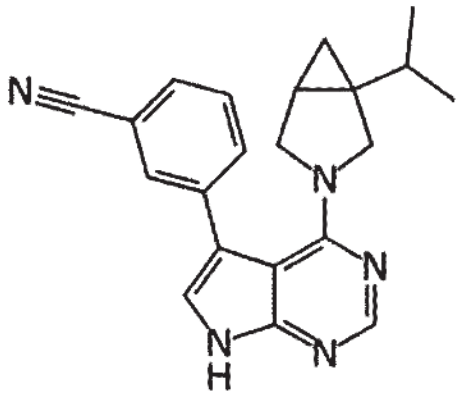
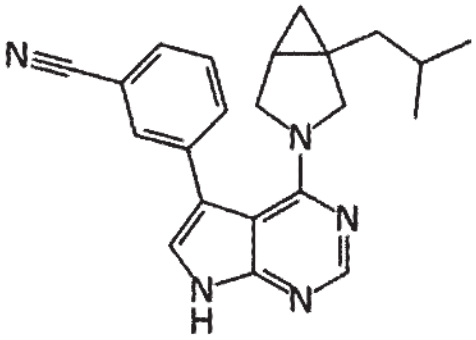
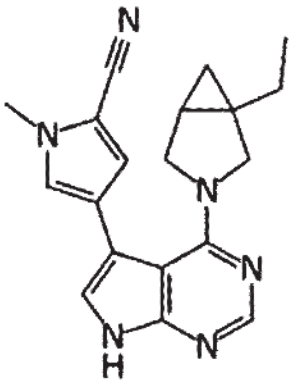
55	
56	
57	

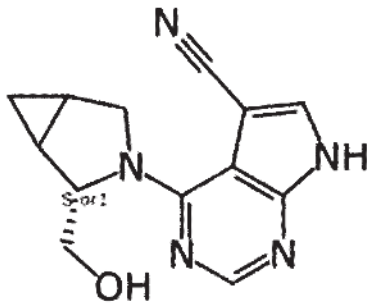
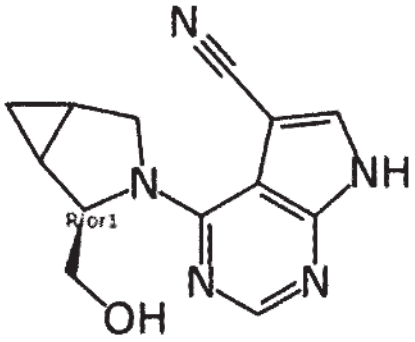
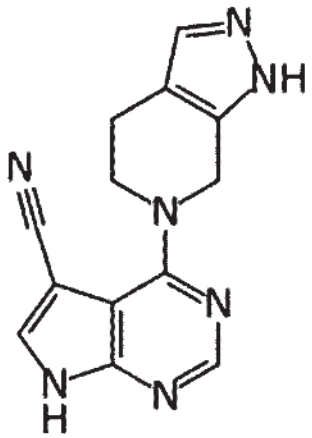
58	
59	
60	

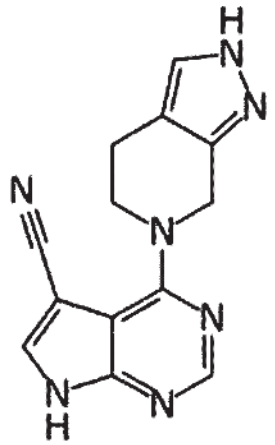
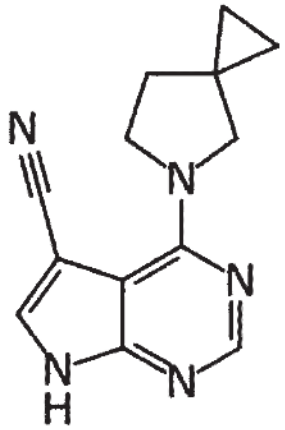
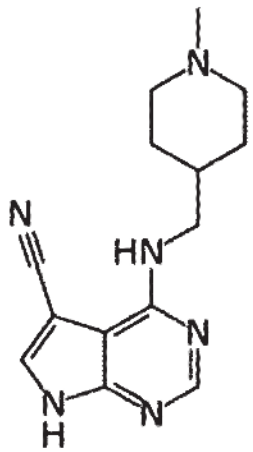
61	
62	
63	

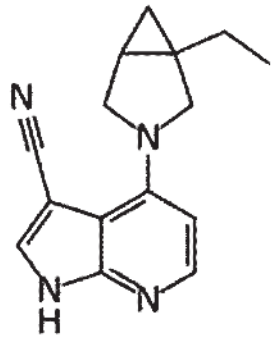
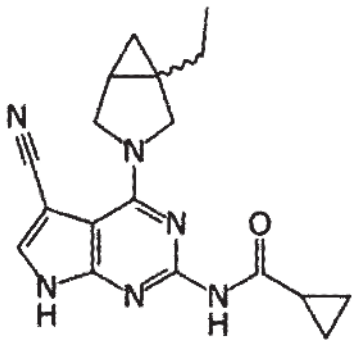
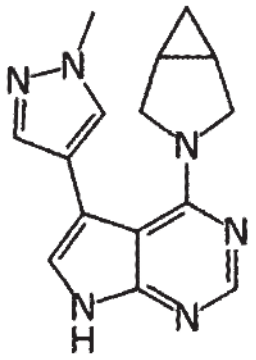
67	
68	
69	

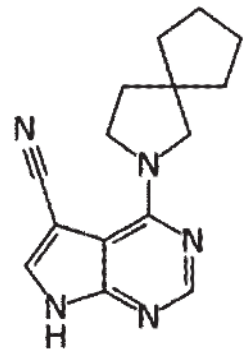
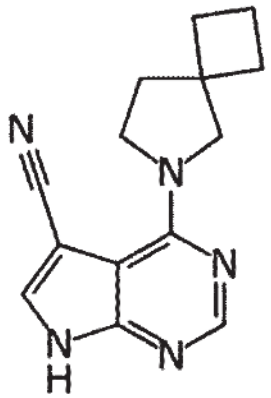
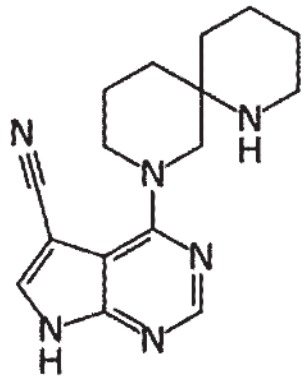
70	
71	
72	

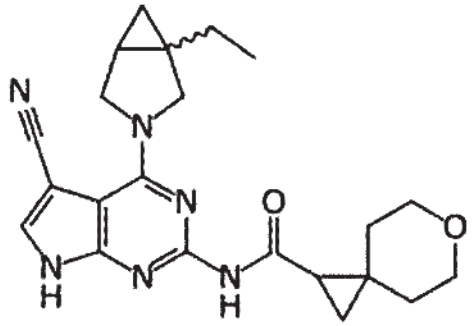
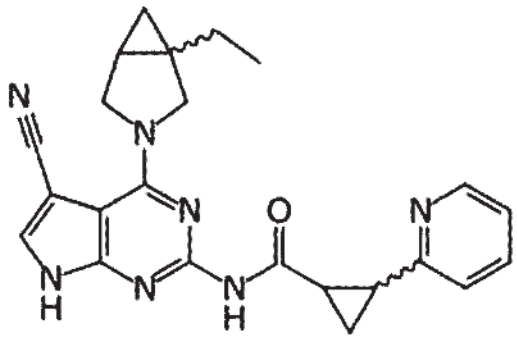
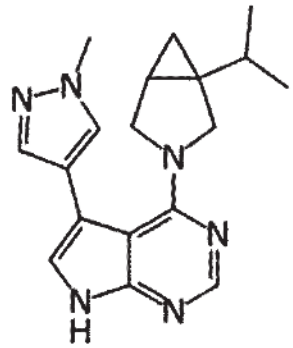
73	
74	
75	

