Title: PERFLUORINATED CYCLOPROPYL FUSED 1,3-OXAZIN-2-AMINE COMPOUNDS AS BETA-SECRETASE INHIBITORS AND METHODS OF USE

Abstract: PERFLUORINATED CYCLOPROPYL FUSED 1,3-OXAZIN-2-AMINE COMPOUNDS AS BETA-SECRETASE INHIBITORS AND METHODS OF USE ABSTRACT OF THE DISCLOSURE The present invention provides a new class of compounds useful for the modulation of beta-secretase enzyme (BACE) activity. The compounds have a general formula I: [INSERT STRUCTURE HERE] I wherein variables A4, A5, A6, A8, each of Ra, Rb, R1, R2, R3 and R7 of Formula I, independently, are defined herein. The invention also provides pharmaceutical compositions comprising the compounds, and uses of the compounds and compositions for treatment of disorders and/or conditions related to A-beta plaque formation and deposition, resulting from the biological activity of BACE. Such BACE mediated disorders include, for example, Alzheimer’s Disease, cognitive deficits, cognitive impairments, schizophrenia and other central nervous system conditions. The invention further provides compounds of Formulas II and III, and sub-formula embodiments thereof, intermediates and methods for preparing compounds of the invention.

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PERFLUORINATED CYCLOPROPYL FUSED 1,3-OXAZIN-2-AMINE COMPOUNDS AS BETA-SECRETASE INHIBITORS AND METHODS OF USE

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Patent Application Nos. 61/775,380, filed on March 08, 2013 and 61/939,580, filed on February 13, 2014, which specifications are hereby incorporated herein by reference in their entireties.

FIELD OF THE INVENTION

The invention relates generally to pharmaceutically active compounds, pharmaceutical compositions and methods of use thereof, to treat beta-secretase mediated diseases and conditions, including, without limitation, Alzheimer's disease, plaque formation and associated central nervous system (CNS) disorders.

BACKGROUND OF THE INVENTION

Alzheimer's disease (AD) affects greater than 12 million aging people worldwide, and importantly, the number affected continues to grow. AD accounts for the majority of dementias clinically diagnosed after the age of 60. AD is generally characterized by the progressive decline of memory, reasoning, judgement and orientation. As the disease progresses, motor, sensory, and vocal abilities are affected until there is global impairment of multiple cognitive functions. The loss of cognitive function occurs gradually, typically leading to a diminished cognition of self, family and friends. Patients with severe cognitive impairment and/or diagnosed as end-stage AD are generally bedridden, incontinent, and dependent on custodial care. The AD patient eventually dies in about nine to ten years, on average, after initial diagnosis. Due to the incapacitating, generally humiliating and ultimately fatal effects of AD, there is a need to treat AD effectively upon diagnosis.

AD is characterized by two major physiological changes in the brain. The first change, beta amyloid plaque formation, supports the "amyloid cascade hypothesis" which conveys the thought that AD is caused by the formation of characteristic beta amyloid peptide (A-beta), or A-beta fragments thereof, deposits in the brain (commonly referred to as beta amyloid "plaques" or "plaque deposits") and in cerebral blood vessels (beta amyloid angiopathy). A wealth of evidence suggests that beta-amyloid and accompanying amyloid plaque formation is central to the pathophysiology of AD and is likely to play an

Several lines of evidence indicate that progressive cerebral deposition of A-beta plays a seminal role in the pathogenesis of AD and can precede cognitive symptoms by years or even decades. Selkoe, Neuron, 6:487 (1991). Release of A-beta from neuronal cells grown in culture and the presence of A-beta in cerebrospinal fluid (CSF) of both normal individuals and AD patients has been demonstrated. Seubert et al., Nature, 359:325-327 (1992). Autopsies of AD patients have revealed large numbers of lesions comprising these 2 factors in areas of the human brain believed to be important for memory and cognition.

Smaller numbers of these lesions in a more restricted anatomical distribution are found in the brains of most aged humans who do not have clinical AD. Amyloid containing plaques and vascular amyloid angiopathy were also found in the brains of individuals with Down's Syndrome, Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-type (HCHWA-D), and other neurodegenerative disorders.

It has been hypothesized that A-beta formation is a causative precursor or factor in the development of AD. More specifically, deposition of A-beta in areas of the brain responsible for cognitive factors is believed to be a major factor in the development of AD. Beta amyloid plaques are primarily composed of amyloid beta peptide (A-beta peptide). A-beta peptide is derived from the proteolytic cleavage of a large transmembrane amyloid precursor protein (APP), and is a peptide comprised of about 39-42 amino acid residues. A-beta 42 (42 amino acids long) is thought to be the major component of these plaque deposits in the brains of Alzheimer's Disease patients. Citron, Trends in Pharmacological Sciences, 25(2):92-97 (2004).

Similar plaques appear in some variants of Lewy body dementia and in inclusion body myositis, a muscle disease. Aβ also forms aggregates coating cerebral blood vessels in cerebral amyloid angiopathy. These plaques are composed of a tangle of regularly ordered fibrillar aggregates called amyloid fibers, a protein fold shared by other peptides such as prions associated with protein misfolding diseases. Research on laboratory rats suggest that the dimeric, soluble form of the peptide is a causative agent in the development of Alzheimer's and is the smallest synaptotoxic species of soluble amyloid
1782.

Several aspartyl proteases, including beta-secretase and gamma-secretase, are
thought to be involved in the processing or cleavage of APP, resulting in the formation of
A-beta peptide. Beta secretase (BACE, also commonly referred to as memapsin) is
thought to first cleave APP to generate two fragments: (1) a first N-terminus fragment
(beta APP) and (2) a second C-99 fragment, which is subsequently cleaved by gamma
secretase to generate the A-beta peptide. APP has also been found to be cleaved by alpha-
secretase to produce alpha-sAPP, a secreted form of APP that does not result in beta-
amyloid plaque formation. This alternate pathway precludes the formation of A-beta
peptide. A description of the proteolytic processing fragments of APP is found, for
example, in U.S. Patent Nos. 5,441,870, 5,712,130 and 5,942,400.

BACE is an aspartyl protease enzyme comprising 501 amino acids and
responsible for processing APP at the beta-secretase specific cleavage site. BACE is
present in two forms, BACE 1 and BACE 2, designated as such depending upon the
specific cleavage site of APP. Beta secretase is described in Sinha et al., Nature, 402:537-
554 (1999) (p510) and PCT application WO 2000/17369. It has been proposed that A-
beta peptide accumulates as a result of APP processing by BACE. Moreover, in vivo
processing of APP at the beta secretase cleavage site is thought to be a rate-limiting step
the BACE enzyme activity is desirable for the treatment of AD.

Studies have shown that the inhibition of BACE may be linked to the treatment
of AD. The BACE enzyme is essential for the generation of beta-amyloid or A-beta.
BACE knockout mice do not produce beta-amyloid and are free from Alzheimer's
associated pathologies including neuronal loss and certain memory deficits. Cole, S.L.,
Vasser, R., Molecular Degeneration 2:22, 2007. When crossed with transgenic mice that
over express APP, the progeny of BACE deficient mice show reduced amounts of A-beta
in brain extracts as compares with control animals (Luo et al., Nature Neuroscience,
4:231-232 (2001)). The fact that BACE initiates the formation of beta-amyloid, and the
observation that BACE levels are elevated in this disease provide direct and compelling
reasons to develop therapies directed at BACE inhibition thus reducing beta-amyloid and
its associated toxicities. To this end, inhibition of beta secretase activity and a
corresponding reduction of A-beta in the brain should provide a therapeutic method for
treating AD and other beta amyloid or plaque related disorders.
Consequently, the approach of regulating or reducing the formation of A-beta peptide formation and deposition as a potential treatment for AD has received tremendous attention, support and commitment from both researchers and investors alike. A small molecule gamma-secretase inhibitor, LY450139 ("Semagacestat"), an A-beta lowering agent, advanced to phase III clinical trials for the treatment of Alzheimer’s Disease. The pharmacokinetics of semagacestat in plasma, as well as the plasma and cerebral spinal fluid (CSF) A-Beta peptide levels as pharmacodynamic responses to semagacestat administration were evaluated in healthy human subjects in single and multiple doses, and pharmacokinetic and pharmacodynamic changes were also assessed in mild to moderate AD patients in two (2) clinical trials (Expert Opin. Pharmacother. (2009), 10 (10); Clin. Neuropharmacol. 2007; 30 (pgs 317-325); and Neurology, 2006, 66 (pgs 602-624)).


\[
\text{NR}^{2a}R^{2b}N\begin{array}{c}R^{4a}\\(R^{4b})\end{array}\text{A}
\]

while WO2012168164 describes "Halogen-Alkyl-1,3-Oxazines as BACE1 and/or BACE2 Inhibitors" and discloses compounds of the general formula:
The lysosomal aspartic protease Cathepsin D (CatD) is ubiquitously expressed in eukaryotic organisms. CatD activity is essential to accomplish the acid-dependent extensive or partial proteolysis of protein substrates within endosomal and lysosomal compartments therein delivered via endocytosis, phagocytosis or autophagocytosis. CatD may also act at physiological pH on small-size substrates in the cytosol and in the extracellular milieu. Mouse and fruit fly CatD knock-out models have highlighted the multi-pathophysiological roles of CatD in tissue homeostasis and organ development.

Inhibition of protein Cathepsin D has been implicated in undesirable side effects. For instance, the inhibition of Cathepsin D is believed to be linked to adverse retinal development and retinal atrophy. Particularly, in mice it was found that cathepsin D is essential for the metabolic maintenance of retinal photoreceptor cells and that its deficiency induces apoptosis of the cells, while the loss of INL neurons is mediated by nitric oxide release from microglial cells. However, in the very same mice, it was also found that no atrophic change was detected in the retina of mice deficient in cathepsin B or L. Mol. Cell. Neurosci., 2003, Feb 22(2): 146-161. Further, Animal models of cathepsin D (CatD) deficiency are characterized by a progressive and relentless neurodegenerative phenotype similar to that observed in Neuronal Ceroid Lipofuscinoses (NCL), a group of pediatric neurodegenerative diseases known collectively as Batten Disease. It has been shown that the targeted deletion of the pro-apoptotic molecule Bax prevents apoptotic markers but not neuronal cell death and neurodegeneration induced by CatD deficiency, which suggests that alterations in the macroautophagy-lysosomal degradation pathway can mediate neuronal cell death in NCL/Batten Disease in the absence of apoptosis. Autophagy, 2007, Sept-Oct;3(5):474-476. Finally, an adverse effect of the inhibition of CatD is evident from the data presented in PLoS One, 2011; 6(7):e21908, published 7-1-2011. The authors of the PLoS One paper found that knock-down of cathepsin D affects the retinal pigment epithelium, impairs swim-bladder ontogenesis and causes premature death in zebrafish. The main phenotypic alterations produced by CatD knock-down in zebrafish were: 1. abnormal development of the eye and of retinal pigment epithelium; 2.
absence of the swim-bladder; 3. skin hyper-pigmentation; 4. reduced growth and premature death. Rescue experiments confirmed the involvement of CatD in the developmental processes leading to these phenotypic alterations.

Moreover, such toxicity findings which, in view of the literature, may have played a role in the termination of a human Bace-mediated Alzheimer's Disease clinical trial. Eli Lilly terminated a phase I clinical trial of LY 281 1376 after rat toxicology studies showed that a higher compound dose given for three months damaged the pigment epithelium of the rat's eye. The retinal layer had inclusions and extensive damage. The Phase I dosing trial was terminated and people brought in for eye assessments did not show any abnormalities. (Alzheimer's Research Forum News, 3-1-2011 reporting on Martin Citron's presentation at the AD/PD Conference 3-2011 in Barcelona, Spain)

Hence, it is desirable to provide compounds which modulate the activity of and are reasonably selective for BACE, while not suffering from undesirable side effects possibly due to intervention with or the reduction and/or direct or indirect inhibition of the expression and/or function of other proteins or biological pathways.

BRIEF DESCRIPTION OF THE INVENTION

The present invention provides a new class of compounds useful for the modulation of beta secretase activity, and as treatment of AD. Particularly, the compounds of the invention are useful for the regulation or reduction of the formation of A-beta peptide and, consequently, the regulation and/or reduction of formation of beta amyloid plaque both on the brain, as well as in the CNS. To this end, the compounds are useful for the treatment of AD and other beta secretase and/or plaque-related and/or mediated disorders. For example, the compounds are useful for the prophylaxis and/or treatment, acute and/or chronic, of AD and other diseases or conditions involving the deposition or accumulation of beta amyloid peptide, and formation of plaque, on the brain.

The compounds provided by the invention, including stereoisomers, tautomers, hydrates, solvates and pharmaceutically acceptable salts thereof, are generally defined by Formula I
wherein each of A\(^4\), A\(^5\), A\(^6\), A\(^8\), R\(^1\), R\(^2\), R\(^3\) and R\(^7\) of Formula I are defined below.

The invention also provides procedures for making compounds of Formula I, and sub-Formulas thereof, as well as intermediates useful in such procedures.

The invention further provides pharmaceutical compositions comprising compounds of the invention, and uses of these compositions in the treatment of beta secretase mediated diseases. For example, and in one embodiment, the invention provides a pharmaceutical composition comprising an effective dosage amount of a compound of Formula I in association with at least one pharmaceutically acceptable excipient.

The foregoing merely summarizes certain aspects of the invention and is not intended, nor should it be construed, as limiting the invention in any way. All patents and other publications recited herein are hereby incorporated by reference in their entirety.

### DETAILED DESCRIPTION OF THE INVENTION

In embodiment 1 of the invention, there are provided compounds, including stereoisomers, tautomers, hydrates, solvates and pharmaceutically acceptable salts thereof, which are generally defined by Formula I:

\[
\text{I}
\]

or a stereoisomer, tautomer, hydrate, solvate or pharmaceutically acceptable salt thereof, wherein

A\(^4\) is CR\(^4\) or N;
A\(^5\) is CR\(^3\) or N;
A-1

A is CR or N;
A is CR or N, provided that no more than two of A, A, A and A is N;
each of R and R, independently, is H, F, Cl, CI-alkyl, C-alkenyl,
C-alkynyl, CN, -CH2OCI-alkyl, -OCI-alkyl, -S(0)C1-alkyl, -NHC1-alkyl or -
C(0)Cl-alkyl, wherein each of the CI-alkyl, C-alkenyl, and CI-alkyl portion of -CH2OCI-alkyl, -OCI-alkyl, -S(0)C1-alkyl, -NHC1-alkyl and -C(0)Cl-alkyl are optionally substituted with 1-4 substituents of F, oxo or OH;
each of R and R, independently, is H, F, Cl, CI-alkyl, C-alkenyl,
C-alkynyl, CN, -CH2OCI-alkyl, -OCI-alkyl, -S(0)C1-alkyl, -NHC1-alkyl or -
C(0)Cl-alkyl, wherein each of the CI-alkyl, C-alkenyl, C-alkenyl, and CI-alkyl portion of -CH2OCI-alkyl, -OCI-alkyl, -S(0)C1-alkyl, -NHC1-alkyl and -C(0)Cl-alkyl are optionally substituted with 1-4 substituents of F, oxo or OH;
R is CI-alkyl, CH2OCI-alkyl, CH2OH, CI-haloalkyl or cyclopropyl, wherein each of the CI-alkyl, CH2OCI-alkyl, CI-haloalkyl and cyclopropyl is optionally substituted with 1-4 F atoms;
each of R, R, and R, independently, is H, halo, haloalkyl, haloalkoxy,
CI-alkyl, CN, OH, OCI-alkyl, S(0)CI-alkyl, NHC1-alkyl or C(0)CI-alkyl;
R is -NH-R, -NH-C(=0)-R, -C(=0)NH-R, -O-R or -S-R;
R is acetyl, CI-alkyl, C-alkenyl, C-alkynyl or a fully or partially unsaturated
3-, 4-, 5-, 6- or 7-membered monocyclic or 8-, 9- or 10-membered bicyclic ring formed of
carbon atoms, said ring optionally including 1-4 heteroatoms if monocyclic or 1-5
heteroatoms if bicyclic, said heteroatoms selected from O, N or S, wherein the CI-alkyl, C-alkenyl, C-alkynyl and ring are optionally substituted, independently, with 1-5
substituents of R; and
each R, independently, is H, halo, haloalkyl, CN, OH, N02, NH2, SF, acetyl,
-C(0)NHCH, oxo, cyclopropylmethoxy, 2-butyloxy, CI-alkyl, C-alkenyl, C-alkynyl, C-alkylamino, CI-dialkylamino, CI-dialkoxyl, CI-thialkoxyl, morpholinyl, pyrazolyl, isoazolyl, dihydropyranyl, pyrrolyl, pyrrolidinyl,
tetrahydropyrrrolyl, piperazinyl, oxetan-3-yl, imidazo-pyridinyl or dioxolyl, wherein each
of the cyclopropylmethoxy, 2-butyloxy, CI-alkyl, C-alkenyl, C-alkynyl, C-alkylamino, CI-dialkylamino, CI-dialkoxyl, CI-thialkoxyl, morpholinyl, pyrazolyl, isoazolyl, dihydropyranyl, pyrrolyl, pyrrolidinyl, oxetan-3-yl or dioxolyl, is optionally substituted independently with 1-5 substituents of F, Cl, CN, N02, NH2, OH,
oxo, CF, CHF, CF, methyl, methoxy, ethyl, ethoxyl, CH2CF, CH2CHF, propyl,
propoxy, isopropyl, isoproxy, cyclopropyl, butyl, butoxyl, cyclobutyl, isobutoxy, tert-butoxy, isobutyl, sec-butyl, tert-butyl, cyclopentyl, cyclohexyl, CI$_3$alkylamino-, CI$_3$dialkylamino, CI$_3$thioalkoxy tetrahydropyranyl, tetrahydropyrrolyl or oxetan-3yl, provided the compound is not

5 N-(3-((IR,5R,6R)-3-amino-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methoxy-1,7-naphthyridin-8-amine or

N-(3-((IR,5R,6R)-3-amino-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-methoxy-2-pyrazinecarboxamide.

In embodiment 2, the invention provides compounds according to embodiment 1, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each of R$^1$ and R$^2$, independently, is H, F, CH$_3$, CH$_2$F, CHF$_2$ or CF$_3$.

In embodiment 3, the invention provides compounds according to any one of embodiments 1 and 2, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each of R$^a$ and R$^b$, independently, is H, F, CH$_3$, CH$_2$F, CHF$_2$ or CF$_3$.

In embodiment 4, the invention provides compounds according to any one of embodiments 1, 2 and 3, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each of R$^1$ and R$^2$, independently, is H, F or CF$_3$.

In embodiment 5, the invention provides compounds according to any one of embodiments 1-4, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each of R$^a$ and R$^b$, independently, is H or F.

In embodiment 6, the invention provides compounds according to any one of embodiments 1-5, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each of R$^1$ and R$^2$, independently, is H, F or CF$_3$; and each of R$^a$ and R$^b$, independently, is H or F.

In embodiment 7, the invention provides compounds according to any one of embodiments 1-6, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each of R$^1$, R$^2$, R$^a$ and R$^b$, independently, is H.

In embodiment 8, the invention provides compounds according to any one of embodiments 1-7, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R$^3$ is CH$_3$, CF$_3$, CH$_2$F or CHF$_2$.

In embodiment 9, the invention provides compounds according to any one of embodiments 1-8, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R$^7$ is -NH-CH$_2$R$^9$ or -NH-C(=0)-R$^9$.
or $R^7$ is

wherein $V$ is NR, O or S; and

each $W$, independently, is CH, CF, CC1, CCH or N.

In embodiment 10, the invention provides compounds according to any one of embodiments 1 and 9, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein

$A^4$ is CR or N;

$A^5$ is CR or N;

$A^6$ is CR or N;

$A^7$, CR or N, provided that no more than one of $A^4$, $A^5$, $A^6$ and $A^7$ is N;

each of $R^4$ and $R^9$, independently, is H, F, Cl, CF$_3$, OCF$_3$, methyl, ethyl, CN, OH, OCH$_3$, SCH$_3$, NHCH$_3$, C(0)CH$_3$ or CH$_2$OCHF$_2$;

each of $R^1$ and $R^2$, independently, is H, F, Cl, CF$_3$, OCF$_3$, methyl, ethyl, CN, OH, OCH$_3$, SCH$_3$, NHCH$_3$, C(0)CH$_3$ or CH$_2$OCHF$_2$;

$R^3$ is C$_{1-4}$alkyl, C$_{1-4}$haloalkyl, CH$_2$OH, CH$_2$OCHF$_2$ or cyclopropyl; and

each of $R^4$, $R^5$, $R^6$ and $R^8$, independently, is H, F, Cl, CF$_2$H, CH$_2$F, CF$_3$, OCF$_3$, methyl, ethyl, CN, OH, OCH$_3$, SCH$_3$, NHCH$_3$, C(0)CH$_3$ or CH$_2$OCHF$_2$.

In embodiment 11, the invention provides compounds according to any one of embodiments 1-9, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein

each of $R^1$ and $R^2$, independently, is H, F or CF$_3$;

each of $R^4$ and $R^5$, independently, is H or F;

$R^3$ is CH$_3$, CF$_3$, CH$_2$F or CHF$_2$; and

$R^7$ is -NH-R$_9$, -NH-C(=0)-R$_9$ or
wherein \( V \) is \( NR, O \) or \( S \); and

each \( W \), independently, is \( CH, CF, CCl, CCH_3 \) or \( N \).

In embodiment 12, the invention provides compounds according to any one of

embodiments 1-11, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein

\[ R^7 \] is \(-NH-C(=0)-R^9 \).

In embodiment 13, the invention provides compounds according to any one of

embodiments 1-11, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein

\[ R^7 \] is

wherein \( V \) is \( NR, O \) or \( S \); and

each \( W \), independently, is \( CH, CF, CCl, CCH_3 \) or \( N \).

In embodiment 14, the invention provides compounds according to any one of

embodiments 1-13, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein

\( A^4 \) is \( CR^4 \);

\( A^5 \) is \( CR^5 \) or \( N \);

\( A^6 \) is \( CR^6 \); and

\( A^8 \) is \( CR^8 \) or \( N \), provided only one of \( A^5 \) and \( A^8 \) is \( N \), and wherein each of \( R^4, R^5, R^6 \) and \( R^8 \), independently, is \( H, F, Cl, CF_3, CF_2H, CH_2F \) or \( CH_3 \).

In embodiment 15, the invention provides compounds, including stereoisomers, tautomers, hydrates, solvates and pharmaceutically acceptable salts thereof, which are generally defined by Formula 1:
or a stereoisomer, tautomer, hydrate, solvate or pharmaceutically acceptable salt thereof,

wherein

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A^4 is CR^4 or N;
A^5 is CR^5 or N;
A^6 is CR^6 or N;
A^8 is CR^8 or N, provided that no more than one of A^4, A^5, A^6 and A^8 is N;
each of R^1 and R^2, independently, is H, F, CH₃, CH₂F, CHF₂ or CF₃;
each of R^4 and R^5, independently, is H, F, CH₃, CH₂F, CHF₂ or CF₃;
R^3 is C₄-alkyl, CH₂OC₄-alkyl, CH₂OH, C₄-haloalkyl or cyclopropyl, wherein
each of the C₄-alkyl, CH₂OC₄-alkyl, C₄-haloalkyl and cyclopropyl is optionally
substituted with 1-4 F atoms;
each of R^4, R^5, R^6 and R^8, independently, is H, halo, haloalkyl, haloalkoxy,

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C₄-alkyl, CN, OH, OC₄-alkyl, S(0)ₜ-C₄-alkyl, NHCl₄-alkyl or C(0)Cl₄-alkyl;
R^7 is -NH-R^9 or -NH-C(=0)-R^9;
or R^7 is

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wherein V is NR^1₀, O or S; and
each W, independently, is CH, CF, CC1, CCH₃ or N;
R^9 is acetyl, C_6-alkyl, C_2-alkenyl, C_2-alkynyl or a fully or partially unsaturated 3-, 4-, 5-, 6- or 7-membered monocyclic or 8-, 9- or 10-membered bicyclic ring formed of carbon atoms, said ring optionally including 1-4 heteroatoms if monocyclic or 1-5 heteroatoms if bicyclic, said heteroatoms selected from O, N or S, wherein the C_1-6-alkyl, C_2-alkenyl, C_2-alkynyl and ring are optionally substituted, independently, with 1-5 substituents of R^10; and
each R^10, independently, is H, halo, haloalkyl, CN, OH, N=O_2, NH_2, SF_5, acetyl, -C(0)NHCH_3, oxo, cyclopropylmethoxy, 2-butylnoxy, C_2-alkenyl, C_2-alkynyl, C_3-cycloalkyl, C_6-alkylamino-, C_6-dialkylamino-, C_6alkoxy, C_6-thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolyl, pyrrolidinyl, tetrahydropyrrolyl, piperazinyl, oxetan-3-yl, imidazo-pyridinyl or dioxolyl, wherein each of the cyclopropylmethoxy, 2-butylnoxy, C_2-alkenyl, C_2-alkynyl, C_3-cycloalkyl, C_6-alkylamino-, C_6-dialkylamino-, C_6alkoxy, C_6-thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolidinyl, oxetan-3-yl or dioxolyl, is optionally substituted independently with 1-5 substituents of F, Cl, CN, N=O_2, NH_2, OH, oxo, CF_3, CHF_2, CH_2F, methyl, methoxy, ethyl, ethoxy, CH_2CF_3, CH_2CHF_2, propyl, propanoyl, isopropinyl, isopropoxy, cyclopropyl, butyl, butoxyl, cyclobutyl, isobutoxy, tert-butoxy, isobutyl, sec-butyl, tert-butyl, cyclopentyl, cyclohexyl, C_3-alkylamino-, C_3-dialkylamino, C_3-thioalkoxyl tetrahydropyranyl, tetrahydropyrrolyl or oxetan-3-yl, provided the compound is not
N-(3-((1R,5R,6R)-3-amino-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methoxy-1,7-naphththyridin-8-amine or N-(3-((1R,5R,6R)-3-amino-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-methoxy-2-pyrazinecarboxamide.

In embodiment 16, the invention provides compounds, including stereoisomers, tautomers, hydrates, solvates and pharmaceutically acceptable salts thereof, which are generally defined by Formula II:
wherein

\[ A^4 \text{ is } CR^4 \text{ or } N; \]
\[ A^5 \text{ is } CR^5 \text{ or } N; \]
\[ A^6 \text{ is } CR^6 \text{ or } N; \]
\[ A^8 \text{ is } CR^8 \text{ or } N, \text{ provided that no more than two of } A^4, A^5, A^6 \text{ and } A^8 \text{ is } N; \]

each of \( R^4 \) and \( R^5 \), independently, is \( H, F, Cl, Ci_{1-6}\text{-alkyl}, C_2\text{-alkenyl}, \) \( C_2\text{-alkynyl}, CN, \) \(-CH_2\text{O}Ci_{1-6}\text{-alkyl}, \) \(-OCi_{1-6}\text{-alkyl}, \) \(-S(0)Ci_{1-6}\text{-alkyl}, \) \(-NH\text{Ci}_{1-6}\text{-alkyl} \) or \( -C(0)Ci_{1-6}\text{-alkyl}, \) wherein each of the \( Ci_{1-6}\text{-alkyl}, C_2\text{-alkenyl}, C_2\text{-alkynyl}, \) and \( Ci_{1-6}\text{-alkyl} \) portion of \( -CH_2\text{O}Ci_{1-6}\text{-alkyl}, \) \(-OCi_{1-6}\text{-alkyl}, \) \(-S(0)Ci_{1-6}\text{-alkyl}, \) \(-NH\text{Ci}_{1-6}\text{-alkyl} \) and \( -C(0)Ci_{1-6}\text{-alkyl} \) are optionally substituted with 1-4 substituents of \( F, oxo \) or \( OH; \)

each of \( R^1 \) and \( R^2 \), independently, is \( H, F, Cl, Ci_{1-6}\text{-alkyl}, C_2\text{-alkenyl}, \) \( C_2\text{-alkynyl}, CN, \) \(-CH_2\text{O}Ci_{1-6}\text{-alkyl}, \) \(-OCi_{1-6}\text{-alkyl}, \) \(-S(0)Ci_{1-6}\text{-alkyl}, \) \(-NH\text{Ci}_{1-6}\text{-alkyl} \) or \( -C(0)Ci_{1-6}\text{-alkyl}, \) wherein each of the \( Ci_{1-6}\text{-alkyl}, C_2\text{-alkenyl}, C_2\text{-alkynyl}, \) and \( Ci_{1-6}\text{-alkyl} \) portion of \( -CH_2\text{O}Ci_{1-6}\text{-alkyl}, \) \(-OCi_{1-6}\text{-alkyl}, \) \(-S(0)Ci_{1-6}\text{-alkyl}, \) \(-NH\text{Ci}_{1-6}\text{-alkyl} \) and \( -C(0)Ci_{1-6}\text{-alkyl} \) are optionally substituted with 1-4 substituents of \( F, oxo \) or \( OH; \)

\( R^3 \) is \( Ci_{1-6}\text{-alkyl}, CH_2\text{O}Ci_{4-alkyl}, CH_2\text{OH, Ci}_{1-6}\text{-haloalkyl or cyclopropyl, wherein each of the } Ci_{1-6}\text{-alkyl, CH}_2\text{O}Ci_{4-alkyl}, Ci_{1-6}\text{-haloalkyl and cyclopropyl is optionally substituted with 1-4 F atoms; } \)
each of \( R^4, R^5, R^6 \) and \( R^8 \), independently, is \( H, \) halo, haloalkyl, haloalkoxy,

\( Ci\text{-4-alkyl}, CN, OH, OCl_{1-4}\text{-alkyl, S(0)}Ci_{1-4}\text{-alkyl, NHCl}_{1-4}\text{-alkyl or C(0)Cl}_{1-4}\text{-alkyl; } \)
\( R^7 \) is \( -NH-R^9, -NH-C(=0)-R^9, -C(=0)NH-R^9; \) or \( R^7 \) is

\[ \text{R}^{10} \text{ or } \text{R}^{11} \]

wherein \( V \) is \( NR^{10}, O \) or \( S; \) and
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each $W$, independently, is CH, CF, CC1, CCH$_3$ or N;

$R\text{^9}$ is acetyl, C$_{1-6}$-alkyl, C*alkenyl, C$_{2-}$alkynyl or a fully or partially unsaturated

3-, 4-, 5-, 6- or 7-membered monocyclic or 8-, 9- or 10-membered bicyclic ring formed of
carbon atoms, said ring optionally including 1-4 heteroatoms if monocyclic or 1-5

heteroatoms if bicyclic, said heteroatoms selected from O, N or S, wherein the C$_{1-6}$-alkyl,
C$_{2-}$alkenyl, C$_{2-}$alkynyl and ring are optionally substituted, independently, with 1-5

substituents of $R\text{^9};$ and

each $R\text{^10}$, independently, is H, halo, haloalkyl, CN, OH, NO$_2$, NH$_2$, SF$_5$, acetyl,
-C(0)NHCH$_3$, oxo, cyclopropylmethoxy, 2-butynyloxy, C$_{1-6}$alkyl, C$_{2-}$alkenyl, C$_{2-}$alkynyl,
cyclopropylmethoxy, 2-butynyloxy, C$_{1-6}$alkyl, C$_{2-}$alkenyl, C$_{2-}$alkynyl, C$_{3-}$morpholinyl, pyrazolyl, isoxazolyl, dihydropryranyl, pyrrolyl, pyrrolidinyl,
tetrahydropyrrolyl, pyrazolyl, isoxazolyl, dihydropryranyl, pyrrolyl, pyrrolidinyl,
tetrahydropyrrolyl, pyrazolyl, isoxazolyl, dihydropryranyl, pyrrolyl, pyrrolidinyl,
tetrahydropyrrolyl, oxetan-3-yl, imidazo-pyridinyl or dioxolyl, wherein each

of the cyclopropylmethoxy, 2-butynyloxy, C$_{1-6}$alkyl, C$_{2-}$alkenyl, C$_{2-}$alkynyl, C$_{3-}$morpholinyl, pyrazolyl,

isoxazolyl, dihydropryranyl, pyrrolidinyl, oxetan-3-yl or dioxolyl, is optionally substituted independently with 1-5 substituents of F, Cl, CN, NO$_2$, NH$_2$, OH,

oxo, CF$_3$, CHF$_2$, CH$_2$F, methyl, methoxy, ethyl, ethoxy, CH$_2$CF$_3$, CH$_2$CHF$_2$, propyl,
propoxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxy, cyclobutyl, isobutoxy, tert-butoxy,
isobutyl, sec-buty1, tert-buty1, cyclopentyl, cyclohexyl, C$_{1-6}$alkylamino-, C$_{1-6}$thioalkoxyl,
dialkylamino, C$_{1-6}$alkylamino-, C$_{1-6}$alkylamino-, C$_{1-6}$alkylamino-, C$_{1-6}$alkylamino-, C$_{1-6}$alkylamino-, C$_{1-6}$alkylamino-

cycloalkyl, C$_{1-6}$alkylamino-, C$_{1-6}$alkylamino-.

In embodiment 17, the invention provides compounds according any one of

embodiments 1 and 16, or a stereoisomer, tautomer or pharmaceutically acceptable salt

thereof, wherein

A$_4$ is CR$_4$ or N;

A$_5$ is CR$_5$ or N;

A$_6$ is CR$_6$ or N;

A$_8$ is CR$_8$ or N, provided no more than one of A$_4$, A$_5$, A$_6$ and A$_8$ isN;

each of R$_4$ and R$_5$, independently, is H, F, CH$_3$, CHF$_2$, CH$_2$F or CF$_3$;

each of R$_1$ and R$_2$, independently, is H, F, CH$_3$, CHF$_2$, CH$_2$F or CF$_3$;

R$_3$ is C$_{1-6}$alkyl, C$_{1-6}$haloalkyl, CH$_2$OH, CH$_2$OCH$_2$F or cyclopropyl; and

each of R$_4$, R$_5$, R$_6$ and R$_8$, independently, is H, F, Cl, CF$_2$H, CH$_2$F, CF$_3$, OCF$_3$,
methyl, ethyl, CN, OH, OCH$_3$, SCH$_3$, NHCH$_3$ or C(0)CH$_3$. 


In embodiment 18, the invention provides compounds according to any one of embodiments 1-6, 7 and 16-17, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein

\[ A^4 \text{ is } C \text{R}^4; \]

\[ A^5 \text{ is } C \text{R}^5; \]

\[ A^6 \text{ is } C \text{R}^6; \]

\[ A^8 \text{ is } C \text{R}^8; \]

wherein each of \( R^4, R^5, R^6 \) and \( R^8 \), independently, is H, F, CF₃, CF₂H, CH₂F or CH₃;

\[ R^3 \text{ is } CH₃, \text{CFH}, \text{CF₂H} \text{ or CHF}_2; \]

and

\[ R^7 \text{ is } -\text{NH}-\text{C}(=\text{O})-R^9 \text{ or} \]

wherein \( V \) is N, R, O or S; and

each \( W \), independently, is CH, CF, CCl or N.

In embodiment 19, the invention provides compounds according to any one of embodiments 16-17, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein \( R^7 \) is -NH-C(=O)-R^9.

In embodiment 20, the invention provides compounds according to any one of embodiments 16-18, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein \( R^7 \) is

wherein \( V \) is N, R, O or S; and

each \( W \), independently, is CH, CF, CCl, CCH₃ or N.

In embodiment 21, the invention provides compounds according to any one of embodiments 16-20, or a stereoisomer or pharmaceutically acceptable salt thereof,
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wherein each of R¹ and R², independently, is H, F or CF₃; and each of R⁸ and R⁹, independently, is H or F.

In embodiment 22, the invention provides compounds according to any one of embodiments 1-12, or a stereoisomer or pharmaceutically acceptable salt thereof, having a Formula I-A

![Chemical Structure](image)

wherein

A⁴ is CR⁴ or N;
A⁵ is CR⁵ or N;
A⁶ is CR⁶ or N;
A⁸ is CR⁸ or N, provided that no more than one of A⁴, A⁵, A⁶ and A⁸ is N;
each of R⁴ and R⁵, independently, is H, F, Cl, Ci-6-alkyl, C₂-alkenyl,
C₂-alkynyl, CN, -CH₂OCi₁₋₄-alkyl, -OCl₁₋₄-alkyl, -S(0)₆C₁₋₄-alkyl, -NHCi₁₋₄-alkyl or -C(0)Ci₁₋₄-alkyl, wherein each of the Ci₁₋₄-alkyl, C₂-alkenyl, C₂-alkynyl, and Ci₁₋₄-alkyl portion of -CH₂OCi₁₋₄-alkyl, -OCl₁₋₄-alkyl, -S(0)₆C₁₋₄-alkyl, -NHCi₁₋₄-alkyl and -C(0)Ci₁₋₄-alkyl are optionally substituted with 1-4 substituents of F, oxo or OH;
each of R¹ and R², independently, is H, F, Cl, Ci₁₋₄-alkyl, C₂-alkenyl,
C₂-alkynyl, CN, -CH₂OCi₁₋₄-alkyl, -OCl₁₋₄-alkyl, -S(0)₆C₁₋₄-alkyl, -NHCi₁₋₄-alkyl or -C(0)Ci₁₋₄-alkyl, wherein each of the Ci₁₋₄-alkyl, C₂-alkenyl, C₂-alkynyl, and Ci₁₋₄-alkyl portion of -CH₂OCi₁₋₄-alkyl, -OCl₁₋₄-alkyl, -S(0)₆C₁₋₄-alkyl, -NHCi₁₋₄-alkyl and -C(0)Ci₁₋₄-alkyl are optionally substituted with 1-4 substituents of F, oxo or OH;
R³ is Ci₁-alkyl, CH₂OCi₁₋₄-alkyl, CH₂OH, Ci₁-haloalkyl or cyclopropyl, wherein each of the Ci₁-alkyl, CH₂OCi₁-alkyl, Ci₁-haloalkyl and cyclopropyl is optionally substituted with 1-4 F atoms;
each of R⁴, R⁵, R⁶ and R⁷, independently, is H, F, Cl or CH₃;
R⁹ is acetyl, Ci₆-alkyl, C₂-alkenyl. C₂-alkynyl or a fully or partially unsaturated 3-, 4-, 5-, 6- or 7-membered monocyclic or 8-, 9- or 10-membered bicyclic ring formed of carbon atoms, said ring optionally including 1-4 heteroatoms if monocyclic or 1-5...
heteroatoms if bicyclic, said heteroatoms selected from O, N or S, wherein the C₆-alkyl, C₃-alkenyl, C₆-alkynyl and ring are optionally substituted, independently, with 1-5 substituents of R₁⁰; and

each R₁⁰, independently, is H, halo, haloalkyl, CN, OH, NO₂, NH₂, SF₅, acetyl, -C(0)NHCH₃, oxo, cyclopropylmethoxy, 2-butynoxy, Cl₆-alkyl, C₆-alkenyl, C₆-alkynyl, C₆-cycloalkyl, Cl₆-alkylamino-, Cl₆-dialkylamino-, Cl₆-thioalkoxy, morpholiny, pyrazoliny, isoxazoliny, dihydropyranly, pyrroliny, pyrroldinyl, tetrahydropyrrolly, piperaziny, oxetan-3-yl, imidazo-pyridinyl or dioxolyl, wherein each of the cyclopropylmethoxy, 2-butynoxy, C₆-alkyl, C₆-alkenyl, C₆-alkynyl, C₆-cycloalkyl, Cl₂-dialkylamino-, Cl₆-dialkylamino-, Cl₆-thioalkoxy, morpholiny, pyrazoliny, isoxazoliny, dihydropyranly, pyrroliny, pyrroldinyl, tetrahydropyrrolly, piperaziny, oxetan-3-yl, imidazo-pyridinyl or dioxolyl, is optionally substituted independently with 1-5 substituents of F, Cl, CN, NO₂, NH₂, OH, oxo, CF₃, CHF₂, CH₂F, methyl, methoxy, ethyl, ethoxy, CH₃CF₃, CH₂CHF₂, propyl, propoxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxy, cyclobutyl, isobutony, tert-butoxy, isobutyl, sec-butyl, tert-butyl, cyclopentyl, cyclohexyl, Cl₆-alkylamino-, Cl₆-dialkylamino-, Cl₆-thioalkoxy tetrahydropyranyl, tetrahydropyrroly or oxetan-3-yl.

In embodiment 23, the invention provides compounds according to any one of embodiments 1-3, 8-20 and 22, or a stereoisomer, tautomer or pharmaceutically acceptable salt thereof, wherein

A⁴ is CR⁴;
A⁵ is CR⁵;
A⁶ is CR⁶;
A⁸ is CR₈, wherein each of R⁴, R⁵, R₆ and R₈, independently, is H, F, Cl, CF₃, CH₂F, CF₃, OCF₃, methyl, ethyl, CN, OH, OCH₃, SCH₃, NHCH₃ or C(0)CH₃;
each of R⁴ and R₅, independently, is H, F, CH₃, CH₂F, CHF₂ or CF₃;
each of R¹ and R², independently, is H, F, CH₃, CH₂F, CHF₂ or CF₃;
R³ is CH₃, C₂H₅, CF₃H or CH₂F;
R⁹ is acetyl, Cl₆-alkyl, C₄-alkenyl, C₄-alkynyl or a fully or partially unsaturated 3-, 4-, 5-, 6- or 7-membered monocyclic or 8-, 9- or 10-membered bicyclic ring formed of carbon atoms, said ring optionally including 1-4 heteroatoms if monocyclic or 1-5 heteroatoms if bicyclic, said heteroatoms selected from O, N or S, wherein the Cl₆-alkyl, C₂₄-alkenyl, C₂₄-alkynyl and ring are optionally substituted, independently, with 1-5 substituents of R₁⁰; and

each R₁⁰, independently, is H, halo, haloalkyl, CN, OH, NO₂, NH₂, SF₅, acetyl,
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- (0)NHCH₃, oxo, cyclopropylmethoxy, 2-butylnyloxy, C₃₋₆alkyl, C₃₋₆alkynyl, C₅₋₆cycloalkyl, C₆₋₁₀alkylamino-, C₆₋₁₀dialkylamino-, C₆₋₁₀thioalkyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolyl, pyrrolidinyl, tetrahydropyranyl, piperazinyl, oxetan-3-yl, imidazo-pyridinyl or dioxolyl, wherein each of the cyclopropylmethoxy, 2-butylnyloxy, C₃₋₆alkyl, C₅₋₆alkynyl, C₅₋₆cycloalkyl, C₆₋₁₀alkylamino-, C₆₋₁₀dialkylamino-, C₆₋₁₀thioalkyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolyl, pyrrolidinyl, oxetan-3-yl or dioxolyl, is optionally substituted independently with 1-5 substituents of F, Cl, CN, N₂, NH₂, OH, oxo, CF₃, CHF₂, CH₂F, methyl, methoxy, ethyl, methoxy, CH₂CF₃, CH₂CHF₂, propyl, propoxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxy, cyclobutyl, isobutoxy, tert-butoxy, isobutyl, sec-butyl, tert-butyl, cyclopentyl, cyclohexyl, C₆₋₁₀alkylamino-, C₆₋₁₀dialkylamino-, C₆₋₁₀thioalkyl tetrahydropyranyl, tetrahydropyrrol or oxetan-3-yl.

In embodiment 24, the invention provides compounds according to any one of embodiments 1-19 and 22-23, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein

A⁴ is CR⁴ or N;
A⁵ is CR⁵ or N;
A⁶ is CR⁶ or N;
A⁸ is CR⁸ or N, wherein each of R⁴, R⁵, R⁶ and R⁸, independently, is H, F, Cl or CH₃, provided no more than one of A⁴, A⁵, A⁶ and A⁸ is N;
each of R¹, R², R³ and R⁸, independently, is H; and
R³ is CF₃, CH₂CF₃, CF₂H or CH₂F.

In embodiment 25, the invention provides compounds according to any one of embodiments 1-12, 16-19 and 22-24, or a stereoisomer or pharmaceutically acceptable salt thereof, having a Formula II-A.

wherein
A is CR₄, wherein R₄ is H, F or Cl;
A₅ is CR₅ or N, wherein R₅ is H, F, CI or CH₃;
A₆ is CH;
A₈ is CR₈ or N, wherein R₈ is H or F, provided that no more than one of A₅ and
A₈ is N;

each of R₄ and R₅, independently, is H or F;
each of R¹ and R₂, independently, is H or F;
R₃ is CH₃, CF₃, CH₂F or CHF₂;
R⁹ is a fully unsaturated 5- or 6-membered monocyclic or 8-, 9- or 10-membered
bicyclic ring formed of carbon atoms, said ring optionally including 1-4 heteroatoms if
monocyclic or 1-5 heteroatoms if bicyclic, said heteroatoms selected from O, N or S,
wherein the ring is optionally substituted, independently, with 1-5 substituents of R₁₀; and
each R₁₀, independently, is H, halo, haloalkyl, CN, OH, N₀₂, NH₂, SF₅, acetyl,
-C(0)NHCH₂-, oxo, cyclopropylmethoxy, 2-butoxyloxy, CI₆alkyl, C₅₋₆alkenyl, C₂₋₆,
-alkyl, C₃₋₄Cycloalkyl, C₁₋₄alkylamino-, C₁₋₄alkylamino-, C₁₋₄alkyloxyl, C₁₋₄thioalkyloxyl,
morpholinyl, pyrazolyl, isoxazolyl, dihydropranyl, pyrrolyl, pyrrolidinyl,
tetrahydropyrrolyl, piperazinyl, oxetan-3-y1, imidazo-pyridinyl or dioxolyl, wherein each
of the cyclopropylmethoxy, 2-butoxyloxy, CI₆alkyl, C₅₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆,
₆Cycloalkyl, CI₆alkylamino-, CI₆dialkylamino-, CI₆alkyloxyl, CI₆thioalkyloxyl,
morpholinyl, pyrazolyl, isoxazolyl, dihydropranyl, pyrrolidinyl, oxetan-3-yl or dioxolyl,
is optionally substituted independently with 1-5 substituents of F, CI, CN, N₀₂, NH₂, OH,
oxo, CF₃, CHF₂, CH₂F, methyl, methoxy, ethyl, ethoxy, CH₂CF₃, CH₃CHF₂, propyl,
proxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxy, cyclobutyl, isobutoxy, tert-
butoxy, isobutyl, sec-butyl, tert-butyl, cyclopentyl, cyclohexyl, CI₆alkylamino-, CI₆,
₃dialkyloxyl, CI₆thioalkyloxyl tetrahedropyranyl, tetrahydroprrolyl or oxetan-3-yl.

In embodiment 26, the invention provides compounds according to embodiment
25, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each of R⁸, R⁹,
R¹ and R₂, independently, is H.

In embodiment 27, the invention provides compounds according any one of
embodiments 25 and 26, or a stereoisomer or pharmaceutically acceptable salt thereof,
wherein R³ is CH₃, CH₂F or CHF₂.

In embodiment 28, the invention provides compounds according to any one of
embodiments 25-27, or a stereoisomer or pharmaceutically acceptable salt thereof,
wherein R³ is CH₂F or CHF₂.
In embodiment 29, the invention provides compounds according to any one of embodiments 25-28, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^3 is CH_2F.

In embodiment 30, the invention provides compounds according to any one of embodiments 25-28, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^3 is CHF_2.

In embodiment 31, the invention provides compounds according to any one of embodiments 25-30, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein A^4 is CF or CCI;

A^5 is CH, CF, CH_3 or N;
A^6 is CH; and
A^8 is CH.

In embodiment 32, the invention provides compounds according to any one of embodiments 25-31, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein A^4 is CF;

A^5 is CH, CF or N;
A^6 is CH; and
A^8 is CH.

In embodiment 33, the invention provides compounds according to any one of embodiments 25-32, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein A^4 is CCI;

A^5 is CH or CF;
A^6 is CH; and
A^8 is CH.

In embodiment 34, the invention provides compounds according to any one of embodiments 25-33, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^9 is a ring selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrazolyl, pyrazolo[3,4-c]pyridinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl or thiienyl, wherein the ring is optionally substituted with 1-5 substituents of R^10; and each R^10, independently, is H, halo, haloalkyl, CN, OH, NO_2, NH_2, SF_5, acetyl, -C(0)NHCH_3, oxo, cyclopropylmethoxy, 2-butylyloxy, C_1alkyl, C_2alkenyl, C_2alkynyl, C_3alkynyl, C_5cycloalkyl, C_6alkylamino-, C_6dialkylamino-, C_6alkoxyl, C_6thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolyl, pyrrolidinyl,
tetrahydropyrrolyl, piperazinyl, oxetan-3-yl, imidazo-pyridinyl or dioxolyl, wherein each of the cyclopropylmethoxy, 2-butyloxy, Cl₆alkyl, C₂₆alkenyl, C₇₆alkynyl, C₃₆
C₆Cycloalkyl, Cl₆alkylamino-, Cl₆dialkylamino-, Cl₆alkoxy, Cl₆thioalkoxy,
morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolidinyl, oxetan-3-yl or dioxolyl,
is optionally substituted independently with 1-5 substituents of F, Cl, CN, N0₂, NH₂, OH,
butyl, methoxy, ethyl, ethoxy, CH₃CF₃, CH₂CH₂F₂, propyl, prooxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxy, cyclobutyl, isobutoxy, tert-butoxy, isobutyl, sec-butyl, tert-butyl, cyclopentyl, cyclohexyl, Cl₆alkylamino-, Cl₆dialkylamino, Cthioalkoxyl
tetrahydropyranyl, tetrahydropyrrolyl or oxetan-3yl.

In embodiment 35, the invention provides compounds according to any one of embodiments 25-33, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R⁹ is a ring selected from pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrazolyl, pyrazolo[3,4-c]pyridinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl or thiényl, wherein the ring is optionally substituted with 1-5 substituents of R¹⁰.

In embodiment 36, the invention provides compounds according to any one of embodiments 25-35 or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R⁹ is

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R¹⁰
N
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; and

each R¹⁰, independently, is H, F, Cl, Br, CF₃, CHF₂, CH₂F, CN, OH,

-C(0)NHCH₃, cyclopropylmethoxy, 2-propynoxy, 2-butyloxy, 2-butynoxy, Cl₆alkyl, C₂₆alkenyl, C₇₆alkynyl, C₃₆Cycloalkyl, Cl₆alkoxy or Cl₆thioalkoxy, wherein each of the cyclopropylmethoxy, 2-propynoxy, 2-butynoxy, Cl₆alkyl, C₂₆alkenyl, C₇₆alkynyl, C₃₆cycloalkyl, Cl₆alkoxy and Cl₆thioalkoxy is optionally substituted independently with 1-5 substituents of F, Cl, CN, N0₂, NH₂, OH, oxo, CF₃, CHF₂, CH₂F, methyl, methoxy, ethyl, ethoxy, CH₃CF₃, CH₂CH₂F₂, propyl, prooxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxy, cyclobutyl, isobutoxy, tert-butoxy, isobutyl, sec-butyl, tert-butyl, Cl₆alkylamino-, Cl₆dialkylamino, Cl₆thioalkoxyl, oxazolyl or thiazolyl.

In embodiment 37, the invention provides compounds according to any one of embodiments 25-36, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R¹ is CHF₂; and R⁹ is
each $R_{10}$, independently, is $H$, $F$, $Cl$, $Br$, $CH_3$, $CHF_2$, $CH_2F$, $CN$, 2-propynloxy, 2-butyloxy or $C_2$alkoxy, wherein the $C_2$alkoxy is optionally substituted independently with 1-5 substituents of $F$, $Cl$, methyl, methoxy, ethyl, ethoxy, oxazolyl or thiazolyl.

In embodiment 38, the invention provides compounds according to any one of embodiments 25-36, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein $R_3$ is $CH_2F$; and $R_9$ is

each $R_{10}$, independently, is $H$, $F$, $Cl$, $Br$, $CH_3$, $CHF_2$, $CH_2F$, $CN$, 2-propynloxy, 2-butyloxy or $C_2$alkoxy, wherein the $C_2$alkoxy is optionally substituted independently with 1-5 substituents of $F$, $Cl$, methyl, methoxy, ethyl, ethoxy, oxazolyl or thiazolyl.

In embodiment 39, the invention provides compounds according to any one of embodiments 25-36, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein $R_3$ is $CHF_2$; and $R_9$ is

each $R_{10}$, independently, is $H$, $F$, $Cl$, $Br$, $CH_3$, $CHF_2$, $CH_2F$, $CN$, 2-propynloxy, 2-butyloxy or $C_2$alkoxy, wherein the $C_2$alkoxy is optionally substituted independently with 1-5 substituents of $F$, $Cl$, methyl, methoxy, ethyl, ethoxy, oxazolyl or thiazolyl.

In embodiment 40, the invention provides compounds according to any one of embodiments 25-36, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein $R_3$ is $CH_2F$; and $R_9$ is
each R\textsuperscript{10}, independently, is H, F, Cl, Br, CH\textsubscript{3}, CHF\textsubscript{2}, CH\textsubscript{2}F, CN, 2-propynloxy, 2-butyloxy or Ci\textsubscript{2}alkoxyl, wherein the Ci\textsubscript{2}alkoxyl is optionally substituted independently with 1-5 substituents of F, Cl, methyl, methoxy, ethyl, ethoxy, oxazolyl or thiazolyl.

In embodiment 41, the invention provides compounds according to any one of embodiments 1-11, 13-18 and 20-21, or a stereoisomer, tautomer, hydrate, solvate or pharmaceutically acceptable salt thereof, having a Formula II-B:

![Formula II-B](image)

wherein

A\textsuperscript{4} is CR\textsuperscript{4}, wherein R\textsuperscript{4} is H, F or Cl;
A\textsuperscript{5} is CR\textsuperscript{5} or N, wherein R\textsuperscript{5} is H, F, Cl or CH\textsubscript{3};
A\textsuperscript{6} is CH;
A\textsuperscript{8} is CR\textsuperscript{8} or N, wherein R\textsuperscript{8} is H or F,

provided that no more than one of A\textsuperscript{5} and A\textsuperscript{8} is N;

each of R\textsuperscript{4} and R\textsuperscript{5}, independently, is H or F;

each of R\textsuperscript{1} and R\textsuperscript{2}, independently, is H or F;

R\textsuperscript{3} is CH\textsubscript{3}, CF\textsubscript{3}, CH\textsubscript{2}F or CHF\textsubscript{2};

R\textsuperscript{9} is a fully unsaturated 5- or 6-membered monocyclic or 8-, 9- or 10-membered bicyclic ring formed of carbon atoms, said ring optionally including 1-4 heteroatoms if monocyclic or 1-5 heteroatoms if bicyclic, said heteroatoms selected from O, N or S, wherein the ring is optionally substituted, independently, with 1-5 substituents of R\textsuperscript{10}; and

each R\textsuperscript{10}, independently, is H, halo, haloalkyl, CN, OH, NO\textsubscript{2}, NH\textsubscript{2}, SF\textsubscript{3}, acetyl, C(0)NHCH\textsubscript{3}, oxo, cyclopropylmethoxy, 2-butyloxy, Ci\textsubscript{2}alkyl, C\textsubscript{2}alkenyl, C\textsubscript{2}alkynyl, C\textsubscript{3}cycloalkyl, Ci\textsubscript{2}alkylamino-, Ci\textsubscript{2}dialkylamino-, Ci\textsubscript{2}alkoxyl, Ci\textsubscript{2}thioalkoxyl,
morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolyl, pyrrolidinyl, tetrahydropyrrolyl, piperazinyl, oxetan-3-y1, imidazo-pyridinyl or dioxyol, wherein each of the cyclopropylmethoxy, 2-butynoxy, C₅alkyl, C₂₋₅alkenyl, C₂₋₅alkynyl, C₃₋₅alkylamino-, C₅₋₁₀alkyloxy, dialkylamino-, cyclopropylmethoxy, isobutoxy, isopropoxy, tert-butoxy, isobutoxy, tert-butoxy, isobutoxy, tert-butoxy, cyclohexyl, cyclopentyl, cyclohexyl, tert-butyl, tert-butyl, tert-butyl, tert-butyl, tert-butyl, cyclohexyl, C₅₋₁₀alkyloxy, C₅₋₁₀alkylamino-, C₅₋₁₀alkyloxy, 1,3-dialkylamino, 1,3-thioalkoxyl, tetrahydropyranyl, tetrahydropyranyl or oxetan-3-y1; and each W, independently, is CH, CF, CC1, CCH₃ or N.

In embodiment 42, the invention provides compounds according to embodiment 40, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each of R¹, R², R³ and R⁴, independently, is H.

In embodiment 43, the invention provides compounds according to any one of embodiments 41 and 42, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R³ is CH₃, CH₂F or CHF₂.

In embodiment 44, the invention provides compounds according to any one of embodiments 41-43, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R³ is CH₂F or CHF₂.

In embodiment 45, the invention provides compounds according to any one of embodiments 41-44, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R³ is CH₃F.

In embodiment 46, the invention provides compounds according to any one of embodiments 41-44, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R³ is CHF₂.

In embodiment 47, the invention provides compounds according to any one of embodiments 41-46, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein A¹ is CF or CC1;

A⁵ is CH, CF, CH₃ or N;
A⁶ is CH; and
A⁸ is CH.

In embodiment 48, the invention provides compounds according to any one of
embodiments 41-47, or a stereoisomer or pharmaceutically acceptable salt thereof,
wherein A^4 is CF;
    A^5 is CH, CF or N;
    A^6 is CH; and
    A^8 is CH.

In embodiment 49, the invention provides compounds according to any one of
embodiments 41-47, or a stereoisomer or pharmaceutically acceptable salt thereof,
wherein A^4 is CCl;
    A^5 is CH or CF;
    A^6 is CH; and
    A^8 is CH.

In embodiment 50, the invention provides compounds according to any one of
embodiments 41-49 or a stereoisomer or pharmaceutically acceptable salt thereof,
wherein

\[
\begin{align*}
\text{each } R^{10}, \text{ independently, is H, F, Cl, Br, }\text{CH}_3, \text{CHF}_2, \text{CH}_2F, \text{CN, 2-propynloxy,}
\text{2-butyloxy or C}^\text{alkoxyl, wherein the C}^\text{alkoxyl is optionally substituted}
\text{independently with 1-5 substituents of F, Cl, methyl, methoxy, ethyl, ethoxy, oxazolyl or}
\text{thiazolyl.}
\end{align*}
\]

In embodiment 51, the invention provides compounds, including stereoisomers,
tautomers, hydrates, solvates and pharmaceutically acceptable salts thereof, which are
generally defined by Formula III:
wherein

\[ \text{A}_4 \text{ is CR}_4 \text{ or N}; \]
\[ \text{A}_5 \text{ is CR}_5 \text{ or N}; \]
\[ \text{A}_6 \text{ is CR}_6 \text{ or N}; \]
\[ \text{A}_8 \text{ is CR}_8 \text{ or N}, \text{ provided that no more than two of } \text{A}_4, \text{A}_5, \text{A}_6 \text{ and } \text{A}_8 \text{ is N}; \]
\[ \text{each of } \text{R}^4 \text{ and } \text{R}^5, \text{ independently, is H, F, CH}_3, \text{CH}_2\text{F, CHF}_2 \text{ or CF}_3; \]
\[ \text{each of } \text{R}^1 \text{ and } \text{R}^2, \text{ independently, is H, F, CH}_3, \text{CH}_2\text{F, CHF}_2 \text{ or CF}_3; \]
\[ \text{R}^3 \text{ is CH}_3, \text{CF}_3, \text{CH}_2\text{F or CHF}_2; \]
\[ \text{each of } \text{R}^4, \text{R}^5, \text{R}^6 \text{ and } \text{R}^8, \text{ independently, is H, F, CI or CH}_3; \]
\[ \text{R}^7 \text{ is } -\text{NH-C(=0)-R}_9 \text{ or } \]
\[ \text{R}^7 \text{ is } \]

wherein \( V \) is NR\(^{10} \), O or S; and

\[ \text{each } \text{W}, \text{ independently, is CH, CF, CCl, CCH}_3 \text{ or N}; \]

\[ \text{R}^9 \text{ is a ring selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, pyrazinyl, pyrazolo[3,4-c]pyridinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl or thienyl, wherein the ring is optionally substituted with 1-5 substituents of } \text{R}^{10}; \text{ and } \]

\[ \text{each } \text{R}^{10}, \text{ independently, is H, halo, haloalkyl, CN, OH, NO}_2, \text{NH}_2, \text{SF}_3, \text{acetyl, } \]
\[ \text{-C(0)NHCH}_3, \text{oxo, cyclopropylmethoxy, 2-buturyloxy, } \text{Cl}_1\text{-alkyl, C}_2\text{-alkenyl, C}_2\text{-alkynyl, C}_3\text{-cycloalkyl, Cl}_1\text{-alkylamino, C}_2\text{-dialkylamino, } \text{Cl}_3\text{-alkoxy, Cl}_6\text{thioalkoxy, morpholinyl, pyrazolyl, isoxazolyl, dihydropryranyl, pyrrolyl, pyrrolidinyl, tetrahydropryrollyl, piperazinyl, oxetan-3-yl, imidazo-pyridinyl or dioxolyl, wherein each } \]

\[ \text{of the cyclopropylmethoxy, 2-buturyloxy, CI1-alkyl, C2-alkenyl, C2-alkynyl, C3-} \]
In embodiment 52, the invention provides compounds including stereoisomers, tautomers, hydrates, solvates and pharmaceutically acceptable salts thereof, according to embodiment 51, which are generally defined by Formula III-A:

![Diagram](attachment:image.png)

wherein

- \( A^4 \) is \( \text{CR}^4 \), wherein \( \text{R}^4 \) is H, F or Cl;
- \( A^5 \) is \( \text{CR}^5 \) or N, wherein \( \text{R}^5 \) is H, F, Cl or CH\(_3\);
- \( A^6 \) is CH;
- \( A^8 \) is \( \text{CR}^8 \) or N, wherein \( \text{R}^8 \) is H or F, provided that no more than one of \( A^5 \) and \( A^8 \) is N;

- each of \( \text{R}^4 \) and \( \text{R}^5 \), independently, is H or F;
- each of \( \text{R}^1 \) and \( \text{R}^2 \), independently, is H or F;
- \( \text{R}^3 \) is CH\(_3\), CH\(_2\)F or CHF\(_2\);
- \( \text{R}^9 \) is a ring selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, pyrazolyl, pyrazolo[3,4-c]pyridinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl or thienyl, wherein the ring is optionally substituted with 1-5 substituents of \( \text{R}^{10} \); and

- each \( \text{R}^{10} \), independently, is H, halo, haloalkyl, CN, OH, NO\(_2\), NH\(_2\), SF\(_3\), acetyl, -C(0)NHCH\(_3\), oxo, cyclopropylmethoxy, 2-butylnoxy, Si-alkyl, C\(_2\)-alkenyl, C\(_2\)-alkynyl, C\(_3\)-cycloalkyl, C\(_{1-6}\)alkylamino-, C\(_{1-6}\)dialkylamino-, C\(_{1-6}\)alkoxy, C\(_{1-6}\)thioalkoxy, morpholinyl, pyrazolyl, isoxazolyl, dihydropryanyl, pyrrolyl, pyrrolidinyl, tetrahydropryrolyl, piperazinyl, oxetan-3-yl, imidazo-pyridinyl or dioxolyl, wherein each
of the cyclopropylmethoxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxy, C_{1-6}thioalkoxy, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolidinyl, oxetan-3-yl or dioxolyl, is optionally substituted independently with 1-5 substituents of F, Cl, CN, N\textsubscript{0}, NH\textsubscript{2}, OH, oxo, CF\textsubscript{3}, CHF\textsubscript{2}, CH\textsubscript{2}F, methyl, methoxy, ethyl, ethoxy, CH\textsubscript{2}CF\textsubscript{3}, CH\textsubscript{2}CHF\textsubscript{2}, propyl, propoxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxy, cyclobutyl, isobutoxy, tert-butoxy, isobutyl, sec-butyl, tert-butyl, cyclopentyl, cyclohexyl, C\textsubscript{1-6}alkylamino-, C\textsubscript{1-6}dialkylamino, C\textsubscript{1-6}thioalkoxyl tetrahydropyranyl, tetrahydropropylyoxy or oxetan-3yl.

In embodiment 53, the invention provides compounds according to any one of embodiments 51-52 or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R\textsuperscript{9} is

![Chemical structure](image)

; and

each R\textsuperscript{10}, independently, is H, F, Cl, Br, CF\textsubscript{3}, CHF\textsubscript{2}, CH\textsubscript{2}F, CN, OH, -C(0)NHCH\textsubscript{3}, cyclopropylmethoxy, 2-propynyloxy, 2-butyloxy, C\textsubscript{1-6}alkyl, C\textsubscript{2-6}alkenyl, C\textsubscript{1-6}cycloalkyl, C\textsubscript{1-6}alkoxy, or C\textsubscript{1-6}thioalkoxy, wherein each of the cyclopropylmethoxy, 2-propynyloxy, 2-butyloxy, C\textsubscript{1-6}alkyl, C\textsubscript{2-6}alkenyl, C\textsubscript{1-6}cycloalkyl, C\textsubscript{1-6}alkoxy and C\textsubscript{1-6}thioalkoxy is optionally substituted independently with 1-5 substituents of F, Cl, CN, N\textsubscript{0}, NH\textsubscript{2}, OH, oxo, CF\textsubscript{3}, CHF\textsubscript{2}, CH\textsubscript{2}F, methyl, methoxy, ethyl, ethoxy, CH\textsubscript{2}CF\textsubscript{3}, CH\textsubscript{2}CHF\textsubscript{2}, propyl, propoxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxy, cyclobutyl, isobutoxy, tert-butoxy, isobutyl, sec-butyl, tert-butyl, C\textsubscript{1-3}alkylamino-, C\textsubscript{1-3}dialkylamino, C\textsubscript{1-3}thioalkoxyl oxazolyl or thiazolyl.

In embodiment 54, the invention provides compounds according to any one of embodiments 51-53, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R\textsuperscript{1} is CHF\textsubscript{2}; and R\textsuperscript{9} is

![Chemical structure](image)

; and

each R\textsuperscript{10}, independently, is H, F, Cl, Br, CH\textsubscript{3}, CHF\textsubscript{2}, CH\textsubscript{2}F, CN, 2-propynyloxy, 2-butyloxy or C\textsubscript{1-6}alkoxy, wherein the C\textsubscript{1-6}alkoxy is optionally substituted
independently with 1-5 substituents of F, Cl, methyl, methoxy, ethyl, ethoxy, oxazolyl or thiazolyl.

In embodiment 55, the invention provides compounds according to any one of embodiments 51-53, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R³ is CH₂F; and R⁹ is

![Chemical Structure](image)

each R¹⁰, independently, is H, F, Cl, Br, CH₃, CHF₂, CH₂F, CN, 2-propynyl, 2-butynyl, or Ci₂alkoxyl, wherein the Ci₂alkoxyl is optionally substituted independently with 1-5 substituents of F, Cl, methyl, methoxy, ethyl, ethoxy, oxazolyl or thiazolyl.

In embodiment 56, the invention provides compounds according to any one of embodiments 51-53 or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R³ is CHF₂; and R⁹ is

![Chemical Structure](image)

each R¹⁰, independently, is H, F, Cl, Br, CH₃, CHF₂, CH₂F, CN, 2-propynyl, 2-butynyl, or Ci₂alkoxyl, wherein the Ci₂alkoxyl is optionally substituted independently with 1-5 substituents of F, Cl, methyl, methoxy, ethyl, ethoxy, oxazolyl or thiazolyl.

In embodiment 57, the invention provides compounds according to any one of embodiments 51-53, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R³ is CH₂F; and R⁹ is

![Chemical Structure](image)

each R¹⁰, independently, is H, F, Cl, Br, CH₃, CHF₂, CH₂F, CN, 2-propynyl, 2-butynyl, or Ci₂alkoxyl, wherein the Ci₂alkoxyl is optionally substituted independently with 1-5 substituents of F, Cl, methyl, methoxy, ethyl, ethoxy, oxazolyl or thiazolyl.
In embodiment 58, the invention provides compounds, including stereoisomers, tautomers, hydrates, solvates and pharmaceutically acceptable salts thereof, which are generally defined by Formula III-B:

$$\text{III-B}$$

wherein

- $A^4$ is CR$^4$, wherein $R^4$ is H, F or Cl;
- $A^5$ is CR$^5$ or N, wherein $R^5$ is H, F, Cl or CH$_3$;
- $A^6$ is CH;
- $A^8$ is CR$^8$ or N, wherein $R^8$ is H or F, provided that no more than one of $A^5$ and $A^8$ is N;
- each of $R^a$ and $R^b$, independently, is H or F;
- each of $R^1$ and $R^2$, independently, is H or F;
- $R^3$ is CH$_3$, CH$_2$F or CHF$_2$;

where each $R^{10}$, independently, is H, F, Cl, Br, CH$_3$, CHF$_2$, CH$_2$F, CN, 2-propynloxy, 2-butyloxy or C$_i$-alkoxyl, wherein the C$_i$-alkoxyl is optionally substituted independently with 1-5 substituents of F, Cl, methyl, methoxy, ethyl, ethoxy, oxazolyl or thiazolyl.
In embodiment 59, the invention provides compounds of formula III-A-1, or a pharmaceutically acceptable salt or tautomer thereof,

![Chemical Structure](III-A-1)

wherein, $\text{A}^4$ is CF;

$\text{A}^5$ is CH, CF, CC1, CCH$_3$ or N;

$\text{A}^6$ is CH;

$\text{A}^8$ is CH or N, provided that no more than one of $\text{A}^5$ and $\text{A}^8$ is N;

each of $\text{R}^4$ and $\text{R}^5$, independently, is H;

each of $\text{R}^1$ and $\text{R}^2$, independently, is H or F;

$\text{R}^3$ is CH$_3$, CH$_2$F or CHF$_2$;

W is CR$_{10}$ or N; and

each $\text{R}^{10}$, independently, is H, halo, haloalkyl, CN, OH, N0$_2$, NH$_2$, SF$_5$, acetyl, -C(0)NHCH$_3$, oxo, cyclopropylmethoxy, 2-butynoxy, Ci$_a$alkyl, C$_2$alkenyl, C$_2$-alkynyl, C$_3$-cycloalkyl, Ci$_a$alkylamino, Ci$_a$alkylamino-, Ci$_a$alkoxy, Ci$_a$thioalkoxy, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolyl, pyrrolidinyl, tetrahydropyrrolyl, piperazinyl, oxetan-3-yl, imidazo-pyridinyl or dioxyol, wherein each of the cyclopropylmethoxy, 2-butynoxy, C$_1$alkyl, C$_2$alkenyl, C$_2$alkynyl, C$_3$. $\delta$Cycloalkyl, C$_1$alkylamino-, C$_1$alkylamino-, C$_1$alkoxy, C$_a$thioalkoxy, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolidinyl, oxetan-3-yl or dioxyol, is optionally substituted independently with 1-5 substituents of F, Cl, CN, N0$_2$, NH$_2$, OH, oxo, CF$_3$, CHF$_2$, CH$_2$F, methyl, methoxy, ethyl, ethoxy, CH$_2$CF$_3$, CH$_2$CHF$_2$, propyl, propoxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxy, cyclobutyl, isobutoxy, tert-butoxy, isobutyl, sec-butyl, tert-butyl, cyclopentyl, cyclohexyl, C$_1$alkylamino-., Ci$_a$

In embodiment 60, the invention provides compounds of formula III-A-2, or a pharmaceutically acceptable salt or tautomer thereof,
wherein

A_4 is CF or CCl;

A_5 is CH, CF, CCl, CCH_3 or N;

A_8 is CH or N, provided no more than one of A_5 and A_8 is N;

R_3 is CH_3, CH_2F or CHF_2;

W is CH or N; and

each R_{10}, independently, is H, F, Cl, Br, CH_3, CHF_2, CH_2F, CN, 2-propynoxy, 2-butynoxy or C_{i_2}alkoxyl, wherein the C_{i_2}alkoxyl is optionally substituted independently with 1-5 substituents of F, Cl, methyl, methoxy, ethyl, ethoxy, oxazolyl or thiazolyl.

In embodiment 61, the invention provides compounds according to any one of embodiments 59-60, or a stereoisomer or pharmaceutically acceptable salt thereof,

wherein R_3 is CHF_2.

In embodiment 62, the invention provides compounds according to any one of embodiments 59-60, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R_3 is CH_2F.

In embodiment 63, the invention provides compounds according to any one of embodiments 59-62, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein W is CH.

In embodiment 64, the invention provides compounds according to any one of embodiments 59-62, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein W is N.

In embodiment 65, the invention provides compounds according to any one of embodiments 59-64, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each R_{10}, independently, is H, F, Cl, Br, CH_3, CHF_2, CH_2F, CN, 2-propynoxy, 2-butynoxy or C_{i_2}alkoxyl, wherein the C_{i_2}alkoxyl is optionally substituted independently with 1-5 substituents of F, oxazolyl or thiazolyl.
In embodiment 66, the invention provides compounds according to any one of embodiments 59-65, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each R^\(15\), independently, is H, F, Cl, Br, CH\(_3\), CHF\(_2\), CH\(_2\)F, CN, 2-propynloxy, 2-butyloxy, -OCHF\(_2\) or -OCH\(_3\).

In embodiment 67, the invention provides compounds according to any one of embodiments 59-66, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein A\(^8\) is CH.

In embodiment 68, the invention provides compounds according to any one of embodiments 59-67, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein A\(^5\) is CH, CF, CC1, CCH\(_3\) or N.

In embodiment 69, the invention provides compounds of formula III-A-3, or a pharmaceutically acceptable salt or tautomer thereof,

![III-A-3](image)

wherein

A\(^5\) is CH, CF, CC1, CCH\(_3\) or N;

R\(^3\) is CH\(_3\), CH\(_2\)F or CHF\(_2\);

W is CH or N; and

each R\(^{10}\), independently, is H, F, Cl, Br, CH\(_3\), CHF\(_2\), CH\(_2\)F, CN, 2-propynloxy, 2-butyloxy or C\(_i\)\(_2\)alkoxyl, wherein the C\(_i\)\(_2\)alkoxyl is optionally substituted independently with 1-5 substituents of F, Cl, methyl, methoxy, ethyl, ethoxy, oxazolyl or thiazolyl.

In embodiment 70, the invention provides compounds according to any one of
embodiment 69, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^3 is CHF_2.

In embodiment 71, the invention provides compounds according to any one of embodiments 69, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^3 is CH.

In embodiment 72, the invention provides compounds according to any one of embodiments 69-71, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein W is CH.

In embodiment 73, the invention provides compounds according to any one of embodiments 69-71, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein W is N.

In embodiment 74, the invention provides compounds according to any one of embodiments 69-74, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each R^6, independently, is H, F, Cl, Br, CH_3, CHF_2, CH_2F, CN, 2-propynyloxy, 2-butynyloxy or Cl_2alkoxyl, wherein the Cl_2alkoxyl is optionally substituted independently with 1-5 substituents of F, oxazolyl or thiazolyl.

In embodiment 75, the invention provides compounds according to any one of embodiments 69-75, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each R^6, independently, is H, F, Cl, Br, CH_3, CHF_2, CH_2F, CN, 2-propynyloxy, 2-butynyloxy, -OCHF_2 or -OCH_3.

In embodiment 77, the invention provides compounds according to any one of embodiments 69-76, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein A^5 is CH, CF, CCH_3 or N.

In embodiment 78, the invention provides compounds according to any one of embodiments 69-77, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein A^5 is CH, CF or N.

In embodiment 79, the invention provides compounds according to any one of embodiments 69-78, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein A^5 is CH or N.

In embodiment 80, the invention provides compounds according to any one of embodiments 69-79, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein A^5 is CH.

In embodiment 81, the invention provides compounds according to any one of
embodiments 69-79, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein A₅ is N.

Similarly, the invention provides compounds of sub-formulas III-C, III-D, III-E and III-F, respectively, as described below.

III-C

III-D

III-E

and

III-F

in conjunction with any of the above or below embodiments, including those described in embodiments A, A-1 to A-4, B, B-1 to B-10, C, C-1 to C-10, D, D-1 to D-4, E, E-1 to E-4, F, F-1 to F-4, G, G-1 to G-4, H, H-1 to H-4, I, I-1 to I-9, J, J-1 to J-8, K, K-1 to K-2, L, M, N-1 to N-2, O-1 to O-2, P-1 to P-2, Q and Q-1 to Q-2 described herein.

The present invention contemplates that the various different embodiments of Formulas I, II and III, and sub-Formulas I-A, I-B, I-C and III-A through III-F thereof, described herein, may comprise the following embodiments with respect to individual variables of A₄, A₅, A₆, A₈, R₁, R₂, R₇, V and W, where applicable, as described below. Hence, these embodiments with respect to individual variables A₄, A₅, A₆, A₈, R₁, R₂, R₇, V and W where applicable, may be applied "in conjunction with any of the other [above and below] embodiments" to create various embodiments of general Formulas I, II and III, and each sub-formula thereof, which are not literally or identically described herein. More specifically, the term "in conjunction with any of the above or below embodiments" includes embodiments A, A-1 to A-4, B, B-1 to B-10, C, C-1 to C-10, D, D-1 to D-4, E, E-1 to E-4, F, F-1 to F-4, G, G-1 to G-4, H, H-1 to H-4, I, I-1 to I-9, J, J-1 to J-9, K, K-1 to K-2, L, M, N-1 to N-2, O-1 to Q-2, P-1 to P-2, Q and Q-1 to Q-2
described herein, as it applies to general Formulas I, II and III, and sub-formulas I-A, I-B and I-C and III-A through III-F, also described herein.

In another embodiment A, the invention includes compounds wherein each of \( R^a \) and \( R^b \), independently, is H, F, Cl, \( C_{i \geq 6} \)-alkyl, \( C_{i \geq 4} \)-alkenyl, \( C_{i \geq 4} \)-alkynyl, CN, -CH\(_2\)OC\(_i \geq 6\)-alkyl, -OC\(_i \geq 6\)-alkyl, -S(0)\(_i \geq 6\)-alkyl, -NHC\(_i \geq 6\)-alkyl or -C(0)\(_i \geq 6\)-alkyl, wherein each of the \( C_i \)-alkyl, \( C_{i \geq 6} \)-alkenyl, \( C_{i \geq 4} \)-alkynyl, and \( C_{i \geq 6} \)-alkyl portion of -CH\(_2\)OC\(_i \geq 6\)-alkyl, -OC\(_i \geq 6\)-alkyl, -S(0)\(_i \geq 6\)-alkyl, -NHC\(_i \geq 6\)-alkyl and -C(0)\(_i \geq 6\)-alkyl are optionally substituted with 1-4 substituents of F, oxo or OH, in conjunction with any of the above or below embodiments.

In another embodiment A-1, the invention includes compounds wherein each of \( R^a \) and \( R^b \), independently, is H, F, Cl, CF\(_3\), OCF\(_3\), methyl, ethyl, CN, OH, OCH\(_3\), SCH\(_3\), NHCH\(_3\), C(0)CH\(_3\) or CH\(_2\)OCHF\(_2\), in conjunction with any of the above or below embodiments.

In another embodiment A-2, the invention includes compounds wherein each of \( R^a \) and \( R^b \), independently, is H, F, CF\(_3\), CH\(_3\), CF\(_2\)H or CH\(_2\)F, in conjunction with any of the above or below embodiments.

In another embodiment A-3, the invention includes compounds wherein \( R^1 \) is H or F, in conjunction with any of the above or below embodiments.

In another embodiment A-4, the invention includes compounds wherein \( R^1 \) is H, in conjunction with any of the above or below embodiments.

