[DESCRIPTION]

[Title of Invention]

COMPOUND HAVING KDM5 INHIBITORY ACTIVITY AND PHARMACEUTICAL USE THEREOF

[Technical Field]

[0001]

The present invention relates to a compound represented by the general formula (I) described hereinbelow having KDM5 inhibitory activity, or a salt thereof, and pharmaceutical use thereof.

[Background Art]

[0002]

Eukaryotic DNA exists in the nucleus as a chromatin structure that is a complex with histone proteins. Histone proteins are subject to modifications such as methylation, acetylation and phosphorylation through various enzymes, and changes in such modifications are known to induce chromatin remodeling and transcriptional alterations. Epigenetic modifications including histone methylation reversively regulate gene expression without altering the nucleotide sequence and play an important role in physiological processes.

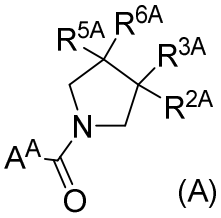
[0003]

KDM5 proteins are members of JARID histone demethylase protein family, which demethylates tri-methylation of the fourth lysine residue of histone H3 protein (H3K4me3). In mammalian species including humans, there are four subfamilies: KDM5A, KDM5B, KDM5C, and KDM5D, which have five conserved domains, namely JmjN, ARID, JmjC, PHDs, and C5HC2 zinc finger. The KDM5 family is widely distributed in blood cells and various organs, in vivo, and particularly, is known to be highly expressed in cancer tissues. Epigenetic aberrations in cancer cells are known to be involved in the cell proliferation and metastasis, and KDM5 inhibitors have been reported to have efficacy against cancer cells. The involvement of epigenetic abnormalities, including histone modifications, has also been reported in other pathologies, such as neuropsychiatric disorders and metabolic diseases. Therefore, compounds with KDM5 inhibitory activity may improve the epigenetic abnormalities and be useful for the prevention and treatment of these diseases.

[0004]

In related art of the present invention, WO2016057924 reports that compounds of formula (A) are useful as inhibitors of one or more histone demethylases such as KDM5.

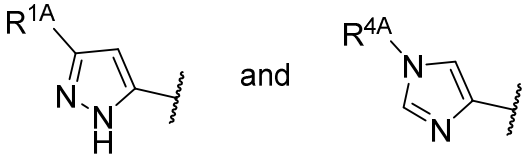
Formula (A):



(A)

or a salt thereof, wherein:

A^A is selected from the group consisting of:



R^{1A} is alkyl, cyclic group, or the like;

R^{2A} is optionally substituted cyclic group, $-OR^{aA}$, $-C(O)N(R^{aA})_2$, or $NR^{aA}R^{bA}$;

R^{aA} and R^{bA} are each independently selected from H, optionally substituted alkyl group, optionally substituted cyclic group, etc.;

R^{3A} is H or alkyl;

R^{4A} is H, alkyl, or cyclic group; and

R^{5A} is H, halo, or alkyl, and

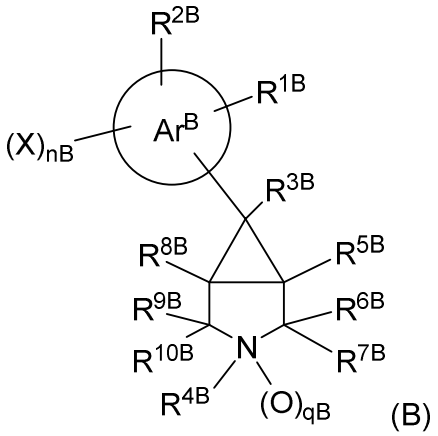
R^{6A} is H, alkyl, or cyclic group;

or R^{5A} and R^{6A} taken together to form cyclic group (where the definitions of the groups are excerpted).

[0005]

In addition, WO2000039089 reports that compounds represented by the following formula (B) are useful as opiate receptors ligands.

Formula (B):



(B)

wherein the Ar^B ring represents an optionally benzo-fused phenyl or 5- or 6- membered heteroaryl ring;

R^{1B} is selected from various substituents;

R^{2B} is H or halogen;

R^{3B} is H, halogen, alkyl group, cyclic group, or the like,

R^{4B} is optionally substituted alkyl, alkenyl or alkynyl,

R^{5B} and R^{8B} are each independently H or C_{1-6} alkyl,

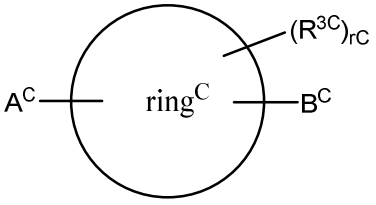
R^{6B}, R^{7B}, R^{9B} and R^{10B} when taken separately are H,

X is halogen, alkyl, alkoxy, or the like (where the definitions of the groups are excerpted) or a pharmaceutically or veterinary acceptable derivative or prodrug thereof.

[0006]

In addition, WO2021010492 reports that compounds of formula (C) are useful as KDM5 inhibitor.

Formula (C):



(C)

wherein $ring^C$ is 3- to 10-membered mono or bicyclic hetero ring containing 1 to 4 nitrogen atoms, one oxygen atom and/or one sulfur atom, which may be substituted with 1 to 3 substituents;

A^C is $R^{1\text{-}1C}$-L^{1C}-, or the like;

B^C is $R^{2\text{-}1C}$-L^{2C}-, or the like;

$R^{1\text{-}1C}$ is a C3-8 cycloalkyl which may be substituted with 1 to 4 substituents, or the like;

L^{1C} is a bond, or carbonyl(-C(=O)-);

L^{2C} is a bond, carbonyl(-C(=O)-), or the like;

R^{2-1C} is 5- or 6-membered monocyclic heterocycle which may be substituted with 1 to 4 substituents, or the like;

R^{3C} is a hydrogen atom, or the like;

r^{C} represents an integer of 0 to 1;

or a salt thereof.

[Citation List]

[Patent Literature]

[0007]

[PTL 1] WO 2016/057924

[PTL 2] WO 2000/039089

[PTL 3] WO 2021/010492

[Summary of Invention]

[Technical Problem]

[0008]

For example, a compound having KDM5 inhibitory activity for the treatment or prevention of diseases such as cancer, Huntington's disease, Alzheimer's disease and the like has been desired.

[Solution to Problem]

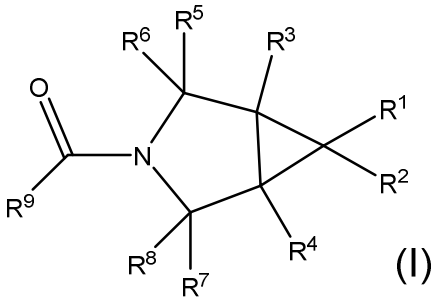
[0009]

The inventors of the present invention have carried out extensive studies in order to achieve the above problem, and as a result, found that the compound represented by the general formula (I) described hereinafter, or a salt thereof can achieve the above object. The inventors have carried out further researches and completed the present invention.

[0010]

Thus the present invention relates to:

[1] A compound represented by the general formula (I):



(I)

wherein R^1 represents Cyc1, -CO-Cyc2 or -CONR^{10}R^{11};

Cyc1 represents a 5 to 9 membered aromatic hetero ring or 5 membered non-aromatic hetero ring, each of which may be substituted with 1 to 5 R^{12};

R^{12} represents (1) C1-4 alkyl, (2) C3-7 cycloalkyl, (3) C1-4 haloalkyl, (4) C1-4 alkoxy, (5) phenyl which may be substituted with 1 to 3 R^{17}, (6) C1-4 alkyl which is substituted with phenyl, (7) dimethylamino, (8) pyridyl or (9) 1-(cyclopropylmethyl)pyrazol-3-yl;

a plurality of R^{12} may be the same or different;

two R^{12} together with an atom to which these R^{12} are attached may form a C3-5 cycloalkane, wherein the carbon atom of C3-5 cycloalkane may be replaced with hetero atom selected from 1 to 2 N, O and S;

R^{17} represents C1-4 alkyl, C1-4 alkoxy or halogen;

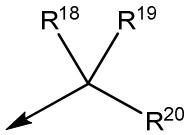
a plurality of R^{17} may be the same or different;

Cyc2 represents a C3-12 mono or bicyclic carbocycle or a 5- to 9-membered mono or bicyclic heterocycle, each of which may be substituted with 1 to 5 R^{13};

R^{13} represents C1-4 alkyl, C1-4 alkoxy or halogen;

a plurality of R^{13} may be the same or different;

R^{10} represents



wherein R^{18} and R^{19} independently represents C1-4 alkyl;

R^{18} and R^{19} together with a carbon atom to which R^{18} and R^{19} are attached may form a C3-5 cycloalkane;

R^{20} represents a hydrogen atom, C1-4 alkyl, C1-4 haloalkyl or nitrile;

(in the group, the arrow indicates the binding to the nitrogen atom of -CON<);

R^{11} represents a hydrogen atom, C1-4 alkyl or 1 to 9 deuterated C1-4 alkyl;

R^2, R^3, R^4, R^5, R^6, R^7 and R^8 independently represent a hydrogen atom, C1-4 alkyl, halogen or C1-4 alkoxy;

R^9 represents imidazole which may be substituted with 1 to 3 R^{14} or pyrazole which may be substituted with 1 to 3 R^{15};

R^{14} represents (1) C1-8 alkyl, (2) C3-7 cycloalkyl which may be substituted with C1-4 alkyl, (3) C1-8 haloalkyl, (4) C1-8 alkyl which is substituted with Cyc3 which may be substituted with 1 to 3 R^{16} or (5) C1-8 alkyl which is substituted with phenoxy;

Cyc3 represents phenyl, C3-7 cycloalkyl, pyridyl, thiazolyl or tetrahydropyranyl;

R^{16} represents C1-4 alkyl, halogen, C1-4 alkoxy or cyano;

a plurality of R^{14} may be the same or different;

a plurality of R^{16} may be the same or different;

R^{15} represents (1) C1-8 alkyl, (2) C3-7 cycloalkyl which may be substituted with C1-4 alkyl, (3) C1-8 haloalkyl, (4) C1-8 alkyl which is substituted with Cyc4 which may be substituted with 1 to 3 R^{21} or (5) C1-8 alkyl which is substituted with phenoxy;

Cyc4 represents phenyl, C3-7 cycloalkyl, pyridyl, thiazolyl or tetrahydropyranyl;

R^{21} represents C1-4 alkyl, halogen, C1-4 alkoxy or cyano;

a plurality of R^{15} may be the same or different;

a plurality of R^{21} may be the same or different;

each hydrogen atom may be a deuterium atom or a tritium atom;

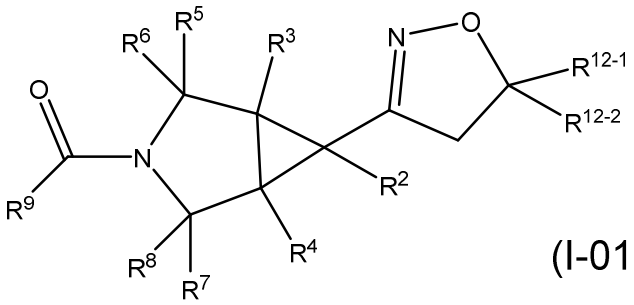
with the proviso that ((1R,5S,6r)-6-(Cyclopropanecarbonyl)-3-azabicyclo[3.1.0] hexan-3-yl)(5-isopropyl-1H-pyrazol-3-yl)methanone, (5-Isopropyl-1H-pyrazol-3-yl)-[(1R,5S)-6-[(2R)-2-methylpyrrolidine-1-carbonyl]-3-azabicyclo[3.1.0]hexan-3-yl]methanone, (5-Isopropyl-1H-pyrazol-3-yl)-[(1S,5R)-6-[(2S)-2-methylpyrrolidine-1-carbonyl]-3-azabicyclo[3.1.0]hexan-3-yl]methanone, [(1S,5R)-6-(2,2-Dimethylpyrrolidine-1-carbonyl)-3-azabicyclo[3.1.0]hexan-3-yl]-(5-isopropyl-1H-pyrazol-3-yl)methanone and (5-Isopropyl-1H-pyrazol-3-yl)-[(1S,5R)-6-(5-methyl-4-phenyl-isoxazol-3-yl)-3-azabicyclo[3.1.0]hexan-3-yl]methanone are excluded;

or a salt thereof;

[2] The compound according to the preceding item [1], wherein R^1 represents Cyc1, and the Cyc1 represents 5 membered non-aromatic hetero ring which may be substituted with 1 to 5 R^{12}, or a salt thereof;

[3] The compound according to the preceding item [2], wherein 5 membered non-aromatic hetero ring represents 4,5-dihydroisoxazole or 4,5-dihydro-1,2,4-oxadiazole, or a salt thereof;

[3-1] The compound according to the preceding item [3], wherein the compound represented by the general formula (I) is represented by the general formula (I-01)



(I-01)

wherein R^{12-1} and R^{12-2} independently represent C1-4 alkyl;

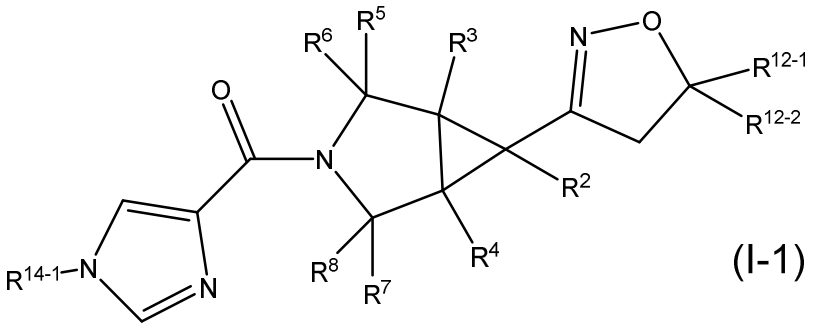
R^{12-1} and R^{12-2} together with an atom to which the R^{12-1} and R^{12-2} are bound may form C3-5 cycloalkane;

other symbols represent the same meaning as described in the preceding item [1];

or a salt thereof;

[4] The compound according to any one of the preceding item [1] to [3] and [3-1], wherein R^9 represents imidazole which may be substituted with 1 to 3 R^{14}, or a salt thereof;

[5] The compound according to any one of the preceding item [1] to [4] and [3-1], wherein the compound represented by the general formula (I) is represented by the general formula (I-1)



(I-1)

wherein R^{12-1} and R^{12-2} independently represent C1-4 alkyl;

R^{12-1} and R^{12-2} together with an atom to which the R^{12-1} and R^{12-2} are bound may form C3-5 cycloalkane;

R^{14-1} represents C1-4 alkyl or C3-5 cycloalkyl which may be substituted with C1-4 alkyl;

other symbols represent the same meaning as described in [1];

or a salt thereof;

[6] The compound according to any one of the preceding item [1] to [5] and [3-1], wherein the compound is:

(1) [(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](1-isopropyl-1H-imidazol-4-yl)methanone;

(2) [(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl][1-(1-methylcyclopropyl)-1H-imidazol-4-yl]methanone;

(3) (1-cyclopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-6-methyl-3-azabicyclo[3.1.0]hex-3-yl]methanone;

(4) (1-cyclopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-methyl-6-(4-oxa-5-azaspiro[2.4]hept-5-en-6-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone;

(5) {1-[(2S)-butan-2-yl]-1H-imidazol-4-yl}[(1R,5S,6S)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone;

(6) [(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-6-methyl-3-azabicyclo[3.1.0]hex-3-yl](1-isopropyl-1H-imidazol-4-yl)methanone;

(7) (1-isopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-methyl-6-(4-oxa-5-azaspiro[2.4]hept-5-en-6-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone ;

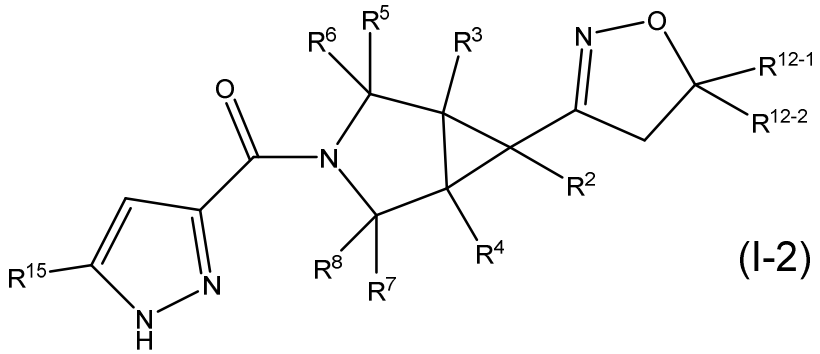
(8) (1-cyclopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(4-oxa-5-azaspiro[2.4]hept-5-en-6-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone or

(9) [1-(1-methylcyclopropyl)-1H-imidazol-4-yl][(1R,5S,6r)-6-(4-oxa-5-azaspiro[2.4]hept-5-en-6-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone;

or a salt thereof;

[7] The compound according to any one of the preceding item [1] to [3] and [3-1], wherein R^9 represents pyrazole which may be substituted with 1 to 3 R^{15} or a salt thereof;

[8] The compound according to any one of the preceding item [1] to [3], [3-1] and [7], wherein the compound represented by the general formula (I) is represented by the general formula (I-2)



(I-2)

wherein all symbols represent the same meaning as described in the preceding item [1] or [5];

or a salt thereof;

[9] The compound according to any one of the preceding item [1] to [3], [3-1], [7] and [8] wherein the compound is:

(1) [(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](5-isopropyl-1H-pyrazol-3-yl)methanone;

(2) (5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(2-oxa-3-azabicyclo[3.1.0]hex-3-en-4-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone;

(3) [5-(1-cyclopropylethyl)-1H-pyrazol-3-yl][(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone;

(4) [(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-6-methyl-3-azabicyclo[3.1.0]hex-3-yl](5-isopropyl-1H-pyrazol-3-yl)methanone or

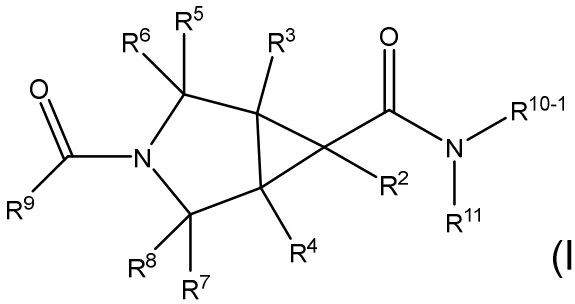
(5) (5-cyclopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-methyl-6-(4-oxa-5-azaspiro[2.4]hept-5-en-6-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

or a salt thereof;

[10] The compound according to the preceding item [1], wherein R^1 represents $-CONR^{10}R^{11}$, or a salt thereof;

[11] The compound according to the preceding item [1] or [10], wherein R^{10} represents isopropyl, tert-butyl, 1,1,1-trifluoro-2-methylpropan-2-yl, 1-methylcyclopropyl, 1-(trifluoromethyl)cyclopropyl or 1-cyanocyclopropyl, or a salt thereof;

[11-1] The compound according to the preceding item [11], wherein the compound represented by the general formula (I) is represented by the general formula (I-02)



(I-02)

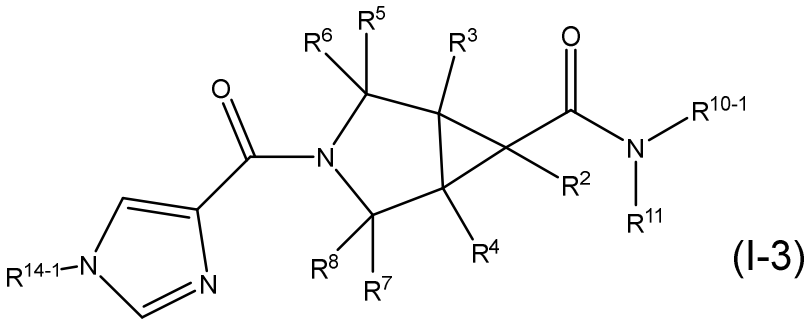
wherein R^{10-1} represents isopropyl, tert-butyl, 1,1,1-trifluoro-2-methylpropan-2-yl, 1-methylcyclopropyl, 1-(trifluoromethyl)cyclopropyl or 1-cyanocyclopropyl;

other symbols represent the same meaning as described in the preceding item [1];

or a salt thereof;

[12] The compound according to the preceding item [10], [11] or [11-1], wherein R^9 represents imidazole which may be substituted with 1 to 3 R^{14}, or a salt thereof;

[13] The compound according to any one of the preceding item [1], [10] to [12] and [11-1], wherein the compound represented by the general formula (I) is represented by the general formula (I-3)



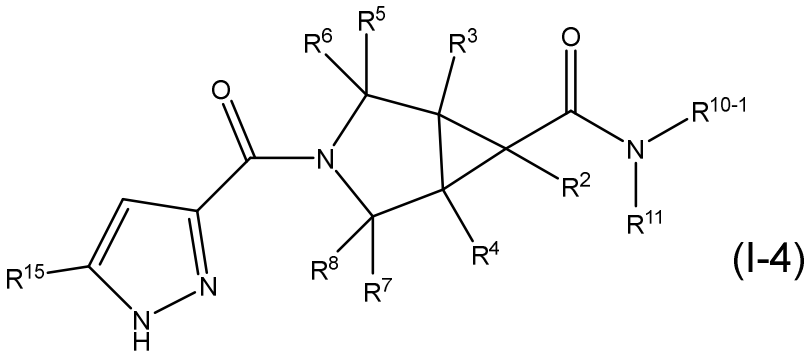
(I-3)

wherein R^{10-1} represents isopropyl, tert-butyl, 1,1,1-trifluoro-2-methylpropan-2-yl, 1-methylcyclopropyl, 1-(trifluoromethyl)cyclopropyl or 1-cyanocyclopropyl;
other symbols represent the same meaning as described in the preceding item [1] or [5];
or a salt thereof;

[14] The compound according to any one of the preceding item [1], [10] to [13] and [11-1], wherein the compound is:
(1) (1R,5S,6r)-N-tert-butyl-6-methyl-3-[1-(propan-2-yl)-1H-imidazole-4-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide ;
(2) (1R,5S,6r)-N-tert-butyl-3-[1-(propan-2-yl)-1H-imidazole-4-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide;
(3) (1R,5S,6r)-N-(propan-2-yl)-3-[1-(propan-2-yl)-1H-imidazole-4-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide or
(4) (1R,5S,6r)-N-(1-cyanocyclopropyl)-3-[1-(propan-2-yl)-1H-imidazole-4-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide
or a salt thereof;

[15] The compound according to the preceding item [10], [11] and [11-1], wherein R^9 represents pyrazole which may be substituted with 1 to 3 R^{15} or a salt thereof;

[16] The compound according to any one of the preceding item [1], [10], [11], [11-1] and [15], wherein the compound represented by the general formula (I) is represented by the general formula (I-4)



(I-4)

wherein all symbols represent the same meaning as described in the preceding item [1] or [13];

or a salt thereof;

[17] The compound according to any one of the preceding item [1], [10], [11], [11-1], [15] and [16], wherein the compound is:

(1) (1R,5S,6r)-N-(propan-2-yl)-3-[5-(propan-2-yl)-1H-pyrazole-3-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide;

(2) (1R,5S,6r)-N-tert-butyl-6-methyl-3-[5-(propan-2-yl)-1H-pyrazole-3-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide;

(3) (1R,5S,6r)-N-tert-butyl-N-methyl-3-[5-(propan-2-yl)-1H-pyrazole-3-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide or

(4) (1R,5S,6r)-N-methyl-N-(1-methylcyclopropyl)-3-[5-(propan-2-yl)-1H-pyrazole-3-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide,

or a salt thereof;

[18] A pharmaceutical composition comprising the compound represented by the general formula (I) according to the preceding item [1] or a salt thereof, and a pharmaceutically acceptable carrier;

[19] The pharmaceutical composition according to the preceding item [18], which is KDM5 inhibitor;

[20] The pharmaceutical composition according to the preceding item [18] or [19], which is a prophylactic and/or therapeutic agent for KDM5-related disease;

[21-1] The pharmaceutical composition according to the preceding item [20], wherein the KDM5-related disease is hyperproliferative disease, cancer, stroke, diabetes, hepatomegaly, cardiovascular disease, multiple sclerosis, Huntington's disease, Alzheimer's disease, cystic fibrosis, viral disease, autoimmune diseases, atherosclerosis, restenosis, psoriasis, rheumatoid arthritis, inflammatory bowel disease, asthma, allergic disorders, inflammation, neurological

disorders, a hormone-related disease, conditions associated with organ transplantation, immunodeficiency disorders, destructive bone disorders, proliferative disorders, infectious diseases, conditions associated with cell death, thrombin-induced platelet aggregation, liver disease, pathologic immune conditions involving T cell activation, CNS disorders, myeloproliferative disorder, Parkinson's disease, Lewy body disease, frontotemporal lobar degeneration, mild cognitive impairment, cognitive impairment, cerebrovascular disease, schizophrenia, depression, anxiety disorder, bipolar disorder, autism spectrum disorder, attention deficit/hyperactivity disorder, learning disabilities, movement disorders, obsessive-compulsive disorder, personality disorder, sleeping disorder, delirium, amyotrophic lateral sclerosis, developmental disorders, intellectual disability, post-traumatic stress disorder, or hepatitis;

[21-2] The pharmaceutical composition according to the preceding item [20], wherein the KDM5-related disease is cancer, or Alzheimer Disease;

[22] A prophylactic and/or therapeutic agent for KDM5-related disease, comprising the compound represented by the general formula (I) according to the preceding item [1] or a salt thereof as an active component, wherein the prophylactic and/or therapeutic agent is administered together with at least one drug selected from the group consisting of donepezil hydrochloride, galantamine hydrobromide, huperzine A, idebenone, levacecarnine hydrochloride, memantine hydrochloride, memantine hydrochloride/donepezil hydrochloride, proteolytic peptide fraction from porcine brain protein, rivastigmine tartrate, tacrine hydrochloride and aducanumab;

[23] A method for prophylaxis and/or therapy of KDM5-related disease, comprising administering to a mammal (preferably, a patient in need thereof) an effective amount of the compound represented by the general formula (I) according to the preceding item [1] or a salt thereof;

[24] The compound represented by the general formula (I) according to the preceding item [1] or a salt thereof for use in prophylaxis and/or therapy of KDM5-related disease; and

[25] Use of the compound represented by the general formula (I) according to the preceding item [1] or a salt thereof in the manufacture of a prophylactic and/or therapeutic agent for KDM5-related disease.

[Advantageous Effects of Invention]

[0011]

The compound represented by the general formula (I) or a salt thereof (hereinafter collectively referred to as the present compound) as disclosed herein has KDM5 inhibitory activity. Therefore, the present compound can be used as a therapeutic and/or prophylactic agent for diseases such as hyperproliferative disease, cancer, stroke, diabetes, hepatomegaly, cardiovascular disease, multiple sclerosis, Huntington's disease, Alzheimer's disease, cystic fibrosis, viral disease, autoimmune diseases, atherosclerosis, restenosis, psoriasis, rheumatoid arthritis, inflammatory bowel disease, asthma, allergic disorders, inflammation, neurological disorders, a hormone-related disease, conditions associated with organ transplantation, immunodeficiency disorders, destructive bone disorders, proliferative disorders, infectious diseases, conditions associated with cell death, thrombin-induced platelet aggregation, liver disease, pathologic immune conditions involving T cell activation, CNS disorders, myeloproliferative disorder, Parkinson's disease, Lewy body disease, frontotemporal lobar degeneration, mild cognitive impairment, cognitive impairment, cerebrovascular disease, schizophrenia, depression, anxiety disorder, bipolar disorder, autism spectrum disorder, attention deficit/hyperactivity disorder, learning disabilities, movement disorders, obsessive-compulsive disorder, personality disorder, sleeping disorder, delirium, amyotrophic lateral sclerosis, developmental disorders, intellectual disability, post-traumatic stress disorder, or hepatitis.

[Description of Embodiments]

[0012]

Examples of “halogen” as used herein include fluorine, chlorine, bromine and iodine atoms.

[0013]

The “C1-4 alkyl” as used herein includes methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl and isobutyl groups.

[0014]

The “1 to 9 deuterated C1-4 alkyl” as used herein includes CH_2D-, CHD_2-, CD_3-, CD_3CD_2-, $CD_3CD_2CD_2$-, $(CD_3)_2CD$-, $CD_3CD_2CD_2CD_2$-, $CD_3CD_2CD(CD_3)$-, $(CD_3)_3C$-, and $(CD_3)_2CDCD_2$- and the like (D means deuterium).

[0015]

The “C1-8 alkyl” as used herein includes methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl, isobutyl, pentyl, 1,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1,3-dimethylbutyl, heptyl and octyl groups.

[0016]

The “C1-4 alkoxy” as used herein includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, sec-butoxy, tert-butoxy and isobutoxy groups.

[0017]

The “C1-4 haloalkyl” as used herein includes fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, 2,2,2-trifluoroethyl, perfluoroethyl, perfluoropropyl, perfluoro(isopropyl), perfluorobutyl, perfluoro(sec-butyl), perfluoro(tert-butyl) and perfluoro(isobutyl) groups and the like.

[0018]

The “C1-8 haloalkyl” as used herein includes fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, 2,2,2-trifluoroethyl, perfluoroethyl, perfluoropropyl, perfluoro(isopropyl), perfluorobutyl, perfluoro(sec-butyl), perfluoro(tert-butyl), perfluoro(isobutyl), perfluoropentyl, perfluorohexyl, perfluoroheptyl and perfluorooctyl groups and the like.

[0019]

Examples of “C3-5 cycloalkyl” as used herein include cyclopropyl, cyclobutyl, and cyclopentyl groups.

[0020]

Examples of “C3-5 cycloalkane” as used herein include cyclopropane, cyclobutane, and cyclopentane rings.

[0021]

Examples of “C3-5 cycloalkane, wherein the carbon atom of C3-5 cycloalkane may be replaced with hetero atom selected from 1 to 2 N, O and S” as used herein include cyclopropane, cyclobutane, cyclopentane, aziridine, oxirane, thiirane, azetidine, oxetane, thietane, pyrrolidine, tetrahydrofuran, tetrahydrothiophene, pyrazolidine, isoxazolidine, isothiazolidine, imidazolidine, oxazolidine, thiazolidine, and 1,3-dioxolane rings and the like.

[0022]

Examples of “C3-7 cycloalkyl” as used herein include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[1.1.0]butyl, bicyclo[2.1.0]pentyl, bicyclo[1.1.1]pentyl, bicyclo[3.1.0]hexyl, bicyclo[2.2.0]hexyl, bicyclo[2.1.1]hexyl,

bicyclo[4.1.0]heptyl, bicyclo[3.2.0]heptyl, bicyclo[2.2.1]heptyl and bicyclo[3.1.1]heptyl groups and the like.

[0023]

Examples of “5 to 9 membered aromatic hetero ring” as used herein include “5 to 9 membered aromatic hetero ring containing 1 to 4 nitrogen atoms, 1 oxygen atoms and/or 1 sulfur atom” and the like. Examples of the “5 to 9 membered aromatic hetero ring containing 1 to 4 nitrogen atoms, 1 oxygen atom and/or 1 sulfur atom” include 1,2,5-oxadiazole, 1,2,5-thiadiazole, 1,2,4-oxadiazole, 1,2,4-thiadiazole, isothiazole, 1,3,4-thiadiazole, benzo[d]isothiazole, isoxazole, 1,3,4-oxadiazole, 1,2,4-triazole, tetrazole, benzo[d]isoxazole, [1,2,3]triazolo[1,5-a]pyridine or [1,2,4]triazolo[4,3-a]pyridine rings and the like.

[0024]

Examples of “5 membered non-aromatic hetero ring” as used herein include “5 membered non-aromatic hetero ring containing 1 to 4 nitrogen atoms, 1 oxygen atom and/or 1 sulfur atom” and the like. Examples of the “5 membered non-aromatic hetero ring containing 1 to 4 nitrogen atoms, 1 oxygen atoms and/or 1 sulfur atom” include 2,3-dihydro-1,2,3-oxadiazole, 2,3-dihydro-1,2,3-thiadiazole, 2,3-dihydro-1,2,4-oxadiazole, 2,3-dihydro-1,2,4-thiadiazole, 2,3-dihydro-1,2,5-oxadiazole, 2,3-dihydro-1,2,5-thiadiazole, 2,3-dihydro-1,3,4-oxadiazole, 2,3-dihydro-1,3,4-thiadiazole, 2,3-dihydro-1H-1,2,3-triazole, 2,3-dihydro-1H-1,2,4-triazole, 2,3-dihydro-1H-imidazole, 2,3-dihydro-1H-pyrazole, 2,3-dihydro-1H-pyrrole, 2,3-dihydro-1H-tetrazole, 2,3-dihydrofuran, 2,3-dihydroisothiazole, 2,3-dihydroisoxazole, 2,3-dihydrooxazole, 2,3-dihydrothiazole, 2,3-dihydrothiophene, 4,5-dihydro-1,2,3-oxadiazole, 4,5-dihydro-1,2,3-thiadiazole, 4,5-dihydro-1,2,4-oxadiazole, 4,5-dihydro-1,2,4-thiadiazole, 4,5-dihydro-1H-1,2,3-triazole, 4,5-dihydro-1H-1,2,4-triazole, 4,5-dihydro-1H-imidazole, 4,5-dihydro-1H-pyrazole, 4,5-dihydro-1H-tetrazole, 4,5-dihydroisothiazole, 4,5-dihydroisoxazole, 4,5-dihydrooxazole and 4,5-dihydrothiazole rings and the like.

[0025]

Examples of “C3-12 mono or bicyclic carbocycle” as used herein include cyclopropane, cyclobutane, cyclopentane, cyclohexane, cyclopentene, cyclohexene, cyclopentadiene, cyclohexadiene, benzene, indene, dihydroindene, naphthalene, dihydronaphthalene, and tetrahydronaphthalene rings and the like.

[0026]

Examples of “5- to 9-membered mono or bicyclic heterocycle” as used herein include “5- to 9-membered mono or bicyclic heterocycles containing 1 to 4 nitrogen atoms, 1 to 2 oxygen atoms and/or 1 sulfur atom” and the like. Examples of the “5- to 9-membered mono or bicyclic heterocycles containing 1 to 4 nitrogen atoms, 1 to 2 oxygen atoms and/or 1 sulfur atom” include pyrrole, imidazole, triazole, tetrazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, furan, pyran, thiophene, thiopyran, oxazole, isoxazole, thiazole, isothiazole, furazan, oxadiazole, oxazine, oxadiazine, thiadiazole, thiazine, thiadiazine, pyrroline, pyrrolidine, imidazoline, imidazolidine, triazoline, triazolidine, tetrazoline, tetrazolidine, pyrazoline, pyrazolidine, dihydropyridine, tetrahydropyridine, piperidine, dihydropyrazine, tetrahydropyrazine, piperazine, dihydropyrimidine, tetrahydropyrimidine, perhydropyrimidine, dihydropyridazine, tetrahydropyridazine, perhydropyridazine, dihydrofuran, tetrahydrofuran, dihydropyran, tetrahydropyran, dihydrothiophene, tetrahydrothiophene, dihydrothiopyran, tetrahydrothiopyran, dihydrooxazole, tetrahydrooxazole (oxazolidine), dihydroisoxazole, tetrahydroisoxazole (isoxazolidine), dihydrothiazole, tetrahydrothiazole (thiazolidine), dihydroisothiazole, tetrahydroisothiazole (isothiazolidine), dihydrofurazan, tetrahydrofurazan, dihydrooxadiazole, tetrahydrooxadiazole (oxadiazolidine), dihydrooxazine, tetrahydrooxazine, dihydrooxadiazine, tetrahydrooxadiazine, dihydrothiadiazole, tetrahydrothiadiazole (thiadiazolidine), dihydrothiazine, tetrahydrothiazine, dihydrothiadiazine, tetrahydrothiadiazine, morpholine, thiomorpholine, oxathiane, dioxolane, dioxane, dioxole, indole, benzimidazole, benztriazole, indazole, benzofuran, benzothiophene, benzoxazole, indoline, dihydrobenzimidazole, dihydrobenztriazole, dihydroindazole, dihydrobenzofuran, dihydrobenzothiophene, and dihydrobenzoxazole, rings and the like.

[0027]



indicates that the bond projects above the plane of the paper (i.e., β-configuration), and the symbol:

In the present invention, unless particularly stated, the symbol:



indicates that the bond projects below the plane of the paper (i.e., α-configuration), and the symbol:



indicates that the bond is the α-configuration, β-configuration or the mixture of these configurations at arbitrary proportions, as apparent to a person skilled in the art.

[0028]

In the present invention, R^1 is preferably, for example, Cyc1 or -$CONR^{10}R^{11}$, more preferably, for example, Cyc1, and particularly preferably, for example, 5 membered non-aromatic hetero ring.

[0029]

In the present invention, Cyc1 is preferably, for example, 5 membered non-aromatic hetero ring which may be substituted with 1 to 5 R^{12}, more preferably, for example, 2,3-dihydro-1,2,5-oxadiazole, 2,3-dihydro-1,2,5-thiadiazole, 4,5-dihydro-1,2,3-oxadiazole, 4,5-dihydro-1,2,3-thiadiazole, 4,5-dihydro-1,2,4-oxadiazole, 4,5-dihydro-1,2,4-thiadiazole, 4,5-dihydro-1H-1,2,3-triazole, 4,5-dihydroisothiazole, or 4,5-dihydroisoxazole, each of which may be substituted with 1 to 5 R^{12}, particularly preferably, for example, 4,5-dihydro-1,2,4-oxadiazole or 4,5-dihydroisoxazole, each of which may be substituted with 1 to 5 R^{12} , and especially preferably, for example, 4,5-dihydroisoxazole which may be substituted with 1 to 5 R^{12}.

[0030]

In the present invention, Cyc1 is also preferably, for example, 5 to 9 membered aromatic hetero ring which may be substituted with 1 to 5 R^{12}, more preferably, for example, 1,2,5-oxadiazole, 1,2,5-thiadiazole, 1,2,4-oxadiazole, 1,2,4-thiadiazole, isothiazole, 1,3,4-thiadiazole, benzo[d]isothiazole, isoxazole, 1,3,4-oxadiazole, 1,2,4-triazole, tetrazole, benzo[d]isoxazole, [1,2,3]triazolo[1,5-a]pyridine or [1,2,4]triazolo[4,3-a]pyridine, each of which may be substituted with 1 to 5 R^{12}, and particularly preferably, for example, isoxazole, 1,3,4-oxadiazole, 1,2,4-triazole, tetrazole, benzo[d]isoxazole, [1,2,3]triazolo[1,5-a]pyridine or [1,2,4]triazolo[4,3-a]pyridine, each of which may be substituted with 1 to 5 R^{12}.

[0031]

In the present invention, R^{12} is preferably, for example, (1) C1-4 alkyl, (2) C3-7 cycloalkyl, (3) C1-4 haloalkyl, (4) C1-4 alkoxy, (5) phenyl which may be substituted with 1 to 3 R^{17}, (6) C1-4 alkyl which is substituted with phenyl, (7) dimethylamino, (8) pyridyl or (9) 1-(cyclopropylmethyl)pyrazol-3-yl, or (10) two R^{12} together with an atom to which these R^{12} are attached may form a C3-5 cycloalkane, more preferably, for example, (1)C1-4 alkyl, (2) C3-7 cycloalkyl, (3) phenyl which may be substituted with 1 to 3 R^{17}, or (4) two R^{12} together with an atom to which these R^{12} are attached may form a C3-5 cycloalkane, and particularly preferably, for example, C1-4 alkyl, or two R^{12} together with an atom to which these R^{12} are attached may form a C3-5 cycloalkane.

[0032]

In the present invention, R^{17} is preferably, for example, C1-4 alkyl or C1-4 alkoxy.

In the present invention, Cyc2 is preferably, for example, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cyclopentene, cyclohexene, cyclopentadiene, cyclohexadiene, benzene, pyrrole, imidazole, triazole, tetrazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, furan, pyran, thiophene, thiopyran, oxazole, isoxazole, thiazole, isothiazole, furazan, oxadiazole, oxazine, oxadiazine, thiadiazole, thiazine, thiadiazine, indole, benzimidazole, benztriazole, indazole, benzofuran, benzothiophene, benzoxazole, indoline, dihydrobenzimidazole, dihydrobenztriazole, dihydroindazole, dihydrobenzofuran, dihydrobenzothiophene, or dihydrobenzoxazole, each of which may be substituted with 1 to 5 R^{13}, and more preferably, for example, cyclopropane, benzene, pyridine, thiophene, thiazole, or indoline, each of which may be substituted with 1 to 5 R^{13}.

[0033]

In the present invention, R^{10} is preferably, for example, isopropyl, tert-butyl, 1,1,1-trifluoro-2-methylpropan-2-yl, 1-methylcyclopropyl, 1-(trifluoromethyl)cyclopropyl or 1-cyanocyclopropyl.

[0034]

In the present invention, R^{13} is preferably, for example, C1-4 alkyl or C1-4 alkoxy.

In the present invention, R^{11} is preferably, for example, a hydrogen atom or C1-4 alkyl.

In the present invention, R^{2} is preferably, for example, a hydrogen atom or C1-4 alkyl.

In the present invention, R^3 is preferably, for example, a hydrogen atom or C1-4 alkyl.

In the present invention, R^4 is preferably, for example, a hydrogen atom or C1-4 alkyl.

In the present invention, R^5 is preferably, for example, a hydrogen atom or C1-4 alkyl.

In the present invention, R^6 is preferably, for example, a hydrogen atom or C1-4 alkyl.

In the present invention, R^7 is preferably, for example, a hydrogen atom or C1-4 alkyl.

In the present invention, R^8 is preferably, for example, a hydrogen atom or C1-4 alkyl.

In the present invention, R^9 is preferably, for example, imidazole which may be substituted with 1 to 3 R^{14}.

In the present invention, R^9 is also preferably, for example, pyrazole which may be substituted with 1 to 3 R^{15}.

[0035]

In the present invention, R^{14} is preferably, for example, (1) C1-8 alkyl, (2) C3-7 cycloalkyl which may be substituted with C1-4 alkyl, (3) C1-8 alkyl which is substituted with Cyc3 which may be substituted with 1 to 3 R^{16} or (4) C1-8 alkyl which is substituted with phenoxy, and more preferably, for example, (1) C1-8 alkyl or (2) C3-7 cycloalkyl which may be substituted with C1-4 alkyl.

[0036]

In the present invention, Cyc3 is preferably, for example, phenyl or C3-7 cycloalkyl.

In the present invention, R^{16} is preferably, for example, C1-4 alkyl or cyano.

[0037]

In the present invention, R^{15} is preferably, for example, (1) C1-8 alkyl, (2) C3-7 cycloalkyl which may be substituted with C1-4 alkyl, (3) C1-8 alkyl which is substituted with Cyc3 which may be substituted with 1 to 3 R^{21}, and more preferably, for example, (1) C1-8 alkyl or (2) C3-7 cycloalkyl which may be substituted with C1-4 alkyl.

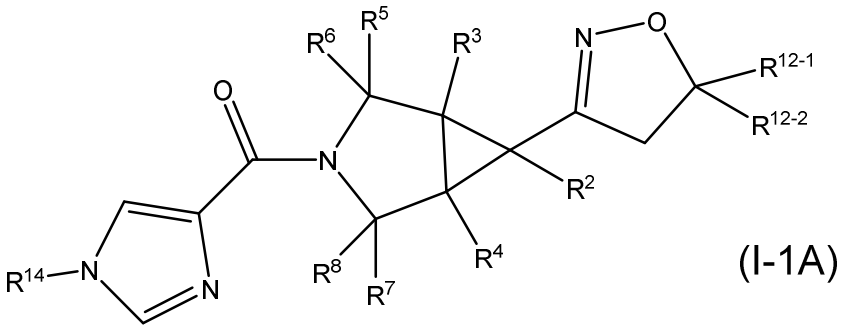
[0038]

In the present invention, Cyc4 is preferably, for example, phenyl or C3-7 cycloalkyl.

In the present invention, R^{21} is preferably, for example, C1-4 alkyl or cyano.

[0039]

In the present invention, examples of the general formula (I) preferably include the general formula (I-1A):

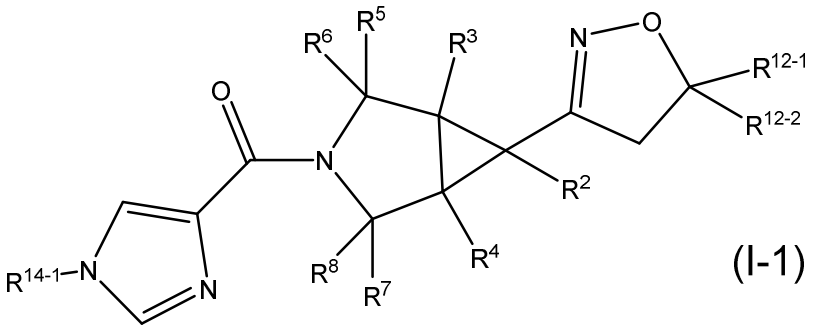


(I-1A)

wherein all symbols have the same meanings as above,

[0040]

In the present invention, examples of the general formula (I) preferably include the general formula (I-1):

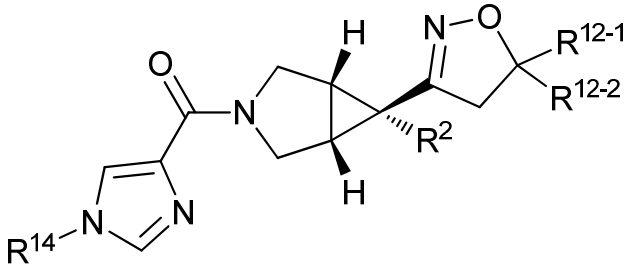


(I-1)

wherein all symbols have the same meanings as above,

[0041]

the general formula (I-1A-1):



(I-1A-1)

wherein R^2 represents a hydrogen atom, or C1-4 alkyl;

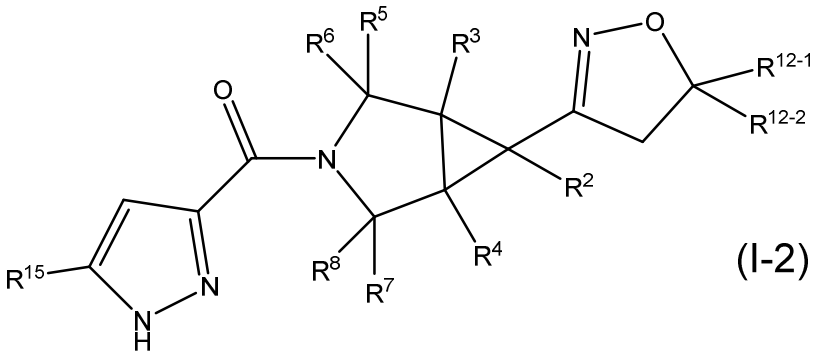
R^{14} represents (1) C1-8 alkyl, (2) C3-7 cycloalkyl which may be substituted with C1-4 alkyl, or (5) C1-8 alkyl which is substituted with phenoxy;

wherein R^{12-1} and R^{12-2} independently represent C1-4 alkyl; and

R^{12-1} and R^{12-2} together with an atom to which the R^{12-1} and R^{12-2} are bound may form C3-5 cycloalkane;

[0042]

the general formula (I-2):

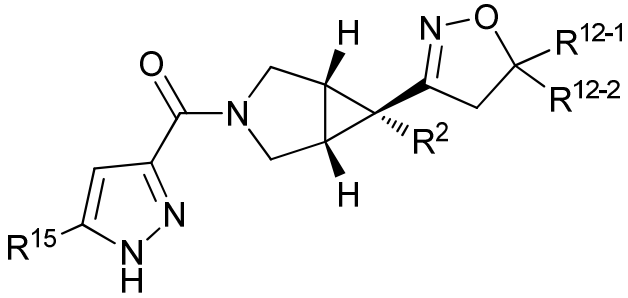


(I-2)

wherein all symbols have the same meanings as above,

[0043]

the general formula (I-2-1):



(I-2-1)

wherein R^2 represents a hydrogen atom, C1-4 alkyl, halogen or C1-4 alkoxy;

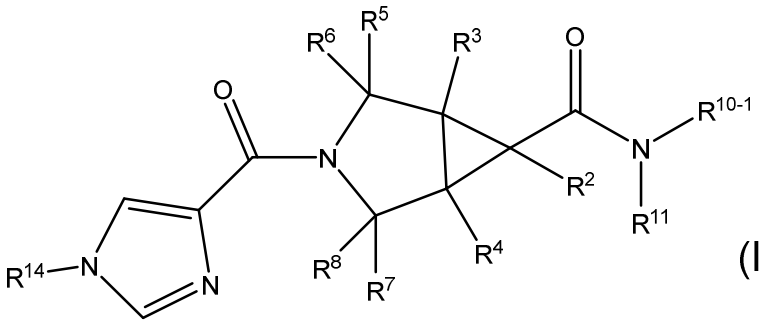
R^{15} represents (1) C1-8 alkyl, or (3) C1-8 haloalkyl;

wherein R^{12-1} and R^{12-2} independently represent C1-4 alkyl; and

R^{12-1} and R^{12-2} together with an atom to which the R^{12-1} and R^{12-2} are bound may form C3-5 cycloalkane;

[0044]

the general formula (I-3A):

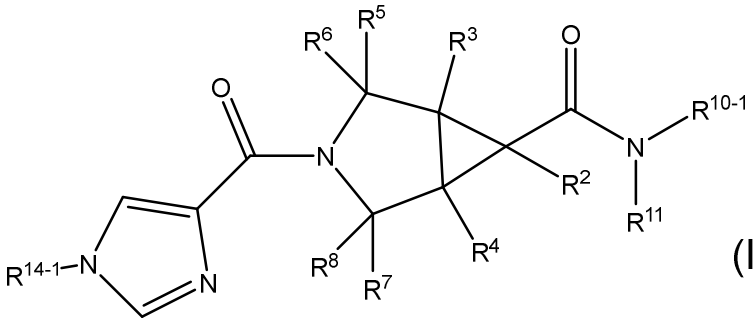


(I-3A)

wherein all symbols have the same meanings as above,

[0045]

the general formula (I-3):

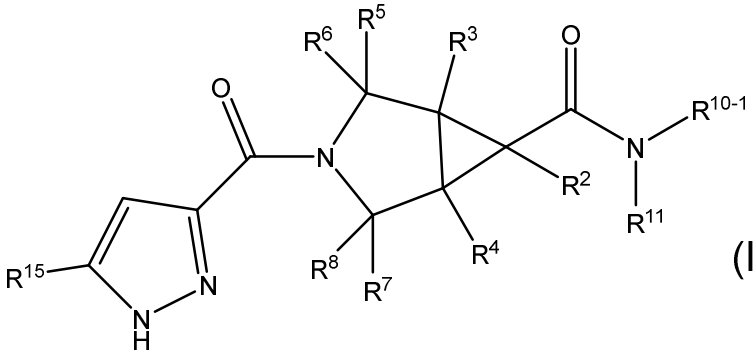


(I-3)

wherein all symbols have the same meanings as above,

[0046]

the general formula (I-4):

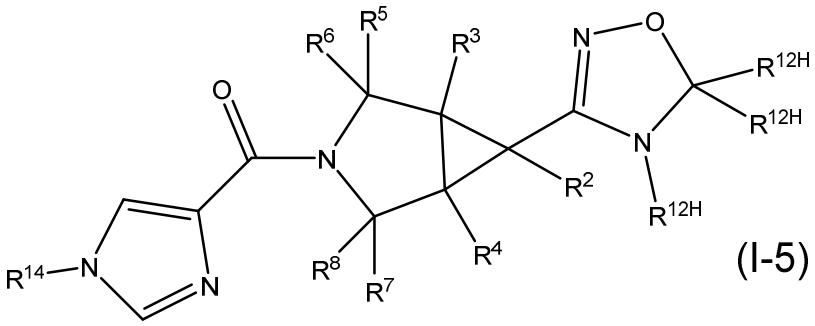


(I-4)

wherein all symbols have the same meanings as above,

[0047]

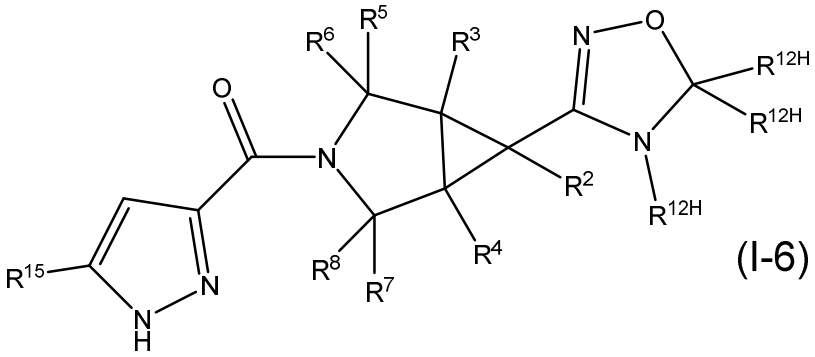
the general formula (I-5):



wherein R^{12H} represents (1) a hydrogen atom, (2) C1-4 alkyl, (3) C3-7 cycloalkyl, (4) C1-4 haloalkyl, (5) C1-4 alkoxy, (6) phenyl which may be substituted with 1 to 3 R^{17}, (7) C1-4 alkyl which is substituted with phenyl, (8) dimethylamino, (9) pyridyl or (10) 1-(cyclopropylmethyl)pyrazol-3-yl, and other symbols have the same meanings as above,

[0048]

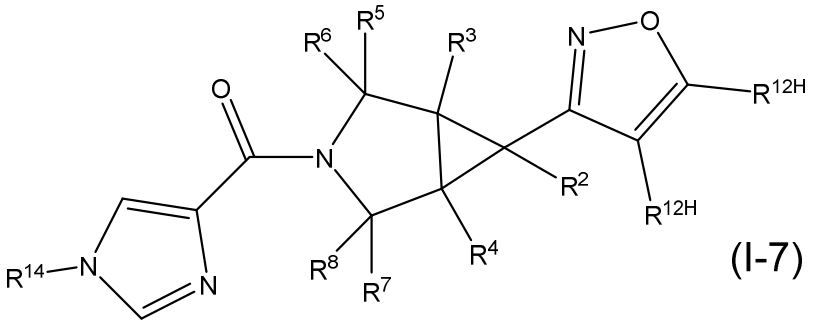
the general formula (I-6):



wherein all symbols have the same meanings as above,

[0049]

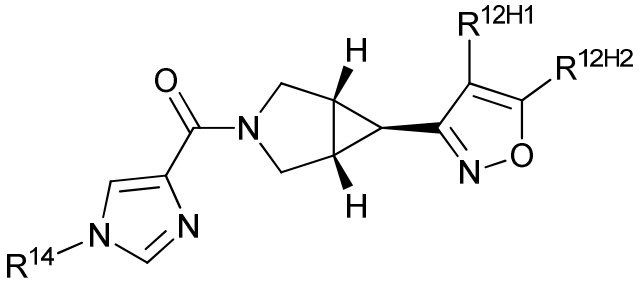
the general formula (I-7):



wherein all symbols have the same meanings as above,

[0050]

the general formula (I-7-1):



(I-7-1)

wherein R^{14} represents (1) C1-8 alkyl, or (3) C1-8 haloalkyl;

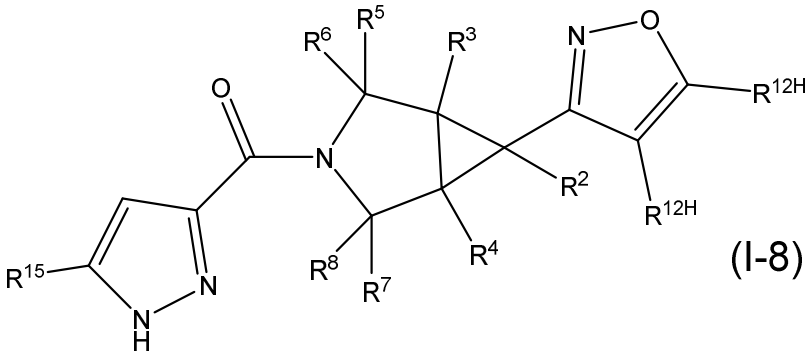
R^{12H1} represents (2) C1-4 alkyl, (3) C3-7 cycloalkyl, (4) C1-4 haloalkyl, (5) C1-4 alkoxy, (6) phenyl which may be substituted with 1 to 3 R^{17}, (7) C1-4 alkyl which is substituted with phenyl, (8) dimethylamino, (9) pyridyl or (10) 1-(cyclopropylmethyl)pyrazol-3-yl; preferably, R^{12H1} represents (2) C1-4 alkyl, (3) C3-7 cycloalkyl, (4) C1-4 haloalkyl, (6) phenyl which may be substituted with 1 to 3 R^{17}, (7) C1-4 alkyl which is substituted with phenyl, (9) pyridyl or (10) 1-(cyclopropylmethyl)pyrazol-3-yl;

R^{12H2} represents (1) a hydrogen atom, (2) C1-4 alkyl, (3) C3-7 cycloalkyl, (4) C1-4 haloalkyl, (5) C1-4 alkoxy, (6) phenyl which may be substituted with 1 to 3 R^{17}, (7) C1-4 alkyl which is substituted with phenyl, (8) dimethylamino, (9) pyridyl or (10) 1-(cyclopropylmethyl)pyrazol-3-yl; preferably, R^{12H2} represents (1) a hydrogen atom, (2) C1-4 alkyl, (4) C1-4 haloalkyl, (7) C1-4 alkyl which is substituted with phenyl, (8) dimethylamino;

and R^{17} represents C1-4 alkyl, C1-4 alkoxy or halogen.

[0051]

the general formula (I-8):

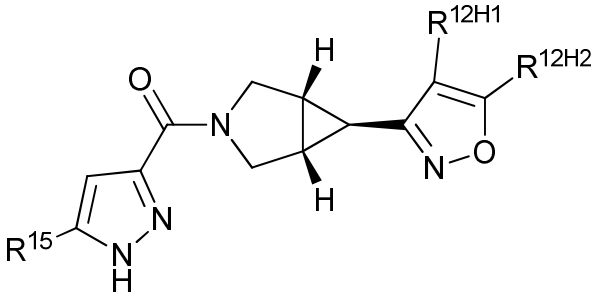


(I-8)

wherein all symbols have the same meanings as above,

[0052]

the general formula (I-8-1):



(I-8-1)

wherein R^{15} represents (1) C1-8 alkyl, or (3) C1-8 haloalkyl;

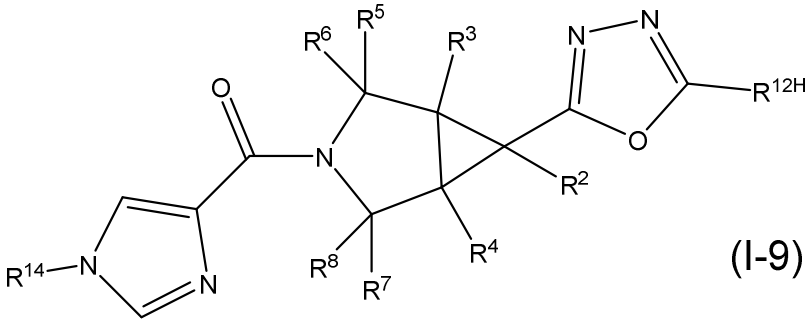
R^{12H1} represents (2) C1-4 alkyl, (3) C3-7 cycloalkyl, (4) C1-4 haloalkyl, (5) C1-4 alkoxy, (6) phenyl which may be substituted with 1 to 3 R^{17}, (7) C1-4 alkyl which is substituted with phenyl, (8) dimethylamino, (9) pyridyl or (10) 1-(cyclopropylmethyl)pyrazol-3-yl; preferably, R^{12H1} represents (2) C1-4 alkyl, (3) C3-7 cycloalkyl, (4) C1-4 haloalkyl, (6) phenyl which may be substituted with 1 to 3 R^{17}, (7) C1-4 alkyl which is substituted with phenyl, (9) pyridyl or (10) 1-(cyclopropylmethyl)pyrazol-3-yl;

R^{12H2} represents (1) a hydrogen atom, (2) C1-4 alkyl, (3) C3-7 cycloalkyl, (4) C1-4 haloalkyl, (5) C1-4 alkoxy, (6) phenyl which may be substituted with 1 to 3 R^{17}, (7) C1-4 alkyl which is substituted with phenyl, (8) dimethylamino, (9) pyridyl or (10) 1-(cyclopropylmethyl)pyrazol-3-yl; preferably, R^{12H2} represents (1) a hydrogen atom, (2) C1-4 alkyl, (4) C1-4 haloalkyl, (7) C1-4 alkyl which is substituted with phenyl, (8) dimethylamino;

and R^{17} represents C1-4 alkyl, C1-4 alkoxy or halogen.

[0053]

the general formula (I-9):

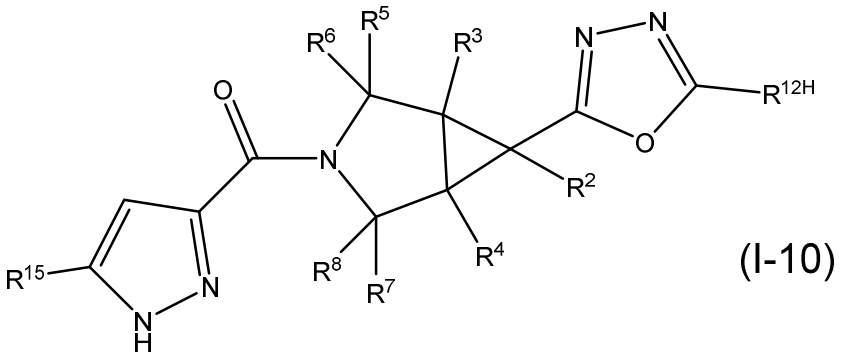


(I-9)

wherein all symbols have the same meanings as above,

[0054]

the general formula (I-10):

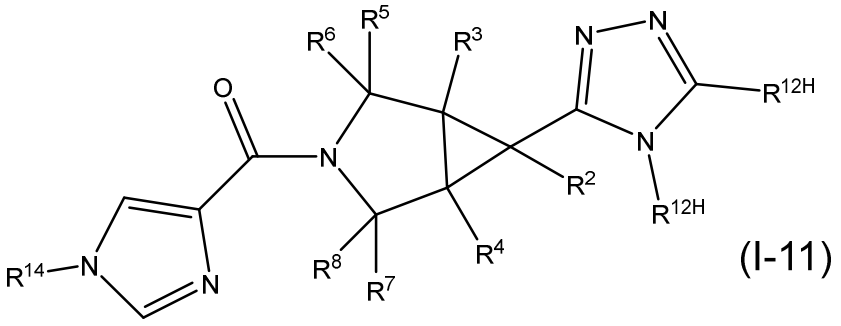


(I-10)

wherein all symbols have the same meanings as above,

[0055]

the general formula (I-11):

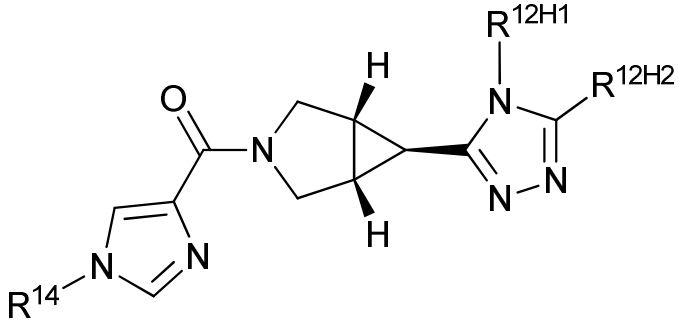


(I-11)

wherein all symbols have the same meanings as above,

[0056]

the general formula (I-11-1):



(I-11-1)

wherein R^{14} represents (1) C1-8 alkyl, or (3) C1-8 haloalkyl;

R^{12H1} represents (2) C1-4 alkyl, (3) C3-7 cycloalkyl, (4) C1-4 haloalkyl, (5) C1-4 alkoxy, (6) phenyl which may be substituted with 1 to 3 R^{17}, (7) C1-4 alkyl which is substituted with phenyl, (8) dimethylamino, (9) pyridyl or (10) 1-(cyclopropylmethyl)pyrazol-3-yl; preferably, R^{12H1} represents (2) C1-4 alkyl, (3) C3-7 cycloalkyl, (4) C1-4 haloalkyl, (6)

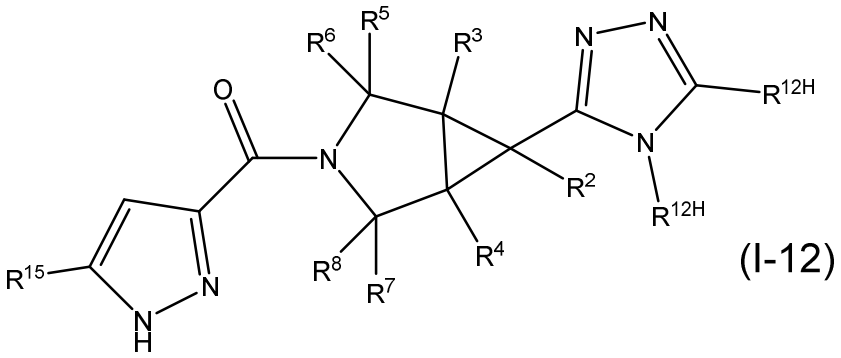
phenyl which may be substituted with 1 to 3 R^{17}, (7) C1-4 alkyl which is substituted with phenyl, (9) pyridyl or (10) 1-(cyclopropylmethyl)pyrazol-3-yl;

R^{12H2} represents (1) a hydrogen atom, (2) C1-4 alkyl, (3) C3-7 cycloalkyl, (4) C1-4 haloalkyl, (5) C1-4 alkoxy, (6) phenyl which may be substituted with 1 to 3 R^{17}, (7) C1-4 alkyl which is substituted with phenyl, (8) dimethylamino, (9) pyridyl or (10) 1-(cyclopropylmethyl)pyrazol-3-yl; preferably, R^{12H2} represents (1) a hydrogen atom, (2) C1-4 alkyl, (4) C1-4 haloalkyl, (7) C1-4 alkyl which is substituted with phenyl, (8) dimethylamino;

and R^{17} represents C1-4 alkyl, C1-4 alkoxy or halogen.

[0057]

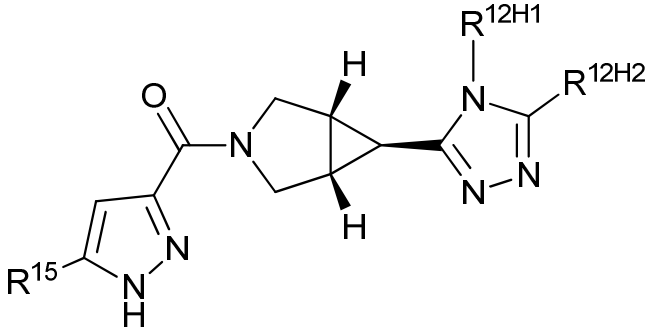
the general formula (I-12):



(I-12)

wherein all symbols have the same meanings as above,

the general formula (I-12-1):



(I-12-1)

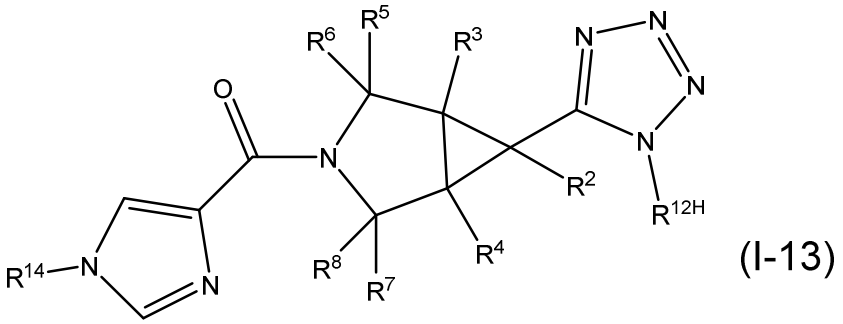
wherein R^{15} represents (1) C1-8 alkyl, or (3) C1-8 haloalkyl;

R^{12H1} represents (2) C1-4 alkyl, (3) C3-7 cycloalkyl, (4) C1-4 haloalkyl, (5) C1-4 alkoxy, (6) phenyl which may be substituted with 1 to 3 R^{17}, (7) C1-4 alkyl which is substituted with phenyl, (8) dimethylamino, (9) pyridyl or (10) 1-(cyclopropylmethyl)pyrazol-3-yl; preferably, R^{12H1} represents (2) C1-4 alkyl, (3) C3-7 cycloalkyl, (4) C1-4 haloalkyl, (6) phenyl which may be substituted with 1 to 3 R^{17}, (7) C1-4 alkyl which is substituted with phenyl, (9) pyridyl or (10) 1-(cyclopropylmethyl)pyrazol-3-yl;

R^{12H2} represents (1) a hydrogen atom, (2) C1-4 alkyl, (3) C3-7 cycloalkyl, (4) C1-4 haloalkyl, (5) C1-4 alkoxy, (6) phenyl which may be substituted with 1 to 3 R^{17}, (7) C1-4 alkyl which is substituted with phenyl, (8) dimethylamino, (9) pyridyl or (10) 1-(cyclopropylmethyl)pyrazol-3-yl; preferably, R^{12H2} represents (1) a hydrogen atom, (2) C1-4 alkyl, (4) C1-4 haloalkyl, (7) C1-4 alkyl which is substituted with phenyl, (8) dimethylamino; and R^{17} represents C1-4 alkyl, C1-4 alkoxy or halogen.

[0058]

the general formula (I-13):

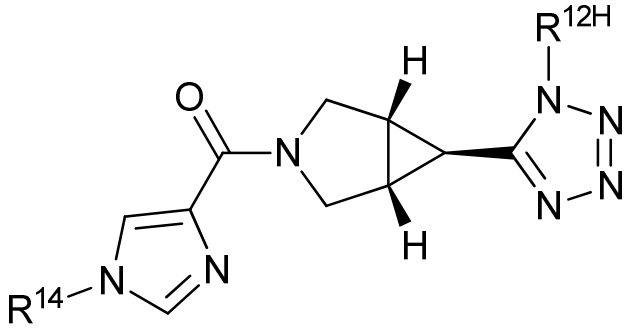


(I-13)

wherein all symbols have the same meanings as above,

[0059]

the general formula (I-13-1):



(I-13-1)

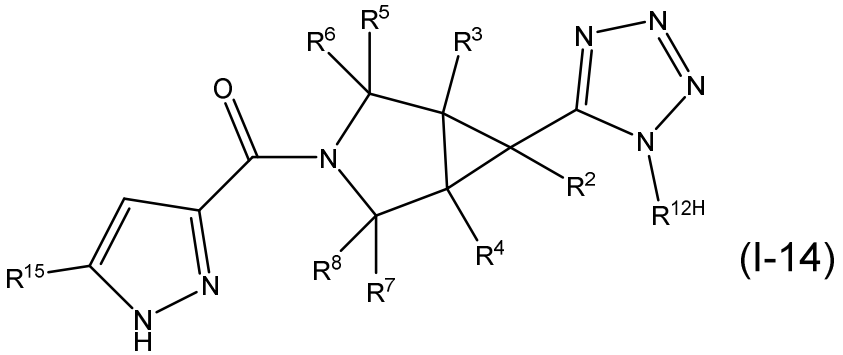
wherein R^{14} represents (1) C1-8 alkyl, or (3) C1-8 haloalkyl;

R^{12H} represents (1) a hydrogen atom, (2) C1-4 alkyl, (3) C3-7 cycloalkyl, (4) C1-4 haloalkyl, (5) C1-4 alkoxy, (6) phenyl which may be substituted with 1 to 3 R^{17}, (7) C1-4 alkyl which is substituted with phenyl, (8) dimethylamino, (9) pyridyl or (10) 1-(cyclopropylmethyl)pyrazol-3-yl; preferably, R^{12H} represents (1) a hydrogen atom, (2) C1-4 alkyl, (4) C1-4 haloalkyl;

and R^{17} represents C1-4 alkyl, C1-4 alkoxy or halogen.

[0060]

the general formula (I-14):

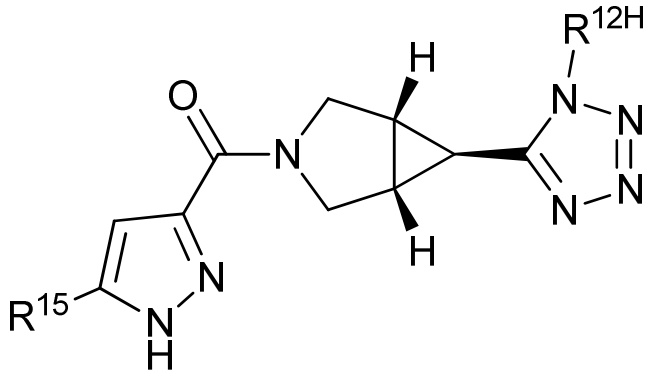


(I-14)

wherein all symbols have the same meanings as above,

[0061]

the general formula (I-14-1):



(I-14-1)

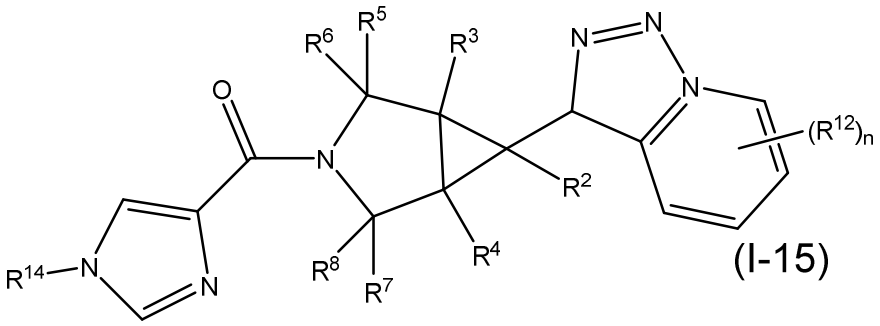
wherein R^{15} represents (1) C1-8 alkyl, or (3) C1-8 haloalkyl;

R^{12H} represents (1) a hydrogen atom, (2) C1-4 alkyl, (3) C3-7 cycloalkyl, (4) C1-4 haloalkyl, (5) C1-4 alkoxy, (6) phenyl which may be substituted with 1 to 3 R^{17}, (7) C1-4 alkyl which is substituted with phenyl, (8) dimethylamino, (9) pyridyl or (10) 1-(cyclopropylmethyl)pyrazol-3-yl; preferably, R^{12H} represents (1) a hydrogen atom, (2) C1-4 alkyl, (4) C1-4 haloalkyl;

and R^{17} represents C1-4 alkyl, C1-4 alkoxy or halogen.

[0062]

the general formula (I-15):

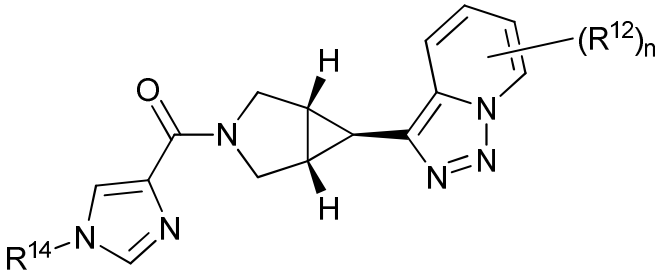


(I-15)

wherein n represents an integer of 0 to 4, and other symbols have the same meanings as above,

[0063]

the general formula (I-15-1):



(I-15-1)

wherein R^{14} represents (1) C1-8 alkyl, or (3) C1-8 haloalkyl;

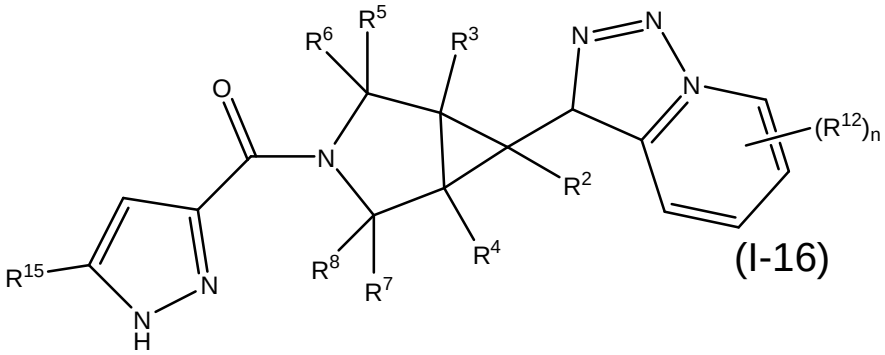
R^{12} represents (1) C1-4 alkyl, (2) C3-7 cycloalkyl, (3) C1-4 haloalkyl, (4) C1-4 alkoxy, (5) phenyl which may be substituted with 1 to 3 R^{17}, (6) C1-4 alkyl which is substituted with phenyl, (7) dimethylamino, (8) pyridyl or (9) 1-(cyclopropylmethyl)pyrazol-3-yl;

n represents an integer of 0 to 4, preferably, n is 0;

and R^{17} represents C1-4 alkyl, C1-4 alkoxy or halogen.

[0064]

the general formula (I-16):

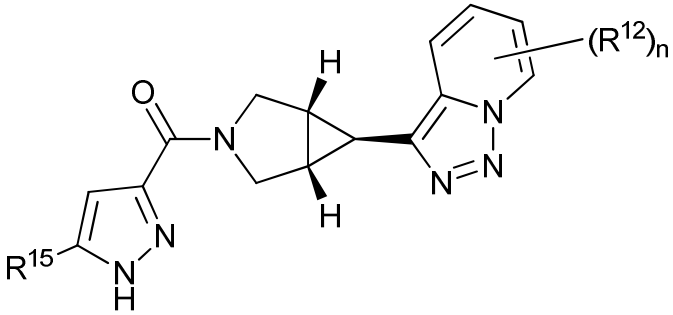


(I-16)

wherein all symbols have the same meanings as above,

[0065]

the general formula (I-16-1):



(I-16-1)

wherein R^{15} represents (1) C1-8 alkyl, or (3) C1-8 haloalkyl;

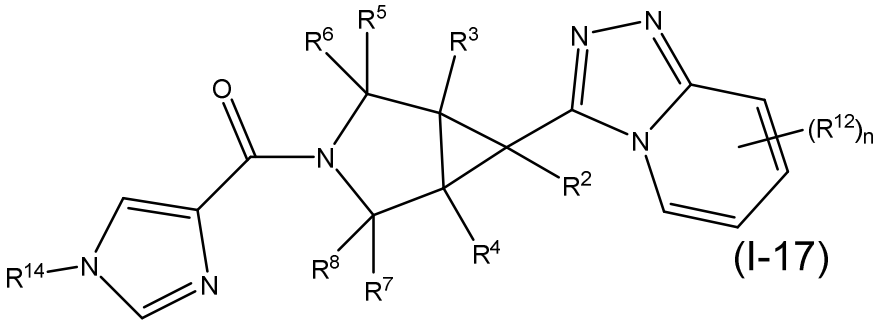
R^{12} represents (1) C1-4 alkyl, (2) C3-7 cycloalkyl, (3) C1-4 haloalkyl, (4) C1-4 alkoxy, (5) phenyl which may be substituted with 1 to 3 R^{17}, (6) C1-4 alkyl which is substituted with phenyl, (7) dimethylamino, (8) pyridyl or (9) 1-(cyclopropylmethyl)pyrazol-3-yl;

n represents an integer of 0 to 4, preferably, n is 0;

and R^{17} represents C1-4 alkyl, C1-4 alkoxy or halogen.

[0066]

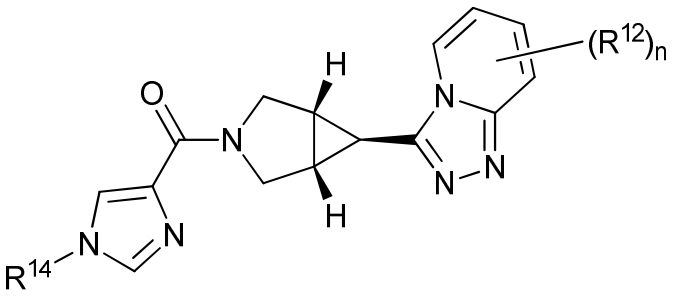
the general formula (I-17):



(I-17)

wherein all symbols have the same meanings as above,

the general formula (I-17-1):



(I-17-1)

wherein R^{14} represents (1) C1-8 alkyl, or (3) C1-8 haloalkyl;

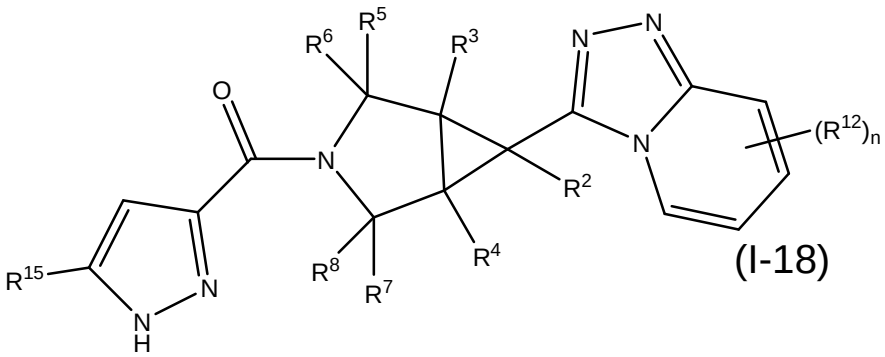
R^{12} represents (1) C1-4 alkyl, (2) C3-7 cycloalkyl, (3) C1-4 haloalkyl, (4) C1-4 alkoxy, (5) phenyl which may be substituted with 1 to 3 R^{17}, (6) C1-4 alkyl which is substituted with phenyl, (7) dimethylamino, (8) pyridyl or (9) 1-(cyclopropylmethyl)pyrazol-3-yl;

n represents an integer of 0 to 4, preferably, n is 0;

and R^{17} represents C1-4 alkyl, C1-4 alkoxy or halogen;

[0067]

the general formula (I-18):

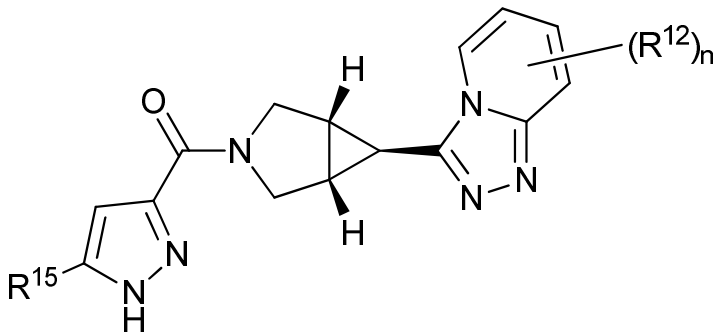


(I-18)

wherein all symbols have the same meanings as above,

[0068]

the general formula (I-18-1):



(I-18-1)

wherein R^{15} represents (1) C1-8 alkyl, or (3) C1-8 haloalkyl;

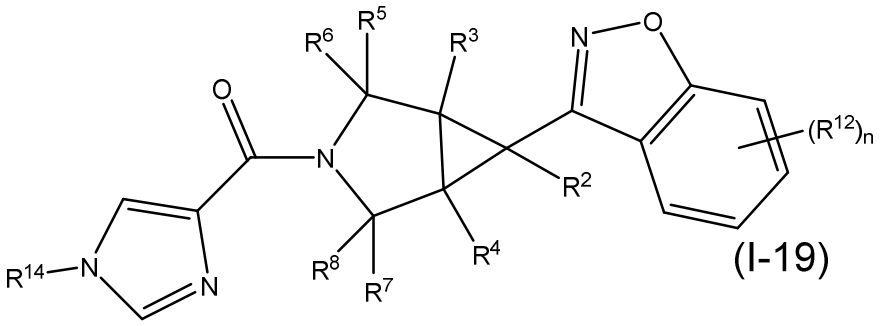
R^{12} represents (1) C1-4 alkyl, (2) C3-7 cycloalkyl, (3) C1-4 haloalkyl, (4) C1-4 alkoxy, (5) phenyl which may be substituted with 1 to 3 R^{17}, (6) C1-4 alkyl which is substituted with phenyl, (7) dimethylamino, (8) pyridyl or (9) 1-(cyclopropylmethyl)pyrazol-3-yl; preferably, R^{12} represents (1) C1-4 alkyl, (2) C3-7 cycloalkyl, (3) C1-4 haloalkyl, (4) C1-4 alkoxy,

n represents an integer of 0 to 4, preferably, n is 1;

and R^{17} represents C1-4 alkyl, C1-4 alkoxy or halogen.

[0069]

the general formula (I-19):

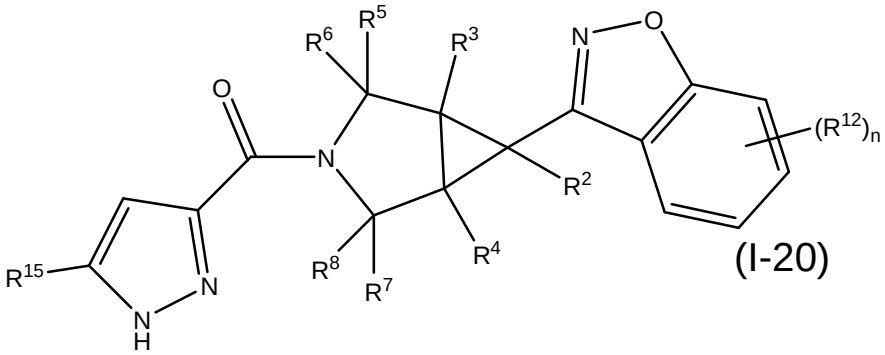


(I-19)

wherein all symbols have the same meanings as above,

[0070]

the general formula (I-20):

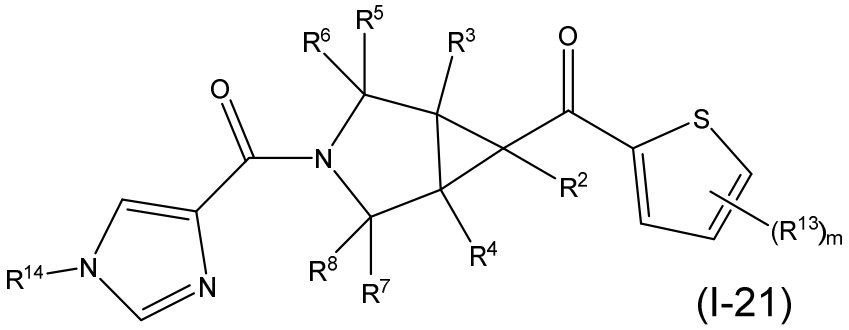


(I-20)

wherein all symbols have the same meanings as above,

[0071]

the general formula (I-21):

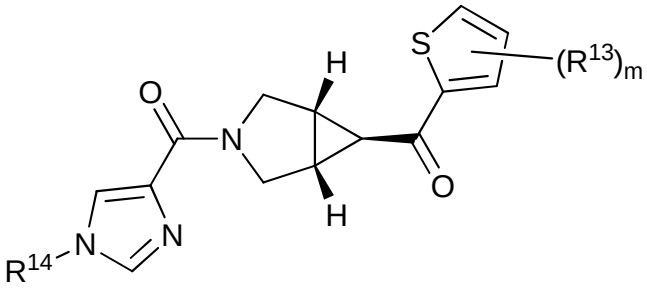


(I-21)

wherein m represents an integer of 0 to 2, and other symbols have the same meanings as above,

[0072]

the general formula (I-21-1):



(I-21-1)

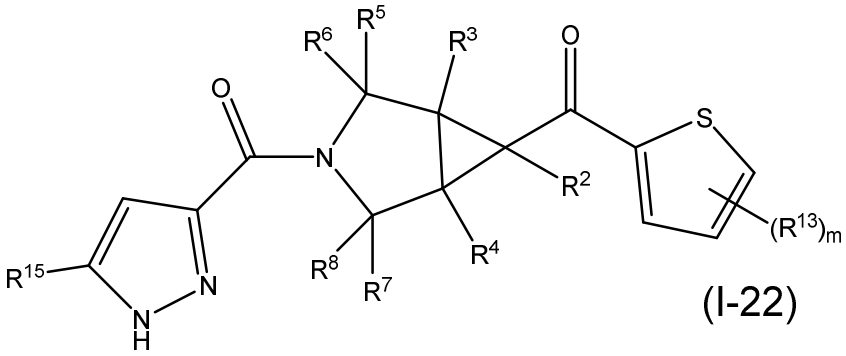
wherein R^{14} represents (1) C1-8 alkyl, or (3) C1-8 haloalkyl;

R^{13} represents C1-4 alkyl, C1-4 alkoxy or halogen; and

m represents an integer of 0 to 2.