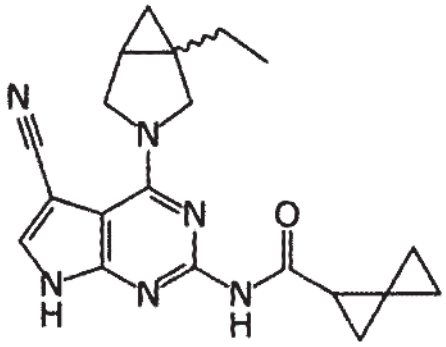
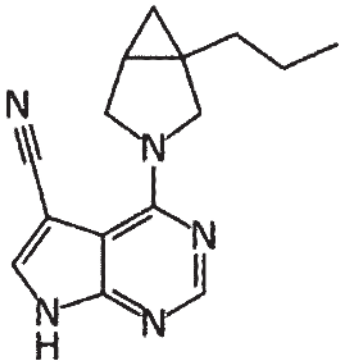
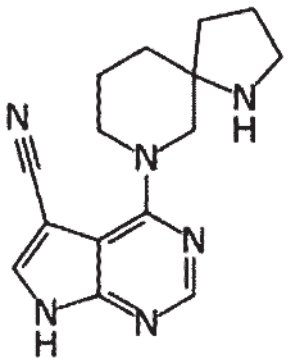
76	
77	
78	

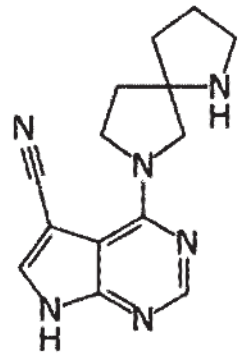
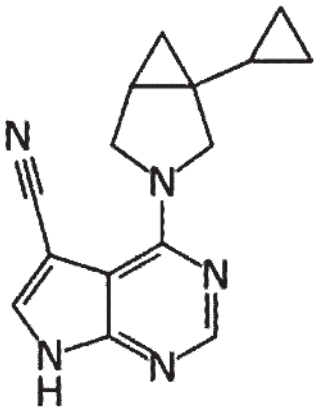
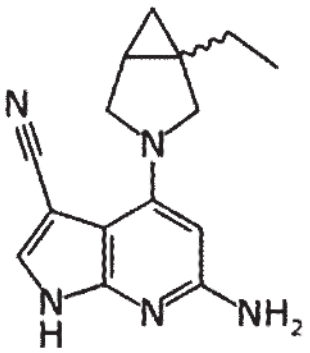
79	
80	
81	

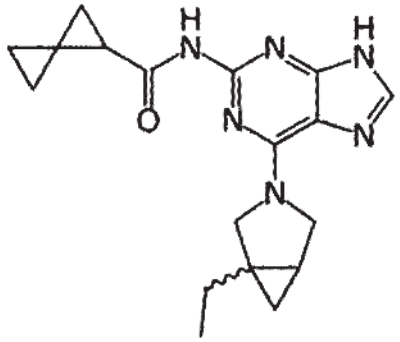
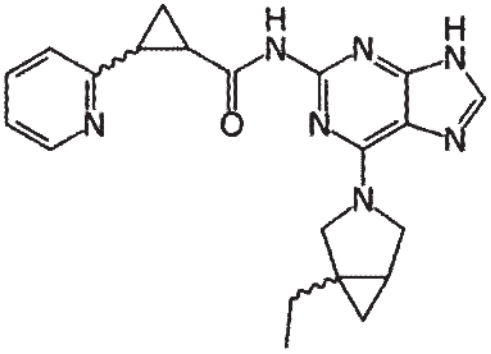
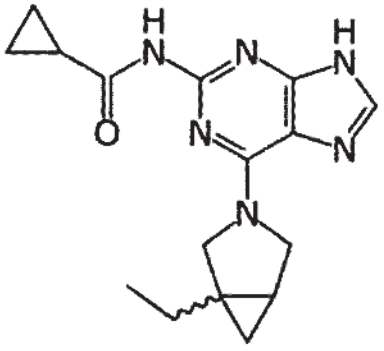
82	
83	
84	

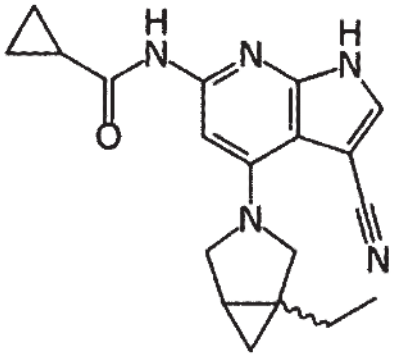
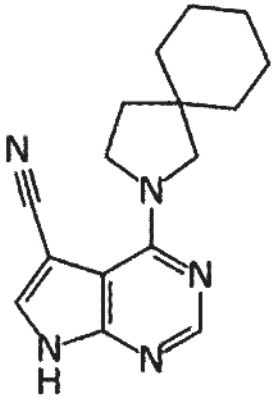
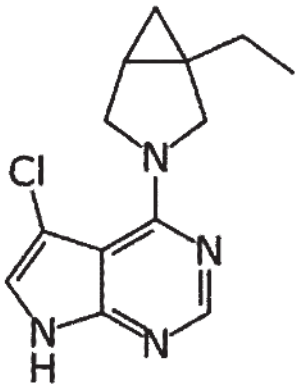
85	
86	
87	

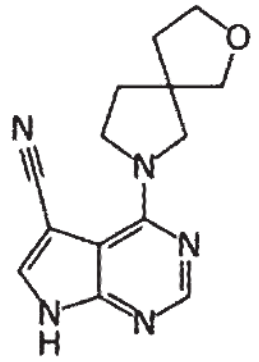
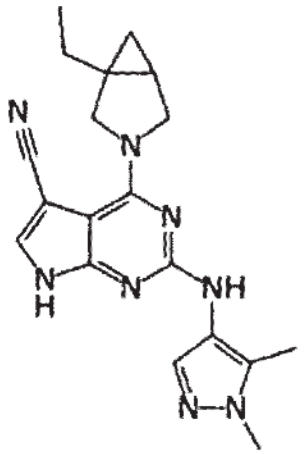
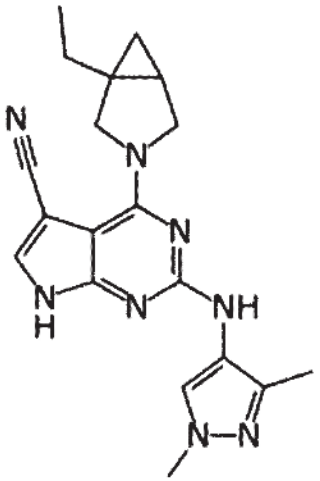
88	
89	
90	

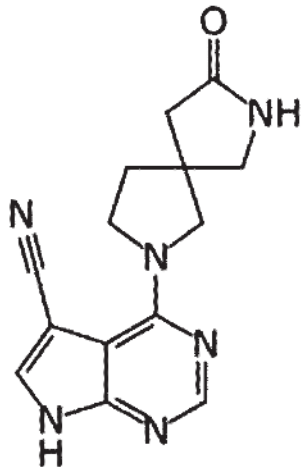
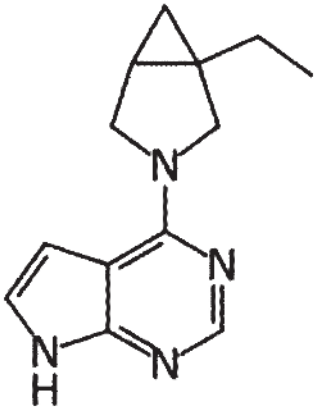
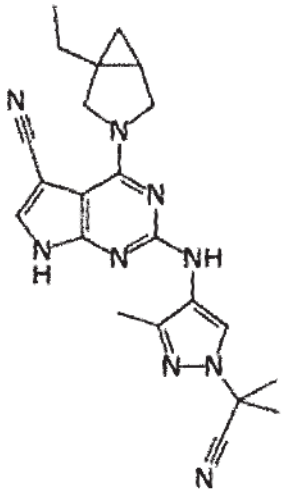
91	
92	
93	