In another embodiment B, the invention includes compounds wherein \( R^1 \) is H, F, Cl, \( C_i \)-alkyl, \( C_{i \geq 6} \)-alkenyl, \( C_{i \geq 4} \)-alkynyl, CN, -CH\(_2\)OC\(_i \geq 6\)-alkyl, -OC\(_i \geq 6\)-alkyl, -S(0)\(_i \geq 6\)-alkyl, -NHC\(_i \geq 6\)-alkyl or -C(0)\(_i \geq 6\)-alkyl, wherein each of the \( C_i \)-alkyl, \( C_{i \geq 6} \)-alkenyl, \( C_{i \geq 4} \)-alkynyl, and \( C_{i \geq 6} \)-alkyl portion of -CH\(_2\)OC\(_i \geq 6\)-alkyl, -OC\(_i \geq 6\)-alkyl, -S(0)\(_i \geq 6\)-alkyl, -NHC\(_i \geq 6\)-alkyl and -C(0)\(_i \geq 6\)-alkyl are optionally substituted with 1-4 substituents of F, oxo or OH, in conjunction with any of the above or below embodiments.

In another embodiment B-1, the invention includes compounds wherein \( R^1 \) is H, F, Cl, \( C_{i \geq 4} \)-alkenyl, \( C_{i \geq 4} \)-alkynyl, CN, -CH\(_2\)OC\(_i \geq 3\)-alkyl, -OC\(_i \geq 3\)-alkyl, wherein each of the \( C_{i \geq 4} \)-alkenyl, \( C_{i \geq 4} \)-alkynyl and \( C_{i \geq 3} \)-alkyl portion of -CH\(_2\)OC\(_i \geq 3\)-alkyl and -OC\(_i \geq 3\)-alkyl are optionally substituted with 1-4 substituents of F, in conjunction with any of the above or below embodiments.

In another embodiment B-2, the invention includes compounds wherein \( R^1 \) is H, F, Cl, CF\(_3\), OCF\(_3\), methyl, ethyl, CN, OH, OCH\(_3\), SCH\(_3\), NHCH\(_3\), C(0)CH\(_3\) or CH\(_2\)OCHF\(_2\), in conjunction with any of the above or below embodiments.
In another embodiment B-3, the invention includes compounds wherein $R^1$ is H, F, CH$_3$, C$_2$H$_5$, CF$_3$, CH$_2$F, CH$_2$OCH$_2$F, CH$_2$OCF$_2$H or CH$_2$OCF$_3$, in conjunction with any of the above or below embodiments.

In another embodiment B-4, the invention includes compounds wherein $R^1$ is H, F, Cl, CF$_3$, CH$_3$, CF$_2$H or CH$_2$F, in conjunction with any of the above or below embodiments.

In another embodiment B-5, the invention includes compounds wherein $R^1$ is H, F, CF$_3$, or CH$_3$, in conjunction with any of the above or below embodiments.

In another embodiment B-6, the invention includes compounds wherein $R^1$ is H, F or CF$_3$, in conjunction with any of the above or below embodiments.

In another embodiment B-7, the invention includes compounds wherein $R^1$ is H or F, in conjunction with any of the above or below embodiments.

In another embodiment B-8, the invention includes compounds wherein $R^1$ is H, in conjunction with any of the above or below embodiments.

In another embodiment B-9, the invention includes compounds wherein $R^1$ is F, in conjunction with any of the above or below embodiments.

In another embodiment B-10, the invention includes compounds wherein $R^1$ is CF$_3$, in conjunction with any of the above or below embodiments.

In another embodiment C, the invention includes compounds wherein $R^2$ is H, F, Cl, Ci-e-alkyl, C$_2$-alkenyl, C$_2$-alkynyl, CN, -CH$_2$OCi$_6$-alkyl, -OCi$_6$-alkyl, -S(0)$_3$Ci$_6$-alkyl, -NHCi$_6$-alkyl or -C(0)Cl$_6$-alkyl, wherein each of the Ci$_6$-alkyl, C$_2$-alkenyl, C$_2$-alkynyl, and Ci-6-alkyl portion of -CH$_2$OCi$_6$-alkyl, -OCi$_6$-alkyl, -S(0)$_3$Ci$_6$-alkyl, -NHCi$_6$-alkyl and -C(0)Cl$_6$-alkyl are optionally substituted with 1-4 substituents of F, oxo or OH, in conjunction with any of the above or below embodiments.

In another embodiment C-1, the invention includes compounds wherein $R^2$ is H, F, Cl, C$_2$-alkenyl, C$_2$-alkynyl, CN, -CH$_2$OCi$_3$-alkyl, -OCi$_3$-alkyl, wherein each of the C$_2$-alkenyl, C$_2$-alkynyl and Ci$_3$-alkyl portion of -CH$_2$OCi$_3$-alkyl and -OCi$_3$-alkyl are optionally substituted with 1-4 substituents of F, in conjunction with any of the above or below embodiments.

In another embodiment C-2, the invention includes compounds wherein $R^2$ is H, F, Cl, CF$_3$, OCF$_3$, methyl, ethyl, CN, OH, OCH$_3$, SCH$_3$, NHCH$_3$, Cl(0)CH$_3$ or CH$_2$OCHF$_2$, in conjunction with any of the above or below embodiments.

In another embodiment C-3, the invention includes compounds wherein $R^2$ is H,
In another embodiment C-4, the invention includes compounds wherein R₂ is H, F, Cl, CF₃, CH₃, CF₂H or CH₂F, in conjunction with any of the above or below embodiments.

In another embodiment C-5, the invention includes compounds wherein R₁ is H, F, CF₃, CH₃, CF₂H or CH₂F, in conjunction with any of the above or below embodiments.

In another embodiment C-6, the invention includes compounds wherein R₁ is H, F or CF₃, in conjunction with any of the above or below embodiments.

In another embodiment C-7, the invention includes compounds wherein R₂ is H or F, in conjunction with any of the above or below embodiments.

In another embodiment C-8, the invention includes compounds wherein R₂ is H, in conjunction with any of the above or below embodiments.

In another embodiment C-9, the invention includes compounds wherein R₂ is F, in conjunction with any of the above or below embodiments.

In another embodiment C-10, the invention includes compounds wherein R₂ is CF₃, in conjunction with any of the above or below embodiments.

In another embodiment D, the invention includes compounds wherein R₁ is Ci₃alkyl, CH₂OCi₃alkyl, CH₂OH, Ci₃h haloalkyl or cyclopropyl, wherein each of the Ci₃alkyl, CH₂OCi₃alkyl, Ci₃h haloalkyl and cyclopropyl is optionally substituted with 1-4 F atoms, in conjunction with any of the above or below embodiments.

In another embodiment D-1, the invention includes compounds wherein R₁ is Ci₃alkyl, Ci₃h haloalkyl, CH₂OH, CH₂OCHF₂ or cyclopropyl, wherein each of the Ci₃alkyl, Ci₃h haloalkyl and cyclopropyl is optionally substituted with 1-4 F atoms, in conjunction with any of the above or below embodiments.

In another embodiment D-2, the invention includes compounds wherein R₁ is Ci₃alkyl, CH₂OH, CH₂OCH₂F, CH₂OCF₂H, or cyclopropyl, wherein each of the Ci₃alkyl and cyclopropyl is optionally substituted with 1-2 F atoms, in conjunction with any of the above or below embodiments.

In another embodiment D-3, the invention includes compounds wherein R₃ is CH₃, CF₃, C₂H₅, CF₂H or CH₂F, in conjunction with any of the above or below embodiments.

In another embodiment D-4, the invention includes compounds wherein R₃ is CF₃, CH₃, CF₂H or CH₂F, in conjunction with any of the above or below embodiments.
In another embodiment E, the invention includes compounds wherein A^4 is CR^4 wherein R^4 is H, halo, haloalkyl, haloalkoxy, Ci_{i-4}-alkyl, CN, OH, OCl_{i-4}-alkyl, S(0)_{6}Ci_{i-4}-alkyl, NHCl_{i-4}-alkyl or C(0)Cl_{i-4}-alkyl, in conjunction with any of the above or below embodiments.

In another embodiment G-1, the invention includes compounds wherein A^6 is 

wherein R^6 is H, halo, haloalkyl, haloalkoxy, Ci_{i-4}-alkyl, CN, OH, OCl_{i-4}-alkyl, S(0)_{6}Ci_{i-4}-alkyl, NHCl_{i-4}-alkyl or C(0)Cl_{i-4}-alkyl, in conjunction with any of the above or below embodiments.
CR\textsuperscript{6} wherein \( R\textsuperscript{6} \) is H, F, Cl, CF\textsubscript{3}, OCF\textsubscript{3}, methyl, ethyl, CN, OH, OCH\textsubscript{3}, SCH\textsubscript{3}, NHCH\textsubscript{3} or C(0)CH\textsubscript{3}, in conjunction with any of the above or below embodiments.

In another embodiment G-2, the invention includes compounds wherein \( A\textsuperscript{6} \) is CR\textsuperscript{6} wherein \( R\textsuperscript{6} \) is H, F, CF\textsubscript{3}, CF\textsubscript{2}H, CH\textsubscript{2}F or CH\textsubscript{3}, in conjunction with any of the above or below embodiments.

In another embodiment G-3, the invention includes compounds wherein \( A\textsuperscript{6} \) is CR\textsuperscript{6} wherein \( R\textsuperscript{6} \) is H or F, in conjunction with any of the above or below embodiments.

In another embodiment G-4, the invention includes compounds wherein \( A\textsuperscript{6} \) is N, in conjunction with any of the above or below embodiments.

In another embodiment H, the invention includes compounds wherein \( A\textsuperscript{8} \) is CR\textsuperscript{8} wherein \( R\textsuperscript{8} \) is H, halo, haloalkyl, haloalkoxy, Cl\textsubscript{4}-alkyl, CN, OH, OC\textsubscript{4}-alkyl, S(0)\textsubscript{4}Cl\textsubscript{4}-alkyl, NHCl\textsubscript{4}-alkyl or C(0)Cl\textsubscript{4}-alkyl, in conjunction with any of the above or below embodiments.

In another embodiment H-1, the invention includes compounds wherein \( A\textsuperscript{8} \) is CR\textsuperscript{8} wherein \( R\textsuperscript{8} \) is H, F, Cl, CF\textsubscript{3}, OCF\textsubscript{3}, methyl, ethyl, CN, OH, OCH\textsubscript{3}, SCH\textsubscript{3}, NHCH\textsubscript{3} or C(0)CH\textsubscript{3}, in conjunction with any of the above or below embodiments.

In another embodiment H-2, the invention includes compounds wherein \( A\textsuperscript{8} \) is CR\textsuperscript{8} wherein \( R\textsuperscript{8} \) is H, F, CF\textsubscript{3}, CF\textsubscript{2}H, CH\textsubscript{2}F or CH\textsubscript{3}, in conjunction with any of the above or below embodiments.

In another embodiment H-3, the invention includes compounds wherein \( A\textsuperscript{8} \) is CR\textsuperscript{8} wherein \( R\textsuperscript{8} \) is H or F, in conjunction with any of the above or below embodiments.

In another embodiment H-4, the invention includes compounds wherein \( A\textsuperscript{8} \) is N, in conjunction with any of the above or below embodiments.

In another embodiment I, the invention includes compounds wherein no more than two of \( A\textsuperscript{4}, A\textsuperscript{5}, A\textsuperscript{6} \) and \( A\textsuperscript{8} \) is N, in conjunction with any of the above or below embodiments.

In another embodiment I-1, the invention includes compounds wherein no more than one of \( A\textsuperscript{4}, A\textsuperscript{5}, A\textsuperscript{6} \) and \( A\textsuperscript{8} \) is N, in conjunction with any of the above or below embodiments.

In another embodiment I-2, the invention includes compounds wherein \( A\textsuperscript{4} \) is CR\textsuperscript{4}, \( A\textsuperscript{5} \) is CR\textsuperscript{5} or N, \( A\textsuperscript{6} \) is CR\textsuperscript{6} and \( A\textsuperscript{8} \) is CR\textsuperscript{8}, in conjunction with any of the above or below embodiments.

In another embodiment, the invention includes compounds wherein \( A\textsuperscript{4} \) is CR\textsuperscript{4} or
N, A^4 is CR^5, A^6 is CR^6 and A^8 is CR^8, in conjunction with any of the above or below embodiments.

In another embodiment 1-3, the invention includes compounds wherein A^4 is N, A^5 is CR^5, A^6 is CR^6 and A^8 is CR^8, in conjunction with any of the above or below embodiments.

In another embodiment 1-4, the invention includes compounds wherein A^4 is CR^4, A^5 is N, A^6 is CR^6, and A^8 is CR^8, in conjunction with any of the above or below embodiments.

In another embodiment 1-5, the invention includes compounds wherein A^4 is CR^4, A^5 is CR^5, A^6 is CR^6, and A^8 is N, in conjunction with any of the above or below embodiments.

In another embodiment 1-6, the invention includes compounds wherein A^4 is CR^5, A^5 is CR^5, A^6 is CR^6, and A^8 is N, in conjunction with any of the above or below embodiments.

In another embodiment 1-7, the invention includes compounds of of Formulas I, II or III, wherein

A^4 is CR^4 or N;
A^5 is CR^5 or N;
A^6 is CR^6 or N;

A^8 is CR^8 or N, provided that no more than one of A^4, A^5, A^6 and A^8 is N;

each of R^4 and R^6, independently, is H, F, Cl, CF_3, OCF_3, methyl, ethyl, CN, OH, OCH_3, SCH_3, NHCH_3, C(0)CH_3 or CH_2OCHF_2;

each of R^1 and R^2, independently, is H, F, Cl, CF_3, OCF_3, methyl, ethyl, CN, OH, OCH_3, SCH_3, NHCH_3, C(0)CH_3 or CH_2OCHF_2;

R^3 is C_3 alkyl, C_3 haloalkyl, CH_2OH, CH_2OCHF_2 or cyclopropyl; and

each of R^4, R^5, R^6 and R^8, independently, is H, F, Cl, CF_2H, CH_2F, CF_3, OCF_3, methyl, ethyl, CN, OH, OCH_3, SCH_3, NHCH_3 or C(0)CH_3, in conjunction with any of the above or below embodiments.

In another embodiment 1-8, the invention includes compounds of Formulas I, II or III, wherein

A^4 is CR^4;
A^5 is CR^5;
A^6 is CR^6; and
A^8 is CR^8; wherein each of R^4, R^5, R^6, and R^8, independently, is H, F, CF_3, CF_2H, CH_2F or CH_3, in conjunction with any of the above or below embodiments.

In another embodiment 1-9, the invention includes compounds of Formulas I, II or III, wherein A^4 is CH, CF or N, A^5 is CH, CF or N, A^6 is CH, CF or N, A^8 is CH, CF or N, one of A^4, A^5, A^6, and A^8 is N, in conjunction with any of the above or below embodiments.

In another embodiment J, the invention includes compounds of Formulas I, II or III, wherein R^7 is -NH-R^9, -NH-C(=O)-R^9, -C(=O)NH-R^9, -O-R^9, -S-R^9; or R^7 is

wherein V is NR^10, O or S; and
each W, independently, is CH, CF, CCl, CCH_3 or N, in conjunction with any of the above or below embodiments.

In another embodiment J-1, the invention includes compounds of Formulas I, II or III, wherein R^7 is -NH-R^9, -NH-C(=O)-R^9 or

wherein V is NR^10, O or S; and
each W, independently, is CH, CF, CCl, CCH_3 or N, in conjunction with any of the above or below embodiments.

In another embodiment J-2, the invention includes compounds of Formulas I, II or III, wherein R^7 is -NH-C(=O)-R^9 or
wherein \( V \) is \( NR^{10} \), O or S; and

each \( W \), independently, is CH, CF, CCl or N, in conjunction with any of
the above or below embodiments.

In another embodiment J-3, the invention includes compounds of Formulas I, II
or III, wherein \( R^7 \) is \(-NH-C(=0)-R^9\), in conjunction with any of the above or below embodiments.

In another embodiment J-4, the invention includes compounds of Formulas I, II
or III, wherein \( R^7 \) is \(-NH-R^9\), in conjunction with any of the above or below

In another embodiment J-5, the invention includes compounds wherein \( R^7 \) is

wherein \( V \) is \( NR^{10} \), O or S; and

each \( W \), independently, is CH, CF, CCl, CCH\(_3\) or N, in conjunction with
any of
the above or below embodiments.

In another embodiment J-6, the invention includes compounds wherein \( R^7 \) is

wherein \( V \) is \( NR^{10} \), O or S; and

each \( W \), independently, is CH, CF, CCl, CCH\(_3\) or N, in conjunction with any of
the above or below embodiments.
In another embodiment J-7, the invention includes compounds wherein R7 is -NH-R9, -O-R9 or -S-R9, in conjunction with any of the above or below embodiments.

In another embodiment J-8, the invention includes compounds wherein R7 is -O-R9 or -S-R9, in conjunction with any of the above or below embodiments.

In another embodiment J-9, the invention includes compounds wherein R7 is -NH-R9, -O-C(=0)-R9, -C(=0)NH-R9, -O-R9 or -S-R9, wherein R9 is acetyl, C1-6-alkyl, C2-4-alkenyl, C2-4-alkynyl or a fully or partially unsaturated 3-, 4-, 5-, 6- or 7-membered monocyclic or 8-, 9- or 10-membered bicyclic ring formed of carbon atoms, said ring optionally including 1-4 heteroatoms if monocyclic or 1-5 heteroatoms if bicyclic, said heteroatoms selected from O, N or S, wherein the C1-6-alkyl, C2-4-alkenyl, C2-4-alkynyl and ring are optionally substituted, independently, with 1-5 substituents of R10, in conjunction with any of the above or below embodiments.

In another embodiment K, the invention includes compounds wherein R9 is acetyl, C1-6-alkyl, C2-4-alkenyl, C2-4-alkynyl or a fully or partially unsaturated 3-, 4-, 5-, 6- or 7-membered monocyclic or 8-, 9- or 10-membered bicyclic ring formed of carbon atoms, said ring optionally including 1-4 heteroatoms if monocyclic or 1-5 heteroatoms if bicyclic, said heteroatoms selected from O, N or S, wherein the C1-6-alkyl, C2-4-alkenyl, C2-4-alkynyl and ring are optionally substituted, independently, with 1-5 substituents of R10, in conjunction with any of the above or below embodiments.

In another embodiment K-1, the invention includes compounds wherein each R9, independently, is acetyl, C1-6-alkyl, C2-4-alkenyl, C2-4-alkynyl or a ring selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrazolyl, isoxazolyl, thiazolyl, naphthyl, quinolinyl, isoquinolinyl, quinazolinyl, naphthyridinyl, phtalazinyl, pyranyl, dihydropyranyl, tetrahydropranyl, furanyl, dihydrofuranyl, tetrahydrofuranyl, thiaryl, pyrrolyl, pyrrolidinyl, tetrahydropropyryrolyl, pipеридинил, пиперазинил, прополинил, азетидинил, 8-оксо-3-аза-бicyclo[3.2.1]окт-3-ил, аза-бicyclo[2.2.1]пент-5-ил, 2-оксо-7-аза-[3.5]-спиронон-7-ил, циклобутил, цикlopентил и циклохексил, wherein the C1-6-alkyl, C2-4-alkenyl, C2-4-alkynyl and ring are optionally substituted, independently, with 1-5 substituents of R10, in conjunction with any of the above or below embodiments.

In another embodiment K-2, the invention includes compounds wherein each R9 is a ring selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrazolyl, pyrazolo[3,4-c]pyridinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl or thienyl, wherein the ring is optionally substituted with 1-5 substituents of R10, in conjunction with any of the above or below embodiments.
In another embodiment K-2, the invention includes compounds of Formulas I, II, and III, and any sub-formula thereof as described herein, wherein R⁹ is a ring selected from the group consisting of phenyl, pyridyl, pyrimidyl, pyrazinyl, pyrazolyl, isoxazolyl, thiazolyl, thiethyl, furanyl and pyrrolyl, wherein the ring is optionally substituted, independently, with 1-3 substituents of R₉, wherein each R₉, independently, is F, Cl, CN, NO₂, NH₂, OH, CF₃, CHF₂, CH₂F, CH₃, -OCH₃, C₂H₅, -OC₂H₅, -CH₂CF₃, -CH₂CHF₂, propyl, proproxy, isopropoxy, cyclopropyl, butyl, butoxy, cyclobutyl, isobutoxy, tert-butoxy, isobutyl, sec-butyl, tert-butyl, cyclopropylmethoxy, 2-butynoxyloxy or oxetan-3yl, in conjunction with any of the above or below embodiments.

In another embodiment L, the present invention provides compounds, and solvates, tautomers, hydrates, stereoisomers and pharmaceutically acceptable salts thereof, as defined by Formulas I, I-A, I-B, I-C or II, wherein

A⁴ is CR⁴ or N;
A⁵ is CR⁵ or N;
A⁶ is CR⁶ or N;
A⁸ is CR⁸ or N, provided no more than one of A⁴, A⁵, A⁶ and A⁸ is N;
each of R⁴ and R⁶, independently, is H, F, CH₃, CH₂F, CHF₂ or CF₃;
each of R⁵ and R⁷, independently, is H, F, CH₃, CH₂F, CHF₂ or CF₃;
R³ is C₃-alkyl, C₃-haloalkyl, CH₂OH, CH₂OCHF₂ or cyclopropyl; and
each of R⁴, R⁵, R⁶ and R⁸, independently, is H, F, Cl, CF₃H, CH₂F, CF₃, OCF₃,
methyl, ethyl, CN, OH, OCH₃, SCH₂, NHCH₂ or C(0)CH₂ in conjunction with any of the above or below embodiments.

In another embodiment M, the present invention provides compounds, and solvates, tautomers, hydrates, stereoisomers and pharmaceutically acceptable salts thereof, as defined by Formulas I and II, wherein

R⁷ is -NH-R⁹, -NH-C(=0)-R⁹ or

wherein V is NR₁⁰, O or S; and
each W, independently, is CH, CF, CCl, CCH$_3$ or N, in conjunction with any of
the above or below embodiments.

In another embodiment N-1, the invention includes compounds of Formula I-A
wherein A$^4$ is CR$^4$;

5  A$^5$ is CR$^5$;

A$^6$ is CR$^6$;

A$^8$ is CR$^8$; wherein each of R$^4$, R$^5$, R$^6$ and R$^8$, independently, is H, F, Cl, CF$_3$,
OCF$_3$, methyl, ethyl, CN, OH, OCH$_3$, SCH$_3$, NHCH$_3$ or C(0)CH$_3$;

each of R$^4$ and R$^5$, independently, is H, F, CH$_3$, CH$_2$F, CHF$_2$ or CF$_3$;

each of R$^1$ and R$^2$, independently, is H, F, CH$_3$, CH$_2$F, CHF$_2$ or CF$_3$;

10  R$^3$ is CH$_3$, C$_2$H$_5$, CF$_2$H or CH$_2$F;

R$^9$ is acetyl, Cl-6-alkyl, C$_2$alkenyl, C$_2$alkynyl or a fully or partially unsaturated
3-, 4-, 5-, 6- or 7-membered monocyclic or 8-, 9- or 10-membered bicyclic ring formed of
carbon atoms, said ring optionally including 1-4 heteroatoms if monocyclic or 1-5
heteroatoms if bicyclic, said heteroatoms selected from O, N or S, wherein the Cl-6-alkyl,
C$_2$alkenyl, C$_2$alkynyl and ring are optionally substituted, independently, with 1-5
substituents of R$^{10}$; and

each R$^{10}$, independently, is H, halo, haloalkyl, CN, OH, N0$_2$, NH$_2$, SF$_3$, acetyl,
-C(0)NHCH$_3$, oxo, cyclopropylmethoxy, 2-butylnoloxyl, Cl$_2$alkyl, C$_2$alkenyl, C$_2$

20  $\_6$alkynyl, C$_2$6cycloalkyl, Cl$_6$alkylaminio-, Cl$_6$alkylaminiao-, Cl$_6$alkoxy, Cl$_6$thiolalkoxy,
morpholinyl, pyrazolyl, isoxazolyl, dihydropranyl, pyrrolyl, pyrrolidinyl,
tetrahydropryrollyl, piperezinyl, oxetan-3-yl, imidazo-pyridinyl or dioxolyl, wherein each of
the cyclopropylmethoxy, 2-butylnoloxyl, Cl$_2$alkyl, C$_2$alkenyl, C$_2$alkynyl, C$_3$
6cycloalkyl, Cl$_6$alkylaminio-, Cl$_6$dialkylaminio-, Cl$_6$alkoxy, Cl$_6$thiolalkoxy,
morpholinyl, pyrazolyl, isoxazolyl, dihydropranyl, pyrrolidinyl, oxetan-3-yl or dioxolyl,
is optionally substituted independently with 1-5 substituents of F, Cl, CN, N0$_2$, NH$_2$, OH,
oxo, CF$_3$, CHF$_2$, CH$_2$F, methyl, methoxy, ethyl, ethoxy, CH$_2$CF$_3$, CH$_2$CHF$_2$, propyl,
propanoyl, isopropyl, isopropanoyl, cyclopropyl, butyl, butoxyl, cyclobutyl, isobutoxyl, tert-
butoxyl, isobutyl, sec-butyl, tert-butyl, cyclopentyl, cyclohexyl, Cl$_6$alkylaminio-, Cl$_6$
3dialkylaminio, Cthioalkoxy tetrahydropryranil, tetrahydropryrollyl or oxetan-3yl.

In another embodiment N-2, the invention includes compounds of Formula I-A
wherein A$^4$ is CR$^4$;

A$^5$ is CR$^5$;

A$^6$ is CR$^6$;
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A\(^8\) is CR\(^8\); wherein each of R\(^4\), R\(^5\), R\(^6\) and R\(^8\), independently, is H, F, CF\(_3\), OCF\(_3\), methyl, ethyl, CN or OCH\(_3\);
each of R\(^4\) and R\(^9\), independently, is H or F;
each of R\(^1\) and R\(^2\), independently, is H, F or CF\(_3\);
5 R\(^3\) is CF\(_3\), CH\(_3\), CF\(_2\)H or CH\(_2\)F;
R\(^9\) is a ring selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, pyridazineyl, pyrazolyl, isoxazolyl, thiazolyl, furyl and pyrryl, wherein the ring is optionally substituted, independently, with 1-3 substituents of R\(^1\)\(^{u}\); and
each R\(^1\)\(^{u}\), independently, is H, halo, haloalkyl, CN, OH, NO\(_2\), NH\(_2\), SF\(_3\), acetyl,
10 -C(0)NHCH\(_3\), oxo, cyclopropylmethoxy, 2-butynoxy, C\(_1\)-alkyl, C\(_2\)-alkenyl, C\(_2\)-alkynyl, C\(_3\)-Cycloalkyl, C\(_1\)-alkylamino-, C\(_1\)-dialkylamino-, C\(_1\)-alkoxy, C\(_1\)-thiaoalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropryranyl, pyrroldinyl, tetrahydropryrol, piperoxynyl, oxetan-3-yl, imidazo-pyridinyl or dioxolyl, wherein each of the cyclopropylmethoxy, 2-butynoxy, C\(_1\)-alkyl, C\(_2\)-alkenyl, C\(_2\)-alkynyl, C\(_3\)-Cycloalkyl, C\(_1\)-alkylamino-, C\(_1\)-dialkylamino-, C\(_1\)-alkoxy, C\(_1\)-thiaoalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropryranyl, pyrroldinyl, oxetan-3-yl or dioxolyl, is optionally substituted independently with 1-5 substituents of F, Cl, CN, N0\(_2\), NH\(_2\), OH, oxo, CF\(_3\), CHF\(_2\), CH\(_2\)F, methyl, methoxy, ethyl, ethoxy, CH\(_2\)CF\(_3\), CH\(_2\)CHF\(_2\), propyl, propoxy, isopropoxy, isopropoxy, cyclopropyl, butyl, butoxyl, cyclobutyl, isobutoxy, tert-butoxy, isobutyl, sec-butyl, tert-butyl, cyclopentyl, cyclohexyl, C\(_1\)-alkylamino-, C\(_1\)-dialkylamino, C\(_1\)-thiaoalkoxyl tetrahydropryranyl, tetrahydropryrol or oxetan-3-yl.

In another embodiment O-1, the invention includes compounds of Formula I-B wherein A\(^4\) is CR\(^4\);
A\(^5\) is CR\(^5\);
25 A\(^6\) is CR\(^6\);
A\(^8\) is CR\(^8\); wherein each of R\(^4\), R\(^5\), R\(^6\) and R\(^8\), independently, is H, F, Cl, CF\(_3\), OCF\(_3\), methyl, ethyl, CN, OH, OCH\(_3\), SCH\(_3\), NHCH\(_3\) or C(0)CH\(_3\);
each of R\(^4\) and R\(^9\), independently, is H, F, CH\(_3\), CHF, CHF\(_2\) or CF\(_3\);
each of R\(^1\) and R\(^2\), independently, is H, F, CH\(_3\), CHF, CHF\(_2\) or CF\(_3\); and
30 R\(^3\) is CH\(_3\), C\(_2\)H\(_5\), CF\(_3\)H or CH\(_2\)F, in conjunction with any of the above or below embodiments with respect to Formula I-B.

In another embodiment 0-2, the invention includes compounds of Formula I-B wherein A\(^4\) is CR\(^4\) or N;
A\(^5\) is CR\(^5\) or N;
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A^6 is CR^6 or N;
A^8 is CR^8 or N, wherein each of R^4, R^5, R^6 and R^8, independently, is H or F and provided no more than one of A^4, A^5, A^6 and A^8 is N;
each of R^1 and R^2, independently, is H, F or CF_3;
each of R^4 and R^5, independently, is H or F; and
R^3 is CF_3, CH_3, CF_2H or CH_2F, in conjunction with any of the above or below embodiments with respect to Formula I-B.

In another embodiment P-1, the invention includes compounds of Formula I-C wherein A^4 is CR^4;
10 A^5 is CR^5;
A^6 is CR^6;
A^8 is CR^8; wherein each of R^4, R^5, R^6 and R^8, independently, is H, F, Cl, CF_3, OCF_3, methyl, ethyl, CN, OH, OCH_3, SCH_3, NHCH_3 or C(0)CH_3;
each of R^4 and R^5, independently, is H, F, CH_3, CH_2F, CHF_2 or CF_3;
each of R^1 and R^2, independently, is H, F, CH_3, CH_2F, CHF_2 or CF_3; and
R^3 is CH_3, C_2H_5, CF_3H or CH_2F, in conjunction with any of the above or below embodiments with respect to Formula I-C.

In another embodiment P-2, the invention includes compounds of Formula I-C wherein A^4 is CR^4 or N;
20 A^5 is CR^5 or N;
A^6 is CR^6 or N;
A^8 is CR^8 or N, wherein each of R^4, R^5, R^6 and R^8, independently, is H or F and provided no more than one of A^4, A^5, A^6 and A^8 is N;
each of R^1 and R^2, independently, is H, F or CF_3;
each of R^4 and R^5, independently, is H or F; and
25 R^3 is CF_3, CH_3, CF_2H or CH_2F, in conjunction with any of the above or below embodiments with respect to Formula I-C.

In another embodiment, the invention provides one or more of the compounds, or a pharmaceutically acceptable salt thereof, of Formulas I, II and III, and sub-formulas thereof, as taught and described herein.

In another embodiment, the invention provides the compound of Formula I, II or III, or a stereoisomer or pharmaceutically acceptable salt thereof, selected from
N-(3-((lR,5S,6R)-3-amino-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-methoxy-2-pyrazinecarboxamide;
Racemic mixture of N-(3-((lR,5R,6R)-3-amino-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-methoxy-2-pyrazinecarboxamide and N-(3-((lS,5S,6S)-3-amino-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-methoxy-2-pyrazinecarboxamide;

N-(3-((lS,5S,6S)-3-amino-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-methoxy-2-pyrazinecarboxamide;

N-(3-((lR,5S,6R)-3-amino-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methoxy-1,7-naphthyridin-8-amine; and

N-(3-((lS,5S,6S)-3-amino-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methoxy-1,7-naphthyridin-8-amine.

Additional generic and specific compounds representative of the invention include:
In embodiment 82, the invention provides a compound, or a pharmaceutically acceptable salt or tautomer thereof, selected from:

- N-(3-((lR,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(prop-2-yn-1-yloxy)pyrazine-2-carboxamide;
- N-(3-((lR,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(but-2-yn-1-yloxy)pyrazine-2-carboxamide;
- N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-3-(methoxymethyl)picolinamide;
- N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-cyanopicolinamide;
- N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-cyano-3-methylpicolinamide;
- N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-cyano-3-methoxypicolinamide;
- N-(3-((lR,S),(5S,R),(6R,S))-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloropicolinamide;
N-(3-((R,S),5(R,S),6(R,S))-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-cyanopicolinamide compound;
N-(3-((IR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-chloro-5-cyanopicolinamide;
N-(3-((IR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3,5-dichloropicolinamide;
N-(3-((IR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-bromopicolinamide;
N-(3-((IR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloropicolinamide;
N-(3-((IR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-methoxypicolinamide;
N-(3-((IR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-2,4-difluorophenyl)-5-methoxypicolinamide;
N-(3-((IR,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-cyanopicolinamide;
N-(3-((IR,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloropicolinamide;
N-(3-((IR,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(oxazol-4-ylmethoxy)pyrazine-2-carboxamide;
N-(3-((IR,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(but-2-yn-1-yl)oxy)pyrazine-2-carboxamide trifluoroacetate;
N-(3-((IR,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(prop-2-yn-1-yl)oxy)pyrazine-2-carboxamide trifluoroacetate;
N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-3-methyl-5-(trifluoromethyl)picolinamide;
N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-3-chloro-5-cyanopicolinamide;
N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-3-fluoropicolinamide;
N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3,5-dichloropicolinamide;
N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(oxazol-2-ylmethoxy)pyrazine-2-carboxamide;
N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(oxazol-4-ylmethoxy)pyrazine-2-carboxamide;
N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(difluoromethyl)-3-methylpicolinamide;
N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(prop-2-yn-1-yl)pyrazine-2-carboxamide;
N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(but-2-yn-1-yl)pyrazine-2-carboxamide;
N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(prop-2-yn-1-yl)pyridin-2-carboxamide;
N-(3-((\(1R,5S,6R\))-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(but-2-yn-1-yloxy)pyrazine-2-carboxamide;
N-(3-\((1R,5S,6R)\)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(fluoromethoxy)-3-methylpicolinamide;
N-(3-\((1R,5S,6R)\)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-bromopyrimidine-2-carboxamide;
N-(3-\((1R,5S,6R)\)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(difluoromethoxy)pyrazine-2-carboxamide;
N-(3-\((1R,5S,6R)\)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(methoxymethyl)pyrazine-2-carboxamide;
N-(3-\((1R,5S,6R)\)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-cyano-3-methoxypicolinamide.
In embodiment 83, the invention provides a compound, or a pharmaceutically acceptable salt or tautomer thereof, selected from:

- **N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-3-methylpicolinamide**;
- **N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-cyano-3-methylpicolinamide**;
- **N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-chloro-5-cyanopicolinamide**;
- **N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-chloro-5-methoxypicolinamide**;
- **N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-bromopicolinamide**;
- **N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloropicolinamide**;
- **N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-cyanopicolinamide**;
- **N-(3-((lS,5R,6S)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-2,4-difluorophenyl)-5-methoxypicolinamide**;
- **N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-cyanopicolinamide**;
- **N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(prop-2-yn-1-yloxy)pyrazine-2-carboxamide trifluoroacetate**;
- **N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-chloropicolinamide**;
- **N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-(oxazol-4-ylmethoxy)pyrazine-2-carboxamide**;
- **N-(3-((lR,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloropicolinamide**;
- **N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluoro-5-methylphenyl)-3-chloro-5-methylpicolinamide**;
N-(3-((lR,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-cyanopicolinamide;
N-(3-((lR,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3,5-dichloropicolinamide;
N-(3-((lR,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(but-2-yn-1-ylxy)pyrazine-2-carboxamide;
N-(3-((lR,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-chloro-5-cyanopicolinamide;
N-(3-((lR,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-chloro-5-methoxypicolinamide;
N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methylpicolinamide;
N-(3-((lR,5S,6R)-3-benzamido-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-methoxypyrazine-2-carboxamide;
N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(difluoromethoxy)-3-methylpicolinamide;
N-(3-((lR,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-cyano-3-methylpicolinamide;
N-(3-((lR,5S,6R)-3-benzamido-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-methoxypyrazine-2-carboxamide;
N-(3-((lR,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-cyano-3-(methoxymethyl)picolinamide; and
N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluoro-5-methylphenyl)-5-cyano-3-methoxypicolinamide.

In embodiment 84, the invention provides a compound, or a pharmaceutically acceptable salt or tautomer thereof, selected from:
In embodiment 85, the invention provides each individual compound according to embodiments 82-84, or a pharmaceutically acceptable salt or tautomer thereof.

For instance, in embodiment 86, the invention provides the compound

and

In embodiment 87, the invention provides the compound

, or a pharmaceutically acceptable salt or tautomer thereof.

In embodiment 88, the invention provides the compound

, or a pharmaceutically acceptable salt or tautomer thereof.
In embodiment 89, the invention provides the compound

5 or a pharmaceutically acceptable salt or tautomer thereof.
In embodiment 90, the invention provides the compound

10 or a pharmaceutically acceptable salt or tautomer thereof.
In embodiment 91, the invention provides the compound

15 or a pharmaceutically acceptable salt or tautomer thereof.
In embodiment 92, the invention provides the compound

In embodiment 93, the invention provides the compound
In embodiment 94, the invention provides the compound, or a pharmaceutically acceptable salt or tautomer thereof.

In embodiment 95, the invention provides the compound, or a pharmaceutically acceptable salt or tautomer thereof.

In embodiment 96, the invention provides the compound, or a pharmaceutically acceptable salt or tautomer thereof.

In embodiment 97, the invention provides the compound, or a pharmaceutically acceptable salt or tautomer thereof.
, or a pharmaceutically acceptable salt or tautomeric thereof.

In embodiment 98, the invention provides the compound

![Chemical structure](image1)

, or a pharmaceutically acceptable salt or tautomeric thereof.

In embodiment 99, the invention provides the compound

![Chemical structure](image2)

, or a pharmaceutically acceptable salt or tautomeric thereof.

In embodiment 100, the invention provides the compound

![Chemical structure](image3)

, or a pharmaceutically acceptable salt or tautomeric thereof.

In embodiment 101, the invention provides the compound

![Chemical structure](image4)

, or a pharmaceutically acceptable salt or tautomeric thereof.

In embodiment 102, the invention provides the compound

![Chemical structure](image5)
In embodiment 103, the invention provides the compound

In embodiment 104, the invention provides the compound

In embodiment 105, the invention provides the compound

In embodiment 106, the invention provides the compound
In embodiment 107, the invention provides the compound

\[
\text{N} = \text{N} \quad \text{O} \\
\text{O} \quad \text{N}
\]

, or a pharmaceutically acceptable salt or tautomer thereof.

In the structures depicted hereinabove, an "-N" in the 1,3-oxazine head group is intended to be an -NH₂ (an amine groups); and lines ending without an atom are understood by persons of ordinary skill in the art to be a -CH₃ group.

In another embodiment, the invention provides the compound of Formula I-A, I-B and I-C, II, II-A, or a stereoisomer or pharmaceutically acceptable salt thereof, as exemplified herein, provided the compound is not

\[
\text{N}=-(\text{(IR,5R,6R)}-3\text{-amino-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl})-4\text{-fluorophenyl})\text{-3-methoxy-1,7-naphthyridin-8-amine or}
\]

\[
\text{N}=-(\text{(IR,5R,6R)}-3\text{-amino-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl})-4\text{-fluorophenyl})\text{-5-methoxy-2-pyrazinecarboxamide.}
\]

All of the possible embodiments described herein for various of the R groups of the compounds of Formula I may be applied, as appropriate, to compounds of Formulas II and III, and any sub-formulas thereof.

In another embodiment, the invention provides each of the Exemplary compounds, and stereoisomers, tautomers, solvates, pharmaceutically acceptable salts, derivatives or prodrugs thereof, and related intermediates, described herein.

In another embodiment, the invention provides the exemplified compounds described herein, and pharmaceutically acceptable salt forms of each thereof.

The invention does not include the following compounds:
DEFINITIONS

The following definitions should assist in understanding the metes and bounds of the invention.

The term "comprising" is meant to be open ended, i.e., all encompassing and non-limiting. It may be used herein synonymously with "having." Comprising is intended to include each and every indicated or recited component or element(s) while not excluding any other components or elements.

The term "Cₐ-palkyl", when used either alone or within other terms such as "haloalkyl" and "alkylamino", embraces linear or branched radicals having a to β number of carbon atoms (such as Ci-Cio; Ci-C₄, or C₁-C₄). Unless otherwise specified, one or more carbon atoms of the "alkyl" radical may be substituted, such as with a cycloalkyl moiety. Examples of "alkyl" radicals include methyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, ethyl, cyclopropylethyl, cyclobutylethyl, cyclopentylethyl, n-propyl, isopropyl, n-butyl, cyclopropylbutyl, isobutyl, sec-butyl, tert-butyl, pentyl, isooamyl, hexyl and the like.

The term "Cₐ-palkenyl", when used alone or in combination, embraces linear or branched radicals having at least one carbon-carbon double bond in a moiety having a number of carbon atoms in the range from a and β. Included within alkenyl radicals are "lower alkenyl" radicals having two to about six carbon atoms and, for example, those radicals having two to about four carbon atoms. Examples of alkenyl radicals include, without limitation, ethenyl, propenyl, allyl, propenyl, butenyl and 4-methylbutenyl. The terms "alkenyl" and "lower alkenyl", embrace radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations, as appreciated by those of ordinary skill in the art.

The term "Cₐ-palkynyl", when used alone or in combination, denotes linear or branched radicals having at least one carbon-carbon triple bond in a moiety having a number of carbon atoms in the range from a and β. Examples of alkynyl radicals include "lower alkynyl" radicals having two to about six carbon atoms and, for example,
lower alkynyl radicals having two to about four carbon atoms. Examples of such radicals include, without limitation, ethynyl, propynyl (propargyl), butynyl, and the like.

The term "C₃₋₅-alkyl", "C₃₋₅-alkenyl" and "C₃₋₅-alkynyl", when used with other terms such as "wherein 1, 2 or 3 carbon atoms of said C₃₋₅-alkyl, C₃₋₅-alkenyl or C₃₋₅-alkynyl is optionally replaced with a heteroatom selected from O, S, S(O), S(O)₂ and N" embraces linear or branched radicals wherein one or more of the carbon atoms may be replaced with a heteroatom. Examples of such "alkyl" radicals include -O-methyl, -O-ethyl, -CH₂-0-CH₃, -CH₂CH₂-0-CH₃, -NH-CH₂, -CH₂CH₂-N(CH₃)-CH₃, -S-(CH₂)₃CH₂, -CH₂CH₂S-CH₃ and the like. Accordingly, such radicals also include radicals encompassed by -OR where R may be defined as a C₃₋₅-alkyl. Examples of such "alkenyl" radicals include -NH-CH₂CH=CH₂, -S-CH₂CH₂CH=CHCH₃ and the like. Similar examples exist for such "alkynyl" radicals, as appreciated by those skilled in the art.

The term "C₃₋₅-palkoxy" or "-OC₃₋₅-palkyl" when used alone or in combination, embraces linear or branched oxygen-containing alkyl radicals each having a to β number of carbon atoms (such as C1-C6). The terms "alkoxy" and "alkoxy", when used alone or in combination, embraces linear or branched oxygen-containing radicals each having alkyl and substituted alkyl portions of one or more carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy, tert-butoxy and neopentoxy. Alkoxo radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy" radicals or with other substitution. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoro-propoxy.

The term "aryl", when used alone or in combination, means a carbocyclic aromatic moiety containing one, two or even three rings wherein such rings may be attached together in a fused manner. Every ring of an "aryl" multi-ring system need not be aromatic, and the ring(s) fused to the aromatic ring may be partially or fully unsaturated and include one or more heteroatoms selected from nitrogen, oxygen and sulfur. Thus, the term "aryl" embraces aromatic radicals such as phenyl, naphthyl, indenyl, tetrahydronaphthyl, dihydrobenzofuranyl, anthracenyl, indanyl, benzodioxazinyl, and the like. The "aryl" group may be substituted, such as with 1 to 5 substituents including lower alkyl, hydroxyl, halo, haloalkyl, nitro, cyano, alkoxy and lower
alkylamino, and the like. Phenyl substituted with -0-CH₂-0- or -0-CH₂-CH₂-0- forms an aryl benzodioxolyl substituent.

The term "Cₘ₋ₘₙ-cycloalkyl", also referred to herein as "carbocyclic", when used alone or in combination, denotes a partially or fully saturated ring radical having a number of carbon atoms in the range from a and β. The "cycloalkyl" may contain one ("monocyclic"), two ("bicyclic") or even three ("tricyclic") rings wherein such rings may be attached together in a fused manner and each formed from carbon atoms. Examples of saturated carbocyclic radicals include saturated 3 to 6-membered monocyclic groups such as cyclopropane, cyclobutane, cyclopentane and cyclohexane.

Cycloalkyls may be substituted as described herein.

The terms "ring" and "ring system" refer to a ring comprising the delineated number of atoms, the atoms being carbon or, where indicated, a heteroatom such as nitrogen, oxygen or sulfur. Where the number of atoms is not delineated, such as a "monocyclic ring system" or a "bicyclic ring system", the numbers of atoms are 3-8 for a monocyclic and 6-12 for a bicyclic ring. The ring itself, as well as any substituents thereon, may be attached at any atom that allows a stable compound to be formed. The term "nonaromatic" ring or ring system refers to the fact that at least one, but not necessarily all, rings in a bicyclic or tricyclic ring system is nonaromatic.

The terms "partially or fully saturated or unsaturated" and "saturated or partially or fully unsaturated" with respect to each individual ring, refer to the ring either as fully aromatic (fully unsaturated), partially aromatic (or partially saturated) or fully saturated (containing no double or triple bonds therein). If not specified as such, then it is contemplated that each ring (monocyclic) in a ring system (if bicyclic or tricyclic) may either be fully aromatic, partially aromatic or fully saturated, and optionally substituted with up to 5 substituents. This includes carbocyclics, heterocyclics, aryl and heteroaryl rings.

The term "halo", when used alone or in combination, means halogens such as fluorine, chlorine, bromine or iodine atoms.

The term "haloalkyl", when used alone or in combination, embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. For example, this term includes monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals such as a perhaloalkyl. A monohaloalkyl radical, for example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo
radicals. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. "Perfluoroalkyl", as used herein, refers to alkyl radicals having all hydrogen atoms replaced with fluoro atoms. Examples include trifluoromethyl and pentafluoroethyl.

The term "heteroaryl", as used herein, either alone or in combination, means a fully unsaturated (aromatic) ring moiety formed from carbon atoms and having one or more heteroatoms selected from nitrogen, oxygen and sulfur. The ring moiety or ring system may contain one ("monocyclic"), two ("bicyclic") or even three ("tricyclic") rings wherein such rings are attached together in a fused manner. Every ring of a "heteroaryl" ring system need not be aromatic, and the ring(s) fused thereto (to the heteroaromatic ring) may be partially or fully saturated and optionally include one or more heteroatoms selected from nitrogen, oxygen and sulfur. The term "heteroaryl" does not include rings having ring members of -0-0-, -O-S- or -S-S-.

Examples of unsaturated heteroaryl radicals, include unsaturated 5- to 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atoms, including for example, pyrrol, imidazol, pyrazol, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl] and tetrazole; unsaturated 7- to 10- membered heterobicyclyl groups containing 1 to 4 nitrogen atoms, including for example, quinolinyl, isoquinolinyl, quinazolinyl, isoquinazolinyl, aza-quinazolinyl, and the like; unsaturated 5- to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranil, 2-furyl, 3-furyl, benzofuryl, etc.; unsaturated 5 to 6-membered heteromonocyclic group containing a sulfur atom, for example, 2-thienyl, 3-thienyl, benzothienyl, etc.; unsaturated 5- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl]; unsaturated 5 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, isothiazolyl, thiadiazolyl [e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl].

The terms "heterocycle" or "heterocyclic", when used alone or in combination, means a partially or fully saturated ring moiety containing one, two or even three rings wherein such rings may be attached together in a fused manner, formed from carbon atoms and including one or more heteroatoms selected from N, O or S. Examples of
saturated heterocyclic radicals include saturated 3 to 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atoms [e.g. pyrrolidinyl, imidazolidinyl, piperidinyl, pyrrolinyl, piperazinyl]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. morpholinyl]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl]. Examples of partially saturated heterocyclic radicals include dihydrothienyl, dihydropyranyl, dihydrofuryl and dihydrothiazolyl.

The term "heterocycle" also embraces radicals where heterocyclic radicals are fused/condensed with aryl radicals: unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo [1,5-b]pyridazinyl]; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl]; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl]; and saturated, partially unsaturated and unsaturated condensed heterocyclic group containing 1 to 2 oxygen or sulfur atoms [e.g. benzofuryl, benzothienyl, 2,3-dihydro-benzo[1,4]dioxinyl and dihydrobenzofuryl]. Examples of heterocyclic radicals include five to ten membered fused or unfused radicals.

Examples of partially saturated and fully saturated heterocyclics include, without limitation, pyrrolidinyl, imidazolidinyl, piperidinyl, pyrrolinyl, pyrazolidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, thiazolidinyl, dihydrothienyl, 2,3-dihydrobenzo[1,4]dioxanyl, indolyl, isoindolyl, dihydrobenzothienyl, dihydrobenzofuryl, isochromanyl, chromanyl, 1,2-dihydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3,4,4a,9,9a-hexahydro-1H-3-aza-fluorenyl, 5,6,7-trihydro-1,2,4-triazolo[3,4-a]isoquinolinyl, 3,4-dihydro-2H-benzo[1,4]oxazinyl, benzo[1,4]dioxanly, 2,3-dihydro-1H-R'-benzo[d]isothiazol-6-yl, dihydropyranyl, dihydrofuryl and dihydrothiazolyl, and the like.

The term "a 3-8 membered monocyclic or 6-12 membered bicyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic or 1-6 heteroatoms if bicyclic, said heteroatoms selected from O, N, or S, wherein said ring system is optionally substituted” refers to a single ring of 3-, 4-, 5-, 6-, 7- or 8-atom memberd or a 6-, 7-, 8-, 9-, 10-, 11 or 12-atom membered bicyclic ring system comprising the delineated number of atoms, the atoms being carbon or, where indicated, a heteroatom such as nitrogen (N), oxygen (O) or sulfur (S). Where the number
of atoms is not delineated, such as a "monocyclic ring system" or a "bicyclic ring system", the numbers of atoms are 3-8 for a monocyclic and 6-12 for a bicyclic ring. The ring or ring system may contain substituents thereon, attached at any atom that allows a stable compound to be formed. A bicyclic ring is intended to include fused ring systems as well as spiro-fused rings. This phrase encompasses carbocyclics, heterocyclics, aryl and heteroaryl rings.

The term "alkylamino" includes "N-alkylamino" where amino radicals are independently substituted with one alkyl radical. Preferred alkylamino radicals are "lower alkylamino" radicals having one to six carbon atoms. Even more preferred are lower alkylamino radicals having one to three carbon atoms. Examples of such lower alkylamino radicals include N-methylamino, and N-ethylamino, N-propylamino, N-isopropylamino and the like.

The term "dialkylamino" includes "N,N-dialkylamino" where amino radicals are independently substituted with two alkyl radicals. Preferred alkylamino radicals are "lower alkylamino" radicals having one to six carbon atoms. Even more preferred are lower alkylamino radicals having one to three carbon atoms. Examples of such lower alkylamino radicals include N,N-dimethylamino, N,N-diethylamino, and the like.

The term "carbonyl", whether used alone or with other terms, such as "aminocarbonyl", denotes -(C=O)-. "Carbonyl" is also used herein synonymously with the term "oxo".

The term "alkythio" or "thioalkoxy" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. An example of "alkythio" or "thioalkoxy" is methylthio,(CH₃S-).

The term "Formula I" includes any sub formulas, such as Formulas II and III. Similar with Formulas II and III, in that they include sub-formulas where described.

The present invention also includes tautomeric forms of compounds of the invention. For example, the invention comprises compounds of formula I as well as their tautomers, as shown:
Similarly, tauatomers of compounds of Formulas I-I and III, and of compounds of sub-formulas of compounds of Formulas I, II and III, are also included in the invention.

The term "pharmaceutically-acceptable" when used with reference to a compound of Formulas I-III is intended to refer to a form of the compound that is safe for administration. For example, a salt form, a solvate, a hydrate, a prodrug or derivative form of a compound of Formulas I-III, which has been approved for mammalian use, via oral ingestion or other routes of administration, by a governing body or regulatory agency, such as the Food and Drug Administration (FDA) of the United States, is pharmaceutically acceptable.

Included in the compounds of Formulas I-III are the pharmaceutically acceptable salt forms of the free-base compounds. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. As appreciated by those of ordinary skill in the art, salts may be formed from ionic associations, charge-charge interactions, covalent bonding, complexation, coordination, etc. The nature of the salt is not critical, provided that it is pharmaceutically acceptable.

Suitable pharmaceutically acceptable acid addition salts of compounds of Formulas I-III may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, hydrofluoric, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, arylaliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which include, without limitation, formic, acetic, adipic, butyric, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, ethanedisulfonic, benzenesulfonic, pantothenic, 2-hydroxyethanesulfonic, toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, camphoric, camphorsulfonic, digluconic, cyclopentanepropionic, dodecylsulfonic, glucoheptanoic, glycerophosphonic, heptanoic, hexanoic, 2-hydroxy-ethanesulfonic, nicotinic, 2-naphthalenesulfonic, oxalic, palmoic, pectinic, persulfuric, 2-phenylpropionic, picric, pivalic propionic, succinic, thiocyanic, undecanoic, stearic, algenic, β-hydroxybutyric, salicylic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formulas I - III include metallic salts, such as salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc, or salts made from organic bases.
including, without limitation, primary, secondary and tertiary amines, substituted amines including cyclic amines, such as caffeine, arginine, diethylamine, N-ethyl piperidine, histidine, glucamine, isopropylamine, lysine, morpholine, N-ethyl morpholine, piperazine, piperidine, triethylamine, disopropylethylamine and trimethylamine. All of these salts may be prepared by conventional means from the corresponding compound of the invention by reacting, for example, the appropriate acid or base with the compound of Formulas I-III.

Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

Additional examples of such salts can be found in Berge et al., J. Pharm. Sci., 66:1 (1977). Conventional methods may be used to form the salts. For example, a phosphate salt of a compound of the invention may be made by combining the desired compound free base in a desired solvent, or combination of solvents, with phosphoric acid in a desired stoichiometric amount, at a desired temperature, typically under heat (depending upon the boiling point of the solvent). The salt can be precipitated upon cooling (slow or fast) and may crystallize (i.e., if crystalline in nature), as appreciated by those of ordinary skill in the art. Further, hemi-, mono-, di, tri- and poly-salt forms of the compounds of the present invention are also contemplated herein. Similarly, hemi-, mono-, di, tri- and poly-hydrated forms of the compounds, salts and derivatives thereof, are also contemplated herein.

The term "pharmaceutically-acceptable derivative" as used herein, denotes a derivative which is pharmaceutically acceptable.

The compound(s) of Formulas I-III may be used to treat a subject by administering the compound(s) as a pharmaceutical composition. To this end, the compound(s) can be combined with one or more excipients, including without limitation, carriers, diluents or adjuvants to form a suitable composition, which is described in more detail herein.

The term "excipient", as used herein, denotes any pharmaceutically acceptable additive, carrier, adjuvant, or other suitable ingredient, other than the active
pharmaceutical ingredient (API), which is typically included for formulation and/or administration purposes. "Diluent" and "adjuvant" are defined hereinafter.

The terms "treat", "treating," "treatment," and "therapy" as used herein refer to therapy, including without limitation, curative therapy, prophylactic therapy, and preventative therapy. Prophylactic treatment generally constitutes either preventing the onset of disorders altogether or delaying the onset of a pre-clinically evident stage of disorders in individuals.

The phrase "effective dosage amount" is intended to quantify the amount of each agent, which will achieve the goal of improvement in disorder severity and the frequency of incidence over treatment of each agent by itself, while avoiding adverse side effects typically associated with alternative therapies. Accordingly, this term is not limited to a single dose, but may comprise multiple dosages required to bring about a therapeutic or prophylactic response in the subject. For example, "effective dosage amount" is not limited to a single capsule or tablet, but may include more than one capsule or tablet, which is the dose prescribed by a qualified physician or medical care giver to the subject.

The term "leaving group" (also denoted as "LG") generally refers to groups that are displaceable by a nucleophile. Such leaving groups are known in the art. Examples of leaving groups include, but are not limited to, halides (e.g., I, Br, F, Cl), sulfonates (e.g., mesylate, tosylate), sulfides (e.g., SCH₂), N-hydroxsuccinimide, N-hydroxybenzotriazole, and the like. Nucleophiles are species that are capable of attacking a molecule at the point of attachment of the leaving group causing displacement of the leaving group. Nucleophiles are known in the art. Examples of nucleophilic groups include, but are not limited to, amines, thiols, alcohols, Grignard reagents, anionic species (e.g., alkoxides, amides, carbanions) and the like.

**GENERAL SYNTHETIC PROCEDURES**

The present invention further comprises procedures for the preparation of compounds of Formulas I-III. The compounds of Formulas I-III can be synthesized according to the procedures described in the following Schemes 1, 2, 3a, 3b, 4 and 5, wherein the substituents are as defined for Formulas I-III above, except where further noted. The synthetic methods described below are merely exemplary, and the compounds of the invention may also be synthesized by alternate routes utilizing alternative synthetic strategies, as appreciated by persons of ordinary skill in the art.
The following list of abbreviations used throughout the specification represent the following and should assist in understanding the invention:

ACN, MeCN - acetonitrile
Aq., aq. - aqueous
Ar - argon (gas)
BOC - tert-butoxycarbonyl
BOP - benzotriazol-1-yl-oxy Hexafluorophosphate
BuLi - Butyllithium
Cs$_2$CO$_3$ - cesium carbonate
CHC$_3$ - chloroform
CH$_2$C$_2$, DCM - dichloromethane, methylene chloride
Cu(I)I - copper(I) iodide
DCC - dicyclohexylcarbodiimide
DEA - diethylamine
DIC - 1,3-diisopropylcarbodiimide
DIEA, DIPEA - diisopropylethylamine
DME - dimethoxyethane
DMF - dimethylformamide
DMAP - 4-dimethylaminopyridine
DMSO - dimethylsulfoxide
EDC, EDCI - 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
Et$_2$O - diethyl ether
EtOAc - ethyl acetate
g, gm - gram
h, hr - hour
⅓ - hydrogen (gas)
H$_2$O - water
HATU - 0-(7-azabenzotriazol-1-yl)-N,N,N',N'-
tetramethyluroniumhexafluorophosphate
HBr - hydrobromic acid
HCl - hydrochloric acid
HOBt - 1-hydroxybenzotriazole hydrate
HOAc - acetic acid
<table>
<thead>
<tr>
<th>Chemical</th>
<th>Formula</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPLC</td>
<td>-</td>
<td>high pressure liquid chromatography</td>
</tr>
<tr>
<td>IPA, IpOH</td>
<td>-</td>
<td>isopropyl alcohol</td>
</tr>
<tr>
<td>$\text{K}_2\text{CO}_3$</td>
<td>-</td>
<td>potassium carbonate</td>
</tr>
<tr>
<td>KI</td>
<td>-</td>
<td>potassium iodide</td>
</tr>
<tr>
<td>LG</td>
<td>-</td>
<td>leaving group</td>
</tr>
<tr>
<td>LDA</td>
<td>-</td>
<td>Lithium diisopropylamide</td>
</tr>
<tr>
<td>LiOH</td>
<td>-</td>
<td>lithium hydroxide</td>
</tr>
<tr>
<td>MgSO$_4$</td>
<td>-</td>
<td>magnesium sulfate</td>
</tr>
<tr>
<td>MS</td>
<td>-</td>
<td>mass spectrum</td>
</tr>
<tr>
<td>MeOH</td>
<td>-</td>
<td>methanol</td>
</tr>
<tr>
<td>$\text{N}_2$</td>
<td>-</td>
<td>nitrogen (gas)</td>
</tr>
<tr>
<td>NaCNBH$_3$</td>
<td>-</td>
<td>sodium cyanoborohydride</td>
</tr>
<tr>
<td>Na$_2$CO$_3$</td>
<td>-</td>
<td>sodium carbonate</td>
</tr>
<tr>
<td>NaHCO$_3$</td>
<td>-</td>
<td>sodium bicarbonate</td>
</tr>
<tr>
<td>NaH</td>
<td>-</td>
<td>sodium hydride</td>
</tr>
<tr>
<td>NaI</td>
<td>-</td>
<td>sodium iodide</td>
</tr>
<tr>
<td>NaBH$_4$</td>
<td>-</td>
<td>sodium borohydride</td>
</tr>
<tr>
<td>NaOH</td>
<td>-</td>
<td>sodium hydroxide</td>
</tr>
<tr>
<td>Na$_2$SO$_4$</td>
<td>-</td>
<td>sodium sulfate</td>
</tr>
<tr>
<td>NH$_4$Cl</td>
<td>-</td>
<td>ammonium chloride</td>
</tr>
<tr>
<td>NH$_4$OH</td>
<td>-</td>
<td>ammonium hydroxide</td>
</tr>
<tr>
<td>P(i-bu)$_3$</td>
<td>-</td>
<td>tri(tert-butyl)phosphine</td>
</tr>
<tr>
<td>Ph$_3$P</td>
<td>-</td>
<td>triphenylphosphine</td>
</tr>
<tr>
<td>Pd/C</td>
<td>-</td>
<td>palladium on carbon</td>
</tr>
<tr>
<td>Pd(PPh$_3$)$_4$</td>
<td>-</td>
<td>palladium(0)triphenylphosphine tetrakis</td>
</tr>
<tr>
<td>Pd(dppf)Cl$_2$</td>
<td>-</td>
<td>palladium(1,1-bis(diphenylphosphinoferrocene)) chloride</td>
</tr>
<tr>
<td>Pd(PhCN)$_2$Cl$_2$</td>
<td>-</td>
<td>palladium di-cyanophenyl dichloride</td>
</tr>
<tr>
<td>Pd(OAc)$_2$</td>
<td>-</td>
<td>palladium acetate</td>
</tr>
<tr>
<td>Pd$_2$(dba)$_3$</td>
<td>-</td>
<td>tris(dibenzylideneacetone) dipalladium</td>
</tr>
<tr>
<td>PyBop</td>
<td>-</td>
<td>benzotriazol-1-yl-oxy-tripyrrolidino-phosphonium hexafluorophosphate</td>
</tr>
</tbody>
</table>
RT,  \(r\) - room temperature
RBF,  \(rbf\) - round bottom flask
TLC,  \(tic\) - thin layer chromatography
TBAF - Tetrabutylammonium fluoride
TBTU - 0-benzotriazol-1-yl-N,N,N,N'-tetramethyluronium tetrafluoroborate
TEA,  \(Et_3N\) - triethylamine
TFA - trifluoroacetic acid
THF - tetrahydrofuran

\(uv\) - ultraviolet light

Scheme 1-A
Scheme 1 describes an exemplary method for preparing compounds 7a and 7b of Formulas I, II and III, wherein each of A¹, A², A₆ and A⁸ is, independently, as defined hereunder, each of R¹ and R², independently, is H, and R³ is CH₃. Beginning with compound 1, aldehyde oxime may be converted to the corresponding chloride using N-chlorosuccinimide under suitable conditions. The chloride of compound 1 may be converted to intermediate 2 by treatment with allyl chloride under suitable conditions and in suitable solvents, to afford racemate 2. Ring closure of intermediate 2 can be effected by treating 2 with a sufficiently strong base, such as potassium t-butoxide, to provide racemic intermediate 3. The (hetero)aryl group can be installed in compounds of Formulas I, II and III, using a Lewis acid, such as a boron agent, with methyllithium lithium bromide under suitable conditions to afford intermediates 4a and 4b as a racemic mixture. The oxazole ring of racemic intermediate 4 can be opened using zinc in acetic acid under suitable conditions to afford intermediates 5a and 5b as a racemic mixture. Racemic mixture 5a and 5b can be re-closed to the corresponding 6-membered ring by treatment of mixture 5a and 5b with benzoylisothiocyanate under suitable conditions and solvent, to provide intermediates 6a and 6b as a racemic mixture. The bromide of intermediates 6a and 6b can be converted to the corresponding amine by first converting the bromide of 6a and 6b to the corresponding azide by conventional methods, such as those described in Example 1 herein. The azide is then reduced with a suitable reducing agent, such as sodium borohydride, under conventional conditions to provide the intermediates 7a and 7b, as a racemic mixture. Intermediates 7a and 7b, either as a racemic mixture or separately, may then be used as described herein to prepare compounds of Formulas I, II and III wherein each of R¹ and R² are H, respectively, R³ is CH₃ and having the desired R₇ group. Such compounds may be prepared using the scheme shown and described hereinbelow and/or using the methods described in the Examples provided herein.
As shown, desired R<sup>3</sup>-amide-linked compounds 10 can be prepared as desired, such as by treatment of aniline 8 with a desired R<sup>2</sup>-carboxylic acid in conjunction with a known acid activating reagent, such as HATU, TBTU or DMTMM (see Method A and B for Example 2) to afford the desired protected amide-linked adduct 9. Compound 9 can be deprotected using known conditions, such as with a base, such as ammonia or DBU in a suitable solvent, to afford final compounds 10 of Formula I and I-A.

Acid activating groups convert the OH of the acid into a strong leaving group "LG." A "leaving group" which may be a halide such as an iodide, bromide, chloride or fluoride. LG may also be a non-halide moiety such as an alkylsulfonate or other known groups which generally form an electrophilic species (E<sup>+</sup>). Coupling reactions generally occur more readily in one or a combination of solvents and a base. Suitable solvents include, without limitation, generally non-nucleophilic, anhydrous solvents such as toluene, CH<sub>2</sub>C<sub>2</sub>, THF, DMF, N,N-dimethylacetamide and the like. The solvent may range in polarity, as appreciated by those skilled in the art. Suitable bases include, for example, tertiary amine bases such as DIEA, TEA, carbonate bases such as Na<sub>2</sub>CO<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub>, CS<sub>2</sub>CO<sub>3</sub>, hydrides such as NaH, KH and the like, alkoxides such as NaOCH<sub>3</sub>, and the like. The base itself may also serve as a solvent. These coupling reactions are generally fast and conversion occurs typically in ambient conditions. However, depending upon the particular substrate, such reactions may require heat, as appreciated by those skilled in the art.
As shown, desired compounds 12 of Formulas I, I-B, II and III can be prepared as shown in scheme 3. First, compound 8 is deprotected using conventional techniques, and the aniline adduct 11 can be functionalized to the desired compound. A desired bicyclic R7 group having a suitable leaving group, such as a chloride (Cl) or other aromatic leaving group, can be reacted with compound 11 in the presence of a suitable acid, such as of sulfuric acid. This allows coupling of the bicyclic heteroaromatic R7 group to the amine to form compounds 12 of Formulas I, I-B, II and III.

Examples

The Examples, described herein below, represent various exemplary starting materials, intermediates and compounds of Formulas I-III, which should assist in a better understanding and appreciation of the scope of the present invention and of the various methods which may be used to synthesize compounds of Formulas I-III. It should be appreciated that the general methods above and specific examples below are illustrative only, for the purpose of assistance and of understanding the present invention, and should not be construed as limiting the scope of the present invention in any manner.

Chromatography:

Unless otherwise indicated, crude product-containing residues were purified by passing the crude material or concentrate through either a Biotage or Isco brand silica gel column (pre-packed or individually packed with SiO2) and eluting the product off the column with a solvent gradient as indicated. For example a description of (330 g SiO2, 0-40% EtOAc/Hexane) means the product was obtained by elution from the column packed with 330gms of silica, with a solvent gradient of 0% to 40% EtOAc in Hexanes.

Preparative HPLC Method:

Where so indicated, the compounds described herein were purified via reverse phase HPLC using one of the following instruments: Shimadzu, Varian, Gilson; utilizing
one of the following two HPLC columns: (a) a Phenomenex Luna or (b) a Gemini column
(5 micron or 10 micron, C18, 150x50 mm)

A typical run through the instrument included: eluting at 45 ml/min with a linear
gradient of 10% (v/v) to 100% MeCN (0.1% v/v TFA) in water (0.1% TFA) over 10 minutes; conditions can be varied to achieve optimal separations.

Proton NMR Spectra:

Unless otherwise indicated, all ¹H NMR spectra were run on a Bruker series 300 MHz instrument or a Bruker series 400 MHz instrument. Where so characterized, all observed protons are reported as parts-per-million (ppm) downfield from tetramethylsilane (TMS) or other internal reference in the appropriate solvent indicated.

Mass Spectra (MS)

Unless otherwise indicated, all mass spectral data for starting materials, intermediates and/or exemplary compounds are reported as mass/charge (m/z), having an (M+H⁺) molecular ion. The molecular ion reported was obtained by electrospray detection method (commonly referred to as an ESI MS) utilizing a PE SCiEX API 150EX MS instrument instrument or an Agilent 1100 series LC/MSD system. Compounds having an isotopic atom, such as bromine and the like, are generally reported according to the detected isotopic pattern, as appreciated by those skilled in the art.

The compounds disclosed and described herein have been named using either (1) the naming convention provided with Chem-Draw Ultra 11.0 software, available in Chem Office, or (2) by the ISIS database software (Advanced Chemistry Design Labs or ACD software).

Example 1
Synthesis of Intermediate li:
Step 1: (g,Z)-5-bromo-2-fluoro-N'-hydroxybenzimidamide (lb)

5-Bromo-2-fluorobenzonitrile (65 g, 325 mmol, Matrix) was suspended in water (325 mL) and hydroxyl ammonium chloride (49.7 g, 715 mmol) was added. The pH was adjusted to pH = 10 by adding 1 M NaOH solution (500 mL), followed by 10 M NaOH (5 mL). The suspension was stirred for 1 h at RT and subsequently heated to 100 °C for 3 hs. The reaction mixture was cooled to 0 °C, upon which a white solid precipitated, which was filtered off. The solid was dissolved in EtOAc and dried over MgSO₄. The solvent was removed under reduced pressure to obtain the title compound as a beige solid (70 g, 300 mmol, 92 % yield) which was taken onto the next step without further purification. MS m/z = 232.9 M⁺. Calculated for C₇H₅BrFN₂O : 233.04

Step 2: (g,Z)-5-bromo-2-fluoro-N-hydroxybenzimidoyl chloride (lc)

(is,Z)-5-Bromo-2-fluoro-N'-hydroxybenzimidamide (lb, 19.9 g, 85 mmol) was suspended in water (100 mL). The suspension was cooled to 5 °C and hydrochloric acid (37%, 42.1 mL, 512 mmol) was added, followed by drop wise addition of a solution of sodium nitrite (5.89 g, 85 mmol, Aldrich) in 30 mL water. The internal reaction temperature was maintained below 5 °C for 4 h and then raised to 30 °C for 1 h. The reaction mixture was cooled to RT. The solid was filtered off and dissolved in CH₂Cl₂. The solution was washed with water and dried over MgSO₄. The solvent was removed under reduced pressure. The residue was dissolved in Et₂O and hexanes. Upon removing the solvent under reduced pressure a fine yellow solid formed which was filtered off and
dried. The solid was identified as title compound (6 g) and taken onto the next step without further purification. MS m/z = 253.9 [M+H]+. Calculated for C₂H₇BrClFNO: 252.47.

Step 3: 3-(5-bromo-2-fluorophenyl)-5-(chloromethyl)-4,5-dihydroisoxazole

 TEA (0.551 ml, 3.96 mmol, Aldrich) was added drop wise to a stirred solution of (Z)-5-bromo-2-fluoro-N-hydroxybenzimidoyl chloride (1 g, 3.96 mmol) at 0°C, followed by a solution of allyl chloride (0.968 ml, 11.88 mmol, Aldrich) in Et₂O (20 mL). The reaction mixture was allowed to stir at RT for 4 hs. 2 M HCl (10 ml) was added, followed by water and EtOAc. The organic phase was separated and dried over MgSO₄.

The solvent was removed under reduced pressure. The crude material was absorbed onto a plug of silica gel and purified by chromatography eluting with a gradient of 3% to 35% EtOAc in hexane, to provide the title compound as colorless oil (0.604 g, 2.065 mmol, 52.1% yield). MS m/z = 293.9 [M+H]+. Calculated for C₁₀H₇BrClFNO 292.53.

Step 4: 4-(5-bromo-2-fluorophenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (1e-rac)

Potassium t-butoxide (176 mg, 1.572 mmol, Aldrich) was added in small portions over a time period of 20 min to a solution of 3-(5-bromo-2-fluorophenyl)-5-(chloromethyl)-4,5-dihydroisoxazole (200 mg, 0.684 mmol, 1e rac) in DMSO (4 mL) cooled with a water bath. After completed, the reaction was quenched by the addition of ice. EtOAc was added and the organic phase was separated. The organic phase was dried over MgSO₄ and the solvent was removed under reduced pressure. The crude material was absorbed onto a plug of silica gel and purified by chromatography, eluting with 3% to 5% EtOAc in hexane, to provide the title compound as a colorless oil (154 mg, 0.601 mmol, 88% yield). MS m/z = 257.9 [M+H]+. Calculated for C₁₀H₇BrFNO: 256.07.

Step 5: [1(S,R),4(S,R),5(S,R)]-4-(5-bromo-2-fluorophenyl)-4-methyl-2-oxa-S-azabicyclo[3.1.0]hex-3-ene (1f-rac)

A solution of 4-(5-bromo-2-fluorophenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (1e rac; 10 g, 39.1 mmol) in DCM (400 mL) was cooled to -78 °C. Boron fluoride diethyl etherate (8.19 ml, 66.4 mmol, Aldrich) was added and the reaction mixture was stirred for 5 min. A solution of methyl lithium bromide (1.5 M solution in Et₂O; 31.2 ml, 46.9 mmol) was added drop wise. The temperature was maintained at -78 °C. After 2 hs, additional methyl lithium bromide solution (31.2 ml, 46.9 mmol) was added drop wise. After 4 hs reaction time, additional boron fluoride diethyl etherate (8.19 ml, 66.4 mmol) and an additional portion of MeLi lithium bromide solution (1.5 M
solution in Et₂O : 31.2 ml, 46.9 mmol) were added. The reaction mixture was stirred for one more hour at -78 °C. The reaction was quenched by the addition of aqueous, saturated ammonium chloride solution. EtOAc was added to the mixture and the organic phase was separated and dried over MgSO₄. The solvent was removed under reduced pressure. The crude material was loaded onto a plug of silica gel and purified by chromatography, eluting with a gradient of 5% to 25% EtOAc in hexane, to provide the title compound as a light-yellow oil (2.48 g, 9.11 mmol, 23.34 % yield). MS m/z = 272.0/274.0 M+/[M+2]+. Calculated for C₁₁H₁₁BrFNO: 272.11

Step 6: [1f/SJO.2iS.Ryi-2-IYS.Ry1-amino-1-i5-bromo-2-fluorophenynethyl]-
cyclopropanol (1g-rac)

[1(S,R),4(S,R),5(S,R)]=4-(5-bromo-2-fluorophenyl)-4-methyl-2-oxa-3-
azabicyclo[3.1.0]hexane (If rac; 5.197 g, 19.10 mmol) was dissolved in glacial acetic acid (49.6 ml, 859 mmol, EMD). Zinc dust (12.49 g, 191 mmol, Aldrich) was added portion wise at RT. The resulting thick suspension was stirred for 1 hour. The reaction mixture was filtered. The filter cake was washed with acetic acid and water. The filtrate was concentrated under reduced pressure. Water was added to the residue and the pH was adjusted to pH 10 with aqueous, saturated potassium carbonate solution. A suspension formed. The solid was filtered off and the filtrate was extracted with CHCl₃, followed by extraction with a solution of 10% MeOH/DCM. The combined organic phases were

concentrated under reduced pressure. The residue was dissolved in DCM and dried over MgSO₄. The solvent was removed under reduced pressure to obtain the title compound as a yellow oil (5.044 g, 18.40 mmol, 96 %, yield), which was used in the next step without further purification. MS m/z = 275.9 [M+H]+. Calculated for C₁₁H₁₃BrFNO: 274.13.

Step 7: N-rrUS.R ),5rS.R),6rS,R)||(5-r5-bromo-2-fluorophenyl)V5-methyl-2-oxa-4-
azabicvclo[4.1.0]hept-3-en-3-yl]benzamide ( lh-rac)

[1(S,R),2(S,R)]=2-[(S,R)-1-amino-1 -(5-bromo-2-
fluorophenyl)ethyl]cyclopropanol (lg rac; 5.044 g, 18.40 mmol) was dissolved in THF (100 mL) and benzoyl isothiocyanate (2.72 mL, 20.24 mmol, Aldrich) was added. The reaction mixture was allowed to stir at RT. After 10 min reaction time, the solvent was removed under reduced pressure to obtain a yellow foam, which was taken up in acetonitrile (100 mL). A solution of 1,3-dicyclohexylcarbodiimide (1 M in DCM, 18.40 mL, 18.40 mmol, Aldrich) was added, followed by triethylamine (0.512 mL, 3.68 mmol, Aldrich). The reaction mixture was heated to 80 °C for 3 hs. The reaction mixture was cooled to room temperature upon which a solid precipitated. The reaction mixture was
filtered and the filtrate was loaded onto a plug of silica gel and purified by chromatography, eluting with a gradient of 5% to 35% EtOAc in hexane, to provide the title compound as a yellow oil (6.438 g, 15.97 mmol, 87% yield; 90% purity). MS m/z = 403.0 M+. Calculated for C_{19}H_{18}BrFN_2O_2: 403.25

Step 8: N-(S,R),5(S,R),6(S,R)-5-amino-2-fluorophenylV5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl]benzamide (li-rac)

A sealable flask was charged with sodium azide (2.322 g, 35.7 mmol, Aldrich), copper(I) iodide (0.453 g, 2.381 mmol, Aldrich) and (+)-sodium L-ascorbate (0.236 g, 1.190 mmol, Acros). The flask was evacuated and backfilled with nitrogen gas. A solution of N-[[l (S,R),5(S,R),6(S,R)]=5-(5-bromo-2-fluorophenyl)-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl]benzamide (li-rac, 4.8 g, 11.90 mmol) in ethanol (40.5 ml) was added, followed by water (16.20 ml). The reaction mixture was purged with nitrogen gas for 2 min. Trans-AyV'-dimethyl-l,2-cyclohexanediamine (0.563 ml, 3.57 mmol, Aldrich) was added and the reaction mixture was heated to 80 °C for 2.5 hs. The reaction was poured into a mixture of aqueous NH_4Cl/NH_4OH (200 mL, 9:1) and subsequently extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in MeOH (150 mL) and sodium borohydride (0.901 g, 23.81 mmol, Aldrich) was added portion wise at RT. Additional portions of sodium borohydride (0.901 g, 23.81 mmol, Aldrich) were added after 1 hs and 2 hs reaction time. Copper(I) iodide (2.2 g, 11.9 mmol, Aldrich) was added, followed by an additional portion sodium borohydride (0.901 g, 23.81 mmol, Aldrich). After 20 min, water was added and the reaction mixture was concentrated under reduced pressure. The remaining aqueous solution was extracted with EtOAc. The organic phase was washed with brine and dried over Na_2SO_4. The filtrate was concentrated and purified by silica gel column (10-100% EtOAc/hexanes) to afford the title compound (2.55 g, 7.51 mmol, 63.1% yield) as a beige solid. MS m/z = 340.1 [M+H]^+. Calculated for C_{19}H_{18}FN_2O_2: 339.36.