[0073]

the general formula (I-22):

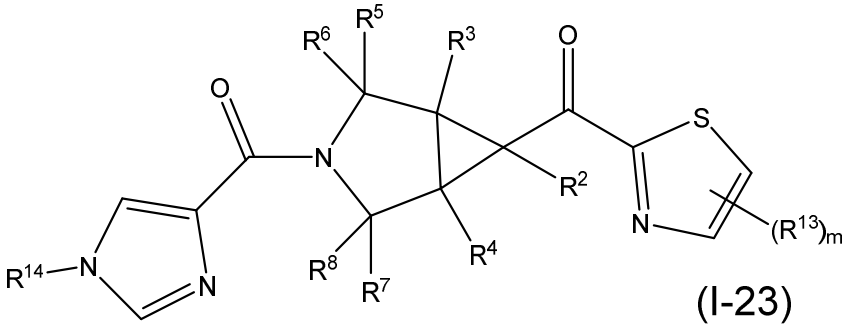


(I-22)

wherein all symbols have the same meanings as above,

[0074]

the general formula (I-23):

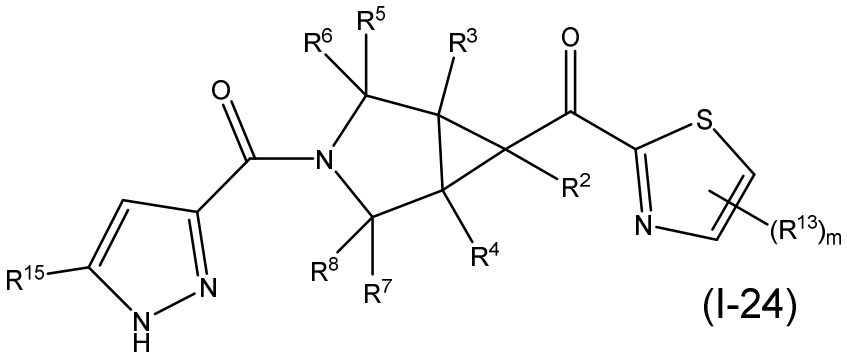


(I-23)

wherein all symbols have the same meanings as above,

[0075]

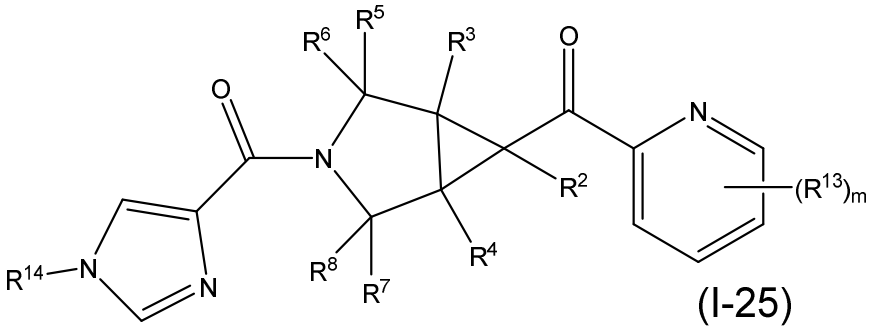
the general formula (I-24):



wherein all symbols have the same meanings as above,

[0076]

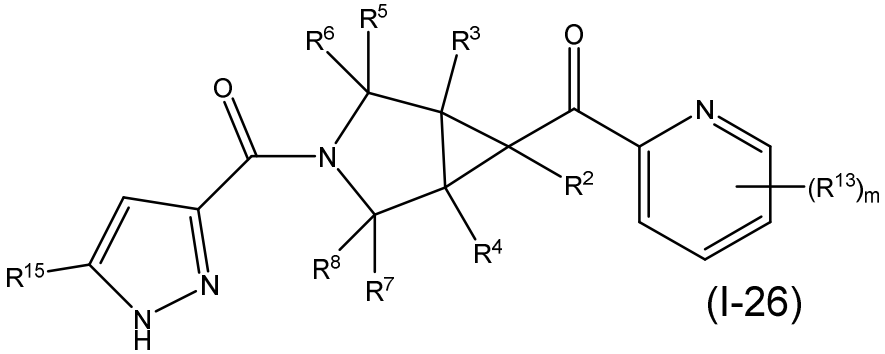
the general formula (I-25):



wherein all symbols have the same meanings as above,

[0077]

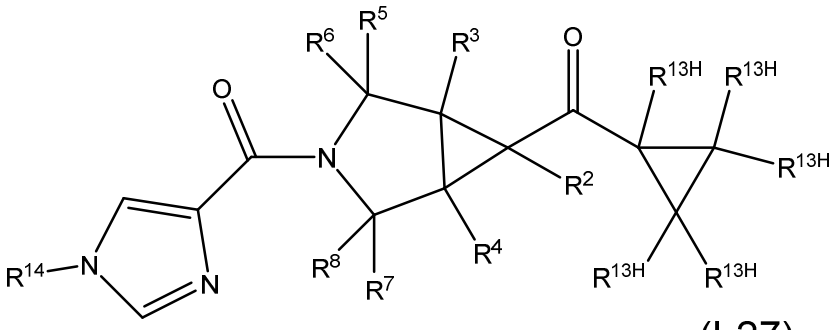
the general formula (I-26):



wherein all symbols have the same meanings as above,

[0078]

the general formula (I-27):

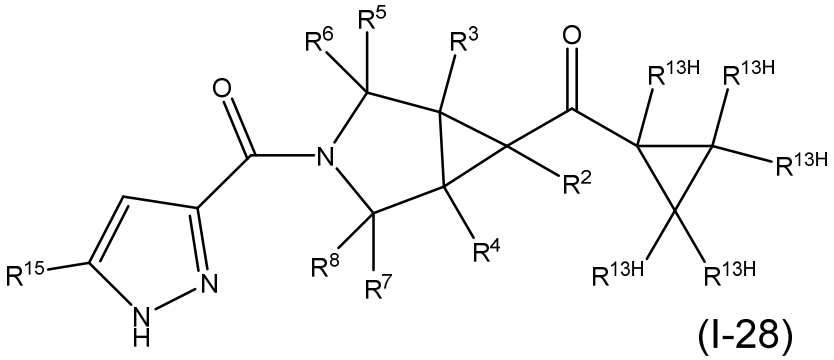


(I-27)

wherein R^{13H} represents a hydrogen atom, C1-4 alkyl, C1-4 alkoxy or halogen, and other symbols have the same meanings as above,

[0079]

the general formula (I-28):

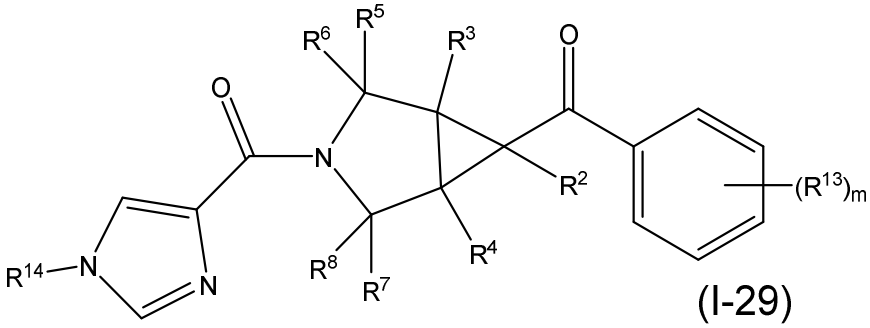


(I-28)

wherein all symbols have the same meanings as above,

[0080]

the general formula (I-29):

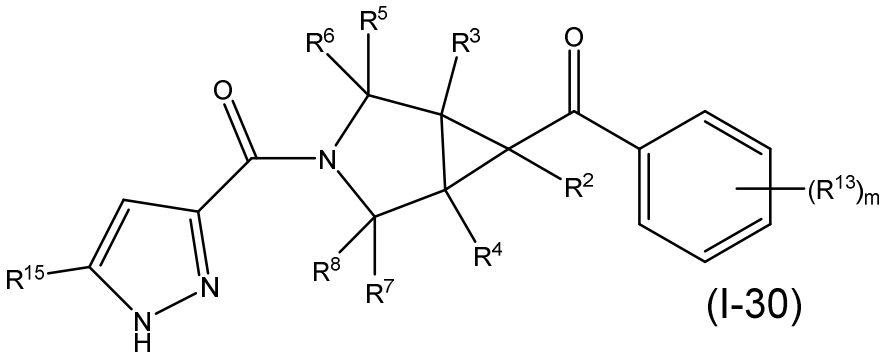


(I-29)

wherein all symbols have the same meanings as above,

[0081]

the general formula (I-30):

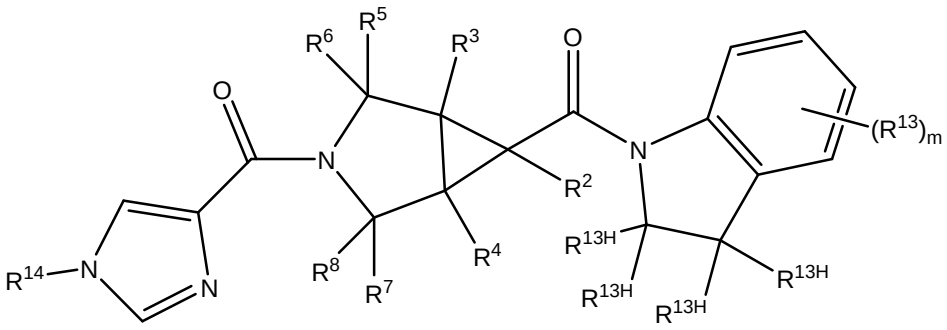


(I-30)

wherein all symbols have the same meanings as above,

[0082]

the general formula (I-31):

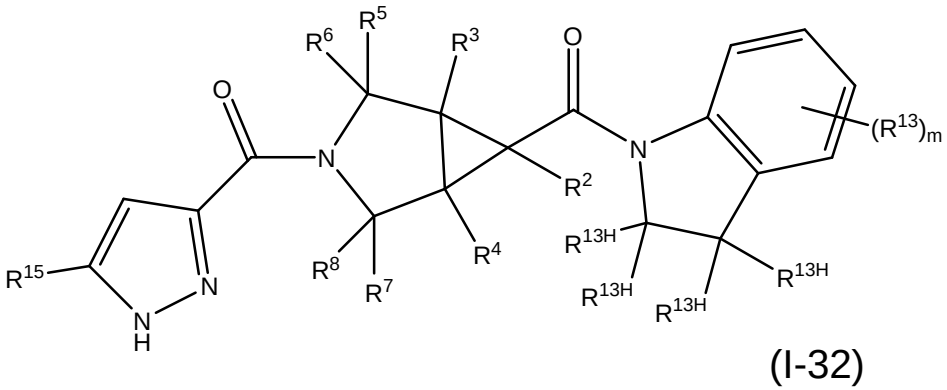


(I-31)

wherein all symbols have the same meanings as above,

[0083]

the general formula (I-32):

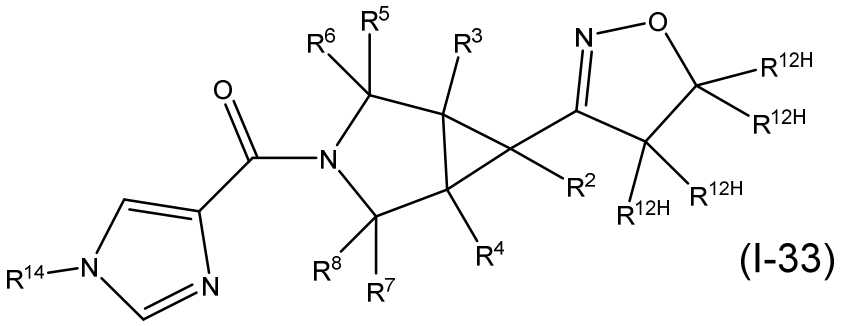


(I-32)

wherein all symbols have the same meanings as above,

[0084]

the general formula (I-33):

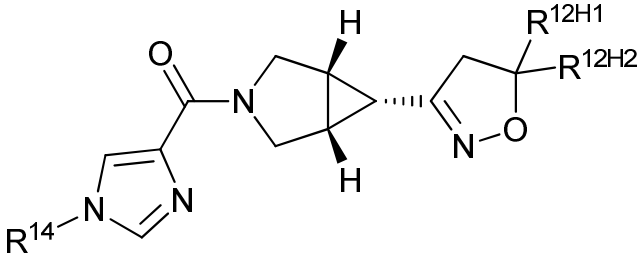


(I-33)

wherein all symbols have the same meanings as above,

[0085]

the general formula (I-33-1):



(I-33-1)

wherein R^{14} represents (1) C1-8 alkyl, or (3) C1-8 haloalkyl;

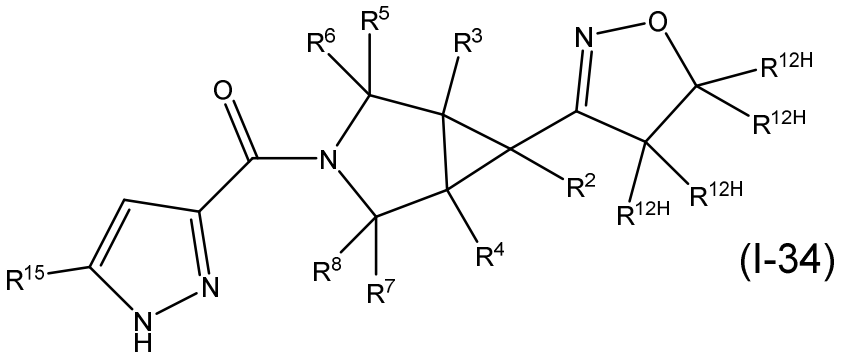
R^{12H1} represents (2) C1-4 alkyl, (3) C3-7 cycloalkyl, (4) C1-4 haloalkyl, (5) C1-4 alkoxy, (6) phenyl which may be substituted with 1 to 3 R^{17}, (7) C1-4 alkyl which is substituted with phenyl, (8) dimethylamino, (9) pyridyl or (10) 1-(cyclopropylmethyl)pyrazol-3-yl; preferably, R^{12H1} represents (2) C1-4 alkyl, (3) C3-7 cycloalkyl, (4) C1-4 haloalkyl, (6) phenyl which may be substituted with 1 to 3 R^{17}, (7) C1-4 alkyl which is substituted with phenyl, (9) pyridyl or (10) 1-(cyclopropylmethyl)pyrazol-3-yl;

R^{12H2} represents (1) a hydrogen atom, (2) C1-4 alkyl, (3) C3-7 cycloalkyl, (4) C1-4 haloalkyl, (5) C1-4 alkoxy, (6) phenyl which may be substituted with 1 to 3 R^{17}, (7) C1-4 alkyl which is substituted with phenyl, (8) dimethylamino, (9) pyridyl or (10) 1-(cyclopropylmethyl)pyrazol-3-yl; preferably, R^{12H2} represents (1) a hydrogen atom, (2) C1-4 alkyl, (4) C1-4 haloalkyl, (7) C1-4 alkyl which is substituted with phenyl, (8) dimethylamino;

and R^{17} represents C1-4 alkyl, C1-4 alkoxy or halogen;

[0086]

the general formula (I-34):

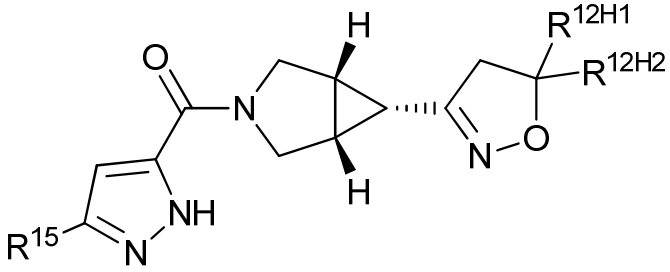


(I-34)

wherein all symbols have the same meanings as above,

[0087]

the general formula (I-34-1):



(I-34-1)

wherein R^{15} represents (1) C1-8 alkyl, or (3) C1-8 haloalkyl;

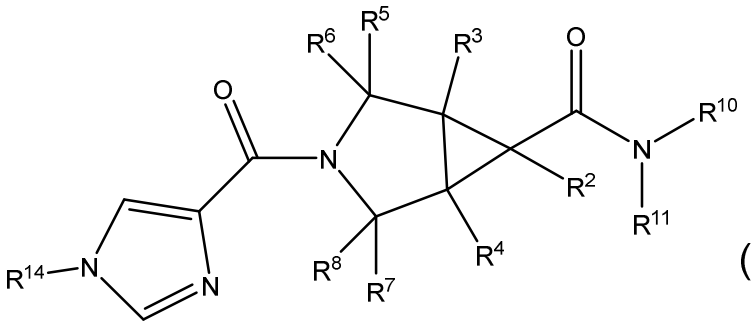
R^{12H1} represents (2) C1-4 alkyl, (3) C3-7 cycloalkyl, (4) C1-4 haloalkyl, (5) C1-4 alkoxy, (6) phenyl which may be substituted with 1 to 3 R^{17}, (7) C1-4 alkyl which is substituted with phenyl, (8) dimethylamino, (9) pyridyl or (10) 1-(cyclopropylmethyl)pyrazol-3-yl; preferably, R^{12H1} represents (2) C1-4 alkyl, (3) C3-7 cycloalkyl, (4) C1-4 haloalkyl, (6) phenyl which may be substituted with 1 to 3 R^{17}, (7) C1-4 alkyl which is substituted with phenyl, (9) pyridyl or (10) 1-(cyclopropylmethyl)pyrazol-3-yl;

R^{12H2} represents (1) a hydrogen atom, (2) C1-4 alkyl, (3) C3-7 cycloalkyl, (4) C1-4 haloalkyl, (5) C1-4 alkoxy, (6) phenyl which may be substituted with 1 to 3 R^{17}, (7) C1-4 alkyl which is substituted with phenyl, (8) dimethylamino, (9) pyridyl or (10) 1-(cyclopropylmethyl)pyrazol-3-yl; preferably, R^{12H2} represents (1) a hydrogen atom, (2) C1-4 alkyl, (4) C1-4 haloalkyl, (7) C1-4 alkyl which is substituted with phenyl, (8) dimethylamino;

and R^{17} represents C1-4 alkyl, C1-4 alkoxy or halogen;

[0088]

the general formula (I-35):

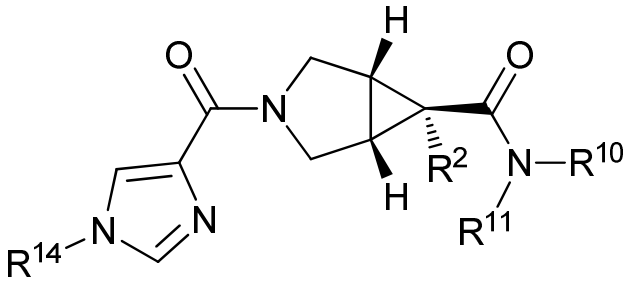


(I-35)

wherein all symbols have the same meanings as above,

[0089]

the general formula (I-35-1):



(I-35-1)

wherein R^2 represents a hydrogen atom, C1-4 alkyl, halogen or C1-4 alkoxy;

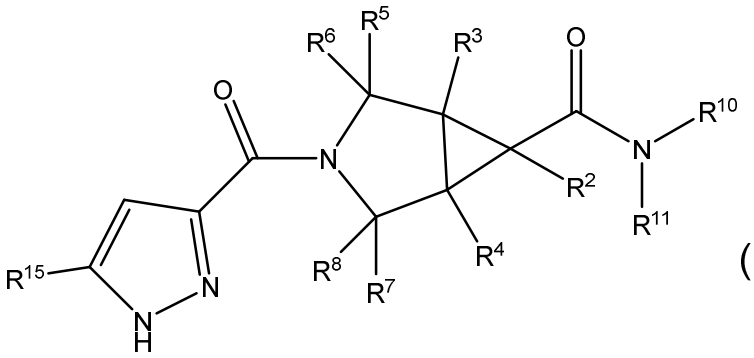
R^{14} represents (1) C1-8 alkyl, or (3) C1-8 haloalkyl;

R^{10} represents C1-8 alkyl, or C1-8 haloalkyl, preferably, R^{10} represents isopropyl, tert-butyl, 1,1,1-trifluoro-2-methylpropan-2-yl; and

R^{11} represents a hydrogen atom or C1-4 alkyl;

[0090]

the general formula (I-36):

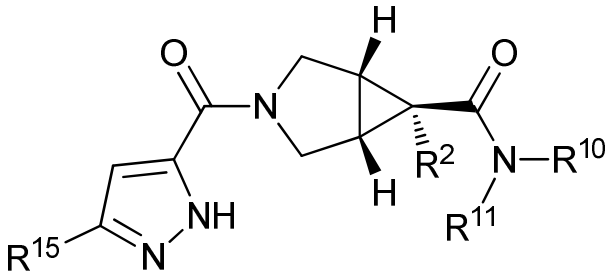


(I-36)

wherein all symbols have the same meanings as above;

[0091]

and the general formula (I-36-1-1):



(I-36-1-1)

wherein R^2 represents a hydrogen atom, C1-4 alkyl, halogen or C1-4 alkoxy;

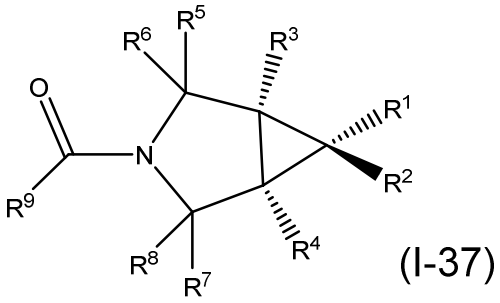
R^{15} represents (1) C1-8 alkyl, or (3) C1-8 haloalkyl;

R^{10} represents C1-8 alkyl, or C1-8 haloalkyl, preferably, R^{10} represents isopropyl, tert-butyl, 1,1,1-trifluoro-2-methylpropan-2-yl; and

R^{11} represents a hydrogen atom or C1-4 alkyl.

[0092]

In the present invention, examples of the general formula (I) preferably include the general formula (I-37):

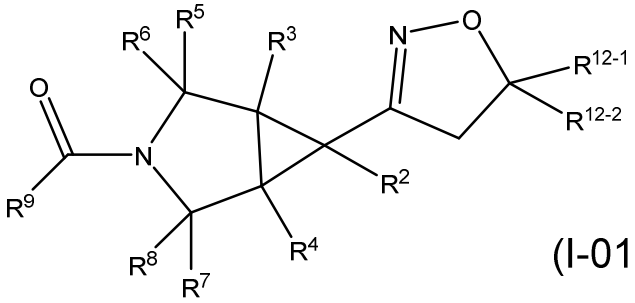


(I-37)

wherein all symbols have the same meanings as above.

[0093]

In the present invention, examples of the general formula (I) preferably include the general formula (I-01):

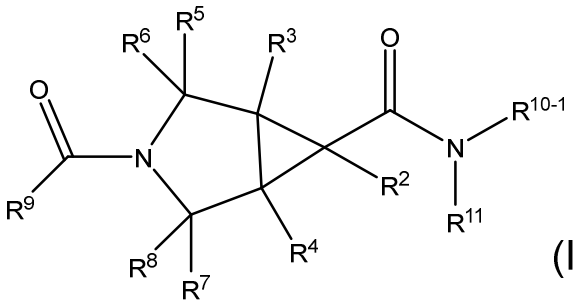


(I-01)

wherein all symbols have the same meanings as above.

[0094]

In the present invention, examples of the general formula (I) preferably include the general formula (I-02):



(I-02)

wherein all symbols have the same meanings as above.

[0095]

In the present invention, the stereo configuration of substituents corresponding to the substituents represented by R^1, R^3 and R^4 on 3-azabicyclo[3.1.0]hexane ring of the general formulae (I-1) to (I-36) is preferably in the same direction, like the general formula (I-37).

[0096]

In the present invention, or in the general formula (I) or (I-1), the compound is preferably, for example:

(1) [(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](1-isopropyl-1H-imidazol-4-yl)methanone;

(2) [(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl][1-(1-methylcyclopropyl)-1H-imidazol-4-yl]methanone;

(3) (1-cyclopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-6-methyl-3-azabicyclo[3.1.0]hex-3-yl]methanone;

(4) (1-cyclopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-methyl-6-(4-oxa-5-azaspiro[2.4]hept-5-en-6-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone;

(5) {1-[(2S)-butan-2-yl]-1H-imidazol-4-yl}[(1R,5S,6S)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone;

(6) [(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-6-methyl-3-azabicyclo[3.1.0]hex-3-yl](1-isopropyl-1H-imidazol-4-yl)methanone;

(7) (1-isopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-methyl-6-(4-oxa-5-azaspiro[2.4]hept-5-en-6-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone ;

(8) (1-cyclopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(4-oxa-5-azaspiro[2.4]hept-5-en-6-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone or

(9) [1-(1-methylcyclopropyl)-1H-imidazol-4-yl][(1R,5S,6r)-6-(4-oxa-5-azaspiro[2.4]hept-5-en-6-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone;

or a salt thereof.

[0097]

In the present invention, or in the general formula (I) or (I-2), the compound is also preferably, for example:

(1) [(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](5-isopropyl-1H-pyrazol-3-yl)methanone;

(2) (5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(2-oxa-3-azabicyclo[3.1.0]hex-3-en-4-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone;

(3) [5-(1-cyclopropylethyl)-1H-pyrazol-3-yl][(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone;

(4) [(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-6-methyl-3-azabicyclo[3.1.0]hex-3-yl](5-isopropyl-1H-pyrazol-3-yl)methanone or

(5) (5-cyclopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-methyl-6-(4-oxa-5-azaspiro[2.4]hept-5-en-6-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

or a salt thereof.

[0098]

In the present invention, or in the general formula (I) or (I-3), the compound is also preferably, for example:

(1) (1R,5S,6r)-N-tert-butyl-6-methyl-3-[1-(propan-2-yl)-1H-imidazole-4-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide ;

(2) (1R,5S,6r)-N-tert-butyl-3-[1-(propan-2-yl)-1H-imidazole-4-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide;

(3) (1R,5S,6r)-N-(propan-2-yl)-3-[1-(propan-2-yl)-1H-imidazole-4-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide or

(4) (1R,5S,6r)-N-(1-cyanocyclopropyl)-3-[1-(propan-2-yl)-1H-imidazole-4-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide

or a salt thereof.

[0099]

In the present invention, or in the general formula (I) or (I-4), the compound is also preferably, for example:

(1) (1R,5S,6r)-N-(propan-2-yl)-3-[5-(propan-2-yl)-1H-pyrazole-3-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide;
(2) (1R,5S,6r)-N-tert-butyl-6-methyl-3-[5-(propan-2-yl)-1H-pyrazole-3-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide;
(3) (1R,5S,6r)-N-tert-butyl-N-methyl-3-[5-(propan-2-yl)-1H-pyrazole-3-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide or
(4) (1R,5S,6r)-N-methyl-N-(1-methylcyclopropyl)-3-[5-(propan-2-yl)-1H-pyrazole-3-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide,
or a salt thereof.

[Isomers]

[0100]

The present invention encompasses all isomers unless otherwise particularly stated. For example, alkyl groups, alkoxy groups and the like include linear and branched groups. Moreover, the present invention encompasses isomers for double bonds, rings and condensed rings (E-forms, Z-forms, cis forms and trans forms), isomers due to asymmetrical carbon atoms (R and S forms, α and β configurations, enantiomers and diastereomers), optically active substances having optical rotating activity (D, L, d and l forms), polar substances which can be separated by chromatography (high polarity substances and low polarity substances), equilibrium compounds, rotamers, mixtures thereof at arbitrary proportions and racemic mixtures. The present invention also encompasses tautomers.

[Salt and solvate]

[0101]

A salt of the compound represented by the general formula (I) disclosed herein encompasses all pharmacologically acceptable salts. The pharmacologically acceptable salt is preferably a water-soluble salt with low toxicity. Examples of appropriate salts include acid addition salts (such as inorganic acid salt [examples: hydrochloride, hydrobromide, hydroiodide, sulphate, phosphate, nitrate and the like], organic acid salts [examples: acetate, trifluoroacetate, lactate, tartrate, oxalate, fumarate, maleate, benzoate, citrate, methanesulphonate, ethanesulphonate, benzenesulphonate, toluenesulphonate, isethionate, glucuronate, gluconate and the like], salts with acidic natural amino acids [examples: aspartate, glutamate and the like] and the like) and the like.

[0102]

A salt also encompasses quaternary ammonium salts. The quaternary ammonium salt represents a compound represented by the general formula (I) in which a nitrogen atom thereof is quaternised with an R^0 group. The R^0 group as used herein represents, for example, a C1-8 alkyl group which may be substituted with a phenyl group.

[0103]

The compound represented by the general formula (I) can be converted to the salt, N-oxide and solvate according to well-known methods.

[0104]

The N-oxide of the compound represented by the general formula (I) represents the compound represented by the general formula (I) in which a nitrogen atom is oxidized. The N-oxide may form salts such as acid addition salts as described above.

[0105]

The compound represented by the general formula (I), a salt thereof or an N-oxide thereof may form a solvate with, for example, water or an alcoholic solvent (such as ethanol). The solvate preferably has low toxicity and is water soluble.

[0106]

The compound represented by the general formula (I) and a salt thereof may be in the form of without forming a solvate or may be in the form of a solvate with a pharmaceutically acceptable solvent such as water and ethanol. The solvate is preferably a hydrate. The compound represented by the general formula (I) or a salt thereof can be converted to the solvate according to well-known methods.

[0107]

The compound represented by the general formula (I) and a salt thereof may form a co-crystal with an appropriate co-crystal former. The co-crystal is preferably pharmaceutically acceptable as formed with a pharmaceutically acceptable co-crystal former. A co-crystal is defined to be a crystal typically formed of 2 or more molecules by intermolecular interaction that is not ionic bonding. The co-crystal may be a complex of a neutral molecule and a salt. Co-crystals may be prepared according to well-known methods such as melt crystallization, recrystallization from a solvent or physical grinding of components together. Appropriate co-crystal formers include those disclosed in WO 2006/007448.

[0108]

In the present invention, all the recitations on the present compound encompass the compound represented by the general formula (I), a salt thereof, a solvate (such as hydrate) thereof, an N-oxide thereof or a co-crystal thereof, or a solvate (such as hydrate), N-oxide or co-crystal of a salt of the compound represented by the general formula (I).

[0109]

Namely, in the present invention, the compound represented by the general formula (I) or a salt thereof encompasses a solvate (such as hydrate), N-oxide or co-crystal of the compound represented by the general formula (I) or a solvate (such as hydrate), N-oxide or co-crystal of a salt of the compound represented by the general formula (I).

[Prodrug]

[0110]

The prodrug of the compound represented by the general formula (I) refers to a compound which is converted *in vivo* to the compound represented by the general formula (I) by the reaction with enzymes, gastric acid and the like. Examples of the prodrug of the compound represented by the general formula (I) include, when the compound represented by the general formula (I) has an amino group, compounds in which the amino group is acylated, alkylated or phosphorylated (e.g. compounds represented by the general formula (I) in which the amino group thereof is converted to eicosanoyl, alanyl, pentylaminocarbonyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonyl, tetrahydrofuranyl, pyrrolidylmethyl, pivaloyloxymethyl, acetoxymethyl, tert-butyl or the like); when the compound represented by the general formula (I) has a hydroxy group, compounds in which the hydroxy group is acylated, alkylated, phosphorylated or converted to borate (e.g. compounds represented by the general formula (I) in which the hydroxy group thereof is converted to acetyl, palmitoyl, propanoyl, pivaloyl, succinyl, fumaryl, alanyl, dimethylaminomethylcarbonyl or the like) and the like. The prodrug of the compound represented by the general formula (I) may be the one which is converted to the compound represented by the general formula (I) under the physiological condition such as those disclosed in “Iyakuhin no Kaihatsu”, vol. 7 “Bunshi Sekkei”, p. 163-198, 1990, Hirokawa Shoten Co. The prodrug of the compound represented by the general formula (I) can be produced by the methods well known *per se*. The prodrug of the compound represented by the general formula (I) may form, similarly to the compound represented by the general formula (I), for example, salts such as acid addition salts, or may form solvates with water or an alcoholic solvent (such as ethanol).

[Labelled compound]

[0111]

In the present invention, the compound represented by the general formula (I), or a salt thereof encompasses a so-called labelled compound in which some or all atoms constituting the compound is substituted with an isotope thereof. The labelled compound may be produced according to the methods well known *per se*. Examples of isotopes which may be used for labelling suitably include, but are not limited to, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{16}N, ^{17}O, ^{18}O, ^{35}S, ^{36}Cl, ^{77}Br, ^{125}I and the like.

[Production method]

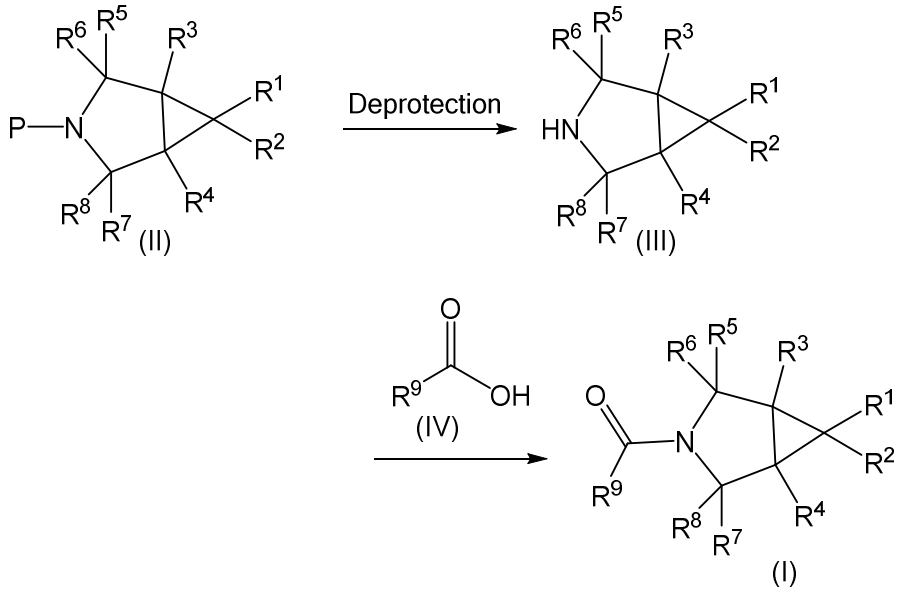
[Method for producing compound of the present invention]

[0112]

The compound represented by the general formula (I) or a salt thereof may be produced by well-known methods, for example, methods described in the following methods represented in Scheme I to XII, methods equivalent to these methods, methods described in Examples, methods equivalent to those described in Examples, or methods described in Comprehensive Organic Transformations: A Guide to Functional Group Preparations, 2nd Edition (Richard C. Larock, John Wiley & Sons Inc., 1999), methods adapted from the foregoing or methods combining the foregoing without limitation. In the production methods described hereinbelow, raw material compounds may be those forming salts. Examples of the salts include those mentioned above as salts of the compound represented by the general formula (I).

[0113]

Scheme I



Wherein the compound represented by the general formula (I) can be produced by subjecting the compound represented by the general formula (III) and the compound represented by the general formula (IV) to an amidation reaction.

[0114]

The amidation is known. For example, it includes the method

(1) via an acyl halide,

(2) via a mixed acid anhydride,

(3) using a condensing agent.

[0115]

These methods are explained as follows.

(1) The method via an acyl halide may be carried out, for example, by reacting a carboxylic acid with an acyl halide (e.g., oxalyl chloride or thionyl chloride) in an organic solvent (e.g., chloroform, dichloromethane, diethyl ether or tetrahydrofuran) or without a solvent at about -20°C to reflux temperature. And then, the obtained acyl halide derivative may be reacted with an amine in an organic solvent (e.g., chloroform, dichloromethane, diethyl ether or tetrahydrofuran) in the presence of a base (e.g., pyridine, triethylamine, dimethylaniline, dimethylaminopyridine or diisopropylethylamine etc.) at about 0 to 40°C. As an alternative, the obtained acyl halide derivative may be reacted with an amine in an organic solvent (e.g., dioxane, tetrahydrofuran) using an alkaline aqueous solution (e.g., sodium hydrogen carbonate, sodium hydroxide) at about -78 to 40°C.

[0116]

(2) The method via a mixed acid anhydride may be carried out, for example, by reacting a carboxylic acid with an acyl halide (e.g., pivaloyl chloride, p-toluenesulfonyl chloride or methanesulfonyl chloride) or an acid derivative (e.g., ethyl chloroformate or isobutyl chloroformate) in an organic solvent (e.g., chloroform, dichloromethane, diethyl ether, tetrahydrofuran) or without a solvent, in the presence of a base (e.g., pyridine, triethylamine, dimethylaniline, dimethylaminopyridine or diisopropylethylamine) at about 0 to 40°C. And then the obtained mixed acid anhydride derivative may be reacted with an amine in an organic solvent (e.g., chloroform, methylene chloride, diethyl ether or tetrahydrofuran), at about 0 to 40°C.

[0117]

(3) The method using a condensing agent may be carried out, for example, by reacting a carboxylic acid with amine in an organic solvent (e.g., chloroform, dichloromethane, dimethylformamide, diethyl ether or tetrahydrofuran) or without a solvent, in the presence or absence of a base (e.g., pyridine, triethylamine, dimethylaniline or dimethylaminopyridine), using a condensing agent (e.g., 1,3-dicyclohexyl carbodiimide (DCC), 1-ethyl-3-[3-(dimethylamino)propyl] carbodiimide (EDC), 1,1'-carbodiimidazole (CDI), 2-chloro-1-methylpyridinium iodide, or 1-propanephosphonic acid cyclic anhydride (PPA)), in the presence or absence of 1-hydroxybenzotriazole (HOBt), at about 0 to 40°C.

[0118]

The reaction described in (1), (2) and (3) may be carried out under an inert gas (e.g., argon, nitrogen) to avoid water in order to obtain a preferable result.

[0119]

The compound represented by the general formula(III) can be produced by subjecting the compound represented by the general formula (II) to a deprotection reaction of protecting group of amino group.

P in the general formula (II) is represented a protecting group of amino group.

P includes such as benzyloxycarbonyl (Z), tert-butoxycarbonyl (Boc), allyloxycarbonyl (Alloc), 1-methyl-1-(4-biphenyl)ethoxycarbonyl (Bpoc), trifluoroacetyl, 9-fluorenylmethoxycarbonyl (Fmoc), benzyl (Bn), p-methoxybenzyl, benzyloxymethyl (BOM) or 2-(trimethylsilyl)ethoxymethyl (SEM) etc.

[0120]

Deprotection reaction of protecting group of amino group can be conducted by suitable condition of each protective group.

For example, a deprotection of tert-butoxycarbonyl (Boc) group can be conducted with acidic reagent (e.g., HCl/dioxane, TFA or MsOH) in solvent (e.g., dioxane or dichloromethane) at 0 ºC to 40 ºC.

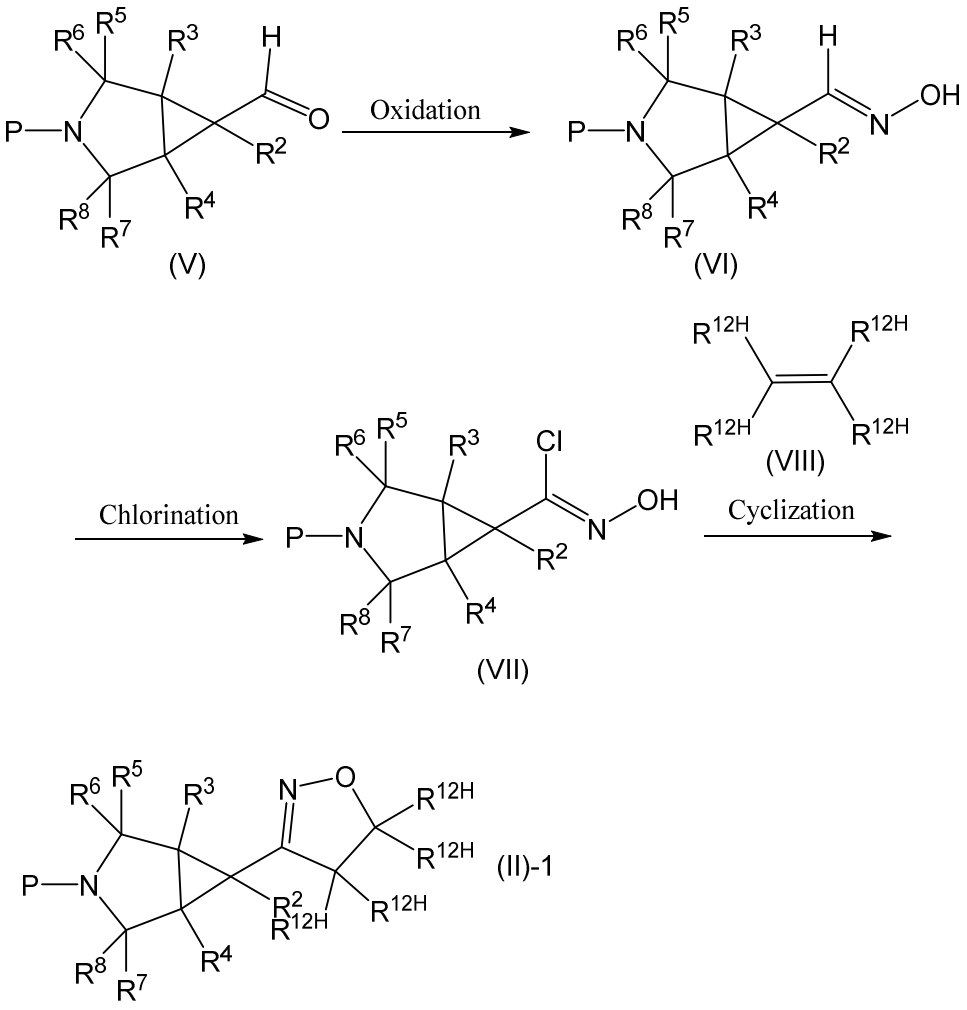
For example, a deprotection of benzyloxycarbonyl (Z) group can be conducted by hydrogenation condition such as hydrogen and catalytic Pd-C in solvent (e.g., MeOH or EtOH etc.) at 20 ºC to 60 ºC.

[0121]

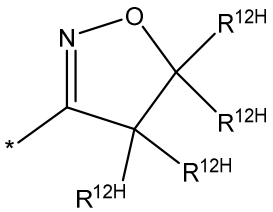
Deprotection reaction of protecting group of amino group is well known and well described in T.W. Greene, *Protective Groups in Organic Synthesis*, Wiley, New York, 1999.

[0122]

Scheme II



Wherein R^1 in the general formula (II) in Scheme I represents:



and

the general formula (II) can be described as the general formula (II)-1 in Scheme II.

[0123]

The compound represented by the general formula (II)-1 can be produced by subjecting the compound represented by the general formula (VII) and the compound represented by the general formula (VIII) to an isoxazoline cyclization reaction.

[0124]

An isoxazoline cyclization reaction can be carried out with base (e.g., trimethylamine or DIPEA) and solvent (e.g., DMF etc.) at 0 ºC to 80 ºC.

The compound represented by the general formula (VII) can be produced by subjecting the compound represented by the general formula (VI) to a chlorination reaction.

[0125]

A chlorination reaction can be carried out with a chlorination reagent (e.g., N-chlorosuccinimide) in solvent (e.g., DMF etc.) at about 0 ºC to 40 ºC.

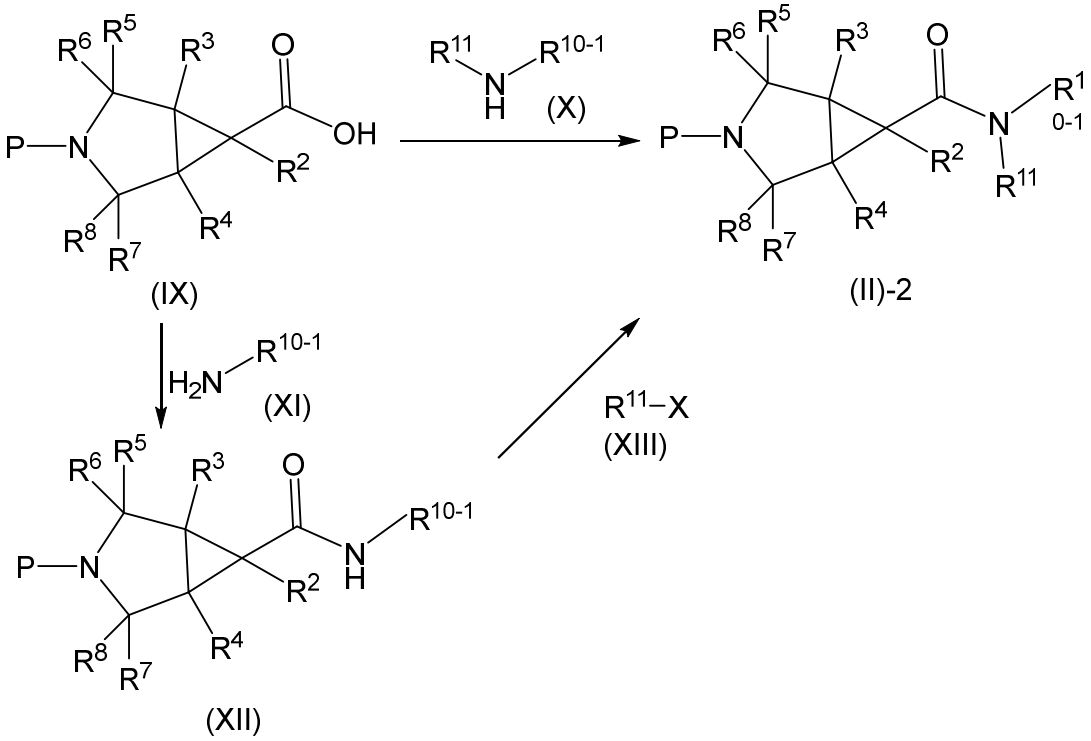
The compound represented by the general formula (VI) can be produced by subjecting the compound represented by the general formula (V) to an oxime forming reaction.

[0126]

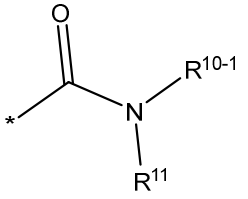
An oxime forming reaction can be carried out with hydroxylamine hydrochloride, potassium acetate and acetic acid in solvent (e.g., EtOH etc.) at about 20 ºC to 40 ºC.

[0127]

Scheme III



Wherein R^1 in the general formula (II) in Scheme I represents



and

the general formula (II) can be described as the general formula (II)-2 in Scheme III.

[0128]

The compound represented by the general formula (II)-2 can be produced by subjecting the compound represented by the general formula (IX) and the compound represented by the general formula (X) to an amidation reaction.

[0129]

An amidation can be carried out by the same method described above for the preparation of the general formula (I) in Scheme I.

The compound represented by the general formula (II)-2 can be produced by subjecting the compound represented by the general formula (XII) and the compound represented by the general formula (XIII) to an alkylation reaction.

[0130]

An alkylation reaction can be carried out with base (e.g., sodium hydride, potassium hydride, lithium hydride, sodium methoxide, sodium ethoxide, potassium tert-butoxide, butyl lithium, LDA, LHMDS, NaHMDS, KHMDS etc.) in solvent (e.g., THF, DMF, DMA, diethyl ether etc) at -78 ºC to 40 ºC.

[0131]

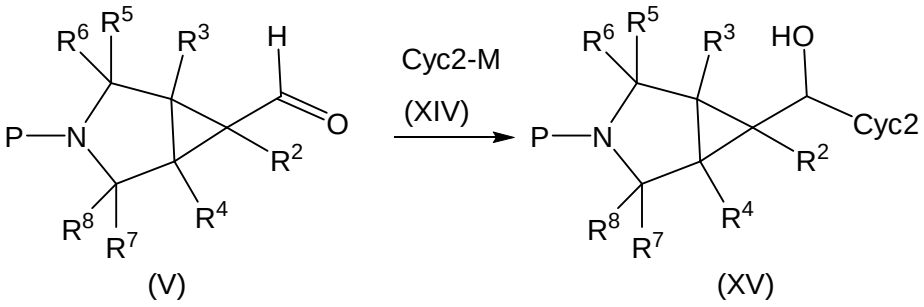
The compound represented by the general formula (XII) can be produced by subjecting the compound represented by the general formula (IX) and the compound represented by the general formula (XI) to an amidation reaction.

[0132]

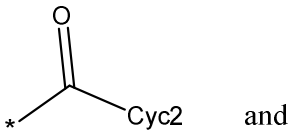
An amidation can be carried out by the same method described above for the preparation of the general formula (I) in Scheme I.

[0133]

Scheme IV



Wherein R^1 in the general formula (II) in Scheme I represents



and

the general formula (II) can be described as the general formula (II)-3 in Scheme IV.

[0134]

The compound represented by the general formula (II)-3 can be produced by subjecting the compound represented by the general formula (XV) to an oxidation reaction of hydroxyl group.

[0135]

The oxidation of hydroxyl group is known. For example, it includes the method

(1) Dess-Martin oxidation

(2) DMSO oxidation

(3) Chromium reagent oxidation.

[0136]

These methods are explained as follows.

(1) The method of Dess-Martin oxidation can be carried out with Dess-Martin Periodinane in solvent (for example methylene chloride) at 0 ºC to 40 ºC.

(2) The method of DMSO oxidation can be carried out with DMSO and its activator (e.g., oxalyl chloride, thionyl chloride or sulfur trioxide pyridinium complex etc.) and base (for example trimethylamine or DIPEA etc) at -78 ºC to 40 ºC.

(3) The method of chromium reagent oxidation is carried out with chromium oxidant (for example PCC or PDC) in solvent (for example dichloromethane) at -20 ºC to 40 ºC.

[0137]

The compound represented by the general formula (XV) can be produced by subjecting the compound represented by the general formula (V) and the compound represented by the general formula (XIV) to an addition reaction.

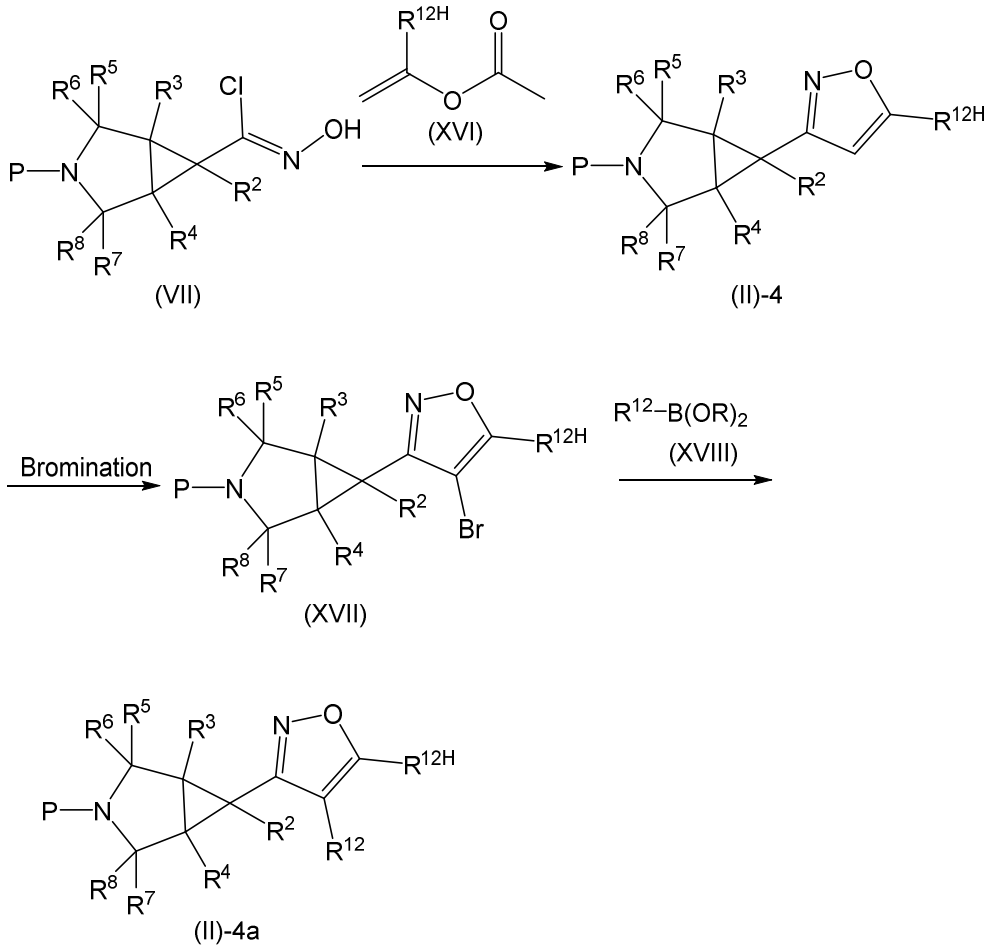
Wherein M in the general formula (XIV) represents metal (e.g., Li, Na or K) or metal halide (MgCl, MgBr, MgI, ZnCl, ZnBr or ZnI).

[0138]

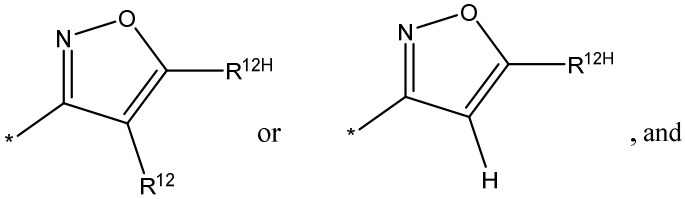
An addition reaction can be carried out in solvent (e.g., THF) at -78 ºC to 0 ºC under inert atmosphere (e.g., dry nitrogen or argon).

[0139]

Scheme V



Wherein R^1 in the general formula (II) in Scheme I represents



the general formula (II) can be described as the general formula (II)-4 and (II)-4a in Scheme V.

[0140]

The compound represented by the general formula (II)-4 can be produced by subjecting the compound represented by the general formula (VII) and the compound represented by the general formula (XVI) to an isoxazole cyclization reaction.

[0141]

An isoxazole cyclization reaction can be carried out with base (for example trimethylamine etc.) in solvent (for example dichloromethane etc.) at -20 ºC to 40 ºC.

[0142]

The compound represented by the general formula (II)-4a can be produced by subjecting the compound represented by the general formula (XVII) and the compound represented by the general formula (XVIII) to a coupling reaction.

[0143]

The coupling reaction is well known and can be carried out by, for example, reacting in an organic solvent (examples: benzene, toluene, dimethylformamide, 1,4-dioxane, tetrahydrofuran, methanol, acetonitrile, dimethoxyethane, acetone or mixed solvents thereof), with a base (examples: sodium ethylate, sodium hydroxide, potassium hydroxide, triethylamine, sodium carbonate, sodium hydrogen carbonate, potassium carbonate, caesium carbonate, thallium carbonate, tripotassium phosphate, caesium fluoride, barium hydroxide, tetrabutylammonium fluoride and the like) or aqueous solutions thereof or mixtures thereof in the presence of a catalyst (examples: bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) ($(A\text{-}taPhos)_2PdCl_2$), tetrakis(triphenylphosphine)palladium ($Pd(PPh_3)_4$), bis(triphenylphosphine)palladium dichloride ($PdCl_2(PPh_3)_2$), palladium acetate ($Pd(OAc)_2$), palladium black, 1,1'-bis(diphenylphosphinoferrocene)dichloropalladium ($PdCl_2(dppf)_2$), diallylpalladium dichloride ($PdCl_2(allyl)_2$), iodophenyl bis(triphenylphosphine)palladium ($PhPdI(PPh_3)_2$) and the like) at room temperature to 150 ºC.

[0144]

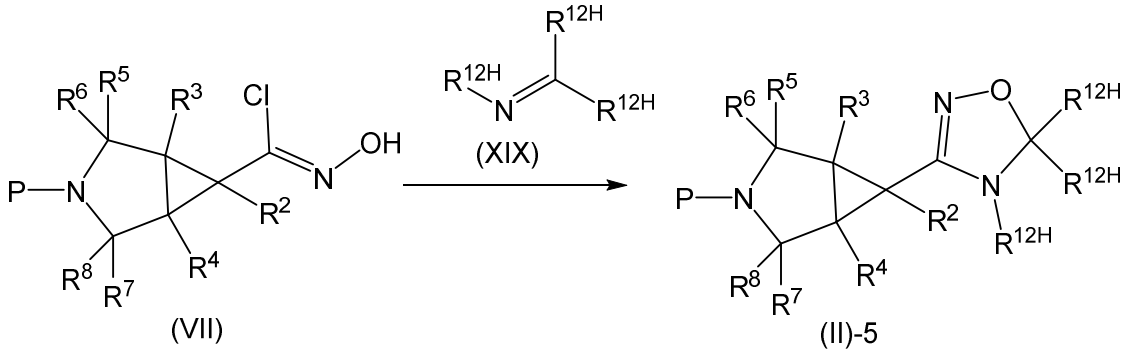
The compound represented by the general formula (XVII) can be produced by subjecting the compound represented by the general formula (II)-4 to a bromination reaction.

[0145]

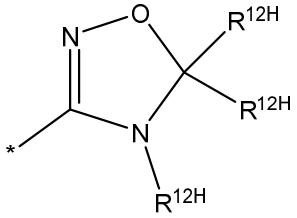
A bromination reaction can be carried out with bromination reagent (e.g., NBS or bromine etc.) in solvent (for example DMF etc.) at -20 ºC to 40 ºC.

[0146]

Scheme VI



Wherein R^1 in the general formula (II) in Scheme I represents



and

the general formula (II) can be described as the general formula (II)-5 in Scheme VI.

[0147]

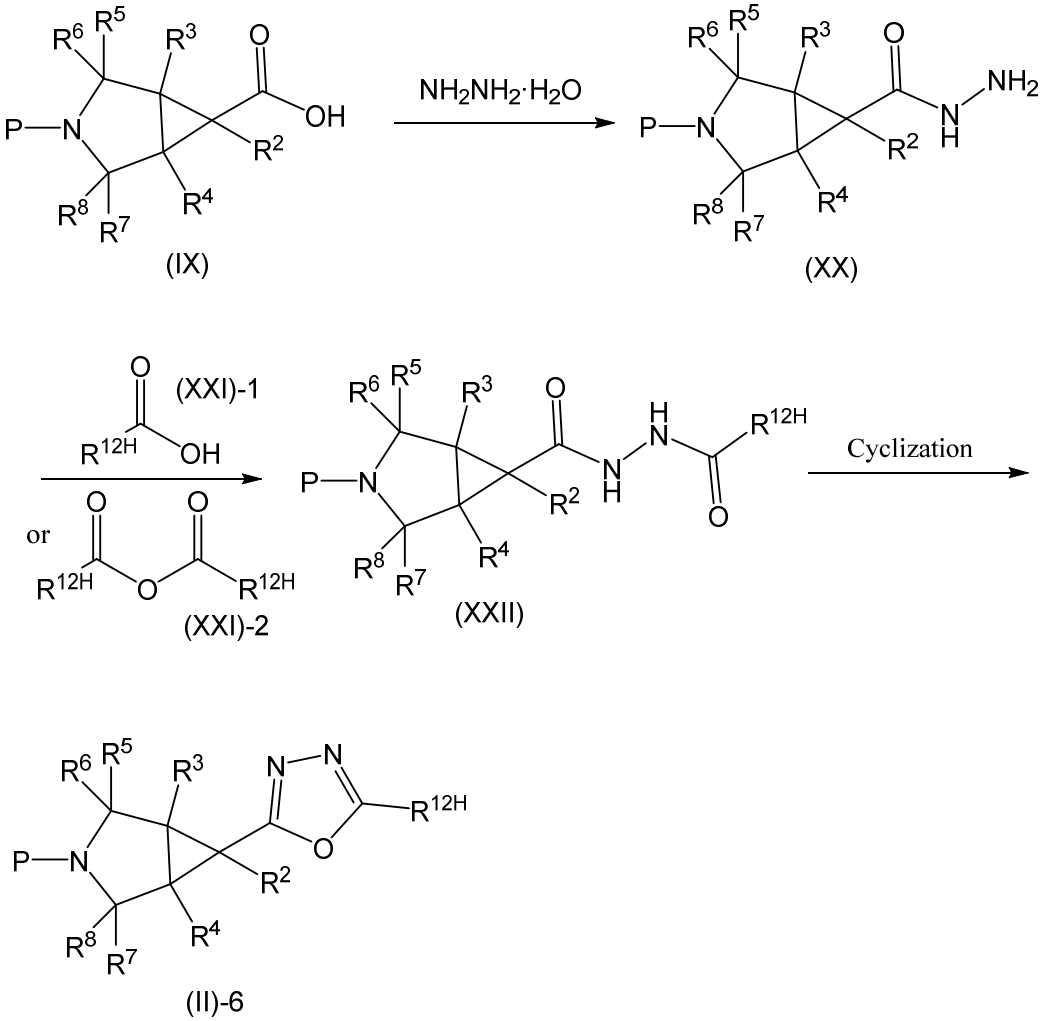
The compound represented by the general formula (II)-5 can be produced by subjecting the compound represented by the general formula (VII) and the compound represented by the general formula (XIX) to a 1,2,4-oxadiazoline cyclization reaction.

[0148]

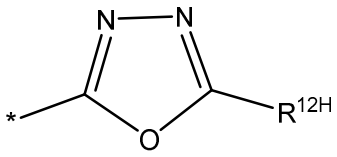
A 1,2,4-oxadiazoline cyclization reaction can be carried out with base (for example trimethylamine etc.) in solvent (for example THF, toluene or DMF etc.) at 0 ºC to 40 ºC.

[0149]

Scheme VII



Wherein R^1 in the general formula (II) in Scheme I represents

 and

the general formula (II) can be described as the general formula (II)-6 in Scheme VII.

[0150]

The compound represented by the general formula (II)-6 can be produced by subjecting the compound represented by the general formula (XXII) to a 1,3,4-oxadiazole cyclization reaction.

[0151]

A 1,3,4-oxadiazole cyclization reaction can be carried out with dehydrating agent (e.g., $POCl_3$ etc.) at 80 ºC to 120 ºC.

The compound represented by the general formula (XXII) can be produced by subjecting the compound represented by the general formula (XX) and the compound represented by the general formula (XXI)-1 or (XXI)-2 to an amidation reaction.

[0152]

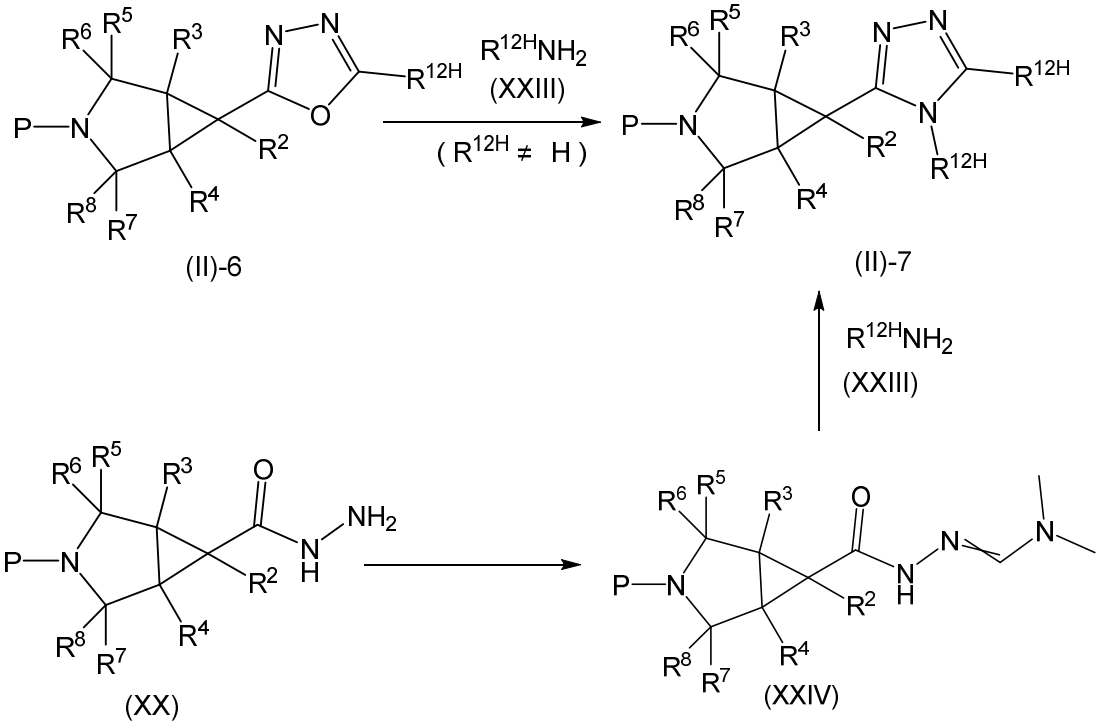
An amidation can be carried out by the same method described above for the preparation of the general formula (I) in Scheme I.

The compound represented by the general formula (XX) can be produced by subjecting the compound represented by the general formula (IX) to an amidation reaction.

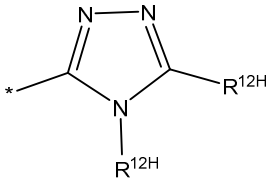
An amidation can be carried out by the same method described above for the preparation of the general formula (I) in Scheme I.

[0153]

Scheme VIII



Wherein R^1 in the general formula (II) in Scheme I represents



and

the general formula (II) can be described as the general formula (II)-7 in Scheme VIII.

[0154]

The compound represented by the general formula (II)-7 can be produced by subjecting the compound represented by the general formula (II)-6 and the compound represented by the general formula (XXIII) to a replacement reaction.

[0155]

A replacement reaction can be carried out with acidic catalyst (e.g., TsOH etc.) in solvent (e.g., xylene etc.) at 120 ºC to 150 ºC.

The compound represented by the general formula (II)-7 can be produced by subjecting the compound represented by the general formula (XXIV) and the compound represented by the general formula (XXIII) to a 1,3,4-triazole cyclization reaction.

A 1,3,4-triazole cyclization reaction can be carried out with acetic acid at 0 ºC to 100 ºC.

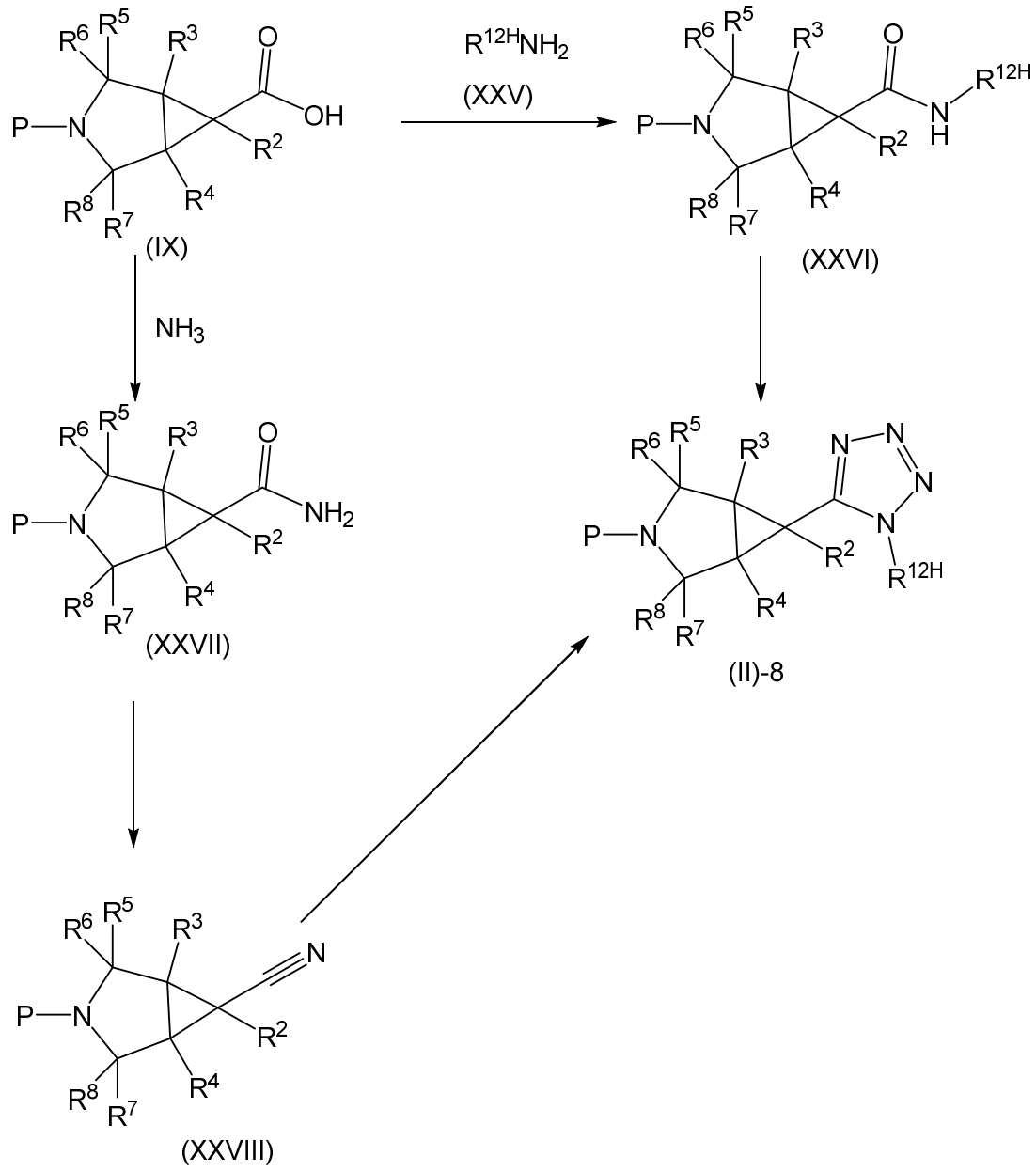
The compound represented by the general formula (XXIV) can be produced by subjecting the compound represented by the general formula (XX) to a hydrazonoformamide formation reaction.

[0156]

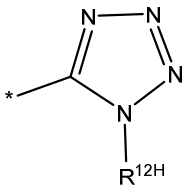
A hydrazonoformamide formation reaction can be carried out with 1,1-dimethoxy-N,N-dimethylmethanamine in solvent (e.g., acetonitrile or DMF etc.) at 100 ºC to 120 ºC.

[0157]

Scheme IX



Wherein R^1 in the general formula (II) in Scheme I represents



and

the general formula (II) can be described as the general formula (II)-8 in Scheme IX.

[0158]

The compound represented by the general formula (II)-8 can be produced by subjecting the compound represented by the general formula (XXVI) to a dehydrative tetrazole cyclization reaction.

A dehydrative tetrazole cyclization reaction can be carried out with Tf_2O and $TMSN_3$ in solvent (e.g., dichloromethane etc.) at 0 ºC to 30 ºC.

[0159]

The compound represented by the general formula (XXVI) can be produced by subjecting the compound represented by the general formula (IX) and the compound represented by the general formula (XXV) to an amidation reaction.

An amidation can be carried out by the same method described above for the preparation of the general formula (I) in Scheme I.

Wherein R^{12} represents H, the compound represented by the general formula (II)-8 can be produced by subjecting the compound represented by the general formula (XXVIII) to a tetrazole cyclization reaction.

A tetrazole cyclization reaction can be carried out with NaN_3 and NH_4Cl in solvent (e.g., DMF etc.) at 100 ºC to 140 ºC.

[0160]

The compound represented by the general formula (XXVIII) can be produced by subjecting the compound represented by the general formula (XXVII) to a nitrile formation reaction.

A nitrile formation reaction can be carried out with dehydration agent (e.g., cyanuric chloride, thionyl chloride or P_2O_5 etc.) in solvent (e.g., DMF, benzene, toluene or xylene etc.) at 100 ºC to 140 ºC.

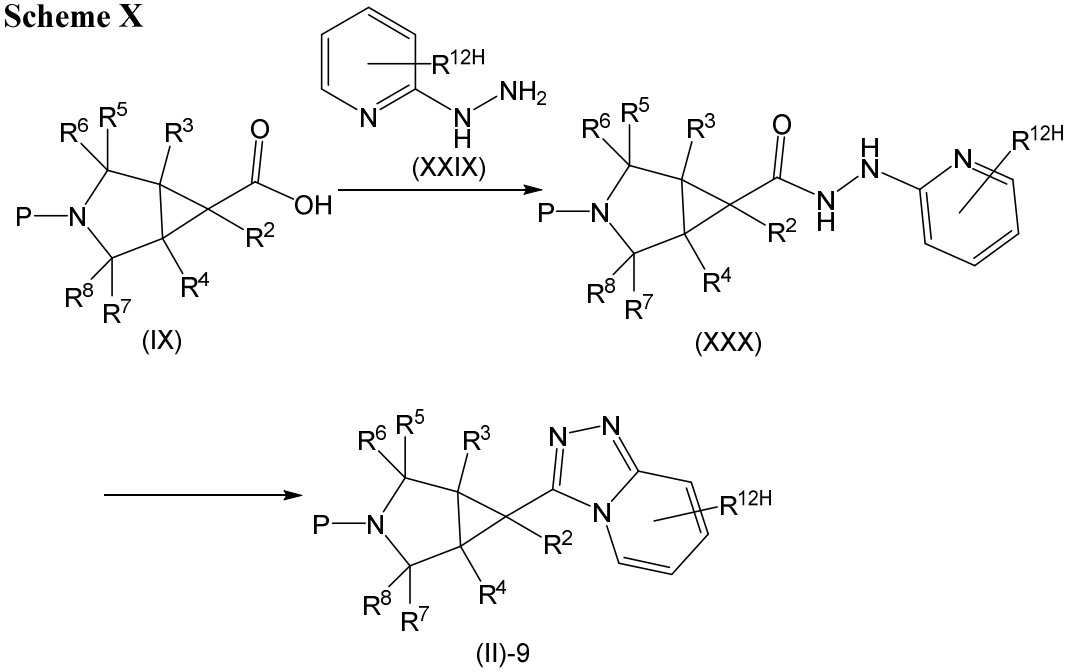
[0161]

The compound represented by the general formula (XXVII) can be produced by subjecting the compound represented by the general formula (IX) and ammonia to an amidation reaction.

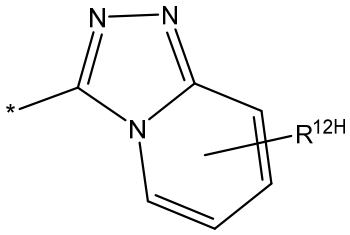
An amidation can be carried out by the same method described above for the preparation of the general formula (I) in Scheme I.

[0162]

Scheme X



Wherein R^1 in the general formula (II) in Scheme I represents



and

,

the general formula (II) can be described as the general formula (II)-9 in Scheme X.

[0163]

The compound represented by the general formula (II)-9 can be produced by subjecting the compound represented by the general formula (XXX) to a [1,2,4]triazolo[4,3-a]pyridine cyclization reaction.

A [1,2,4]triazolo[4,3-a]pyridine cyclization reaction can be carried out with Burgess reagent in solvent (e.g., acetonitrile etc.) at 100 ºC to 140 ºC.

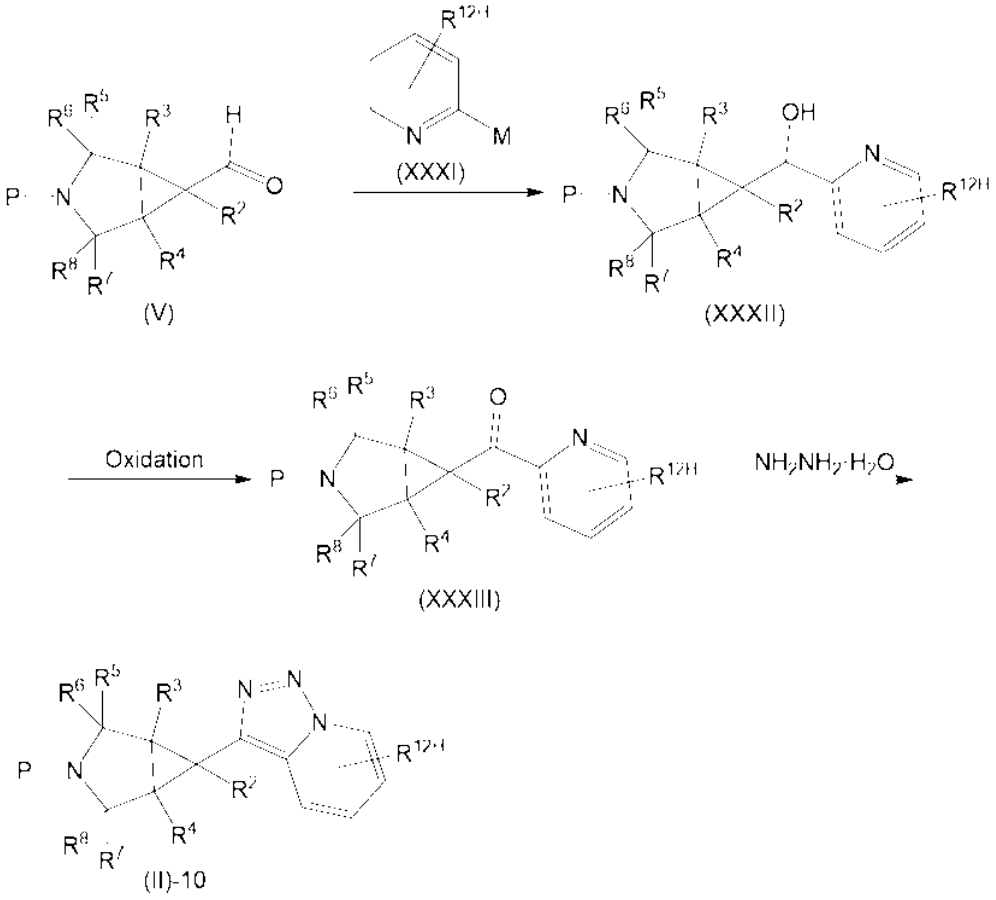
[0164]

The compound represented by the general formula (XXX) can be produced by subjecting the compound represented by the general formula (IX) and the compound represented by the general formula (XXIX) to an amidation reaction.

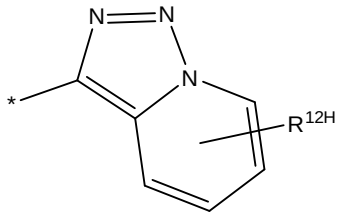
An amidation can be carried out by the same method described above for the preparation of the general formula (I) in Scheme I.

[0165]

Scheme XI



Wherein R^1 in the general formula (II) in Scheme I represents



and

the general formula (II) can be described as the general formula (II)-10 in Scheme XI.

[0166]

The compound represented by the general formula (II)-10 can be produced by subjecting the compound represented by the general formula (XXXIII) to a [1,2,3]triazolo[1,5-a]pyridine cyclization reaction.

A [1,2,4]triazolo[4,3-a]pyridine cyclization reaction can be carried out with hydrazine hydrate at 50 ºC to 70 ºC, followed by the treatment of cupper acetate in solvent (e.g., ethylacetate etc.) at 20 ºC to 40 ºC.

[0167]

The compound represented by the general formula (XXXIII) can be produced by subjecting the compound represented by the general formula (XXXII) to an oxidation reaction of hydroxyl group.

An oxidation reaction of hydroxyl group can be carried out by the same method described above for the preparation of the general formula (II)-3 in Scheme IV.

[0168]

The compound represented by the general formula (XXXII) can be produced by subjecting the compound represented by the general formula (V) and the compound represented by the general formula (XXXI) to an addition reaction.

An addition reaction can be carried out by the same method described above for the preparation of the general formula (XV) in Scheme IV.

[0169]

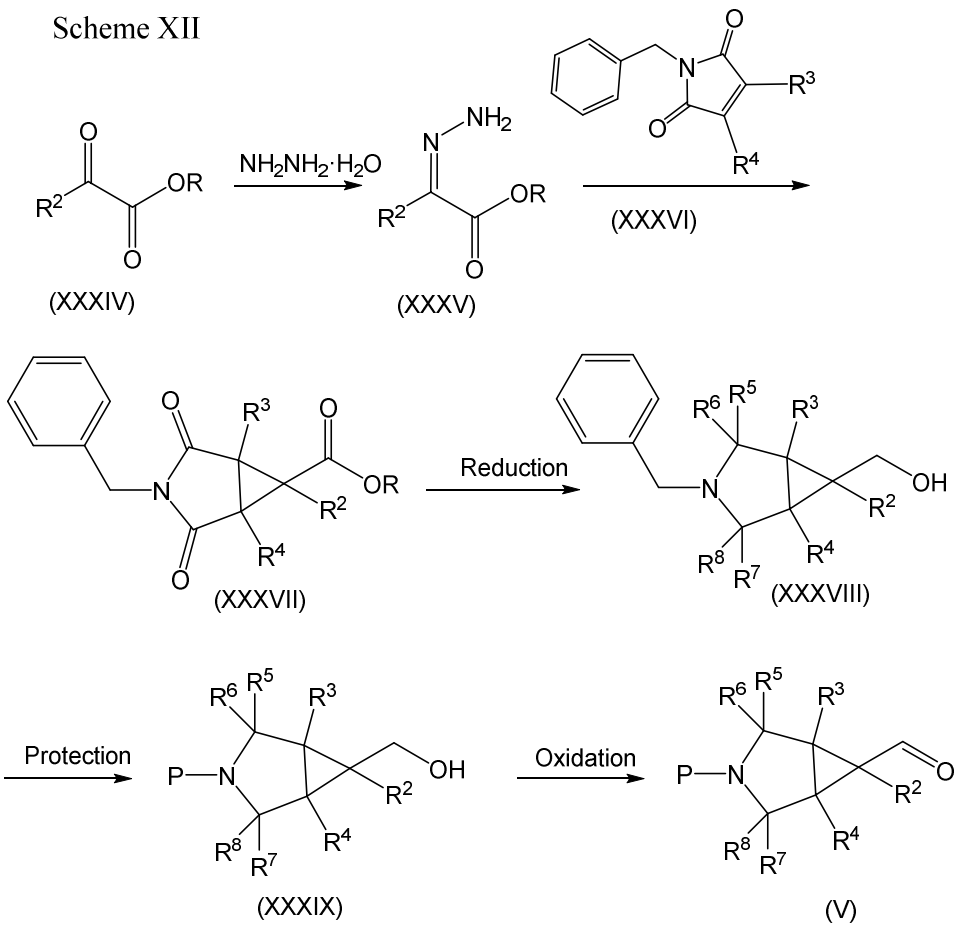
Wherein the compounds represented by the general formula (IV), (VIII), (X), (XI), (XIII), (XIV), (XVI), (XVIII), (XIX), (XXI)-1, (XXI)-2, (XXIII), (XXV), (XXVII), (XXIX) and (XXXI) can be available commercially, or easily prepared from commercial chemicals by well-known method described in, for example, Comprehensive Organic Transformations: A Guide to Functional Group Preparations, 2nd Edition (Richard C. Larock, John Wiley & Sons Inc., 1999) and the like.

[0170]

Wherein the compound represented by the general formula (V) can be available commercially or prepared by the method described in Scheme XII.

[0171]

Scheme XII



Wherein the compound represented by the general formula (V) can be produced by subjecting the compound represented by the general formula (XXXIX) to an oxidation reaction of hydroxyl group.

[0172]

An oxidation reaction of hydroxyl group can be carried out by the same method described above for the preparation of the general formula (II)-3 in Scheme IV.

[0173]

The compound represented by the general formula (XXXIX) can be produced by subjecting the compound represented by the general formula (XXXVIII) to a protection exchange reaction.

A protection exchange reaction can be carried out with hydrogen gas, Pd catalyst (e.g., Pd-C or $Pd(OH)_2$-C etc.) and $(Boc)_2O$ in solvent (e.g., MeOH, EtOH or THF etc.) at 20 ºC to 40 ºC.

[0174]

The compound represented by the general formula (XXXVIII) can be produced by subjecting the compound represented by the general formula (XXXVII) to an ester reduction reaction.

An ester reduction reaction can be carried out with reductant (e.g., $LiAlH_4$, DIBAL-H, Red-Al etc.) in solvent (e.g., THF, diethylether or DME etc.) at -20 ºC to 20 ºC.

[0175]

The compound represented by the general formula (XXXVII) can be produced by subjecting the compound represented by the general formula (XXXVIII) and to an imide reduction reaction.

An imide reduction reaction can be carried out with borane reductant (e.g., BH_3 THF, BH_3 Me_2S or B_2H_6 etc.) in solvent (e.g., THF, diethylether or DME etc.) at 20 ºC to 80 ºC.

[0176]

The compound represented by the general formula (XXXVII) can be produced by subjecting the compound represented by the general formula (XXXV) and the compound represented by the general formula (XXXVI) to a cyclopropanation reaction.

A cyclopropanation reaction can be carried out with MnO_2 in solvent (e.g., dioxane etc) at 20 ºC to 100 ºC.

[0177]

The compound represented by the general formula (XXXV) can be produced by subjecting the compound represented by the general formula (XXXIV) to a hydrazone formation reaction.

A hydrazone formation reaction can be carried out with hydrazine hydrate and acetic acid in water at 0 ºC to 40 ºC.

[0178]

Wherein the compound represented by the general formula (XXXIV) and (XXXVI) can be available commercially, or easily prepared from commercial chemicals by well-known method described in, for example, Comprehensive Organic Transformations: A Guide to Functional Group Preparations, 2nd Edition (Richard C. Larock, John Wiley & Sons Inc., 1999) and the like.

[0179]

In the reactions exemplified herein, any heating means such as water bath, oil bath, sand bath and microwave may be used.

[0180]

In the reactions exemplified herein, a solid phase-supported reagent supported on a polymer (such as polystyrene, polyacrylamide, polypropylene and polyethylene glycol) may be used, if appropriate.

[0181]

The products from the reactions exemplified herein may be purified by a conventional purification means, for example, distillation under normal or reduced pressure, chromatography (such as high performance liquid chromatography, thin layer chromatography or column chromatography) using silica gel, an ion exchange resin, scavenger resin or magnesium silicate, or by washing or recrystallization. Purification may be carried out after each reaction step or after a series of reactions.

[Toxicity]

[0182]

The present compound has low toxicity and thus can be safely used as a medicament.

[Application to medicaments]

[0183]

The present compound has KDM5 inhibitory activity, and thus can be used as an agent for prophylaxis and/or therapy of KDM5-related diseases in mammals, particularly in humans.

[0184]

Examples of such diseases include hyperproliferative disease, cancer, stroke, diabetes, hepatomegaly, cardiovascular disease, multiple sclerosis, Huntington's disease, Alzheimer's disease, cystic fibrosis, viral disease, autoimmune diseases, atherosclerosis, restenosis, psoriasis, rheumatoid arthritis, inflammatory bowel disease, asthma, allergic disorders, inflammation, neurological disorders, a hormone-related disease, conditions associated with organ transplantation, immunodeficiency disorders, destructive bone disorders, proliferative disorders, infectious diseases, conditions associated with cell death, thrombin-induced platelet aggregation, liver disease, pathologic immune conditions involving T cell activation, CNS disorders, myeloproliferative disorder, Parkinson's disease, Lewy body disease, frontotemporal lobar degeneration, mild cognitive impairment, cognitive impairment, cerebrovascular disease, schizophrenia, depression, anxiety disorder, bipolar disorder, autism spectrum disorder, attention deficit/hyperactivity disorder, learning disabilities, movement

disorders, obsessive-compulsive disorder, personality disorder, sleeping disorder, delirium, amyotrophic lateral sclerosis, developmental disorders, intellectual disability, post-traumatic stress disorder, and hepatitis and the like.

[0185]

Among others, the present compound is useful for prophylaxis and/or therapy of cancer, Huntington's disease, Alzheimer's disease, Parkinson's disease, Lewy body disease, frontotemporal lobar degeneration, mild cognitive impairment, cognitive impairment, cerebrovascular disease, schizophrenia, depression, anxiety disorder, bipolar disorder, autism spectrum disorder, attention deficit/hyperactivity disorder, learning disabilities, movement disorders, obsessive-compulsive disorder, personality disorder, sleeping disorder, delirium, amyotrophic lateral sclerosis, developmental disorders, intellectual disability, post-traumatic stress disorder, or hepatitis. The present compound is particularly suitable for prophylaxis and/or therapy of cancer and Alzheimer's disease.

[0186]

In addition to having a strong KDM5 inhibitory activity, the present compound is excellent in metabolic stability and can be present in the brain at a high concentration.

[0187]

Examples of test methods for evaluating the pharmacological activity of the present compounds include an evaluation system of improvement of cognitive impairment in mice. For example, improvement of cognitive impairment by the present compounds may be evaluated by using the following method.

[0188]

Mice (16 to 23-month old male C57BL/6 mice (Charles River Laboratories Japan, Inc.)) are used. A test compound and its vehicle are orally administered once daily for 2 weeks. After that, the cognitive function will be assessed by the novel object recognition (NOR) test using a plastic cage (ECON cage, CL-0107, 345 mm * 403 mm * 177 mm, CLEA Japan, Inc.) with a video camera as the experimental apparatus. The evaluation is performed in a dark room and the light intensity is adjusted to approximately 20 lux near the experimental apparatus. To acclimatize animals to the evaluation environment, the mice are moved to the evaluation room at least 1 hour prior to the start of the trial. The study will be conducted over 3 days. For acclimation to the experimental apparatus on Day 1, the mice are placed in a cage and allowed to move freely for 10 minutes. In the acquisition trial on Day 2, two identical objects (familiar objects) are placed on the cage and performed in the same way

for 10 minutes. The two objects are placed apart on a line parallel to the long side of one cage. The distance between the object and the inner wall of the two adjacent surfaces is 10 cm. In the test trial on Day 3, one of the objects used in the acquisition trial is replaced by a novel object with a different color and shape, and the animals behave in the same manner for 10 minutes. The test trials start 24 hours (Acceptable range: 23 to 25 hours) after the acquisition trials. From the video images recorded in the test trials, the exploration time for each object is measured. From the exploration time of familiar and novel objects, the total exploration time and the novel object recognition rate are calculated by the following equation.

[0189]

Total exploration time (seconds) = Exploration Time for familiar object + Exploration time for novel object

Recognition index (%) = 100 * (Exploration time for novel object / Total exploration time)

[0190]

Examples of test methods for evaluating the pharmacological activity of the present compounds include the clonogenic assay and the cytotoxicity assay in cancer cells. For example, efficacy of the present compounds in cancer cells may be evaluated by using the following methods.

[0191]

MCF-7, T47D and MBA-MB231 human breast cancer cells are purchased from ATCC with certification. Cells are cultured for at most 10–12 passages, then replaced by cells from early passages, kept in liquid nitrogen since collection. Cells are grown in adherence in high glucose Dulbecco's Modified Eagle Medium (DMEM) with 1% penicillin/streptomycin, 2 mM L-glutamine, 10% previously inactivated fetal bovine serum. Cells are maintained at 37 °C and 5% CO_2 in an incubator and routinely passaged removing DMEM, washing with PBS and detaching them using a suitable amount of Trypsin/EDTA.

[0192]

For the clonogenic assay, one hour after treatment with the compound, cells are exposed to X-ray using a MLG 300/6-D apparatus (Gilardoni) set to 200 V and 6 mA, in order to produce an equivalent absorbed dose of 1cGy/s. Afterwards, cells are harvested, counted and then diluted in the growth medium containing the compound. Appropriate cell numbers are seeded in quadruplicate according to the doubling time of the cell line and to radiation dose. Twenty-four hours after this seeding, the medium with the compound is replaced with

fresh DMEM and cells are then incubated for 14 days (enough time to allow at least six cell divisions). After this period of growth, cells are washed twice with PBS and then fixed and stained with a suitable volume of a solution made of 0.3% Methylene Blue and 80% Ethanol for 30 min at room temperature. After washing cells twice with ddH2O, plates are pictured with ChemiDoc XRS+ Imaging System (Bio-Rad) in colorimetric mode. Radiation-dose response curves to X-ray for DMSO and the compound samples are calculated using surviving fraction. Plating efficiency and surviving fraction are calculated as follows:

Plating efficiency = number of colonies counted/number of cells plated

Surviving fraction = Plating efficiency/plating efficiency of sham sample

[0193]

For the cytotoxicity assay, Cell Counting Kit-8 (#CK04, DOJINDO) is used according to the manufacturer's instructions. MCF-7 T47D or MDA-MB231 cell suspension (5000 cells/100μL/well) is dispensed in a 96-well plate. After 24 hours, the compound or DMSO is added in growth medium and then cells are irradiated. Forty-eight hours post irradiation, 10 μL of CCK-8 solution is added to each well of the plate and incubated again for 1 hour. The absorbance at 450 nm is read using a VICTOR2 1420 reader (Perkin Elmer).

[0194]

Examples of test methods for evaluating the pharmacological activity of the present compounds include the primary human hepatocytes (PHH) assay for inhibition of hepatitis B virus antigen (HbsAg). For example, efficacy of the present compounds in the PHH assay may be evaluated by using the following methods.

[0195]

Primary human hepatocytes (PHH) (Bioreclamation IVT) are plated on collagen-coated flasks using Plating Media (Life Technologies) containing William's Medium E supplemented with 1% penicillin/streptomycin, 4 pg/mL human recombinant insulin, 2 mM GlutaMAX, 15 mM HEPES, 1 μM dexamethasone, 5% fetal bovine serum, and 0.2% Antibiotic Mix. After a 4-hour incubation at 37 °C, cells are switched to Maintenance Media (Life Technologies) containing William's Medium E supplemented with 0.5% penicillin/streptomycin, 6.25 pg/mL human recombinant insulin, 6.25 pg/mL human transferrin, 6.25 ng/mL selenous acid, 1.25mg/mL bovine serum albumin, 5.35 pg/mL linoleic acid, 2 mM GlutaMAX, 15 mM HEPES, 0.1 μM dexamethasone, 2% fetal bovine serum, 2% DMSO, and 0.2% Antibiotic Mix. On the next day, PHH are infected with 500 genome equivalent per cell of genotype D (AD38-derived) HBV in Maintenance Media supplemented

with 4% PEG 8000 (Promega). After 24 hour incubation, cells are washed three times with William's Medium E and fed with fresh Maintenance Media. At 3 days after infection, infected PHH cells are seeded on 96-well plates pre-coated with collagen at a density of 65000 cells per well containing serially diluted solutions of compounds or DMSO (1 % final concentration) in a final volume of 125 μΐ of Maintenance Media (Life Technologies). Media with compounds is replenished every 2-3 days. After an incubation time of 12 days, secreted HBsAg in the supernatant are measured using a multiplex chemiluminescent (Mesoscale discovery, MSD) assay using capture and detection antibody pairs specific for HBsAg. EC50 values are calculated from the fit of the dose-response curves to a four-parameter equation.

[0196]

Examples of test methods for evaluating the pharmacological activity of the present compounds include an evaluation system of improvement of the depressive symptoms in the social defeat stress model. For example, efficacy of the present compounds in the social defeat model may be evaluated by using the following methods.

[0197]

Eight-week-old male DBA/2 mice are used for the study. The social defeat stress is given to the mice. The test mice are placed in a highly aggressive CD-1 mouse cage for 5 minutes. At this time, CD-1 mice will attack the test mice unilaterally (Physical Stress). After 5 minutes, CD-1 mice and test mice are separated by a transparent acrylic plate and maintained for 24 hours (psychological stress burden). This process is done for 5 consecutive days. The compound or vehicle is orally administrated 2 hours before the social defeat stress in each day. After that, the social interaction test and the sucrose preference test are conducted.

[0198]

For the social interaction test, CD-1 mice as a novel mouse are placed in a box of 42 cm square (Target Area). Test mice (DBA/2 mouse) are placed in the boxes and the time spent in the target area for 3 minutes is measured by a video tracking system (Any-Maze Software). Time contacting with a novel mouse is reduced in depressed animals.

[0199]

For the sucrose preference test, bottles containing 1% sucrose solution and normal water are given simultaneously. The amount of sucrose solution and normal water consumed over 4 h is measured, and the percentage of sucrose water consumed (sucrose preference) is

used as an indicator of anhedonia. Animals usually prefer sweet sucrose, but animals in the anhedonia state, a condition of depression, have reduced preference for sucrose.

[0200]

Upon using the present compound for pharmaceutical purposes, the present compound may be used not only as a single drug but also as a combined drug with an additional active component, for example those listed hereinbelow, for the purposes of, for example, (1) supplementing and/or enhancement of the effect thereof for prophylaxis, therapy and/or amelioration of symptoms, (2) improvement of the kinetics and absorption, reduction of the dosage thereof and/or (3) alleviation of side-effects thereof.

[0201]

When the present compound is used for prophylaxis and/or therapy of Alzheimer's disease, examples of the drugs which may be used in combination with the present compound include symptomatic agents, for example those known to modify cholinergic transmission such as M1 and M3 muscarinic receptor agonists or allosteric modulators, M2 muscarinic antagonists, M4 agonists or positive allosteric modulators (PAMs), acetylcholinesterase inhibitors (such as tetrahydroaminoacridine, donepezil hydrochloride and rivastigmine), nicotinic receptor agonists or allosteric modulators (such as α7 agonists or allosteric modulators or α4β2 agonists or allosteric modulators), PPAR agonists (such as PPARy agonists), 5-HT_4 receptor agonists or partial agonists, histamine H3 antagonists, 5-HT_6 receptor antagonists or $5HT_{1A}$ receptor ligands and NMDA receptor antagonists or modulators, 5-HT_{2A} antagonists, 5-HT_7 antagonists, Dl agonists or PAMs, D4 agonists or PAMs, D5 agonists or PAMs, GABA-A a5 inverse agonists or negative allosteric modulators (NAMs), GABA-A a2/3 agonists or PAMs, mGluR2 modulators (PAMs or NAMs), mGluR3 PAMs, mGluR5 PAMs, PDE 1 inhibitors, PDE 2 inhibitors, PDE 4 inhibitors, PDE 5 inhibitors, PDE 9 inhibitors, PDE 10 inhibitors, GlyTl inhibitors, DAAO inhibitors, ASCI inhibitors, AMPA modulators, SIRT1 activators or inhibitors, AT4 antagonists, GalRl antagonists, GalR3 ligands, adenosine Al antagonists, adenosine A2a antagonists, a2A antagonists or agonists, selective and unselective norepinephrine reuptake inhibitors (SNRIs), or potential disease modifying agents such as gamma secretase inhibitors or modulators, alpha secretase activators or modulators, amyloid aggregation inhibitors, amyloid antibodies, tau aggregation inhibitors or tau phosphorylation/kinase inhibitors, tau dephosphorylation / phosphatase activators, mitogen-activated protein kinase kinase 4 (MKK4/MEK4/MAP2K4) inhibitors, c-Jun N-terminal kinase (JNK) inhibitors, casein kinase inhibitors, MK2 (mitogen

activated protein kinase-activated protein kinase 2) inhibitors, MARK (microtubule affinity regulating kinase) inhibitors, CDK5 (cyclin dependent kinase 5) inhibitors, GSK-3 (glycogen synthase kinase-3) inhibitors and tau-tubulin kinase- 1 (TTBK1) inhibitors. Further examples of such other therapeutic agents may be calcium channel blockers, HMG-CoA (3-hydroxy-3-methyl-glutaryl-CoA) reductase inhibitors (statins) and lipid lowering agents, NGF (nerve growth factor) mimics, antioxidants, GPR3 ligands, plasmin activators, neprilysin (NEP) activators, IDE (insulin degrading enzyme) activators, melatonin MT1 and/or MT2 agonists, TLX/NR2E1 (tailless X receptor) ligands, GluRl ligands, RAGE (receptor for advanced glycation end-products) antagonists, EGFR (epidermal growth factor receptor) inhibitors, FPRL-1 (formyl peptide-like receptor- 1) ligands, GABA antagonists, and MICAL (molecule interacting with casL) inhibitors, e.g. oxidoreductase inhibitors, CB1 antagonists/inverse agonists, non-steroidal anti-inflammatory drugs (NSAIDs), anti-inflammatory agents (for example agents that could be used to treat neuroinflammation either by enhancing or reducing neuroinflammation), amyloid precursor protein (APP) ligands, anti-amyloid vaccines and/or antibodies, agents that promote or enhance amyloid efflux and/or clearance, histone deacetylase (HDAC) inhibitors, EP2 antagonists, 11-beta HSD1 (hydroxy steroid dehydrogenase) inhibitors, liver X receptor (LXR) agonists or PAMs, lipoprotein receptor-related protein (LRP) mimics and/or ligands and/or enhancers and/or inhibitors, butyryl cholinesterase inhibitors, kynurenic acid antagonists and/or inhibitors of kynurenine aminotransferase (KAT), orphanin FQ / nociceptin (NOP) / opioid-like receptor 1 (ORL1) antagonists, excitatory amino acid transporter (EAAT) ligands (activators or inhibitors), and plasminogen activator inhibitor- 1 (PAI- 1) inhibitors, niacin and/or GPR109 agonists or PAMs in combination with cholesterol lowering agents and/or HMGCoA reductase inhibitors (statins), dimebolin or similar agents, antihistamines, metal binding / chelating agents, antibiotics, growth hormone secretagogues, cholesterol lowering agents, vitamin E, cholesterol absorption inhibitors, cholesterol efflux promoters and/or activators, and insulin upregulating agents, and the like.

[0202]

The present compound may alternatively be used in combination with, for example, donepezil hydrochloride, galantamine hydrobromide, huperzine A, idebenone, levacecarnine hydrochloride, memantine hydrochloride, memantine hydrochloride/donepezil hydrochloride, proteolytic peptide fraction from porcine brain protein, rivastigmine tartrate, tacrine hydrochloride, aducanumab (genetical recombination) or the like.

[0203]

The combined drug of the present compound and an additional drug may be administered in the form of a concomitant drug containing both components in one formulation, or separate formulations may be administered by the same or different routes of administration. It is not necessary that separate formulations are administered simultaneously and separate formulations may be administered sequentially with a time difference. When the formulations are sequentially administered, the order or administration is not particularly limited and may be appropriately adjusted so that desired efficacy of drugs can be obtained.

[0204]

The dosage of the additional drug which is used in combination with the present compound may be appropriately increased or decreased according to the clinical dosage thereof or a similar drug. The ratio between the present compound and the additional drug may be appropriately adjusted by considering the age and weight of the subject, the administration method, the time of administration, the target disease and condition and the like. Generally, 1 part by weight of the present compound may be combined with the additional drug in an amount ranging from 0.01 to 100 parts by weight. A plurality of the additional drug may be used. The additional drug may be, in addition to those mentioned above, a drug having the same mechanism as those mentioned above. Such an additional drug includes not only the one which has been discovered by now but also the one which will be discovered in future.

[0205]

The dosage of the present compound may vary according to the age, weight, condition, therapeutic effect, administration method, treatment period and the like. The present compound may be orally administered to an adult once to several times daily at the amount of 0.1 mg to 300 mg per administration, parenterally administered to an adult once to several times daily at the amount of 0.1 mg to 150 mg per administration or intravenously and continuously administered over 1 hour to 24 hours daily.

[0206]

As described above, the dosage may vary according to various conditions, and thus the amount less than the dosage described above may be sufficient in some cases and the amount exceeding the above dosage may be required in other cases.