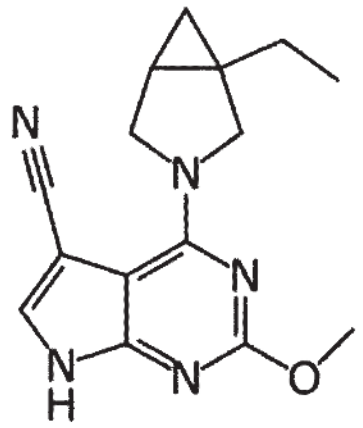
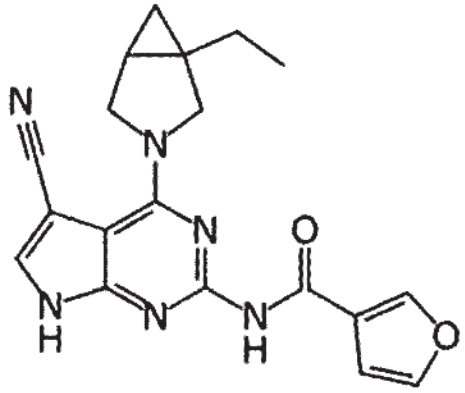
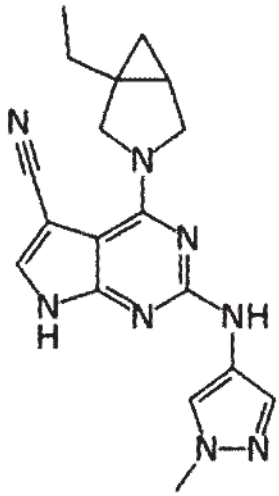
94	
95	
96	

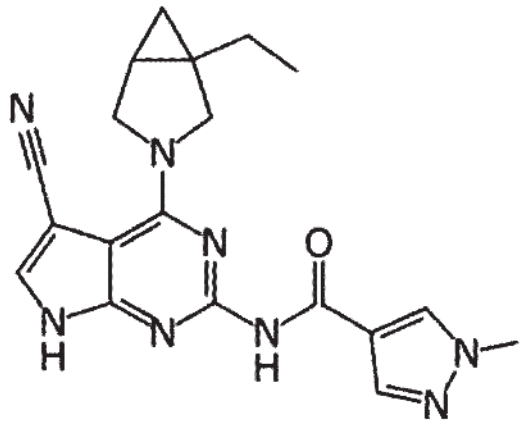
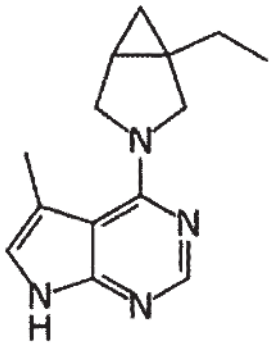
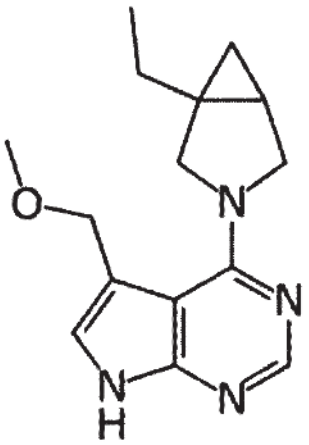
97	
98	
99	

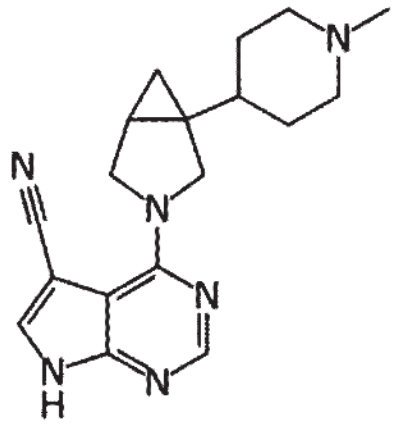
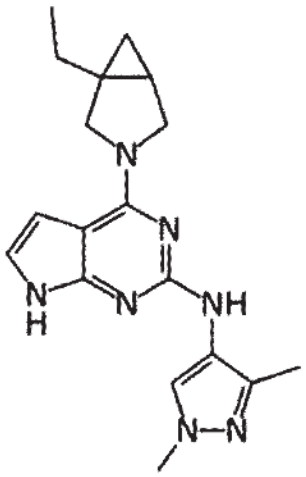
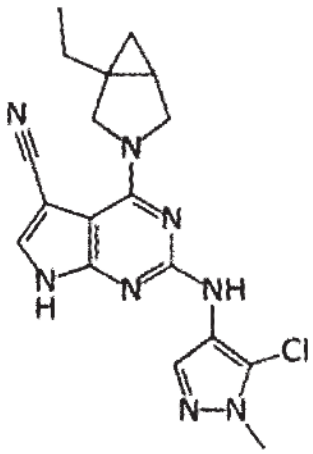
100	
101	
102	