Step 9: N-[[l (S,R),5(S,R),6(S,R)]=5-(5-azido-2-fluorophenyl)-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl]benzamide (li-rac)

A solution of N-[[l (S,R),5(S,R),6(S,R)]=5-(5-amino-2-fluorophenyl)-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl]benzamide (li-rac, 0.7 g, 2.063 mmol) in ammonia (2M solution in methanol: 30.9 ml, 61.9 mmol, Aldrich) was heated to 80 °C. After 12 hs, additional ammonia (2M solution in methanol; 30.9 ml, 61.9 mmol, Aldrich) was added
and the reaction mixture was heated for 24 hs. The solvent was removed under reduced pressure and water (50 mL) and 1N HCl (50 mL) were added to the residue. The solution was extracted with EtOAc. The aqueous acidic phase was neutralized (pH = 7) by the addition of aqueous saturated bicarbonate solution. The aqueous phase was extracted 4 times with EtOAc. The combined organic phases were dried over MgSO4 and the solvent was removed under reduced pressure to obtain the title compound (350 mg), which was taken onto the next step without further purification. MS m/z = 236.1 [M+H]+. Calculated for C12H14FN3O: 235.26

**Example 2**

Step 1: N-[3-[(S,R),5(S,R),6(S,R)]]-3-benzamido-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yll-4-fluorophenyll-5-methoxypyrazine-2-carboxamide (2a-rac)

To a solution of N-[1 (S,R),5(S,R),6(S,R)]-5-(5-amino-2-fluorophenyl)-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yll benzamide (li-rac; 0.620 g, 1.827 mmol) in DMF (8.0 mL) were added 5-methoxypyrazine-2-carboxylic acid (0.282 g, 1.827 mmol, Ark Pharm), 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-f]pyridinium 3-oxid hexafluorophosphate (1.042 g, 2.74 mmol, Aldrich) and di-isopropylethylamine (0.636 mL, 3.65 mmol, Aldrich). The reaction was stirred at ambient temperature for 25 min. Water (50mL) was added and the resulting suspension was stirred for 15 min, and then filtered. The solid was dried to afford the title compound as a yellow solid (0.75 g, 1.577 mmol, 86% yield). MS m/z = 476.0 [M+H]+. Calculated for C23H22FN4O4: 475.47

Step 2: N-[3-[(S,R),5(S,R),6(S,R)]-3-amino-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yll 4-fluorophenyll-5-methoxypyr-2-carboxamide (Example 2b-rac)
A sealable vial was charged with N-[3-[(1(S,R),5(S,R),6(S,R))-3-benzamido-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl]-4-fluorophenyl]-5-methoxy pyrazine-2-carboxamide (2a rac; 1.28 g, 2.69 mmol) and ammonia (2.0 M solution in methanol; 30 ml, 60.0 mmol, Aldrich). The reaction mixture was heated to 80°C for 34 hours. The reaction mixture was filtered. The filter cake was rinsed with MeOH and dried to afford the title compound as a tan solid (230 mg, 0.62 mmol, 46% yield).

**MS m/z = 372.0 [M+H]^+**. Calculated for C_{18}H_{21}FN_{0.5}: 371.37

^1H NMR (400 MHz, DMSO-d$_6$) δ ppm 0.36 (td, J=6.36, 2.74 Hz, 1 H) 0.59 (dt, J=9.44, 6.24 Hz, 1 H) 1.57 (s, 3 H) 1.69 (dd, J=6.75, 3.23 Hz, 1 H) 3.96 - 4.07 (m, 4 H) 5.36 (s, 2 H) 7.11 (dd, J=11.74, 8.80 Hz, 1 H) 7.70 (dt, J=8.22, 3.72 Hz, 1 H) 8.02 (dd, J=7.24, 2.74 Hz, 1 H) 8.40 (d, J=1.37 Hz, 1 H) 8.88 (d, J=1.7 Hz, 1 H) 10.33 (s, 1 H)

**Step 3:** N-(3-((1S,5S,6S)-3-amino-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-methoxy pyrazine-2-carboxamide (Example 2b-A) and N-(3-((1R,5R,6R)-3-amino-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-methoxy pyrazine-2-carboxamide (Example 2b-B).

N-(3-[(1(S,R),5(S,R),6(S,R))-3-amino-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl]-4-fluorophenyl]-5-methoxy pyrazine-2-carboxamide (2b rac, 230 mg) was subjected to chromatography using supercritical C$_{0.2}$ (additives 40% methanol with 20 mM NH$_4$) on an ODS H column (21 x 250 mm, 5 µm) eluting at a flow rate 70 ml/min (100 bar pressure, 40°C column temperature). The first peak (retention time = 1.19 min) provided (1S,5S,6S)-5-(2-fluoro-5-(3-methoxy-1,7-naphthyridin-8-y1)amino)phenyl)-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (Example 2b-A, 108 mg, 0.28 mmol, 47% yield; 99% de; 99% ee) as a tan powder. The second peak (retention time = 2.28 min) provided (1R,5R,6R)-5-(2-fluoro-5-(3-methoxy-1,7-naphthyridin-8-y1)amino)phenyl)-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (Example 2b-B; 106 mg, 0.28 mmol, 46% yield; 99% de; 99% ee) as a tan powder.

**MS m/z = 372. 1 [M+H]^+**. Calculated for C$_{18}$H$_{21}$FN$_{0.5}$: 371.37 (for both enantiomers)

^1H NMR (Example 2-A; 400 MHz, CHLOROFORM -J) δ ppm 0.51 (td, J=6.94, 2.93 Hz, 1 H) 0.69 (dt, J=9.68, 6.60 Hz, 1 H) 0.79 - 0.95 (m, 1 H) 1.72 (s, 4 H) 1.79 - 1.91 (m, 1 H) 3.95 - 4.14 (m, 4 H) 7.06 (dd, J=11.44, 8.71 Hz, 1 H) 7.65 (dd, J=6.85, 2.74 Hz, 1 H) 7.97 - 8.05 (m, 1 H) 8.14 (d, J=1.17 Hz, 1 H) 9.02 (d, J=1.7 Hz, 1 H) 9.51 (br. s., 1 H)

^1H NMR (Example 2-B; 400 MHz, CHLOROFORM-J) δ ppm 0.51 (td, J=6.94, 2.93 Hz, 1 H) 0.69 (dt, J=9.83, 6.63 Hz, 1 H) 1.72 (s, 4 H) 1.84 (ddt, J=10.32, 6.97, 6.97, 3.91 Hz, 1 H) 3.95 - 4.13 (m, 4 H) 7.06 (dd, J=11.35, 8.80 Hz, 1 H) 7.65 (dd, J=6.94, 2.84 Hz, 1
Example 3

\[
\begin{align*}
\text{Me}^+\text{NO}^- & \quad \text{step 1} \quad \text{Me}^+\text{NO}^- \text{Cl}^- \\
3a & \quad \rightarrow \quad 3b \text{ (rac)} & 3b \text{ (rac)} & \rightarrow \quad 3c \text{ (rac)} \\
\text{Me} & \quad \text{step 2} \quad \text{Me} & \quad \text{step 3} \quad \text{Me} & \quad \text{step 4} \quad \text{Me} & \quad \text{step 5} \quad \text{Me} & \quad \text{step 6} \quad \text{Me} & \quad \text{step 7} \quad \text{Me} & \quad \text{step 8} \quad \text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} \\
\text{3a} & \quad \rightarrow \quad 3c (\text{rac}) & \text{3d (rac)} & \text{3e (rac)} & \text{3f (rac)} & \text{3g (rac)} & \text{3h (rac)} & \text{3h-A} & \text{3h-B} \\
\end{align*}
\]

Step 1: 5-(Chloromethyl)-3-methyl-4,5-dihydroisoxazole (3b-rac)

To a solution of acetaldehyde oxime (2.070 mL, 33.9 mmol, Aldrich) in THF (30 mL)/Chloroform (15 mL) was added N-chlorosuccinimide (4.75 g, 35.6 mmol, Aldrich) in one portion, followed by dropwise addition of pyridine (1.369 mL, 16.93 mmol, Aldrich) at rt. After completed addition the reaction mixture was allowed to stir at RT for 4 hrs. The solid was filtered off and the filtrate was cooled to 0 °C. Additional solid precipitated out. The solution was decanted off and concentrated under reduced pressure to give a light-yellow oil, which was taken onto the next step assuming 100 % theoretical yield (according to WO2008062739). The oil was dissolved in Et\textsubscript{2}O (100 mL) and THF (5 mL). Allyl chloride (8.28 mL, 102 mmol, Aldrich) was added, followed by triethylamine (4.71 mL, 33.9 mmol, Aldrich). The reaction mixture was cooled to 0 °C. The reaction mixture was allowed to warm up to RT and stirred for 3 days. The reaction mixture was filtered and the filtrate was washed with aqueous saturated ammonium chloride solution, followed by water. The organic phase was separated and dried over MgSO\textsubscript{4}. The solvent was removed under reduced pressure. The crude material was loaded onto a plug of silica gel and purified by chromatography eluting with a gradient of 5% to
35% EtOAc in hexane, to provide a yellow oil, which was dissolved in EtOAc and washed with aqueous CuSO$_4$ solution. The organic phase was separated and dried over MgSO$_4$. The solvent was removed under reduced pressure to obtain the title compound as a yellow oil (1.9 g, 14.22 mmol, 42.0 % yield). MS m/z = 134.0 [M+H]$^+$. Calculated for C$_7$H$_{16}$BrFNO: 133.58.

Step 2: [(S,R),(S,R)]-4-methyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (3c-rac)

Potassium 2-methylpropan-2-olate (63.8 g, 568 mmol, Aldrich) was added portion wise to a solution of 5-(chloromethyl)-3-methyl-4,5-dihydroisoxazole (3b rac; 33 g, 247 mmol) in DMSO (618 mL) cooled with a water bath. The reaction was quenched after 30 min by the addition of ice. Et$_2$O was added and the organic phase was separated. The organic phase was washed with aqueous saturated LiCl solution and dried over MgSO$_4$. The Et$_2$O was removed by distillation under ambient pressure. The remaining liquid was distilled under reduced pressure and the title compound was obtained as a colorless oil (13 g, 134 mmol, 54.2 % yield; boiling point 85 °C at 35 Torr). GCMS m/z = 97 M$^+$. Calculated for C$_7$H$_{16}$NO: 97.12.

Step 3: [(S,R),(S,R)]-4-methyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (3d-rac)

A solution of 4-bromo-1-fluoro-2-iodobenzene (8.52 g ml, 28.3 mmol, Matrix Scientific) in ether (20 ml) was cooled to -78 °C before adding a solution of n-butyllithium (2.5M in hexanes; 11.33 ml, 28.3 mmol, Aldrich) drop wise. The reaction mixture was stirred at -78 °C for 30 minutes. In a separate flask, a solution of [(S,R),(S,R)]-4-methyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (1.1 g, 11.33 mmol, 3c rac) in toluene (110 ml) was cooled to -78 °C before adding boron fluoride diethyl etherate (1.677 ml, 13.59 mmol, Aldrich) drop wise. The solution was stirred at -78 °C for 15 minutes. The aryl-lithium solution was added to the isoxazoline solution drop wise via cannula. Upon complete addition the reaction was warmed to RT and stirred for 16 hours. The reaction was quenched with aqueous saturated ammonium chloride solution and diluted with water and EtOAc. The aqueous layer was washed with additional EtOAc and the organic layers were combined, washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography using a gradient of 5-30% EtOAc in Hexanes to afford the title compound (1.969 g, 7.24 mmol, 63.9 % yield). MS m/z = 272.0 [M+H]$^+$. Calculated for C$_{13}$H$_{16}$BrFNO: 272.11.
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Step 4: rUS.R\(2(S,R)\)-(2-r(R,S))-1-amino-1-(5-bromo-2-fluorophenylmethyl)cyclopropanol (3e-rac)

\(11(S,R)\)-(4(R,S),5(S,R))-4-(5-bromo-2-phenolyl)-4-methyl-2-oxa-3-azabicyclo[3.1.0]hexane (2.5 g, 9.11 mmol, 3d rac) was dissolved in glacial acetic acid. The reaction was heated to 40 °C for 3.5 hours. The reaction was cooled to RT, filtered and the filter cake was washed with additional HOAc. The filtrate was concentrated under reduced pressure. The crude residue was dissolved in water and the solution was basified to pH=10 by the addition of saturated sodium bicarbonate aqueous solution and a few drops of 2M NaOH solution. The basic solution was extracted with chloroform three times. The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure to afford the title compound as a yellow solid. (2.4209 g, 8.83 mmol, 97 % yield). MS m/z = 274 [M+H]*. Calculated for C_{14}H_{16}BrFNO: 274.129

Step 5: N-rUS.R\(5(S,R)\)-5-(5-bromo-2-fluorophenyl)-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl benzamide (3f-rac)

The title compound was prepared using a procedure similar to that described in step 7 for the synthesis of lh-rac, but using \([l(S,R),2(S,R)]\)-2-\([l(S,R)\)-1-amino-1-(5-bromo-2-fluorophenylmethyl)cyclopropanol (3e-rac). MS m/z = 403.0 [M+H]*. Calculated for C_{19}H_{18}BrFNO_{2}: 403.245

Step 6: N-rUS.R\(5(S,R)\)-5-(5-amino-2-fluorophenyl)benzamide (3g-rac)

The title compound was prepared using a procedure similar to that described in step 8 for the synthesis of li-rac, but using N-[\([l(S,R),5(S,R),6(S,R)]\)-5-\([l(S,R)\)-5-amino-2-fluorophenyl]-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl benzamide (3f-rac). MS m/z = 340.1 [M+H]*. Calculated for C_{19}H_{18}FN_{2}O_{2}: 339.364

Step 7: N-rUni(S,R)-N-(S,R)-N-(5(S,R)-5-(5-amino-2-fluorophenyl)-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl benzamide (3g-rac)

The title compound was prepared using a procedure similar to that described in step 9 for the synthesis of lk-rac, but using N-[\([l(S,R),5(S,R),6(S,R)]\)-5-(5-amino-2-fluorophenyl)-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl benzamide (3g-rac). MS m/z = 236.0 [M+H]*. Calculated for C_{12}H_{10}FN_{2}O: 235.25
Step 8: (0.5S,6R)-5-(5-amino-2-fluorophenyl)-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (3h-A) and (1S,5R,6S)-5-(5-amino-2-fluorophenyl)-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (3h-B)

N-[1(S,R),5(R,S),6(S,R)]-5-(5-amino-2-fluorophenyl)-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (3h-A) and (1S,5R,6S)-5-(5-amino-2-fluorophenyl)-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (3h-B) was subjected to chromatography using supercritcal CO₂ (additives 22% EtOH with 20 mM NH₃) on a CHIRALPAK AD-H SFC column (21 x 250 mm, 5 µm) eluting at a flow rate 70 ml/min (100 bar pressure, 40 °C column temperature). The first peak (retention time = 1.57 min) provided (Example 3h-A, 454 mg, 1.930 mmol, 41% yield; 99% de; 99% ee) as a white powder. The second peak (retention time = 2.31 min) provided (Example 3h-B, 464 mg, 1.972 mmol, 42% yield; 99% de; 99% ee) as a white powder. MS m/z = 236.2 [M+H]+. Calculated for C₁₂H₁₄FN₃O₂ (rac) = 235.1 12 (for both enantiomers)

³H NMR (400 MHz, CHLORORFORM-J) δ ppm 0.76 - 0.84 (m, 1 H) 0.94 (td, J=6.80, 2.64 Hz, 1 H) 1.58 (d, J=1.37 Hz, 3 H) 1.71 - 1.80 (m, 1 H) 3.54 (br. s, 4 H) 3.88 (ddd, J=7.48, 6.02, 2.74 Hz, 1 H) 6.51 (dt, J=8.22, 3.42 Hz, 1 H) 6.73 (dd, J=6.85, 2.93 Hz, 1 H) 6.83 (dd, J=11.84, 8.51 Hz, 1 H)

Example 4

Step 1: [1(R,S),4(S,R),5(R,S)]-4-(6-bromo-3-fluoropyridin-2-yl)-4-methyl-2-oxa-3-azabicyclo[3.1.0]hexane (4a rac)

A solution of n-butyllithium solution, (1.6M in hexane; 3.22 ml, 5.15 mmol) was added dropwise to solution of 2-bromo-5-fluoropyridine (0.906 g, 5.15 mmol) in Et₂O (20 mL; anhydrous) at -78 °C. The reaction mixture was allowed to stir for 25 min at -78 °C. An additional flask was charged with 4-methyl-2-oxa-3-azabicyclo[3.1.0]hexene (0.25 g, 2.57 mmol, 3c-rac) and toluene (20 mL). The solution was cooled to -78 °C and boron fluoride diethyl etherate (0.477 ml, 3.86 mmol) was added. The solution was stirred for 15 minutes and then transferred via cannula to the heteroaryl lithium solution. Upon complete addition the reaction mixture was stirred at -78 °C for 20 min and then allowed to warm gradually to 10 °C. After 1 h, the reaction mixture was quenched by the addition
of aq. sat ammonium chloride solution. EtOAc was added and the organic extract was washed with brine and dried over MgSO₄. The solution was filtered and concentrated in vacuo to give the crude material. The crude material was absorbed onto a plug of silica gel and purified by silica gel chromatography, eluting with a gradient of 5% to 45% EtOAc in hexane, to provide the title compound as a single diastereoisomer (0.226 g, 0.828 mmol, 32.1 % yield, >95% de). MS m/z = 274.9 [M+H]+.

**Steps 2: ddr(R.S), r5R.S)-2-rrS.RV1 -amino-1-(6-bromo-3-fluoropyridin-2-yl)-4-methyl-2-oxa-3-azabicyclo[4.1.0]hept-3-en-3-yl)-4-methyl-2-oxa-3-azabicyclo[4.1.0]hept-3-en-3-yl)benzamide (4b rac)**

A flask was charged with [1(R,S),4(S,R),5(R,S)]-4-(6-bromo-3-fluoropyridin-2-yl)-4-methyl-2-oxa-3-azabicyclo[4.1.0]hept-3-en-3-yl)benzamide (4d rac)

The title compound was prepared using a procedure similar to that described in step 7 for the synthesis of lb-rac, but using [1(R,S), (2S,R)]-2-[(S,R)-1-amino-1-(6-bromo-3-fluoropyridin-2-yl)ethyl]cyclopropanol (4b rac). MS m/z = 403.9 [M+H]+.

**Step 4: ddr(R,S), (5S,R), i6R.S)-5-i6-bromo-3-fluoropyridin-2-yl)-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)benzamide (4d rac)**

To a solution of N-[(1R,S), (5S,R), (6R,S)]-5-(6-bromo-3-fluoropyridin-2-yl)-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)benzamide (4d rac) in MeOH (49.5 ml) was added DBU (3.36 mL, 22.3 mmol). The reaction mixture was heated to 70 °C over night. Upon cooling, a white solid precipitated out, which was filtered off. The solid was taken up in EtOAc (70 mL), washed with saturated ammonium chloride solution (70 mL) and brine. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure to afford the title compound (1.67 g, 5.56 mmol, 75.0 % yield) as a fine white solid.

MS m/z = 301.9 [M+H]+.
Example 5

Step 1: r(S,R),4(R,S),5(S,R)]-4-(5-Bromo-2-fluoropyridin-3-yl)-5-methyl-2-oxa-3-azabicyclo[3.1.0]hexane (5a rac)

A solution of 3,5-dibromo-2-fluoropyridine (4.88 g, 19.14 mmol) and toluene (55 mL) under argon atmosphere was cooled to 0 °C. A solution of isopropylmagnesium chloride lithium chloride (1.3 M solution in THF, 14.8 mL, 19.24 mmol) was added dropwise. The resulting mixture was stirred at 0 °C for 30 min and then cooled to -78 °C. In a separate flask, a solution of 4-methyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (3c rac, 0.93 g, 9.57 mmol) and toluene (53 mL) under argon atmosphere was cooled to -78 °C and boron trifluoride diethyl etherate (3.54 mL, 28.7 mmol) was added dropwise. The reaction mixture was stirred at -78 °C for 15 min and added via syringe to the 3,5-dibromo-2-fluoropyridine-Grignard mixture. The resulting mixture was allowed to warm to RT and stirred for additional 2 h. The reaction was quenched with aqueous saturated NH4Cl solution and partitioned between EtOAc and water. The organic layer was dried over MgSO4). The filtrate was concentrated in vacuo and the residue was purified by silica gel chromatography (0% to 25% EtOAc/Hexanes) to afford the title compound as a tan solid. MS m/z = 272.9, 275.0 [M+H]+.

Step 2 and 3: r([S,R].5(R,S).6(S,R)].5-(5-Bromo-2-fluoropyridin-3-yl)-5-methyl-2-

oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)benzamide (5c rac).

The title compound was prepared using procedures similar to that described in steps 6 and 7 for the synthesis of 1h-rac, but using [l(S,R).4(R,S).5(S,R)].4-(5-Bromo-2-

fluoropyridin-3-yl)-4-methyl-2-oxa-3-azabicyclo[3.1.0]hexane (5a rac). MS m/z = 404.0, 406.0 [M+H]+.
Step 4: tert-Butyl benzoyl[(S,R),5(R,S),6(S,R)]1-5-(5-bromo-2-fluoropyridin-3-yl)-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl]carbamate (5d rac)

To a solution of N-[(S,R),5(R,S),6(S,R)]-5-(5-bromo-2-fluoropyridin-3-yl)-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl]benzamide (5c rac, 0.718 g, 1.77 mmol) in DCM (8.9 mL, 1.77 mmol) under argon atmosphere was added di-tert-butyl dicarbonate (0.46 g, 2.13 mmol), followed by 4-(dimethylamino)-pyridine (0.11 g, 0.88 mmol). The reaction mixture was stirred at room temperature for 1 h. CH₂Cl₂ was added. The phases were separated and the aqueous layer was back-extracted with C₄ ḳ₄. The combined organic extracts were washed with water, dried over MgSO₄ and the filtrate was concentrated in vacuo. The residue was purified by silica gel chromatography (0% to 15% EtOAc/Hexanes) afforded the title compound as a colorless foam. MS m/z = 503.9, 506.0 [M+H]^+.

Step 5: tert-butyl [(l(S,R),5(R,S),6(S,R)]-5-(5-bromo-2-fluoropyridin-3-yl)-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl]carbamate (5e rac)

To a solution of tert-butyl benzoyl [(l(S,R),5(R,S),6(S,R)]-5-(5-bromo-2-fluoropyridin-3-yl)-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl]carbamate (5d rac; 486 mg, 0.964 mmol) in MeOH (6 mL) was added potassium carbonate (0.029 mL, 0.482 mmol) and the resulting reaction mixture was stirred at RT for 30 min. The reaction mixture was cooled to -78°C and quenched with aqueous saturated ammonium chloride solution, followed by extraction with EtOAc (2 x 20 mL). The combined organic extracts were dried over MgSO₄ and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (0%-100% EtOAc/hexane) to give 368 mg of the title compound as a white solid. MS (ESI, positive ion) m/z: 400.1, 401.9 (M+H).

Step 6: (l(S,R),5(R,S),6(S,R)]-5-(5-bromo-2-fluoropyridin-3-yl)-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-ene-3-amine (5f rac)

To a solution of tert-butyl ((l(S,R),5(R,S),6(S,R)]-5-(5-bromo-2-fluoropyridin-3-yl)-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl]carbamate (5e rac, 368 mg, 0.919 mmol) in DCM (2.5 mL) was added trifluoroacetic acid (0.956 mL, 12.87 mmol). The resulting mixture was stirred at room temperature for 45 min. Additional trifluoroacetic acid (0.5 mL) was added and the mixture reaction was stirred at RT for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in DCM (10 mL). The solution was cooled to -50°C and aqueous saturated NaHCO₃ solution (4 mL) was added dropwise. The reaction mixture was stirred at RT for 10 min, followed by
extraction with DCM (2 x 15 mL). The combined organic extracts were dried over MgSO₄ and concentrated in vacuo. The residue was absorbed onto silica gel. Purification by silica gel flash column chromatography (0%-20% ammonia in MeOH 2M/DCM) gave 267 mg of the title compound as a light yellow solid. MS (ESI, positive ion) m/z: 300.0, 302.0 (M+H).

**Example 6**

Step 1: 5-(Chloromethyl)-3-(fluoromethyl)-4,5-dihydroisoxazole (6b rac)

To a solution of (5-(chloromethyl)-4,5-dihydroisoxazol-3-yl)methanol (1.58 g, 10.56 mmol, 6a rac, Tetrahedron 1986, 42, 5267) in DCM (30 mL) at -78 °C was added (diethylamino)sulfur trifluoride (1.60 ml, 12.11 mmol). The reaction mixture was stirred at -78 °C for 10 min, warmed from -78 °C to room temperature over 15 min, stirred at room temperature for 1 h and quenched with saturated aq. saturated NaHCO₃ solution. The reaction mixture was diluted with diethyl ether and water. The aqueous phase was extracted with diethyl ether (4 x) and the combined organic extracts were washed with...
brine (1 x), dried over MgSO₄, filtered, and concentrated in vacuo to give a dark red oil.

Purification by flash column chromatography on silica gel (20% diethyl ether in pentane) gave the title compound (0.79 g, 49% yield).

**Step 2:** 4-(fluoromethyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (6c rac)

To a solution of 5-(chloromethyl)-3-(fluoromethyl)-4,5-dihydroisoxazole (0.78 g, 5.13 mmol, 6b rac) in THF (25 mL) at 0 °C was added potassium tert-butoxide, (1.0M solution in THF; 5.50 ml, 5.50 mmol). The reaction mixture was stirred at 0 °C for 20 min and additional potassium tert-butoxide solution (0.50 mL) was added. Stirring was continued at 0 °C for additional 20 min. The reaction mixture was warmed to RT, stirred for 20 min and quenched with saturated NH₄Cl solution. The reaction mixture was diluted with diethyl ether and water. The aqueous phase was extracted with diethyl ether (3 x). The combined organic extracts were washed with brine and dried over MgSO₄. The filtrate was concentrated under reduced pressure to give a dark red oil. Purification by flash column chromatography on silica gel (20% diethyl ether in pentane) gave the title compound (0.57 g, 96% yield).

**Step 3:** 4-(5-bromo-2-fluorophenyl)-4-(fluoromethyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (6d rac)

To a solution of 4-bromo-1-fluoro-2-iodobenzene (22.1 g, 73.6 mmol) in Et₂O (150 mL) at -78 °C was added n-butyllithium (1.6 M in hexane, 46.0 mL, 73.6 mmol).

The solution was stirred at -78 °C for 15 min. An additional flask was charged with a solution of [1(S,R),5(S′,R′)]-4-(fluoromethyl)-2-oxa-3-azabicyclo[3.1.0]hexane (6c rac, 4.21 g, 36.6 mmol) and boron trifluoride diethyl etherate (4.65 mL, 36.7 mmol) in PhMe (170 mL) at -78 °C. The second solution was added dropwise via cannula over 10 min to the aryl lithium solution. The reaction mixture was stirred at -78 °C for 30 min and quenched with aqueous saturated NH₄Cl solution. The reaction mixture was warmed to RT and diluted with EtOAc and water. The aqueous phase was extracted with EtOAc (2 x) and the combined organic extracts were washed with brine and dried over MgSO₄. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel flash column chromatography (5% to 20% EtOAc in hexanes) to give the title compound (9.58 g, 33.0 mmol, 90% yield) as a yellow oil. LC/MS (ESI) m/z = 289.90 (M+H).

**Steps 4-5:** N-(iR,S)-1(5S,R)-iS,iR-3-bromo-2-fluorophenyl-i5-bromo-2-fluoromethyl-i5-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)benzamide (6f-rac)
The title compound was prepared following procedures similar to those described in steps 2 and 3 for the synthesis of 4c rac, but using \( \{l(R,S),4(S,R),5(R,S)\}\)-4-(5-bromo-2-fluorophenyl)-4-(fluoromethyl)-2-oxa-3-azabicyclo[4.1.0]hept-3-en-3-amine \( (6g-B, 0.61 \text{ g}, 1.9 \text{ mmol}) \), sodium azide \( (0.388 \text{ g}, 6.0 \text{ mmol}, \text{ rac}) \) for synthesis of 6d rac. MS \( m/z = 422.9 \ [\text{M} + \text{H}]^+ \).

5 Step 6: \( \{1(S,R),5(R,S),6(S,R)\}\)-5-(5-Bromo-2-fluorophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine \( (6g-rac) \)

The title compound was prepared following a procedure similar to that described in step 4 for the synthesis of 4d rac, but using \( \{N-(\{1(R,S), (5S,R), (6R,S)\}\)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl\)benzamide \( (6f-rac) \) MS \( m/z = 316.9 \ [\text{M} + \text{H}]^+ \). Calculated for \( \text{C}_{12}\text{H}_{13}\text{BrF}_2\text{N}_2\text{O} 316.0 \) for \( \{1^6.S,5^6.R\}\)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine \( (6g-A) \) and \( \{1^6.S,5^6.S\}\)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine \( (6g-B) \)

15 \( \{1^6.S,5^6.S\}\)-5-(5-Bromo-2-fluorophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine \( (6g-rac, 493 \text{ mg}, 1.39 \text{ mmol}) \) was subjected to chromatography using supercritical \( \text{CO}_2 \) (additives 35% MeOH with 20 mM NH\(_3\)) on a Chiralpak ICH \( (20 \times 250 \text{ mm}, 5 \mu\text{m}) \) eluting at a flow rate 75 mL/min (100 bar pressure, ambient column temperature).

The first peak (retention time = 1.97 min) provided \( \{\text{Example} 6g-A; 220 \text{ mg}, 0.69 \text{ mmol, 45% yield; }>99\% \text{ de; }>99\% \text{ ee}\} \) as a light yellow solid. LC/MS \( \text{(ESI)} \) \( m/z = 317.0 \) \( \{\text{M} + \text{H}\}\). Calculated for \( \text{C}_{12}\text{H}_{13}\text{BrF}_2\text{N}_2\text{O} 316.0 \)

1H NMR \( \text{(CD}_3\text{OD)} \) \( \delta = 7.59 \) (dd, \( J = 7.0, 2.5 \text{ Hz}, 1\text{H} \)), 7.51 (ddd, \( J = 8.6, 4.2, 2.6 \text{ Hz}, 1\text{H} \)), 7.11 (ddd, \( J = 11.7, 8.6 \text{ Hz}, 1\text{H} \)), 4.67 - 4.80 (m, 1\text{H})), 4.51 - 4.65 (m, 1\text{H})), 3.96 - 4.12 (m, 1\text{H})), 1.63 - 1.80 (m, 1\text{H})), 1.17 (td, \( J = 6.8, 2.6 \text{ Hz}, 1\text{H} \)), 0.92 (dt, \( J = 9.4, 6.7 \text{ Hz}, 1\text{H} \)).

25 The second peak (retention time = 3.00 min) provided \( \{\text{Example} 6g-B; 210 \text{ mg}, 0.66 \text{ mmol, 43% yield; }>99\% \text{ de; }>99\% \text{ ee}\} \) as a light yellow solid. MS \( m/z = 316.9 \) \{\text{M} + \text{H}\}. Calculated for \( \text{C}_{12}\text{H}_{13}\text{BrF}_2\text{N}_2\text{O} 316.0 \)

1H NMR \( \text{(CD}_3\text{OD)} \) \( \delta = 7.59 \) (dd, \( J = 7.0, 2.3 \text{ Hz}, 1\text{H} \)), 7.45 - 7.55 (m, 1\text{H})), 7.10 (ddd, \( J = 11.7, 8.8 \text{ Hz}, 1\text{H} \)), 4.67 - 4.79 (m, 1\text{H})), 4.51 - 4.65 (m, 1\text{H})), 3.95 - 4.16 (m, 1\text{H})), 1.60 - 1.86 (m, 1\text{H})), 1.17 (td, \( J = 6.7, 2.4 \text{ Hz}, 1\text{H} \)), 0.84 - 1.00 (m, 1\text{H})).

30 Step 8: \( \{1^7.S,5^7.S,6^7.R\}\)-5-(5-amino-2-fluorophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine \( (6h-B) \)

To a mixture of \( \{1^7.S,5^7.S,6^7.R\}\)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine \( (6g-B, 0.61 \text{ g}, 1.9 \text{ mmol}) \), sodium azide \( (0.388 \text{ g}, \text{ rac}) \)...
5.96 mmol), (+)-sodium 1-ascorbate (0.080 g, 0.41 mmol), copper(I) iodide (0.086 g, 0.45 mmol) and (1S,2S)-dimethylcyclohexane-1,2-diamine (0.075 mL, 0.47 mmol) under argon atmosphere were added EtOH (2.40 mL) and water (1.2 mL). The reaction mixture was heated at 70 °C for 1.5 h. The cooled reaction mixture was poured into a mixture of 10:1 NH4Cl/ammonium hydroxide and diluted with C4 H4. The aqueous layer was extracted with CH2Cl2 (3x) and the combined organic extracts were washed with aqueous saturated NH4Cl solution. The solution was dried over MgSO4 and the filtrate was concentrated in vacuo to give a yellow solid, which was dissolved in THF (8.4 mL) and water (2.8 mL). Trimethylphosphine (1.0 M solution in THF, 1.924 mL, 1.924 mmol) was added and the reaction mixture was stirred at RT for 20 min. The reaction was diluted with CH2Cl2 and water. The phases were separated and the aqueous layer was extracted with C4 H4. The combined organic extracts were dried over MgSO4 and the filtrate was purified by silica gel flash column chromatography (0% to 5% 2 M NH3 in MeOH/CH2Cl2) to afford the title compound (0.4473 g, 1.766 mmol, 92% yield) as a maize color solid. MS m/z = 254.0 [M+H]+. Calculated for C12H11F2N3O 253.1.


The title compound was prepared following a procedure similar to that described in step 8 for the synthesis of [(1S,5S,6a)-5-(5-amino-2-fluorophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (6h-B), but using [(5S,6H,R),5(5amino-2-fluorophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (6g-rac) MS m/z = 254.0 [M+H]+.

Example 7:

A solution of 2-chloro-5-fluoropyridine (1.8 mL, 17.75 mmol) in diethyl ether (50 mL) under nitrogen atmosphere was cooled to -78 °C. A solution of n-butyllithium (2.5 M in hexanes, 6.8 ml, 17.00 mmol) was added dropwise and the solution was stirred for
20 minutes. In a separate flask, 4-(fluoromethyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (1.0 g, 8.69 mmol, 6c rac) was dissolved in dry toluene (10 mL) and cooled to -78 °C under nitrogen atmosphere. Boron fluoride diethyl etherate (1.2 ml, 9.72 mmol) was added dropwise and the reaction mixture was stirred for 5 minutes. The solution of the pyridyl anion was transferred to the isoxazole/boron trifluoride mixture via cannula. The reaction mixture was stirred for additional 25 minutes and then quenched by addition of saturated ammonium chloride solution (10 mL). The reaction mixture was allowed to warm to rt and diethyl ether (200 mL) was added. The organic layer was separated, washed with brine (70 mL) and dried over magnesium sulfate. The filtrate was concentrated under reduced pressure and the crude residue was purified using silica chromatography (0-100% ethyl acetate/hexanes) to give the title compound (1.30 g, 5.27 mmol, 60.7% yield, >95% de). MS m/z = 246.9 [M+H]+.

**Step 2:** \( \eta(1R,S), r2R.S)1-2-rrS.RV1-amino-1 -r6-chloro-3-fluoropyridin-2-ylV2 fluorooethylDcyclopropanol (7b rac) 

The title compound was prepared using a procedure similar to that described in step 2 for the synthesis of 4b-rac, but using \([(1R,S), (4S,R), (5R,S)]-4-(6-Chloro-3-fluoropyridin-2-yl)-4-(fluoromethyl)-2-oxa-3-azabicyclo[3.1.0]hexane (7a rac). MS m/z = 249.1 [M+H]+.

**Step 3:** \( N-r(1R.S), (5S,R), r6R.S)1-5-r6-Chloro-3-fluoropyridin-2-ylV5-rfluoromethylIV2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)benzamide (7c rac) 

The title compound was prepared using a procedure similar to that described in step 7 for the synthesis of li-rac, but using \([(1R,S), (2R,S)]-2-((S,R)-l-amino-1-(6-chloro-3-fluoropyridin-2-yl)-2-fluoroethyl)cyclopropanol (7b rac). MS m/z = 377.9 [M+H]+.

**Step 4:** \( N-r(1R.S), (5S,R), r6R.S)1-5-r6-amino-3-fluoropyridin-2-ylV5-rfluoromethylIV2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)benzamide (7d rac) 

The title compound was prepared using a procedure similar to that described in step 8 for the synthesis of li-rac, but using \(-[(1R,S), (5S,R), (6R,S)]-5-(6-Chloro-3-fluoropyridin-2-yl)-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)benzamide (7c rac). MS m/z = 359.0 [M+H]+.

**Example 8**
Step 1: r i r S . R 4 R . S ) l-5-r5-bromo-2-fluoropyridin-3-ylV5-rfluoromethylV2-
oxa-3-azabicvclo[4.1.0]hept-3-en-3-amine (8f rac)

To a solution of diisopropylamine (3.65 mL, 26.1 mmol) in THF (25 mL) under nitrogen atmosphere, cooled to 0°C, was added a solution of butyllithium (1.6M in hexane, 16.29 mL, 26.1 mmol) dropwise. After completed addition, the reaction mixture was stirred at 0°C for 10 min. Then, the mixture was cooled to -78°C and 5-bromo-2-
fluoropyridine (3.00 mL, 26.1 mmol) was added dropwise. The reaction mixture was stirred at -78°C for 30 min, followed by the addition of NNN',N'-tetra-methyl-
ethylenediamine (3.90 mL, 26.1 mmol). The resulting mixture was stirred at -78°C for 5 min. In an additional flask, a solution of [l(R,S),5(R,S)]-4-(fluoromethyl)-2-oxa-3-
azabicclo[3.1.0]hex-3-ene (6c rac, 1.5 g, 13.03 mmol) in toluene (37.5 mL) was treated with boron trifluoride diethyl etherate (1.608 mL, 13.03 mmol) at -78°C under nitrogen atmosphere. After 10 min, this solution was added dropwise via cannula to the aryl lithium solution. The resulting reaction mixture was then stirred at -78°C for 1 h. The reaction was quenched with aqueous saturated NH₄C₁ solution and diluted with EtOAc. The organic extract was dried over MgSO₄ and the filtrate was concentrated in vacuo. The residue was absorbed onto silica gel and purified by silica gel flash column chromatography (0%-35% EtOAc/heptane) to give 1259 mg of the title compound as a light yellow solid. MS (ESI, positive ion) m/z: 290.9, 292.9 (M+H).
The title compound was prepared following procedures similar to those described in steps 2 to 6 for the synthesis of 6f rac, but using \([l(S,R),4(R,S),5(S,R)]-4-(5-bromo-2-fluoropyridin-3-yl)-2-(fluoromethyl)-2-oxa-3-azabicyclo[3.1.0]hexane\) (8a rac) MS (ESI, positive ion) m/z: 317.9, 320.9 (M+H).

**Step 7**: \((lS,5R,6S)-5-(5-bromo-2-fluoropyridin-3-yl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine\) (8f-A)

\[\text{[l(S,R),5(R,S),6(S,R)-5-(5-bromo-2-fluoropyridin-3-yl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (8f-B)}\]

\([l(S,R),5(R,S),6(S,R)-5-(5-bromo-2-fluoropyridin-3-yl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (8f-A)\) and \((IR,5S,6R)-5-(5-bromo-2-fluoropyridin-3-yl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (8f-B)\) were subjected to chromatography using supercritical \(\text{CO}_2 (25\% \text{ MeOH})\) on a IC-H column (21.2 x 250 nm, 5 \(\mu\)m) eluting at a flow rate 80 mL/min (209 bar, 40°C column temperature). The first peak (retention time = 3.7 min) provided \((IS,5R,6S)-5-(5-bromo-2-fluoropyridin-3-yl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (8f-A, 108 mg, 0.40 mmol, 63% yield, 99% de; 99% ee) as a white solid. MS (ESI, positive ion) m/z: 317.9, 320.9 (M+H).

\[^1\text{H NMR (MeOH)}\] \(\delta: 8.22-8.24 \text{ (m, 1H), 8.06 (dd, J=8.6, 2.5 Hz, 1H), 4.52-4.76 (m, 2H), 4.04-4.09 (m, 1H), 1.64-1.71 (m, 1H), 1.13 (td, J=6.8, 2.6 Hz, 1H), 0.93 (dt, J=9.6, 6.7 Hz, 1H). The second peak (retention time = 4.5 min) provided (IR,5S,6R)-5-(5-bromo-2-fluoropyridin-3-yl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (8f-B, 112 mg, 0.352 mmol, 65% yield, 99% de; 99% ee) as a light yellow solid. MS (ESI, positive ion) m/z: 317.9, 320.9 (M+H).

\[^1\text{H NMR (MeOH)}\] \(\delta: 8.24-8.27 \text{ (m, 1H), 8.08 (dd, J=8.6, 2.5 Hz, 1H), 4.54-4.80 (m, 2H), 4.12 (br. s., 1H), 1.67-1.74 (m, 1H), 1.13-1.20 (m, 1H), 0.97 (dt, J=9.5, 6.7 Hz, 1H).}

**Step 8**: \((IR,5S,6R)-5-(5-amino-2-fluoropyridin-3-yl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (8g-B)

A sealable vial was charged with (IR,5S,6R)-5-(5-bromo-2-fluoropyridin-3-yl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (8f-B, 0.1016 g, 0.319 mmol), trifluoroacetamide (0.072 g, 0.639 mmol), copper(I) iodide (0.018 g, 0.096 mmol) and potassium carbonate (0.177 g, 1.278 mmol), followed by dioxane (1.8 mL) andtrans-N,N'-dimethylcyclohexane-1,2-diamine (0.015 mL, 0.096 mmol). The reaction mixture was purged with nitrogen for 5 min and then heated at 120 °C for 20 h. The cooled reaction mixture was diluted with CH2Cl2 and washed with aqueous saturated NaHCO3 solution. The layers were separated and the aqueous layer was extracted with 15% MeOH/CH2Cl2. The combined organic extracts were dried over MgSO4 and the filtrate
A-1813-WO-PCT

was concentrated in vacuo. The residue was purified by silica gel flash chromatography (1% to 10% MeOH/CH₂Cl₂) afforded the title compound (0.061 g, 0.240 mmol, 75% yield) as a tan amorphous solid. MS (ESI, positive ion) m/z: 255.1 (M+H)

Example 9

Step 1: n[(1S,4R,5S)4-i5-bromo-2-chloropheny4-i5-fluoromethiv2-oxa-3-azabicvclo[3.1.0]hexane (9a rac)

A flame dried round bottom flask was charged with 4-bromo-1-chloro-2iodobenzene (33.1 g, 104 mmol) and Et₂O (206 mL). The solution was cooled to -78 °C and a solution of n-butyllithium solution (2.5 M in hexanes, 41.7 mL, 104 mmol) was added dropwise. The reaction mixture was stirred at -78 °C for 15 minutes. A second flame dried round bottom flask was charged with a solution of 4-(fluoromethyl)-2-oxa-3azabicyclo[3.1.0]hex-3-ene (6c rac; 6 g, 52.1 mmol) in toluene (229 mL) and cooled to -78 °C. Boron trifluoride diethyl etherate (6.61 mL, 52.1 mmol) was added, the reaction mixture was stirred for 5 minutes at -78 C and added via cannula to the aryllithium species. The reaction mixture was stirred at -78 °C for 10 minutes. The reaction was quenched with saturated ammonium chloride solution and warmed to RT. The reaction mixture was diluted with water and EtOAc. The organic layer was separated and the aqueous layer was washed with additional EtOAc. The combined organic layers were
washed with brine and dried over magnesium sulfate. The filtrate was concentrated under reduced pressure and the crude material was purified via silica gel chromatography, eluting with 5-45% EtOAc:Hexanes to afford the title compound (10.1 g, 33.2 mmol, 63.8 % yield). MS m/z = 305.9 [M+H]+. Calculated for C11H8BrClFNO: 306.6

Step 2: [[1(R,S), 2R,S]-]-2-rrS.RV1-amino-1-(5-bromo-2-chlorophenyl)1V2-
fluoroethylDecypropanol  (6b rac)

To a solution of [(1R,S), (4S,R), (5R,S)]-4-(5-bromo-2-chlorophenyl)-4-(fluoromethyl)-2-oxa-3-azabicyclo[4.1.0]hept-3-en-3-yl)benzamide (9d-A, 876 mg, 2.34 mmol, 41.7 %yield; 99%

N-((1R,S), (5S,R), (6R,S))-5-5-amino-2-chlorophenyl)5-fluoromethyl)-2-oxa-3-azabicyclo[4.1.0]hept-3-en-3-yl)benzamide  

The title compound was prepared following procedures similar to those described in steps 7 and 8 for the synthesis of li rac, but using [(1R,S), (2R,S)]-2-((S,R)-1-amino-1-(5-bromo-2-chlorophenyl)-2-fluoroethyl)cyclopropanol  (6b rac) MS m/z = 374.0 [M+H]+. Calculated for C10H12BrFNO: 373.8

Step 5: N-((1S,5R,6S)-5-(5-amino-2-chlorophenyl)-5-(fluoromethyl)-2-oxa-4-
azabicyclo[4.1.0]hept-3-en-3-yl)benzamide  (6b-A) & N-((1R,5S,6R)-5-(5-amino-2-
chlorophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)benzamide  

N-((1R,S), (5S,R), (6R,S))-5-(5-amino-2-chlorophenyl)-5-(fluoromethyl)-2-oxa-4-
azabicyclo[4.1.0]hept-3-en-3-yl)benzamide  (9d, 2.1g) was subjected to chromatography using supercritical C02 (additives 35% MeOH with 20 mM NH3) on a Chiralpak OD column (2.1 x 250 mm, 10 μηι) eluting at a flow rate 70 ml/min (130 bar pressure, 40 °C column temperature). The first peak (retention time = 1.45 min) provided N-((1S,5R,6S)-5-(5-amino-2-chlorophenyl)-5-(fluoromethyl)-2-oxa-4-
azabicyclo[4.1.0]hept-3-en-3-yl)benzamide  (9d-A, 876 mg, 2.34 mmol, 41.7 %yield; 99%
de; 99% ee) as a light yellow powder. The second peak (retention time = 2.14 min) provided N-((1R,5S,6R)-5-(5-amino-2-chlorophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (9d-B, 932 mg, 2.49 mmol, 44.4 yield; 99% de; 99% ee) as a light yellow powder. MS m/z = 374.0 [M+H]+. Calculated for C_{10}H_{10}ClF_{1}N_{2}O_{2}: 373.8 for both enantiomers.

Step 6: [Y1R,S],(5S,R), (6R,S)-5-(5-amino-2-chlorophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (9e-A) and (lR,5S,6R)-5-(5-amino-2-chlorophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (9e-B).

The title compound was prepared following a procedure similar to that described in steps 4 for the synthesis of 4d rac, but using N-((1R,5S,6R)-5-(5-amino-2-chlorophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (9d rac) MS m/z = 269.9 [M+H]+. Calculated for C_{10}H_{10}ClF_{1}N_{2}O_{2}: 269.7.

Step 7: [(1S,5R,6S)-5-(5-amino-2-chlorophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (9e-A) and (lR,5S,6R)-5-(5-amino-2-chlorophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (9e-B).

[(1R,S),(5S,R), (6R,S)-5-(5-amino-2-chlorophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (9e rac, 130 mg) was subjected to chromatography using supercritical C0_{2} (additives 35% (MeOH with 20 mM NH_{3}) on a Chiralpak ODH column (20 x 250 mm, 10 µm) eluting at a flow rate 70 ml/min (172 bar pressure, 40 °C column temperature). The first peak (retention time = 1.71 min) provided [(1S,5R,6S)-5-(5-amino-2-chlorophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (9e-A, 33 mg, 0.12 mmol, 25 % yield; 99% de; 99% ee) as a light yellow powder. The second peak (retention time = 2.42 min) provided (IR,5S,6R)-5-(5-amino-2-chlorophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (9e-B, 33 mg, 0.12 mmol, 25 % yield; 99% de; 99% ee) as a light yellow powder.

MS m/z = 270.0 [M+H]+ (for both enantiomers)

Peak 1: ^{1}H NMR (300 MHz, DMSO-d_{6}) δ ppm 0.68 - 0.85 (m, 1 H) 0.92 (td, J=6.58, 2.63 Hz, 1 H) 1.70 (dt, J=9.90, 6.96 Hz, 1 H) 3.80 - 3.94 (m, 2 H) 4.48 - 4.65 (m, 1 H) 4.68 - 4.83 (m, 1 H) 5.16 (s, 2 H) 5.55 (s, 13 H) 6.45 (dd, J=8.40, 2.85 Hz, 7 H) 6.87 (d, J=2.78 Hz, 1 H) 7.01 (d, J=8.48 Hz, 1 H)

Peak 2: ^{1}H NMR (300 MHz, DMSO-d_{6}) δ ppm 0.79 (dt, J=9.68, 6.27 Hz, 1 H) 0.92 (td, J=6.58, 2.78 Hz, 1 H) 1.70 (dt, J=9.79, 7.09 Hz, 1 H) 3.73 - 3.96 (m, 1 H) 4.39 - 4.65 (m, 1 H) 4.68 - 4.84 (m, 1 H) 5.16 (s, 2 H) 5.54 (s, 2 H) 6.45 (dd, J=8.48, 2.78 Hz, 1 H) 6.87 (d, J=2.92 Hz, 1 H) 7.01 (d, J=8.33 Hz, 7 H)
A solution of 1-bromo-2,6-difluorobenzene (2.51 ml, 16.94 mmol) in Et20 (25 ml) was cooled to -78 °C and a solution of n-butyllithium (2.5M in hexanes, 6.78 ml, 16.94 mmol) was added dropwise. The resulting mixture was stirred at -78 °C for 20 min. A second flask was charged with a solution of 4-(fluoromethyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (6c rac, 1.3 g, 11.29 mmol) in toluene (5 mL). The reaction mixture was cooled to -78 °C and boron trifluoride diethyl etherate (1.464 ml, 11.86 mmol) was added. The reaction mixture was stirred for 5 min at -78 °C and transferred via cannula to the aryllithium solution. The resulting reaction mixture was stirred at -78 °C for 30 min. The reaction was quenched with saturated NH4Cl solution. The reaction mixture was allowed to warm to room temperature and diluted with EtOAc and water. The organic layer was separated and the aqueous phase was extracted with EtOAc (2x). The combined organic layers were dried over Na2SO4 and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluting with 0-15% EtOAc/hexanes, to afford the title compound (2.02 g, 8.81 mmol, 78 % yield). MS m/z = 230 [M+H]+. Calculated for C16H10F3NO: 229.07

Step 2-4: [R,S]. (5S.R), i6R.S)l-5-i2.6-difluoropheniy5-(fluoromethiy2-oxa-4-azabicyclo [4.1.0]hept-3-en-3-amine (10d rac)
The title compound was prepared following procedures similar to those described in steps 2 to 4 for the synthesis of 4d rac, but using [(1R,S), (4S,R), (5R,S)]-4-(2,6-difluorophenyl)-4-(fluoromethyl)-2-oxa-3-azabicyclo[3.1.0]hexane (10a rac)

MS m/z = 256.9 [M+H]^+. Calculated for C_{17}H_{11}F_3N_2O : 256.08

Step 5: [(1R,S), (5S,R), (6R,S)]-5-(2,6-difluoro-3-nitrophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (10e rac)

A solution of [(1R,S), (5S,R), (6R,S)]-5-(2,6-difluoro-3-nitrophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (10e rac, 0.111 g, 0.368 mmol) in EtOH (5 mL) was purged with Nitrogen followed by the addition of palladium (10% wt. on activated carbon, 0.196 g, 0.184 mmol) and acetic acid (0.128 mL, 2.21 mmol). The reaction mixture was purged with Hydrogen for 35 min. The reaction mixture was filtered through celite and the filtrate was concentrated under reduced pressure. The residue was dissolved in DCM and washed with 10% aqueous Na_2CO_3 solution. The organic layer was dried over Na_2SO_4 and the filtrate was concentrated to afford the title compound (0.082 g, 0.302 mmol, 82% yield).

Step 6: [(1R,S), (5S,R), (6R,S)]-5-(3-amino-2,6-difluorophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (10f rac)

A solution of [(1R,S), (5S,R), (6R,S)]-5-(2,6-difluoro-3-nitrophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (10e rac, 0.111 g, 0.368 mmol) in EtOH (5 mL) was purged with Nitrogen followed by the addition of palladium (10% wt. on activated carbon, 0.196 g, 0.184 mmol) and acetic acid (0.128 mL, 2.21 l mmol). The reaction mixture was purged with Hydrogen for 35 min. The reaction mixture was filtered through celite and the filtrate was concentrated under reduced pressure. The residue was dissolved in DCM and washed with 10% aqueous Na_2CO_3 solution. The organic layer was dried over Na_2SO_4 and the filtrate was concentrated to afford the title compound (0.082 g, 0.302 mmol, 82% yield).
[(1R,S), (5S,R), (6R,S)]-5-(2,6-difluorophenyl)-5-(fluoromethyl)-2-oxa-4-
azabicyclo[4.1.0]hept-3-en-3-amine \( \text{Example 10d-A} \) was subjected to chromatography using supercritical \( \text{CO}_2 \) (additive 35% MeOH with 20 mM NH\(_3\)) on a IC column (21 x 250 mm, 5 \( \mu \text{m} \)) eluting at a flow rate 50 ml/min (100 bar pressure, 40 \( ^\circ \text{C} \) column temperature). The first peak (retention time = 1.13 min) provided \((1R,5S,6R)-5-(2,6-difluorophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine\) \( \text{Example 10d-A} \); 571 mg, mmol, 48% yield; 99% de; 99% ee) as a light-yellow powder, MS \( m/z = 256.9 \) [M+H]^+. 

Step 8-9: \((1R,5S,6R)-5-(3-amino-2,6-difluorophenyl)-5-(fluoromethyl)-2-oxa-4-
azabicyclo[4.1.0]hept-3-en-3-amine\) \( \text{Example 10d-B} \) was prepared following procedures similar to those described in steps 5 and 6 for the synthesis of \( \text{Example 10d-A} \), but using \((1R,5S,6R)-5-(2,6-difluorophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine\) \( \text{Example 10d-A} \). MS \( m/z = 272.0 \) [M+H]^+. 

The title compound was prepared following procedures similar to those described in steps 5 and 6 for the synthesis of \( \text{Example 10d-A} \), but using \((1S,5R,6S)-5-(3-amino-2,6-difluorophenyl)-5-(fluoromethyl)-2-oxa-4-
azabicyclo[4.1.0]hept-3-en-3-amine\) \( \text{Example 10d-B} \). MS \( m/z = 271.9 \) [M+H]^+. 

**Example 11**
**Step 1**: \( \text{r} \text{R}. \text{S}, \text{(4S.R)}, \text{(5R.S)} \text{l}-4-(23\text{-difuoerophenyl})-4-(\text{fluoromethyl})-2\text{-oxa-3-azabicyclo[3.1.0]} \text{hexane} \) (1 a rac)

A solution of n-butyllithium (2.5 M in hexanes, 35.4 mL, 89 mmol) was added to a solution of l-bromo-2,3-difluorobenzene (16.10 g, 83 mmol) in diethyl ether (60 mL) under nitrogen atmosphere at -78 °C. The resulting reaction mixture was stirred for 15 minutes. An additional flask was charged with 4-(fluoromethyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (6c rac, 6 g, 52.1 mmol) and toluene (30 mL). The reaction mixture was placed under nitrogen atmosphere and cooled to -78 °C. Boron fluoride diethyl etherate (7.08 mL, 57.3 mmol) was added and the solution was stirred for 5 minutes. This solution was transferred via cannula to the aryl lithium solution. The resulting reaction mixture was stirred for 25 minutes. The reaction was quenched by addition of saturated NH\(_4\)Cl solution and subsequently partitioned between water and ethyl acetate. The organic phase was dried over sodium sulfate and the filtrate evaporated under reduced pressure. The residue was purified by flash chromatography (hexane to DCM = 4:1 to 3:1 to 1:1) to give the title compound (6.5g, 28.4 mmol, 54.4 % yield). MS 
\[ m/z = 230 \text{ [M+H]}^+ \].

**Step 2**: \( \text{r} \text{R}. \text{S}, \text{r} \text{R}. \text{S}, \text{l}-2\text{-rt} \text{r} \text{S}. \text{R} \text{V} \text{V}-\text{amino}-1-(23\text{-difuoerophenyl})\text{V}2-	ext{fluoroethvDiczpropanol} \) (1 b rac)

The title compound was prepared following a procedure similar to that described in step 2 for the synthesis of 4b rac, but using \([(1R,S), (4S,R), (5R,S)]4-(23\text{-difuoerophenyl})-4-(\text{fluoromethyl})-2\text{-oxa-3-azabicyclo[3.1.0]} \text{hexane} \) (1 a rac)_MS m/z = 232 [M+H]^+.

**Step 3**: \( \text{N}-(\text{(1R,S)}, \text{r} \text{S}, \text{R}, \text{r} \text{S}, \text{S}) \text{V}5\text{-r}2,3\text{-difuoerophenyl} \text{V}5-(\text{fluoromethyl})\text{V}2\text{-oxa-4-azabicyclo[4.1.0]}\text{hept-3-en-3-yl} \) benzamide (1 c rac)

To a solution of \([(1R,S),(2R,S)]2-(\text{S},\text{R})\text{l}-\text{amino}-1-(23\text{-difuoerophenyl})-2\text{-fluoroethyl}\text{cyclopropanol} \) (11b rac, 6.46 g, 27.9 mmol) in dry tetrahydrofuran (30 mL) under nitrogen was added benzoyl isothiocyanate (3.76 mL, 27.9 mmol) dropwise. After 10 minutes, N.N-diisopropylethylamine (1 mL) was added and the reaction mixture was stirred for an additional 10 minutes. Additional N,N-diisopropylethylamine (9.72 mL, 55.9 mmol) was added followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide HCl (5.89 g, 30.7 mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with DCM (100 mL) and water (100 mL), the phases were separated and the organic phase was dried over magnesium sulfate. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography.
to give the title compound (8.2 g, 22.76 mmol, 81% yield) as a sticky, light yellow tar.

**Step 4:** \([(R,S),(5S,R),(6R,S)]-5-(2,3-difluorophenyl)-5-(fluoromethyl)-2-oxa-4-
azabicvclo[4.1.0]hept-3-en-3-amine (11d rac)

The title compound was prepared following a procedure similar to that described in step 4 for the synthesis of 4d rac, but using N-\([(1R,S),(5S,R),(6R,S)]-5-(2,3-
difluorophenyl)-5-(fluoromethyl)-2-oxa-4-azabicvclo[4.1.0]hept-3-en-3-yl)benzamide (11c rac). MS \(m/z = 257 \ [M+H]^+\).

**Step 5:** \([(1R,S),(5S,R),(6R,S)]-5-(2,3-difluoro-5-nitrophenyl)-5-(fluoromethyl)-2-oxa-4-
azabicvclo[4.1.0]hept-3-en-3-amine (11e rac)

\([(R,S),(5S,R),(6R,S)]-5-(2,3-difluorophenyl)-5-(fluoromethyl)-2-oxa-4-
azabicvclo[4.1.0]hept-3-en-3-amine (11d rac, 5.4 g, 21.08 mmol) was dissolved in concentrated sulfuric acid (25 mL) and the solution was cooled to 0°C. Sodium nitrate (2.69 g, 31.6 mmol) was added in one portion and the reaction mixture was stirred for 5 minutes at 0°C. The cold bath was removed and the reaction mixture was allowed warm to room temperature. After 10 minutes, ice (-100 mL) was added, and the reaction mixture was poured into a mixture of dichloromethane (200 mL), water (200 mL), ice (-100 mL), and tribasic potassium phosphate (65 g). The resulting mixture was stirred for 5 minutes, followed by the addition of saturated sodium bicarbonate solution (50 mL).

The organic phase was separated and the aqueous phase was extracted with ethyl acetate (2 x 150 mL). The combined organic extracts were dried over magnesium sulfate and the filtrate was concentrated under reduced pressure and taken into the next step without further purification.

**Step 6:** \([(1R,S),(5S,R),(6R,S)]-5-(5-amino-2,3-difluorophenyl)-5-(fluoromethyl)-2-oxa-4-
azabicvclo[4.1.0]hept-3-en-3-amine (11f rac)

The residue obtained in step 5 was dissolved in acetic acid (40 mL) and treated with zinc dust (13.78 g, 211 mmol). The reaction mixture was stirred for 30 minutes and the slurry was filtered. The filter cake was washed with ethyl acetate (200 mL). The combined filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (100% DCM to DCM/EtOAc = 4:1 to DCM/EtOAc 2:1 to DCM/EtOAc 1:1 to 100% EA) to give the title compound (5.2 g, 19.17 mmol, 91% yield). MS \(m/z = 272.1 \ [M+H]^+\).
Step 1: \(|Y1R.S), (5S,R)i6R,S|5-(3-fluoro-2-methoxy-5-nitrophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine \(12a\) (rac)

To a solution of \([(1R,S), (5S,R),(6R,S)]5-(2,3-difluoro-5-nitrophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine \(11e\) (rac, 500 mg, 1.660 mmol) in MeOH (10 mL) was added potassium carbonate (459 mg, 3.32 mmol). The reaction mixture was heated to 60 °C for 1 h. The reaction mixture was cooled to rt and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (100% DCM to DCM/EtOAc = 4:1 to DCM/EtOAc 1:1) to give the title compound (420 mg, 1.341 mmol, 81% yield). MS *m/z* = 313.9 [M+1]*. Calculated for \(C_{13}H_{13}F_2N_3O_4\): 313.3.

Step 2: \([(1R,S), (5S,R),(6R,S)]5-(5-amino-3-fluoro-2-methoxyphenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine \(12b\) (rac)

A suspension of \([(1R,S), (5S,R),(6R,S)]5-(3-fluoro-2-methoxy-5-nitrophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine \(12a\) (rac, 160 mg, 0.511 mmol) and palladium (10% on activated carbon, 109 mg, 0.102 mmol) in EtOH (20 mL) was purged with Nitrogen, followed by Hydrogen. The flask was fitted with a balloon filled with Hydrogen and the reaction mixture was stirred overnight. The reaction mixture was filtered through a pad of celite and the filter cake was rinsed with EtOAc. The filtrate was absorbed onto silica gel and purified by flash chromatography (100% EtOAc to EtOAc/MeOH = 10:1) to give the title compound (140 mg, 0.494 mmol, 97% yield). MS *m/z* = 284.0 [M+1]*. Calculated for \(\frac{3}{4} H_{13}F_2N_3O_8\): 283.2.

\(^1H\) NMR (400 MHz, CHLOROFORM-d) \(\delta = 6.54 - 6.46 \text{ (m, 1 H)}, 6.41 \text{ (dd, } J = 2.7, 12.9 \text{ Hz, 1 H)}, 4.74 \text{ (s, 1 H)}, 4.63 \text{ (s, 1 H)}, 3.88 \text{ (d, } J = 1.8 \text{ Hz, 3 H)}, 3.77 - 3.62 \text{ (m, 1 H)}, 1.76 \text{ (td, } J = 12, 9.7 \text{ Hz, 1 H}), 1.13 \text{ (dt, } J = 2.8, 6.8 \text{ Hz, 1 H}), 0.90 - 0.79 \text{ (m, 1 H)}.

Example 13
Step 1: r[(R,S), (S,R), (6R,S)]-5-(3-fluoro-2-(methylthio)-5-nitrophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (13a rac)

[(1R,S), (5S,R), (6R,S)]-5-(2,3-difluoro-5-nitrophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (11e rac, 0.100 g, 0.332 mmol) was dissolved in MeOH (0.75 mL) and S-methyl benzothioate (0.056 g, 0.365 mmol) was added to the solution, followed by a solution of sodium methoxide (0.5M solution in methanol, 0.730 mL, 0.365 mmol). The reaction mixture was stirred at room temperature for 30 min and subsequently partitioned between EtOAc and water. The aqueous layer was separated and extracted with EtOAc. The combined organic layers were washed with brine, dried over sodium sulfate, and the filtrate was concentrated under reduced pressure. The crude material was purified by column chromatography, eluting with a gradient of 10-100% EtOAc/Hexanes to obtain the title compound (81 mg, 74% yield).

Step 2: r[(R,S), (S,R), (6R,S)]-5-(3-amino-3-fluoro-2-(methylthio)phenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (13b rac)

A flask was charged with [(1R,S), (5S,R), (6R,S)]-5-(3-fluoro-2-(methylthio)-5-nitrophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (13a rac, 0.073 g, 0.222 mmol), palladium (10% wt. on activated carbon, 1.963 µl, 0.022 mmol), EtOAc (600 µl) and MeOH (600 µl). The reaction mixture was purged with Nitrogen, followed by Hydrogen. The flask was fitted with a balloon filled with hydrogen and the reaction mixture was stirred at rt overnight. The reaction mixture was filtered through a pad of celite and the filter cake was washed with EtOAc. The filtrate was concentrated under reduced pressure to obtain the title compound. MS m/z=299.9 [M+H]^+. Calculated forC_{19}H_{15}F_2N_3O:S 299.3
Step 1: \( \text{L}(S,R,4(R,S),5(S,R)) \text{-4-}r\text{2-chloro-3-fluorophenyl}^V\text{4-fluoromethyl}^V\text{2-oxa-3-}
\text{azabicyclo[3.1.0]hexane} \ (14a \text{ rac}) \\
To a cooled (-78 °C, internal) solution of 1-bromo-2-chloro-3-fluorobenzene (18.02 g, 86 mmol) in Et2O (90 mL) was added a solution of n-butyllithium (2.5M in toluene, 34.0 mL, 85 mmol) over a period of 20 min. After completed addition, the reaction mixture was stirred for additional 30 min at that temperature. In a separate flask, a cooled (-78 °C) solution of 6c (4.0 g, 34.8 mmol) in toluene (24 mL) was treated with boron trifluoride diethyl etherate (4.3 mL, 34.8 mmol). The reaction mixture was stirred at that temperature for 20 min. This solution was added via cannula to the organolithium mixture. After 30 min, the reaction was quenched with 5% aq KHSO4 solution (75 mL) and the reaction mixture was allowed to warm to rt. The layers were separated and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine and dried over Na2SO4. The filtrate was absorbed onto silica gel and purified by flash chromatography, eluting with a gradient 0:1 → 1:4 EtOAc:hexane, to give the title compound as a light-yellow crystalline solid (4.87 g, 57%). MS \( m/z = \) 245.9, 248.0 \([\text{M+H}]^+\). Calculated for C11H12ClF2NO: 245.6 

Steps 2-6: \( \text{[L(S),5(R),6(S,R)]-5-(5-amino-2-chloro-3-fluorophenyl)-5-(fluoromethyl)-}
\text{2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine} \ (14f \text{ rac}) \\
The title compound was prepared following procedures similar to those described in steps 2-6 for the synthesis of 11f rac, but using \( \text{[L(S,R,4(R,S),5(S,R))]-4-(2-chloro-3-fluorophenyl)-4-(fluoromethyl)-2-oxa-3-}
\text{azabicyclo[3.1.0]hexane} \ (14a \text{ rac}) \text{ MS } \( m/z = \) 287.9, 290.0 \([\text{M+H}]^+\). Calculated for C12H12ClF2N3O: 287.7
Step 1: \((IR.S), (4S.R), i5R.S)\-4-i3-chloro-2-fluorophenyl\)-4-fluoromethyl\)-2-oxa-3-azabicyclo[3.1.0]hexane (15a rac)

A solution of n-butyllithium (2.5M in hexanes, 5.21 ml, 13.03 mmol) was added dropwise to a cooled (-78°C) solution of 1-bromo-3-chloro-2-fluorobenzene (2.73 g, 13.03 mmol) in Et20 (40 mL). The resulting reaction mixture was stirred at -78°C for 20 min. In a separate flask, a solution of 4-(fluoromethyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (6c rac, 1.0 g, 8.69 mmol) in toluene (10 mL) was cooled to -78°C. Boron trifluoride diethyl etherate (1.126 ml, 9.12 mmol) was added and the reaction mixture was stirred for 5 min. This solution was subsequently transferred via cannula to the aryl lithium solution. The resulting reaction mixture was stirred at -78°C for 30 min. The reaction was quenched with aqueous saturated NH4Cl solution and allowed to warm to room temperature. EtOAc and water were added. The aqueous phase was separated and extracted with EtOAc. The combined organic layers were dried over Na2SO4 and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel
chromatography (0-10% EtOAc/hexanes) to afford the title compound (1.81 g, 7.37 mmol, 85% yield). MS m/z = 245.9 [M+H]^+. Calculated for C_{13}H_{10}ClF_2NO: 245.04.

Steps 2-4: [(1R,S), (5S,R), (6R,S)]-5-(3-chloro-2-fluorophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (Example 15d-B). MS m/z = 272.9 [M+H]^+. Calculated for C_{12}H_{11}ClF_2N_2O : 272.05.

Step 5-6: [(1R,S), (5S,R), (6R,S)]-5-(5-amino-3-chloro-2-fluorophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (15f rac).

The title compound was prepared following procedures similar to those described in steps 2-4 for the synthesis of 11d rac, but using [(1R,S), (4S,R), (5R,S)]-4-(3-chloro-2-fluorophenyl)-4-(fluoromethyl)-2-oxa-3-azabicyclo[3.1.0]hexane (15a rac). MS m/z = 287.9 [M+H]^+. Calculated for C_{12}H_{15}ClF_2N_2O : 287.06.

Step 7: [(1S,5R,6S)-5-(3-chloro-2-fluorophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (15d-A) and (IR,5S,6R)-5-(3-chloro-2-fluorophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (15d-B) was subjected to chromatography using supercritical C0_2 (additives 30% MeOH with 20 mM NH_3) on a IC column (30 x 250 mm, 5 µm) eluting at a flow rate 120 ml/min (158 bar pressure, 40 °C column temperature). The first peak (retention time = 1.28 min) provided [(1R,S), (5S,R), (6R,S)]-5-(3-chloro-2-fluorophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (Example 15d-A; 863 mg, 3.17 mmol, 39% yield; 99% de; 99% ee) as a light-yellow powder. MS m/z = 272.9 [M+H]^+. The second peak (retention time = 1.93 min) provided [(IR,5S,6R)-5-(3-chloro-2-fluorophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (Example 15d-B; 878 mg, 3.22 mmol, 40% yield; 99% de; 99% ee) as a light-yellow powder. MS m/z = 272.9 [M+H]^+.

Steps 8-9: [(IR,5S,6R)-5-(5-amino-3-chloro-2-fluorophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (15f rac).

The title compound was prepared following procedures similar to those described in steps 5-6 for the synthesis of 15f rac, but using [(IR,5S,6R)-5-(3-chloro-2-fluorophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (Example 15d-B). MS m/z = 287.9 [M+H]^+. Calculated for C_{12}H_{15}ClF_2N_2O : 287.06.
Step 1: 5-(Chloromethyl)-3-(difluoromethyl)-4,5-dihydroisoxazole (16a rac)

A solution of dimethyl sulfoxide (35.6 ml, 501 mmol) in DCM (50 mL) was added dropwise to a solution of oxalyl chloride (20.47 ml, 231 mmol) in DCM (400 mL) at -78 °C. This solution was stirred for 10 min before a solution of (5-(chloromethyl)-4,5-dihydroisoxazol-3-yl)methanol (15.0 g, 100 mmol, synthesized according to Tetrahedron 1986, 42, 5267) in DCM (50 mL) was added dropwise. This mixture was stirred for 15 minutes at -78 °C before triethylamine (13.98 ml, 100 mmol) was added dropwise. The dry ice bath was removed and replaced with an ice bath. After 30 min, water and Et₂O were added and the layers were separated. The organic layer was washed with water, dried over MgSO₄ and the filtrate was concentrated in vacuo. The residue was dissolved in DCM (300 mL), the solution was cooled to -78 °C solution and (diethylamino)sulfur trifluoride (39.7 ml, 301 mmol) was added. The dry ice bath was replaced with an ice bath and the reaction mixture was stirred for 30 min. The reaction
was quenched by addition of aqueous saturated \( \text{NaHCO}_3 \) solution, and the resulting biphasic mixture was separated. The aqueous layer was extracted with DCM. The combined organic extracts were dried over \( \text{MgSO}_4 \) and the filtrate was concentrated in vacuo to give an oil. The oil was purified by silica gel chromatography (0 to 60% Et\(_2\)O/hexane gradient) to give the title compound (11.0 g, 65% yield for the two steps).

Step 2: 4-(Difluoromethyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (16b rac)

A solution of potassium tert-butoxide (1.0 M in THF, 66.3 mL, 66.3 mmol) was added dropwise to a solution of 5-(chloromethyl)-3-(difluoromethyl)-4,5-dihydroisoxazole (16a rac, 9.0 g, 53.1 mmol) in THF (70 mL) at 0 °C. The reaction mixture was stirred for 30 min, then aqueous saturated \( \text{NH}_4\text{Cl} \) solution was added slowly. The mixture was extracted with Et\(_2\)O (2x), and the combined organic extracts were dried over MgSO\(_4\). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-60% Et\(_2\)O/pentane gradient) to give the title compound as an oil (5.29 g, 75% yield).

\[ ^{1}H \text{ NMR (300 MHz, CHLOROFORM -d) d ppm 6.43-6.45 (s, 1 H) 5.08 (td, J=5.41, 2.34 Hz, 1 H) 2.75-2.83 (m, 1 H) 1.04-1.14 (m, 1 H) 0.38 (dd, J=1.90, 1.61 Hz, 1 H) } \]

Step 3: \( \eta^{1}[(R,S), 4(S,R), 5rR.S)]4r5-bromo-2-fluorophenylV4-rdifluoromethylV2-oxa-3-azabicyclo[3.1.0]hexane \) (16c rac)

A solution of n-butyllithium (2.5 M in hexanes, 49.6 mL, 124 mmol) was added slowly over 20 min to a stirred solution of 4-bromo-1-fluoro-2-iodobenzene (37.7 g, 125 mmol) in diethyl ether (240 mL) at -78 °C under a nitrogen atmosphere. The reaction mixture was stirred at -78 °C for 15 min. A separate flask was charged with a solution of 4-(difluoromethyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (8.25 g, 62.0 mmol) in toluene (280 mL) and cooled to -78 °C. Boron trifluoride diethyl etherate (7.80 mL, 63.2 mmol) was added and after stirring the reaction mixture for 5 min at -78 °C, it was transferred via cannula to the aryl lithium solution. The reaction mixture was stirred at -78 °C for 1 h and subsequently quenched with saturated aqueous \( \text{NH}_4\text{Cl} \) solution. The mixture was warmed to RT and diluted with EtOAc and water. The organic layer was separated. The aqueous layer was extracted once more with EtOAc. The combined organic layers were washed with brine, dried over MgSO\(_4\). The filtrate was concentrated in vacuo and the resulting crude product was purified via silica gel flash column chromatography eluting with 0 to 20% EtOAc in heptane to give the title compound as a light orange solid (15.14 g, 79% yield).
Steps 4-6: [(R.S), (5.S,R), (6R.S),]-5-(5-bromo-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (16f-A) provided (Example 16f-A; 3.54 g, 10.6 mmol, 38% yield; >99% de; >99% ee) as a white solid.

LC/MS (ESI\(^{+}\)) m/z = 334.9 (M+H\(^{+}\)).

Calculated for C\(_{12}\)H\(_{10}\)BrF\(_{3}\)N\(_{2}\)O 334.0. 1\(^{H}\) NMR (400 MHz, CDCl\(_{3}\)) \(\delta\) 0.95 (dt, \(J = 9.34, 6.97\) Hz, 1H), 1.28-1.42 (m, 1H), 1.78 (dt, \(J = 9.49, 7.09\) Hz, 1H), 3.89-3.94 (m, 1H), 4.42 (br s, 2H), 6.13 (t, \(J = 56.70\) Hz, 1H), 6.97 (dd, \(J = 11.54, 8.61\) Hz, 1H), 7.42 (ddd, \(J = 8.61, 4.30, 2.54\) Hz, 1H), 7.65 (dd, \(J = 6.85\) Hz, 1H). The second peak (retention time = 6.26 min) provided (Example 16f-B; 3.52 g, 10.5 mmol, 38% yield; >99% de; >98.4% ee) as a white solid. LC/MS m/z = 334.9 [M+H]+. Calculated for C\(_{12}\)H\(_{10}\)BrF\(_{3}\)N\(_{2}\)O 334.0. 1\(^{H}\) NMR (400 MHz, CDCl\(_{3}\)) \(\delta\) 0.95 (dt, \(J = 9.44, 6.92\) Hz, 1H), 1.37 (t, \(J = 7.04\) Hz, 1H), 1.78 (dt, \(J = 9.54, 7.16\) Hz, 1H), 3.89-3.94 (m, 1H), 4.45 (br s, 2H), 6.15 (t, \(J = 56.10\) Hz, 1H), 6.97 (dd, \(J = 11.54, 8.80\) Hz, 1H), 7.42 (ddd, \(J = 8.61, 4.21, 2.64\) Hz, 1H), 7.65 (dd, \(J = 7.04, 2.54\) Hz, 1H).

Step 8: [(S,R),6S(5bromo)-2-fluorophenyl]-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (16g-B).

The title compound was prepared following a procedure similar to that described in step 1 for the synthesis of 6h-B, but using [(1R,5S,6R)-5-(5-amino-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (16f-B)] MS m/z = 272.0 [M+H]+.

The title compound was prepared following a procedure similar to that described in step 9 for the synthesis of 6h rac, but using [(1R,S), (5S,R), (6R,S)]-5-(5-bromo-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (16f rac). MS m/z = 272.0 [M+H]+.

5. **Step 10**: tert-butyl ((1P,5S,6h')-5-(5-bromo-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)carbamate (16h-B)

To a solution of (1P,5S,6h')-5-(5-bromo-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (16f-B, 1.22 g, 3.64 mmol) in dioxane (10 mL) at room temperature was added saturated aqueous NaHCO₃ (15 mL) and di-tert-butyl dicarbonate (0.975 g, 4.47 mmol). The reaction mixture was heated to 40 °C for 2 h. Additional di-tert-butyl dicarbonate (1.02 g, 4.68 mmol) was added. Stirring at 40 °C was continued for 1 d. The reaction mixture was cooled to RT and diluted with EtOAc. The organic phase was washed with brine and dried over MgSO₄. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (40 g, 5% to 50% EtOAc in hexanes) to give the title compound (1.47 g, 3.38 mmol, 93% yield) as a white solid. MS m/z = 434.9 [M+H]+. Calculated for C₁₇H₁₉BrF₃N₂O₃ 434.0.

6. **Step 11**: ferf-butyl ((1P,5S,6h')-5-(5-amo-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)carbamate (16i-B)

To a mixture of tert-butyl ((1P,5S,6h')-5-(5-bromo-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)carbamate (16h-B, 1.47 g, 3.38 mmol), copper(I) iodide (0.139 g, 0.730 mmol), (+)-sodium 1-ascorbate (0.131 g, 0.661 mmol), and sodium azide (0.688 g, 10.6 mmol) were added EtOH (4.6 mL) and water (2.3 mL). The reaction mixture was purged with Nitrogen for 10 min, followed by the addition of (1R,2R)-(-)-N^+V^-dimethylcyclohexane-1,2-diamine (0.110 mL, 0.698 mmol). The reaction mixture was heated to 70 °C for 1.5 h and cooled to RT. The reaction mixture was poured into 10:1 saturated NH₄Cl/ammonium hydroxide, and diluted with EtOAc. The aqueous phase was extracted with EtOAc (2 x) and the combined organic extracts were washed with brine and dried over MgSO₄. The filtrate was concentrated under reduced pressure to give a solid, which was dissolved in THF (12 mL) and water (4 mL). A solution of trimethyl phosphine (1.0 M in THF, 3.40 mL, 3.40 mmol) was added and the reaction mixture was stirred at RT for 15 min. The reaction mixture was diluted with EtOAc and water, the aqueous phase was separated and extracted with EtOAc. The combined organic extracts were washed with brine and dried over MgSO₄. The filtrate
was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (20% to 70% EtOAc in heptane) to give the title compound (1.03 g, 2.77 mmol, 82% yield) as a white solid. MS m/z = 372.0 [M+H]+. Calculated for C_{17}H_{26}F_{3}N_{2}O_{3} 371.1.