[0207]

When the present compound is used for prophylaxis and/or therapy of the above diseases as a single drug or a combined drug with the additional drug, the present substance which is an active component is generally formulated with a pharmaceutically acceptable carrier such as various additives or solvents and the obtained formulation is administered systemically or locally and orally or parenterally. The pharmaceutically acceptable carrier as used herein means a substance other than an active component that is generally used for medicinal formulations. The pharmaceutically acceptable carrier preferably does not exhibit pharmacological activity, is harmless and does not prevent the therapeutic effect of the active component at the dosage of the formulation. The pharmaceutically acceptable carrier may also be used in order to increase the usefulness of the active component and the formulation, to facilitate production of the formulation, to stabilize the quality or to improve the usability. Specifically, the substances described in “Iyakuhin Tenkabutsu Jiten”, 2000, Yakuji Nippo Ltd. (Ed. IPEC Japan) may be appropriately selected according to the need.

[0208]

Examples of the dosage form include oral administration formulations (examples: tablets, capsules, granules, powders, oral liquids, syrups, oral jelly formulations and the like), oral cavity formulations (examples: tablets for the oral cavity, spray formulations for the oral cavity, semi-solid formulations for the oral cavity, oral rinse and the like), formulations for injection (examples: injections and the like), formulations for dialysis (examples: agents for dialysis and the like), formulations for inhalation (examples: agents for inhalation and the like), ophthalmic formulations (examples: ophthalmic solutions, ophthalmic ointments and the like), otological formulations (examples: ear drops and the like), nasologic formulations (examples: nasal drops and the like), rectal formulations (examples: suppositories, semi-solid formulations for rectal administration, enema formulations and the like), vaginal formulations (examples: vaginal tablets, vaginal suppositories and the like), skin formulations (examples: topical solid formulations, topical liquids, spray formulations, ointments, creams, gels, plasters and pressure sensitive adhesives and the like) and the like.

[Oral administration formulations]

[0209]

Examples of an oral administration formulation include tablets, capsules, granules, powders, oral liquids, syrups, oral jelly formulations and the like. The oral administration

formulation may be classified into rapidly disintegrating formulations for which the release of an active component from the formulations is not particularly controlled and release-controlled formulations for which the release is controlled according to the purposes by adjusting the dosage design and production method, such as enteric formulations and sustained release formulations. The enteric formulations refer to a formulation which is designed to release an active component mainly in the small intestine rather than in the stomach with the purpose of prevention of decomposition of the active component in the stomach or reduction of stimulation of the stomach by the active component. The enteric formulation may be generally produced by providing a coating of an acid-insoluble enteric base. The sustained release formulations refer to a formulation for which the release rate, release time and release site of an active component from the formulation is controlled with the purpose of reduction in the frequency of administration or reduction of side effects. The sustained release formulation may be generally produced by using an appropriate agent for sustained release. Among the oral administration formulations, capsules, granules, tablets may be provided with an appropriate coating film of a saccharide, sugar alcohol, polymer compound and the like with the purpose of easy ingestion or prevention of decomposition of an active component.

(1) Tablets

[0210]

Tablets are an orally administered solid formulation having a certain shape. Examples thereof include those generally referred to as tablets such as plain tablets, film-coated tablets, sugar-coated tablets, multilayered tablets and dry-coated tablets as well as orally disintegrating tablets, chewable tablets, effervescent tablets, dispersible tablets, soluble tablets and the like. Plain tablets may be generally produced according to the following procedure (a), (b) or (c):

(a) An active component is mixed with an additive such as a vehicle, a binding agent and a disintegrating agent to obtain a homogeneous mixture which is granulated by an appropriate method using water or a solution containing a binding agent, mixed with a lubricant and the like, compressed and moulded;

(b) An active component is mixed with an additive such as a vehicle, a binding agent and a disintegrating agent to obtain a homogeneous mixture which is then directly compressed and moulded, or granules prepared with an additive are mixed with an active component, a

lubricant and the like to obtain a homogeneous mixture which is then compressed and moulded;

(c) An active component is mixed with an additive such as a vehicle and a binding agent to obtain a homogeneous mixture which is then wetted and kneaded with a solvent, moulded in a certain mould and dried by an appropriate method. Film-coated tablets may be generally produced by providing appropriate thin coating films of a polymer and the like to plain tablets. Sugar-coated tablets may be generally produced by providing coating films containing a saccharide or sugar alcohol to plain tablets. Multilayerd tablets may be produced by stacking layers of powder granules having different compositions and compressing and moulding the product according to an appropriate method. Dry-coated tablets may be produced by coating inner core tablets with outer layers having different compositions. Tablets may be formed as enteric tablets or sustained release tablets according to appropriate well-known methods. Orally disintegrating tablets, chewable tablets, effervescent tablets, dispersible tablets and soluble tablets are the tablets to which unique functions are imparted by appropriately selecting additives, and may be produced according to the production procedures described above for the tablets. Orally disintegrating tablets refer to a tablet ingested by rapid dissolution or disintegration in the oral cavity; chewable tablets refer to a tablet ingested by chewing; effervescent tablets refer to a tablet which is dissolved or dispersed in water with rapid effervescence; dispersible tablets refer to a tablet which is ingested after dispersion in water; and the soluble tablets refer to a tablet which is ingested after dissolution in water. The effervescent tablets may be produced by using an additive which is an appropriate acidic substance, carbonate salt, hydrogen carbonate salt and the like.

(2) Capsules

[0211]

Capsules are a formulation containing a capsule shell filled with an active component or an active component coated with a capsule base. Examples thereof include hard capsules, soft capsules and the like. Hard capsules may be produced by mixing an active component with an additive such as a vehicle to obtain a homogeneous mixture, or obtaining granules or moulded substance by an appropriate method, which is then directly, or after appropriately being moulded, added to a capsule shell. Soft capsules may be produced by capsulating and moulding a mixture of an active component and an additive into a certain shape with an

appropriate capsule base such as gelatine having an increased plasticity by addition of glycerol, D-sorbitol or the like. Capsules may be formed as enteric capsules or sustained release capsules according to appropriate well-known methods. A capsule base may be added with a colorant, a preservative or the like.

(3) Granules

[0212]

Granules are a granulated formulation. Examples thereof include those generally referred to as granules as well as effervescent granules. Granules may be generally produced according to the following procedure (a), (b) or (c):

(a) A powder active component is mixed with an additive such as a vehicle, a binding agent or a disintegrating agent to obtain a homogeneous mixture which is then granulated by an appropriate method;

(b) A granulated active component is mixed with an additive such as a vehicle to obtain a homogeneous mixture;

(c) A granulated active component is mixed with an additive such as a vehicle to obtain a homogeneous mixture which is then granulated by an appropriate method. Granules may be optionally provided with a film or may be formed as enteric granules or sustained release granules using appropriate well-known methods. Effervescent granules may be produced by using an additive which is an appropriate acidic substance, carbonate salt, hydrogen carbonate salt and the like. The effervescent granules refer to a granule which is dissolved or dispersed in water with rapid effervescence. The granules may also be formed as fine granules by controlling the particle size.

(4) Powders

[0213]

Powders are powdery formulations and may be generally produced by mixing an active component with an additive such as a vehicle to obtain a homogeneous mixture.

(5) Oral liquids

[0214]

Oral liquids are a formulation in the form of solution or flowable and viscous gel. Examples thereof include those generally referred to as oral liquids as well as elixirs,

suspensions, emulsions, lemonades and the like. Oral liquids may be generally produced by mixing an active component with an additive and purified water to homogeneously dissolve, emulsify or suspend the active component and optionally filtering the product. Elixirs refer to a clear oral liquid containing ethanol having sweet taste and aroma. Elixirs may be generally produced by dissolving a solid active component or an infusion thereof in ethanol, purified water, a flavouring agent and sucrose, an additional saccharide or a sweetening agent and obtaining a clear liquid by filtration or other methods. Suspensions refer to an oral liquid in which an active component is finely and homogeneously suspended. Suspensions may be generally produced by suspending a solid active component in a suspending agent or an additional additive and purified water or oil and homogenising the whole product according to an appropriate method. Emulsions refer to an oral liquid in which an active component is finely and homogeneously emulsified. Emulsions may be generally produced by adding an emulsifying agent and purified water to a liquid active component and emulsifying and homogenising the whole product according to an appropriate method. Lemonades refer to a clear oral liquid having sweet taste and sour taste.

(6) Syrups

[0215]

Syrups are a viscous liquid or solid formulation containing a saccharide or a sweetening agent. Examples thereof include agents for syrups. Syrups may be generally produced by dissolving, mixing, suspending or emulsifying an active component in a solution of sucrose, other saccharides or a sweetening agent or solely a syrup and optionally boiling the product followed by filtering while heating. Formulations for syrups refer to a granular or powdery formulation to which water is added to provide syrups and may be sometimes referred to as dry syrups. Formulations for syrups may be generally produced according to the production procedures described above for the granules or powders by using a saccharide or a sweetening agent as an additive.

(7) Oral jelly formulations

[0216]

Oral jelly formulations are a shaped gel formulation without flowability. Oral jelly formulations may be generally produced by mixing an active component with an additive and

a polymer gel base, allowing formation of gel and shaping into a certain shape according to appropriate methods.

[Oral cavity formulations]

(1) Tablets for the oral cavity

[0217]

Tablets for the oral cavity are a formulation having a certain shape which is administered to the oral cavity. Examples thereof include troches, sublingual tablets, buccal tablets, adhering tablets, chewing gum tablets and the like. Tablets for the oral cavity may be generally produced according to the production procedures described for the tablets. Troches refer to a tablet for the oral cavity which is gradually dissolved or disintegrated in the oral cavity and is applied locally to the oral cavity or pharynx; sublingual tablets refer to a tablet for the oral cavity to be rapidly dissolved under the tongue to allow absorption of an active component through oral mucosa; buccal tablets refer to a tablet for the oral cavity to be gradually dissolved between the molars and cheeks to allow absorption of an active component through oral mucosa; adhering tablets refer to a tablet for the oral cavity which is adhered to oral mucosa; and chewing gum tablets refer to a tablet for the oral cavity to be chewed to release an active component.

(2) Spray formulations for the oral cavity

[0218]

Spray formulations for the oral cavity are a formulation to spray an active component in the form of mist, powder, foam or paste. Spray formulations for the oral cavity may be generally produced by dissolving or suspending an active component and an additive in a solvent or the like, optionally filtering thereof and packing the product into a container together with liquefied gas or compressed gas, or by preparing a solution or suspension with an active component and an additive and packing the product into a container to which a spraying pump is attached.

(3) Semi-solid formulations for the oral cavity

[0219]

Semi-solid formulations for the oral cavity are a formulation to be applied to the oral mucosa. Examples thereof include creams, gels, ointments and the like. Semi-solid

formulations for the oral cavity may be generally produced by emulsifying an active component together with an additive in purified water and an oil component such as petrolatum, or by mixing an active component and an additive with a base such as a polymer gel or an oil or fat and obtaining a homogeneous mixture. Creams refer to a semi-solid formulation in the form of an oil-in-water or water-in-oil emulsion and lipophilic formulations in the form of a water-in-oil emulsion may also be referred to as oil-based creams. Creams may be generally produced by preparing an oil phase from petrolatum or a higher alcohol or a mixture thereof with an additive such as an emulsifying agent, separately preparing a water phase from purified water or a mixture thereof with an additive such as an emulsifying agent, adding an active component either to the oil phase or the water phase, heating both phases and mixing the oil phase and the water phase until homogeneity to obtain an emulsion. Gels refer to a gel formulation and examples thereof include water-based gels, oil-based gels and the like. Water-based gels may be produced by dissolving or suspending an active component in an additive such as a polymer compound and purified water and allowing crosslinking by heating and cooling or addition of a gel-forming agent. Oil-based gels may be produced by mixing an active component with a liquid oil base such as a glycol or a higher alcohol and an additive. Ointments refer to a semi-solid formulation containing an active component dissolved or dispersed in a base. Examples thereof include oil- or fat-based ointments, water-soluble ointments and the like. Oil- or fat-based ointments may be generally produced by melting an oil- or fat-based base such as an oil or fat, a wax and a hydrocarbon including paraffin by heating, dissolving or dispersing an active component therein and mixing and kneading to obtain a homogeneous mixture. Water-soluble ointments may be generally produced by melting a water-soluble base such as macrogol by heating and mixing and kneading an active component therein to obtain a homogeneous mixture.

(4) Oral rinses

[0220]

Oral rinses are a liquid formulation to be applied locally to the oral cavity or pharynx and may include solid formulations which are dissolved upon use. Oral rinses may be generally produced by homogeneously dissolving an active component in a solvent and an additive and optionally filtering the solution. Solid formulations which are dissolved upon

use may be generally produced according to the production procedures described for the tablets and granules.

[Formulations for injection]

(1) Injections

[0221]

Injections are an aseptic formulation in the form of solution, suspension or emulsion or solid to be dissolved or suspended upon use, which are directly administered to body tissues and organs such as under the skin, in the muscle or to a vessel. Examples thereof include those generally referred to as injections as well as lyophilised injections, powder injections, pre-filled syringes, cartridges, transfusions, implantable injections, sustained release injections and the like. Injections may be generally produced according to the following procedure (a) or (b):

(a) An active component or a mixture of an active component with an additive is dissolved, suspended or emulsified in water for injection or another aqueous solvent or a non-aqueous solvent and the product is packed into a container for injection which is then sterilised;

(b) An active component or a mixture of an active component with an additive is dissolved, suspended or emulsified in water for injection or another aqueous solvent or a non-aqueous solvent and the product is subjected to aseptic filtration or the product is homogeneously prepared in an aseptic manner and is charged into a container for injection which is then sealed. Lyophilised injections may be generally produced by dissolving an active component or an active component together with an additive such as a vehicle in water for injection, subjecting the solution to aseptic filtration, charging the solution in a container for injection followed by lyophilisation or lyophilising the solution in a container dedicated for lyophilisation followed by packing the product in a container for injection. Powder injections may be generally produced by aseptic filtration and crystallization to obtain powder which is directly or a mixture thereof with a sterilized additive is charged into a container for injection. Pre-filled syringes may be generally produced by charging an active component or a solution, suspension or emulsion of an active component and an additive into a syringe. Cartridges refer to an injection in the form of a cartridge containing a drug solution to be placed in a dedicated syringe. Cartridges containing a drug solution may be generally produced by charging an active component or a solution, suspension or emulsion of an active component and an additive into a cartridge. Transfusions refer to an injection generally of

100 mL or more which is intravenously administered. Implantable injections refer to an injection in the form of a solid or gel, which is to be applied using an implantable tool or by surgery under the skin or in the muscle in order to release an active component over a long period of time. Implantable injections may be generally produced by forming a pellet, microsphere or gel with a biodegradable polymer compound. Sustained release injections refer to an injection applied in the muscle in order to release an active component over a long period of time and may be generally produced by dissolving or suspending an active component in a vegetable oil or obtaining a microsphere suspension with a biodegradable polymer compound.

[Formulations for dialysis]

(1) Agents for dialysis

[0222]

Agents for dialysis are a liquid formulation or a solid formulation dissolved upon use to be used for peritoneal dialysis or haemodialysis. Examples thereof include agents for peritoneal dialysis, agents for haemodialysis and the like. Agents for peritoneal dialysis refer to an aseptic agent for dialysis used for peritoneal dialysis and may be generally produced by charging a solution of an active component and an additive in a solvent at a certain volume or a mixture of an active component and an additive into a container, sealing the same and optionally sterilizing the same. Solid formulations to be dissolved upon use may be generally produced according to the production procedures described above for the tablets and granules. Agents for haemodialysis refer to an agent for dialysis used for haemodialysis and may be generally produced by charging a solution of an active component and an additive in a solvent at a certain volume or a mixture of an active component and an additive into a container. Solid formulations to be dissolved upon use may be generally produced according to the production procedures described above for the tablets and granules.

[Formulations for inhalation]

(1) Agents for inhalation

[0223]

Agents for inhalation are a formulation applied to the bronchus or lung by inhaling aerosols of an active component. Examples thereof include powder agents for inhalation, liquid agents for inhalation, aerosols for inhalation and the like. Powder agents for

inhalation refer to a formulation to be inhaled as aerosols of solid particles at a predetermined amount, and may be generally produced by preparing fine particles of an active component and optionally mixing thereof with an additive such as lactose to obtain a homogeneous mixture. Liquid agents for inhalation refer to a liquid agent for inhalation to be applied by a nebuliser and the like and may be generally produced by homogeneously dissolving or suspending an active component in a solvent, an appropriate tonicity agent, a pH-controlling agent and the like and optionally filtering the product. Aerosols for inhalation refer to a metered-dose agent for inhalation to spray a predetermined amount of active component packed in a container together with a propellant. Aerosols for inhalation may be generally produced by preparing a solution or suspension from an active component, a solvent, an appropriate dispersant, a stabilising agent and the like and charging the product in a pressure resistant container attached with a flow regulating valve together with a liquid propellant.

[Ophthalmic formulations]

(1) Ophthalmic solutions

[0224]

Ophthalmic solutions are a liquid aseptic formulation or a solid aseptic formulation to be dissolved or suspended upon use, which is applied to ophthalmic tissue such as conjunctival sac. Ophthalmic solutions may be generally produced by charging a solution or suspension of an active component and an additive in a solvent or the like at a certain volume or a mixture of an active component and an additive in a container.

(2) Ophthalmic ointments

[0225]

Ophthalmic ointments are a semi-solid aseptic formulation to be applied to ophthalmic tissue such as conjunctival sac, and may be generally produced by charging a homogeneous mixture of a base such as petrolatum and a solution or fine powder of an active component in a container.

[Otological formulations]

(1) Ear drops

[0226]

Ear drops are a liquid or semi-solid formulation or a solid formulation to be dissolved or suspended upon use, which is administered to the external ear or middle ear. Ear drops are generally produced by charging a solution or suspension of an active component and an additive in a solvent or like at a certain volume or a mixture of an active component and an additive in a container.

[Nasologic formulations]

(1) Nasal drops

[0227]

Nasal drops are a formulation to be administered to the nasal cavity or nasal mucosa and examples thereof include nasal powders, nasal liquids and the like. Nasal powders refer to a fine powder nasal drop to be administered to the nasal cavity and may be generally produced by making appropriately fine powder of an active component and optionally mixing the active component with an additive to obtain a homogeneous mixture. Nasal liquids refer to a nasal drop which is liquid or solid to be dissolved or suspended upon use and is administered to the nasal cavity. Nasal liquids may be generally produced by dissolving or suspending an active component in a solvent and an additive and optionally filtering the product. An additive for nasal liquids which may be used includes a tonicity agent, a pH controlling agent and the like.

[Rectal formulations]

(1) Suppositories

[0228]

Suppositories are a semi-solid formulation having a certain shape, which is applied in the rectum and releases an active component by melting at body temperature or gradually dissolving or dispersing in water. Suppositories may be generally produced by dissolving or homogeneously dispersing a homogeneous mixture of an active component with an additive such as a dispersant and an emulsifying agent in a base liquefied by heating and the like, charging a predetermined amount of the product in a container and solidifying/moulding the same. A base for suppositories which may be generally used includes oil- or fat-based bases and hydrophilic bases.

(2) Semi-solid formulations for rectal administration

[0229]

Semi-solid formulations for rectal administration are a formulation applied around or in the anus and examples thereof include rectal creams, rectal gels, rectal ointments and the like. Semi-solid formulations for rectal administration may be generally produced by emulsifying an active component together with an additive in purified water and an oil component such as petrolatum, or by homogeneously mixing an active component and an additive with a base which is a polymer gel or an oil or fat. Rectal creams may be generally produced by preparing an oil phase from petrolatum or a higher alcohol or a mixture thereof with an additive such as an emulsifying agent, separately preparing a water phase from purified water or a mixture thereof with an additive such as an emulsifying agent, adding an active component either to the oil phase or the water phase, heating both phases and mixing the oil phase and the water phase until homogeneity to obtain an emulsion. Rectal gels refer to a gel formulation and examples thereof include water-based gels, oil-based gels and the like. Water-based gels may be produced by dissolving or suspending an active component in an additive such as a polymer compound and purified water and allowing crosslinking by heating and cooling or addition of a gel-forming agent. Oil-based gels may be produced by mixing an active component with a liquid oil base such as a glycol or a higher alcohol and an additive. Rectal ointments refer to a semi-solid formulation containing an active component dissolved or suspended in a base and examples thereof include oil- or fat-based ointments, water-soluble ointments and the like. Oil- or fat-based ointments may be generally produced by melting an oil- or fat-based base such as an oil or fat, a wax and a hydrocarbon including paraffin by heating, dissolving or suspending an active component therein and mixing and kneading to obtain a homogeneous mixture. Water-soluble ointments may be generally produced by melting a water-soluble base such as macrogol by heating and mixing and kneading an active component therein to obtain a homogeneous mixture.

(3) Enema formulations

[0230]

Enema formulations are a liquid or viscous gel formulation to be applied through the anus. Enema formulations are generally produced by dissolving or suspending an active component in a solvent or the like at a certain volume using purified water or an appropriate aqueous solvent and charging the product in a container. An additive which may be used for

enema formulations includes a dispersant, a stabilising agent, a pH controlling agent and the like.

[Vaginal formulations]

(1) Vaginal tablets

[0231]

Vaginal tablets are a solid formulation having a certain shape, which is applied in the vagina and releases an active component by gradually dissolving or dispersing in water. Vaginal tablets may be generally produced according to the production procedures described above for the tablets.

(2) Vaginal suppositories

[0232]

Vaginal suppositories are a semi-solid formulation having a certain shape, which is applied in the vagina and releases an active component by melting at body temperature or gradually dissolving or dispersing in water. Vaginal suppositories may be generally produced according to the production procedures described above for the rectal suppositories and the like.

[Skin formulations]

(1) Topical solid formulations

[0233]

Topical solid formulations are a solid formulation to be applied or spread on skin including the scalp or nails and examples thereof include topical powders. Topical powders refer to a topical solid powder formulation and may be generally produced by mixing an active component with an additive such as a vehicle to obtain a homogeneous mixture which is then formed into powders.

(2) Topical liquids

[0234]

Topical liquids are a liquid formulation to be applied on skin including the scalp or nails and examples thereof include liniments, lotions and the like. Topical liquids may be generally produced by dissolving, emulsifying or suspending an active component in a

solvent, an additive and the like and optionally filtering the product. Liniments refer to a liquid or muddy topical liquid to be rubbed into the skin. Lotions refer to a topical liquid containing an active component dissolved, emulsified or finely dispersed in an aqueous liquid. Lotions may be generally produced by preparing a solution, suspension or emulsion of an active component, an additive and purified water to obtain a homogeneous product.

(3) Spray formulations

[0235]

Spray formulations are a formulation to spray an active component in the form of mist, powder, foam or paste on the skin and examples thereof include topical aerosols, pump spray formulations and the like. Spray formulations may be generally produced by preparing a solution or suspension of an active component, optionally filtering the product and charging the product in a container. Topical aerosols refer to a spray formulation which sprays an active component together with liquefied gas or compressed gas packed in a container. Topical aerosols may be generally produced by preparing a solution or suspension of an active component and packing the product into a pressure resistant container attached with a continuous injection valve together with a liquid propellant. An additive such as a dispersant and a stabilising agent may be optionally added to topical aerosols. Pump spray formulations refer to a spray formulation which sprays an active component in a container by means of a pump. Pump spray formulations may be generally produced by dissolving or suspending an active component and an additive and charging the product in a container to which a pump is attached.

(4) Ointments

[0236]

Ointments are a semi-solid formulation to be applied on the skin containing an active component dissolved or dispersed in a base. Examples thereof include oil- or fat-based ointments, water soluble ointments and the like. Oil- or fat-based ointments may be generally produced by melting an oil- or fat-based base such as an oil or fat, a wax and a hydrocarbon including paraffin by heating, dissolving or suspending an active component therein and mixing and kneading to obtain a homogeneous mixture. Water soluble ointments may be generally produced by melting a water-soluble base such as macrogol by heating and mixing and kneading an active component therein to obtain a homogeneous mixture.

(5) Creams

[0237]

Creams are a semi-solid formulation in the form of an oil-in-water or water-in-oil emulsion to be applied on the skin and lipophilic formulations in the form of a water-in-oil emulsion may also be referred to as oil-based creams. Creams may be generally produced by preparing an oil phase from petrolatum or a higher alcohol or a mixture thereof with an additive such as an emulsifying agent, separately preparing a water phase from purified water or a mixture thereof with an additive such as an emulsifying agent, adding an active component either to the oil phase or the water phase, heating both phases and mixing the oil phase and the water phase until homogeneity to obtain an emulsion.

(6) Gels

[0238]

Gels are a gel formulation to be applied on the skin and examples thereof include water-based gels and oil-based gels. Water-based gels may be generally produced by dissolving or suspending an active component in an additive such as a polymer compound and purified water and allowing crosslinking by heating and cooling or addition of a gel-forming agent. Oil-based gels may be produced by mixing an active component with a liquid oil base such as a glycol or a higher alcohol and an additive.

(7) Plasters and pressure sensitive adhesives

[0239]

Plasters and pressure sensitive adhesives are a formulation to be adhered on the skin and examples thereof include tapes and cataplasms. Plasters and pressure sensitive adhesives may be generally produced by homogeneously mixing an active component with a base which is a polymer compound or a mixture thereof, spreading the mixture on a support or a liner (release material) and shaping the same. Plasters and pressure sensitive adhesives may be formed as transdermal absorption formulations by using a release-controlled film. An additive such as an adhesive or an absorption-promoting agent may be optionally used for plasters and pressure sensitive adhesives. Tapes refer to a plaster and pressure sensitive adhesive containing a base that contains little water and examples thereof include plasters and the like. Tapes may be generally produced with a base which is a water insoluble natural or

synthetic polymer compound such as a resin, a plastic, a rubber or the like by spreading on a fabric or spreading on or incorporating into a plastic film an active component or a homogeneous mixture of an active component and an additive and shaping the product. Tapes may also be produced by incorporating a mixture of an active component and a base or another additive into a release material made of a release-controlled film, a support and a liner (release material) and shaping the same. Cataplasms refer to a plaster and pressure sensitive adhesive containing a base which contains water and may be generally produced by homogeneously mixing an active component with a liquid substance such as purified water or glycerol or homogeneously mixing and kneading a natural or synthetic polymer compound such as a water soluble polymer or a water-absorbable polymer and purified water together with an active component, spreading the mixture on a fabric or the like and shaping the same.

[0240]

Unless otherwise defined, all technical and scientific terms and abbreviations used herein have the same meanings as those commonly understood by a person skilled in the art to which the present invention belongs.

[0241]

Contents of all patent literatures and non patent literatures or references explicitly cited herein may be incorporated herein as a part of the present specification.

[Examples]

[0242]

The present invention is hereinafter specifically described by way of Examples and Biological Examples which do not limit the present invention. The present compounds and compounds described in Examples are denominated according to the IUPAC nomenclature. Naming according to the IUPAC nomenclature can be done using, for example, ACD/Name (version 2019.2.0, available from Advanced Chemistry Development Inc.), ACD/Name Batch (version 12.02.45356, available from Advanced Chemistry Development Inc.) or ChemDraw Professional (version 17.1.0.105 or 18.0.0.231, available from PerkinElmer Inc.) In each of the following Examples, the name of the objective compound of the Example is described subsequently to the number of the Example, and the compound is sometimes referred to as the “title compound”.

Analytical methods

[0243]

^{1}H NMR spectra were recorded on Bruker DRX -400 instruments and are calibrated using residual undeuterated solvent ($CHCl_3$, DMSO, MeOH at 7.26, 2.50 and 3.31 ppm for ^{1}H NMR, respectively). Chemical shifts (δ) are quoted in parts per million (ppm) and referenced to the appropriate NMR solvent peak(s) and are assigned in accordance with numbered diagrams; with resonances described as s (singlets), d (doublets), t (triplets), q (quartets), combinations thereof (i.e. td indicates a triplet of doublets) or m (multiplets) and br s (broad singlet).

[0244]

The Liquid Chromatography Mass Spectroscopy (LCMS) systems used are:

General LCMS Procedures

Method 1

Simadzu LC20-MS2010, Agilent Pursit 5 C_{18} 20 × 2.0 mm at 50°C. Elution with A: 1.5 mL of TFA in 4 L water; B: 0.75 mL of TFA in acetonitrile. Gradient:

Gradient - Time	flow mL/min	%A	%B
0.00	1.5	95	5
0.70	1.5	5	95
1.10	1.5	5	95
1.11	1.5	95	5
1.50	1.5	95	5

Detection - MS, UV 220, 254nm. MS ionization method - Electrospray (positive ion).

Method 2:

Simadzu LC20-MS2010, Xbridge Shield RP-18,5 um,2.1 x 50mm at 50°C. Elution with A: 0.8 mL of NH_3-H2O in 4 L water; B: acetonitrile. Gradient:

Gradient - Time	flow mL/min	%A	%B
0.00	1.0	50	50
2.00	1.0	0	100
2.48	1.0	0	100
2.49	1.0	5	50
3.00	1.0	50	50

Detection - MS, UV 220, 254nm. MS ionization method - Electrospray (positive ion).

Column: XBridge C18 3.5um 2.1 x 50mm;

[0245]

The High Performance Liquid Chromatography (HPLC) systems used are:

General HPLC Procedures

Method 1

SHIMADZU 20A, Ultimate C_{18} 3.0 x 50 mm,3um at 40 °C. Elution with A: 2.75 mL of TFA in 4 L water; B: 2.5 mL of TFA in acetonitrile. Gradient:

Gradient - Time	flow mL/min	%A	%B
0.00	1.2	70	30
6.00	1.2	10	90
8.00	1.2	10	90
8.01	1.2	70	30
10.00	1.2	70	30

Detection - MS, UV 220, 254nm. MS ionization method - Electrospray (positive ion).

Method 2

SHIMADZU 20A, Ultimate C_{18} 3.0 x 50 mm,3um at 40 °C. Elution with A: 2.75 mL of TFA in 4 L water; B: 2.5 mL of TFA in acetonitrile. Gradient:

Gradient - Time	flow mL/min	%A	%B
0.00	1.2	90	10
6.00	1.2	20	80
8.00	1.2	20	80
8.01	1.2	90	10
10.00	1.2	90	10

Detection - MS, UV 220, 254nm. MS ionization method - Electrospray (positive ion).

Method 3:

SHIMADZU LC20-MS2020, Xbridge Shield RP-18, 5 um, 2.1 x 50 mm at 50 °C. Elution with A: 0.8 mL of $NH_3 \cdot H_2O$ in 4 L water; B: acetonitrile. Gradient:

Gradient - Time	flow mL/min	%A	%B
0.00	0.8	90	10
6.00	0.8	20	80
6.50	0.8	20	80

6.51	0.8	90	10
7.00	0.8	90	10

Detection - MS, UV 220, 254nm. MS ionization method - Electrospray (positive ion).

[0246]

The chiral Supercritical Fluid Chromatography (SFC) systems used are:

Chiral SFC Procedures

Method 1:

Column: ChiralPak AD-3 150 × 4.6 mm I.D., 3 um

Mobile phase: A: CO_2 B:IPA (0.05% DEA)

Isocratic: 40% B

Flow rate: 2.5 mL/min Column temp.:40 °C

Back pressure: 100 bar

Method 2:

Column: Chiralcel OJ-3 150 × 4.6 mm I.D., 3 um

Mobile phase: A: CO_2 B: EtOH (0.05% DEA)

Gradient: from 5 % to 40 % of B in 5 min and from 40 % to 5 % of B in 0.5 min, hold 5 % of B for 1.5 min

Flow rate: 2.5 mL/min

Column temp.: 35 °C

ABPR: 1500 psi

Method 3:

Column: Chiralcel OD-3 150 × 4.6 mm I.D., 3 um

Mobile phase: A: CO_2 B: EtOH (0.05 % DEA)

Gradient: from 5 % to 40 % of B in 5 min and from 40 % to 5 % of B in 0.5 min, hold 5 % of B for 1.5 min

Flow rate: 2.5 mL/min

Column temp.: 35 °C

ABPR: 1500 psi

[0247]

Abbreviations

2-MeTHF = 2-methyl tetrahydrofuran;

4A MS = molecular sieves, 4A;

DAST = N,N-diethylaminosulfur trifluoride;

DCM = dichloromethane;

DE = diethyl ether;

DEA = diethylamine;

DIPEA = diisopropyl ethylamine;

DMF = N,N-dimethylformamide;

DMP = Dess-Martin periodinane;

DMSO = dimethyl sulfoxide;

dppf = 1,1'-Ferrocenebis(diphenylphosphine);

EA = ethyl acetate;

EDCI = 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide;

HATU =1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate;

MTBE = methyl tert-butyl ether;

NBS = N-bromosuccinimide;

NCS = N-chlorosuccinimide;

PE = petroleum ether;

TBHP = tert-butyl hydroperoxide;

TEA = triethylamine;

TFA = trifluoroacetic acid;

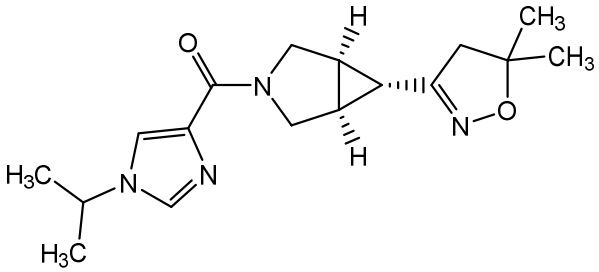
THF = tetrahydrofuran;

TLC = thin layer chromatography; and

X-Phos = 2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl.

[0248]

Example 1 [(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](1-isopropyl-1H-imidazol-4-yl)methanone



tert-butyl (1R,5S,6r)-6-[(E)-(hydroxyimino)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-formyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (Pharmablock Inc., catalog No. PBG0012)(2 g, 9.47 mmol) in EtOH (20 mL) were added AcOH (0.54 mL, 9.47 mmol, 1.0 eq.), KOAc (0.93 g, 9.47 mmol, 1.0 eq.). Then $NH_2OH{\cdot}HCl$ (0.47 mL, 11.36 mmol) was added to the mixture. The mixture was stirred at 25 ^oC for 2h to give white suspension. The reaction mixture was poured into H_2O (40 mL) and extracted with EtOAc (40 mL x 3). The combined organic layers were washed with brine (60 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound as white solid.

TLC : Rf=0.4, PE:EtOAc = 3 : 1;

LC-MS Method1 0.694 min, MS (m/z) 170.8 (M –tBu, + H^+);

^1H NMR (400MHz, CHLOROFORM-d) δ = 7.16 (d, J = 7.6 Hz, 0.5H), 6.13 (d, J = 8.8 Hz, 0.5H), 3.75-3.55 (m, 2H), 3.50-3.35 (m, 2H), 2.23-2.15 (m, 0.5H), 2.10 (s, 1.5H), 1.80 (brs, 1H), 1.44 (s, 9H).

[0249]

tert-butyl (1R,5S,6r)-6-[(Z)-chloro(hydroxyimino)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-[(E)-(hydroxyimino)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (2.2g, 9.72 mmol) in DMF (18.4 mL) were added N-chlorosuccinimide (1363 mg, 10.21 mmol), the mixture was stirred at 20 °C for 2h. The mixture was poured into H_2O (90 mL), extracted by EtOAc (50 mL x 3). The organic phase was washed with brine (50 mL x 3), dried over anhydrous Na_2SO_4, concentrated to give the title compound as a white solid.

LC-MS Method1 0.780 min, MS (m/z) 245.9 (M + H^+).

^1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.42 (s, 1H), 3.75 (d, J=11.2 Hz, 1H), 3.64 (d, J = 10.8 Hz, 1H), 3.38 (d, J = 10.8 Hz, 2H), 2.06 (s, 2H), 1.76 (t, J = 3.2 Hz, 1H), 1.45 (s, 9H).

[0250]

tert-butyl (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-[(Z)-chloro(hydroxyimino)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (100 mg, 0.38 mmol) and Et_3N (0.19 mL, 1.15 mmol) in DMF (1.0 mL) was added 2-methylprop-1-ene (0.72 mL, 1.15 mmol) (15 % in isopropyl ether), and the mixture was stirred at 20 °C for 16 h. The reaction mixture was poured into H_2O (20 mL), extracted with EtOAc (20 mL x 3). The organic phase was washed with brine (20 mL x 3), dried over anhydrous Na_2SO_4, concentrated to give the title compound (100 mg, 0.356 mmol, 92.9 % yield) as a yellow oil.

LC-MS Method1 0.852 min, MS (m/z): 281 ($M + H^+$).

^{1}H NMR (400 MHz, DIMETHYL SUlFOXIDE-d6) δ ppm 3.50 (d, J=11.1 Hz, 2H), 3.30 (d, J = 10.8 Hz, 2H), 2.61 (s, 2H), 1.91 (t, J = 2.7 Hz, 2H), 1.40-1.38 (m, 1H), 1.37 (s, 9H), 1.23 (s, 6H).

[0251]

(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride

The mixture of tert-butyl (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (100 mg, 0.36 mmol) in HCl/Dioxane (2.0 mL, 8.0 mmol, 4.0 M) was stirred at 20 °C for 0.5 h. The mixture was concentrated to afford the title compound (100 mg, 0.46 mmol, 129 % yield, crude) as a yellow oil.

LC-MS Method1 0.232 min, MS (m/z): 181 ($M - HCl + H^+$).

^{1}H NMR (400 MHz, DIMETHYL SUlFOXIDE-d6) δ ppm 9.53 (brs, 1H), 9.06 (brs, 1H), 3.40-3.26 (m, 4H), 2.60 (s, 2H), 2.12 (brs, 2H), 1.99 (m, 1H), 1.23 (s, 6H).

[0252]

[(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](1-isopropyl-1H-imidazol-4-yl)methanone

To a solution of (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (100 mg, 0.46 mmol), 1-isopropylimidazole-4-carboxylic acid (92 mg, 0.6 mmol) and DIPEA (0.38 mL, 2.31 mmol) in DMF (3.0 mL) was added HATU (194 mg, 0.51 mmol), and the mixture was stirred at 20°C for 16h. The mixture was poured into H_2O (30 mL), extracted by EtOAc. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, concentrated to give a residue. The residue was purified

by Prep-HPLC (NH_3) to afford the title compound (4 mg, 0.012 mmol, 2.7 % yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$-*d*) : δ ppm 1.38 (s, 6 H) 1.46 (t, *J*=3.5 Hz, 1 H) 1.51 (d, *J*=6.8 Hz, 6 H) 1.98 (br d, *J*=3.5 Hz, 1 H) 2.08 (br d, *J*=3.0 Hz, 1 H) 2.64 (s, 2 H) 3.62 (dd, *J*=12.5, 4.5 Hz, 1 H) 3.95 (dd, *J*=11.9, 3.6 Hz, 1 H) 4.20 (d, *J*=12.5 Hz, 1 H) 4.36 (dt, *J*=13.5, 6.7 Hz, 1 H) 4.75 (d, *J*=12.0 Hz, 1 H) 7.47 (d, *J*=1.3 Hz, 1 H) 7.67 (d, *J*=1.5 Hz, 1 H)

LCMS Method 1 0.65 mins MS (m/z) 317.0 [$M+H^+$]

[0253]

Example 2 [(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](1-methyl-1H-imidazol-4-yl)methanone

[(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](1-methyl-1H-imidazol-4-yl)methanone

To a mixture of 1-methyl-1H-imidazole-4-carboxylic acid (52.47 mg, 0.42 mmol), EDCI (79.76 mg, 0.42 mmol) in Pyridine (1.0 mL) was added (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (91 mg, 0.42 mmol). The suspension was stirred at 20 °C for 8 hr. The reaction mixture was concentrated in vacuum. The residue was purified by prep-HPLC (NH_3) and lyophilized to afford the title compound (17.45 mg, 21.8 % yield) as yellow solid.

LC-MS Method1: 0.691 min, MS (m/z): 289.2 ($M + H^+$).

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.56 (d, *J*=1.25 Hz, 1 H), 7.38 (s, 1 H), 4.70 (d, *J*=12.05 Hz, 1 H), 4.19 (d, *J*=12.30 Hz, 1 H), 3.94 (dd, *J*=12.05, 4.02 Hz, 1 H), 3.72 (s, 3 H), 3.61 (dd, *J*=12.55, 4.27 Hz, 1 H), 2.64 (s, 2 H), 2.05 - 2.11 (m, 1 H), 1.95 - 2.01 (m, 1 H), 1.46 (t, *J*=3.39 Hz, 1 H), 1.38 (s, 6 H)

[0254]

Example 3 [(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](1-ethyl-1H-imidazol-4-yl)methanone

ethyl 1-ethyl-1H-imidazole-4-carboxylate

A mixture of ethyl (2Z)-3-(dimethylamino)-2-isocyanoacrylate and ethylamine(1608.2 mg, 35.67 mmol, 1.60mL, 20 *eq*) was stirred at 40 °C for 16 hr. The

solution was then concentrated in vacuum. The residue was purified by prep-TLC (PE:EtOAc=0:1, Rf=0.2) to afford the title compound (126 mg, crude) as yellow oil.

LC-MS Method1: 0.259 min, MS (m/z): 168.8($M + H^+$).

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.64 (s, 1H), 7.51 (s, 1H), 4.37 (q, J = 7.2 Hz, 2H), 4.04 (q, J = 7.2 Hz, 2H), 1.39 (t, J = 7.2 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H).

[0255]

1-ethyl-1H-imidazole-4-carboxylic acid

To a mixture of ethyl 1-ethyl-1H-imidazole-4-carboxylate in H_2O (0.5 mL) and THF (1.5 mL) was added $LiOH·H_2O$ (47.16 mg, 1.12 mmol, 1.5 *eq*). The suspension was stirred at 40 °C for 6 hr. The residue was diluted with H_2O (1 mL), extracted with EtOAc (5mLx4). The afforded H_2O layer was acidified with 1 N HCl aq. to pH=5, The combined organic layers were concentrated and then lyophilized to afford the title compound (70 mg, crude) as yellow solid.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.69 (s, 1H), 7.45 (s, 1H), 3.98 (q, J = 7.2 Hz, 2H), 1.33 (t, J = 7.2 Hz, 3H).

[0256]

[(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](1-ethyl-1H-imidazol-4-yl)methanone

To a mixture of 1-ethyl-1H-imidazole-4-carboxylic acid in Pyridine (1 mL) were added EDCI (95.54 mg, 0.50 mmol) and (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (72 mg, 0.33mmol). The suspension was stirred at 20 °C for 16 hr. The solution was purified by Prep-HPLC (NH_3) and lyophilized to afford the title compound (23.69 mg, 23.58% yield) as yellow solid.

LC-MS Method1: 2.045min, MS (m/z): 303.2 ($M + H^+$).

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.54 (d, *J*=1.25 Hz, 1 H) 7.35 (d, *J*=1.25 Hz, 1 H) 4.65 (d, *J*=12.05 Hz, 1 H) 4.12 (d, *J*=12.30 Hz, 1 H) 3.94 (q, *J*=7.28 Hz, 2 H) 3.87 (dd, *J*=12.05, 4.02 Hz, 1 H) 3.54 (dd, *J*=12.55, 4.27 Hz, 1 H) 2.57 (s, 2 H) 2.00 (dt, *J*=7.47, 3.92 Hz, 1 H) 1.91 (br d, *J*=3.76 Hz, 1 H) 1.37 - 1.44 (m, 4 H) 1.30 (s, 7 H)

[0257]

Example 4 (1-cyclopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

methyl 1-cyclopropyl-1H-imidazole-4-carboxylate

To a suspension of 2,2'-bipyridine (618.79 mg, 3.96 mmol), $Cu(OAc)_2$ (720.01 mg, 3.96 mmol), Na_2CO_3 (840.54 mg, 7.93 mmol) in DCE (30 mL) were added methyl 1H-imidazole-4-carboxylate (500 mg, 3.96 mmol) and cyclopropylboronic acid (681.15 mg, 7.93 mmol). The mixture was stirred at 70 °C for 16 h under O_2. TLC (PE:EtOAc = 1:4) showed the reaction was completed. The reaction mixture was cooled to 23 °C. The solid was removed by filtration and the filtrate was concentrated under vacuum. The residue was purified by flash column (PE to 20% EtOAc in PE). The combined organic layers were concentrated under reduced pressure to afford the title compound (140 mg, 0.8425 mmol, 21.249% yield) as a brown oil.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.66 (s, 1H), 7.60 (s, 1H), 3.87 (s, 3H), 3.42-3.36 (m, 1H), 1.10-0.90 (m, 4H).

[0258]

1-cyclopropyl-1H-imidazole-4-carboxylic acid

To a solution of methyl 1-cyclopropyl-1H-imidazole-4-carboxylate (140 mg, 0.84 mmol) in THF (3 mL) and H_2O (1 mL) was added $LiOH·H_2O$ (0.06 mL, 1.1 mmol). The resulting mixture was stirred at 20-25 °C for 2 h to give white suspension. TLC (PE:EtOAc = 1:4) showed the reaction was completed (Rf = 0). The reaction mixture was concentrated directly. The residue was acidified with 1 M HCl aq. to pH = 6, then the combined organic layers were lyophilized to afford the title compound (120 mg, 0.7887 mmol, 93.618% yield) as a white solid.

[0259]

(1-cyclopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a solution of 1-cyclopropyl-1H-imidazole-4-carboxylic acid (120 mg, 0.79 mmol) in DMF (3 mL) were added at HATU (361.82 mg, 0.95 mmol), Et_3N (0.51 mL, 3.94mmol), (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (142.16 mg, 0.79 mmol). The resulting mixture was stirred at 20-25 °C for 14 hours. The residue was purified by prep-HPLC (HCl). The combined organic layers were concentrated and then lyophilized to afford the title compound (4.8 mg, 0.0137 mmol, 1.7347% yield) as a light yellow gum.

LC-MS Method1: 315.0 [$M+H^+$]

^{1}H NMR (400MHz, METHANOL-d_4) δ = 8.68 - 8.33 (m, 1H), 7.91 (br s, 1H), 4.10 - 3.84 (m, 3H), 3.60 (br d, *J*=4.8 Hz, 2H), 2.63 (s, 2H), 2.16 - 1.99 (m, 2H), 1.44 (br s, 1H), 1.24 (s, 7H), 1.07 (d, *J*=6.5 Hz, 4H).

[0260]

Example 5 (1-cyclobutyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

ethyl 1-cyclobutyl-1H-imidazole-4-carboxylate

A mixture of ethyl (2Z)-3-(dimethylamino)-2-isocyanoacrylate (400 mg, 2.38mmol) and cyclobutanamine (1.02mL, 11.89mmol) was heated at 50ºC for 16 hr. The mixture was concentrated in vacuum, then the residue was purified by flash column (0-100% EA in PE, 0.5% NH_3-H_2O) to give the title compound (420mg, 2.1624mmol, 90.923% yield) as yellow oil.

LC-MS Method1 0.568 min, MS (M/Z) 194.9 ($M + H^+$).

[0261]

1-cyclobutyl-1H-imidazole-4-carboxylic acid

To a mixture of ethyl 1-cyclobutyl-1H-imidazole-4-carboxylate (100 mg, 0.5100mmol) in THF (0.8578mL) and H_2O (1.0722mL) was added $LiOH·H_2O$ (0.09mL, 1.54mmol). The resulting suspension was then stirred at 20ºC for 3.5 hr. TLC (100%EA) showed new spot (Rf=0) and the reactant was consumed completely. The aqueous phase was washed with DCM (3mL×2) and acidified with 1N HCl to pH=2. The residual aqueous solution was lyophilized to give the title compound (160mg, 0.9628mmol, 187.01% yield) as pale yellow solid.

^{1}H NMR (400 MHz, D_2O) δ ppm 8.77 (s, 1H), 8.03 (s, 1H), 4.85-4.75 (m, 1H), 2.50-2.40 (m, 2H), 2.40-2.30 (m, 2H), 1.90-1.75 (m, 2H).

[0262]

(1-cyclobutyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a mixture of 1-cyclobutyl-1H-imidazole-4-carboxylic acid (110 mg, 0.5400mmol) in DMF (0.9736mL) were added HATU (247.8mg, 0.6500mmol), DIPEA (0.45mL, 2.7mmol) and (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (97.36mg, 0.5400mmol). The resulting mixture was stirred at 20ºC for 4 hr.

The reaction mixture was diluted with H_2O (5mL), extracted with EtOAc (5mL×2). The combined organic layers were separated, then dried over Na_2SO_4 and concentrated in vacuum to give crude oil. The crude oil was purified by prep-TLC (EA/MeOH=10/1), then Prep-HPLC (NH_3) and lyophilized to give the title compound (12.15mg, 0.0370mmol, 6.8494% yield) as pale yellow solid.

LC-MS Method1: 328.9 [$M+H^+$]

^{1}H NMR (400MHz, DMSO-d_6) δ = 8.03 (d, *J*=1.3 Hz, 1H), 7.99 (s, 1H), 4.96 - 4.89 (m, 1H), 4.75 (br d, *J*=12.0 Hz, 1H), 4.12 (br d, *J*=12.3 Hz, 1H), 3.99 (br d, *J*=9.0 Hz, 1H), 3.66 (br s, 1H), 2.83 (s, 2H), 2.57 (t, *J*=8.7 Hz, 4H), 2.25 (br d, *J*=11.3 Hz, 1H), 2.17 (br s, 1H), 2.00 - 1.90 (m, 2H), 1.60 - 1.57 (m, 1H), 1.44 (s, 6H)

[0263]

Example 6 [1-(bicyclo[1.1.1]pent-1-yl)-1H-imidazol-4-yl][(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

ethyl 1-(bicyclo[1.1.1]pent-1-yl)-1H-imidazole-4-carboxylate

To a mixture of ethyl (2Z)-3-(dimethylamino)-2-isocyanoacrylate (100 mg, 0.5900mmol) in 1-Butanol (0.40 mL) were added bicyclo[1.1.1]pentan-1-amine (284.42mg, 2.38mmol) and Et_3N (0.58mL, 4.46mmol). The resulting mixture was heated at 76ºC for 16 hr. The reaction mixture was diluted with H_2O (5mL) and extracted with EtOAc (5mL×3). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum to give the title compound (100 mg, crude product) as yellow oil.

[0264]

1-(bicyclo[1.1.1]pent-1-yl)-1H-imidazole-4-carboxylic acid

To a mixture of ethyl 1-(bicyclo[1.1.1]pent-1-yl)-1H-imidazole-4-carboxylate (100 mg, 0.4800mmol) in H_2O (1mL) and MeOH (0.80 mL) was added LiOH.H_2O (0.06mL, 0.9700mmol). The reaction was stirred at 25ºC for 16 hr. The aqueous phase was washed with DCM (3mL×2) and acidified with 1N HCl to pH = 2. The aqueous solution was lyophilized to give the title compound (50mg, 0.2806mmol, crude product) as pale yellow solid.

[0265]

[1-(bicyclo[1.1.1]pent-1-yl)-1H-imidazol-4-yl][(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a mixture of 1-(bicyclo[1.1.1]pent-1-yl)-1H-imidazole-4-carboxylic acid (59.54mg, 0.2800mmol) in DMF (0.50 mL) were added HATU (137.86mg, 0.3600mmol), DIPEA (0.18mL, 1.11mmol) and (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (50 mg, 0.2800mmol). The resulting mixture was stirred at 20ºC for 4 hr. The reaction mixture was diluted with H_2O (5mL) and extracted with EtOAc (5mL×2), The combined organic layers were separated, washed with brine (8mL), dried over Na_2SO_4 and concentrated in vacuum to give crude oil. The crude oil was purified by prep-HPLC (NH_3) to give the title compound (2.4mg, 0.0071mmol, 2.5416% yield) as yellow solid.

^{1}H NMR (400MHz, DMSO-d_6) δ = 7.76 (d, *J*=1.0 Hz, 1H), 7.71 (d, *J*=1.3 Hz, 1H), 4.53 (br d, *J*=11.8 Hz, 1H), 3.93 (br d, *J*=12.0 Hz, 1H), 3.81 (br dd, *J*=3.6, 11.9 Hz, 1H), 3.47 (br dd, *J*=3.6, 11.9 Hz, 1H), 2.65 (s, 2H), 2.24 (s, 6H), 2.08 - 1.93 (m, 3H), 1.40 (t, *J*=3.4 Hz, 1H), 1.26 - 1.25 (m, 1H), 1.25 (s, 5H).

[0266]

Example 7 (1-cyclopentyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

ethyl 1-cyclopentyl-1H-imidazole-4-carboxylate

A mixture of ethyl (2Z)-3-(dimethylamino)-2-isocyanoacrylate (200 mg, 1.19mmol) and cyclopentyl amine (0.58mL, 5.95mmol) was heated at 50ºC for 16 hr. The mixture was concentrated in vacuum. The residue was purified by flash column (0-100% EA in PE, 0.5% NH_3H_2O) to give the title compound (240mg, 1.1524mmol, 96.912% yield) as yellow oil. LC-MS Method1 0.668 min, MS (M/Z) 209.1 ($M + H^+$).

[0267]

1-cyclopentyl-1H-imidazole-4-carboxylic acid

To a mixture of ethyl 1-cyclopentyl-1H-imidazole-4-carboxylate (100 mg, 0.4800mmol) in THF (0.80 mL) and H_2O (1mL) was added $LiOH·H_2O$ (0.08mL, 1.44mmol). The reaction mixture was stirred at 25ºC for 3.5 hr. The aqueous phase was washed with DCM (3 mL × 2) and acidified with 1N HCl to pH=2. The residual aqueous solution was lyophilized to give the title compound (150mg, crude product) as pale yellow solid.

^{1}H NMR (400 MHz, D_2O) δ ppm 8.73 (s, 1H), 7.90 (s, 1H), 4.75-4.70 (m, 1H), 2.25-2.10 (m, 2H), 1.90-1.60 (m, 6H).

[0268]

(1-cyclopentyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a mixture of 1-cyclopentyl-1H-imidazole-4-carboxylic acid (60.38mg, 0.2800mmol) in DMF (0.50 mL) were added HATU (137.86mg, 0.3600mmol), DIPEA (0.18mL, 1.11mmol) and (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (50 mg, 0.2800mmol). The resulting mixture was stirred at 20ºC for 4 hr. The reaction mixture was diluted with H_2O (5mL) and extracted with EtOAc (5mL×2). The combined organic layers were separated, washed with brine (8mL), dried over Na_2SO_4 and concentrated in vacuum to give crude oil. The crude oil was purified by prep-TLC (EA/MeOH=10/1), then prep-HPLC (NH_3) and lyophilized to give the title compound (11mg, 0.0321mmol, 4.6614% yield) as white solid.

^{1}H NMR (400MHz, DMSO-d_6) δ = 7.78 (d, *J*=1.3 Hz, 1H), 7.73 (d, *J*=1.3 Hz, 1H), 4.66 - 4.51 (m, 2H), 3.93 (br d, *J*=12.3 Hz, 1H), 3.81 (br d, *J*=6.5 Hz, 1H), 3.47 (br d, *J*=11.8 Hz, 1H), 2.65 (s, 2H), 2.19 - 2.03 (m, 3H), 1.99 (br d, *J*=6.0 Hz, 1H), 1.79 (br s, 4H), 1.64 (br s, 2H), 1.25 (s, 7H)

[0269]

Example 8 (1-cyclohexyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

ethyl 1-cyclohexyl-1H-imidazole-4-carboxylate

A mixture of ethyl (2Z)-3-(dimethylamino)-2-isocyanoacrylate (200 mg, 1.19mmol) and cyclohexyl amine (0.68mL, 5.95mmol) was heated at 50 ºC for 16 hr. The mixture was concentrated in vacuum. The residue was purified by flash column (0-100% EA in PE, 0.5% NH_3H_2O) to give the title compound (280mg, 1.2597mmol, 105.93% yield) as yellow oil. LC-MS Method1 0.719 min, MS (m/z) 223.1 ($M + H^+$).

[0270]

1-cyclohexyl-1H-imidazole-4-carboxylic acid

To a mixture of ethyl 1-cyclohexyl-1H-imidazole-4-carboxylate (110 mg, 0.4900mmol) in THF (0.80 mL) and H_2O (1mL) was added $LiOH·H_2O$ (0.09mL, 1.48mmol), then stirred at 25ºC for 5 hr. TLC (100%EA) showed new spot (Rf=0) and the reactant was consumed completely. the aqueous phase was washed with DCM (3mL×2) and acidified with

1N HCl to pH=2. The residual aqueous solution was lyophilized to give the title compound (190mg, crude product) as pale yellow solid.

^{1}H NMR (400 MHz, Methanol-d_4) δ ppm 9.05 (s, 1H), 8.30 (s, 1H), 4.36-4.30 (m, 1H), 2.20-2.17 (m, 2H), 1.92-1.82 (m, 2H), 1.80-1.73 (m, 3H), 1.60-1.40 (m, 2H), 1.40-1.25 (m, 1H).

[0271]

(1-cyclohexyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a mixture of 1-cyclohexyl-1H-imidazole-4-carboxylic acid (64.27mg, 0.2800mmol) in DMF (0.50 mL) were added HATU (106.05mg, 0.2800mmol), DIPEA (0.18mL, 1.11mmol) and (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (50 mg, 0.2800mmol). The resulting mixture was stirred at 20ºC for 4 hr. The reaction mixture was diluted with H_2O (5mL) and extracted with EtOAc (5mL×2). The combined organic layers were separated, dried over Na_2SO_4 and concentrated in vacuum to give crude oil. The crude oil was purified by prep-TLC (EA/MeOH=10/1) then lyophilized to give the title compound (9.5mg, 0.0267mmol, 9.6077% yield) as white powder.

^{1}H NMR (400MHz, DMSO-d_6) δ = 7.77 (d, *J*=5.5 Hz, 2H), 4.58 (br d, *J*=12.0 Hz, 1H), 4.14 - 4.02 (m, 1H), 3.93 (br d, *J*=12.0 Hz, 1H), 3.80 (br d, *J*=8.5 Hz, 1H), 3.51 - 3.43 (m, 1H), 2.64 (s, 2H), 2.05 (br s, 1H), 1.95 (br d, *J*=12.3 Hz, 3H), 1.80 (br d, *J*=13.3 Hz, 2H), 1.72 - 1.61 (m, 3H), 1.41 - 1.29 (m, 3H), 1.25 (s, 7H)

[0272]

Example 9 [(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl][1-(1,1,1-trifluoropropan-2-yl)-1H-imidazol-4-yl]methanone

ethyl 1-(1,1,1-trifluoropropan-2-yl)-1H-imidazole-4-carboxylate

To a solution of 1,1,1-trifluoro-2-propanamine (403.4mg, 3.57mmol) in 2-MeTHF (3 mL, 1.19mmol) was added n-BuLi (1.43mL, 3.57mmol) at -78 °C. The reaction mixture was stirred at -78 °C for 15 min. Then ethyl (2Z)-3-(dimethylamino)-2-isocyanoacrylate (200 mg, 1.19mmol) was added. The reaction mixture was allowed to warm to 25 °C for 0.5 hr to give black solution. The reaction mixture was poured into EtOH (5 mL) and concentrated. The crude product was purified by flash column (PE to 100% EtOAc in PE). The afforded

residue was purified by prep-TLC (EtOAc) to give the title compound (50mg, 0.2117mmol, 17.802% yield) as brown oil.

[0273]

1-(1,1,1-trifluoropropan-2-yl)-1H-imidazole-4-carboxylic acid

To a solution of ethyl 1-(1,1,1-trifluoropropan-2-yl)-1H-imidazole-4-carboxylate (50 mg, 0.2100mmol) in THF (1.5mL) and H_2O (0.3mL, 16.67mmol) was added hydroxylithium hydrate (26.65mg, 0.6400mmol). The mixture was stirred at 20°C for 3h to give black solution. LCMS showed the starting material (50 mg, 0.2100mmol) was remained. The mixture was stirred at 40°C for 12h to give black solution. The reaction mixture was concentrated directly. The afforded H_2O layer was acidified with 1 N HCl aq. to pH=5-6 and lyophilized to give the title compound (30mg, 0.1441mmol, 68.086% yield) as brown solid.

[0274]

[(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl][1-(1,1,1-trifluoropropan-2-yl)-1H-imidazol-4-yl]methanone

To a solution of 1-(1,1,1-trifluoropropan-2-yl)-1H-imidazole-4-carboxylic acid (30 mg, 0.1400mmol) in DMF (1.5mL) were added HATU (66.12mg, 0.1700mmol), DIPEA (0.12mL, 0.7200mmol). The mixture was stirred for 30 min. Then (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (36.48mg, 0.1400mmol) was added to the mixture. The mixture was stirred at 25°C for 3h to give brown solution. The reaction mixture was concentrated directly. The residue was purified by prep-HPLC (NH_3) to give the title compound (16.87mg, 0.0455mmol, 17.802% yield) as white powder.

LC-MS Method1: 371.1 [$M+H^+$]

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.72 (1 H, s) 7.53 (1 H, s) 4.59 - 4.78 (2 H, m) 4.19 (1 H, dd, *J*=12.80, 5.77 Hz) 3.95 (1 H, dd, *J*=12.05, 7.91, 4.14 Hz) 3.63 (1 H, br d, *J*=12.30 Hz) 2.65 (2 H, s) 2.09 (1 H, m d, *J*=3.76 Hz) 2.01 (1 H, m d, *J*=6.53 Hz) 1.76 (3 H, d, *J*=7.28 Hz) 1.44 - 1.50 (1 H, m) 1.38 (6 H, s)

[0275]

Example 10 [(1R,5S,6S)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]{1-[(2S)-3-methylbutan-2-yl]-1H-imidazol-4-yl}methanone

(R)-2-methyl-N-[(1E)-2-methylpropylidene]-2-propanesulfinamide

To a solution of (*R*)-t-BuS(O)NH_2 (8403.83mg, 69.34mmol) in THF (36.369mL) were added 2-methylpropanal (6.3mL, 69.34mmol) and $Ti(OEt)_4$ (21.57mL, 104.01mmol) at 20 °C. The resulting mixture was stirred at 60 °C for 0.5 hours to give yellow solution. H_2O (3 mL) was added dropwise and it was stirred at 20 °C for 5mins, then it was filtered through a pad of celite and concentrated in vacuum to give the title compound (8330mg, 47.521mmol, 68.535% yield) as white solid. It was used directly for the next step.

LC-MS Method1 0.825 min, MS (m/z) 176.2 ($M + H^+$).

[0276]

(R)-2-methyl-N-[(2S)-3-methyl-2-butanyl]-2-propanesulfinamide

To a stirred solution of (R)-2-methyl-N-[(1E)-2-methylpropylidene]-2-propanesulfinamide (2500 mg, 14.26mmol) in THF (30mL) cooled to -40 °C was added MeMgBr (5.7mL, 17.11mmol) dropwise. The reaction was stirred at -40 °C for 3hr and warmed up to 20 ° C slowly over 13 hr. TLC (DCM/EA=6/1, RF=0.3) showed two new spot. H_2O (30 mL) was added and it was extracted with EtOAc (30 mLx2). The combined organic layer dried over Na_2SO_4 and concentrated in vacuum to give a yellow oil. The crude was purified by silica gel chromatography (PE/EA= 10/1 to 3/1) to give the title compound (2200 mg, 11.498mmol, 80.623% yield) as colorless oil.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 3.35-3.10 (m, 1H), 2.90-2.75 (m, 1H), 1.80-1.60 (m, 1H), 1.21 (d, J = 6.8 Hz, 3H), 1.20 (s, 9H), 0.886 (d, J = 6.8 Hz, 3H), 0.871 (d, J = 6.8 Hz, H).

[0277]

(2*S*)-3-methyl-2-butanamine

A solution of (R)-2-methyl-N-[(2S)-3-methyl-2-butanyl]-2-propanesulfinamide (2200 mg, 11.5mmol) in HCl/MeOH (10 mL, 40mmol) was stirred at 20 °C for 4hr to give a colorless solution. The reaction mixture was evaporated in vacuum to give a white solid. It was triturated with toluene/PE= 1/6 to give the title compound (1350 mg, 10.921 mmol) as white solid.

[0278]

ethyl 1-[(2S)-3-methylbutan-2-yl]-1H-imidazole-4-carboxylate

To a 5 mL microwave vial were added (2S)-3-methyl-2-butanamine (500 mg, 4.04mmol), ethyl (2Z)-3-(dimethylamino)-2-isocyanoacrylate (680.27mg, 4.04mmol), 1-Butanol (3mL) and Et_3N (0.84mL, 6.07mmol). The reaction mixture was irradiated with microwave at 130 °C for 1hr to give a brown solution. H_2O (30 mL) was added and it was

extracted with EtOAc (30 mLx2). The combined organic layer dried over Na_2SO_4 and concentrated in vacuum to give a yellow oil. The crude was purified by silica gel chromatography (PE/EA= 10/1 to 3/2) to give the title compound (161mg, 0.7657mmol, 18.931% yield) as brown oil.

LC-MS Method1 0.691 min, MS (m/z) 211.2 ($M + H^+$).

[0279]

1-[(2S)-3-methylbutan-2-yl]-1H-imidazole-4-carboxylic acid

A stirred solution of ethyl 1-[(2S)-3-methylbutan-2-yl]-1H-imidazole-4-carboxylate (150.0 mg, 0.7600mmol) in 1,4-Dioxane (3mL) was added a solution of $LiOH·H_2O$ (48.11mg, 1.15mmol). The reaction mixture was stirred at 20 ° C for 4hr to give a yellow solution. H_2O (10 mL) was added and it was extracted with EtOAc (10 mLx2). The H_2O phase was adjusted to 5 with 1M HCl aq. and lyophilized to give the title compound (110mg, 0.6037mmol, 78.98% yield) as brown solid.

LC-MS Method1 0.306 min, MS (m/z) 183.0 ($M + H^+$).

[0280]

[(1R,5S,6S)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]{1-[(2S)-3-methylbutan-2-yl]-1H-imidazol-4-yl}methanone

To a stirred solution of 1-[(2S)-3-methylbutan-2-yl]-1H-imidazole-4-carboxylic acid (100 mg, 0.5500mmol) and HATU (251.76mg, 0.6600mmol) in DMF (3mL) was added N-ethyl-N-isopropylpropan-2-amine (0.47mL, 2.74mmol). After stirred for 30 mins, (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (138.94mg, 0.5500mmol) was added and the reaction was stirred at 20 ° C for 16hr to give a yellow solution. H_2O (30 mL) was added and it was extracted with EtOAc (30 mLx2). The combined organic layer dried over Na_2SO_4 and concentrated in vacuum to give a yellow oil. The crude was purified by Prep-HPLC (NH_3) and lyophilized to give the title compound (108.71mg, 0.3156mmol, 57.509% yield) as white solid.

LC-MS Method1: 345.3 [$M+H^+$]

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.61 (d, J=1.00 Hz, 1H), 7.40 (d, J=1.25 Hz, 1H), 4.76 (br d, J=12.05 Hz, 1H), 4.18 (d, J=12.55 Hz, 1H), 3.94 (br dd, J=4.02, 11.80 Hz, 1H), 3.84 (quin, J=7.09 Hz, 1H), 3.61 (dd, J=4.27, 12.55 Hz, 1H), 2.64 (s, 2H), 2.07 (br dd, J=3.51, 7.28 Hz, 1H), 1.95-1.99 (m, 1H), 1.87-1.94 (m, 1H), 1.47 (d, J=6.78 Hz, 4H), 1.36 (s, 6H), 0.96 (d, J=6.78 Hz, 3H), 0.78 (d, J=6.53 Hz, 3H)

[0281]

Example 11 {1-[(2R)-butan-2-yl]-1H-imidazol-4-yl}[(1R,5S,6R)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

ethyl 1-[(2R)-butan-2-yl]-1H-imidazole-4-carboxylate

A mixture of ethyl (2Z)-3-(dimethylamino)-2-isocyanoacrylate (300 mg, 1.78mmol) and (2*R*)-2-butanamine (0.54mL, 5.35mmol) was stirred at 50 °C for 16 h to give brown mixture. TLC (PE:EA=1:1) showed new spot (Rf = 0.2) was detected. The mixture was concentrated to give a residue. The residue was purified by flash column (PE:EA=1:0 to 1:4) to afford the title compound (240mg, 1.2229mmol, 68.562% yield) as brown solid.
LC-MS Method1 0.586 min, MS (m/z) 196.9 ($M + H^+$).

[0282]

1-[(2*R*)-butan-2-yl]-1H-imidazole-4-carboxylic acid

To a mixture of ethyl 1-[(2R)-butan-2-yl]-1H-imidazole-4-carboxylate (240 mg, 1.22mmol) in THF (3mL) and H_2O (1.5mL) was added $LiOH·H_2O$ (0.11mL, 1.83mmol). The reaction mixture was stirred at 25 °C for 16 h to give yellow mixture. TLC (PE: EtOAc = 1: 1) showed most of the starting material was consumed. The reaction mixture was diluted with H_2O (15 mL) and extracted with EtOAc (8 mL × 5). The aqueous phase was acidified with 1 N HCl aq. to pH = 4. The resulting aqueous phase was dried in vacuum to afford the title compound (200 mg, 1.1891mmol, 97.236% yield) (crude) as yellow oil.

[0283]

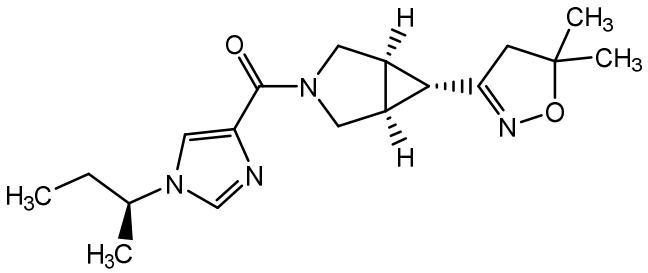
{1-[(2R)-butan-2-yl]-1H-imidazol-4-yl}[(1R,5S,6R)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a mixture of (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (70 mg, 0.3900mmol) in DMF (1mL) were added 1-[(2*R*)-butan-2-yl]-1H-imidazole-4-carboxylic acid (65.32mg, 0.3900mmol), DIPEA (0.26mL, 1.55mmol) and HATU (178.16mg, 0.4700mmol). The reaction mixture was stirred at 25 °C for 16 h to give brown mixture. The reaction mixture was concentrated in vacuo to give a residue. The residue was purified by prep-HPLC (NH_3). The afforded flows were combined, concentrated to remove most of CH_3CN and lyophilized to afford the title compound (4.09mg, 0.0108mmol, 2.7864% yield) as yellow solid.
LC-MS Method1: 331.1 [$M+H^+$]

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 8.91 (br s, 1 H), 8.19 (br s, 1 H), 4.31 - 4.44 (m, 1 H), 4.15 (br d, J=11.3 Hz, 1 H), 3.96 (br d, J=12.8 Hz, 1 H), 3.90 (br d, J=9.0 Hz, 1 H), 3.50 - 3.65 (m, 1 H), 2.65 (s, 2 H), 2.16 (br d, J=3.3 Hz, 1 H), 2.07 (br d, J=3.5 Hz, 1 H), 1.82 (quin, J=7.2 Hz, 2 H), 1.55 (t, J=3.4 Hz, 1 H), 1.48 (d, J=6.8 Hz, 3 H), 1.26 (s, 6 H), 0.76 (t, J=7.4 Hz, 3 H)

[0284]

Example 12 {1-[(2S)-butan-2-yl]-1H-imidazol-4-yl}[(1R,5S,6S)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone



ethyl 1-[(2S)-butan-2-yl]-1H-imidazole-4-carboxylate

A mixture of ethyl (2Z)-3-(dimethylamino)-2-isocyanoacrylate (300 mg, 1.78mmol) and (S)-butan-2-amine (0.54mL, 5.35mmol) was stirred at 50 ^{o}C for 12 h to give brown mixture. TLC(PE:EA=1:1) showed new spot(Rf = 0.2) was detected. The mixture was concentrated to give a residue. The residue was purified by flash column (PE:EA=1: 0 to 1: 4) to afford the title compound (160mg,0.8153mmol, 45.708% yield) as yellow solid.
LC-MS Method1 0.580 min, MS (m/z) 196.1 ($M + H^+$).

[0285]

1-[(2S)-butan-2-yl]-1H-imidazole-4-carboxylic acid

To a mixture of ethyl 1-[(2S)-butan-2-yl]-1H-imidazole-4-carboxylate (160 mg, 0.8200mmol) in THF (4mL) and H_2O (2mL) was added $LiOH·H_2O$ (0.07mL, 1.22mmol). The reaction mixture was stirred at 20 ^{o}C for 16 h to give yellow mixture. The reaction mixture was diluted with H_2O (15 mL) and extracted with EtOAc (8 mL × 5). The aqueous phase was acidified with 1 N HCl aq. to pH =4. The resulting aqueous phase was dried in vacuum to afford the title compound (150mg,0.8918mmol, 109.39% yield) (crude) as yellow solid.

[0286]

{1-[(2S)-butan-2-yl]-1H-imidazol-4-yl}[(1R,5S,6S)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a mixture of (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (70 mg, 0.3900mmol) in DMF (1.5mL) were added 1-[(2S)-butan-2-yl]-1H-imidazole-4-carboxylic acid (65.32mg, 0.3900mmol), DIPEA (0.26mL, 1.55mmol) and HATU (178.16mg, 0.4700mmol). The reaction mixture was stirred at 25 ^{o}C for 16 h to give brown mixture. LCMS showed the starting material was consumed. The reaction mixture was filtered. The filtrate was purified by prep-HPLC (NH_3). The afforded flows were combined, concentrated to remove most of CH_3CN and lyophilized to afford the title compound (34.59mg,0.1002mmol, 25.797% yield) as white solid.

LC-MS Method2 1.516 min, MS (m/z) 331.2 [$M+H^+$]

^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.64 (s, 1 H), 7.44 (s, 1 H), 4.76 (br d, J=12.0 Hz, 1 H), 4.19 (br d, J=12.5 Hz, 1 H), 4.02 - 4.10 (m, 1 H), 3.95 (br d, J=7.8 Hz, 1 H), 3.58 - 3.65 (m, 1 H), 2.64 (s, 2 H), 2.08 (br s, 1 H), 1.93 - 2.01 (m, 1 H), 1.93 - 2.01 (m, 1 H), 1.74 - 1.84 (m, 2 H), 1.49 (d, J=6.8 Hz, 3 H), 1.47 (br s, 1 H), 1.37 (s, 6 H), 0.85 (t, J=7.4 Hz, 3 H)

[0287]

Example13 [(1R,5S,6S)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]{1-[(2S)-4-methylpentan-2-yl]-1H-imidazol-4-yl}methanone

(R)-2-methyl-N-[(2E)-1,3-dimethylbutanylidene]-2-propanesulfinamide

To a mixture of 4-methyl-2-pentanone (1.25mL, 9.98mmol) in THF (10mL) were added (R)-2-methylpropane-2-sulfinamide (1210.06mg, 9.98mmol) and $Ti(OEt)_4$ (3414.54mg, 14.98mmol). The reaction mixture was stirred at 60 ^{o}C for 2 h to give colorless mixture. The reaction mixture was diluted with EtOAc (30 mL). The mixture was added to H_2O (10 mL) and stirred for 1 min to give yellow suspension. The suspension was filtered. The filtrate was washed with H_2O (20 mL × 3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to afford the title compound (900 mg, 4.4261mmol, 44.332% yield) as colorless oil.

LC-MS Method1 0.778 min, MS (m/z) 204.0 ($M + H^+$).

[0288]

(R)-2-methyl-N-[(2S)-4-methylpentan-2-yl]-2-propanesulfinamide

To a mixture of (R)-2-methyl-N-[(2E)-1,3-dimethylbutanylidene]-2-propanesulfinamide (900 mg, 4.43mmol) in THF (9mL) was added L-selectride (13.28mL, 13.28mmol) at 0°C. The reaction mixture was stirred at 25 °C for 2 h to give colorless

mixture. TLC (PE: EtOAc = 2:1) showed one new spot (Rf = 0.2) was detected. The reaction quenched by H_2O (3 mL). The reaction mixture was concentrated in vacuo to give a residue. The residue was purified by flash column (PE to 30% EtOAc in PE) to afford the title compound (260mg, 1.026mmol, 45.252% yield) as colorless oil.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 3.50-3.30 (m, 1H), 2.81 (d, J = 8.0 Hz, 1H), 1.80-1.60 (m, 1H), 1.60-1.30 (m, 2H), 1.28 (d, J = 6.4 Hz, 3H), 1.21 (s, 9H), 0.90 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H).

[0289]

(2*S*)-4-methyl-2-pentanamine hydrochloride

A solution of (R)-2-methyl-N-[(2S)-4-methylpentan-2-yl]-2-propanesulfinamide (610 mg, 2.97mmol) in MeOH/HCl (10 mL, 2.97mmol) was stirred at 25 ^{o}C for 2 h to give colorless mixture. The reaction mixture was concentrated in vacuo to give a residue. The residue was triturated with PE (20 mL) and dried in vacuo to give the title compound (240mg, 1.7436mmol, 58.698% yield) as white solid.

[0290]

ethyl 1-[(2S)-4-methylpentan-2-yl]-1H-imidazole-4-carboxylate

To a mixture of (2S)-4-methyl-2-pentanamine hydrochloride (240 mg, 1.74mmol) in 1-Butanol (2.5mL) were added ethyl (2Z)-3-(dimethylamino)-2-isocyanoacrylate (293.25mg, 1.74mmol) and Et_3N (0.34mL, 2.62mmol). The reaction mixture was stirred at 130 ^{o}C for 1 h with a microwave system to give brown mixture. TLC (PE: EtOAc = 1: 1) showed one new spot (Rf = 0.2) was detected. The reaction mixture was concentrated in vacuo to give a residue. The residue was purified by prep-TLC (PE: EtOAc = 1: 1) to afford the title compound (60mg, 0.2675mmol, 15.342% yield) as yellow oil.

LC-MS Method1 0.681 min, MS (m/z) 225.0 ($M + H^+$).

[0291]

1-[(2*S*)-4-methylpentan-2-yl]-1H-imidazole-4-carboxylic acid

To a mixture of ethyl 1-[(2S)-4-methylpentan-2-yl]-1H-imidazole-4-carboxylate (60 mg, 0.2700mmol) in THF (1.5mL) and H_2O (0.50 mL) was added $LiOH·H_2O$ (0.02mL, 0.4000mmol). The reaction mixture was stirred at 40 ^{o}C for 16 h to give a yellow mixture. TLC (PE: EtOAc = 1: 1) showed the starting material was consumed completely. The reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (3 mL × 2). The aqueous phase was acidified with 1 N HCl aq. to pH = 5 and lyophilized to afford the title compound (50mg, 0.2548mmol, 95.244% yield) as yellow solid.

[0292]

[(1R,5S,6S)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]{1-[(2S)-4-methylpentan-2-yl]-1H-imidazol-4-yl}methanone

To a mixture of 1-[(2*S*)-4-methylpentan-2-yl]-1H-imidazole-4-carboxylic acid (50 mg, 0.2500mmol) in Pyridine (2.5mL) was added EDCI (58.61mg, 0.3100mmol). The mixture was stirred at 25 °C for 10 min and followed by addition of (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (55.21mg, 0.2500mmol). The mixture was allowed to stirred at 25 °C for 16 h to give a yellow mixture. LCMS showed the starting material was consumed completely. The reaction mixture concentrated in vacuo to give a residue. The residue was purified by prep-HPLC (NH_3). The afforded flows were combined, concentrated to remove most of CH_3CN and lyophilized to afford the title compound (16.26mg, 0.0449mmol, 17.643% yield) as yellow solid.
LC-MS Method1: 359.2 [$M+H^+$]
^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.64 (s, 1 H), 7.46 (s, 1 H), 4.76 (br d, J=12.0 Hz, 1 H), 4.13 - 4.33 (m, 2 H), 3.95 (dd, J=12.0, 3.8 Hz, 1 H), 3.62 (dd, J=12.3, 4.0 Hz, 1 H), 2.64 (s, 2 H), 2.08 (br d, J=3.5 Hz, 1 H), 1.98 (br d, J=3.5 Hz, 1 H), 1.68 - 1.78 (m, 1 H), 1.50 - 1.57 (m, 2 H), 1.47 (d, J=6.8 Hz, 4 H), 1.38 (s, 6 H), 0.92 (d, J=6.5 Hz, 3 H), 0.87 (d, J=6.8 Hz, 3 H)

[0293]

Example 14 (1-((S)-1-cyclopropylethyl)-1H-imidazol-4-yl)((1R,5S,6S)-6-(5,5-dimethyl-4,5-dihydroisoxazol-3-yl)-3-azabicyclo[3.1.0]hexan-3-yl)methanone

ethyl 1-[(1*S*)-1-cyclopropylethyl]-1H-imidazole-4-carboxylate

Around bottom flask was charged with (S)-1-cyclopropylethanamine hydrochloride (903.81mg, 7.43mmol), Et_3N (1.57mL, 11.15mmol), ethyl (2Z)-3-(dimethylamino)-2-isocyanoacrylate (250 mg, 1.49mmol) and 1-Butanol (0.50 mL). The resulting mixture was stirred at 70°C for 36 hours to give yellow solution. The reaction mixture was poured into H_2O (30 mL) and extracted with EtOAc (30 mL x 2). The combined organic layers were washed with brine (30 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a yellow oil. The crude product was purified by flash column (PE to 100% EtOAc in PE) to give the title compound (100 mg, 0.4802mmol, 32.304% yield) as yellow oil.
LC-MS Method1 0.652 min, MS (m/z) 209.2 ($M + H^+$).

[0294]

1-[(1*S*)-1-cyclopropylethyl]-1H-imidazole-4-carboxylic acid

To a solution of ethyl 1-[(1S)-1-cyclopropylethyl]-1H-imidazole-4-carboxylate (150 mg, 0.7200mmol) in H_2O (0.50 mL), THF (0.50 mL), MeOH (0.50 mL) was added hydroxylithium hydrate (60.44mg, 1.44mmol). The resulting mixture was stirred at 20-25°C for 14 hours to give white suspension. The reaction mixture was poured into H_2O and extracted with EtOAc (20 mL x 4). The combined organic layers were washed with brine (20 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (150mg, crude product) as yellow oil.

LC-MS Method1 0.227 min, MS (m/z) 180.9 ($M + H^+$).

[0295]

(1-((S)-1-cyclopropylethyl)-1H-imidazol-4-yl)((1R,5S,6S)-6-(5,5-dimethyl-4,5-dihydroisoxazol-3-yl)-3-azabicyclo[3.1.0]hexan-3-yl)methanone

To a solution of 1-[(1S)-1-cyclopropylethyl]-1H-imidazole-4-carboxylic acid (70 mg, 0.3900mmol) in DMF (3mL) were added HATU (193.06mg, 0.5000mmol) and N-ethyl-N-isopropylpropan-2-amine (0.33mL, 1.94mmol) at 20 ºC for 30 min. (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (98.35mg, 0.3900mmol) was added. The resulting mixture was stirred at 20-25°C for 14 hours to give yellow solution. The reaction mixture was poured into sat. NH_4Cl aq. (50 mL) and extracted with EtOAc (50 mL x 4). The combined organic layers were washed with brine (50 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (FA) to give the title compound (10.65mg, 0.0311mmol, 8.0061%yield) as yellow oil.

LC-MS Method1: 343.1 [$M+H^+$]

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.70 (s, 1H), 7.64 (s, 1H), 4.63 (br d, *J*=10.0 Hz, 1H), 4.19 (br d, *J*=12.5 Hz, 1H), 3.95 (br dd, *J*=3.4, 11.2 Hz, 1H), 3.63 (br d, *J*=11.5 Hz, 1H), 3.48 - 3.43 (m, 1H), 2.64 (s, 2H), 2.08 (br s, 2H), 1.58 (d, *J*=6.8 Hz, 3H), 1.47 (t, *J*=3.4 Hz, 1H), 1.36 (s, 6H), 1.19 - 1.13 (m, 1H), 0.75 - 0.61 (m, 2H), 0.36 (q, *J*=4.9 Hz, 2H)

[0296]

Example 15 {1-[(1R)-1-cyclopropylethyl]-1H-imidazol-4-yl}[(1R,5S,6R)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

ethyl 1-[(1*R*)-1-cyclopropylethyl]-1H-imidazole-4-carboxylate

To a solution of ethyl (2Z)-3-(dimethylamino)-2-isocyanoacrylate (500 mg, 2.97mmol) in 1-Butanol (1 mL) was added (1*R*)-1-cyclopropylethanamine (253.14mg, 2.97mmol) at 20 °C. The reaction mixture was irradiated with microwave at 130 °C for 40 min to give a yellow solution. The reaction mixture was poured into sat. NH_4Cl aq. (50 mL) and extracted with EtOAc (50 mL x 4). The combined organic layers were washed with sat. aq. (50 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica column (PE to PE:EtOAc=1:1) to give the title compound (190 mg, 0.9123mmol, 30.689% yield) as yellow oil.

LC-MS Method1 0.608 min, MS (m/z) 209.0 ($M + H^+$).

[0297]

1-[(1*R*)-1-cyclopropylethyl]-1H-imidazole-4-carboxylic acid

To a solution of ethyl 1-[(1R)-1-cyclopropylethyl]-1H-imidazole-4-carboxylate (190 mg, 0.9100mmol) in H_2O (1.9mL), THF (1.9mL), MeOH (1.9mL) was added hydroxylithium hydrate (76.56mg, 1.82mmol) at 20 °C. The resulting mixture was stirred at 20 - 25°C for 2 hours to give white suspension. The reaction mixture was poured into H_2O and extracted with EtOAc (20 mL x 4). The combined organic layers were washed with sat. aq. (20 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (180mg, 0.9989mmol, 109.49% yield) as yellow oil.

LC-MS Method1 0.214 min, MS (m/z) 180.0 ($M + H^+$).

[0298]

{1-[(1R)-1-cyclopropylethyl]-1H-imidazol-4-yl}[(1R,5S,6R)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a solution of 1-[(1R)-1-cyclopropylethyl]-1H-imidazole-4-carboxylic acid (70 mg, 0.3900mmol) in DMF (2mL) were added HATU (193.06mg, 0.5000mmol) and N-ethyl-N-isopropylpropan-2-amine (0.33mL, 1.94mmol) at 20 °C. The reaction mixture was stirred for 30 min. (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (98.35mg, 0.3900mmol) was added. The resulting mixture was stirred at 20-25°C for 14 hours to give yellow solution. The reaction mixture was poured into sat. NH_4Cl aq. (50 mL) and extracted with EtOAc (50 mL x 4). The combined organic layers were washed with sat. aq. (50 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (FA) to give the title compound (14.08mg, 0.0411mmol, 10.585% yield) as yellow oil.

LC-MS Method1: 343.3 [M+H$^+$]

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.70 (d, *J*=1.3 Hz, 1H), 7.64 (s, 1H), 4.65 (br d, *J*=11.5 Hz, 1H), 4.19 (br d, *J*=12.3 Hz, 1H), 3.94 (br dd, *J*=3.8, 11.8 Hz, 1H), 3.62 (br dd, *J*=4.1, 12.4 Hz, 1H), 3.45 (dd, *J*=6.8, 8.8 Hz, 1H), 2.64 (s, 2H), 2.11 - 2.05 (m, 2H), 1.58 (d, *J*=6.8 Hz, 3H), 1.46 (t, *J*=3.4 Hz, 1H), 1.36 (s, 6H), 1.19 - 1.13 (m, 1H), 0.77 - 0.70 (m, 1H), 0.65 - 0.60 (m, 1H), 0.36 (q, *J*=5.4 Hz, 2H)

[0299]

Example 16 (1-((S)-1-cyclobutylethyl)-1H-imidazol-4-yl)((1R,5S,6S)-6-(5,5-dimethyl-4,5-dihydroisoxazol-3-yl)-3-azabicyclo[3.1.0]hexan-3-yl)methanone

(R)-N-[(E)-cyclobutylmethylene]-2-methyl-2-propanesulfinamide

To a mixture of cyclobutane aldehyde (1.07mL, 11.89mmol) in THF (15mL) were added (R)-2-methylpropane-2-sulfinamide (1.44g, 11.89mmol) and $Ti(OEt)_4$ (4065.62mg, 17.83mmol). The reaction mixture was stirred at 60 ^{o}C for 2 h to give yellow mixture. TLC(PE: EtOAc = 10: 1) showed the starting material was consumed completely, one new spot was(Rf = 0.2) detected. The reaction mixture was diluted with EtOAc(40 mL). The mixture was added to H_2O (10 mL) and stirred for 1 min to give white suspension. The suspension was filtered. The filtrate was washed with H_2O (20 mL × 3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to afford the title compound (1.77g,9.4501mmol, 79.494% yield) as colorless oil.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.12 (d, J = 4.8 Hz, 1H), 3.45-3.30 (m, 1H), 2.35-2.10 (m, 4H), 2.10-2.00 (m, 1H), 2.00-1.90 (m, 1H), 1.20 (s, 9H).

[0300]

(R)-N-[(1S)-1-cyclobutylethyl]-2-methyl-2-propanesulfinamide

To a solution of (R)-N-[(E)-cyclobutylmethylene]-2-methyl-2-propanesulfinamide (0.5g, 2.67mmol) in THF (6mL) was added chloro(methyl)magnesium (2.67mL, 8.01mmol) at -40 ^{o}C. The reaction mixture was stirred at -40 ^{o}C for 2 h to give yellow mixture. TLC (DCM: EtOAc = 1: 1) showed the starting material was consumed completely, one new spot(Rf = 0.3) was detected. The reaction mixture quenched with NH_4Cl (eq., 25 mL) and then extracted with EtOAc (15 mL × 3). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to give a

residue. The residue was purified by flash column (DCM to 20 % EtOAc in DCM) to afford the title compound (360mg, 1.7704mmol, 66.32% yield) as colorless oil.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 3.35-3.15 (m, 1H), 2.84 (d, J = 8.0 Hz, 1H), 2.40-2.20 (m, 1H), 2.10-1.90 (m, 1H), 2.00-1.90 (m, 1H), 1.90-1.60 (m, 4H), 1.20 (s, 9H), 1.18 (d, J = 6.8 Hz, 3H).

[0301]

(1*S*)-1-cyclobutylethanamine hydrochloride

A solution of (R)-N-[(1S)-1-cyclobutylethyl]-2-methyl-2-propanesulfinamide (360 mg, 1.77mmol) in MeOH/HCl (0.44mL, 1.77mmol) was stirred at 25 °C for 2 h to give colorless mixture. TLC (DCM: EtOAc = 1: 1) showed the starting material was consumed completely. The reaction mixture was concentrated in vacuo to give the title compound (330mg, 2.4329mmol, 137.42% yield) as yellow solid.

[0302]

ethyl 1-[(1*S*)-1-cyclobutylethyl]-1H-imidazole-4-carboxylate

To a mixture of (1S)-1-cyclobutylethanamine hydrochloride (240 mg, 1.77mmol) in 1-Butanol (2mL) were added ethyl (2Z)-3-(dimethylamino)-2-isocyanoacrylate (297.59mg, 1.77mmol) and Et_3N (0.37mL, 2.65mmol). The reaction mixture was stirred at 130 °C for 1 h used MW to give brown mixture. LCMS showed the starting material was consumed completely. TLC (PE: EtOAc = 2:1) showed one new spot (Rf= 0.2) was detected. The reaction mixture was concentrated in vacuo to give a residue. The residue was purified by prep-TLC (100% EtOAc) to afford the title compound (36mg, 0.1620mmol, 9.1533% yield) as brown solid.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.61 (s, 1H), 7.50 (s, 1H), 4.37 (q, J = 6.8 Hz, 2H), 4.15-4.00 (m, 1H), 2.70-2.50 (m, 1H), 2.20-2.10 (m, 1H), 2.00-1.60 (m, 5H), 1.40 (d, J = 6.8 Hz, 3H), 1.39 (t, J = 6.8Hz, 3H).

[0303]

1-[(1*S*)-1-cyclobutylethyl]-1H-imidazole-4-carboxylic acid

To a mixture of ethyl 1-[(1*S*)-1-cyclobutylethyl]-1H-imidazole-4-carboxylate (36 mg, 0.1600mmol) in THF (1.5mL) and H_2O (0.50 mL) was added $LiOH·H_2O$ (0.01mL, 0.2400mmol). The reaction mixture was stirred at 25 °C for 16 h to give brown mixture. TLC(PE: EtOAc = 1: 1) showed the starting material was consumed completely. The reaction mixture was diluted with H_2O (4 mL) and extracted with EtOAc (2 mL ×2). The

aqueous phase was acidified with 1 N HCl aq. to pH = 4 and lyophilized to the title compound (31mg, 0.1596mmol, 98.547% yield) as brown solid.

^{1}H NMR (400MHz, DMSO-d_6) δ = 7.91 (s, 1H), 7.84 (s, 1H), 4.40-4.20 (m, 1H), 2.75-2.65 (m, 1H), 2.15-2.00 (m, 1H), 1.95-1.60 (m, 5H), 1.38 (d, J = 6.8 Hz, 3H).

[0304]

(1-((S)-1-cyclobutylethyl)-1H-imidazol-4-yl)((1R,5S,6S)-6-(5,5-dimethyl-4,5-dihydroisoxazol-3-yl)-3-azabicyclo[3.1.0]hexan-3-yl)methanone

To a solution of 1-[(1*S*)-1-cyclobutylethyl]-1H-imidazole-4-carboxylic acid (30 mg, 0.1500mmol) in DMF (1.5mL) were added HATU (70.86mg, 0.1900mmol), DIPEA (99.81mg, 0.7700mmol). The mixture was stirred for 10 min. Then (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (39.1mg, 0.1500mmol) was added to the mixture. The mixture was stirred at 25°C for 12h to give brown solution. The reaction mixture was concentrated directly. The residue was purified by prep-HPLC (NH_3) to give the title compound (25.52mg, 0.0716mmol, 46.352% yield) as brown solid.

LC-MS Method1: 357.1 [$M+H^+$]

^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.61 (1 H, d, J=1.25 Hz), 7.42 (1 H, d, J=1.25 Hz), 4.76 (1 H, d, J=12.05 Hz), 4.19 (1 H, d, J=12.55 Hz), 3.99 - 4.08 (1 H, m), 3.94 (1 H, dd, J=12.17, 4.14 Hz), 3.61 (1 H, dd, J=12.55, 4.27 Hz), 2.64 (2 H, s), 2.53 - 2.63 (1 H, m), 2.05 - 2.18 (2 H, m), 1.94 - 2.01 (1 H, m), 1.85 - 1.94 (2 H, m), 1.67 - 1.84 (3 H, m), 1.46 (1 H, br s), 1.36 - 1.41 (9 H, m)

[0305]

Example 17 {1-[(1R)-1-cyclobutylethyl]-1H-imidazol-4-yl}[(1R,5S,6R)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

ethyl 1-[(1R)-1-cyclobutylethyl]-1H-imidazole-4-carboxylate

To a solution of ethyl (2Z)-3-(dimethylamino)-2-isocyanoacrylate (100 mg, 0.5900mmol) in Et_3N (0.58mL, 4.46mmol) was added the mixture of (1R)-1-cyclobutylethanamine hydrochloride (241.94mg, 1.78mmol) in 1-Butanol (0.30 mL). The resulting mixture was stirred at 70 °C for 16 hours to give yellow mixture. TLC (PE: EtOAc= 1: 1) showed one new spot (Rf = 0.3) was detected. The reaction mixture was concentrated in

vacuo to give a residue. The residue was purified by prep-TLC (PE: EtOAc = 1: 1) to afford the title compound (25mg, 0.1125mmol, 18.916% yield) as yellow oil.

LC-MS Method1 0.667 min, MS (m/z) 222.9 ($M + H^+$).