103	
104	
105	

106	
107	
108	

109	
110	
111	

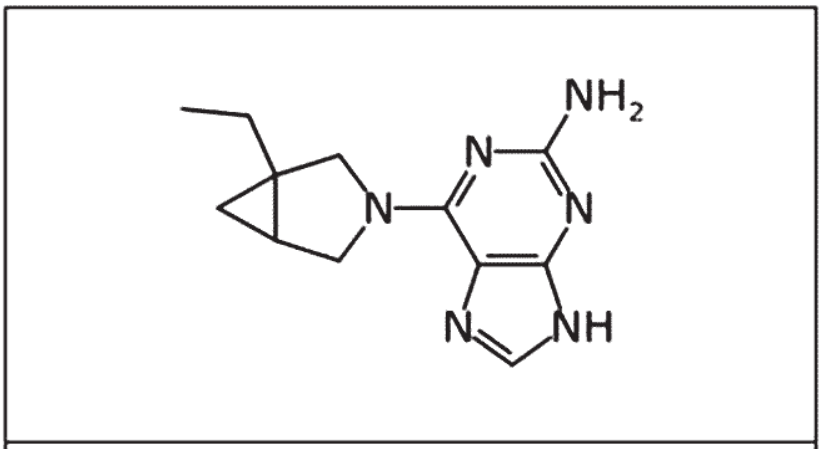
112	
113	
114	

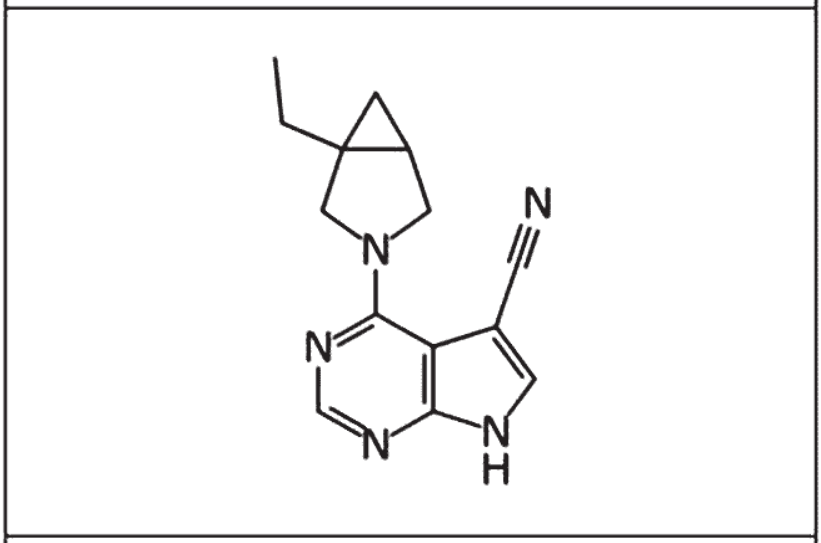
115	
116	
117	

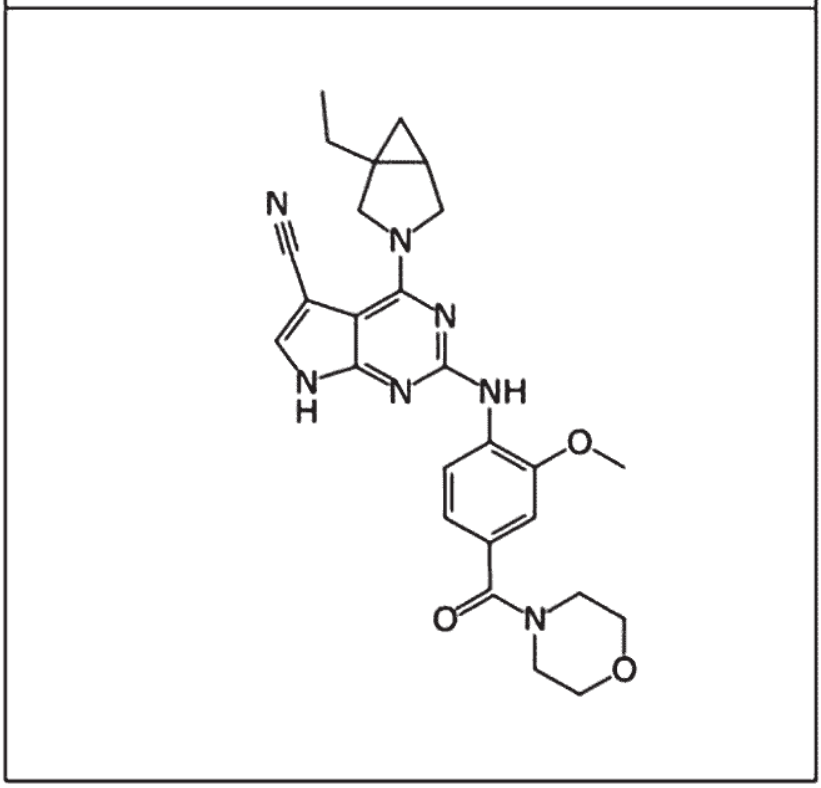
【Claim 11】

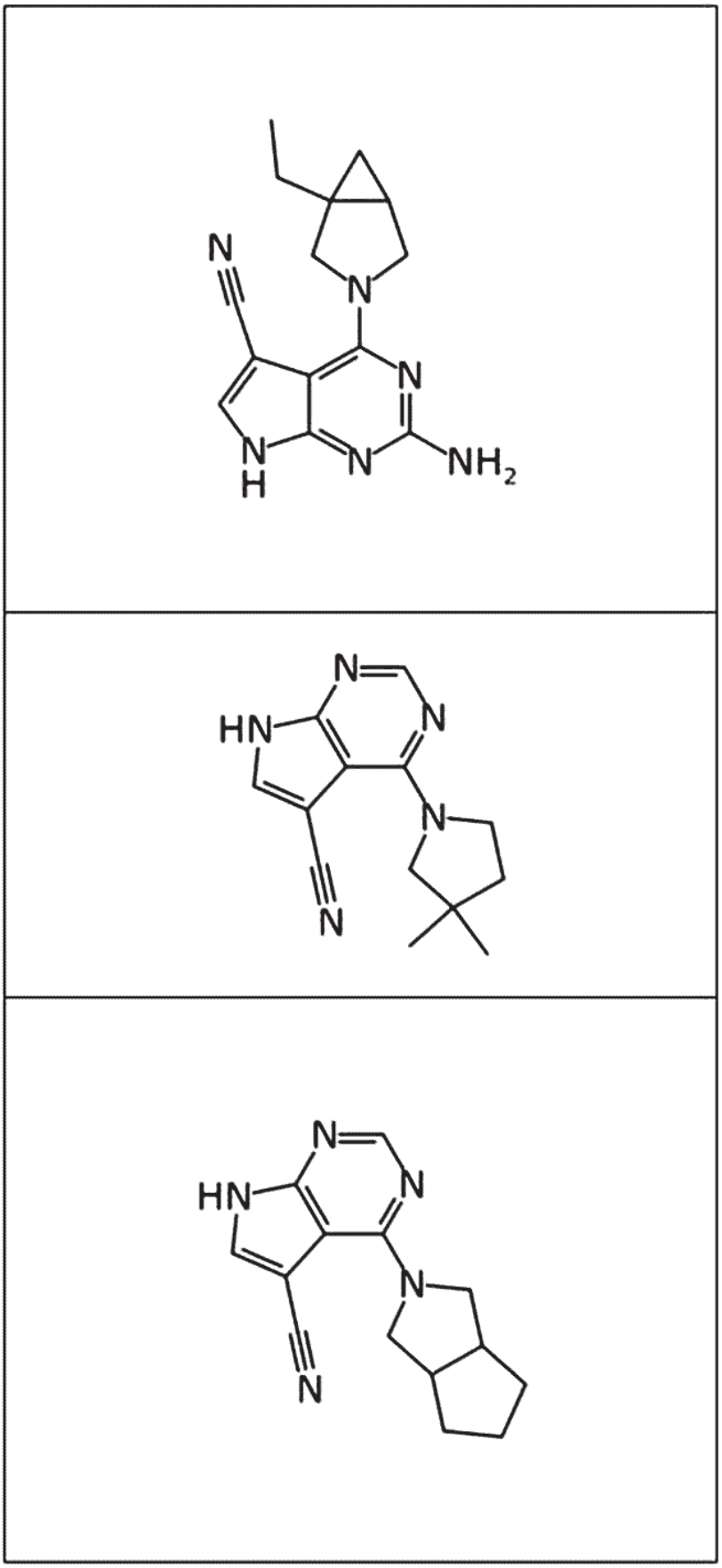
The compound selected from the group consisting of the following compounds, or a

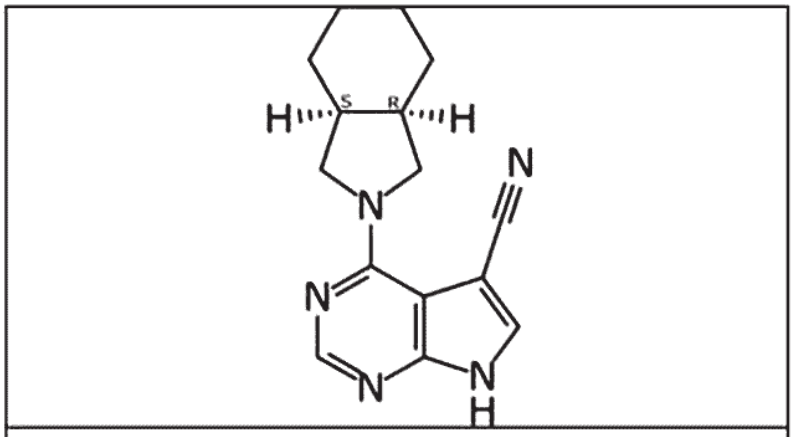
pharmaceutically acceptable salt thereof, according to claim 10:

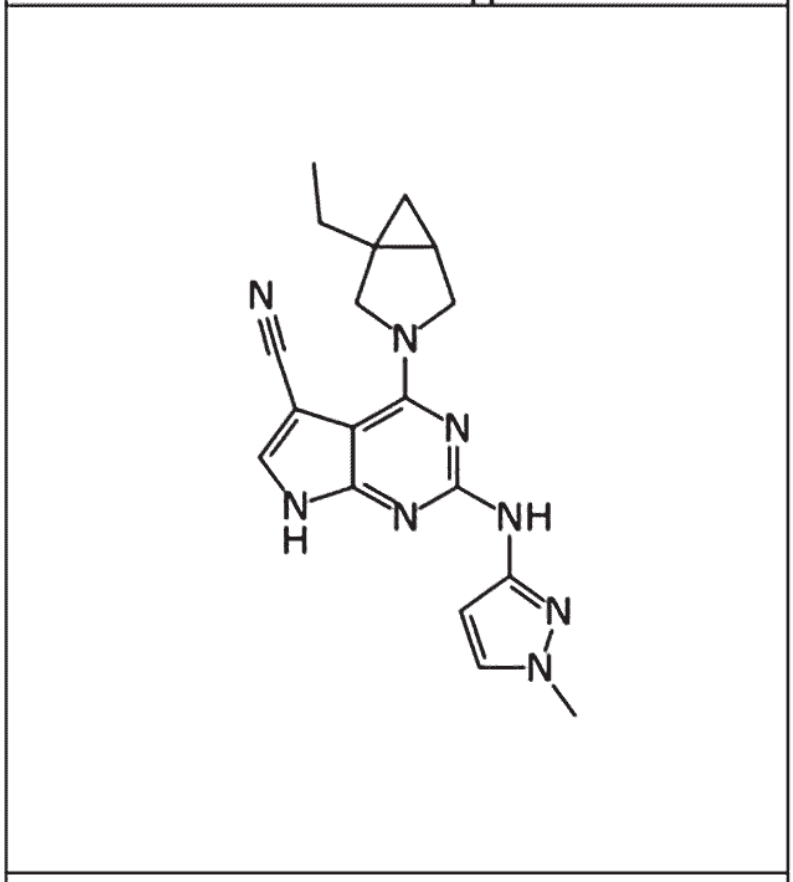

NH2
N
N
N
N
NH

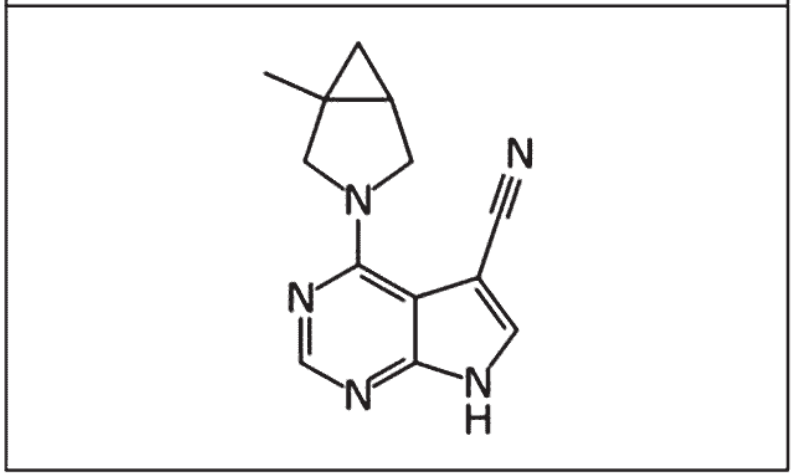

N
N
N
N
N
H

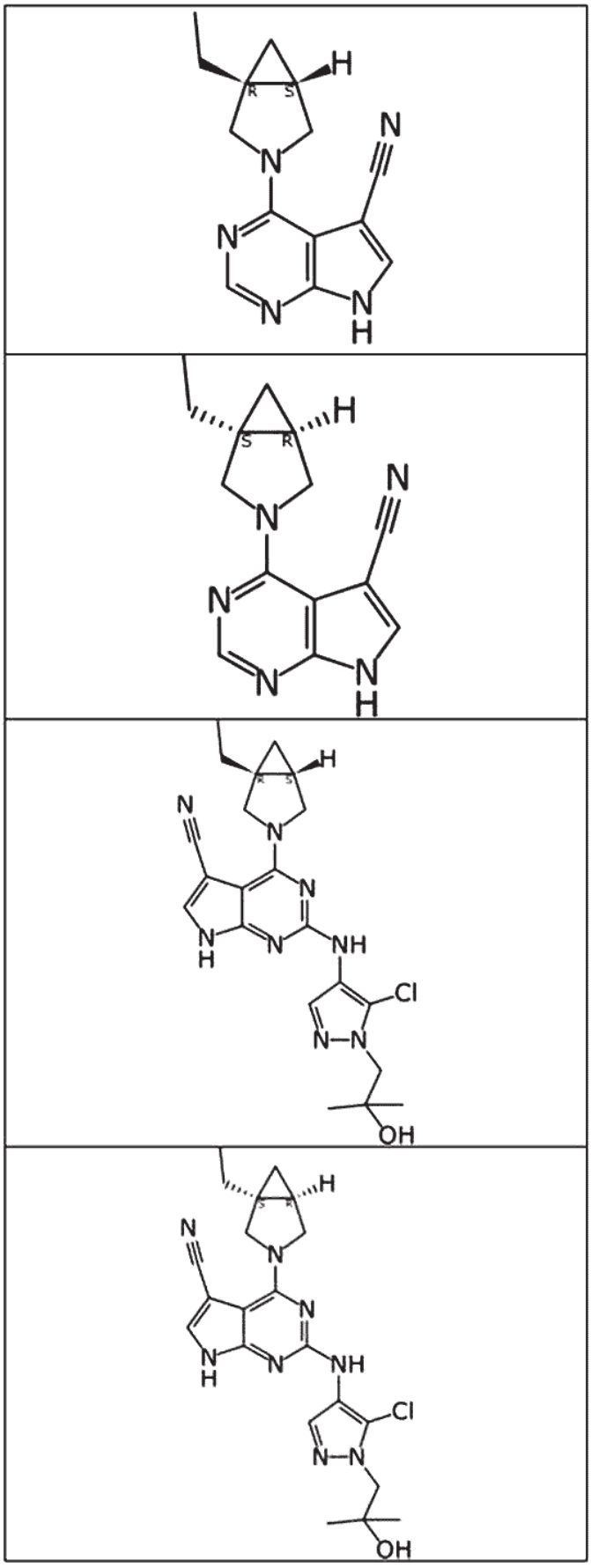

N
N
N
N
H
N
NH
O
O
N
O

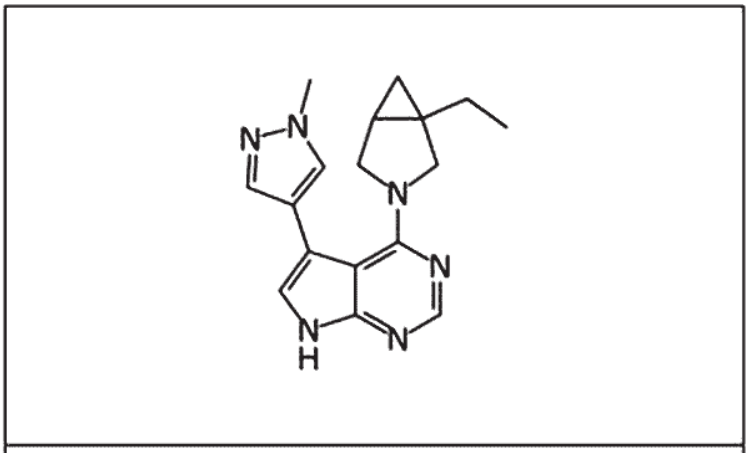


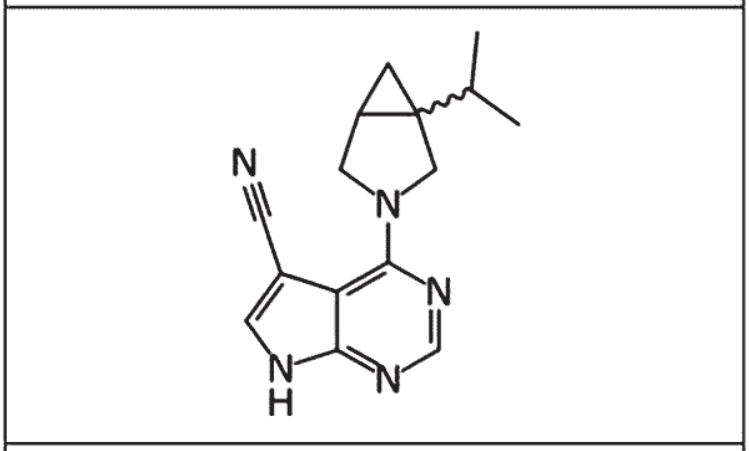


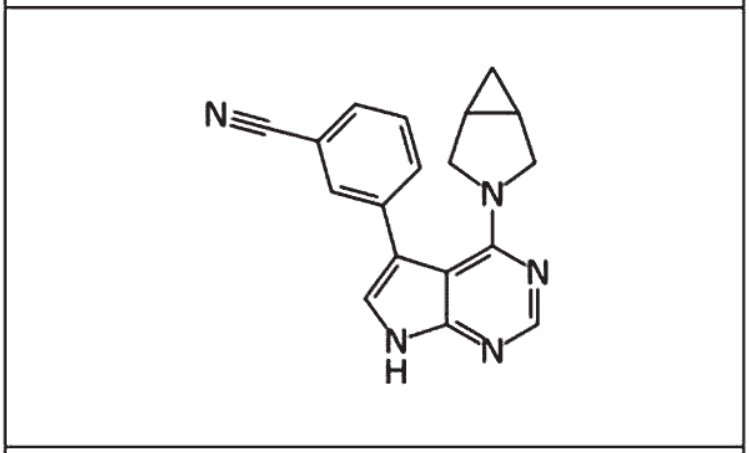


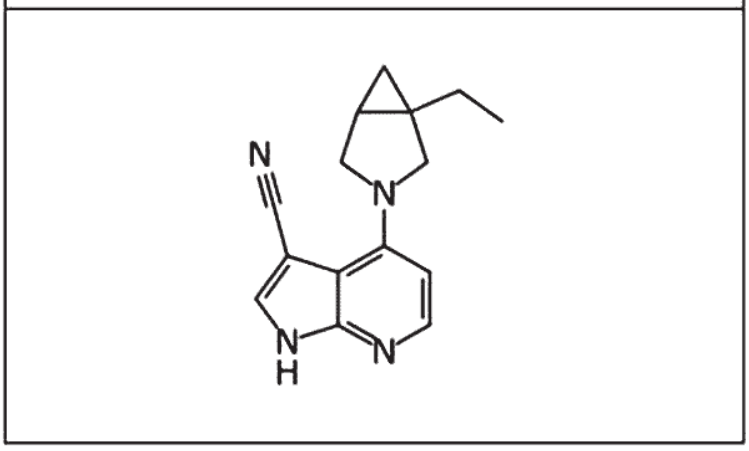


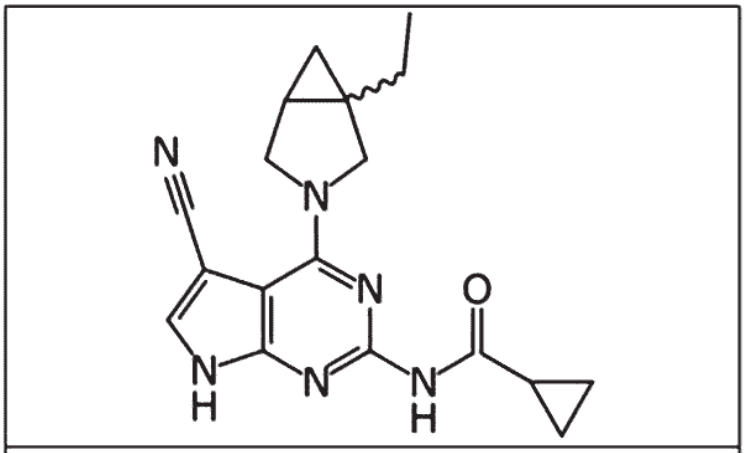


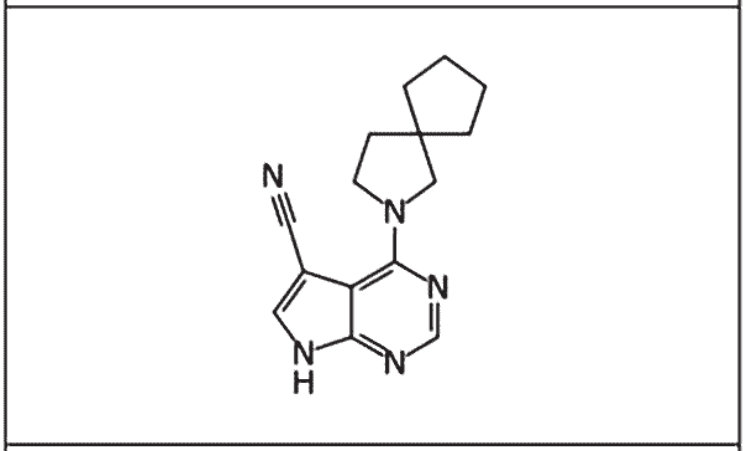


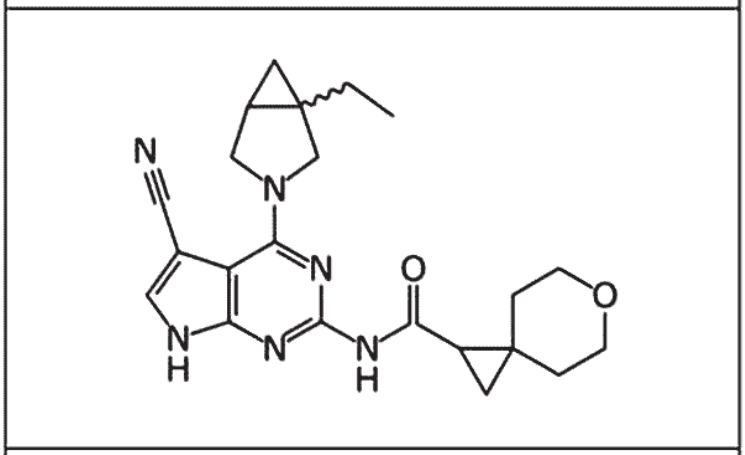


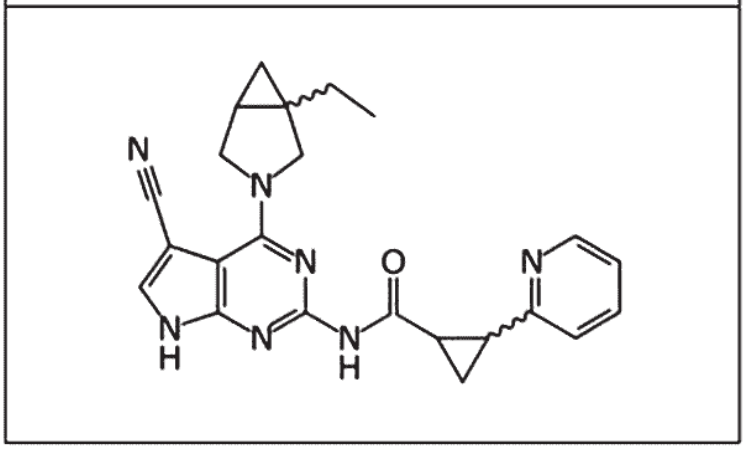


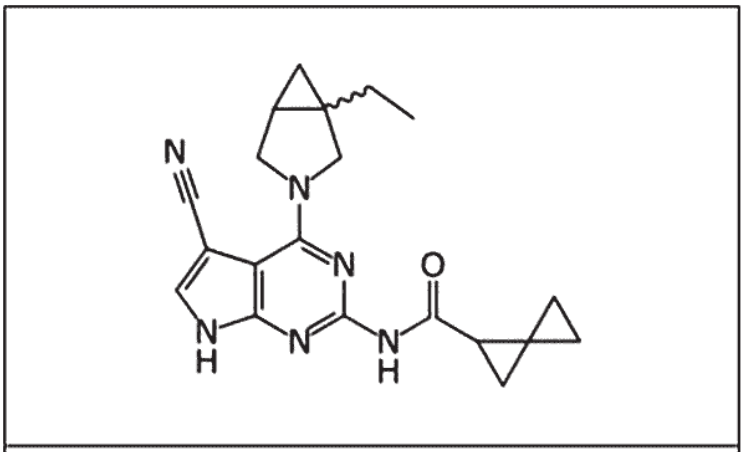


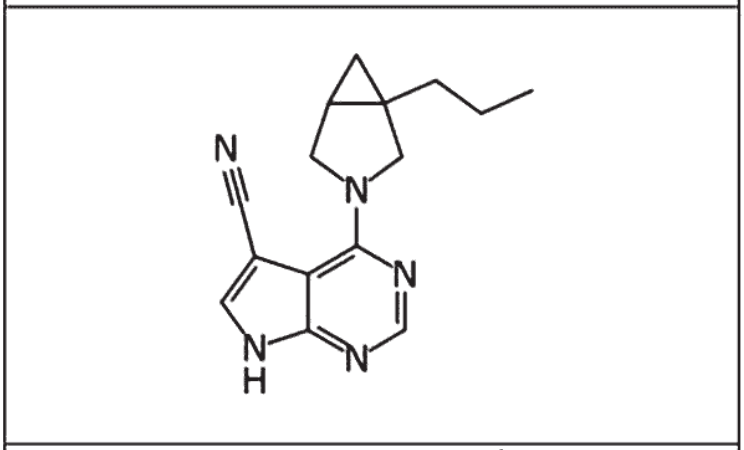


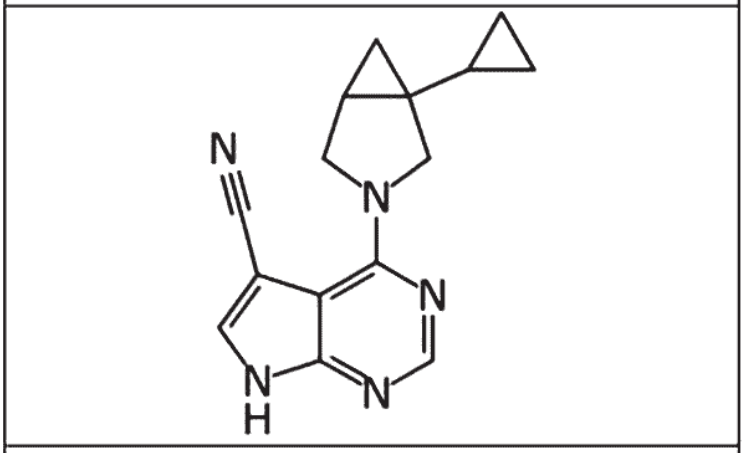


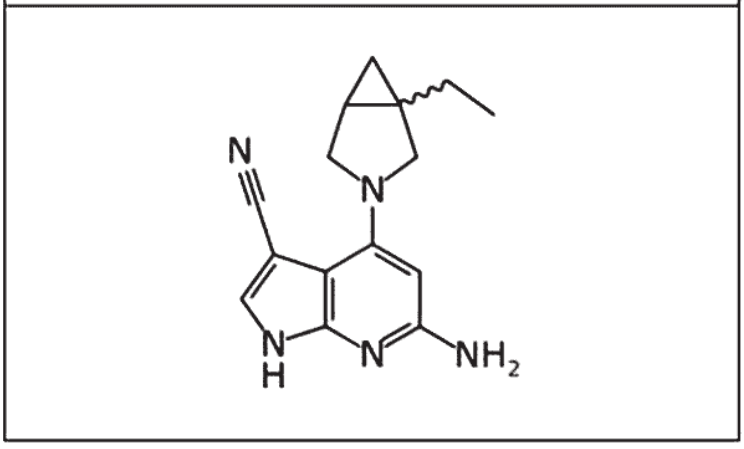


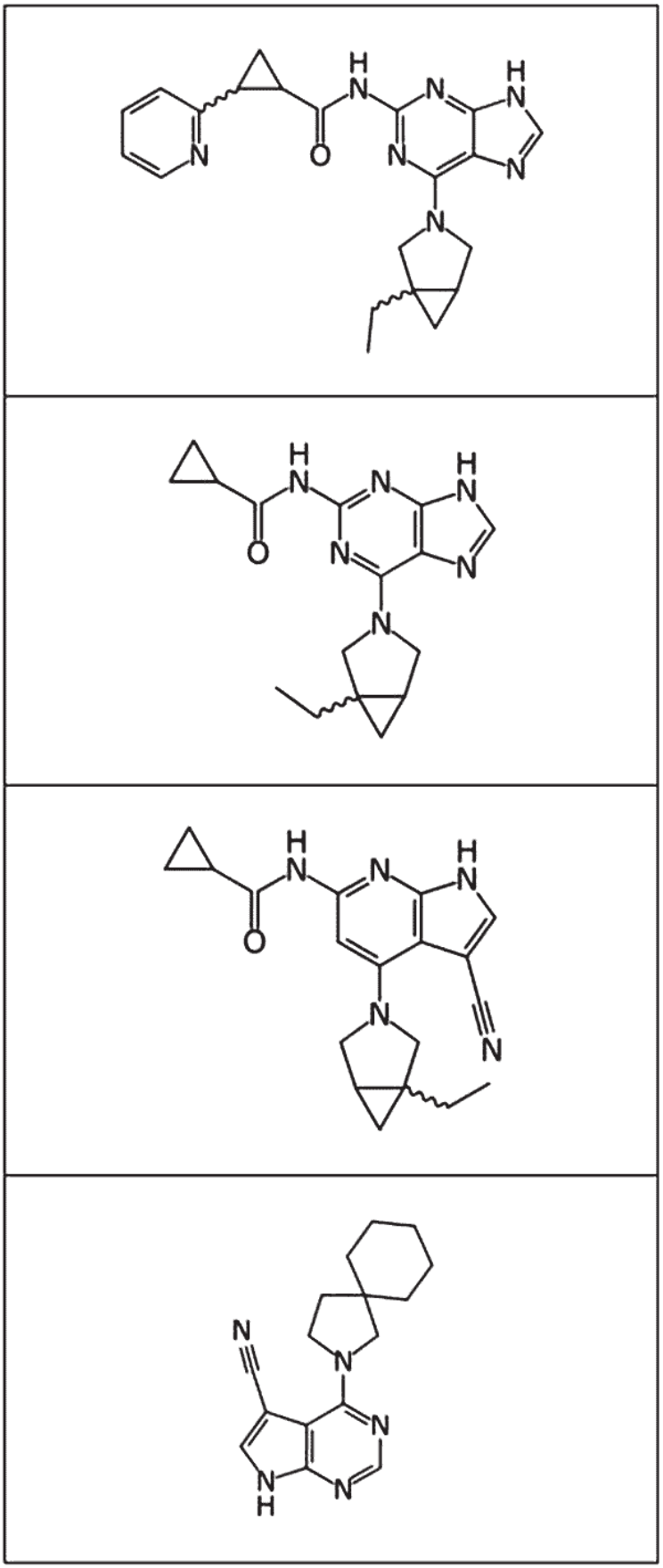


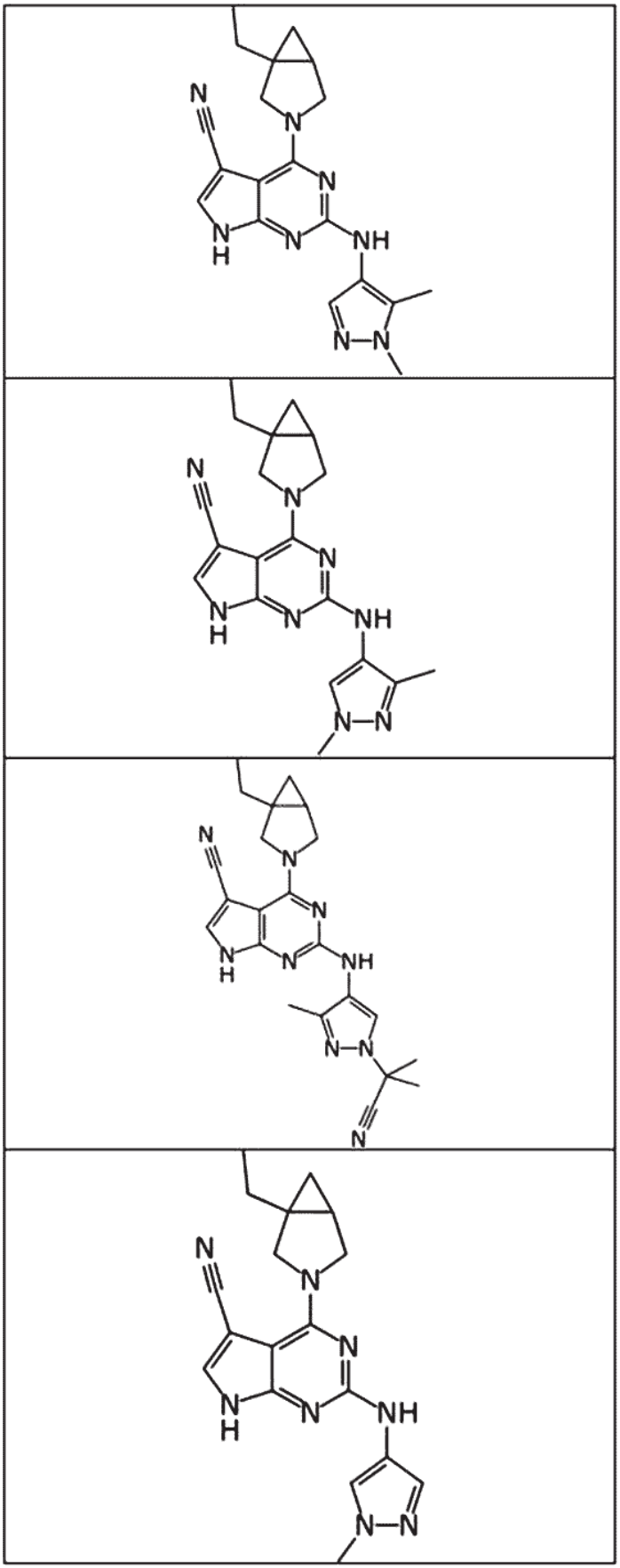


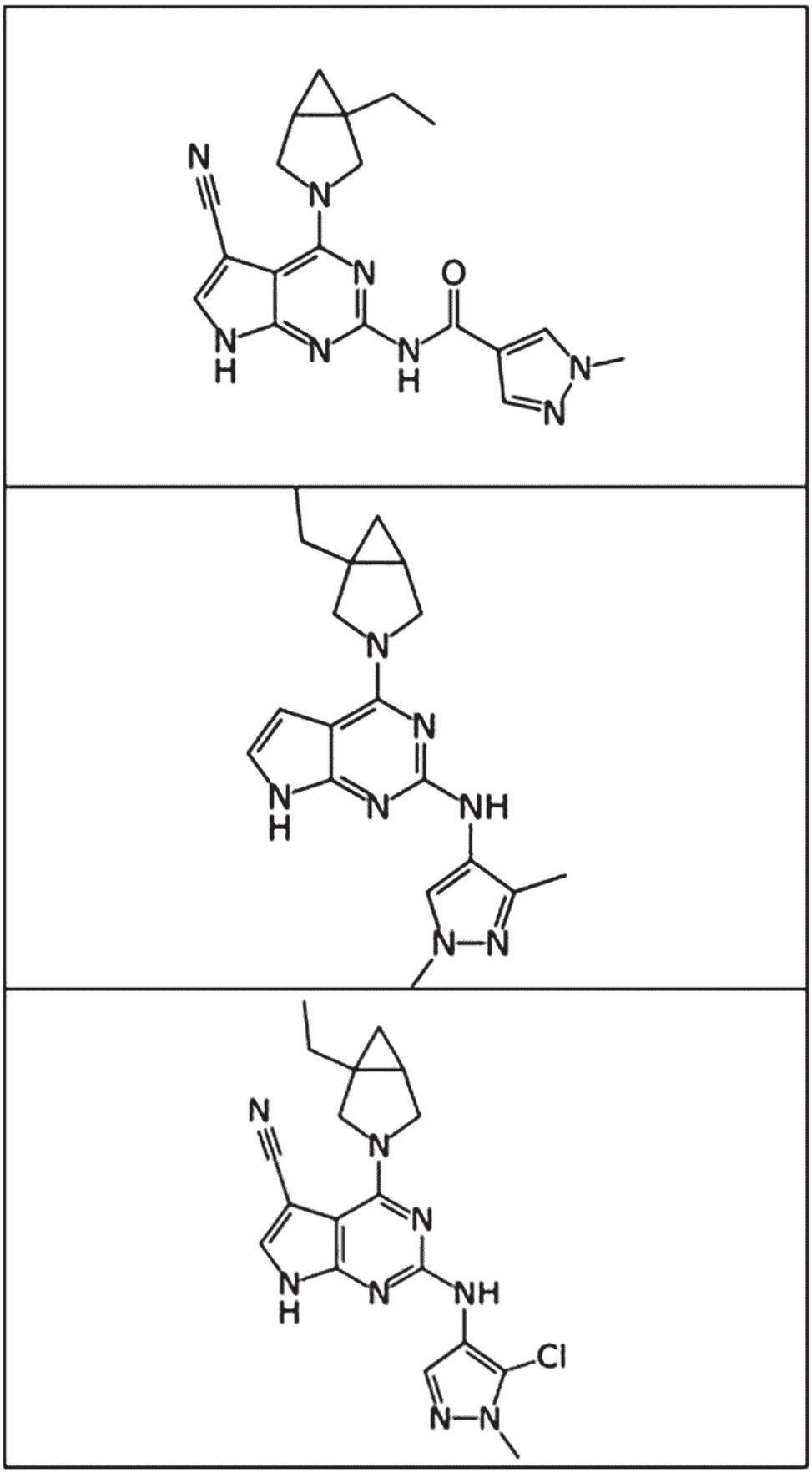