**Example 17:**

![Chemical structure image]

**Step 1:** \((1R,S), (4S,R), (5S,R)\)-4-(6-bromo-3-fluoropyridin-2-yl)-5-(difluoromethyl)-2-oxa-3-azabicyclo[3.1.0]hexane (17a rac)

A flame dried RBF was charged with 2-bromo-5-fluoropyridine (10.23 g, 58.2 mmol) and diethyl ether (240 mL). The solution was cooled to -78 °C before adding a solution of n-butyllithium (2.5M in hexane, 23.26 ml, 58.2 mmol) dropwise. The reaction mixture was stirred at -78 °C for 30 min. A second flask was charged with a solution of 4-(difluoromethyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (16b rac, 3.87 g, 29.1 mmol) in DCM (100 mL) and cooled to -78 °C solution. Boron fluoride diethyl etherate (3.59 ml, 29.1 mmol) was added and after 15 min, this reaction mixture was transferres via cannula to the aryl lithium solution. Upon complete addition the reaction mixture was stirred at -78 °C for 30 minutes and then gradually warmed to RT for 2 hours. The reaction was diluted with water and DCM. The organic layer was separated, washed with brine and dried over magnesium sulfate. The filtrate was concentrated under reduced pressure and the crude material was purified via silica gel flash chromatography using a gradient of 5-40% EtOAc in hexanes to afford the title compound (3.74 g, 12.10 mmol, 41.6% yield) as a brown solid. MS m/z=308.9 M+. Calculated for C_{15}H_{3}BrF_{3}N_{2}O: 309.1

**Steps 2-4:** \((1R,S), (5S,R), (6R,S)\)-5-(6-bromo-3-fluoropyridin-2-yl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (17d rac)
The title compound was prepared following procedures similar to those described in steps 2-4 for the synthesis of 4d rac, but using [(1R,S), (4S,R), (5R,S)]-4-(6-bromo-3-fluoropyridin-2-yl)-4-(difluoromethyl)-2-oxa-3-azabicyclo[3.1.0]hexane (17a rac). MS m/z=335.9 M⁺. Calculated for C₁₁H₉BrF₃N₃O: 336.1 for both enantiomers.

Step 5: [(1R,5S,6R)-5-(6-bromo-3-fluoropyridin-2-yl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (17d-A) and (1S,5R,6S)-5-(6-bromo-3-fluoropyridin-2-yl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (17d-B)]

[(1R,S), (5S,R), (6R,S)]-5-(6-bromo-3-fluoropyridin-2-yl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (17d rac) was subjected to chromatography using supercritical CO₂ (additives 12% MeOH with 20 mM NH₃) on an ODH column (20 x 250 mm, 5 µm) eluting at a flow rate 75 ml/min (100 bar pressure, 40 °C column temperature). The first peak (retention time = 1.02 min) provided (Example 17d-A): 510 mg, 1.518 mmol, 43% yield; 99% de; 99% ee) as a white powder. The second peak (retention time = 1.29 min) provided (Example 17d-B): 490 mg, 1.458 mmol, 41% yield; 99% de; 99% ee) as a white powder. MS m/z=335.9 M⁺. Calculated for C₁₁H₉BrF₃N₃O: 336.1 for both enantiomers.

Example 18

Step 1: [(R,S), r4S,R,r5S,R]-4-r5-bromo-2-fluoropyridin-3-yl-V4-(difluoromethyl)IV2-oxa-3-azabicyclo[3.1.0]hexane (18a rac)

A solution of n-butyllithium (9.39 mL, 15.03 mmol, 1.60 M in hexanes) was added to a solution of diisopropylamine (2.106 mL, 15.03 mmol) in THF (30 mL) at 0 °C
under a nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 10 min and then cooled to -78 °C. 5-Bromo-2-fluoropyridine (1.729 mL, 15.03 mmol) was added dropwise, the reaction mixture was stirred at -78 °C for 30 min, followed by the addition of N,N,N',N'-tetramethylethanediamine (2.249 mL, 15.03 mmol). A separate flask was charged with a solution of 4-(difluoromethyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (16b rac, 1.00 g, 7.51 mmol) in toluene (20 mL) and cooled to -78 °C solution. Boron fluoride diethyl etherate (0.927 mL, 7.51 mmol) and after 3 min, this reaction mixture was transferred via cannula to the aryl lithium solution. Upon complete addition the reaction mixture was stirred at -78 °C for 1 h, then allowed to warm to 0 °C and quenched with saturated aqueous ammonium chloride solution. The biphasic mixture was extracted with EtOAc. The organic layer was separated, washed with brine and dried over magnesium sulfate. The filtrate was concentrated in vacuo and the resulting crude residue was purified via silica gel flash column chromatography (eluent: 0% to 30% EtOAc in hexanes) to yield a 2:1 mixture of the regioisomers [(1R,S), (4S,R),(5R,S)]-4-(5-bromo-2-fluoropyridin-3-yl)-4-(difluoromethyl)-2-oxa-3-azabicyclo[3.1.0]hexane (18a rac) and [(1R,S), (4S,R),(5R,S)]-4-(5-bromo-2-fluoropyridin-4-yl)-4-(difluoromethyl)-2-oxa-3-azabicyclo[3.1.0]hexane as a yellow solid (1.164 g). The mixture was taken onto the next step. MS m/z = 308.9 [M+H]+. (for both regioisomers) Calculated for C10H8BrF3N2O : 307.977.

Steps 2: r[(IR,S),(2R,S)]-2-((S,R)-l-amino-l-(5-bromo-2-fluoropyridin-3-yl)-2,2-difluoroethanol (18b rac)

To a stirred solution of a 2:1 mixture of [(1R,S), (4S,R),(5R,S)]-4-(5-bromo-2-fluoropyridin-3-yl)-4-(difluoromethyl)-2-oxa-3-azabicyclo[3.1.0]hexane (18a rac) and [(1R,S), (4S,R),(5R,S)]-4-(5-bromo-2-fluoropyridin-4-yl)-4-(difluoromethyl)-2-oxa-3-azabicyclo[3.1.0]hexane (0.879 g, 2.84 mmol) in trifluoroacetic acid (10.6 mL, 142 mmol) was added zinc dust (1.86 g, 28.4 mmol). The reaction mixture was stirred at room temperature for 1.5 h before being diluted with DCM and filtered. The filtrate was diluted with saturated aqueous sodium bicarbonate and brought to pH 9 with 1 M aqueous NaOH. The organic layer was separated, and the aqueous layer was extracted once more with DCM. The combined organic layers were dried over magnesium sulfate and the filtrate was concentrated under reduced pressure. The resulting crude residue was purified via silica gel flash column chromatography (eluent: 0 to 50% EtOAc in hexanes) to give [(IR,S),(2R,S)]-2-((S,R)-l-amino-l-(5-bromo-2-fluoropyridin-3-yl)-2,2-
difluoroethyl)cyclopropanol (0.322 g, 1.04 mmol, 36.4% yield) as a light yellow oil that partially solidified upon standing. MS m/z = 312.8 [M+H]+.

Steps 3-6: [l(R,S),5(S,R),6(R,S)]-5-(5-amino-2-fluoropyridin-3-yl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (18f rac).

The title compound was prepared following procedures similar to those described in steps 3-5 for the synthesis of 5e rac, and step 8 for the synthesis of 8g-B but using [(lR,S),(2R,S)]-2-((S,R)-l-amino-l-(5-bromo-2-fluoropyridin-3-yl)-2,2-difluoroethyl)cyclopropanol (18b rac). MS m/z = 273.0 [M+H]+. Calculated for C_{11}H_{11}F_{3}N_{2}O: 272.088

Example 19

Step 1: r(1R,S), (4S,R), i5R,S)i-4-i2-chlorophenviy4-idifluoromethviy2-oxa-3-

azabicyclo[3.1.0]hexane (19a rac)

A solution of n-butyllithium (2.5M in hexanes, 9.80 mL, 24.50 mmol) was added dropwise to a stirred solution of 1-chloro-2-iodobenzene (3.00 mL, 24.62 mmol) in toluene (24 mL) and THF (8 mL) at -70 °C. After completed addition, the reaction
mixture was stirred at -70 °C for 5 min. Subsequently, a solution of 4-(difluoromethyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (16b rac, 1.4582 g, 9.97 mmol) in toluene (6 mL) was added over a period of 9 min. After 5 min stirring at that temperature boron fluoride diethyl etherate (1.30 mL, 10.26 mmol) was added and the resulting reaction mixture was stirred at -70 °C for additional 30 min. A solution of saturated aqueous NH₄Cl (20 mL) was added and the cold bath was removed, allowing the reaction mixture to warm up to rt. The mixture was partitioned between water (20 mL) and EtOAc (10 mL). The aqueous phase was extracted with EtOAc (2 x 30 mL). The combined organic phases were washed with saturated aqueous sodium bicarbonate (50 mL), water (50 mL) brine (50 mL). The organic phase was dried over sodium sulfate and the filtrate was concentrated in vacuo. The crude product was purified by silica gel flash chromatography (EtOAc in hexanes 0 % - 20 %) to afford 1.3566 g of the title compound as a yellow oil. MS m/z = 245.9 [M+H]^+

1H NMR (400MHz, CHLOROFORM-d) δ = 8.10 - 8.02 (m, 1 H), 7.45 - 7.27 (m, 3 H), 7.12 - 6.80 (m, 1 H), 6.27 (d, J = 5.5 Hz, 1 H), 4.08 - 4.00 (m, 1 H), 2.73 - 2.64 (m, 1 H), 1.37 (dd, J = 2.6, 5.0 Hz, 1 H), 0.71 (dt, J = 5.5, 8.5 Hz, 1 H).

Steps 2-6: [(IR,S),(5S,R),(6R,S)]-4-(5-amino-2-chlorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (19f-rac)

The title compound was prepared following procedures similar to those described in steps 2-6 for the synthesis of IOf rac, but using [(IR,S),(4S,R),(5R,S)]-4-(2-chlorophenyl)-4-(difluoromethyl)-2-oxa-3-azabicyclo[3.1.0]hexane (19a rac) MS m/z = 287.9 [M+H]^+

1H NMR (400 MHz, CDCl3): δ 7.15 (d, J=8.4 Hz, 1 H), 7.02 (d, J=2.7 Hz, 1 H), 6.81 (t, J=57.7 Hz, 1 H), 6.55 (dd, J=8.4, 2.7 Hz, 1 H), 4.66 (br s, 2 H), 3.82 (t, J=5.7 Hz, 2 H), 3.69 (br s, 2 H), 2.00 - 2.11 (m, 1 H), 1.32 (t, J=6.8 Hz, 1 H), 0.93 (dt, J=9.7, 6.8 Hz, 1 H)

Step 7: [(IR,S),(5S,6S)]-5-(5-amino-2-chlorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (19f-A) and [(IR,S,6R)]-5-(5-amino-2-chlorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (19f-B)

[(IR,S),(5S,R),(6R,S)]-5-(5-amino-2-chlorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (16f rac; 0.96 g) was subjected to chromatography using supercritical CO₂ (additives 25% (MeOH with 20 mM NH₄Cl) on a Chiralpak OJ-H column (20 x 250 mm, 5 µm) eluting at a flow rate 50 ml/min (165 bar pressure, 40 °C column temperature). The first peak (retention time = 0.87 min) provided (IR,S,6S)-5-(5-amino-2-chlorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (19f-A).
amine (19f-A, 380 mg, 1.32 mmol, 40% yield; 99% de; 99% ee) as a light-yellow powder. 

\(^1\)H NMR (300MHz, DMSO-\(d_6\)) = 7.04 (d, J = 8.3 Hz, 1 H), 6.91 - 6.43 (m, 3 H), 5.80 (s, 2 H), 5.23 (s, 2 H), 3.88 (br. s., 1 H), 1.86 (q, J = 8.1 Hz, 1 H), 1.02 (br. s., 1 H), 0.93 - 0.81 (m, 1 H). Residual MeOH. MS \(m/z\) = 287.9 [M]+

The second peak (retention time = 1.22 min) provided (IR,5S,6R)-5-(5-amino-2-chlorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine

(19f-B, 380 mg, 1.32 mmol, 40% yield; 99% de; 99% ee) as a light-yellow powder. 

\(^1\)H NMR (300MHz, DMSO-\(d_6\)) = 7.05 (d, J = 8.5 Hz, 1 H), 6.92 - 6.44 (m, 3 H), 5.80 (s, 2 H), 5.23 (s, 2 H), 3.94 - 3.83 (m, 1 H), 1.93 - 1.80 (m, 1 H), 1.02 (t, J = 6.7 Hz, 1 H), 0.87 (td, J = 6.3, 9.4 Hz, 1 H). Residual MeOH.

MS \(m/z\) = 287.9 [M+H] +

**Step 8:** (1S,2S)-2-((R)-l-amino-l-(2-chlorophenyl)-2,2-difluoroethyl)cyclopropanol

(l9b-A) and (IR,2R)-2-((S)-l-amino-l-(2-chlorophenyl)-2,2-difluoroethyl)cyclopropanol

(l9b-B)

[(lR,S),(2R,S)]-2-((S,R)-l-amino-l-(2-chlorophenyl)-2,2-difluoroethyl)cyclopropanol (19b-rac; 17.4 g) was subjected to chromatography using supercritical \(CO_2\) (additives 25% (MeOH with 20 mM NH\(_3\)) on a Chiralpak AD-H column (30 x 250 mm, 5 \(\mu\)m) eluting at a flow rate 120 ml/min (165 bar pressure, 40 °C column temperature). The first peak (retention time = 1.03 min) provided (IR,2S)-2-((R)-l-amino-l-(2-chlorophenyl)-2,2-difluoroethyl)cyclopropanol (19b-A, 6.39 g, 25.7 mmol, 40% yield; 99% de, 99% ee). MS \(m/z\) = 248.0 [M]+. The second peak (retention time = 1.51 min) provided (IR,2R)-2-((S)-l-amino-l-(2-chlorophenyl)-2,2-difluoroethyl)cyclopropanol (19b-B, 6.39 g, 25.7 mmol, 40% yield; 99% de, 99% ee). MS \(m/z\) = 248.0 [M+H] +

**Steps 9-11:** (IR,5S,6R)-5-(2-chloro-5-nitrophenyl)-5-(difluoromethyl)-2-oxa-4-

azabicclo[4.1.0]hept-3-en-3-amine (19e-B)

The title compound was prepared following procedures similar to those described in steps 3-5 for the synthesis of 19e-rac, but using (IR,2R)-2-((S)-l-amino-l-(2-chlorophenyl)-2,2-difluoroethyl)cyclopropanol (19b-B). 

\(^1\)H NMR (400 MHz, CHLOROFORM-d) \(\delta\) ppm 8.68 - 8.70 (m, 1 H) 8.11 - 8.16 (m, 1 H) 7.60 (dd, J=8.90, 1.66 Hz, 1 H) 6.85 (s, 1 H) 6.71 (s, 1 H) 6.56 - 6.58 (m, 1 H) 3.91 - 3.97 (m, 1 H) 1.94 - 2.02 (m, 1 H) 1.37 - 1.43 (m, 1 H) 1.02 - 1.10 (m, 1 H)MS \(m/z\) = 317.9 [M]+

Example 20
Step 1: 

A solution of 1-bromo-2,3-difluorobenzene (1.1 ml, 9.83 mmol) in diethyl ether (60 mL) under nitrogen atmosphere was cooled to -78°C. A solution of n-butyllithium (2.5 M in hexanes, 4 ml, 10.00 mmol) was added dropwise and the reaction stirred for 20 minutes at -78°C. A second flask was charged with a solution of 4-(difluoromethyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (1.0 g, 7.51 mmol, 16b rac) in toluene (20 mL) under nitrogen atmosphere and cooled to -78°C. Boron fluoride diethyl etherate (1.0 ml, 8.10 mmol) was added and the reaction mixture stirred for 5 minutes. This solution was added to the aryl lithium solution via cannula. Upon complete addition, the reaction was stirred for 10 minutes and then quenched by addition of aqueous citric acid solution (10%; 5 mL). Water (50 mL) and ethyl acetate (100 mL) were added and the organic layer was separated and dried over magnesium sulfate. The solvent was evaporated under reduced pressure and the crude residue was purified using silica chromatography (0-100% ethyl acetate/hexanes) to give the title compound (1.33 g, 5.38 mmol, 71.6% yield).

MS m/z = 248.0 [M+H]

Steps 2-6: [Y1R,S). (4S,R), (5S,R)]-5-(5-amino-2,3-difluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (20f rac)

The title compound was prepared following procedures similar to those described in steps 2-6 for the synthesis of 10f rac, but using [(1R,S), (4S,R), (5R,S)]-4-(difluoromethyl)-4-(2,3-difluorophenyl)-2-oxa-3-azabicyclo[3.1.0]hexane (20a rac).

MS m/z = 290.0 [M+H]
Step 7: (lS,5R,6S)-5-(5-amino-2,3-difluorophenyl)-5-(difluoromethyl)-2-oxa-4-
azabicyclo[4.1.0]hept-3-en-3-amine (20f-A) and (IR,5S,6R)-5-(5-amino-2,3-
difluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (20f-B)

[(1R,S), (5S,R), (6R,S)]-5-(5-amino-2,3-difluorophenyl)-5-(difluoromethyl)-2-oxa-
azabicyclo[4.1.0]hept-3-en-3-amine (20f rac; 2.0 g) was subjected to
chromatography using supercritical CO₂ (additives 15% (EtOH with 20 mM NH₃) on a
Chiralpak OJ-H column (21 x 250 mm, 5 µm) eluting at a flow rate 50 ml/min (100 bar
pressure, 40 °C column temperature). The first peak (retention time = 2.7 min) provided
((lS,5R,6S)-5-(5-amino-2,3-difluorophenyl)-5-(difluoromethyl)-2-oxa-4-
azabicyclo[4.1.0]hept-3-en-3-amine (20f-A, 830 mg, 2.87 mmol, 41.5 yield; 99% de;
99% ee) as a light-yellow powder.

H NMR (CHLOROFORM-d) δ: 6.54 (ddd, J=5.2, 3.0, 1.8 Hz, 1H), 6.44 (ddd, J=1 1.2,
6.2, 2.9 Hz, 1H), 6.14 (td, J=56.1, 1.0 Hz, 1H), 4.91 (br. s., 2H), 3.81-3.94 (m, 1H), 3.66
(br. s., 2H), 1.72-1.84 (m, 1H), 1.33-1.43 (m, 1H), 0.85-0.97 (m, 1H)

F NMR (CHLOROFORM-d) δ: -127.37 (dd, J=275.9, 10.9 Hz, IF), -129.71 (dd,
J=275.9, 7.5 Hz, IF), -137.53 (d, J=21.8 Hz, IF), -150.81 (dd, J=21.9, 10.6, 7.5 Hz, IF)
MS m/z = 290.0 [M+H]

The second peak (retention time = 3.4 min) provided (IR,5S,6R)-5-(5-amino-2,3-
difluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (20f-B,
840 mg, 2.90 mmol, 42% yield; 99% de; 99% ee) as a light-yellow powder.

H NMR (CHLOROFORM-d) δ: 6.54 (ddd, J=5.2, 3.0, 1.8 Hz, 1H), 6.44 (ddd, J=1 1.3,
6.3, 2.9 Hz, 1H), 6.14 (td, J=55.9, 1.0 Hz, 1H), 4.84 (br. s., 2H), 3.84-3.93 (m, 1H), 3.64
(br. s., 2H), 1.73-1.84 (m, 1H), 1.33-1.42 (m, 1H), 0.86-0.97 (m, 1H)

F NMR (CHLOROFORM-d) δ: -127.40 (dd, J=275.9, 10.9 Hz, IF), -129.72 (dd,
J=275.9, 7.5 Hz, IF), -137.53 (d, J=21.8 Hz, IF), -150.80 (dd, J=21.8, 10.9, 7.5 Hz, IF)
MS m/z = 290.0 [M+H]⁺.
Step 1: rR,S), r4S.R, r5R.S |-4-r5-bromo-2-fluoro-3-methylphenylV4-rdifluoromethylV2-oxa-3-azabicyclo [3.1.0] hexane (21a rac)

A flask was charged with a solution of 5-bromo-2-fluoro-1-iodo-3-methylbenzene (24.16 g, 77 mmol) in diethyl ether (143 ml) and the solution was cooled to -78 °C. A solution of n-butyllithium (2.5 M in hexanes, 30.7 ml, 77 mmol) was added dropwise and the reaction mixture was stirred at -78 °C for 15 min. A separate flask was charged with a solution of [(1R,S), (5R,S)]-4-(difluoromethyl)-2-oxa-3-azabicyclo [3.1.0] hex-3-ene (16b rac, 6.6 g, 45.1 mmol) in toluene (158 ml) and the solution was cooled to -78 °C. Boron trifluoride diethyl etherate (5.72 ml, 45.1 mmol) was added dropwise and the reaction mixture was stirred at -78 °C for 5 min. This reaction mixture was transferred via cannula within 14 min to the aryl lithium solution. The reaction mixture was stirred at -78 °C for 2 h, followed by quenching with saturated ammonium chloride solution. The reaction mixture was warmed to RT and diluted with water and EtOAc. The organic layer was separated and the aqueous layer was washed with additional EtOAc. The combined organic layers were washed with brine, dried over magnesium sulfate and the filtrate was concentrated under reduced pressure. The crude material was triturated with diethyl ether and the solids collected by vacuum filtration were washed with cold diethyl ether to afford a pale yellow solid. The filtrate was concentrated under reduced pressure and trituration was repeated to afford a second crop. The two crops were combined to afford the title compound (11.15 g, 34.6 mmol, 77% yield).

MS m/z = 321.8 [M+H]+. Calculated for C12H16BrF3NO: 322.1

Step 2: r(R,S), (2R,S)-2-r(S,RV1-amino-l-(5-bromo-2-fluoro-3-methylphenylV2.2-difluoroethylVcyclopropanol (21b rac)

The title compound was prepared following a procedure similar to that described in step 2 for the synthesis of 4b rac, but using [(1R,S), (4S,R),(5R,S)]-4-(5-bromo-2-

fluoro-3-methylphenyl)-4-(difluoromethyl)-2-oxa-3-azabicyclo[3.1.0]hexane (21a rac).

**MS m/z = 323.9 [M+H]⁺. Calculated C₁₂H₁₅BrF₃NO: 324.1**

**Step 3:** (1S,2S)-2-((R)-1-amino-1-(5-bromo-2-fluoro-3-methylphenyl)-2,2-difluoroethyl)cyclopropanol (21b-A) and (1R,2R)-2-((S)-1-amino-1-(5-bromo-2-fluoro-3-methylphenyl)-2,2-difluoroethyl)cyclopropanol (21b-B) _MS m/z = 323.9 [M+H]⁺._

[(1R,S), (2R,S)-2-[(S,R)-1-amino-1-(5-bromo-2-fluoro-3-methylphenyl)-2,2-difluoroethyl]cyclopropanol (21b rac, 13 g) was subjected to chromatography using supercritical CO₂ (additives 25% (EtOH with 20 mM NH₃) on a Chiralpak ADH column (30 x 250 mm, 5 µm) eluting at a flow rate 120 ml/min (100 bar pressure, 40 °C column temperature). The first peak (retention time = 0.8 min) provided (1S,2S)-2-((R)-1-amino-1-(5-bromo-2-fluoro-3-methylphenyl)-2,2-difluoroethyl)cyclopropanol (21b-A, 5.3 g, 20.3 mmol, 40.5% yield; 99% de; 99% ee) as a light yellow powder. The second peak (retention time = 1.52 min) provided (1R,2R)-2-((S)-1-amino-1-(5-bromo-2-fluoro-3-methylphenyl)-2,2-difluoroethyl)cyclopropanol (21b-B, 5.2 g, 20.0 mmol, 40.0% yield; 99% de; 99% ee) as a light yellow powder. MS m/z = 323.9 [M+H]⁺. Calculated C₁₂H₁₅BrF₃NO: 324.1 for both enantiomers.

**Steps 4 and 5:** N-((1R,5S,6R)-5-(5-amino-2-fluoro-3-methylphenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)benzamide (21d-B)

The title compound was prepared following procedures similar to those described in steps 3 and 4 for the synthesis of 4d rac, but using (1R,2R)-2-((S)-1-amino-1-(5-bromo-2-fluoro-3-methylphenyl)-2,2-difluoroethyl)cyclopropanol (21b-B) _MS m/z = 390.0 [M+H]⁺._

**Step 6:** (1R,5S,6R)-5-(5-amino-2-fluoro-3-methylphenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)benzamide (21d-B) _MS m/z = 286.0 [M+H]⁺

**Example 2**
Step 1: ([R.S]. (4S.R). (5R.S)-l-4-(3-bromophenyl)-4-(difluoromethyl)-2-oxa-3-
azabicyclo[3.1.0]hexane (23a rac)

A flask was charged with a solution of 1,3-dibromobenzene (2.72 ml, 22.54 mmol) in diethyl ether (40 ml) and cooled to -78 °C. A solution of n-butyllithium (2.5M in hexanes, 2.034 ml, 22.54 mmol) was added dropwise and the reaction mixture was allowed to stir at -78 °C for 1 hour. A separate flask was charged with a solution of 4-
difluoromethyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (16b rac, 1.000 g, 7.51 mmol) in toluene (37.6 ml) and cooled to -78 °C. Boron trifluoride etherate (1.020 ml, 8.26 mmol) was added and the reaction mixture was allowed to stir for additional 5 minutes. The aryl lithium solution was transferred via cannula to this reaction mixture and the resulting reaction mixture was allowed to stir at -78 °C for 30 minutes. The reaction mixture was quenched with aqueous saturated NH4Cl solution and then allowed to warm to room temperature. Ethyl acetate (200 ml) was added, the layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over sodium sulfate and the filtrate was concentrated in vacuo. The crude material was absorbed on silica gel and purified by silica gel chromatography, eluting with a gradient of 0-20% ethyl acetate/hexanes, to provide the title compound (1.392 g, 4.80 mmol, 63.9 % yield) as a tan oil. MS mix = 290.9 [M+H]^+. Calculated for C_{11}H_{19}BrF_{2}NO: 288.9.

^{1}H NMR (300 MHz, CHLOROFORM-d) δ ppm 7.84 (t, J=1.97 Hz, 1 H) 7.46 - 7.64 (m, 2 H) 7.24 - 7.32 (m, 1 H) 5.92 (s, 1 H) 4.08 - 4.17 (m, 1 H) 2.21 (dd, J=4.75, 4.17 Hz, 1 H) 1.36 - 1.43 (m, 1 H) 0.73 - 0.82 (m, 1 H)

Step 2-4: N-[([R.S]. (5S.R). r6R.SV5-r3-aminophenylV5-rdifluoromethylV2-oxa-4-
azabicyclo[4.1.0]hept-3-en-3-yl]benzamide (23d rac)
The title compound was prepared following procedures similar to those described in steps 2 to 4 for the synthesis of 
\[ ([1R,S], (4S,R), (5R,S)]-4-(3-bromophenyl)-4-(difluoromethyl)-2-oxa-3-azabicyclo[3.1.0]hexane (23a rac) \]

\[ \text{MS } m/z = 358 \ [\text{M+H}]^+. \text{ Calculated for } C_{18}H_{17}F_{2}N_{2}O_{2}: \ 357. \]

**Step 5:** \[ N-((1S,5R,6S)-5-(3-aminophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)benzamide (23d-A) \]

and \[ N-((1R,5S,6R)-5-(3-aminophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)benzamide (23d-B) \]

N-[(1R,S), (5S,R), (6R,S)-5-(3-aminophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl]benzamide (23d, 0.787 g, 2.202 mmol) was subjected to chromatography using supercritical CO\(_2\) (20% methanol with 20 mM ammonia) on a chiralcel OD-H column (21 x 250 mm, 5 \( \mu \)m) eluting at a flow rate 70 ml/min (165 bar pressure, 40 °C column temperature). The first peak (retention time = 1.49 min) provided N-[(1S,5R,6S)-5-(3-aminophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl]benzamide (23d-A, 0.350 g, 0.979 mmol, 44.5 % yield; >98% de) as off-white solid. MS m/z = 358 [M+H]^+. Calculated for C\(_{18}\)H\(_{17}\)F\(_2\)N\(_2\)O\(_2\): 357.

\[ ^{1}H \text{ NMR (400 MHz, CHLOROFORM-d)} \text{ d ppm } 8.22 - 8.27 (m, 2 H) 7.49 - 7.55 (m, 1 H) 7.41 - 7.47 (m, 2 H) 7.18 - 7.27 (m, 1 H) 6.83 (d, J=8.61 Hz, 1 H) 6.74 (br. s., 1 H) 6.68 - 6.74 (m, 2 H) 6.00 - 6.02 (m, 1 H) 4.26 (m, 1 H) 1.99 (m, 1 H) 1.69 (m, 1 H) 1.21 - 1.27 (m, 1 H).

The second peak (retention time = 1.76) provided N-[(1R,5S,6R)-5-(3-aminophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl]benzamide (23d-B, 0.325 g, 0.909 mmol, 41.3 % yield; >97% de) as off-white solid. MS m/z = 358 [M+H]^+. Calculated for C\(_{18}\)H\(_{17}\)F\(_2\)N\(_2\)O\(_2\): 357.

\[ ^{1}H \text{ NMR (400 MHz, CHLOROFORM-d)} \text{ d ppm } 8.24 (d, J=7.04 Hz, 2 H) 7.53 (br. s., 1 H) 7.48 - 7.52 (m, 1 H) 7.39 - 7.46 (m, 2 H) 7.17 - 7.23 (m, 1 H) 6.81 (s, 1 H) 6.66 - 6.74 (m, 2 H) 6.00 (s, 1 H) 4.20 - 4.27 (m, 1 H) 1.91 - 1.99 (m, 1 H) 1.61 - 1.68 (m, 1 H) 1.17 - 1.25 (m, 1 H).

Example 24
Step 1: (S,R)-5-(chloromethyl)-3-(trifluoromethyl)-4,5-dihydroisoxazole (24a rac)

A solution of 2,2,2-trifluoro-A^-hydroxyacetimidoyl bromide (13.0 g, 40.6 mmol, WO2008 135826) and 3-chloroprop-1-lene (10.0 mL, 123 mmol) in diethyl ether (50 mL) was cooled to 5 °C. A solution of triethylamine (11.4 mL, 82 mmol) in diethyl ether (200 mL) was added over a period of 3 h, keeping the internal temperature below 10 °C. The cold bath was removed and the reaction mixture was stirred at rt for 2 h. The precipitate was filtered off and the filtrate was washed with water (300 mL) and brine (300 mL). The organic phase was dried over sodium sulfate and the filtrate was concentrated in vacuo. The crude product was purified by silica gel column chromatography (ether in hexanes 0 to 40%) to afford the title compound (3.16 g, 16.8 mmol) as a clear oil. 1H NMR (300MHz, CHLOROFORM-d) δ = 5.11 (dd, J = 4.2, 6.7, 10.9 Hz, 1 H), 3.75 - 3.57 (m, 2 H), 3.41 - 3.09 (m, 2 H).

Step 2: V(R,S)-5(R,S)-l-4-(trifluorometlyl)-2-oxa-3-azabicyclo[3, 1.011iex-3-ene (24b rac)

A solution of potassium 2-methylpropan-2-olate (1M in THF, 20.2 mL, 20.2 mmol) was added over a period of 30 min to a stirred solution of (S,77)-5-(chloromethyl)-3-(trifluoromethyl)-4,5-dihydroisoxazole (24a rac, 3.16 g, 16.8 mmol) in tetrahydrofuran (50 mL) at 0 °C. After 45 min, the reaction was quenched by addition of aqueous saturated ammonium chloride solution. The cold bath was removed and the reaction mixture was further diluted with aqueous saturated ammonium chloride solution and diethyl ether. The phases were separated and the aqueous phase was extracted with diethyl ether. The combined organic phases were washed with water, brine and dried over sodium sulfate. The filtrate was concentrated in vacuo and the crude product was purified by silica gel column chromatography (ether in pentanes 0 to 50%) to afford the title compound (1.50 g, 9.93 mmol) containing residual tetrahydrofuran and pentane. 1H NMR
A-1 813-WO-PCT - 130 -

(300MHz, CHLOROFORM-d) δ = 5.18 (dt, J = 2.2, 5.4 Hz, 1 H), 2.85 - 2.69 (m, 1 H), 1.19 - 1.08 (m, 1 H), 0.46 (dt, J = 1.9, 4.1 Hz, 1 H).

**Step 3:** [(7\(^{7}\),6\(^{6}\),4\(^{4}\),5\(^{5}\),11\(^{11}\),4-((5-bromo-2-fluoro)phenyl)-4-(trifluoromethyl)-2-oxa-3-azabicclo[3.1.0]hexane (24c rac). LC/MS (ESI) m/z = 290 (M+H).

Example 25

A flask was charged with a solution of 4-bromo-l-fluoro-2-iodobenzene (5.00 ml, 16.6 mmol) in diethyl ether (25 mL) and the solution was cooled to -78 °C. A solution of n-butyllithium (2.5 M in hexanes, 6.50 ml, 16.25 mmol) was added dropwise and the reaction mixture was stirred at this temperature for 15 min. A separate flask was charged with a solution of [l(i,h),s(R,S)]-4-(trifluoromethyl)-2-oxa-3-azabicclo[3.1.0]hex-3-ene (24b rac, 1.25 g, 8.27 mmol) in toluene (73 mL) and cooled to -78 °C. Boron trifluoride diethyl etherate (1.05 ml, 8.51 mmol) was added and the reaction mixture was stirred for 5 min at -78 °C. This solution was added via cannula to the aryl lithium solution. The resulting reaction mixture was stirred at that temperature for 40 min and then quenched by adding aqueous saturated ammonium chloride. The cold bath was removed and the reaction mixture was allowed to warm to rt. The reaction mixture was diluted with water and ethyl acetate. The layers were separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine and dried over sodium sulfate. The filtrate was concentrated in vacuo and the crude product was purified by silica gel column chromatography (ethyl acetate in hexanes 0 - 30%) to afford the title compound (1.36 g, 4.16 mmol) as a pale orange solid. LC/MS (ESI\(^{+}\)) m/z = 326 (M+H).

Steps 4-7: ri(P,S),5(S,7?),6(6?,8?)-5-(5-amino-2-fluorophenyl)-5-(trifluoromethyl)-2-oxa-4-azabicclo[4.1.0]1,01hept-3-en-3-amine (24 g rac)

The title compound was prepared following procedures similar to those described in steps 2 to 4 for the synthesis of 4d rac, and step 9 for the synthesis of 6h rac, but using r1(P',y),4r3?,7?)-5-(5-bromo-2-fluorophenyl)-4-(trifluoromethyl)-2-oxa-3-azabicclo[3.1.0]hexane (24c rac). LC/MS (ESI\(^{+}\)) m/z = 290 (M+H).

Example 25
A flask was charged with a solution of 1,3-dibromobenzene (1.90 mL, 15.72 mmol) in Et₂O (30 mL) and the solution was cooled to -78 °C. A solution of n-butyllithium (2.5 M in hexanes, 6.20 mL, 15.50 mmol) was added dropwise and the reaction mixture was stirred at this temperature for 40 min. A separate flask was charged with a solution of [l(R,S),5(R,S)]-4-(trifluoromethyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (24b rac, 1.90 g, 7.92 mmol) in toluene (70 mL) and cooled to -78 °C. Boron trifluoride diethyl etherate (1.0 mL, 8.10 mmol) was added and the reaction mixture was stirred for 40 min at -78 °C. This solution was added via cannula to the aryl lithium solution. The resulting reaction mixture was stirred at that temperature for 40 min and then quenched by adding aqueous saturated ammonium chloride. The cold bath was removed and the reaction mixture was allowed to warm to rt. The reaction mixture was diluted with water and ethyl acetate. The layers were separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine and dried over sodium sulfate. The filtrate was concentrated in vacuo and the crude material was purified by silica gel chromatography, eluting with 10-30% EtOAc in hexanes, to provide the title compound (0.502 g, 1.63 mmol) as a brown oil. LC/MS (ESI⁺) m/z = 308.3 (M+H).

Steps 2-5: [l(S,R),5(R,S)]-6(S,R)-5-(3-aminophenyl)-5-(trifluoromethyl)-2-oxa-4-hept-3-en-3-amine (25e rac)

The title compound was prepared following procedures similar to those described in steps 2 to 4 for the synthesis of 4d rac, and step 9 for the synthesis of 6h rac, but using [l(R,S),4(S,R),5(R,S)]-4-(3-bromophenyl)-4-(trifluoromethyl)-2-oxa-3-azabicyclo[3.1.0]hexane (25a rac), LC/MS (ESI⁺) m/z = 272.0 (M+H).
Step 1-2: 4-(Methoxymethyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (26b rac)

To a solution of (5-(chloromethyl)-4,5-dihydroisoxazol-3-yl)methanol (6c rac, 2.2 g, 14.71 mmol) in THF (40 mL) was added sodium hydride (60% dispersion in mineral oil, 0.372 ml, 17.65 mmol). The resulting mixture was stirred for 15 min followed by dropwise addition of methyl iodide (1.005 ml, 16.18 mmol). After 15 min, the reaction mixture was carefully quenched with aqueous saturated ammonium chloride solution and diluted with water. The phases were separated and the aqueous phase was extracted with Et20. The combined organic layers were dried over Na2SO4 and the filtrate was concentrated under reduced pressure to afford the title compound as a pale yellow oil. The oil was dissolved in THF (20 mL) and the solution was cooled 0 °C. A solution of potassium tert-butoxide (1M in THF, 17.65 ml, 17.65 mmol) was added dropwise and the reaction mixture was stirred for 30 min at 0 °C. The mixture was quenched with aqueous saturated ammonium chloride solution, the phases were separated and the aqueous phase was extracted with EtOAc. The combined organic layers were dried over Na2SO4 and the filtrate was concentrated under reduced pressure to afford the title compound as an orange oil as MS m/z = 128.1[M+H]+. Calculated for C_{10}N_{0.5}O_{2}: 127.06.

Step 3: (R,S,R,S)-4-(3-bromo-5-fluorophenyl)-4-(methoxymethyl)-2-oxa-3-azabicyclo[3.1.0]hexane (26c rac)

A flask was charged with a solution of 4-bromo-l-fluoro-2-iodobenzene (3.55 ml, 11.80 mmol) in Et20 (40 mL) and the solution was cooled to - 78 °C. A solution of n-butyllithium (2.5M in hexanes, 4.72 ml, 11.80 mmol) was added dropwise and the reaction mixture was stirred at this temperature for 20 min. A separate flask was charged with a solution of 4-(methoxymethyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (26b rac, 1.0 g, 7.87 mmol) in toluene (10 mL)
and cooled to -78 °C. Boron trifluoride diethyl etherate (1.019 ml, 8.26 mmol) was added dropwise and the resulting reaction mixture was stirred at -78 °C for 5 min. This solution was added via cannula to the aryl lithium solution. The resulting reaction mixture was stirred at that temperature for 30 min and subsequently quenched with aqueous saturated ammonium chloride solution. The reaction mixture was allowed to warm to room temperature and diluted with EtOAc and water. The aqueous phase was extracted with EtOAc (2x) and the combined organics were dried over Na₂SO₄. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel chromatography (0-10% EtOAc/hexanes) to afford the title compound as a light yellow oil (0.500 g, 1.655 mmol, 21.04% yield). MS m/z = 301.9 [M+H]+. Calculated for C₁₂H₁₁BrFNO₂: 301.01.

Steps 4-7: [Y1R.S), (5S.R), (6R,S)]-5-(5-amino-2-fluorophenyl)-5-(methoxymethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (26g rac).

The title compound was prepared following procedures similar to those described in steps 2 to 4 for the synthesis of 4d rac, and step 9 for the synthesis of 6h rac, but using [(1R,S), (4S,R), (5R,S)]-4-(5-bromo-2-fluorophenyl)-4-(methoxymethyl)-2-oxa-3-azabicyclo[3.1.0]hexane (26c rac). MS m/z = 266 [M+H]+. Calculated for C₁₃H₁₆FN₃O₂: 265.12.

Example 27

Step 1: (IR,5S,6R)-5-(difluoromethyl)-5-(2-methyl-5-nitrophenyl)-2-oxa-4-

Step 2: [101hept-3-en-3-amine (27a-B)]

A flask was charged with (IR,5S,6R)-5-(2-chloro-5-nitrophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (19e-B 0.248 g, 0.781 mmol), cesium carbonate (0.763 g, 2.342 mmol) and a solvent mixture of THF (14.87 ml)/water (0.74 ml). The reaction mixture was purged with nitrogen gas for 5 min. Then 1,1'-bis(diphenylphosphino)ferrocene palladium(II) dichloride dichloromethane adduct
(0.064 g, 0.078 mmol) and methylboronic acid (0.935 g, 15.61 mmol) were added. The flask was fitted with a reflux condenser, and the reaction mixture was heated under reflux overnight. Additional methylboronic acid (0.935 g, 15.61 mmol) and 1,1'-bis(diphenylphosphino)ferrocene palladium(II)dichloride dichloromethane adduct (0.064 g, 0.078 mmol) were added and stirring was continued at 88 °C overnight. The reaction mixture was cooled to ambient temperature and diluted with ethyl acetate (50 ml). The mixture was filtered through a pad of celite and the filter cake was rinsed with dichloromethane (2x). The combined organic extracts were concentrated in vacuo and the crude material was purified by silica gel chromatography, eluting with a gradient of 0-55% ethyl acetate/hexanes, to provide a mixture of (IR,5S,6R)-5-(difluoromethyl)-5-(2-methyl-5-nitrophenyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (27a-B, 0.225 g, 0.757 mmol) and (IR,5S,6R)-5-(difluoromethyl)-5-(3-nitrophenyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (0.229 g, 77:23 ratio). MS m/z = 298 [M+H]+. Calculated for C_{13}H_{10}F_{2}N_{3}O_{3}: 297. 

**Step 2:** (IR,5S,6R)-5-(5-amino-2-methylphenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (27b-B)

A flask was charged with a 77:23 mixture of (IR,5S,6R)-5-(difluoromethyl)-5-(2-methyl-5-nitrophenyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (27a-B, 0.225 g, 0.757 mmol) and (IR,5S,6R)-5-(difluoromethyl)-5-(3-nitrophenyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (0.229 g, 77:23 ratio). Glacial acetic acid (0.262 ml, 4.54 mmol) and TFA (0.394 ml, 5.30 mmol) were added, followed by zinc (0.247 g, 3.78 mmol). The reaction mixture was allowed to stir for 30 min and was then diluted with methanol (5 ml). The suspension was filtered and the filtrate was concentrated in vacuo. The crude material was purified by chromatography, eluting with a gradient of 0-10% MeOH/DCM, to provide a 85:15 mixture of (IR,5S,6R)-5-(5-amino-2-methylphenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (27b-B, 0.13 g) as off-white solid. The mixture was used in the next step without further purification.

MS m/z = 268 [M+H]+. Calculated for C_{13}H_{12}F_{2}N_{3}O: 267.

MS m/z = 254 [M+H]+. Calculated for C_{12}H_{12}F_{2}N_{3}O: 253.
Step 1: To a flame dried RBF was added a solution of n-butyllithium (2.5 M in hexanes; 3.01 ml, 7.51 mmol) and diethyl ether (15 ml). The solution was cooled to -78 °C, and 2-fluoro-6-iodotoluene (0.981 ml, 7.51 mmol) was added dropwise and the reaction was stirred at -78 °C for 10 minutes. A -78 °C premixed solution of 4-(difluoromethyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (1.00 g, 7.51 mmol) and boron trifluoride diethyl etherate (0.927 ml, 7.51 mmol) in toluene (10 ml) was added to the reaction via syringe. The reaction was stirred at -78 °C for 10 minutes, quenched with saturated ammonium chloride and warmed to RT. The reaction was diluted with water and EtOAc. The organic layer was separated and concentrated under reduced pressure. The crude residue was purified via silica gel flash chromatography eluting with 0-20% ethyl acetate in hexanes to afford 4-(difluoromethyl)-4-(3-fluoro-2-methylphenyl)-2-oxa-3-azabicyclo[3.1.0]hexane (28a rac) (807 mg, 3.33 mmol, 44.3% yield).

LC/MS (ESI) m/z = 244.1 (M+H).

Step 2: To a solution of 4-(difluoromethyl)-4-(3-fluoro-2-methylphenyl)-2-oxa-3-azabicyclo[3.1.0]hexane (0.81 g, 3.33 mmol) in acetic acid, glacial (7.69 ml, 133 mmol) was added zinc (1.306 g, 19.98 mmol) portionwise at RT followed by trifluoroacetic acid (2.474 ml, 33.3 mmol). The reaction was stirred at RT for 1 hour. The reaction was filtered through a pad of celite and concentrated under vacuum. The residue was dissolved in iced water and the solution was basified by the addition of 5N NaOH to pH
12. The basic aqueous layer was back extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate, and concentrated to dryness to afford the title compound 2-(l-amino-2,2-difluoro-l-(3-fluoro-2-methylphenyl)ethyl)cyclopropanol (0.61 g, 2.487 mmol, 74.7 % yield). LC/MS (ESI⁻) m/z = 246.1 (M+H).

Step 3: N-{(1R,S), (5S,R), (6R,S)}-l-(5-(difluormethyl)lV5-(3-fluoro-2-methyl)Dlienvn-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)benzamide (28c rac)

To a solution of 2-(l-amino-2,2-difluoro-l-(3-fluoro-2-methylphenyl)ethyl)cyclopropanol (0.61 g, 2.487 mmol) in dry THF (10 mL) under nitrogen was added benzyol isothiocyanate (0.7 ml, 5.20 mmol) dropwise and the reaction was stirred for 30 min. Diisopropylethylamine (1.73 l ml, 9.95 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.954 g, 4.97 mmol) were added and the reaction stirred at room temperature for 1 hour and then warmed to 60 °C for another 12 hr. The reaction mixture was diluted with dichloromethane and water. The phases were mixed, separated, and the organic was evaporated to dryness under reduced pressure. The crude residue was purified via silica gel flash chromatography eluting with 0-30% ethyl acetate in hexane afforded the title compound N-{(5-(difluoromethyl)-5-(3-fluoro-2-methylphenyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)benzamide (0.8 g, 2.137 mmol, 86 % yield). LC/MS (ESI⁺) m/z = 375.0 (M+H).

Step 4: (1R,S), (5S,R), (6R,S)-l-(5-(difluorometlivn-5-(3-fluoro-2-metliylDlienvn-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)benzamide (28d rac)

N-{(5-(difluoromethyl)-5-(3-fluoro-2-methylphenyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)benzamide (1.0 g, 2.67 mmol) was dissolved in methanol (50 mL) under nitrogen and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.798 ml, 5.34 mmol) was added. The reaction was heated to 40 °C. After 18 hours, the reaction mixture was concentrated to dryness under reduced pressure and the residue partitioned between water and ethyl acetate. The organic layer was isolated and concentrated under reduced pressure. The crude residue was purified via silica gel flash chromatography eluting with 0-60% ethyl acetate in hexanes afforded the title compound 5-(difluoromethyl)-5-(3-fluoro-2-methylphenyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)benzamide (0.470 g, 1.739 mmol, 65.1 % yield). LC/MS (ESI⁻) m/z = 270.9 (M+H).

Step 5: (1R,S), (5S,R), (6R,S)-l-(5-(difluorometlivn-5-(3-fluoro-2-metliylDlienvn-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)benzamide (28e rac)

5-(Difluoromethyl)-5-(3-fluoro-2-methylphenyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)benzamide (0.470 g, 1.739 mmol) was dissolved in sulfuric acid, 95%o (5 mL) and
cooled in an ice bath. Sodium nitrate (0.177 g, 2.087 mmol) was added in one portion and the reaction stirred for 5 minutes. The reaction was warmed to rt and stirred for 1 hr and poured into a mixture of dichloromethane (50 mL), iced water (90 mL), and potassium phosphate tribasic (20.02 g, 87 mmol). The mixture was stirred for 5 minutes then saturated sodium bicarbonate was added slowly until pH 8. The phases were separated and the aqueous extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried over magnesium sulfate and evaporated under reduced pressure. The crude residue was purified via silica gel flash chromatography eluting with 0-30% hexane to ethyl acetate to afford the title compound 5-(difluoromethyl)-5-(3-fluoro-2-methyl-5-nitrophenyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (0.22 g, 0.698 mmol, 40.1 % yield). LC/MS (ESI+) m/z = 316.1 (M+H).

**Step 6:** IY1R.S1 (5S,R). (6R,S)-5-(5-amino-3-fluoro-2-methylphenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4. 1.0]hept-3-en-3-amine (200 mg, 0.634 mmol) was dissolved in THF (20 mL). 10% palladium on carbon (135 mg, 0.127 mmol) was added and the reaction mixture was put under a balloon of 3/4 and stirred at 18 °C for 4h. The mixture was filtered through a pad of celite, washing well with ethyl acetate. The filtrate was concentrated under vacuum to yield crude 5-(5-amino-3-fluoro-2-methylphenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4. 1.0]hept-3-en-3-amine (140 mg, 0.491 mmol, 77 % yield) as a gray foam. LC/MS (ESI+) m/z = 286.2 (M+H)

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**Synthesis of 8-Chloro-3-methoxy-1,7-naphthyridine**

**Step 1:** 3-chloro-5-methoxypicolinonitrile

To a solution of 3,5-dichloropicolinonitrile (22.5 g, 130 mmol) in DMF (500 mL) at 0 °C was added sodium methoxide (6.67 g, 124 mmol) slowly. The reaction was stirred for 5 minutes at 0 °C, then it was allowed to warm to RT and stir for 30 minutes. The solution was partitioned between water and EtOAc. The organic layer was washed with water and concentrated. The crude product was purified via silica gel
chromatography, eluting with 0-75 % ethyl acetate in heptanes, to afford a 1:1 ratio of the desired isomer 3-chloro-5-methoxypicolinonitrile and 5-chloro-3-methoxypicolinonitrile (7.0 g, 41.5 mmol). The material was used without further purification. MS m/z = 169 (M+H).

5 **Step 2: 5-Methoxy-3-((triethylsilyl)ethynyl)picolinonitrile**

A sealed vessel was charged with bis(acetonitrile)palladium (II) chloride (0.154 g, 0.593 mmol), dicyclohexyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphine (0.848 g, 1.780 mmol), cesium carbonate (25.1 g, 77 mmol), the product of Intermediate 1, step 1 (5 g, 29.7 mmol), and ACN (60 mL). The vessel was flushed with argon, sealed, and stirred at RT for 25 minutes. To the reaction was added triethyl(ethynyl)silane (5.41 g, 38.6 mmol), and the vessel was resealed and stirred at 90 °C for 3 hours. The solution was concentrated, and the residue was purified via silica gel chromatography, eluting with 0-50 % ethyl acetate in heptanes, to afford the title compound (3.8 g, 13.9 mmol). MS m/z = 273 (M+H)+.

15 **Step 3: 3-(2,2-Dimethoxyethyl)-5-methoxypicolinonitrile**

A pressure vessel was charged with 5-methoxy-3-((triethylsilyl)ethynyl)picolinonitrile (3.8 g, 13.95 mmol) and sodium methoxide (0.5 M in methanol, 69.7 mL, 34.9 mmol). The vessel was sealed and stirred at 55 °C for 2 hours. The reaction was concentrated to afford the title intermediate (3.1 g, 13.95 mmol).

20 **Step 4: 3-(2,2-dimethoxyethyl)-5-methoxypicolinamide**

To a 1 L round-bottomed flask was added 3-(2,2-dimethoxyethyl)-5-methoxypicolinonitrile (8.550 g, 38.5 mmol), water (480 ml), and acetone (120 ml). An aqueous solution of sodium carbonate (3M; 154 ml, 462 mmol) was added followed by hydrogen peroxide (35 wt. % solution in water; 138 ml, 1347 mmol). The tan mixture was stirred vigorously at rt for 2 h. The organic solvent was removed under reduced pressure and the aqueous residue was extracted with DCM (3x). The combined organic fractions were dried over sodium sulfate. The filtrate was concentrated under reduced pressure to afford 3-(2,2-dimethoxyethyl)-5-methoxypicolinamide (8.200 g, 34.1 mmol, 89 % yield) as an off-white solid that was advanced without further purification. MS m/z = 263.2 (M+Na)+

**Step 5: 3-Methoxy-1,7-naphthyridin-8(7H)-one**

To a mixture of 3-(2,2-dimethoxyethyl)-5-methoxypicolinamide (6.74 g, 28.1 mmol) in toluene (112 ml) was added 4-methylbenzene sulfonic acid (monohydrate; 0.534 g, 2.81 mmol). The reaction mixture was heated to reflux for 20 h. The reaction
mixture was cooled to rt and concentrated in vacuo to a volume of ca. 15 mL. The residue was triturated with heptanes and filtered to afford 3-methoxy-1,7-naphthyridin-8(7H)-one (4.53 g, 25.7 mmol, 92 % yield) as a crude, tan solid that was advanced without further purification. MS m/z = 177.1 [M+H]⁺.

Step 6: 8-Chloro-3-methoxy-1,7-naphthyridine

To a mixture of 3-methoxy-1,7-naphthyridin-8(7H)-one (4.50 g, 25.5 mmol) in acetonitrile (102 ml) was added phosphorus oxychloride (11.69 ml, 128 mmol). The reaction mixture was heated to 85 °C for 5h. The solution was cooled to rt and concentrated in vacuo. The resulting brown residue was partitioned between CH2C12 and aqueous saturated NaHCO3 solution; the aqueous layer was back-extracted with DCM (3x). The combined organic extracts were dried over sodium sulfate, the filtrate was concentrated in vacuo, and the residue was purified by silica gel chromatography (5% - 30% of 9:1 DCM:MeOH in DCM ) to afford 8-chloro-3-methoxy-1,7-naphthyridine (3.00 g, 15.41 mmol, 60.3 % yield) as an off-white solid. MS m/z = 195 (M+H) +.

Intermediate 2

Synthesis of 3,8-Dichloro-1,7-naphthyridine

Step 1: 3-Bromo-5-chloropicolinonitrile

A microwave vial was charged with copper (I) cyanide (1.089 g, 12.16 mmol), 2,3-dibromo-5-chloropyridine (3 g, 11.06 mmol), and propionitrile (15 mL). The vial was capped and irradiated in a microwave reactor at 150 °C for 2.5 hours. The solution was concentrated, diluted with DCM (25 mL), and filtered. The filtrate was concentrated, and the residue was purified by silica gel chromatography, eluting with 0-30% EtOAc in heptanes, to afford the title compound (2 g, 9.20 mmol). MS m/z = 219 (M+H) +.

Step 2: 5-Chloro-3-((trimethylsilyl)ethynyl)picolinonitrile

A pressure vessel was charged with TEA (7.65 mL, 55.2 mmol), ethynyltrimethylsilane (2.32 mL, 16.6 mmol), copper (I) iodide (0.263 g, 1.380 mmol), palladium (0) tetrakis(triphenylphosphine) (0.558 g, 0.483 mmol), 3-bromo-5-chloropicolinonitrile (3.0 g, 13.8 mmol), and DMF (50 ml). The vessel was flushed with argon, sealed, stirred at ambient temperature for 15 minutes, and then heated at 50 °C for 4 hours. The solution was diluted with water and extracted with EtOAc. The combined
organic layers were concentrated, and the residue was purified by silica-gel chromatography, eluting 0-50% ethyl acetate in hexane, to afford the title compound (1.3 g, 5.5 mmol). MS m/z = 235 (M+H)⁺.

**Step 3: 5-Chloro-3-(2,2-dimethoxyethyl)picolinonitrile**

A pressure vessel was charged with 5-chloro-3-((trimethylsilyl)ethynyl)picolinonitrile (2 g, 8.52 mmol) and sodium methoxide (0.5 M in methanol, 42.6 mL, 21.30 mmol), sealed, and stirred at 55 °C for one hour. The solution was concentrated, and the residue was purified via silica gel chromatography, eluting with 10% methanol in DCM to afford the title compound (1.7 g, 7.50 mmol). MS m/z = 227 (M+H)⁺.

**Step 4: 3-Chloro-1,7-naphthyridin-8(7H)-one**

To a solution of 5-chloro-3-(2,2-dimethoxyethyl)picolinonitrile (1.7 g, 7.50 mmol) in acetone (50 mL) and water (150 mL) was added aqueous saturated sodium carbonate (37.5 mL, 113 mmol) and 30% aqueous hydrogen peroxide (38.3 mL, 375 mmol). The reaction was stirred at RT for one hour, concentrated to remove most of the acetone, and extracted with DCM. The combined organic layers were concentrated. To a solution of this intermediate (1.8 g, 7.36 mmol) in benzene (20 mL) was added p-toluenesulfonic acid (0.350 g, 1.839 mmol) and the reaction was sonicated for 10 minutes. The solution was stirred overnight at 80 °C and concentrated. The crude product was purified via silica gel, eluting with 0-100% (80/20/1 ethyl acetate/methanol/ammonium hydroxide) in EtOAc, to the title intermediate (1.1 g, 6.1 mmol). MS m/z = 181 (M+H)⁺.

**Step 5: 3,8-Dichloro-1,7-naphthyridine**

A suspension of 3-chloro-1,7-naphthyridin-8(7H)-one (250 mg, 1.384 mmol) in phosphorus oxychloride (1.94 mL, 20.8 mmol) was stirred at 95 °C for one hour. The solution was concentrated to afford the title compound (276 mg, 1.39 mmol). MS m/z = 199 (M+H)⁺.

![Intermediate 3](image)

**Synthesis of 5-Chloro-2-methoxypyrido|3,4-b|pyrazine**

**Step 1: 5-Chloropyrido|3,4-b|pyrazin-2(1H)-one**
A suspension 2-chloropyridine-3,4-diamine (2.5 g, 17.41 mmol) and a 50% solution of ethyl glyoxalate in toluene (3.45 mL, 17.41 mmol) in ethanol (34.8 mL) was stirred at reflux for 24 hours. The solution was cooled to -20 °C for 16 hours, and the resulting precipitate was collected by vacuum filtration and rinsed with ethanol. The crude product was purified via reverse-phase HPLC, eluting with 5-50% acetonitrile/0.1% trifluoroacetic acid in water/0.1% TFA, to afford the title compound (570 mg, 3.14 mmol). MS m/z = 182 (M+H)⁺.

**Step 2: 2,5-Dichloropyrido[3,4-\(\beta\)]pyrazine**

A suspension of 5-chloropyrido[3,4-Z]>pyrazin-2(1H)-one (0.57 g, 3.14 mmol) in phosphorus oxychloride (10.24 mL, 110 mmol) was stirred at 110 °C for two hours, and then concentrated. The residue was dissolved in DCM, washed with saturated sodium bicarbonate, dried over anhydrous sodium sulfate, filtered, and concentrated to afford the title compound (580 mg, 2.90 mmol). MS m/z = 200 (M+H)⁺.

**Step 3: 5-Chloro-2-methoxypyrid|3,4-\(\gamma\)|pyrazine**

To a solution of 2,5-dichloropyrido[3,4-Z]>pyrazine (580 mg, 2.90 mmol) in NN-dimethylformamide (10 mL) was added a 0.5-M solution of sodium methoxide in methanol (6.09 mL, 3.04 mmol), and the reaction was stirred at RT for 5 minutes. The solution was diluted with water and extracted with ethyl acetate. The organic layer was dried with sodium sulfate, filtered and concentrated to afford the title compound (550 mg, 2.81 mmol). MS m/z = 196 (M+H)⁺.

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**Synthesis of 8-Chloro-1,7-naphthyridine-3-carbonitrile**

A screw-cap vial was charged with 3-chloro-1,7-naphthyridin-8(7H)-one (100 mg, 0.554 mmol), zinc cyanide (52.7 μmol, 0.831 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (45.5 mg, 0.111 mmol), tris(dibenzylideneacetone)dipalladium(0) (40.6 mg, 0.044 mmol), DMF (2.74 mL) and water (28 μL). The vial was purged with argon, sealed, and stirred at 110 °C for 1 hour. The mixture was filtered through a pad of Celite, which was rinsed with methanol and dimethylsulfoxide. The combined filtrates were concentrated, and a few drops of water were added. The resulting solids were collected by vacuum filtration, rinsed with water and dried. The solids were suspended in...
toluene (3.5 mL), and phosphorus oxychloride (98 µL, 1.052 mmol) and DIPEA (122 µL, 0.701 mmol) were added. The reaction was stirred at 120 °C for 1.5 hours, cooled to RT, diluted with EtOAc, and washed with 2 M aqueous sodium carbonate. The organic portion was dried over anhydrous sodium sulfate, filtered and concentrated. The crude material was purified by silica gel chromatography, eluting with 5-50% EtOAc in heptanes, to provide the title compound (50 mg, 0.264 mmol) as a white solid. LC/MS (ESI+) m/z = 190 (M+H)+.

Intermediate 5

Step 1: methyl 5-(2.2.2-trifluoroethoxy)picolinate

To a solution of methyl 5-hydroxypicolinate (0.50 g, 3.27 mmol, Frontier Scientific) in DMF (5 mL) were added cesium carbonate (1.383 g, 4.24 mmol, Aldrich) and 2,2,2-trifluoroethyl ester (0.909 ml, 3.92 mmol) and the resulting suspension was stirred at RT for 1 hour. The reaction was diluted with water and EtOAc. The organic layer was washed with 1M LiCl (aq) solution and brine before drying over magnesium sulfate and concentrating under reduced pressure to afford the crude title compound as a yellow oil, which was used directly in the next step without further purification. M/S m/z= 236.0 [M+H]+. Calculated for C₉H₆F₃N0₃: 235.160

Step 2: 5-(2.2.2-trifluoroethoxy)picolinic acid

The crude material from the previous reaction was taken up in THF (5 mL) and lithium hydroxide, 2.0M, (aq) (4.90 ml, 9.80 mmol) was added. The reaction was stirred at RT for 16 hours. The reaction was diluted with water and acidified with 1.0N HCl (aq) solution was added until pH=1 (by pH paper). The solution was extracted with DCM and the organic layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure to afford the title compound as a white solid. (0.194 g, 0.877 mmol, 26.9 % yield). M/S m/z=221.9 [M+H]+. Calculated for C₉H₆F₃N0₃: 221.133

¹H NMR (300 MHz, DMSO-δ6) δ ppm 5.00 (q, J=8.77 Hz, 2 H) 7.66 (dd, J=8.77, 2.92 Hz, 1 H) 8.07 (d, J=8.77 Hz, 1 H) 8.50 (d, J=2.92 Hz, 1 H) 13.00 (br. S., 1 H)
Step 1: Synthesis of 5-chloro-3-methylpicolinonitrile

A mixture of 2-bromo-5-chloro-3-methylpyridine (45 g, 218 mmol), zinc cyanide (8.30 mL, 131 mmol), tris(dibenzylideneacetone) dipalladium (0) (4.99 g, 5.45 mmol), and 1,1'-bis(diphenylphosphino)ferrocene (6.04 g, 10.90 mmol) in dimethylacetamide (40 mL) was heated to 110 °C for 4 hours. The reaction mixture was cooled to RT, diluted with water and extracted with ethyl acetate. The organic phase obtained was concentrated under reduced pressure and residue purified by chromatography on silica gel using ISCO eluting with 0-60% EtOAc/hex to afford the title compound 5-chloro-3-methylpicolinonitrile (25.4 g, 166 mmol, 76% yield). LC/MS (ESI+) m/z = 153.1 (M+H).

Step 2: Synthesis of 5-chloro-3-methylpicolinic acid

To a solution of 5-chloro-3-methylpicolinonitrile (24.0 g, 157 mmol) in EtOH (100 mL) was added NaOH (5.0 N, 110 mL, 550 mmol). The resulting mixture was refluxed at 90 °C for 18 h. After cooling to RT, the reaction mixture was concentrated, diluted with water and the pH of the solution was adjusted to 4 by addition of 5N HCl. The solid that precipitated was filtered and set aside. The filtrate was extracted with EtOAc (2X). The aqueous layer was again acidified with 5N HCl to pH 4 and extracted with EtOAc (2X). The EtOAc extracts were combined, dried, and concentrated. The solid obtained from all the workup steps were combined and dried in a high vac oven at 40 °C for 12 h to give the title compound 5-chloro-3-methylpicolinic acid (24.1 g, 140 mmol, 89% yield). LC/MS (ESI+) m/z = 172.0 (M+H)+; 1H NMR (400 MHz, CHLOROFORM -J) δ ppm 11.29 (br. s., 1 H), 8.41 (d, J=1.76 Hz, 1 H), 7.73 (d, J=1.76 Hz, 1 H), 2.75 (s, 3 H).

Intermediate 7

Synthesis of 3,8-Dichloro-5-fluoro-1,7-naphthyridine

Step 1: 3-chloro-5-fluoro-6-methoxy-6,7-dihydro-1,7-naphthyridin-8(5//)-one

A pressure bottle was charged with 3-chloro-1,7-naphthyridin-8(7//)-one (15 g, 83 mmol, Anichem), methanol (34.6 mL), ACN (173 mL) and 1-chloromethyl-4-fluoro-
1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (30.9 g, 87 mmol), and the mixture was heated at 45 °C for 15 hours. Water and ethyl acetate were added, and the layers were separated. The aqueous portion was extracted twice with ethyl acetate and once with DCM, and the combined organic layers were dried with anhydrous sodium sulfate, filtered and concentrated. The crude solid was triturated with a minimum amount of ethyl acetate and filtered. The title intermediate was isolated as an off-white solid (15.34 g, 80%) as a 3:1 mixture of diastereomers.

**Step 2: 3,8-dichloro-5-fluoro-1,7-naphthyridine**

A vial was charged with 3-chloro-5-fluoro-6-methoxy-6,7-dihydro-1,7-naphthyridin-8(5//)-one (7.5 g, 32.5 mmol), acetonitrile (130 mL) and phosphorus oxychloride (9.09 mL, 98 mmol), and the mixture was stirred at 75 °C for 15 hours. The mixture was concentrated, and the crude material was purified by silica gel chromatography, eluting with 0-50% ethyl acetate in heptanes, to provide the title compound (5.57 g, 25.7 mmol, 79% yield) as a white solid. LC/MS (ESI⁺) m/z = 217(M+H)⁺.

**Synthesis of 8-Chloro-5-fluoro-3-methoxy-1,7-naphthyridine**

Using an analogous sequence of reactions to those described for Intermediate 7, 3-methoxy-1,7-naphthyridin-8(7H)-one was converted to the title compound. LC/MS (ESI⁺) m/z = 213 (M+H)⁺.

**Synthesis of 4,7-Dichloropyrido[3.2-J]pyrimidine**

To a suspension of 5-chloro-2-cyano-3-nitopyridine (1.274 mL, 10.9 mmol) in water (22 mL) was added 28% aqueous ammonium hydroxide (3.94 mL, 28.3 mmol), and the reaction was stirred at RT for 20 minutes. Sodium hydrosulfite (2.68 mL, 32.7 mmol) was added, and the reaction mixture was stirred at RT for 70 minutes. The yellow
precipitate was collected by vacuum filtration to provide the title compound (1.097 g, 6.39 mmol) as yellow solid. $^1$H-NMR (400 MHz, DMSO-$_d$6): $\delta$ 7.88 (br. s, 1 H), $\delta$ 7.73 (s, 1 H), $\delta$ 7.39 (br. s, 1 H), $\delta$ 7.23 (s, 1 H), $\delta$ 7.06 (br. s, 2 H). LC/MS (ESI$^+$) $m/z = 172$ (M+H)$^+$.  

5 **Step 2: 7-Chloropyrido[3.2-$d$]pyrimidin-4(1/$f$)-one**

A suspension of 3-amino-5-chloropicolinamide (1.1 g, 6.41 mmol) in triethyl orthoformate (15.99 mL, 96 mmol) was stirred at 155°C for 22 hours. After cooling to RT, the yellow precipitate was collected by vacuum filtration and washed with hexanes to yield the title intermediate (1.03 g, 5.67 mmol) as a yellow solid. $^1$H NMR (400 MHz, DMSO-$_d$6) $\delta$ ppm 8.20 (s, 1 H) 8.27 (d, J=2.35 Hz, 1 H) 8.80 (d, J=2.25 Hz, 1 H) 12.68 (br. s., 1 H). LC/MS (ESI$^+$) $m/z = 182$ (M+H)$^+$.  

10 **Step 3: 4J-Dichloropyrido[3.2-$d$]pyrimidine**

To a mixture of 7-chloropyrido[3.2-$d$]pyrimidin-4(1/$f$)-one (250 mg, 1.377 mmol) in toluene (12 mL) were added DIPEA (0.73 mL, 4.20 mmol) and phosphorus oxychloride (0.391 mL, 4.27 mmol), and the reaction was stirred at reflux for 1 hour. After cooling to RT, the reaction mixture was concentrated to provide the title compound. LC/MS (ESI$^+$) $m/z = 200$ (M+H)$^+$.  

20 **Synthesis of 4-Chloro-7-methoxypyrido[3.2-$d$]pyrimidine**

**Step 1: 7-Methoxypyrido[3.2-$d$]pyrimidin-4(1/$f$)-one**

A microwave vial was charged with 7-chloropyrido[3.2-$d$]pyrimidin-4(1/$f$)-one (110mg, 0.606 mmol), a 0.5 M solution of sodium methoxide in methanol (3.65 mL, 1.817 mmol) and sodium methoxide (327 mg, 6.06 mmol). The vial was capped and irradiated in a microwave reactor at 145°C for 30 minutes. The reaction was neutralized with saturated aqueous ammonium chloride (3 mL), concentrated, and diluted with cold water. The resulting precipitate was collected by vacuum filtration and dried in vacuo to provide the title compound (107 mg, 0.604 mmol) as pink solid. $^1$H NMR (400 MHz, DMSO-$_d$6) $\delta$ ppm 3.95 (s, 3 H) 7.49 (d, J=2.74 Hz, 1 H) 8.11 (s, 1 H) 8.47 (d, J=2.74 Hz, 1 H). LC/MS (ESI$^+$) $m/z = 178$ (M+H)$^+$.  

30 **Step 2: 4-Chloro-7-methoxypyrido[3.2-$d$]pyrimidine**
Using an analogous reaction to that described for Intermediate 9, step 3, 7-methoxypyrido[3,2-i]pyrimidin-4(1H)-one was converted to the title compound. LC/MS (ESI⁺) m/z = 196 (M+H)⁺.

Intermediate 11

5

Synthesis of 4-Chloro-5-fluoro-7-methoxyquinazoline

Step 1: 2-Amino-6-fluoro-4-methoxybenzonitrile

Ammonia gas was bubbled through a solution of 2,6-difluoro-4-methoxybenzonitrile (1.0 g, 5.91 mmol) in dimethylsulfoxide (11.83 mL) for 10 minutes. The reaction was then sealed and stirred at 90 °C for 24 hours. The reaction mixture was cooled to RT and concentrated in vacuo to afford a tan residue. The residue was triturated with water, collected by vacuum filtration, and dried in vacuo to afford the title intermediate (0.9 g, 5.42 mmol) as a white solid. LC/MS (ESI⁺) m/z = 167 (M+H)⁺.

Step 2: 5-Fluoro-7-methoxyquinazolin-4-ol

To a mixture of formic acid (11.43 mL, 298 mmol) and sulfuric acid (0.866 mL, 16.25 mmol) was added 2-amino-6-fluoro-4-methoxybenzonitrile (0.9 g, 5.42 mmol) in portions. The reaction mixture was stirred at 100 °C for 1 hour, cooled to ambient temperature, and poured into 80 mL of an ice-water mixture. The resulting precipitate was collected by vacuum filtration and dried in vacuo to provide the title intermediate (0.8 g, 4.12 mmol) as an off-white solid. LC/MS (ESI⁺) m/z = 195 (M+H)⁺.

Step 3: 4-Chloro-5-fluoro-7-methoxyquinazoline

To a suspension of 5-fluoro-7-methoxyquinazolin-4-ol (0.125 g, 0.644 mmol) in thionyl chloride (1.410 mL, 19.31 mmol) was added AyV-dimethylformamide (0.028 mL, 0.361 mmol). The reaction was stirred at 80 °C for 6 hours and concentrated in vacuo.

The residue was suspended in saturated aqueous sodium bicarbonate and extracted with dichloromethane. The organic layer was concentrated in vacuo to generate the title compound (0.13 g, 0.611 mmol) as a yellow solid. LC/MS (ESI⁺) m/z = 213 (M+H)⁺.

Intermediate 12

F

Cl

MeO

F

N

MeO

F

N

F

F

COOH
Synthesis of 5-(Difluoromethyl)picolinic acid

Step 1: 5-Formylpicolinonitrile

A suspension of 2-bromo-5-formylpyridine (940 mg, 5.05 mmol) and copper (I) cyanide (233 μL, 7.58 mmol) in DMF (8.4 mL) was stirred at 120°C for 1.5 hours, cooled to RT, and partitioned between water and EtOAc. The solids were removed from the aqueous layer by filtration, and the filtrate was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The crude product was purified by silica-gel chromatography, eluting with a gradient of 40%-60% (40% ethyl acetate in heptane) in heptane, to provide the title compound (236 mg, 1.786 mmol) as white solid. LC/MS (ESI+) m/z = 133 (M+H)⁺.

Step 2: 5-(Difluoromethyl)picolinonitrile

To a solution of 5-formylpicolinonitrile (74 mg, 0.560 mmol) in toluene (0.25 mL) was added bis(2-methoxymethyl)aminosulfur trifluoride (0.258 mL, 1.400 mmol), and the reaction was stirred at RT overnight. The reaction mixture was carefully quenched with saturated aqueous sodium bicarbonate, diluted with water, and extracted with DCM. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The crude material was purified by silica-gel chromatography, eluting with a gradient of 40% to 60% (40% ethyl acetate/heptane) in heptane, to provide the title compound (48 mg, 0.311 mmol) as white solid. LC/MS (ESI⁺) m/z = 155 (M+H)⁺.

Step 3: 5-(Difluoromethyl)picolinic acid

A suspension of 5-(difluoromethyl) picolinonitrile (48 mg, 0.311 mmol) in 12 N aqueous hydrochloric acid (4.3 mL, 140 mmol) was stirred at 110°C for 1.5 hours. After cooling to ambient temperature, the reaction mixture was concentrated and treated with DIPEA (2 mL). The mixture was concentrated and dried in vacuo to provide the title compound in quantitative yield. LC/MS (ESI⁺) m/z = 174 (M+H)⁺.

Intermediate 13

Synthesis of 5-methoxy-3-methylpyrazine-2-carboxylic acid

Step 1: Methyl 3-methylpyrazine-2-carboxylate

In a 2-L flask, 3-methylpyrazine-2-carboxylic acid (Matrix, 19.95 g, 144 mmol) was suspended in MeOH (500 mL). The suspension was cooled in an ice-water bath, and
concentrated sulfuric acid (Fluka, 27.3 mL, 506 mmol) was added over a time period of 5 min. The reaction mixture was heated to 80 °C for 5 h. The reaction mixture was concentrated under reduced pressure and the residue was taken up in DCM (750 mL). The excess acid was neutralized carefully with of aqueous NaOH (5N or 5M, 200 mL). The aqueous layer was separated and extracted with DCM (250 mL). The combined organic layers were combined, dried over MgSO₄ and concentrated to afford 16.15 g of the title compound (106 mmol, 73%). MS m/z=153 [M+H]⁺. Calculated for C₇H₆N₂O₂: 152.

**Step 2: 3-(Methoxycarbonyl)-2-methylpyrazine 1-oxide**

In a 1-L flask, the methyl 3-methylpyrazine-2-carboxylate (step 1, 16.08 g, 106 mmol) was suspended in CHCl₃ (300 mL). 3-chlorobenzoperoxoic acid (Aldrich, 24.62 g, 143 mmol) was added. The reaction mixture was heated to 70 °C for 16 h. The reaction mixture was quenched with saturated NaHCO₃ (200 mL). The layers were separated, and the aqueous layer was further extracted with DCM (2 x 100 mL). The combined organic layers were dried over MgSO₄, and the filtrate was concentrated to afford the title compound. MS m/z=169 [M+H]⁺. Calculated for C₇H₆N₂O₃: 168.

**Step 3: Methyl 5-chloro-3-methylpyrazine-2-carboxylate**

In a 1-L flask, the crude 3-(methoxycarbonyl)-2-methylpyrazine 1-oxide (step 2, 17.77 g, 106 mmol) was dissolved in DMF(300 mL). Neat phosphoryl trichloride (29.6 mL, 317 mmol) was added. The reaction mixture was heated to 100 °C. After 1 h, the reaction mixture was concentrated to remove most of the DMF. The flask was cooled in an ice water bath, and 1 M aqueous Na₂CO₃ (300 mL) was added slowly, followed by 80% EtOAc-hexane (400 mL). The mixture was filtered through Celite. The resulting filtrate was partitioned and the aqueous phase was extracted further with 80% EtOAc-hexane (2 x 250 mL). The combined organic layers were dried over MgSO₄ and concentrated. The material was purified through silica gel using 11% EtOAc-hexane to afford the title compound (4.29 g, 23 mmol, 22%). MS m/z=187 [M+H]⁺. Calculated for C₇H₆ClN₂O₂: 186. ¹H NMR in CDCl₃ δ: 8.51 (s, 1H), 4.01 (s, 3H), 2.86 (s, 3H).

**Step 4: 5-Methoxy-3-methylpyrazine-2-carboxylic acid**

A flask was charged with sodium (0.813 g, 35.4 mmol), purged with Argon, and placed in a room temperature water bath. Methanol (47.7 mL, 1179 mmol) was added slowly. After 40 min, methyl 5-chloro-3-methylpyrazine-2-carboxylate (step 3, 2.2 g, 11.79 mmol) was added. The vessel was sealed and heated to 45 °C for 1.5 hs. Sodium hydroxide (1M, 12.97 mL, 12.97 mmol) was added and heating was continued for 1.5 hs. The reaction mixture was concentrated under reduced pressure and the residue was
dissolved in a minimum amount of water (50 mL). The aqueous phase was extracted with diethyl ether (15 mL), which was discarded. The aqueous phase was acidified with HCl (5M, 11 mL, 55 mmol). The mixture was extracted with DCM (3 x 60 mL). The combined organic extracts were dried over MgSO₄ and the filtrate was concentrated to afford the title compound (2.0 g, 100%). MS m/z = 169 [M+H]+. Calculated for C₇H₈N₂O₃: 168.

**Intermediate 14**

**Synthesis of 3-methyl-5-(2,2,2-trifluoroethoxy)pyrazine-2-carboxylic acid**

The title compound was synthesized according to Intermediate 13, using 2,2,2-trifluoroethanol (Aldrich) in Step 4. MS m/z = 237 (M+H)+.

**Intermediate 15**

**Synthesis of 5-chloro-3-methoxypicolinic acid**

In a 1-L flask, 5-chloro-3-nitropicolinonitrile (Oakwood, 6.67 g, 36.3 mmol) was dissolved in MeOH (185 mL). The solution was cooled to 0 °C, and sodium hydroxide (3M, 36.3 mL, 109 mmol) was added. The reaction mixture was warmed to room temperature and stirred overnight. The reaction was concentrated under reduced pressure and the residue was taken up in absolute ethanol (100 mL). NaOH (5M, 3 equiv, 109 mmol, 22 mL) was added, and the reaction mixture was heated to 100 °C for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was taken up in water (100 mL). The aqueous layer was extracted with diethyl ether (30 mL), which was discarded. The aqueous phase was acidified with HCl (5M, 55 mL), saturated with NaCl, and extracted with EtOAc (5 x 75 mL). The combined organic extracts were dried over MgSO₄ and the filtrate was concentrated under reduced pressure. The resulting solid was triturated with diethyl ether to afford the title compound (5.63 g, 30 mmol, 83%). MS
5

Synthesis of 5-cyano-3-methoxypicolinic acid

Step 1: Methyl 5-chloro-3-methoxypicolinate

In a 350-mL resealable vessel, 5-chloro-3-methoxypicolinic acid (intermediate 14, 7.5 g, 40.0 mmol) was dissolved in MeOH (120 mL). The solution was cooled to 0 °C, and concentrated sulfuric acid (7.57 mL, 140 mmol) was added. The vessel was sealed and heated to 95 °C for 1.5 h. The reaction mixture was cooled to 0 °C, and quenched with Na₂CO₃ (1M, 140 mL). The reaction mixture was concentrated under reduced pressure and the residue was extracted with EtOAc (3 x 100 mL). The combined organics extracts were dried over MgSO₄ and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (gradient 20% - 33% EtOAc/hexane) to afford the title compound as a yellow solid (5.59 g, 27.7 mmol, 67%). MS m/z=202 [M+H]⁺. Calculated for C₇H₆ClN₂O₂: 201. ¹H NMR in CDCl₃ δ: 8.24 (d, 1H, J = 1.9), 7.37 (d, 1H, J = 1.9), 3.97 (s, 3H), 3.94 (s, 3H).