[0306]

1-[(1R)-1-cyclobutylethyl]-1H-imidazole-4-carboxylic acid

To a mixture of ethyl 1-[(1R)-1-cyclobutylethyl]-1H-imidazole-4-carboxylate (25 mg, 0.1100mmol) in THF (0.75 mL) and H_2O (0.25 mL) was added $LiOH \cdot H_2O$ (0.01mL, 0.1700mmol). The reaction mixture was stirred at 40 °C for 16 h to give yellow mixture. TLC (PE: EtOAc = 1:1) showed starting material was consumed completely. The reaction mixture was diluted with H_2O (6 mL) and concentrated to remove most of THF. The aqueous phase was acidified with 1 N HCl aq. to pH = 5 and lyophilized to afford the title compound (21mg, 0.1081mmol, 96.131% yield) as yellow solid.

LC-MS Method1 0.414 min, MS (m/z) 194.9 ($M + H^+$).

[0307]

{1-[(1R)-1-cyclobutylethyl]-1H-imidazol-4-yl}[(1R,5S,6R)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a mixture of 1-[(1R)-1-cyclobutylethyl]-1H-imidazole-4-carboxylic acid (21 mg, 0.1100mmol) in DMF (0.50 mL) were added HATU (49.6mg, 0.1300mmol) and DIPEA (0.09mL, 0.5400mmol). The mixture was stirred at 50 °C for 30 min and followed by addition of (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (29.23mg, 0.1600mmol). The mixture was stirred at 25 °C for 16 h to give a yellow mixture. The reaction mixture was purified by prep-HPLC (NH_3). The afforded flows were combined, concentrated to remove most of CH_3CN and lyophilized to afford the title compound (1.64mg, 0.0046mmol, 4.2553% yield) as yellow solid.

LC-MS Method1: 357.1 [$M+H^+$]

^{1}H NMR (400 MHz, METHANOL-d4) δ ppm 7.73 (s, 1 H), 7.68 (s, 1 H), 4.42 (br d, J=11.3 Hz, 1 H), 4.18 - 4.29 (m, 1 H), 4.11 (br d, J=12.8 Hz, 1 H), 3.94 (br dd, J=12.2, 3.9 Hz, 1 H), 3.60 (br dd, J=12.4, 3.6 Hz, 1 H), 2.73 (s, 2 H), 2.62 - 2.71 (m, 1 H), 2.10 - 2.20 (m, 2 H), 2.03 - 2.10 (m, 1 H), 1.78 - 1.94 (m, 4 H), 1.72 (br t, J=8.5 Hz, 1 H), 1.49 (t, J=3.4 Hz, 1 H), 1.40 (d, J=6.5 Hz, 3 H), 1.34 (s, 6 H), 0.89 (br d, J=9.8 Hz, 1 H)

[0308]

Example 18 (1-((S)-1-cyclopentylethyl)-1H-imidazol-4-yl)((1R,5S,6S)-6-(5,5-dimethyl-4,5-dihydroisoxazol-3-yl)-3-azabicyclo[3.1.0]hexan-3-yl)methanone

(1-((S)-1-cyclopentylethyl)-1H-imidazol-4-yl)((1R,5S,6S)-6-(5,5-dimethyl-4,5-dihydroisoxazol-3-yl)-3-azabicyclo[3.1.0]hexan-3-yl)methanone

To a solution of 1-[(1S)-1-cyclopentylethyl]-1H-imidazole-4-carboxylic acid (50 mg, 0.2400mmol, prepared with the same protocol described in Example 19 using (R)-2-methylpropane-2-sulfinamide instead of (S)-2-methylpropane-2-sulfinamide) in DMF (5mL) were added HATU (137.68mg, 0.3600mmol) and Et_3N (0.12mL, 0.9600mmol). The mixture was stirred at 25°C for 30min. Then (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (43.28mg, 0.2400mmol) was added. The resulting mixture was stirred at 25°C for 3 hours to give a brown solution. The reaction mixture was concentrated in vacuum to remove most of DMF. The crude product was purified by Prep-HPLC (NH_3) and lyophilized to give the title compound (70mg, 0.1889mmol, 78.697% yield) as a white solid.

LC-MS Method1: 371.3 [$M+H^+$]

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.65 (d, *J*=1.1 Hz, 1H), 7.44 (d, *J*=0.9 Hz, 1H), 4.76 (br d, *J*=11.9 Hz, 1H), 4.19 (br d, *J*=12.6 Hz, 1H), 3.95 (br dd, *J*=3.9, 11.9 Hz, 1H), 3.87 (qd, *J*=6.8, 9.5 Hz, 1H), 3.62 (br dd, *J*=4.1, 12.5 Hz, 1H), 3.66 - 3.57 (m, 1H), 2.64 (s, 2H), 2.20 - 2.04 (m, 2H), 2.02 - 1.94 (m, 1H), 1.88 (dtd, *J*=3.9, 7.6, 11.7 Hz, 1H), 1.64 - 1.55 (m, 3H), 1.49 (d, *J*=6.8 Hz, 6H), 1.38 (s, 6H), 1.23 (qd, *J*=8.8, 12.6 Hz, 1H), 1.14 - 1.01 (m, 1H)

[0309]

Example 19 {1-[(1R)-1-cyclopentylethyl]-1H-imidazol-4-yl}[(1R,5S,6R)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

(S)-N-[(E)-cyclopentylmethylene]-2-methyl-2-propanesulfinamide

To a mixture of cyclopentyl aldehyde in THF (20 mL) were added (S)-2-methylpropane-2-sulfinamide (2.47 g, 20.38 mmol), titanium(IV) ethanolate (6.97 g, 30.57 mmol). The suspension was stirred at 20 °C for 16 hr. The reaction mixture was diluted with EtOAc(60 mL). The mixture was added to H_2O (10 mL) and stirred for 1 min to give white suspension. The suspension was filtered. The filtrate was washed with H_2O (30 mLx3), dried

with anhydrous Na_2SO_4, filtered and concentrated in vacuum to afford the title compound (3.6 g, crude) as yellow liquid.

LC-MS Method1: 0.833 min, MS (m/z): 201.9 ($M + H^+$).

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.92 (t, d = 4.8 Hz, 1H), 2.90-2.80 (m, 1H), 1.90-1.75 (m, 3H), 1.75-1.50 (m, 5H), 1.15 (s, 9H).

[0310]

(S)-N-[(1R)-1-cyclopentylethyl]-2-methyl-2-propanesulfinamide

To a mixture of (S)-N-[(E)-cyclopentylmethylene]-2-methyl-2-propanesulfinamide in THF (20 mL) was added MeMgCl (742.96 mg, 9.93 mmol, 3.31 mL) dropwise for 10 min at -40 °C under N_2. The suspension was stirred at 20 °C for 16 hr. The residue was diluted with NH_4Cl (15 mL), extracted with EtOAc (30 mLx4), washed with saturated NaCl (30 mLx2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The solution was purified by flash column (PE to 30% EtOAc in PE) to afford the title compound (595 mg, crude) as yellow liquid.

LC-MS Method1: 0.827 min, MS (m/z): 218 ($M + H^+$).

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 3.20-3.05 (m, 1H), 2.82 (brd, J = 8.4 Hz, 1H), 1.90-1.40 (m, 8H), 1.20 (d, J = 7.2 Hz, 3H), 1.14 (s, 9H).

[0311]

(1R)-1-cyclopentylethanamine hydrochloride

To a mixture of (S)-N-[(1R)-1-cyclopentylethyl]-2-methyl-2-propanesulfinamide was added MeOH/HCl (5 mL). The suspension was stirred at 25 ℃ for 1 hr. The residue was concentrated in vacuum to afford the title compound (257 mg, crude) as yellow solid.

[0312]

ethyl 1-[(1R)-1-cyclopentylethyl]-1H-imidazole-4-carboxylate

To a mixture of (1R)-1-cyclopentylethanamine hydrochloride (52.0 mg, 0.35 mmol) was added 1-Butanol (0.5 mL). Then ethyl (2Z)-3-(dimethylamino)-2-isocyanoacrylate (58.44 mg, 0.35 mmol), Et_3N (52.64 mg, 0.52 mmol, 0.07 mL) was added into the solution. The suspension was subjected to reaction in microwave reactor (time: 1 hr, temp: 130 °C). The residue was concentrated in vacuum to afford the title compound (77 mg, crude) as yellow oil.

LC-MS Method1: 0.690 min, MS (m/z): 237.0 ($M + H^+$).

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.57 (s, 1H), 7.43 (s, 1H), 4.30 (q, J = 6.8 Hz, 2H), 3.80-3.70 (m, 1H), (q, J = 7.2 Hz, 2H), 1.70-1.40 (m, 8H), 1.42 (d, J = 6.8 Hz, 2H), 1.32 (t, J = 7.2 Hz, 3H).

[0313]

1-[(1R)-1-cyclopentylethyl]-1H-imidazole-4-carboxylic acid

To a mixture of ethyl 1-[(1R)-1-cyclopentylethyl]-1H-imidazole-4-carboxylate in H_2O (0.5 mL) and THF (1.5 mL) was added $LiOH \cdot H_2O$ (20.5 mg, 0.49 mmol, 1.5 *eq*). The suspension was stirred at 20 °C for 2 hr. The residue was diluted with H_2O (1 mL), extracted with EtOAc (5mLx4). The afforded H_2O layer was acidified with 1 N HCl aq. to pH=5. The combined organic layers were concentrated and then lyophilized to afford the title compound (39 mg, crude) as yellow solid.

LC-MS Method1: 0.571 min, MS (m/z): 209 ($M + H^+$).

[0314]

{1-[(1R)-1-cyclopentylethyl]-1H-imidazol-4-yl}[(1R,5S,6R)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a mixture of 1-[(1R)-1-cyclopentylethyl]-1H-imidazole-4-carboxylic acid (30.0 mg, 0.14 mmol) in Pyridine (0.5 mL) were added EDCI (27.6 mg, 0.14 mmol) and(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (26.0 mg, 0.14mmol). The suspension was stirred at 20 °C for 16 hr. The reaction mixture was quenched with H_2O (10 mL). The residue was diluted with EtOAc (20 mLx3), washed with saturated NaCl (5 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The solution was purified by prep-HPLC (NH_3) and lyophilized to afford the title compound (1.88 mg, 3.5% yield) as white solid.

LC-MS Method1: 3.486min, MS (m/z): 371.3 ($M + H^+$).

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.58 (d, *J*=1.25 Hz, 1 H), 7.36 (s, 1 H), 4.70 (br d, *J*=12.30 Hz, 1 H), 4.12 (d, *J*=12.30 Hz, 1 H), 3.87 (br d, *J*=12.30 Hz, 1 H), 3.79 (dd, *J*=9.41, 6.65 Hz, 1 H), 3.54 (br d, *J*=8.53 Hz, 1 H), 2.57 (s, 2 H), 1.80 - 2.10 (m, 4 H), 1.51 - 1.60 (m, 2 H), 1.41 (br d, *J*=6.78 Hz, 9 H), 1.30 (s, 7 H), 1.18 (s, 7 H).

[0315]

Example 20 [(1R,5S,6S)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]{1-[(1S)-1-(tetrahydro-2H-pyran-4-yl)ethyl]-1H-imidazol-4-yl}methanone

(R)-2-methyl-N-[(E)-tetrahydro-2H-pyran-4-ylmethylene]-2-propanesulfinamide

A 100 mL round-bottom flask was charged with tetrahydro-2H-pyran-4-carbaldehyde (5000 mg, 43.81mmol), (R)-2-methylpropane-2-sulfinamide (5309.27mg, 43.81mmol), $Ti(OEt)_4$ (13.5mL, 65.71mmol) and THF (25mL). The reaction was heated at 60 ^oC for 30min under N_2 protection to give a yellow solution. TLC (PE/EA= 3/1 , Rf =0.4) showed a new spot was detected. H_2O (3 mL) was added dropwise and it was stirred at 20 ^oC for 5mins, then it was filtrated through a pad of celite and the filtrate concentrated in vacuum to give the title compound (8700 mg, 40.031mmol, 91.383% yield) as white solid.
LC-MS Method1 0.745 min, MS (m/z) 218.1 ($M + H^+$).

[0316]

(R)-2-methyl-N-[(1S)-1-(tetrahydro-2H-pyran-4-yl)ethyl]-2-propanesulfinamide

A round-bottom flask charged with (R)-2-methyl-N-[(E)-tetrahydro-2H-pyran-4-ylmethylene]-2-propanesulfinamide (3000 mg, 13.8mmol) and THF (30mL) was cooled to -48 ^oC, MeMgBr (5.06mL, 15.18mmol) was added dropwise to the mixture. The reaction was stirred at this temperature for 2hr to give a yellow solution. H_2O (30 mL) was added and it was extracted with EtOAc (30 mLx2). The combined organic layer dried over Na_2SO_4 and concentrated in vacuum to give a yellow oil. The crude was purified by silica gel chromatography (DCM/EA= 3/1 to 1/1) to give the title compound (1700 mg, 7.2846mmol, 52.772% yield) as colorless oil.
^1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 4.05-3.95 (m, 2H), 3.40 (dt, J = 4.0, 1.6 Hz, 2H), 3.25-3.10 (m, 1H), 2.90 (d, J = 7.6 Hz, 1H), 1.85-1.75 (m, 1H), 1.70-1.20 (m, 4H), 1.29 (d, J = 6.8 Hz, 3H), 1.25 (s, 9H).

[0317]

(1S)-1-(tetrahydro-2H-pyran-4-yl)ethanamine hydrochloride

A 100ml round-bottom flask was charged with (R)-2-methyl-N-[(1S)-1-(tetrahydro-2H-pyran-4-yl)ethyl]-2-propanesulfinamide (1700 mg, 7.28 mmol) and HCl/MeOH (10 mL, 7.28 mmol). The reaction mixture was stirred at 25 ^oC for 3hr to give a colorless oil. It was evaporated in vacuum to give the title compound (1250mg, 7.5456mmol, 103.58% yield) as colorless oil.

[0318]

ethyl 1-[(1S)-1-(tetrahydro-2H-pyran-4-yl)ethyl]-1H-imidazole-4-carboxylate

A microwave tube was charged with ethyl (2Z)-3-(dimethylamino)-2-isocyanoacrylate (400.29mg, 2.38mmol), (1S)-1-(tetrahydro-2H-pyran-4-yl)ethanamine hydrochloride (394.27mg, 2.38mmol), triethylamine (0.5mL, 3.57mmol) and 1-Butanol

(0.6004mL). It was irradiated with microwave at 130 °C for 1hr to give a brown solution. H_2O (15 mL) was added and it was extracted with EtOAc (15mLx2). The combined organic layer dried over Na_2SO_4 and concentrated in vacuum to give a yellow oil. The crude was purified by silica gel chromatography (PE/EA= 1/1 to 0/1) to give the title compound (135mg, 0.5351mmol, 22.481% yield) as yellow oil.

LC-MS Method1 0.638, MS (m/z) 253.2 ($M + H^+$).

[0319]

1-[(1S)-1-(tetrahydro-2H-pyran-4-yl)ethyl]-1H-imidazole-4-carboxylic acid

A 100 mL round-bottom flask was charged with ethyl 1-[(1S)-1-(tetrahydro-2H-pyran-4-yl)ethyl]-1H-imidazole-4-carboxylate (130 mg, 0.5200mmol), hydroxylithium hydrate (43.24mg, 1.03mmol), THF (3mL). It was stirred at 20 °C for 3hr to give a yellow solution. H_2O (15 mL) was added and it was extracted with EtOAc (15 mLx2). The aqueous phase was lyophilized to give the title compound (110mg, 0.4905mmol, 95.199% yield) as yellow solid. It was directly used in the next step.

[0320]

[(1R,5S,6S)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]{1-[(1S)-1-(tetrahydro-2H-pyran-4-yl)ethyl]-1H-imidazol-4-yl}methanone

To a mixture of 1-[(1S)-1-(tetrahydro-2H-pyran-4-yl)ethyl]-1H-imidazole-4-carboxylic acid (110 mg, 0.4900mmol) and HATU (243.77mg, 0.6400mmol) in DMF (5mL) was added N-ethyl-N-isopropylpropan-2-amine (0.59mL, 3.43mmol). After stirred for 30min, (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (384.3mg, 0.7400mmol) was added. The reaction mixture was stirred for another 16hr to give a yellow solution. H_2O (30 mL) was added and it was extracted with EtOAc (30 mLx2). The combined organic layer dried over Na_2SO_4 and concentrated in vacuum to give a yellow oil. The crude was purified by Prep-HPLC (NH_3). The afforded flows were concentrated in vacuum to remove most of CH_3CN and lyophilized to give the title compound (9.57mg, 0.0248mmol, 5.0482% yield) as white solid.

LC-MS Method1: 387.3 [$M+H^+$]

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.12 - 1.17 (m, 1 H) 1.23 (dd, *J*=12.30, 4.02 Hz, 1 H) 1.37 (s, 6 H) 1.46 (br d, *J*=3.01 Hz, 1 H) 1.50 (d, *J*=6.78 Hz, 3 H) 1.68 (br d, *J*=13.05 Hz, 1 H) 1.78 (br d, *J*=8.78 Hz, 1 H) 1.94 - 1.99 (m, 1 H) 2.04 - 2.11 (m, 1 H) 2.63 (s, 2 H) 3.25 (td, *J*=11.80, 2.26 Hz, 1 H) 3.36 (td, *J*=11.92, 2.01 Hz, 1 H) 3.61 (dd, *J*=12.42,

3.89 Hz, 1 H) 3.81 - 3.88 (m, 1 H) 3.92 (br t, *J*=11.80 Hz, 2 H) 4.02 (br dd, *J*=11.54, 3.76 Hz, 1 H) 4.18 (br d, *J*=13.05 Hz, 1 H) 4.75 (dd, *J*=12.05, 4.27 Hz, 1 H) 7.40 (s, 1 H) 7.62 (s, 1 H)

[0321]

Example 21 [(1R,5S,6S)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]{1-[(1S)-1-phenylethyl]-1H-imidazol-4-yl}methanone

ethyl 1-[(1S)-1-phenylethyl]-1H-imidazole-4-carboxylate

A mixture of ethyl isocyanoacetate (1.0 g, 8.84mmol) and 1,1-dimethoxy-N,N-dimethylmethanamine (1.53mL, 11.49mmol) was stirred at 0 °C for 3 h. TLC (PE:EA=3: 1) showed ethyl 2-isocyanoacetate (1.g, 8.84mmol) (Rf=0.6) was consumed completely and new spot (Rf=0.4) was detected. (S)-1-phenylethanamine (4.5mL, 35.36mmol) was added to the mixture. The obtained mixture was stirred at 50°C for 16 h to give brown mixture. TLC (PE:EA=1: 1) showed new spot(Rf = 0.1) was detected. The mixture was concentrated to give a residue. The residue was purified by flash column (PE: EA=1:0 to 0:1) to afford the title compound (0.9300g, 3.807mmol, 43.06% yield)(PE:EA=1:1,Rf=0.1) as a brown oil.
LC-MS Method1 0.685 min, MS (m/z) 244.9 ($M + H^+$).

[0322]

1-[(1S)-1-phenylethyl]-1H-imidazole-4-carboxylic acid

To a mixture of ethyl 1-[(1S)-1-phenylethyl]-1H-imidazole-4-carboxylate (930 mg, 3.81mmol) in THF (6mL) and H_2O (3mL) was added $LiOH \cdot H_2O$ (0.33mL, 5.71mmol). The reaction mixture was stirred at 20 ºC for 16 h to give yellow mixture. TLC (PE:EtOAc = 1:1) showed the starting material was consumed completely. The reaction mixture was diluted with H_2O (15 mL) and extracted with EtOAc (8 mL × 5). The aqueous phase was acidified with 1 N HCl aq. to pH = 4. The resulting aqueous phase was dried in vacuum to afford the title compound (900 mg, 4.162mmol, 109.33% yield) (crude) as brown solid.
LC-MS Method1 0.539 min, MS (m/z) 216.9 ($M + H^+$).

[0323]

[(1R,5S,6S)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]{1-[(1S)-1-phenylethyl]-1H-imidazol-4-yl}methanone

To a mixture of (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (100 mg, 0.5500mmol) in DMF (2mL) were added 1-[(1S)-1-phenylethyl]-1H-imidazole-4-carboxylic acid (143.96mg, 0.6700mmol), DIPEA

(0.37mL, 2.22mmol) and HATU (254.51mg, 0.6700mmol). The reaction mixture was stirred at 25 ^{o}C for 16 h to give brown mixture. TLC (DCM: MeOH = 40: 1, a drop of Et_3N) showed one new spot (Rf = 0.5) was detected. The reaction mixture was diluted with H_2O (10 mL). The resulting mixture was extracted with EtOAc (5 mL×4). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to give a residue. The residue was purified by prep-TLC (DCM: MeOH = 40: 1, 1% Et_3N in the solvent) to give crude product. The crude product was purified by prep-HPLC (NH_3). The afforded flows were combined, concentrated to remove most of CH_3CN and lyophilized to afford the title compound (3.85mg, 0.0102mmol, 1.8336% yield) as white solid.

LC-MS Method1: 379.1 [$M+H^+$]

^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.67 (br s, 1 H), 7.48 (s, 1 H), 7.31 - 7.40 (m, 3 H), 7.18 (br d, J=6.5 Hz, 2 H), 5.35 (q, J=6.9 Hz, 1 H), 4.75 (br d, J=8.0 Hz, 1 H), 4.18 (br d, J=12.3 Hz, 1 H), 3.88 - 4.01 (m, 1 H), 3.61 (br d, J=8.8 Hz, 1 H), 2.64 (s, 2 H), 2.07 (br s, 1 H), 1.98 (br s, 1 H), 1.88 (d, J=7.0 Hz, 3 H), 1.46 (br s, 1 H), 1.38 (s, 6 H), 1.26 (s, 1 H)

[0324]

Example 22 2-[(1S)-1-(4-{[(1R,5S,6S)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]carbonyl}-1H-imidazol-1-yl)ethyl]benzonitrile

(R)-N-[(E)-(2-bromophenyl)methylene]-2-methyl-2-propanesulfinamide

A 100 mL round-bottom flask was charged with 2-bromobenzaldehyde (2000 mg, 10.81mmol), (R)-2-methylpropane-2-sulfinamide (1310.13mg, 10.81mmol), $Ti(OEt)_4$ (3.33mL, 16.21mmol) and THF (9.2536mL). The reaction was heated at 60 ^{o}C for 30min under N_2 protection to give a yellow solution. TLC (PE/EA= 3/1, Rf =0.4) showed a new spot was detected. H_2O (3 mL) was added dropwise and it was stirred at 20 ^{o}C for 5 min, then it was filtrate through a pad of celite and concentrated in vacuum to give the title compound (3050mg, 10.583mmol, 97.903% yield) as white solid.

[0325]

(R)-N-[(1S)-1-(2-bromophenyl)ethyl]-2-methyl-2-propanesulfinamide

A round-bottom flask charged with(R)-N-[(E)-(2-bromophenyl)methylene]-2-methyl-2-propanesulfinamide (3000 mg, 10.41mmol) and THF (25mL) was cooled to -48 ^{o}C, and chloro(methyl)magnesium (4.16mL, 12.49mmol) was added dropwise to the mixture. The reaction was stirred at this temperature for 2hr to give a yellow solution. H_2O (30 mL) was

added and it was extracted with EtOAc (30 mLx2). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuum to give a yellow oil. The crude was purified by silica gel chromatography (DCM/EA= 10/1 to 3/1) to give the title compound (960mg, 3.1553mmol, 30.312% yield) as white solid.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.54 (d, J = 8.0 Hz, 1H), 7.43 (dd, J = 8.0, 0.8 Hz, 1H), 7.40-7.20 (m, 1H), 7.20-7.10 (m, 1H), 5.05-4.95 (m, 1H), 3.37 (d, J = 4.0 Hz, 1H), 1.54 (d, J = 6.8 Hz, 3H), 1.21 (s, 9H).

[0326]

(1S)-1-(2-bromophenyl)ethanamine hydrochloride

A solution of (R)-N-[(1S)-1-(2-bromophenyl)ethyl]-2-methyl-2-propanesulfinamide (900 mg, 2.96 mmol) in HCl/MeOH (105.31mg, 2.96 mmol) was stirred at 30 ^{o}C for 16 hr to give a colorless solution. The reaction mixture was evaporated in vacuum to give the title compound (700 mg, 2.95 mmol, 100.04% yield) as yellow oil. It was used directly in the next step.

LC-MS Method1 0.592 min, MS (m/z) 202.1 ($M + H^+$).

[0327]

ethyl 1-[(1S)-1-(2-bromophenyl)ethyl]-1H-imidazole-4-carboxylate

A 8 mL microwave vial was charged with (1S)-1-(2-bromophenyl)ethanamine hydrochloride (780 mg, 3.3mmol), ethyl (2Z)-3-(dimethylamino)-2-isocyanoacrylate (554.61mg, 3.3mmol), Et_3N (0.69mL, 4.95mmol) and 1-Butanol (3mL). The reaction was irradiated with microwave at 130 ^{o}C for 1h to give a brown red solution. The reaction mixture was diluted with saturated Na_2CO_3 aq.(10 mL) and extracted with EtOAc (20mL x2). The combined organic layer dried over Na_2SO_4 and concentrated in vacuum to give a yellow oil. The crude was purified by silica gel chromatography (DCM/EA= 10/1 to 6/1) to give the title compound (230mg, 0.7117mmol, 21.581% yield) as yellow oil.

LC-MS Method1 0.726 min, MS (m/z) 324.9 ($M + H^+$).

[0328]

ethyl 1-[(1S)-1-(2-cyanophenyl)ethyl]-1H-imidazole-4-carboxylate

A 50mL round-bottom flask was charged with ethyl 1-[(1S)-1-(2-bromophenyl)ethyl]-1H-imidazole-4-carboxylate (180 mg, 0.5600mmol), $Zn(CN)_2$ (130.78mg, 1.11mmol), $Pd_2(dba)_3$ (25.5mg, 0.0300mmol), $P(t\text{-}Bu)_3.HBF_4$ (32.32mg, 0.1100mmol), Zn (14.57mg, 0.2200mmol) and DMF (2mL). The reaction mixture was stirred at 120°C for 16h to give a yellow solution. H_2O (15 mL) was added and it was extracted with

EtOAc (20 mLx2). The combined organic layer dried over Na_2SO_4 and concentrated in vacuum to give a yellow oil. The reaction mixture was evaporated in vacuum to give the title compound (60mg, 0.2228mmol, 40.004% yield) as yellow oil. It was used directly in the next step.

[0329]

1-[(1S)-1-(2-cyanophenyl)ethyl]-1H-imidazole-4-carboxylic acid

To a mixture of ethyl 1-[(1S)-1-(2-cyanophenyl)ethyl]-1H-imidazole-4-carboxylate (150 mg, 0.5600mmol) in 1,4-Dioxane (5mL) was added a solution of $LiOH \cdot H_2O$ (46.74mg, 1.11mmol) in H_2O (1.5mL, 0.5600mmol). It was reacted at 20 °C for 16 h to give a yellow solution. The reaction mixture was evaporated in vacuum to give the title compound (160mg, 0.6632mmol, 119.07% yield) as white solid.

LC-MS Method1 0.688 min, MS (m/z) 242.2 ($M + H^+$).

[0330]

2-[(1S)-1-(4-{[(1R,5S,6S)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]carbonyl}-1H-imidazol-1-yl)ethyl]benzonitrile

To a solution of 1-[(1S)-1-(2-cyanophenyl)ethyl]-1H-imidazole-4-carboxylic acid (50 mg, 0.2100mmol) in DMF (2mL) were added N-ethyl-N-isopropylpropan-2-amine (0.18mL, 1.04mmol) and HATU (118.85mg, 0.3100mmol) at 20 °C. After stirred for 30 min, (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (52.47mg, 0.21 mmol) was added and stirred for 16hr to give black suspension. H_2O (30 mL) was added and it was extracted with EtOAc (30 mLx2). The combined organic layer dried over Na_2SO_4 and concentrated in vacuum to give a yellow oil. The crude was purified by Prep-HPLC (NH_3). The afforded flows were concentrated in vacuum to remove most of CH_3CN and lyophilized to give the title compound (37.35 mg, 0.0926 mmol) as white solid.

LC-MS Method1: 404.3 [$M+H^+$]

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.70 (dd, J=1.00, 7.53 Hz, 1H), 7.67 (d, J=1.51 Hz, 1H), 7.56-7.63 (m, 2H), 7.41-7.48 (m, 1H), 7.20 (d, J=8.03 Hz, 1H), 5.78 (q, J=7.03 Hz, 1H), 4.73 (dd, J=2.89, 12.17 Hz, 1H), 4.16 (d, J=12.55 Hz, 1H), 3.93 (br d, J=10.29 Hz, 1H), 3.60 (dd, J=4.14, 12.42 Hz, 1H), 2.63 (d, J=2.26 Hz, 2H), 2.07 (br d, J=3.51 Hz, 1H), 1.95-1.99 (m, 1H), 1.94 (d, J=7.03 Hz, 3H), 1.45 (br d, J=3.26 Hz, 1H), 1.36 (s, 6H)

[0331]

Example 23 3-[(1S)-1-(4-{[(1R,5S,6S)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]carbonyl}-1H-imidazol-1-yl)ethyl]benzonitrile

(R)-N-[(E)-(3-cyanophenyl)methylene]-2-methyl-2-propanesulfinamide

To a solution of (R)-2-methylpropane-2-sulfinamide (4621.37mg, 38.13mmol) in THF (20mL) were added 3-formylbenzonitrile (5000 mg, 38.13mmol) and tetraethoxytitanium (11.86mL, 57.2mmol) at 60 °C. The resulting mixture was stirred at 60°C for 0.5 hours to give yellow solution. H_2O (3 mL) was added dropwise and it was stirred for 5min. Then solid was filtered through a pad of celite and the filtrate was concentrated in vacuum to afford the title compound (7630mg, 32.562mmol, 85.398% yield) as white solid. It was used directly for the next step without further purification.

LC-MS Method1 0.858 min, MS (m/z) 235.2 ($M + H^+$).

[0332]

(R)-N-[(1S)-1-(3-cyanophenyl)ethyl]-2-methyl-2-propanesulfinamide

To a solution of (R)-N-[(E)-(3-cyanophenyl)methylene]-2-methyl-2-propanesulfinamide (3000 mg, 12.8mmol) in THF (32.054mL) was added chloro(methyl)magnesium (4.69mL, 14.08mmol) at -48 °C. The resulting mixture was stirred at -40°C for 14 hours to give yellow solution. The reaction mixture was poured into sat. NH_4Cl aq. (30 mL) and extracted with EtOAc (30 mL x 4). The combined organic layers were washed with brine (30 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (960mg, 3.8345mmol, 29.95% yield) as yellow solid.

LC-MS Method1 0.845 min, MS (m/z) 251.2 ($M + H^+$).

[0333]

3-[(1S)-1-aminoethyl]benzonitrile hydrochloride

To (R)-N-[(1S)-1-(3-cyanophenyl)ethyl]-2-methyl-2-propanesulfinamide (960 mg, 3.83mmol) was added HCl/MeOH (10 mL, 3.83mmol) at 20 °C. The resulting mixture was stirred at 20-25°C for 0.5 hours to give yellow solution. The reaction mixture was evaporated in vacuum to give the title compound (643 mg, crude product) as yellow oil.

LC-MS Method1 0.258 min, MS (m/z) 147. ($M –HCl + H^+$).

[0334]

ethyl 1-[(1S)-1-(3-cyanophenyl)ethyl]-1H-imidazole-4-carboxylate

To a solution of 3-[(1S)-1-aminoethyl]benzonitrile hydrochloride (250 mg, 1.49mmol) in 1-Butanol (2.5mL) were added Et_3N (0.31mL, 2.23mmol) and ethyl (2Z)-3-

(dimethylamino)-2-isocyanoacrylate (271.49mg, 1.49mmol) The reaction mixture was irradiated with microwave at 130 °C for 60 min to give a yellow solution. The reaction mixture was poured into sat. NH_4Cl aq. (30 mL) and extracted with EtOAc (30 mL x 2). The combined organic layers were washed with brine (30 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (90mg, 0.3342mmol, 22.484% yield) as yellow oil.

LC-MS Method1 0.732 min, MS (m/z) 270.2 ($M + H^+$).

[0335]

1-[(1S)-1-(3-cyanophenyl)ethyl]-1H-imidazole-4-carboxylic acid

To a solution of ethyl 1-[(1S)-1-(3-cyanophenyl)ethyl]-1H-imidazole-4-carboxylate (90 mg, 0.3300mmol) was added hydroxylithium hydrate (28.05mg, 0.6700mmol) in THF (0.90 mL), H_2O (0.90 mL) and MeOH (0.90 mL) at 20 °C. The resulting mixture was stirred at 20-25°C for 14 hours to give yellow solution. The reaction mixture was poured into H_2O and extracted with EtOAc (20 mL x 4). The aqueous layers were concentrated and lyophilized to afford the title compound (132 mg, crude product) as white solid.

LC-MS Method1 0.468 min, MS (m/z) 241.9 ($M + H^+$).

[0336]

3-[(1S)-1-(4-{[(1R,5S,6S)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]carbonyl}-1H-imidazol-1-yl)ethyl]benzonitrile

To a solution of 1-[(1S)-1-(3-cyanophenyl)ethyl]-1H-imidazole-4-carboxylic acid (60 mg, 0.2500mmol) in DMF (1.8mL) were added HATU (123.6mg, 0.3200mmol) and N-ethyl-N-isopropylpropan-2-amine (0.3mL, 1.74mmol) at 20 °C. The reaction mixture was stirred at 20 °C for 30 min. Then (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (62.96mg, 0.2500mmol) was added. The resulting mixture was stirred at 20-25°C for 14 hours to give yellow solution. The reaction mixture was poured into sat. NH_4Cl aq. (80 mL) and extracted with EtOAc (50 mL x 4). The combined organic layers were washed with sat. aq. (50 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (FA) to the title compound (10mg, 0.0248mmol, 9.9654% yield) as white solid.

LC-MS Method1: 404.2 [$M+H^+$]

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.63 (br d, *J*=7.8 Hz, 2H), 7.52 - 7.46 (m, 2H), 7.44 (s, 1H), 7.37 (br d, *J*=8.0 Hz, 1H), 5.40 (q, *J*=6.9 Hz, 1H), 4.73 (br d, *J*=12.3 Hz, 1H),

4.17 (br d, *J*=12.3 Hz, 1H), 3.98 - 3.91 (m, 1H), 3.64 - 3.58 (m, 1H), 2.64 (s, 2H), 2.08 (br s, 1H), 1.98 (br d, *J*=3.3 Hz, 1H), 1.90 (d, *J*=7.0 Hz, 3H), 1.46 (t, *J*=3.3 Hz, 1H), 1.36 (s, 6H)

[0337]

Example 24 4-[(1S)-1-(4-{[(1R,5S,6S)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]carbonyl}-1H-imidazol-1-yl)ethyl]benzonitrile

(R)-N-[(E)-(4-cyanophenyl)methylene]-2-methyl-2-propanesulfinamide

To a solution of (R)-2-methylpropane-2-sulfinamide (4621.37mg, 38.13mmol) in THF (20mL) were added 4-formylbenzonitrile (5000 mg, 38.13mmol) and tetraethoxytitanium (13.05g, 57.2mmol) at 60 °C. The resulting mixture was stirred at 60°C for 0.5 hours to give yellow solution. H_2O (3 mL) was added dropwise and it was stirred for 5mins. Then the solid was removed by filtration through a pad of celite and the filtrate was concentrated in vacuum to give the title compound (8340mg, 35.592mmol, 93.345% yield) as white solid.

LC-MS Method1 0.858 min, MS (m/z) 234.8 ($M + H^+$).

[0338]

(R)-N-[(1S)-1-(4-cyanophenyl)ethyl]-2-methyl-2-propanesulfinamide

To a solution of (R)-N-[(E)-(4-cyanophenyl)methylene]-2-methyl-2-propanesulfinamide (2340 mg, 9.99mmol) in THF (30mL) was added chloro(methyl)magnesium (4.99mL, 14.98mmol) at -48 °C. The resulting mixture was stirred at -40°C for 14 hours to give yellow solution. The mixture was quenched with NH_4Cl and the aqueous layer was extracted with EA (30 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and then concentrated in vacuum. The crude product was purified by silica column (PE to PE:EtOAc=1:1). The afforded solid was triturated with EtOAc/hexane (20 mL/10 mL) and dried in air to give the title compound (1310mg, 5.2325mmol, 52.396% yield) as yellow solid.

LC-MS Method1 0.732 min, MS (m/z) 250.9 ($M + H^+$).

[0339]

4-[(1S)-1-aminoethyl]benzonitrile hydrochloride

To (R)-N-[(1S)-1-(4-cyanophenyl)ethyl]-2-methyl-2-propanesulfinamide (1310 mg, 5.23mmol) was added HCl/MeOH (10 mL, 5.23mmol) at 20 °C. The resulting mixture was

stirred at 20-25°C for 0.5 hours to give yellow solution. The reaction mixture was evaporated in vacuum to give the title compound (1 g, crude product) as a yellow oil.
LC-MS Method1 0.302 min, MS (m/z) 146.8 ($M + H^+$).

[0340]

ethyl 1-[(1S)-1-(4-cyanophenyl)ethyl]-1H-imidazole-4-carboxylate

To a solution of ethyl (2Z)-3-(dimethylamino)-2-isocyanoacrylate (300 mg, 1.78mmol) in 1-Butanol (3mL) were added Et_3N (0.38mL, 2.68mmol) and 4-[(1S)-1-aminoethyl]benzonitrile hydrochloride (300 mg, 1.78mmol). The reaction mixture was irradiated with microwave at 130 °C for 60 min to give a yellow solution. The reaction mixture was poured into sat. NH_4Cl aq. (30 mL) and extracted with EtOAc (30 mL x 2). The combined organic layers were washed with sat. aq. (30 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (110mg, 0.4085mmol, 22.9% yield) as yellow oil.
LC-MS Method1 0.732 min, MS (m/z) 270.2 ($M + H^+$).

[0341]

1-[(1S)-1-(4-cyanophenyl)ethyl]-1H-imidazole-4-carboxylic acid

To a solution of ethyl 1-[(1S)-1-(4-cyanophenyl)ethyl]-1H-imidazole-4-carboxylate (110 mg, 0.4100mmol) in THF (1.1mL), H_2O (1.1mL) and MeOH (1.1mL) was added hydroxylithium hydrate (34.28mg, 0.8200mmol) at 20 °C. The resulting mixture was stirred at 20-25°C for 14 hours to give yellow solution. The reaction mixture was poured into H_2O and extracted with EtOAc (20 mL x 4). The aqueous layer was concentrated and lyophilized to afford the title compound (130 mg, crude product) as yellow solid.
LC-MS Method1 0.443 min, MS (m/z) 241.9 ($M + H^+$).

[0342]

4-[(1S)-1-(4-{[(1R,5S,6S)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]carbonyl}-1H-imidazol-1-yl)ethyl]benzonitrile

To a solution of 1-[(1S)-1-(4-cyanophenyl)ethyl]-1H-imidazole-4-carboxylic acid (100 mg, 0.4100mmol) in DMF (3mL) were added HATU (206.01mg, 0.5400mmol) and N-ethyl-N-isopropylpropan-2-amine (0.5mL, 2.9mmol) at 20 °C. The reaction mixture was stirred for 30 min. Then (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (104.94mg, 0.4100mmol) was added. The resulting mixture was stirred at 20-25°C for 14 hours to give yellow solution. The reaction mixture was poured into sat. NH_4Cl aq. (20 mL) and extracted with EtOAc (20 mL x 3). The crude product

was purified by Prep-HPLC (FA) to give the title compound (2mg, 0.0050mmol, 1.1958% yield) as yellow solid.

LC-MS Method1: 404.2 [$M+H^+$]

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.66 (br d, *J*=8.0 Hz, 3H), 7.51 (br d, *J*=9.0 Hz, 1H), 7.23 (br s, 2H), 5.42 (br d, *J*=7.0 Hz, 1H), 4.72 (br s, 1H), 4.17 (br d, *J*=12.8 Hz, 1H), 3.93 (br d, *J*=12.0 Hz, 1H), 3.61 (br d, *J*=14.8 Hz, 1H), 2.63 (s, 2H), 2.08 (br s, 1H), 1.98 (br s, 1H), 1.90 (br d, *J*=7.0 Hz, 3H), 1.47 (br s, 1H), 1.37 (s, 6H)

[0343]

Example 25 [(1R,5S,6S)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]{1-[(1S)-1-(2-pyridinyl)ethyl]-1H-imidazol-4-yl}methanone

ethyl 1-[(1S)-1-(2-pyridinyl)ethyl]-1H-imidazole-4-carboxylate

The mixture of (1S)-1-(2-pyridinyl)ethanamine (500 mg, 4.09mmol) and ethyl (2Z)-3-(dimethylamino)-2-isocyanoacrylate (137.67mg, 0.8200mmol) was stirred at 50 °C for 16 h. The reaction mixture was concentrated directly. The residue was purified by prep-TLC (PE:EtOAc=0:1) to give the title compound as brown oil.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.61 (d, J = 4.0 Hz, 1H), 7.78 (d, J = 1.2 Hz, 1H), 7.70-7.60 (m, 2H), 7.30-7.20 (m, 1H), 7.02 (d, J = 8.0 Hz, 1H), 5.50-5.35 (m, 1H), 4.36 (q, J= 6.8 Hz, 2H), 1.94 (d, J = 7.6 Hz, 3H), 1.38 (t, J = 6.8 Hz, 3H).

[0344]

1-[(1S)-1-(2-pyridinyl)ethyl]-1H-imidazole-4-carboxylic acid

To a solution of ethyl 1-[(1S)-1-(2-pyridinyl)ethyl]-1H-imidazole-4-carboxylate (160 mg, 0.6500mmol) in THF (5mL) and H_2O (1 mL, 55.56mmol) was added $LiOH·H_2O$ (0.11mL, 1.96mmol). The mixture was stirred at 20℃ for 12h to give brown suspension. LCMS showed the starting material consumed up. The reaction mixture was concentrated. The afforded H_2O layer was acidified with 1 N HCl aq. to pH=5-7 and lyophilized to give the title compound (130mg, 0.5985mmol, 91.746% yield) as white solid.

[0345]

[(1R,5S,6S)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]{1-[(1S)-1-(2-pyridinyl)ethyl]-1H-imidazol-4-yl}methanone

To a solution of 1-[(1S)-1-(2-pyridinyl)ethyl]-1H-imidazole-4-carboxylic acid (130 mg, 0.6000mmol) in DMF (2mL) were added HATU (274.55mg, 0.7200mmol), DIPEA

(0.49mL, 2.99mmol), (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (108 mg, 0.6000mmol). The mixture was stirred at 30°C for 3h to give brown solution. The reaction mixture was concentrated directly. The residue was purified by prep-HPLC (NH_3) and the afforded flows were combined, concentrated to remove most of CH_3CN and lyophilized to give the title compound (48.15mg, 0.1269mmol, 21.202% yield) as light yellow solid.

LC-MS Method1: 380.0 [$M+H^+$]

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 8.60 (1 H, d, *J*=4.63 Hz), 7.74 (1 H, br d, *J*=2.38 Hz), 7.67 (1 H, td, *J*=7.75, 1.50 Hz), 7.60 (1 H, s), 7.24 (1 H, dd, *J*=7.44, 4.82 Hz), 7.03 (1 H, d, *J*=7.88 Hz), 5.43 (1 H, q, *J*=7.00 Hz), 4.74 (1 H, dd, *J*=12.07, 3.69 Hz), 4.18 (1 H, d, *J*=12.51 Hz), 3.90 - 4.01 (1 H, m), 3.61 (1 H, dd, *J*=12.51, 4.13 Hz), 2.64 (2 H, s), 2.07 (1 H, br d, *J*=3.38 Hz), 1.97 (1 H, br dd, *J*=7.13, 3.50 Hz), 1.92 (3 H, d, *J*=7.00 Hz), 1.45 (1 H, t, *J*=3.31 Hz), 1.31 - 1.43 (6 H, m)

[0346]

Example 26 [(1R,5S,6S)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]{1-[(1S)-1-(4-pyridinyl)ethyl]-1H-imidazol-4-yl}methanone

(1R)-1-(4-pyridinyl)ethyl 4-methylbenzenesulfonate

To a solution of (1R)-1-(4-pyridinyl)ethanol in THF (5 mL) was added NaH (148.11 mg, 6.17 mmol) at 0°C. The mixture was stirred at 0 °C for 0.5 h. 4-methylbenzene-1-sulfonyl chloride (0.29 mL, 1.95mmol) was added and the mixture was stirred at 20-25 °C for 16 h. The reaction mixture was poured into H_2O (10 mL) and extracted with EtOAc (10 mL x 4). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column (PE to 30% EtOAc in PE) to afford the title compound (330 mg, 1.1899 mmol, 73.267% yield) as a white solid.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.54 - 8.48 (m, 2H), 7.69 (d, *J*=8.5 Hz, 2H), 7.25 (d, *J*=8.0 Hz, 2H), 7.13 - 7.10 (m, 2H), 5.54 (q, *J*=6.6 Hz, 1H), 2.42 (s, 3H), 1.59 (d, *J*=6.8 Hz, 3H)

[0347]

ethyl 1-[(1S)-1-(4-pyridinyl)ethyl]-1H-imidazole-4-carboxylate

To a solution of (1R)-1-(4-pyridinyl)ethyl 4-methylbenzenesulfonate (280 mg, 1.01 mmol) in DMF (11.2 mL) were added methyl 1H-imidazole-5-carboxylate (127.32 mg, 1.01

mmol) and Cs_2CO_3 (164.47 mg, 0.50 mmol). The mixture was stirred at 40 °C for 16 h. The reaction mixture was poured into H_2O (10 mL) and extracted with EtOAc (15 mL x 4). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (DCM:MeOH = 10:1) to afford the title compound (28 mg, 0.1211 mmol, 11.993% yield) as a yellow oil.

LC-MS Method1: 232.1 $[M+H]^+$

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.64 - 8.60 (m, 2H), 7.68 - 7.59 (m, 2H), 7.05 - 7.01 (m, 2H), 5.39 (q, *J*=7.0 Hz, 1H), 3.95 - 3.84 (m, 3H), 1.91 (d, *J*=7.3 Hz, 3H)

[0348]

1-[(1S)-1-(4-pyridinyl)ethyl]-1H-imidazole-4-carboxylic acid

To a solution of ethyl 1-[(1S)-1-(4-pyridinyl)ethyl]-1H-imidazole-4-carboxylate (50 mg, 0.22 mmol) in THF (2 mL) and H_2O (1 mL) was added $LiOH·H_2O$ (13.61 mg, 0.32 mmol). The mixture was stirred at 20-25 °C for 2 h. The reaction mixture was concentrated directly. The reaction mixture was acidified with 1 N HCl aq. to pH = 6 and then lyophilized to afford the title compound (40 mg, 0.1841 mmol, 85.167% yield) as a yellow oil.

^{1}H NMR (400MHz, DMSO-d_6) δ = 8.59 - 8.50 (m, 2H), 7.95 (s, 1H), 7.83 (s, 1H), 7.25 (d, *J*=6.3 Hz, 2H), 5.66 (q, *J*=7.1 Hz, 1H), 1.81 (d, *J*=7.3 Hz, 3H)

[0349]

[(1R,5S,6S)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]{1-[(1S)-1-(4-pyridinyl)ethyl]-1H-imidazol-4-yl}methanone

To a solution of 1-[(1S)-1-(4-pyridinyl)ethyl]-1H-imidazole-4-carboxylic acid (20 mg, 0.09 mmol) in Pyridine (1 mL) were added EDCI (26.48 mg, 0.14 mmol) and (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (19.95 mg, 0.0900mmol). The resulting mixture was stirred at 20-25 °C for 16 h. The reaction mixture was concentrated directly. The residue was purified by prep-HPLC (NH_3). The afforded flows were combined, concentrated to remove most of CH_3CN and lyophilized to afford the title compound (24.99 mg, 0.0659 mmol, 71.527% yield) as a yellow solid.

LC-MS Method1: 380.1 $[M+H]^+$

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.61 (d, *J*=5.8 Hz, 2H), 7.68 (s, 1H), 7.51 (s, 1H), 7.03 (d, *J*=5.8 Hz, 2H), 5.36 (q, *J*=6.9 Hz, 1H), 4.76 (dd, *J*=2.9, 12.2 Hz, 1H), 4.19 (br d, *J*=12.3 Hz, 1H), 4.02 - 3.89 (m, 1H), 3.62 (dd, *J*=4.1, 12.7 Hz, 1H), 2.64 (s, 2H), 2.13 - 1.96 (m, 2H), 1.90 (d, *J*=7.3 Hz, 3H), 1.48 (t, *J*=3.4 Hz, 1H), 1.38 (s, 6H)

[0350]

Example 27 [(1R,5S,6S)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]{1-[(1S)-1-(1,3-thiazol-2-yl)ethyl]-1H-imidazol-4-yl}methanone

ethyl 1-[(1S)-1-(1,3-thiazol-2-yl)ethyl]-1H-imidazole-4-carboxylate

To a solution of (1S)-1-(1,3-thiazol-2-yl)ethanamine (131.19mg, 0.7800mmol) in 1-Butanol (1.4mL) were added ethyl (2Z)-3-(dimethylamino)-2-isocyanoacrylate (100 mg, 0.7800mmol) and Et_3N (0.16mL, 1.17mmol) at 25°C. The resulting mixture was subjected to reaction in microwave reactor (time: 1h, temp: 130°C). The reaction mixture was poured into H_2O (5 mL) and extracted with EA (5 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a crude product. The crude product was purified by Prep-TLC (EA) to give the title compound (50mg, 0.1990mmol, 25.507% yield) as a yellow oil.

[0351]

1-[(1S)-1-(1,3-thiazol-2-yl)ethyl]-1H-imidazole-4-carboxylic acid

To a solution of ethyl 1-[(1S)-1-(1,3-thiazol-2-yl)ethyl]-1H-imidazole-4-carboxylate (50mg, 0.2000mmol) in THF (3mL) and H_2O (1mL) was added $LiOH·H_2O$ (41.75mg, 0.9900mmol). The reaction mixture was stirred at 25°C for 16 hours to give a yellow mixture. The reaction mixture was concentrated in vacuum to remove most of THF. The residue was diluted with H_2O (5 mL) and acidified with 0.5 M HCl aq. to pH = 6. Then the solution was lyophilized to give the title compound as a yellow solid.

[0352]

[(1R,5S,6S)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]{1-[(1S)-1-(1,3-thiazol-2-yl)ethyl]-1H-imidazol-4-yl}methanone

To a solution of 1-[(1S)-1-(1,3-thiazol-2-yl)ethyl]-1H-imidazole-4-carboxylic acid (44mg, 0.2000mmol) in Pyridine (2mL) was added EDCI (56.67mg, 0.3000mmol). The mixture was stirred at 25°C under N_2 for 10min. Then (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (42.71mg, 0.2000mmol) was added. The resulting mixture was stirred at 25°C for 2 hours to give a yellow solution. The reaction mixture was poured into H_2O (5 mL) and extracted with EA (5 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was purified by

Prep-HPLC (NH_3) to give the title compound (60mg, 0.1557mmol, 78.975% yield) as a white solid.

LC-MS Method1: 386.2 [$M+H^+$]

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.79 (d, *J*=3.3 Hz, 1H), 7.75 (s, 1H), 7.62 (s, 1H), 7.35 (d, *J*=3.3 Hz, 1H), 5.70 (q, *J*=6.9 Hz, 1H), 4.73 (dd, *J*=8.8, 11.9 Hz, 1H), 4.18 (br d, *J*=12.3 Hz, 1H), 3.99 - 3.91 (m, 1H), 3.61 (dd, *J*=4.2, 12.7 Hz, 1H), 2.64 (s, 2H), 2.11 - 2.06 (m, 1H), 2.03 (d, *J*=7.0 Hz, 3H), 2.00 - 1.95 (m, 1H), 1.37 (s, 6H)

[0353]

Example 28 [(1R,5S,6S)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]{1-[(1S)-1-(1,3-thiazol-5-yl)ethyl]-1H-imidazol-4-yl}methanone

(R)-2-methyl-N-[(E)-1,3-thiazol-5-ylmethylene]-2-propanesulfinamide

To a mixture of 5-formylthiazole (2.14mL, 17.68mmol) in THF (20mL) were added (R)-2-methylpropane-2-sulfinamide (2142.48mg, 17.68mmol) and $Ti(OEt)_4$ (6045.61mg, 26.52mmol). The reaction mixture was stirred at 60 ^oC for 2 h to give yellow mixture. TLC (PE: EtOAc = 2: 1) showed the starting material was consumed completely, and one new spot was (Rf = 0.5) detected. The reaction mixture was diluted with EtOAc (30 mL). The mixture was added H_2O (10 mL) and stirred for 1 min to give yellow suspension. The suspension was filtered. The filtrate was washed with H_2O (20 mL × 3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to afford the title compound (3.77g,17.428mmol, 98.59% yield) as yellow solid.

[0354]

(R)-2-methyl-N-[(1S)-1-(1,3-thiazol-5-yl)ethyl]-2-propanesulfinamide

To a mixture of (R)-2-methyl-N-[(E)-1,3-thiazol-5-ylmethylene]-2-propanesulfinamide (3.77g, 17.43mmol) in THF (37mL) was added chloro(methyl)magnesium (9.88mL, 29.63mmol) at -40°C. The reaction mixture was stirred at 25 ^oC for 16 h to give black brown mixture. TLC (100% EtOAc) showed the starting material was consumed completely, and one new spot (Rf = 0.3) was detected. The reaction mixture was quenched with NH_4Cl (60 mL). The resulting mixture was extracted with EtOAc (40 mL × 4). The combined organic phase was washed with brine (80 mL × 2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to give a residue. The residue was

purified by flash column (10% EtOAc in PE to 100% EtOAc) to afford the title compound (1.7g, 7.3159mmol, 41.978% yield) as brown oil.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.77 (s, 1H), 7.84 (s, 1H), 5.00-4.60 (m, 1H), 3.52 (d, J = 3.2 Hz, 1H), 1.69 (d, J = 6.4 Hz, 3H), 1.23 (s, 9H).

[0355]

(1S)-1-(1,3-thiazol-5-yl)ethanamine

A solution of (R)-2-methyl-N-[(1S)-1-(1,3-thiazol-5-yl)ethyl]-2-propanesulfinamide (500 mg, 2.15mmol) in MeOH/HCl (8 mL, 2.15mmol) was stirred at 25 ºC for 2 h to give brown mixture. TLC (100% EtOAc) showed the starting material was consumed completely. The reaction mixture was concentrated in vacuo to give a residue. The residue was triturated with MTBE (20 mL) and dried in vacuo to give the title compound (504mg, 3.0609mmol, 142.25% yield) (crude) as brown solid.

[0356]

ethyl 1-[(1S)-1-(1,3-thiazol-5-yl)ethyl]-1H-imidazole-4-carboxylate

To a mixture of (1S)-1-(1,3-thiazol-5-yl)ethanamine (350 mg, 2.13mmol) in 1-Butanol (3.5mL) were added ethyl (2Z)-3-(dimethylamino)-2-isocyanoacrylate (357.5mg, 2.13mmol) and Et_3N (0.41mL, 3.19mmol). The reaction mixture was stirred at 130 ºC for 1 h used MW to give brown mixture. The reaction mixture was concentrated in vacuo to give a residue. The residue was purified by prep-TLC (100% EtOAc) to afford the title compound (46mg, 0.1830mmol, 8.6116% yield) as brown solid.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.83 (s, 1H), 7.81 (s, 1H), 7.66 (s, 1H), 7.62 (s, 1H), 5.75-5.60 (m, 1H), 4.37 (q, J = 7.6 Hz, 2H), 2.00 (d, J = 7.2 Hz, 3H), 1.39 (t, J = 7.6 Hz, 3H).

[0357]

1-[(1S)-1- (1,3-thiazol-5-yl)ethyl]-1H-imidazole-4-carboxylic acid

To a mixture ethyl 1-[(1S)-1-(1,3-thiazol-5-yl)ethyl]-1H-imidazole-4-carboxylate (46 mg, 0.1800mmol) in THF (1.5mL) and H_2O (0.50 mL) was added $LiOH·H_2O$ (0.02mL, 0.2700mmol). The reaction mixture was stirred at 25 ºC for 16 h to give yellow mixture. The reaction mixture was diluted with H_2O (4 mL) and extracted with EtOAc (2 mL × 3). The aqueous phase was acidified with 1 N HCl aq. to pH = 5 and lyophilized to afford the title compound (40mg, 0.1792mmol, 97.882% yield) as brown solid.

^{1}H NMR (400MHz, DMSO-d_6) δ = 9.06 (s, 1H), 7.93 (s, 1H), 7.90 (s, 1H), 7.76 (s, 1H), 6.05-5.95 (m, 1H), 1.89 (d, J = 6.8 Hz, 3H).

[0358]

[(1R,5S,6S)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]{1-[(1S)-1-(1,3-thiazol-5-yl)ethyl]-1H-imidazol-4-yl}methanone

To a mixture of 1-[(1S)-1-(1,3-thiazol-5-yl)ethyl]-1H-imidazole-4-carboxylic acid (40 mg, 0.1800mmol) in DMF (0.8286mL) were added HATU (82.2mg, 0.2200mmol) and DIPEA (0.15mL, 0.9000mmol). The mixture was stirred at 50 ^{o}C for 30 min and followed by addition of (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (48.44mg, 0.2700mmol). The mixture was stirred at 25 °C for 16 h to give a yellow mixture. The reaction mixture was purified by prep-HPLC (NH_3). The afforded flows were combined, concentrated to remove most of CH_3CN and lyophilized to afford the title compound (14.11mg, 0.0366 mmol, 20.34% yield) as yellow solid.

LC-MS Method1: 386.1 [$M+H^+$]

^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.80 (s, 1 H), 7.79 (s, 1 H), 7.67 (s, 1 H), 7.52 (d, J=1.4 Hz, 1 H), 5.68 (d, J=7.0 Hz, 1 H), 4.71 (t, J=11.3 Hz, 1 H), 4.16 (dd, J=12.6, 1.9 Hz, 1 H), 3.87 - 3.99 (m, 1 H), 3.60 (dd, J=12.6, 4.2 Hz, 1 H), 2.63 (s, 2 H), 2.08 (dt, J=7.3, 3.7 Hz, 1 H), 1.98 (d, J=7.0 Hz, 4 H), 1.45 (br d, J=4.0 Hz, 1 H), 1.37 (s, 6 H).

[0359]

Example 29 [(1R,5S,6S)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]{1-[(2S)-1-phenylpropan-2-yl]-1H-imidazol-4-yl}methanone

(2R)-1-phenyl-2-propanyl 4-methylbenzenesulfonate

To a solution of (2R)-1-phenyl-2-propanol (400 mg, 2.94mmol) in DCM (5mL) were added Et_3N (0.45mL, 3.23mmol) and 4-methylbenzene-1-sulfonyl chloride (0.44mL, 2.94mmol). The reaction was stirred at 20 ^{o}C for 16 hr to give a yellow solution. TLC (PE/EA=10/1, rf = 0.3) showed a new major spot. H_2O (30 mL) was added and it was extracted with DCM (30 mLx2). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuum to give a yellow oil. The crude was purified by silica gel chromatography (PE/EA= 1/0 to 10/1) to give the title compound (680mg, 2.3418mmol, 79.731% yield) as a white solid.

[0360]

methyl 1-[(2S)-1-phenylpropan-2-yl]-1H-imidazole-4-carboxylate

A solution of methyl 1H-imidazole-4-carboxylate (300 mg, 2.38mmol) and (2R)-1-phenyl-2-propanyl 4-methylbenzenesulfonate (690.78mg, 2.38mmol) in DMF (4mL) was stirred at 80 ^{o} C for 16hr to give a yellow solution. H_2O (30 mL) was added and it was extracted with EtOAc (30 mLx2). The combined organic layer dried over Na_2SO_4 and concentrated in vacuum to give a yellow oil. The crude was purified by silica gel chromatography (DCM/EA= 10/1 to 3/1) to give the title compound (120mg, 0.4912mmol, 20.649% yield)

^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.61 (s, 1H), 7.35-7.15 (m, 5H), 6.95-6.85 (m, 2H), 4.45-4.35 (m, 1H), 3.88 (s, 3H), 3.10-2.90 (m, 2H), 1.56 (d, J = 6.8 Hz, 3H).

[0361]

1-[(2S)-1-phenylpropan-2-yl]-1H-imidazole-4-carboxylic acid

To a stirred solution of methyl 1-[(2S)-1-phenylpropan-2-yl]-1H-imidazole-4-carboxylate (120 mg, 0.4900mmol) in 1,4-Dioxane (3mL) was added a solution of $LiOH·H_2O$ (41.22mg, 0.9800mmol) in H_2O (1 mL, 0.4900mmol). The reaction mixture as stirred at 20 ^{o}C for 16 h to give a colorless oil. TLC (PE/EA =1/1, Rf=0) showed a new spot. The reaction mixture was evaporated in vacuum and lyophilized to give the title compound (110mg, 0.4777mmol, 97.252% yield) as white solid.

[0362]

[(1R,5S,6S)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]{1-[(2S)-1-phenylpropan-2-yl]-1H-imidazol-4-yl}methanone

To a stirred solution of 1-[(2S)-1-phenylpropan-2-yl]-1H-imidazole-4-carboxylic acid (100 mg, 0.4300mmol) and HATU (199.24mg, 0.5200mmol) in DMF (3mL) was added N-ethyl-N-isopropylpropan-2-amine (0.37mL, 2.17mmol). After stirred for 30 mins, (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (109.95mg, 0.4300mmol) was added and the reaction was stirred at 20 ^{o}C for 16hr to give a yellow solution. H_2O (30 mL) was added and it was extracted with EtOAc (30 mLx2). The combined organic layer dried over Na_2SO_4 and concentrated in vacuum to give a yellow oil. The crude was purified by Prep-HPLC (NH_3). The afforded flows were concentrated in vacuum to remove most of CH_3CN and lyophilized to give the title compound (104.7mg, 0.2668mmol, 61.424% yield) as white solid.

LC-MS Method1: 393.3 [$M+H^+$]

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.64 (s, 1H), 7.21-7.26 (m, 3H), 7.17 (br s, 1H), 6.96 (br d, J=7.03 Hz, 2H), 4.69 (br d, J=12.05 Hz, 1H), 4.30-4.38 (m, 1H), 4.18 (br d,

J=10.54 Hz, 1H), 3.86-3.95 (m, 1H), 3.60 (br dd, J=3.89, 12.42 Hz, 1H), 2.94-3.04 (m, 2H), 2.63 (s, 2H), 2.06 (br d, J=3.51 Hz, 1H), 1.97 (br d, J=3.51 Hz, 1H), 1.54 (d, J=6.78 Hz, 3H), 1.46 (br d, J=11.29 Hz, 1H), 1.37 (s, 6H)

[0363]

Example 30 [(1R,5S,6S)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]{1-[(2S)-4-phenylbutan-2-yl]-1H-imidazol-4-yl}methanone

(R)-2-methyl-N-[(1E)-1-methyl-3-phenylpropanylidene]-2-propanesulfinamide

To a mixture of 4-phenyl-2-butanone (1.01mL, 6.75mmol) in THF (10mL) were added (R)-2-methylpropane-2-sulfinamide (817.81mg, 6.75mmol) and $Ti(OEt)_4$ (2307.69mg, 10.12mmol). The reaction mixture was stirred at 60 ^oC for 16 h to give yellow mixture. The reaction mixture was diluted with EtOAc (30 mL). The mixture was added to H_2O (10 mL) and stirred for 1 min to give yellow suspension. The suspension was filtered. The filtrate was washed with H_2O (20 mL×3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to give a residue. The residue was purified by flash column (PE to 30% EtOAc in PE) to give the title compound (570mg, 2.2674mmol, 33.603% yield) as yellow oil.
LC-MS Method1 0.823 min, MS (m/z) 252 ($M + H^+$).

[0364]

(R)-2-methyl-N-[(2S)-4-phenylbutan-2-yl]-2-propanesulfinamide

To a mixture of (R)-2-methyl-N-[(1E)-1-methyl-3-phenylpropanylidene]-2-propanesulfinamide (570 mg, 2.27mmol) in THF (6mL) was added L-selectride (6.8mL, 6.8mmol) at 0 °C. The mixture was stirred at 25 ^oC for 3 h to give colorless mixture. TLC (PE: EtOAc = 2: 1) showed one new spot (Rf = 0.3) was detected. The reaction was quenched by H_2O (3 mL). The reaction mixture was concentrated in vacuo to give a residue. The residue was purified by flash column (PE to 30% EtOAc in PE) to afford the title compound (260mg, 1.026mmol, 45.252% yield) as yellow oil.
^1H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.40-7.25 (m, 2H), 7.25-7.10 (m, 3H), 3.41 (qn, J = 6.8 Hz, 1H), 2.93 (d, J = 7.2 Hz, 1H), 2.80-2.55 (m, 2H), 1.95-1.75 (m, 2H), 1.33 (d, J = 6.8 Hz, 3H), 1.24 (s, 9H).

[0365]

(2S)-4-phenyl-2-butanamine

A solution of (R)-2-methyl-N-[(2S)-4-phenylbutan-2-yl]-2-propanesulfinamide (260 mg, 1.03mmol) in MeOH/HCl (5 mL, 1.03mmol) was stirred at 25 °C for 1 h to give yellow mixture. The reaction mixture was concentrated in vacuo to afford the title compound (190mg, 1.0232mmol, 99.724% yield) (crude) as yellow solid.

[0366]

ethyl 1-[(2S)-4-phenylbutan-2-yl]-1H-imidazole-4-carboxylate

To a mixture of (2S)-4-phenyl-2-butanamine (190 mg, 1.02mmol) in 1-Butanol (2mL) were added ethyl (2Z)-3-(dimethylamino)-2-isocyanoacrylate (172.09mg, 1.02mmol) and Et_3N (0.2mL, 1.53mmol). The reaction mixture was heated in microwave system at 130 °C for 1 h to give brown mixture. TLC (PE: EtOAc = 1: 1) showed one new spot (Rf = 0.2) was detected. The reaction mixture was concentrated in vacuo to give a residue. The residue was purified by prep-TLC (PE: EtOAc=1: 1) to afford the title compound (40mg, 0.1469mmol, 14.354% yield) as brown oil.

LC-MS Method1 0.718 min, MS (m/z) 273 ($M + H^+$).

[0367]

1-[(2S)-4-phenylbutan-2-yl]-1H-imidazole-4-carboxylic acid

To a mixture of ethyl 1-[(2S)-4-phenylbutan-2-yl]-1H-imidazole-4-carboxylate (40 mg, 0.1500mmol) in THF (1.5mL) and H_2O (0.50 mL) was added $LiOH·H_2O$ (0.01mL, 0.2200mmol). The reaction mixture was stirred at 40 °C for 16 h to give yellow mixture. TLC (PE:EtOAc = 1: 1) showed the starting material was consumed completely. The reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (3 mL × 2). The aqueous phase was acidified with 1 N HCl aq. to pH = 5 and lyophilized to afford the title compound (30mg, 0.1228mmol, 83.612% yield) as yellow solid.

LC-MS Method1 0.677 min, MS (m/z) 245 ($M + H^+$).

[0368]

[(1R,5S,6S)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]{1-[(2S)-4-phenylbutan-2-yl]-1H-imidazol-4-yl}methanone

To a mixture of 1-[(2S)-4-phenylbutane-2-yl]1H-imidazole-4-carboxylic acid (30 mg, 0.1200mmol) in Pyridine (1.5mL) was added EDCI (28.25mg, 0.1500mmol). The mixture was stirred at 25 °C for 10 min and followed by addition of (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (26.61mg, 0.1200mmol). The mixture was stirred at 25 °C for 16 h to give a yellow mixture. LCMS

showed the starting material was consumed completely. The reaction mixture was concentrated in vacuo to give a residue. The residue was purified by prep-HPLC (NH_3). The afforded flows were combined, concentrated to remove most of CH_3CN and lyophilized to afford the title compound (16.26mg, 0.0449mmol, 17.643% yield) as yellow solid.

LC-MS Method1: 407.2 [$M+H^+$]

^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.68 (s, 1 H), 7.43 (s, 1 H), 7.28 - 7.32 (m, 2 H), 7.19 - 7.24 (m, 1 H), 7.12 (s, 1 H), 7.10 (s, 1 H), 4.78 (dd, J=11.8, 3.8 Hz, 1 H), 4.21 (br d, J=12.5 Hz, 1 H), 4.04 - 4.15 (m, 1 H), 3.97 (br d, J=11.5 Hz, 1 H), 3.63 (dd, J=12.4, 3.9 Hz, 1 H), 2.65 (s, 2 H), 2.39 - 2.60 (m, 2 H), 2.05 - 2.19 (m, 3 H), 1.99 (br d, J=3.5 Hz, 1 H), 1.50 (d, J=6.8 Hz, 3 H), 1.46 - 1.49 (m, 1 H), 1.38 (s, 6 H)

[0369]

Example 31 [(1R,5S,6S)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]{1-[(2S)-1-phenoxypropan-2-yl]-1H-imidazol-4-yl}methanone

tert-butyl [(2S)-1-phenoxypropan-2-yl]carbamate

To a solution of phenol (0.51mL, 5.84mmol), tert-butyl [(2S)-1-hydroxypropan-2-yl] carbamate (1024.08mg, 5.84mmol), PPh_3 (2299.32mg, 8.77mmol) in Toluene (12mL) was slowly added DIAD (1.73mL, 8.77mmol). The reaction mixture was stirred at 20 ^{o} C for 16hr to give a yellow solution. TLC (PE/EA =10/1, Rf =0.8) showed a new spot. H_2O (30 mL) was added and it was extracted with EtOAc (30 mLx2). The combined organic layer dried over Na_2SO_4 and concentrated in vacuum to give a yellow oil. The crude was purified by silica gel chromatography (PE/EA= 10/1 to 3/1) to give the title compound (600 mg, 2.3874mmol, 40.85% yield) as white solid.

[0370]

(2S)-1-phenoxy-2-propanamine hydrochloride

To a solution of tert-butyl [(2S)-1-phenoxypropan-2-yl]carbamate (1100 mg, 4.38mmol) in MeOH (1mL) was added HCl/dioxane (5 mL, 20mmol) and the reaction mixture was stirred at 20 ^{o} C for 3hr to give a colorless solution. LCMS showed a new peak gives the desired ms. The reaction mixture was evaporated in vacuum to give the title compound (800 mg, 4.2628mmol, 97.393% yield) as yellow solid. It was used directly in the next step.

LC-MS Method1 0.498 min, MS (m/z) 151.8 ($M + H^+$).

[0371]

ethyl 1-[(2S)-1-phenoxypropan-2-yl]-1H-imidazole-4-carboxylate

To a 5 mL MW vial were added (2S)-1-phenoxy-2-propanamine hydrochloride (1100 mg, 5.86mmol), ethyl (2Z)-3-(dimethylamino)-2-isocyanoacrylate (985.82mg, 5.86mmol),1-Butanol (3mL) and Et_3N (1.22mL, 8.79mmol). The reaction was irradiated with microwave at 130 ^oC for 1hr to give a brown solution. LCMS showed a new peak gives the desired ms. The reaction was diluted with sat. Na_2CO_3 aq. (20 mL). H_2O (30 mL) was added and it was extracted with EtOAc (30 mLx2). The combined organic layer dried over Na2SO4 and concentrated in vacuum to give a yellow oil. The crude was purified by silica gel chromatography (PE/EA= 10/1 to 1/1) to give the title compound (310mg, 1.1301mmol, 19.28% yield) as white solid.

LC-MS Method1 0.765 min, MS (m/z) 275.2 ($M + H^+$).

[0372]

1-[(2S)-1-phenoxypropan-2-yl]-1H-imidazole-4-carboxylic acid

A stirred solution of ethyl 1-[(2S)-1-phenoxypropan-2-yl]-1H-imidazole-4-carboxylate (310 mg, 1.13mmol) in 1, 4-Dioxane (3mL) was added a solution of $LiOH·H_2O$ (61.64mg, 1.47mmol) in H_2O. The reaction mixture was stirred at 20 ^oC for 16hr to give a yellow solution. LCMS showed a new peak give the desired ms. H_2O (30 mL) was added and it was extracted with EtOAc (30 mL). Then aqueous layer was acidified by 1M HCl aq. and lyophilized to give the title compound (240mg, 0.9746mmol, 86.241% yield) as a yellow solid.

LC-MS Method1 0.645 min, MS (m/z) 247.2 ($M + H^+$).

[0373]

[(1R,5S,6S)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]{1-[(2S)-1-phenoxypropan-2-yl]-1H-imidazol-4-yl}methanone

A stirred solution of 1-[(2S)-1-phenoxypropan-2-yl]-1H-imidazole-4-carboxylic acid (130 mg, 0.5300mmol) and N-ethyl-N-isopropylpropan-2-amine (0.45mL, 2.64mmol) in DMF (2mL) was added HATU (300.9mg, 0.7900mmol). After stirred for 30 mins, (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (114.4mg, 0.5300mmol) was added to give a brown solution. H_2O (30 mL) was added and it was extracted with EtOAc (30 mLx2). The combined organic layer dried over Na_2SO_4 and concentrated in vacuum to give a yellow oil. The crude was purified by prep-HPLC (NH_3). The afforded flows were concentrated in vacuum to remove most of CH_3CN

and lyophilized to give the title compound (51.22mg, 0.1254mmol, 23.752% yield) as white solid.

LC-MS Method1: 409.3 [$M+H^+$]

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.33 (s, 6 H) 1.47 (br s, 1 H) 1.64 (d, *J*=7.03 Hz, 3 H) 2.00 - 2.15 (m, 2 H) 2.72 (s, 2 H) 3.53 - 3.67 (m, 1 H) 3.92 (br d, *J*=8.53 Hz, 1 H) 4.10 (br d, *J*=12.30 Hz, 1 H) 4.15 - 4.28 (m, 2 H) 4.37 (br d, *J*=10.79 Hz, 1 H) 4.75 (br dd, *J*=11.04, 6.78 Hz, 1 H) 6.88 (br d, *J*=8.03 Hz, 2 H) 6.92 (br t, *J*=7.53 Hz, 1 H) 7.24 (br t, *J*=7.65 Hz, 2 H) 7.82 (br d, *J*=6.78 Hz, 2 H)

[0374]

Example 32 [(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl][1-(pentan-3-yl)-1H-imidazol-4-yl]methanone

ethyl 1-(pentan-3-yl)-1H-imidazole-4-carboxylate

The mixture of pentan-3-amine (1.73mL, 14.86mmol) and ethyl (2Z)-3-(dimethylamino)-2-isocyanoacrylate (500 mg, 2.97mmol) was stirred at 80°C for 16 hours. The crude product was purified by flash column (PE: EA=2:1) to give the title compound (500 mg, 2.3779mmol, 79.988% yield) as a brown oil.

[0375]

1-(pentan-3-yl)-1H-imidazole-4-carboxylic acid

To a solution of ethyl 1-(pentan-3-yl)-1H-imidazole-4-carboxylate in THF (15mL) and H_2O (5mL) was added $LiOH·H_2O$ (0.41mL, 7.13mmol). The reaction mixture was stirred at 40°C for 16 hours to give a yellow mixture. The reaction mixture was concentrated in vacuum to remove most of THF. The residue was diluted with H_2O (5 mL) and acidified with 0.5 M HCl aq. to pH = 6. Then the solution was lyophilized to give the title compound as a yellow solid.

[0376]

[(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl][1-(pentan-3-yl)-1H-imidazol-4-yl]methanone

To a solution of 1-(pentan-3-yl)-1H-imidazole-4-carboxylic acid (50mg, 0.2700mmol) in DMF (5mL) were added HATU (157.35mg, 0.4100mmol) and Et_3N (0.14mL, 1.1mmol) and the reaction mixture was stirred for 15 min at 25°C. Then (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride

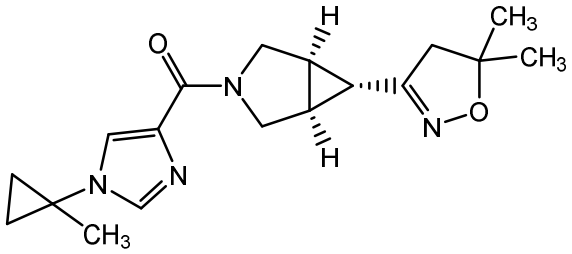
(49.46mg, 0.2700mmol) was added. The resulting mixture was stirred for 2 hours at 25°C to give a brown solution, and then concentrated in vacuum to remove most of DMF to give a crude product. The crude product was purified by Prep-HPLC (NH_3) to give the title compound as a white solid.

LC-MS Method1: 345.3 [$M+H^+$]

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.61 (d, *J*=1.3 Hz, 1H), 7.40 (d, *J*=1.3 Hz, 1H), 4.80 (d, *J*=12.0 Hz, 1H), 4.20 (d, *J*=12.5 Hz, 1H), 3.95 (dd, *J*=4.0, 11.8 Hz, 1H), 3.74 (tt, *J*=4.8, 9.5 Hz, 1H), 3.62 (dd, *J*=4.3, 12.3 Hz, 1H), 2.65 (s, 2H), 2.13 - 2.05 (m, 1H), 2.02 - 1.95 (m, 1H), 1.91 - 1.79 (m, 2H), 1.78 - 1.69 (m, 2H), 1.48 (t, *J*=3.4 Hz, 1H), 1.38 (s, 6H), 0.82 (t, *J*=7.3 Hz, 6H)

[0377]

Example 33 [(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl][1-(1-methylcyclopropyl)-1H-imidazol-4-yl]methanone



ethyl 1-(1-methylcyclopropyl)-1H-imidazole-4-carboxylate

To a solution of ethyl (2Z)-3-(dimethylamino)-2-isocyanoacrylate (469.02 mg, 2.79 mmol) in 1-Butanol (5.5 mL) were added 1-methylcyclopropanamine (300 mg, 2.79 mmol) and Et_3N (0.54 mL, 4.18 mmol). The resulting mixture was subjected to reaction in microwave reactor (time: 1 h, temp: 130 °C). TLC (PE:EtOAc = 0:1) showed the reaction was completed (Rf = 0.5). The reaction mixture was concentrated directly. The crude product was purified by flash column (PE to 40% EtOAc in PE) to afford the title compound (118 mg, 0.6075 mmol, 21.786% yield) as a brown oil.

LC-MS Method1: 0.568 min, MS (m/z) 194.9 [$M+H]^+$

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.71 - 7.69 (m, 1H), 7.60 (s, 1H), 4.36 (q, *J*=7.0 Hz, 2H), 1.58 (s, 3H), 1.38 (t, *J*=7.2 Hz, 3H), 1.17 - 1.12 (m, 2H), 0.96 - 0.91 (m, 2H)

[0378]

1-(1-methylcyclopropyl)-1H-imidazole-4-carboxylic acid

To a solution of ethyl 1-(1-methylcyclopropyl)-1H-imidazole-4-carboxylate (118 mg, 0.61 mmol) in THF (1.5 mL) and H_2O (0.50 mL) was added $LiOH·H_2O$ (0.05 mL, 0.79 mmol). The resulting mixture was stirred at 20-25 ºC for 2 h. The reaction mixture was concentrated directly. The residue was acidified with 1 M HCl aq. to pH = 6 and then lyophilized to afford the title compound (100 mg, 0.6018 mmol, 99.05% yield) as a yellow solid.

^{1}H NMR (400MHz, DMSO-d_6) δ = 7.81 (d, *J*=1.0 Hz, 1H), 7.65 (s, 1H), 1.55 - 1.47 (m, 3H), 1.13 - 1.07 (m, 2H), 0.91 - 0.85 (m, 2H)

[0379]

[(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl][1-(1-methylcyclopropyl)-1H-imidazol-4-yl]methanone

To a solution of 1-(1-methylcyclopropyl)-1H-imidazole-4-carboxylic acid (100 mg, 0.60 mmol) in DMF (2 mL) were added HATU (276.06 mg, 0.72 mmol) and Et_3N (0.39 mL, 3.01 mmol). The mixture was stirred at 20-25ºC for 0.5 h. The mixture was added (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (108.47 mg, 0.60 mmol). The reaction mixture was stirred at 20-25ºC for 1 h. LCMS showed the desired MS (as a major peak). The residue was purified by prep-HPLC (NH_3). The afforded flows were combined, concentrated to remove most of CH_3CN and lyophilized to afford the title compound (60.45 mg, 0.1841 mmol, 30.589% yield) as a yellow solid.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.68 (d, J=1.5 Hz, 1H), 7.52 (d, J=1.3 Hz, 1H), 4.70 (d, J=11.8 Hz, 1H), 4.18 (d, J=12.5 Hz, 1H), 3.92 (dd, J=4.0, 12.0 Hz, 1H), 3.60 (dd, J=4.1, 12.4 Hz, 1H), 2.63 (s, 2H), 2.07 (br dd, J=3.5, 7.0 Hz, 1H), 2.01 - 1.92 (m, 1H), 1.57 (s, 3H), 1.45 (t, J=3.4 Hz, 1H), 1.37 (s, 6H), 1.16 - 1.10 (m, 2H), 0.95 - 0.89 (m, 2H)

LC-MS Method1 0.606 min, MS (m/z) 329.0 [$M+H^+$]

[0380]

Example 34 [(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl][1-(1-methylcyclobutyl)-1H-imidazol-4-yl]methanone

ethyl 1-(1-methylcyclobutyl)-1H-imidazole-4-carboxylate

To a mixture of ethyl (2Z)-3-(dimethylamino)-2-isocyanoacrylate (200 mg, 1.19mmol) in 1-Butanol (0.50 mL) were added 1-methylcyclobutanamine (583.25mg, 4.76mmol) and Et_3N (1.15mL, 8.92mmol). The resulting mixture was heated at 76ºC for 16

hr. The reaction mixture was diluted with H_2O (5mL) and extracted with EtOAc (5 mL × 3). The combined organic layers were separated, washed with brine (10mL), dried over Na_2SO_4 and concentrated in vacuum to give crude oil. The crude oil was purified by prep-TLC (100% EA) to give the title compound (50mg, 0.2401mmol, 20.19% yield) as yellow oil.

LC-MS Method1 0.665 min, MS (m/z) 209.2 ($M + H^+$).

[0381]

1-(1-methylcyclobutyl)-1H-imidazole-4-carboxylic acid

To a mixture of ethyl 1-(1-methylcyclobutyl)-1H-imidazole-4-carboxylate (50 mg, 0.2400mmol) in H_2O (0.4952mL) and MeOH (0.3961mL) was added $LiOH·H_2O$ (0.04mL, 0.7200mmol). The resulting mixture was stirred at 25ºC for 5 hr. The aqueous phase was washed with DCM (3mL × 2) and acidified with 1N HCl to pH = 2. The aqueous solution was lyophilized to give the title compound (50mg, 0.2775mmol, 115.57% yield) as pale yellow solid.

[0382]

[(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl][1-(1-methylcyclobutyl)-1H-imidazol-4-yl]methanone

To a mixture of 1-(1-methylcyclobutyl)-1H-imidazole-4-carboxylic acid (48.08mg, 0.2200mmol) in DMF (0.40 mL) were added HATU (137.86mg, 0.3600mmol), DIPEA (0.18mL, 1.11mmol) and (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (40 mg, 0.2200mmol). The resulting mixture was stirred at 20ºC for 4 hr. The reaction mixture was diluted with H_2O (5mL) and extracted with EtOAc (5mL×2), then washed with brine (8mL). The combined organic layers were separated, then dried over Na_2SO_4 and concentrated in vacuum to give crude oil. The crude oil was purified by prep-HPLC (NH_3) and then lyophilized to give the title compound (3mg, 0.0088mmol, 3.9478% yield) as pale yellow solid.

^{1}H NMR (400MHz, CD_3OD) δ = 7.74 (s, 1H), 7.67 (s, 1H), 4.41 (br d, *J*=12.0 Hz, 1H), 4.09 (br d, *J*=12.3 Hz, 1H), 3.93 (br dd, *J*=3.8, 11.8 Hz, 1H), 3.59 (br dd, *J*=3.9, 12.4 Hz, 1H), 2.71 (s, 2H), 2.63 - 2.52 (m, 2H), 2.30 (tt, *J*=3.0, 8.9 Hz, 2H), 2.14 - 2.08 (m, 1H), 2.07 - 1.92 (m, 3H), 1.68 (s, 3H), 1.48 (t, *J*=3.4 Hz, 1H), 1.32 (s, 6H).

[0383]

Example 35 [(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](1-propyl-1H-imidazol-4-yl)methanone

ethyl 1-propyl-1H-imidazole-4-carboxylate

To a solution of ethyl (2Z)-3-(dimethylamino)-2-isocyanoacrylate (500 mg, 2.97 mmol) in 1-Butanol (0.5 M, 64.98 mmol) were added propan-1-amine (2.97 mL, 1.78 mmol, 1.0 eq.) and Et_3N (0.25 mL, 1.78 mmol, 0.6 eq.). The mixture was stirred at 130 °C for 6 hr, and then concentrated to give a residue. The residue was purified by silica gel chromatography (n-hexane / EtOAc = 60 / 40 to 0 / 100 and then MeOH / EtOAc = 5 / 95) to give the title compound (214 mg, 1.17 mmol, 39.5 % yield) as a brown oil.

LC-MS Method1 0.662 min, MS (m/z) 183.0 ($M + H^+$).

^1H NMR (400 MHz, CHLOROFORM-d) δ 7.60 (d, J = 1.2 Hz, 1H), 7.47 (d, J = 1.2 Hz, 1H), 4.36 (q, J = 7.2 Hz, 2H), 3.93 (t, J = 6.9 Hz, 2H), 1.90-1.80 (m, 2H), 1.39 (t, J = 6.9 Hz, 3H), 0.94 (t, J = 9.6 Hz, 3H).

[0384]

1-propyl-1H-imidazole-4-carboxylic acid

To a stirred solution of ethyl 1-propyl-1H-imidazole-4-carboxylate (214 mg, 1.17 mmol) in THF (1.7 mL, 660 mM) was added a solution of LiOH (70.3 mg, 2.94 mmol, 2.5 eq.) in H_2O (0.6 mL). The reaction mixture was stirred at 40 °C for 12 hr. The reaction mixture was diluted with H_2O and extracted with DCM. The aqueous phase was acidified with 1 N HCl (aq) to pH = 5. The resulting aqueous phase was dried in vacuum to afford the title compound (133 mg, 0.86 mmol, 73.4 % yield) (crude) as beige solid.

^1H NMR (400 MHz, DMSO-d_6) δ 7.81 (d, J = 1.5 Hz, 1H), 7.72 (d, J = 1.5 Hz, 1H), 3.94 (t, J = 6.9 Hz, 2H), 1.80-1.60 (m, 2H), 0.78 (t, J = 7.5 Hz, 3H).

[0385]

[(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](1-propyl-1H-imidazol-4-yl)methanone

To a stirred solution of 1-propyl-1H-imidazole-4-carboxylic acid (45.0 mg, 0.14 mmol) and HATU (53.2 mg, 0.14 mmol, 1.0 eq.) in THF (0.7 mL, 200 mM) was added DIPEA (0.12 mL, 0.7 mmol, 5.0 eq.). After stirred at 50 °C for 30 min, (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (33.4 mg, 0.154 mmol, 1.1 eq.) was added and the reaction was stirred at 20 ^{o} C for 16 hr to give a yellow solution. H_2O was added and it was extracted with DCM. The combined organic layer dried over Na_2SO_4 and concentrated in vacuum to give a yellow oil. The crude was purified by silica gel chromatography (EtOAc / DCM = 99 / 1 to 70 / 30) to give the title compound (23 mg, 0.072 mmol, 51.9 % yield) as a beige powder.

LC-MS Method1 0.757 min, MS (m/z) 317.0 ($M + H^+$).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.59 (d, J = 1.5 Hz, 1H), 7.39 (d, J = 1.5 Hz, 1H), 4.73 (d, J = 11.2 Hz, 1H), 4.18 (d, J = 11.2 Hz, 1H), 4.00-3.85 (m, 1H), 3.91 (t, J = 7.2 Hz, 2H), 3.65-3.55 (m, 1H), 2.64 (s, 2H), 2.10-2.05 (m, 1H), 2.05-1.90 (m, 1H), 1.90-1.70 (m, 2H), 1.50-1.45 (m, 1H), 1.37 (s, 6H), 0.91 (t, 3H, J = 7.2 Hz, 3H).

[0386]

Example 36 [(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](1-isobutyl-1H-imidazol-4-yl)methanone

ethyl 1-isobutyl-1H-imidazole-4-carboxylate

To a solution of ethyl (2Z)-3-(dimethylamino)-2-isocyanoacrylate (1.50 g, 8.92 mmol) in 1-Butanol (17.8 mL, 0.5 M) were added 2-methylpropan-1-amine (1.0 mL, 9.8 mmol, 1.1 eq.) and Et_3N (0.74 mL, 5.35 mmol, 0.6 eq.). The mixture was stirred at 130 °C. for 6 hr and then concentrated to give a residue. The residue was purified by silica gel chromatography (n-hexane / EtOAc = 60 / 40 to 0 / 100 and then MeOH / EtOAc = 5 / 95) to give the title compound (455 mg, 2.3 mmol, 26.0 % yield) as a brown oil.

LC-MS Method1 0.743 min, MS (m/z) 197.0 ($M + H^+$).

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.58 (d, J = 1.2 Hz, 1H), 7.44 (d, J = 1.2 Hz, 1H), 4.36 (q, J = 7.2 Hz, 2H), 3.75 (d, J = 7.8 Hz, 2H), 2.15-1.95 (m, 1H), 1.39 (t, J = 7.2 Hz, 3H), 0.93 (d, J = 6.6 Hz, 6H).

[0387]

1-isobutyl-1H-imidazole-4-carboxylicacid

A stirred solution of ethyl 1-isobutyl-1H-imidazole-4-carboxylate (450 mg, 2.3 mmol) in THF (3.5 mL, 660 mM) was added a solution of LiOH (137 mg, 5.7 mmol, 2.5 eq.) in H_2O (1.2 mL). The reaction mixture was stirred at 40 °C for 12 hr, and then diluted with H_2O and extracted with DCM. The aqueous phase was acidified with 1 N HCl (aq) to pH = 5. The resulting aqueous phase was dried in vacuum to afford the title compound (440 mg, 2.15 mmol, 93.8 % yield) (crude) as yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.50 brs, 1H), 8.10 (d, J = 1.2 Hz, 1H), 3.91 (d, J = 6.9 Hz, 2H), 2.15-1.95 (m, 1H), 0.82 (d, J = 6.6 Hz, 6H).

[0388]

[(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](1-isobutyl-1H-imidazol-4-yl)methanone

To a stirred solution of 1-isobutyl-1H-imidazole-4-carboxylicacid (65.0 mg, 0.15 mmol) and HATU (56.8 mg, 0.15 mmol, 1.0 eq.) in THF (0.7 mL, 200 mM) was added DIPEA (0.13 mL, 0.75 mmol, 5.0 eq.). After stirred at 50 °C for 30 min, (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (35.6 mg, 0.164 mmol, 1.1 eq.) was added and the reaction was stirred at 50 º C for 1 hr to give a yellow solution. H_2O was added and it was extracted with DCM. The combined organic layer dried over Na_2SO_4 and concentrated in vacuum to give a yellow oil. The crude was purified by silica gel chromatography (EtOAc / DCM = 99 / 1 to 80 / 20) to give the title compound (36.2 mg, 0.11 mmol, 73.4 % yield) as a white powder.

LC-MS Method1 0.800 min, MS (m/z) 331.1 ($M + H^+$).

^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.57 (d, J = 1.8 Hz, 1H), 7.36 (d, J = 1.8Hz, 1H), 4.74 (d, J = 12.3 Hz, 1H), 4.18 (d, J = 12.3 Hz, 1H), 3.93 (dd, J = 12.3, 4.2 Hz, 1H), 3.73 (d, J = 7.2 Hz, 2H), 3.61 (dd, J = 12.3, 4.2 Hz, 1H), 2.64 (s, 2H), 2.15-1.95 (m, 3H), 1.50-1.40 (m, 1H), 1.37 (s, 6H), 0.92 (d, J = 6.6 Hz, 6H).

[0389]

Example 37 (1-isopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(5-methyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

tert-butyl (1R,5S,6r)-6-(5-methyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

The mixture of tert-butyl (1R,5S,6r)-6-[(Z)-chloro(hydroxyimino)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (200 mg, 0.77 mmol) in DMF (2 mL) were added prop-1-ene (4.6 mL, 2.3 mmol) and Et_3N (0.38 mL, 2.3 mmol). The resulting mixture was stirred at 20°C for 16 hr to give pale yellow mixture. The reaction mixture was diluted with H_2O (10 mL), then extracted with EtOAc (10 mL×2). The combined organic layers were separated, then dried over Na_2SO_4 and concentrated in vacuum to give the title compound (130 mg, crude) as pale yellow oil.

LC-MS Method1 0.825 min, MS (m/z) 267.0 ($M + H^+$).

[0390]

(1R,5S,6r)-6-(5-methyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride

To tert-butyl (1R,5S,6r)-6-(5-methyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (130 mg, 0.49 mmol) was added HCl/dioxane (3. mL, 0.49 mmol). The reaction mixture was stirred at 0 ºC for 30 min to give pale yellow mixture. The reaction mixture was concentrated to dryness directly to give the title compound (90mg, crude).

[0391]

(1-isopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(5-methyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a mixture of (1R,5S,6r)-6-(5-methyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (50 mg, 0.30 mmol) in DMF (0.50 mL) were added DIPEA (0.2 mL, 1.2 mmol), 1-isopropylimidazole-4-carboxylic acid (46.38mg, 0.30 mmol) and HATU (148.6mg, 0.39 mmol). The resulting mixture was stirred at 20ºC for 16 hr to give brown mixture. TLC (PE/EtOAc = 0/1) showed a series of new spots and 1-isopropylimidazole-4-carboxylic acid (46.38mg, 0.30 mmol) was consumed completely. LCMS detected desired MS. The reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (5 mL×2), then washed with H_2O (5 mL) and brine (5 mL×2). The combined organic layers were separated, then dried over Na_2SO_4 and concentrated in vacuum to give crude product. The crude product was purified by prep-HPLC (NH_3) to give the title compound (5mg, 0.0165 mmol, 5.4972 % yield) as white solid.

^{1}H NMR (400MHz, MeOH) δ = 7.69 (br d, *J*=14.6 Hz, 2H), 4.76 - 4.73 (m, 1H), 4.74 - 4.73 (m, 1H), 4.42 (td, *J*=6.6, 13.4 Hz, 1H), 4.26 (br d, *J*=11.4 Hz, 1H), 4.08 - 3.98 (m, 1H), 3.86 (br dd, *J*=3.6, 11.6 Hz, 1H), 3.54 (br d, *J*=9.9 Hz, 1H), 3.02 - 2.89 (m, 1H), 2.44 (dd, *J*=8.1, 16.9 Hz, 1H), 2.13 - 1.95 (m, 2H), 1.42 (d, *J*=6.6 Hz, 6H), 1.18 (d, *J*=6.3 Hz, 3H)

[0392]

Example 38 (1-isopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(4-oxa-5-azaspiro[2.4]hept-5-en-6-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

tert-butyl (1R,5S,6r)-6-(4-oxa-5-azaspiro[2.4]hept-5-en-6-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-[(Z)-chloro(hydroxyimino)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (0.24 mL, 24.32 mmol) were added methylenecyclopropane (300 mg, 1.22 mmol) in THF (15 mL) and Et_3N (0.51 mL, 3.65 mmol). The reaction mixture was stirred at 0 ^oC for 16 hr to give a yellow solution. LCMS showed a new peak gives the desired MS. The reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (30 mL x2). The combined organic layer dried over Na_2SO_4 and concentrated to give the title compound (260mg, 0.9341 mmol, 76.809 % yield) as yellow oil.

LC-MS Method1 0.845min, MS (m/z) 279 ($M + H^+$).