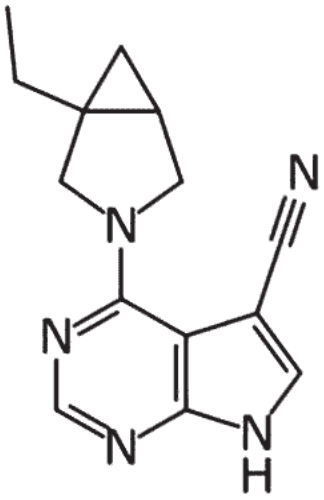






【Claim 12】

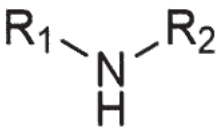
The following compound, or a pharmaceutically acceptable salt thereof, according to claim 10:



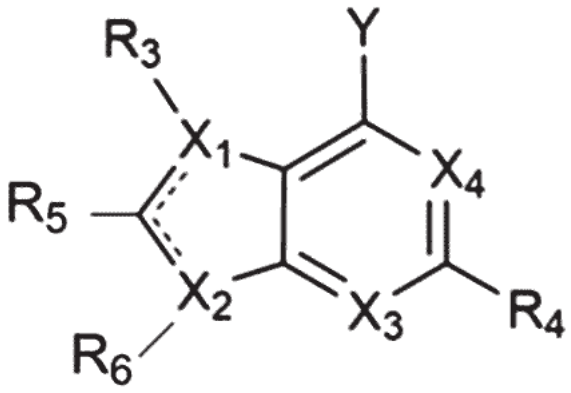
【Claim 13】

A method for preparing the compound or a pharmaceutically acceptable salt thereof according to claim 1, comprising a step of reacting a compound of Formula 2 below and a compound of Formula 3 below:

[Formula 2]



[Formula 3]



wherein

····· are each independently absent or a single bond,

X_1 to X_4 are each independently C or N,

Y is halogen,

R_1 and R_2 are each independently hydrogen, alkyl, -O-alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -alkyl-cycloalkyl, -alkyl-heterocycloalkyl, -alkyl-aryl or -alkyl-heteroaryl, or