Step 2: Methyl 5-cyano-3-methoxypicolinate

In a 350-mL resealable vessel, Pd₂dba₃ (1.487 g, 1.623 mmol), dicyclohexyl(2',6'-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine (1.444 g, 3.52 mmol), dicyanozinc (3.18 g, 27.1 mmol), and methyl 5-chloro-3-methoxypicolinate (step 1, 5.455 g, 27.1 mmol) were taken up in DMF (80 mL). The reaction mixture was purged with Argon and subsequently heated to 120 °C for 2 h. Upon cooling, the reaction mixture was concentrated under reduced pressure. The residue was filtered through Celite, and the filter cake was rinsed with 1% MeOH/DCM. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel chromatography (33%-40% EtOAc/hexane) to afford the title compound as a white solid (4.51 g, 23.5 mmol, 87%). MS m/z=193 [M+H]⁺. Calculated for C₉H₈N₂O₂: 192. ¹H NMR in CDCl₃ δ: 8.51 (d, 1H, J = 1.6), 7.55 (d, 1H, J = 1.6), 4.00 (s, 3H), 3.97 (s, 3H).

Step 3: 5-Cyano-3-methoxypicolinic acid
In a 1-L flask, the methyl 5-cyano-3-methoxypicolinate (step 2, 4.51 g, 23.5 mmol) was taken up in THF (74 mL). The suspension was cooled to 0 °C, and sodium hydroxide (1M, 24.64 mL, 24.64 mmol) was added. After 1 h, the reaction was concentrated under reduced pressure. The residue was taken up in 100 mL of water, and the aqueous phase was extracted with diethyl ether (50 mL), which was discarded. The aqueous phase was acidified with HCl (5M, 5.16 mL, 25.8 mmol). The aqueous phase was extracted with DCM (11 x 150 mL). The combined organic extracts were dried over MgSO4 and the filtrate was concentrated under reduced pressure to afford the title compound as a white solid. MS m/z=179 [M+H]+. Calculated for C9H6N2O3: 178.1

NMR in CDCl3 δ: 8.48 (d, 1H, J = 1.6), 7.71 (d, 1H, J = 1.6), 4.08 (s, 3H).

Intermediate 17

Synthesis of 5-cyano-3-methylpicolinic acid

To a solution of tert-butyl 5-cyano-3-methylpicolinate (synthesized according to procedure described in WO2012095521; 4.18 g, 19.15 mmol) in dichloromethane (96 mL) was added TFA (Aldrich, 148 mL, 1915 mmol). The reaction mixture was stirred at room temperature for 2 hrs. The reaction mixture was concentrated under reduced pressure and the residue was triturated with EtOAc. The yellow slurry was concentrated under reduced pressure. The residue was triturated with 30 mL of methyl tert-butyl ether (30 mL) and hexanes (50mL) to yield 5-cyano-3-methylpicolinic acid (2.91 g, 17.95 mmol, 94% yield) as yellow solid. MS m/z=163.2 [M+H]+. Calculated for C8H6N2O2: 162.0

Intermediate 18

Step 1: 3-Chloro-5-fluoro-6-methoxy-6,7-dihydro-1,7-naphthyridin-8(5H)-one

A pressure bottle was charged with 3-chloro-1,7-naphthyridin-8(7H)-one (Anichem, 15 g, 83 mmol), MeOH (34 mL), acetonitrile (173 mL) and 1-(chloromethyl)-4-fluoro-1,4-diazabicyclo[2.2.2]octane-1,4-diium tetrafluoroborate (Aldrich, 30.9 g, 87
mmol). The mixture was heated to 45-50 °C. After 6 h, additional 1-(chloromethyl)-4-fluoro-1,4-diazabicyclo[2.2.2]octane, 1,4-diiium tetrafluoroborate (2.5 g) was added and heating was continued overnight. Water and EtOAc were added to the cooled reaction mixture and the layers were separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried over MgSO₄. The filtrate was concentrated under reduced pressure and the residue was triturated with EtOAc. The solid was filtered off and the title compound (15.34 g, 66.5 mmol, 80% yield) was isolated as a white solid. MS m/z = 208 [M+H]. Calculated for C₁₀H₇ClFN₃: 207.0

Synthesis of 5-chloropicolinamide

**Step 2:** 5-Fluoro-6-methoxy-8-oxo-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carbonitrile

A pressure bottle was charged with Pd(dba)₃ (Strem, 1.032 g, 1.127 mmol), 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (Strem 1.157 g, 2.82 mmol), zinc cyanide (Alfa Aesar, 2.482 g, 21.14 mmol), 3-chloro-5-fluoro-6-methoxy-6,7-dihydro-1,7-naphthyridin-8(5H)-one (step 1, 3.25 g, 14.09 mmol) and DMF (70 ml). The bottle was purged with Argon and the reaction mixture was heated to 110 °C for 1 h. The crude reaction mixture was filtered through a pad of Celite and the filtercake was washed with MeOH. The combined filtrates were concentrated under reduced pressure. The residue was triturated with DCM. The solid was filtered off and washed with DCM. The title compound (2.27 g, 10.26 mmol, 72.8% yield) was obtained as an off-white solid. MS m/z = 222 [M+H]. Calculated for C₁₀H₇FN₂: 221.1

**Step 3:** 8-Chloro-5-fluoro-1,7-naphthyridine-3-carbonitrile

A pressure bottle was charged with 5-fluoro-6-methoxy-8-oxo-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carbonitrile (step 3, 2.27 g, 10.26 mmol), acetonitrile (41 ml) and phosphorus oxychloride (Aldrich, 3.35 ml, 35.9 mmol). The bottle was sealed and the reaction mixture was heated to 75 °C overnight. The reaction mixture was concentrated and the crude material was purified by silica gel chromatography (gradient 0-20% (10 MeOH in DCM)/DCM to afford the title compound (1.2 g, 5.78 mmol, 56.3% yield) as a white solid. MS m/z = 208 [M+H]. Calculated for C₉H₅ClFN₃: 207.0

**Intermediate 19 (Method R)**

Synthesis of 5-chloropicolinamide
A 500-mL RBF was charged with 5-chloro-2-pyridinecarboxylic acid (Ark Pharm, 10.00 g, 63.5 mmol) and thionyl chloride (Aldrich, 100 ml, 1371 mmol). A catalytic amount of DMF (0.2 ml) was added and the reaction mixture was heated to 80 °C under Argon atmosphere for 4 hours. The reaction mixture was cooled to RT and concentrated under reduced pressure. The residue was diluted with DCM (100 ml) and added slowly to a stirred solution of ammonium hydroxide (131 ml, 3364 mmol) at 0 °C. After completed addition, the reaction mixture was allowed to stir an additional 10 min. The reaction mixture was concentrated under reduced pressure and the precipitate was filtered off. The solid was washed with water and dried to give the title compound (8.686 g, 55.5 mmol, 87 % yield) as an off-white solid. MS m/z=157 [M+H]+. Calculated for C_{6}H_{4}ClN_{2}O : 156

Intermediate 20

Synthesis of 5-cyanopicolinamide

The title compound was synthesized according to Method R starting from 5-cyanopicolinic acid (Aldrich). MS m/z = 147.9 [M+H]+Calculated for C_{6}H_{4}N_{3}O : 147

Intermediate 21

Synthesis of 5-chloro-3-methylpicolinamide

The title compound was synthesized according to Method R starting from 5-chloro-3-methylpicolinic acid (intermediate 17). MS m/z = 171.1 [M+H]+Calculated for C_{7}H_{7}ClN_{2}O : 170

Intermediate 22
Synthesis of 3-chloro-5-cyanopicolinamide

The title compound was synthesized according to Method R starting from 3-chloro-5-cyanopicolinic acid (Bionet Research). MS \( m/z = 181.9 \ [M+H]^+ \). Calculated for \( C_7H_4ClN_3O \) : 181

\[ \text{Intermediate 23} \]

Synthesis of 3-chloro-5-(trifluoromethyl)picolinamide

The title compound was synthesized according to Method R starting from 3-chloro-5-(trifluoromethyl)picolinic acid (Ark Pharm). MS \( m/z = 224.9 \ [M+H]^+ \). Calculated for \( C_7H_4ClF_3N_2O \) : 224

\[ \text{Intermediate 24} \]

Synthesis of 4-chloro-1-(difluoromethyl)-1H-pyrazole-3-carboxamide

The title compound was prepared according to Method R starting from 4-chloro-1-(difluoromethyl)-1H-pyrazole-3-carboxylic acid (WO201 169934). MS \( m/z = 196 \ [M+H] \).

\[ \text{Intermediate 25} \]

Synthesis of 3-chloro-5-methoxypicolinic acid

Step 1: methyl 3-chloro-5-methoxypicolinate

In a 1-L flask, methyl 3-chloro-5-hydroxypicolinate (Afferchim, 25.00 g, 133 mmol) and cesium carbonate (87 g, 267 mmol) were suspended in DMF (200 mL) and iodomethane (41.7 mL, 666 mmol) was added drouise. A water-cooled condenser was attached, and the reaction vessel was heated in a 55 °C oil bath. After 3 h the reaction was concentrated under reduced pressure. The residue was taken up in 1.2 L of 80% EtOAc-hexane and 500 mL brine. The mixture was filtered through Celite. The filtrate was
transferred into a separation funnel. The organic layer was separated, washed with brine (100 mL), dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 30% to 40% EtOAc-hexane, affording the title compound (19.1 g) as a tan solid. MS m/z = 202 (M+H).

**Step 2: 3-chloro-5-methoxypicolinic acid**

Using an analogous reaction to that described for Intermediate 5, step 2 methyl 3-chloro-5-methoxypicolinate was converted to the title compound. MS m/z = 188 (M+H).

**Synthesis of 3-chloro-5-methoxypicolinamide**

The title compound was synthesized according to procedure R starting from 3-chloro-5-methoxypicolinic acid (intermediate 25). MS m/z = 187 (M+H).

**Synthesis of 3,5-dichloropicolinamide**

The title compound was synthesized according to Method R, starting from 3,5-dichloropyridine-2-carboxylic acid (Matrix Scientific). MS m/z = 190.9 [M+H]+.

**Step 1: Sodium-5-methoxypicolinate**
A microwave vial was charged with methyl 5-methoxypicolinate (9.700 g, 58.0 mmol, synthesized according to Tetrahedron Letters 2011, 52, 122-124) and sodium hydroxide solution (10 N; 58.0 ml, 580 mmol). The reaction mixture was stirred and heated in a CEM Voyager microwave (Large-Scale Unit) at 120 °C for 11 min (150 watts, Powermax feature on). Subsequently, the reaction mixture was allowed to stir for 10 minutes at ambient temperature. The precipitate was collected by filtration and the solid was rinsed with hexanes. The solid was dried to obtain sodium 5-methoxypicolinate (9.83 g, 56.1 mmol, 97 % yield) as a light-yellow solid. MS m/z = 175.9 [M+H]^+. Calculated for C_7H_6NNaO_3: 175. 1H NMR (400 MHz, MeOH) δ ppm 8.23 (d, J=2.93 Hz, 1 H) 8.06 (d, J=8.61 Hz, 1 H) 7.39 (dd, J=8.80, 2.93 Hz, 1 H) 3.91 (s, 3 H)

Step 2: 5-methoxypicolinamid

The title compound was synthesized according to Method R, starting from sodium-5-methoxypicolinate. MS m/z = 153 [M+H]^+. Calculated for C_7H_5N_2O_2: 152.

![Intermediate 29]

Step-1: Synthesis of 6-chloro-5-methylpyridine-3-amine

Iron (Fe) powder (9.75 g, 0.174 mol, Sigma-Aldrich) was added in portions over a period of 2h to a stirred solution of 2-chloro-3-methyl-5-nitropyridine (10 g, 0.058 mol, Combi-blocks) in acetic acid/water (29 mL: 88 mL). After 3h, the reaction mixture was filtered through celite and the filter cake was washed with ethyl acetate. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with aqueous sodium bicarbonate, brine and dried over Na2SO4. The solvent was removed under reduced pressure to yield 6-chloro-5-methylpyridine-3-amine as a brown solid (8.0g; 97%). MS m/z = 142.03 [M+H]^+

1H-NMR (300MHZ, DMSO-d6): δ 7.54 (d, J=30 Hz, 1H), 6.91-6.90 (dd, J = 0.6 Hz & 2.7 Hz, 1H), 5.39 (s, 2H), 2.17 (s, 3H)

Step 2: Synthesis of 6-chloro-5-methylpyridine-3-ylacetate

In a 100 mL R.B. flask, Boron trifluoride diethyl etherate (1.8 mL, 0.0143 mol, Sigma Aldrich) was added drop wise to a cooled mixture (-15°C) of 6-chloro-5-methylpyridine-3-amine (1.0 g, 0.0070 mol) in DME (7.5 mL) and dichloromethane (2.5
mL). Then tert-butyl nitrite (0.85 g, 0.0082 mol, Sigma-Aldrich) was added drop wise and the reaction mixture was stirred at -10°C for 25 min. The reaction mixture was allowed to warm to 0°C and stirred for additional 20 min. The reaction mixture was diluted with pentane (50 mL) and the tetrafluoroborate diazonium salt was collected by filtration. The salt was dissolved in acetic anhydride (10 mL) and heated at 95°C for 2h. The reaction mixture was cooled to ambient temperature and then partitioned between ethyl acetate (50 mL) and sat.aq.sodium bicarbonate solution (100 mL). The aqueous solution was separated and extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to afford a brown oil. This oil was purified by column chromatography on silica gel, eluting with 5% ethyl acetate in petroleum ether to give 6-chloro-5-methylpyridine-3-yl acetate as pale yellow oil (780 mg, 62%). MS m/z = 185.02 [M+H]+

'H-NMR (300MHZ, DMSO-d₆): δ 8.13 (d, J = 2.4Hz, 1H), 7.72 (d, J = 2.7 Hz 1H), 2.34(s, 3H), 2.30 (s, 3H)

Step-3: Synthesis of 6-chloro-5-methylpyridine-3-ol

Potassium carbonate (1.10 g, 0.0081 mol) was added to a stirred solution of 6-chloro-5-methylpyridine-3-yl acetate (750 mg, 0.004 mol) in MeOH (15 mL) at RT. The reaction mixture was stirred for 1h at ambient temperature. The reaction mixture was concentrated under reduced pressure and the residue was diluted with minimum amounts of water and neutralized with IN HCl (15 mL). After neutralization, the solution was extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated to give 6-chloro-5-methylpyridine-3-ol as a off white solid (500 mg, 89%). MS m/z = 143.01 [M+H]+.

'H-NMR (300MHZ, DMSO-d₆): δ 10.09 (s, 1H), 7.76 (d, J= 3Hz, 1H), 7.18 (d, J=3.6 Hz, 1H), 2.24 (s, 3H).

Step 4: Synthesis of 2-chloro-5-((4-methoxybenzyl)oxy)-3-methylpyridine

A mixture of 6-chloro-5-methylpyridin-3-ol (250 mg, 0.0017 mol), 1-(chloromethyl)-4-methoxybenzene (0.328 g, 0.0020 mol, Sigma Aldrich), and potassium carbonate (0.482 g, 0.0034 mol) in DMF (5 mL) was allowed to stir for 3h at 60°C. After completion of the reaction, reaction mixture was cooled to ambient temperature and poured into ice cold water (25 mL). The obtained solid was filtered, washed with water (2 x 10 mL) and dried to obtain 2-chloro-5-((4-methoxybenzyl)oxy)-3-methylpyridine as an off white solid (400 mg, 87%).

MS m/z = 263.9 [M+H]+.
\[ H-NMR \ (300 \text{ MHz}, \text{ CDC1}_3): \ \delta \ 7.96 \ (d, \ J = 2.7 \text{ Hz}, \ 1H), \ 7.34 \ (d, \ J = 8.7 \text{ Hz}, \ 2H), \ 7.15 \ (d, \ J = 3 \text{ Hz}, \ 1H), \ 6.94 - 6.89 \ (m, \ 2H), \ 4.99 \ (s, \ 2H), \ 3.81 \ (s, \ 3H), \ 2.33 \ (s, \ 3H). \]

**Step 3:** Synthesis of 5-((4-methoxybenzyl)oxy)-3-methyl-2-vinylpyridine

A 25 mL sealable tube was charged with a mixture of 2-chloro-5-(difluoromethoxy)-3-methylpyridine (330 mg, 0.0012 mmol), toluene (10 mL), and tributyl(vinyl)stannane (447 mg, 0.0015 mmol). The reaction mixture was purged with Argon for 10 min. Then Pd(PPh\(_3\))\(_4\) (0.0018 mol, Alfa- Aesar) was added and the reaction mixture was allowed to stir for 16h at 100°C. The reaction mixture was cooled to ambient temperature and filtered through celite. The filter cake was washed with ethyl acetate and concentrated to get a crude residue. The residue was purified by column chromatography using silica and eluting with 5-10% ethyl acetate in petroleum ether to give 5-((4-methoxybenzyl)oxy)-3-methyl-2-vinylpyridine as an off white solid (250 mg, 65%). MS m/z = 256.1 [M+H]+.

\[ H-NMR \ (300 \text{ MHz}, \text{ CDC1}_3): \ \delta \ 8.20 \ (d, \ J = 2.7 \text{ Hz}, \ 1H), \ 7.37-7.33 \ (m, \ 2H), \ 7.02 \ (d, \ J = 2.7 \text{ Hz}, \ 1H), \ 6.94-6.87 \ (m, \ 3H), \ 6.21 \ (dd, \ J = 1.8 \text{ Hz} \& 16.8 \text{ Hz}, \ 1H), \ 5.39 \ (dd, \ J = 2.1 \text{ Hz} \& 10.5 \text{ Hz}, \ 1H), \ 5.01 \ (s, \ 2H), \ 3.81 \ (s, \ 3H), \ 2.33 \ (s, \ 3H). \]

**Step 4:** Synthesis of 5-methyl-6-vinylpyridin-3-ol

Trifluoroacetic acid (1.25 mL, 5 times) was added to a stirred solution of 5-((4-methoxybenzyl)oxy)-3-methyl-2-vinylpyridine (250 mg, 0.00098 mmol) in anisole (0.5 mL). The reaction mixture was stirred for 2h at ambient temperature. After completion of the reaction, the reaction mixture was concentrated and quenched with saturated NaHC03 solution (2 mL). The reaction mixture was extracted with ethyl acetate (2 x 10 mL) and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude residue was triturated with pentane to afford 5-methyl-6-vinylpyridin-3-ol as an off white solid (100 mg, 76%). MS m/z = 136.15 [M+H]+.

\[ H-NMR \ (400 \text{ MHz}, \text{ CDC1}_3): \ \delta \ 9.86 \ (s, \ 1H), \ 7.96 \ (d, \ J = 2.8 \text{ Hz}, \ 1H), \ 6.94-6.86 \ (m, \ 2H), \ 6.07 \ (dd, \ J = 2.4 \text{ Hz} \& 16.8 \text{ Hz}, \ 1H), \ 5.26 \ (dd, \ J = 2.8 \text{ Hz} \& 10.4 \text{ Hz}, \ 1H), \ 2.25 \ (s, \ 3H). \]

**Step 5:** Synthesis of 5-(but-2-yn-1-yloxy)-3-methyl-2-vinylpyridine

A reaction mixture of of 5-methyl-6-vinylpyridin-3-ol (100 mg, 0.00074 mmol), sodium 1-bromobut-2-yn (118 mg, 0.00088 mol, Alfa- Aesar) and cesium carbonate (361 mg, 0.0011 mol) in DMF (2 mL) was stirred for 2h at 80°C. After completion of the reaction, reaction mixture was cooled to ambient temperature, poured into ice-cold water (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were
washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The crude residue was purified by column chromatography using silica gel and eluting with 0-10% ethyl acetate in petroleum ether to give 5-(but-2-yn-1-yloxy)-3-methyl-2-vinylpyridine as an off white solid (85 mg, 61.5%). MS m/z = 188.3 [M+H]+.

\[ ^1H-NMR \text{ (400MHz, CDCl}_3\text{):} \delta \text{ 8.21 (d, } J = 2.8 \text{ Hz, 1H), 7.03} \text{ (d, } J = 2.4 \text{ Hz, 1H), 6.96-6.89 (m, 1H), 6.22 (dd, } J = 2.4 \text{ Hz & 17.2 Hz, 1H), 5.40 (dd, } J = 2 \text{ Hz & 10.8 Hz, 1H),} \]
\[ \text{4.68-4.67 (m, 2H), 2.35 (s, 3H), 1.85 (t, } J = 2.4 \text{ Hz, 3H).} \]

**Step 8:** Synthesis of 5-(but-2-yn-1-yloxy)-3-methylpicolinaldehyde

OSO₄ (2.5 wt.% sol. in tert-Butanol) (0.86 mL, 0.0027 mol) was added to a stirred solution of 5-(but-2-yn-1-yloxy)-3-methyl-2-vinylpyridine (5.1 g, 0.027 mol) in acetone/water (100:100 mL) at 0 °C. The reaction mixture was allowed to stir for 30 min at ambient temperature. Then NaClO₃ (23.2 g, 0.108 mol) was added and the reaction mixture was allowed to stir for additional 4h at ambient temperature. The reaction mixture was diluted with ice cold water (200 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel, eluting with 5-10% EtOAc in pet ether to give 5-(but-2-yn-1-yloxy)-3-methylpicolinaldehyde as an off white solid (3.6 g, 69.9%). MS m/z = 189.9 [M+H]+.

\[ ^1H-NMR \text{ (400MHz, CDCl}_3\text{):} \delta \text{ 10.10 (s, 1H), 8.37 (d, } J = 2.8 \text{ Hz, 1H), 7.13} \text{ (d, } J = 2.8} \]
\[ \text{Hz, 1H), 4.77 (d, } J = 2.4 \text{ Hz, 2H), 2.67 (s, 3H), 1.86 (t, } J = 2 \text{ Hz, 3H).} \]

**Step 9:** Synthesis of 5-(but-2-yn-1-yloxy)-3-methylpicolinic acid

A stirred solution of 5-(but-2-yn-1-yloxy)-3-methylpicolinaldehyde (3.6 g, 0.019 mol) in water (216 mL)/acetone (36 mL) was treated with sulphamic acid (2.5 g, 0.025 mol) and 85% sodium chlorite (2.65 g, 0.029 mol). The reaction mixture was allowed to stir for 2h at ambient temperature. The reaction mixture was extracted with ethyl acetate (2 x 100 mL). The combined organic layer was washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The crude residue was triturated with n-pentane to get 5-(but-2-yn-1-yloxy)-3-methylpicolinaldehyde as an off white solid (3.2 g, 82 %). MS m/z = 206.3 [M+H]+.

\[ ^1H-NMR \text{ (400MHz, CD3OD):} \delta \text{ 8.16 (d, } J = 2.8 \text{ Hz, 1H), 7.38} \text{ (d, } J = 2.4 \text{ Hz, 1H), 4.84-4.82(m, 2H), 2.63} \text{ (s, 3H), 1.83 (t, } J = 2 \text{ Hz, 3H).} \]
Step 1: Synthesis of 2-chloro-3-methyl-5-(2,2,2-trifluoroethoxy)pyridine

Tert-butyl nitrite (1.60 g, 0.0156 mol, Sigma-Aldrich) was added drop wise to a stirred solution of 6-chloro-5-methylpyridine-3-amine (2.0 g, 0.0140 mol) in trifluoroethanol (10.05 g, 0.100 mol) and TFA (2.42 g, 0.0212 mol) at ambient temperature, followed by slow addition of potassium carbonate (4.40 g). The reaction mixture was stirred at ambient temperature for 1h. The reaction mixture was poured into ice-cold water and extracted with ethyl acetate (2 x 300 mL). The combined organic layer were washed with brine, dried over sodium sulfate and concentrated. The crude residue was purified by silica gel column chromatography, eluting with 5% ethyl acetate in petroleum ether to give 2-chloro-3-methyl-5-(2,2,2-trifluoroethoxy)pyridine (1.30 g, 41.13 % yield) as a reddish oil. MS m/z = 225.02 [M+H]+

\[ \text{H-NMR (400MHz, CDCl}_3\text{): } \delta 7.96 (d, J=3.2 Hz, 1H), 7.19 (d, J = 2.8 Hz, 1H), 7.87 - 4.41-4.35 (m, 2H), 2.37 (s, 3H). \]

Step 2: Synthesis of 3-methyl-5-(2,2,2-trifluoroethoxy)-2-vinylpyridine

Using an analogous reaction to that described for Intermediate 29, step 5

2-chloro-3-methyl-5-(2,2,2-trifluoroethoxy)pyridine was converted to 3-methyl-5-(2,2,2-trifluoroethoxy)-2-vinylpyridine. MS m/z = 217.07 [M+H]+

\[ \text{H-NMR (400MHz, CDCl}_3\text{): } \delta 8.18 (d, J = 2.8 Hz, 1H), 7.03 (d, J = 3.2 Hz, 1H), 6.96-6.89(m, 2H), 6.26 - 6.21 (dd, J = 2Hz, 16.8 Hz, 1H), 5.45-5.42 (dd, J = 2 Hz, 10.8 Hz, 1H), 4.42-4.36 (m, 2H), 2.36 (s, 3H). \]

Step 3: Synthesis of 3-methyl-5-(2,2,2-trifluoroethoxy)picinaldehyde

Using an analogous reaction to that described for Intermediate 29, step 8

3-methyl-5-(2,2,2-trifluoroethoxy)-2-vinylpyridine was converted to 3-methyl-5-(2,2,2-trifluoroethoxy)picinaldehyde. MS m/z = 219.05 [M+H]+

\[ \text{H-NMR (400MHz, CDCl}_3\text{): } \delta 10.11 (s, 1H), 8.36 (dd, J = 2.4 Hz, 1H), 7.11 (dd, J = 2.8 Hz, 1H), 4.51-4.46 (m, 2H), 2.67 (s, 3H). \]
Step 4: Synthesis of 3-methyl-5-(2,2,2-trifluoroethoxy) picolinic acid.

Using an analogous reaction to that described for Intermediate 34, step 9 3-methyl-5-(2,2,2-trifluoroethoxy) picolinaldehyde was converted to 3-methyl-5-(2,2,2-trifluoroethoxy) picolinic acid. MS m/z = 235.05 [M+H]+.

Step 3: Ethyl 3,5-dimethoxypyrazine-2-carboxylate

To a solution of lithium diisopropylamide (2.0 M heptane/tetrahydrofuran/ethylbenzene, 11.10 mL, 22.20 mmol) in THF (75 mL) at -78 °C was added a solution of 2,6-dichloropyrazine-carboxylic acid (1.44 g, 9.67 mmol) in THF (20 mL) at room temperature over 20 min. The reaction mixture was stirred at -78 °C for 1.5 h and added via cannula to a 3-neck flask containing dry ice at -78 °C. The reaction mixture was warmed from -78 °C to room temperature over 21 h and quenched with 5 M HCl. The mixture was partitioned between brine and EtOAc. The aqueous phase was acidified to pH 3.5 with 5 M HCl. The aqueous phase was extracted with EtOAc (6 x) and the combined organic extracts were washed with brine (1 x), dried over MgSO4, filtered, and concentrated. Purification by flash column chromatography on silica gel (5% to 10% MeOH in DCM) gave 3,5-dichloropyrazine-2-carboxylic acid (0.408 g, 2.11 mmol, 22% yield) as a light brown solid. LC/MS (ESI+) m/z = 193.0 (M+H)+.

Step 2: Methyl 3,5-dichloropyrazine-2-carboxylate

To a solution of 3,5-dichloropyrazine-2-carboxylic acid (0.304 g, 1.58 mmol) in MeOH (5 mL) and diethyl ether (5 mL) at room temperature was added trimethylsilyldiazomethane (2.0 M solution in hexanes, 4.00 mL, 8.00 mmol). The reaction mixture was stirred at RT for 30 min and concentrated. Purification by flash column chromatography on silica gel (5% to 20% EtOAc in hexanes) gave methyl 3,5-dichloropyrazine-2-carboxylate (0.312 g, 1.51 mmol, 96% yield) as a white solid. LC/MS (ESI+) m/z = 207.0 (M+H)+.

Step 3: Ethyl 3,5-dimethoxypyrazine-2-carboxylate
To a solution of methyl 3,5-dichloropyrazine-2-carboxylate (0.312 g, 1.51 mmol) in THF (4.5 mL) at RT was added sodium hydride (60% wt. dispersion, 0.199 g, 4.98 mmol) and methanol (0.200 mL, 4.94 mmol). The reaction mixture was stirred at RT for 30 min, diluted with EtOAc, and quenched with saturated NH₄Cl. The reaction mixture was partitioned between brine and EtOAc. The aqueous phase was extracted with EtOAc (3 x) and the combined organic extracts were washed with brine (1 x), dried over MgSO₄, filtered, and concentrated. Purification by flash column chromatography on silica gel (10% to 50% EtOAc in hexanes) gave ethyl 3,5-dimethoxypyrazine-2-carboxylate (0.314 g, 1.48 mmol, 98% yield) as an off white solid. LC/MS (ESI) \( m/z = 199.1 \) (M+H)⁺.

**Step 4: 3,5-dimethoxypyrazine-2-carboxylic acid**

To a solution of ethyl 3,5-dimethoxypyrazine-2-carboxylate (0.314 g, 1.48 mmol) in MeOH (5 mL) at room temperature was added potassium hydroxide (0.135 g, 2.41 mmol). The reaction mixture was stirred at RT for 17 h, quenched with 5 M HCl (0.48 mL), and diluted with EtOAc. The solid was removed by filtration and the filtrate was concentrated. Purification by flash column chromatography on silica gel (10% MeOH in DCM) gave 3,5-dimethoxypyrazine-2-carboxylic acid (0.261 g, 1.42 mmol, 96% yield) as a white solid. LC/MS (ESI⁺) \( m/z = 185.1 \) (M+H)⁺.

**Synthesis of 5-chloro-3-methylpyrazine-2-carboxylic acid**

A solution of methyl 5-chloro-3-methylpyrazine-2-carboxylate (0.117 g, 0.627 mmol) (Step 3 of Intermediate 24) and sodium hydroxide 5N (0.150 mL, 0.752 mmol) in dioxane (5 mL) was stirred at room temperature for 30 minutes. The reaction mixture was acidified with 2N HCl to pH 4 and extracted with EtOAc (2X). The combined organic extracts were dried over Na₂SO₄ and the filtrate was concentrated to afford the title compound (91.0 mg, 84%). MS \( m/z = 172.9 \) (M+H)⁺.

**Intermediate 33 (Method S)**
Synthesis of 5-(but-2-yn-1-yloxy)picolinic acid

Step 1: Methyl 5-(but-2-yn-1-yloxy)picolinate

A solution of methyl 5-hydroxypyridine-2-carboxylate (1.5 g, 9.8 mmol, Molbridge) in THF (39 ml) under argon was cooled to 0 °C and 2-butyn-1-ol (1.5 ml, 20 mmol, Aldrich), triphenylphosphine (2.95 g, 11.2 mmol, Aldrich) and diisopropyl azodicarboxylate (2.2 ml, 11.2 mmol, Aldrich) were added consecutively. The reaction mixture was stirred at RT for 2 h. Additional diisopropyl azodicarboxylate (1 ml) was added and the reaction mixture was stirred at RT for another 1 h. The reaction mixture was diluted with C3H6 and washed with saturated NaHCO3 solution; the aqueous layer was back-extracted with C3H6. The combined organic extracts were dried over MgSO4 and concentrated in vacuo. Purification by silica gel chromatography (0% to 50% EtOAc/Hexanes) afforded the title compound as a light tan solid. MS m/z = 206.0 [M+H]+.

Step 2: 5-(But-2-yn-1-yloxy)picolinic acid

Using an analogous reaction to that described for Intermediate 5, step 2 methyl 5-(but-2-yn-1-yloxy)picolinate was converted to 5-(But-2-yn-1-yloxy)picolinic acid MS m/z = 192.1 [M+H]+.

Synthesis of 5-(prop-2-yn-1-yloxy)picolinic acid

The title compound was synthesized analogously according to Method S starting from propargyl alcohol (Aldrich). MS m/z = 178.1 [M+H]+.
Synthesis of 5-((3-cyclopropylprop-2-yn-1-yl)oxy)picolinic acid

**Step 1: 3-Cyclopropylprop-2-yn-1-ol**

To a solution of cyclopropylacetylene (0.833 mL, 9.83 mmol, Aldrich) in THF (20 mL) at -78°C under N₂ was added butyllithium (6.15 mL, 9.83 mmol, Aldrich) dropwise. After completed addition, the mixture was stirred at -78°C for 30 min, followed by slow addition of a solution of paraformaldehyde powder (600 mg, 9.83 mmol, Aldrich) in THF (7 mL). The reaction mixture was then stirred at -78°C for 2 h and allowed to warm up to room temperature overnight. The reaction mixture was quenched with saturated ammonium chloride (20 mL) at 0°C. The mixture was then extracted with diethyl ether (2 x 20 mL). The combined organic extracts were dried over MgSO₄ and concentrated to a volume of approximately 3 mL. The mixture was then purified by silica gel flash column chromatography, (0%-50% diethyl ether/pentane) to give 760 mg of the title compound as a colorless liquid containing diethyl ether, which was used in the next step.

**HNMR (MeOH) δ:** 4.13 (d, J=2.0 Hz, 2H), 1.26-1.30 (m, 1H), 0.74-0.83 (m, 2H), 0.59-0.67 (m, 2H).

**Step 2: 5-((3-Cyclopropylprop-2-yn-1-yl)oxy)picolinic acid**

The title compound was synthesized analogously according to Method KS starting from methyl 5-hydroxypicolinate (Molbridge) and 3-cyclopropylprop-2-yn-1-ol. MS m/z: 218 (M+H).

Intermediate 36

**Synthesis of 5-(Oxazol-2-ylmethoxy)picolinic acid**

The title compound was synthesized analogously according to Method S starting from methyl 5-hydroxypicolinate (Molbridge) and oxazol-2-ylmethanol (AstaTech). MS m/z = 237.9 [M+H]⁺. Calculated for C₁₀H₇N₃O₂S. ¹H NMR (400 MHz, DMSO-d₆) δ ppm
A synthesis of 5-(Thiazol-2-ylmethoxy)picolinic acid

The title compound was synthesized according to the above method starting from 1,3-thiazol-2-ylmethanol (Maybridge Chemical Co., Ltd.). MS m/z = 236.9 [M+H]⁺. Calculated for C₁₀H₇N₂O₃S: 293.084.

Step 1: 5-hydroxy-3-methylpicolinonitrile

A resealable vessel was charged with Pd₂dba₃ (0.893 g, 0.975 mmol, Strem), dicyclohexyl(2',6'-dimethoxy-[l,l'-biphenyl]-2-yl)phosphine (0.858 g, 2.090 mmol, Strem), dicyanozinc (1.636 g, 13.93 mmol), and 6-chloro-5-methylpyridin-3-ol (2.00 g, 13.93 mmol, step 3 intermediate 34). The solids were taken up in DMF (45 mL) and the reaction mixture was purged with Argon. The vessel was sealed and heated in a 110 °C oil bath. After 21 h, the reaction was filtered through Celite and the filter cake was rinsed with 5% MeOH-DCM. The filtrate was concentrated and the residue was purified by silica gel chromatography, eluting with 40% to 50% EtOAc-hexane to afford the title compound (676 mg, 32%). MS m/z = 135 (M+H)⁺.

Step 2: 5-hydroxy-3-methylpicolinic acid

5-Hydroxy-3-methylpicolinonitrile (0.570 g, 4.25 mmol) was taken up in concentrated aqueous HCl (28.3 mL, 340 mmol). The reaction mixture was heated in a 110 °C oil bath. After 24 h, the reaction was concentrated to afford the title compound (650 mg). The residue was used as is. MS m/z = 154 (M+H)⁺.

Step 3: methyl 5-hydroxy-3-methylpicolinate
A sealable reaction vessel was charged with 5-hydroxy-3-methylpicolinic acid (0.651 g, 4.25 mmol) and MeOH (35 mL). The reaction vessel was placed in a water bath, and concentrated sulfuric acid (0.854 mL, 15.94 mmol) was added. The vessel was sealed and heated in a 95 °C oil bath. After 24 h, the reaction mixture was concentrated and the residue was taken up in 30 mL of 0.5M aqueous Na₂CO₃. The aqueous phase was extracted with 10% MeOH- EtOAc (100 mL). The aqueous layer was separated and saturated with NaCl. The aqueous phase was extracted with 10% MeOH-EtOAc (7 x 100 mL). The combined organic fractions were dried over MgSO₄ and concentrated. The residue was purified by silica gel chromatography, eluting with 3% to 4% MeOH-DCM to afford the title compound (593 mg). MS m/z = 168 (M+H)⁺.

Step 4: 4-methylpent-2-yne-1,4-diol

In a 1-L flask, potassium hydroxide (23.52 g, 419 mmol) was suspended in diethyl ether (338 mL). The suspension was cooled to 0 °C and propargyl alcohol (10.0 mL, 168 mmol, Aldrich) was added. After 1 h, acetone (36.9 mL, 503 mmol) was added and the mixture was stirred overnight at rt. The reaction mixture was cooled in an ice/water bath and acidified with aqueous HC1 (5M; 90 mL). The reaction mixture was diluted with 100 mL of water. The layers were separated. The aqueous layer was saturated with NaCl and extracted with EtOAc (2 x 100 mL). The combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluting with 70% to 80% EtOAc-hexane to afford the title compound (564 mg). 1H NMR (400 MHz, CDC1₃) δ ppm 4.29 (d, J = 6.1 Hz, 2 H), 2.05 (d, J = 6.1 Hz, 1 H), 1.73 (m, 1 H), 1.53 (s, 6 H).

Step 5: methyl 5-((4-hydroxy-4-methylpent-2-yn-1-yl)oxy)-3-methylpicolinate

The title compound was synthesized analogously according to Method S starting from methyl 5-hydroxy-3-methylpicolinate and 4-methylpent-2-yne-1,4-diol. MS m/z = 264 (M+H)⁺.

Step 6: 5-((4-hydroxy-4-methylpent-2-yn-1-yl)oxy)-3-methylpicolinic acid

Using an analogous reaction to that described for Intermediate 5, step 2 methyl 5-((4-hydroxy-4-methylpent-2-yn-1-yl)oxy)-3-methylpicolinate was converted into the title compound. MS m/z = 250 (M+H)⁺.
Synthesis of 5-(Cyanomethoxy)-3-methylpicolinic acid

**Step 1:** Methyl 5-(cyanomethoxy)-3-methylpicolinate

To a suspension of methyl 5-hydroxy-3-methylpicolinate (0.8063 g, 4.82 mmol, step 3 intermediate 38) and cesium carbonate (0.772 ml, 9.65 mmol, Alfa Aesar) in DMF (48.2 ml) was added bromoacetonitrile (0.336 ml, 4.82 mmol, Sigma-Aldrich Chemical Company, Inc.). The reaction mixture was stirred for 4 h at rt. The reaction mixture was diluted with aqueous, saturated sodium bicarbonate solution and extracted with EtOAc. The organic extract was washed with aqueous, saturated sodium bicarbonate solution, brine and dried over MgSO₄. The filtrate was concentrated in vacuo. MS m/z = 207.1 [M+H]+. Calculated for C₇H₈O₃: 206.069. ¹H NMR (400 MHz, CHLOROFORM-J) δ ppm 2.67 (s, 3 H) 3.98 (s, 3 H) 4.88 (s, 2 H) 7.20 (d, J=2.35 Hz, 1 H) 8.32 (br. s., 1 H)

**Step 2:** 5-(Cyanomethoxy)-3-methylpicolinic acid

To a solution of methyl 5-(cyanomethoxy)-3-methylpicolinate (0.895 g, 4.34 mmol) and sodium iodide (0.354 ml, 8.68 mmol, Sigma-Aldrich Chemical Company, Inc.) in acetonitrile (4.34 ml) was added chlorotrimethylsilane (1.102 ml, 8.68 mmol, Strem Chemicals, Inc.). The reaction mixture was heated to 70 °C and allowed to stir overnight. The reaction mixture was concentrated under reduced pressure and the residue was diluted with water and extracted with EtOAc. The organic extract was washed with water, 10% sodium thiosulfate solution and dried over MgSO₄. The filtrate was concentrated in vacuo to give 5-(cyanomethoxy)-3-methylpicolinic acid which was used without further purification. MS m/z = 192.9 [M+H]+. Calculated for C₇H₆N₂O₃: 192.03

**Synthesis of 5-(Thiazol-4-ylmethoxy)pyrazine-2-carboxylic acid**

**Step 1:** Thiazol-4-ylmethanol

Intermediate 40 (Method T)

Synthesis of 5-(Thiazol-4-ylmethoxy)pyrazine-2-carboxylic acid

**Step 1:** Thiazol-4-ylmethanol
To a solution of thiazole-4-carboxaldehyde (0.810 ml, 9.67 mmol, Combi-Blocks Inc.) in MeOH (48.3 ml) at 0 °C was added sodium borohydride (0.341 ml, 9.67 mmol, Sigma-Aldrich Chemical Company, Inc.) in portions. The reaction mixture was allowed to stir for 1 hour. Saturated aqueous ammonium chloride solution was carefully added and the reaction mixture was filtered. The filtrate was concentrated in vacuo. The solid was taken up in 10% MeOH/DCM and filtered through a plug of silica gel to provide thiazol-4-ylmethanol (0.826 g, 7.18 mmol, 74.3% yield) as a yellow oil. MS m/z = 116.0 [M+H]+. Calculated for C₅H₇NOS: 115.099. ¹H NMR (400 MHz, CHLOROFORM -J) δ ppm 2.58 (br. s., 1 H) 7.27 - 7.30 (m, 1 H) 8.83 (d, J=1.76 Hz, 1 H)

Step 2: Methyl 5-(thiazol-4-ylmethoxy)pyrazine-2-carboxylate

A RBF was charged with methyl 5-chloropyrazine-2-carboxylate (1.239 g, 7.18 mmol, Ark Pharm), thiazol-4-ylmethanol (0.8266 g, 7.18 mmol), cesium carbonate (0.689 ml, 8.61 mmol, Alfa Aesar) and DMF (20.51 ml). The reaction mixture was stirred at 40 °C for 3 days. The reaction mixture was allowed to cool to rt and was diluted with water and extracted with EtOAc. The organic extract was washed with water, satd NaCl, dried over MgSO₄, and concentrated in vacuo. The crude product was adsorbed onto a plug of silica gel and purified by silica gel flah chromatography, eluting with a gradient of 10% to 100% EtOAc in hexane, to provide methyl 5-(thiazol-4-ylmethoxy)pyrazine-2-carboxylate (0.7606 g, 3.03 mmol, 42.2 % yield). MS m/z = 252.1 [M+H]+. Calculated for C₁₀H₈N₅O₃S: 251.036. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 3.89 (s, 2 H) 5.60 (s, 1 H) 7.86 (d, J=1.96 Hz, 1 H) 8.46 (d, J=1.37 Hz, 1 H) 8.86 (d, J=1.37 Hz, 1 H) 9.14 (d, J=1.96 Hz, 1 H)

Step 3: 5-(Thiazol-4-ylmethoxy)pyrazine-2-carboxylic acid

To a solution of methyl 5-(thiazol-4-ylmethoxy)pyrazine-2-carboxylate (0.7606 g, 3.03 mmol) in 1,4-dioxane (15.14 ml) was added a 1N solution of sodium hydroxide (4.54 ml, 4.54 mmol) at rt. The reaction mixture was allowed to stir for 16 hours. Hydrogen chloride(4.0M solution in 1,4-dioxane; 1.135 ml, 4.54 mmol, Sigma Aldrich) was added and after 10 minutes, the reaction mixture was concentrated in vacuo to give the title compound. MS m/z = 237.9 [M+H]+. Calculated for C₉H₇N₃O₃S: 237.021. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 5.59 (s, 2 H) 7.86 (d, J=1.96 Hz, 1 H) 8.45 (d, J=1.17 Hz, 1 H) 8.83 (d, J=1.37 Hz, 1 H) 9.14 (d, J=1.96 Hz, 1 H)
Synthesis of 5-(Oxazol-2-ylmethoxy)pyrazine-2-carboxylic acid

The title compound was synthesized according to the above method T starting from oxazol-2-ylmethanol (Asatech, Inc.). MS m/z = 221.9 [M+H]+. Calculated for C_{7}H_{7}N_{0}4: 221.044.

Intermediate 42

Synthesis of 5-(Thiazol-5-ylmethoxy)pyrazine-2-carboxylic acid

The title compound was synthesized according to the above method T starting from 5-(hydroxymethyl)thiazole (Oakwood Products, Inc.). MS m/z = 237.9 [M+H]+. Calculated for C_{7}H_{7}N_{0}3S: 237.02.

Intermediate 43

Synthesis of 5-(Oxazol-5-ylmethoxy)pyrazine-2-carboxylic acid

The title compound was synthesized according to the above method T starting from 1,3-oxazol-5-methanol (Combi-Blocks Inc.). MS m/z = 222.1 [M+H]+. Calculated for C_{7}H_{7}N_{0}4: 221.04.

Intermediate 44
Synthesis of 5-(Oxazol-4-ylmethoxy)pyrazine-2-carboxylic acid

The title compound was synthesized according to the above method T starting from oxazol-4-ylmethanol (J&W Pharmlab). MS m/z = 221.9 [M+H]⁺. Calculated for C₉H₇N₂O₄: 221.04.

Intermediate 45

Synthesis of 5-(Thiazol-2-ylmethoxy)pyrazine-2-carboxylic acid

The title compound was synthesized according to the above method T starting from 1,3-thiazol-2-ylmethanol (Maybridge Chemical Co., Ltd.). MS m/z = 237.9 [M+H]⁺. Calculated for C₉H₇N₂O₄S: 237.02.

Intermediate 46

Synthesis of (S)-5-(But-3-yn-2-yloxy)pyrazine-2-carboxylic acid

The title compound was synthesized according to the above method T starting from (S)-(-)-3-butyn-2-ol (Alfa Aesar, A Johnson Matthey Company). MS m/z = 192.5 [M+H]⁺. Calculated for C₅H₃N₂O₃: 192.05

Intermediate 47

Synthesis of (R)-5-(But-3-yn-2-yloxy)pyrazine-2-carboxylic acid

The title compound was synthesized according to the above method T starting from (R)-(++)-3-butyn-2-ol (Aldrich). MS m/z = 193 [M+H]⁺. Calculated for C₅H₄N₂O₃: 192.05
Synthesis of 5-isopropoxypyrazine-2-carboxylic acid

To a rt solution of sodium t-butoxide (1.41 g, 14.67 mmol) in THF (20 mL) was added 2-propanol (1.250 mL, 16.33 mmol) dropwise. After 10 min a solution of methyl 5-chloro-2-pyrazinecarboxylate (1.70 g, 9.85 mmol, Ark Pharm) in THF (10 mL) was added dropwise. After 1.5 h, the reaction was quenched with saturated aq NH4CI and extracted with EtOAc (3x). The aqueous layer was concentrated under reduced pressure and the resulting solid was treated with aqueous HCl. The solution was extracted with DCM (3x) and the combined organic layers were purified by flash chromatography, eluting with 0.5% TFA in iPrOH:CH2Cl2 (0:1 → 1:9) to give a white crystalline solid. (497 mg, 2.7 mmol, 28%). MS m/z=183 [M+H]+. Calculated for C8H14N2O3: 182.

Synthesis of 2-(l-Fluoroethyl)oxazole-4-carboxylic acid

Step 1: Methyl 2-(2-fluoropropanamido)-3-hydroxypropanoate

A rbf was charged with DL-serine methyl ester hydrochloride (1.49 g, 9.57 mmol, Sigma-Aldrich Chemical Company, Inc.), HATU (4.37 g, 11.49 mmol, Sigma-Aldrich Chemical Company, Inc.) and DCM (22 mL). 2-Fluoropropionic acid (0.75 ml, 9.57 mmol, Alfa Aesar, A Johnson Matthey Company) and triethylamine (3.3 ml, 23.93 mmol, Sigma-Aldrich Chemical Company, Inc.) were added and the reaction mixture was allowed to stir at rt overnight. The reaction mixture was diluted with water and extracted with DCM. The organic extract was washed with water, aqueous saturated NaHCO3 solution, brine, and dried over MgSO4. The solution was concentrated in vacuo and the crude product was purified by silica gel chromatography, eluting with a gradient of 1% to 10% MeOH in DCM, to provide methyl 2-(2-fluoropropanamido)-3-hydroxypropanoate (0.69 g, 3.60 mmol, 38 % yield).
Step 2: Methyl 2-(1-fluoroethyl)oxazole-4-carboxylate

A solution of methyl 2-(2-fluoropropanamido)-3-hydroxypropanoate (0.69 g, 3.60 mmol) in DCM (36.0 ml) was cooled to -20 °C and deoxo-fluor (50% in THF; 0.73 ml, 3.96 mmol, Fluka Chemie GmbH) was added dropwise. The reaction mixture was allowed to stir for 1 hour. Bromotrichloromethane (1.276 ml, 12.96 mmol, Sigma-Aldrich Chemical Company, Inc.) was added followed by addition of DBU (1.936 ml, 12.96 mmol, TCI). The reaction mixture was allowed to warm to 0 °C and stirred for 3 h. The reaction was quenched by the addition of aqueous, saturated NaHCC\(^{+}\) solution and extracted with \(\text{CH}_2\text{Cl}_2\). The organic extract was washed with water, brine and dried over MgSO\(_4\). The solvent was removed in vacuo and the crude product was purified by silica gel chromatography, eluting with a gradient of 1% to 10% 2M NH\(_3\)-MeOH in \(\text{CH}_2\text{Cl}_2\), to provide methyl 2-(1-fluoroethyl)oxazole-4-carboxylate \((0.2746 \text{ g}, 1.586 \text{ mmol}, 44.1 \% \text{ yield})\). MS \(m/z = 173.9 \ [M]^+\); Calculated for \(\text{C}_7\text{H}_8\text{FN}_0\_3\): 173.049

Step 3: 2-(1-Fluorooethyl)oxazole-4-carboxylic acid

Using an analogous reaction to that described for Intermediate 5, step 2 methyl 2-(1-fluoroethyl)oxazole-4-carboxylate was converted into the title compound. MS \(m/z = 159.9 \ [M+H]^+\). Calculated for \(\text{C}_7\text{H}_8\text{FN}_0\_3\): 159.03

### Intermediate 50

![Intermediate 50](image)

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### Synthesis of 4-Chloro-1-isopropyl-1H-pyrazole-3-carboxylic acid

Step 1: Methyl 1-isopropyl-1H-pyrazole-3-carboxylate

To a solution of 1-isopropyl-1H-pyrazole-3-carboxylic acid (0.9757 g, 6.33 mmol, Matrix Scientific) in MeOH (31.6 ml) in a glass pressure vessel was added sulfuric acid (0.355 ml, 6.33 mmol Sigma Aldrich). The vessel was sealed and the rxn was brought to reflux to stir. (NOTE: A portable blast shield was used.) Rxn was allowed to stir for 5 hours. The rxn was concentrated in vacuo. The residue was diluted with water and extracted with EtOAc. The organic extract was washed with water, dried over MgSO\(_4\), filtered and concentrated in vacuo to give methyl 1-isopropyl-1H-pyrazole-3-carboxylate.
Step 2: Methyl 4-chloro-1-isopropyl-1H-pyrazole-3-carboxylate

To a solution of methyl 1-isopropyl-1H-pyrazole-3-carboxylate (0.8073 g, 4.80 mmol) in DMF (9.60 ml) was added n-chlorosuccinimide (3.20 g, 24.00 mmol, Sigma Aldrich). The reaction mixture was heated to 70 °C for 4.5 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic extract was washed with water, brine, dried over MgSO$_4$, filtered and concentrated in vacuo. The crude product was purified by silica gel chromatography, eluting with a gradient of 10% to 30% EtOAc in hexane, to provide methyl 4-chloro-1-isopropyl-1H-pyrazole-3-carboxylate (0.2705 g, 1.335 mmol, 27.8 % yield) as an off-white solid. MS $m/z = 203.0$[M+H]$. Calculated for C$_7$H$_5$ClN$_2$: 202.05. $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ ppm 1.42 (d, $J=6.85$ Hz, 6 H) 3.80 (s, 3 H) 4.55 (dt, $J=13.30$, 6.65 Hz, 1 H) 8.23 (s, 1 H)

Step 3: 4-chloro-1-isopropyl-1H-pyrazole-3-carboxylic acid

Using an analogous reaction to that described for Intermediate 5, step 2 methyl 4-chloro-1-isopropyl-1H-pyrazole-3-carboxylate was converted into the title compound. MS $m/z = 188.9$ [M+H]$. Calculated for C$_7$H$_5$ClN$_2$: 188.035. $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ ppm 1.41 (d, $J=6.65$ Hz, 6 H) 4.52 (quin, $J=6.70$ Hz, 1 H) 8.17 (s, 1 H) 12.89 (br. s., 1 H)

Intermediate 51

25 Synthesis of 2-(difluoromethyl)thiazole-4-carboxylic acid

Step 1: 2,5-difluoroethanethioamide

To a solution of difluoroacetonitrile (0.650 ml, 9.45 mmol) in MeOH (20 mL) was added ammonium sulfide (40-48 wt.% solution in water; 2.00 mL, 11.74 mmol) dropwise at rt. After stirring over 2.5 days the reaction mixture was concentrated to dryness to give 1.023 g (97%) of an orange amorphous solid. The material was carried on
to the next step without further purification. MS m/z=180 [M+H]^+. Calculated for C_2H_3F_2NS: 179.

**Step 2. ethyl 2-(difluoromethyl)thiazole-4-carboxylate**

A mixture of 2,2-difluoroethanethioamide (1.023 g, 9.21 mmol) and ethyl bromopyruvate (1.150 mL, 9.21 mmol) in EtOH (20 mL) was heated to 50 °C for 2 h. The reaction mixture was cooled to rt and purified by silica gel flash chromatography, eluting with EtOAc:hexanes (0:1 → 1:1) to give 964 mg (51%) of a brown oil. MS m/z=208 [M+H]^+. Calculated for C_7H_4F_2N_2O_2S: 207.

**Step 3. 2-(difluoromethyl)thiazole-4-carboxylic acid**

Using an analogous reaction to that described for Intermediate 5, step 2 ethyl 2-(difluoromethyl)thiazole-4-carboxylate was converted into the title compound. MS m/z=180 [M+H]^+. Calculated for C_3H_4F_2NO_2S: 179.

**Intermediate 52**

\[
\begin{align*}
F &-F \\
O &\equiv N \\
O &\equiv C - OH
\end{align*}
\]

**Synthesis of 2-(difluoromethyl)oxazole-4-carboxylic acid**

**Step 1. methyl 2-(difluoromethyl)-4,5-dihydrooxazole-4-carboxylate**

To a cooled (0 °C) solution of sodium methoxide (25 wt % solution in methanol; 0.230 mL, 1.032 mmol) and MeOH (20 mL) was added dropwise difluoroacetonitrile (0.690 mL, 10.03 mmol) while maintaining an internal temperature of <1 °C. After 20 min DL-serine methyl ester hydrochloride (1.55 g, 9.96 mmol) was added followed by MeOH (20 mL) and the reaction was allowed to warm to rt overnight. Subsequently, the reaction was heated to 55 °C for 5 h. The reaction was cooled to rt and partitioned between DCM/water. The aqueous layer was extracted with DCM (3x) and the combined organic layers were washed with water and dried over MgSO4. The filtrate was concentrated in vacuo to give 1.59 g (89%) of a light-brown oil. MS m/z=180 [M+H]^+. Calculated for C_8H_7F_2N_3O_3: 179.

**Step 2. methyl 2-(difluoromethyl)oxazole-4-carboxylate**

To a cooled (0 °C) suspension of copper(II) bromide (5.95 g, 26.6 mmol) in DCM (50 mL) was added hexamethylenetetramine (3.73 g, 26.6 mmol, Aldrich) followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (4.0 mL, 26.8 mmol, Aldrich). After 20 min a
solution of methyl 2-(difluoromethyl)-4,5-dihydrooxazole-4-carboxylate (1.59 g, 8.88 mmol) in DCM (5 mL) was added and the reaction mixture was allowed to warm to rt and stirred for 2 h. The mixture mixture was filtered and the filtrate was concentrated to dryness. The residue was partitioned between EtOAc and 1:1 satd NH₄Cl-conc NH₄OH. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were washed consecutively with 1:1 satd NH₄Cl-conc NH₄OH (1x), 10% citric acid (1x), satd NaHC03 (1x) and brine (1x). The filtrate was purified by silica gel flash chromatography, eluting with 25% EtOH/EtOAc:hexanes (0:1 → 1:0) to give 708 mg (45%) of a white crystalline solid. MS m/z=178 [M+H]^+.

Calculated for C₇H₈F₂N₂O₃: 177.

Step 3. 2-(difluoromethyl)oxazole-4-carboxylic acid

Using an analogous reaction to that described for Intermediate 5, step 2 methyl 2-(difluoromethyl)oxazole-4-carboxylate was converted into the title compound. MS m/z=164 [M+H]^+. Calculated for C₅H₃F₂NO₃: 163.

Intermediate 53

Synthesis of 2-(cyclopropylethynyl)oxazole-4-carboxylic acid

Step 1. ethyl 2-(cyclopropylethynyl)oxazole-4-carboxylate

A mixture of 2-bromo-oxazol-4-carboxylic ethyl ester (0.967 g, 4.40 mmol, Combi-Blocks), trans-dichlorobis(triphenylphosphine)palladium (II) (0.201 g, 0.286 mmol, Strem) and copper (I) iodide (0.165 g, 0.866 mmol, Aldrich) in toluene (15 ml) was purged with argon for 10 min. Ethynylcyclopropane (1.00 ml, 11.80 mmol) and triethylamine (1.70 ml, 12.22 mmol) were added. After 2.5 h, the reaction mixture was partitioned between CH₂Cl₂ and water. The aqueous layer was extracted with CH₂Cl₂ (3x). The combined organic layers were washed with brine. The solvent was removed under reduced pressure and the residue and was purified by silica gel flash chromatography, eluting with (EtOAc):hexanes (0:1 → 2:3) to give 452 mg (50%) of a light-orange oil. MS m/z=206 [M+H]^+. Calculated for C₁₁H₁₈N₂O₃: 205.
Step 2. 2-(cyclopropylethynyl)oxazole-4-carboxylic acid

Using an analogous reaction to that described for Intermediate 5, step 2 ethyl 2-(cyclopropylethynyl)oxazole-4-carboxylate was converted into the title compound. MS m/z=178 [M+H]+. Calculated for C₇H₇NO₃: 177.

Intermediate 54

Synthesis of 7-bromo-2-methyl-2H-pyrazolo[3.4-c]pyridine

Step 1. 7-bromo-1H-pyrazolo[3.4-c]pyridine

To a cooled (13 °C) mixture of 3-amino-2-bromo-4-picoline (4.5 g, 24.06 mmol, Combi-Blocks) and potassium acetate (3.09 g, 31.5 mmol) in AcOH (100 mL) was added a solution of sodium nitrite (2.01 g, 29.1 mmol) in water (10 mL) dropwise. Upon complete addition the reaction mixture was allowed to slowly warm to rt for 66 h. A solution of NaN₃ (706 mg) in water (3 mL) was added to the reaction mixture and the reaction mixture was stirred for 5 h. The solvent was removed under reduced pressure and the residue was basified with saturated NaHCO₃. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were washed with water then brine, and dried over MgSO₄. The filtrate was purified by silica gel flash chromatography, eluting with EtOAc:hexanes (0:1 → 1:1) to give a white crystalline solid (1.38 g, 7.0 mmol, 29%). MS m/z=198 [M+H]+. Calculated for C₇H₄BrN₃: 198.

Step 2. 7-bromo-2-methyl-2H-pyrazolo[3.4-c]pyridine

To a suspension of sodium hydride (57% in mineral oil; 0.052 g, 1.235 mmol) in DMF (4 mL) was added 7-bromo-1H-pyrazolo[3.4-c]pyridine (0.197 g, 0.995 mmol) in portions at room temperature. After 30 min iodomethane (0.070 mL, 1.127 mmol) was added. After 1.5 h the reaction was quenched with water (20 mL) and the solution was extracted with EtOAc (3x). The combined organic layers were purified by silica gel flash chromatography, eluting with MeOH (0:1 → 1:19) to give an off-white crystalline solid (19 mg, 0.09 mmol, 9%). MS m/z=214 [M+H]+. Calculated for C₇H₉BrN₃: 212.

Intermediate 56
Synthesis of 5-chloro-3-(prop-1-en-2-yl)picolinic acid

A microwave glass vessel was charged with 3-bromo-5-chloropicolinonitrile (0.5 g, 2.3 mmol), tetrakis(triphenylphosphine)palladium(0) (0.13 g, 0.15 mmol) and sodium carbonate (0.731 g, 6.90 mmol). The vial was evacuated and back-filled with nitrogen. Dioxane (10 mL) and water (3 mL) were added. The reaction mixture was degassed and isopropenylboronic acid pinacol ester (0.474 mL, 2.53 mmol) was added. The reaction mixture was heated to 90 °C for 2 hrs. The reaction mixture was partitioned between water and EtOAc. The organic phase was dried over MgSO₄ and concentrated in vacuo. The residue was dissolved in EtOH (7 mL) and NaOH (5M, 3 mL). The solution was heated to 115 °C for 1.5 hrs. The reaction mixture was partitioned between water and EtOAc. The organic phase was discarded and the aq. phase was acidified with aq. 2M HCl and extracted with EtOAc. The organic phase was dried over MgSO₄ and concentrated under reduced pressure to obtain the title compound as a light-yellow solid (0.373 g, 82%). MS m/z= 198.1 [M+H]+. Calculated for C₉H₅ClNO₂: 197.024

Intermediate 57

Synthesis of 5-chloro-3-isopropylpicolinic acid

A sealable vial was charged with 5-chloro-3-(prop-1-en-2-yl)picolinic acid (373 mg, 1.887 mmol) and EtOH (100 mL). The solution was purged with Nitrogen. Pt on activated carbon (479 mg, 0.245 mmol) was added, followed by glacial acetic acid (0.4 mL). The reaction mixture was evacuated, backfilled with hydrogen and stirred for 30 min at rt. The reaction mixture was filtered through a pad of celite to obtain the title compound as a white solid. The product contained minor amounts of dehalogenated product. The product was used in the next step without further purification. MS m/z= 200.1 [M+H]+. Calculated for C₉H₉ClNO₂ 199.040

Intermediate 58
Synthesis of 3-bromo-5//-cyclopenta|b|pyridin-7(6/f)-one

Step 1:
To a mixture of 3-bromo-6,7-dihydro-5//-cyclopenta[£]pyridine (1.83 g, 9.24 mmol) and potassium acetate (0.980 g, 9.99 mmol) in acetic acid (30 mL, 520 mmol) was added benzaldehyde (1.90 mL, 18.7 mmol). The reaction mixture was heated to 145 °C (oil bath temperature) in a sealed pressure tube for 3 d, cooled to room temperature and additional benzaldehyde (4 mL) and KOAc (1.83 g) were added. The reaction mixture was heated to 145 °C (oil bath temperature) in a sealed pressure tube for 2 d and cooled to room temperature. The reaction mixture was diluted with EtOAc. The organic phase was washed with 5 M NaOH, water and brine and dried over MgSO4. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (5% to 10% EtOAc in heptane) to give (is)-7-benzylidene-3-bromo-6,7-dihydro-5//-cyclopenta[b]pyridine (1.57 g, 5.49 mmol, 59% yield) as a yellow solid. MS m/z = 286.0 [M+H]+. Calculated for C17H12BrN2 285.0.

Step 2:
A solution of (ii)-7-benzylidene-3-bromo-6,7-dihydro-5//-cyclopenta[b]pyridine (1.61 g, 5.63 mmol) in MeOH (75 mL) and DCM (75 mL) was cooled to -78 °C and a stream of ozone in oxygen was bubbled through the solution for 10 min until the solution turned light blue. Oxygen was pass through the solution for 10 min until the solution turned colorless. Triphenylphosphine (3.63 g, 13.8 mmol) was added and the reaction mixture was allowed to warm to room temperature. The reaction mixture was stirred at room temperature for 1.5 h and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (80 g, 30% to 70% EtOAc in heptane) to give 3-bromo-5//-cyclopenta[6]pyridin-7(6//)-one (1.14 g, 5.38 mmol, 96% yield) as a yellow solid. MS m/z = 211.9 [M+H]+. Calculated for C7BrNO 211.0.
Synthesis of 5-bromo-2-fluoro-1-iodo-3-methylbenzene

A PFA plastic round bottom flask was charged with a solution of hydrogen fluoride pyridine (70 wt% HF, 100 ml, 1150 mmol). The solution was cooled to 0 °C and 4-bromo-2-iodo-6-methylaniline (9.2 g, 29.5 mmol, Organic Letters 2009, 11, 249-251) was added portion wise. After 15 minutes, sodium nitrite (1.032 g, 32.4 mmol) was added and the reaction mixture was stirred at 0 °C for additional 15 minutes. The reaction mixture was allowed to warm to room temperature and stirred for 15 minutes, followed by heating at 90 °C for 3 hour. The reaction mixture was then cooled to room temperature and quenched with water and diethyl ether. The organic layer was separated, washed with brine and dried over magnesium sulfate. The filtrate was concentrated under reduced pressure. The crude material was purified via silica gel chromatography eluting with hexanes to afford the title compound (8.45 g, 26.8 mmol, 91% yield) as a brown solid. 1H NMR (300 MHz, CHLOROFORM-d) δ ppm 2.29 (s, 3 H) 7.27 - 7.34 (m, 1 H) 7.64 - 7.75 (m, 1 H)

Intermediate 60

Synthesis of 1-bromo-4-fluoro-5-iodo-2-(((4-methoxybenzyl)-oxy)-methyl)-benzene

A solution of n-Butyllithium (2.5M in hexanes, 42.9 mL, 107 mmol) was added drop wise to a solution of freshly distilled 2,2,6,6-tetramethylpiperidine (18.11 mL, 107 mmol) in THF (220 mL) at -78 °C. The solution was warmed to 0 °C for 30 minutes and then cooled again to -78 °C. In a separate flask, a solution of 2-bromo-5-fluorobenzyl alcohol (10 g, 48.8 mmol) in THF (60 mL) was cooled to -78 °C and was transferred via cannula to the LiTMP solution. The resulting reaction mixture was stirred for 2 h at -78 °C. Subsequently, a solution of iodine (14.86 g, 58.5 mmol) in THF (60 mL) was added dropwise and the reaction mixture was stirred 40 minutes before the reaction was quenched with saturated aqueous ammonium chloride at -78 °C. After diluting with aqueous sodium thiosulfate and EtOAc, the layers were separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with saturated aqueous ammonium chloride, water, brine, and dried over sodium sulfate. The filtrate was concentrated in vacuo and the resulting crude product was taken up in in THF (48 ml) and DMF (8 ml) and cooled to 0 °C. Sodium hydride (60% in mineral oil, 0.341 g, 8.52 mmol) was added in one portion and after 15 minutes, 4-methoxybenzyl chloride (1.253
ml, 9.23 mmol) was added and the solution was stirred overnight at room temperature. The reaction mixture was cooled to 0 °C and quenched with IN HCl. After dilution with water and EtOAc, the layers were separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with aqueous lithium bromide solution, brine, and dried over sodium sulfate. The filtrate was concentrated in vacuo to give the crude material. The crude material was purified by silica gel chromatography, eluting with 1:30 Et₂O in heptane, to afford 1-bromo-4-fluoro-5-iodo-2-(((4-methoxybenzyl)oxy)methyl)benzene as a ~2:1 mixture with 1-bromo-4-fluoro-2-(((4-methoxybenzyl)oxy)methyl)benzene. LC/MS (ESI) m/z = 472.9/474.8 (M+Na).

**Synthesis of 4-(prop-1-yn-1-yl)-1H-pyrazole**

A sealable vial was charged with a solution of tert-butyl 4-bromo-1H-pyrazole-1-carboxylate (Ig, 4.05 mmol) and triethylamine (2.81 mL, 20.24 mmol) in DMF (6.75 mL). The solution was purged with nitrogen for 10 minutes. Copper (I) iodide (0.077 g, 0.405 mmol) and tetrakis(triphenylphosphine)palladium (0.234 g, 0.202 mmol) were added and 1-propyne was bubbled through the solution for 2 min. The reaction mixture was heated at 70 °C overnight. The reaction was poured into a 9:1 mixture of aqueous saturated ammonium chloride/ammonium hydroxide and the mixture was extracted with EtOAc. The combined organic extracts were washed with a 9:1 mixture of aqueous saturated ammonium chloride/ammonium hydroxide, aqueous lithium bromide solution, brine, and dried over sodium sulfate. The filtrate was concentrated in vacuo and the residue was purified by silica gel chromatography, eluting with 1:9 EtOAc in heptane, to provide tert-butyl 4-(prop-1-yn-1-yl)-1H-pyrazole-1-carboxylate, which was taken up in MeOH and treated with excess solid K₂CO₃ for 15 minutes. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure The crude material was partitioned between DCM and water. The layers were separated and the aqueous layer was extracted with DCM. The combined organic extracts were washed with brine and dried over sodium sulfate. The filtrate was concentrated in vacuo to afford 4-(prop-1-yn-1-yl)-1H-pyrazole. LC/MS (ESI) m/z = 107.0 (M+H).
Synthesis of 4-(cyclopropylethynyl)-1H-pyrazole

The title compound was synthesized according to the procedure described for 4-(prop-1-yn-1-yl)-1H-pyrazole (intermediate 61) above, but using cyclopropylacetylene. LC/MS (EST) m/z = 133.1 (M+H).

The following carboxylic acid intermediates were synthesized according to existing literature procedures, as listed below:

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A-1813-WO-PCT - 183 -

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| 79 | ![Chemical Structure](image2.png) | J. Med. Chem. 2013, 56, 3980 |
| 80 | ![Chemical Structure](image3.png) | J. Med. Chem. 2013, 56, 3980 |

Intermediate 81

5 **Synthesis of 5-((tert-butoxycarbonyl)(methyl)amino)pyrimidine-2-carboxylic acid**

**Step 1: Methyl 5-aminopyrimidine-2-carboxylate**

A suspension of 5-aminopyrimidine-2-carboxylic acid (Goldenbridge Pharma, Inc.; 5.70 g, 41.0 mmol) in MeOH (120 mL) was cooled in an ice-water bath and treated dropwise with thionyl chloride (8.97 mL, 123 mmol). The resulting suspension was heated at reflux for 20 h and then concentrated to give a yellow solid. The solid was dissolved in saturated aqueous NaHCO₃ (60 mL) and extracted into EtOAc using a Gregar Extractor. The extract was concentrated to give methyl 5-aminopyrimidine-2-carboxylate (4.26 g, 68% yield) as an off-white solid. ¹H NMR (400 MHz, CDCl₃): δ 8.32 (s, 2H), 4.35 (br s, 2H), 4.02 (s, 3H).

10 **Step 2: Methyl 5-((tert-butoxycarbonyl)amino)pyrimidine-2-carboxylate**

A solution of methyl 5-aminopyrimidine-2-carboxylate (1.37 g, 8.96 mmol) in DMF (15 mL) was treated with di-tert-butyl dicarbonate (2.15 g, 9.86 mmol) and stirred at ambient temperature for 5 min. DMAP (0.11 g, 0.90 mmol) was added and the solution was stirred at ambient temperature for 20 h. The resulting suspension was concentrated and purified by flash chromatography on silica gel eluting with a gradient of 0 to 40% EtOAc in DCM to give methyl 5-((tert-butoxycarbonyl)amino)pyrimidine-2-carboxylate.
Step 3: Methyl 5-((tert-butoxycarbonyl)(methyl)amino)pyrimidine-2-carboxylate

A solution of methyl 5-((tert-butoxycarbonyl)(methyl)amino)pyrimidine-2-carboxylate (1.31 g, 5.16 mmol) in DMF (13 mL) was treated with cesium carbonate (2.19 g, 6.71 mmol) followed by iodomethane (0.64 mL, 10.32 mmol). The resulting suspension was stirred at ambient temperature for 5 h. The suspension was diluted with DCM (50 mL), filtered, concentrated, and purified by flash chromatography on silica gel eluting with a gradient of 0 to 40% EtOAc in DCM to give methyl 5-((tert-butoxycarbonyl)(methyl)amino)pyrimidine-2-carboxylate (1.16 g, 84% yield) as a white solid. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.01 (s, 2H), 6.78 (br. s, 1H), 4.05 (s, 3H), 1.54 (s, 9H).

Step 4: 5-((tert-butoxycarbonyl)(methyl)amino)pyrimidine-2-carboxylate

A solution of methyl 5-((tert-butoxycarbonyl)(methyl)amino)pyrimidine-2-carboxylate (1.16 g, 4.35 mmol) in THF (15 mL) was treated with a 1.0 M aqueous solution of LiOH (4.6 mL, 4.6 mmol) and the solution was stirred at ambient temperature for 16 h. The mixture was concentrated and lyophilized from 1,4-dioxane to give lithium 5-((tert-butoxycarbonyl)(methyl)amino)pyrimidine-2-carboxylate (1.16 g, 100% yield) as a white powder. $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 8.63 (s, 2H), 3.24 (s, 3H), 1.43 (s, 9H).

Intermediate 82

Synthesis of a mixture of 3-fluoro-5-methoxypicolinic acid and 5-fluoro-3-methoxypicolinic acid

Step 1: Mixture of 3-fluoro-5-hydroxypicolinic acid and 5-fluoro-3-hydroxypicolinic acid

To a sealable tube was added 3,5-difluoropyridine-2-carboxylic acid (2.0 g, 12.57 mmol, Lancaster Synthesis Ltd.), lithium hydroxide hydrate (5.28 g, 126 mmol, Aldrich), and water (50 mL). The resulting mixture was stirred at 100 °C for 20 h. Then the mixture was cooled to RT and TFA (5.0 mL, 67.3 mmol, Aldrich) was added to the
mixture. The mixture was concentrated and dried in vacuo overnight to provide 12.6 g of a crude product mixture of 3-fluoro-5-hydroxypicolinic acid and 5-fluoro-3-hydroxypicolinic acid, as a white solid, used directly in the next step. MS (ESI, positive ion) m/z: 158.1 (M+H) observed for both isomers.

**Step 2: Mixture of methyl 3-fluoro-5-methoxypicolinate and methyl 5-fluoro-3-methoxypicolinate**

To a solution of 3-fluoro-5-hydroxypicolinic acid (1.98 g, 12.57 mmol) and 5-fluoro-3-hydroxypicolinic acid in DMF (100 mL, Aldrich) was added cesium carbonate (2.5 mL, 31.4 mmol, Aldrich) and iodomethane, stabilized (1.7 mL, 27.7 mmol, Alfa Aesar, A Johnson Matthey Company). The reaction was stirred at room temperature for 48 hours. Cesium carbonate (20.48 g, 62.8 mmol, Aldrich) and iodomethane, stabilized (3.4 mL, 55.4 mmol, Alfa Aesar) were added. The resulting mixture was stirred at room temperature for 16 hours. The mixture was diluted with H₂O (500 mL) and extracted with EtOAc (2 x 500 mL). The combined extracts were washed with H₂O (1 x 500 mL), dried over MgSO₄, concentrated, and dried in vacuo to give 1.18 g of products as a mixture of methyl 3-fluoro-5-methoxypicolinate and methyl 5-fluoro-3-methoxypicolinate as a light yellow solid. MS (ESI, positive ion) m/z: 186.1 (M+H) observed for both isomers.

**Step 3: Mixture of 3-fluoro-5-methoxypicolinic acid and 5-fluoro-3-methoxypicolinic acid**

To a solution of methyl 3-fluoro-5-methoxypicolinate (1.18 g, 6.37 mmol) and methyl 5-fluoro-3-methoxypicolinate in MeOH (30 mL, Aldrich) and water (10 mL) at 0 °C was added lithium hydroxide hydrate (0.53 g, 12.74 mmol, Aldrich). After addition, the mixture was then stirred at room temperature for 1 h. The mixture was concentrated and H₂O (25 mL) was added. The resulting mixture was adjusted to pH=5-6 by HCl (2N). The mixture was concentrated and dried. The residue was dissolved in MeOH (100 mL), adsorbed onto silica, and purified by silica gel flash chromatography using a gradient of 0%-40% MeOH in DCM to give 1.67 g (white solid) of products as a mixture of 3-fluoro-5-methoxypicolinic acid and 5-fluoro-3-methoxypicolinic acid. MS (ESI, positive ion) m/z: 172.1 (M+H) observed for both isomers.

Intermediate 83
Synthesis of 5-cyanopyrimidine-2-carboxylic acid

Step 1: methyl 5-bromopyrimidine-2-carboxylate

To a solution of 5-bromopyrimidine-2-carboxylic acid (3.22 g, 15.9 mmol) in MeOH (50 mL) at room temperature was added acetyl chloride (4.0 mL, 56.3 mmol). The reaction mixture was heated to reflux for 15 min, cooled to room temperature and concentrated under reduced pressure. The reaction mixture was diluted with saturated NaHCO₃ (30 mL) and EtOAc, and transferred to a separatory funnel. The aqueous phase was extracted with EtOAc (4 x) and the combined organic extracts were washed with brine (1 x), dried over MgSO₄, filtered, and concentrated to give methyl 5-bromopyrimidine-2-carboxylate (2.30 g, 10.6 mmol, 67% yield) as a white solid. LC/MS (ESI⁺) m/z = 216.9 (M+H). Calculated for C₇H₆N₂O₂ 216.0.

Step 2: methyl 5-cyanopyrimidine-2-carboxylate

To a mixture of methyl 5-bromopyrimidine-2-carboxylate (2.30 g, 10.6 mmol) and copper (I) cyanide (1.92 g, 21.4 mmol) in a 100 mL round bottom flask was added DMA (21 mL). The reaction mixture was degassed by bubbling nitrogen through the solution for 5 min. The reaction mixture was heated to 110 °C for 2 d and cooled to room temperature. The reaction mixture was diluted with EtOAc and water and filtered through a glass frit (medium). The filtrate was transferred to a separatory funnel. The aqueous phase was extracted with EtOAc (4 x) and the combined organic extracts were washed with brine (1 x), dried over MgSO₄, filtered, concentrated to give a yellow oil. Purification by flash column chromatography on silica gel (80 g, 5% to 50% EtOAc in heptane) gave methyl 5-cyanopyrimidine-2-carboxylate (0.83 g, 5.08 mmol, 48% yield) as a white solid. LC/MS (ESI⁺) m/z = 164.0 (M+H). Calculated for C₇H₈N₂O₂ 163.0.