[0393]

6-[(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl]-4-oxa-5-azaspiro[2.4]hept-5-ene TFA salt

To a solution of tert-butyl (1R,5S,6r)-6-(4-oxa-5-azaspiro[2.4]hept-5-en-6-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (260 mg, 0.93 mmol) in DCM (16.25 mL) was added 2,2,2-trifluoroacetic acid (0.07 mL, 0.93 mmol). The reaction mixture was stirred at 10 ^oC for 3 hr to give a yellow solution. LCMS showed a new peak give the desired MS. The reaction mixture was evaporated in vacuum to give the title compound (272mg, 0.9307 mmol, 99.64 % yield) as yellow oil. The product was used directly in the next step.

LC-MS Method1 0.178 min, MS (m/z) 179.1 ($M + H^+$).

[0394]

(1-isopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(4-oxa-5-azaspiro[2.4]hept-5-en-6-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

A 100 ml round-bottom flask was charged with 1-isopropylimidazole-4-carboxylic acid (143.49mg, 0.93 mmol), HATU (426.97mg, 1.12 mmol), DMF (4.5916 mL) and N-ethyl-N-isopropylpropan-2-amine (0.48 mL, 2.79 mmol). After stirred for 30min, 6-[(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl]-4-oxa-5-azaspiro[2.4]hept-5-ene TFA salt (272 mg, 0.93 mmol) was added. The reaction mixture was stirred at 10 ^oC for 16 hr to give a yellow solution. LCMS showed the reactant was completely consumed and the desired MS. The reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (30 mL x 2). The combined organic layer dried over Na_2SO_4 and concentrated to give yellow oil. The crude was purified by prep- HPLC (FA). The afford flows were concentrated in vacuum to remove most of CH_3CN and lyophilized to give the title compound (14.67mg, 0.0467 mmol, 5.0137 % yield) as white solid.

LC-MS Method1: 315.1 [$M+H^+$]

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.67 (s, 1H), 7.48 (s, 1H), 4.73 (br d, *J*=12.0 Hz, 1H), 4.41 - 4.27 (m, 1H), 4.20 (br d, *J*=12.4 Hz, 1H), 3.95 (br dd, *J*=4.0, 12.0 Hz, 1H), 3.62 (br dd, *J*=4.0, 12.0 Hz, 1H), 2.96 (s, 2H), 2.80 (s, 1H), 2.12 (br d, *J*=3.0 Hz, 1H), 2.03 (br d, *J*=3.5 Hz, 1H), 1.50 (d, *J*=6.4 Hz, 6H), 1.14 - 1.08 (m, 2H), 0.73 - 0.67 (m, 2H)

[0395]

Example 39 (1-isopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(5-oxa-6-azaspiro[3.4]oct-6-en-7-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

tert-butyl (1R,5S,6r)-6-(5-oxa-6-azaspiro[3.4]oct-6-en-7-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a mixture of tert-butyl (1R,5S,6r)-6-[(E)-(hydroxyimino)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate in DMF (1.5 mL) was added methylenecyclobutane (78.4 mg, 1.15 mmol). The suspension was stirred at 20 °C for 16 hr. The reaction mixture was quenched with H_2O (10 mL). The residue was diluted with EtOAc (20 mLx3), washed with saturated NaCl (5 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to afford the title compound (46 mg, crude) as yellow powder.
LC-MS Method1: 0.818 min, MS (m/z): 237.0 ($M-56 + H^+$).

[0396]

7-[(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl]-5-oxa-6-azaspiro[3.4]oct-6-ene TFA salt

A mixture of tert-butyl (1R,5S,6r)-6-(5-oxa-6-azaspiro[3.4]oct-6-en-7-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (46.0 mg, 0.16 mmol) in DCM (1.5 mL) was added 2,2,2-trifluoroacetic acid (17.9 mg, 0.16 mmol). The suspension was stirred at 20 °C for 2 hr. The reaction mixture was concentrated under reduced pressure to give the title compound.
LC-MS Method1: 0.822 min, MS (m/z): 193.0 ($M + H^+$).

[0397]

(1-isopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(5-oxa-6-azaspiro[3.4]oct-6-en-7-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a mixture of 7-[(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl]-5-oxa-6-azaspiro[3.4]oct-6-ene TFA salt (30.0 mg, 0.16 mmol) in Pyridine (0.5 mL) were added EDCI (29.9 mg, 0.16 mmol) and 1-isopropylimidazole-4-carboxylic acid (24.1 mg, 0.16 mmol). The suspension was stirred at 20 °C for 16 hr. The reaction mixture was quenched with H_2O (10 mL). The residue was diluted with EtOAc (20 mLx3), washed with saturated

NaCl (5 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The solution was purified by prep-HPLC (NH_3) and lyophilized to afford the title compound (6.49 mg, 12.7 % yield) as yellow solid.

LC-MS Method1: 2.386 min, MS (m/z): 329.2 ($M + H^+$).

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.69 (d, *J*=1.51 Hz, 1 H), 7.49 (d, *J*=1.51 Hz, 1 H), 4.75 (d, *J*=12.05 Hz, 1 H), 4.37 (dt, *J*=13.43, 6.84 Hz, 1 H), 4.20 (d, *J*=12.80 Hz, 1 H), 3.93 - 3.99 (m, 1 H), 3.63 (dd, *J*=12.92, 3.89 Hz, 1 H), 2.96 (s, 2 H), 2.48 (dt, *J*=12.55, 9.66 Hz, 2 H), 2.07 - 2.18 (m, 4 H), 2.02 (br d, *J*=9.03 Hz, 1 H), 1.76 - 1.85 (m, 1 H), 1.52 (d, *J*=6.78 Hz, 7 H), 1.49 (t, *J*=3.51 Hz, 1 H).

[0398]

Example 40 {(1R,5S,6r)-6-[5-(difluoromethyl)-5-methyl-4,5-dihydro-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hex-3-yl}(1-isopropyl-1H-imidazol-4-yl)methanone

tert-butyl (1R,5S,6r)-6-[5-(dihydroxymethyl)-5-methyl-4,5-dihydro-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-[(Z)-chloro(hydroxyimino)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (200 mg, 0.77 mmol) and methacrylaldehyde (0.32 mL, 3.84 mmol) in DMF (3 mL) was added Et_3N (0.22 mL, 1.53 mmol). The reaction was stirred at 20°C for 12h to give pale yellow solution. The reaction was diluted with EtOAc (15 mL), stirred with saturated $NaHCO_3$ (10 mL) for 5min. The aqueous layer was extracted with EtOAc (10 mL x 2). The combined DCM layer was dried over Na_2SO_4 and concentrated in vacuum to give the title compound (240mg, 0.7683 mmol, crude) as pale brown oil.

[0399]

tert-butyl (1R,5S,6r)-6-[5-(difluoromethyl)-5-methyl-4,5-dihydro-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-[5-(dihydroxymethyl)-5-methyl-4,5-dihydro-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (240 mg, 0.77 mmol) in DCM (10 mL) was added DAST (371.11mg, 2.31 mmol) at -78°C. The reaction was allowed to warm to 20°C and stirred for further 12h to give pale brown solution. The reaction was re-cooled to -78°C, treated with additional DAST (300 mg) and then allowed to warm to 20°C and stirred for further 12h to give pale brown solution. The reaction was cooled to 0°C, diluted with DCM (20 mL), and quenched with saturated $NaHCO_3$ (8 mL). The organic layer was

collected, dried over Na_2SO_4, and concentrated in vacuum to give crude oil, which was purified by prep-HPLC (HCl). The afforded eluent was treated with saturated $NaHCO_3$ (2 mL) and concentrated to remove MeCN. The residue was extracted with EtOAC (10 mL x 2). The combined EtOAc layer was dried over Na_2SO_4 and concentrated in vacuum to give the title compound (55mg, 0.1739 mmol, 22.628 % yield) as pale brown gum.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 5.58 (t, *J*=56 Hz, 1H), 3.65 (d, J = 11.2 Hz, 1H), 3.56 (d, J = 11.2 Hz, 1H), 3.36-3.32 (m, 2H), 3.04 (dd, J = 17.2, 6.0 Hz, 1H), 2.60 (d, J = 17.2 Hz, 1H), 2.00-1.85 (m, 3H), 1.37 (s, 9H). 1.37 (s, 3H).

[0400]

{(1R,5S,6r)-6-[5-(difluoromethyl)-5-methyl-4,5-dihydro-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hex-3-yl}(1-isopropyl-1H-imidazol-4-yl)methanone

To a solution of tert-butyl (1R,5S,6r)-6-[5-(difluoromethyl)-5-methyl-4,5-dihydro-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (55 mg, 0.17 mmol) in DCM (2 mL) was added $MeSO_3H$ (33.38mg, 0.35 mmol). The reaction was stirred at 20°C for 1h to give pale yellow solution. DMF (1 mL) was added, followed by 1-isopropylimidazole-4-carboxylic acid (32.17mg, 0.21 mmol), HATU (66.47mg, 0.17 mmol) and Et_3N (0.12 mL, 0.87 mmol). The resultant mixture was stirred at 20°C for 12h to give yellow mixture. The reaction was concentrated and purified by prep-HPLC (NH_3). The afforded eluent was concentrated and lyophilized to give the title compound (7.01mg, 0.0199 mmol, 11.442 % yield) as a pale yellow solid.

LC-MS Method1: 353.0 [$M+H^+$]

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.60 (d, *J*=1.4 Hz, 1H), 7.40 (d, *J*=1.4 Hz, 1H), 5.78 - 5.37 (m, 1H), 4.70 (d, *J*=12.1 Hz, 1H), 4.28 (quin, *J*=6.7 Hz, 1H), 4.13 (d, *J*=12.4 Hz, 1H), 3.87 (br d, *J*=10.0 Hz, 1H), 3.54 (dd, *J*=3.9, 12.4 Hz, 1H), 3.05 (d, *J*=17.4 Hz, 1H), 2.61 (br dd, *J*=7.8, 17.6 Hz, 1H), 2.04 (br s, 1H), 1.99 - 1.89 (m, 1H), 1.43 (d, *J*=6.6 Hz, 6H), 1.38 (m, 3H)

[0401]

Example 41 [(1R,5S,6r)-6-(5-ethyl-5-methyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](1-isopropyl-1H-imidazol-4-yl)methanone

tert-butyl (1R,5S,6r)-6-(5-ethyl-5-methyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-[(Z)-chloro(hydroxyimino)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate in DMF (1.5 mL) were added 2-methylbut-1-ene (403.48 mg, 5.75 mmol), Et_3N (116.4 mg, 1.15 mmol, 0.16 mL). The suspension was stirred at 20 °C for 16 hr. The reaction mixture was quenched with H_2O (10 mL). The residue was extracted with EtOAc (20 mL x 3). The combined organic layers were washed with saturated NaCl (5 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-TLC (PE:EtOAc=2:1, Rf=0.5) to afford the title compound (76 mg, crude) as yellow powder.

LC-MS Method1: 0.833 min, MS (m/z): 239.0 ($M - 56 + H^+$).

[0402]

(1R,5S,6r)-6-(5-ethyl-5-methyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane TFA salt

A mixture of compound tert-butyl (1R,5S,6r)-6-(5-ethyl-5-methyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (76.0 mg, 0.26 mmol), 2,2,2-trifluoroacetic acid (29.4mg, 0.16 mmol) in DCM (1 mL) was stirred at 20 °C for 2 hr. The reaction mixture was concentrated under reduced pressure to afford the title compound as brown oil.

LC-MS Method1: 0.357min, MS (m/z): 195.0 ($M + H^+$).

[0403]

[(1R,5S,6r)-6-(5-ethyl-5-methyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](1-isopropyl-1H-imidazol-4-yl)methanone

A solution of (1R,5S,6r)-6-(5-ethyl-5-methyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane TFA salt (50.0 mg, 0.26 mmol) in Pyridine (2 mL) were added EDCI (49.3 mg, 0.26 mmol), 1-isopropylimidazole-4-carboxylic acid (39.7 mg, 0.26 mmol). The suspension was stirred at 20 °C for 16 hr. The reaction mixture was quenched with H_2O (10 mL). The residue was extracted with EtOAc (20 mL x 3), washed with saturated NaCl (5 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (NH_3) and lyophilized to afford the title compound (5.77 mg, 6.8 % yield) as yellow solid.

LC-MS Method1: 2.693 min, MS (m/z): 331.2 ($M + H^+$).

^1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.59 (s, 1 H), 7.40 (s, 1 H), 4.64 (s, 1 H), 4.28 (s, 1 H), 4.12 (br d, *J*=12.63 Hz, 1 H), 3.86 (br d, *J*=12.38 Hz, 1 H), 3.51 - 3.57 (m, 1 H), 2.59 - 2.65 (m, 1 H), 2.44 - 2.51 (m, 1 H), 2.00 (br s, 1 H), 1.90 (br s, 1 H), 1.54 - 1.61 (m, 3

H), 1.46 - 1.50 (m, 7 H), 1.43 (d, *J*=6.63 Hz, 7 H), 1.38 (t, *J*=3.25 Hz, 1 H), 1.25 (s, 4 H), 1.18 (s, 3 H), 0.85 (t, *J*=7.44 Hz, 4 H).

[0404]

Example 42 {(1R,5S,6r)-6-[(5R)-5-ethyl-5-methyl-4,5-dihydro-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hex-3-yl}(1-isopropyl-1H-imidazol-4-yl)methanone

Example 43 {(1R,5S,6r)-6-[(5S)-5-ethyl-5-methyl-4,5-dihydro-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hex-3-yl}(1-isopropyl-1H-imidazol-4-yl)methanone

The compounds in Examples 42 and 43 were obtained during the course of the preparation in Example 41, respectively. They were isolated from the final step of Example 41 by SFC purification, which are {(1R,5S,6r)-6-[(5R)-5-ethyl-5-methyl-4,5-dihydro-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hex-3-yl}(1-isopropyl-1H-imidazol-4-yl)methanone (63.41 mg, 0.19 mmol, 9.3 % yield) and {(1R,5S,6r)-6-[(5S)-5-ethyl-5-methyl-4,5-dihydro-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hex-3-yl}(1-isopropyl-1H-imidazol-4-yl)methanone (69.78 mg, 0.21 mmol, 10.2 % yield) as white solid.
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.66 (s, 1H), 7.48 (s, 1H), 4.74 (br d, *J*=11.8 Hz, 1H), 4.36 (spt, *J*=6.7 Hz, 1H), 4.19 (d, *J*=12.5 Hz, 1H), 3.94 (dd, *J*=4.0, 12.0 Hz, 1H), 3.61 (dd, *J*=4.1, 12.4 Hz, 1H), 2.74 - 2.63 (m, 1H), 2.60 - 2.48 (m, 1H), 2.15 - 2.02 (m, 1H), 2.01 - 1.90 (m, 1H), 1.66 - 1.58 (m, 2H), 1.50 (d, *J*=6.8 Hz, 6H), 1.45 (t, *J*=3.4 Hz, 1H), 1.32 (s, 3H), 0.92 (t, *J*=7.5 Hz, 3H)

[0405]

Example 44 (1-isopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(2-oxa-3-azabicyclo[3.1.0]hex-3-en-4-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

ethyl (1R,5S,6r)-3-azabicyclo[3.1.0]hexane-6-carboxylate hydrochloride

To 6-ethyl 3-(tert-butyl) (1R,5S,6r)-3-azabicyclo[3.1.0]hexane-3,6-dicarboxylate (3.5g, 13.71 mmol) was added HCl/dioxane (50. mL, 3 mmol). The mixture was stirred at 30°C for 2h to give brown solution. TLC (PE:EtOAc=5:1) showed a new spot. The reaction mixture was concentrated directly to give the title compound (2.5g, 13.044 mmol, 95.15 % yield) as a black solid.

6-ethyl 3-[2-(trimethylsilyl)ethyl] (1R,5S,6r)-3-azabicyclo[3.1.0]hexane-3,6-dicarboxylate

To a solution of ethyl (1R,5S,6r)-3-azabicyclo[3.1.0]hexane-6-carboxylate hydrochloride (2.5g, 13.04 mmol) in DCM (20.27 mL) was added DIPEA (10.78 mL, 65.22 mmol) at 0°C. Then 2,5-dioxopyrrolidin-1-yl (2-(trimethylsilyl)ethyl) carbonate (4.06g, 15.65 mmol) in DCM (20.27 mL) was added to the mixture, which was stirred at 30°C for 12h to give brown suspension. TLC (PE:EtOAc=3:1) showed a new spot. The reaction mixture was concentrated directly. The crude product was purified by flash column (PE to 20 % EtOAc in PE) to give the title compound (3.5g, 11.688 mmol, 89.609 % yield) as yellow oil.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 4.20-4.10 (m, 4H), 3.73 (d, J = 11.2 Hz, 1H), 3.65 (d, J = 11.2 Hz, 1H), 3.49 (t, J = 11.2 Hz, 2H), 2.12 (s, 2 H), 1.48 (d, J = 3.2 Hz, 1H), 1.28 (t, J = 6.8 Hz, 3H), 1.00-0.90 (, 2H), 0.03 (s, 9H).

[0406]

2-(trimethylsilyl)ethyl (1R,5S,6r)-6-(hydroxymethyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of 6-ethyl 3-[2-(trimethylsilyl)ethyl] (1R,5S,6r)-3-azabicyclo[3.1.0]hexane-3,6-dicarboxylate (3.5g, 11.69 mmol) in THF (40 mL) was added $LiAlH_4$ (0.67g, 17.53 mmol) at 0°C. The mixture was stirred at 0°C for 20 min to give white suspension. TLC (PE:EtOAc=1:1) showed the reaction was completed. The reaction mixture was poured into H_2O (0.6 mL), 1N NaOH aq (0.6 mL), H_2O (1.8 ml) and filtered. The filtrate was concentrated to give yellow oil. The crude product was purified by flash column (PE to 40 % EtOAc in PE) to give the title compound (1.2g, 4.662 mmol, 39.885 % yield) as colorless oil.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 4.15 (dd, J = 8.8, 7.6 Hz, 2H), 3.67 (d, J = 10.8 Hz, 1H), 3.60 (d, J = 10.8 Hz, 1H), 3.60-3.45 (m, 2H), 3.41 (dt, J = 8.0, 4.0 Hz, 2H), 1.50-1.40 (m, 3H), 1.00-0.85 (m, 3H), 0.03 (s, 9H).

[0407]

2-(trimethylsilyl)ethyl (1R,5S,6r)-6-formyl-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of 2-(trimethylsilyl)ethyl (1R,5S,6r)-6-(hydroxymethyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (1.2g, 4.66 mmol) in DCM (15 mL) was added DMP (2.97g, 6.99 mmol), $NaHCO_3$ (979.14mg, 11.66 mmol) at 0°C. The mixture was stirred at 30°C for 2 h. TLC (PE:EtOAc=1:1) showed the reaction was completed. The reaction mixture were poured into H_2O (40 mL) and extracted with EtOAc (30 mL x 4). The combined organic layers were washed with $NaHCO_3$.aq. (50 mL) and Na_2SO_3.aq. (50 mL),

dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column (PE to 30 % EtOAc in PE) to give the title compound (0.8200g, 3.2108 mmol, 68.871 % yield) as brown oil.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 9.46 (d, J = 4.0 Hz, 1H), 4.17 (dd, J = 7.6, 4.0 Hz, 2H), 3.80 (d, J = 11.6 Hz, 1H), 3.60 (d, J = 11.6 Hz, 1H), 3.54 (t, J = 11.6 Hz, 2H), 2.24 S, 2H), 1.83 (dd, J = 6.4, 3.2 Hz, 1H), 0.99 (dd, J = 7.6, 4.0 Hz, 2H), 0.03 (s, 9H).

[0408]

2-(trimethylsilyl)ethyl (1R,5S,6r)-6-[(E)-(hydroxyimino)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of 2-(trimethylsilyl)ethyl (1R,5S,6r)-6-formyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (820 mg, 3.21 mmol) in EtOH (10 mL) were added KOAc (315.11mg, 3.21 mmol), HOAc (0.18 mL, 3.21 mmol), $NH_2OH{\cdot}HCl$ (0.17 mL, 4.17 mmol). The mixture was stirred at 25 ºC for 3h to give white suspension. TLC (PE:EtOAc=2:1) showed the reaction was completed. The reaction mixture was removed under reduced pressure. H_2O (40 mL) was added to the residue and the mixture was extracted with EtOAc (30 mL x 4). The combined organic phases were washed with saturated sodium hydrogen carbonate (30 mL x 2) and saturated brine (40 mLx2) and dried over Na2SO4. The solvent was removed under reduced pressure to give the title compound (850mg, 3.1435 mmol, 97.904 % yield) as brown oil.

[0409]

2-(trimethylsilyl)ethyl (1R,5S,6r)-6-[(Z)-chloro(hydroxyimino)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of 2-(trimethylsilyl)ethyl (1R,5S,6r)-6-[(E)-(hydroxyimino)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (850 mg, 3.14 mmol) in DMF (9 mL) was added NCS (503.7mg, 3.77 mmol). The mixture was stirred at 25°C for 3h to give brown solution. TLC (PE:EtOAc=2:1) showed the reaction was completed. The reaction mixture was poured into H_2O (40 mL) and extracted with EtOAc (30 mL x 4). The combined organic layers were washed with brine (50 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column (PE to 30 % EtOAc in PE) to give the title compound (750mg, 2.4602 mmol, 78.264 % yield) as colorless oil.

[0410]

2-(trimethylsilyl)ethyl (1R,5S,6r)-6-[5-(chloromethyl)-4,5-dihydro-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of 2-(trimethylsilyl)ethyl (1R,5S,6r)-6-[(Z)-chloro(hydroxyimino)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (400 mg, 1.31 mmol) in DMF (5.3333 mL) were added 3-chloroprop-1-ene (0.54 mL, 6.56 mmol) and Et_3N (0.51 mL, 3.94 mmol). The mixture was stirred at 25°C for 12h to give brown solution. TLC (PE:EtOAc=3:1) showed the reaction was completed. H_2O (40 mL) was added to the mixture, which was extracted with EtOAc (30 mL x 4). The combined organic phases were washed with saturated brine (40 mLx2) and dried over Na_2SO_4. The solvent was removed under reduced pressure. The crude product was purified by flash column (PE to 20 % EtOAc in PE) to give the title compound (160mg, 0.4639 mmol, 35.354 % yield) as colorless oil.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 4.85-4.75 (m, 1H), 4.16 (dd, J = 9.2, 7.2 Hz, 2H), 3.76 (d, J = 11.2 Hz, 1H), 3.70 (d, J = 11.2 Hz, 1H), 3.61 (dd, J = 7.2, 4.0 Hz, 1H), 3.55-3.40 (m, 3H), 3.15-3.05 (m, 1H), 2.95-2.80 (m, 1H), 52.00 (brs, 2H), 1.50 (brs, 1H), 1.00 (dd, J = 9.2, 7.2 Hz, 2H), 0.05 (s, 9H).

[0411]

4-[(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl]-2-oxa-3-azabicyclo[3.1.0]hex-3-ene

To a solution of 2-(trimethylsilyl)ethyl (1R,5S,6r)-6-[5-(chloromethyl)-4,5-dihydro-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (20 mg, 0.06 mmol) in DMSO (1 mL) was added t-BuOK (13.01mg, 0.12 mmol). The mixture was stirred at 20°C for 30 min to give brown solution. The reaction mixture was lyophilized directly to give the title compound (8mg, 0.0487 mmol, 84.022 % yield) as brown solid.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 4.90-4.80 (m, 1H), 4.04 (d, J = 12.4 Hz, 1H), 3.80-3.60 (m, 2H), 3.40-3.30 (m, 1H), 2.40-2.30 (m, 1H), 2.20-1.90 (m, 2H), 1.60-1.50 (m, 1H), 1.00-0.85 (m, 2H), 0.40-0.30 (m, 1H).

[0412]

(1-isopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(2-oxa-3-azabicyclo[3.1.0]hex-3-en-4-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a solution of 4-[(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl]-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (30 mg, 0.18 mmol) and 1-isopropylimidazole-4-carboxylic acid (27.75mg, 0.18 mmol) in Pyridine (2.9557 mL) was added EDCI (44.86mg, 0.23 mmol). The mixture was stirred at 25°C for 3h to give yellow solution. LCMS showed the desire MS as a major peak. The reaction mixture was concentrated directly. The residue was purified by

prep-HPLC (NH_3) to give the title compound (7.58mg, 0.0252 mmol, 14.02 % yield) as yellow solid.

LC-MS Method1: 301.2 [$M+H^+$]

^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.68 (1 H, d, J=1.51 Hz), 7.48 (1 H, d, J=1.25 Hz), 4.85 (1 H, td, J=5.33, 2.13 Hz), 4.78 (1 H, br d, J=10.79 Hz), 4.36 (1 H, m, J=13.49, 6.68 Hz), 4.23 (1 H, br d, J=11.80 Hz), 3.98 (1 H, br dd, J=12.05, 4.52 Hz), 3.60 - 3.70 (1 H, m), 2.36 (1 H, dt, J=8.85, 4.49 Hz), 1.98 - 2.15 (2 H, m), 1.66 (1 H, br d, J=3.51 Hz), 1.51 (6 H, d, J=6.78 Hz), 0.85 - 0.89 (1 H, m), 0.31 (1 H, br s)

[0413]

Example 45 (1-isopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(1-methyl-2-oxa-3-azabicyclo[3.1.0]hex-3-en-4-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

2-(trimethylsilyl)ethyl (1R,5S,6r)-6-[5-(chloromethyl)-5-methyl-4,5-dihydro-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of 2-(trimethylsilyl)ethyl (1R,5S,6r)-6-[(Z)-chloro(hydroxyimino)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (150 mg, 0.49 mmol) in DMF (2 mL) were added 3-chloro-2-methylprop-1-ene (0.24 mL, 2.46 mmol) and Et_3N (0.19 mL, 1.48 mmol). The mixture was stirred at 25°C for 12h to give brown mixture. The reaction mixture was poured into H_2O (10 mL) and extracted with EtOAc (15 mL x 4). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (150 mg, 0.4179 mmol, 84.931 % yield) as brown oil.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 4.25-4.10 (m, 2H), 3.80-3.60 (m, 2H), 3.55-3.45 (m, 4H), 3.05 (d, J = 9.2 Hz, 1H), 2.65 (d, J = 9.2 Hz, 1H), 2.00-1.90 (m, 1H), 1.55-1.45 (m, 2H), 1.05 (s, 3H), 1.50-1.40 (m, 1H), 0.99 (t, J = 8.0 Hz, 2H), 0.04 (s, 9H).

[0414]

4-[(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl]-1-methyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene

To a solution of 2-(trimethylsilyl)ethyl (1R,5S,6r)-6-[5-(chloromethyl)-5-methyl-4,5-dihydro-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (130 mg, 0.36 mmol) in DMSO (4 mL) was added t-BuOK (81.28mg, 0.72 mmol). The mixture was stirred at 20°C for 30 min to give brown solution. The reaction mixture was lyophilized directly to give the title compound (60mg, 0.3366 mmol, 92.95 % yield) as brown solid.

[0415]

(1-isopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(1-methyl-2-oxa-3-azabicyclo[3.1.0]hex-3-en-4-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a solution of 4-[(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl]-1-methyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (60 mg, 0.34 mmol) and 1-isopropylimidazole-4-carboxylic acid (51.9mg, 0.34 mmol) in Pyridine (5 mL) was added EDCI (129.07mg, 0.67 mmol). The mixture was stirred at 25°C for 3h to give yellow solution. The mixture was concentrated directly. The residue was purified by prep-HPLC (NH_3). The afforded solid was purified by prep-TLC (DCM:MeOH =15 :1) to give the title compound (11.96mg, 0.0380 mmol, 11.301 % yield) as light yellow solid.

LC-MS Method1: 315.2 [$M+H^+$]

^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.67 (1 H, s), 7.48 (1 H, s), 4.75 (1 H, br d, J=12.05 Hz), 4.36 (1 H, m, J=13.43, 6.84 Hz), 4.22 (1 H, br d, J=12.30 Hz), 3.97 (1 H, br d, J=12.05 Hz), 3.64 (1 H, br d, J=12.30 Hz), 2.08 (2 H, br d, J=3.76 Hz), 2.01 (1 H, br s), 1.67 (3 H, s), 1.51 (6 H, d, J=6.78 Hz), 0.90 (1 H, dd, J=9.41, 5.14 Hz), 0.33 - 0.43 (1 H, m)

[0416]

Example 46 (1-isopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(4,5,5-trimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

tert-butyl (1R,5S,6r)-6-(4,5,5-trimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of Et_3N (0.36 mL, 2.18 mmol) and 2-methylbut-2-ene (1.16 mL, 10.92 mmol) in THF was added tert-butyl (1R,5S,6r)-6-[(Z)-chloro(hydroxyimino)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (200 mg, 0.73 mmol). The mixture was stirred at 20 °C for 16 hr. The mixture was diluted with H_2O (15 mL) and extracted with EtOAc (15 mL x 3). The organic phase was washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated to give a residue. The residue was purified by flash column (PE:EtOAc=1:0-0:1) to afford the title compound (100 mg, 0.3397 mmol, 46.663 % yield) as a yellow oil.

[0417]

(1R,5S,6r)-6-(4,5,5-trimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane TFA salt

A mixture of tert-butyl (1R,5S,6r)-6-(4,5,5-trimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (160 mg, 0.54 mmol) in TFA (0.5 mL, 0.54 mmol) and DCM (2 mL) was stirred at 20ºC for 40 min. The reaction mixture was concentrated in vacuum and then lyophilized to give the title compound (100 mg, crude product) as yellow oil.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 3.60-3.40 (m, 4H), 2.30-2.20 (m, 2H), 2.00-1.70 (m, 2H), 1.24 (s, 3H), 1.15 (s, 3H), 0.95 (d, J = 7.6 Hz, 3H).

[0418]

(1-isopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(4,5,5-trimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a mixture of 1-isopropylimidazole-4-carboxylic acid (39.68mg, 0.26 mmol) in DMF (1 mL) were added HATU (127.91mg, 0.33 mmol) and DIPEA (0.21 mL, 1.29 mmol). The mixture was heated at 50ºC for 30 min. (1R,5S,6r)-6-(4,5,5-trimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane TFA salt (50 mg, 0.26 mmol) was added the mixture. The resulting mixture was stirred at 20ºC for 4 hr. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL×2), then washed with brine (10 mL). The combined organic layers were separated, then dried over Na_2SO_4 and concentrated in vacuum to give crude oil. The crude oil was purified by prep-HPLC (NH_3) and lyophilized to give the title compound (6mg, 0.0182 mmol, 7.0554 % yield) as white solid.

^{1}H NMR (400MHz, DMSO) δ = 7.98 (d, *J*=2.8 Hz, 2H), 4.79 (br d, *J*=12.5 Hz, 1H), 4.65 (td, *J*=6.8, 13.2 Hz, 1H), 4.17 - 4.10 (m, 1H), 4.01 (br d, *J*=13.1 Hz, 1H), 3.65 (br s, 1H), 3.02 (br d, *J*=6.5 Hz, 1H), 2.30 - 2.07 (m, 2H), 1.60 (d, *J*=6.5 Hz, 6H), 1.47 (br s, 1H), 1.48 - 1.45 (m, 1H), 1.40 (s, 3H), 1.31 (s, 3H), 1.22 (d, *J*=7.5 Hz, 3H)

[0419]

Example 47 (1-isopropyl-1H-imidazol-4-yl){(1R,5S,6r)-6-[(4S)-4,5,5-trimethyl-4,5-dihydro-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hex-3-yl}methanone

Example 48 (1-isopropyl-1H-imidazol-4-yl){(1R,5S,6r)-6-[(4R)-4,5,5-trimethyl-4,5-dihydro-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hex-3-yl}methanone

To a solution of 1-isopropylimidazole-4-carboxylic acid (476.15 mg, 3.09mmol) in Pyridine (8 mL) were added EDCI (592.06 mg, 3.09 mmol) and (1R,5S,6r)-6-(4,5,5-trimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane (400 mg, 2.06 mmol). The

resulting mixture was stirred at 20-25 °C for 2 h. LCMS showed the desired MS (as a major peak). The reaction mixture was concentrated directly. The residue was purified by prep-HPLC (NH_3). The afforded flows were combined, concentrated to remove most of CH_3CN and lyophilized. The product was chirally separated by SFC and lyophilized to afford (1-isopropyl-1H-imidazol-4-yl){(1R,5S,6r)-6-[(4S)-4,5,5-trimethyl-4,5-dihydro-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hex-3-yl}methanone (48.84 mg, 0.15 mmol, 7.2 % yield) and (1-isopropyl-1H-imidazol-4-yl){(1R,5S,6r)-6-[(4R)-4,5,5-trimethyl-4,5-dihydro-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hex-3-yl}methanone (52.66 mg, 0.1594 mmol, 7.7403% yield) both as yellow gum.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.68 (br s, 1H), 7.49 (s, 1H), 4.85 - 4.64 (m, 1H), 4.48 - 4.29 (m, 1H), 4.27 - 4.12 (m, 1H), 4.03 - 3.88 (m, 1H), 3.71 - 3.54 (m, 1H), 2.78 (quin, *J*=7.2 Hz, 1H), 2.30 - 1.95 (m, 2H), 1.65 (br s, 3H), 1.52 (s, 6H), 1.31 (d, *J*=2.8 Hz, 3H), 1.28 - 1.18 (m, 4H), 1.10 (br d, *J*=7.3 Hz, 3H)

[0420]

Example 49 (1-isopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(4-methoxy-5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

tert-butyl (1R,5S,6s)-6-ethynyl-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-formyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (2000 mg, 9.47 mmol) in MeOH (8 mL) were added K_2CO_3 (2616.87mg, 18.93 mmol) and 1-diazo-1-dimethoxyphosphoryl-propan-2-one (1818.71mg, 9.47 mmol). The reaction mixture was stirred at 20°C for 16 hr to give a light yellow mixture. TLC (PE/EtOAc=3:1) showed a new spot. The reaction mixture was diluted with H_2O (300 mL) and extracted with EtOAc (100 mL x 2). The organic layer was washed with brine (100 mL x 2) and dried over anhydrous sodium sulfate to give a residue. The residue was purified by silica column (PE/EtOAc=3:1) to give the title compound (1800 mg, 8.6843 mmol, 91.733 % yield) as white solid.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 3.35 (d, J = 11.2 Hz, 1H), 3.57 (d, J = 11.2 Hz, 1H), 3.36-3.30 (m, 2H), 1.88 (s, 1H), 1.84-1.80 (m, 2H), 1.42 (s, 9H), 1.12-1.09 (m, 1H).

[0421]

tert-butyl (1R,5S,6s)-6-(3-hydroxy-3-methyl-1-butyn-1-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6s)-6-ethynyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (1800 mg, 8.68 mmol) in THF (90 mL) was added n-BuLi (0.2 mL, 9.55 mmol) at -78°C. The reaction mixture was stirred for 30min at -78°C. The acetone (1109.65mg, 19.11 mmol) was added to the reaction mixture. Then the reaction mixture was stirred at 25°C for 16 hr to give a yellow mixture. The reaction mixture was quenched with H_2O (100 mL) and extracted with EtOAc (100 mL x 2). The organic layer was washed with brine (100 mL) and dried over anhydrous sodium sulfate to give a residue. The residue was purified by silica column (PE/EtOAc=3:1) to give the title compound as white solid.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 3.63 (d, J = 11.2 Hz, 1H), 3.55 (d, J = 11.2 Hz, 1H), 3.40-3.10 (m, 2H), 1.83 (s, 1H), 1.78-1.60 (m, 2H), 1.47 (s, 6H), 1.42 (s, 9H), 1.10-1.09 (m, 1H).

[0422]

<u>tert-butyl (1R,5S,6r)-6-(5,5-dimethyl-2-oxido-4-oxo-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate</u>

To a solution of tert-butyl (1R,5S,6s)-6-(3-hydroxy-3-methyl-1-butyn-1-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (900 mg, 3.39 mmol) in MeCN (36 mL) were added t-BuONO (699.11mg, 6.78 mmol) and $Pd(OAc)_2$ (152.3mg, 0.68 mmol). The reaction mixture was stirred at 25°C for 16 hr to give a yellow mixture. TLC (PE/EtOAc=3:1) showed a new spot. The reaction mixture was diluted with H_2O (200 mL) and extracted with EtOAc (100 mL x 2). The organic layer was washed with brine (200 mL), filtered and dried over anhydrous sodium sulfate to give a residue. The residue was purified by silica column (PE/EtOAc=3:1) to give the title compound (600 mg, 1.9333 mmol, 57 % yield) as yellow solid.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 3.72 (d, J = 11.2 Hz, 1H), 3.65 (d, J = 11.2 Hz, 1H), 3.47-3.40 (m, 2H), 2.40-2.20 (m, 2H), 1.60 (s, 1H), 1.49 (s, 6H), 1.44 (s, 9H).

[0423]

<u>tert-butyl (1R,5S,6r)-6-(4-hydroxy-5,5-dimethyl-2-oxido-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate</u>

To a solution of tert-butyl (1R,5S,6r)-6-(5,5-dimethyl-2-oxido-4-oxo-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (650 mg, 2.09 mmol) in THF (10 mL) was added a solution of $NaBH_4$ (87.15mg, 2.3 mmol) in MeOH (3 mL) at 0°C. The reaction mixture was stirred at 0°C for 2 hr to give a white mixture. The reaction mixture was quenched with H_2O (100 mL) and extracted with EtOAc (100 mL x 2). The organic layer was

dried over anhydrous sodium sulfate to give the title compound (570mg, 1.8248 mmol, 87.128 % yield) as colorless oil.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 4.25 (d, J = 11.2 Hz, 1H), 4.20 (d, J = 11.2 Hz, 1H), 3.70-3.50 (m, 2H), 3.50-3.40 (m, 2H), 2.25-2.15 (m, 1H), 2.15-2.00 (m, 1H), 1.70 (d, J = 3.2 Hz, 1H), 1.43 (s, 9H), 1.43 (s, 3H), 1.35 (s, 3H).

[0424]

tert-butyl (1R,5S,6r)-6-(4-methoxy-5,5-dimethyl-2-oxido-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-(4-hydroxy-5,5-dimethyl-2-oxido-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (400 mg, 1.28 mmol) in THF (20 mL) was added NaH (36.88mg, 1.54 mmol) at 0°C and stirred at 0°C for 0.5 hr to give a yellow mixture. MeI (0.11 mL, 1.79 mmol) was added to the reaction mixture. The reaction mixture was stirred at 20°C for 16 hr to give a light yellow mixture. TLC (PE/EtOAc=1:1) showed a new spot. The reaction mixture was quenched with H_2O (100 mL) and extracted with EtOAc (50 mL x 3). The organic layer was concentrated to give a residue. The residue was purified by silica column (PE/EtOAc=1:1) to give the title compound (380mg, 1.1643 mmol, 90.916 % yield) as colorless oil.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 4.02 (d, J = 4.0 Hz, 1H), 3.80-3.60 (m, 2H), 3.50-3.35 (m, 2H), 3.41 (s, 3H), 2.15-2.00 (m, 2H), 1.69 (s, 1H), 1.43 (s, 9H), 1.39 (s, 3H), 1.37 (s, 3H).

[0425]

tert-butyl (1R,5S,6r)-6-(4-methoxy-5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

A solution of tert-butyl (1R,5S,6r)-6-(4-methoxy-5,5-dimethyl-2-oxido-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (380 mg, 1.16 mmol) in $P(MeO)_3$ (1. mL, 1.16 mmol) was stirred at 110°C for 16 hr to give a yellow mixture. TLC (PE/EtOAc=1:1) showed a new spot. The reaction mixture was diluted with EtOAc (200 mL) and washed with H2O (100 mL x 3). The organic layer was concentrated to give a residue. The residue was purified by silica column (PE/EtOAc=1:1) to give the title compound (320mg, 1.031 mmol, 88.551 % yield) as colorless oil.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 4.01 (d, J = 11.2 Hz, 1H), 3.80-3.60 (m, 2H), 3.46 (s, 3H), 3.46-3.30 (m, 2H), 2.20-2.00 (m, 2H), 1.64 (s, 1H), 1.46 (s, 9H), 1.35 (s, 3H), 1.29 (s, 3H).

[0426]

(1R,5S,6r)-6-(4-methoxy-5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane TFA salt

To a solution of tert-butyl (1R,5S,6r)-6-(4-methoxy-5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (200 mg, 0.64 mmol) in DCM (4 mL) was added TFA (0.8 mL, 0.64 mmol). The reaction mixture was stirred at 25°C for 1 hr to give a colorless mixture. The reaction mixture was removed the solvent to give a residue. The residue was used for the next step directly.

LC-MS Method1 0.323 min, MS (m/z) 211.0 ($M + H^+$).

[0427]

(1-isopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(4-methoxy-5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a solution of 1-isopropylimidazole-4-carboxylic acid (49.12mg, 0.32 mmol), HATU (91.62mg, 0.48 mmol) in DMF (2.393 mL) was added DIPEA (0.16 mL, 0.96 mmol). The reaction mixture was stirred at 15°C for 30 min. Then (1R,5S,6r)-6-(4-methoxy-5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane TFA salt (67 mg, 0.32 mmol) was added to the reaction. The reaction mixture was stirred at 15°C for 0.5 hr to give a yellow mixture. LCMS showed the desired MS. The reaction mixture was purified by prep-HPLC (NH_3) to give the title compound (65.26mg, 0.1884 mmol, 59.122 % yield) as white powder

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.67 (s, 1H), 7.47 (s, 1H), 4.75 (dd, *J*=12.0, 16.8 Hz, 1H), 4.35 (m, 1H), 4.21 (m, 1H), 4.05 - 3.92 (m, 2H), 3.66 - 3.58 (m, 1H), 2.25 - 2.17 (m, 1H), 2.07 (m, 1H), 1.50 (d, *J*=6.8 Hz, 6H), 1.47 (m, 1H), 1.35 (s, 3H), 1.28 (d, *J*=4.4 Hz, 3H)

[0428]

Example 50 [(1R,5S,6r)-6-(4-isobutyl-5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](1-isopropyl-1H-imidazol-4-yl)methanone

tert-butyl (1R,5S,6r)-6-(4-isobutyl-5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-[(Z)-chloro(hydroxyimino)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (200 mg, 0.77 mmol) and Et_3N (0.3 mL, 2.3 mmol) in DMF (2.8571 mL) was added 2,5-dimethylhex-2-ene (258.23mg, 2.3 mmol). The mixture

was stirred at 25°C for 12h. LCMS showed the desired mass was detected. The reaction mixture was poured into H_2O (50 mL), extracted by EtOAc (40 mL x 3). The organic phase was washed with H_2O (30 mL x 3) and brine (50 mL), dried over anhydrous Na_2SO_4, concentrated to give the title compound (150 mg, 58.1 % yield) as colorless oil.

[0429]

(1R,5S,6r)-6-(4-isobutyl-5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane TFA salt

The solution of tert-butyl (1R,5S,6r)-6-(4-isobutyl-5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (150 mg, 0.45 mmol) in HCl/Dioxane (10. mL, 0.45 mmol) was stirred at 15 ℃ for 1 h. TLC (PE:EtOAc=3:1) showed the starting material (Rf=0.3) was consumed completely and a new spot (Rf=0) was found. LCMS showed the desired MS. The reaction mixture was concentrated under reduced pressure to give the title compound (105mg,0.3110 mmol, 69.757 % yield, crude) as a white solid. The crude product was used directly for next step.

LC-MS Method1 0.725, MS (m/z) 237.1 ($M + H^+$).

[0430]

[(1R,5S,6r)-6-(4-isobutyl-5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](1-isopropyl-1H-imidazol-4-yl)methanone

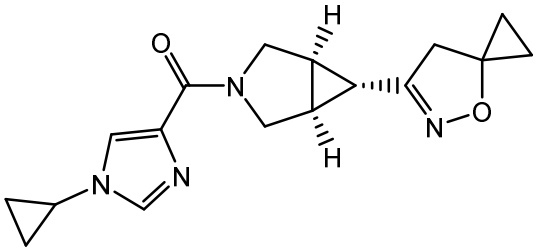
To a solution of (1R,5S,6r)-6-(4-isobutyl-5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane TFA salt (105 mg, 0.44 mmol) and DIPEA (0.22 mL, 1.33 mmol) in DMF (3 mL) were added HATU (202.58mg, 0.53 mmol) and 1-isopropylimidazole-4-carboxylic acid (68.49mg, 0.44 mmol). The mixture was stirred at 20 °C for 12 h. LCMS showed the desired mass was detected. The reaction mixture was poured into H_2O (30 mL), extracted by EtOAc (20 mL x 3). The organic phase was washed by brine, dried over anhydrous Na_2SO_4 and concentrated to give a residue. The residue was purified by prep-HPLC (NH_3) to give the title compound (4.86mg, 0.0130 mmol, 2.9368 % yield) as an off-white solid.

LC-MS Method1: 372.0 [$M+H^+$]

^{1}H NMR (400MHz, METHANOL-d_4) δ = 9.11 (s, 1H), 8.21 (br s, 1H), 4.77 - 4.69 (m, 2H), 4.13 - 4.00 (m, 3H), 3.72 (br dd, *J*=4.4, 12.4 Hz, 1H), 3.01 - 2.92 (m, 1H), 2.36 - 2.25 (m, 1H), 2.20 - 2.06 (m, 1H), 1.79 - 1.71 (m, 1H), 1.63 (d, *J*=6.8 Hz, 6H), 1.36 (d, *J*=2.4 Hz, 3H), 1.21 (s, 3H), 0.97 (br d, *J*=6.5 Hz, 6H), 0.90 - 0.87 (m, 3H)

[0431]

Example 51 (1-cyclopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(4-oxa-5-azaspiro[2.4]hept-5-en-6-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone



(1-cyclopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(4-oxa-5-azaspiro[2.4]hept-5-en-6-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To the mixture of 6-[(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl]-4-oxa-5-azaspiro[2.4]hept-5-ene hydrochloride (49.0 mg, 0.27 mmol) in Pyridine (1.5 mL) were added EDCI (52.7 mg, 0.27 mmol) and 1-cyclopropylimidazole-4-carboxylic acid (41.83 mg, 0.27 mmol). The suspension was stirred at 20 °C for 16 hr. The solution was purified by prep-HPLC (NH_3) and lyophilized to afford the title compound (6.79mg, 7.9 % yield) as yellow solid.

LC-MS Method1: 2.058 min, MS (m/z): 313.2 ($M + H^+$).

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.56 (d, *J*=1.38 Hz, 1 H) 7.43 (d, *J*=1.25 Hz, 1 H) 4.63 (d, *J*=12.01 Hz, 1 H) 4.12 (d, *J*=12.38 Hz, 1 H) 3.87 (dd, *J*=11.82, 3.94 Hz, 1 H) 3.55 (dd, *J*=12.88, 4.38 Hz, 1 H) 3.26 - 3.33 (m, 1 H) 2.89 (s, 2 H) 2.05 (br d, *J*=3.50 Hz, 1 H) 1.93 - 1.99 (m, 1 H) 1.45 (br d, *J*=3.63 Hz, 1 H) 1.18 (s, 3 H) 1.02 - 1.07 (m, 2 H) 0.95 - 0.99 (m, 3 H) 0.90 - 0.94 (m, 2 H) 0.61 - 0.66 (m, 2 H)

[0432]

Example 52 [1-(1-methylcyclopropyl)-1H-imidazol-4-yl][(1R,5S,6r)-6-(4-oxa-5-azaspiro[2.4]hept-5-en-6-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

[1-(1-methylcyclopropyl)-1H-imidazol-4-yl][(1R,5S,6r)-6-(4-oxa-5-azaspiro[2.4]hept-5-en-6-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a solution of 1-(1-methylcyclopropyl)-1H-imidazole-4-carboxylic acid (37.3 mg, 0.22 mmol) in DMF (1.5 mL) were added HATU (110.87 mg, 0.29 mmol) and Et_3N (0.09 mL, 0.67 mmol). The mixture was stirred at 20-25°C for 0.5 h. To the mixture was added 6-[(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl]-4-oxa-5-azaspiro[2.4]hept-5-ene hydrochloride (40

mg, 0.22 mmol). The resulting mixture was stirred for 2 h. The residue was purified by prep-HPLC (NH_3). The afforded flows were combined, concentrated to remove most of CH_3CN and lyophilized to afford the title compound (11.21 mg, 0.0343 mmol, 15.303 % yield) as a yellow solid.

LC-MS Method1: 327.2 [$M+H^+$]

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.69 (d, *J*=1.3 Hz, 1H), 7.53 (d, *J*=1.3 Hz, 1H), 4.73 (br d, *J*=12.0 Hz, 1H), 4.21 (br d, *J*=12.3 Hz, 1H), 3.95 (br dd, *J*=4.0, 12.0 Hz, 1H), 3.62 (br dd, *J*=4.0, 12.5 Hz, 1H), 2.97 (s, 2H), 2.13 (br d, *J*=3.5 Hz, 1H), 2.07 - 2.01 (m, 1H), 1.58 (s, 3H), 1.53 (t, *J*=3.4 Hz, 1H), 1.18 - 1.08 (m, 4H), 0.98 - 0.89 (m, 2H), 0.75 - 0.68 (m, 2H)

[0433]

Example 53 (1-isopropyl-1H-imidazol-4-yl){(1R,5S,6r)-6-[(1S,5S)-1-methyl-2-oxa-3-azabicyclo[3.1.0]hex-3-en-4-yl]-3-azabicyclo[3.1.0]hex-3-yl}methanone

Example 54 (1-isopropyl-1H-imidazol-4-yl){(1R,5S,6r)-6-[(1R,5R)-1-methyl-2-oxa-3-azabicyclo[3.1.0]hex-3-en-4-yl]-3-azabicyclo[3.1.0]hex-3-yl}methanone

The compound produced in Example 45 was applied for SFC chiral separation to afford (1-isopropyl-1H-imidazol-4-yl){(1R,5S,6r)-6-[(1S,5S)-1-methyl-2-oxa-3-azabicyclo[3.1.0]hex-3-en-4-yl]-3-azabicyclo[3.1.0]hex-3-yl}methanone (22.30 mg), and (1-isopropyl-1H-imidazol-4-yl){(1R,5S,6r)-6-[(1R,5R)-1-methyl-2-oxa-3-azabicyclo[3.1.0]hex-3-en-4-yl]-3-azabicyclo[3.1.0]hex-3-yl}methanone (21.47 mg) as white solid.

[0434]

(1-isopropyl-1H-imidazol-4-yl){(1R,5S,6r)-6-[(1S,5S)-1-methyl-2-oxa-3-azabicyclo[3.1.0]hex-3-en-4-yl]-3-azabicyclo[3.1.0]hex-3-yl}methanone

LC-MS Method1: 315.2 [$M+H^+$]

^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.67 (1 H, s), 7.48 (1 H, s), 4.75 (1 H, br d, J=12.05 Hz), 4.36 (1 H, m, J=13.43, 6.84 Hz), 4.22 (1 H, br d, J=12.30 Hz), 3.97 (1 H, br d, J=12.05 Hz), 3.64 (1 H, br d, J=12.30 Hz), 2.08 (2 H, br d, J=3.76 Hz), 2.01 (1 H, br s), 1.67 (3 H, s), 1.51 (6 H, d, J=6.78 Hz), 0.90 (1 H, dd, J=9.41, 5.14 Hz), 0.33 - 0.43 (1 H, m)

[0435]

(1-isopropyl-1H-imidazol-4-yl){(1R,5S,6r)-6-[(1R,5R)-1-methyl-2-oxa-3-azabicyclo[3.1.0]hex-3-en-4-yl]-3-azabicyclo[3.1.0]hex-3-yl}methanone

LS-MS method1: 315.2 [$M+H^+$]

^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.67 (1 H, s), 7.48 (1 H, s), 4.75 (1 H, br d, J=12.05 Hz), 4.36 (1 H, m, J=13.43, 6.84 Hz), 4.22 (1 H, br d, J=12.30 Hz), 3.97 (1 H, br d, J=12.05 Hz), 3.64 (1 H, br d, J=12.30 Hz), 2.08 (2 H, br d, J=3.76 Hz), 2.01 (1 H, br s), 1.67 (3 H, s), 1.51 (6 H, d, J=6.78 Hz), 0.90 (1 H, dd, J=9.41, 5.14 Hz), 0.33 - 0.43 (1 H, m)

[0436]

Example 55 (1-isopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(5-methyl-4-phenyl-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

tert-butyl (1R,5S,6r)-6-(4-bromo-5-methyl-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-(5-methyl-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (2.46g, 9.31mmol, from Example 56) in DMF (25mL) was added NBS (1.66g, 9.31mmol) at 0 to 5°C. The reaction was stirred at 15°C for 5 hours to give a yellow solution. LCMS showed the reaction was completed. The reaction was diluted with H_2O (150 mL) and extracted with EA (40 mL x 3). The combined organic layers were washed with NH_4Cl aq. (40 mL x2), $NaHCO_3$ aq. (40 mL) and brine (40 mL), dried over Na_2SO_4, filtered and concentrated to afford the title compound (2.9g , 90.786% yield) as light yellow oil.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 3.75-3.60 (m, 2H), 3.55-3.40 (m, 2H), 2.38 (s, 3H), 2.20-2.00 (m, 2H), 1.70-1.65 (m, 1H), 1.46 (s, 9H).

[0437]

tert-butyl (1R,5S,6r)-6-(5-methyl-4-phenyl-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

A mixture of tert-butyl (1R,5S,6r)-6-(4-bromo-5-methyl-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (100 mg, 0.29 mmol), phenylboronic acid (42.63mg, 0.35 mmol) and $NaHCO_3$ (73.43mg, 0.87 mmol) in DMF (1.5 mL) and H_2O (0.2 mL) was purged with N_2. Then, $Pd(dppf)Cl_2$ (21.32mg, 0.03 mmol) was added and the mixture was purged with N_2 and heated at 90°C under N_2 atmosphere for 12h to give black mixture. The mixture was diluted with EtOAc (20 mL) and H_2O (10 mL). The solid was filtered off. The organic layer was washed with H_2O (10 mL) and brine (10 mL), then, dried over Na_2SO_4 and concentrated in vacuum to give brown oil. The brown oil was purified by prep-TLC

(PE/EtOAc=6/1) to give the title compound (50mg, 0.1469 mmol, 50.411 % yield) as a white solid.

LC-MS Method1 0.943 min, MS (m/z) 340.9 ($M + H^+$).

[0438]

(1R,5S,6r)-6-(5-methyl-4-phenyl-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride

A mixture of tert-butyl (1R,5S,6r)-6-(5-methyl-4-phenyl-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (50 mg, 0.15 mmol) in 4M HCl/dioxane (5. mL, 0.15 mmol) was stirred at 0°C for 50min to give colorless solution. The reaction was concentrated in vacuum to give the title compound (50mg, 0.1807 mmol, 123 % yield) as pale yellow gum, which was used directly in the next step.

[0439]

(1-isopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(5-methyl-4-phenyl-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a solution of 1-isopropylimidazole-4-carboxylic acid (36.21mg, 0.23 mmol) in DMF (2 mL) were added HATU (82.88mg, 0.22 mmol), Et_3N (0.06 mL, 0.45 mmol) and (1R,5S,6r)-6-(5-methyl-4-phenyl-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (50 mg, 0.18 mmol) at 20°C. The reaction was stirred at 20°C for 4h to give pale brown solution. The reaction was concentrated in vacuum to give pale brown gum, which was purified by prep-HPLC (NH_3). The fluent was concentrated and lyophilized to give the title compound (32.53mg, 0.0864 mmol, 47.831 % yield) as pale yellow solid.

LC-MS Method1: 377.0 [$M+H^+$]

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.57 (d, *J*=1.3 Hz, 1H), 7.40 - 7.33 (m, 3H), 7.28 (d, *J*=7.4 Hz, 1H), 7.25 - 7.21 (m, 2H), 4.59 (d, *J*=12.1 Hz, 1H), 4.26 (spt, *J*=6.8 Hz, 1H), 4.07 (d, *J*=12.6 Hz, 1H), 3.96 (dd, *J*=4.4, 11.9 Hz, 1H), 3.62 (dd, *J*=4.2, 12.6 Hz, 1H), 2.33 (s, 3H), 2.32 - 2.28 (m, 1H), 2.13 - 2.06 (m, 1H), 1.53 - 1.53 (m, 1H), 1.41 (d, *J*=6.6 Hz, 6H)

[0440]

Example 56 (1-isopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(5-methyl-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

tert-butyl (1R,5S,6r)-6-(5-methyl-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-[(Z)-chloro(hydroxyimino)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (0.5g, 1.92 mmol) and prop-1-en-2-yl acetate (1.04

mL, 9.59 mmol) in DCM (6 mL) was added Et_3N (0.8 mL, 5.75 mmol) drop-wise at 0°C. The reaction was then stirred at 20°C for 12h to give pale yellow solution. LCMS showed the desired MS. The solution was diluted with DCM (30 mL) and washed with H_2O (15 mL x 2), saturated $NaHCO_3$ (15 mL) and brine (15 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuum to give the title compound (460mg, 1.7403 mmol, 90.747 % yield) as pale yellow oil, which was used directly in the next step.

[0441]

(1R,5S,6r)-6-(5-methyl-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane TFA salt

To a solution of tert-butyl (1R,5S,6r)-6-(5-methyl-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (235 mg, 0.89 mmol) in DCM (5 mL) was added 2,2,2-trifluoroacetic acid (1. mL, 13.06 mmol). The reaction mixture was stirred at 20 °C for 3hr to give a yellow solution. The reaction mixture was evaporated in vacuum to give the title compound (260mg, 0.9345 mmol, 105.11 % yield) as yellow oil. It used directly in the next step.

[0442]

(1-isopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(5-methyl-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

A 100 mL round-bottom flask was charged with 1-isopropylimidazole-4-carboxylic acid (70 mg, 0.45 mmol), N-ethyl-N-isopropylpropan-2-amine (0.24 mL, 1.41 mmol), HATU (190.94mg, 0.50 mmol) and DMF (3 mL). After stirring for 30min, (1R,5S,6r)-6-(5-methyl-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane TFA salt (126.33mg, 0.45 mmol) was added. The reaction mixture was stirred at 20 °C for 16hr to give a yellow solution. H_2O (30 mL) was added and it was extracted with EtOAc (30 mL x 2). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuum to give a yellow oil. The crude was purified by prep-HPLC (NH_3). The afforded flows were concentrated in vacuum to remove most of CH_3CN and lyophilized to give the title compound (13.06mg, 0.0383 mmol, 8.4313 % yield) as white solid.

LC-MS Method1: 301.1 [$M+H^+$]

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.22 (br s, 1H), 8.35 (s, 1H), 6.07 (s, 1H), 4.66 (td, *J*=6.64, 13.35 Hz, 1H), 4.11 (br d, *J*=10.76 Hz, 1H), 4.02 (br d, *J*=12.63 Hz, 1H), 3.98 (br dd, *J*=4.06, 10.82 Hz, 1H), 3.63 (br dd, *J*=4.19, 12.57 Hz, 1H), 2.34 (s, 3H), 2.14-2.20 (m, 1H), 2.05-2.10 (m, 1H), 1.84 (t, *J*=3.38 Hz, 1H), 1.51 (d, *J*=6.63 Hz, 6H)

[0443]

Example 57 [(1R,5S,6r)-6-(1,2-benzoxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](1-isopropyl-1H-imidazol-4-yl)methanone

N-phenoxyacetamide

To a solution of (aminooxy)benzene (200 mg, 1.37 mmol) in THF (3 mL) was added Ac_2O (280.49mg, 2.75 mmol) at 0°C. The mixture was stirred at 20°C for 3 h to give brown suspension. The reaction mixture was concentrated directly. The crude product was purified by flash column (PE to 20 % EtOAc in PE) to give the title compound (170mg, 1.1246 mmol, 81.868 % yield) as white solid.

^{1}H NMR (400MHz, DMSO-d6) δ = 11.67 (brs, 1H), 7.35-7.25 (m, 2H), 7.05-6.95 (m, 3H), 1.92 (s, 3H).

[0444]

tert-butyl (1R,5S,6r)-6-(1,2-benzoxazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of N-phenoxyacetamide (50 mg, 0.33 mmol) in tert-Amyl alcohol (1.5 mL, 0.33 mmol) were added $Pd(TFA)_2$ (9.92mg,0.03 mmol), tert-butyl 6-formyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (139.76mg, 0.66 mmol) and TBHP (0.17 mL, 0.83 mmol). The mixture was stirred at 60 °C under N_2 for 12h to give brown solution. The reaction mixture was poured into $NaHSO_3$ aq. (20 mL) and extracted with EtOAc (20 mL x 4). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (PE:EtOAc=6:1) to give the title compound (20mg,0.0666 mmol, 20.131 % yield) as white gum.

[0445]

3-[(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl]-1,2-benzoxazole hydrochloride

To a solution of tert-butyl (1R,5S,6r)-6-(1,2-benzoxazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (20 mg, 0.07 mmol) was added HCl/dioxane (2.0 mL, 8 mmol). The mixture was stirred at 20°C for 1h to give colorless solution. TLC (PE:EtOAc=5:1) showed the reaction was completed. The reaction mixture was concentrated directly to give the title compound (15mg, 0.0634 mmol, 95.168 % yield) as brown gum.

[0446]

[(1R,5S,6r)-6-(1,2-benzoxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](1-isopropyl-1H-imidazol-4-yl)methanone

To a solution of 1-isopropylimidazole-4-carboxylic acid (22.08mg, 0.14 mmol) in DMF (1.5 mL) were added HATU (43.79mg, 0.11 mmol), IEA (0.06 mL, 0.38 mmol) and 3-[(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl]-1,2-benzoxazole hydrochloride (30 mg, 0.10 mmol). The mixture was stirred at 20°C for 1h to give brown solution. LCMS showed the desire MS and a part of 3-[(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl]-1,2-benzoxazole hydrochloride was remained. The mixture was stirred at 20°C for 12 h to give brown solution. LCMS showed the desire MS as major peak. The mixture was poured into H_2O (15 mL) and extracted with EtOAc (15 mL x 5). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4 and concentrated to dryness. The residue was purified by prep-TLC (MeOH:EtOAc=1:11) and the afforded solid was triturated with MTBE (2 mL) and dried in air to give as brown solid. The residue was purified by prep-HPLC (NH_3). The afforded flows were combined, concentrated to remove most of CH3CN and lyophilized to give the title compound (10mg, 0.0297 mmol, 31.14 % yield) as white solid.

LC-MS Method1: 336.9 [$M+H^+$]

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.73 (1 H, d, *J*=1.25 Hz), 7.68 (1 H, d, *J*=8.03 Hz), 7.47 - 7.57 (3 H, m), 7.31 (1 H, dd, *J*=7.91, 3.89 Hz), 4.91 (1 H, br d, *J*=12.05 Hz), 4.34 - 4.40 (2 H, m), 4.08 (1 H, br dd, *J*=12.05, 3.76 Hz), 3.74 (1 H, br dd, *J*=12.55, 4.02 Hz), 2.45 - 2.53 (1 H, m), 2.31 - 2.41 (1 H, m), 2.07 (1 H, t, *J*=3.26 Hz), 1.53 (6 H, d, *J*=6.53 Hz)

[0447]

Example 58 [(1R,5S,6r)-6-(4-cyclopropyl-5,5-dimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](1-isopropyl-1H-imidazol-4-yl)methanone

N-cyclopropyl-2-propanimine

To a solution of cyclopropylamine (0.24 mL, 3.5 mmol) and acetone (1017.34mg, 17.52 mmol) in DMF (2.5 mL) was added 4A MS (2000 mg, 3.5 mmol). The mixture was stirred at 110°C for 4 hr without monitor. The mixture was filtered to give the title compound (2000 mg, 2.0585 mmol, 58.759 % yield). The crude product was used directly for next step.

[0448]

tert-butyl (1R,5S,6r)-6-(4-cyclopropyl-5,5-dimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of Et_3N (0.36 mL, 2.18 mmol) and N-cyclopropyl-2-propanimine (5000 mg, 5.15 mmol) was added tert-butyl (1R,5S,6r)-6-[(Z)-chloro(hydroxyimino)methyl]-3-

azabicyclo[3.1.0]hexane-3-carboxylate (200 mg, 0.73 mmol). The mixture was stirred at 20 °C for 16 hr. LCMS showed the desired mass. The mixture was diluted with H_2O (50 mL) and extracted by EtOAc (30 mL x 2). The organic phase was washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated to give a residue. The residue was purified by flash column (PE:EtOAc=1:0-0:1) to afford the title compound (80mg,0.2489 mmol, 34.192 % yield) as a yellow oil

^{1}H NMR (400MHz, DMSO-d6) δ = 11.67 (brs, 1H), 7.35-7.25 (m, 2H), 7.05-6.95 (m, 3H), 1.92 (s, 3H).

[0449]

(1R,5S,6r)-6-(4-cyclopropyl-5,5-dimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)-3-azabicyclo[3.1.0]hexane TFA salt

To a solution of tert-butyl (1R,5S,6r)-6-(4-cyclopropyl-5,5-dimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (80 mg, 0.25 mmol) in DCM (4.4444 mL) was added TFA (0.44 mL, 5.98 mmol). The mixture was stirred at 20 °C for 4 h. TLC (PE:EtOAc=1:1) showed a new spot (Rf=0) was detected. The mixture was concentrated to afford the title compound (55mg, 0.2485 mmol, 99.851 % yield) as yellow oil. The crude was used for next step directly.

[0450]

[(1R,5S,6r)-6-(4-cyclopropyl-5,5-dimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](1-isopropyl-1H-imidazol-4-yl)methanone

To a solution of (1R,5S,6r)-6-(4-cyclopropyl-5,5-dimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)-3-azabicyclo[3.1.0]hexane TFA salt (55 mg, 0.25 mmol), 1-isopropylimidazole-4-carboxylic acid (42.15mg, 0.27 mmol) and DIPEA (0.14 mL, 0.87 mmol) in DMF (2.4444 mL) was added HATU (142.52mg, 0.37 mmol). The mixture was stirred at 20 °C for 1 hr to give a brown mixture. LCMS showed the starting material was consumed and the desired peak was detected. The reaction mixture was diluted with H_2O (50 mL) and extracted by EtOAc (25 mL x 3). The organic phase was washed with brine (50 mL x 3), dried over anhydrous Na_2SO_4 and concentrated to give a residue. The residue was purified by Prep-HPLC (NH_3) to afford the title compound (7.32mg, 0.0205 mmol, 8.2398 % yield) as white solid.

LC-MS Method1: 358.0 [$M+H^+$]

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.68 (d, *J*=1.6 Hz, 1H), 7.47 (d, *J*=1.2 Hz, 1H), 4.75 (d, *J*=12.0 Hz, 1H), 4.35 (spt, *J*=6.7 Hz, 1H), 4.16 (d, *J*=12.6 Hz, 1H), 3.96 (dd, *J*=4.3,

11.9 Hz, 1H), 3.64 (dd, *J*=4.4, 12.8 Hz, 1H), 2.32 - 2.26 (m, 1H), 2.23 (td, *J*=3.8, 7.3 Hz, 1H), 2.03 (td, *J*=3.8, 7.4 Hz, 1H), 1.50 (d, *J*=6.8 Hz, 6H), 1.46 (d, *J*=6.0 Hz, 6H), 1.43 (t, *J*=3.6 Hz, 1H), 0.75 - 0.68 (m, 4H)

[0451]

Example 59 (1-isopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(4,5,5-trimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

N-methyl-2-propanimine

To a solution of methylamine (1.3 mL, 32.2 mmol) and acetone (9349.65mg, 160.98 mmol) in DMF (22.976 mL) was added 4A MS (3000 mg, 32.2 mmol). The mixture was stirred at 110°C for 4 h. The mixture was filtered to give the title compound (2000 mg, 2.8121 mmol, 8.7345 % yield). The crude product was used directly for next step.

[0452]

tert-butyl (1R,5S,6r)-6-(4,5,5-trimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of Et_3N (0.36 mL, 2.18 mmol) and N-methyl-2-propanimine (258.86mg, 3.64 mmol) was added tert-butyl (1R,5S,6r)-6-[(Z)-chloro(hydroxyimino)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (200 mg, 0.73 mmol). The mixture was stirred at 20 °C for 16 hr. LCMS showed desired mass. The mixture was diluted with H_2O (50 mL) and extracted by EtOAc (30 ml x 2). The organic phase was washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated to give a residue. The residue was purified by flash column (PE:EtOAc=1:0-0:1) to afford the title compound (140mg, 0.4740 mmol, 65.109 % yield) (PE:EtOAc=1:1, Rf=0.3) as a yellow oil. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 3.70 (d, J = 11.2 Hz, 1H), 3.60 (d, J = 11.2 Hz, 1H), 3.50-3.40 (m, 2H), 2.78 (s, 3H), 2.10-2.00 (m, 1H), 2.00-1.90 (m, 1H), 1.44 (s, 9H), 1.41 (s, 6H). 1.16-1.14 (m, 1H).

[0453]

(1R,5S,6r)-6-(4,5,5-trimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)-3-azabicyclo[3.1.0]hexane TFA salt

To a solution of tert-butyl (1R,5S,6r)-6-(4,5,5-trimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (140 mg, 0.47 mmol) in DCM (2.8 mL) was added TFA (0.56 mL, 7.54 mmol). The reaction mixture was stirred at 15°C for 16 hr to

give a brown mixture. LCMS showed the starting material was consumed up. The reaction mixture was concentrated to give the title compound as a brown oil. The residue was used for the next step directly.

LC-MS Method1 0.214 min, MS (m/z) 195.9 ($M + H^+$).

[0454]

(1-isopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(4,5,5-trimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a solution of 5-isopropyl-1H-pyrazole-3-carboxylic acid (72.64mg, 0.47 mmol) in DMF (3.5385 mL) were added HATU (135.48mg, 0.71 mmol) and DIPEA (182.7 mg, 1.41 mmol). The reaction mixture was stirred at 15°C for 30 min. Then (1R,5S,6r)-6-(4,5,5-trimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)-3-azabicyclo[3.1.0]hexane TFA salt (92 mg, 0.47 mmol) was added to the reaction. The reaction mixture was stirred at 15°C for 0.5 hr to give a yellow mixture. LCMS showed the desired MS. The reaction mixture was purified by prep-HPLC (NH_3) to give the title compound (18.72mg, 0.0565 mmol, 11.989 % yield) as white powder.

LC-MS Method1: 331.9 [$M+H^+$]

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.67 (d, *J*=1.2 Hz, 1H), 7.47 (d, *J*=1.2 Hz, 1H), 4.75 (d, *J*=12.0 Hz, 1H), 4.35 (spt, *J*=6.7 Hz, 1H), 4.19 (d, *J*=12.4 Hz, 1H), 3.94 (dd, *J*=4.3, 12.0 Hz, 1H), 3.62 (dd, *J*=4.4, 12.8 Hz, 1H), 2.76 (s, 3H), 2.20 (td, *J*=3.7, 7.3 Hz, 1H), 2.06 - 2.00 (m, 1H), 1.50 (d, *J*=6.4 Hz, 6H), 1.40 (d, *J*=4.0 Hz, 6H), 1.15 (t, *J*=3.4 Hz, 1H)

[0455]

Example 60 [(1R,5S,6r)-6-(4-ethyl-5,5-dimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](1-isopropyl-1H-imidazol-4-yl)methanone

tert-butyl (1R,5S,6r)-6-(4-ethyl-5,5-dimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of Et_3N (0.36 mL, 2.18 mmol) and N-ethylpropan-2-imine (309.93mg, 3.64 mmol) was added tert-butyl (1R,5S,6r)-6-[(Z)-chloro(hydroxyimino)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (200 mg, 0.73 mmol). The mixture was stirred at 20 °C for 16 hr. LCMS showed the desired mass. The mixture was diluted with H_2O (50 mL) and extracted by EtOAc (30 mL x 2). The organic phase was washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated to give a residue. The residue was

purified by flash column (PE:EtOAc=1:0-0:1) to afford the title compound (140mg,0.4525 mmol, 62.158 % yield) (PE:EtOAc=1:1, Rf=0.3) as a yellow oil.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 3.68 (d, J = 11.2 Hz, 1H), 3.58 (d, J = 11.2 Hz, 1H), 3.45-3.30 (m, 2H), 3.18 (q, J = 6.8 Hz, 2H), 2.30-2.20 (m, 1H), 2.00-1.90 (m, 1H), 1.45 (s, 9H), 1.42 (s, 3H), 1.21 (t, J = 6.8 Hz, 3H), 1.14-1.13 (m, 1H).

[0456]

(1R,5S,6r)-6-(4-ethyl-5,5-dimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)-3-azabicyclo[3.1.0]hexane TFA salt

To a solution of tert-butyl (1R,5S,6r)-6-(4-ethyl-5,5-dimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (140 mg, 0.45 mmol) in DCM (2.6731 mL) was added TFA (0.53 mL, 7.2 mmol). The reaction mixture was stirred at 15°C for 16 hr to give a brown mixture. LCMS showed the starting material was consumed up. The reaction mixture was concentrated to give the title compound as brown oil. The residue was used for the next step directly.

LC-MS Method1 0.785 min, MS (m/z) 309.9 ($M + H^+$).

[0457]

[(1R,5S,6r)-6-(4-ethyl-5,5-dimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](1-isopropyl-1H-imidazol-4-yl)methanone

To a solution of 1-isopropylimidazole-4-carboxylic acid (69.24mg, 0.45 mmol) in DMF (3.373 mL) were added HATU (129.15mg, 0.67 mmol) and DIPEA (0.22 mL, 1.35 mmol). The reaction mixture was stirred at 15°C for 30 min. Then the (1R,5S,6r)-6-(4-ethyl-5,5-dimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)-3-azabicyclo[3.1.0]hexane TFA salt (94 mg, 0.45 mmol) was added to the reaction. The reaction mixture was stirred at 15°C for 0.5 hr to give a yellow mixture. LCMS showed the desired MS. The reaction mixture was purified by prep-HPLC (NH_3) to give the title compound (9.9mg, 0.0287 mmol, 6.3809 % yield) as off-white solid.

LC-MS Method1: 346.0 [$M+H^+$]

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.67 (d, *J*=1.2 Hz, 1H), 7.47 (d, *J*=1.2 Hz, 1H), 4.73 (d, *J*=12.0 Hz, 1H), 4.35 (m, 1H), 4.17 (d, *J*=12.6 Hz, 1H), 3.96 (dd, *J*=4.0, 12.0 Hz, 1H), 3.64 (dd, *J*=4.0, 12.6 Hz, 1H), 3.16 (m, 2H), 2.24 (m, 1H), 2.05 (m, 1H), 1.50 (d, *J*=6.8 Hz, 6H), 1.42 (d, *J*=5.6 Hz, 6H), 1.19 (t, *J*=7.2 Hz, 3H), 1.14 (t, *J*=3.4 Hz, 1H)

[0458]

Example 61 (1-isopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

tert-butyl (1R,5S,6r)-6-{[2-(2-pyridinyl)hydrazino]carbonyl}-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a mixture of (1R,5S,6r)-3-{[(tert-butyl)oxy]carbonyl}-3-azabicyclo[3.1.0]hexane-6-carboxylic acid (300 mg, 1.32 mmol) in DMF (5 mL) were added 2-hydrazinylpyridine (144.06 mg, 1.32 mmol), Et_3N (0.2 mL,1.45 mmol), and HATU (555.13 mg, 1.45 mmol). The reaction mixture was stirred at 15°C for 16 h to give brown mixture. The reaction mixture was concentrated in vacuo to give a residue. The residue was purified by silica column (SiO_2, petroleum ether: Ethyl acetate = 6:1 to 0:1) to give the title compound (418 mg, 1.3129 mmol, 99.459 % yield) as yellow gum.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.55 (dd, J = 4.4, 1.6 Hz, 1H), 8.27 (dd, J = 9.2, 1.2 Hz, 1H), 8.03 (d, J = 4.8 Hz, 1H), 7.57 (t, J = 9.2 Hz, 1H), 7.29 (dd, J = 8.4, 4.4 Hz, 1H), 6.80-6.70 (m, 1H), 3.60-3.50 (m, 2H), 3.40-3.30 (m, 3H), 2.10-2.00 (m, 2H), 1.47-1.46 (m, 1H), 1.35 (s, 9H).

[0459]

tert-butyl (1R,5S,6r)-6-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a mixture of tert-butyl (1R,5S,6r)-6-{[2-(2-pyridinyl)hydrazino]carbonyl}-3-azabicyclo[3.1.0]hexane-3-carboxylate (200 mg, 0.63 mmol) in MeCN (4 mL) was added Burgess Reagent (149.7 mg, 0.63 mmol). The reaction mixture was stirred at 90°C for 12h to give yellow mixture. TLC (DCM/MeOH = 10/1) showed the starting materials was consumed completely and a new spot was detected. The reaction mixture was concentrated in vacuo to give residue. The residue was purified by prep-TLC (DCM/MeOH=10/1) to afford the title compound (64mg, 0.2131 mmol, 33.919 % yield) as yellow solid.

LC-MS Method1 0.668, MS (m/z) 300.9 ($M + H^+$).

[0460]

3-[(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl][1,2,4]triazolo[4,3-a]pyridine TFA salt

To a solution of tert-butyl (1R,5S,6r)-6-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (66.2 mg, 0.22 mmol) in DCM (2 mL) was added TFA (0.2 mL, 2.61 mmol). The reaction mixture was stirred at 25°C for 2 h to give yellow

mixture. The reaction mixture was concentrated in vacuo to give the title compound. The crude product was used directly in the next step.

[0461]

(1-isopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a mixture of 3-[(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl][1,2,4]triazolo[4,3-a]pyridine TFA salt (40 mg, 0.20 mmol) in DMF (2 mL) were added 1-isopropylimidazole-4-carboxylic acid (30.8 mg, 0.20 mmol), Et_3N (0.11 mL, 0.80 mmol), and HATU (114.55mg, 0.30 mmol). The reaction mixture was stirred at 25°C for 12 h to give yellow mixture. The crude product was purified by prep-HPLC (NH_3) to give the title compound (8.6 mg, 12.8 % yield) as yellow gum.

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.97 (d, *J*=7.0 Hz, 1H), 7.68 - 7.62 (m, 2H), 7.44 (s, 1H), 7.18 - 7.14 (m, 1H), 6.79 (t, *J*=6.8 Hz, 1H), 4.90 (d, *J*=12.0 Hz, 1H), 4.40 - 4.19 (m, 2H), 4.00 (dd, *J*=4.1, 12.1 Hz, 1H), 3.69 (dd, *J*=4.1, 12.5 Hz, 1H), 2.50 (td, *J*=3.7, 7.3 Hz, 1H), 2.31 (td, *J*=3.7, 7.2 Hz, 1H), 1.88 (t, *J*=3.3 Hz, 1H), 1.45 (d, *J*=6.8 Hz, 6H).

[0462]

Example 62 (1-isopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-([1,2,3]triazolo[1,5-a]pyridin-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

tert-butyl (1R,5S,6r)-6-[hydroxy(2-pyridinyl)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-formyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (0.61 mL, 1.42 mmol) in THF (6 mL) was added bromo(2-pyridyl)magnesium (3.2 mL, 2.13 mmol) at 15°C. The reaction mixture was stirred at 0°C for 4 hr to give a brown mixture. LCMS showed the desired MS. TLC (PE/EtOAc=1:2) showed a new spot. The reaction mixture was quenched with H_2O (30 mL) and extracted with EtOAc (30 mL x 2). The organic layer was washed with brine (30 mL x 2), dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column (PE/EtOAc=1:2) to give the title compound (200 mg, 0.6888 mmol, 48.505 % yield) as light yellow gum.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.53 (d, J = 8.4 Hz, 1H), 7.75-7.65 (m, 1H), 7.40-7.30 (m, 1H), 7.25-7.20 (m, 1H), 4.60-4.25 (m, 2H), 3.60-3.45 (m, 2H), 3.40-3.30 (m, 2H), 1.80-1.60 (m, 2H), 1.43 (s, 9H), 1.00-0.90 (m, 1H).

[0463]

tert-butyl (1R,5S,6r)-6-(2-pyridinylcarbonyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-[hydroxy(2-pyridinyl)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (200 mg, 0.69 mmol) in DCM (4.1931 mL) was added DMP (292.15mg, 0.69 mmol) at 15°C. The reaction mixture was stirred at 15°C for 20 min to give a white mixture. TLC (PE/EtOAc=1:1) showed a new spot. The reaction mixture was quenched with $NaHCO_3$ (30 mL) and extracted with DCM (30 mL x 2). The organic layer was washed with brine (30 mL x 2), dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column (PE/EtOAc=1:1) to give the title compound (200 mg, 0.6936 mmol, 100.7 % yield) as white solid.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.77 (d, J = 4.0 Hz, 1H), 8.10-7.90 (m, 2H), 7.70 (dd, J = 4.8, 3.6 Hz, 1H), 3.57 (d, J = 11.2 Hz, 2H), 3.50-3.40 (m, 2H), 3.24 (s, 1H), 2.23 (s, 2H), 1.41 (s, 3H).

[0464]

tert-butyl (1R,5S,6r)-6-([1,2,3]triazolo[1,5-a]pyridin-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-(2-pyridinylcarbonyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (100 mg, 0.35 mmol) in EtOH (2.0973 mL) was added hydrazine hydrate (26.04mg, 0.52 mmol). The reaction mixture was stirred at 60°C for 6 hr to give a colorless mixture. Then copper acetate (3.45mg, 0.02 mmol), ethyl acetate (10 mL) was added to the reaction mixture. Then the reaction mixture was stirred at 20°C for 1 hr to give a colorless mixture. LCMS showed the desired MS. The reaction mixture was concentrated to give a residue. The residue was purified by prep-TLC (PE/EtOAc=1:1) to give the title compound (20mg, 0.0666 mmol, 19.2 % yield) as colorless oil

LC-MS Method1 0.832 min, MS (m/z) 301.2 ($M + H^+$).

^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.65 (d, J = 7.2Hz, 1H), 7.69 (dd, J = 7.6, 1.2 Hz, 1H), 7.19 (dd, J = 8.0, 5.6 Hz, 1H), 6.95 (t, J = 6.0 Hz, 1H), 3.84 (d, J = 11.2 Hz, 1H), 3.75 (d, J = 11.2 Hz, 1H), 3.60-3.50 (m, 2H), 2.35-2.25 (m, 1H), 2.20-2.10 (m, 1H), 1.95-1.90 (m, 1H), 1.48 (s, 9H).

[0465]

3-[(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl][1,2,3]triazolo[1,5-a]pyridine TFA salt

To a solution of tert-butyl (1R,5S,6r)-6-([1,2,3]triazolo[1,5-a]pyridin-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (30 mg, 0.10 mmol) in DCM (3.14 mL) was added TFA (0.01 mL, 0.10 mmol). The reaction mixture was stirred at 20°C for 16 hr to give a colorless mixture. TLC (PE/EtOAc=1:1) showed a new spot. The reaction mixture was removed the solvent to give the title compound. The residue was used for the next step directly.

LC-MS Method1 0.289 min, MS (m/z) 200.9 ($M + H^+$).

[0466]

(1-isopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-([1,2,3]triazolo[1,5-a]pyridin-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a solution of 1-isopropylimidazole-4-carboxylic acid (23.1mg, 0.15 mmol) in DMF (1.1251 mL) were added HATU (43.08mg, 0.22 mmol) and DIPEA (0.07 mL, 0.45 mmol). The reaction mixture was stirred at 15°C for 30 min. Then 3-[(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl][1,2,3]triazolo[1,5-a]pyridine TFA salt (30 mg, 0.15 mmol) was added to the reaction. The reaction mixture was stirred at 15°C for 0.5 hr to give a yellow mixture. LCMS showed the desired MS. The reaction mixture was purified by prep-HPLC (FA) to give the title compound (14.4mg, 0.0428 mmol, 28.573 % yield) as white powder.

LC-MS Method1: 337.1 [$M+H^+$]

^{1}H NMR (400MHz, DMSO-d_6) δ = 8.94 (d, *J*=7.2 Hz, 1H), 8.12 - 7.73 (m, 3H), 7.35 - 7.22 (m, 1H), 7.10 (m, 1H), 4.77 - 4.41 (m, 2H), 4.22 - 3.85 (m, 2H), 3.60 (br s, 1H), 2.35 - 2.24 (m, 1H), 2.20 - 2.08 (m, 2H), 1.44 (br d, *J*=5.6 Hz, 6H)

[0467]

Example 63 (1-isopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(1H-tetrazol-5-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

tert-butyl (1R,5S,6r)-6-carbamoyl-3-azabicyclo[3.1.0]hexane-3-carboxylate

A solution of (1R,5S,6r)-3-{[(tert-butyl)oxy]carbonyl}-3-azabicyclo[3.1.0]hexane-6-carboxylic acid (1000 mg, 4.4mmol), 1H-benzo[d][1,2,3]triazol-1-ol (713.47mg, 5.28mmol), N-ethyl-N-isopropylpropan-2-amine (0.91mL, 5.28mmol) and EDCI (1012.23mg, 5.28mmol) in DCM (10mL) was stirred at 10 ^{o}C for 30min. Then it was cooled to 0 ^{o}C and NH_3/EtOH (5

mL, 40mmol) was added drop-wise to stirred for 16hr to give a white suspension. TLC (DCM/MeOH =10/1 Rf =0.1) showed a new spot was detected. H_2O (10 mL) was added and it was extracted with EtOAc (10 mLx2). The combined organic layer dried over Na_2SO_4 and concentrated in vacuum to give the title compound (1050mg, 4.6405mmol, 105.46% yield) as white solid.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 5.59 (brs, 1H), 5.29 (brs, 1H), 3.61 (d, J = 11.2 Hz, 1H), 3.59 (d, J = 11.2 Hz, 1H), 3.45-3.35 (m, 2H), 2.27 (t, J = 7.2 Hz, 1H), 2.01 (brs, 2H), 1.37 (s, 9H).

[0468]

<u>tert-butyl (1R,5S,6r)-6-cyano-3-azabicyclo[3.1.0]hexane-3-carboxylate</u>

To a solution of tert-butyl (1R,5S,6r)-6-carbamoyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (620 mg, 2.74mmol)in DMF (12.4mL) was added 2,4,6-trichloro-1,3,5-triazine (0.57mL, 5.48mmol). The reaction mixture was stirred at15 ^{o}C for 16hr to give a yellow solution. TLC (PE/EA =3/1 Rf =0.2) showed a new spot was detected. H_2O(30 mL) was added and it was extracted with EtOAc (30 mLx2). The combined organic layer dried over Na2SO4 and concentrated in vacuum to give the title compound as a yellow oil. The crude was purified by silica gel chromatography (PE/EA= 10/1 to 3/1) to give the title compound (380mg, 1.8246mmol, 66.591% yield) as colorless oil.

[0469]

<u>tert-butyl (1R,5S,6r)-6-(1H-tetrazol-5-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate</u>

A mixture of tert-butyl (1R,5S,6r)-6-cyano-3-azabicyclo[3.1.0]hexane-3-carboxylate (330 mg, 1.58mmol), ammonia hydrochloride (169.52mg, 3.17mmol) and NaN_3 (206.02mg, 3.17mmol) in DMF (7.3333mL) was stirred at 120 ^{o}C for 24 hr to give a yellow solution. TLC (EA, Rf =0.1) showed a new spot was detected. H_2O (10 mL) was added and it was extracted with EtOAc (15 mLx3). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuum to give the title compound (380mg, 1.5123mmol, 95.437% yield) as yellow oil.

^{1}H NMR (400MHz, DMSO-d_6) δ ppm 7.95 (brs, 1H), 3.70-3.40 (m, 4H), 2.15 (brs, 2H), 1.96 (t, J = 3.2 Hz, 1H), 1.40 (s, 9H).

[0470]

<u>(1R,5S,6r)-6-(1H-tetrazol-5-yl)-3-azabicyclo[3.1.0]hexane TFA salt</u>

tert-butyl (1R,5S,6r)-6-(1H-tetrazol-5-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (120 mg, 0.4800mmol) was dissolved in HCl/dioxane (2 mL, 0.4800mmol) and it was stirred

at 15 °C for 2hr to give a colorless solution. The reaction was evaporated in vacuum to give the title compound as a colorless oil. It was directly used in the next step.

[0471]

(1-isopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(1H-tetrazol-5-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

A 100 mL round-bottom flask was charged with 1-isopropylimidazole-4-carboxylic acid (60 mg, 0.39 mmol), HATU (163.66mg, 0.43 mmol), N-ethyl-N-isopropylpropan-2-amine (0.27 mL, 1.56 mmol) and DMF (3 mL). After stirred for 30min, (1R,5S,6r)-6-(1H-tetrazol-5-yl)-3-azabicyclo[3.1.0]hexane TFA salt (103.21mg, 0.39 mmol) was added. The reaction mixture was stirred at 20 °C for 16 hr to give a yellow solution. H_2O (10 mL) was added and it was extracted with EtOAc (10 mL x 2). The H_2O layer was purified by Prep-HPLC (NH_3). The afforded flows were concentrated in vacuum to remove most of CH_3CN and lyophilized to give the title compound (37.35mg, 0.13 mmol, 33.402 % yield) as white solid.

LC-MS Method1: 288.0 [$M+H^+$]

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.14 (br s, 1H), 8.32 (s, 1H), 4.65 (td, *J*=6.64, 13.35 Hz, 1H), 4.17 (br d, *J*=10.88 Hz, 1H), 3.98-4.08 (m, 2H), 2.42 (br d, *J*=3.25 Hz, 1H), 2.32 (br d, *J*=3.75 Hz, 1H), 2.13 (t, *J*=3.31 Hz, 1H), 1.50 (d, *J*=6.63 Hz, 6H)

[0472]

Example 64 (1R,5S,6r)-N-(propan-2-yl)-3-[1-(propan-2-yl)-1H-imidazole-4-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide

tert-butyl (1R,5S,6r)-6-(isopropylcarbamoyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of (1R,5S,6r)-3-{[(tert-butyl)oxy]carbonyl}-3-azabicyclo[3.1.0]hexane-6-carboxylic acid (100 mg, 0.44 mmol) in DMF (1.5 mL) were added HATU (201.87 mg, 0.5300 mmol), Et_3N (0.22 mL, 1.32 mmol) and propan-2-amine (52.02 mg, 0.8800 mmol). The mixture was stirred at 20°C for 12h to give yellow solution. TLC (PE:EtOAc = 1:1) showed a new spot (Rf = 0, 0.7). The reaction mixture was poured into H_2O (10 mL) and extracted with EtOAc (10 mL x 4). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the title compound (110 mg 0.4099 mmol, 93.157 % yield) (crude) as a white solid.

[0473]

(1R,5S,6r)-N-isopropyl-3-azabicyclo[3.1.0]hexane-6-carboxamide TFA salt

To a solution of (1R,5S,6r)-3-{[(tert-butyl)oxy]carbonyl}-3-azabicyclo[3.1.0]hexane-6-carboxylic acid (110 mg, 0.4100 mmol) in DCM (2.8947 mL) was added TFA (0.58 mL, 7.79 mmol). The resulting mixture was stirred at 20 to 25°C for 30 min to give yellow solution. TLC (PE:EtOAc = 1:1) showed a new spot (Rf = 0, 0.4). The reaction mixture was filtered and concentrated under reduced pressure to afford the title compound (110 mg, 0.3897 mmol, 95.072 % yield) (crude) as yellow oil.

[0474]

(1R,5S,6r)-N-(propan-2-yl)-3-[1-(propan-2-yl)-1H-imidazole-4-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide

To a solution of 1-isopropylimidazole-4-carboxylic acid (120.16 mg, 0.78 mmol) in DMF (2 mL) were added HATU (193.68 mg, 0.51 mmol), Et_3N (0.19 mL, 1.17 mmol) and (1R,5S,6r)-N-isopropyl-3-azabicyclo[3.1.0]hexane-6-carboxamide TFA salt (110 mg, 0.39 mmol). The resulting mixture was stirred at 20 to 25°C for 12 hours to give yellow solution. The reaction mixture was poured into H_2O (10 mL) and extracted with EtOAc (10 mL x 4). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (NH_3). The afforded flows were combined and concentrated to remove most of CH_3CN and lyophilized to afford the title compound (50.32 mg, 0.1653 mmol, 42.42 % yield) as white solid.

LC-MS Method1: 305.2 [$M+H^+$]

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.65 (d, *J*=1.3 Hz, 1H), 7.47 (d, *J*=1.3 Hz, 1H), 5.41 (br d, *J*=7.8 Hz, 1H), 4.74 (d, *J*=11.8 Hz, 1H), 4.35 (spt, *J*=6.7 Hz, 1H), 4.17 - 4.02 (m, 2H), 3.90 (dd, *J*=4.0, 12.0 Hz, 1H), 3.61 (dd, *J*=4.0, 12.5 Hz, 1H), 2.19 (td, *J*=3.7, 7.2 Hz, 1H), 2.10 (td, *J*=3.4, 7.3 Hz, 1H), 1.50 (d, *J*=6.8 Hz, 6H), 1.16 - 1.13 (m, 6H)

[0475]

Example 65 (1R,5S,6r)-N-tert-butyl-3-[1-(propan-2-yl)-1H-imidazole-4-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide

tert-butyl (1R,5S,6r)-6-[(tert-butyl)carbamoyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of (1R,5S,6r)-3-{[(tert-butyl)oxy]carbonyl}-3-azabicyclo[3.1.0]hexane-6-carboxylic acid (200 mg, 0.88 mmol) in Pyridine (2 mL) was added 2-methylpropan-2-amine (0.11 mL, 1.06 mmol). The reaction mixture was stirred at 20 °C for 0.5 hr to give a

mixture. Then the EDCI (337.41mg, 1.76 mmol) was added to the reaction mixture. The reaction mixture was stirred at 20°C for 2 hr to give a brown mixture. TLC (PE/EtOAc=1:1) showed a new spot. The reaction mixture was diluted with H2O (10 mL) and extracted with EtOAc (20 mL x 2). The organic layer was dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (PE/EtOAc=1:1) to give the title compound (200 mg, 0.7083 mmol, 80.48 % yield) as white solid.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 5.43 (brs, 1H), 3.64 (d, J = 11.2 Hz, 1H), 3.55 (d, J = 11.2 Hz, 1H), 3.45-3.35 (m, 2H), 1.99 (s, 2H), 1.43 (s, 9H), 1.34 (s, 9H), 1.10-1.05 (m, 1H).

[0476]

(1R,5S,6r)-N-(tert-butyl)-3-azabicyclo[3.1.0]hexane-6-carboxamide TFA salt

To a solution of tert-butyl (1R,5S,6r)-6-[(tert-butyl)carbamoyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (100 mg, 0.35 mmol) in DCM (1.3333 mL) was added TFA (0.01 mL, 0.07 mmol). The reaction mixture was stirred at 20°C for 16 hr to give a colorless mixture. LCMS showed the desired MS. The reaction mixture was removed the solvent to give the title compound. The compound was used for the next step directly.

LC-MS Method1 0.293 min, MS (m/z) 182.9 ($M + H^+$).

[0477]

(1R,5S,6r)-N-tert-butyl-3-[1-(propan-2-yl)-1H-imidazole-4-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide

To a solution of 1-isopropylimidazole-4-carboxylic acid (54.14mg, 0.35 mmol) in Pyridine (2.6371 mL) was added EDCI (134.63mg, 0.70 mmol). The reaction mixture was stirred at 15°C for 30 min. Then (1R,5S,6r)-N-(tert-butyl)-3-azabicyclo[3.1.0]hexane-6-carboxamide TFA salt (64 mg, 0.35 mmol) was added to the reaction. The reaction mixture was stirred at 15°C for 0.5 hr to give a yellow mixture. The reaction mixture was quenched with H_2O and the resulting residue was purified by prep-HPLC (NH_3) to give the title compound (37.57mg, 0.1180 mmol, 33.602 % yield) as light yellow solid.