R_1 and R_2 are heterocycloalkyl formed by linking R_1 and R_2 together,

R_3 is absent, or is hydrogen, halo, cyano, alkyl, -alkyl-O-alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl,

R_4 is hydrogen, halo, cyano, $-NH_2$, -alkyl, -alkyl-O-alkyl, -O-alkyl, $-N(R_{4A})(R_{4B})$, $-N(R_{4D})C(=O)(R_{4C})$, cycloalkyl, heterocycloalkyl, aryl or heteroaryl,

wherein R_{4A} to R_{4D} are each independently hydrogen, alkyl, cycloalkyl, heterocycloalkyl, -cycloalkyl-heteroaryl, heteroaryl, aryl or -aryl-C(=O)-heterocycloalkyl,

R_5 is hydrogen, cyano, alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl,

R_6 is absent, or is hydrogen, cyano, alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl,

wherein the cycloalkyl, heterocycloalkyl, aryl or heteroaryl may be substituted with

one or more selected from the group consisting of halo, NH_2, cyano, haloalkyl, alkyl, alkenyl, alkynyl, -alkynyl-alkyl, -O-alkyl, -alkyl-CN, -alkyl-OH, -alkyl-O-alkyl, -alkyl-NH_2, -alkyl-N(alkyl)(alkyl), -alkyl-cycloalkyl, NH_2, -N(alkyl)(alkyl), -C(=O)-NH_2, -C(=O)-heteroaryl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein the cycloalkyl, heterocycloalkyl, aryl or heteroaryl may be unsubstituted or substituted with alkyl or -OH, wherein the alkyl may be unsubstituted or substituted with halo.

【Claim 14】

A pharmaceutical composition for preventing or treating a disease mediated by or associated with LRRK2, comprising the compound or a pharmaceutically acceptable salt thereof according to claim 1.

【Claim 15】

The pharmaceutical composition according to claim 14, wherein the disease mediated by or associated with LRRK2 is Parkinson's disease.