Step 3: 5-cyanopyrimidine-2-carboxylic acid

To a solution of methyl 5-cyanopyrimidine-2-carboxylate (0.11 g, 0.644 mmol) in THF (2.6 mL) at 0 °C was added a solution of lithium hydroxide monohydrate (30 mg, 0.715 mmol) in water (0.5 mL). The reaction mixture was stirred at 0 °C for 20 min and 1 M HCl (0.70 mL) was added. The reaction mixture was concentrated under reduced pressure and dried under high vacuum to give methyl 5-cyanopyrimidine-2-carboxylate (0.11 g, 0.644 mmol) as a white solid that was used without further purification. LC/MS (ESI⁻) m/z = 148.0 (M-H). Calculated for C₇H₈N₂O₂ 149.0.

Intermediate 84
Synthesis of 5-ethynylpicolinic acid

Step 1: Methyl 5-((triethylsilyl)ethynyl)picolinate

A glass microwave reaction vessel was charged with methyl 5-bromopyridine-2-carboxylate (0.95 ml, 6.94 mmol, Alfa Aesar), (triethylsilyl) acetylene (3.73 ml, 20.81 mmol, Sigma-Aldrich), tetrakis(triphenylphosphine) palladium (0.61 g, 0.527 mmol, Strem Chemicals), triethylamine (4.82 ml, 34.7 mmol, Sigma-Aldrich Chemical), and copper (I) iodide (0.04 ml, 1.040 mmol, Sigma-Aldrich). The reaction mixture was stirred and heated in a Biotage Initiator microwave reactor at 70 °C for 30 min. The reaction mixture was filtered through celite and concentrated. The reaction mixture was diluted with saturated NH₄Cl and extracted with EtOAc. The organic extract was washed with water and brine, dried over MgSO₄, filtered and concentrated in vacuo. The crude product was adsorbed onto a plug of silica gel and chromatographed through a silica gel column, eluting with a gradient of 0% to 40% EtOAc in hexane, to provide methyl 5-((triethylsilyl)ethynyl)picolinate (1.68 g, 6.09 mmol, 88% yield). MS m/z [M+H]+ = 276.0. Calculated from C₁₅H₂₁NO₂S₁: 275.418

Step 2: 5-Ethynylpicolinic acid

To a solution of methyl 5-((triethylsilyl)ethynyl)picolinate (1.68 g, 6.05 mmol) in THF (12.11 ml) was added TBAF, 1.0M in THF (6.68 ml, 6.68 mmol, Sigma Aldrich). The reaction was allowed to stir for 6 hours at RT. The reaction was concentrated. The crude product was adsorbed onto a plug of silica gel and chromatographed through silica gel column eluting with a gradient of 10% to 100% EtOAc in hexane followed by 1% AcOH in EtOAc, to afford 5-ethynylpicolinic acid (0.05 g, 0.37 mmol, 6.10% yield). MS m/z [M+H]+ = 147.9. Calculated from C₉H₅NO₂: 147.131

Intermediate 85

Synthesis of 5-(Prop-1-yn-1-yl)picolinic acid

Step 1: Methyl 5-bromopicolinate
A-1 8 1 3-WO-PCT - 188 -

To a suspension of 5-bromopicolinic acid (2.0 g, 9.94 mmol) in MeOH (2 ml) and toluene (20 ml) was added TMS-diazomethane (20M in diethyl ether; 5.47 ml, 10.94 mmol, Matrix Scientific) dropwise. The reaction was stirred at room temperature for 3 hours. An additional 0.2 eq (0.99 mL) of TMS-diazomethane was added and the reaction stirred for 1.5 hours. The reaction was concentrated and the brown solid was carried to next step without further work up. MS m/z [M+H]^+ = 217.9. Calculated from C_{17}H_{18}BrN_{2}O_{2}: 216.032

Step 2: Methyl 5-(prop-l-yn-l-yl)picolinate

To a solution of methyl 5-bromopicolinate (0.60g, 2.77 mmol) in toluene (50 mL) was added tributyl(prop-l-yn-l-yl)stannane (1.01 mL, 3.32 mmol, Sigma Aldrich) and tetrakis(triphenylphosphine)palladium (0.04 g, 0.036 mmol, Strem Chemicals, Inc.). The reaction was stirred overnight at 100 °C. The reaction was allowed to cool to rt and concentrated. The residue was adsorbed onto a plug of 10% w/w KF Silica and chromatographed with a silica gel column eluting with a gradient of 10% to 100% EtOAc in hexane, to provide methyl 5-(prop-l-yn-l -yl)picolinate (0.18, 1.05 mmol, 37.8 % yield). MS m/z [M+H]^+ = 176.0. Calculated from C_{10}H_{14}N_{2}O_{2}: 175.184

Step 3: 5-(Prop-l-yn-l-yl)picolinic acid

To a solution of methyl 5-(prop-l-yn-l -yl)picolinate (0.18 g, 1.05 mmol) in tetrahydrofuran (3.48 ml) was added sodium hydroxide 1.0 N solution (1.05 mL, 1.045 mmol, Sigma). The reaction was stirred for 1.5 hours at room temperature. Hydrogen chloride (4.0M solution in 1,4-dioxane; 0.26 ml, 1.05 mmol, Sigma Aldrich) was added and the reaction stirred for an additional 10 minutes. The reaction was concentrated in vacuo to provide 5-(prop-l-yn-l -yl)picolinic acid as a light yellow solid. The material was used without further purification assuming theoretical yield. MS m/z [M+H]^+ = 162.1. Calculated from C_{3}H_{5}N_{2}O: 161.157

Intermediate 86

![Intermediate 86](image)

Synthesis of 5-chloro-3-(fluoromethyl)picolinic acid

Step 1: Methyl 5-chloro-2-vinylnicotinate

A sealable vial was charged with methyl 2,5-dichloronicotinate (100 mg, 0.49 mmol, Bionet Research), tributyl(vinyl)stannane (156 µl, 0.53 mmol) and N,N-
diethylefornamide (1 mL) at RT under nitrogen atmosphere. 2,6-Di tert-butyl-4-methylphenol (Aldrich, 5 mg) was added, followed by dichlorobis(triphenylphosphine)palladium(II) (Strem, 68 mg, 0.10 mmol) and the reaction mixture was heated to 80°C for 1 hour. The reaction mixture was cooled to RT and partitioned between EtOAc (50 mL) and water (50 mL). The organic phase was separated and washed with water (2x25 mL) and brine (30 mL). The combined organic layers were dried over anhydrous magnesium sulfate and the filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (5-35% EtOAc/hexamnes) to obtain the title compound as a colorless oil (96 mg).

1H NMR (300 MHz, CHLOROFORM-J) δ ppm 3.95 (s, 3 H) 3.97 - 4.00 (m, 1 H) 5.55 - 5.69 (m, 1 H) 6.43 - 6.58 (m, 1 H) 7.51 - 7.67 (m, 1 H) 8.12 - 8.23 (m, 1 H) 8.59 - 8.69 (m, 1 H)

Step 2: (5-Chloro-2-vinylpyridin-3-yl)methanol

A solution of methyl 5-chloro-2-vinylnicotinate (0.21 g, 1.06 mmol) in DCM (5 ml) was cooled to -45 °C. A solution of disobutylaluminum hydride (1M in hexane, 1.6 ml, 1.59 mmol, Aldrich) was added dropwise. After 15 min, the reaction mixture was quenched by the addition of a saturated aqueous solution of potassium sodium tartrate (3 mL). DCM was added, followed by water. The organic phase was separated, washed with water and dried over MgSO₄. The filtrate was concentrated under reduced pressure. The crude material was absorbed onto a plug of silica gel and purified by chromatography, eluting with a gradient of 5% to 55% EtOAc in hexane, to provide the title compound (77 mg) as a white solid. LC/MS m/z = 170.1 [M+H]+.

Step 3: 5-Chloro-3-(fluoromethyl)-2-vinylpyridine

To a solution of triethylamine trihydrofluoride (Aldrich, 1.9 mL, 12 mmol) in DCM (30 mL) at -78 °C, was added Xalfluor-E (4.1 g, 18 mmol, Aldrich), followed by a solution of (5-chloro-2-vinylpyridin-3-yl)methanol (2 g, 12 mmol) in DCM (40 mL). The cold bath was removed and the reaction mixture was allowed to warm from -78 °C to rt over a period of 15 min. The reaction was quenched by the addition of aqueous saturated bicarbonate solution. After 15 min stirring at rt, the reaction mixture was diluted with EtOAc and water. The organic phase was separated and dried over MgSO₄. The filtrate was absorbed onto a plug of silica gel and purified by chromatography through, eluting with a gradient of 5% to 45% EtOAc in hexane, to provide the title compound as colorless oil (1.22 g). LC/MS m/z = 172.1 [M+H]+.

Step 4: 5-Chloro-3-(fluoromethyl)picolinaldehyde
To a solution of 5-chloro-3-(fluoromethyl)-2-vinylpyridine (65 mg, 0.38 mmol) in THF (2.3 mL) and water (3.5 mL) was added a solution of osmium tetroxide (2.5 wt% in 2-methyl-2-propanol, 80 µl, 0.038 mmol, Aldrich). After 5 min, sodium meta-periodate (122 mg, 0.568 mmol, Aldrich) was added in one portion and the reaction mixture was allowed to stir for 1 h. The reaction mixture was partitioned between brine and EtOAc.

The organic phase was separated and dried over MgSO₄. The filtrate was absorbed onto a plug of silica gel and purified by chromatography, eluting with a gradient of 5% to 45% EtOAc in hexane, to provide the title compound as grey solid (55 mg).

1H NMR (300 MHz, CHLOROFORM-J) δ ppm 5.81 (s, 1 H) 5.97 (s, 1 H) 8.02 - 8.21 (m, 1 H) 8.63 - 8.82 (m, 1 H) 10.03 - 10.19 (m, 1 H)

Step 5: 5-chloro-3-(fluoromethyl)picolinic acid

To a solution of 5-chloro-3-(fluoromethyl)picinaldehyde (55 mg, 0.32 mmol) in THF (2 mL) and water (4 mL) was added solid NaOH (13 mg) at 0 °C. After 10 min, KMNO₄ (100 mg) was added in one portion. After additional 10 min, the reaction mixture was filtered through a pad of celite. The celite was washed with 1 M HCl (10 mL), water and EtOAc. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic layers were dried over MgSO₄ and the filtrate was concentrated under reduced pressure. The title compound was obtained as a yellow residue and taken onto the next step without further purification. LC/MS m/z = 172.1 [M+H]+.

Intermediate 87

Synthesis of 6-chlorofuro[3,2-b]pyridin-3(2//-)one

Step 1: ethyl 2-((5-chloro-2-cyanopyridin-3-yl)oxy)acetate

To a mixture of cesium carbonate (1.63 g, 5.01 mmol) and 5-chloro-3-fluoropicolinonitrile (0.784 g, 5.01 mmol) was added NMP (5 mL) and ethyl glycolate (0.52 mL, 5.49 mmol). The reaction mixture was stirred at RT for 20 min, heated to 80 °C for 1 h and additional ethyl glycolate (0.10 mL) was added. Stirring was continued at 80 °C for 2 h and the reaction mixture was cooled to RT. The reaction was and diluted with EtOAc and water. The aqueous phase was extracted with EtOAc (2 x) and the combined organic extracts were washed with brine (1 x), dried over MgSO₄, filtered, and
concentrated. Purification by flash column chromatography on silica gel eluthing with a gradient of 0% to 15% EtOAc in DCM gave ethyl 2-((5-chloro-2-cyanopyridin-3-y1)oxy)acetate (0.83 g, 3.46 mmol, 69 % yield) as a white solid. LC/MS (ESI⁺) m/z = 240.9 (M+H). Calculated for C10H11ClN02 240.0.

Step 2: ethyl 3-amino-6-chlorofuro[3,2-f]pyridine-2-carboxylate

The HCl salt of ethyl 2-((5-chloro-2-cyanopyridin-3-yl)oxy)acetate was formed by the addition of HCl (4 M in dioxane, 6.0 mL, 24 mmol) to a solution of ethyl 2-((5-chloro-2-cyanopyridin-3-yl)oxy)acetate in EtOH (15 mL). The solution was concentrated under reduced pressure. To a suspension of sodium hydride (60 wt% dispersion in mineral oil, 0.60 g, 14.9 mmol) in PhMe (45 mL) at RT was added ethanol (0.88 mL, 15.00 mmol). The mixture was stirred at room temperature for 20 min and added via cannula to ethyl 2-((5-chloro-2-cyanopyridin-3-yl)oxy) acetate hydrochloride (1.27 g, 4.58 mmol). The reaction mixture was stirred at RT for 40 min and quenched with saturated NH₄Cl. The reaction mixture was diluted with EtOAc and water. The aqueous phase was extracted with EtOAc (2 x) and the combined organic extracts were washed with brine (1 x), dried over MgSO₄, filtered, and concentrated to give ethyl 3-amino-6-chlorofuro[3,2-f]pyridine-2-carboxylate (0.84 g, 3.47 mmol, 76 % yield) as a yellow solid which was used without further purification. LC/MS (ESI⁺) m/z = 240.9 (M+H). Calculated for C₈H₇ClN0₂ 240.0.

Step 3: 6-chlorofuro[3,2-f]pyridin-3(2H)-one

A solution of ethyl 3-amino-6-chlorofuro[3,2-f]pyridine-2-carboxylate (0.81 g, 3.35 mmol) in hydrochloric acid (5.0 M in water, 50.0 mL, 3.35 mmol) was heated to reflux for 4 h and cooled to RT. The pH was adjusted to 7 with saturated NaHCO₃. The aqueous phase was extracted with EtOAc (3 x) and the combined organic extracts were dried over MgSO₄, filtered, and concentrated. Purification by flash column chromatography on silica gel eluthing with a gradient of 0% to 100% EtOAc in DCM gave 6-chlorofuro[3,2-f]pyridin-3(2H)-one (0.12 g, 0.68 mmol, 20 % yield) as a yellow solid. LC/MS (ESI⁺) m/z = 170.0 (M+H). Calculated for C₇H₄ClN0₂ 169.0.

Synthesis of 3-bromo-6,7-dihydroquinolin-8(5H)-one
Step 1: (ii)-8-benzylidene-3-bromo-5,6,7,8-tetrahydroquinoline

To a mixture of 3-bromo-5,6,7,8-tetrahydroquinoline (0.58 g, 2.73 mmol) (prepared according to: J. Am. Chem. Soc. 2011, 133, 12285) and potassium acetate (2.94 g, 30.0 mmol) in acetic acid (9.50 mL, 165 mmol) in a pressure tube was added benzaldehyde (2.80 mL, 27.7 mmol). The reaction mixture was heated to 150 °C (oil bath temperature) for 8 d and cooled to room temperature. The reaction was diluted with EtOAc and washed with 5 M NaOH (1 x), water (1 x), brine (1 x), dried over MgSO₄, filtered, and concentrated. Purification by flash column chromatography on silica gel eluting with a gradient of 0% to 10% EtOAc in heptane gave 1.29 g of a 2.5:1 mixture of (ii)-8-benzylidene-3-bromo-5,6,7,8-tetrahydroquinoline (1.29 g, 4.30 mmol) and benzaldehyde as a yellow oil that was used without further purification. LC/MS (ESI⁺) m/z = 300.0 (M+H). Calculated for C₁₀H₁₄BrN 299.0.

Step 2: 3-bromo-6,7-dihydroquinolin-8(5H)-one

A solution of (ii)-8-benzylidene-3-bromo-5,6,7,8-tetrahydroquinoline (0.82 g, 2.5:1 mixture with benzaldehyde) in MeOH (40 mL) and DCM (40 mL) was cooled to -78 °C and ozone was bubbled through the solution for 5 min until the solution turned light blue. Oxygen was passed through the solution for 10 min until the solution turned colorless and triphenylphosphine (1.03 g, 3.93 mmol) was added. The solution was removed from the dry ice/acetone bath and allowed to warm to RT. The reaction mixture was stirred at RT for 1 h. The reaction mixture was concentrated. Purification by flash column chromatography on silica gel eluting with 30% to 70% EtOAc in heptane) gave 3-bromo-6,7-dihydroquinolin-8(5H)-one (0.460 g, 2.04 mmol, 75 % yield) as a white solid. LC/MS (ESI⁺) m/z = 225.9 (M+H). Calculated for C₇H₆BrNO 225.0.

Intermediate 89

Synthesis of 3-Methylenevclobutanecarbaldehyde

Step 1: N-methoxy-N-methyl-3-methylenevclobutanecarboxamide

To a solution of 3-methylenevclobutanecarboxylic acid (525 mg, 4.68 mmol, Frontiers Scientific Services) in DMF (5 mL, aldrich) was added a solution of N,O-dimethyl hydroxylamine hydrochloride (0.55 g, 5.62 mmol, Aldrich) and triethylamine (0.78 mL, 5.62 mmol, Aldrich) in DMF (5 mL, Aldrich). The reaction was cooled to 0 °C
and propylphosphonic anhydride solution (50 wt. % in DMF; 4.47 mL, 7.02 mmol, Alfa Aesar) was added. The reaction was stirred at RT for 16 h. The reaction was quenched with saturated NaHCO₃ (10 mL) and stirred at RT for 5 min. The reaction was extracted with EtOAc (2 x 30 mL) and the combined organic extracts were washed with saturated ammonium chloride (2 x 40 mL), dried over MgSO₄, and concentrated. The residue was dissolved in diethyl ether (5 mL) and the solution mixture was washed with H₂O (2 x 10 mL), dried over MgSO₄, concentrated, and dried in vacuo to give 398 mg of the title compound as a light yellow liquid. MS (ESI, positive ion) m/z: 156.1 (M+H).

Step 2: 3-Methylenecyclobutanecarbaldehyde

To a solution of N-methoxy-N-methyl-3-methylenecyclobutanecarboxamide (0.11 g, 0.71 mmol) in diethyl ether (2 mL, Aldrich) at 0 °C under Ar(g) was added lithium aluminium hydride (1.0 M solution in THF; 0.851 mL, 0.851 mmol, Aldrich) dropwise. After completed addition, the reaction was stirred at 0 °C for 45 min. The reaction was quenched with a solution of KHSO₄ (1M, aq) at 0 °C and gradually warmed to room temperature and stirred for 30 min. The reaction was extracted with diethyl ether (2 x 10 mL) and the combined organic extracts were dried over MgSO₄, concentrated, and dried in vacuo to afford 68 mg of the title compound as a light yellow liquid, which was used directly in the next step without further purification. 1H NMR (CHLOROFORM-d) δ: 9.79 (d, J=2.3 Hz, 1H), 4.68-4.80 (m, 2H), 3.08-3.24 (m, 1H), 2.84-3.02 (m, 4H).

Syntesis of I-(Trifluoromethyl)cyclopropanecarbaldehyde

Step 1: N-methoxy-N-methyl-l-(trifluoromethyl)cyclopropanecarboxamide

To a solution of N,O-Dimethyl hydroxylamine hydrochloride (0.48 g, 4.87 mmol, Aldrich) in DMF (15 mL, Aldrich) was added triethylamine (0.68 mL, 4.87 mmol, Aldrich). After completed addition the reaction was stirred at RT for 5 min. 1-trifluoromethylcyclopropane-l-carboxylic acid (0.5 g, 3.24 mmol, Alfa Aesar, A Johnson Matthey Company) was added and the reaction was stirred at room temperature for 1 min. The reaction was cooled to 0 °C and propylphosphonic anhydride solution (50 wt. % in DMF; 3.10 mL, 4.87 mmol, Acros Organics) was added dropwise. The resulting mixture
was stirred at room temperature for 5 days. The reaction was quenched with saturated NaHCC>3 and stirred at RT for 5 min. The reaction was extracted with diethyl ether (2 x 40 mL) and the combined organic extracts were washed with saturated ammonium chloride, water, dried over MgSO₄, and concentrated to give 229 mg of the title compound as a light yellow liquid. MS (ESI, positive ion) m/z: 198.1 (M+H).

Step 2: 1-(Trifluoromethyl)cyclopropanecarbaldehyde

To a solution of N-methoxy-N-methyl-1-(trifluoromethyl)cyclopropanecarboxamide (0.23 g, 1.162 mmol) in diethyl ether (3 mL, aldrich) at 0 °C under Ar(g) was added lithium aluminium hydride (1.0 M solution in THF; 1.39 mL, 1.39 mmol, aldrich) dropwise. After completed addition the reaction was then stirred at 0 °C for 45 min. The reaction was quenched with a solution of KHSO₄ (1M) at -78 °C and gradually warmed to RT and stirred for 30 min. The reaction was extracted with diethyl ether (2 x 10 mL). The combined organic extracts were dried over MgSO₄, concentrated, and dried in vacuo to afford 62 mg of the title compound as a light yellow liquid, which was used in the next step without further purification. 1H NMR (CHLOROFORM-d) δ: 9.69 (s, 1H), 1.43 (m, 2H), 1.21 (t, J=7.0 Hz, 2H)

**Intermediate 91**

20 Synthesis of 4-chloro-7-(trifluoromethyl)pyrido[3,2-d]pyrimidine

**Step 1: 3-nitro-5-(trifluoromethyl)picolinonitrile**

A microwave reaction vial was charged with 2-chloro-3-nitro-5-(trifluoromethyl)pyridine (2 g, 8.83 mmol), NMP (4.41 ml) and CuCN (0.830 g, 9.27 mmol). The vial was sealed and the mixture was irradiated in the MW at 175 °C for 15 min. Upon cooling to RT, the reaction mixture was poured onto ice and EtOAc was added. The mixture was filtered through Celite, washing with EtOAc and a small amount of MeOH. The layers of the filtrate were separated, and the aqueous portion was extracted again with EtOAc. The combined organic portions were dried with sodium sulfate, filtered and concentrated. The crude material was purified by silica gel chromatography, using a gradient of 0-30% EtOAc in heptane to provide 3-nitro-5-(trifluoromethyl)picolinonitrile (645 mg, 2.97 mmol, 33.7 % yield) as a yellow oil that solidified upon standing. LC/MS (ES⁺) m/z = 218.1 (M+H).
Step 2: 3-nitro-5-(trifluoromethyl)pyridinamide

A round bottom flask was charged with 3-nitro-5-(trifluoromethyl)picolinonitrile (910 mg, 4.19 mmol) and sulfuric acid (4192 µL, 4.19 mmol), and the mixture was stirred at 60 °C for 16 h. Upon cooling to RT the crude mixture was poured onto ice, and the resulting solids were filtered, washed with water and dried. 3-nitro-5-(trifluoromethyl)pyridinamide (850 mg, 3.62 mmol, 86 % yield) was isolated as a light yellow solid. LC/MS (ESI+) \( m/z = 236.1 \) (M+H).

Step 3: 3-amino-5-(trifluoromethyl)picolinamide

A round bottom flask was charged with 3-nitro-5-(trifluoromethyl)picolinamide (850 mg, 3.62 mmol) and wet 5 wt. % Pd/C (769 mg, 0.362 mmol) and was purged with nitrogen. EtOAc (7230 µL) and then MeOH (7230 µL) were added, and the flask was evacuated and filled with hydrogen. The reaction was stirred at RT under hydrogen atmosphere for 17 h. The mixture was filtered through Celite and washed with EtOAc and MeOH. The filtrate was concentrated to provide 3-amino-5-(trifluoromethyl)picolinamide (720 mg, 3.51 mmol, 97 % yield) as a white solid. LC/MS (ESI+) \( m/z = 206.1 \) (M+H).

Step 4: 7-(trifluoromethyl)pyrido[3,2-d]pyrimidin-4(3H)-one

A vial was charged with 3-amino-5-(trifluoromethyl)picolinamide (615 mg, 3.00 mmol) and triethyl orthoformate (2496 µL, 14.99 mmol). The vial was sealed and the mixture was heated at 120 °C for 17 h. Upon cooling, the heterogeneous mixture was filtered and the solids were washed with heptane. 7-(trifluoromethyl)pyrido[3,2-d]pyrimidin-4(3H)-one (540 mg, 2.51 mmol, 84 % yield) was isolated as a tan solid. LC/MS (ESI+) \( m/z = 216.0 \) (M+H).

Step 5: 4-chloro-7-(trifluoromethyl)pyrido[3,2-d]pyrimidine

A pressure bottle was charged with 7-(trifluoromethyl)pyrido[3,2-d]pyrimidin-4(3H)-one (540 mg, 2.51 mmol), toluene (10.000 mL) and Hunig's base (1.315 mL, 7.53 mmol). POCl₃ (0.702 mL, 7.53 mmol) was added, and the bottle was sealed. The mixture was heated to 115 °C for 4 h. After cooling to RT, the mixture was diluted with EtOAc and water, and the layers were separated. The aqueous portion was extracted with additional EtOAc, and the combined organic portions were washed with saturated sodium bicarbonate, dried over sodium sulfate, filtered and concentrated. 4-chloro-7-(trifluoromethyl)pyrido[3,2-d]pyrimidine (560 mg, 2.397 mmol, 96 % yield) was isolated as a brown solid. LC/MS (ESI+) \( m/z = 234.0 \) (M+H).
Methods to synthesize final compounds

General Amidation Procedures:

The following four (4) methods were used to couple the aniline core intermediates to desired acid intermediates or other intermediates as presented herein, to prepare the final compounds of the invention.

Method A: Triphenylphosphine (T3P) procedure

Example 28: Synthesis of N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-3-methoxypicolinamide

A solution of 1-propanephosphonic acid cyclic anhydride (50 wt% in EtOAc, 0.352 ml, 0.553 mmol) was added to a solution of ((lR,5S,6R)-5-(5-amino-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (16g-B, 0.075 g, 0.277 mmol) and 5-chloro-3-methoxypicolinic acid (0.062 g, 0.332 mmol) in EtOAc (2 mL) at room temperature. The reaction mixture was stirred at rt for 12 h, diluted with aqueous saturated NaHCO3 solution and extracted with EtOAc. The organic phase dried over MgSO4 and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography using (0-100% EtOAc/heptane) to give the title compound (0.082 g, 0.186 mmol, 67.3 % yield). MS m/z = 441.1 [M+H]+

1H NMR (400 MHz, DMSO-d6) δ ppm 10.51 (s, 1 H), 8.26 (d, J=1.76 Hz, 1 H), 7.91 - 7.91 (m, 3 H), 7.20 (dd, J=1.64, 9.29 Hz, 1 H), 5.99 - 6.37 (m, 1 H), 5.86 (s, 2 H), 3.98 (t, J=5.38 Hz, 1 H), 3.89 (s, 3 H), 1.63 - 1.76 (m, 1 H), 1.12 (br. s., 1 H), 0.82 - 0.96 (m, 1 H)

Method B: DMTMM procedure

Example 29: Synthesis of N-(3-((l[R,S],5(S,R),6(R,S)l-3-amino-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-((4-hydroxy-4-methylpent-2-vn-l -yl)oxy)-3-methylpicolinamide
4-(4,6-Dimethoxy-1,3,5-triazet-2-yl)-4-methylpiperidino-4-methyl chloride (32.3 mg, 0.117 mmol) was added to a stirring solution of [I(S,R),5(S,R),6(S,R)]-5-(5-amino-2-fluorophenyl)-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (lk-rac) (lk rac, 25 mg, 0.106 mmol), and 5-((4-hydroxy-4-methylpent-2-yn-1-yl)oxy)-3-methylpicolinic acid (intermediate 38, 27.8 mg, 0.112 mmol) in THF (1 mL) and MeOH (0.250 mL). The reaction mixture was stirred at RT for 2.5 hrs. The reaction mixture was concentrated under reduced pressure and the residue was purified via silica gel flash column chromatography eluting with 0 to 10% (2 M NH₃ in MeOH) in DCM to yield the title compound as a white solid. MS m/z = 467.1 [M+H]+

1H NMR (400 MHz, CHLOROFORM-d) δ ppm 0.84 (dt, J=9.63, 6.63 Hz, 1 H) 0.97 (td, J=6.90, 2.64 Hz, 1 H) 1.51 (s, 6 H) 1.64 (s, 3 H) 1.74 - 1.83 (m, 1 H) 2.76 (s, 3 H) 3.31 (br. s., 3H) 3.89 - 3.96 (m, 1 H) 4.78 (s, 2 H) 7.04 (dd, J=1.54, 8.80 Hz, 1 H) 7.13 (d, J=2.74 Hz, 1H) 7.41 (dd, J=7.14, 2.64 Hz, 1 H) 7.90 - 7.96 (m, 1 H) 8.10 (d, J=2.74 Hz, 1 H) 9.98 (s, 1 H)

Method C: DMTMM procedure followed by deprotection of benzoyl group


A solution of N-([(lR,S),(5S,R),(6R,S)]-5-(5-amino-2-fluoro-3-methylphenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4. 1.0]hept-3-en-3-yl)benzamide (21d-rac, 220 mg, 0.565 mmol) and 5-chloro-2-pyridinecarboxylic acid (134 mg, 0.848 mmol) in THF (1983 µl)/MβOH (991 µl) was cooled to 0 °C before adding 4-(4,6-dimethoxy-1,3,5-
The reaction mixture was stirred at 0 °C for 15 minutes and then overnight at RT. The reaction was quenched with saturated sodium bicarbonate solution and diluted with water and EtOAc. The organic layer was washed with brine, dried over magnesium sulfate and the filtrate was concentrated under reduced pressure. The crude residue was taken up in MeOH (3 mL) and 1,8-diazabicyclo-[5.4.0]undec-7-ene (186 µL, 1.243 mmol) was added. The reaction mixture was heated to 50 °C for 6 hours and additional 12 h at rt. The precipitate was filtered off, suspended in water (5 mL) and MeOH (2 mL) and stirred vigorously for 10 minutes. The solid was filtered and dried under high vac to afford the title compound (155.6 mg, 0.366 mmol, 64.8% yield) as a white solid. MS m/z = 424.9 [M+H]+.

1H NMR (300 MHz, DMSO-d6) δ ppm: 0.82 - 0.99 (m, 1 H), 1.07 - 1.22 (m, 1 H), 1.63 - 1.81 (m, 1 H), 3.94 - 4.09 (m, 1 H), 5.83 (s, 2 H), 5.97 - 6.49 (m, 1 H), 7.80 (d, J=4.82 Hz, 2 H), 8.08 - 8.26 (m, 2 H), 8.78 (d, J=1.61 Hz, 1 H) 10.56 (s, 1 H).

Method D: HATU procedure

Example 31: Synthesis of N-(3-(r(1R,S), (5S,R), (6R,S)l-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-5-fluoro-4-methoxyphenyl)-5-chloropicolinamide

To a solution of [(1R,S), (5S,R), (6R,S)]-5-(5-amino-3-fluoro-2-methoxyphenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (12b rac, 80 mg, 0.282 mmol) and 5-chloropicolinic acid (102 mg, 0.650 mmol) in DMF (1 mL) was added 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-f]pyridinium 3-oxid hexafluorophosphate (247 mg, 0.650 mmol) and diisopropylethylamine (0.196 mL, 1.130 mmol). The reaction mixture was stirred at RT overnight and then quenched with aqueous, saturated NaHCO₃ solution. The reaction mixture was extracted with DCM and dried over Na₂SO₄. The filtrate was concentrated under reduced pressure and the residue was purified by flash column (DCM/EtOAc = 4:1 to 3:1) to afford 5-chloro-N-[(1R,S), (5S,R), (6R,S)]-5-(5-chloropicolinamido)-3-fluoro-2-methoxyphenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)picolinamide (140 mg, 0.249
mmol). The product was dissolved 5 mL 2N NH₃/MeOH and heated to 60° C overnight. The reaction mixture was cooled to rt, the solvent was evaporated under reduced pressure and the residue was purified by flash column (EtOAc/DCM = 1:2 to 1:1 to EtOAc) to give the title compound as a light yellow solid (90 mg, 0.213 mmol, 75% yield). MS

m/z = 422.9 [M+H]+

1H NMR (400MHz ,CHLOROFORM-d) δ ppm = 9.79 (br. s., 1 H), 8.55 (s, 1 H), 8.22 (d, J = 8.4 Hz, 1 H), 8.01 (d, J = 13.5 Hz, 1 H), 7.87 (d, J = 8.6 Hz, 1 H), 7.24 (br. s., 1 H), 4.97 - 4.58 (m, 2 H), 4.00 (s, 3 H), 3.95 (br. s., 1 H), 1.79 (q, J = 7.7 Hz, 1 H), 1.20 - 1.11 (m, 1 H), 0.96 - 0.84 (m, 1 H)

Examples 32-293

Using procedures analogous or similar to one of the general amidation procedures A-D described above, the appropriate aniline and carboxylic acid intermediates were reacted to provide the examples listed in Table 1.

<table>
<thead>
<tr>
<th>Example #</th>
<th>Method</th>
<th>Compound Name</th>
<th>Structure</th>
<th>Analytical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td>D</td>
<td>N-(3-((1S,5R,6S)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-chloropicolinamide</td>
<td><img src="image" alt="Structure" /></td>
<td>MS m/z = 410.8 [M]+ 1H NMR (400 MHz, CHLOROFORM-d) δ 9.59-9.79 (m, 1H), 8.48 (s, 1H), 8.11-8.23 (m, 1H), 7.96-8.07 (m, 1H), 7.86 (d, J=8.41 Hz, 1H), 7.26 (br. s., 1H), 4.70-4.84 (m, 2H), 4.44-4.70 (m, 2H), 3.94 (br. s., 1H), 1.71 (br. s., 1H), 1.22 (br. s., 1H), 0.77-1.01 (m, 1H)</td>
</tr>
<tr>
<td>33</td>
<td>A</td>
<td>N-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(prop-2-yn-1- yloxy)pyrazine-2-carboxamide</td>
<td><img src="image" alt="Structure" /></td>
<td>MS m/z = 432.1 [M+H]+ 1H NMR (400 MHz, DMSO-d6) δ ppm 10.73 (s, 1H), 8.91 (d, J=1.17 Hz, 1H), 8.49 (s, 1H), 7.97 (ddd, J=12.47, 6.80, 2.45 Hz, 1H), 7.81 - 7.92 (m, 1H), 5.66 (s, 2H), 5.14 (d, J=2.35 Hz, 2H), 4.32 - 4.82 (m, 2H), 4.00 - 4.15 (m, 1H), 3.64 (t, J=2.35 Hz, 1H), 1.47 - 1.70 (m, 1H), 0.99 (td, J=6.50, 2.64 Hz, 1H), 0.86 (dt, J=9.49, 6.41 Hz, 1H)</td>
</tr>
</tbody>
</table>
A-1813-WO-PCT

34 A
N-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-oxa-4-
azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-
difluorophenyl)-5-(prop-2-yn-1-yl)oxo)pyrazine
-2-carboxamide

MS \( m/z = 432.1 \) [M+H]+

1H NMR (400 MHz, CDCl3) d ppm 10.73 (s, 1 H), 8.91 (d, J=1.17 Hz, 1 H), 8.89 (d, J=3.17 Hz, 1 H), 7.97 (dd, J=12.32, 6.85, 2.54 Hz, 1 H), 7.82 - 7.91 (m, 1 H), 5.66 (s, 2 H), 5.14 (d, J=2.35 Hz, 2 H), 4.34 - 4.78 (m, 2 H), 3.97 - 4.17 (m, 1 H), 3.64 (d, J=4.89 Hz, 1 H), 1.46 - 1.66 (m, 1 H), 0.99 (dt, J=6.46, 2.74 Hz, 1 H), 0.86 (dt, J=9.49, 6.50 Hz, 1 H)

35 A
N-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-
azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-
difluorophenyl)-5-(but-2-yn-1-yl)oxo)pyrazine
-2-carboxamide

MS \( m/z = 446.1 \) [M+H]+

1H NMR (400 MHz, CDCl3) d ppm 9.49 (br. s., 1 H), 8.99 (s, 1 H), 8.17 (s, 1 H), 7.97 - 8.11 (m, 1 H), 7.26 (s, 1 H), 5.04 (br. s., 2 H), 4.71 - 4.82 (m, 1 H), 4.57 - 4.69 (m, 1 H), 4.01 (br. s., 1 H), 1.89 (br. s., 3 H), 1.77 (q, J=7.89 Hz, 1 H), 1.24 (br. s., 1 H), 0.97 (q, J=7.37 Hz, 1 H)

36 A
N-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-
azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-
difluorophenyl)-5-(but-2-yn-1-yl)oxo)pyrazine
-2-carboxamide

MS \( m/z = 446.1 \) [M+H]+

1H NMR (400 MHz, CDCl3) d ppm 9.49 (br. s., 1 H), 8.99 (s, 1 H), 8.17 (s, 1 H), 7.97 - 8.11 (m, 1 H), 7.26 (s, 1 H), 5.04 (br. s., 2 H), 4.71 - 4.82 (m, 1 H), 4.57 - 4.69 (m, 1 H), 4.01 (br. s., 1 H), 1.89 (br. s., 3 H), 1.77 (q, J=7.89 Hz, 1 H), 1.24 (br. s., 1 H), 0.97 (q, J=7.37 Hz, 1 H)

37 A
N-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-
azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-
difluorophenyl)-5-cyanopicolinamide

MS \( m/z = 402.2 \) [M+H]+

1H NMR (400 MHz, CDCl3) d ppm 9.70 (br. s., 1 H), 8.82 (s, 1 H), 8.38 (s, 1 H), 8.19 (d, J=8.02 Hz, 1 H), 7.86 - 8.06 (m, 1 H), 7.26 (br. s., 1 H), 4.53 - 4.89 (m, 4 H), 3.95 (br. s., 1 H), 1.71 (q, J=7.63 Hz, 1 H), 1.22 (br. s., 1 H), 0.93 (q, J=7.37 Hz, 1 H)

38 A
N-((1R,5S,6S)-3-amino-5-(fluoromethyl)-2-oxa-4-
azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-
difluorophenyl)-5-cyanopicolinamide

MS \( m/z = 402.2 \) [M+H]+

1H NMR (400 MHz, CDCl3) d ppm 9.70 (br. s., 1 H), 8.82 (s, 1 H), 8.38 (s, 1 H), 8.19 (d, J=8.02 Hz, 1 H), 7.86 - 8.06 (m, 1 H), 7.26 (br. s., 1 H), 4.53 - 4.89 (m, 4 H), 3.95 (br. s., 1 H), 1.71 (q, J=7.63 Hz, 1 H), 1.22 (br. s., 1 H), 0.93 (q, J=7.37 Hz, 1 H)
<p>| | | | |</p>
<table>
<thead>
<tr>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
</table>
| 39 | A | N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-bromopicolinamide | MS m/z = 457 [M+H]+  
1H NMR (400 MHz, CHLOROFORM-d) d ppm 9.78 (br. s., 1 H), 8.62 (d, J=1.96 Hz, 1 H), 8.14 (s, 1 H), 7.97 - 8.08 (m, 2 H), 7.28 (d, J=2.93 Hz, 1 H), 4.75 (s, 1 H), 4.63 (s, 1 H), 3.97 (t, J=6.16 Hz, 1 H), 1.63 - 1.80 (m, 1 H), 1.21 (td, J=6.94, 2.54 Hz, 1 H), 0.93 (dt, J=9.34, 6.87 Hz, 1 H) |
| 40 | A | N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-bromopicolinamide | MS m/z = 457 [M+H]+  
1H NMR (400 MHz, CHLOROFORM-d) d ppm 9.76 (br. s., 1 H), 8.62 (d, J=1.76 Hz, 1 H), 8.14 (s, 1 H), 7.97 - 8.07 (m, 2 H), 7.27 (br. s., 1 H), 4.74 (s, 1 H), 4.62 (s, 1 H), 4.50 (br. s., 2 H), 3.95 (t, J=6.16 Hz, 1 H), 1.63 - 1.81 (m, 1 H), 1.20 (td, J=6.85, 2.54 Hz, 1 H), 0.84 - 0.98 (m, 1 H) |
| 41 | A | N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-methoxypicolinamide | MS m/z = 407.2 [M+H]+  
1H NMR (400 MHz, CHLOROFORM-d) d ppm 9.81 (s, 1 H), 8.15 - 8.25 (m, 2 H), 8.06 (ddd, J=1.83, 6.94, 2.54 Hz, 1 H), 7.32 (dd, J=8.61, 2.74 Hz, 1 H), 7.26 (s, 1 H), 4.51 - 4.90 (m, 2 H), 3.96 - 4.03 (m, 1 H), 3.94 (s, 3 H), 1.65 - 1.81 (m, 1 H), 1.15 - 1.30 (m, 1 H), 0.95 (dt, J=9.49, 6.90 Hz, 1 H). NH2 is broad and not accounted for. |
| 42 | A | N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-3-(methoxymethyl)picolinamide | MS m/z = 455.1 [M+H]+  
1H NMR (400 MHz, CHLOROFORM-d) d ppm 9.86 (br. s., 1 H), 8.27 (br. s., 1 H), 8.17 (br. s., 1 H), 7.92 (d, J=6.06 Hz, 1 H), 7.49 (d, J=6.26 Hz, 1 H), 7.00 (t, J=10.07 Hz, 1 H), 6.03 - 6.42 (m, 1 H), 4.85 - 5.14 (m, 4 H), 3.91 (br. s., 1 H), 3.54 (s, 3 H), 1.83 - 1.96 (m, 1 H), 1.43 (br. s., 1 H), 0.95 (q, J=7.30 Hz, 1 H) |
<table>
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<th>No.</th>
<th>Compounds</th>
<th>MS m/z</th>
<th>NMR Data (400 MHz, CHLOROFORM-d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>43</td>
<td>N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-3-methylpicolinamide</td>
<td>425.2[M+H]+</td>
<td>1H NMR: 9.89 (s, 1H), 8.24 (s, 1H), 7.87 - 8.04 (m, 1H), 7.61 (s, 1H), 7.48 (dd, J=6.65, 2.35 Hz, 1H), 7.01 (dd, J=1.35, 9.00 Hz, 1H), 6.01 - 6.45 (m, 1H), 4.96 (br. s., 2H), 3.92 (t, J=5.67 Hz, 1H), 2.75 (s, 3H), 1.82 - 1.97 (m, 1H), 1.35 - 1.53 (m, 1H), 0.86 - 1.03 (m, 1H)</td>
</tr>
<tr>
<td>44</td>
<td>N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-cyano-3-methylpicolinamide</td>
<td>416.1[M+H]+</td>
<td>1H NMR: 9.86 (s, 1H), 8.54 (s, 1H), 7.84 - 8.03 (m, 2H), 7.49 (dd, J=6.65, 2.54 Hz, 1H), 7.00 (dd, J=1.35, 8.80 Hz, 1H), 6.02 - 6.48 (m, 1H), 4.99 (br. s., 2H), 3.79 - 3.99 (m, 1H), 2.82 (s, 3H), 1.82 - 1.93 (m, 1H), 1.43 (t, J=6.16 Hz, 1H), 0.80 - 1.05 (m, 1H)</td>
</tr>
<tr>
<td>45</td>
<td>N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-cyano-3-methoxy-picolinamide</td>
<td>432.2[M+H]+</td>
<td>1H NMR: 9.59 (br. s., 1H), 8.34 (s, 1H), 8.01 (d, J=8.02 Hz, 1H), 7.49 - 7.67 (m, 2H), 7.08 (t, J=10.17 Hz, 1H), 6.00 - 6.49 (m, 1H), 4.97 (br. s., 2H), 3.84 - 4.00 (m, 4H), 1.82 - 1.94 (m, 1H), 1.42 (br. s., 1H), 0.96 (q, J=7.63 Hz, 1H)</td>
</tr>
<tr>
<td>46</td>
<td>N-(3-((lR,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-4-chloro-1-(difluoromethyl)-1H-pyrazole-3-carboxamide</td>
<td>450.1[M+H]+</td>
<td>1H NMR (400 MHz, CHLOROFORM-d) d ppm 8.45 (br. s., 1H), 8.00 (ddd, J=11.59, 6.99, 2.54 Hz, 1H), 7.90 (s, 1H), 7.25 (s, 1H), 7.11 - 7.18 (m, 1H), 4.48 - 4.84 (m, 2H), 3.95 (t, J=6.26 Hz, 1H), 1.59 - 1.82 (m, 1H), 1.20 (td, J=6.94, 2.54 Hz, 1H), 0.76 - 0.99 (m, 1H). Note NH2 is broad from 5-3 ppm</td>
</tr>
<tr>
<td>47</td>
<td>N-(3-((lS,S,6S)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-4-chloro-1-(difluoromethyl)-1H-pyrazole-3-carboxamide</td>
<td>450.1[M+H]+</td>
<td>1H NMR (400 MHz, CHLOROFORM-d) δ 8.48 (br. s., 1H), 8.02 (dd, J=6.94, 11.64 Hz, 1H), 8.01 (dd, J=7=6.94, 11.64 Hz, 1H), 7.90 (s, 1H), 7.10 - 7.16 (m, 1H), 4.56-4.79 (m, 2H), 3.96 (t, J=6.36 Hz, 1H), 1.68-1.76 (m, 1H), 1.21 (dt, J=7=2.54, 6.85 Hz, 1H), 0.88-0.97 (m, 1H)</td>
</tr>
</tbody>
</table>
| 48 | D | N-(3-((1S,5S,6S)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-4-chloropyrazole-3-carboxamide | MS m/z = 410.8 [M]+  
1H NMR (400 MHz, CHLOROFORM-d) δ 8.48 (br. s., 1H), 8.02 (dd, J=6.94, 11.64 Hz, 1H), 8.01 (dd, J=7.90, 11.64 Hz, 1H), 7.90 (s, 1H), 7.10-7.16 (m, 2H), 4.56-4.79 (m, 3H), 3.96 (t, J=6.36 Hz, 1H), 1.68-1.76 (m, 2H), 1.21 (dt, J=2.54 Hz, 6.85 Hz, 1H), 1.07-0.97 (m, 1H) |
| 49 | A | N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-cyano-3-methylpicolinamide | MS m/z = 415.8 [M]+  
1H NMR (400 MHz, CHLOROFORM-d) δ 9.70 (br. s., 1H), 8.63 (s, 1H), 8.47 (s, 1H), 8.14-8.19 (m, J=8.41 Hz, 1H), 7.95-8.02 (m, 2H), 7.26 (br. s., 1H), 4.49-4.92 (m, 4H), 3.94 (br. s., 1H), 1.72 (q, J=7.96 Hz, 1H), 1.22 (t, J=6.46 Hz, 1H), 0.91 (q, J=7.37 Hz, 1H) |
| 50 | A | N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-cyano-3-methylpicolinamide | MS m/z = 415.8 [M]+  
1H NMR (400 MHz, CHLOROFORM-d) δ 9.91-10.10 (m, J=8.41 Hz, 1H), 7.99-8.07 (m, 1H), 7.94 (s, 1H), 7.14 (br. s., 1H), 4.56-4.81 (m, 4H), 3.95 (br. s., 1H), 2.84 (s, 3H), 1.73 (q, J=7.96 Hz, 1H), 1.11-1.34 (m, 2H), 0.83-0.99 (m, 1H) |
| 51 | A | N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-cyano-3-methylpicolinamide | MS m/z = 458.9 [M]+  
1H NMR (400 MHz, CHLOROFORM-d) δ 9.90 (br. s., 1H), 8.63 (s, 1H), 7.99-8.07 (m, 1H), 7.94 (s, 1H), 7.14 (br. s., 1H), 4.56-4.81 (m, 4H), 3.95 (br. s., 1H), 2.84 (s, 3H), 1.73 (q, J=7.96 Hz, 1H), 1.11-1.34 (m, 2H), 0.83-0.99 (m, 1H) |
| 52 | A | N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(trifluoromethyl)picolinamide | MS m/z = 458.9 [M]+  
1H NMR (400 MHz, CHLOROFORM-d) δ 9.91-10.10 (m, 1H), 8.53-8.68 (m, 1H), 7.98-8.10 (m, 1H), 7.82-7.93 (m, 1H), 7.10-7.21 (m, 1H), 4.26-5.17 (m, 3H), 3.74-4.08 (m, 1H), 2.86 (s, 4H), 1.57-1.91 (m, 1H), 1.09-1.38 (m, 1H), 0.79-1.06 (m, 1H) |
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<th>Index</th>
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<th>Compound Details</th>
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<tr>
<td>53 A</td>
<td>N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloropyrazine-2-carboxamide</td>
<td><strong>MS</strong> <em>m/z</em> = 425.9[M]+ 1H NMR (300 MHz, CHLOROFORM-d) δ ppm 9.52 (s, 1 H), 8.25 (s, 1 H), 7.88 - 8.00 (m, 1 H), 7.45 (d, <em>J</em>=4.97 Hz, 1 H), 6.89 - 7.06 (m, 1 H), 5.97 - 6.50 (m, 1 H), 4.78 - 5.40 (br. s., 2 H), 3.91 (br. s., 1 H), 3.00 (s, 3 H), 1.81 - 1.96 (m, 1 H), 1.43 (br. s., 1 H), 0.84 - 1.05 (m, 1 H)</td>
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<td>54 A</td>
<td>N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-6-chloropyrazine-2-carboxamide</td>
<td><strong>MS</strong> <em>m/z</em> = 425.9 [M]+ 1H NMR (300 MHz, CHLOROFORM-d) δ ppm 9.42 (s, 1 H), 8.64 (s, 1 H), 7.93-8.01 (m, 1 H), 7.51 (dd, <em>J</em>=2.05, 6.43 Hz, 1 H), 6.97-7.05 (m, 1 H), 6.42-6.05 (t, 1 H), 4.92 (br. s., 2 H), 3.93 (m, 1 H), 3.00 (s, 3 H), 1.83-1.93 (m, 1 H), 1.39-1.47 (m, 1 H), 0.92-1.02 (m, 1 H)</td>
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<td>55 B</td>
<td>N-(3-((1R,S,5S,R,6(R,S))-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloropicolinamide</td>
<td><strong>MS</strong> <em>m/z</em> = 411.0[M+H]+ 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 9.03 - 1.01 (m, 1 H) 1.39 - 1.45 (m, 1 H) 1.83 - 1.91 (m, 1 H) 3.91 - 3.97 (m, 1 H) 4.67 (br. s., 2 H) 6.24 (t, <em>J</em>=56.10 Hz, 1 H) 7.09 (dd, <em>J</em>=1.54, 8.80 Hz, 1 H) 7.64 (dd, <em>J</em>=6.85, 2.74 Hz, 1 H) 7.87 (dd, <em>J</em>=8.41, 2.35 Hz, 1 H) 7.99 (ddd, <em>J</em>=8.80, 4.11, 2.93 Hz, 1 H) 8.21 (d, <em>J</em>=8.22 Hz, 1 H) 8.52 (d, <em>J</em>=2.15 Hz, 1 H) 9.79 (s, 1 H)</td>
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<td>56 B</td>
<td>N-(3-((1R,5S,6R)-3-amino-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(but-2-yn-1-yloxy)-3-methylpicolinamide</td>
<td><strong>MS</strong> <em>m/z</em> = 422.9 [M]+ 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 0.89 (dt, <em>J</em>=9.59, 6.65 Hz, 1 H) 1.01 (td, <em>J</em>=6.99, 2.64 Hz, 1 H) 1.68 (s, 3 H) 1.83 (dt, <em>J</em>=9.44, 7.31 Hz, 1 H) 1.88 (t, <em>J</em>=2.25 Hz, 3 H) 2.78 (s, 3 H) 3.96 - 4.01 (m, 1 H) 4.40 (br. s., 2 H) 4.75 (q, <em>J</em>=2.20 Hz, 2 H) 7.04 (dd, <em>J</em>=1.64, 8.90 Hz, 1 H) 7.14 (d, <em>J</em>=2.54 Hz, 1 H) 7.44 (dd, <em>J</em>=7.14, 2.64 Hz, 1 H) 7.92 (ddd, <em>J</em>=8.71, 4.11, 2.84 Hz, 1 H) 8.14 (d, <em>J</em>=2.74 Hz, 1 H) 10.01 (s, 1 H)</td>
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| 57 | B | N-((3-((1S,5R,6S)-3-amino-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(but-2-yn-1-yloxy)-3-methylpicolinamide | MS \( m/z = 422.9 \) [M]+  
1H NMR (400 MHz, CHLOROFORM-d) \( \delta \) ppm 0.88 (dt, \( J=9.73, 6.48 \) Hz, 1 H) 1.00 (td, \( J=6.90, 2.64 \) Hz, 1 H) 1.67 (s, 3 H) 1.81 (dt, \( J=9.98, 7.30 \) Hz, 1 H) 1.88 (t, \( J=2.35 \) Hz, 3 H) 2.78 (s, 3 H) 3.97 (ddd, \( J=7.48, 6.1 \) Hz, 1 H) 4.09 (br. s., 2 H) 4.75 (q, \( J=2.35 \) Hz, 2 H) 7.04 (dd, \( J=1.74, 8.80 \) Hz, 1 H) 7.14 (d, \( J=2.54 \) Hz, 1 H) 7.43 (dd, \( J=7.04, 2.74 \) Hz, 1 H) 7.92 (ddd, \( J=8.80, 4.11, 2.74 \) Hz, 1 H) 8.14 (d, \( J=2.74 \) Hz, 1 H) 10.00 (s, 1 H) |

| 58 | B | N-((3-((1(R,S),5(S,R),6(R,S))-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-methoxy-3-methylpyrazine-2-carboxamide | MS \( m/z = 422.0[M+H]+ \)  
1H NMR (400 MHz, DMSO-d6) \( \delta \) ppm 0.92 (dt, \( J=9.34, 6.48 \) Hz, 1 H) 1.12 - 1.18 (m, 1 H) 1.70 - 1.77 (m, 1 H) 2.76 (s, 3 H) 3.97 - 4.05 (m, 1 H) 4.00 (s, 3 H) 5.86 (s, 2 H) 6.19 (t, \( J=56.10 \) Hz, 1 H) 7.20 (dd, \( J=1.74, 8.80 \) Hz, 1 H) 7.82 - 7.87 (m, 1 H) 7.90 (dd, \( J=7.04, 2.54 \) Hz, 1 H) 8.24 (s, 1 H) 10.45 (s, 1 H) |

| 59 | B | N-((3-((1(R,S),5(S,R),6(R,S))-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-cyanopicolinamide compound | MS \( m/z = 401.9[M]+ \)  
1H NMR (400 MHz, DMSO-d6) \( \delta \) ppm 0.92 (dt, \( J=9.34, 6.48 \) Hz, 1 H) 1.13 - 1.19 (m, 1 H) 1.74 (dt, \( J=9.29, 7.09 \) Hz, 1 H) 4.00 - 4.06 (m, 1 H) 5.86 (s, 2 H) 6.20 (t, \( J=55.90 \) Hz, 1 H) 7.24 (dd, \( J=1.74, 8.80 \) Hz, 1 H) 7.89 (ddd, \( J=8.80, 4.11, 2.93 \) Hz, 1 H) 8.06 (dd, \( J=7.04, 2.74 \) Hz, 1 H) 8.29 (dd, \( J=8.22, 0.59 \) Hz, 1 H) 8.58 (dd, \( J=8.22, 1.96 \) Hz, 1 H) 9.20 (dd, \( J=2.00, 0.78 \) Hz, 1 H) 10.86 (s, 1 H) |

| 60 | B | N-((3-((1S,5R,6S)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloropicolinamide | MS \( m/z = 410.9[M]+ \)  
1H NMR (400 MHz, CHLOROFORM-d) \( \delta \) ppm 0.91 - 0.99 (m, 1 H) 1.40 - 1.46 (m, 1 H) 1.87 (dt, \( J=9.44, 7.12 \) Hz, 1 H) 3.89 - 3.95 (m, 1 H) 4.85 (br. s., 2 H) 6.24 (t, \( J=55.80 \) Hz, 1 H) 7.04 (dd, \( J=1.54, 8.80 \) Hz, 1 H) 7.62 (dd, \( J=6.65, 2.74 \) Hz, 1 H) 7.85 (dd, \( J=8.41, 2.35 \) Hz, 1 H) 7.94 (ddd, \( J=8.75, 4.16, 2.74 \) Hz, 1 H) 8.17 (d, \( J=8.22 \) Hz, 1 H) 8.45 (d, \( J=2.15 \) Hz, 1 H) 9.71 (s, 1 H) |
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<td>61</td>
<td>N-(3-((1R,5S,6S)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-3'-chloro-3'-methylpyrazine-2-carboxamide</td>
<td>463.9[M]+</td>
<td>0.86 - 0.98 (m, 1 H) 1.12 - 1.19 (m, 1 H) 1.73 (q, J=7.56 Hz, 1 H) 2.81 (s, 3 H) 3.99 - 4.07 (m, 1 H) 5.85 (br. s., 2 H) 6.19 (t, J=56.10 Hz, 1 H) 7.18 (dd, J=1 1.15, 9.39 Hz, 1 H) 7.42 (d, J=9.39 Hz, 1 H) 7.69 (d, J=9.59 Hz, 1 H) 7.84 - 7.91 (m, 1 H) 7.96 - 8.02 (m, 1 H) 8.68 (s, 1 H) 10.24 (s, 1 H)</td>
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<td>62</td>
<td>N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-5-cyanopicolinamide</td>
<td>435.8 [M+H]+</td>
<td>1.09 - 1.15 (m, 1 H) 1.66 - 1.75 (m, 1 H) 3.95 - 4.00 (m, 1 H) 5.93 (s, 2 H) 6.19 (t, J=55.80 Hz, 1 H) 7.26 (dd, J=1 1.74, 8.80 Hz, 1 H) 7.75 (dd, J=6.94, 2.64 Hz, 1 H) 7.80 - 7.85 (m, 1 H) 8.81 (d, J=1 1.76 Hz, 1 H) 9.11 (d, J=1 1.76 Hz, 1 H) 10.95 (s, 1 H)</td>
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<td>63</td>
<td>N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-methoxy-3-methylpyrazine-2-carboxamide</td>
<td>422.1 [M+H]+</td>
<td>1.05 - 1.12 (m, 1 H) 1.58 - 1.68 (m, 1 H) 2.81 (t, J=55.80 Hz, 1 H) 3.89 - 3.95 (m, 1 H) 4.04 (s, 3 H) 4.64 (br. s., 2 H) 6.22 (t, J=55.80 Hz, 1 H) 7.05 (t, J=10.30 Hz, 1 H) 7.48 (d, J=6.26 Hz, 1 H) 7.90 (s, 1 H) 7.97 - 8.03 (m, 1 H) 9.70 (s, 1 H)</td>
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<td>64</td>
<td>N-(3-((1S,5R,6S)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-methoxy-3-methylpyrazine-2-carboxamide</td>
<td>422.1 [M+H]+</td>
<td>1.05 - 1.12 (m, 1 H) 1.58 - 1.68 (m, 1 H) 2.81 (t, J=55.80 Hz, 1 H) 3.89 - 3.95 (m, 1 H) 4.04 (s, 3 H) 4.67 (br. s., 2 H) 6.22 (t, J=55.90 Hz, 1 H) 7.04 (t, J=10.60 Hz, 1 H) 7.48 (d, J=6.26 Hz, 1 H) 7.90 (s, 1 H) 7.97 - 8.03 (m, 1 H) 9.69 (s, 1 H)</td>
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<td>65</td>
<td>N-(3-((1S,5R,6S)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-carboxamide</td>
<td>402.0 [M+H]+</td>
<td>0.92 (dt, J=9.39, 6.46 Hz, 1 H) 1.12 - 1.18 (m, 1 H) 1.73 (dt, J=9.15, 6.97 Hz, 1 H) 3.99 - 4.06 (m, 1 H) 5.88 (s, 2 H) 6.20 (t, J=56.10 Hz, 1 H)</td>
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<tr>
<td>cyanopicolinamide</td>
<td>7.24 (dd, J=1.93, 8.80 Hz, 1 H) 7.88 (ddd, J=8.80, 4.11, 2.93 Hz, 1 H) 8.06 (dd, J=7.04, 2.74 Hz, 1 H) 8.28 (dd, J=8.22, 0.78 Hz, 1 H) 8.59 (dd, J=8.22, 1.96 Hz, 1 H) 9.21 (dd, J=2.05, 0.88 Hz, 1 H) 10.88 (s, 1 H)</td>
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<td>N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-chloro-5-cyanopicolinamide</td>
<td>MS m/z = 436.0 [M+H]+&lt;br&gt;1H NMR (400 MHz, DMSO-d6) δ ppm 0.90 (dt, J=9.29, 6.50 Hz, 1 H) 1.10 - 1.15 (m, 1 H) 1.67 - 1.75 (m, 1 H) 3.95 - 4.01 (m, 1 H) 5.93 (s, 2 H) 6.19 (t, J=55.90 Hz, 1 H) 7.26 (dd, J=1.74, 8.80 Hz, 1 H) 7.75 (dd, J=7.04, 2.74 Hz, 1 H) 7.83 (ddd, J=8.75, 4.06, 2.84 Hz, 1 H) 8.81 (d, J=1.57 Hz, 1 H) 9.11 (d, J=1.57 Hz, 1 H) 10.95 (s, 1 H)</td>
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<td>N-(3-((1S,5R,6S)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-chloro-5-cyanopicolinamide</td>
<td>MS m/z = 436.0 [M+H]+&lt;br&gt;1H NMR (400 MHz, DMSO-d6) δ ppm 0.90 (dt, J=9.19, 6.46 Hz, 1 H) 1.09 - 1.15 (m, 1 H) 1.67 - 1.75 (m, 1 H) 3.95 - 4.02 (m, 1 H) 5.93 (s, 2 H) 6.19 (t, J=55.90 Hz, 1 H) 7.26 (dd, J=1.83, 8.90 Hz, 1 H) 7.75 (dd, J=6.85, 2.74 Hz, 1 H) 7.83 (ddd, J=8.75, 4.06, 2.84 Hz, 1 H) 8.81 (d, J=1.76 Hz, 1 H) 9.11 (d, J=1.56 Hz, 1 H) 10.95 (s, 1 H)</td>
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<td>N-(3-((1R,5S,6R)-3-amino-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloropicolinamide</td>
<td>MS m/z = 375.0 [M]+&lt;br&gt;1H NMR (400 MHz, DMSO-d6) δ ppm 0.78 (dd, J=8.02, 4.50 Hz, 2 H) 1.49 (s, 3 H) 1.58 (q, J=7.82 Hz, 1 H) 3.88 - 3.97 (m, 1 H) 5.44 (br. s., 2 H) 7.14 (dd, J=1.93, 8.80 Hz, 1 H) 7.75 - 7.80 (m, 1 H) 7.85 (dd, J=7.43, 2.74 Hz, 1 H) 8.14 (d, J=8.41 Hz, 1 H) 8.19 (dd, J=8.41, 2.35 Hz, 1 H) 8.78 (d, J=1.76 Hz, 1 H) 10.57 (s, 1 H)</td>
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<td>N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-6-chloro-3-methyl limidazo [1,2-a]pyridine-2-carboxamide</td>
<td>MS m/z = 463.9 [M]+&lt;br&gt;1H NMR (400 MHz, DMSO-d6) δ ppm 0.92 (q, J=6.80 Hz, 1 H) 1.07 - 1.21 (m, 1 H) 1.74 (q, J=7.69 Hz, 1 H) 2.81 (s, 3 H) 3.99 - 4.07 (m, 1 H) 5.85 (s, 2 H) 6.19 (t, J=55.90 Hz, 1 H) 7.18 (dd, J=11.64, 9.10 Hz, 1 H) 7.42 (dd, J=9.58, 1.37 Hz, 1 H) 7.69 (d, J=9.59 Hz, 1 H) 7.84 - 7.92 (m, 1 H) 7.95 - 8.03 (m, 1 H) 8.68 (s, 1 H) 10.24 (s, 1 H)</td>
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| 70 | B | N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-chloro-5-methoxypicolinamide | MS *m/z* = 440.8 [M]+  
1H NMR (400 MHz, DMSO-d6)  
δ ppm 0.91 (dt, J=9.24, 6.53 Hz, 1 H)  
1.08 - 1.18 (m, 1 H) 1.67 - 1.76 (m, 1 H) 3.93 (s, 3 H) 3.96 - 4.03 (m, 1 H)  
5.86 (s, 2 H) 6.19 (t, J=56.10 Hz, 1 H) 7.17 - 7.24 (m, 1 H)  
7.72 (d, J=2.54 Hz, 1 H) 7.87 - 8.73 (m, 2 H) 8.34 (d, J=2.54 Hz, 1 H) 10.57 (s, 1 H) |
| 71 | B | N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3,5-dichloropicolinamide | MS *m/z* = 444.8 [M]+  
1H NMR (400 MHz, DMSO-d6)  
δ ppm 0.90 (dt, J=9.19, 6.46 Hz, 1 H) 1.10 - 1.16 (m, 1 H) 1.67 - 1.75 (m, 1 H) 3.96 - 4.01 (m, 1 H) 5.89 (s, 2 H)  
6.19 (t, J=56.10 Hz, 1 H) 7.23 (dd, J=1.93, 8.80 Hz, 1 H) 7.77 (dd, J=6.94, 2.64 Hz, 1 H)  
7.79 - 7.84 (m, 1 H) 8.44 (d, J=1.96 Hz, 1 H) 8.72 (d, J=1.96 Hz, 1 H) 10.78 (s, 1 H) |
| 72 | B | N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-methoxypyrazine-2-carboxamide | MS *m/z* = 407.9 [M]+  
1H NMR (400 MHz, DMSO-d6)  
δ ppm 0.91 (dt, J=9.29, 6.50 Hz, 1 H) 1.12 - 1.18 (m, 1 H) 1.69 - 1.76 (m, 1 H) 4.02 (s, 3 H) 3.99 - 4.05 (m, 1 H)  
5.85 (s, 2 H) 6.19 (t, J=56.10 Hz, 1 H) 7.21 (dd, J=1.74, 8.80 Hz, 1 H) 7.85 (ddd, J=8.80, 4.11, 2.93 Hz, 1 H)  
8.03 (dd, J=7.04, 2.74 Hz, 1 H) 8.41 (d, J=1.37 Hz, 1 H) 8.89 (d, J=1.17 Hz, 1 H) 10.52 (s, 1 H) |
| 73 | B | N-(5-((1(R,S),5(S,R),6(R,S))-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoropyridin-3-yl)-5-chloropicolinamide | MS *m/z* = 411.8 [M]+  
1H NMR (400 MHz, CHLOROFORM-d)  
δ ppm 1.05 (dt, J=9.44, 6.92 Hz, 1 H) 1.41 - 1.47 (m, 1 H) 1.92 (dt, J=9.73, 7.16 Hz, 1 H)  
4.02 (dd, J=6.75, 2.74 Hz, 1 H) 4.84 (br. s., 2 H) 6.19 (t, J=55.40 Hz, 1 H)  
7.90 (dd, J=8.41, 2.35 Hz, 1 H) 8.24 (d, J=8.41 Hz, 1 H) 8.37 (dd, J=8.41, 2.60 Hz, 1 H) 8.58 (d, J=1.96 Hz, 1 H) |
| 74 | B | N-(3-(((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-bromopicolinamide | MS m/z = 454.7 [M]+  
I/H NMR (400 MHz, DMSO-d6) δ ppm 0.92 (dt, J=9.24, 6.53 Hz, 1 H) 1.12 - 1.18 (m, 1 H) 1.69 - 1.78 (m, 1 H) 3.99 - 4.05 (m, 1 H) 5.86 (s, 2 H) 6.19 (t, J=56.10 Hz, 1 H) 7.22 (dd, J=1 1.84, 8.90 Hz, 1 H) 7.84 - 7.90 (m, 1 H) 8.03 (dd, J=7.04, 2.74 Hz, 1 H) 8.08 (d, J=8.22 Hz, 1 H) 8.32 (dd, J=8.41, 2.35 Hz, 1 H) 8.86 (d, J=2.15 Hz, 1 H) 10.69 (s, 1 H) |
| 75 | B | N-(5-((1(R,S),5(S,R),6(R,S))-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoropyridin-3-yl)-5-cyanopicolinamide | MS m/z = 402.9 [M]+  
I/H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.03 (dt, J=9.54, 6.97 Hz, 1 H) 1.40 - 1.46 (m, 1 H) 1.89 (dt, J=9.68, 7.09 Hz, 2 H) 3.98 (td, J=6.80, 2.54 Hz, 1 H) 4.71 (br. s., 2 H) 6.18 (t, J=55.80 Hz, 1 H) 8.22 (dd, J=8.22, 1.96 Hz, 1 H) 8.34 (dd, J=8.41, 2.74 Hz, 1 H) 8.42 (dd, J=8.10, 0.60 Hz, 1 H) 8.69 - 8.72 (m, 1 H) 8.90 (dd, J=1.70, 0.70 Hz, 1 H) 9.87 (s, 1 H) |
| 76 | B | N-(3-(((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloropicolinamide | MS m/z = 410.9 [M]+  
I/H NMR (400 MHz, CHLOROFORM-d) δ ppm 0.92 - 1.00 (m, 1 H) 1.39 - 1.46 (m, 1 H) 1.87 (dt, J=9.44, 7.12 Hz, 1 H) 3.90 - 3.95 (m, 1 H) 4.82 (br. s., 2 H) 6.24 (t, J=56.10 Hz, 1 H) 7.04 (dd, J=1 1.44, 8.90 Hz, 1 H) 7.63 (dd, J=6.65, 2.74 Hz, 1 H) 7.85 (dd, J=8.41, 2.35 Hz, 1 H) 7.95 (ddd, J=8.80, 4.11, 2.93 Hz, 1 H) 8.18 (d, J=8.41 Hz, 1 H) 8.46 (d, J=2.15 Hz, 1 H) 9.72 (s, 1 H) |
| 77 | B | N-(3-(((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-cyanopicolinamide | MS m/z = 420.0 [M+H]+  
I/H NMR (400 MHz, DMSO-d6) δ ppm 0.92 (dt, J=9.19, 6.46 Hz, 1 H) 1.12 - 1.18 (m, 1 H) 1.73 (dt, J=9.24, 6.92 Hz, 1 H) 3.99 - 4.06 (m, 1 H) 5.89 (s, 2 H) 6.20 (t, J=55.90 Hz, 1 H) 7.24 (dd, J=1 1.74, 8.80 Hz, 1 H) 7.88
| 78 | B | N-(3-((1 S,5R,6S)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-2,4-difluorophenyl)-5-methoxypicolinamide |
| 79 | A | N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-2,4-difluorophenyl)-5-methoxypicolinamide |
| 80 | A | N-(3-((1R,5S,6R)-3-amino-5-(methoxymethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-methoxypyrazine-2-carboxamide |
| 81 | A | N-(3-((1 S,5R,6S)-3-amino-5-(methoxymethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-methoxypyrazine-2-carboxamide |

**MS** $m/z = 406.9$ [M]+

$^1$H NMR (300 MHz, DMSO-d$_6$) δ ppm 0.80 - 0.98 (m, 2 H) 1.47 - 1.65 (m, 1 H) 3.94 (s, 3 H) 4.05 - 4.17 (m, 1 H) 4.28 - 4.97 (m, 2 H) 5.56 (s, 2 H) 7.04 - 7.14 (m, 1 H) 7.63 (dd, $J=8.77, 2.78$ Hz, 1 H) 8.00 - 8.04 (m, 1 H) 8.02 - 8.11 (m, 1 H) 8.13 (d, $J=7.87$ Hz, 1 H) 8.44 (d, $J=2.48$ Hz, 1 H) 10.14 (s, 1 H).

**MS** $m/z = 401.9$ [M]+

$^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 0.78 (dt, $J=9.63, 6.33$ Hz, 1 H) 0.88 - 0.96 (m, 1 H) 1.49 - 1.61 (m, 1 H) 3.23 (s, 3 H) 3.48 - 3.75 (m, 2 H) 3.98 - 4.04 (m, 4 H) 5.42 (s, 2 H) 7.08 (dd, $J=8.77, 2.87$ Hz, 1 H) 7.95 (dd, $J=7.34, 2.64$ Hz, 1 H) 8.41 (d, $J=1.37$ Hz, 1 H) 8.89 (d, $J=1.17$ Hz, 1 H) 10.43 (s, 1 H).

**MS** $m/z = 401.9$ [M]+

$^1$H NMR (300 MHz, DMSO-d$_6$) δ ppm 0.80 - 0.89 (m, 1 H) 0.95 - 1.03 (m, 1 H) 1.56 - 1.69 (m, 1 H) 3.29 (s, 3 H) 3.54 - 3.82 (m, 2 H) 4.02 - 4.13 (m, 4 H) 5.48 (s, 2 H) 7.15 (dd, $J=1.93, 8.80$ Hz, 1 H) 7.76 - 7.87 (m, 1 H) 8.01 (dd, $J=7.34, 2.64$ Hz, 1 H)
| 82  | A      | N-((1R,5S,6R)-3-amino-5-(methoxymethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloropicolinamide | MS m/z = 404.9 [M]+  
\( ^1H \) NMR (400 MHz, DMSO-\( d_6 \)) \( \delta \) ppm 0.71 - 0.86 (m, 1 H) 0.88 - 0.98 (m, 1 H) 1.51 - 1.65 (m, 1 H) 3.24 (s, 3 H) 3.53 (d, J=9.78 Hz, 1 H) 3.72 (d, J=9.19 Hz, 1 H) 4.02 (br. s., 1 H) 5.43 (br. s., 2 H) 7.10 (t, J=10.37 Hz, 1 H) 7.79 (br. s., 1 H) 7.96 (d, J=6.85 Hz, 1 H) 8.10 - 8.27 (m, 2 H) 8.79 (s, 1 H) 10.61 (s, 1 H). |
| 83  | A      | N-((1S,5R,6S)-3-amino-5-(methoxymethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloropicolinamide | MS m/z = 404.9 [M]+  
\( ^1H \) NMR (400 MHz, DMSO-\( d_6 \)) \( \delta \) ppm 0.73 - 0.98 (m, 2 H) 1.51 - 1.64 (m, 1 H) 3.24 (s, 3 H) 3.48 - 3.60 (m, 1 H) 3.72 (d, J=8.80 Hz, 1 H) 4.02 (br. s., 1 H) 5.43 (br. s., 2 H) 7.10 (t, J=9.78 Hz, 1 H) 7.78 (br. s., 1 H) 7.96 (d, J=7.24 Hz, 1 H) 8.18 (q, J=8.15 Hz, 2 H) 8.79 (s, 1 H) 10.61 (s, 1 H). |
| 84  | A      | N-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3,5-dimethoxy pyrazine-2-carboxamide | MS m/z = 437.9 [M]+  
\( ^1H \) NMR (300 MHz, DMSO-\( d_6 \)) \( \delta \) ppm 0.90 - 1.03 (m, 1 H) 1.20 (br. s., 1 H) 1.72 - 1.84 (m, 1 H) 4.07 (d, J=3.80 Hz, 7 H) 5.82 (s, 2 H) 6.25 (dt, J=56.42, 1 H) 1.00 Hz, 1 H) 7.25 (dd, J=11.91, 8.70 Hz, 1 H) 7.82 - 7.94 (m, 1 H) 8.00 (s, 1 H) 10.36 (s, 1 H). |
| 85  | A      | N-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-5-chloro-4-fluorophenyl)-5-methoxy pyrazine-2-carboxamide | MS m/z = 423.9 [M]+  
\( ^1H \) NMR (300 MHz, DMSO-\( d_6 \)) \( \delta \) ppm 0.77 - 0.93 (m, 1 H) 0.93 - 1.06 (m, 1 H) 1.47 - 1.66 (m, 1 H) 3.95 - 4.14 (m, 4 H) 4.31 - 4.79 (m, 2 H) 5.67 (s, 2 H) 8.02 (d, J=4.24 Hz, 1 H) 8.11 (d, J=6.10 Hz, 1 H) 8.42 (s, 1 H) 8.90 (s, 1 H) 10.71 (s, 1 H). |
| 86  | A      | N-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-5-chloro-4-fluorophenyl)-5-cyano-3-methoxy picolinamide | MS m/z = 447.8 [M]+  
\( ^1H \) NMR (300 MHz, DMSO-\( d_6 \)) \( \delta \) ppm 0.78 - 0.90 (m, 1 H) 0.93 - 1.03 (m, 1 H) 1.46 - 1.60 (m, 1 H) 3.93 (s, 3 H) 4.02 (br. s., 1 H) 4.38 - 4.71 (m, 2 H) 5.70 (s, 2 H) 7.67 (d, J=5.99 Hz, 1 H) 8.07 (d, J=4.82 Hz, 1 H) 8.23 (s, 1 H). |
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<th>Mass Spectrometry Data</th>
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<td>87 A</td>
<td>N-(3-((lR,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-5-chloro-4-fluorophenyl)-5-(difluoromethoxy)-3-methylpicolinamide</td>
<td>$\delta$ ppm: 0.85 - 0.98 (m, 1 H) 0.99 - 1.11 (m, 1 H) 1.61 (q, $\delta$=8.04 Hz, 1 H) 2.66 (s, 3 H) 4.11 (br. s., 1 H) 4.42 - 4.83 (m, 2 H) 5.74 (s, 2 H) 7.45 (t, $\delta$=71.90 Hz, 1 H) 7.79 (s, 1 H) 7.90 (d, $\delta$=3.80 Hz, 1 H) 8.19 (d, $\delta$=6.14 Hz, 1 H) 8.50 (s, 1 H) 10.78 (s, 1 H).</td>
<td>$m/z = 472.8$ [M]+</td>
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<td>88 A</td>
<td>N-(3-((lR,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-5-chloro-4-fluorophenyl)-5-cyanopicolinamide</td>
<td>$\delta$ ppm: 0.79 - 0.93 (m, 1 H) 0.93 - 1.05 (m, 1 H) 1.48 - 1.64 (m, 1 H) 4.00 - 4.13 (m, 1 H) 4.35 - 4.78 (m, 2 H) 5.68 (s, 2 H) 8.05 (d, $\delta$=7.45 Hz, 1 H) 8.14 (d, $\delta$=5.70 Hz, 1 H) 8.29 (d, $\delta$=8.04 Hz, 1 H) 8.59 (d, $\delta$=8.04 Hz, 1 H) 9.21 (s, 1 H).</td>
<td>$m/z = 417.9$ [M]+</td>
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<td>89 A</td>
<td>N-(3-((lR,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-5-chloro-4-fluorophenyl)-5-methoxy-3-methylpyrazine-2-carboxamide</td>
<td>$\delta$ ppm: 0.79 - 0.91 (m, 1 H) 0.92 - 1.06 (m, 1 H) 1.46 - 1.65 (m, 1 H) 4.00 (s, 3 H) 4.02 - 4.10 (m, 1 H) 4.36 - 4.76 (m, 2 H) 5.67 (s, 2 H) 7.86 (d, $\delta$=5.70 Hz, 1 H) 8.12 (d, $\delta$=6.58 Hz, 1 H) 8.25 (s, 1 H) 10.63 (s, 1 H).</td>
<td>$m/z = 437.9$ [M]+</td>
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<td>90 A</td>
<td>N-(3-((lR,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-5-chloro-4-fluorophenyl)-5-(2,2,2-trifluoroethoxy)pyrazine-2-carboxamide</td>
<td>$\delta$ ppm: 0.79 - 0.92 (m, 1 H) 0.93 - 1.05 (m, 1 H) 1.48 - 1.63 (m, 1 H) 3.99 - 4.13 (m, 1 H) 4.36 - 4.79 (m, 2 H) 5.17 (q, $\delta$=8.82 Hz, 2 H) 5.67 (s, 2 H) 8.04 (d, $\delta$=5.99 Hz, 1 H) 8.12 (d, $\delta$=5.70 Hz, 1 H) 8.63 (s, 1 H) 8.93 (s, 1 H) 10.80 (s, 1 H).</td>
<td>$m/z = 491.9$ [M]+</td>
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<td>91 A</td>
<td>N-(3-((lR,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-5-chloro-4-fluorophenyl)-5-cyano-</td>
<td>$\delta$ ppm: 0.79 - 0.92 (m, 1 H) 0.93 - 1.06 (m, 1 H) 1.46 - 1.63 (m, 1 H) 2.56 (s, 3 H) 3.98 - 4.10 (m, 1 H) 4.38 - 4.75 (m, 2 H) 5.69 (s, 2 H) 7.81 (br. s., 1 H).</td>
<td>$m/z = 431.9$ [M]+</td>
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<td>92</td>
<td>B</td>
<td>N-((3-((1R,5S,6S)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-chloropicolinamide</td>
<td>MS $m/z = 427.0$ [M+H]+&lt;br&gt;HNMR (400 MHz, DMSO-d$_6$) d ppm 10.74 (br, s, 1 H) 8.78 - 8.80 (m, 1 H) 8.14 - 8.26 (m, 3 H) 7.92 (dd, J=8.71, 2.64 Hz, 1 H) 7.44 - 7.50 (m, 1 H) 6.85 - 6.88 (m, 1 H) 6.70 - 6.75 (m, 1 H) 6.57 - 6.60 (m, 1 H) 5.81 - 5.89 (m, 2 H) 3.98 (t, J=7.14 Hz, 1 H) 1.85 - 1.93 (m, 1 H) 1.07 - 1.15 (m, 1 H) 0.91 - 1.00 (m, 1 H)</td>
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<td>93</td>
<td>B</td>
<td>N-((3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-cyanopicolinamide</td>
<td>MS $m/z = 418.0$ [M+H]+&lt;br&gt;HNMR (400 MHz, CHLOROFORM-d) d ppm 9.64 - 9.71 (m, 1 H) 8.94 - 8.96 (m, 1 H) 8.94 (s, 1 H) 7.94 - 8.01 (m, 1 H) 7.69 - 7.74 (m, 1 H) 7.06 - 7.13 (m, 1 H) 6.38 (s, 1 H) 6.24 (s, 1 H) 6.10 (s, 1 H) 3.91 - 3.96 (m, 1 H) 1.83 - 1.91 (m, 1 H) 1.40 - 1.46 (m, 1 H) 0.93 - 1.01 (m, 1 H)</td>
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<td>94</td>
<td>B</td>
<td>N-((3-((1R,5R,6S)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-cyanopicolinamide</td>
<td>MS $m/z = 418.0$ [M+H]+&lt;br&gt;HNMR (400 MHz, CHLOROFORM-d) d ppm 9.64 - 9.71 (m, 1 H) 8.94 - 8.96 (m, 1 H) 8.94 (s, 1 H) 7.94 - 8.01 (m, 1 H) 7.69 - 7.74 (m, 1 H) 7.06 - 7.13 (m, 1 H) 6.38 (s, 1 H) 6.24 (s, 1 H) 6.10 (s, 1 H) 3.91 - 3.96 (m, 1 H) 1.83 - 1.91 (m, 1 H) 1.40 - 1.46 (m, 1 H) 0.93 - 1.01 (m, 1 H)</td>
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| 95 | B | N-((3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(prop-2-yn-1-yl)oxy)pyrazine-2-carboxamide trifluoroacetate | MS $m/z = 431.0$ [M]+<br>HNMR (400 MHz, DMSO-d$_6$): δ 10.85 (s, 1 H), 10.70 (br s, 1 H), 9.47 (br s, 1 H), 8.93 (d, J=1.4 Hz, 1 H), 8.52 (d, J=1.4 Hz, 1 H), 8.24 (br s, 1 H), 8.18 (dd, J=7.2, 2.5 Hz, 1 H), 7.96 - 8.07 (m, 1 H), 7.44 (dd, J=1.9, 9.0 Hz, 1 H), 6.58 - 6.93 (m, 1 H), 5.12 - 5.22 (m, 2 H), 4.69 (br s, 1 H), 3.62 - 3.71 (m, 1 H), 2.04 - 2.19 (m, 1 H), 1.63 (br s, 1 H), 1.30 (q, J=7.9 Hz, 1 H); 19F NMR (377 MHz, DMSO-d$_6$):
δ -73.76 (s, 3 F), -117.16 (s, 1 F), -126.50 (d, J=279 Hz, 1 F), -128.54 (d, J=279 Hz, 1 H).