LC-MS Method1: 319.0 [$M+H^+$]

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.63 (d, *J*=1.2 Hz, 1H), 7.46 (d, *J*=1.2 Hz, 1H), 5.44 (s, 1H), 4.72 (d, *J*=11.2 Hz, 1H), 4.34 (spt, *J*=6.7 Hz, 1H), 4.11 (d, *J*=12.4 Hz, 1H), 3.87 (dd, *J*=3.6, 11.8 Hz, 1H), 3.58 (dd, *J*=4.4, 12.8 Hz, 1H), 2.16 - 2.09 (m, 1H), 2.04 (td, *J*=3.5, 7.3 Hz, 1H), 1.49 (d, *J*=6.8 Hz, 6H), 1.33 (s, 9H), 1.10 (t, *J*=3.1 Hz, 1H)

[0478]

Example 66 (1R,5S,6r)-N-tert-butyl-N-methyl-3-[1-(propan-2-yl)-1H-imidazole-4-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide

tert-butyl (1R,5S,6r)-6-[methyl(tert-butyl)carbamoyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-[(tert-butyl)carbamoyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (50 mg, 0.18 mmol) in DMF (2.4909 mL) was added NaH (8.5mg, 0.35 mmol) at 20 °C. Then the reaction mixture was stirred at 20°C for 1 hr. Then MeI (0.04 mL, 0.71 mmol) in DMF (2.4909 mL) was added. The reaction mixture was stirred at 50°C for 2 hr to give a light yellow mixture. TLC (PE/EtOAc=1:1) showed the new spot. The reaction mixture was quenched with H_2O (10 mL) and extracted with EtOAc (10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure to give the title compound (52mg, 0.1754 mmol, 99.077 % yield) as brown oil

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 3.66 (d, J = 11.2 Hz, 1H), 3.60 (d, J = 11.2 Hz, 1H), 3.50-3.40 (m, 2H), 3.02 (s, 3H), 2.10-2.00 (m, 1H), 2.00-1.90 (m, 1H), 1.50-1.40 (m, 1H), 1.44 (s, 9H), 1.38 (s, 9H),

[0479]

(1R,5S,6r)-N-methyl-N-(tert-butyl)-3-azabicyclo[3.1.0]hexane-6-carboxamide TFA salt

To a solution of tert-butyl (1R,5S,6r)-6-[methyl(tert-butyl)carbamoyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (52 mg, 0.18 mmol) in DCM (1 mL) was added TFA (0.1 mL, 1.35 mmol). The reaction mixture was stirred at 20°C for 16 hr to give a brown mixture. TLC (PE/EtOAc=1:1) showed a new spot. The reaction mixture was concentrated under reduced pressure to give the title compound and it was used for the next step directly.

[0480]

(1R,5S,6r)-N-tert-butyl-N-methyl-3-[1-(propan-2-yl)-1H-imidazole-4-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide

To a solution of 1-isopropylimidazole-4-carboxylic acid (78.54mg, 0.51 mmol) in Pyridine (3.826 mL) was added EDCI (195.32mg, 1.02 mmol). The reaction mixture was stirred at 15°C for 30 min. Then (1R,5S,6r)-N-methyl-N-(tert-butyl)-3-

azabicyclo[3.1.0]hexane-6-carboxamide TFA salt (100 mg, 0.51 mmol) was added to the reaction. The reaction mixture was stirred at 15°C for 0.5 hr to give a yellow mixture. LCMS showed the desired MS. The reaction mixture was purified by prep-HPLC (NH_3) to give the title compound (16.42mg, 0.0494 mmol, 9.6952 % yield) as light yellow solid.

LC-MS Method1: 333.0 [$M+H^+$]

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.66 (d, *J*=1.2 Hz, 1H), 7.47 (d, *J*=1.2 Hz, 1H), 4.66 (d, *J*=12.0 Hz, 1H), 4.40 - 4.31 (m, 1H), 4.11 (d, *J*=12.8 Hz, 1H), 3.97 (dd, *J*=4.3, 12.0 Hz, 1H), 3.65 (dd, *J*=4.3, 12.8 Hz, 1H), 3.00 (s, 3H), 2.20 (td, *J*=3.8, 7.5 Hz, 1H), 2.05 (td, *J*=3.8, 7.4 Hz, 1H), 1.50 (d, *J*=6.8 Hz, 6H), 1.38 (s, 9H)

[0481]

Example 67 (1R,5S,6r)-N-methyl-N-(1-methylcyclopropyl)-3-[1-(propan-2-yl)-1H-imidazole-4-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide

tert-butyl (1R,5S,6r)-6-[(1-methylcyclopropyl)carbamoyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a mixture of (1R,5S,6r)-3-{[(tert-butyl)oxy]carbonyl}-3-azabicyclo[3.1.0]hexane-6-carboxylic acid (500 mg, 2.2 mmol) in DCM (20 mL) were added Et_3N (0.73 mL, 4.4 mmol) and HATU (1.26g, 3.3 mmol). After 10 min, 1-methylcyclopropanamine hydrochloride (236.69mg, 2.2 mmol) was added. The resulting mixture was stirred at 20ºC for 6 hours to give brown mixture. LCMS showed the desired peak was found. The reaction was diluted with H_2O (20 mL) and extracted with EtOAc (30 ml x 3). The combined organic layers were separated, then dried over Na_2SO_4 and concentrated in vacuum to give brown oil. The crude oil was purified by prep-TLC (PE/EtOAc=1/1) to give the title compound (590mg, 2.1044 mmol, 95.651 % yield) as white solid.

LC-MS Method1: 227.0 [$M+H^+$].

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 6.15 - 5.95 (m, 1H), 3.70 - 3.59 (m, 1H), 3.58 - 3.48 (m, 1H), 3.45 - 3.25 (m, 2H), 2.07 - 1.96 (m, 2H), 1.46 - 1.40 (m, 9H), 1.36 (s, 3H), 1.13 - 1.04 (m, 1H), 0.78 - 0.70 (m, 2H), 0.65 - 0.57 (m, 2H)

[0482]

tert-butyl (1R,5S,6r)-6-[methyl(1-methylcyclopropyl)carbamoyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a mixture of tert-butyl (1R,5S,6r)-6-[(1-methylcyclopropyl)carbamoyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (100 mg, 0.4000mmol) in THF (5 mL) was added NaH (23.78mg, 0.5900mmol). The reaction mixture was then stirred at 0ºC for 15 min. Then MeI (0.03mL, 0.4800mmol) was added. The reaction mixture was stirred at 15ºC for 16 hr. TLC (PE/EA=1/1) showed a new spot (Rf=0.5) and the reaction was completed. The mixture was diluted with H_2O (20 mL), extracted with EA (10mL×2), and then washed with H_2O (10mL) and NH_4Cl (10mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum to give crude oil. The crude oil was purified by prep-TLC (PE/EA=1/1) to give the title compound (100 mg, 0.3755mmol, 94.732% yield) as off-white solid.

LC-MS Method1 0.825 min, MS (m/z) 295 ($M + H^+$).

[0483]

(1R,5S,6r)-N-methyl-N-(1-methylcyclopropyl)-3-azabicyclo[3.1.0]hexane-6-carboxamide TFA salt

To a solution of tert-butyl (1R,5S,6r)-6-[methyl(1-methylcyclopropyl)carbamoyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (100 mg, 0.34 mmol) in DCM (2 mL) was added TFA (0.15 mL, 2.04 mmol) at 20°C. The mixture was stirred at 20 °C for 2 hours. LCMS showed the desired peak was found. The reaction mixture was concentrated under reduced pressure to give the title compound (100 mg, crude product) as yellow oil.

LC-MS Method1: 195.0 [$M+H^+$].

[0484]

(1R,5S,6r)-N-methyl-N-(1-methylcyclopropyl)-3-[1-(propan-2-yl)-1H-imidazole-4-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide

To a mixture of 1-isopropylimidazole-4-carboxylic acid (75 mg, 0.49 mmol) in DCM (5 mL) were added HATU (278.97mg, 0.73 mmol) and Et_3N (0.16 mL, 0.97 mmol). The mixture was stirred at 20 ºC for 10 min under N_2. Then (1R,5S,6r)-N-methyl-N-(1-methylcyclopropyl)-3-azabicyclo[3.1.0]hexane-6-carboxamide TFA salt (94.51mg, 0.49 mmol) in DCM (3 mL) was added. The resulting mixture was stirred at 20ºC for 16 hr to give brown mixture. LCMS showed the desired peak was found. The reaction was diluted with H_2O (20 mL) and extracted with DCM (20 mL). The combined organic layers were separated, then dried over Na_2SO_4 and concentrated in vacuum to give brown oil. The brown oil was purified by prep-HPLC (FA). The afforded flows were combined, concentrated to remove

most of CH_3CN, added NH_3H_2O (0.5 mL) and lyophilized to afford the title compound (20mg, 0.0605 mmol, 12.442 % yield) as yellow solid.

LC-MS Method1: 331.1 [$M+H^+$].

^{1}H NMR (400MHz, DMSO-d_6) δ = 7.80 (br s, 2H), 4.66 - 4.37 (m, 2H), 4.00 - 3.78 (m, 2H), 3.50 (br d, *J*=5.1 Hz, 1H), 2.77 (s, 3H), 2.13 - 1.92 (m, 2H), 1.91 - 1.83 (m, 1H), 1.40 (d, *J*=6.6 Hz, 6H), 1.28 (s, 3H), 1.09 - 0.54 (m, 4H)

[0485]

Example 68 (1R,5S,6r)-N-(1-cyanocyclopropyl)-3-[1-(propan-2-yl)-1H-imidazole-4-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide

ethyl (1R,5S,6r)-3-azabicyclo[3.1.0]hexane-6-carboxylate TFA salt

To a mixture of 6-ethyl 3-(tert-butyl) (1R,5S,6r)-3-azabicyclo[3.1.0]hexane-3,6-dicarboxylate (600 mg, 2.35 mmol) in DCM (10 mL) was added TFA (1 mL, 13.46 mmol). The reaction was stirred at 25 °C for 3 h to give brown mixture. The reaction mixture was concentrated in vacuo to give the title compound (300 mg, crude).

[0486]

ethyl (1R,5S,6r)-3-[(1-isopropyl-1H-imidazol-4-yl)carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxylate

To a solution of ethyl (1R,5S,6r)-3-azabicyclo[3.1.0]hexane-6-carboxylate TFA salt (300 mg, 1.18 mmol) in THF (4 mL) were added Et_3N (0.81 mL, 5.88 mmol), 1-isopropylimidazole-4-carboxylic acid (181.16 mg, 1.18 mmol) and HATU (583.98 mg, 1.53 mmol). The resulting mixture was stirred at 20 °C for 12 h to give yellow mixture. The reaction mixture was concentrated and purified by silica column to give the title compound (170 mg, crude) as light yellow gum.

LC-MS Method1 0.598 min, MS (m/z) 291.9 ($M + H^+$).

[0487]

(1R,5S,6r)-3-[(1-isopropyl-1H-imidazol-4-yl)carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid

To a mixture of ethyl (1R,5S,6r)-3-[(1-isopropyl-1H-imidazol-4-yl)carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxylate (170 mg, 0.58 mmol) in THF/H_2O (4 mL, 3/1) was added hydroxylithium hydrate (31.83 mg, 0.76 mmol). The reaction was stirred at 25 °C for

12 h to give yellow mixture. TLC showed the starting material was consumed up. The reaction mixture was concentrated in vacuo to give the title compound (153 mg, crude) as light yellow solid.

LC-MS Method1 0.218 min, MS (m/z) 263.9 ($M + H^+$).

[0488]

(1R,5S,6r)-N-(1-cyanocyclopropyl)-3-[1-(propan-2-yl)-1H-imidazole-4-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide

To a solution (1R,5S,6r)-3-[(1-isopropyl-1H-imidazol-4-yl)carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid (153 mg, 0.58 mmol) in DMF (2 mL) were added HATU (244.37 mg, 0.64 mmol), Et_3N (0.3 mL, 2.32 mmol) and 1-aminocyclopropanecarbonitrile hydrochloride (82.68mg, 0.70 mmol). The reaction mixture was stirred at 25 °C for 12 h to give yellow mixture. The reaction mixture was concentrated in vacuo to give residue. The crude product was purified by prep-HPLC (NH_3) to give the title compound (5.98 mg) as a white solid

LC-MS Method1: 328.1 [$M+H^+$]

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.56 (d, *J*=1.0 Hz, 1H), 7.40 (d, *J*=1.1 Hz, 1H), 6.69 (s, 1H), 4.63 (d, *J*=12.1 Hz, 1H), 4.37 - 4.23 (m, 1H), 4.02 (d, *J*=12.5 Hz, 1H), 3.81 (dd, *J*=3.9, 11.9 Hz, 1H), 3.52 (dd, *J*=4.1, 12.6 Hz, 1H), 2.22 - 2.15 (m, 1H), 2.11 - 2.03 (m, 1H), 1.46 (br d, *J*=2.5 Hz, 2H), 1.43 (d, *J*=6.8 Hz, 6H), 1.18 (br d, *J*=4.1 Hz, 2H), 1.13 (t, *J*=3.1 Hz, 1H)

[0489]

Example 69 (1R,5S,6r)-N-(1-cyanocyclopropyl)-N-methyl-3-[1-(propan-2-yl)-1H-imidazole-4-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide

(1R,5S,6r)-N-(1-cyanocyclopropyl)-N-methyl-3-[1-(propan-2-yl)-1H-imidazole-4-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide

To a mixture of (1R,5S,6r)-N-(1-cyanocyclopropyl)-3-[(1-isopropyl-1H-imidazol-4-yl)carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide (15 mg, 0.05 mmol) in DMF (0.50 mL)/THF (0.50 ml) was added NaH (2.75mg, 0.07 mmol) under ice-cooling. The reaction mixture was stirred for 0.3 h. Then MeI (19.51mg, 0.14 mmol) was added. The mixture was stirred at 30°C for 3 h. The reaction mixture was concentrated directly. Then the residue was purified by prep-HPLC (NH_3) to afford the title compound (2.8 mg, 0.0176 mmol, 38.356 % yield) as white solid.

LC-MS Method1: 341.9 [$M+H^+$]

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.63 (br s, 1H), 7.41 (s, 1H), 4.64 (br s, 1H), 4.34 - 4.22 (m, 1H), 4.11 - 3.92 (m, 2H), 3.66 (br s, 1H), 3.00 - 2.85 (m, 3H), 2.28 (br s, 1H), 2.12 (br s, 1H), 1.84 (br s, 1H), 1.44 (d, *J*=6.8 Hz, 7H), 1.18 (s, 4H)

[0490]

Example 70 (1R,5S,6r)-3-[1-(propan-2-yl)-1H-imidazole-4-carbonyl]-N-[1-(trifluoromethyl)cyclopropyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide

tert-butyl (1R,5S,6r)-6-{[1-(trifluoromethyl)cyclopropyl]carbamoyl}-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of (1R,5S,6r)-3-{[(tert-butyl)oxy]carbonyl}-3-azabicyclo[3.1.0]hexane-6-carboxylic acid (200 mg, 0.88 mmol) in DMF (3 mL) were added HATU (370.09 mg, 0.97 mmol), Et_3N (0.34 mL, 2.64 mmol) and 1-(trifluoromethyl)cyclopropanamine hydrochloride (170.61 mg, 1.06 mmol). The resulting mixture was stirred at 25 ºC for 12 h. TLC (PE:EtOAc = 1:1) showed the reaction was completed. The reaction mixture was poured into H_2O (10 ml) and extracted with EtOAc (10 ml×3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column (PE to 40 % EtOAc in PE) to afford the title compound (328 mg, 0.9811 mmol, 111.48 % yield, crude product) as a white solid.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 6.47 (s, 1H), 3.68 - 3.53 (m, 2H), 3.41 (br d, *J*=11.3 Hz, 2H), 2.12 - 2.03 (m, 2H), 1.48 - 1.46 (m, 1H), 1.44 (s, 9H), 1.31 (br s, 2H), 1.19 (t, *J*=3.1 Hz, 1H), 1.10 (br d, *J*=5.5 Hz, 2H)

[0491]

(1R,5S,6r)-N-[1-(trifluoromethyl)cyclopropyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide TFA salt

To a solution of tert-butyl (1R,5S,6r)-6-{[1-(trifluoromethyl)cyclopropyl]carbamoyl}-3-azabicyclo[3.1.0]hexane-3-carboxylate (50 mg, 0.15 mmol) in DCM (2 mL) was added 2,2,2-trifluoroacetic acid (0.3 mL, 3.92 mmol). The resulting mixture was stirred at 20 to 25 ºC for 2 h. TLC (PE:EtOAc = 1:1) showed the reaction was completed. The mixture was concentrated by purging with N_2 to afford the title compound (30 mg, 0.1281 mmol, 85.645 % yield) as a white solid.

[0492]

(1R,5S,6r)-3-[1-(propan-2-yl)-1H-imidazole-4-carbonyl]-N-[1-(trifluoromethyl)cyclopropyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide

To a solution of 1-isopropylimidazole-4-carboxylic acid (19.75 mg, 0.13 mmol) in DMF (2 mL) were added Et_3N (0.08 mL, 0.64 mmol), HATU (58.76 mg, 0.15 mmol) and (1R,5S,6r)-N-[1-(trifluoromethyl)cyclopropyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide TFA salt (30 mg, 0.13 mmol). The resulting mixture was stirred at 20 to 25 ºC for 16 h. The mixture was filtered and the filtrate was purified by prep-HPLC (NH_3). The afforded flows were combined, concentrated to remove most of CH_3CN and lyophilized to afford the title compound (3.97 mg, 0.0107 mmol, 8.3687 % yield) as a white solid.

LC-MS Method1: 371.1 [$M+H^+$]

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.67 (s, 1H), 7.49 (s, 1H), 6.13 (br s, 1H), 4.77 (br d, *J*=12.0 Hz, 1H), 4.43 - 4.31 (m, 1H), 4.16 (br d, *J*=12.8 Hz, 1H), 3.90 (dd, *J*=3.9, 12.3 Hz, 1H), 3.62 (dd, *J*=3.5, 13.3 Hz, 1H), 2.23 (br d, *J*=3.8 Hz, 1H), 2.15 (br d, *J*=3.3 Hz, 1H), 1.52 (d, *J*=6.6 Hz, 7H), 1.37 - 1.32 (m, 2H), 1.27 (s, 2H), 1.21 (br s, 2H), 1.13 (br d, *J*=7.6 Hz, 2H)

[0493]

Example 71 (1R,5S,6r)-N-methyl-3-[1-(propan-2-yl)-1H-imidazole-4-carbonyl]-N-[1-(trifluoromethyl)cyclopropyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide

tert-butyl (1R,5S,6r)-6-{methyl[1-(trifluoromethyl)cyclopropyl]carbamoyl}-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a mixture of tert-butyl (1R,5S,6r)-6-{[1-(trifluoromethyl)cyclopropyl]carbamoyl}-3-azabicyclo[3.1.0]hexane-3-carboxylate (180 mg, 0.54 mmol) in DMF (2.52 mL) was added NaH (19.38 mg, 0.81 mmol) under ice-cooling after stirring for 0.5 h. Then MeI (382.1 mg, 2.69 mmol) was added. The mixture was stirred at 30 °C for 3 h. TLC (PE:EtOAc = 5:1) showed the reaction was completed (Rf = 0.2). The reaction mixture was poured into H_2O (10 mL) and extracted with EtOAc (10 mL x 4). The combined organic layers were washed with sat. aq. (10 mL x 4), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the title compound (180 mg, 0.5167 mmol, 95.973 % yield) as a yellow oil.

[0494]

(1R,5S,6r)-N-methyl-N-[1-(trifluoromethyl)cyclopropyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide TFA salt

To a solution of tert-butyl (1R,5S,6r)-6-{methyl[1-(trifluoromethyl)cyclopropyl]carbamoyl}-3-azabicyclo[3.1.0]hexane-3-carboxylate (220 mg, 0.63 mmol) in DCM (3 mL) was added 2,2,2-trifluoroacetic acid (0.3 mL, 3.92 mmol). The resulting mixture was stirred at 20 to 25°C for 2 h. TLC (PE:EtOAc = 5:1) showed the reaction was completed. The mixture was concentrated by purging with N_2 to afford the title compound (150 mg, 0.6043 mmol, 95.681 % yield) as a brown solid.

[0495]

(1R,5S,6r)-N-methyl-3-[1-(propan-2-yl)-1H-imidazole-4-carbonyl]-N-[1-(trifluoromethyl)cyclopropyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide

To a solution of 1-isopropylimidazole-4-carboxylic acid (93.16 mg, 0.60 mmol) in DMF (2 mL) were added HATU (277.21 mg, 0.73 mmol) and Et_3N (0.39 mL, 3.02 mmol). The mixture was stirred at 20 to 25°C for 0.5 h. (1R,5S,6r)-N-methyl-N-[1-(trifluoromethyl)cyclopropyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide TFA salt (150 mg, 0.60 mmol) was added and the reaction mixture was stirred at 20-25°C for 16 h. The mixture was then filtered and the filtrate was concentrated. The residue was purified by prep-HPLC (NH_3). The afforded flows were combined, concentrated to remove most of CH_3CN and lyophilized to afford the title compound (36.84 mg, 0.0958 mmol, 15.86 % yield) as a yellow solid.

LC-MS Method1: 385.0 [$M+H^+$]

^{1}H NMR (400MHz, DMSO-d_6) δ = 7.79 (br d, *J*=8.3 Hz, 2H), 4.59 - 4.39 (m, 2H), 3.94 - 3.74 (m, 2H), 3.52 (br d, *J*=12.0 Hz, 1H), 3.15 (s, 1H), 2.89 (s, 3H), 2.17 (br s, 1H), 2.06 (br s, 1H), 1.95 (br s, 1H), 1.80 (br s, 1H), 1.72 - 1.51 (m, 2H), 1.40 (d, *J*=6.8 Hz, 7H)

[0496]

Example 72 (1R,5S,6r)-3-[1-(propan-2-yl)-1H-imidazole-4-carbonyl]-N-(1,1,1-trifluoro-2-methylpropan-2-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide

tert-butyl (1R,5S,6r)-6-[(1,1,1-trifluoro-2-methylpropan-2-yl)carbamoyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of (1R,5S,6r)-3-{[(tert-butyl)oxy]carbonyl}-3-azabicyclo[3.1.0]hexane-6-carboxylic acid (100 mg, 0.44 mmol) and HATU (126.53mg, 0.66 mmol) in DMF (3.3046

mL) was added DIPEA (0.22 mL, 1.32 mmol). The reaction mixture was stirred at 15°C for 30 min. Then 1,1,1-trifluoro-2-methyl-propan-2-amine (55.93mg, 0.44 mmol) was added. The reaction mixture was stirred at 15 °C for 0.5 hr to give a yellow mixture. LCMS showed the desired MS. TLC (PE/EtOAc=1:1) showed a new spot. The reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (30 mL x 2). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by silica column (PE/EtOAc=1:1) to give the title compound (90 mg, 0.2676 mmol, 60.81 % yield) as white solid.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 5.75 (s, 1H), 3.65 (d, J = 11.2 Hz, 1H), 3.57 (d, J = 11.2 Hz, 1H), 3.45-3.35 (m, 2H), 2.02 (brs, 2H), 1.59 (s, 6H), 1.45 (s, 9H).

[0497]

(1R,5S,6r)-N-(1,1,1-trifluoro-2-methylpropan-2-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide TFA salt

To a solution of tert-butyl (1R,5S,6r)-6-[(1,1,1-trifluoro-2-methylpropan-2-yl)carbamoyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (90 mg, 0.27 mmol) in DCM (2 mL) was added TFA (9.53mg, 0.27 mmol). The reaction mixture was stirred at 25 °C for 0.5 hr to give a colorless mixture. TLC (PE/EtOAc=1:1) showed a new spot. The solvent was removed by evaporation to afford the title compound as yellow oil.

[0498]

(1R,5S,6r)-3-[1-(propan-2-yl)-1H-imidazole-4-carbonyl]-N-(1,1,1-trifluoro-2-methylpropan-2-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide

To a solution of 1-isopropylimidazole-4-carboxylic acid (41.12mg, 0.27 mmol) and HATU (76.69mg, 0.40 mmol) in DMF (2.0028 mL) was added DIPEA (0.13 mL, 0.80 mmol). The reaction mixture was stirred at 15°C for 30 min. Then (1R,5S,6r)-N-(1,1,1-trifluoro-2-methylpropan-2-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide TFA salt (63 mg, 0.27 mmol) was added to the reaction. The reaction mixture was stirred at 15 °C for 0.5 hr to give a yellow mixture. LCMS showed the desired MS. The reaction mixture was purified by prep-HPLC (NH_3) to give the title compound (37.38mg, 0.1004 mmol, 37.639 % yield) as light yellow solid.

LC-MS Method1: 373.2 [$M+H^+$]

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.64 (d, *J*=1.2 Hz, 1H), 7.46 (d, *J*=1.2 Hz, 1H), 5.70 (s, 1H), 4.74 (d, *J*=12.0 Hz, 1H), 4.35 (m, 1H), 4.14 (d, *J*=12.3 Hz, 1H), 3.87 (dd, *J*=3.9,

11.9 Hz, 1H), 3.58 (dd, *J*=3.9, 12.4 Hz, 1H), 2.19 - 2.01 (m, 2H), 1.57 (d, *J*=5.5 Hz, 6H), 1.49 (d, *J*=6.8 Hz, 6H), 1.20 (t, *J*=3.0 Hz, 1H)

[0499]

Example 73 (1R,5S,6r)-N-methyl-3-[1-(propan-2-yl)-1H-imidazole-4-carbonyl]-N-(1,1,1-trifluoro-2-methylpropan-2-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide

tert-butyl (1R,5S,6r)-6-[methyl(1,1,1-trifluoro-2-methylpropan-2-yl)carbamoyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-[(1,1,1-trifluoro-2-methylpropan-2-yl)carbamoyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (160 mg, 0.48 mmol) in THF (7.4294 mL) was added NaH (13.7mg, 0.57 mmol) at 0°C and the mixture was stirred at 0°C for 0.5 hr to give a yellow mixture. MeI (0.04 mL, 0.67 mmol) was added to the reaction mixture. The reaction mixture was stirred at 20°C for 16 hr to give a light yellow mixture. TLC (PE/EtOAc=1:1) showed a new spot. LCMS showed the desired MS. The reaction mixture was quenched with H_2O (100 mL) and extracted with EtOAc (50 mL x 3). The organic layer was concentrated to give a residue. The residue was purified by silica column (PE/EtOAc=1:1) to give the title compound (150mg, 0.4281 mmol, 89.996 % yield) as colorless oil.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 3.66 (d, J = 11.2 Hz, 1H), 3.55 (d, J = 11.2Hz, 1H), 3.50-3.40 (m, 2H), 3.15 (s, 3H), 2.20-2.10 (m, 1H), 2.10-2.00 (m, 1H), 1.66 (s, 6H), 1.60-1.50 (m, 1H), 1.44 (s, 9H).

[0500]

(1R,5S,6r)-N-methyl-N-(1,1,1-trifluoro-2-methylpropan-2-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide TFA salt

To a solution of tert-butyl (1R,5S,6r)-6-[methyl(1,1,1-trifluoro-2-methylpropan-2-yl)carbamoyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (100 mg, 0.29 mmol) in DCM (2.1332 mL) was added TFA (10.16mg, 0.29 mmol). The reaction mixture was stirred at 25 °C for 0.5 hr to give a colorless mixture. TLC (PE/EtOAc=1:1) showed a new spot. The reaction mixture was removed the solvent to give the title compound. It was used for the next step directly.

[0501]

(1R,5S,6r)-N-methyl-3-[1-(propan-2-yl)-1H-imidazole-4-carbonyl]-N-(1,1,1-trifluoro-2-methylpropan-2-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide

To a solution of 1-isopropylimidazole-4-carboxylic acid (43.74mg, 0.28 mmol), HATU (81.58mg, 0.43 mmol) in DMF (2.1306 mL) was added DIPEA (0.14 mL, 0.85 mmol). The reaction mixture was stirred at 15 °C for 30 min. Then (1R,5S,6r)-N-methyl-N-(1,1,1-trifluoro-2-methylpropan-2-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide TFA salt (71 mg, 0.28 mmol) was added to the reaction. The reaction mixture was stirred at 15 °C for 0.5 hr to give a yellow mixture. LCMS showed the desired MS. The reaction mixture was purified by prep-HPLC (NH_3) to give the title compound (72.14mg, 0.1867 mmol, 65.805 % yield) as white powder.

LC-MS Method1: 387.2 [$M+H^+$]

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.67 (d, *J*=1.6 Hz, 1H), 7.47 (d, *J*=1.2 Hz, 1H), 4.71 (d, *J*=12.3 Hz, 1H), 4.35 (m, 1H), 4.13 (d, *J*=12.5 Hz, 1H), 3.96 (dd, *J*=4.4, 12.2 Hz, 1H), 3.65 (dd, *J*=4.4, 12.7 Hz, 1H), 3.12 (s, 3H), 2.24 (m, 1H), 2.11 (m, 1H), 1.65 (s, 6H), 1.56 (t, *J*=3.1 Hz, 1H), 1.50 (d, *J*=6.8 Hz, 6H)

[0502]

Example 74 [(1R,5S,6r)-6-(2,2-dimethyl-2,3-dihydro-1H-indole-1-carbonyl)-3-azabicyclo[3.1.0]hexan-3-yl][1-(propan-2-yl)-1H-imidazol-4-yl]methanone

2,2-dimethylindoline

To a solution of 2,2-dimethyl-1,2-dihydro-3H-indol-3-one (270 mg, 1.67 mmol) and trichloroalumane (223.33 mg, 1.67 mmol) in THF (5 mL) was added $LiAlH_4$ (95.47 mg, 2.51 mmol) at 0°C under N_2. The reaction mixture was stirred at 20 °C under N_2 for 2 hours. TLC (PE:EtOAc = 4:1) showed the reaction was completed. The reaction mixture was basified with $NaHCO_3$ aq. to pH = 8, extracted with EtOAC (10 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (PE:EtOAc = 4:1) to afford the title compound (60 mg, 0.4076 mmol, 24.333 % yield) (crude) as yellow oil.

[0503]

tert-butyl (1R,5S,6r)-6-[(2,2-dimethyl-2,3,3a,7a-tetrahydro-1H-indol-1-yl)carbonyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of (1R,5S,6r)-3-{[(tert-butyl)oxy]carbonyl}-3-azabicyclo[3.1.0]hexane-6-carboxylic acid (92.62 mg, 0.41 mmol) in DCM (1 mL) were added HATU (233.71 mg, 0.61 mmol) and Et_3N (0.11 mL, 0.82 mmol). The mixture was stirred at 20°C for 10 minute under N_2. Then 2,2-dimethylindoline (60 mg, 0.41 mmol) was added. The resulting mixture was stirred at 20 °C for 16 h to give brown mixture. The reaction mixture was poured into H_2O (10 mL) and extracted with EtOAc (10 mL x 4). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give brown oil. The residue was purified by prep-TLC (PE:EtOAc = 4:1) to afford the title compound (45 mg, 0.1262 mmol, 30.975 % yield) as a brown oil.

[0504]

(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl(2,2-dimethyl-2,3,3a,7a-tetrahydro-1H-indol-1-yl)methanone TFA salt

To a solution of tert-butyl (1R,5S,6r)-6-[(2,2-dimethyl-2,3,3a,7a-tetrahydro-1H-indol-1-yl)carbonyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (45 mg, 0.13 mmol) in DCM (4 mL) was added TFA (1 mL, 13.46 mmol). The resulting mixture was stirred at 20 to 25°C for 1h. The reaction mixture was purged with N_2 to remove the solvent to afford the title compound (32 mg, 0.1248 mmol, 98.884 % yield) as brown oil.

[0505]

[(1R,5S,6r)-6-(2,2-dimethyl-2,3-dihydro-1H-indole-1-carbonyl)-3-azabicyclo[3.1.0]hexan-3-yl][1-(propan-2-yl)-1H-imidazol-4-yl]methanone

To a solution of 1-isopropylimidazole-4-carboxylic acid (25.02 mg, 0.16 mmol) in DMF (1.5 mL) were added HATU (57.27 mg, 0.15 mmol), Et_3N (0.07 mL, 0.50 mmol) and (1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl(2,2-dimethyl-2,3,3a,7a-tetrahydro-1H-indol-1-yl)methanone TFA salt (32 mg, 0.12 mmol). The resulting mixture was stirred at 20 to 25°C for 12 hours to give green solution. The reaction mixture was poured into H_2O (10 mL) and extracted with EtOAc (10 mL x 4). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (NH_3). The afforded flows were combined, concentrated to remove most of CH_3CN and lyophilized to afford the title compound (18 mg, 0.0459 mmol, 36.738 % yield) as white solid.

LC-MS Method1: 393.0 [$M+H^+$]

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.68 (s, 1H), 7.48 (s, 1H), 7.26 - 7.20 (m, 1H), 7.18 - 7.13 (m, 2H), 7.00 - 6.95 (m, 1H), 4.78 (d, *J*=12.4 Hz, 1H), 4.36 (td, *J*=6.8, 13.5 Hz,

1H), 4.22 (br d, *J*=12.5 Hz, 1H), 4.07 (dd, *J*=4.5, 12.3 Hz, 1H), 3.77 (dd, *J*=4.2, 13.3 Hz, 1H), 2.97 (br s, 2H), 2.46 (dd, *J*=3.6, 7.2 Hz, 1H), 2.30 (br d, *J*=3.3 Hz, 1H), 1.93 (br s, 1H), 1.56 (br s, 2H), 1.56 - 1.52 (m, 4H), 1.50 (d, *J*=6.6 Hz, 6H)

[0506]

Example 75 cyclopropyl{(1R,5S,6r)-3-[(1-isopropyl-1H-imidazol-4-yl)carbonyl]-3-azabicyclo[3.1.0]hex-6-yl}methanone

tert-butyl (1R,5S,6r)-6-[cyclopropyl(hydroxy)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-formyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (500 mg, 2.37 mmol) in THF (5 mL) was drop wise added bromo(cyclopropyl)magnesium (7.1 mL, 3.55 mmol) at 0 °C. The mixture was stirred at 0 °C for 45 min. The mixture was poured into H_2O (40 mL) slowly and extracted by EtOAc (20 mL x 3). The organic phase was washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give the title compound (600 mg, 2.36 mmol) as yellow oil.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 3.75-3.50 (m, 2H), 3.45-3.30 (m, 2H), 2.75-2.55 (m, 2H), 1.57 (s, 2H), 1.44 (s, 9H), 1.10-0.90 (m, 1H), 1.90-1.80 (m, 1H), 0.60-0.45 (m, 2H), 0.30-0.20 (m, 2H).

[0507]

tert-butyl (1R,5S,6r)-6-(cyclopropylcarbonyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-[cyclopropyl(hydroxy)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (550 mg, 2.17 mmol) in DCM (11 mL) was added DMP (1.01 g, 2.39 mmol) at 0 °C. The mixture was stirred at 20 °C for 2 h. TLC (PE:EtOAc = 3:1) showed the starting material (Rf =0.3) was consumed completely and a new spot (Rf =0.6) was detected. The mixture was poured into H_2O (30 mL) slowly, extracted by DCM (25 mL x 3). The organic phase was washed with saturated $NaHCO_3$ (30 mL x 2) and brine (35 mL x 1), dried over anhydrous Na_2SO_4 and concentrated to give a residue. The residue was purified by SiO_2 flash column (PE:EtOAc=10:1-1:1) to afford the title compound (280 mg, 1.11 mmol, 51.3 % yield) as a white solid.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 3.70 (d, J = 11.2 Hz, 1H), 3.61 (d, J = 11.2 Hz, 1H), 3.45-3.40 (m, 2H), 2.10 (s, 2H), 2.10-2.00 (m, 1H), 1.92 (s, 1H), 1.46 (s, 9H), 1.10-1.00 (m, 2H), 0.95-0.90 (m, 2H).

[0508]

(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl(cyclopropyl)methanone

To a solution of tert-butyl (1R,5S,6r)-6-(cyclopropylcarbonyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (80 mg, 0.32 mmol) in DCM (5 mL) was added TFA (1 mL, 13.4 mmol). The mixture was stirred at 25 °C for 2 h. TLC (PE:EtOAc=3:1) showed a new spot (Rf=0) was detected. The mixture was concentrated to afford the title compound (80 mg, 0.52 mmol) as a yellow oil. The crude was used for next directly.

[0509]

cyclopropyl{(1R,5S,6r)-3-[(1-isopropyl-1H-imidazol-4-yl)carbonyl]-3-azabicyclo[3.1.0]hex-6-yl}methanone

To a solution of (1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl(cyclopropyl)methanone (75 mg, 0.5 mmol) and DIPEA (0.41 mL, 2.48 mmol) in DMF (2 mL) was added HATU (189 mg, 0.5 mmol) and 1-isopropylimidazole-4-carboxylic acid (76.4 mg, 0.5 mmol). The mixture were stirred at 20 °C for 16 h. The mixture was diluted with H2O (50 mL), extracted by EtOAc (25 mL x 3). The organic phase was washed by brine (50 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by Prep-HPLC (NH_3) to afford the title compound (7 mg, 0.024 mmol, 4.91% yield) as a white solid.

LC-MS Method1: 288.1 [$M+H^+$]

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.68 (d, *J*=1.5 Hz, 1 H) 7.48 (d, *J*=1.4 Hz, 1 H) 4.75 (d, *J*=12.1 Hz, 1 H) 4.36 (dt, *J*=13.4, 6.7 Hz, 1 H) 4.17 (d, *J*=12.8 Hz, 1 H) 3.95 (dd, *J*=12.2, 3.9 Hz, 1 H) 3.63 (dd, *J*=12.6, 4.1 Hz, 1 H) 2.26 (dt, *J*=7.1, 3.5 Hz, 1 H) 2.16 (dt, *J*=7.2, 3.5 Hz, 1 H) 1.98 - 2.06 (m, 1 H) 1.93 (t, *J*=3.0 Hz, 1 H) 1.51 (d, *J*=6.6 Hz, 6 H) 1.02 - 1.08 (m, 2 H) 0.88 - 0.94 (m, 2 H)

[0510]

Example 76 (1-isopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(2-thienylcarbonyl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

tert-butyl (1R,5S,6r)-6-(2-thienylcarbonyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a mixture of 2-bromothiophene (0.28 mL, 2.84 mmol) in THF (5 mL) was added n-BuLi (1.42 mL, 3.55 mmol) dropwise at -78ºC. The reaction mixture was stirred at -78 ºC for 1h. Then tert-butyl (1R,5S,6r)-6-formyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (500 mg, 2.37 mmol) was added at -78ºC. The resulting mixture was stirred at 25ºC for 30 min. The reaction mixture was diluted with H_2O (10 mL) and then extracted with EtOAc (10 mL×2). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum to give crude oil. The crude oil was purified by flash column (0-30 %EtOAc in PE) to give the title compound (30mg, 0.1023 mmol, 4.3205 % yield) as pale yellow oil.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.75 (s, 1H), 7.60 (s, 1H), 7.09 (s, 1H), 3.80-3.50 (m, 2H), 3.50-3.40 (m, 2H), 2.31 (s, 1H), 2.23 (brs, 2H), 1.40 (s, 9H).

[0511]

(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl(2-thienyl)methanone TFA salt

The mixture of tert-butyl (1R,5S,6r)-6-(2-thienylcarbonyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (30 mg, 0.10 mmol) in DCM (0.50 mL) and TFA (0.1 mL, 0.10 mmol) was stirred at 25°C for 2 hr. The reaction mixture was concentrated to dryness to give the title compound (19mg, 0.0983 mmol, 96.139 % yield) as yellow oil.

[0512]

(1-isopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(2-thienylcarbonyl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a mixture of (1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl(2-thienyl)methanone TFA salt (19 mg, 0.10 mmol) in Pyridine (0.50 mL) were added EDCI (22.61mg, 0.12 mmol) and 1-isopropylimidazole-4-carboxylic acid (15.16mg, 0.10 mmol). The resulting mixture was stirred at 20°C for 16 hr. The reaction mixture was diluted with H_2O (5 mL) and then extracted with EtOAc (5 mL×3). The combined organic layers were washed with brine (10 mL), then dried over Na_2SO_4 and concentrated in vacuum to give the residue. The residue was purified by prep-TLC (EtOAc/MeOH=20/1, 0.05 %$NH_3.H_2O$) to afford the title compound (5mg, 0.0152 mmol, 15.439 % yield) as white solid.

^{1}H NMR (400MHz, CD_3OD) δ = 8.02 (d, *J*=3.0 Hz, 1H), 7.84 (d, *J*=4.8 Hz, 1H), 7.77 (br d, *J*=7.5 Hz, 2H), 7.22 - 7.18 (m, 1H), 4.50 (br d, *J*=8.3 Hz, 2H), 4.14 (br d, *J*=13.1 Hz, 1H), 4.01 (br s, 1H), 3.71 (br s, 1H), 2.59 (s, 1H), 2.38 (br d, *J*=17.8 Hz, 2H), 1.51 (d, *J*=6.5 Hz, 6H), 1.46 (s, 1H), 1.44 - 1.42 (m, 1H).

[0513]

Example 77 (1-isopropyl-1H-imidazol-4-yl){(1R,5S,6r)-6-[(4-methyl-2-thienyl)carbonyl]-3-azabicyclo[3.1.0]hex-3-yl}methanone

tert-butyl (1R,5S,6r)-6-[hydroxy(4-methyl-2-thienyl)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (compound 1) and tert-butyl(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl(4-methyl-2-thienyl)methanone (compound 2)

To a solution of 3-methylthiophene (0.24 mL, 2.55 mmol) in THF (5 mL) was dropwise added 2.5 M n-BuLi in n-Hexane (1.02 mL, 2.55 mmol) at -78°C. The mixture was stirred at -78ºC for 0.5 hour under N_2. Then, tert-butyl (1R,5S,6r)-6-formyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (742.43mg, 3.51 mmol) was added at -78°C. The resulting solution was warmed to 25°C and stirred for 1 hour to give a brown solution. The reaction mixture was diluted with EtOAc and quenched with saturated NH_4Cl solution carefully. The resulting mixture was poured into H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column (PE:EtOAc=30:1) to give the title compound 1 (660mg, 2.133 mmol, 83.76 % yield) as a yellow oil and the title compound 2 (100 mg,0.3253 mmol, 12.774 % yield) as a yellow solid.

[0514]

tert-butyl (1R,5S,6r)-6-[(4-methyl-2-thienyl)carbonyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-[hydroxy(4-methyl-2-thienyl)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (660mg, 2.13 mmol) in DCM (8 mL) was added DMP (1357.05mg, 3.2 mmol) at 0°C. The mixture was stirred at 25°C for 2 hours to give a white suspension. The reaction mixture was poured into H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with $NaHCO_3$.aq. (20 mL) and Na_2SO_3 aq. (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. The crude product was purified by flash column chromatography (PE: EtOAc=30:1) to give the title compound (500 mg, 1.6265 mmol, 76.253 % yield).

[0515]

(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl(4-methyl-2-thienyl)methanone TFA salt

To a solution of tert-butyl (1R,5S,6r)-6-[(4-methyl-2-thienyl)carbonyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (100 mg, 0.33 mmol) in DCM (5 mL) was added TFA (0.75 mL, 9.76 mmol). The resulting mixture was stirred at 25 °C for 2 hours to give a yellow solution. The reaction mixture was evaporated in vacuum to give the title compound (60mg, 0.2894 mmol, 88.98 % yield) as a yellow oil. It was directly used in the next step.

[0516]

(1-isopropyl-1H-imidazol-4-yl){(1R,5S,6r)-6-[(4-methyl-2-thienyl)carbonyl]-3-azabicyclo[3.1.0]hex-3-yl}methanone

To a solution of (1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl(4-methyl-2-thienyl)methanone TFA salt (130 mg, 0.63 mmol) in DMF (4 mL) were added HATU (359.63mg, 0.94 mmol) and Et_3N (0.16 mL, 1.25 mmol). The mixture was stirred at 25ºC for 10 min under N_2. Then, 1-isopropylimidazole-4-carboxylic acid (193.37mg, 1.25 mmol) in DMF (2 mL) was added, the resulting mixture was stirred at 25 ºC for 16 hours to give a yellow mixture. The reaction mixture was poured into H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. The crude product was purified by Prep-HPLC (NH_3) and lyophilized to give the title compound (200 mg, 0.5823 mmol, 92.857 % yield) as a yellow solid.

LC-MS Method1: 344.2 [$M+H^+$]

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.72 (d, *J*=1.3 Hz, 1H), 7.59 (d, *J*=1.0 Hz, 1H), 7.49 (d, *J*=1.3 Hz, 1H), 7.24 (s, 1H), 4.79 (d, *J*=12.3 Hz, 1H), 4.38 (spt, *J*=6.7 Hz, 1H), 4.23 (d, *J*=12.8 Hz, 1H), 4.03 (dd, *J*=4.0, 12.3 Hz, 1H), 3.71 (dd, *J*=3.8, 12.8 Hz, 1H), 2.51 - 2.41 (m, 1H), 2.37 - 2.31 (m, 2H), 2.29 (s, 3H), 1.52 (d, *J*=6.8 Hz, 6H)

[0517]

Example 78 (1-isopropyl-1H-imidazol-4-yl){(1R,5S,6r)-6-[(4-methoxy-2-thienyl)carbonyl]-3-azabicyclo[3.1.0]hex-3-yl}methanone

tert-butyl (1R,5S,6r)-6-[hydroxy(4-methoxy-2-thienyl)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of 3-methoxy thiophen (0.18 mL, 2.13 mmol) in THF (3 mL) was added 2.5 M n-BuLi in n-Hexane (0.85 mL, 2.13 mmol) at -78 °C. The mixture was stirred at -78 °C for 0.5 h under N_2. tert-butyl (1R,5S,6r)-6-formyl-3-azabicyclo[3.1.0]hexane-3-

carboxylate (300 mg, 1.42 mmol) was added at -78 °C. The resulting mixture was stirred at 20 to 25 °C for 2 h. The reaction mixture was poured into sat. NH_4Cl aq. (2 mL) and the aqueous layer was extracted with EtOAc (10 mL x 4). The combined organic layers were washed with sat. aq. (10 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column (PE to 30 % EtOAc in PE) to afford the title compound (380 mg, 1.1677 mmol, 82.231 % yield) as a yellow gum.

[0518]

tert-butyl (1R,5S,6r)-6-[(4-methoxy-2-thienyl)carbonyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-[hydroxy(4-methoxy-2-thienyl)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (380 mg, 1.17 mmol) in THF (4 mL) was added MnO_2 (507.61 mg, 5.84 mmol). The mixture was stirred at 50 °C for 16 h. TLC (PE:EtOAc = 2:1) showed new spots and the starting material was remained. The mixture was then filtered and the filtrate was concentrated in vacuum. The residue was purified by prep-TLC (PE:EtOAc = 2:1) to afford the title compound (60 mg, 0.1855 mmol, 15.888 % yield) as a colorless oil. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.43 (d, *J*=1.8 Hz, 1H), 6.64 (d, *J*=1.6 Hz, 1H), 3.85 (s, 3H), 3.75 (br d, *J*=11.4 Hz, 1H), 3.65 (br d, *J*=10.9 Hz, 1H), 3.50 (br d, *J*=8.9 Hz, 2H), 2.29 (s, 3H), 1.48 (s, 9H)

[0519]

(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl(4-methoxy-2-thienyl)methanone TFA salt

To a solution of tert-butyl (1R,5S,6r)-6-[(4-methoxy-2-thienyl)carbonyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (70 mg, 0.22 mmol) in DCM (3.5 mL) was added 2,2,2-trifluoroacetic acid (0.35 mL, 4.57 mmol). The resulting mixture was stirred at 20 to 25°C for 1 h. TLC (PE:EtOAc = 2:1) showed the reaction was completed (Rf = 0). The mixture was concentrated by purging with N_2 to afford the title compound (48 mg, 0.2150 mmol, 99.318 % yield) as a purple solid.

[0520]

(1-isopropyl-1H-imidazol-4-yl){(1R,5S,6r)-6-[(4-methoxy-2-thienyl)carbonyl]-3-azabicyclo[3.1.0]hex-3-yl}methanone

To a solution of 1-isopropylimidazole-4-carboxylic acid (33.14 mg, 0.21 mmol) in Pyridine (2 mL) were added EDCI (61.81 mg, 0.32 mmol) and (1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl(4-methoxy-2-thienyl)methanone TFA salt(48 mg, 0.21 mmol) at 20 to 25 °C for 2 h. The reaction mixture was concentrated directly. The residue was purified by

prep-HPLC (NH_3) to afford crude product. The crude product was purified by prep-TLC (DCM:MeOH = 10:1) to afford the title compound (5.73 mg, 0.0159 mmol, 7.4158 % yield) as a white solid.

LC-MS Method1: 360.0 [$M+H^+$]

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.72 (s, 1H), 7.54 - 7.48 (m, 1H), 7.40 (d, *J*=1.5 Hz, 1H), 6.63 (d, *J*=1.8 Hz, 1H), 4.79 (d, *J*=12.3 Hz, 1H), 4.38 (td, *J*=6.9, 13.3 Hz, 1H), 4.23 (d, *J*=12.5 Hz, 1H), 4.04 (dd, *J*=4.0, 12.0 Hz, 1H), 3.83 (s, 3H), 3.71 (dd, *J*=3.8, 12.5 Hz, 1H), 2.46 (br d, *J*=3.3 Hz, 1H), 2.35 (br d, *J*=6.3 Hz, 1H), 2.32 - 2.27 (m, 1H), 1.52 (d, *J*=6.5 Hz, 8H)

[0521]

Example 79 (1-isopropyl-1H-imidazol-4-yl){(1R,5S,6r)-6-[(4-methyl-1,3-thiazol-2-yl)carbonyl]-3-azabicyclo[3.1.0]hex-3-yl}methanone

tert-butyl (1R,5S,6r)-6-[hydroxy(4-methyl-1,3-thiazol-2-yl)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of 2-bromo-4-methyl-1,3-thiazole (74.48uL, 0.71 mmol) in THF (2 mL) was added 2.5 M n-BuLi in n-Hexane (0.34 mL, 0.86 mmol) at -78°C. The mixture was stirred at -78ºC for 0.5 h under N_2. Then to the reaction mixture added tert-butyl (1R,5S,6r)-6-formyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (210.89mg, 1 mmol) at -78°C. The resulting solution was warmed to 25°C and stirred for 1 h to give a brown solution. LCMS showed the desire MS. The reaction mixture was poured into NH_4Cl aq. (20 mL) and extracted with EtOAc (20 mL x 4). The combined organic layers were washed with brine (50 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column (PE to 20 % EtOAc in PE) to give the title compound (220mg, 0.7087 mmol, 99.396 % yield) as brown oil.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.68 (s, 1H), 5.00-4.85 (m, 1H), 4.06 (t, J = 10.8 Hz, 2H), 3.90-3.75 (m, 2H), 2.85 (s, 3H), 2.25-2.00 (m, 2H), 1.84 (s, 9H), 1.70-1.60 (m, 1H), 1.55-1.50 (m, 1H).

[0522]

tert-butyl (1R,5S,6r)-6-[(4-methyl-1,3-thiazol-2-yl)carbonyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-[hydroxy(4-methyl-1,3-thiazol-2-yl)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (220 mg, 0.71 mmol) in DCM (4 mL) was added DMP (450.91mg, 1.06 mmol) at 0°C. The mixture was stirred at 25°C for 3h to give white suspension. The reaction mixture was filtered. The filtrate was washed with $NaHCO_3$ aq. (50 mL x 2) and Na_2SO_3.aq. (50 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (220mg, 0.7134 mmol, 100.65 % yield) as brown oil.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.27 (s, 1H), 3.78 (d, J = 11.2 Hz, 1H), 3.72 (d, J = 11.2 Hz, 1H), 3.55-3.45 (m, 2H), 3.15-3.10 (m, 1H), 2.57 (s, 3H), 2.35 (brs, 2H), 1.48 (s, 9H).

[0523]

(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl(4-methyl-1,3-thiazol-2-yl)methanone TFA salt

To a solution of tert-butyl (1R,5S,6r)-6-[(4-methyl-1,3-thiazol-2-yl)carbonyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (100 mg, 0.32 mmol) in DCM (5 mL) was added TFA (1. mL, 0.32 mmol). The mixture was stirred at 25 °C for 30 min to give brown solution. TLC (PE:EtOAc=3:1) showed the reaction was completed. The reaction mixture was concentrated directly to give the title compound (100 mg, 0.3103 mmol, 95.687 % yield, TFA salt) as brown oil.

[0524]

(1-isopropyl-1H-imidazol-4-yl){(1R,5S,6r)-6-[(4-methyl-1,3-thiazol-2-yl)carbonyl]-3-azabicyclo[3.1.0]hex-3-yl}methanone

To a solution of 1-isopropylimidazole-4-carboxylic acid (47.83mg, 0.31 mmol) in DMF (2 mL) were added HATU (142.34mg, 0.37 mmol) and DIPEA (200.5mg, 1.55 mmol). The mixture was stirred at 25 °C for 20 min. Then (1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl(4-methyl-1,3-thiazol-2-yl)methanone TFA salt (100 mg, 0.31 mmol, TFA salt) was added. The mixture was stirred at 25 °C for 2h to give brown solution. The mixture was stirred at 25 °C for 12h to give brown solution. The reaction mixture was concentrated directly. The residue was purified by prep-HPLC (NH_3) to give the title compound (20.22mg, 0.0587 mmol, 18.921 % yield) as yellow solid.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.72 (1 H, d, *J*=1.51 Hz), 7.48 (1 H, d, *J*=1.51 Hz), 7.24 (1 H, d, *J*=0.75 Hz), 4.81 (1 H, d, *J*=12.30 Hz), 4.33 - 4.43 (1 H, m), 4.28 (1 H, d, *J*=13.05 Hz), 4.07 (1 H, dd, *J*=12.30, 4.02 Hz), 3.72 (1 H, dd, *J*=12.80, 4.02 Hz), 3.12 (1 H, t,

J=3.14 Hz), 2.53 (4 H, d, *J*=0.75 Hz), 2.40 (1 H, dt, *J*=7.09, 3.61 Hz), 1.52 (6 H, d, *J*=6.53 Hz)

[0525]

Example 80 (1-isopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(2-pyridinylcarbonyl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

bromo(2-pyridinyl)magnesium

To a solution of 2-bromopyridine (0.61mL, 6.33mmol) in THF (10mL) was added chloro(isopropyl)magnesium (3.2mL, 6.33mmol) at 15 °C. The reaction mixture was stirred at 0 °C for 4 hr to give the title compound as a mixture. The reaction mixture was used for the next step without further purification.

[0526]

tert-butyl (1R,5S,6r)-6-[hydroxy(2-pyridinyl)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-formyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (0.61mL, 1.42mmol) in THF (6mL) was added bromo(2-pyridinyl)magnesium (3.2mL, 2.13mmol) at 15 °C. The reaction mixture was stirred at 0 °C for 4 hr to give a brown mixture. TLC (PE/EA=1:2) showed a new spot. The reaction mixture was quenched with H_2O (30 mL) and extracted with EtOAc (30mLx2). The organic layer was washed with brine (30 mLx2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column (PE/EA=1:2) to give the title compound (460mg, 1.5842mmol, 111.56% yield) as light yellow gum.

^{1}H NMR (400MHz, DMSO-d_6) δ 8.47 (dd, J = 4.4, 0.8 Hz, 1H), 7.78 (t, J = 5.6 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.30-7.20 (m, 1H), 5.41(d, J = 4.8 Hz, 1H), 4.27 (t, J = 5.6 Hz, 1H), 3.40-3.20 (m, 4H), 1.62 (brs, 2H), 1.37 (s, 9H), 1.85-1.75 (m, 1H).

[0527]

tert-butyl (1R,5S,6r)-6-[(2-pyridinyl)carbonyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-[hydroxy(2-pyridinyl)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (460 mg, 1.58mmol) in DCM (9.6442mL) was added DMP (671.94mg, 1.58mmol) at 15 °C. The reaction mixture was stirred at 15 °C for 20 min to give a white mixture. TLC (PE/EA=1:1) showed a new spot. The reaction mixture was quenched with $NaHCO_3$ (30 mL) and extracted with DCM (30 mLx2). The organic layer was washed with brine (30mLx2), dried over anhydrous Na_2SO_4, filtered and concentrated under

reduced pressure to give a residue. The residue was purified by silica gel column (PE/EA=1:1) to give the title compound (340mg, 1.1792mmol, 74.431% yield) as white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.77 (dd, J = 4.4, 0.8 Hz, 1H), 8.02 (t, J = 5.6 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.70-7.60 (m, 1H), 3.57 (d, J = 11.4 Hz, 1H), 3.50-3.25 (m, 3H), 3.25-3.20 (m, 1H), 2.22 (brs, 2H), 1.41 (s, 9H), 1.85-1.75 (m, 1H).

[0528]

(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl(2-pyridinyl)methanone TFA salt

To a solution of tert-butyl (1R,5S,6r)-6-[(2-pyridinyl)carbonyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (58 mg, 0.20 mmol) in DCM (1.5 mL) was added TFA (0.02 mL, 0.20 mmol). The reaction mixture was stirred at 20 °C for 2 hr to give a colorless mixture. The reaction mixture was concentrated under reduced pressure to give the title compound. It was used for the next step directly.

LC-MS Method1: 0.268 min, MS (m/z): 189.0 ($M + H^+$).

[0529]

(1-isopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(2-pyridinylcarbonyl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

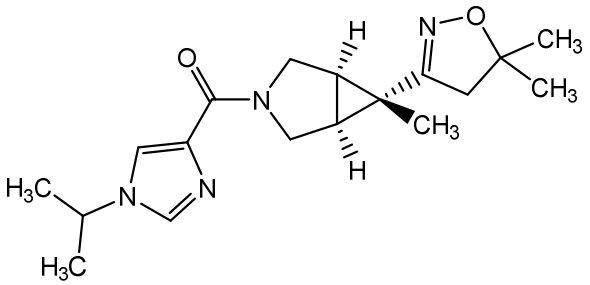
To a solution of (1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl(2-pyridinyl)methanone TFA salt (37 mg, 0.20 mmol) in Pyridine (1.5 mL) were added 1-isopropylimidazole-4-carboxylic acid (45.46 mg, 0.29 mmol) and EDCI(56.52 mg, 0.29 mmol). The reaction mixture was stirred at 20 °C for 16 hr. The solution was purified by prep-HPLC (NH_3) and lyophilized to afford the title compound (7.52 mg, 11.79 % yield) as yellow solid.

LC-MS Method1: 0.363 min, MS (m/z): 325.2 ($M + H^+$).

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.68 (d, *J*=4.77 Hz, 1 H), 8.02 (d, *J*=7.78 Hz, 1 H), 7.81 - 7.86 (m, 1 H), 7.71 (s, 1 H), 7.45 - 7.49 (m, 2 H), 4.79 (d, *J*=12.30 Hz, 1 H), 4.37 (dt, *J*=13.36, 6.74 Hz, 1 H), 4.28 (d, *J*=12.80 Hz, 1 H), 4.08 (dd, *J*=12.17, 3.89 Hz, 1 H), 3.73 (dd, *J*=12.80, 4.02 Hz, 1 H), 3.45 (t, *J*=3.01 Hz, 1 H), 2.44 - 2.49 (m, 1 H), 2.36 (dt, *J*=7.28, 3.64 Hz, 1 H), 1.52 (d, *J*=6.53 Hz, 6 H)

[0530]

Example 81 [(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-6-methyl-3-azabicyclo[3.1.0]hex-3-yl](1-isopropyl-1H-imidazol-4-yl)methanone



ethyl (2E)-2-hydrazonopropanoate

Hydrazine hydrate (0.86g, 17.22mmol) was slowly added to a mixture of glacial HOAc (1.4mL, 24.5mmol) and H_2O (1.4mL, 77.78mmol) at 0 °C. Then ethyl 2-oxopropanoate (0.95mL, 8.61mmol) was added at room temperature. MeOH (0.5 mL) was added in order to obtain a homogeneous solution. The mixture was stirred at 25 °C for 6 h to give yellow solution. TLC (PE:EtOAc=1:1) showed the reaction was completed. The reaction mixture was removed under reduced pressure. H_2O (40 mL) was added to the residued and the mixture was extracted with EtOAc (30 mL x 4). The combined organic phases were washed with saturated sodium hydrogen carbonate (30 mL x2), saturated brine (40 mL x2) and dried over Na_2SO_4. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (PE to 20% EtOAc in PE) to give the title compound (930mg, 7.1456mmol, 82.975% yield) as colorless oil.

LC-MS Method1 0.348 min, MS (m/z) 130.8 [$M+H^+$].

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 5.93 (brs, 2H), 4.28 (q, J = 6.8 Hz, 2H), 1.99 (s, 3H), 1.37 (t, J = 6.8 Hz, 3H).

[0531]

ethyl 3-benzyl-6-methyl-2,4-dioxo-3-azabicyclo[3.1.0]hexane-6-carboxylate

To a solution of ethyl (2E)-2-hydrazonopropanoate (2.5g, 19.21mmol) in 1,4-Dioxane (30mL) was added MnO_2 (10.02g, 115.25mmol). The mixture was stirred at 20 °C for 1.5 h and then filtered through a pad of Celite. To the filtrate was added 1-benzyl-1H-pyrrole-2,5-dione (3.6g, 19.21mmol). The reaction was stirred at 20 °C for 2 h and at 100 °C for 16 h to give yellow solution. TLC (PE:EtOAc=5:1) showed the reaction was completed. The reaction mixture was concentrated directly. The crude product was purified by flash column (PE to 10% EtOAc in PE). The afforded solid was triturated with EtOAc/PE (2 mL/20 mL) and dried in air to give the title compound (1.28g, 4.4551mmol, 23.193% yield) as colorless solid.

LC-MS Method1 0.827 min, MS (m/z) 287.9 [$M+H^+$].

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.45-7.25 (m, 5H), 4.57 (s, 2H), 4.15 (q, J= 6.8 Hz, 2H), 2.89 (s, 2H), 1.25 (t, J = 6.8 Hz, 3H), 1.14 (s, 3H).

[0532]

ethyl 3-benzyl-6-methyl-3-azabicyclo[3.1.0]hexane-6-carboxylate

To a solution of ethyl 3-benzyl-6-methyl-2,4-dioxo-3-azabicyclo[3.1.0]hexane-6-carboxylate (2.5g, 8.7mmol) (crude) in THF (25mL) was added BORANE DIMETHYL SULFIDE COMPLEX (3.48mL, 34.81mmol) at 25 ℃. The mixture was stirred at 70 ℃ for 2h to give colorless suspension. TLC (PE:EtOAc=5:1) showed the reaction was completed. The reaction mixture was added dropwise into MeOH/HCl (12 N) (8:1 = 5mL) and the mixture was stirred for 30 min. Then the mixture was concentrated directly. The crude product was purified by flash column (PE to 10% EtOAc in PE) to the title compound (600 mg, 2.3136mmol, 26.588% yield) as colorless oil.

LC-MS Method1 0.781 min, MS (m/z) 260.1 [M+H$^+$].

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.50-7.30 (m, 5H), 4.10 (q, J = 6.8 Hz, 2H), 4.05 (s, 2H), 3.36 (dt, J = 12.0, 1.2 Hz, 2H), 2.98 (d, J = 5.2 Hz, 1H), 2.88 (d, J = 5.2 Hz, 1H), 2.45-2.40 (m, 1H), 2.20-2.10 (m, 1H), 1.40 (s, 9H), 1.25 (t, J = 6.8 Hz, 3H), 0.70 (s, 1H).

[0533]

[(1R,5S,6r)-3-benzyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl]methanol

To a solution of ethyl 3-benzyl-6-methyl-3-azabicyclo[3.1.0]hexane-6-carboxylate (600 mg, 2.31mmol) in THF (8mL) was added LiAlH4 (131.87mg, 3.47mmol) at 0°C. The mixture was stirred at 0 °C for 10 min to give white suspension. TLC (PE:EtOAc=5:1) showed the reaction was completed. To the reaction mixture was added H_2O (0.15 mL), 1N NaOH aq (0.15mL), H_2O (0.5 ml) continuously and filtered. The filtrate was concentrated to give colorless oil. The crude product was purified by flash column chromatography (PE to 30% EtOAc in PE) to give the title compound (270mg, 1.2425mmol, 53.703% yield) colorless oil.

LC-MS Method1 1.643 min, MS (m/z) 218.2 [M+H$^+$].

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.55-7.50 (m, 2H), 7.45-7.40 (m, 3H), 4.03 (s, 2H), 3.40-3.25 (m, 2H), 3.30 (s, 2H), 3.00-2.90 (m, 2H), 1.60-1.55 (m, 2H), 1.27 (s, 3H). The relative configuration was determined by NoE experiments.

[0534]

tert-butyl (1R,5S,6r)-6-(hydroxymethyl)-6-methyl-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of [(1R,5S,6r)-3-benzyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl]methanol (100 mg, 0.4600mmol) in MeOH (3mL) was added $Pd(OH)_2$ (30 mg, 0.4600mmol). The mixture was stirred at 20°C under H_2 (15 psi) for 12 h to give black solution. TLC (PE:EtOAc=1:1) showed the reaction was completed. The reaction mixture was filtered and the filtrate was concentrated. The residue was diluted with DCM (3 mL) and di-tert-butyl dicarbonate (150.65mg, 0.6900mmol) was added into the solution. The mixture was stirred at 20 °C for 30 min to give colorless solution. The reaction mixture was concentrated directly. The crude product was purified by flash column (PE to 30% EtOAc in PE) to give the title compound (35mg, 0.1540mmol, 33.462% yield) as white solid.
LC-MS Method1 0.710 min, MS (m/z) 171.8 [$M–tBu+H^+$].
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 3.60-3.45 (m, 2H), 3.45-3.35 (m, 2H), 1.50-1.45 (m, 2H), 1.49 (s, 9H), 1.04 (s, 3H).

[0535]

<u>tert-butyl (1R,5S,6r)-6-formyl-6-methyl-3-azabicyclo[3.1.0]hexane-3-carboxylate</u>

To a solution of tert-butyl (1R,5S,6r)-6-(hydroxymethyl)-6-methyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (70 mg, 0.3100mmol) in DCM (2mL) was added DMP (143.68mg, 0.3400mmol) at 0°C. The mixture was stirred at 20 °C for 2 h to give white suspension. TLC (PE:EtOAc=1:1) showed the reaction was completed. The reaction mixture was poured into H_2O (20 mL) and extracted with EtOAc (20 mL x 4). The combined organic layers were washed with $NaHCO_3$.aq. (50 mL), Na_2SO_3.aq. (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (62mg, 0.2752mmol, 89.366% yield) as yellow gum.
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.96 (s, 1H), 3.70-3.55 (m, 2H), 3.48 (d, J = 11.4 Hz, 1H), 3.40 (d, J = 11.4 Hz, 1H), 2.15 (d, J = 2.0 Hz, 1H), 1.45 (s, 9H), 1.72 (s, 3H).

[0536]

<u>tert-butyl (1R,5S,6r)-6-[(E)-(hydroxyimino)methyl]-6-methyl-3-azabicyclo[3.1.0]hexane-3-carboxylate</u>

To a solution of tert-butyl (1R,5S,6r)-6-formyl-6-methyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (62 mg, 0.2800mmol) in EtOH (1.5mL) were added HOAc (15.73uL, 0.2800mmol), KOAc (26.97mg, 0.2800mmol) and hydroxylamine hydrochloride (0.01mL, 0.3300mmol). The mixture was stirred at 20 °C for 2h to give yellow suspension. TLC (PE:EtOAc=3:1) showed the reaction was completed. The reaction mixture was poured into H_2O (20 mL) and extracted with EtOAc (15 mL x 4). The combined organic layers were

washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (65mg,0.2705mmol, 98.286% yield) as yellow solid.
LC-MS Method1 0.727 min, MS (m/z) 185.0 [M–tBu+H^+].
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.03 (s, 1H), 3.65-3.50 (m, 2H), 3.46 (d, J = 11.2 Hz, 1H), 3.39 (d, J = 11.2 Hz, 1H), 1.80 (d, J = 2.4 Hz, 2H), 1.45 (s, 9H), 1.15 (s, 3H).

[0537]

tert-butyl (1R,5S,6r)-6-[(Z)-chloro(hydroxyimino)methyl]-6-methyl-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-[(E)-(hydroxyimino)methyl]-6-methyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (65 mg, 0.2700mmol) in DMF (1.5mL) was added NCS (39.73mg, 0.3000mmol). The mixture was stirred at 20 °C for 14 h to give brown solution. The mixture was poured into H_2O (15 mL) and extracted with EtOAc (15 mL x 5). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4 and concentrated to dryness to give the title compound (70mg, 0.2548mmol, 94.193% yield) as yellow oil.
LC-MS Method1 0.802 min, MS (m/z) 218.9 [M–tBu+H^+].
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.55 (s, 1H), 3.66-3.55 (m, 2H), 3.47 (d, J = 9.0 Hz, 1H), 3.39 (d, J = 9.0 Hz, 1H), 2.15-2.08 (m, 2H) , 1.44 (s, 9H), 1.22 (s, 3H).

[0538]

tert-butyl (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-6-methyl-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-[(Z)-chloro(hydroxyimino)methyl]-6-methyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (70 mg, 0.2500mmol) in DMF (1.5mL) were added Et_3N (0.13mL, 0.7600mmol) and 2-methylprop-1-ene (0.48mL, 0.7600mmol, 2.4 M in THF). The mixture was stirred at 20 °C for 12h to give brown solution. The mixture was poured into H_2O (15 mL) and extracted with EtOAc (15 mL x 5). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4 and concentrated to dryness to give the title compound (70mg, 0.2378mmol, 93.325% yield) as yellow oil.
LC-MS Method1 0.810 min, MS (m/z) 295.1 [M+H^+].
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 3.60-3.55 (m, 2H), 3.46 (d, J = 8.7 Hz, 1H), 3.38 (d, J = 8.7 Hz, 1H), 2.64 (s, 2H), 2.00-1.92 (m, 2H) , 1.45 (s, 9H), 1.36 (s, 6H), 1.16 (s, 3H).

[0539]

(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-6-methyl-3-azabicyclo[3.1.0]hexane TFA salt

To a solution of tert-butyl (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-6-methyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (70 mg, 0.2400mmol) in DCM (5mL) was added TFA (1 mL, 13.46mmol). The mixture was stirred at 20 °C for 30 min to give yellow solution. The reaction mixture was concentrated directly to give the title compound (70 mg crude) as yellow oil.

LC-MS Method1 0.268 min, MS (m/z) 194.9 [$M+H^+$].

^{1}H NMR (400 MHz, DIMETHYL SUlFOXIDE-d6) δ ppm 9.58 (brs, 1H), 8.85 (brs, 1H), 3.65-3.50 (m, 2H), 3.20-3.10 (m, 2H), 2.68 (s, 2H), 2.25 (m, 2H), 1.25 (s, 6H), 1.18 (s, 3H).

[0540]

[(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-6-methyl-3-azabicyclo[3.1.0]hex-3-yl](1-isopropyl-1H-imidazol-4-yl)methanone

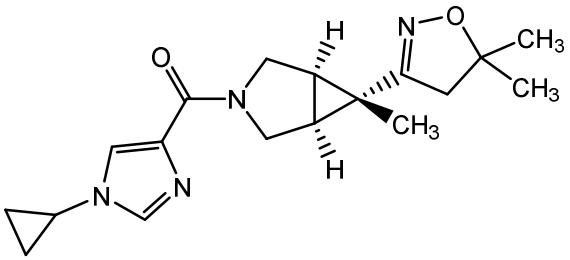
To a solution of 1-isopropylimidazole-4-carboxylic acid (61.11mg, 0.4000mmol) in DMF (2mL) were added HATU (179.08mg, 0.4700mmol), Et_3N (0.2mL, 1.44mmol), and (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-6-methyl-3-azabicyclo[3.1.0]hexane TFA salt (70 mg, 0.3600mmol). The mixture was stirred at 20 ℃ for 12h to give brown solution. The reaction mixture was concentrated directly. The residue was purified by prep-HPLC (NH_3). The afforded flows were combined, concentrated to remove most of CH_3CN and lyophilized to give the title compound (11.6mg, 0.0351mmol, 9.7431% yield) as brown solid.

LC-MS Method1 0.610 min, MS (m/z) 331.1 [$M+H^+$]

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.69 (1 H, s), 7.48 (1 H, s), 4.17 - 4.44 (3 H, m), 3.79 - 3.95 (2 H, m), 2.66 (2 H, d, *J*=1.63 Hz), 2.12 - 2.19 (1 H, m), 1.99 - 2.05 (1 H, m), 1.51 (6 H, dd, *J*=6.69, 1.56 Hz), 1.38 (6 H, s), 1.19 (3 H, d, *J*=1.75 Hz)

[0541]

Example 82 (1-cyclopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-6-methyl-3-azabicyclo[3.1.0]hex-3-yl]methanone



(1-cyclopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-6-methyl-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a solution of 1-cyclopropyl-1H-imidazole-4-carboxylic acid (14.81 mg, 0.10 mmol) in Pyridine (0.75 mL) was added EDCI (27.98 mg, 0.15 mmol). The mixture was stirred for 20 minute. Then (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-6-methyl-3-azabicyclo[3.1.0]hexane TFA salt; (30 mg, 0.10 mmol) was added. The mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated directly. The residue was purified by prep-HPLC (NH_3). The afforded flows were combined, concentrated to remove most of CH_3CN and lyophilized to afford the title compound (9.93 mg, 0.0302 mmol, 31.073% yield) as a yellow gum.

LC-MS Method2 3.650 min, MS (m/z) 329.2 $[M+H]^+$

^1H NMR (400MHz, CHLOROFORM-d) δ = 7.66 (d, *J*=1.5 Hz, 1H), 7.51 (d, *J*=1.3 Hz, 1H), 4.32 - 4.19 (m, 2H), 3.91 - 3.78 (m, 2H), 3.37 (tt, *J*=3.8, 7.2 Hz, 1H), 2.66 (s, 2H), 2.14 (dd, *J*=4.9, 8.2 Hz, 1H), 2.06 - 1.96 (m, 1H), 1.38 (s, 7H), 1.18 (s, 3H), 1.09 - 0.96 (m, 4H)

[0542]

Example 83 [(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-6-methyl-3-azabicyclo[3.1.0]hex-3-yl][1-(1-methylcyclopropyl)-1H-imidazol-4-yl]methanone

[(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-6-methyl-3-azabicyclo[3.1.0]hex-3-yl][1-(1-methylcyclopropyl)-1H-imidazol-4-yl]methanone

To a solution of 1-(1-methylcyclopropyl)-1H-imidazole-4-carboxylic acid (42.77mg, 0.2600mmol) in DMF (1.5mL) were added HATU (127.14mg, 0.3300mmol) and DIPEA (0.21mL, 1.29mmol). The mixture was stirred for 30 min. Then (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-6-methyl-3-azabicyclo[3.1.0]hexane TFA salt (50 mg, 0.2600mmol) was added. The mixture was stirred at 25 °C for 3 h to give brown solution. The

reaction mixture was concentrated directly. The residue was purified by prep-HPLC (NH_3) to give the title compound (33.31mg, 0.0973mmol, 37.794% yield) as brown solid.
LC-MS Method1: 343.3 [$M+H^+$]
^{1}H NMR (400MHz, DMSO-d_6) δ = 7.71 (s, 1H), 7.53 (d, *J*=1.2 Hz, 1H), 4.32 - 4.20 (m, 2H), 3.89 – 3.80 (m, 2H), 2.66 (s, 3H), 2.16 – 1.99 (m, 2H), 1.57 (s, 3H), 1.37 (s, 6H), 1.17 (s, 3H), 1.33 – 1.31 (m, 2H), 0.94 – 0.91 (m, 2H).

[0543]

Example 84 (1-isopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-methyl-6-(4-oxa-5-azaspiro[2.4]hept-5-en-6-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

tert-butyl (1R,5S,6r)-6-methyl-6-(4-oxa-5-azaspiro[2.4]hept-5-en-6-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

tert-butyl (1R,5S,6r)-6-[(Z)-chloro(hydroxyimino)methyl]-6-methyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (300 mg, 1.09mmol) was added gradually to a solution of methylenecyclopropane (0.24mL, 9.96mmol) in THF (13.469mL). Then, Et_3N (0.46mL, 3.28mmol) was added. The reaction mixture was stirred at 0 °C. for 16 hr to give a yellow solution. The reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (30 mLx2). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuum to give a residue. The residue was purified by silica column (PE/EA=2:1) to give the title compound (200 mg, 0.6841mmol, 62.647% yield) as white solid.
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 3.65-3.55 (m, 2H), 3.47 (d, J = 11.2 Hz, 1H), 3.39 (d, J = 11.2 Hz, 1H), 2.96 (s, 2H), 2.10-1.95 (m, 2H), 1.48 (s, 9H), 1.20 (s, 3H), 1.15-1.05 (m, 2H), 0.75-0.65 (m, 2H).

[0544]

6-[(1R,5S,6r)-6-methyl-3-azabicyclo[3.1.0]hex-6-yl]-4-oxa-5-azaspiro[2.4]hept-5-ene TFA salt

To a solution of tert-butyl (1R,5S,6r)-6-methyl-6-(4-oxa-5-azaspiro[2.4]hept-5-en-6-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (200 mg, 0.6800mmol) in DCM (11.901mL) was added 2,2,2-trifluoroacetic acid (0.05mL, 0.6800mmol). The reaction mixture was stirred at 10 °C for 1 hr to give a yellow solution. TLC (PE/EA=1:1) showed a new spot. The reaction mixture was evaporated in vacuum to give the title compound (200 mg, 0.6530mmol, 95.458% yield) as yellow oil.

[0545]

(1-isopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-methyl-6-(4-oxa-5-azaspiro[2.4]hept-5-en-6-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

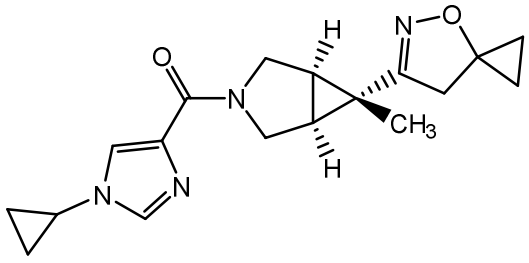
A 100 ml round- bottom flask was charged with 1-isopropylimidazole-4-carboxylic acid (50.34mg, 0.3300mmol), HATU (149.78mg, 0.3900mmol), N-ethyl-N-isopropylpropan-2-amine (0.17mL, 0.9800mmol) and DMF (1.6108mL). After stirred for 30min, 6-[(1R,5S,6r)-6-methyl-3-azabicyclo[3.1.0]hex-6-yl]-4-oxa-5-azaspiro[2.4]hept-5-ene TFA salt (100 mg, 0.3300mmol) was added. The reaction mixture was stirred at 10 °C for 1 hr to give a yellow solution. LCMS showed reactant was completely consumed and the desired MS. The reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (30 mLx2). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuum to give a residue as yellow oil. The crude was purified by Prep-HPLC (NH_3). The afford flows was concentrated in vacuum to remove most of CH_3CN and lyophilized to give the title compound (52.53mg, 0.1600mmol, 48.99% yield) as white solid.

LC-MS Method1: 329.2 [$M+H^+$]

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.69 (d, *J*=1.6 Hz, 1H), 7.48 (d, *J*=1.2 Hz, 1H), 4.39 - 4.22 (m, 3H), 3.89 - 3.84 (m, 2H), 2.98 (s, 2H), 2.20 (m, 1H), 2.06 (m, 1H), 1.50 (d, *J*=6.4 Hz, 6H), 1.22 (s, 3H), 1.16 - 1.07 (m, 2H), 0.74 - 0.67 (m, 2H)

[0546]

Example 85 (1-cyclopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-methyl-6-(4-oxa-5-azaspiro[2.4]hept-5-en-6-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone



(1-cyclopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-methyl-6-(4-oxa-5-azaspiro[2.4]hept-5-en-6-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a solution of 1-cyclopropylimidazole-4-carboxylic acid (25.12mg, 0.1700mmol) in DMF (1mL) were added HATU (71.11mg, 0.1900mmol) and DIPEA (100.16mg, 0.7800mmol). The mixture was stirred at 25 °C for 0.5h. Then 6-[(1R,5S,6r)-6-methyl-3-azabicyclo[3.1.0]hex-6-yl]-4-oxa-5-azaspiro[2.4]hept-5-ene TFA salt (50 mg, 0.1600mmol)

was added to the mixture. The mixture was stirred at 25°C for 12h to give brown solution. LCMS showed the desire MS as a major peak. The reaction mixture was concentrated directly. The residue was purified by prep-HPLC (NH_3) to give the title compound (11.52mg, 0.0353mmol, 20% yield) as brown solid.

LC-MS Method2 1.763 min, MS (m/z) 327.2 [$M+H^+$]

^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.66 (1 H, d, J=1.25 Hz), 7.51 (1 H, d, J=1.25 Hz), 4.18 - 4.35 (2 H, m), 3.82 - 3.92 (2 H, m), 3.37 (1 H, tt, J=7.31, 3.73 Hz), 2.99 (2 H, s), 2.20 (1 H, dd, J=8.16, 5.14 Hz), 2.01 - 2.12 (1 H, m), 1.19 - 1.24 (3 H, m), 1.09 - 1.17 (2 H, m), 0.96 - 1.08 (4 H, m), 0.67 - 0.76 (2 H, m)

[0547]

Example 86 [1-(1-methylcyclopropyl)-1H-imidazol-4-yl][(1R,5S,6r)-6-methyl-6-(4-oxa-5-azaspiro[2.4]hept-5-en-6-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

[1-(1-methylcyclopropyl)-1H-imidazol-4-yl][(1R,5S,6r)-6-methyl-6-(4-oxa-5-azaspiro[2.4]hept-5-en-6-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a solution of 1-(1-methylcyclopropyl) imidazole-4-carboxylic acid (37.98mg, 0.2300mmol) in DMF (2mL) were added HATU (104.22mg, 0.2700mmol) and DIPEA (0.19mL, 1.14mmol). The mixture was stirred at 25 °C for 30 min. Then 6-[(1R,5S,6r)-6-methyl-3-azabicyclo[3.1.0]hex-6-yl]-4-oxa-5-azaspiro[2.4]hept-5-ene TFA salt (70 mg, 0.2300mmol) was added to the mixture. The mixture was stirred at 25 °C for 3h to give brown solution. The reaction mixture was concentrated directly. The residue was purified by prep-HPLC (NH_3) to give the title compound (15.64mg, 0.0459mmol, 20.102% yield) as brown solid.

LC-MS Method1: 341.3 [$M+H^+$]

^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.65 (2 H, br d, J=6.25 Hz) 4.10 - 4.26 (2 H, m) 3.77 - 3.92 (2 H, m) 3.00 (2 H, s) 2.20 - 2.29 (1 H, m) 2.07 - 2.15 (1 H, m) 1.59 (3 H, s) 1.17 - 1.23 (3 H, m) 1.08 - 1.17 (4 H, m) 0.93 - 1.00 (2 H, m) 0.69 - 0.76 (2 H, m)

[0548]

Example 87 (1R,5S,6r)-N-tert-butyl-6-methyl-3-[1-(propan-2-yl)-1H-imidazole-4-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide

(1R,5S,6r)-6-methyl-3-{[(tert-butyl)oxy]carbonyl}-3-azabicyclo[3.1.0]hexane-6-carboxylic acid

To a solution of tert-butyl (1R,5S,6r)-6-formyl-6-methyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (100 mg, 0.44 mmol) in 1-BuOH (1.7 mL, 0.44 mmol), THF (1.7 mL), and H_2O (0.60 mL) were added 2-methylbut-2-ene (0.94 mL, 8.88 mmol), $NaClO_2$ (160.58 mg, 1.78 mmol) and NaH_2PO_4 (490.02 mg, 3.55 mmol). The resulting mixture was stirred at 20 to 25 °C for 16 h. TLC (PE:EtOAc = 2:1) showed the reaction was completed (Rf = 0.5). The reaction mixture was poured into H_2O (10 mL) and extracted with EtOAc (10 mL x 4). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the title compound (167 mg, 0.6921 mmol, 155.93% yield) as a white solid.
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 3.66 - 3.56 (m, 2H), 3.47 - 3.34 (m, 2H), 2.26 - 2.18 (m, 2H), 1.47 - 1.42 (m, 9H), 1.17 (s, 3H)

[0549]

tert-butyl (1R,5S,6r)-6-methyl-6-[(tert-butyl)carbamoyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of (1R,5S,6r)-6-methyl-3-{[(tert-butyl)oxy]carbonyl}-3-azabicyclo[3.1.0]hexane-6-carboxylic acid (100 mg, 0.41 mmol) in Pyridine (1 mL) was added EDCI (119.18 mg, 0.62 mmol). The mixture was stirred at 20 to 25 °C for 0.5 h. Then 2-methylpropan-2-amine (0.04 mL, 0.41 mmol) was added. The resulting mixture was stirred at 20 to 25 °C for 16 h. TLC (PE:EA=1:1) showed the reaction was completed. The crude product was purified by flash column (PE to 30% EtOAc in PE) to afford the title compound (50 mg, 0.1687 mmol, 40.7% yield) as a brown solid.
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 3.67 - 3.55 (m, 2H), 3.36 (d, *J*=11.9 Hz, 1H), 3.28 (d, *J*=11.8 Hz, 1H), 2.15 - 2.04 (m, 2H), 1.48 - 1.42 (m, 9H), 1.48 - 1.42 (m, 1H), 1.39 - 1.30 (m, 9H), 1.13 (s, 3H)

[0550]

(1R,5S,6r)-6-methyl-N-(tert-butyl)-3-azabicyclo[3.1.0]hexane-6-carboxamide TFA salt

A solution of tert-butyl (1R,5S,6r)-6-methyl-6-[(tert-butyl)carbamoyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (50 mg, 0.17 mmol) in DCM (1 mL) and 2,2,2-trifluoroacetic acid (0.1 mL, 1.31 mmol) was stirred at 20 to 25 °C for 1 h. TLC (PE:EtOAc = 1:1) showed the reaction was completed (Rf = 0.3). The reaction mixture was concentrated by purging with N_2 to afford the title compound (30 mg, 0.1528 mmol, 90.604% yield) as a brown oil.

[0551]

(1R,5S,6r)-N-tert-butyl-6-methyl-3-[1-(propan-2-yl)-1H-imidazole-4-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide

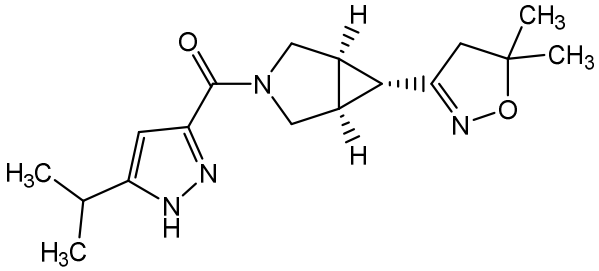
To a solution of 1-isopropylimidazole-4-carboxylic acid (23.56 mg, 0.15 mmol) in DMF (0.50 mL) were added HATU (75.96 mg, 0.20 mmol) and Et_3N (0.06 mL, 0.46 mmol). The mixture was stirred at 20 to 25 °C for 0.5 h. Then (1R,5S,6r)-6-methyl-N-(tert-butyl)-3-azabicyclo[3.1.0]hexane-6-carboxamide TFA salt (30 mg, 0.15 mmol) was added to the mixture. The resulting mixture was stirred at 20 to 25°C for 2 h. LCMS showed the desired MS (as a major peak). The residue was purified by prep-HPLC (NH_3). The afforded flows were combined, concentrated to remove most of CH_3CN and lyophilized to afford the title compound (10.28 mg, 0.0309 mmol, 20.233% yield) as an off-white solid.

LC-MS Method1: 333.1 [$M+H^+$]

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.69 (s, 1H), 7.48 (s, 1H), 5.58 (s, 1H), 4.36 (td, *J*=6.7, 13.4 Hz, 1H), 4.24 (d, *J*=2.3 Hz, 2H), 3.94 - 3.85 (m, 1H), 3.74 (d, *J*=13.3 Hz, 1H), 2.30 - 2.25 (m, 1H), 2.12 (dd, *J*=5.4, 8.2 Hz, 1H), 1.51 (d, *J*=6.8 Hz, 6H), 1.36 (s, 9H), 1.15 (s, 3H)

[0552]

Example 88 [(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](5-isopropyl-1H-pyrazol-3-yl)methanone



[(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](5-isopropyl-1H-pyrazol-3-yl)methanone

To a solution of 5-isopropyl-1H-pyrazole-3-carboxylic acid (21.34mg, 0.1400mmol) in DMF (1mL) were added HATU (63.13mg, 0.1700mmol), DIPEA (0.08mL, 0.4800mmol) and (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (30 mg, 0.1400mmol). The mixture was stirred at 25 °C for 12 h to give brown solution. TLC (PE:EtOAc=1:3) showed a new spot. The reaction mixture was poured into

H_2O (10 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (PE:EtOAc=1:3) and lyophilized to give the title compound (18.42mg,0.0570mmol, 41.171% yield) as white powder.

LC-MS Method1 0.781 min, MS (m/z) 317.0 [$M+H^+$]

^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 6.41 (s, 1 H), 4.13 - 4.28 (m, 2 H), 3.95 (br dd, J=11.17, 4.14 Hz, 1 H), 3.69 (br dd, J=12.92, 4.39 Hz, 1 H), 3.06 (quin, J=6.84 Hz, 1 H), 2.66 (s, 2 H), 2.15 (br dd, J=7.40, 3.39 Hz, 1 H), 2.02 - 2.08 (m, 1 H), 1.47 (t, J=3.26 Hz, 1 H), 1.38 (s, 6 H), 1.27 - 1.31 (m, 6 H)

[0553]

Example 89 (5-sec-butyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

ethyl 5-methyl-2,4-dioxoheptanoate

To a solution of 3-methylpentan-2-one (0.61mL, 4.99mmol) and diethyl oxalate (0.81mL, 5.99mmol) in THF (20mL) was added NaH (239.62mg, 5.99mmol) at 0°C. The reaction was allowed to warm to 20 °C and stirred for further 6h to give pale brown solution. The reaction was cooled to 0 °C, treated with H_2O (30 mL), acidified with 2M HCl to pH=6 and extracted with EA (20 mL x 2). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuum to give the title compound (1000 mg, 4.9943mmol) as pale brown liquid.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 14.60 (brs, 1H), 6.40 (s, 1H), 4.26 (q, J = 6.8 Hz, 2H), 2.55-2.40 (m, 1H), 1.60-1.50 (m, 1H), 1.50-1.35 (m, 1H), 1.38 (t, J = 6.8 Hz, 3H), 1.10 (d, J = 7.4 Hz, 3H), 0.82 (t, J = 6.8 Hz, 3H).

[0554]

ethyl 5-sec-butyl-1H-pyrazole-3-carboxylate

To a solution of ethyl 5-methyl-2,4-dioxoheptanoate (1000 mg, 4.99mmol) in EtOH (20mL) was added hydrazine hydrate (275.01mg, 5.49mmol) at 20 °C. After stirred for 20min, the reaction was heated at 60 °C for further 4h to give yellow mixture. The mixture was concentrated in vacuum to give crude oil. The oil was diluted with EA (40 mL), washed with H_2O (30 mL x 2) and brine (30 mL), then, dried over Na_2SO_4 and concentrated in vacuum to give the title compound (950mg, 4.8408mmol, 96.927% yield) as pale yellow oil.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 6.55 (s, 1H), 4.31 (q, J = 6.8 Hz, 2H), 2.80-2.35 (m, 1H), 1.70-1.50 (m, 2H), 1.37 (t, J = 6.8 Hz, 3H), 1.31 (d, J = 7.4 hz, 3H), 0.82 (t, J = 6.8 Hz, 3H).

[0555]

5-sec-butyl-1H-pyrazole-3-carboxylic acid

To a solution of ethyl 5-sec-butyl-1H-pyrazole-3-carboxylate (950 mg, 4.84mmol) in MeOH (15mL) and H_2O (5mL) was added $LiOH·H_2O$ (0.42mL, 7.26mmol). The reaction was stirred at 20 °C for 12 h to give yellow mixture. The mixture was concentrated to remove MeOH. The residue was diluted with H_2O (5 mL) and washed with DCM (5 mL x 2). The aqueous layer was cooled to 0 °C and acidified with 2M HCl to pH=6. The precipitate was collected and concentrated in vacuum to give the title compound (420mg, 2.4972mmol, 51.586% yield) as a white solid.

[0556]

(5-sec-butyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a solution of 5-sec-butyl-1H-pyrazole-3-carboxylic acid (50 mg, 0.3000mmol) in DMF (1.5mL) were added HATU (125.02mg, 0.3300mmol), (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane TFA salt (70.87mg, 0.3300mmol) and Et_3N (0.1mL, 0.7400mmol). The reaction was stirred at 20 °C for 12h to give pale yellow mixture. The mixture was concentrated in vacuum and purified by prep-HPLC (HCl). The afforded eluent was concentrated and lyophilized to give the title compound (10.38mg, 0.0314mmol, 10.567% yield) as pale yellow solid.

LC-MS Method1: 331.0 [$M+H^+$]

^{1}H NMR (400MHz, DMSO-d_6) δ = 6.51 - 6.28 (m, 1H), 4.30 (br d, *J*=11.9 Hz, 1H), 3.94 (d, *J*=12.3 Hz, 1H), 3.83 (dd, *J*=4.2, 11.8 Hz, 1H), 2.80 - 2.71 (m, 1H), 2.65 (s, 2H), 2.08 (td, *J*=3.7, 7.4 Hz, 1H), 2.00 (td, *J*=3.8, 7.3 Hz, 1H), 1.65 - 1.51 (m, 2H), 1.47 - 1.41 (m, 1H), 1.25 (s, 6H), 1.20 (d, *J*=6.9 Hz, 3H), 0.80 (t, *J*=7.4 Hz, 3H)

[0557]

Example 90 [5-(1-cyclopropylethyl)-1H-pyrazol-3-yl][(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

methyl 5-acetyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-3-carboxylate

A solution of methyl 5-bromo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-3-carboxylate (1500 mg, 4.47mmol, Tetrahedron 2015, 71(39), 7250), tributyl(1-ethoxyvinyl)stannane (1938.94mg, 5.37mmol) and $PdCl_2$(dppf) (163.68mg, 0.2200mmol) in1,4-Dioxane (25mL) was heated to 9 ^{o}C for 16 hr give a yellow solution. 1M HCl aq. (3 mL) was added to be stirred for 10 min. Then the reaction was diluted with H_2O (20 mL) and it was extracted with EtOAc (30 mLx2). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuum to give a yellow oil. The crude was purified by silica gel chromatography (PE/EA= 10/1 to 3/1) to give the title compound (580mg, 1.9436mmol, 43.443% yield) as white solid.

LC-MS Method1 0.972 min, MS (m/z) 299.0 ($M + H^+$).

[0558]

methyl 5-{(1E)-N-[(4-methylphenyl)sulfonyl]ethanehydrazonoyl}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-3-carboxylate

A 100 mL round-bottom flask was charged with methyl 5-acetyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-3-carboxylate (810 mg, 2.71mmol), 4-methylbenzenesulfonohydrazide (505.5mg, 2.71mmol), 4-methylbenzenesulfonic acid (0.02mL, 0.1400mmol) and MeOH (10mL). The reaction was stirred at 40 ^{o}C for 16 hr to give a yellow solution. The reaction mixture was evaporated in vacuum to give the title compound (1250mg, 2.6788mmol, 98.688% yield) as yellow oil. It used directly in the next step.

LC-MS Method1 1.012 min, MS (m/z) 467.1 ($M + H^+$).

[0559]

methyl 5-(1-cyclopropylethyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-3-carboxylate

A round-bottom flask was charged with methyl 5-{(1E)-N-[(4-methylphenyl)sulfonyl]ethanehydrazonoyl}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-3-carboxylate (500 mg, 1.07mmol), cyclopropylboronic acid (138.06mg, 1.61mmol), K_2CO_3 (222.14mg, 1.61mmol) and 1,4-Dioxane (10mL). The reaction was heated to 110 ^{o}C for 2hr to give a white suspension. TLC (PE/EA =10/1, Rf =0.7) showed a new spot. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated in vacuum to give a colorless oil. The crude was purified by silica gel chromatography (PE/EA= 10/1 to 3/1) to give the title compound (230mg, 0.6904mmol, 64.43% yield) as colorless oil.

LC-MS Method1 1.105 min, MS (m/z) 325.2 ($M + H^+$).

[0560]

methyl 5-(1-cyclopropylethyl)-1H-pyrazole-3-carboxylate

A round-bottom flask was charged with methyl 5-(1-cyclopropylethyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-3-carboxylate (230 mg, 0.7100mmol), 2,2,2-trifluoroacetic acid (0.05mL, 0.7100mmol) and DCM (10mL). The reaction mixture was stirred at 20 ^{o}C for 2 hr to give a yellow solution. The reaction mixture was evaporated in vacuum to give the title compound (130mg, 0.6693mmol, 94.428% yield) as yellow oil.
LC-MS Method1 0.785 min, MS (m/z) 195.2 ($M + H^+$).

[0561]

5-(1-cyclopropylethyl)-1H-pyrazole-3-carboxylic acid

A 100 mL round-bottom flask was charged with methyl 5-(1-cyclopropylethyl)-1H-pyrazole-3-carboxylate (130 mg, 0.6700mmol), hydroxylithium hydrate (84.25mg, 2.01mmol), H_2O (1.3mL), THF (1.3mL) and MeOH (1.3mL). The reaction mixture was stirred under N_2 atmosphere for 3 hr to give a yellow solution. H_2O (30 mL) was added and pH value was adjusted to 3 with 1M HCl. It was extracted with EtOAc (30 mLx2). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuum to give the title compound (120mg, 0.6659mmol, 99.495% yield) as yellow oil.
LC-MS Method1 0.732 min, MS (m/z) 181.2 ($M + H^+$).

[0562]

[5-(1-cyclopropylethyl)-1H-pyrazol-3-yl][(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a solution of 5-(1-cyclopropylethyl)-1H-pyrazole-3-carboxylic acid (80 mg, 0.4400mmol) in DMF (2mL) were added HATU (203.67mg, 0.5300mmol) and N-ethyl-N-isopropylpropan-2-amine (0.46mL, 2.66mmol). After stirred for 30 min, (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane TFA salt (278.26mg, 0.5300mmol) was added. The reaction mixture was stirred for 16 hr to give a yellow solution. H_2O (30 mL) was added and it was extracted with EtOAc (30 mLx2). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuum to give a yellow oil. The crude was purified by Prep-TLC (DCM/EA= 3/1) and lyophilized to give the title compound (16.86mg, 0.0459mmol, 10.346% yield) as white solid.
LC-MS Method1: 343.0 [$M+H^+$]
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.55 (s, 1H), 3.33 (d, J = 11.2 Hz, 1H), 3.20 (d, J = 11.2 Hz, 1H), 3.95-3.85 (m, 1H), 3.70-3.60 (m, 1H), 2.65 (s, 2H), 2.20-2.10 (m, 2H), 2.05-2.00 (m,

1H), 1.45-1.40 (m, 1H), 1.38 (s, 9H), 0.95-0.85 (m, 1H), 0.58 (d, J = 7.6 Hz, 2H), 0.30-0.20 (m, 2H).

[0563]

Example 91 [5-(1-cyclobutylethyl)-1H-pyrazol-3-yl][(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

N'-[(1E)-1-cyclobutylethylidene]-4-methylbenzenesulfonohydrazide

A solution of 1-cyclobutylethanone (350 mg, 3.57 mmol) and $TsNHNH_2$ (664.16 mg, 3.57 mmol) in MeOH (7 mL) was stirred at 25 °C for 4 hr. The solvent was concentrated by reduce pressure to give the crude product. The crude product was triturated by (PE:EtOAc=10:1, 10 mL) to afford the title compound (820 mg, 3.0785 mmol, 86.322% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.86 (d, J =8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 3.10-2.90 (m, 1H), 2.43 (s, 3H), 2.10-2.00 (m, 6H), 1.68 (s, 3H).

[0564]

3-(1-cyclobutylvinyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-5-carboxylic acid

To a solution of methyl 3-bromo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-5-carboxylate (300 mg, 0.89 mmol), N'-[(1E)-1-cyclobutylethylidene]-4-methylbenzenesulfonohydrazide (238.34 mg, 0.89 mmol) and t-BuOLi (214.89 mg, 2.68 mmol) in 1,4-Dioxane (5 mL) were added XPhos (42.66 mg, 0.09 mmol) and $Pd_2(dba)_3$ (40.97 mg, 0.04 mmol) at 25 °C under N_2. The mixture was stirred at 110 °C for 12 hr. The mixture was poured into H_2O (10 mL), and then adjusted pH to 4 to 5 by 1M HCl and extracted by EtOAc (10 mLx3). The organic phase was washed by brine (15 mL), then dried over anhydrous Na_2SO_4 and the solvent was removed. The residue was purified by SiO_2 column chromatography (PE:EtOAc=1:0-5:1, 0.5%FA) to afford the title compound (200 mg,0.6202mmol, 69.313% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.23 (s, 1H), 7.05 (s, 1H), 5.81 (s, 2H), 5.81 (s, 1H), 3.70-3.60 (m, 2H), 3.00-2.80 (m, 2H), 2.30-1.90 (m, 6H), 1.00-0.90 (m, 2H), 0.03 (s, 9H).

[0565]

3-(1-cyclobutylethyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-5-carboxylic acid

To a solution of 3-(1-cyclobutylvinyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-5-carboxylic acid (200 mg, 0.62 mmol) in MeOH (4 mL) was added Pd/C (100 mg)

under N_2. The mixture was stirred at 25 °C under H_2 (15 psi) for 12 hr. The mixture was filtered through Celite and the filtrate was concentrated to give the title compound (200 mg, 0.6164 mmol, 99.377% yield) as a colorless oil. The crude was used directly for next step.
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.77 (s, 2H), 5.80-5.70 (m, 2H), 3.60-3.50 (m, 2H), 2.80-2.70 (m, 1H), 2.45-2.30 (m, 1H), 2.20-2.00 (m, 1H), 1.80-1.60 (m, 5H), 1.43 (d, J = 6.8 Hz, 3H), 0.80-0.70 (m, 2H), 0.06 (s, 9H).

[0566]

methyl 3-(1-cyclobutylethyl)-1H-pyrazole-5-carboxylate

To a solution of 3-(1-cyclobutylethyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-5-carboxylic acid (100 mg, 0.310 mmol) in MeOH (4 mL) was added TFA (175.69 mg, 1.54 mmol) at 25 °C. The mixture was stirred at 60 °C for 12 hr. The mixture was stirred at 70 °C for 6 hr. The mixture was concentrated to give the crude title compound (100 mg, 0.2881 mmol, 93.486% yield) as yellow oil. The crude was used directly for next step.
LC-MS Method1: 0.818 min, MS (m/z) 209.1 ($M + H^+$).

[0567]

3-(1-cyclobutylethyl)-1H-pyrazole-5-carboxylic acid

To a solution of methyl 3-(1-cyclobutylethyl)-1H-pyrazole-5-carboxylate (100 mg, 0.480 mmol) in THF (1 mL) and H_2O (2 mL) was added $LiOH·H_2O$ (80.59 mg, 1.92 mmol). The mixture was stirred at 20 °C for 2 hr. The mixture was diluted with H_2O (10 mL), adjusted pH to 4 to 5 by 1M HCl and extracted by EA (10mL x 3). The combined organic layer was dried over Na_2SO_4 and the solvent was removed to give the title compound (80 mg, 0.4119 mmol, 85.779% yield) as a yellow oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.66 (s, 1H), 2.90-2.70 (m, 1H), 2.50-2.30 (m, 1H), 2.00-1.50 (m, 6H), 1.25 (d, J = 6.8 Hz, 3H).

[0568]

[5-(1-cyclobutylethyl)-1H-pyrazol-3-yl][(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a solution of 3-(1-cyclobutylethyl)-1H-pyrazole-5-carboxylic acid (120 mg, 0.62 mmol) and EDCI (130 mg, 0.68 mmol) in Pyridine (5 mL) was added (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane TFA salt (120 mg, 0.67 mmol). The mixture was stirred at 20 °C for 2 h. The reaction mixture was concentrated to give a residue. The residue was purified by Prep-HPLC (NH_3) to give the title compound (10 mg, 0.028 mmol) as a white solid.

LC-MS Method1: 357.1 [M+H$^+$]

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.44 (s, 1 H) 4.32 (d, J=11.6 Hz, 1 H) 4.20 (d, J=12.6 Hz, 1 H) 3.92 (dd, J=11.4, 4.3 Hz, 1 H) 3.65 (dd, J=12.6, 4.3 Hz, 1 H) 3.60 - 3.70 (m, 1 H)2.82-2.78 (m, 1 H) 2.66 (s, 2 H) 2.35 - 2.46 (m, 1 H) 1.73 - 2.17 (m, 8 H) 1.44 (t, J=3.4 Hz, 1 H) 1.38 (s, 6 H) 1.18 (d, J=7.0 Hz, 3 H)

[0569]

Example 92 (5-cyclopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

(5-cyclopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a stirred solution of 5-cyclopropyl-1H-pyrazole-3-carboxylic acid (23.0 mg, 0.151 mmol) and HATU (57.5 mg, 0.151 mmol) in THF (0.76 mL) was added DIPEA (0.13 mL, 0.756 mmol). After stirred at 50 °C for 30 min, (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (36.0 mg, 0.166 mmol) was added and the reaction was stirred at 50 ºC for 1 hr to give a yellow solution. H_2O was added and it was extracted with DCM. The combined organic layer was dried over Na_2SO_4 and concentrated in vacuum to give a yellow oil. The crude was purified by silica gel chromatography (EtOAc / DCM = 99 / 1 to 80 / 20) to give the title compound (14.7 mg, 0.047 mmol, 47.5 % yield) as a beige powder.

LC-MS Method1: 315.0[M+H$^+$]

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 6.30 (s, 1H), 4.23 (d. J=11.7 Hz, 1H), 4.18 (d. J=12.9 Hz, 1H), 3.88 (dd, J=11.1, 4.2 Hz, 1H), 3.64 (dd, J=12.9, 4.5 Hz, 1H), 2.65 (s, 2H), 2.15-2.01 (m, 2H), 1.92-1.87 (m, 1H),1.42 (t, J=3.0 Hz, 1H), 1.37 (s, 6H), 0.99-0.94 (m, 2H), 0.77-0.72 (m, 2H)

[0570]

Example 93 (5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(5-methyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

(5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(5-methyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a mixture of (1R,5S,6r)-6-(5-methyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (50 mg, 0.3000mmol) in DMF (0.50 mL) were added DIPEA (0.2mL, 1.2mmol), 5-isopropyl-1H-pyrazole-3-carboxylic acid (46.38mg, 0.3000mmol) and HATU (148.6mg, 0.3900mmol). The resulting mixture was stirred at 20 ºC for 16 hr to give brown mixture. TLC (PE/EA=0/1) showed new spots and the reactant was consumed completed. The reaction mixture was diluted with H_2O (5mL), extracted with EtOAc (5mL×2), and then washed with H_2O (5mL) and brine (5mL×2). The combined organic layers were separated, then dried over Na_2SO_4 and concentrated in vacuum to give crude product. The crude product was purified by prep-HPLC (NH_3) to give the title compound (2.11mg, 0.0070mmol, 2.3198% yield) as white solid.

^{1}H NMR (400MHz, $CDCl_3$) δ = 6.40 (s, 1H), 4.63 - 4.56 (m, 1H), 4.23 (br d, *J*=11.3 Hz, 1H), 4.13 (d, *J*=12.8 Hz, 1H), 3.84 (dd, *J*=4.3, 11.5 Hz, 1H), 3.58 (dd, *J*=4.0, 12.8 Hz, 1H), 2.98 - 2.88 (m, 2H), 2.47 - 2.38 (m, 1H), 2.08 (br d, *J*=3.5 Hz, 1H), 1.98 (br s, 1H), 1.28 - 1.20 (m, 12H)

[0571]

Example 94 {(1R,5S,6r)-6-[5,5-dimethyl-4-(3-methylphenyl)-4,5-dihydro-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hex-3-yl}(5-isopropyl-1H-pyrazol-3-yl)methanone

tert-butyl (1R,5S,6r)-6-[5,5-dimethyl-4-(3-methylphenyl)-4,5-dihydro-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-[(Z)-chloro(hydroxyimino)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (220 mg, 0.8400mmol) and 1-methyl-3-(2-methyl-1-propen-1-yl)benzene (246.78mg, 1.69mmol) in DCM (5mL) was added triethylamine (0.23mL, 1.69mmol). The reaction mixture was stirred at 10 ºC for 16 hr to give a yellow solution. TLC (PE/EA =3/1 Rf =0.7) showed a new spot was detected. H_2O (15 mL) was added and it was extracted with EtOAc (15 mLx2). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuum to give a yellow oil. The crude was purified by silica gel chromatography (PE/EA= 1/0 to 3/1) to give the title compound (120mg, 0.3239mmol, 38.385% yield) as yellow oil.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.40-7.30 (m, 1H), 7.20-7.10 (m, 1H), 6.80-6.70 (m, 2H), 3.62 (s, 1H), 3.55-3.35 (m, 2H), 3.35-3.20 (m, 2H), 2.29 (s, 3H), 1.70-1.60 (m, 1H), 1.32 (s, 9H), 1.108 (s, 3H), 0.86 (s, 3H), 0.60-0.50 (m, 2H).

[0572]

(1R,5S,6r)-6-[5,5-dimethyl-4-(3-methylphenyl)-4,5-dihydro-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hexane TFA salt

A solution of tert-butyl (1R,5S,6r)-6-[5,5-dimethyl-4-(3-methylphenyl)-4,5-dihydro-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (120 mg, 0.3200mmol) in HCl/dioxane (2 mL, 0.3200mmol) was stirred at 10 ^{o}C for 3 hr to give a yellow solution. It was evaporated in vacuum to give the title compound (110mg, 0.3585mmol, 110.69% yield) as yellow oil

[0573]

{(1R,5S,6r)-6-[5,5-dimethyl-4-(3-methylphenyl)-4,5-dihydro-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hex-3-yl}(5-isopropyl-1H-pyrazol-3-yl)methanone

To a solution of 5-isopropyl-1H-pyrazole-3-carboxylic acid (12 mg, 0.0800mmol) and N-ethyl-N-isopropylpropan-2-amine (0.04mL, 0.2300mmol) in DMF (1mL) was added HATU (32.73mg, 0.0900mmol). After stirred for 30 min, (1R,5S,6r)-6-[5,5-dimethyl-4-(3-methylphenyl)-4,5-dihydro-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hexane TFA salt (20.3mg, 0.0700mmol) was added to be stirred for 16 hr to give a yellow solution. H_2O (30 mL) was added and it was extracted with EtOAc (30 mLx2). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuum to give a yellow oil. The crude was purified by Prep-HPLC (FA). The afford flows were concentrated in vacuum to remove most of CH_3CN and lyophilized to give the title compound (1.25mg,0.0031mmol, 3.9505% yield) as white solid.

LC-MS Method1: 407.1 [M+H$^+$]

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.22 (d, *J*=7.50 Hz, 1H), 7.11 (br d, *J*=7.38 Hz, 1H), 6.81-6.87 (m, 2H), 6.40 (s, 1H), 4.10-4.20 (m, 1H), 3.98-4.08 (m, 1H), 3.84 (ddd, *J*=4.44, 11.29, 19.54 Hz, 1H), 3.70 (d, *J*=3.00 Hz, 1H), 3.57 (td, *J*=4.60, 12.57 Hz, 1H), 2.99 (td, *J*=6.86, 13.91 Hz, 1H), 2.35 (s, 3H), 2.29 (td, *J*=3.86, 7.41 Hz, 1H), 2.13 (td, *J*=3.77, 7.35 Hz, 1H), 2.01 (td, *J*=3.81, 7.13 Hz, 1H), 1.89 (td, *J*=3.85, 7.32 Hz, 1H), 1.39 (s, 3H), 1.27 (d, *J*=7.00 Hz, 6H), 0.94 (s, 3H)

[0574]

Example 95 (5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(4-oxa-5-azaspiro[2.4]hept-5-en-6-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

(5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(4-oxa-5-azaspiro[2.4]hept-5-en-6-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

A 100 ml round-bottom flask was charged with 5-isopropyl-1H-pyrazole-3-carboxylic acid (125 mg, 0.8100mmol), HATU (371.96mg, 0.9700mmol), DMF (4mL), N-ethyl-N-isopropylpropan-2-amine (0.42mL, 2.43mmol) and DMF (4mL). After stirred for 30 min, 6-[(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl]-4-oxa-5-azaspiro[2.4]hept-5-ene hydrochloride (236.95mg, 0.8100mmol) was added .The reaction mixture was stirred at 10 °C for 16 hr to give a yellow solution. H_2O (20 mL) was added and it was extracted with EtOAc (30 mLx2). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuum to give a yellow oil. The crude was purified by Prep- HPLC (FA). The afford flows were concentrated in vacuum to remove most of CH_3CN and lyophilized to give the title compound (36.35mg,0.1156mmol, 14.261% yield) as white solid.

LC-MS Method1: 315.1 [$M+H^+$]

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 6.48 (s, 1H), 4.29-4.34 (m, 1H), 4.21 (d, *J*=12.55 Hz, 1H), 3.93 (dd, *J*=4.52, 11.54 Hz, 1H), 3.66 (dd, *J*=4.39, 12.67 Hz, 1H), 3.00-3.06 (m, 1H), 2.98 (s, 2H), 2.19 (td, *J*=3.58, 7.40 Hz, 1H), 2.08 (td, *J*=3.89, 7.28 Hz, 1H), 1.50 (t, *J*=3.39 Hz, 1H), 1.30 (d, *J*=7.03 Hz, 6H), 1.09-1.14 (m, 2H), 0.65-0.74 (m, 2H)

[0575]

Example 96 (5-isopropyl-1H-pyrazol-3-yl){(1R,5S,6r)-6-[(1S,5S)-2-oxa-3-azabicyclo[3.1.0]hex-3-en-4-yl]-3-azabicyclo[3.1.0]hex-3-yl}methanone

(5-isopropyl-1H-pyrazol-3-yl){(1R,5S,6r)-6-[(1S,5S)-2-oxa-3-azabicyclo[3.1.0]hex-3-en-4-yl]-3-azabicyclo[3.1.0]hex-3-yl}methanone

12 mg of (5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(2-oxa-3-azabicyclo[3.1.0]hex-3-en-4-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone (Example 97) was sent for SFC chiral separation to afford the title compound (4.95 mg)

LC-MS Method1: 301.2 [$M+H^+$]

^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 10.27 (1 H, br s), 6.41 (1 H, s), 4.79 (1 H, td, J=5.33, 2.13 Hz), 4.27 (1 H, br d, J=11.04 Hz), 4.16 (1 H, dd, J=12.67, 1.38 Hz), 3.82 - 3.93 (1 H, m), 3.60 (1 H, br dd, J=12.55, 5.02 Hz), 2.95 (1 H, spt, J=6.94 Hz), 2.25 - 2.36 (1 H, m), 2.13 - 2.21 (1 H, m), 2.08 (1 H, br s), 1.96 - 2.21 (1 H, m), 1.96 - 2.03 (1 H, m), 1.57 (1 H, t, J=3.39 Hz), 1.23 (6 H, d, J=7.03 Hz), 0.81 (1 H, dt, J=9.29, 5.52 Hz), 0.24 (1 H, br d, J=2.51 Hz)

[0576]

Example 97 (5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(2-oxa-3-azabicyclo[3.1.0]hex-3-en-4-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

(5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(2-oxa-3-azabicyclo[3.1.0]hex-3-en-4-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a solution of 5-isopropyl-1H-pyrazole-3-carboxylic acid (25.82mg, 0.1700mmol) in DMF (2.0833mL) were added HATU (75.67mg, 0.2000mmol) and DIPEA (0.08mL, 0.4600mmol). The mixture was stirred at 25 °C for 30 min. Then 4-[(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl]-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (25 mg, 0.1500mmol) was added to the mixture. The mixture was stirred at 25 °C for 3 h to give brown solution. The reaction mixture was concentrated directly. The residue was purified by prep-HPLC (NH_3) to give the title compound (21.39mg, 0.0712mmol, 46.774% yield) as white solid.

LC-MS Method1: 301.2 [$M+H^+$]

^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 10.27 (1 H, br s), 6.41 (1 H, s), 4.79 (1 H, td, J=5.33, 2.13 Hz), 4.27 (1 H, br d, J=11.04 Hz), 4.16 (1 H, dd, J=12.67, 1.38 Hz), 3.82 - 3.93 (1 H, m), 3.60 (1 H, br dd, J=12.55, 5.02 Hz), 2.95 (1 H, spt, J=6.94 Hz), 2.25 - 2.36 (1 H, m), 2.13 - 2.21 (1 H, m), 2.08 (1 H, br s), 1.96 - 2.21 (1 H, m), 1.96 - 2.03 (1 H, m), 1.57 (1 H, t, J=3.39 Hz), 1.23 (6 H, d, J=7.03 Hz), 0.81 (1 H, dt, J=9.29, 5.52 Hz), 0.24 (1 H, br d, J=2.51 Hz)

[0577]

Example 98 [(1R,5S,6r)-6-(4-isobutyl-5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](5-isopropyl-1H-pyrazol-3-yl)methanone

[(1R,5S,6r)-6-(4-isobutyl-5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](5-isopropyl-1H-pyrazol-3-yl)methanone

To a solution of (1R,5S,6r)-6-(4-isobutyl-5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride (300 mg, 1.27 mmol) and DIPEA (1.05mL, 6.35mmol) in DMF (8.5 mL) were added HATU (578 mg, 1.52 mmol) and 5-isopropyl-1H-pyrazole-3-carboxylic acid (195 mg, 1.27 mmol), and the mixture was stirred at 20 °C for 12 hr. LCMS showed the desired mass was detected. The reaction mixture was poured into H_2O

(30 mL) and extracted by EtOAc (20mLx3). The organic phase was washed by brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated to give a residue. The residue was purified by Prep-HPLC (NH_3) to afford the title compound (12 mg, 0.03 mmol, 2.53% yield) as a white solid.

LC-MS Method1: 373.2 [$M+H^+$]

^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 0.93 - 1.01 (m, 6 H) 1.19 (d, *J*=1.6 Hz, 3 H) 1.30 (d, *J*=6.9 Hz, 9 H) 1.35 (d, *J*=2.1 Hz, 3 H) 1.41 - 1.49 (m, 2 H) 1.69 - 1.79 (m, 1 H) 1.98 - 2.25 (m, 3 H) 2.95 (br t, *J*=7.2 Hz, 1 H) 2.99 - 3.08 (m, 1 H) 3.57 - 3.69 (m, 1 H) 3.93 (br d, *J*=12.0 Hz, 1 H) 4.01 - 4.15 (m, 1 H) 4.37 (br dd, *J*=11.9, 5.4 Hz, 1 H) 6.45 (s, 1 H)

[0578]

Example 99 (5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(4,5,5-trimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

(5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(4,5,5-trimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a mixture of 5-isopropyl-1H-pyrazole-3-carboxylic acid (39.68mg, 0.2600mmol) in DMF (0.4639mL) were added HATU (127.91mg, 0.3300mmol) and DIPEA (0.21mL, 1.29mmol). The mixture was heated at 50 ºC for 30 min. (1R,5S,6r)-6-(4,5,5-trimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane TFA salt (50 mg, 0.2600mmol) was added. The resulting mixture was stirred at 20 ºC for 4 hr. The reaction mixture was diluted with H_2O (10mL), extracted with EtOAc (10mL×2), and then washed with brine (10mL). The combined organic layers were separated, then dried over Na_2SO_4 and concentrated in vacuum to give crude oil. The crude oil was purified by prep-HPLC (NH_3) and lyophilized to give the title compound (4.91mg, 0.0149mmol, 5.7737% yield) as white solid.

^{1}H NMR (400MHz, MeOD) δ = 6.47 (s, 1H), 4.39 (br d, *J*=12.0 Hz, 1H), 4.12 (dd, *J*=5.4, 12.7 Hz, 1H), 3.95 (br d, *J*=12.5 Hz, 1H), 3.64 (br d, *J*=12.8 Hz, 1H), 3.16 - 3.01 (m, 1H), 2.92 (q, *J*=7.2 Hz, 1H), 2.25 - 2.00 (m, 2H), 1.37 (br s, 1H), 1.36 - 1.27 (m, 12H), 1.22 (s, 3H)

[0579]

Example 100 [(1R,5S,6r)-6-(5-ethyl-5-methyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](5-isopropyl-1H-pyrazol-3-yl)methanone

[(1R,5S,6r)-6-(5-ethyl-5-methyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](5-isopropyl-1H-pyrazol-3-yl)methanone

To a mixture of 5-isopropyl-1H-pyrazole-3-carboxylic acid (23.81mg, 0.1500mmol) in DMF (0.2783mL) were added HATU (76.75mg, 0.2000mmol), DIPEA (0.13mL, 0.7700mmol) and (1R,5S,6r)-6-(5-ethyl-5-methyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane TFA salt (30 mg, 0.1500mmol). The resulting mixture was stirred at 20 ºC for 4 hr. The reaction mixture was diluted with H_2O (5mL), extracted with EtOAc (5mL×2), and then washed with brine (8mL). The combined organic layers were separated, then dried over Na_2SO_4 and concentrated in vacuum to give crude oil. The crude oil was purified by prep-HPLC (NH_3) and lyophilized to give the title compound (1.82mg, 0.0055mmol, 3.5669% yield) as white solid.

^{1}H NMR (400MHz, MeOD) δ = 6.47 (br s, 1H), 4.37 (br s, 1H), 4.12 (d, *J*=12.8 Hz, 1H), 3.95 (dd, *J*=3.8, 12.3 Hz, 1H), 3.64 (dd, *J*=4.4, 12.4 Hz, 1H), 3.08 - 3.01 (m, 1H), 2.87 - 2.74 (m, 1H), 2.73 - 2.59 (m, 1H), 2.19 - 2.04 (m, 2H), 1.68 - 1.60 (m, 2H), 1.52 - 1.48 (m, 1H), 1.32 - 1.30 (m, 9H), 0.94 (t, *J*=7.5 Hz, 3H)

[0580]

Example 101 (5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(4-methoxy-5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

(5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(4-methoxy-5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a solution of 5-isopropyl-1H-pyrazole-3-carboxylic acid (49.12mg, 0.3200mmol) in DMF (2.393mL) were added HATU (91.62mg, 0.4800mmol) and DIPEA (0.16mL, 0.9600mmol). The reaction mixture was stirred at 15 °C for 30 min. Then (1R,5S,6r)-6-(4-methoxy-5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane TFA salt (67 mg, 0.3200mmol) was added to the reaction. The reaction mixture was stirred at 15 °C for 0.5 hr to give a yellow mixture. LCMS showed the desired MS. The reaction mixture was purified by prep-HPLC (NH_3) to give the title compound (43.85mg, 0.1266mmol, 39.725% yield) as white powder.

LC-MS Method1: 347.2 [$M+H^+$]

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 6.48 (s, 1H), 4.31 (br d, *J*=11.0 Hz, 1H), 4.22 (m, 1H), 4.03 (d, *J*=16.1 Hz, 1H), 3.93 (m, 1H), 3.66 (m, 1H), 3.45 (s, 3H), 3.02 (m, 1H), 2.30 - 2.19 (m, 1H), 2.11 (m, 1H), 1.47 - 1.42 (m, 1H), 1.35 (s, 3H), 1.30 (d, *J*=7.0 Hz, 9H)

[0581]

Example 102 (5-isopropyl-1H-pyrazol-3-yl){(1R,5S,6r)-6-[6a-methyl-4,5,6,6a-tetrahydro-3aH-cyclopenta[d][1,2]oxazol-3-yl]-3-azabicyclo[3.1.0]hex-3-yl}methanone

tert-butyl (1R,5S,6r)-6-[6a-methyl-4,5,6,6a-tetrahydro-3aH-cyclopenta[d][1,2]oxazol-3-yl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a mixture of tert-butyl (1R,5S,6r)-6-[(Z)-chloro(hydroxyimino)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (100 mg, 0.3800mmol) and 1-methylcyclopent-1-ene (0.61mL, 5.75mmol) in tert-Butyl methyl ether (4mL) was added Et_3N (0.07mL, 0.3800mmol) in tert-Butyl methyl ether (1mL) dropwise over 1 h. The mixture was stirred at 20 ºC for 5 hr. TLC (PE/EA=3/1) showed a major new spot (Rf=0.4) and the reaction was completed. The mixture was washed with H_2O (10mL) and then extracted with EtOAc (10mL×2). The combined organic layer was dried over Na_2SO_4 and concentrated to give crude oil. The crude oil was purified by prep-TLC (PE/EA=3/1) to give the title compound (40mg, 0.1305mmol, 34.037% yield) as pale yellow solid.

LC-MS Method1 1.077 min, MS (m/z) 307.1 ($M + H^+$).

[0582]

3-[(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl]-6a-methyl-4,5,6,6a-tetrahydro-3aH-cyclopenta[d][1,2]oxazole hydrochloride

A mixture of tert-butyl (1R,5S,6r)-6-[6a-methyl-4,5,6,6a-tetrahydro-3aH-cyclopenta[d][1,2]oxazol-3-yl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (40 mg, 0.1300mmol) in HCl/dioxane (5 mL, 4 M) was stirred at 20 ºC for 2 hr. The mixture was concentrated to dryness with EA (15mL) directly to give the title compound (26.9mg, crude product) as pale yellow solid.

LC-MS Method1 0.535 min, MS (m/z) 207.0 ($M + H^+$).

[0583]

(5-isopropyl-1H-pyrazol-3-yl){(1R,5S,6r)-6-[6a-methyl-4,5,6,6a-tetrahydro-3aH-cyclopenta[d][1,2]oxazol-3-yl]-3-azabicyclo[3.1.0]hex-3-yl}methanone

To a mixture of (3aR,6aR)-3-[(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl]-6a-methyl-4,5,6,6a-tetrahydro-3aH-cyclopenta[d][1,2]oxazole hydrochloride (26.9mg, 0.1300mmol) in DMF (1.5mL) were added 5-isopropyl-1H-pyrazole-3-carboxylic acid (20.1mg, 0.1300mmol), DIPEA (0.06mL, 0.3900mmol) and HATU (64.42mg, 0.1700mmol), and the mixture was stirred at 20 °C for 16 hr. TLC (PE/EA=0/1) showed a major new spot (Rf=0.6) and the reaction was completed. The mixture was diluted with H_2O (10 mL) and EA (10mL×2). The combined organic layer was separated, then dried over Na_2SO_4 and concentrated in vacuum to give crude oil. The crude oil was purified by prep-TLC (PE/EA=0/1) to give the title compound (28mg, 0.0818mmol, 62.702% yield) as pale yellow solid.

^{1}H NMR (400MHz, DMSO-d_6) δ = 13.05 - 12.79 (m, 1H), 6.37 (s, 1H), 4.35 (br dd, *J*=4.0, 12.0 Hz, 1H), 4.01 - 3.91 (m, 1H), 3.82 (br d, *J*=11.8 Hz, 1H), 3.55 - 3.53 (m, 1H), 3.48 (br d, *J*=12.8 Hz, 1H), 3.12 (br d, *J*=3.3 Hz, 1H), 2.97 (td, *J*=7.1, 13.7 Hz, 1H), 2.09 - 1.94 (m, 1H), 2.07 - 1.90 (m, 1H), 1.90 - 1.73 (m, 4H), 1.68 - 1.49 (m, 3H), 1.42 - 1.30 (m, 4H), 1.22 (d, *J*=7.0 Hz, 8H).

[0584]

Example 103 (5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(5-methyl-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

(5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(5-methyl-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

A 100 mL round-bottom flask was charged with 5-isopropyl-1H-pyrazole-3-carboxylic acid (70 mg, 0.4500mmol), N-ethyl-N-isopropylpropan-2-amine (0.24mL, 1.41mmol), HATU (190.94mg, 0.5000mmol) and DMF (3mL). After stirring for 30 min, (1R,5S,6r)-6-(5-methyl-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane TFA salt (126.33mg, 0.4500mmol) was added. The reaction mixture was stirred at 20 ^oC for 16 hr to give a yellow solution. LCMS showed a new peak gives the desired ms. H_2O (30 mL) was added and it was extracted with EtOAc (30 mLx2). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuum to give a yellow oil. The crude was purified by Prep-HPLC (FA). The afforded flows were concentrated in vacuum to remove most of CH_3CN and lyophilized to give the title compound (13.52mg, 0.0448mmol, 9.8741% yield) as white solid.

LC-MS Method1: 301.1 [$M+H^+$]

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 6.48 (br s, 1H), 5.75 (s, 1H), 4.21-4.33 (m, 2H), 3.96 (br dd, *J*=3.81, 10.94 Hz, 1H), 3.69 (br dd, *J*=3.69, 12.44 Hz, 1H), 3.04 (td, *J*=6.83, 13.73 Hz, 1H), 2.36 (s, 3H), 2.15 (br d, *J*=3.38 Hz, 1H), 2.04-2.09 (m, 1H), 1.75 (t, *J*=3.06 Hz, 1H), 1.30 (d, *J*=6.88 Hz, 6H)

[0585]

Example 104 {(1R,5S,6r)-6-[5-(difluoromethyl)-4-methyl-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hex-3-yl}(5-isopropyl-1H-pyrazol-3-yl)methanone

tert-butyl (1R,5S,6r)-6-[1-hydroxypropyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-formyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (500 mg, 2.37mmol) in THF (10mL) was added bromo(ethyl)magnesium (1.6mL, 4.73mmol, 3M in Et_2O) drop-wise at -78°C. The reaction was allowed to warm to 0 °C and stirred for further 20 min to give pale yellow mixture. The reaction was quenched with H_2O (15 mL), diluted with EA (30 mL) and acidified with 2N HCl to pH=5. The aqueous layer was extracted with EA (20 mL x 2). The combined EA layer was dried over Na_2SO_4 and concentrated in vacuum to give the title compound (590mg, 2.4448mmol, crude) as pale yellow oil.

[0586]

tert-butyl (1R,5S,6r)-6-propionyl-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a mixture of tert-butyl (1R,5S,6r)-6-[1-hydroxypropyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (590 mg, 2.44mmol) and $NaHCO_3$ (410.77mg, 4.89mmol) in DCM (25mL) was added Dess-Martin's reagent (1555.4mg, 3.67mmol) at 0 °C. The mixture was stirred at 20 °C for 12 h to give white mixture. The mixture was diluted with DCM (30 mL) and H_2O (20 mL) and basified with saturated $NaHCO_3$ to pH=8. The aqueous layer was extracted with DCM (20 mL). The combined DCM layer was dried over Na_2SO_4 and concentrated in vacuum to give crude product which was purified by flash column (PE/EA=1/0 to 3/1) to give the title compound (500 mg, 2.0893mmol, 85.461% yield) as pale yellow oil.

[0587]

tert-butyl (1R,5S,6r)-6-(4-ethoxy-2-methyl-3,4-dioxobutanoyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-propionyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (500 mg, 2.09mmol) in THF (10mL) was added LHMDS (2.5mL, 2.51mmol, 1 M in THF) at -78 °C. The reaction was stirred at -78 °C for 1 h. Then, a solution of diethyl oxalate (0.34mL, 2.51mmol) in THF (2mL) was added at -78°C. The reaction was allowed to warm to 20 °C and stirred for further 12 h to give pale yellow solution. The reaction was cooled to 0 °C, diluted with EA (30 mL), quenched with H_2O (15 mL) and acidified with 2M HCl to pH=6. The aqueous layer was extracted with EA (20 mL x 2). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuum to give pale yellow oil. The crude oil was purified by flash column (PE/EA=1/0 to 4/1) to give the title compound (300 mg, 0.8840mmol, 42.308% yield) as pale yellow oil. Meanwhile, about 160 mg of B76-2a was recovered.

[0588]

tert-butyl (1R,5S,6r)-6-[(1E)-4-ethoxy-N-hydroxy-2-methyl-3,4-dioxobutanimidoyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of NaOH (42.43mg, 1.06mmol) in H_2O (2mL) was added hydroxylamine hydrochloride (0.04mL, 1.06mmol) at 0°C. After stirred for 5min, the reaction was added to a solution of tert-butyl (1R,5S,6r)-6-(4-ethoxy-2-methyl-3,4-dioxobutanoyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (300 mg, 0.8800mmol) in THF (2mL) drop-wise at 0 °C. The reaction was stirred at 20 °C for 12 h to give pale yellow suspension. The suspension was diluted with EA (20 mL) and H_2O (10 mL) and adjusted with 2M HCl to pH=7. The aqueous layer was extracted with EA (15 mL x 2). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuum to give the title compound (300 mg, 0.8465mmol, 95.762% yield) as pale yellow oil.

[0589]

tert-butyl (1R,5S,6r)-6-[5-(ethoxycarbonyl)-4-methyl-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-[(1E)-4-ethoxy-N-hydroxy-2-methyl-3,4-dioxobutanimidoyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (300 mg, 0.8500mmol) and Et_3N (0.15mL, 1.1mmol) in DCM (8mL) was added methanesulfonyl chloride (126.06mg, 1.1mmol) at 0°C. The reaction was stirred at 20 °C for 4 h to give pale yellow solution. The reaction was cooled to 0 °C and treated with additional MsCl (60 uL) and Et_3N (0.8 mL). The reaction was stirred at 20 °C for further 1 h to give pale yellow solution. The reaction was

concentrated in vacuum. The residue was purified by prep-TLC (PE/EA=3/1) to give the title compound (75mg, 0.2230mmol, 26.339% yield) as pale yellow gum.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 4.36 (q, J = 6.8 Hz, 2H), 3.80-3.55 (m, 2H), 3.50-3.40 (m, 2H), 2.23 (s, 3H), 2.15-2.10 (m, 1H), 2.10-2.00 (m, 1H), 1.60-1.50 (m, 1H), 1.40 (s, 9H), 1.02 (t, J = 6.8 Hz, 3H).

[0590]

tert-butyl (1R,5S,6r)-6-[5-(hydroxymethyl)-4-methyl-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-[5-(ethoxycarbonyl)-4-methyl-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (100 mg, 0.3000mmol) in THF (4mL) was added $LiALH_4$ (20.33mg, 0.5400mmol) at 0 °C. The reaction was stirred at 0 °C for 20min to give white mixture. The mixture was quenched with H_2O (3 drops), diluted with EA (20 mL) and stirred with Na_2SO_4 (10 g) for 10min. The solid was filtered off. The filtrate was concentrated in vacuum to give the title compound (80mg, 0.2718mmol, 91.423% yield) as pale yellow oil.

[0591]

tert-butyl (1R,5S,6r)-6-(5-formyl-4-methyl-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a mixture of tert-butyl (1R,5S,6r)-6-[5-(hydroxymethyl)-4-methyl-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (80 mg, 0.2700mmol) and $NaHCO_3$ (57.08mg, 0.6800mmol) in DCM (4mL) was added Dess-Martin reagent (172.91mg, 0.4100mmol) at 0°C. The mixture was stirred at 20 °C for 12 h to give white mixture. The mixture was diluted with DCM (15 mL) and H_2O (10 mL) and basified with saturated $NaHCO_3$ to pH=8. The organic layer was collected, concentrated and purified by prep-TLC (PE/EA=3/1, rf=0.5) to give the title compound (45mg, 0.1539mmol, 56.639% yield) as colorless oil.

[0592]

tert-butyl (1R,5S,6r)-6-[5-(difluoromethyl)-4-methyl-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-(5-formyl-4-methyl-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (45 mg, 0.1500mmol) in DCM (3mL) was added DAST (74.35mg, 0.4600mmol) drop-wise at -78 °C. The reaction was allowed to warm to 20 °C and stirred for further 12 h to give pale yellow solution. The reaction was diluted with DCM (10 mL), cooled to 0°C, treated with H_2O (5 mL) and saturated $NaHCO_3$ (3 mL). The

aqueous layer was extracted with EA (10 mL x 2). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum to give the title compound (55mg, 0.1750mmol) as pale yellow oil.

[0593]

(1R,5S,6r)-6-[5-(difluoromethyl)-4-methyl-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hexane TFA salt

A solution of tert-butyl (1R,5S,6r)-6-[5-(difluoromethyl)-4-methyl-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (55 mg, 0.1700mmol) in DCM (2mL) was treated with TFA (0.2mL, 0.1700mmol) and stirred at 20 °C for 10 min to give pale brown solution. The reaction was concentrated in vacuum to give the title compound (60mg, 0.2801mmol, TFA salt) as pale brown oil.

[0594]

{(1R,5S,6r)-6-[5-(difluoromethyl)-4-methyl-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hex-3-yl}(5-isopropyl-1H-pyrazol-3-yl)methanone

To a solution of (1R,5S,6r)-6-[5-(difluoromethyl)-4-methyl-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hexane TFA salt (60 mg, 0.1800mmol) and 5-isopropyl-1H-pyrazole-3-carboxylic acid (28.2mg, 0.1800mmol) in DMF (1mL) were added HATU (69.93mg, 0.1800mmol) and Et_3N (0.05mL, 0.3700mmol) at 0 °C. The reaction was stirred at 20 °C for 12 h to give pale yellow solution. The reaction was concentrated in vacuum to give pale yellow oil, which was purified by prep-TLC (PE/EA=1/2) twice to give desired product. The product was lyophilized to give the title compound (21.2mg, 0.0605mmol, 33.078% yield) as a white solid.

LC-MS Method1: 350.9 [$M+H^+$]

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 10.05 (s, 1H), 6.78 - 6.48 (m, 1H), 6.45 (s, 1H), 4.31 (br d, *J*=10.3 Hz, 1H), 4.21 (d, *J*=12.5 Hz, 1H), 3.92 (dd, *J*=4.4, 11.4 Hz, 1H), 3.64 (dd, *J*=4.3, 12.8 Hz, 1H), 2.96 (td, *J*=6.9, 13.8 Hz, 1H), 2.29 (td, *J*=3.8, 7.4 Hz, 1H), 2.13 (td, *J*=3.7, 7.3 Hz, 1H), 2.06 (t, *J*=2.0 Hz, 3H), 1.26 - 1.21 (m, 6H)

[0595]

Example 105 {(1R,5S,6r)-6-[4-(dimethylamino)-5-methyl-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hex-3-yl}(5-isopropyl-1H-pyrazol-3-yl)methanone

tert-butyl (1R,5S,6r)-6-[4-(ethoxycarbonyl)-5-methyl-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

A round-bottom flask was charged with tert-butyl (1R,5S,6r)-6-[(E)-(hydroxyimino)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (600 mg, 2.3mmol), methyl 3-oxobutanoate (0.5mL, 4.6mmol) and triethylamine (0.96mL, 6.9mmol) and DMF (12mL). The reaction mixture was stirred at 20 ^{o}C for 16 hr to give a yellow solution. LCMS showed a major peak gives the desired ms. H_2O (30 mL) was added and it was extracted with EtOAc (30 mLx2). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuum to give the title compound (950mg, 2.947mmol, 128.06% yield) as yellow oil. It was directly used in the next step.

LC-MS Method1 0.925, MS (m/z) 308.0 ($M - CH_2CH_3 + H^+$).

[0596]

5-methyl-3-[(1R,5S,6r)-3-{[(tert-butyl)oxy]carbonyl}-3-azabicyclo[3.1.0]hex-6-yl]-1,2-oxazole-4-carboxylic acid

A 100 mL round-bottom flask was charged with tert-butyl (1R,5S,6r)-6-[4-(ethoxycarbonyl)-5-methyl-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (380 mg, 1.18mmol), hydroxylithium hydrate (148.39mg, 3.54mmol) and THF (6mL). The reaction mixture was stirred at 20 ^{o}C for 16 hr to give a yellow solution. The reaction was diluted with H_2O (15mL). pH was adjusted to 3 with 1M HCl aq. and the reaction mixture was extracted with EtOAc (30mL x2). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuum to give the title compound (330mg, 1.0703mmol, 90.794% yield) as yellow oil.

[0597]

tert-butyl (1R,5S,6r)-6-(4-{[(benzyloxy)carbonyl]amino}-5-methyl-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

A round-bottom flask was charged with 5-methyl-3-[(1R,5S,6r)-3-{[(tert-butyl)oxy]carbonyl}-3-azabicyclo[3.1.0]hex-6-yl]-1,2-oxazole-4-carboxylic acid (300 mg, 0.9700mmol), DPPA (401.65mg, 1.46mmol), Et_3N (0.41mL, 2.92mmol) and Toluene (2.7273mL). The reaction mixture was stirred at 110 ^{o}C for 2 hr, and then phenylmethanol (0.4mL, 3.89mmol) was added. The reaction mixture was stirred at 110 ^{o}C for 10 min to give a yellow solution. H_2O (30 mL) was added and it was extracted with EtOAc (30 mLx2). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuum to give a yellow

oil. The crude was purified by silica gel chromatography (PE/EA= 10/1 to 3/1) to give the title compound (160mg, 0.3870mmol, 39.771% yield) as yellow oil.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.45-7.20 (m, 5H), 5.12 (brs, 2H), 3.80-3.25 (m, 4H), 2.25 (brs, 3H), 2.00-1.90 (m, 1H), 1.50-1.40 (m, 1H), 1.39 (s, 9H).

[0598]

tert-butyl (1R,5S,6r)-6-(4-amino-5-methyl-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

A round-bottom flask was charged with tert-butyl (1R,5S,6r)-6-(4-{[(benzyloxy)carbonyl]amino}-5-methyl-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (1200 mg, 2.9mmol), Pd/C (120 mg, 2.9mmol) and MeOH (10mL). The reaction mixture was stirred under molecular hydrogen (15 psi) atmosphere to give a black suspension. The suspension was filtrated through a pad of celite and the filtrate was concentrated in vacuum to give the title compound as yellow solid.

LC-MS Method1 0.765 min, MS (m/z) 280.1 ($M + H^+$).

[0599]

tert-butyl (1R,5S,6r)-6-[4-(dimethylamino)-5-methyl-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-(4-amino-5-methyl-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (100 mg, 0.3600mmol) in MeOH (2.8571mL) was added formaldehyde (1 mL, 2.15mmol). After stirring for 15min, $NaBH_3CN$ (134.98mg, 2.15mmol) was added to give a yellow solution. H_2O (30 mL) was added and it was extracted with EtOAc (30 mLx2). The combined organic layer dried over Na_2SO_4 and concentrated in vacuum to give the title compound (150 mg, crude) as yellow oil. It was directly used in the next step.

[0600]

3-[(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl]-N,N,5-trimethyl-1,2-oxazol-4-amine TFA salt

A round-bottom flask was charged with tert-butyl (1R,5S,6r)-6-[4-(dimethylamino)-5-methyl-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (150 mg, 0.4900mmol), 2,2,2-trifluoroacetic acid (0.04mL, 0.4900mmol), DCM (6mL) and 2,2,2-trifluoroacetic acid (0.04mL, 0.4900mmol). The reaction mixture was stirred at 30 ^{o}C under N_2 protection to give a yellow solution. The reaction mixture was evaporated in vacuum to give the title compound (220mg, 0.5054mmol, 103.56% yield) as yellow oil. It was directly used in the next step.

LC-MS Method1 0.443 min, MS (m/z) 207.9 ($M + H^+$).

[0601]

{(1R,5S,6r)-6-[4-(dimethylamino)-5-methyl-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hex-3-yl}(5-isopropyl-1H-pyrazol-3-yl)methanone

To a solution of 5-isopropyl-1H-pyrazole-3-carboxylic acid (80 mg, 0.5200mmol) and HATU (238.05mg, 0.6200mmol) in DMF (2mL) was added N-ethyl-N-isopropylpropan-2-amine (0.36 mL, 2.08mmol). After stirring for 15 min, 3-[(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl]-N,N,5-trimethyl-1,2-oxazol-4-amine TFA salt (225.89mg, 0.5200mmol) was added and the reaction mixture was stirred for 16 hr to give a yellow solution. H_2O (30 mL) was added and it was extracted with EtOAc (30 mLx2). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuum to give a yellow oil. The crude was purified by Prep-HPLC (NH_3). The afforded flows were concentrated in vacuum to remove most of CH_3CN and lyophilized to give the title compound (38.86mg, 0.1132mmol, 21.807% yield) as white solid.

LC-MS Method1: 344.2 [$M+H^+$]

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 6.49 (s, 1H), 4.19-4.37 (m, 2H), 3.99 (dd, *J*=4.39, 11.17 Hz, 1H), 3.71 (dd, *J*=4.52, 12.55 Hz, 1H), 3.03 (td, *J*=7.00, 13.87 Hz, 1H), 2.71 (s, 6H), 2.32-2.40 (m, 4H), 2.14 (td, *J*=3.83, 7.40 Hz, 1H), 1.68 (t, *J*=3.51 Hz, 1H), 1.30 (d, *J*=7.03 Hz, 6H)

[0602]

Example 106 (5-isopropyl-1H-pyrazol-3-yl){(1R,5S,6r)-6-[5-methyl-4-(2-pyridinyl)-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hex-3-yl}methanone

tert-butyl (1R,5S,6r)-6-[5-methyl-4-(2-pyridinyl)-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-(4-bromo-5-methyl-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (100 mg, 0.29mmol) in 1,4-Dioxane (2mL) were added tributyl(2-pyridyl)stannane (214.52mg, 0.58mmol), X-Phos (27.78mg, 0.0600mmol) and X-Phos-Pd-G2 (22.92mg, 0.0300mmol) under N_2. The resulting mixture was stirred at 110 °C for 16 hours to give a black brown solution. LCMS showed the reaction was completed. The reaction was diluted with EA (15 mL) and filtered through a pad of Celite. The filtrate was concentrated and the residue was purified by prep-TLC (EA/PE=1/1, Rf=0.5) to afford the title compound (71mg, 71.379% yield) as a light yellow solid.

[0603]

(1R,5S,6r)-6-[5-methyl-4-(2-pyridinyl)-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hexane hydrochloride

A solution of tert-butyl (1R,5S,6r)-6-[5-methyl-4-(2-pyridinyl)-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (71 mg, 0.2100mmol) in 4M HCl in MeOH (1 mL, 0.2100mmol) was stirred at 15 °C for 10 min to give a light yellow solution. TLC showed the starting material was consumed up and a new spot was detected. The reaction was concentrated to afford the title compound (62mg, 123.55% yield) as a light yellow gum.

[0604]

(5-isopropyl-1H-pyrazol-3-yl){(1R,5S,6r)-6-[5-methyl-4-(2-pyridinyl)-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hex-3-yl}methanone

To a solution of (1R,5S,6r)-6-[5-methyl-4-(2-pyridinyl)-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hexane hydrochloride (62 mg, 0.26mmol) in DMF (1mL) were added 5-isopropyl-1H-pyrazole-3-carboxylic acid (39.61mg, 0.26mmol), DIPEA (0.13mL, 0.77mmol) and HATU (146.46mg, 0.39mmol) at 0 to 5 °C. The resulting mixture was stirred at 15 °C for 16 hours to give a light brown solution. The reaction was diluted with H_2O (15 mL) and extracted with EA (5 mL x 3). The combined organic layers were washed with NH_4Cl aq. (5 mL x 2) and brine (5 mL), dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by prep-TLC (EA/MeOH=12/1, Rf=0.6) and lyophilized to afford the title compound (34mg, 35.057% yield) as a white solid.

LC-MS Method1: 378.1 [$M+H^+$]

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.29 (d, *J*=6.88 Hz, 6 H) 1.92 (t, *J*=3.44 Hz, 1 H) 2.18 (dt, *J*=7.41, 3.86 Hz, 1 H) 2.46 (dt, *J*=7.44, 3.91 Hz, 1 H) 2.55 (s, 3 H) 2.97 - 3.08 (m, 1 H) 3.73 (dd, *J*=12.69, 4.44 Hz, 1 H) 3.99 (dd, *J*=11.13, 4.38 Hz, 1 H) 4.20 (d, *J*=12.76 Hz, 1 H) 4.28 (br d, *J*=11.13 Hz, 1 H) 6.44 (s, 1 H) 7.23 (dd, *J*=7.32, 5.19 Hz, 1 H) 7.38 (d, *J*=7.88 Hz, 1 H) 7.75 (td, *J*=7.75, 1.75 Hz, 1 H) 8.66 (d, *J*=4.63 Hz, 1 H)

[0605]

Example 107 [(1R,5S,6r)-6-{4-[1-(cyclopropylmethyl)-1H-pyrazol-3-yl]-5-methyl-1,2-oxazol-3-yl}-3-azabicyclo[3.1.0]hex-3-yl](5-isopropyl-1H-pyrazol-3-yl)methanone

3-bromo-1-(cyclopropylmethyl)-1H-pyrazole

To a solution of 3-bromopyrazole (1.g, 6.8mmol) in DMF (10mL) were added K_2CO_3 (1.88g, 13.61mmol) and (bromomethyl)cyclopropane (0.66mL, 6.8mmol). The reaction was stirred at 15 °C for 3 hours to give a white suspension. LCMS showed about half of the starting material was remained and the reaction was stirred for 16 hours to give a white suspension. TLC (PE/EA=5/1, Rf=0.7, I_2) showed most of the starting material was consumed and a new spot was detected. The reaction was diluted with H_2O (90 mL) and extracted with EA (10 mL x 3). The combined organic layers were washed with NH_4Cl aq. (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered and concentrated to afford a mixture of the title compounds and its isomer as colorless oil (1.36g, 99.413% yield).

Isomer a: ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.49 (d, J = 1.2 Hz, 1H), 6.28 (d, J = 1.2 Hz, 1H), 4.03 (d, J = 6.8 Hz, 2H), 1.40-1.20 (m, 2H), 0.60-0.50 (m, 1H), 0.45-0.40 (m, 1H).

Isomer b; ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.39 (d, J = 1.2 Hz, 1H), 6.26 (d, J = 1.2 Hz, 1H), 3.92 (d, J = 6.8 Hz, 2H), 1.40-1.20 (m, 2H), 0.70-0.60 (m, 1H), 0.40-0.35 (m, 1H).

[0606]

1-(cyclopropylmethyl)-3-(tributylstannyl)-1H-pyrazole

To a solution of the mixture of 3-bromo-1-(cyclopropylmethyl)-1H-pyrazole and its isomer (1.39g, 6.91mmol) in THF (15mL) was added n-BuLi (3.04mL, 7.6mmol) dropwise at -75 to -70°C. After stirring for 1 hour at -75 to -70°C, tributyl(chloro)stannane (2.48g, 7.6mmol) in THF (5mL) was added to the reaction at -75 to -70°C. The resulting mixture was stirred at 15 °C for 16 hours to give a light yellow solution. The reaction was quenched with NH_4Cl aq (5 mL). The mixture was diluted with H_2O (50 mL) and extracted with EA (15 mL x 3). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column (eluted with 5% EA in PE, EA/PE=1/9) to afford the title compound (525 mg, Rf=0.45) as colorless oil. LC-MS Method1 1.060 min, MS (m/z) 413.0 ($M + H^+$).

[0607]

tert-butyl (1R,5S,6r)-6-{4-[1-(cyclopropylmethyl)-1H-pyrazol-3-yl]-5-methyl-1,2-oxazol-3-yl}-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-(4-bromo-5-methyl-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (300 mg, 0.87mmol) in 1,4-Dioxane (3mL) were added 1-(cyclopropylmethyl)-3-(tributylstannyl)-1H-pyrazole (431.31mg, 1.05mmol), X-Phos

(83.34mg, 0.17mmol) and X-Phos-Pd-G2 (68.77mg, 0.09mmol) under N_2. The resulting mixture was stirred at 100 °C for 16 hours to give a black brown solution. The reaction was diluted with EA (30 mL) and filtered through a pad of celite. The filtrate was concentrated and purified by flash column (8% EA in PE, PE/EA=3/1, Rf=0.5) to afford the title compound (205mg, 16.47% yield) as a light yellow solid.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.50 (d, J = 2.0 Hz, 1H), 6.40 (d, J = 2.0 Hz, 1H), 4.00 (d, J = 3.2 Hz, 2H), 3.79 (d, J = 11.2 Hz, 1H), 3.70 (d, J = 11.2 Hz, 1H), 3.50-3.40 (m, 2H), 2.38 (s, 3H), 2.11 (m, 2H), 1.70-1.65 (m, 1H), 1.47 (s, 9H),.70-0.60 (m, 1H), 0.55-0.50 (m, 2H), 0.45-0.35 (m, 2H).

[0608]

(1R,5S,6r)-6-{4-[1-(cyclopropylmethyl)-1H-pyrazol-3-yl]-5-methyl-1,2-oxazol-3-yl}-3-azabicyclo[3.1.0]hexane hydrochloride

A solution of tert-butyl (1R,5S,6r)-6-{4-[1-(cyclopropylmethyl)-1H-pyrazol-3-yl]-5-methyl-1,2-oxazol-3-yl}-3-azabicyclo[3.1.0]hexane-3-carboxylate (205 mg, 0.5300mmol) in 4M HCl in MeOH (3 mL, 0.5300mmol) was stirred at 15 °C for 15 min to give a colorless solution. LCMS showed the starting material was consumed up and one new peak with desired mass was detected. The reaction was concentrated to afford the title compound (77.8mg, 51.312% yield) as an off-white solid.

LC-MS Method1 0.652 min, MS (m/z) 284.9 ($M + H^+$).

[0609]

[(1R,5S,6r)-6-{4-[1-(cyclopropylmethyl)-1H-pyrazol-3-yl]-5-methyl-1,2-oxazol-3-yl}-3-azabicyclo[3.1.0]hex-3-yl](5-isopropyl-1H-pyrazol-3-yl)methanone

To a solution of (1R,5S,6r)-6-{4-[1-(cyclopropylmethyl)-1H-pyrazol-3-yl]-5-methyl-1,2-oxazol-3-yl}-3-azabicyclo[3.1.0]hexane hydrochloride (77.8mg, 0.27mmol) in DMF (1mL) were added 5-isopropyl-1H-pyrazole-3-carboxylic acid (42.18mg, 0.27mmol), DIPEA (0.23mL, 1.37mmol) and HATU (155.95mg, 0.41mmol). The resulting mixture was stirred at 15 °C for 16 hours to give a brown solution. The reaction was diluted with H_2O (20 mL) and extracted with EA (5 mL x 3). The combined organic layers were washed with NH_4Cl aq. (8 mL) and brine (8 mL), dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by prep-TLC (EA/MeOH=10/1) and lyophilized to afford the title compound (21.33mg, 18.54% yield) as a white solid.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.35 (q, *J*=5.02 Hz, 2 H) 0.57 - 0.66 (m, 2 H) 1.21 - 1.27 (m, 1 H) 1.30 (d, *J*=7.03 Hz, 7 H) 2.00 (t, *J*=3.51 Hz, 1 H) 2.18 (dt, *J*=7.40, 3.83

Hz, 1 H) 2.41 (dt, *J*=7.40, 3.83 Hz, 1 H) 2.52 (s, 3 H) 3.02 (dt, *J*=13.74, 6.81 Hz, 1 H) 3.71 (dd, *J*=12.67, 4.39 Hz, 1 H) 3.97 (d, *J*=7.03 Hz, 2 H) 4.21 - 4.34 (m, 2 H) 6.31 (d, *J*=2.26 Hz, 1 H) 6.46 (s, 1 H) 7.53 (d, *J*=2.26 Hz, 1 H)

[0610]

Example 108 [(1R,5S,6r)-6-(1,2-benzoxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](5-isopropyl-1H-pyrazol-3-yl)methanone

[(1R,5S,6r)-6-(1,2-benzoxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](5-isopropyl-1H-pyrazol-3-yl)methanone

To a solution of 5-isopropyl-1H-pyrazole-3-carboxylic acid (10.75mg, 0.0700mmol) in DMF (1mL) were added HATU (33.71mg, 0.0900mmol), DIPEA (0.03mL, 0.1900mmol) and 3-[(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl]-1,2-benzoxazole (15 mg, 0.0600mmol). The mixture was stirred at 20 °C for 12 h to give yellow solution. LCMS showed the desired MS. The reaction mixture was poured into H_2O (15 mL) and extracted with EtOAc (20 mL x 4). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (PE:EtOAc=1 :1) and lyophilized to give the title compound (5.1mg,0.0152mmol, 23.924% yield) as white solid.

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 12.96 (br s, 1 H), 7.99 (br d, J=7.78 Hz, 1 H), 7.56 - 7.75 (m, 2 H), 7.36 (br t, J=7.78 Hz, 1 H), 6.42 (s, 1 H), 4.50 (br d, J=12.05 Hz, 1 H), 4.10 (br d, J=12.30 Hz, 1 H), 3.96 (br d, J=11.80 Hz, 1 H), 3.61 (br d, J=8.03 Hz, 1 H), 2.93 - 3.04 (m, 1 H), 2.42 (br s, 1 H), 2.22 (br s, 1 H), 1.23 (br d, J=6.53 Hz, 6 H)

[0611]

Example 109 (5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(4,5,5-trimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

(5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(4,5,5-trimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a solution of 5-isopropyl-1H-pyrazole-3-carboxylic acid (72.64mg, 0.4700mmol) in DMF (3.5385mL) was added HATU (135.48mg, 0.7100mmol). The reaction mixture was stirred at 15 °C for 30 min. Then (1R,5S,6r)-6-(4,5,5-trimethyl-4,5-dihydro-1,2,4-oxadiazol-

3-yl)-3-azabicyclo[3.1.0]hexane (92 mg, 0.4700mmol) was added. The reaction mixture was stirred at 15 °C for 0.5 hr to give a yellow mixture. LCMS showed the desired MS. The reaction mixture was purified by prep-HPLC (NH_3) to give the title compound (14.45mg, 0.0436mmol, 9.254% yield) as white powder.

LC-MS Method1: 332.0 [$M+H^+$]

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 10.62 (br s, 1H), 6.49 (s, 1H), 4.35 (br d, *J*=10.4 Hz, 1H), 4.22 (d, *J*=12.8 Hz, 1H), 3.99 - 3.89 (m, 1H), 3.65 (dd, *J*=4.0, 12.8 Hz, 1H), 3.02 (m, 1H), 2.78 (s, 3H), 2.33 (m, 1H), 2.04 (m, 1H), 1.41 (d, *J*=7.3 Hz, 6H), 1.30 (d, *J*=7.0 Hz, 6H), 1.14 (t, *J*=3.5 Hz, 1H)

[0612]

Example 110 [(1R,5S,6r)-6-(4-ethyl-5,5-dimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](5-isopropyl-1H-pyrazol-3-yl)methanone

[(1R,5S,6r)-6-(4-ethyl-5,5-dimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](5-isopropyl-1H-pyrazol-3-yl)methanone

To a solution of 5-isopropyl-1H-pyrazole-3-carboxylic acid (69.24mg, 0.4500mmol) in DMF (3.373mL) were added HATU (129.15mg, 0.6700mmol) and DIPEA (171.4 mg, 1.35 mmol). The reaction mixture was stirred at 15 °C for 30 min. Then (1R,5S,6r)-6-(4-ethyl-5,5-dimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)-3-azabicyclo[3.1.0]hexane TFA salt (94 mg, 0.4500mmol) was added. The reaction mixture was stirred at 15 °C for 0.5 hr to give a yellow mixture. LCMS showed the desired MS. The reaction mixture was purified by prep-HPLC (NH_3) to give the title compound (41.23mg, 0.1194mmol, 26.574% yield) as white powder.

LC-MS Method1: 346.0 [$M+H^+$]

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 10.80 (br s, 1H), 6.50 (s, 1H), 4.35 (br s, 1H), 4.21 (d, *J*=12.8 Hz, 1H), 3.97 (dd, *J*=4.3, 11.6 Hz, 1H), 3.67 (dd, *J*=4.4, 12.8 Hz, 1H), 3.18 (q, *J*=7.3 Hz, 2H), 3.02 (td, *J*=6.9, 13.8 Hz, 1H), 2.41 (td, *J*=3.9, 7.4 Hz, 1H), 2.05 (td, *J*=3.6, 7.2 Hz, 1H), 1.43 (d, *J*=12.8 Hz, 6H), 1.30 (d, *J*=6.8 Hz, 6H), 1.20 (t, *J*=7.2 Hz, 3H), 1.14 (t, *J*=3.4 Hz, 1H)

[0613]

Example 111 [(1R,5S,6r)-6-(4-cyclopropyl-5,5-dimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](5-isopropyl-1H-pyrazol-3-yl)methanone

[(1R,5S,6r)-6-(4-cyclopropyl-5,5-dimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](5-isopropyl-1H-pyrazol-3-yl)methanone

To a solution of (1R,5S,6r)-6-(4-cyclopropyl-5,5-dimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)-3-azabicyclo[3.1.0]hexane TFA salt (90 mg, 0.41 mmol), 5-isopropyl-1H-pyrazole-3-carboxylic acid (68.9 mg, 0.45 mmol) and DIPEA (0.34 mL, 2.03 mmol) in DMF (4 mL) was added HATU (171 mg, 0.45 mmol). The mixture was stirred at 20 °C for 16 h. The reaction mixture was diluted with H_2O (50 mL) and extracted by EA (25 mL x 3). The organic phase was washed with brine (50 mL x 3), dried over anhydrous Na_2SO_4 and concentrated to give a residue. The residue was purified by Prep-HPLC (NH_3) to afford the title compound (20 mg, 0.056 mmol, 13.7 % yield) as a white solid.

LC-MS Method1: 358.1 [$M+H^+$]

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 10.39 (br s, 1 H) 6.51 (s, 1 H) 4.14 - 4.39 (m, 2 H) 3.96 (dd, *J*=11.4, 4.4 Hz, 1 H) 3.69 (dd, *J*=12.6, 4.4 Hz, 1 H) 3.03 (spt, *J*=6.9 Hz, 1 H) 2.28 - 2.37 (m, 2 H) 2.06 (dt, *J*=7.2, 3.8 Hz, 1 H) 1.48 (d, *J*=8.9 Hz, 6 H) 1.43 (t, *J*=3.5 Hz, 1 H) 1.31 (d, *J*=6.9 Hz, 6 H) 0.67 - 0.77 (m, 4 H)

[0614]

Example 112 [(1R,5S,6r)-6-(5,5-dimethyl-4-phenyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](5-isopropyl-1H-pyrazol-3-yl)methanone

N-phenyl-2-propanimine

To a solution of aniline (0.2 mL, 2.15 mmol) in Toluene (4.6 mL) was added acetone (374.19 mg, 6.44 mmol), followed by 4A MS (200 mg). Then the mixture was stirred at 110 °C for 3 h. The mixture was filtered and the filtrate was concentrated to dryness to give the title compound (300 mg, crude) as yellow oil, which was used to next step without purification.

[0615]

tert-butyl (1R,5S,6r)-6-(5,5-dimethyl-4-phenyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-[(Z)-chloro(hydroxyimino)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (115.23 mg, crude) in DMF (3 mL) was added Et_3N (0.3 mL, 2.34 mmol), followed by N-phenyl-2-propanimine (186.64 mg, crude) at 20 °C and

then the mixture was stirred at 25 °C for 1 h. The mixture was poured into H_2O (5 mL) and extracted with EtOAc (5 mL x 5). The combined organic layer was washed with brine (5 mL), dried over Na_2SO_4 and concentrated to dryness. The residue was purified by silica gel column (EA in PE from 0% to 50%) to give the title compound (140 mg, 0.3917 mmol, 83.849% yield) as white solid.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.40-7.20 (m, 3H), 7.20-7.10 (m, 2H), 3.50-3.25 (m, 4H), 2.25-2.00 (m, 2H), 1.40 (brs, 3H), 1.37 (brs, 3H), 1.30 (s, 9H), 0.89 (s, 1H).

[0616]

(1R,5S,6r)-6-(5,5-dimethyl-4-phenyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)-3-azabicyclo[3.1.0]hexane TFA salt

A solution of tert-butyl (1R,5S,6r)-6-(5,5-dimethyl-4-phenyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (70 mg, 0.20 mmol) in TFA (0.5 mL)/DCM (2.5 mL) was stirred at 20 °C for 0.5 h. The mixture was concentrated to give the title compound (73 mg, crude as TFA salt) which was used to next step without purification.

[0617]

[(1R,5S,6r)-6-(5,5-dimethyl-4-phenyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](5-isopropyl-1H-pyrazol-3-yl)methanone

To a solution of 3-isopropyl-1H-pyrazole-5-carboxylic acid (39.4mg, 0.26 mmol) and Et_3N (0.17 mL, 0.98 mmol) in DMF (2 mL) was added HATU (89.64 mg, 0.24 mmol) at 15 °C and then the mixture was stirred at 15 °C for 20 min. To the mixture was added (1R,5S,6r)-6-(5,5-dimethyl-4-phenyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)-3-azabicyclo[3.1.0]hexane TFA salt (73 mg, crude as TFA salt) at 15 °C and then the resulting mixture was stirred at 15 °C for 16 h. The mixture was concentrated to remove Et_3N and the residue was purified by prep-HPLC (NH_3) and then lyophilized for 16 h to give the title compound (40.08 mg, 0.1019 mmol, 51.816% yield) as white solid.

LC-MS Method1: 394.0 [$M+H^+$]

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 10.32 (brs, 1H), 7.44 - 7.32 (m, 3H), 7.19 (d, *J*=7.6 Hz, 2H), 6.43 (s, 1H), 4.30 - 4.00 (m, 1H), 3.97 - 3.90 (m, 2H), 3.65 (dd, *J*=4.4, 12.8 Hz, 1H), 3.05 - 2.96 (m, 1H), 2.48 - 2.40 (m, 1H), 2.22 - 2.15 (m, 1H), 1.51 (s, 3H), 1.45 (s, 3H), 1.29 (d, *J*=6.8 Hz, 6H), 0.99 (t, *J*=3.2 Hz, 1H).

[0618]

Example 113 {(1R,5S,6r)-6-[5,5-dimethyl-4-(3-methylphenyl)-4,5-dihydro-1,2,4-oxadiazol-3-yl]-3-azabicyclo[3.1.0]hex-3-yl}(5-isopropyl-1H-pyrazol-3-yl)methanone

{(1R,5S,6r)-6-[5,5-dimethyl-4-(3-methylphenyl)-4,5-dihydro-1,2,4-oxadiazol-3-yl]-3-azabicyclo[3.1.0]hex-3-yl}(5-isopropyl-1H-pyrazol-3-yl)methanone

To a solution of 5-isopropyl-1H-pyrazole-3-carboxylic acid (57.61mg, 0.3700mmol) in DMF (2mL) were added HATU (166.66mg, 0.4400mmol), DIPEA (0.18mL, 1.09mmol) and (1R,5S,6r)-6-[5,5-dimethyl-4-(3-methylphenyl)-4,5-dihydro-1,2,4-oxadiazol-3-yl]-3-azabicyclo[3.1.0]hexane TFA salt (120 mg, 0.3100mmol, TFA salt). The mixture was stirred at 20 °C for 12 h to give yellow solution. The mixture was poured into H_2O (15 mL) and extracted with EtOAc (15 mL x 5). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4 and concentrated to dryness. The residue was purified by prep-TLC (EtOAc) and lyophilized to give the title compound (65.74mg, 0.1613mmol, 51.808% yield) as white solid.

LC-MS Method1: 408.1 [$M+H^+$]

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 9.97 - 10.66 (1 H, m), 7.24 - 7.27 (1 H, m), 7.13 (1 H, d, *J*=7.75 Hz), 6.92 - 7.00 (2 H, m), 6.40 (1 H, s), 4.11 (1 H, br d, *J*=10.88 Hz), 3.87 - 3.97 (2 H, m), 3.64 (1 H, dd, *J*=12.69, 4.44 Hz), 2.94 - 3.06 (1 H, m), 2.38 - 2.47 (1 H, m), 2.37 (3 H, s), 2.18 (1 H, dt, *J*=7.35, 3.77 Hz), 1.49 (3 H, s), 1.43 (3 H, s), 1.28 (6 H, d, *J*=6.88 Hz), 0.97 (1 H, t, *J*=3.50 Hz)

[0619]

Example 114 {(1R,5S,6r)-6-[5,5-dimethyl-4-(4-methylphenyl)-4,5-dihydro-1,2,4-oxadiazol-3-yl]-3-azabicyclo[3.1.0]hex-3-yl}(5-isopropyl-1H-pyrazol-3-yl)methanone

N-(4-methylphenyl)-2-propanimine

To a solution of 4-amino toluene (0.18 mL, 1.87 mmol) in Toluene (4 mL) was added acetone (325.23 mg, 5.6 mmol), followed by 4A MS (200 mg). Then the mixture was stirred at 110 °C for 5 h. Without monitoring. The mixture was filtered and the filtrate was concentrated to dryness to give the title compound (300 mg, crude) as yellow oil, which was used to next step without purification.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.25 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.0 Hz, 2H), 3.53 (brs, 6H), 2.35 (s, 3H).

[0620]

tert-butyl (1R,5S,6r)-6-[5,5-dimethyl-4-(4-methylphenyl)-4,5-dihydro-1,2,4-oxadiazol-3-yl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-[(Z)-chloro(hydroxyimino)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (115.23 mg, crude reaction from above) in DMF (3 mL) was added Et_3N (0.3 mL, 2.34 mmol), followed by N-(4-methylphenyl)-2-propanimine (206.3 mg, crude) at 20 °C and then the mixture was stirred at 25 °C for 1 h. The mixture was poured into H_2O (5 mL) and extracted with EtOAc (5 mL x 5). The combined organic layer was washed with brine (5 mL), dried over Na_2SO_4 and concentrated to dryness. The residue was purified by silica gel column (EA in PE from 0% to 50%) to give the title compound (150 mg, 0.4038mmol, 86.448% yield) as white solid.

^1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.21 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 8.0 Hz, 2H), 3.50-3.30 (m, 4H), 2.39 (s, 3H), 2.20-2.10 (m, 1H), 2.10-2.00 (m, 1H), 1.47 (s, 6H), 1.38 (s, 9H), 0.95-0.90 (m, 1H).

[0621]

(1R,5S,6r)-6-[5,5-dimethyl-4-(4-methylphenyl)-4,5-dihydro-1,2,4-oxadiazol-3-yl]-3-azabicyclo[3.1.0]hexane TFA salt

A solution of tert-butyl (1R,5S,6r)-6-[5,5-dimethyl-4-(4-methylphenyl)-4,5-dihydro-1,2,4-oxadiazol-3-yl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (120 mg, 0.3200mmol) in TFA (1 mL)/DCM (5 mL) was stirred at 20 °C for 0.5 h. The mixture was concentrated to give the title compound (124.49mg, crude), it was used to next step without purification.

[0622]

{(1R,5S,6r)-6-[5,5-dimethyl-4-(4-methylphenyl)-4,5-dihydro-1,2,4-oxadiazol-3-yl]-3-azabicyclo[3.1.0]hex-3-yl}(5-isopropyl-1H-pyrazol-3-yl)methanone

To a solution of 3-isopropyl-1H-pyrazole-5-carboxylic acid (64.49 mg, 0.420 mmol) and Et_3N (0.28 mL, 1.61 mmol) in DMF (2 mL) was added HATU (158.95 mg, 0.420 mmol) at 15 °C and then the mixture was stirred at 15 °C for 20 min. To the mixture was added (1R,5S,6r)-6-[5,5-dimethyl-4-(4-methylphenyl)-4,5-dihydro-1,2,4-oxadiazol-3-yl]-3-azabicyclo[3.1.0]hexane TFA salt (124 mg, 0.320 mmol, TFA salt) at 15 °C and then the resulting mixture was stirred at 15 °C for 2 h. The mixture was concentrated to remove Et_3N (about 3 mL of DMF remained). Precipitate solids were collected by filtration and the cake was washed with MeCN (0.5 mL x 2) to give the title compound (18.1 mg, 0.0444 mmol, 13.804% yield) as white solid. The filtrate was purified by prep-HPLC (NH_3) and then

lyophilized to give the title compound (34.44 mg, 0.0845 mmol, 26.266% yield) as white solid.

LC-MS Method1: 408.0 [$M+H^+$]

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 10.75 - 9.95 (m, 1H), 7.20 (br d, *J*=8.0 Hz, 1H), 7.07 (d, *J*=8.0 Hz, 2H), 6.62 - 6.17 (m, 1H), 4.40 – 3.55 (m, 4H), 3.11 - 2.93 (m, 1H), 2.49 - 2.05 (m, 5H), 1.45 (d, *J*=27.6 Hz, 6H), 1.29 (d, *J*=7.2 Hz, 6H), 0.96 (t, *J*=3.2 Hz, 1H).

[0623]

Example 115 (5-isopropyl-1H-pyrazol-3-yl){(1R,5S,6r)-6-[4-(4-methoxyphenyl)-5,5-dimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl]-3-azabicyclo[3.1.0]hex-3-yl}methanone

N-(4-methoxyphenyl)propan-2-imine

To a solution of 4-methoxyaniline (0.83mL, 8.12mmol) in toluene (10mL) was added acetone(1.41g, 24.36mmol), followed by 4A MS (1.g, 8.12mmol). Then the mixture was stirred at 110 °C for 5 h to give brown suspension. The mixture was filtered and the filtrate was concentrated to dryness to give the title compound (1.5g, 9.1901mmol, 113.18% yield) as brown oil, which was used to next step without purification.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 6.75 (d, J = 8.0 Hz, 2H), 6.65 (d, J = 8.0 Hz, 2H), 3.77 (s, 3H), 2.15 (s, 6H).

[0624]

tert-butyl (1R,5S,6r)-6-[4-(4-methoxyphenyl)-5,5-dimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-[(Z)-chloro(hydroxyimino)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate in DMF (2mL) was added Et_3N (0.48mL, 2.88mmol), followed by N-(4-methoxyphenyl)propan-2-imine (375.62mg, 2.3mmol) at 20 °C and then the mixture was stirred at 25 °C for 1 h to give brown solution. The mixture was poured into H_2O (15 mL) and extracted with EtOAc (15 mL x 5). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4 and concentrated to dryness. The residue was purified by silica gel column (EA in PE from 0% to 50%) to give the title compound (140mg, 0.3613mmol, 62.802% yield) as brown oil.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.11 (d, J = 8.0 Hz, 2H), 6.93 (d, J = 8.0 Hz, 2H), 3.83 (s, 3H), 3.50-3.30 (m, 4H), 2.20-2.10 (m, 1H), 2.10-2.00 (m, 1H), 1.45 (s, 3H), 1.42 (s, 3H), 1.40 (s, 9H), 0.95-0.90 (m, 1H).

[0625]

(1R,5S,6r)-6-[4-(4-methoxyphenyl)-5,5-dimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl]-3-azabicyclo[3.1.0]hexane TFA salt

To a solution of tert-butyl (1R,5S,6r)-6-[4-(4-methoxyphenyl)-5,5-dimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (140 mg, 0.3600mmol) in DCM (5mL) was added TFA (1 mL, 13.46mmol). The mixture was stirred at 20 °C for 0.5 h to give black solution. TLC (PE:EtOAc=1:1) showed the reaction was completed. The reaction mixture was concentrated directly to give the title compound (140mg, 0.3488mmol, 96.534% yield, TFA, salt) as brown gum.

[0626]

(5-isopropyl-1H-pyrazol-3-yl){(1R,5S,6r)-6-[4-(4-methoxyphenyl)-5,5-dimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl]-3-azabicyclo[3.1.0]hex-3-yl}methanone

To a solution of 5-isopropyl-1H-pyrazole-3-carboxylic acid (64.53mg, 0.4200mmol) in DMF (2mL) were added HATU (186.68mg, 0.4900mmol), DIPEA (0.2mL, 1.22mmol) and (1R,5S,6r)-6-[4-(4-methoxyphenyl)-5,5-dimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl]-3-azabicyclo[3.1.0]hexane TFA salt (140 mg, TFA,salt 0.3500mmol). The mixture was stirred at 20 °C for 12 h to give brown solution. The mixture was poured into H_2O (15 mL) and extracted with EtOAc (15 mL x 5). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4 and concentrated to dryness. The residue was purified by prep-HPLC (FA). The afforded flows were combined, concentrated to remove most of CH_3CN and lyophilized to give the title compound (59.06mg, 0.1395mmol, 39.981% yield) as brown solid.

LC-MS Method1: 404.3 [$M+H^+$]

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.11 (2 H, d, *J*=8.76 Hz), 6.91 (2 H, d, *J*=8.75 Hz), 6.39 (1 H, s), 4.92 (2 H, br s), 3.96 - 4.06 (1 H, m), 3.84 - 3.95 (2 H, m), 3.83 (3 H, s), 3.62 (1 H, br dd, *J*=12.63, 4.25 Hz), 3.06 (1 H, dt, *J*=13.88, 6.94 Hz), 2.35 - 2.45 (1 H, m), 2.12 - 2.23 (1 H, m), 1.44 (6 H, d, *J*=15.01 Hz), 1.30 (6 H, d, *J*=6.88 Hz), 0.97 (1 H, t, *J*=3.13 Hz)

[0627]

Example 116 (5-isopropyl-1H-pyrazol-3-yl){(1R,5S,6r)-6-[4-(3-methoxyphenyl)-5,5-dimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl]-3-azabicyclo[3.1.0]hex-3-yl}methanone

(5-isopropyl-1H-pyrazol-3-yl){(1R,5S,6r)-6-[4-(3-methoxyphenyl)-5,5-dimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl]-3-azabicyclo[3.1.0]hex-3-yl}methanone

To a solution of 5-isopropyl-1H-pyrazole-3-carboxylic acid (64.53mg, 0.4200mmol) in DMF (2mL) were added HATU (186.68mg, 0.4900mmol), DIPEA (0.2mL, 1.22mmol) and (1R,5S,6r)-6-[4-(3-methoxyphenyl)-5,5-dimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl]-3-azabicyclo[3.1.0]hexane TFA salt(140 mg, 0.3500mmol, TFA salt). The mixture was stirred at 20 °C for 12 h to give brown solution. The mixture was poured into H_2O (15 mL) and extracted with EtOAc (15 mL x 5). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4 and concentrated to dryness. The residue was purified by prep-HPLC (NH_3). The afforded flows were combined, concentrated to remove most of CH_3CN and lyophilized to give the title compound (62.38mg, 0.1473mmol, 42.229% yield) to give white solid.

LC-MS Method1: 424.0 [$M+H^+$]

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 10.34 (1 H, br s), 7.28 - 7.33 (1 H, m), 6.86 (1 H, dd, *J*=8.41, 1.88 Hz), 6.75 (1 H, dd, *J*=7.91, 1.13 Hz), 6.70 (1 H, t, *J*=2.13 Hz), 6.45 - 6.45 (1 H, m), 6.42 (1 H, br s), 4.14 (1 H, br s), 3.88 - 3.99 (2 H, m), 3.82 (3 H, s), 3.65 (1 H, dd, *J*=12.80, 4.27 Hz), 3.00 (1 H, dt, *J*=13.80, 6.90 Hz), 2.42 (1 H, dt, *J*=7.47, 3.92 Hz), 2.14 - 2.21 (1 H, m), 1.42 - 1.53 (6 H, m), 1.28 (6 H, d, *J*=6.78 Hz), 1.02 (1 H, t, *J*=3.39 Hz)

[0628]

Example 117 [(1R,5S,6r)-6-(4-benzyl-5,5-dimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](5-isopropyl-1H-pyrazol-3-yl)methanone

N-benzyl-2-propanimine

To a solution of benzylamine (0.5 mL, 4.67 mmol) and acetone (1 mL, 14 mmol) in Toluene (5 mL) was added 4AMS (3 g), and the mixture was stirred at 110 °C for 4 h without monitor. The mixture was filtered and the filtrate was concentrated to give the title compound (330 mg, 2.24 mmol) as a colorless oil. The product was used directly for next step.

[0629]

tert-butyl (1R,5S,6r)-6-(4-benzyl-5,5-dimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-[(Z)-chloro(hydroxyimino)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (150 mg, 0.58 mmol) and Et_3N (0.29 mL, 1.73mmol)

in DMF (2 mL) was added N-benzyl-2-propanimine (330 mg, 2.24 mmol). The mixture was stirred at 20 °C for 2 h. The reaction was diluted with H_2O (50 mL) and extracted by EtOAc (20 mL x 3). The organic phase was washed three times with brine, dried over anhydrous Na_2SO_4 and concentrated to give a residue. The residue was purified by flash column (PE:EA = 1:0 - 1:1) to give the title compound (50 mg, 0.1346 mmol, 23.3 % yield) (PE:EA=3:1, Rf=0.5) as a pale yellow solid.

[0630]

(1R,5S,6r)-6-(4-benzyl-5,5-dimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)-3-azabicyclo[3.1.0]hexane TFA salt

To a solution of tert-butyl (1R,5S,6r)-6-(4-benzyl-5,5-dimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (50 mg, 0.13 mmol) in DCM (3 mL) was added TFA (0.3 mL, 4.04 mmol), and the mixture was stirred at 20 °C for 1 h. The reaction mixture was concentrated to give the title compound (50 mg, 0.18mmol) as a yellow oil.

[0631]

[(1R,5S,6r)-6-(4-benzyl-5,5-dimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](5-isopropyl-1H-pyrazol-3-yl)methanone

To a solution of (1R,5S,6r)-6-(4-benzyl-5,5-dimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)-3-azabicyclo[3.1.0]hexane TFA salt (50 mg, 0.1800mmol), HATU (84.5 mg, 0.22 mmol) and DIPEA (0.15 mL, 0.92 mmol) in DMF (3 mL) was added 5-isopropyl-1H-pyrazole-3-carboxylic acid

(34.0 mg, 0.22 mmol), and the mixture was stirred at 20 °C for 16 hr. The mixture was diluted with H_2O (30 mL) and extracted by EA (20 mL x 2), and the organic phase was washed by brine (30 mLx3), dried over anhydrous Na_2SO_4 and concentrated to give a residue. The residue was purified by Prep-HPLC (FA) to afford the title compound (2.5 mg) as a white solid.

LC-MS Method1: 357.1 [$M+H^+$]

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.28 - 7.32 (m, 5 H) 6.38 (br s, 1 H) 4.29 (s, 2 H) 3.88 (br d, *J*=12.8 Hz, 1 H) 3.78 - 3.83 (m, 1 H) 3.69 - 3.76 (m, 1 H) 3.49 (br dd, *J*=12.6, 4.1 Hz, 1 H) 3.04 (dt, *J*=13.7, 6.8 Hz, 1 H) 2.10 - 2.16 (m, 1 H) 2.03 (dt, *J*=7.2, 3.7 Hz, 1 H) 1.44 (d, *J*=6.3 Hz, 6 H) 1.31 (dd, *J*=6.8, 2.3 Hz, 6 H) 0.97 (t, *J*=3.3 Hz, 1 H)

[0632]

Example 118 (5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(7a-methyl-5,6,7,7a-tetrahydropyrrolo[1,2-d][1,2,4]oxadiazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

5-methyl-3,4-dihydro-2H-pyrrole

To a solution of 4-chlorobutanenitrile (1.83mL, 19.31mmol) in 2-methoxy-2-methyl-propane (20 mL, 23.18mmol) was added bromo(methyl)magnesium (2763.65mg, 23.18mmol) drop-wise at 0 °C. It was allowed to reach room temperature. After 15min, THF (10mL) was added drop-wise over 5min. H_2O (30 mL) was added and it was extracted with MTBE (30 mLx2). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuum to give the title compound (800 mg, 9.6235mmol, 49.826% yield) as yellow oil. It was directly used in the next step.

[0633]

tert-butyl (1R,5S,6r)-6-(7a-methyl-5,6,7,7a-tetrahydropyrrolo[1,2-d][1,2,4]oxadiazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

A 100 mL round-bottom flask was charge with tert-butyl (1R,5S,6r)-6-[(Z)-chloro(hydroxyimino)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (250 mg, 0.9600mmol), 5-methyl-3,4-dihydro-2H-pyrrole (500 mg, 6.01mmol), triethylamine (0.4mL, 2.88mmol) and DMF (12.5mL). The reaction was stirred at 20 °C for 16 hr to give a yellow solution. H_2O (30 mL) was added and it was extracted with EtOAc (30 mLx2). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuum to give the title compound (300 mg, 0.9760mmol, 101.78% yield) as yellow oil. It was directly used in the next step. LC-MS Method1 0.810 min, MS (m/z) 307.9 ($M + H^+$).

[0634]

3-[(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl]-7a-methyl-5,6,7,7a-tetrahydropyrrolo[1,2-d][1,2,4]oxadiazole TFA salt

A 100 mL round-bottom flask was charged with tert-butyl (1R,5S,6r)-6-(7a-methyl-5,6,7,7a-tetrahydropyrrolo[1,2-d][1,2,4]oxadiazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (250 mg, 0.8100mmol), 2,2,2-trifluoroacetic acid (1 mL, 13.06mmol) and DCM (10mL). The reaction was stirred at 20 °C for 3 hr to give a yellow solution. The reaction mixture was evaporated in vacuum to give the title compound (260mg, 0.8092mmol, 99.498% yield) as red oil. It was directly use in the next step.

[0635]

(5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(7a-methyl-5,6,7,7a-tetrahydropyrrolo[1,2-d][1,2,4]oxadiazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

A 100 mL round-bottom flask was charged with 5-isopropyl-1H-pyrazole-3-carboxylic acid (130 mg, 0.8400mmol), HATU (354.6mg, 0.9300mmol), N-ethyl-N-isopropylpropan-2-amine (0.58mL, 3.37mmol) and DMF (6.5mL). After stirred for 30 min, 3-[(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl]-7a-methyl-5,6,7,7a-tetrahydropyrrolo[1,2-d][1,2,4]oxadiazole TFA salt (270.93mg, 0.8400mmol) was added. The reaction mixture was stirred at 20 ^{o}C for 16 hr to give a yellow solution. H_2O (30 mL) was added and it was extracted with EtOAc (30 mLx2). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuum to give a yellow oil. The crude was purified by Prep-HPLC (NH_3). The afforded flows were concentrated in vacuum to remove most of CH_3CN and lyophilized to give the title compound (32.74mg, 0.0950mmol, 11.269% yield) as white solid.

LC-MS Method1: 344.1 [$M+H^+$]

^{1}H NMR (400 MHz, DMSO-d_6) δ 6.36 (br s, 1H), 4.20-4.44 (m, 1H), 3.95 (br s, 1H), 3.80 (br s, 1H), 3.45-3.57 (m, 2H), 2.97 (ddd, *J*=6.32, 9.01, 11.44 Hz, 2H), 2.03-2.15 (m, 1H), 1.95 (br s, 1H), 1.85-1.91 (m, 1H), 1.80-1.85 (m, 1H), 1.69-1.76 (m, 1H), 1.57-1.66 (m, 1H), 1.35 (s, 3H), 1.22 (d, *J*=6.88 Hz, 6H)

[0636]

Example 119 (5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(5-methyl-1,3,4-oxadiazol-2-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

ethyl (1R,5S,6r)-3-[(5-isopropyl-1H-pyrazol-3-yl)carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxylate

To a solution of 5-isopropyl-1H-pyrazole-3-carboxylic acid (1.69g, 10.96mmol) in DMF (20mL) were added HATU (5.41g, 14.24mmol), DIPEA (5.43mL, 32.87mmol) and ethyl (1R,5S,6r)-3-azabicyclo[3.1.0]hexane-6-carboxylate (2.1g, 10.96mmol). The mixture was stirred at 15 ^{o}C for 4 h to give brown solution. The reaction mixture was poured into H_2O (100 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (250 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column (PE to 40% EtOAc in PE) to give brown solid. The afforded solid was triturated with EtOAc/PE (10 mL/20 mL) and dried in air to give the title compound (1.45g,4.9768mmol, 45.422% yield) as white solid.

^{1}H NMR (400MHz, CHLOROFORM-d) δ ppm = 10.58 (brs, 1H), 6.47 (s, 1H), 4.35 (d, J = 11.2 Hz, 1H), 4.20 (d, J = 11.2 Hz, 1H), 4.20 (q, J = 6.8 Hz, 2H), 3.95 (d, J = 11.6, 4.0 Hz, 1H), 3.68 (d, J = 11.6, 4.0 Hz, 1H), 3.02 (qn, J = 3.6 Hz, 1H), 2.30-2.15 (m, 2H), 1.50-1.45 (m, 1H), 1.31 (d, J = 6.8 Hz, 6H), 1.26 (t, J = 6.8 Hz, 3H).

[0637]

(1R,5S,6r)-3-[(5-isopropyl-1H-pyrazol-3-yl)carbonyl]-3-azabicyclo[3.1.0]hexane-6-carbohydrazide

To a solution of ethyl (1R,5S,6r)-3-[(5-isopropyl-1H-pyrazol-3-yl)carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxylate (450 mg, 1.54mmol) in EtOH (4mL) was added hydrazine hydrate (236.69mg, 4.63mmol). The mixture was stirred at 80 ^{o}C for 13 h under N_2 to give white suspension. LCMS showed the desire MS and a part of the starting material was remained. Then hydrazine hydrate (236.69mg, 4.63mmol) was added to the mixture. The mixture was stirred at 80 ^{o}C for 13 h under N_2 to give white suspension. LCMS showed the desire MS and a part of the starting material was remained. Then hydrazine hydrate (236.69mg, 4.63mmol) was added to the mixture. The mixture was stirred at 80 ^{o}C for 13h under N_2 to give white suspension. LCMS showed desire MS and a part of the starting material was remained. The reaction mixture was concentrated directly. The afforded solid was triturated with PE (15 mL) and dried in air to give the title compound (390mg,1.4063mmol, 91.051% yield) as white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.96 (brs, 1H), 9.06 (s, 1H), 6.37 (brs, 1H), 4.50-3.80 (m, 6H), 3.50-3.40 (m, 1H), 3.00-2.90 (m, 1H), 2.05-1.95 (m, 1H), 1.95-1.85 (m, 1H), 1.25 (d, J = 7.2 Hz, 6H), 0.90-0.80 (m, 1H).

[0638]

(1R,5S,6r)-N'-acetyl-3-[(5-isopropyl-1H-pyrazol-3-yl)carbonyl]-3-azabicyclo[3.1.0]hexane-6-carbohydrazide

To a mixture of (1R,5S,6r)-3-[(5-isopropyl-1H-pyrazol-3-yl)carbonyl]-3-azabicyclo[3.1.0]hexane-6-carbohydrazide (270 mg, 0.9700mmol) in DCM (10mL) were added acetic anhydride (119.27mg, 1.17mmol) and Et_3N (0.34mL, 1.95mmol). The reaction mixture was stirred at 15 ^{o}C for 12 h to give white suspension. The suspension was filtered. The filter cake was washed with DCM (5 mL × 3) and dried in vacuo to afford the title compound (250mg, 0.7828mmol, 80.404% yield) as white solid.

[0639]

(5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(5-methyl-1,3,4-oxadiazol-2-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

A solution of (1R,5S,6r)-N'-acetyl-3-[(5-isopropyl-1H-pyrazol-3-yl)carbonyl]-3-azabicyclo[3.1.0]hexane-6-carbohydrazide (250 mg, 0.7800mmol) in $POCl_3$ (5 mL, 69.14mmol) was stirred at 90 °C for 4 h to give brown mixture. TLC showed one new spot (Rf = 0.3) was detected. The reaction mixture was concentrated in vacuo to give a residue. The residue was dissolved with DCM (15 mL). The resulting mixture was washed with $NaHCO_3$ (eq., 15 mL×2). The aqueous phase was extracted with DCM (10 mL×3). The combined organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to give a residue. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 10: 1) and lyophilized to afford the title compound (120mg, 0.3799mmol, 48.535% yield) as yellow powder.