96  B  N-(3-(((lR,S), (5S,R), (6R,S))-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4. 1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-(but-2-yn-1-yl)oxy)pyrazine-2-carboxamide trifluoroacetate

MS m/z = 446.0 [M+H]+

1H NMR (400 MHz, DMSO-d6): d 10.83 (s, 1 H), 10.77 (br s, 1 H), 9.45 (br s, 1 H), 8.92 (d, J=1.2 Hz, 1 H), 8.49 (d, J=1.2 Hz, 1 H), 8.37 (br s, 1 H), 8.18 (dd, J=7.1, 1.4 Hz, 1 H), 8.02 (m, 1 H), 7.44 (dd, J=1.9, 9.0 Hz, 1 H), 6.74 (t, J=51 Hz, 1 H), 5.12 (q, J=2.2 Hz, 2 H), 4.68 (br s, 1 H), 2.12 (q, J=8.1 Hz, 1 H), 1.87 (t, J=2.3 Hz, 3 H), 1.63 (t, J=6.3 Hz, 1 H), 1.30 (q, J=8.1 Hz, 1 H); 19F NMR (377 MHz, DMSO-d6): d -73.82 (s, 3 F), -117.20 (br s, 1 F), -126.48 (d, J=287 Hz, 1 F), -128.55 (d, J=287 Hz, 1 F).

97  B  N-(3-(((lR,S), (5S,R), (6R,S))-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4. 1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-cyanopicolinamide trifluoroacetate

MS m/z = 427.0 [M+H]+

1H NMR (400 MHz, CD3OD): d 8.75 (d, J=2.2 Hz, 1 H), 8.43 (d, J=2.3 Hz, 1 H), 8.24 (d, J=8.4 Hz, 1 H), 8.12 (dd, J=8.4, 2.3 Hz, 1 H), 7.87 (dd, J=8.7, 2.4 Hz, 1 H), 7.64 (d, J=8.8 Hz, 1 H), 7.11 (t, J=54.8 Hz, 1 H), 4.61 (td, J=6.7, 2.5 Hz, 1 H), 2.45 (dt, J=9.8, 7.2 Hz, 1 H), 1.66 (t, J=7.7 Hz, 1 H), 1.42 (dd, J=9.9, 8.3, 6.5 Hz, 1 H); 19F NMR (377 MHz, CD3OD): d -76.95 (br s, 3 F), -127.45 (d, J=280.1 Hz, 1 F), -129.82 (d, J=281.9 Hz, 1 F).

98  B  N-(3-(((lR,S), (5S,R), (6R,S))-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4. 1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-cyanopicolinamide trifluoroacetate

MS m/z = 418.0 [M+H]+

1H NMR (400 MHz, CD3OD): d 9.09 (dd, J=2.0, 0.8 Hz, 1 H), 8.43 - 8.50 (m, 1 H), 8.37 - 8.42 (m, 1 H), 7.90 (dd, J=8.6, 2.5 Hz, 1 H), 7.66 (d, J=8.6 Hz, 1 H), 7.11 (t, J=54.8 Hz, 1 H), 4.62 (td, J=6.7, 2.7 Hz, 1 H), 2.45 (dt, J=9.9, 7.2 Hz, 1 H), 1.66 (t, J=7.7 Hz, 1 H), 1.43 (dd, J=9.9, 8.3, 6.3 Hz, 1 H); 19F NMR (377 MHz, CD3OD): d -76.97 (br s, 3 F), -127.42 (d, J=283.1 Hz, 1 F), -129.82 (d, J=284.3 Hz, 1 F).
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<td>99</td>
<td>B</td>
<td>N-(3-((IR,5S,6R)-3-amino-5-&lt;br&gt;(difluoromethyl)-2-oxa-&lt;br&gt;4-azabicyclo[4.1.0]hept-&lt;br&gt;3-en-5-yl)-4-chlorophenyl)-5-&lt;br&gt;chloropicolinamide</td>
<td>426.8 [M]+</td>
<td>m/z = 426.8 [M]+&lt;br&gt;1H NMR (400 MHz, DMSO-d6) d ppm 10.75 (s, 1 H) 8.78 - 8.80 (m, 1 H) 8.14 - 8.25 (m, 3 H) 7.91 (br. s., 1 H) 7.44 - 7.50 (m, 1 H) 6.87 (s, 1 H) 6.73 (s, 1 H) 6.57 - 6.60 (m, 1 H) 5.82 - 5.87 (m, 2 H) 3.95 - 4.02 (m, 1 H) 1.85 - 1.93 (m, 1 H) 1.07 - 1.14 (m, 1 H) 0.91 - 0.99 (m, 1 H)</td>
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<td>100</td>
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<td>N-(3-((IR,5S,6R)-3-amino-5-&lt;br&gt;(difluoromethyl)-2-oxa-&lt;br&gt;4-azabicyclo[4.1.0]hept-&lt;br&gt;3-en-5-yl)-4-chlorophenyl)-5-&lt;br&gt;methoxypicolinamide</td>
<td>422.9 [M]+</td>
<td>m/z = 422.9 [M]+&lt;br&gt;1H NMR (400 MHz, CDC13): δ 9.82 (s, IH), 8.20 (s, IH), 8.17-8.19 (m, IH), 8.01 (dd, J=2.74, 8.61 Hz, IH), 7.78 (d, J=2.74 Hz, IH), 7.28-7.39 (m, 2H), 6.83 (t, J=55.95 Hz, IH), 4.70 (br. s., 2H), 3.94 (s, 3H), 3.82-3.90 (m, IH), 2.08 (td, J=7.14, 9.78 Hz, IH), 1.38 (t, J=7.04 Hz, IH), 0.91-1.03 (m, IH); 19F NMR (377 MHz, CDC13): δ -126.39 (d, J=278.35 Hz, IF), -129.09 (d, J=278.40 Hz, IF),</td>
</tr>
<tr>
<td>101</td>
<td>A</td>
<td>N-(3-((IR,5S,6R)-3-amino-5-&lt;br&gt;(difluoromethyl)-2-oxa-&lt;br&gt;4-azabicyclo[4.1.0]hept-&lt;br&gt;3-en-5-yl)-4-chlorophenyl)-5-&lt;br&gt;methoxy-3-methylpicolinamide</td>
<td>437.0 [M]+</td>
<td>m/z = 437.0 [M]+&lt;br&gt;1H NMR (400 MHz, CDC13): δ 10.04 (s, IH), 8.04 (d, J=8.79 Hz, IH), 8.00 (s, IH), 7.64 (d, J=2.54 Hz, IH), 7.30 (d, J=8.80 Hz, IH), 7.05 (d, J=2.35 Hz, IH), 6.82 (t, J=55.95 Hz, IH), 4.79 (br. s., 2H), 3.92 (s, 3H), 3.82-3.89 (m, IH), 2.77 (s, 3H), 2.09 (td, J=7.19, 9.68 Hz, IH), 1.38 (t, J=7.04 Hz, IH), 0.97 (td, J=6.82, 9.63 Hz, IH); 19F NMR (377 MHz, CDC13): δ -126.34 (d, J=278.40 Hz, IF), -129.10 (d, J=278.30 Hz, IF)</td>
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<td>102</td>
<td>B</td>
<td>N-(3-((IR,5S,6R)-3-amino-5-&lt;br&gt;(difluoromethyl)-2-oxa-&lt;br&gt;4-azabicyclo[4.1.0]hept-&lt;br&gt;3-en-5-yl)-4-chlorophenyl)-5-(oxazol-4-ylmethoxy)pyrazine-2-carboxamide</td>
<td>490.9 [M]+</td>
<td>m/z = 490.9 [M]+&lt;br&gt;1H NMR (400 MHz, CDC13): δ 9.42 (s, IH), 8.98 (s, IH), 8.13 (s, IH), 7.99 (dd, J=2.54, 8.61 Hz, IH), 7.93 (s, IH), 7.82 (s, IH), 7.74 (d, J=2.35 Hz, IH), 7.31 (d, J=8.61 Hz, IH), 6.82 (t, J=55.20 Hz, IH), 5.46 (s, 2H), 4.88 (br s, 2H), 3.87 (t, J=5.58 Hz, IH), 2.05-2.14 (m, IH), 1.39 (br s, IH), 0.92-1.04 (m, IH); 19F NMR (377 MHz, CDC13): δ -126.1 (d, J=278.40 Hz, IF), -129.2 (d, J=278.30 Hz, IF),</td>
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103 A  N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-methoxypyrimidine-2-carboxamide

MS m/z = 407.9 [M]+
1H NMR (400 MHz, CDCl3): δ 9.56-9.89 (m, 2H), 7.90-8.08 (m, 1H), 7.67-7.83 (m, 1H), 7.05-7.17 (m, 1H), 6.24 (t, J=54.80 Hz, 1H), 4.49 (br s, 2H), 4.02 (s, 3H), 3.93-3.99 (m, 1H), 1.85-1.91 (m, 1H), 1.39-1.48 (m, 1H), 0.92-1.05 (m, 1H); 19F NMR (377 MHz, CDCl3): δ -115.77 (dd, J=8.35, 10.73 Hz, 1F), -127.43 (d, J=287.29 Hz, 1F), -129.55 (d, J=275.96 Hz, 1F).

104 A  N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-methoxypyrimidine-2-carboxamide

MS m/z = 424.0 [M+H]+
1H NMR (400 MHz, CDCl3): δ 9.81 (s, 1H), 8.51 (s, 2H), 8.02 (dd, J=2.54, 8.61 Hz, 1H), 7.91 (d, J=2.54 Hz, 1H), 7.41 (d, J=8.61 Hz, 1H), 6.84 (t, J=55.40 Hz, 1H), 4.73 (br s, 2H), 4.03 (s, 3H), 3.89-3.93 (m, 1H), 2.11 (td, J=7.24, 9.78 Hz, 1H), 1.40 (t, J=7.24 Hz, 1H), 1.01 (td, J=6.75, 9.78 Hz, 1H); 19F NMR (377 MHz, CDCl3): δ -126.31 (d, J=278.95 Hz, 1F), -128.99 (d, J=278.95 Hz, 1F).

105 C  N-(6-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-5-fluoropyridin-2-yl)-5-chloropicolinamide

MS m/z = 394 [M+H]+
1H NMR (CHLOROFORM-d) Shift: 8.63 (d, J=2.3 Hz, 1H), 8.34 (dd, J=8.9, 3.0 Hz, 1H), 8.24 (d, J=8.4 Hz, 1H), 7.91 (dd, J=8.4, 2.3 Hz, 1H), 7.50 (dd, J=10.5, 8.9 Hz, 1H), 5.11 (ddt, J=46.6, 8.6, 1.0 Hz, 1H), 4.60 (dd, J=46.9, 8.6 Hz, 1H), 4.12-4.21 (m, 1H), 1.57-1.83 (m, 3H), 1.18 (td, J=6.9, 2.3 Hz, 1H), 1.02 (dt, J=9.8, 6.7 Hz, 1H).

106 C  N-(6-((lS,5R,6S)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-5-fluoropyridin-2-yl)-5-chloropicolinamide

MS m/z = 394 [M+H]+
1H NMR (CHLOROFORM-d) Shift: 8.63 (t, J=2.2 Hz, 1H), 8.33 (dt, J=8.8, 2.8 Hz, 1H), 8.25 (dd, J=8.3, 2.2 Hz, 1H), 7.92 (dt, J=8.3, 2.6 Hz, 1H), 7.46-7.55 (m, 1H), 5.10 (ddd, J=46.8, 8.6, 2.0 Hz, 1H), 4.60 (ddd, J=46.9, 8.6, 2.2 Hz, 1H), 4.10-4.22 (m, 1H), 1.57-1.83 (m, 3H), 1.10-1.22 (m, 1H), 0.96-1.06 (m, 1H).
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<th>No.</th>
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<th>MS ( m/z = )</th>
<th>Spectroscopic Data</th>
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<td>107</td>
<td>N-(3-(((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-chloropicolinamide</td>
<td>428.9 [M]+</td>
<td>1H NMR (CHLOROFORM-d) Shift: 9.70 (br. s, 1H), 8.48 (dd, J=1.8, 0.4 Hz, 1H), 8.19 (dd, J=8.3, 0.4 Hz, 1H), 8.03 (dd, J=11.7, 6.9, 2.7 Hz, 1H), 7.87 (dd, J=8.3, 2.3 Hz, 1H), 7.24-7.30 (m, 1H), 6.18 (td, J=55.7, 1.0 Hz, 1H), 4.76 (br. s, 2H), 3.94 (td, J=6.8, 2.8 Hz, 1H), 1.80-1.92 (m, 1H), 1.38-1.47 (m, 1H), 0.93-1.03 (m, 1H)</td>
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<td>108</td>
<td>N-(3-(((1S,5R,6S)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-chloropicolinamide</td>
<td>428.9 [M]+</td>
<td>1H NMR (CHLOROFORM-d) Shift: 9.69 (br. s, 1H), 8.48 (d, J=2.0 Hz, 1H), 8.18 (d, J=8.3 Hz, 1H), 8.03 (dd, J=11.7, 7.0, 2.8 Hz, 1H), 7.87 (dd, J=8.3, 2.3 Hz, 1H), 6.18 (td, J=55.8, 1.2 Hz, 1H), 4.82 (br. s, 2H), 3.93 (td, J=6.8, 2.6 Hz, 1H), 3.49 (s, 1H), 1.79-1.93 (m, 1H), 1.38-1.47 (m, 1H), 0.92-1.03 (m, 1H)</td>
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<td>109</td>
<td>N-(3-(((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-cyanopicolinamide</td>
<td>419.9 [M]+</td>
<td>1H NMR (CHLOROFORM-d) Shift: 9.62 (br. s, 1H), 8.80 (dd, J=2.0, 0.8 Hz, 1H), 8.37 (dd, J=8.2, 0.7 Hz, 1H), 8.20 (dd, J=8.1, 2.0 Hz, 1H), 8.02 (dd, J=11.5, 6.9, 2.8 Hz, 1H), 7.21-7.28 (m, 1H), 6.20 (td, J=55.8, 1.3 Hz, 1H), 4.94 (br. s, 2H), 3.86-3.98 (m, 1H), 1.77-1.92 (m, 1H), 1.38-1.49 (m, 1H), 0.91-1.08 (m, 1H)</td>
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<td>110</td>
<td>N-(3-(((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-4-chloro-1-(difluoromethyl)-1H-pyrazole-3-carboxamide</td>
<td>467.9 [M]+</td>
<td>1H NMR (MeOH) Shift: 8.40 (s, 1H), 7.93 (dd, J=11.8, 6.9, 2.7 Hz, 1H), 7.37-7.80 (m, 2H), 6.22 (t, J=55.8 Hz, 1H), 4.04-4.14 (m, 1H), 1.84-1.95 (m, 1H), 1.28-1.41 (m, 1H), 0.95-1.06 (m, 1H)</td>
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<td>111</td>
<td>N-(3-(((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(prop-2-yn-1-yl)oxy)pyrazine-2-carboxamide</td>
<td>449.9 [M]+</td>
<td>1H NMR (CHLOROFORM-d) Shift: 9.00 (d, J=1.3 Hz, 1H), 8.22 (d, J=1.3 Hz, 1H), 8.09 (dd, J=11.7, 6.9, 2.7 Hz, 1H), 7.23 (dt, J=5.3, 2.4 Hz, 1H), 6.18 (td, J=55.7, 0.9 Hz, 1H), 5.09 (d, J=2.5 Hz, 2H), 3.91-4.00 (m, 1H), 2.58 (t, J=2.4 Hz, 1H), 2.45 (br. s., 3H), 1.78-1.91 (m, 1H), 1.40 (t, J=5.8 Hz, 3H)</td>
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</table>
| 112 B | N-(3-(((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-methoxyprazin-2-carboxamide | ![Chemical Structure](image) **MS** $m/z = 425.9$ [M+H]$^+$  
1H NMR (CHLOROFORM-d) Shift: 9.32 (br. s, 1H), 8.95 (d, J=1.3 Hz, 1H), 7.92-8.10 (m, 2H), 7.22 (dt, J=5.2, 2.5 Hz, 1H), 6.18 (td, J=5.7, 1.0 Hz, 1H), 4.88 (br. s., 2H), 4.07 (s, 3H), 3.86-3.98 (m, 1H), 1.79-1.91 (m, 1H), 1.42 (t, J=6.4 Hz, 1H), 0.91-1.02 (m, 1H) |
| 113 B | N-(3-(((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-cyanopicolinamide | ![Chemical Structure](image) **MS** $m/z = 419.9$ [M]$^+$  
1H NMR (CHLOROFORM-d) Shift: 9.51 (br. s, 1H), 8.76 (d, J=0.8 Hz, 1H), 8.35 (d, J=8.2 Hz, 1H), 8.19 (dd, J=8.2, 1.8 Hz, 1H), 7.98 (dd, J=11.4, 7.0, 2.5 Hz, 1H), 7.16-7.21 (m, 1H), 6.22 (t, J=5.8 Hz, 1H), 5.20 (br. s., 2H), 3.88-3.95 (m, 1H), 1.80-1.89 (m, 1H), 1.42-1.49 (m, 1H), 0.81-1.08 (m, 1H) |
| 114 B | N-(3-(((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-4-chloro-1-(difluoromethyl)-1H-pyrazole-3-carboxamide | ![Chemical Structure](image) **MS** $m/z = 467.8$ [M]$^+$  
1H NMR (CHLOROFORM-d) Shift: 8.46 (s, 1H), 8.00-8.11 (m, 1H), 7.90 (s, 1H), 6.87-7.31 (m, 2H), 6.16 (td, J=55.7, 1.3 Hz, 1H), 4.96 (br. s., 1H), 3.88-3.97 (m, 1H), 1.79-1.90 (m, 1H), 1.37-1.45 (m, 1H), 0.91-1.03 (m, 1H) |
| 115 B | N-(3-(((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(prop-2-yn-1-yl)oxoyprazin-2-carboxamide | ![Chemical Structure](image) **MS** $m/z = 449.9$ [M]$^+$  
1H NMR (CHLOROFORM-d) Shift: 9.00 (d, J=1.3 Hz, 1H), 8.20 (d, J=1.2 Hz, 1H), 8.07 (ddd, J=11.7, 6.9, 2.6 Hz, 1H), 7.24 (dt, J=5.3, 2.4 Hz, 1H), 6.17 (td, J=55.5, 1.3 Hz, 1H), 5.09 (d, J=2.3 Hz, 2H), 3.91-3.99 (m, 1H), 2.56 (t, J=2.4 Hz, 1H), 1.80-1.90 (m, 2H), 1.61 (br. s., 2H), 1.40 (t, J=6.3 Hz, 1H), 0.93-1.04 (m, 1H) |
| 116 | B | N-(3-((R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-(fluorophenyl)-5-bromopicolinamid | MS m/z = 472.8 [M]+  
IH NMR (CHLOROFORM-d)  
Shift:  
9.55 (br, s, IH), 8.51 (d, J=1.8 Hz, IH), 7.91-8.12 (m, 3H), 7.15-7.24 (m, IH), 6.22 (tdd, J=56.0, 0.7 Hz, IH), 5.23 (br, s, 2H), 3.86-3.95 (m, IH), 1.80-1.90 (m, IH), 1.40-1.49 (m, IH), 0.91-1.02 (m, IH) |
| 117 | B | N-(3-((R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-(fluorophenyl)-5-chloropicolinamide | MS m/z = 393 [M]+H+  
IH NMR (400 MHz, CDC13) δ 0.87-0.95 (m, IH), 1.19-1.27 (m, 1H), 1.72-1.80 (m, 1H), 3.95 (ddd, J = 6.11, 4.84, 1.37 Hz, 1H), 4.35 (br, 2H), 4.58-4.69 (m, IH), 4.70-4.82 (m, IH), 7.07 (dd, J = 11.54, 8.80 Hz, IH), 7.63 (dd, J = 6.85, 2.74 Hz, IH), 7.84-7.92 (m, IH), 7.92-7.96 (m, IH), 8.20 (d, J = 8.41 Hz, IH), 8.51 (d, J = 1.76 Hz, IH), 9.77 (s, IH) |
| 118 | B | N-((S,5R,6S)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-(fluorophenyl)-5-chloropicolinamide | MS m/z = 393 [M]+H+  
IH NMR (400 MHz, CDC13) δ 0.91 (d, J = 9.59 Hz, IH), 1.21 (d, J = 2.54 Hz, IH), 1.75 (d, J = 9.78 Hz, IH), 3.90-4.00 (m, IH), 4.36 (s br, 2H), 4.58-4.69 (m, IH), 4.70-4.81 (m, IH), 7.08 (dd, J = 11.54, 8.80 Hz, IH), 7.63 (dd, J = 6.85, 2.74 Hz, IH), 7.86 (dd, J = 8.41, 2.35 Hz, IH), 7.95 (td, J = 4.40, 1.17 Hz, IH), 8.22 (d, J = 8.41 Hz, IH), 8.53 (d, J = 2.35 Hz, IH), 9.79 (br s, IH) |
| 119 | A | N-(3-((R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-(fluorophenyl)-5-chloropyrimidine-2-carboxamide | MS m/z = 412.0 [M]+H+  
IH NMR (400MHz, CHLOROFORM-d) δ = 9.63 (s, 1H), 8.82 (s, 2H), 7.98 (ddd, J = 2.9, 4.1, 8.8 Hz, 1H), 7.68 (dd, J = 2.7, 6.7 Hz, 1H), 7.07 (dd, J = 8.8, 11.5 Hz, 1H), 6.43 - 6.04 (m, 1H), 4.76 (br, s, 2H), 3.92 (br, s, 1H), 1.86 (td, J = 7.1, 9.3 Hz, 1H), 1.48 - 1.38 (m, 1H), 1.01 - 0.90 (m, 1H) |
| 120 | A | N-(3-((R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-(fluorophenyl)-3-methyl- | MS m/z =490.1 [M]+H+  
¾ NMR (400 MHz, CHLOROFORM) δ ppm 0.78 - 1.03 (m, 1H), 1.39 - 1.54 (m, 1H), 1.76 - 2.01 (m, 1H), 2.89 (s, 3H), 3.79 - 4.02 (m, 1H), 4.67 - 5.08 (m, 2H), 5.32 (br, 2H) |
5-(2,2,2-trifluoroethoxy)pyrazine-2-carboxamide

**121 B**

N-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluoro-5-methylphenyl)-5-chloropicolinamide

MS *m/z* = 424.9 [M+H]+

1H NMR (300 MHz. CHLOROFORM-d) δ 0.92 - 1.05 (m, 1 H) 1.39 - 1.47 (m, 1 H) 1.84 - 1.94 (m, 1 H) 2.31 (d, J=2.48 Hz, 3 H) 3.94 - 4.02 (m, 1 H) 6.06 - 6.48 (m, 2 H) 7.45 (dd, J=6.14, 2.92 Hz, 1 H) 7.84 - 7.93 (m, 2 H) 8.19 - 8.24 (m, 1 H) 8.53 (d, J=1.75 Hz, 1 H) 9.74 (s, 1 H)

**122 C**

N-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-(difluoromethyl)-3-methylpicolinamide

MS *m/z* = 439 [M+H]+

1H NMR (400 MHz, CHLOROFORM-d) δ ppm 0.80 - 0.92 (m, 1 H) 0.95 - 1.05 (m, 1 H) 1.97 - 2.07 (m, 1 H) 2.86 (s, 3 H) 3.96 (d, J=4.70 Hz, 1 H) 4.78 - 4.89 (m, 1 H) 4.90 - 5.00 (m, 1 H) 6.52 - 7.02 (m, 2 H) 7.40 (d, J=8.80 Hz, 1 H) 7.76 (d, J=14.08 Hz, 2 H) 8.04 (d, J=9.00 Hz, 1 H) 8.58 (br. s., 1 H) 10.20 (br. s., 1 H)

**123 C**

N-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluoro-5-methylphenyl)-5-chloropicolinamide

MS *m/z* = 424.9 [M]+

1H NMR (300 MHz, CHLOROFORM-d) δ ppm 0.92 - 1.05 (m, 1 H) 1.39 - 1.47 (m, 1 H) 1.84 - 1.94 (m, 1 H) 2.31 (d, J=2.48 Hz, 3 H) 3.94 - 4.02 (m, 1 H) 6.06 - 6.48 (m, 2 H) 7.45 (dd, J=6.14, 2.92 Hz, 1 H) 7.84 - 7.93 (m, 2 H) 8.19 - 8.24 (m, 1 H) 8.53 (d, J=1.75 Hz, 1 H) 8.74 (s, 1 H)

**124 C**

N-((1S,5R,6S)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluoro-5-methylphenyl)-5-chloropicolinamide

MS *m/z* = 424.9 [M]+

1H NMR (300 MHz, CHLOROFORM-d) δ ppm 0.92 - 1.05 (m, 1 H) 1.39 - 1.48 (m, 1 H) 1.87 - 1.94 (m, 1 H) 2.30 (d, J=2.63 Hz, 3 H) 3.96 (s, J=5.55 Hz, 1 H) 6.07 - 6.49 (m, 1 H) 7.44 (dd, J=6.36, 2.70 Hz, 1 H) 7.83 - 7.94 (m, 2 H) 8.21 (d, J=8.33 Hz, 1 H) 8.52 (d, J=2.34 Hz, 1 H) 9.73 (s, 1 H)
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| 125 | C | N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-3-methyl-5-(trifluoromethyl)picolinamide | MS m/z = 457 [M+H]+  
1H NMR (300 MHz, DMSO-d6) δ ppm 0.80 - 0.90 (m, 1 H) 0.93 (d, J=3.80 Hz, 1 H) 1.60 - 1.74 (m, 1 H) 2.59 (s, 3 H) 3.90 - 4.00 (m, 1 H) 4.65 (s, 1 H) 4.80 (s, 1 H) 5.60 (s, 2 H) 7.43 (d, J=8.48 Hz, 1 H) 7.86 (dd, J=8.62, 2.48 Hz, 1 H) 8.01 (d, J=2.34 Hz, 1 H) 8.29 (s, 1 H) 8.90 (s, 1 H) 10.75 (s, 1 H) |
| 126 | C | N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-(difluoromethoxy)-3-methylpicolinamide | MS m/z = 454.9 [M]+  
1H NMR (300 MHz, DMSO-d6) δ ppm 0.68 - 1.09 (m, 2 H) 1.67 (br. s., 1 H) 2.59 (br. s., 3 H) 3.97 - 4.16 (m, 1 H) 4.54 - 4.71 (m, 1 H) 4.72 - 4.90 (m, 1 H) 5.59 (br. s., 2 H) 7.00 - 7.53 (m, 2 H) 7.61 - 7.91 (m, 2 H) 7.92 - 8.17 (m, 1 H) 8.25 - 8.56 (m, 1 H) 10.58 (br. s., 1 H) |
| 127 | B | N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-3-chloro-5-cyanopicolinamide | MS m/z = 433.8 [M]+  
1H NMR (300 MHz, CHLOROFORM-d) δ 0.94 - 1.06 (m, 1 H) 1.12 - 1.22 (m, 1 H) 1.96 - 2.10 (m, 1 H) 3.89 - 4.04 (m, 1 H) 4.71 - 4.89 (m, 1 H) 4.90 - 5.08 (m, 1 H) 7.40 (d, J=7.89 Hz, 1 H) 7.69 (br. s., 1 H) 8.07 (d, J=9.50 Hz, 1 H) 8.16 (br. s., 1 H) 8.74 (br. s., 1 H) 9.73 (br. s., 1 H) |
| 128 | C | N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-chloro-3-(methoxymethyl)picolinamide | MS m/z = 452.9 [M]+  
1H NMR (300 MHz, CHLOROFORM-d) δ ppm 0.92 - 1.04 (m, 1 H) 1.17 (s, 1 H) 1.94 - 2.05 (m, 1 H) 3.56 (s, 3 H) 3.89 - 4.00 (m, 1 H) 4.73 - 4.86 (m, 1 H) 4.90 - 5.01 (m, 1 H) 5.10 (s, 1 H) 7.41 (d, J=8.77 Hz, 1 H) 7.72 (s, 1 H) 8.01 (d, J=7.45 Hz, 1 H) 8.22 (s, 1 H) 8.44 (s, 1 H) 10.06 (s, 1 H) |
| 129 | B | N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-3-fluoropicolinamide | MS m/z = 428. [M]+  
1H NMR (300 MHz, CHLOROFORM-d) δ ppm 0.94 - 1.07 (m, 1 H) 1.44 (br. s., 1 H) 1.86 - 1.97 (m, 1 H) 4.00 (br. s., 1 H) 6.02 - 6.44 (m, 1 H) 7.03 - 7.18 (m, 1 H) 7.50 - 7.71 (m, 2 H) 7.97 - 8.06 (m, 1 H) 8.38 (s, 1 H) 9.64 (br. s., 1 H) |
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<td>130</td>
<td>N-(3-((IR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-methoxy-3-methylpicolinamide</td>
<td>407 [M+H]+</td>
<td>0.91 - 1.04 (m, 1H) 1.22 (d, J=6.28 Hz, 1H) 1.74 - 1.86 (m, 1H) 4.00 (s, 3H) 4.08 (br. s., 1H) 5.92 (s, 2H) 6.03 - 6.51 (m, 1H) 7.18 - 7.34 (m, 1H) 7.68 (d, J=8.92 Hz, 1H) 7.94 (d, J=6.58 Hz, 1H) 8.19 (d, J=8.77 Hz, 1H) 8.45 (s, 1H) 10.52 (s, 1H)</td>
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<td>131</td>
<td>N-(3-((IR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-methoxy-3-methylpicolinamide</td>
<td>421 [M+H]+</td>
<td>0.84 - 0.98 (m, 1H) 1.11 - 1.22 (m, 1H) 1.67 - 1.81 (m, 1H) 2.62 (s, 3H) 3.91 (s, 3H) 3.97 - 4.07 (m, 1H) 5.86 (s, 2H) 5.96 - 6.42 (m, 1H) 7.13 - 7.25 (m, 1H) 7.41 (s, 1H) 7.87 (d, J=6.14 Hz, 2H) 8.22 (s, 1H) 10.35 - 10.47 (m, 1H)</td>
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<td>132</td>
<td>N-(3-((IR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluoro-5-methylphenyl)-5-cyano-3-methylpicolinamide</td>
<td>430 [M+H]+</td>
<td>0.86 - 1.07 (m, 1H) 1.08 - 1.26 (m, 1H) 1.63 - 1.87 (m, 1H) 2.32 (s, 3H) 2.60 (s, 3H) 4.04 (br. s., 1H) 5.90 (s, 2H) 6.05 - 6.55 (m, 1H) 7.69 (d, J=3.95 Hz, 1H) 7.84 (d, J=6.14 Hz, 1H) 8.44 (s, 1H) 9.03 (s, 1H) 10.70 (s, 1H)</td>
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<td>133</td>
<td>N-(3-((IR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluoro-5-methylphenyl)-3-chloro-5-cyano picolinamide</td>
<td>449.9 [M]+</td>
<td>0.80 - 1.02 (m, 1H) 1.11 (br. s., 1H) 1.69 (q, J=7.70 Hz, 1H) 2.27 (s, 3H) 3.83 - 4.05 (m, 1H) 5.87 (s, 2H) 5.99 - 6.44 (m, 1H) 7.52 (d, J=5.12 Hz, 1H) 7.75 (d, J=6.14 Hz, 1H) 8.79 (s, 1H) 9.09 (s, 1H) 10.83 (s, 1H)</td>
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A-1813-WO-PCT

MS \textit{m/z} = 454.9 \text{ [M]+}

\textit{1H NMR} (300 MHz, DMSO-d\textsubscript{6}) \delta ppm 0.83 - 0.95 (m, 1 H) 1.06 - 1.15 (m, 1 H) 1.62 - 1.75 (m, 1 H) 2.25 (s, 3 H) 3.89 (s, 3 H) 3.93 - 4.01 (m, 1 H) 5.83 (s, 2 H) 6.01 - 6.41 (m, 1 H) 7.56 (d, \textit{J}=5.55 Hz, 1 H) 7.73 (d, \textit{J}=4.97 Hz, 1 H) 7.83 (s, 1 H) 8.25 (s, 1 H) 10.41 (s, 1 H)

MS \textit{m/z} = 458.9 \text{ [M]+}

\textit{1H NMR} (300 MHz, DMSO-d\textsubscript{6}) \delta ppm 0.77 - 0.99 (m, 1 H) 1.03 - 1.21 (m, 1 H) 1.58 - 1.81 (m, 1 H) 2.26 (s, 3 H) 3.83 - 4.05 (m, 1 H) 5.86 (s, 2 H) 5.97 - 6.49 (m, 1 H) 7.54 (d, \textit{J}=4.97 Hz, 1 H) 7.75 (d, \textit{J}=5.99 Hz, 1 H) 8.43 (s, 1 H) 8.71 (s, 1 H) 10.69 (s, 1 H)

\textit{1H NMR} (400 MHz, DMSO-d\textsubscript{6}) \delta ppm 0.81 - 1.03 (m, 2 H), 1.62 (dt, \textit{J}=9.73, 6.97 Hz, 1 H), 3.94 - 4.06 (m, 1 H) 4.71 (dt, \textit{J}=47.8, 9.0 Hz, 2 H), 5.62 (s, 2 H), 8.03 (dd, \textit{J}=1.25, 2.45 Hz, 1 H), 8.09 (br. s., 1 H), 8.29 (dd, \textit{J}=8.22, 0.78 Hz, 1 H), 8.58 (dd, \textit{J}=1.7 Hz, 1 H), 9.21 (d, \textit{J}=1.17 Hz, 1 H), 11.09 (s, 1 H).

\textit{1H NMR} (400 MHz, DMSO-d\textsubscript{6}) \delta ppm 0.83 - 0.98 (m, 2 H), 1.62 (q, \textit{J}=7.69 Hz, 1 H), 2.56 (s, 3 H), 3.98 (br. s., 1 H), 4.60 - 4.81 (m, 2 H), 5.63 (br. s., 2 H), 7.87 (s, 1 H), 7.99 (d, \textit{J}=11.15 Hz, 1 H), 8.41 (s, 1 H), 8.99 (s, 1 H), 11.00 (br. s., 1 H)
| 138 | B | N-3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chloro-5-fluorophenyl)-5-cyano-3-methylpicolinamide | ![Chemical Structure](image1) | MS m/z = 432 [M+H]^+  1H NMR (400 MHz, DMSO-d6) δ ppm 0.81 - 0.99 (m, 2H), 1.62 (q, J=7.70 Hz, 1 H), 2.56 (s, 3 H), 3.96 (br. s., 1 H), 4.71 (dq, J=47.9, 9.0 Hz, 2 H), 5.63 (br. s., 2 H), 7.87 (s, 1 H), 7.99 (d, J=11.15 Hz, 1 H), 8.41 (s, 1 H), 8.99 (s, 1 H), 11.01 (s, 1 H) |
| 139 | B | N-3-((1S,5R,6S)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chloro-5-fluorophenyl)-5-cyano-3-methylpicolinamide | ![Chemical Structure](image2) | MS m/z = 431.9 [M]^+  1H NMR (400 MHz, DMSO-d6) δ ppm 0.81 - 0.99 (m, 2 H), 1.62 (q, J=7.70 Hz, 1 H), 2.56 (s, 3 H), 3.96 (br. s., 1 H), 4.71 (dq, J=47.9, 9.0 Hz, 2 H), 5.63 (br. s., 2 H), 7.87 (s, 1 H), 7.99 (d, J=11.15 Hz, 1 H), 8.41 (s, 1 H), 8.99 (s, 1 H), 11.01 (s, 1 H) |
| 140 | B | N-3-((1R,5S,R,6R,S)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chloro-5-fluorophenyl)-5-(prop-2-yloxy)pyrazine-2-carboxamide | ![Chemical Structure](image3) | MS m/z = 448 [M+H]^+  1H NMR (400 MHz, DMSO-d6) δ ppm 0.85 - 1.01 (m, 2 H), 1.63 (dt, J=9.73, 7.07 Hz, 1 H), 3.66 (t, J=2.35 Hz, 1 H), 3.98 - 4.07 (m, 1 H), 4.55 - 4.88 (m, 2 H), 5.16 (d, J=2.54 Hz, 2 H), 5.63 (s, 2 H), 8.02 (dd, J=11.25, 2.45 Hz, 1 H), 8.10 (s, 1 H), 8.51 (d, J=1.17 Hz, 1 H), 8.94 (d, J=1.37 Hz, 1 H), 10.82 (s, 1 H) |
| 141 | B | N-3-((1S,R),(5S,R),(6R,S))-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-5-fluoro-(methylthio)phenyl)-5-chloropicolinamide | ![Chemical Structure](image4) | MS m/z = 439 [M+H]^+  1H NMR (400 MHz, DMSO-d6) δ ppm 0.90 - 1.06 (m, 1 H) 1.14 - 1.33 (m, 1 H) 1.54 (m, 1 H) 3.46 (s, 3 H) 3.78 - 3.92 (m, 1 H) 4.50 - 4.76 (m, 1 H) 4.80 (m, 1 H) 5.67 (br. s., 2 H) 8.06 (d, J=14.28 Hz, 1 H) 8.15 - 8.26 (m, 2 H) 8.30 (s, 1 H) 8.82 (s, 1 H) 11.12 (br. s., 1 H) |
| 142 | B | N-3-((1R,S),(5S,R),(6R,S))-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-chloropicolinamide | ![Chemical Structure](image5) | MS m/z = 410 [M]^+  1H NMR (400 MHz, CHLOROFORM-d) δ ppm 0.90 - 1.06 (m, 1 H) 8.58 (s, 1 H) 8.23 (d, J=8.6 Hz, 1 H) 8.11 - 8.00 (m, 1 H) 7.90 (d, J=8.4 Hz, 1 H) 4.78 - 4.67 (m, 1 H) 4.69 - 4.58 (m, 1 H) 4.09 - 3.95 (m, 1 H) 1.80 - 1.74 (m, 1 H) 1.24 (t, J=6.9 Hz, 1 H) 1.03 - 0.91 (m, 1 H) |
| 143 | D | N-(3-(((S,S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-methoxypyrazine-2-carboxamide | MS m/z = 408 [M+H]+  
1H NMR (400 MHz)  
CHLOROFORM-d  
  d = 9.51 (s, 1 H), 9.01 (s, 1 H), 8.15 (s, 1 H), 8.08 (ddd, J = 2.5, 6.8, 11.7 Hz, 1 H), 4.79 - 4.69 (m, 1 H), 4.67 - 4.57 (m, 1 H), 4.05 (s, 3H), 4.00 (t, J = 6.2 Hz, 1 H), 1.80 - 1.71 (m, 1 H), 1.21 (dt, J = 2.6, 7.0 Hz, 1 H), 1.01 - 0.92 (m, 1 H) |
| 144 | D | N-(3-(((S,S,6S)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-methoxypyrazine-2-carboxamide | MS m/z = 407.9 [M]+  
1H NMR (400 MHz)  
CHLOROFORM-d  
  d = 9.47 (br. s., 1H), 8.99 (s, 1H), 8.12 (s, 1H), 7.99 - 8.09 (m, 1H), 4.55 - 4.82 (m, 2H), 4.07 (s, 3H), 3.98 (br. s., 1H), 1.74 (q, J = 6.9 Hz, 1H), 1.16 - 1.26 (m, 3H), 0.88 - 1.02 (m, 1H) |
| 145 | D | N-(3-(((S,S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-5-fluoro-4-methoxyphenyl)-5-chloropicolinamide | MS m/z = 422.9 [M]+  
1H NMR (400 MHz)  
CHLOROFORM-d  
  d = 9.78 (br. s., 1H), 8.54 (s, 1H), 8.22 (d, J = 8.22 Hz, 1H), 8.00 (d, J = 13.69 Hz, 1H), 7.87 (d, J = 8.41 Hz, 1H), 7.24 (br. s., 1H), 4.64 - 4.84 (m, 2H), 3.99 (s, 3H), 3.94 (br. s., 1H), 1.72 - 1.82 (m, 1H), 1.15 (t, J = 6.65 Hz, 1H), 0.89 (q, J = 7.63 Hz, 1H) |
| 146 | D | N-(3-(((S,S,6S)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-5-fluoro-4-methoxyphenyl)-5-chloropicolinamide | MS m/z = 422.9 [M]+  
1H NMR (400 MHz)  
CHLOROFORM-d  
  d = 9.77 (br. s., 1H), 8.53 (s, 1H), 8.22 (d, J = 8.41 Hz, 1H), 7.99 (d, J = 13.50 Hz, 1H), 7.87 (d, J = 8.22 Hz, 1H), 7.24 (br. s., 1H), 4.63 - 4.91 (m, 2H), 3.99 (s, 3H), 3.93 (br. s., 1H), 1.77 (q, J = 7.89 Hz, 1H), 1.15 (t, J = 6.85 Hz, 1H), 0.89 (q, J = 7.37 Hz, 1H) |
| 147 | B | N-(3-(((S,S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-isopropoxypyrazine-2-carboxamide | MS oxa = 436 [M+H]+  
1H NMR (300 MHz, DMSO-d6)  
ppm 10.50 (s, 1H), 8.86 (d, J=1.32 Hz, 1H), 8.33 (d, J=1.32 Hz, 1H), 8.03 (dd, J=7.09, 2.56 Hz, 1H), 7.77 - 7.93 (m, 1H), 7.21 (dd, J=1.84, 8.92 Hz, 1H), 5.96 - 6.52 (m, 1H), 5.85 (br. s., 2H), 5.36 (spt, J=6.16 Hz, 1H), 4.03 (br. s., 1H), 1.73 (d, J=7.45 Hz, 1H), 1.37 (d, J=6.14 Hz, 6H), 1.16 (d, J=5.99 Hz, 1H), 0.92 (d,
| 148 | B | N-((IR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-((R)-but-3-yl)oxo/pyrazine-2-carboxamide | MS m/z = 446 [M+H]⁺  
1H NMR (300 MHz, DMSO-d6) d ppm 10.55 (s, 1 H), 8.90 (d, J=1.32 Hz, 1 H), 8.45 (d, J=1.17 Hz, 1 H), 8.04 (dd, J=7.02, 2.63 Hz, 1 H), 7.76 - 7.93 (m, 1 H), 7.21 (dd, J=1.84, 8.92 Hz, 1 H), 5.97 - 6.46 (m, 1 H), 5.72 - 5.92 (m, 3 H), 3.98 - 4.10 (m, 1 H), 3.59 (d, J=2.05 Hz, 1 H), 1.67 - 1.81 (m, 1 H), 1.63 (d, J=6.58 Hz, 3 H), 1.05 - 1.26 (m, 1 H), 0.92 (dt, J=9.21, 6.50 Hz, 1 H) |
| 149 | B | N-((IR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(difluoromethyl)thiazole-4-carboxamide | MS m/z = 433 [M+H]⁺  
1H NMR (300 MHz, DMSO-d6) d ppm 10.47 (s, 1 H), 8.72 (s, 1 H), 7.96 (dd, J=7.09, 2.70 Hz, 1 H), 7.79 (ddd, J=8.84, 4.17, 2.78 Hz, 1 H), 7.43 (t, J=54.08 Hz, 1 H), 7.21 (dd, J=1.91, 8.84 Hz, 1 H), 6.19 (t, J=55.83 Hz, 1 H), 5.85 (s, 2 H), 3.94 - 4.11 (m, 1 H), 1.72 (dt, J=9.28, 6.83 Hz, 1 H), 1.07 - 1.26 (m, 1 H), 0.91 (dt, J=9.32, 6.45 Hz, 1 H) |
| 150 | B | N-((IR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(difluoromethyl)oxazole-4-carboxamide 2,2,2 trifluoroacetate | MS m/z = 416.9 [M+H]⁺  
1H NMR (400 MHz, CD3OD) d ppm 8.75 (s, 1 H), 8.16 (dd, J=7.04, 2.54 Hz, 1 H), 7.84 (ddd, J=9.00, 4.30, 2.54 Hz, 1 H), 7.37 (dd, J=1.84, 8.90 Hz, 1 H), 7.04 (t, J=5.18 Hz, 1 H), 6.69 (t, J=53.60 Hz, 1 H), 4.65 (td, J=6.70, 2.84 Hz, 1 H), 2.26 (dt, J=9.73, 7.07 Hz, 1 H), 1.70 (t, J=7.63 Hz, 1 H), 1.41 (td, J=9.05, 6.36 Hz, 1 H) |
| 151 | A | N-((IR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(cyclopropylethynyl)oxazole-4-carboxamide | MS m/z = 431 [M+H]⁺  
1H NMR (400 MHz, DMSO-d6) d ppm 10.30 (s, 1 H), 8.75 (s, 1 H), 7.97 (dd, J=7.04, 2.74 Hz, 1 H), 7.69 - 7.82 (m, 1 H), 7.18 (dd, J=11.84, 8.90 Hz, 1 H), 6.18 (t, J=56.14 Hz, 1 H), 5.83 (br. s., 2 H), 4.01 (t, J=54.8 Hz, 1 H), 1.62 - 1.80 (m, 2 H), 1.09 - 1.19 (m, 1 H), 0.98 - 1.09 (m, 2 H), 0.81 - 0.95 (m, 3 H) |
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MS m/z = 424.9 [M+H]^+

1H NMR (400 MHz, DMSO-d6) δ ppm 10.77 (s, 1 H), 8.91 (d, J=1.37 Hz, 1 H), 8.43 (d, J=1.17 Hz, 1 H), 8.08 (s, 1 H), 8.00 (dd, J=1.25, 2.45 Hz, 1 H), 5.62 (br. s., 2 H), 4.47 - 4.93 (m, 2 H), 3.94 - 4.11 (m, 1 H), 4.03 (s, 3 H), 1.52 - 1.69 (m, 1 H), 0.81 - 1.04 (m, 2 H)

N-(3-((1S,5R,6S)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chloro-5-fluorophenyl)-5-methoxyprazin-2-carboxamide compound with N-(3-((1S,5R,6S)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chloro-5-fluorophenyl)-5-methoxyprazin-2-carboxamide (1:1)

MS m/z = 473[M+H]^+

1H NMR (400 MHz, DMSO-d6) δ ppm 11.02 (s, 1 H), 10.36 (br. s., 1 H), 8.46 (d, J=2.35 Hz, 1 H), 8.13 (dd, J=1.35, 2.15 Hz, 1 H), 7.99 (s, 1 H), 7.76 (d, J=2.15 Hz, 1 H), 7.46 (t, J=73.00 Hz, 1 H), 5.21 (dd, J=46.36, 9.19 Hz, 1 H), 4.98 (dd, J=46.36, 10.17 Hz, 1 H), 4.61 (m, J=6.46, 6.46 Hz, 1 H), 3.87 (br. s., 1 H), 2.62 (s, 3 H), 1.81 - 1.97 (m, 1 H), 1.51 - 1.68 (m, 1 H), 1.05 - 1.13 (m, 1 H)

N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chloro-5-fluorophenyl)-5-(difluoromethoxy)-3-methylpicolinamide compound with N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chloro-5-fluorophenyl)-5-(difluoromethoxy)-3-methylpicolinamide (1:1)

MS m/z = 430 [M+H]^+

1H NMR (300 MHz, DMSO-d6) δ ppm 10.47 (s, 1 H), 7.81 (dd, J=6.87, 2.19 Hz, 1 H), 7.73 (m, J=8.48, 3.65 Hz, 1 H), 7.31 (s, 1 H), 7.22 (dd, J=1.69, 8.92 Hz, 1 H), 7.07 (t, J=5.45 Hz, 1 H), 6.18 (t, J=5.59 Hz, 1 H), 5.86 (br. s, 2 H), 4.12 (s, 3 H), 4.00 (m, 1 H), 1.61 - 1.82 (m, 1 H), 1.13 (br. s., 1 H), 0.82 - 1.01 (m, 1 H)
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<td>155</td>
<td>N-(3-((1S,5R,6S)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chloro-5-fluorophenyl)-5-methoxy pyrazine-2-carboxamide</td>
<td>$m/z = 424.1 , [M+H]^+$</td>
<td>1H NMR (400 MHz, DMSO-d6) δ ppm: 10.77 (s, 1 H), 8.91 (d, J=1.17 Hz, 1 H), 8.43 (d, J=1.37 Hz, 1 H), 8.08 (s, 1 H), 8.00 (dd, J=11.25, 2.45 Hz, 1 H), 5.63 (br. s., 2 H), 4.46 - 4.92 (m, 2 H), 4.03 (s, 3 H), 3.96 - 4.02 (m, 1 H), 1.61 (dt, J=9.68, 7.09 Hz, 1 H), 0.95 (td, J=6.50, 2.64 Hz, 1 H), 0.83 - 0.92 (m, 1 H)</td>
</tr>
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<td>156</td>
<td>N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chloro-5-fluorophenyl)-5-methoxy pyrazine-2-carboxamide</td>
<td>$m/z = 424.1 , [M+H]^+$</td>
<td>1H NMR (400 MHz, DMSO-d6) δ ppm: 10.76 (s, 1 H), 8.91 (d, J=1.37 Hz, 1 H), 8.43 (d, J=1.17 Hz, 1 H), 8.08 (s, 1 H), 8.00 (dd, J=11.25, 2.45 Hz, 1 H), 5.62 (br. s., 2 H), 4.49 - 4.94 (m, 2 H), 4.03 (s, 3 H), 3.97 - 4.02 (m, 1 H), 1.61 (dt, J=9.73, 7.07 Hz, 1 H), 0.95 (td, J=6.60, 2.84 Hz, 1 H), 0.84 - 0.92 (m, 1 H)</td>
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<td>157</td>
<td>N-(3-((1S,5R,6S)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chloro-5-fluorophenyl)-5-(difluoromethoxy)-3-methyl picolinamide</td>
<td>$m/z = 473.1 , [M+H]^+$</td>
<td>1H NMR (400 MHz, DMSO-d6) δ ppm: 10.80 (s, 1 H), 8.44 (s, 1 H), 8.01 (d, J=11.15 Hz, 1 H), 7.90 (br. s., 1 H), 7.73 (s, 1 H), 7.44 (t, J=72.97 Hz, 1 H), 5.63 (br. s., 2 H), 4.55 - 4.89 (m, 2 H), 3.93 - 4.07 (m, 1 H), 2.60 (s, 3 H), 1.62 (q, J=7.69 Hz, 1 H), 0.81 - 1.03 (m, 2 H)</td>
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<td>158</td>
<td>N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chloro-5-fluorophenyl)-5-(difluoromethoxy)-3-methyl picolinamide</td>
<td>$m/z = 473.1 , [M+H]^+$</td>
<td>1H NMR (400 MHz, DMSO-d6) δ ppm: 10.80 (s, 1 H), 8.44 (s, 1 H), 8.00 (d, J=11.15 Hz, 1 H), 7.90 (s, 1 H), 7.73 (s, 1 H), 7.44 (t, J=73.16 Hz, 1 H), 5.62 (s, 2 H), 4.52 - 4.89 (m, 2 H), 3.89 - 4.06 (m, 1 H), 2.60 (s, 3 H), 1.62 (q, J=7.69 Hz, 1 H), 0.81 - 1.01 (m, 2 H)</td>
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<td>159</td>
<td>N-(3-((1S,R,5(R,S),6(S,R))-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chloro-5-fluorophenyl)-3-methyl-5-(2,2,2-trifluoroethoxy) pyrazine-2-carboxamide</td>
<td>$m/z = 505.9 , [M+H]^+$</td>
<td>1H NMR (300 MHz, DMSO-d6) δ ppm: 10.78 (s, 1 H), 8.44 (s, 1 H), 8.00 (d, J=11.40 Hz, 1 H), 7.93 (s, 1 H), 5.63 (s, 2 H), 5.14 (q, J=8.96 Hz, 2 H), 4.78 (dd, J=28.79, 9.50 Hz, 1 H), 4.63 (dd, J=28.65, 9.06 Hz, 1 H), 3.86 - 4.08 (m, 1 H), 2.77 (s, 3 H), 1.50 - 1.72 (m, 1 H), 0.76 - 1.05 (m, 2 H)</td>
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**MS** $m/z = 476.0 [M+H]^{-}$

$^1$H NMR (400 MHz, DMSO-d$_6$) d ppm 0.86 - 0.99 (m, 1 H) 1.15 (br. s., 1 H) 1.73 (q, $J=7.0$ Hz, 1 H) 4.02 (br. s., 1 H) 5.16 (q, $J=8.93$ Hz, 2 H) 5.85 (br. s., 2 H) 6.00 - 6.37 (m, 1 H) 7.22 (dd, $J=11.64, 8.90$ Hz, 1 H) 7.85 (dt, $J=8.6, 1.34$ Hz, 1 H) 8.04 (dd, $J=6.94, 2.64$ Hz, 1 H) 8.62 (d, $J=1.17$ Hz, 1 H) 8.92 (d, $J=1.17$ Hz, 1 H) 10.62 (s, 1 H)

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**161**

B N-3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2,2,2-trifluoroethoxy)pyrazine-2-carboxamide

**MS** $m/z = 442.0 [M+H]^{-}$

$^1$H NMR (400 MHz, DMSO-d$_6$) d ppm 0.91 (dt, $J=9.24, 6.53$ Hz, 1 H) 1.09 - 1.19 (m, 1 H) 1.47 (d, $J=6.65$ Hz, 5 H) 1.67 - 1.76 (m, 1 H) 3.97 - 4.04 (q, $J=5.15$ Hz, 1 H) 4.57 (quin, $J=6.70$ Hz, 1 H) 5.84 (s, 1 H) 6.00 - 6.35 (m, 1 H) 7.18 (dd, $J=1.84, 8.90$ Hz, 1 H) 7.68 - 7.79 (m, 1 H) 7.87 (dd, $J=7.04, 2.54$ Hz, 1 H) 8.22 (s, 1 H) 10.06 (s, 1 H)

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**162**

B N-3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-((S)-but-3-yn-2-yl)oxy)pyrazine-2-carboxamide

**MS** $m/z = 446.0 [M+H]^{-}$

$^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ ppm 0.93 (br. s., 1 H) 1.73 (d, $J=5.87$ Hz, 2 H) 3.59 (d, $J=8.15$ Hz, 1 H) 5.73 - 5.91 (m, 3 H) 5.98 - 6.41 (m, 1 H) 7.22 (t, $J=10.37$ Hz, 1 H) 7.86 (d, $J=8.02$ Hz, 1 H) 8.04 (d, $J=4.89$ Hz, 1 H) 8.45 (d, $J=1.37$ Hz, 1 H) 8.90 (d, $J=1.17$ Hz, 1 H) 10.55 (br. s., 1 H)

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**163**

B N-3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-4-chloro-1-(difluoromethyl)-1H-pyrazole-3-carboxamide

**MS** $m/z = 449.9 [M+H]^{-}$

$^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ ppm 0.92 (br. s., 1 H) 1.14 (br. s., 1 H) 1.71 (br. s., 1 H) 4.01 (br. s., 1 H) 5.86 (br. s., 2 H) 5.97 - 6.40 (m, 1 H) 7.21 (t, $J=9.68$ Hz, 1 H) 7.66 - 7.82 (m, 1 H) 7.88 (s, 2 H) 8.77 (s, 7 H) 10.57 (br. s., 1 H)

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**164**

B N-3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-4-chloro-1-(difluoromethyl)-1H-pyrazole-3-carboxamide

**MS** $m/z = 43.19 [M+H]^{+}$

$^1$H NMR (400 MHz, DMSO-d$_6$) d ppm 0.84 (dt, $J=9.5, 6.4$ Hz, 1 H) 0.95 - 1.06 (m, 1 H) 1.50 - 1.62 (m, 1 H) 3.97 - 4.08 (m, 1 H) 4.41 - 4.73 (m, 2 H) 7.17 (dd, $J=1.19, 8.8$ Hz, 1 H) 7.67 - 8.05 (m, 1 H) 7.84 (dd, $J=7.0, 2.5$ Hz, 1 H) 7.88 (t, $J=58.5$ Hz, 1 H) 8.76 (s, 1 H) 10.54 (s, 1 H)
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<th>NMR Details</th>
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<td>165</td>
<td>B</td>
<td>N-(3-((IR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(thiazol-2-ylmethoxy)pyrazine-2-carboxamide</td>
<td>491.0 [M+H]^+</td>
<td>1H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.03 - 1.14 (m, 1 H) 1.26 (s, 1 H) 1.44 - 1.53 (m, 1 H) 1.90 - 2.03 (m, 1 H) 4.07 (br. s., 1 H) 5.81 (s, 1 H) 6.10 - 6.44 (m, 1 H) 7.16 (dd, J=1.54, 9.00 Hz, 1 H) 7.42 (d, J=3.13 Hz, 1 H) 7.69 (dd, J=6.75, 2.64 Hz, 1 H) 7.85 (d, J=3.13 Hz, 1 H) 7.98 - 8.06 (m, 1 H) 8.28 (d, J=1.17 Hz, 1 H) 9.05 (d, J=1.17 Hz, 1 H) 9.54 (s, 1 H)</td>
</tr>
<tr>
<td>166</td>
<td>B</td>
<td>N-(3-((IR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-methyloxazole-4-carboxamide</td>
<td>380.9 [M+H]^+</td>
<td>1H NMR (400 MHz, CHLOROFORM-d) δ ppm 0.91 - 1.06 (m, 1 H) 1.43 (t, J=6.75 Hz, 1 H) 1.88 (dt, J=9.49, 7.09 Hz, 1 H) 2.50 (s, 3 H) 3.90 - 4.02 (m, 1 H) 6.05 - 6.42 (m, 1 H) 7.08 (dd, J=1.54, 8.80 Hz, 1 H) 7.62 (dd, J=6.75, 2.64 Hz, 1 H) 7.90 (ddd, J=8.75, 4.06, 2.84 Hz, 1 H) 8.15 (s, 1 H) 8.65 (s, 1 H)</td>
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<td>167</td>
<td>B</td>
<td>N-(3-((IR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(oxazol-2-ylmethoxy)pyrazine-2-carboxamide</td>
<td>475.0 [M+H]^+</td>
<td>1H NMR (400 MHz, DMSO-d6) δ ppm 0.86 - 0.97 (m, 1 H) 1.15 (br. s., 1 H) 1.67 - 1.78 (m, 1 H) 3.96 - 4.05 (m, 1 H) 5.61 (s, 2 H) 5.84 (s, 2 H) 6.01 - 6.36 (m, 1 H) 7.21 (dd, J=1.83, 8.90 Hz, 1 H) 7.29 (d, J=0.59 Hz, 1 H) 7.85 (dt, J=7.29, 4.18 Hz, 1 H) 8.03 (dd, J=7.14, 2.64 Hz, 1 H) 8.19 (d, J=0.78 Hz, 1 H) 8.53 (d, J=1.37 Hz, 1 H) 8.88 (d, J=1.37 Hz, 1 H) 10.56 (s, 1 H)</td>
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<td>168</td>
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<td>N-(3-((IR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(fluoromethyl)oxazole-4-carboxamide</td>
<td>398.9 [M+H]^+</td>
<td>1H NMR (400 MHz, DMSO-d6) δ ppm 0.91 (dt, J=9.39, 6.46 Hz, 1 H) 1.07 - 1.19 (m, 1 H) 1.64 - 1.77 (m, 1 H) 3.96 - 4.06 (m, 1 H) 5.48 - 5.71 (m, 2 H) 5.84 (s, 2 H) 6.00 - 6.37 (m, 1 H) 7.19 (dd, J=1.74, 8.80 Hz, 1 H) 7.73 - 7.82 (m, 1 H) 7.96 (dd, J=7.14, 2.64 Hz, 1 H) 8.88 (d, J=1.56 Hz, 1 H) 10.34 (s, 1 H)</td>
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| Page | A-N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(thiazol-4-ylmethoxy)pyrazine-2-carboxamide | MS m/z = 490.9 [M+H]^+  
1H NMR (400 MHz, DMSO-d6) d ppm 0.91 (dt, J=9.39, 6.36 Hz, 1 H) 1.15 (t, J=4.89 Hz, 1 H) 1.64 - 1.78 (m, 1 H) 4.02 (t, J=5.38 Hz, 1 H) 5.62 (s, 2 H) 5.85 (s, 2 H) 6.02 - 6.37 (m, 1 H) 7.21 (dd, J=1.84, 8.90 Hz, 1 H) 7.80 - 7.87 (m, 1 H) 7.88 (d, J=1.76 Hz, 1 H) 8.03 (dd, J=7.04, 2.74 Hz, 1 H) 8.47 (d, J=1.17 Hz, 1 H) 8.91 (d, J=1.96 Hz, 1 H) 10.54 (s, 1 H) |
| 169 | B-N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(thiazol-5-ylmethoxy)pyrazine-2-carboxamide | MS m/z = 490.9 [M+H]^+  
1H NMR (400 MHz, DMSO-d6) d ppm 0.86 - 1.00 (m, 1 H) 1.15 (br. s., 1 H) 1.65 - 1.79 (m, 1 H) 3.96 - 4.08 (m, 1 H) 5.78 (s, 2 H) 5.84 (s, 2 H) 6.01 - 6.37 (m, 1 H) 7.21 (dd, J=1.83, 8.71 Hz, 1 H) 7.85 (dt, J=7.29, 4.18 Hz, 1 H) 8.03 (dd, J=7.14, 2.64 Hz, 1 H) 8.10 (d, J=0.59 Hz, 1 H) 8.46 (d, J=1.37 Hz, 1 H) 8.93 (d, J=1.37 Hz, 1 H) 9.15 (s, 1 H) 10.55 (s, 1 H) |
| 170 | B-N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(oxazol-5-ylmethoxy)pyrazine-2-carboxamide | MS m/z = 475.0 [M+H]^+  
1H NMR (400 MHz, CHLOROFORM-d) d ppm 1.12 - 1.23 (m, 1 H) 1.53 - 1.67 (m, 1 H) 2.01 - 2.17 (m, 1 H) 4.15 - 4.29 (m, 1 H) 5.54 (s, 2 H) 6.15 - 6.51 (m, 1 H) 7.18 (dd, J=11.54, 9.00 Hz, 1 H) 7.76 (dd, J=6.65, 2.54 Hz, 1 H) 7.93 (s, 1 H) 7.98 (dt, J=8.80, 3.42 Hz, 1 H) 8.21 (d, J=1.17 Hz, 1 H) 9.03 (d, J=1.17 Hz, 1 H) 9.56 (s, 1 H) |
| 171 | B-N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(thiazol-2-ylmethoxy)picolinamide | MS m/z = 490.0 [M+H]^+  
1H NMR (400 MHz, CHLOROFORM-d) d ppm 0.99 (q, J=7.69 Hz, 1 H) 1.44 (br. s., 1 H) 1.89 (q, J=7.69 Hz, 1 H) 3.97 (br. s., 1 H) 5.52 (s, 2 H) 6.09 - 6.43 (m, 1 H) 7.10 (t, J=10.17 Hz, 1 H) 7.45 (br. s., 1 H) 7.48 (d, J=8.80 Hz, 1 H) 7.65 (d, J=6.65 Hz, 1 H) 7.86 (br. s., 1 H) 8.01 (d, J=7.82 Hz, 1 H) 8.22 (d, J=8.80 Hz, 1 H) 8.35 (s, 1 H) 9.81 (s, 1 H) |
173 B N-(3-((3R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4. 1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(oxazol-2-ylmethoxy)picolinamide

MS m/z = 474. 0 [M+H]+
1H NMR (400 MHz, CHLOROFORM-d) d ppm 0.89 - 1.05 (m, 1 H) 1.44 (br. s., 1 H) 1.88 (q, J=7.76 Hz, 1 H) 3.91 - 4.15 (m, 3 H) 5.29 (s, 2 H) 6.08 - 6.44 (m, 1 H) 7.10 (t, J=10.47 Hz, 1 H) 7.21 (s, 1 H) 7.50 (d, J=8.61 Hz, 1 H) 7.66 (d, J=6.46 Hz, 1 H) 7.74 (s, 1 H) 7.94 - 8.05 (m, 1 H) 8.23 (d, J=8.61 Hz, 1 H) 8.35 (s, 1 H) 9.81 (s, 1 H)

174 B N-(3-((3R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4. 1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(oxazol-4-ylmethoxy)pyrazine-2-carboxamide

MS m/z = 475.0 [M+H]+
1H NMR (400 MHz, CHLOROFORM-d) d ppm 0.94 - 1.06 (m, 1 H) 1.38 - 1.48 (m, 1 H) 1.82 - 1.98 (m, 1 H) 3.93 - 4.05 (m, 1 H) 5.47 (s, 2 H) 6.06 - 6.42 (m, 1 H) 7.12 (dd, J=11.54, 9.00 Hz, 1 H) 7.65 (dd, J=6.65, 2.54 Hz, 1 H) 7.82 (s, 1 H) 7.94 (s, 1 H) 7.99 (dt, J=8.5 1, 3.47 Hz, 1 H) 8.19 (s, 1 H) 9.02 (s, 1 H) 9.48 (s, 1 H)

175 B N-(3-((3R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4. 1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(1-fluoroethyl)oxazole-4-carboxamide

MS m/z = 413.0 [M+H]+
1H NMR (400 MHz, CHLOROFORM-d) d ppm 1.31 - 1.44 (m, 1 H) 1.72 (br. s., 1 H) 1.77 - 1.92 (m, 2 H) 2.16 - 2.30 (m, 1 H) 4.42 (br. s., 1 H) 5.58 - 5.82 (m, 1 H) 6.23 - 6.59 (m, 1 H) 7.21 (t, J=10.27 Hz, 1 H) 7.83 (d, J=7.04 Hz, 1 H) 8.33 (s, 1 H) 8.84 (br. s., 1 H) 120768-50-1

176 B N-(3-((3R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4. 1.0]hept-3-en-5-yl)-4-fluorophenyl)-4-methyl thiophene-2-carboxamide

MS m/z = 395.9 [M+H]+
1H NMR (400 MHz, DMSO-d6) d ppm 0.90 (q, J=6.91 Hz, 1 H) 1.13 (br. s., 1 H) 1.64 - 1.79 (m, 1 H) 2.27 (s, 3 H) 4.00 (br. s., 1 H) 5.84 (s, 2 H) 5.97 - 6.37 (m, 1 H) 7.19 (t, J=10.27 Hz, 1 H) 7.44 (s, 1 H) 7.69 (d, J=7.04 Hz, 1 H) 7.83 (br. s., 2 H) 10.27 (s, 1 H)

177 B N-(3-((3R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4. 1.0]hept-3-en-5-yl)-4-fluorophenyl)-4-chlorothiophene-2-carboxamide

MS m/z = 415.9 [M+H]+
1H NMR (400 MHz, DMSO-d6) d ppm 0.90 (dt, J=9.29, 6.50 Hz, 1 H) 1.08 - 1.18 (m, 1 H) 1.72 (dt, J=9.34, 6.87 Hz, 1 H) 3.95 - 4.04 (m, 1 H) 5.86 (s, 2 H) 6.00 - 6.35 (m, 1 H) 7.22 (dd, J=11.74, 8.80 Hz, 1 H) 7.64 - 7.74 (m, 1 H) 7.82 (dd, J=6.94, 2.64 Hz, 1 H) 7.91 (d, J=1.37 Hz, 1 H) 8.03
178 B N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-4-cyanothiophene-2-carboxamide

\[
\text{MS m/z } = 406.9 \text{ [M+H]}^+ \\
\text{1H NMR (400 MHz, DMSO-d6) d ppm 0.82 - 0.98 (m, 1 H) 1.13 (br. s., 1 H) 1.64 - 1.79 (m, 1 H) 3.99 (br. s., 1 H) 5.86 (s, 2 H) 5.99 - 6.35 (m, 1 H) 7.23 (t, J=10.66 Hz, 1 H) 7.69 (br. s., 1 H) 7.80 (d, J=6.65 Hz, 1 H) 8.32 (s, 1 H) 8.80 (s, 1 H) 10.54 (s, 1 H)}
\]
183 C  N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-(fluoromethoxy)picolinamide

MS m/z = 422.9 [M+H]⁺
1H NMR (400 MHz, CHLOROFORM-d) δ ppm 0.98 (dt, J=9.78, 6.65 Hz, 1 H) 1.17 (td, J=7.04, 2.74 Hz, 1 H) 1.99 (dt, J=9.88, 7.19 Hz, 1 H) 3.89 - 3.99 (m, 1 H) 4.75 - 5.01 (m, 2 H) 5.69 - 5.93 (m, 2 H) 7.42 (d, J=8.80 Hz, 1 H) 7.58 (dd, J=8.61, 2.74 Hz, 1 H) 7.83 (d, J=2.74 Hz, 1 H) 8.01 (dd, J=8.61, 2.54 Hz, 1 H) 8.28 (d, J=8.80 Hz, 1 H) 8.41 (d, J=2.74 Hz, 1 H) 9.88 (s, 1 H)

184 B  N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(cyanomethoxy)3-methylpicolinamide

MS m/z = 446.0 [M+H]⁺
1H NMR (400 MHz, ACETONITRILE-d3) δ ppm 1.18 - 1.31 (m, 1 H) 1.57 (br. s., 1 H) 2.04 - 2.12 (m, 2 H) 2.73 (s, 3 H) 3.28 (s, 1 H) 4.39 (br. s., 1 H) 5.02 (s, 2 H) 6.26 - 6.65 (m, 1 H) 7.25 (t, J=10.47 Hz, 1 H) 7.38 (br. s., 1 H) 7.84 (d, J=7.04 Hz, 1 H) 7.94 (br. s., 1 H) 8.25 (br. s., 1 H) 10.10 (br. s., 1 H)

185 B  N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3,5-dimethylpicolinamide

MS m/z = 405.0 [M+H]⁺
1H NMR (400 MHz, CHLOROFORM-d) δ ppm 0.99 (q, J=7.50 Hz, 1 H) 1.43 (br. s., 1 H) 1.91 (q, J=7.82 Hz, 1 H) 2.39 (s, 3 H) 2.76 (s, 3 H) 3.98 (br. s., 1 H) 6.05 - 6.45 (m, 1 H) 7.10 (t, J=10.27 Hz, 1 H) 7.43 (s, 1 H) 7.54 (d, J=6.85 Hz, 1 H) 8.08 (d, J=8.22 Hz, 1 H) 8.24 (s, 1 H) 10.19 (br. s., 1 H)

186 B  N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(difluoromethyl)3-methylpicolinamide

MS m/z = 440.9 [M+H]⁺
1H NMR (400 MHz, CHLOROFORM-d) δ ppm 0.95 - 1.07 (m, 1 H) 1.39 - 1.52 (m, 1 H) 1.85 - 1.99 (m, 1 H) 2.85 (s, 3 H) 3.98 (t, J=5.38 Hz, 1 H) 6.04 - 6.43 (m, 1 H) 6.55 - 6.95 (m, 1 H) 7.09 (dd, J=11.35, 9.00 Hz, 1 H) 7.57 (dd, J=6.55, 2.45 Hz, 1 H) 7.78 (s, 1 H) 8.04 (dd, J=7.82, 3.72 Hz, 1 H) 8.54 (s, 1 H)
| 187 | B | **N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-6-methoxypyridazine-3-carboxamide** | **MS m/z = 408.0 [M+H]⁺**

1H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.02 (q, J=7.82 Hz, 1 H) 1.46 (br. s., 1 H) 1.86 (q, J=7.82 Hz, 1 H) 3.95 - 4.07 (m, 1 H) 4.24 (s, 3 H) 6.07 - 6.45 (m, 1 H) 7.09 - 7.21 (m, 2 H) 7.69 (d, J=6.26 Hz, 1 H) 8.00 (d, J=8.61 Hz, 1 H) 8.28 (d, J=9.00 Hz, 1 H) 9.88 (br. s., 1 H) |

| 188 | B | **N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(trifluoromethyl)picolinamide** | **MS m/z = 459.0 [M+H]⁺**

1H NMR (300 MHz, CHLOROFORM-d) δ ppm 0.93 - 1.08 (m, 1 H) 1.45 (br. s., 1 H) 1.84 - 2.00 (m, 1 H) 2.87 (s, 3 H) 3.98 (br. s., 1 H) 5.99 - 6.47 (m, 1 H) 6.99 - 7.16 (m, 1 H) 7.57 (d, J=6.87 Hz, 1 H) 7.89 (s, 1 H) 7.95 - 8.10 (m, 1 H) 8.65 (s, 1 H) 10.07 (s, 1 H) |

| 189 | B | **N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(2,2,2-trifluoroethoxy)picolinamide** | **MS m/z = 489.0 [M+H]⁺**

1H NMR (300 MHz, CHLOROFORM-d) δ ppm 0.88 - 1.11 (m, 1 H) 1.43 (br. s., 1 H) 1.79 - 2.00 (m, 1 H) 2.80 (s, 3 H) 3.96 (br. s., 1 H) 4.47 (q, J=7.80 Hz, 2 H) 5.98 - 6.50 (m, 1 H) 7.03 - 7.12 (m, 1 H) 7.15 (br. s., 1 H) 7.52 (d, J=5.99 Hz, 1 H) 7.97 - 8.10 (m, 1 H) 8.12 (br. s., 1 H) 9.98 (br. s., 1 H) |

| 190 | B | **N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-methylpicolinamide** | **MS m/z = 391.0 [M+H]⁺**

1H NMR (400 MHz, CHLOROFORM-d) δ ppm 0.98 (q, J=7.76 Hz, 1 H) 1.43 (br. s., 1 H) 1.89 (q, J=7.69 Hz, 2 H) 2.44 (s, 3 H) 3.97 (br. s., 1 H) 4.56 (br. s., 2 H) 6.05 - 6.44 (m, 1 H) 7.11 (t, J=10.17 Hz, 1 H) 7.69 (d, J=6.65 Hz, 2 H) 8.02 (d, J=6.26 Hz, 1 H) 8.16 (d, J=7.82 Hz, 1 H) 8.41 (s, 1 H) 9.96 (br. s., 1 H) |
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<tr>
<th>Page</th>
<th>MS m/z</th>
<th>NMR Conditions</th>
<th>Assignments</th>
</tr>
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| 191  | 457.0  | [M+H]^+        | 1H NMR (400 MHz, CHLOROFORM-d)  
δ ppm: 0.95 - 1.10 (m, 1 H), 1.38 - 1.54 (m, 1 H), 1.92 (dt, J=9.54, 7.6 Hz, 1 H), 2.02 (t, J=13.60 Hz, 1 H), 3.91 - 4.10 (m, 1 H), 5.02 (br. s., 1 H), 6.03 - 6.47 (m, 1 H), 7.11 (dd, J=1.54, 8.80 Hz, 1 H), 7.67 (dd, J=6.75, 2.64 Hz, 1 H), 7.69 - 7.73 (m, 1 H), 8.27 (d, J=8.61 Hz, 1 H), 8.44 (d, J=1.96 Hz, 1 H), 9.85 (s, 1 H) |
<p>| 192  | 384    | [M+H]^+        | 1H NMR (400 MHz, DMSO-d6) d ppm: 10.82 (s, 1 H), 9.20 (s, 1 H), 8.58 (d, J=8.22 Hz, 1 H), 8.28 (d, J=8.22 Hz, 1 H), 8.01 (d, J=6.85 Hz, 1 H), 7.85 (d, J=7.63 Hz, 1 H), 7.19 (t, J=10.37 Hz, 1 H), 5.65 (br. s., 2 H), 4.40 - 4.75 (m, 2 H), 4.04 (br. s., 1 H), 1.58 (q, J=7.63 Hz, 1 H), 1.00 (br. s., 1 H), 0.75 - 0.90 (m, 1 H) |
| 193  | 427.1  | [M+H]^+        | 1H NMR (400 MHz, DMSO-d6) d ppm: 10.75 (s, 1 H), 8.72 (d, J=1.96 Hz, 1 H), 8.43 (d, J=2.15 Hz, 1 H), 7.68 - 7.82 (m, 2 H), 7.19 (d, J=1.74, 8.80 Hz, 1 H), 5.73 (br. s., 2 H), 4.37 - 4.76 (m, 2 H), 4.00 (t, J=5.48 Hz, 1 H), 1.48 - 1.63 (m, 1 H), 1.00 (td, J=6.46, 2.54 Hz, 1 H), 0.83 (dt, J=9.39, 6.36 Hz, 1 H) |
| 194  | 390.2  | [M+H]^+        | 1H NMR (400 MHz, DMSO-d6) d ppm: 10.50 (s, 1 H), 8.89 (d, J=1.17 Hz, 1 H), 8.41 (d, J=1.17 Hz, 1 H), 7.99 (dd, J=7.34, 2.64 Hz, 1 H), 7.76 - 7.87 (m, 1 H), 7.17 (dd, J=1.93, 8.80 Hz, 1 H), 5.79 (br. s., 2 H), 4.39 - 4.77 (m, 2 H), 3.94 - 4.12 (m, 4 H), 1.43 - 1.70 (m, 1 H), 1.02 (td, J=6.41, 2.64 Hz, 1 H), 0.85 (dt, J=9.44, 6.43 Hz, 1 H) |
| 195  | 389.2  | [M+H]^+        | 1H NMR (400 MHz, DMSO-d6) d ppm: 10.44 (s, 1 H), 8.39 (d, J=2.74 Hz, 1 H), 8.12 (d, J=8.80 Hz, 1 H), 7.96 (dd, J=7.24, 2.74 Hz, 1 H), 7.81 - 7.88 (m, 1 H), 7.61 (dd, J=8.70, 2.84 Hz, 1 H) |</p>
<table>
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<th>196</th>
<th>B</th>
<th>N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-cyano-3-methylpicolinamide</th>
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|     |   | **MS m/z = 397.9 [M+H]^+**  
|     |   | 1H NMR (400 MHz, DMSO-d6) d ppm 10.71 (s, 1 H), 8.97 (d, J=1.37 Hz, 1 H), 8.39 (d, J=1.17 Hz, 1 H), 7.78 - 7.86 (m, 2 H), 7.18 (dd, J=11.74, 8.80 Hz, 1 H), 5.70 (br. s., 2 H), 4.32 - 4.73 (m, 2 H), 3.97 - 4.05 (m, 1 H), 2.54 (s, 3 H), 1.49 - 1.62 (m, 1 H), 1.00 (d, J=6.46, 2.54 Hz, 1 H), 0.78 - 0.89 (m, 1 H). |