LC-MS Method1: 301.9 [$M+H^+$]

^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 9.99 - 10.47 (m, 1 H), 6.53 (s, 1 H), 4.45 (br d, J=10.6 Hz, 1 H), 4.29 (d, J=12.8 Hz, 1 H), 3.99 (dd, J=11.6, 4.0 Hz, 1 H), 3.72 (dd, J=12.7, 4.1 Hz, 1 H), 2.99 - 3.09 (m, 1 H), 2.49 (s, 3 H), 2.35 - 2.43 (m, 1 H), 2.26 - 2.34 (m, 1 H), 1.96 (t, J=3.4 Hz, 1 H), 1.31 (d, J=6.9 Hz, 6 H)

[0640]

Example 120 (5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(4-methyl-4H-1,2,4-triazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

N'-({(1R,5S,6r)-3-[(5-isopropyl-1H-pyrazol-3-yl)carbonyl]-3-azabicyclo[3.1.0]hex-6-yl}carbonyl)-N,N-dimethylhydrazonoformamide

To a solution of (1R,5S,6r)-3-[(5-isopropyl-1H-pyrazol-3-yl)carbonyl]-3-azabicyclo[3.1.0]hexane-6-carbohydrazide (390 mg, 1.41mmol) in DMF (4mL) was added 1,1-dimethoxy-N,N-dimethylmethanamine (0.2mL, 1.48mmol). The mixture was stirred at 100 °C for 15 h to give yellow solution. The reaction mixture was concentrated directly to give the title compound (450mg, 1.3538mmol, 96.265% yield) as white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.94 (brs, 1H), 10.10 (s, 1H), 7.66 (s, 1H), 6.36 (brs, 1H), 4.40-4.30 (m, 1H), 4.00-3.70 (m, 2H), 3.50-3.40 (m, 1H), 3.00-2.90 (m, 1H), 2.80-2.75 (m, 1H), 2.76 (s, 6H), 2.00-1.80 (m, 2H), 1.21 (d, J= 7.2 Hz, 6H), 1.25-1.20 (m, 1H).

[0641]

(5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(4-methyl-4H-1,2,4-triazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a solution of N'-({(1R,5S,6r)-3-[(5-isopropyl-1H-pyrazol-3-yl)carbonyl]-3-azabicyclo[3.1.0]hex-6-yl}carbonyl)-N,N-dimethylhydrazonoformamide (200 mg, 0.6000mmol) in THF (4mL) was added methanamine (0.49mL, 12.03mmol). Then HOAc (2 mL, 0.6000mmol) was added to the mixture at 0 ºC. The mixture was stirred at 100°C to give colorless solution. The reaction mixture was concentrated directly. The residue was purified by prep-HPLC (HCl) to give the title compound (37.05mg, 0.1234mmol, 20.501% yield) as white solid.

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 9.39 (br s, 1 H), 6.42 (s, 1 H), 4.46 (br d, J=11.88 Hz, 1 H), 4.10 (br d, J=12.51 Hz, 1 H), 3.95 (br dd, J=12.01, 3.88 Hz, 1 H), 3.85 (s, 3 H), 3.60 (br dd, J=12.44, 4.06 Hz, 1 H), 2.97 (spt, J=6.90 Hz, 1 H), 2.47 (br s, 2 H), 2.16 (t, J=3.25 Hz, 1 H), 1.22 (d, J=6.75 Hz, 6 H)

[0642]

Example 121 (5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(4-phenyl-4H-1,2,4-triazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

(5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(4-phenyl-4H-1,2,4-triazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a solution of (1R,5S,6r)-3-[(5-isopropyl-1H-pyrazol-3-yl)carbonyl]-3-azabicyclo[3.1.0]hexane-6-carbohydrazide in MeCN (2mL) was added 1,1-dimethoxy-N,N-dimethylmethanamine (21.52mg, 0.1800mmol). The mixture was stirred at 50 °C for 30 min. Then aniline (0.03mL, 0.3600mmol) was added to the mixture, followed by AcOH (2 mL). The mixture was stirred at 120 °C for 5 h to give colorless solution. The residue was purified by prep-HPLC (HCl). The afforded flows were combined, concentrated to remove most of CH_3CN and lyophilized to give the title compound (24.12mg,0.0666mmol, 36.912% yield) as white solid.

LC-MS Method1: 362.9 [$M+H^+$]

^{1}H NMR (400 MHz, *DMSO-d*$_6$) δ ppm 9.28 - 9.55 (1 H, m), 7.58 - 7.70 (5 H, m), 6.34 (1 H, s), 4.26 (1 H, br d, *J*=12.01 Hz), 3.81 - 3.92 (2 H, m), 3.54 (1 H, dd, *J*=12.44, 4.19 Hz), 2.93 (1 H, dt, *J*=13.85, 6.89 Hz), 2.54 - 2.58 (1 H, m), 2.39 (1 H, dt, *J*=7.19, 3.66 Hz), 1.68 (1 H, t, *J*=3.31 Hz), 1.19 (6 H, d, *J*=7.00 Hz)

[0643]

Example 122 {(1R,5S,6r)-6-[4-(4-fluorophenyl)-4H-1,2,4-triazol-3-yl]-3-azabicyclo[3.1.0]hex-3-yl}(5-isopropyl-1H-pyrazol-3-yl)methanone

{(1R,5S,6r)-6-[4-(4-fluorophenyl)-4H-1,2,4-triazol-3-yl]-3-azabicyclo[3.1.0]hex-3-yl}(5-isopropyl-1H-pyrazol-3-yl)methanone

To a solution of (1R,5S,6r)-3-[(5-isopropyl-1H-pyrazol-3-yl)carbonyl]-3-azabicyclo[3.1.0]hexane-6-carbohydrazide in MeCN (2mL) was added 1,1-dimethoxy-N,N-dimethylmethanamine (47.96mg, 0.3600mmol). The mixture was stirred at 80 °C for 30 min. Then 4-fluoroaniline (0.07mL, 0.7200mmol) and AcOH (216.36mg, 3.61mmol) were added. The mixture was stirred at 90 °C for 5 h to give colorless solution. The reaction mixture was concentrated directly. The residue was purified by prep-HPLC (HCl) to give the title compound (5.67mg, 0.0149mmol, 4.1333% yield) as gray solid.

LC-MS Method1: 381.0 [$M+H^+$]

^{1}H NMR (400 MHz, *DMSO-d*$_6$) δ ppm 12.92 (1 H, br s), 8.67 (1 H, s), 7.62 (2 H, br dd, *J*=8.91, 4.89 Hz), 7.35 - 7.51 (2 H, m), 6.33 (1 H, s), 4.28 (1 H, br d, *J*=12.05 Hz), 3.80 - 3.94 (2 H, m), 3.52 (1 H, br d, *J*=8.03 Hz), 2.85 - 3.01 (1 H, m), 2.19 (1 H, br s), 1.92 - 2.04 (1 H, m), 1.51 (1 H, br s), 1.13 - 1.27 (6 H, m)

[0644]

Example 123 [(1R,5S,6r)-6-(4,5-dimethyl-4H-1,2,4-triazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](5-isopropyl-1H-pyrazol-3-yl)methanone

[(1R,5S,6r)-6-(4,5-dimethyl-4H-1,2,4-triazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](5-isopropyl-1H-pyrazol-3-yl)methanone

To a solution of (5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(5-methyl-1,3,4-oxadiazol-2-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone (30 mg, 0.1000mmol) in xylene (2 mL, 0.1000mmol) were added methylamine (0.74mL, 1.99mmol) and TsOH (1.71mg, 0.0100mmol). The mixture was stirred at 140 °C for 12 h to give brown solution. The reaction mixture was concentrated directly. The residue was purified by prep-HPLC (HCl). The afforded flows were combined, concentrated to remove most of CH_3CN and lyophilized to give the title compound (11.82mg, 0.0376mmol, 37.765% yield) as light yellow solid.

LC-MS Method1: 314.9 [M+H$^+$]

^{1}H NMR (400 MHz, *DMSO-d*$_6$) δ ppm 6.41 (1 H, s), 4.44 (1 H, br d, *J*=11.80 Hz), 4.09 (1 H, d, *J*=12.30 Hz), 3.94 (1 H, br dd, *J*=11.92, 4.14 Hz), 3.71 (3 H, s), 3.59 (1 H, br dd, *J*=12.55, 4.27 Hz), 2.96 (1 H, dt, *J*=13.80, 6.90 Hz), 2.56 (3 H, s), 2.38 (1 H, br d, *J*=3.76 Hz), 2.29 - 2.35 (1 H, m), 2.28 (1 H, s), 2.14 (1 H, t, *J*=3.39 Hz), 1.21 (6 H, dd, *J*=7.03, 1.00 Hz)

[0645]

Example 124 [(1R,5S,6r)-6-(4-cyclobutyl-5-methyl-4H-1,2,4-triazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](5-isopropyl-1H-pyrazol-3-yl)methanone

[(1R,5S,6r)-6-(4-cyclobutyl-5-methyl-4H-1,2,4-triazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](5-isopropyl-1H-pyrazol-3-yl)methanone

To a mixture of (5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(5-methyl-1,3,4-oxadiazol-2-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone (30 mg, 0.1000mmol) in o-Xylene (1mL) were added TsOH (0.17mg, 0mmol) and cyclobutanamine (0.02mL, 0.2000mmol). The reaction mixture was stirred at 140 ℃ for 16 h to give brown mixture. The reaction mixture was concentrated in vacuo to give a residue. The residue was purified by prep-HPLC (HCl). The afforded flows were combined, concentrated to remove most of CH_3CN and lyophilized to afford the title compound (10.71mg, 0.0302mmol, 30.351% yield) as yellow solid.

LC-MS Method1: 355.0 [M+H$^+$]

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 6.42 (s, 1 H), 4.85 - 4.98 (m, 1 H), 4.45 (br d, J=12.0 Hz, 1 H), 4.05 (d, J=12.3 Hz, 1 H), 3.93 (br dd, J=11.9, 4.1 Hz, 2 H), 3.61 (br s, 1 H), 3.58 (br s, 1 H), 2.91 - 3.01 (m, 1 H), 2.63 - 2.69 (m, 2 H), 2.60 (s, 3 H), 2.42 - 2.45 (m, 1 H), 2.36 (br d, J=3.8 Hz, 1 H), 2.04 (t, J=3.4 Hz, 1 H), 1.84 (td, J=10.2, 5.0 Hz, 2 H), 1.22 (d, J=7.0 Hz, 6 H)

[0646]

Example 125 [(1R,5S,6r)-6-(4-cyclohexyl-5-methyl-4H-1,2,4-triazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](5-isopropyl-1H-pyrazol-3-yl)methanone

tert-butyl (1R,5S,6r)-6-(cyclohexylcarbamoyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of (1R,5S,6r)-3-{[(tert-butyl)oxy]carbonyl}-3-azabicyclo[3.1.0]hexane-6-carboxylic acid (500 mg, 2.2mmol) in DMF (6mL) were added HATU (1086.86mg, 2.86mmol), cyclohexanamine (0.28mL, 2.42mmol) and Et_3N (0.91mL, 5.5mmol). The mixture was stirred at 20 °C for 12 h to give gray suspension. TLC (PE:EtOAc=1:1) showed the reaction was completed. The reaction mixture was poured into H_2O (15 mL) and filtered. The filter cake was washed with H_2O (15 mL x 2) and dried in air to give the title compound (650mg, 2.1075mmol, 95.791% yield) as white solid.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 5.48 (d, J = 8.0 Hz, 1H), 3.85-3.70 (m, 1H), 3.67 (d, J = 11.2 Hz, 1H), 3.59 (d, J = 11.2 Hz, 1H), 3.45-3.35 (m, 2H), 2.04 (brs, 2H), 1.91 (brd, J = 9.6 Hz, 2H), 1.80-1.70 (m, 2H), 1.65-1.55 (m, 1H), 1.44 (s, 9H), 1.50-1.20 (m, 2H), 1.25-1.05 (m, 4H).

[0647]

tert-butyl (1R,5S,6r)-6-(cyclohexylcarbamothioyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-(cyclohexylcarbamoyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (600 mg, 1.95mmol) in THF (6mL) was added 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide (802.59mg, 1.98mmol). The mixture was stirred at 20 °C for 12 h to give brown solution. TLC (PE:EtOAc=5:1) showed a new spot. The reaction mixture was poured into H_2O (20 mL) and extracted with EtOAc (20 mL x 4). The combined organic layers were washed with brine (50 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column (PE to 10% EtOAc in PE) to give the title compound (350mg, 1.0786mmol, 55.446% yield) as gray solid.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.58 (brd, J = 7.2 Hz, 1H), 4.50-4.35 (m, 1H), 3.65 (d, J = 11.2 Hz, 1H), 3.57 (d, J = 11.2 Hz, 1H), 3.50-3.40 (m, 2H), 2.45-2.35 (m, 2H), 2.15-2.05 (m, 2H), 1.80-1.50 (m, 4H), 1.45 (s, 9H), 1.50-1.40 (m, 2H), 1.30-1.10 (m, 4H).

[0648]

tert-butyl (1R,5S,6r)-6-[(Z)-(cyclohexylimino)(methylthio)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-(cyclohexylcarbamothioyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (300 mg, 0.9200mmol), 1-methyl-4-(methylsulfonyl)benzene (0.12mL, 0.9300mmol) in DMF (6mL) was added tert-butoxypotassium (124.49mg, 1.11mmol). The mixture was stirred at 20 °C for 9 h to give

yellow solution. The reaction mixture was poured into H_2O (20 mL) and extracted with EtOAc (20 mL x 4). The combined organic layers were washed with brine (50 mL X 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (300 mg, 0.8862mmol, 95.855% yield) as a light yellow solid.

LC-MS Method1 0.693 min, MS (m/z) 339.0 ($M + H^+$).

[0649]

tert-butyl (1R,5S,6r)-6-(4-cyclohexyl-5-methyl-4H-1,2,4-triazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-[(Z)-(cyclohexylimino)(methylthio)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (300 mg, 0.8900mmol) and acetohydrazide (98.48mg, 1.33mmol) in THF (5mL) was added 2,2,2-trifluoroacetic acid (0.03mL, 0.4400mmol). The mixture was stirred at 75 °C for 16 h to give colorless solution. The reaction mixture was poured into H_2O (20 mL) and extracted with EtOAc (20 mL x 4). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column (EtOAc/MeOH=1/0 to 5/1) to give the title compound (280mg, 0.8082mmol, 91.189% yield) as colorless gum.

LC-MS Method1 0.718 min, MS (m/z) 347.1 (M + H+).

[0650]

(1R,5S,6r)-6-(4-cyclohexyl-5-methyl-4H-1,2,4-triazol-3-yl)-3-azabicyclo[3.1.0]hexane hydrochloride

A solution of tert-butyl (1R,5S,6r)-6-(4-cyclohexyl-5-methyl-4H-1,2,4-triazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (130 mg, 0.3800mmol) in HCl/dioxane (0.09mL, 0.3800mmol) was stirred at 20 °C for 30 min to give colorless solution. LCMS showed the desire MS and the starting material was consumed up. The reaction mixture was concentrated directly to give the title compound (100 mg, 0.3536mmol, 94.238% yield) as yellow gum.

[0651]

[(1R,5S,6r)-6-(4-cyclohexyl-5-methyl-4H-1,2,4-triazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](5-isopropyl-1H-pyrazol-3-yl)methanone

To a solution of 5-isopropyl-1H-pyrazole-3-carboxylic acid (65.42mg, 0.4200mmol) in DMF (1.7422mL) were added HATU (188.11mg, 0.5000mmol), Et_3N (0.18mL, 1.06mmol) and (1R,5S,6r)-6-(4-cyclohexyl-5-methyl-4H-1,2,4-triazol-3-yl)-3-azabicyclo[3.1.0]hexane

hydrochloride (100 mg, 0.3500mmol). The mixture was stirred at 20 °C for 12 h to give yellow solution. LCMS showed the desire MS and the starting material was consumed up. The reaction mixture was poured into H_2O (20 mL) and extracted with EtOAc (20 mL x 4). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (HCl). The afforded flows were combined, concentrated to remove most of CH_3CN and lyophilized to give yellow solid(crude). The residue was purified by prep-TLC (EtOAc) and lyophilized to give the title compound as a white solid.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 10.84 - 11.67 (1 H, m), 6.53 (1 H, s), 4.46 (1 H, br d, *J*=10.76 Hz), 4.26 (1 H, br d, *J*=12.76 Hz), 3.96 - 4.12 (2 H, m), 3.76 (1 H, br dd, *J*=12.88, 4.25 Hz), 3.02 - 3.18 (1 H, m), 2.74 (1 H, br s), 2.51 (3 H, br s), 2.11 (1 H, br s), 1.89 - 2.00 (5 H, m), 1.79 (1 H, br d, *J*=13.76 Hz), 1.67 - 1.75 (2 H, m), 1.38 - 1.50 (2 H, m), 1.33 (6 H, dd, *J*=6.88, 1.63 Hz), 1.25 (1 H, br d, *J*=6.38 Hz)

[0652]

Example 126 (5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(5-methyl-4-phenyl-4H-1,2,4-triazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

(5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(5-methyl-4-phenyl-4H-1,2,4-triazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a mixture of (5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(5-methyl-1,3,4-oxadiazol-2-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone (30 mg, 0.1000mmol) in o-Xylene (1mL) were added aniline (0.02mL, 0.2000mmol) and TsOH (0.17mg, 0mmol). The reaction mixture was stirred at 140 ^{o}C for 16 h to give brown mixture. The reaction mixture was concentrated in vacuo to give a residue. The residue was purified by prep-HPLC (HCl). The afforded flows were combined, concentrated to remove most of CH_3CN and lyophilized to afford the title compound (18.55mg, 0.0493mmol, 49.496% yield) as white powder.

LC-MS Method1: 377.0 [$M+H^+$]

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 7.54 - 7.79 (m, 5 H), 6.32 (s, 1 H), 4.17 (br d, J=12.0 Hz, 1 H), 3.85 (br dd, J=11.8, 4.1 Hz, 2 H), 3.74 (br d, J=12.4 Hz, 2 H), 2.93 (dt, J=13.9, 7.1 Hz, 1 H), 2.68 (br d, J=1.8 Hz, 1 H), 2.35 (s, 3 H), 2.28 (dt, J=7.5, 3.6 Hz, 1 H), 1.45 (t, J=3.3 Hz, 1 H), 1.19 (d, J=6.9 Hz, 6 H)

[0653]

Example 127 {(1R,5S,6r)-6-[4-(4-fluorophenyl)-5-methyl-4H-1,2,4-triazol-3-yl]-3-azabicyclo[3.1.0]hex-3-yl}(5-isopropyl-1H-pyrazol-3-yl)methanone

{(1R,5S,6r)-6-[4-(4-fluorophenyl)-5-methyl-4H-1,2,4-triazol-3-yl]-3-azabicyclo[3.1.0]hex-3-yl}(5-isopropyl-1H-pyrazol-3-yl)methanone

To a solution of (5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(5-methyl-1,3,4-oxadiazol-2-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone (25 mg, 0.0800mmol) in p-Xylene (0.50 mL) were added 4-fluoroaniline (0.02mL, 0.1700mmol) and TsOH (0.14mg, 0mmol). The mixture was stirred at 140 °C for 12 h to give brown solution. The reaction mixture was concentrated directly. The residue was purified by prep-HPLC (HCl). The afforded flows were combined, concentrated to remove most of CH_3CN and lyophilized to give the title compound (13.91mg, 0.0353mmol, 42.506% yield) as white solid.

LC-MS Method1: 395.0 [$M+H^+$]

^{1}H NMR (400 MHz, *DMSO-d*$_6$) δ ppm 7.76 (1 H, dd, *J*=8.69, 4.82 Hz), 7.73 - 7.80 (1 H, m), 7.55 (2 H, t, *J*=8.63 Hz), 6.30 - 6.37 (1 H, m), 4.18 (1 H, br d, *J*=12.01 Hz), 3.86 (1 H, br dd, *J*=11.94, 4.06 Hz), 3.75 (1 H, br d, *J*=12.51 Hz), 3.51 (1 H, br dd, *J*=12.44, 4.06 Hz), 2.88 - 2.99 (1 H, m), 2.39 (3 H, s), 2.31 - 2.37 (1 H, m), 1.53 (1 H, t, *J*=3.25 Hz), 1.19 (6 H, d, *J*=7.00 Hz)

[0654]

Example 128 (5-isopropyl-1H-pyrazol-3-yl){(1R,5S,6r)-6-[5-methyl-4-(4-methylphenyl)-4H-1,2,4-triazol-3-yl]-3-azabicyclo[3.1.0]hex-3-yl}methanone

(5-isopropyl-1H-pyrazol-3-yl){(1R,5S,6r)-6-[5-methyl-4-(4-methylphenyl)-4H-1,2,4-triazol-3-yl]-3-azabicyclo[3.1.0]hex-3-yl}methanone

To a mixture of (5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(5-methyl-1,3,4-oxadiazol-2-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone (20 mg, 0.0700mmol) in o-Xylene (1mL) were added p-toluidine (0.01mL, 0.1300mmol) and TsOH (0.11mg). The reaction mixture was stirred at 140 °C for 12 h to give brown mixture. The reaction mixture was concentrated in vacuo to give a residue. The residue was purified by prep-HPLC (HCl). The afforded flows were combined, concentrated to remove most of CH_3CN and lyophilized to afford the title compound (11.42mg, 0.0278mmol, 41.954% yield) as yellow solid.

LC-MS Method1: 391.0 [M+H$^+$]

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 7.49 - 7.53 (m, 2 H), 7.45 - 7.49 (m, 2 H), 6.33 (s, 1 H), 4.20 (br d, J=12.1 Hz, 1 H), 3.86 (br dd, J=12.0, 4.3 Hz, 2 H), 3.75 (br d, J=12.4 Hz, 1 H), 2.93 (dt, J=13.9, 6.9 Hz, 1 H), 2.46 (br d, J=3.1 Hz, 1 H), 2.41 (s, 3 H), 2.34 (s, 3 H), 2.29 (dt, J=7.4, 3.8 Hz, 1 H), 1.46 (t, J=3.4 Hz, 1 H), 1.19 (d, J=6.9 Hz, 6 H)

[0655]

Example 129 {(1R,5S,6r)-6-[4-(4-ethylphenyl)-5-methyl-4H-1,2,4-triazol-3-yl]-3-azabicyclo[3.1.0]hex-3-yl}(5-isopropyl-1H-pyrazol-3-yl)methanone

{(1R,5S,6r)-6-[4-(4-ethylphenyl)-5-methyl-4H-1,2,4-triazol-3-yl]-3-azabicyclo[3.1.0]hex-3-yl}(5-isopropyl-1H-pyrazol-3-yl)methanone

To a mixture of (5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(5-methyl-1,3,4-oxadiazol-2-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone (20 mg, 0.0700mmol) in o-Xylene (0.9535mL) were added 4-ethylaniline (0.02mL, 0.1300mmol) and TsOH (0.11mg). The reaction mixture was stirred at 140 ^{o}C for 12 h to give brown mixture. LCMS showed the starting material was consumed completely. The reaction mixture was concentrated in vacuo to give a residue. The residue was purified by prep-HPLC (HCl). The afforded flows were combined, concentrated to remove most of CH_3CN and lyophilized to afford the title compound (9.41mg, 0.0229mmol, 34.521% yield) as white powder.

LC-MS Method1: 405.0 [M+H$^+$]

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 7.47 - 7.57 (m, 4 H), 6.25 - 6.40 (m, 1 H), 4.18 (br d, J=11.9 Hz, 1 H), 3.86 (br dd, J=11.9, 4.1 Hz, 2 H), 3.75 (br d, J=12.5 Hz, 1 H), 3.49 (br s, 2 H), 2.87 - 2.97 (m, 1 H), 2.66 - 2.76 (m, 2 H), 2.36 (s, 3 H), 2.28 - 2.33 (m, 2 H), 1.46 (t, J=3.3 Hz, 1 H), 1.16 - 1.25 (m, 9 H)

[0656]

Example 130 (5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(6-methyl[1,2,4]triazolo[4,3-a]pyridin-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

tert-butyl (1R,5S,6r)-6-{[2-(5-methyl-2-pyridinyl)hydrazino]carbonyl}-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a mixture of (1R,5S,6r)-3-{[(tert-butyl)oxy]carbonyl}-3-azabicyclo[3.1.0]hexane-6-carboxylic acid (300 mg, 1.32mmol) in DMF (5mL) were added 2-hydrazino-5-methylpyridine (162.58mg, 1.32mmol), Et_3N (0.24mL, 1.45mmol) and HATU (551.79mg, 1.45mmol). The reaction mixture was stirred at 15 ^oC for 16 h to give brown mixture. The reaction mixture was concentrated in vacuo to give a residue. The residue was purified by column chromatography (SiO_2, PE/EA=6/1) to give the title compound (330mg, 0.9928mmol, 75.206% yield) as yellow solid.

LC-MS Method1 0.639 min, MS (m/z) 332.9 ($M + H^+$).

[0657]

tert-butyl (1R,5S,6r)-6-(6-methyl[1,2,4]triazolo[4,3-a]pyridin-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a mixture of tert-butyl (1R,5S,6r)-6-{[2-(5-methyl-2-pyridinyl)hydrazino]carbonyl}-3-azabicyclo[3.1.0]hexane-3-carboxylate (270 mg, 0.8100mmol) in MeCN (5mL) was added Burgess reagent (387.13mg, 1.62mmol). The reaction mixture was stirred at 90 ^oC for 12 h. TLC showed the starting material was consumed completely, and one new spot was detected. The reaction mixture was concentrated in vacuo to give a residue. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 10: 1) to afford the title compound (130mg, 0.4135mmol, 50.908% yield) as yellow solid.

LC-MS Method1 0.693 min, MS (m/z) 314.9 ($M + H^+$).

[0658]

3-[(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl]-6-methyl[1,2,4]triazolo[4,3-a]pyridine TFA salt

To a solution of tert-butyl (1R,5S,6r)-6-(6-methyl[1,2,4]triazolo[4,3-a]pyridin-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (130 mg, 0.4100mmol) in DCM (4mL) was added TFA (1 mL, 13.46mmol). The reaction mixture was stirred at 15 ^oC for 2 h to give yellow mixture. TLC (DCM: MeOH = 10:1) showed the starting material was consumed completely. The reaction mixture was concentrated in vacuo to give the title compound (135mg, 0.4112mmol, 99.446% yield) as yellow oil.

[0659]

(5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(6-methyl[1,2,4]triazolo[4,3-a]pyridin-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a mixture of 3-[(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl]-6-methyl[1,2,4]triazolo[4,3-a]pyridine TFA salt (130 mg, 0.4000mmol) in DMF (3.0297mL) were added 5-isopropyl-1H-pyrazole-3-carboxylic acid (61.05mg, 0.4000mmol), DIPEA

(0.2mL, 1.19mmol) and HATU (180.57mg, 0.4800mmol). The reaction mixture was stirred at 15 °C for 12 h to give brown mixture. LCMS showed the starting material was consumed completely. The reaction mixture was purified by prep-HPLC (HCl). The afforded flows were combined, concentrated to remove most of CH_3CN and lyophilized to afford the title compound (25.34mg, 0.0698mmol, 17.624% yield) as white solid.

LC-MS Method1: 350.9 [$M+H^+$]

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 1.23 (dd, *J*=6.9, 1.2 Hz, 6 H), 2.37 (d, *J*=3.6 Hz, 1 H), 2.40 (s, 3 H), 2.44 (br d, *J*=1.9 Hz, 1 H), 2.47 (dd, *J*=3.4, 1.6 Hz, 1 H), 2.93 - 3.03 (m, 1 H), 3.62 (br s, 1 H), 3.66 (br d, *J*=3.5 Hz, 1 H), 4.00 (br dd, *J*=11.9, 4.2 Hz, 1 H), 4.21 (d, *J*=12.4 Hz, 1 H), 4.53 (br d, *J*=11.8 Hz, 1 H), 6.45 (s, 1 H), 7.78 (d, *J*=9.5 Hz, 1 H), 7.91 (d, *J*=9.3 Hz, 1 H), 8.86 (s, 1 H).

[0660]

Example 131 (5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(6-methoxy[1,2,4]triazolo[4,3-a]pyridin-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

2-hydrazino-5-methoxypyridine

2-chloro-5-methoxypyridine (1.5.g, 7.98mmol) and hydrazine hydrate (20.g, 379.54mmol) was combined and heated slowly to 140°C. The reaction mixture was stirred at 140 °C for 16 hours. LCMS showed the desired peak was found. The mixture was concentrated under reduced pressure to afford a residue. The residue was purified by Combi Flash with silica gel (MeOH/DCM=1/10) to give the title compound (650mg, 4.6709mmol, 58.548% yield) as yellow oil.

LC-MS Method1 0.192min, MS (m/z) 140.0 ($M + H^+$).

[0661]

tert-butyl (1R,5S,6r)-6-{[2-(5-methoxy-2-pyridinyl)hydrazino]carbonyl}-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a mixture of (1R,5S,6r)-3-{[(tert-butyl)oxy]carbonyl}-3-azabicyclo[3.1.0]hexane-6-carboxylic acid (979.85mg, 4.31mmol) and HATU (2.46g, 6.47mmol) in DCM (20mL) was added Et_3N (1.43mL, 8.62mmol), and the resulting mixture was stirred at 20 °C for 10 min. Then 2-hydrazino-5-methoxypyridine (600 mg, 4.31mmol) was added. The resulting mixture was stirred at 20 °C under N_2 for 16 hours to give brown mixture. The reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (30 mlx3). The organic layer was

washed with brine (20 mL), dried over Na_2SO_4 and concentrated in vacuum to give brown oil. The crude oil was purified by prep-TLC (PE/EA=1/1) to give the title compound (400 mg, 1.1481mmol, 26.628% yield) as yellow solid.

LC-MS Method1: 349.1 [$M+H^+$].

[0662]

tert-butyl (1R,5S,6r)-6-(6-methoxy[1,2,4]triazolo[4,3-a]pyridin-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-{[2-(5-methoxy-2-pyridinyl)hydrazino]carbonyl}-3-azabicyclo[3.1.0]hexane-3-carboxylate (380 mg, 1.09mmol) in MeCN (20mL) was added Burgess reagent (649.78mg, 2.73mmol). The mixture was stirred at 95 °C under N_2 for 16 hours. The reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by Combi Flash with silica gel (EtOAc/PE=1/1) to give the title compound (120mg, 0.3133mmol, 28.723% yield) as yellow solid.

LC-MS Method1: 331.0 [$M+H^+$].

[0663]

3-[(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl]-6-methoxy[1,2,4]triazolo[4,3-a]pyridine TFA salt

To a solution of tert-butyl (1R,5S,6r)-6-(6-methoxy[1,2,4]triazolo[4,3-a]pyridin-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (100 mg, 0.30 mmol) in DCM (3mL) was added TFA (0.13mL, 1.82mmol) at 20°C. The mixture was stirred at 20 °C for 16 hours. The reaction mixture was concentrated to give the title compound (100 mg, 0.4343mmol, 143.48% yield) as yellow oil.

LC-MS Method1: 230.95 [$M+H^+$].

[0664]

(5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(6-methoxy[1,2,4]triazolo[4,3-a]pyridin-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a mixture of 5-isopropyl-1H-pyrazole-3-carboxylic acid (65 mg, 0.42 mmol) in DCM (3 mL) were added HATU (241.77mg, 0.6300mmol) and Et_3N (0.14mL, 0.8400mmol), and the mixture was stirred at 20 ºC for 10 min under N_2. Then, 3-[(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl]-6-methoxy[1,2,4]triazolo[4,3-a]pyridine TFA salt (97.08mg, 0.4200mmol) in DCM (2 mL) was added. The resulting mixture was stirred at 20 ºC for 16 hr to give brown mixture. The reaction was diluted with H_2O (20mL) and extracted with DCM

(20mL). The combined organic layers were separated, then dried over Na_2SO_4 and concentrated in vacuum to give brown oil. The brown oil was purified by prep-HPLC (FA) and the afforded flows were lyophilized to afford the title compound (40.47mg, 0.1054mmol, 24.997% yield) as pale yellow solid.

LC-MS Method1: 367.0 [$M+H^+$].

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.11 (s, 1H), 7.65 (d, *J*=10.0 Hz, 1H), 7.39 (s, 1H), 7.06 (dd, *J*=2.0, 10.0 Hz, 1H), 6.57 (s, 1H), 4.55 (d, *J*=11.5 Hz, 1H), 4.44 (d, *J*=12.5 Hz, 1H), 4.10 (dd, *J*=3.8, 11.8 Hz, 1H), 3.89 (s, 3H), 3.84 - 3.73 (m, 1H), 3.07 (td, *J*=7.2, 13.8 Hz, 1H), 2.82 - 2.74 (m, 1H), 2.31 - 2.29 (m, 1H), 1.89 (br s, 1H), 1.33 (d, *J*=6.8 Hz, 6H)

[0665]

Example 132 (5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-([1,2,3]triazolo[1,5-a]pyridin-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

(5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-([1,2,3]triazolo[1,5-a]pyridin-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a solution of 5-isopropyl-1H-pyrazole-3-carboxylic acid (25.64mg, 0.1700mmol) in DMF (1.2489mL) were added HATU (47.82mg, 0.2500mmol) and DIPEA (64.5 mg, 0.50 mmol). The reaction mixture was stirred at 15 °C for 30 min. Then 3-[(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl]-l[1,2,3]triazolo[1,5-a]pyridine TFA salt (33.3mg, 0.1700mmol) was added. The reaction mixture was stirred at 15 °C for 0.5 hr to give a yellow mixture. LCMS showed the desired MS. The reaction mixture was purified by prep-HPLC (NH_3) to give the title compound (18.6mg, 0.0553mmol, 33.249% yield) as white powder.

LC-MS Method1: 336.9 [$M+H^+$]

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.64 (d, *J*=7.2 Hz, 1H), 7.67 (d, *J*=8.8 Hz, 1H), 7.19 (dd, *J*=6.8, 8.3 Hz, 1H), 6.94 (dt, *J*=1.0, 6.9 Hz, 1H), 6.52 (s, 1H), 4.42 (br d, *J*=11.3 Hz, 1H), 4.35 (d, *J*=12.8 Hz, 1H), 4.05 (dd, *J*=4.4, 11.1 Hz, 1H), 3.77 (dd, *J*=4.4, 12.6 Hz, 1H), 3.09 - 2.98 (m, 1H), 2.49 (td, *J*=3.8, 7.4 Hz, 1H), 2.30 (td, *J*=3.8, 7.4 Hz, 1H), 1.96 (t, *J*=3.4 Hz, 1H), 1.31 (d, *J*=6.8 Hz, 6H).

[0666]

Example 133 (5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(5-methyl[1,2,3]triazolo[1,5-a]pyridin-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

bromo(4-methyl-2-pyridinyl)magnesium

To a solution of 2-bromo-4-methylpyridine (0.67mL, 6.33mmol) in THF (10mL) was added chloro(isopropyl)magnesium (3.2mL, 6.33mmol) at 15 °C. The reaction mixture was stirred at 0 °C for 4 hr to give the title compound as a mixture. The reaction mixture was used for the next step without further purification.

[0667]

tert-butyl (1R,5S,6r)-6-[hydroxy(4-methyl-2-pyridinyl)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-formyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (300 mg, 1.42mmol) in THF (3mL) was added bromo(4-methyl-2-pyridinyl)magnesium (418.2mg, 2.13mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 hr to give a light yellow mixture. TLC (EA) showed a new spot. The reaction mixture was quenched with H_2O (30 mL) and extracted with EtAOc (30 mLx2). The organic layer was washed with brine (30 mLx2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column (PE/EA=1:0 to 1:2) to give the title compound (400 mg, 1.3141mmol, 92.542% yield) as light yellow gum.

^{1}H NMR (400MHz, DMSO-d_6) δ = 8.31 (d, J = 5.2 Hz, 1H), 7.30 (s, 1H), 7.08 (d, J = 5.2 Hz, 1H), 5.36 (d, J = 4.8 Hz, 1H), 4.50-4.40 (m, 1H), 3.45-3.35 (m, 4H), 2.32 (s, 3H), 1.65-1.50 (m, 2H), 1.34 (s, 9H), 0.85-0.80 (m, 1H).

[0668]

tert-butyl (1R,5S,6r)-6-[(4-methyl-2-pyridinyl)carbonyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-[hydroxy(4-methyl-2-pyridinyl)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (300 mg, 0.9900mmol) in DCM (6mL) was added DMP (418.04mg, 0.9900mmol) at 15 °C. The reaction mixture was stirred at 15 °C for 20 min to give a white mixture. TLC (PE/EA=1:1) showed a new spot. The combined reaction mixture was quenched with $NaHCO_3$ (30 mL) and extracted with EtOAc (30 mLx2). The organic layer was washed with brine (30 mLx2), dried over anhydrous Na_2SO_4, filtered and

concentrated under reduced pressure to give a crude product as light yellow solid. The crude product was purified by silica column (PE/EA=1:1) to give the title compound (300 mg, 0.9922mmol, 100.66% yield) as white solid.

^{1}H NMR (400MHz, DMSO-d_6) δ = 8.60 (d, J = 4.8 Hz, 1H), 7.76 (s, 1H), 7.51 (d, J = 4.8 Hz, 1H), 4.50-4.40 (m, 1H), 3.57 (d, J = 11.2 Hz, 2H), 3.45-3.35 (m, 2H), 3.25-3.20 (m, 1H), 2.40 (s, 3H), 2.20 (brs, 2H), 1.40 (s, 9H).

[0669]

tert-butyl (1R,5S,6r)-6-(5-methyl[1,2,3]triazolo[1,5-a]pyridin-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of tert-butyl (1R,5S,6r)-6-[(4-methyl-2-pyridinyl)carbonyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (150 mg, 0.5000mmol) in EtOH (3mL) was added hydrazine hydrate (37.25mg, 0.7400mmol). The reaction mixture was stirred at 60 °C for 6 hr to give a colorless mixture. Then copper acetate (4.94mg, 0.0200mmol) and ethyl acetate (14.304mL) were added. Then the reaction mixture was stirred at 20 °C for 1 hr to give a colorless mixture. The reaction mixture was concentrated to give a residue. The residue was purified by prep-TLC (PE/EA=1:1) to give the title compound (50mg, 0.1590mmol, 32.06% yield) as colorless oil.

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.51 (d, J = 7.2 Hz, 1H), 7.43 (s, 1H), 6.75 (dd, J = 7.2, 1.6 Hz, 1H), 3.84 (d, J = 11.2 Hz, 1H), 3.75 (d, J = 11.2 Hz, 1H), 3.45-3.35 (m, 2H), 2.43 (s, 3H), 2.35-2.35 (m, 1H), 2.20-2.10 (m, 1H), 1.95-1.90 (m, 1H), 1.48 (s, 9H).

[0670]

3-[(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl]-5-methyl[1,2,3]triazolo[1,5-a]pyridine TFA salt

To a solution of tert-butyl (1R,5S,6r)-6-(5-methyl[1,2,3]triazolo[1,5-a]pyridin-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate in DCM (5mL) was added TFA (0.01mL, 0.1600mmol). The reaction mixture was stirred at 20 °C for 16 hr to give a colorless mixture. LCMS showed the desired MS. The solvent was removed from the reaction mixture to give the title compound. The product was used for the next step directly.

LC-MS Method1 0.398 min, MS (m/z) 214.9 ($M + H^+$).

[0671]

(5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(5-methyl[1,2,3]triazolo[1,5-a]pyridin-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a solution of 5-isopropyl-1H-pyrazole-3-carboxylic acid (24.46mg, 0.1600mmol) in DMF (1.1917mL) was added HATU (45.63mg, 0.2400mmol). The reaction mixture was

stirred at 15 °C for 30 min. Then 3-[(1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl]-5-methyl[1,2,3]triazolo[1,5-a]pyridine TFA salt (34 mg, 0.1600mmol) and DIPEA (61.52 mg, 0.476 mmol) were added. The reaction mixture was stirred at 15 °C for 0.5 hr to give a yellow mixture. LCMS showed the desired MS. The reaction mixture was purified by prep-HPLC (NH_3) to give the title compound (22.4mg, 0.0639mmol, 40.285% yield) as white powder.
LC-MS Method1: 350.9 [$M+H^+$]
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.52 (d, *J*=7.2 Hz, 1H), 7.41 (s, 1H), 6.76 (dd, *J*=1.6, 7.2 Hz, 1H), 6.51 (s, 1H), 4.40 (br d, *J*=10.8 Hz, 1H), 4.34 (d, *J*=12.4 Hz, 1H), 4.03 (dd, *J*=4.4, 11.2 Hz, 1H), 3.76 (dd, *J*=4.4, 12.4 Hz, 1H), 3.04 (spt, *J*=6.9 Hz, 1H), 2.47 - 2.44 (m, 1H), 2.42 (s, 3H), 2.26 (td, *J*=3.8, 7.4 Hz, 1H), 1.91 (t, *J*=3.4 Hz, 1H), 1.31 (d, *J*=7.2 Hz, 6H)

[0672]

Example 134 (5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(1H-tetrazol-5-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

(5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(1H-tetrazol-5-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a solution of 5-isopropyl-1H-pyrazole-3-carboxylic acid (90 mg, 0.5800mmol) in DMF (6mL) were added N-ethyl-N-isopropylpropan-2-amine (0.4mL, 2.34mmol) and HATU (266.2mg, 0.7000mmol). After stirred for 30 min, (1R,5S,6r)-6-(1H-tetrazol-5-yl)-3-azabicyclo[3.1.0]hexane TFA salt (79.42mg, 0.5300mmol) was added and the reaction mixture was stirred at 15 °C for 16 hr to give a red solution. H_2O (30 mL) was added and it was extracted with EtOAc (30 mLx2). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuum to give yellow oil. The crude was purified by prep-HPLC (FA) to give the title compound (13.3mg,0.0463mmol, 7.9295% yield) as white solid.
LC-MS Method1: 288.0 [$M+H^+$]
^{1}H NMR (400 MHz, DMSO-d_6) δ 6.41 (s, 1H), 4.42 (br d, *J*=12.05 Hz, 1H), 4.05 (d, *J*=12.30 Hz, 1H), 3.90 (dd, *J*=3.89, 11.92 Hz, 1H), 3.57 (br dd, *J*=4.02, 12.30 Hz, 1H), 2.96 (td, *J*=6.96, 13.68 Hz, 1H), 2.26-2.35 (m, 1H), 2.21 (m, 1H), 1.97 (t, *J*=3.26 Hz, 1H), 1.22 (d, *J*=7.03 Hz, 7H)

[0673]

Example 135 (5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(1-phenyl-1H-tetrazol-5-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

tert-butyl (1R,5S,6r)-6-(phenylcarbamoyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

A solution of (1R,5S,6r)-3-{[(tert-butyl)oxy]carbonyl}-3-azabicyclo[3.1.0]hexane-6-carboxylic acid (500 mg, 2.2mmol), HOBt (356.74mg, 2.64mmol), aniline (0.45mL, 2.64mmol) and EDCI (506.12mg, 2.64mmol) in DCM (5mL) was stirred at 10 °C for 30 min. Then it was cooled to 0 °C and aniline (0.3mL, 3.3mmol) was added drop-wise to be stirred for 16 hr to give a white suspension. TLC (DCM/MeOH =10/1 Rf =0.1) showed a new spot was detected. H_2O (10 mL) was added and it was extracted with EtOAc (10 mLx2). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuum to give a white solid. The crude was purified by silica gel chromatography (PE/EA= 10/1 to 3/1) to give the title compound (590mg, 1.9513mmol, 88.688% yield) as white solid.
LC-MS Method1 0.858 min, MS (m/z) 303.0 ($M + H^+$).

[0674]

(1R,5S,6r)-N-phenyl-3-azabicyclo[3.1.0]hexane-6-carboxamide hydrochloride

A solution of tert-butyl (1R,5S,6r)-6-(phenylcarbamoyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (640 mg, 2.12mmol) in HCl/dionane (6 mL, 2.12mmol) was stirred at 10 °C for 3 hr to give a yellow solution. The reaction mixture was evaporated in vacuum to give the title compound (500 mg, 2.0946mmol, 98.96% yield) as white solid.
LC-MS Method1 0.285 min, MS (m/z) 203.0 ($M + H^+$).

[0675]

(1R,5S,6r)-3-benzyl-N-phenyl-3-azabicyclo[3.1.0]hexane-6-carboxamide

To a solution of (1R,5S,6r)-N-phenyl-3-azabicyclo[3.1.0]hexane-6-carboxamide hydrochloride (500 mg, 2.09mmol) and benzaldehyde (0.25mL, 2.51mmol) in DCM (15mL) and MeOH (5mL) was added triethylamine (0.29mL, 2.09mmol). After stirring for 5 min, sodium triacetoxyhydroborate (887.86mg, 4.19mmol) was added. The reaction mixture was stirred at 10 °C for 16 hr to give a yellow solution. TLC (DCM/MeOH =10/1 Rf =0.6) showed a new spot was detected. H_2O (30 mL) was added and it was extracted with EtOAc (30 mLx2). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo to give a yellow oil. The crude was purified by silica gel chromatography (DCM/MeOH = 10/1 to 3/1) to give the title compound (600 mg, 2.0522mmol, 97.976% yield) as white solid.
LC-MS Method1 0.692 min, MS (m/z) 293.2 ($M + H^+$).

[0676]

(1R,5S,6r)-3-benzyl-6-(1-phenyl-1H-tetrazol-5-yl)-3-azabicyclo[3.1.0]hexane

To a solution of (1R,5S,6r)-3-benzyl-N-phenyl-3-azabicyclo[3.1.0]hexane-6-carboxamide (330 mg, 1.13mmol) in DCM (10 mL) was added Tf_2O (0.39mL, 2.26mmol). After stirred for 5 min, $TMSN_3$ (0.59mL, 4.51mmol) was added and the reaction was stirred for 16 hr to give a yellow solution. H_2O (30 mL) was added and it was extracted with EtOAc (30 mLx2). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuum to give the title compound (298mg, 0.9389mmol, 83.184% yield) as yellow solid.

LC-MS Method1 0.712 min, MS (m/z) 318.1 ($M + H^+$).

[0677]

(1R,5S,6r)-6-(1-phenyl-1H-tetrazol-5-yl)-3-azabicyclo[3.1.0]hexane

To a solution of (1R,5S,6r)-3-benzyl-6-(1-phenyl-1H-tetrazol-5-yl)-3-azabicyclo[3.1.0]hexane (500 mg, 1.58mmol) in MeOH (15 mL) was added Pd/C (50.0 mg). It was stirred at 10 ^oC for under H_2 atmosphere for 3 hr to give a yellow solid. It was filtered through a pad of celite and the filtrate was concentrated in vacuum to give the title compound (400 mg, 1.76mmol, 111.72% yield) as white solid.

LC-MS Method1 0.538 min, MS (m/z) 228.0 ($M + H^+$).

[0678]

(5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(1-phenyl-1H-tetrazol-5-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

A solution of 5-isopropyl-1H-pyrazole-3-carboxylic acid (50 mg, 0.3200mmol), N-ethyl-N-isopropylpropan-2-amine (0.17mL, 0.9700mmol) and HATU (74.61mg, 0.3900mmol) in DMF (2mL) was stirred at 10 ^oC for 30 min. Then (1R,5S,6r)-6-(1-phenyl-1H-tetrazol-5-yl)-3-azabicyclo[3.1.0]hexane (66.34mg, 0.2900mmol) was added and the reaction mixture was stirred for 16 hr to give a yellow solution. H_2O (10 mL) was added and it was extracted with EtOAc (10 mLx2). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuum to give a yellow oil. The crude was purified by silica gel chromatography (DCM/EA= 3/1 to 1/2) to give the title compound (21.25mg, 0.0584mmol, 3.5987% yield) as a white solid.

LC-MS Method1: 364.1 [$M+H^+$]

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.94 (br s, 1H), 7.64-7.72 (m, 5H), 6.35 (s, 1H), 4.38 (br d, *J*=12.30 Hz, 1H), 3.90-3.98 (m, 2H), 3.58 (br dd, *J*=4.27, 12.55 Hz, 1H), 2.91-2.97 (m, 1H), 2.35 (br dd, *J*=3.76, 7.78 Hz, 1H), 1.79 (br s, 1H), 1.20 (d, *J*=6.78 Hz, 6H)

[0679]

Example 136 (1R,5S,6r)-N-(propan-2-yl)-3-[5-(propan-2-yl)-1H-pyrazole-3-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide

(1R,5S,6r)-3-[(5-isopropyl-1H-pyrazol-3-yl)carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid

To a solution of ethyl (1R,5S,6r)-3-[(5-isopropyl-1H-pyrazol-3-yl)carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxylate (400 mg, 1.37mmol) in THF (5mL) and H_2O (1 mL, 1.37mmol) was added $LiOH·H_2O$ (172.82mg, 4.12mmol). The mixture was stirred at 25 ^oC for 3 h to give brown suspension. The reaction was poured into H_2O (20 mL) and acidified with 1 N HCl to pH=3 to 4 and extracted with EtOAc (100 mL x 3). The combined organic layers was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give as the title compound (310mg,1.1774mmol, 85.76% yield) white solid.

[0680]

(1R,5S,6r)-N-(propan-2-yl)-3-[5-(propan-2-yl)-1H-pyrazole-3-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide

To a mixture of (1R,5S,6r)-3-[(5-isopropyl-1H-pyrazol-3-yl)carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid (50 mg, 0.19 mmol) in DMF (1.5mL) were added isopropyl amine (16.55mg, 0.1900mmol), HATU (86.6mg, 0.2300mmol) and DIPEA (0.06mL, 0.3800mmol). The mixture was stirred at 100 °C for 16 h to give brown mixture. LCMS showed the starting material was consumed completely. The reaction mixture was filtered and the filtrate was purified by prep-HPLC (FA). The afforded flows were combined, concentrated to remove most of CH_3CN and lyophilized to afford the title compound (6.83mg, 0.0205mmol, 10.819% yield) as white powder.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 6.45 (s, 1 H), 4.09 - 4.19 (m, 2 H), 3.95 (br dd, J = 11.1, 4.3 Hz, 1 H), 3.69 (br dd, J = 12.5, 4.3 Hz, 2 H), 3.10 (dt, J = 13.9, 7.1 Hz, 1 H), 3.03 (s, 3 H), 2.23 - 2.31 (m, 1 H), 2.09 - 2.17 (m, 1 H), 1.60 (br s, 1 H), 1.40 (s, 9 H), 1.33 (d, J = 6.9 Hz, 6 H)

[0681]

Example 137 (1R,5S,6r)-N-tert-butyl-N-methyl-3-[5-(propan-2-yl)-1H-pyrazole-3-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide

(1R,5S,6r)-N-tert-butyl-N-methyl-3-[5-(propan-2-yl)-1H-pyrazole-3-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide

To a mixture of (1R,5S,6r)-3-[(5-isopropyl-1H-pyrazol-3-yl)carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid (100 mg, 0.3800mmol) in DMF (2mL) were added tert-butyl methylamine (22.45mg, 0.3800mmol), HATU (173.19mg, 0.4600mmol) and DIPEA (0.13mL, 0.7600mmol). The mixture was stirred at 30 °C for 16 h to give yellow suspension. LCMS showed the starting material was consumed completely. The suspension was filtered and the filter cake was washed with EtOAc (3 mL). The filter cake was dried in vacuo to afford the title compound (72.08mg, 0.2368mmol, 62.347% yield) as white solid.

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 13.07 (s, 1 H), 12.94 (s, 1 H), 7.87 (d, J = 7.5 Hz, 1 H), 6.45 - 6.52 (m, 1 H), 6.50 (d, J = 1.6 Hz, 1 H), 6.35 (d, J = 1.9 Hz, 1 H), 4.29 (d, J = 12.0 Hz, 1 H), 3.86 - 3.97 (m, 1 H), 3.72 - 3.84 (m, 2 H), 3.39 - 3.49 (m, 1 H), 2.89 - 3.05 (m, 1 H), 1.90 - 1.96 (m, 1 H), 1.85 (dt, J = 7.4, 3.6 Hz, 1 H), 1.30 (t, J = 3.1 Hz, 1 H), 1.18 - 1.23 (m, 6 H), 1.02 (dd, J = 6.5, 4.6 Hz, 6 H)

[0682]

Example 138 (1R,5S,6r)-N-methyl-N-(1-methylcyclopropyl)-3-[5-(propan-2-yl)-1H-pyrazole-3-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide

(1R,5S,6r)-N-methyl-N-(1-methylcyclopropyl)-3-[5-(propan-2-yl)-1H-pyrazole-3-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide

To a solution of (1R,5S,6r)-N-methyl-N-(1-methylcyclopropyl)-3-azabicyclo[3.1.0]hexane-6-carboxamide hydrochloride (80 mg,0.4100mmol) in DMF (3.2mL) were added 5-isopropyl-1H-pyrazole-3-carboxylic acid (63.49mg, 0.4100mmol), HATU (203.43mg, 0.5400mmol) and Et_3N (0.2mL, 1.24mmol). The mixture was stirred at 20 °C for 16 hr. TLC (PE/EA=0/1) showed a new spot (rf=0.5) and the reaction was completed. The mixture was diluted with H_2O (10 mL) and extracted with EA (10mL×2). The combined organic layers were washed with H_2O (5mL) and NH_4Cl (5mL), dried over Na_2SO_4 and

concentrated in vacuum to give crude oil. The crude oil was purified by prep-TLC (PE/EA=0/1) to give crude product. The crude product was purified by prep-HPLC (FA) to give the title compound (20.8mg, 0.0630mmol, 15.287% yield) as white powder.

LC-MS Method1: 341.0 [$M+H^+$]

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 6.44 (br s, 1H), 4.13 (br s, 1H), 4.04 (d, *J*=12.8 Hz, 1H), 3.94 (dd, *J*=4.0, 11.3 Hz, 1H), 3.68 (dd, *J*=4.1, 12.8 Hz, 1H), 3.01 - 2.92 (m, 1H), 2.84 (s, 3H), 2.03 - 1.87 (m, 1H), 1.28 (s, 3H), 1.24 (d, *J*=6.9 Hz, 6H), 1.21 - 1.14 (m, 1H), 0.98 - 0.66 (m, 3H), 0.58 (br s, 1H)

[0683]

Example 139 [(1R,5S,6r)-6-(2,2-dimethyl-2,3-dihydro-1H-indole-1-carbonyl)-3-azabicyclo[3.1.0]hexan-3-yl][5-(propan-2-yl)-1H-pyrazol-3-yl]methanone

[(1R,5S,6r)-6-(2,2-dimethyl-2,3-dihydro-1H-indole-1-carbonyl)-3-azabicyclo[3.1.0]hexan-3-yl][5-(propan-2-yl)-1H-pyrazol-3-yl]methanone

To a solution of 5-isopropyl-1H-pyrazole-3-carboxylic acid and EDCI (55.95mg, 0.2900mmol) in Pyridine (3mL) was added (1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl(2,2-dimethyl-2,3,3a,7a-tetrahydro-1H-indol-1-yl)methanone TFA salt (49.88mg, 0.1900mmol), and the reaction mixture was stirred at 20 °C under N_2 for 16 hours. LCMS showed the desired peak was found. The reaction was diluted with H_2O (30mL) and extracted with EtOAc (20mLx3). The combined organic layers were separated, then dried over Na_2SO_4 and concentrated in vacuum to give brown oil. The brown oil was purified by prep-HPLC (NH_3) and the afforded flows were combined, concentrated to remove most of CH_3CN and lyophilized to afford the title compound (36.39mg, 0.0927mmol, 47.647% yield) as white solid.

LC-MS Method1: 393.1 [$M+H^+$].

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.23 - 6.89 (m, 4H), 6.50 (s, 1H), 4.34 (br d, *J*=11.5 Hz, 1H), 4.29 - 4.20 (m, 1H), 4.05 (dd, *J*=4.3, 11.6 Hz, 1H), 3.81 (dd, *J*=4.4, 12.9 Hz, 1H), 3.13 - 2.87 (m, 3H), 2.54 (td, *J*=3.7, 7.3 Hz, 1H), 2.32 (td, *J*=3.7, 7.2 Hz, 1H), 1.93 (br s, 1H), 1.61 (s, 3H), 1.53 (br s, 3H), 1.30 (d, *J*=7.0 Hz, 6H)

[0684]

Example 140 (5-isopropyl-1H-pyrazol-3-yl){(1R,5S,6r)-6-[(4-methyl-2-thienyl)carbonyl]-3-azabicyclo[3.1.0]hex-3-yl}methanone

(5-isopropyl-1H-pyrazol-3-yl){(1R,5S,6r)-6-[(4-methyl-2-thienyl)carbonyl]-3-azabicyclo[3.1.0]hex-3-yl}methanone

To a solution of (1R,5S,6r)-3-azabicyclo[3.1.0]hex-6-yl(4-methyl-2-thienyl)methanone TFA salt (60 mg, 0.2900mmol) in DMF(2mL) were added HATU (165.98mg, 0.4300mmol) and Et_3N (0.07mL, 0.5800mmol), and the mixture was stirred at 20 ºC for 10 min under N_2. Then, 5-isopropyl-1H-pyrazole-3-carboxylic acid (44.62mg, 0.2900mmol) in DMF (1mL) was added, and the resulting mixture was stirred at 20 ºC for 16 hours to give a yellow mixture. The reaction mixture was poured into H_2O (5 mL) and extracted with EA (5 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by Prep-HPLC (NH_3) and lyophilized to give the title compound (90mg, 0.2621mmol, 90.535% yield) as a white solid.

LC-MS Method1: 344.2 [$M+H^+$]

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 10.33 (br s, 1H), 7.60 (d, *J*=0.8 Hz, 1H), 7.26 (s, 1H), 6.53 (s, 1H), 4.37 (br d, *J*=11.5 Hz, 1H), 4.26 (d, *J*=13.1 Hz, 1H), 4.02 (dd, *J*=4.1, 11.7 Hz, 1H), 3.74 (dd, *J*=4.1, 12.9 Hz, 1H), 3.04 (td, *J*=6.8, 13.7 Hz, 1H), 2.49 (td, *J*=3.5, 7.2 Hz, 1H), 2.38 (td, *J*=3.6, 7.3 Hz, 1H), 2.34 - 2.31 (m, 1H), 2.30 (s, 3H), 1.32 (d, *J*=6.8 Hz, 6H)

[0685]

Example 141 [(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-6-methyl-3-azabicyclo[3.1.0]hex-3-yl](5-isopropyl-1H-pyrazol-3-yl)methanone

[(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-6-methyl-3-azabicyclo[3.1.0]hex-3-yl](5-isopropyl-1H-pyrazol-3-yl)methanone

To a solution of 5-isopropyl-1H-pyrazole-3-carboxylic acid (38.5mg, 0.2500mmol) in DMF (1.5mL) were added HATU (112.84mg, 0.3000mmol), DIPEA (0.13mL, 0.7900mmol) and (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-6-methyl-3-azabicyclo[3.1.0]hexane TFA salt (70 mg, 0.2300mmol). The mixture was stirred at 20 °C for 12 h to give brown solution. The mixture was poured into H_2O (15 mL) and extracted with EtOAc (15 mL x 5). The combined organic layer was washed with brine (50 mL), dried over

Na_2SO_4 and concentrated to dryness. The residue was purified by prep-TLC (PE:EtOAc=1:1) to give white solid. The residue was purified by prep-HPLC (NH_3). The afforded flows were combined, concentrated to remove most of CH_3CN and lyophilized to give the title compound (3.63mg, 0.0110mmol, 4.8386% yield) as a white solid.

LC-MS Method1: 331.0 [$M+H^+$]

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 6.50 (1 H, s), 4.09 - 4.18 (1 H, m), 4.01 (1 H, br d, *J*=11.54 Hz), 3.81 - 3.95 (2 H, m), 3.03 (1 H, dt, *J*=13.93, 7.09 Hz), 2.68 (2 H, s), 2.22 (1 H, dd, *J*=8.16, 5.40 Hz), 2.06 (1 H, dd, *J*=7.91, 4.14 Hz), 1.38 (6 H, d, *J*=2.26 Hz), 1.31 (6 H, d, *J*=7.03 Hz), 1.17 (3 H, s)

[0686]

Example 142 [5-(1-cyclopropylethyl)-1H-pyrazol-3-yl][(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-6-methyl-3-azabicyclo[3.1.0]hex-3-yl]methanone

[5-(1-cyclopropylethyl)-1H-pyrazol-3-yl][(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-6-methyl-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a stirred solution of (1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-6-methyl-3-azabicyclo[3.1.0]hexane TFA salt (40 mg, 0.2200mmol) and HATU (110.32mg, 0.2900mmol) in DMF (1mL) was added DIPEA (0.23mL, 1.33mmol). After stirred for 30 min, 5-(1-cyclopropylethyl)-1H-pyrazole-3-carboxylic acid (68.44mg, 0.2200mmol) was added. The reaction mixture was stirred at 20 ^{o}C for 16 h to give a yellow solution. LCMS showed a new peak gives the desired ms. H_2O (30 mL) was added and it was extracted with EtOAc (30 mLx2). The combined organic layer dried over Na2SO4 and concentrated in vacuum to give a yellow oil. The crude was purified by prep-HPLC (NH_3). The afforded flows were concentrated in vacuum to remove most of CH_3CN and lyophilized to give the title compound (16.69mg, 0.0468mmol, 21.093% yield) as white solid.

LC-MS Method1: 357.2 [$M+H^+$]

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 6.58 (s, 1H), 4.11-4.17 (m, 1H), 4.00-4.08 (m, 1H), 3.82-3.92 (m, 2H), 2.67 (s, 2H), 2.21 (dd, J=5.40, 7.91 Hz, 1H), 2.13 (dd, J=7.03, 9.03 Hz, 1H), 2.04 (dd, J=5.02, 7.03 Hz, 1H), 1.36-1.40 (m, 9H), 1.17 (d, J=0.75 Hz, 3H), 0.88-0.97 (m, 1H), 0.58 (br d, J=7.28 Hz, 2H), 0.20-0.31 (m, 2H)

[0687]

Example 143 (5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-methyl-6-(4-oxa-5-azaspiro[2.4]hept-5-en-6-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

(5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-methyl-6-(4-oxa-5-azaspiro[2.4]hept-5-en-6-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

A 100 mL round- bottom flask was charged with 5-isopropyl-1H-pyrazole-3-carboxylic acid (50.34mg, 0.3300mmol), HATU (149.78mg, 0.3900mmol), N-ethyl-N-isopropylpropan-2-amine (0.17mL, 0.9800mmol) and DMF (1.6108mL). After stirred for 30 min, 6-[(1R,5S,6r)-6-methyl-3-azabicyclo[3.1.0]hex-6-yl]-4-oxa-5-azaspiro[2.4]hept-5-ene TFA salt (100 mg, 0.3300mmol) was added. The reaction mixture was stirred at 10 °C for 1 hr to give a yellow solution. The reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (30 mLx2). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuum to give a residue as yellow oil. The crude was purified by Prep- HPLC (NH_3). The afford flows was concentrated in vacuum to remove most of CH_3CN and lyophilized to give the title compound (48.63mg, 0.1481mmol, 45.353% yield) as white solid.

LC-MS Method1: 329.2 [$M+H^+$]

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 6.50 (s, 1H), 4.19 - 4.10 (m, 1H), 4.03 (br d, *J*=11.9 Hz, 1H), 3.94 - 3.84 (m, 2H), 3.06 - 2.98 (m, 3H), 2.26 (m, 1H), 2.16 - 2.07 (m, 1H), 1.30 (d, *J*=7.2 Hz, 6H), 1.20 (s, 3H), 1.15 - 1.10 (m, 2H), 0.74 - 0.69 (m, 2H)

[0688]

Example 144 (5-cyclopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-methyl-6-(4-oxa-5-azaspiro[2.4]hept-5-en-6-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

(5-cyclopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-methyl-6-(4-oxa-5-azaspiro[2.4]hept-5-en-6-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone

To a solution of 5-cyclopropyl-1H-pyrazole-3-carboxylic acid (21.86mg, 0.1400mmol) in Pyridine (1.5mL) were added EDCI (62.59mg, 0.3300mmol) and 6-[(1R,5S,6r)-6-methyl-3-azabicyclo[3.1.0]hex-6-yl]-4-oxa-5-azaspiro[2.4]hept-5-ene TFA salt (40 mg, 0.1300mmol). The mixture was stirred at 25 °C for 2 h to give a yellow solution. LCMS showed the desire MS as a major peak. The reaction mixture was concentrated directly. The residue was purified by prep-HPLC (NH_3) to give the title compound (11.2mg, 0.0343mmol, 26.275% yield) as yellow solid.

LC-MS Method1: 327.1 [M+H$^+$]

^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 6.35 (1 H, s), 4.07 - 4.16 (1 H, m), 3.95 - 4.02 (1 H, m), 3.83 - 3.95 (2 H, m), 3.01 (2 H, s), 2.27 (1 H, dd, J=8.16, 5.40 Hz), 2.12 (1 H, dd, J=7.40, 4.64 Hz), 1.88 - 1.95 (1 H, m), 1.18 - 1.22 (3 H, m), 1.11 - 1.17 (2 H, m), 0.95 - 1.02 (2 H, m), 0.71 - 0.79 (4 H, m)

[0689]

Example 145 (1R,5S,6r)-N-tert-butyl-6-methyl-3-[5-(propan-2-yl)-1H-pyrazole-3-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide

(1R,5S,6r)-N-tert-butyl-6-methyl-3-[5-(propan-2-yl)-1H-pyrazole-3-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide

To a solution of 5-isopropyl-1H-pyrazole-3-carboxylic acid (15.71 mg, 0.10 mmol) in DMF (0.50 mL) were added HATU (50.64 mg, 0.13 mmol) and Et_3N (0.04 mL, 0.31 mmol). The mixture was stirred at 20 to 25 °C for 0.5 h. Then (1R,5S,6r)-6-methyl-N-(tert-butyl)-3-azabicyclo[3.1.0]hexane-6-carboxamide TFA salt (20 mg, 0.10 mmol) was added to the mixture. The resulting mixture was stirred at 20 to 25 °C for 2 h. LCMS showed the desired MS (as a major peak). The residue was purified by prep-HPLC (NH_3). The afforded flows were combined, concentrated to remove most of CH_3CN and lyophilized to afford the title compound (6.94 mg, 0.0209 mmol, 20.489% yield) as a white solid.

LC-MS Method1: 333.3 [M+H$^+$]

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 6.49 (s, 1H), 5.59 (s, 1H), 4.13 (dd, *J*=5.7, 11.9 Hz, 1H), 3.95 - 3.86 (m, 2H), 3.79 - 3.71 (m, 1H), 3.03 (td, *J*=6.9, 13.8 Hz, 1H), 2.33 (dd, *J*=5.4, 8.1 Hz, 1H), 2.18 (dd, *J*=5.4, 8.0 Hz, 1H), 1.36 (s, 9H), 1.31 (d, *J*=6.9 Hz, 6H), 1.14 (s, 3H)

[0690]

Biological Example 1:

Biochemical KDM5A inhibition assay

Using 384-well white Greiner784075 (Greiner), representative compounds were characterized for their inhibition of KDM5A using HTRF® technology (Cisbio Bioassays). Briefly, the test compounds, reference compounds, and DMSO control (typical compound concentration range 1pM-10μM, final assay concentration (FAC*) of DMSO 0.5%) were added

to 384-well plate by the Echo® acoustic dispensing platform (Labcyte). Five (5) μl of KDM5A protein (produced by the method described in Nat Chem Biol 12, 531–538 (2016)). (5-20 nM FAC*) in assay buffer (50 mM MES, 50 mM NaCl, 1 mM TCEP, 0.01 % v/v Tween 20, 0.03% BSA, pH 6.5) was added to wells and plates were incubated for 10-20 minutes at 25 dgrees celsius. Then, 5 μl of alpha-ketoglutaric acid (100 μM FAC*), biotin-labelled H3K4-Me3 substrate (Anaspec Cat #AS-64357-1; 200 nM FAC*), $Fe(II)SO_4$ (100 μM FAC*) and ascorbic acid (2 mM FAC*) in assay buffer was added to wells and plates were incubated for 20 minutes at room temperature. The reaction was stopped with the addition of 10 μl of anti-H3K4-Me2-Eu(K) (Cisbio Bioassays Cat #61KA2KAH; 0.75 nM FAC**) + Streptavidin XL665 (Cisbio Bioassays Cat #610SAXLB; 25 nM FAC**) in HTRF detection buffer (Cisbio Bioassays Cat # 62SDBRDF). The mixture was incubated for 30 minutes at room temperature before 340 nm excitation and measurement of dual emission at 620 nm and 665 nm.

*FAC: final assay concentration calculated based on 10 μl of the assay buffer

**FAC: final assay concentration calculated based on 20 μl of the detection buffer

The raw data (a 665 nm and a 620 nm reading from each well) for individual assay plates were analyzed. The ratio of emissions was calculated using the following calculation:

Ratio = (665 nm emission / 620 nm emission) x 10000.

Using DMSO control (maximum response or 0 % inhibition) and 1 μM reference control compound (minimum response or 100 % inhibition), percentage inhibition values for each well were calculated using the median values of the minimum and maximum control wells and the following calculation:

% Inhibition = (Well ratio –max control ratio) / (min control ratio –max control ratio) x 100.

Compound IC_{50} values were calculated from graphs of % inhibition plotted against compound concentration, using a four parameter curve fit.

[Results]

[0691]

The present compounds exhibited a strong KDM5 inhibitory activity. IC_{50} values (μM) of representative present compounds are shown in the table below. IC_{50} values (μM) of comparative compound, (R)-N-(1-(3-isopropyl-1H-pyrazole-5-carbonyl)pyrrolidin-3-yl)cyclopropane carboxamide (the compound of Examples 29 described in PTL 1(the pamphlet of International Publication No. WO2016057924)) was 0.02 μM.

EXAMPLE No.	IC_{50} value (μ M)
Example 1	0.02
Example 9	0.4
Example 12	0.06
Example 22	0.4
Example 24	0.2
Example 27	1.0
Example 33	0.03
Example 40	0.2
Example 51	0.02
Example 55	0.02
Example 56	0.2
Example 59	0.02
Example 60	0.2
Example 62	0.01
Example 63	0.01
Example 65	0.02
Example 66	0.03
Example 69	0.2
Example 75	0.4
Example 76	0.06
Example 77	0.02
Example 81	0.06

EXAMPLE No.	IC_{50} value (μ M)
Example 82	0.03
Example 84	0.03
Example 85	0.02
Example 87	0.04
Example 88	0.07
Example 90	0.05
Example 93	0.2
Example 96	0.03
Example 103	0.2
Example 104	0.04
Example 106	0.04
Example 110	0.05
Example 119	0.3
Example 121	0.04
Example 124	0.04
Example 131	0.01
Example 132	0.04
Example 134	0.004
Example 136	0.05
Example 138	0.8
Example 144	0.02
Example 145	0.09

[0692]

Biological Example 2:

Metabolic stability in human liver microsomes

Human liver microsome (BD Gentest Corporation, Cat No. # 452161) incubations were conducted in duplicate in 96-well plates. Each well contains 40 μL of 0.1 M potassium phosphate buffer (pH 7.4), 4.125 mM $MgCl_2$, 0.625 mg/mL liver microsomes, and test compound (1.25 μM). After 5-min preincubation at 37°C, 10 uL of 5.0 mM NADPH in 0.1M potassium phosphate buffer was added to initiate the enzymatic reaction. The final component concentrations are 0.1M potassium phosphate buffer (pH 7.4), 1.0 mM NADPH, 3.3 mM $MgCl_2$, 0.5 mg/mL liver microsomes, and test compound (1.0 μM). Reactions were terminated at 0 and 60 min by adding 200 μL of ice-cold acetonitrile containing internal standard.

LC-MS/MS analysis was conducted as specified below.

LC	System	ACQUITY UPLC H-Class PLUS System (Waters)
	Column	ACQUITY UPLC BEH C18 Column 2.1 mm ID × 50 mm (Waters)
	Elution conditions	Column temperature: 25°C Mobile phase: A: water (0.1% formic acid) B: acetonitrile (0.1% formic acid) Gradient program: Time (min) 0 1.20 1.40 1.41 1.50 Mobile phase B (%) 10 90 90 10 10 Flow rate: 0.6mL/min
MS	System	API4000 (AB Sciex)
	Condition	Electrospray ionization, positive ion mode, multiple reaction monitoring mode

The remaining at 60 min (%) of test compound was calculated from the peak area ratio (test compound / internal standard) of samples collected 0 and 60 min after the start of the reaction according to the formula described below.

Remaining at 60 min (%) = peak area ratio of sample collected at 60 min / peak area ratio of sample collected at 0min × 100

[0693]

[Results]

The present compounds were stable against hepatic metabolism. The metabolic stability in human liver microsomes of representative present compounds are shown in the table below.

EXAMPLE No.	Metabolic stability in human liver microsomes（% remaining at 60 min）
Example 1	95
Example 9	93
Example12	100
Example 24	101
Example 27	97
Example 33	103
Example 40	103
Example 51	95
Example 59	100
Example 60	102
Example 62	83
Example 65	93
Example 66	89
Example 69	89
Example 75	102
Example 81	100
Example 82	104
Example 84	92
Example 85	98
Example 87	99
Example 88	95
Example 90	100
Example 93	86
Example 96	83
Example 110	85
Example 119	102
Example 121	114
Example 124	97
Example 131	84
Example 136	97
Example 144	101
Example 145	99

[0694]

Biological Example 3:

Brain concentration in mice

Test compounds were orally administered to mice (C57BL/6) at 1 or 3 mg/kg. Brain samples were collected 2h after the administration and homogenized with 3-fold volumes of distilled water.

LC-MS/MS analysis was conducted as specified below. Standard calibration samples were prepared using the same matrix and analyzed in the same manner.

Extraction procedure		Mix 40 μL of sample with 40 μL of acetonitrile and 160 μL of acetonitrile/ethanol (7:3) containing internal standard, and stir the mixture. Transfer all to a deproteinization filter plate for suction filtration and inject the filtrate to a LC system.
LC	System	Prominence UFLC$_{XR}$ (Shimadzu Corporation)
	Column	Shim-pack XR-ODSII 2.0 mm ID × 75 mm (Shimadzu Corporation)
	Elution conditions	Column temperature: 40°C Mobile phase: A: 0.2% formic acid 5 mM ammonium acetate aqueous solution B: acetonitrile Gradient program: Time (min) 0 1.5 3.0 3.1 4 Mobile phase B (%) 10 90 90 10 10 Flow rate: 0.5 mL/min
MS	System	API4000 (AB Sciex)
	Condition	Electrospray ionization, positive ion mode, multiple reaction monitoring mode

Standard calibration samples were analyzed to calculate a regression equation from the peak area ratio (test compound / internal standard). The peak area ratio was determined for a measurement sample and assigned to the regression equation to calculate an assay value.

[0695]

[Results]

The Unbound-Brain Concentration of the present compounds was high. The Unbound-Brain Concentration at 2h at 1 mg/kg of representative present compounds are shown in the table below. Values with * are obtained by proportional calculation from the 3 mg/kg data. Unbound-Brain Concentration at 2h of comparative compound, (R)-N-(1-(3-isopropyl-1H-pyrazole-5-carbonyl)pyrrolidin-3-yl)cyclopropane carboxamide (the compound of Examples 29 described in PTL 1(the pamphlet of International Publication No. WO2016057924)) was 2.5 ng/g.

EXAMPLE No.	Unbound-Brain Concentration at 2h at 1 mg/kg (ng/g)
Example 1	93.7*
Example 12	10.8
Example 33	62.1
Example 51	55.3
Example 81	21.9
Example 82	57.4
Example 85	76.7
Example 88	39.5*

[0696]

Formulation Example 1:

Tablets containing 5 mg of [(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](5-isopropyl-1H-pyrazol-3-yl)methanone

The following components can be mixed and compressed to tablets according to standard methods to obtain 10,000 tablets each containing 5 mg of the active component.

· [(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](5-isopropyl-1H-pyrazol-3-yl)methanone: 50 g

· Carboxymethylcellulose calcium (disintegrating agent): 20 g

· Magnesium stearate (lubricant): 10 g

· Microcrystalline cellulose: 920 g

[0697]

Formulation Example 2:

Tablets containing 5 mg of [(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](1-isopropyl-1H-imidazol-4-yl)methanone

The following components can be mixed and compressed to tablets according to standard methods to obtain 10,000 tablets each containing 5 mg of the active component.

· [(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](1-isopropyl-1H-imidazol-4-yl)methanone:50 g

· Carboxymethylcellulose calcium (disintegrating agent): 20 g

· Magnesium stearate (lubricant): 10 g

· Microcrystalline cellulose: 920 g

[0698]

Formulation Example 3:

Injections containing 20 mg of [(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](5-isopropyl-1H-pyrazol-3-yl)methanone

The following components can be mixed according to the standard method, and the solution can be then sterilised according to the standard method, divided into ampoules at 5-mL aliquot and lyophilised according to the standard method to obtain 10,000 ampoules each containing 20 mg of the active component.

· [(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](5-isopropyl-1H-pyrazol-3-yl)methanone: 200 g

· Mannitol: 20 g

· Distilled water: 50 L

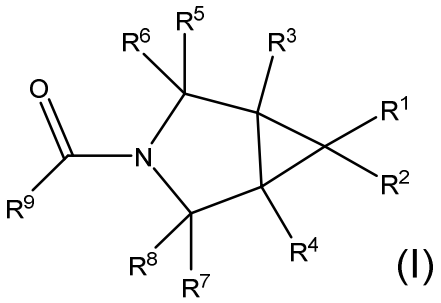
[Industrial Applicability]

[0699]

The present compound has KDM5 inhibitory activity, and thus is useful as a prophylactic and/or therapeutic agent for cancer, Huntington's disease, Alzheimer's disease and the like.

[Claims]

[Claim 1] A compound represented by the general formula (I):



(I)

wherein R^1 represents Cyc1, -CO-Cyc2 or -CONR^{10}R^{11};

Cyc1 represents a 5 to 9 membered aromatic hetero ring or a 5 membered non-aromatic hetero ring, each of which may be substituted with 1 to 5 R^{12};

R^{12} represents (1) C1-4 alkyl, (2) C3-7 cycloalkyl, (3) C1-4 haloalkyl, (4) C1-4 alkoxy, (5) phenyl which may be substituted with 1 to 3 R^{17}, (6) C1-4 alkyl which is substituted with phenyl, (7) dimethylamino, (8) pyridyl or (9) 1-(cyclopropylmethyl)pyrazol-3-yl;

a plurality of R^{12} may be the same or different;

two R^{12} together with an atom to which these R^{12} are attached may form a C3-5 cycloalkane, wherein the carbon atom of C3-5 cycloalkane may be replaced with hetero atom selected from 1 to 2 N, O and S;

R^{17} represents C1-4 alkyl, C1-4 alkoxy or halogen;

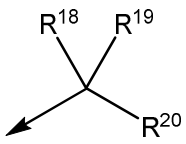
a plurality of R^{17} may be the same or different;

Cyc2 represents a C3-12 mono or bicyclic carbocycle or a 5 to 9 membered mono or bicyclic heterocycle, each of which may be substituted with 1 to 5 R^{13};

R^{13} represents C1-4 alkyl, C1-4 alkoxy or halogen;

a plurality of R^{13} may be the same or different;

R^{10} represents



wherein R^{18} and R^{19} independently represents C1-4 alkyl;

R^{18} and R^{19} together with a carbon atom to which R^{18} and R^{19} are attached may form a C3-5 cycloalkane;

R^{20} represents a hydrogen atom, C1-4 alkyl, C1-4 haloalkyl or nitrile;

in the group, the arrow indicates the binding to the nitrogen atom of -CON<;

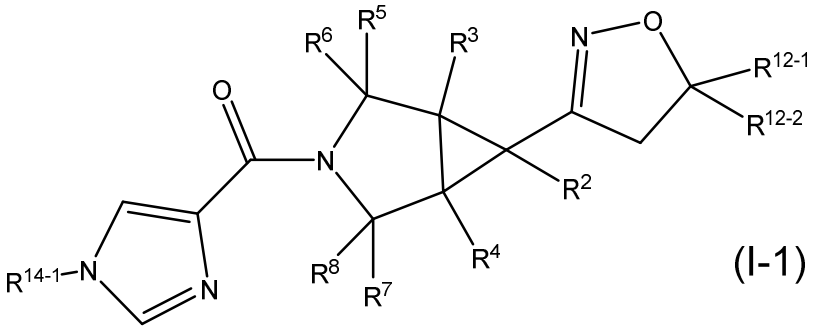
R^{11} represents a hydrogen atom, C1-4 alkyl or 1 to 9 deuterated C1-4 alkyl;
R^2, R^3, R^4, R^5, R^6, R^7 and R^8 independently represent a hydrogen atom, C1-4 alkyl, halogen or C1-4 alkoxy;
R^9 represents imidazole which may be substituted with 1 to 3 R^{14} or pyrazole which may be substituted with 1 to 3 R^{15};
R^{14} represents (1) C1-8 alkyl, (2) C3-7 cycloalkyl which may be substituted with C1-4 alkyl, (3) C1-8 haloalkyl, (4) C1-8 alkyl which is substituted with Cyc3 which may be substituted with 1 to 3 R^{16} or (5) C1-8 alkyl which is substituted with phenoxy;
Cyc3 represents phenyl, C3-7 cycloalkyl, pyridyl, thiazolyl or tetrahydropyranyl;
R^{16} represents C1-4 alkyl, halogen, C1-4 alkoxy or cyano;
a plurality of R^{14} may be the same or different;
a plurality of R^{16} may be the same or different;
R^{15} represents (1) C1-8 alkyl, (2) C3-7 cycloalkyl which may be substituted with C1-4 alkyl, (3) C1-8 haloalkyl, (4) C1-8 alkyl which is substituted with Cyc4 which may be substituted with 1 to 3 R^{21} or (5) C1-8 alkyl which is substituted with phenoxy;
Cyc4 represents phenyl, C3-7 cycloalkyl, pyridyl, thiazolyl or tetrahydropyranyl;
R^{21} represents C1-4 alkyl, halogen, C1-4 alkoxy or cyano;
a plurality of R^{15} may be the same or different;
a plurality of R^{21} may be the same or different; and
each hydrogen atom may be a deuterium atom or a tritium atom;
with the proviso that ((1R,5S,6r)-6-(Cyclopropanecarbonyl)-3-azabicyclo[3.1.0]hexan-3-yl)(5-isopropyl-1H-pyrazol-3-yl)methanone, (5-Isopropyl-1H-pyrazol-3-yl)-[(1R,5S)-6-[(2R)-2-methylpyrrolidine-1-carbonyl]-3-azabicyclo[3.1.0]hexan-3-yl]methanone, (5-Isopropyl-1H-pyrazol-3-yl)-[(1S,5R)-6-[(2S)-2-methylpyrrolidine-1-carbonyl]-3-azabicyclo[3.1.0]hexan-3-yl]methanone, [(1S,5R)-6-(2,2-Dimethylpyrrolidine-1-carbonyl)-3-azabicyclo[3.1.0]hexan-3-yl]-(5-isopropyl-1H-pyrazol-3-yl)methanone and (5-Isopropyl-1H-pyrazol-3-yl)-[(1S,5R)-6-(5-methyl-4-phenyl-isoxazol-3-yl)-3-azabicyclo[3.1.0]hexan-3-yl]methanone are excluded;
or a salt thereof.

[Claim 2] The compound according to claim 1, wherein R^1 represents Cyc1, and the Cyc1 represents the 5 membered non-aromatic hetero ring which may be substituted with 1 to 5 R^{12}, or a salt thereof.

[Claim 3] The compound according to claim 2, wherein the 5 membered non-aromatic hetero ring represents 4,5-dihydroisoxazole or 4,5-dihydro-1,2,4-oxadiazole, or a salt thereof.

[Claim 4] The compound according to any one of claims 1 to 3, wherein R^9 represents imidazole which may be substituted with 1 to 3 R^{14}, or a salt thereof.

[Claim 5] The compound according to any one of claims 1 to 4, wherein the compound represented by the general formula (I) is represented by the general formula (I-1)



(I-1)

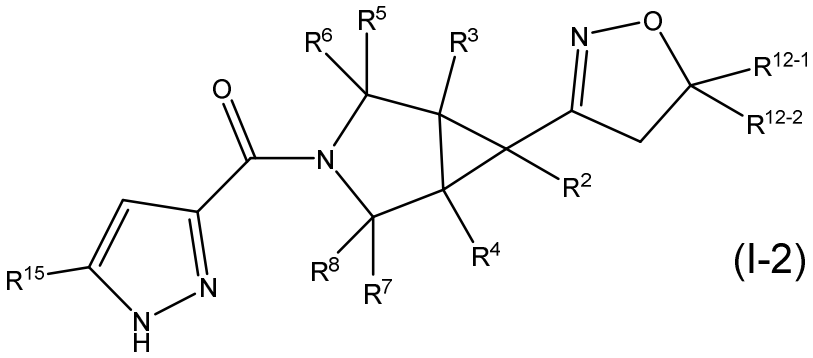
wherein R^{12-1} and R^{12-2} independently represent C1-4 alkyl;
R^{12-1} and R^{12-2} together with an atom to which the R^{12-1} and R^{12-2} are bound may form C3-5 cycloalkane;
R^{14-1} represents C1-4 alkyl or C3-5 cycloalkyl which may be substituted with C1-4 alkyl;
other symbols represent the same meaning as described in claim 1;
or a salt thereof.

[Claim 6] The compound according to any one of claims 1 to 5, wherein the compound is:
(1) [(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](1-isopropyl-1H-imidazol-4-yl)methanone;
(2) [(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl][1-(1-methylcyclopropyl)-1H-imidazol-4-yl]methanone;
(3) (1-cyclopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-6-methyl-3-azabicyclo[3.1.0]hex-3-yl]methanone;
(4) (1-cyclopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-methyl-6-(4-oxa-5-azaspiro[2.4]hept-5-en-6-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone;
(5) {1-[(2S)-butan-2-yl]-1H-imidazol-4-yl}[(1R,5S,6S)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone;

(6) [(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-6-methyl-3-azabicyclo[3.1.0]hex-3-yl](1-isopropyl-1H-imidazol-4-yl)methanone;
(7) (1-isopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-methyl-6-(4-oxa-5-azaspiro[2.4]hept-5-en-6-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone;
(8) (1-cyclopropyl-1H-imidazol-4-yl)[(1R,5S,6r)-6-(4-oxa-5-azaspiro[2.4]hept-5-en-6-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone; or
(9) [1-(1-methylcyclopropyl)-1H-imidazol-4-yl][(1R,5S,6r)-6-(4-oxa-5-azaspiro[2.4]hept-5-en-6-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone;
or a salt thereof.

[Claim 7] The compound according to any one of claims 1 to 3, wherein R^9 represents pyrazole which may be substituted with 1 to 3 R^{15}, or a salt thereof.

[Claim 8] The compound according to any one of claims 1 to 3 and 7, wherein the compound represented by the general formula (I) is represented by the general formula (I-2)



(I-2)

wherein all symbols represent the same meaning as described in claim 1 or claim 5;
or a salt thereof.

[Claim 9] The compound according to any one of claims 1 to 3, 7 and 8 wherein the compound is:
(1) [(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl](5-isopropyl-1H-pyrazol-3-yl)methanone;
(2) (5-isopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-(2-oxa-3-azabicyclo[3.1.0]hex-3-en-4-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone;
(3) [5-(1-cyclopropylethyl)-1H-pyrazol-3-yl][(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone;

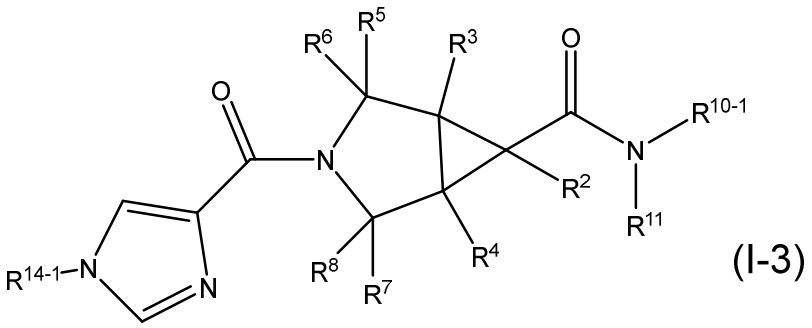
(4) [(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-6-methyl-3-azabicyclo[3.1.0]hex-3-yl](5-isopropyl-1H-pyrazol-3-yl)methanone; or
(5) (5-cyclopropyl-1H-pyrazol-3-yl)[(1R,5S,6r)-6-methyl-6-(4-oxa-5-azaspiro[2.4]hept-5-en-6-yl)-3-azabicyclo[3.1.0]hex-3-yl]methanone;
or a salt thereof.

[Claim 10] The compound according to claim 1, wherein R^1 represents $-CONR^{10}R^{11}$, or a salt thereof.

[Claim 11] The compound according to claim 10, wherein R^{10} represents isopropyl, tert-butyl, 1,1,1-trifluoro-2-methylpropan-2-yl, 1-methylcyclopropyl, 1-(trifluoromethyl)cyclopropyl or 1-cyanocyclopropyl, or a salt thereof.

[Claim 12] The compound according to claim 10 or 11, wherein R^9 represents imidazole which may be substituted with 1 to 3 R^{14}, or a salt thereof.

[Claim 13] The compound according to any one of claims 1 and 10 to 12, wherein the compound represented by the general formula (I) is represented by the general formula (I-3)



(I-3)

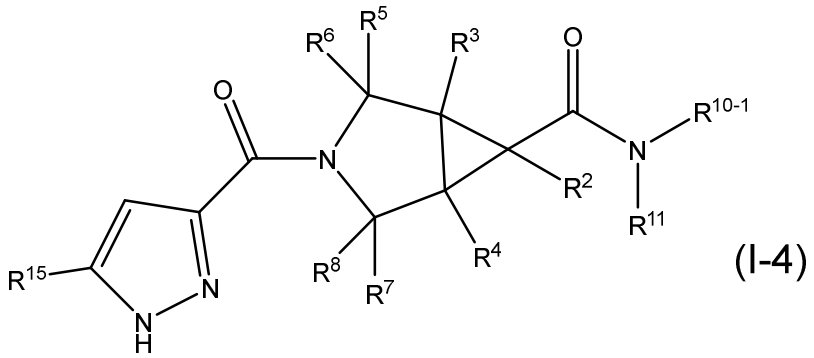
wherein R^{10-1} represents isopropyl, tert-butyl, 1,1,1-trifluoro-2-methylpropan-2-yl, 1-methylcyclopropyl, 1-(trifluoromethyl)cyclopropyl or 1-cyanocyclopropyl;
other symbols represent the same meaning as described in claim 1 or claim 5;
or a salt thereof.

[Claim 14] The compound according to any one of claims 1 and 10 to 13, wherein the compound is:

(1) (1R,5S,6r)-N-tert-butyl-6-methyl-3-[1-(propan-2-yl)-1H-imidazole-4-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide;
(2) (1R,5S,6r)-N-tert-butyl-3-[1-(propan-2-yl)-1H-imidazole-4-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide;
(3) (1R,5S,6r)-N-(propan-2-yl)-3-[1-(propan-2-yl)-1H-imidazole-4-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide; or
(4) (1R,5S,6r)-N-(1-cyanocyclopropyl)-3-[1-(propan-2-yl)-1H-imidazole-4-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide;
or a salt thereof.

[Claim 15] The compound according to claim 10 or 11, wherein R^9 represents pyrazole which may be substituted with 1 to 3 R^{15}, or a salt thereof.

[Claim 16] The compound according to any one of claims 1, 10, 11 and 15, wherein the compound represented by the general formula (I) is represented by the general formula (I-4)



(I-4)

wherein all symbols represent the same meaning as described in claim 1 or claim 13;
or a salt thereof.

[Claim 17] The compound according to any one of claims 1, 10, 11, 15 and 16, wherein the compound is:
(1) (1R,5S,6r)-N-(propan-2-yl)-3-[5-(propan-2-yl)-1H-pyrazole-3-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide;
(2) (1R,5S,6r)-N-tert-butyl-6-methyl-3-[5-(propan-2-yl)-1H-pyrazole-3-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide;
(3) (1R,5S,6r)-N-tert-butyl-N-methyl-3-[5-(propan-2-yl)-1H-pyrazole-3-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide; or

(4) (1R,5S,6r)-N-methyl-N-(1-methylcyclopropyl)-3-[5-(propan-2-yl)-1H-pyrazole-3-carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide;
or a salt thereof.

[Claim 18] A pharmaceutical composition comprising the compound represented by the general formula (I) according to claim 1 or a salt thereof, and a pharmaceutically acceptable carrier.

[Claim 19] The pharmaceutical composition according to claim 18, which is a KDM5 inhibitor.

[Claim 20] The pharmaceutical composition according to claim 18 or 19, which is a prophylactic and/or therapeutic agent for a KDM5-related disease.

[Claim 21] The pharmaceutical composition according to claim 20, wherein the KDM5-related disease is cancer, or Alzheimer Disease.

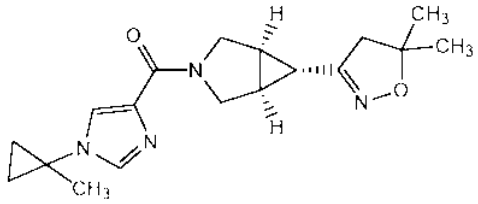
[Claim 22] The compound represented by the general formula (I) according to claim 1 or a salt thereof, or the pharmaceutical composition according to claim 18, for use as a medicament.

[Claim 23] Use of the compound represented by the general formula (I) according to claim 1 or a salt thereof in the manufacture of a prophylactic and/or therapeutic agent for a KDM5-related disease, wherein the KDM5-related disease is hyperproliferative disease, cancer, stroke, diabetes, hepatomegaly, cardiovascular disease, multiple sclerosis, Huntington's disease, Alzheimer's disease, cystic fibrosis, viral disease, autoimmune diseases, atherosclerosis, restenosis, psoriasis, rheumatoid arthritis, inflammatory bowel disease, asthma, allergic disorders, inflammation, neurological disorders, a hormone-related disease, conditions associated with organ transplantation, immunodeficiency disorders, destructive bone disorders, proliferative disorders, infectious diseases, conditions associated with cell death, thrombin-induced platelet aggregation, liver disease, pathologic immune conditions involving T cell activation, CNS disorders, myeloproliferative disorder, Parkinson's disease, Lewy body disease, frontotemporal lobar degeneration, mild cognitive impairment, cognitive

impairment, cerebrovascular disease, schizophrenia, depression, anxiety disorder, bipolar disorder, autism spectrum disorder, attention deficit/hyperactivity disorder, learning disabilities, movement disorders, obsessive-compulsive disorder, personality disorder, sleeping disorder, delirium, amyotrophic lateral sclerosis, developmental disorders, intellectual disability, post-traumatic stress disorder, or hepatitis.

[Claim 24] The use of claim 23, wherein the prophylactic and/or therapeutic agent is to be administered together with at least one drug selected from the group consisting of donepezil hydrochloride, galantamine hydrobromide, huperzine A, idebenone, levacecarnine hydrochloride, memantine hydrochloride, memantine hydrochloride/donepezil hydrochloride, proteolytic peptide fraction from porcine brain protein, rivastigmine tartrate, tacrine hydrochloride and aducanumab.

[Claim 25] [(1R,5S,6r)-6-(5,5-dimethyl-4,5-dihydro-1,2-oxazol-3-yl)-3-azabicyclo[3.1.0]hex-3-yl][1-(1-methylcyclopropyl)-1H-imidazol-4-yl]methanone



or a salt thereof.