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<th>197</th>
<th>B</th>
<th>N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(prop-2-yn-1-yl)oxy)pyrazine-2-carboxamide</th>
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|     |   | **MS m/z = 414.1 [M+H]^+**  
|     |   | 1H NMR (400 MHz, DMSO-d6) d ppm 10.53 (s, 1 H), 8.99 (s, 1 H), 8.48 (s, 1 H), 7.99 (dd, J=7.24, 2.35 Hz, 1 H), 7.72-7.89 (m, 1 H), 7.17 (dd, J=11.74, 8.80 Hz, 1 H), 5.69 (br. s., 2H), 5.14 (d, J=2.35 Hz, 2 H), 4.36 - 4.80 (m, 2 H), 3.90 - 4.12 (m, 1 H), 1.50 - 1.64 (m, 1H), 1.24 (s, 1H), 0.92 - 1.06 (m, 1H), 0.84 (dt, J=9.44, 6.43 Hz, 1 H). |

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<th>198</th>
<th>B</th>
<th>N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-3-methylpicolinamide</th>
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|     |   | **MS m/z = 407.1 [M+H]^+**  
|     |   | 1H NMR (400 MHz, DMSO-d6) d ppm 10.55 (s, 1 H), 8.57 (d, J=1.56 Hz, 1 H), 8.01 (d, J=0.78 Hz, 1 H), 7.77 - 7.86 (m, 2 H), 7.16 (dd, J=11.74, 8.80 Hz, 1 H), 5.63 (br. s., 2 H), 4.40 - 4.71 (m, 2 H), 4.00 (t, J=5.28 Hz, 1 H), 2.55 (s, 3 H), 1.51 - 1.61 (m, 1 H), 0.95 - 1.02 (m, 1 H), 0.78 - 0.88 (m, 1 H). |

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<th>199</th>
<th>B</th>
<th>N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(but-2-yn-1-yl)oxy)pyrazine-2-carboxamide</th>
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|     |   | **MS m/z = 428.1 [M+H]^+**  
|     |   | 1H NMR (400 MHz, DMSO-d6) d ppm 10.51 (s, 1 H), 8.89 (d, J=1.17 Hz, 1 H), 8.45 (d, J=1.37 Hz, 1 H), 7.99 (dd, J=7.34, 2.64 Hz, 1 H), 7.78 - 7.85 (m, 1 H), 7.17 (dd, J=11.74, 8.80 Hz, 1 H), 5.63 (br. s., 2 H), 5.09 (d, J=2.35 Hz, 2 H), 4.39 - 4.74 (m, 2 H), 4.00 - 4.08 (m, 1 H), 1.86 (t, J=2.35 Hz, 3 H), 1.53 - 1.62 (m, 1 H), 0.93 - 1.03 (m, 1 H), 0.83 (dt, J=9.39, 6.43 Hz, 1 H). |
| 200 B | N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-6-chloro-3-methylimidazo[1,2-a]pyridine-2-carboxamide |
| 201 B | N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(difluoromethyl)-3-methylpicolinamide |
| 202 A | N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)isoquinoline-3-carboxamide |
| 203 B | N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(but-2-yn-1-yloxy)picolinamide |

6.36 Hz, 1 H).
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<th>Mass Spectrometry</th>
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<td>204 A N-(5-((IR,5S,6R)-3-amino-5-((fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoropyridin-3-yl)-5-cyanopicolinamide</td>
<td><img src="image" alt="Structure A" /></td>
<td>4.04 (t, J=5.58 Hz, 1H), 1.85 (t, J=2.25 Hz, 3H), 1.52 - 1.63 (m, 1H), 1.00 (td, J=6.26, 2.35 Hz, 1H), 0.84 (dt, J=9.49, 6.3 Hz, 1H).</td>
<td>MS m/z = 385 [M+H]^+</td>
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<td>205 B N-(3-((IR,5S,6R)-3-amino-5-((fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(prop-2-yn-1-yloxy)picolinamide</td>
<td><img src="image" alt="Structure B" /></td>
<td>1H NMR (400 MHz, DMSO-d6) δ ppm 11.21 (s, 1H), 9.17 - 9.26 (m, 1H), 8.64 (s, 1H), 8.58 (dd, J=16.38, 8.56, 2.05 Hz, 2H), 8.30 (d, J=8.22 Hz, 1H), 7.52 (s, 2H), 4.44 - 4.71 (m, 2H), 4.01 - 4.10 (m, 1H), 1.49 - 1.62 (m, 1H), 1.00 (td, J=6.46, 2.54 Hz, 1H), 0.86 (dt, J=9.54, 6.3 Hz, 1H).</td>
<td>MS m/z = 413 [M+H]^+</td>
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<td>206 A N-(5-((IR,5S,6R)-3-amino-5-((fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoropyridin-3-yl)-5-(prop-2-yn-1-yloxy)pyrazine-2-carboxamide</td>
<td><img src="image" alt="Structure C" /></td>
<td>1H NMR (400 MHz, DMSO-d6) δ ppm 10.46 (s, 1H), 8.44 (d, J=2.74 Hz, 1H), 8.14 (d, J=8.61 Hz, 1H), 7.97 (dd, J=7.24, 2.54 Hz, 1H), 7.79 - 7.88 (m, 1H), 7.66 (dd, J=8.70, 2.84 Hz, 1H), 7.16 (dd, J=1, 1.74, 8.80 Hz, 1H), 5.63 (br. s., 2H), 5.03 (d, J=2.35 Hz, 2H), 4.39 - 4.74 (m, 2H), 4.03 (t, J=5.38 Hz, 1H), 3.70 (t, J=2.35 Hz, 1H), 1.53 - 1.62 (m, 1H), 0.99 (td, J=6.36, 2.54 Hz, 1H), 0.83 (dt, J=9.49, 6.41 Hz, 1H).</td>
<td>MS m/z = 415, 1 [M+H]^+</td>
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<td>207 A N-(5-((IR,5S,6R)-3-amino-5-((fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoropyridin-3-yl)-4-chloro-1-(difluoromethyl)-1H-</td>
<td><img src="image" alt="Structure D" /></td>
<td>1H NMR (400 MHz, DMSO-d6) δ ppm 10.84 (s, 1H), 8.78 (s, 1H), 8.53 (s, 1H), 8.38 (dd, J=9.10, 2.45 Hz, 1H), 7.72 - 8.07 (m, 1H), 5.74 (br. s., 2H), 4.44 - 4.69 (m, 2H), 4.04 (t, J=5.38 Hz, 1H), 1.48 - 1.60 (m, 1H).</td>
<td>MS m/z = 433 [M+H]^+</td>
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<td>MS m/z</td>
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<td>208 B</td>
<td>N-(3-((1R,S),5(S),6(R),S)]-3-amino-5-(trifluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)phenyl)-5-chloropicolinamide</td>
<td>410.9 [M+H]^+</td>
<td>1H NMR (300MHz, CHLOROFORM-d) δ = 9.88 (s, 1 H), 8.58 (d, J = 2.0 Hz, 1 H), 8.26 (d, J = 8.3 Hz, 1 H), 7.98 (s, 1 H), 7.93 - 7.79 (m, 2 H), 7.48 - 7.39 (m, 2 H), 4.53 (br. s, 2 H), 4.03 - 3.98 (m, 1 H), 1.91 (td, J = 7.0, 9.7 Hz, 1 H), 1.53 (s, J = 6.4 Hz, 1 H), 1.12 - 0.99 (m, 1 H).</td>
</tr>
<tr>
<td>209 A</td>
<td>N-(3-((1R,S),5(S),6(R),S)]-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-(difluoromethoxy)-3-methylpyridinamide</td>
<td>472.9 [M+H]^+</td>
<td>1H NMR (300MHz, DMSO-d6) δ = 10.61 (s, 1 H), 8.43 (d, J = 2.5 Hz, 1 H), 8.07 (d, J = 2.5 Hz, 1 H), 7.89 (dd, J = 2.6, 8.6 Hz, 1 H), 7.72 (d, J = 2.3 Hz, 1 H), 7.69 - 7.12 (m, 2 H), 6.95 - 6.48 (m, 1 H), 5.84 (s, 2 H), 4.03 - 3.88 (m, 1 H), 2.59 (s, 3 H), 1.87 (td, J = 7.0, 9.6 Hz, 1 H), 1.08 (br. s, 1 H), 0.94 (td, J = 6.4, 9.5 Hz, 1 H).</td>
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<td>210 A</td>
<td>N-(3-((1R,S),5(S),6(R),S)]-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-(but-2-yn-1-yloxy)pyrazine-2-carboxamide</td>
<td>461.8 [M+H]^+</td>
<td>1H NMR (300MHz, DMSO-d6) δ = 10.59 (s, 1 H), 8.89 (d, J = 1.2 Hz, 1 H), 8.46 (d, J = 1.3 Hz, 1 H), 8.22 (d, J = 2.6 Hz, 1 H), 7.89 (dd, J = 2.6, 8.6 Hz, 1 H), 7.45 (d, J = 8.6 Hz, 1 H), 6.96 - 6.43 (m, 1 H), 5.91 - 5.75 (m, 2 H), 5.09 (q, J = 2.2 Hz, 2 H), 4.04 - 3.89 (m, 1 H), 1.94 - 1.77 (m, 4 H), 1.10 (s, 1 H), 0.94 (td, J = 6.4, 9.5 Hz, 1 H).</td>
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<td>211 B</td>
<td>N-(3-((1R,S),5(S),6(R)]-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-3,5-dichloropicolinamide</td>
<td>460.8 [M+H]^+</td>
<td>1H NMR (300MHz, DMSO-d6) δ = 10.88 (br. s, 1 H), 8.73 (d, J = 1.9 Hz, 1 H), 8.45 (d, J = 2.0 Hz, 1 H), 7.97 (d, J = 2.6 Hz, 1 H), 7.86 (dd, J = 2.6, 8.6 Hz, 1 H), 7.48 (d, J = 8.6 Hz, 1 H), 6.93 - 6.50 (m, 1 H), 5.87 (s, 2 H), 4.01 - 3.87 (m, 1 H), 1.87 (td, J = 6.9, 9.6 Hz, 1 H), 1.06 (br. s, 1 H), 0.94 (td, J = 6.4, 9.4 Hz, 1 H).</td>
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212 A  N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-(bromopicolinamide)  

MS m/z = 472.9 [M+H]+  
IH NMR (300MHz ,DMSO-d6) d = 10.61 (s, 1 H), 8.43 (d, J = 2.5 Hz, 1 H), 8.07 (d, J = 2.5 Hz, 1 H), 7.89 (dd, J = 2.6, 8.6 Hz, 1 H), 7.72 (d, J = 2.2 Hz, 1 H), 7.69 - 7.11 (m, 2 H), 6.97 - 6.45 (m, 1 H), 5.84 (s, 2 H), 4.02 - 3.87 (m, 3 H), 1.87 (td, J = 7.0, 9.5 Hz, 1 H), 1.14 - 1.02 (m, 1 H), 0.94 (td, J = 6.4, 9.5 Hz, 1 H).

213 A  N-(3-((I S,5R,6S)-3-amino-5-(difluoromethyl)-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-(bromopicolinamide)  

MS m/z = 472.9 [M+H]+  
IH NMR (300MHz ,DMSO-d6) d = 10.61 (s, 1 H), 8.43 (d, J = 2.5 Hz, 1 H), 8.07 (d, J = 2.5 Hz, 1 H), 7.89 (dd, J = 2.6, 8.7 Hz, 1 H), 7.72 (d, J = 2.3 Hz, 1 H), 7.69 - 7.09 (m, 2 H), 6.96 - 6.44 (m, 1 H), 5.84 (s, 2 H), 4.02 - 3.86 (m, 1 H), 2.59 (s, 3 H), 1.87 (td, J = 7.0, 9.6 Hz, 1 H), 1.15 - 1.02 (m, 1 H), 0.94 (td, J = 6.4, 9.5 Hz, 1 H).

214 B  N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-(but-2-yloxy)pyrazine-2-carboxamide  

MS m/z = 470.7 [M+H]+  
IH NMR (300MHz ,DMSO-d6) d = 10.74 (s, 1 H), 8.87 (dd, J = 0.7, 2.3 Hz, 1 H), 8.33 (dd, J = 2.3, 8.4 Hz, 1 H), 8.22 (d, J = 2.6 Hz, 1 H), 8.08 (dd, J = 0.6, 8.5 Hz, 1 H), 7.91 (dd, J = 2.6, 8.6 Hz, 1 H), 7.46 (d, J = 8.6 Hz, 1 H), 6.95 - 6.46 (m, 1 H), 5.84 (s, 2 H), 4.02 - 3.91 (m, 1 H), 1.88 (td, J = 6.8, 9.7 Hz, 1 H), 1.14 - 1.04 (m, 1 H), 0.94 (td, J = 6.4, 9.5 Hz, 1 H).

215 A  N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-(but-2-yn-1-yl)oxypyrazine-2-carboxamide  

MS m/z = 461.9 [M+H]+  
IH NMR (300MHz ,DMSO-d6) d = 10.59 (s, 1 H), 8.89 (d, J = 1.3 Hz, 1 H), 8.46 (d, J = 1.3 Hz, 1 H), 8.22 (d, J = 2.5 Hz, 1 H), 7.89 (dd, J = 2.6, 8.6 Hz, 1 H), 7.45 (d, J = 8.6 Hz, 1 H), 6.98 - 6.41 (m, 1 H), 5.83 (s, 2 H), 5.09 (q, J = 2.2 Hz, 2 H), 4.05 - 3.88 (m, 1 H), 1.95 - 1.74 (m, 4 H), 1.09 (br. s., 1 H), 0.94 (td, J = 6.4, 9.5 Hz, 1 H).

216 A  N-(3-((I S,5R,6S)-3-amino-5-(difluoromethyl)-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-(but-2-
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| 217 N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-3-methyl-5-(trifluoromethyl)picolinamide | **MS m/z = 474.9 [M+H]^+**  
1H NMR (300MHz, DMSO-d6) d = 6.96 - 6.47 (m, 1 H), 5.83 (s, 2 H), 5.09 (q, J = 2.3 Hz, 2 H), 4.04 - 3.84 (m, 1 H), 1.94 - 1.76 (m, 4 H), 1.09 (br. s., 1 H), 0.94 (td, J = 6.5, 9.4 Hz, 1 H). |
| 218 N-(3-((1(S,R),5(S,R),6(R,S))-3-amino-5-(trifluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloropicolinamide compound | **MS m/z = 428.9 [M+H]^+**  
1H NMR (300MHz, CHLOROFORM-d) d = 8.51 (dd, J = 0.6, 2.3 Hz, 1 H), 8.22 (dd, J = 0.7, 8.4 Hz, 1 H), 8.09 - 8.00 (m, 1 H), 7.87 (dd, J = 2.4, 8.4 Hz, 1 H), 7.80 - 7.74 (m, 1 H), 7.11 (dd, J = 8.8, 11.9 Hz, 1 H), 4.70 (br. s., 2 H), 4.02 - 3.93 (m, 1 H), 2.41 - 2.30 (m, 1 H), 1.50 (t, J = 6.4 Hz, 1 H), 1.10 - 0.98 (m, 1 H). |
| 219 N-(3-((1(S,R),5(R,S),6(S,R))-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-(prop-2-yn-1-yl)oxy)pyrazine-2-carboxamide | **MS m/z = 447.9 [M+H]^+**  
1H NMR (300MHz, DMSO-d6) d = 8.66 (s, 1 H), 8.49 (s, 1 H), 8.49 (s, 1 H), 8.23 (br. s., 1 H), 7.89 (d, J = 8.5 Hz, 1 H), 7.46 (d, J = 8.2 Hz, 1 H), 6.97 - 6.43 (m, 1 H), 5.83 (br. s., 2 H), 5.14 (br. s., 2 H), 3.97 (br. s., 1 H), 3.64 (br. s., 1 H), 1.87 (d, J = 7.2 Hz, 1 H), 1.24 - 0.77 (m, 2 H). |
| 220 N-(3-((1(R,S),5(S,R),6(R,S))-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-4-chloro-1-(difluoromethyl)-1H-pyrazole-3-carboxamide | **MS m/z = 465.8 [M+H]^+**  
1H NMR (300MHz, DMSO-d6) d = 8.66 (s, 1 H), 8.77 (s, 1 H), 8.14 - 7.66 (m, 3 H), 7.45 (d, J = 8.6 Hz, 1 H), 6.96 - 6.47 (m, 1 H), 5.84 (s, 2 H), 3.96 (br. s., 1 H), 1.93 - 1.79 (m, 1 H), 1.08 (br. s., 1 H), 1.00 - 0.88 (m, 1 H). |
| No. | A-N-(3-((1R,5S,6R)-3-amino-5-((difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-(prop-2-yn-1-yl)oxo)pyrazine-2-carboxamide | MS m/z = 447.9 [M+H]+  
1H NMR (300MHz, DMSO-d6) d = 10.61 (s, 1 H), 8.91 (d, J = 1.3 Hz, 1 H), 8.49 (d, J = 1.3 Hz, 1 H), 8.23 (d, J = 2.6 Hz, 1 H), 7.89 (dd, J = 2.6, 8.6 Hz, 1 H), 7.45 (d, J = 8.6 Hz, 1 H), 6.97 - 6.48 (m, 1 H), 5.83 (s, 2 H), 5.14 (d, J = 2.3 Hz, 2 H), 4.03 - 3.93 (m, 1 H), 3.64 (t, J = 2.3 Hz, 1 H), 1.88 (td, J = 7.0, 9.6 Hz, 1 H), 1.09 (br. s., 1 H), 0.95 (td, J = 6.4, 9.5 Hz, 1 H) |
| 222 | A-N-(3-((1S,5R,6S)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-(prop-2-yn-1-yl)oxo)pyrazine-2-carboxamide | MS m/z = 447.8 [M+H]+  
1H NMR (300MHz, DMSO-d6) d = 10.67 (s, 1 H), 8.96 (d, J = 1.3 Hz, 1 H), 8.55 (d, J = 1.3 Hz, 1 H), 8.29 (d, J = 2.6 Hz, 1 H), 7.95 (dd, J = 2.6, 8.7 Hz, 1 H), 7.52 (d, J = 8.5 Hz, 1 H), 7.02 - 6.56 (m, 1 H), 5.89 (br. s., 2 H), 5.20 (d, J = 2.3 Hz, 2 H), 4.04 (br. s., 1 H), 3.70 (t, J = 2.4 Hz, 1 H), 2.00 - 1.87 (m, 1 H), 1.16 (br. s., 1 H), 1.07 - 0.95 (m, 1 H) |
| 223 | A-N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-cyano-3-methylpicolinamide | MS m/z = 43.19 [M+H]+  
1H NMR (300MHz, DMSO-d6) d = 10.82 (s, 1 H), 8.98 (d, J = 1.5 Hz, 1 H), 8.40 (d, J = 1.2 Hz, 1 H), 8.05 (d, J = 2.6 Hz, 1 H), 7.88 (dd, J = 2.6, 8.6 Hz, 1 H), 7.47 (d, J = 8.6 Hz, 1 H), 6.96 - 6.50 (m, 1 H), 5.85 (s, 2 H), 3.95 (t, J = 5.4 Hz, 1 H), 2.55 (s, 3 H), 1.87 (td, J = 6.9, 9.9 Hz, 1 H), 1.08 (br. s., 1 H), 0.94 (td, J = 6.3, 9.5 Hz, 1 H) |
| 224 | A-N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-4-chloro-1-(difluoromethyl)-1H-pyrazole-3-carboxamide | MS m/z = 465.8 [M+H]+  
1H NMR (300MHz, METHANOL-d4) d = 8.28 (s, 1 H), 7.86 (d, J = 2.6 Hz, 1 H), 7.73 (dd, J = 2.6, 8.6 Hz, 1 H), 7.68 - 7.24 (m, 2 H), 6.95 - 6.50 (m, 1 H), 3.96 - 3.85 (m, 1 H), 2.05 - 1.91 (m, 1 H), 1.18 (t, J = 6.9 Hz, 1 H), 0.90 (td, J = 6.8, 9.3 Hz, 1 H) |
N-(3-((1\,S,5R,6S)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chloro-1-(difluoromethyl)-1H-pyrazole-3-carboxamide

MS m/z = 465.8 [M+H]+
1H NMR (300MHz, CDCl3) δ = 8.40 (s, 1H), 7.98 (d, J = 2.5 Hz, 1H), 7.84 (dd, J = 2.6, 8.6 Hz, 1H), 7.80 - 7.36 (m, 2H), 7.08 - 6.60 (m, 1H), 4.08 - 3.97 (m, 1H), 2.17 - 2.01 (m, 1H), 1.35 - 1.26 (m, 1H), 1.01 (d, J = 6.8, 9.4 Hz, 1H).

N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-methoxypyrazine-2-carboxamide

MS m/z = 423.8 [M+H]+
1H NMR (400MHz, DMSO-d6) δ = 10.50 (s, 1H), 8.82 (s, 1H), 8.35 (s, 1H), 8.15 (br. s., 1H), 7.82 (d, J = 8.6 Hz, 1H), 7.39 (s, 1H), 6.85 - 6.46 (m, 1H), 5.76 (br. s., 2H), 3.96 (s, 3H), 3.90 (br. s., 1H), 1.80 (q, J = 7.6 Hz, 1H), 1.02 (br. s., 1H), 0.87 (q, J = 6.9 Hz, 1H).

N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-chloro-5-cyanopicolinamide

MS m/z = 417.8, [M+H]+
1H NMR (MeOH) δ: 8.95 (d, J = 1.8 Hz, 1H), 8.54 (d, J = 1.8 Hz, 1H), 7.80 - 7.91 (m, 1H), 7.76 (dd, J = 7.0, 2.7 Hz, 1H), 7.19 (dd, J = 11.9, 8.8 Hz, 1H), 4.77 (d, J = 3.7 Hz, 1H), 4.66 (d, J = 2.5 Hz, 1H), 3.99 - 4.24 (m, 1H), 1.66 - 1.90 (m, 1H), 1.11 - 1.25 (m, 1H), 0.83 - 1.02 (m, 1H).

N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-chloro-5-cyanopicolinamide

MS m/z = 418.0, [M+H]+
1H NMR (MeOH) δ: 8.94 (d, J = 1.6 Hz, 1H), 8.52 (d, J = 1.8 Hz, 1H), 7.83 (dt, J = 8.8, 3.4 Hz, 1H), 7.75 (dd, J = 6.9, 2.6 Hz, 1H), 7.18 (dd, J = 11.7, 8.8 Hz, 1H), 4.76 (d, J = 6.7 Hz, 1H), 4.64 (d, J = 6.5 Hz, 1H), 4.07 (br. s., 1H), 1.77 (d, J = 9.6 Hz, 1H), 1.12 - 1.22 (m, 1H), 0.84 - 1.00 (m, 1H).

N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-chloro-5-methoxypicolinamide

MS m/z = 422.9 [M+H]+
1H NMR (MeOH) δ: 8.32 (d, J = 2.5 Hz, 1H), 7.83 (dt, J = 8.7, 3.4 Hz, 1H), 7.73 - 7.80 (m, 1H), 7.62 (d, J = 2.3 Hz, 1H), 7.17 (dd, J = 11.8, 8.9 Hz, 1H), 4.72 - 4.84 (m, 1H), 4.59 - 4.71 (m, 1H), 4.10 (br. s., 1H), 3.99 (s, 3H), 1.68 - 1.91 (m, 1H), 1.12 - 1.27 (m, 1H), 0.82 - 1.05 (m, 1H).
| 230 | B | N-(5-((1S,5R,6S)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoropyridin-3-yl)-5-chloropicolinamide | MS m/z = 394.1 [M+H]⁺  
1H NMR (MeOH) d: 8.70 - 8.75 (m, 1H), 8.63 - 8.67 (m, 1H), 8.42 - 8.50 (m, 1H), 8.19 - 8.25 (m, 1H), 8.05 - 8.10 (m, 1H), 4.70 - 4.80 (m, 1H), 4.56 - 4.67 (m, 1H), 4.05 - 4.19 (m, 1H), 1.67 - 1.79 (m, 1H), 1.10 - 1.24 (m, 1H), 0.86 - 1.01 (m, 1H) |
| 231 | B | N-(5-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoropyridin-3-yl)-5-chloropicolinamide | MS m/z = 394.1 [M+H]⁺  
1H NMR (MeOH) d: 8.74 (d, J = 2.2 Hz, 1H), 8.64 - 8.70 (m, 1H), 8.49 (dd, J = 8.8, 2.5 Hz, 1H), 8.24 (d, J = 8.4 Hz, 1H), 8.10 (dd, J = 8.4, 2.3 Hz, 1H), 4.78 (s, 1H), 4.66 (s, 1H), 4.13 (br s., 1H), 1.75 (d, J = 9.6 Hz, 1H), 1.12 - 1.23 (m, 1H), 0.90 - 1.04 (m, 1H) |
| 232 | A | N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(prop-2-yn-1-yl)oxy)picolinamide | MS m/z = 431[M+H]⁺  
1H NMR (MeOH) d: 8.41 (d, J = 2.7 Hz, 1H), 8.17 (d, J = 8.8 Hz, 1H), 7.86 (dd, J = 6.7, 2.9 Hz, 2H), 7.61 (dd, J = 8.7, 2.8 Hz, 1H), 7.16 (dd, J = 11.7, 9.6 Hz, 1H), 5.91 - 6.54 (m, 1H), 4.94 (s, 2H), 3.91 - 4.16 (m, 1H), 3.08 (t, J = 2.3 Hz, 1H), 1.74 - 2.00 (m, 1H), 1.33 (br s., 1H), 0.83 - 1.07 (m, 1H) |
| 233 | A | N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(but-2-yn-1-yl)oxy)picolinamide | MS m/z = 445.1[M+H]⁺  
1H NMR (MeOH) d: 8.38 (d, J = 2.7 Hz, 1H), 8.16 (d, J = 8.6 Hz, 1H), 7.86 (dd, J = 6.5, 3.3 Hz, 2H), 7.58 (dd, J = 8.6, 2.7 Hz, 1H), 7.16 (dd, J = 11.7, 9.6 Hz, 1H), 6.07 - 6.49 (m, 1H), 4.86 (d, J = 2.3 Hz, 2H), 4.01 - 4.11 (m, 1H), 1.78 - 1.98 (m, 4H), 1.33 (br s., 1H), 0.98 (d, J = 9.4 Hz, 1H) |
| 234 | A | N-(5-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoropyridin-3-yl)-5-(difluoromethyl)-3-methylpicolinamide | MS m/z = 424[M+H]⁺  
1H NMR (MeOH) d: 8.69 (s, 1H), 8.63 (s, 1H), 8.41 (dd, J = 8.8, 2.5 Hz, 1H), 7.96 (s, 1H), 6.76 - 7.15 (m, 1H), 4.76 (br s., 1H), 4.64 (d, J = 2.2 Hz, 1H), 4.11 (t, J = 5.4 Hz, 1H), 2.74 (s, 3H), 1.60 - 1.81 (m, 1H), 1.09 - 1.22 (m, 1H), 0.84 - 1.01 (m, 1H) |
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<th>N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoropyridin-3-yl)-5-bromopicolinamide</th>
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|     |   | **MS m/z = 437.9 [M+H]^+**  
|     |   | **IH NMR (MeOH)**  
|     |   | d: 8.81 (d, J = 2.0 Hz, IH), 8.64 (s, IH), 8.46 (dd, J = 8.8, 2.5 Hz, IH), 8.23 (dd, J = 8.4, 2.2 Hz, IH), 8.07 - 8.18 (m, IH), 4.75 (d, J = 1.8 Hz, IH), 4.63 (d, J = 2.5 Hz, IH), 4.10 (t, J = 5.7 Hz, IH), 1.61 - 1.80 (m, IH), 1.16 (dd, J = 6.8, 2.4 Hz, IH), 0.95 (dt, J = 9.6, 6.7 Hz, IH) |

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<th>N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2,2,2-trifluoroethoxy)picolinamide</th>
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|     |   | **MS m/z = 475[M+H]^+**  
|     |   | **IH NMR (MeOH)** Shift: 8.49 (d, J=2.7 Hz, IH), 8.23 (d, J=8.8 Hz, IH), 7.85-7.93 (m, 2H), 7.69 (dd, J=8.7, 2.8 Hz, IH), 7.21 (dd, J=1.6, 8.7 Hz, IH), 6.16-6.49 (m, IH), 4.80 (q, J=8.2 Hz, 2H), 4.12 (t, J=5.4 Hz, IH), 1.89-1.99 (m, IH), 1.38 (t, J=5.8 Hz, IH), 0.98-1.10 (m, IH) |

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|     |   | **MS m/z = 457.1[M+H]^+**  
|     |   | **IH NMR (MeOH)** d: 8.40 (d, J = 2.5 Hz, IH), 7.88 (ddd, J = 8.8, 4.3, 2.8 Hz, IH), 7.82 (dd, J = 6.9, 2.6 Hz, IH), 7.61 (s, IH), 7.18 - 7.27 (m, IH), 6.86 - 7.17 (m, IH), 6.11 - 6.48 (m, IH), 3.99 - 4.17 (m, IH), 2.73 (s, 3H), 1.83 - 2.01 (m, IH), 1.36 (br. s., IH), 0.91 - 1.09 (m, IH) |

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<th>N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)pypyrazine-2-carboxamide</th>
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|     |   | **MS m/z = 382.1[M+H]^+**  
<p>|     |   | <strong>IH NMR (MeOH)</strong> d: 7.66 (br. s., IH), 7.58 (d, J=6.8 Hz, IH), 7.07 (t, J=10.0 Hz, IH), 6.06-6.41 (m, IH), 4.01 (br. s., IH), 2.35 (t, J=1.4 Hz, IH), 1.78-1.91 (m, 5H), 1.72 (d, J=1.2 Hz, IH), 1.44-1.58 (m, 2H), 1.20-1.41 (m, 4H), 0.90-1.01 (m, IH) |</p>
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| 240    | N-(3-((IR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-methoxyacetamide | ![Chemical Structure](image) | MS m/z = 344.1 [M+H]^+  
IH NMR (MeOH) : 7.29-7.74 (m, 2H), 7.11 (t, J=10.2 Hz, IH), 6.07-6.41 (m, IH), 4.02 (s, 3H), 3.47 (s, 3H), 1.84 (q, J=7.5 Hz, IH), 1.30 (br. s., IH), 0.88-1.01 (m, IH) |
| 241 A  | N-(3-((IR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-cyclohexylacetamide | ![Chemical Structure](image) | MS m/z = 396.1 [M+H]^+  
IH NMR (MeOH) : 7.67 (br. s., IH), 7.57 (d, J=6.8 Hz, IH), 7.08 (t, J=10.6 Hz, IH), 6.06-6.41 (m, IH), 4.01 (br. s., IH), 2.22 (d, J=7.2 Hz, 2H), 1.64-1.88 (m, 7H), 1.13-1.40 (m, 4H), 0.89-1.11 (m, 3H) |
| 242 A  | N-(3-((IR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)tetrahydro-2H-pyran-4-carboxamide | ![Chemical Structure](image) | MS m/z = 384.1 [M+H]^+  
IH NMR (MeOH) : 7.31-7.71 (m, 2H), 7.02-7.21 (m, IH), 6.06-6.41 (m, IH), 4.00 (d, J=8.6 Hz, 3H), 3.48 (t, J=1.7 Hz, 2H), 2.62 (t, J=1.6 Hz, IH), 1.68-1.93 (m, 5H), 1.29 (br. s., IH), 0.86-1.01 (m, IH) |
| 243 A  | N-(3-((IR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)cyclohex-1-enecarboxamide | ![Chemical Structure](image) | MS m/z = 380.1 [M+H]^+  
IH NMR (MeOH) : 7.63-7.72 (m, 2H), 7.12 (dd, J=1.8, 8.7 Hz, IH), 6.70 (dt, J=3.7, 2.1 Hz, IH), 6.11-6.45 (m, IH), 3.99-4.09 (m, IH), 2.32-2.40 (m, 2H), 2.27 (dd, J=6.2, 2.6 Hz, 2H), 1.82-1.93 (m, IH), 1.65-1.79 (m, 4H), 1.33 (d, J=4.5 Hz, IH), 0.99 (dt, J=9.4, 6.7 Hz, IH) |
| 244 A  | (S,R)-N-(3-((IR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)tetrahydrofuran-2-carboxamide | ![Chemical Structure](image) | MS m/z = 370.1 [M+H]^+  
IH NMR (MeOH) : 7.67-7.76 (m, 2H), 7.14 (dd, J=1.7, 8.8 Hz, IH), 6.08-6.45 (m, IH), 4.44 (dd, J=7.8, 6.3 Hz, IH), 4.08-4.15 (m, IH), 4.02-4.07 (m, IH), 3.92-3.98 (m, IH), 2.36 (dq, J=12.4, 7.5 Hz, IH), 2.10 (dq, J=13.1, 6.6 Hz, IH), 1.94-2.03 (m, 2H), 1.83-1.91 (m, IH), 1.33 (t, J=6.0 Hz, IH), 0.99 (dt, J=9.4, 6.7 Hz, IH) |
| 245 A  | N-(3-((IR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-1-(4-chlorophenyl)cyclopropa necarboxamide | ![Chemical Structure](image) | MS m/z = 450 [M+H]^+  
IH NMR (MeOH) : 7.46-7.52 (m, 4H), 7.38-7.45 (m, 2H), 7.04-7.13 (m, IH), 6.05-6.39 (m, IH), 3.97-4.05 (m, IH), 1.84 (dt, J=9.4, 6.9 Hz, IH), 1.60 (q, J=3.7 Hz, 2H), 1.30 (t, J=6.5 Hz, IH), 1.20 (q, J=3.7 Hz, 2H), 0.96 (dt, J=9.4, 6.7 Hz, IH) |
| 246 | A | N-(3-((1R,5S,6R)-3-amino-5-<br> (difluoromethyl)-2-oxa-<br> 4-azabicyclo[4.1.0]hept-<br> 3-en-5-yl)-4-<br> fluorenyl)-1-(4-chlorophenyl)carboxamide | ![Chemical Structure](image1.png) | MS m/z = 464.1[M+H]^+<br>1H NMR (MeOH-d<sub>4</sub>) 7.53-7.62 (m, 2H), 7.43-7.49 (m, 2H), 7.33-7.39 (m, 2H), 7.07 (dd, J=11.7, 8.8 Hz, 1H), 6.03-6.39 (m, 1H), 3.93-4.04 (m, 1H), 2.82-2.94 (m, 2H), 2.54 (d, J=7.2 Hz, 2H), 1.86-2.03 (m, 2H), 1.75-1.86 (m, 1H), 1.23-1.34 (m, 1H), 0.89-1.01 (m, 1H) |
| 247 | A | N-(3-((1R,5S,6R)-3-amino-5-<br> (difluoromethyl)-2-oxa-<br> 4-azabicyclo[4.1.0]hept-<br> 3-en-5-yl)-4-<br> fluorenyl)-3-<br> methoxypropamide | ![Chemical Structure](image2.png) | MS m/z = 358.1[M+H]^+<br>1H NMR (MeOH-d<sub>4</sub>) 7.31-7.76 (m, 2H), 7.04-7.22 (m, 1H), 6.01-6.44 (m, 1H), 3.92-4.07 (m, 1H), 3.72 (t, J=6.1 Hz, 2H), 3.36 (s, 3H), 2.61 (t, J=6.2 Hz, 2H), 1.75-1.90 (m, 1H), 1.31 (br.s., 1H), 0.96 (s, 1H) |
| 248 | A | N-(3-((1R,5S,6R)-3-amino-5-<br> (difluoromethyl)-2-oxa-<br> 4-azabicyclo[4.1.0]hept-<br> 3-en-5-yl)-4-<br> fluorenyl)-1-methyl-<br> 6-oxo-1,6-<br> dihydropyridine-3-<br> carboxamide | ![Chemical Structure](image3.png) | MS m/z = 407 [M+H]^+<br>1H NMR (MeOH-d<sub>4</sub>) 8.86 (d, J=2.5 Hz, 1H), 8.06 (dd, J=9.4, 2.7 Hz, 1H), 7.78 (sdd, J=8.8, 4.2, 2.8 Hz, 1H), 7.71 (dd, J=6.8, 2.7 Hz, 1H), 7.17 (dd, J=11.7, 8.8 Hz, 1H), 6.61 (d, J=9.4 Hz, 1H), 6.09-6.45 (m, 1H), 3.98-4.11 (m, 1H), 3.67 (s, 3H), 1.79-1.93 (m, 1H), 1.34 (t, J=6.6 Hz, 1H), 1.00 (dt, J=9.6, 6.7 Hz, 1H) |
| 249 | A | N-(3-((1R,5S,6R)-3-amino-5-<br> (difluoromethyl)-2-oxa-<br> 4-azabicyclo[4.1.0]hept-<br> 3-en-5-yl)-4-<br> fluorenyl)-1-methyl-<br> 2-oxo-1,2-<br> dihydropyridine-4-<br> carboxamide | ![Chemical Structure](image4.png) | MS m/z = 407 [M+H]^+<br>1H NMR (MeOH-d<sub>4</sub>) 7.80 (d, J=6.3 Hz, 3H), 7.20 (dd, J=11.7, 9.0 Hz, 1H), 7.03 (s, 1H), 6.78 (dd, J=6.9, 1.9 Hz, 1H), 6.07-6.50 (m, 1H), 4.09 (br.s., 1H), 3.64 (s, 3H), 1.79-1.97 (m, 1H), 1.36 (br.s., 1H), 0.95-1.09 (m, 1H) |
| 250 | A | N-(3-((1R,5S,6R)-3-amino-5-<br> (difluoromethyl)-2-oxa-<br> 4-azabicyclo[4.1.0]hept-<br> 3-en-5-yl)-4-<br> fluorenyl)-5-(3-<br> cyclopropylprop-2-yn-1-<br> yloxy)pyridinamide | ![Chemical Structure](image5.png) | MS m/z = 471.1 [M+H]^+<br>1H NMR (MeOH-d<sub>4</sub>) 8.37 (br.s., 1H), 8.15 (d, J=8.6 Hz, 1H), 7.85 (d, J=5.9 Hz, 2H), 7.56 (d, J=8.4 Hz, 1H), 7.16 (t, J=10.5 Hz, 1H), 6.06-6.43 (m, 1H), 4.85 (s, 2H), 4.05 (br.s., 1H), 1.83-1.95 (m, 1H), 1.19-1.40 (m, 3H), 0.97 (d, J=7.8 Hz, 1H), 0.79 (d, J=7.2 Hz, 2H), 0.62 (br.s., 2H) |
| 251 | A | N-(3-((1R,5S,6R)-3-amino-5-((difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3,3,3-trifluoropropanamide | \[
\text{MS } m/z = 382 \ [\text{M+H}^+] \\
1H NMR (MeOH) : 7.70 (d, J=8.4 Hz, 1H), 7.60 (d, J=6.5 Hz, 1H), 7.12 (t, J=10.3 Hz, 1H), 6.05-6.43 (m, 1H), 4.03 (br, s, 1H), 3.34 (s, 2H), 1.84 (q, J=7.5 Hz, 1H), 1.30 (br, s, 1H), 0.96 (q, J=7.5 Hz, 1H)
\] |
| 252 | A | N-(3-((1R,5S,6R)-3-amino-5-((difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(4-chlorophenyl)propanamide | \[
\text{MS } m/z = 438 \ [\text{M+H}^+] \\
1H NMR (MeOH) : 7.66 (br, s, 1H), 7.56 (t, J=7.7 Hz, 1H), 7.35-7.41 (m, 2H), 7.28-7.35 (m, 2H), 7.07 (t, J=10.4 Hz, 1H), 6.03-6.40 (m, 1H), 3.99 (br, s, 1H), 3.80 (q, J=7.1 Hz, 1H), 1.81 (d, J=7.2 Hz, 1H), 1.49 (d, J=6.8 Hz, 3H), 1.17-1.34 (m, 1H), 0.88-1.01 (m, 1H)
\] |
| 253 | A | (R,S)-N-(3-((1R,5S,6R)-3-amino-5-((difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)tetrahydrofuranyl-3-carboxamide | \[
\text{MS } m/z = 370.1 \ [\text{M+H}^+] \\
1H NMR (MeOH) : 7.66-7.97 (m, 1H), 7.43-7.62 (m, 1H), 7.09 (t, J=10.5 Hz, 1H), 6.00-6.44 (m, 1H), 3.75-4.05 (m, 4H), 3.34 (s, 1H), 3.17 (quin, J=7.3 Hz, 1H), 2.14-2.25 (m, 2H), 1.83 (q, J=7.4 Hz, 1H), 1.29 (br, s, 1H), 0.86-1.01 (m, 1H)
\] |
| 254 | A | N-(3-((1R,5S,6R)-3-amino-5-((difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(tert-butoxy)acetamide | \[
\text{MS } m/z = 386.1 \ [\text{M+H}^+] \\
1H NMR (MeOH) : 7.65 (d, J=6.3 Hz, 2H), 7.11 (t, J=10.3 Hz, 1H), 6.01-6.42 (m, 1H), 3.85-4.14 (m, 3H), 1.85 (q, J=7.5 Hz, 1H), 1.29 (s, 9H), 1.17-1.28 (m, 1H), 0.95 (q, J=7.6 Hz, 1H)
\] |
| 255 | A | N-(3-((1R,5S,6R)-3-amino-5-((difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-methoxyethoxyacetamide | \[
\text{MS } m/z = 388.1 \ [\text{M+H}^+] \\
1H NMR (MeOH) : 7.69 (d, J=5.9 Hz, 2H), 7.12 (t, J=10.1 Hz, 1H), 6.03-6.42 (m, 1H), 4.11 (s, 2H), 4.02 (br, s, 1H), 3.75 (d, J=2.2 Hz, 2H), 3.63 (br, s, 2H), 3.43 (s, 3H), 1.78-1.88 (m, 1H), 1.30 (br, s, 1H), 0.91-1.00 (m, 1H)
\] |
| 256 | A | N-(3-((1R,5S,6R)-3-amino-5-((difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-phenoxyacetamide | \[
\text{MS } m/z = 406.1 \ [\text{M+H}^+] \\
1H NMR (MeOH) : 7.67-7.74 (m, 2H), 7.31 (t, J=7.7 Hz, 2H), 7.13 (t, J=10.3 Hz, 1H), 6.95-7.07 (m, 3H), 6.11-6.44 (m, 1H), 4.65 (s, 2H), 4.05 (br, s, 1H), 1.87 (q, J=7.6 Hz, 1H), 1.32 (m, 1H), 1.28-1.37 (m, 1H), 0.98 (q, J=7.4 Hz, 1H)
\] |
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<th>- 250 -</th>
</tr>
</thead>
</table>
| **257 A** | (R,S)-N-(3-((1R,5S,6R)-3-amino-5- (difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4- fluorophenyl)-2- methoxypropanamide | ![Chemical Structure](image) | MS m/z = 358 [M+H]^+  
1H NMR (MeOH) 7: 7.70 (d, J=6.8 Hz, 2H), 7.12 (t, J=10.4 Hz, 1H), 6.00-6.45 (m, 1H), 4.04 (br, s, 1H), 3.87 (q, J=6.8 Hz, 1H), 3.42 (s, 3H), 1.86 (q, J=7.5 Hz, 1H), 1.40 (d, J=6.8 Hz, 3H), 1.32 (br, s, 1H), 0.91-1.02 (m, 1H) |
| **258 A** | N-(3-((1R,5S,6R)-3-amino-5- (difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4- fluorophenyl)-3-oxocyclobutanecarboxamide | ![Chemical Structure](image) | MS m/z = 368 [M+H]^+  
1H NMR (MeOH) 7: 7.54-7.85 (m, 2H), 7.12 (t, J=10.2 Hz, 1H), 5.91-6.46 (m, 1H), 4.05 (br, s, 1H), 3.35 (d, J=5.7 Hz, 3H), 1.76-1.95 (m, 1H), 1.32 (br, s, 1H), 0.75-0.98 (m, 1H) |
| **259 A** | N-(3-((1R,5S,6R)-3-amino-5- (difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4- fluorophenyl)-5-((R,S)-1-cyanoethoxy)picolinamide | ![Chemical Structure](image) | MS m/z = 446.1 [M+H]^+  
1H NMR (MeOH) 7: 8.51 (d, J=2.7 Hz, 1H), 8.26 (d, J=8.8 Hz, 1H), 7.87-7.93 (m, 2H), 7.74 (dd, J=8.7, 2.8 Hz, 1H), 7.20 (dd, J=11.7, 9.2 Hz, 1H), 6.11-6.48 (m, 1H), 5.49 (q, J=6.7 Hz, 1H), 4.07-4.12 (m, 1H), 1.88-1.96 (m, 1H), 1.85 (d, J=6.7 Hz, 3H), 1.34-1.40 (m, 1H), 1.01 (dt, J=9.5, 6.8 Hz, 1H) |
| **260 A** | N-(3-((1R,5S,6R)-3-amino-5- (difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4- fluorophenyl)cyclopropa necarboxamide | ![Chemical Structure](image) | MS m/z = 340 [M+H]^+  
1H NMR (MeOH) 7: 7.67 (dd, J=5.2, 3.6 Hz, 1H), 7.59 (dd, J=6.9, 2.6 Hz, 1H), 7.09 (dd, J=11.7, 8.8 Hz, 1H), 6.06-6.42 (m, 1H), 3.98-4.07 (m, 1H), 1.81-1.90 (m, 1H), 1.72-1.79 (m, 1H), 1.31 (t, J=5.8 Hz, 1H), 0.92-1.00 (m, 3H), 0.86 (dt, J=7.8, 3.1 Hz, 2H) |
| **261 A** | N-(3-((1R,5S,6R)-3-amino-5- (difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4- fluorophenyl)-5-chloropyrazine-2-carboxamide | ![Chemical Structure](image) | MS m/z = 412.0 [M+H]^+  
1H NMR (MeOH) 7: 9.16 (d, J=1.2 Hz, 1H), 8.80 (d, J=1.4 Hz, 1H), 7.81 - 8.02 (m, 2H), 7.21 (dd, J=11.8, 9.3 Hz, 1H), 6.00 - 6.54 (m, 1H), 4.08 (br, s, 1H), 1.91 (d, J=9.4 Hz, 1H), 1.36 (br, s, 1H), 0.93 - 1.08 (m, 1H) |
| **262 A** | N-(3-((1R,5S,6R)-3-amino-5- (difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4- fluorophenyl)-3- | ![Chemical Structure](image) | MS m/z = 400.1 [M+H]^+  
1H NMR (MeOH) 7: 7.71-7.80 (m, 2H), 7.63-7.69 (m, 2H), 7.45-7.56 (m, 3H), 7.17 (dd, J=11.7, 8.8 Hz, 1H), 6.13-6.47 (m, 1H), 4.04-4.10 (m, 1H), 1.85-1.92 (m, 1H), 1.33-1.37 (m, 1H), 0.93-1.08 (m, 1H), 0.86-0.87 (m, 2H) |
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<th>No.</th>
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<th>MS m/z</th>
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<td>263</td>
<td><img src="image1.png" alt="Structure Image" /></td>
<td>N-(3-((1R,5S),(5S,R),(6R,S))-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)phenyl)-5-chloropicolinamide</td>
<td>392.9 [M+H]^+</td>
<td>1H NMR (400 MHz, CHLOROFORM-d) d ppm 9.83 - 9.88 (m, 1 H) 8.55 (s, 1 H) 8.22 - 8.27 (m, 1 H) 7.85 - 7.93 (m, 2 H) 7.81 (d, J=7.43 Hz, 1 H) 7.80 (br. s., 1 H) 7.35 - 7.44 (m, 2 H) 5.78 (s, 1 H) 3.94 - 4.01 (m, 1 H) 1.72 - 1.81 (m, 1 H) 1.38 - 1.43 (m, 1 H) 0.94 - 1.02 (m, 1 H)</td>
</tr>
<tr>
<td>264</td>
<td><img src="image2.png" alt="Structure Image" /></td>
<td>N-(3-((1S,5R,6S))-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)phenyl)-5-chloropicolinamide</td>
<td>392.9 [M+H]^+</td>
<td>1H NMR (400 MHz, CHLOROFORM-d) d ppm 9.84 (br. s., 1 H) 8.50 - 8.56 (m, 1 H) 8.22 (br. s., 1 H) 7.77 - 7.95 (m, 4 H) 7.34 - 7.43 (m, 3 H) 5.78 (br. s., 1 H) 3.94 - 4.02 (m, 2 H) 1.74 - 1.81 (m, 1 H) 1.42 (t, J=7.63 Hz, 1 H) 0.94 - 1.01 (m, 1 H)</td>
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<td>265</td>
<td><img src="image3.png" alt="Structure Image" /></td>
<td>N-(3-((1R,5S,6R))-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)phenyl)-5-chloropicolinamide</td>
<td>392.9 [M+H]^+</td>
<td>1H NMR (400 MHz, CHLOROFORM-d) d ppm 9.76 (br. s., 1 H) 8.41 - 8.50 (m, 1 H) 8.15 (d, J=8.41 Hz, 1 H) 7.82 - 7.87 (m, 1 H) 7.75 - 7.82 (m, 1 H) 7.66 - 7.75 (m, 1 H) 7.26 - 7.35 (m, 2 H) 5.68 - 5.73 (m, 1 H) 3.85 - 3.93 (m, 1 H) 1.65 - 1.74 (m, 1 H) 1.29 - 1.36 (m, 1 H) 0.85 - 0.95 (m, 1 H)</td>
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<tr>
<td>266</td>
<td><img src="image4.png" alt="Structure Image" /></td>
<td>N-(3-((1R,5S,6R))-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-methylpyrazine-2-carboxamide</td>
<td>392 [M+H]^+</td>
<td>1H NMR (400 MHz, CHLOROFORM-d) d ppm 9.59 - 9.63 (m, 1 H) 9.33 - 9.36 (m, 1 H) 8.42 (s, 1 H) 7.97 (br. s., 1 H) 7.67 (br. s., 1 H) 7.08 - 7.15 (m, 1 H) 6.24 (s, 1 H) 3.99 (t, J=7.92 Hz, 1 H) 2.66 - 2.71 (m, 3 H) 1.86 - 1.94 (m, 1 H) 1.44 (t, J=7.73 Hz, 1 H) 0.97 - 1.04 (m, 1 H)</td>
</tr>
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<td>267</td>
<td><img src="image5.png" alt="Structure Image" /></td>
<td>N-(3-((1R,5S,6R))-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-phenylpropiolamide</td>
<td>456.9 [M+H]^+</td>
<td>1H NMR (400 MHz, CHLOROFORM-d) d ppm 9.64 - 9.71 (m, 1 H) 8.94 - 8.96 (m, 1 H) 8.94 (s, 1 H) 7.94 - 8.01 (m, 1 H) 7.69 - 7.74 (m, 1 H) 7.06 - 7.13 (m, 1 H) 6.24 (s, 1 H) 3.91 - 3.96 (m, 1 H)</td>
</tr>
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</table>
bromopyrimidine-2-carboxamide

1.83 - 1.91 (m, 1 H) 1.40 - 1.46 (m, 1 H) 0.93 - 1.01 (m, 1 H)

268 B N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(trifluoromethyl)pyrazine-2-carboxamide

MS m/z = 446 [M+H]^+. 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 9.55 - 9.59 (m, 2 H) 8.93 (s, 1 H) 7.98 (br. s., 1 H) 7.69 (d, J=7.24 Hz, 1 H) 7.08 - 7.13 (m, 1 H) 6.22 - 6.25 (m, 1 H) 4.00 (t, J=8.02 Hz, 1 H) 1.91 (br. s., 1 H) 1.45 (t, J=8.22 Hz, 1 H) 1.02 (br. s., 1 H)

269 B N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-methylphenyl)-5-cyanopicolinamidine

MS m/z = 398 [M+H]^+. 1H NMR (300 MHz, CHLOROFORM-d) δ ppm 9.83 (br. s., 1 H) 8.88 (s, 1 H) 8.42 (d, J=8.04 Hz, 1 H) 8.19 (d, J=8.04 Hz, 1 H) 8.08 (s, 1 H) 7.70 (d, J=7.89 Hz, 1 H) 7.18 - 7.24 (m, 1 H) 6.19 (t, J=56.20 Hz, 1 H) 4.06 (br. s., 1 H) 2.59 (s, 3 H) 1.87 (d, J=8.48 Hz, 1 H) 1.47 (br. s., 1 H) 1.01 (d, J=8.62 Hz, 1 H)

270 C N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-chloropicolinamidine

MS m/z = 409.1 [M+H]^+. 1H NMR (300 MHz, DMSO-d6) ppm 6.86 - 1.14 (m, 2 H) 1.52 - 1.83 (m, 1 H) 3.76 - 4.14 (m, 1 H) 4.46 - 5.02 (m, 2 H) 5.44 - 5.70 (m, 2 H) 7.14 - 7.55 (m, 1 H) 7.79 - 7.99 (m, 1 H) 8.17 (s, 3 H) 8.65 - 9.03 (m, 1 H) 10.53 - 10.96 (m, 1 H)

271 C N-(3-((1S,5R,6S)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-chloropicolinamidine

MS m/z = 409.1 [M+H]^+. 1H NMR (300 MHz, DMSO-d6) ppm 0.74 - 1.07 (m, 2 H) 1.52 - 1.84 (m, 1 H) 3.97 (br. s., 1 H) 4.46 - 4.98 (m, 2 H) 7.42 (d, J=8.62 Hz, 1 H) 7.88 (dd, J=8.55, 2.27 Hz, 1 H) 8.04 - 8.30 (m, 3 H) 8.79 (d, J=1.75 Hz, 1 H) 10.70 (s, 1 H)

272 C N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-methoxypyrazine-2-
<p>| | | | |</p>
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<td>273</td>
<td>C</td>
<td>N-(3-((1S,5R,6S)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-methoxyprazin2e-carboxamide</td>
<td>8.42 (d, J= 1.17 Hz, 1 H) 8.89 (d, J= 1.32 Hz, 1 H) 10.53 (s, 1 H)</td>
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<tr>
<td>274</td>
<td>C</td>
<td>N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-bromopicolinamide</td>
<td>300 MHz, DMSO-d&lt;sub&gt;6&lt;/sub&gt; ppm 0.78 - 1.01 (m, 2 H) 1.67 (dt, 7=9.76, 6.96 Hz, 1 H) 3.93 - 4.00 (m, 1 H) 4.02 (s, 3 H) 4.54 - 4.95 (m, 2 H) 5.59 (s, 2 H) 7.41 (d, 7=8.62 Hz, 1 H) 7.86 (dd, 7=8.62, 2.63 Hz, 1 H) 8.16 (d, 7=2.63 Hz, 1 H) 8.42 (d, 7=1.32 Hz, 1 H) 10.89 (d, 7=1.32 Hz, 1 H) 10.53 (s, 1 H)</td>
</tr>
<tr>
<td>275</td>
<td>C</td>
<td>N-(3-((1S,5R,6S)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5- bromopicolinamide</td>
<td>300 MHz, DMSO-d&lt;sub&gt;6&lt;/sub&gt; ppm 0.81 - 0.99 (m, 2 H) 1.67 (dt, 7=9.57, 7.05 Hz, 1 H) 3.97 (br. s., 1 H) 4.57 - 4.89 (m, 2 H) 5.59 (s, 2 H) 7.42 (d, 7=8.62 Hz, 1 H) 7.88 (dd, 7=8.62, 2.63 Hz, 1 H) 8.08 (d, 7=8.33 Hz, 1 H) 8.16 (d, 7=2.68 Hz, 1 H) 8.33 (dd, 7=8.40, 2.27 Hz, 1 H) 8.87 (d, 7=2.19 Hz, 1 H) 10.70 (s, 1 H)</td>
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<td>276</td>
<td>C</td>
<td>N-(3-((1R,S,5S,R),(6R,S))-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chloropicolamide</td>
<td>300 MHz, DMSO-d&lt;sub&gt;6&lt;/sub&gt; ppm 0.78 - 1.05 (m, 2 H) 1.43 - 1.61 (m, 1 H) 1.62 - 1.83 (m, 1 H) 3.97 (br. s., 1 H) 4.46 - 4.99 (m, 2 H) 5.60 (br. s., 2 H) 7.42 (d, 7=8.62 Hz, 1 H) 7.88 (d, 7=8.33 Hz, 1 H) 8.08 - 8.34 (m, 3 H) 8.79 (s, 1 H) 10.69 (br. s., 1 H)</td>
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<td>277</td>
<td>B</td>
<td>N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5 -</td>
<td>300 MHz, DMSO-d&lt;sub&gt;6&lt;/sub&gt; ppm 0.95 (br. s., 2 H) 1.73 (br. s., 1 H) 4.11 (br. s., 1 H) 4.62 - 5.04 (m, 2 H) 7.49 (d, 7=8.48 Hz, 1 H) 7.94 (d, 7=9.21 Hz, 1 H) 8.21 (d, 7=2.19 Hz, 1 H)</td>
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<td>N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-ene-5-yl)-4-chlorophenyl)-5-cyanopicolinamide</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>MS m/z = 400.1 [M+H]^+.&lt;br&gt;(^1)H NMR (300 MHz, DMSO-d&lt;sub&gt;6&lt;/sub&gt;)&lt;br&gt;ppm 0.71 - 1.13 (m, 2 H) 1.53 - 1.83 (m, 1 H) 4.00 (br. s., 1 H) 4.53 - 4.95 (m, 13 H) 5.39 - 5.90 (m, 2 H) 7.45 (d, J=8.62 Hz, 1 H) 7.90 (dd, J=8.62, 2.63 Hz, 1 H) 8.11 - 8.38 (m, 2 H) 8.58 (dd, J=8.18, 2.05 Hz, 1 H) 9.21 (d, J=1.17 Hz, 1 H) 10.88 (s, 7 H)</td>
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<td>N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-ene-5-yl)-4-chlorophenyl)-5-(prop-2-yn-1-yloxy)pyrazine-2-carboxamide</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>MS m/z = 430.1 [M+H]^+.&lt;br&gt;(^1)H NMR (300 MHz, DMSO-d&lt;sub&gt;6&lt;/sub&gt;)&lt;br&gt;ppm 0.93 (br. s., 2 H) 1.71 (br. s., 1 H) 3.64 (t, J=2.41 Hz, 1 H) 3.92 - 4.23 (m, 1 H) 4.58 - 4.96 (m, 2 H) 5.14 (d, J=2.34 Hz, 2 H) 5.75 (s, 1 H) 7.45 (d, J=8.48 Hz, 1 H) 7.89 (d, J=7.45 Hz, 1 H) 8.18 (d, J=2.34 Hz, 1 H) 8.49 (d, J=1.32 Hz, 1 H) 8.91 (d, J=1.32 Hz, 1 H) 10.61 (br. s., 1 H)</td>
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<td>N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-ene-5-yl)-4-chlorophenyl)-5-(prop-2-yn-1-yloxy)pyrazine-2-carboxamide</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>MS m/z = 430.1 [M+H]^+.&lt;br&gt;(^1)H NMR (300 MHz, DMSO-d&lt;sub&gt;6&lt;/sub&gt;)&lt;br&gt;ppm 0.77 - 1.04 (m, 2 H) 1.55 - 1.78 (m, 1 H) 3.64 (t, J=2.34 Hz, 1 H) 3.98 (br. s., 1 H) 4.55 - 4.89 (m, 2 H) 5.14 (d, J=2.48 Hz, 2 H) 5.60 (br. s., 2 H) 7.42 (d, J=8.62 Hz, 1 H) 7.86 (dd, J=8.62, 2.48 Hz, 1 H) 8.17 (d, J=2.48 Hz, 1 H) 8.49 (d, J=1.32 Hz, 1 H) 8.90 (d, J=1.17 Hz, 1 H) 10.57 (s, 6 H)</td>
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<td>N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-ene-5-yl)-4-chlorophenyl)-3,5-dichloropicolinamide</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>MS m/z = 443.0 [M+H]^+.&lt;br&gt;(^1)H NMR (300 MHz, DMSO-d&lt;sub&gt;6&lt;/sub&gt;)&lt;br&gt;ppm 0.71 - 1.07 (m, 2 H) 1.58 - 1.81 (m, 1 H) 3.94 (br. s., 1 H) 4.56 - 4.72 (m, 1 H) 4.74 - 4.89 (m, 1 H) 5.62 (br. s., 2 H) 7.44 (d, J=8.62 Hz, 1 H) 7.81 (dd, J=8.55, 2.56 Hz, 1 H) 7.92 (d, J=2.48 Hz, 1 H) 8.44 (d, J=2.05 Hz, 1 H) 8.73 (d, J=2.05 Hz, 1 H) 10.83 (s, 1 H)</td>
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<td>282</td>
<td>B</td>
<td>N-(3-((IR,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-methoxypicolinamide</td>
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<td>283</td>
<td>B</td>
<td>N-(3-((IR,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-cyano-3-methympicolinamide</td>
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<td>284</td>
<td>B</td>
<td>N-(3-((IR,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-3-chloro-5-methympicolinamide</td>
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<td>285</td>
<td>B</td>
<td>N-(3-((IR,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-(but-2-yn-1-yl)oxy)pyrazine-2-carboxamide</td>
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<td>286</td>
<td>B</td>
<td>N-(3-((IR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-6-chloropicolinamide</td>
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**287 B**
N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-4-chloropicolinamide

MS m/z = 411.1 [M+H]+.

1H NMR (400 MHz, DMSO-d6)
ppm 0.74 - 1.04 (m, 1 H) 1.15 (br. s., 1 H) 1.58 - 1.86 (m, 1 H) 4.03 (br. s., 1 H) 5.85 (br. s., 2 H) 6.00 - 6.42 (m, 1 H) 7.22 (dd, J=1.84, 8.90 Hz, 1 H) 7.79 - 7.95 (m, 2 H) 8.04 (dd, J=7.04, 2.74 Hz, 1 H) 8.15 (d, J=1.96 Hz, 1 H) 8.72 (d, J=5.28 Hz, 1 H) 10.73 (s, 1 H)

**288 B**
N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-isopropylpicolinamide

MS m/z = 419.1 [M+H]+.

1H NMR (300 MHz, DMSO-d6)
ppm 0.85 - 0.98 (m, 1 H) 1.07 (s, 1 H) 1.10 - 1.20 (m, 2 H) 1.23 (dd, J=6.87, 0.88 Hz, 5 H) 1.64 - 1.78 (m, 1 H) 1.99 (s, 1 H) 3.57 (quin., J=6.87 Hz, 1 H) 3.89 - 4.09 (m, 2 H) 5.86 (br. s., 2 H) 5.98 - 6.46 (m, 1 H) 7.12 - 7.29 (m, 1 H) 7.53 (dd, J=8.04, 4.68 Hz, 1 H) 7.82 - 7.89 (m, 2 H) 7.95 (dd, J=7.97, 1.39 Hz, 1 H) 8.49 (dd, J=4.68, 1.46 Hz, 1 H) 10.59 (s, 1 H)

**289 B**
N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloropicolinamide

MS m/z = 453.2 [M+H]+.

1H NMR (300 MHz, DMSO-d6)
ppm 0.79 - 1.01 (m, 1 H) 1.09 - 1.18 (m, 2 H) 1.24 (d, J=6.87 Hz, 6 H) 1.62 - 1.82 (m, 1 H) 3.51 (quin., J=6.87 Hz, 1 H) 3.85 - 4.13 (m, 2 H) 5.87 (s, 2 H) 5.99 - 6.43 (m, 1 H) 7.21 (dd, J=1.62, 8.55 Hz, 1 H) 7.73 - 7.92 (m, 2 H) 8.09 (d, J=2.19 Hz, 1 H) 8.54 (d, J=2.19 Hz, 1 H) 10.63 (s, 1 H)

**290 B**
N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-bromo-3-(difluoromethyl)picolinamide

MS m/z = 505 [M+H]+.

1H NMR (400 MHz, DMSO-d6)
ppm 0.81 - 1.02 (m, 1 H) 1.08 - 1.22 (m, 2 H) 1.14 (br. s., 1 H) 1.66 - 1.79 (m, 1 H) 3.94 - 4.10 (m, 1 H) 5.82 - 5.89 (m, 2 H) 5.86 (br. s., 2 H) 6.00 - 6.41 (m, 1 H) 7.16 - 7.29 (m, 1 H) 7.53 - 7.98 (m, 3 H) 8.51 (s, 1 H) 9.02 (s, 1 H) 10.85 (s, 1 H)

**291 B**
N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-phenylpicolinamide

MS m/z = 453.2 [M+H]+.

1H NMR (300 MHz, DMSO-d6)
ppm 0.77 - 1.05 (m, 1 H) 1.10 - 1.34 (m, 1 H) 1.60 - 1.86 (m, 1 H) 3.92 - 4.12 (m, 1 H) 5.87 (s, 2 H) 5.98 - 6.44 (m, 1 H) 7.10 - 7.33 (m, 1 H) 7.41 - 7.72 (m, 3 H) 7.84 (d, J=7.60 Hz, 2 H)
| 292 | B | N-(3-(((R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-ene-5-yl)-4-fluorophenyl)-3-methylpicolinamide | ![Chemical Structure](image) | MS m/z = 377.1 [M+H]^+.

$^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 0.86 - 0.99 (m, 1 H) 1.09 - 1.23 (m, 1 H) 1.65 - 1.81 (m, 1 H) 3.17 (d, $J$=5.5 Hz, 2 H) 3.97 - 4.13 (m, 1 H) 5.86 (s, 2 H) 5.98 - 6.43 (m, 1 H) 7.14 - 7.31 (m, 1 H) 7.61 - 7.75 (m, 1 H) 7.84 - 7.95 (m, 1 H) 8.00 - 8.20 (m, 3 H) 8.62 - 8.84 (m, 1 H) 10.57 - 10.77 (m, 1 H) |

| 293 | B | N-(3-(((R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-ene-5-yl)-4-fluorophenyl)-3-methylpicolinamide | ![Chemical Structure](image) | MS m/z = 391.1 [M+H]^+.

$^3$N NMR (300 MHz, DMSO-$d_6$) δ ppm 0.76 - 1.01 (m, 1 H) 1.06 - 1.25 (m, 1 H) 1.59 - 1.83 (m, 1 H) 2.56 (s, 3 H) 3.86 - 4.10 (m, 1 H) 5.85 (s, 2 H) 5.96 - 6.45 (m, 1 H) 7.08 - 7.30 (m, 1 H) 7.46 - 7.58 (m, 1 H) 7.88 (br. s., 3 H) 8.41 - 8.65 (m, 1 H) 10.57 (s, 1 H) |

| 294 | A | N-(3-(((R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-ene-5-yl)-4-methylphenyl)-5-methoxyphenyl)-2-carboxamide | ![Chemical Structure](image) | MS m/z = 404.0 [M+H]^+.

$^1$H NMR (400 MHz, CHLOROFORM-d) δ ppm 9.51 (br. s., 1 H) 9.01 (s, 1 H) 8.15 (s, 1 H) 8.08 (s, 1 H) 7.64 (s, 1 H) 7.19 (d, $J$=7.84 Hz, 1 H) 6.00 - 6.41 (m, 1 H) 4.04 - 4.13 (m, 4 H) 2.58 (s, 3 H) 1.65 - 1.78 (m, 1 H) 1.45 - 1.55 (m, 1 H) 0.99 - 1.06 (m, 1 H) |

| 295 | A | N-(3-(((R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-ene-5-yl)-4-methylphenyl)-5-chloropicolinamide | ![Chemical Structure](image) | MS m/z = 407.0 [M+H]^+.

$^1$H NMR (400 MHz, CHLOROFORM-d) δ ppm 9.81 (br. s., 1 H) 8.55 (s, 1 H) 8.24 (d, $J$=8.22 Hz, 1 H) 8.08 (s, 1 H) 7.83 - 7.92 (m, 1 H) 7.68 (d, $J$=7.82 Hz, 1 H) 7.20 (d, $J$=8.22 Hz, 1 H) 6.20 (t, $J$=5.62 Hz, 1 H) 4.07 (br. s., 1 H) 2.59 (s, 3 H) 1.73 - 1.98 (m, 1 H) 1.48 (t, $J$=5.87 Hz, 1 H) 0.83 - 1.08 (m, 1 H) |
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<td>N-(3-((l S,5R,6S)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-bromopicolinamide</td>
<td><img src="image1" alt="Structure" /></td>
<td>MS m/z = 455.0 [M+H]+&lt;br&gt;(\text{\textsuperscript{1}H NMR (400 MHz, CHLOROFORM-d)}) δ ppm 0.95 (dd, J=16.04, 6.85 Hz, 1 H) 1.42 (br. s., 1 H) 1.86 (dd, J=15.85, 8.61 Hz, 1 H) 3.89 - 3.95 (m, 1 H) 4.63 (br. s., 2 H) 6.23 (t, J=55.90 Hz, 1 H) 7.06 (t, J=10.20 Hz, 1 H) 7.63 (d, J=6.43 Hz, 1 H) 7.93 - 8.00 (m, 1 H) 8.01 (d, J=8.57 Hz, 1 H) 8.12 (d, J=8.41 Hz, 1 H) 8.59 (s, 1 H) 9.74 (br. s., 1 H)</td>
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<td>297</td>
<td>N-(3-((lR,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-chloro-3-methoxypicolinamide</td>
<td><img src="image2" alt="Structure" /></td>
<td>MS m/z = 439.0 [M+H]+&lt;br&gt;(\text{\textsuperscript{1}H NMR (300MHz, DMSO)}) Shift = 10.56 (s, IH) 8.27 (s, IH) 7.94 (s, IH) 7.85 (s, IH) 7.81 (d, J=8.8 Hz, IH) 7.40 (d, J=8.5 Hz, IH) 5.59 (s, 2H) 4.80 (s, IH) 4.64 (s, IH) 3.99 - 3.87 (m, 4H) 1.72 - 1.62 (m, IH) 0.93 (d, J=4.8 Hz, IH) 0.90 - 0.80 (m, 1H)</td>
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<td>N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluoro-5-methylphenyl)-5-cyanopyrimidine-2-carboxamide</td>
<td><img src="image3" alt="Structure" /></td>
<td>MS m/z = 416.9 [M+H]+&lt;br&gt;(\text{\textsuperscript{1}H NMR (300MHz, DMSO)}) Shift = 10.86 (s, IH) 9.52 (s, 2H) 7.84 - 7.69 (m, 2H) 6.44 - 6.01 (m, 2H) 5.84 (s, 2H) 4.00 (br. s., IH) 2.27 (s, 3H) 1.77 - 1.65 (m, 5H) 1.13 (br. s., IH) 0.90 (d, J=7.9 Hz, IH)</td>
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<td>299</td>
<td>N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluoro-5-methylphenyl)-5-methoxy-3-methylpyrazine-2-carboxamide</td>
<td><img src="image4" alt="Structure" /></td>
<td>MS m/z = 422.1 [M+H]+&lt;br&gt;(\text{\textsuperscript{1}H NMR (300MHz, DMSO)}) Shift = 10.39 (s, IH) 8.88 (d, J=1.3 Hz, IH) 8.41 (d, J=1.3 Hz, IH) 7.96 - 7.55 (m, 2H) 6.49 - 5.98 (m, 2H) 5.82 (s, 2H) 4.02 (s, 3H) 2.26 (d, J=2.2 Hz, 3H) 1.83 - 1.63 (m, 5H) 1.13 (br. s., IH) 1.01 - 0.80 (m, 1H)</td>
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<td>N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluoro-5-methylphenyl)-5-methoxy-3-methylpyrazine-2-carboxamide</td>
<td><img src="image5" alt="Structure" /></td>
<td>MS m/z = 436.1 [M+H]+&lt;br&gt;(\text{\textsuperscript{1}H NMR (300MHz, DMSO)}) Shift = 10.35 (s, IH) 8.23 (s, IH) 7.84 - 7.76 (m, IH) 7.71 - 7.62 (m, IH) 6.43 - 6.02 (m, 2H) 5.83 (s, 2H) 4.07 - 3.90 (m, 4H) 2.74 (s, 3H) 2.26 (s, 3H) 1.77 - 1.65 (m, 5H) 1.18 - 1.07 (m, J=3.7 Hz, IH) 0.98 - 0.84 (m, IH)</td>
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<td>301 A</td>
<td>N-((3-((1R,5S,6R)-3-aminooxo-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-methoxy-3-methylpyrazine-2-carboxamide</td>
<td>MS m/z = 420 [M+H]^+ 3(^{1})H NMR (300MHz, DMSO) Shift = 10.88 (br. s., IH), 8.22 (s., IH), 8.08 - 7.95 (m, 2H), 7.49 (d, J=8.8 Hz, IH), 4.98 (d, J=13.2 Hz, IH), 4.82 (d, J=12.9 Hz, IH), 4.25 (br. s., IH), 3.99 (s, 3H), 2.74 (s, 3H), 1.91 (br. s., IH), 1.10 - 0.88 (m, 2H)</td>
<td></td>
</tr>
<tr>
<td>302 A</td>
<td>N-((3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluoro-5-methylphenyl)-5-chloro-3-fluoropicolinamide</td>
<td>MS m/z = 443 [M+H]^+ 3(^{1})H NMR (300MHz, DMSO) Shift = 10.60 (s, IH), 8.73 - 8.60 (m, IH), 8.32 (dd, J=1.9, 10.2 Hz, IH), 7.79 - 7.61 (m, 2H), 6.47 - 5.98 (m, IH), 5.85 (s, 2H), 4.08 - 3.91 (m, IH), 2.26 (d, J=2.2 Hz, 3H), 1.75 - 1.65 (m, IH), 1.16 - 1.08 (m, IH), 0.96 - 0.85 (m, IH)</td>
<td></td>
</tr>
<tr>
<td>303 A</td>
<td>N-((3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluoro-5-methylphenyl)-5-chloro-3-methylpyridinamide</td>
<td>MS m/z = 439.1 [M+H]^+ 3(^{1})H NMR (300MHz, DMSO) Shift = 10.52 (s, IH), 8.57 (d, J=2.0 Hz, IH), 8.02 (d, J=1.8 Hz, IH), 7.80 (d, J=3.8 Hz, IH), 7.65 (dd, J=2.8, 6.6 Hz, IH), 6.52 - 5.75 (m, 3H), 4.04 (br. s., IH), 3.96 - 3.90 (m, IH), 2.55 (s, 3H), 2.26 (d, J=2.0 Hz, 3H), 1.70 - 1.68 (m, IH), 1.21 - 1.11 (m, IH), 0.99 - 0.90 (m, IH)</td>
<td></td>
</tr>
<tr>
<td>304 A</td>
<td>N-((3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluoro-5-methylphenyl)-5-methoxypyridinamide</td>
<td>MS m/z = 421.1 [M+H]^+ 3(^{1})H NMR (300MHz, DMSO) Shift = 10.34 (s, IH), 8.39 (d, J=2.8 Hz, IH), 8.12 (d, J=8.8 Hz, IH), 7.79 (t, J=5.8 Hz, 2H), 7.62 (dd, J=2.9, 8.8 Hz, IH), 6.45 - 6.00 (m, IH), 5.83 (s, 2H), 4.05 - 3.97 (m, IH), 3.94 (s, 3H), 2.26 (d, J=2.2 Hz, 3H), 1.78 - 1.66 (m, IH), 1.14 (br. s., IH), 0.97 - 0.86 (m, IH)</td>
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<tr>
<td>305 A</td>
<td>N-((3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluoro-5-methylphenyl)-5-methoxypyridinamide</td>
<td>MS m/z = 435 [M+H]^+ 3(^{1})H NMR (300MHz, DMSO) Shift = 10.31 (s, IH), 8.22 (d, J=2.6 Hz, IH), 7.92 - 7.74 (m, IH), 7.68 - 7.57 (m, IH), 7.41 (d, J=2.6 Hz, IH), 6.41 - 6.01 (m, IH), 5.84 (s, 2H), 4.04 - 3.95 (m, IH), 3.91 (s, 3H), 2.62 (s, 3H), 2.26 (d, J=2.0 Hz, 3H), 1.77 - 1.66 (m, IH), 1.17 - 1.09 (m, IH), 0.96 - 0.84 (m, IH)</td>
<td></td>
</tr>
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</table>
306 A N-(3-((1R,5S,6R)-3-amino-5- (difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept- 3-en-5-yl)-4- fluorophenyl)-3-fluoro- 5-methoxypicolinamide

MS m/z = 425.1 [M+H]^+
1H NMR (400 MHz, MeOH-d4) δ:
8.26 (d, J=1.6 Hz, 1H), 7.82-7.89 (m, 2H), 7.41 (dd, J=12.7, 2.3 Hz, 1H), 7.18 (dd, J=11.8, 9.3 Hz, 1H), 6.12- 6.46 (m, 1H), 4.03-4.11 (m, 1H), 4.00 (s, 3H), 1.84-1.97 (m, 1H), 1.35 (t, J=5.8 Hz, 1H), 1.00 (dt, J=9.5, 6.8 Hz, 1H)

307 A N-(3-((1R,5S,6R)-3-amino-5- (difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept- 3-en-5-yl)-4- fluorophenyl)-5-fluoro- 3-methoxypicolinamide

MS m/z = 425.1 [M+H]^+
1H NMR (400 MHz, MeOH-d4) δ:
8.18 (d, J=2.2 Hz, 1H), 7.85-7.91 (m, 1H), 7.80 (dd, J=6.9, 2.6 Hz, 1H), 7.76-7.82 (m, 1H), 7.59 (dd, J=10.7, 2.2 Hz, 1H), 7.18 (dd, J=11.7, 8.8 Hz, 1H), 6.12-6.45 (m, 1H), 4.03-4.10 (m, 1H), 4.00 (s, 3H), 1.87-1.93 (m, 1H), 1.35 (t, J=6.7 Hz, 1H), 1.00 (dt, J=9.4, 6.7 Hz, 1H)

308 A N-(3-((1R,5S,6R)-3-amino-5- (difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept- 3-en-5-yl)-4- fluorophenyl)-5-chloro- 3-(fluoromethyl)picolinamide

MS m/z = 442.9 [M+H]^+
1H NMR (300 MHz, DMSO-d6) δ ppm 0.85 - 0.97 (m, 1H) 1.10 - 1.27 (m, 3 H, contains EtOAc) 1.66 - 1.81 (m, 1 H) 3.96 - 4.09 (m, 2 H, contains EtOAc) 5.80 - 6.41 (m, 5 H) 7.15 - 7.27 (m, 1 H) 7.79 - 7.87 (m, 1 H) 7.90 - 7.97 (m, 1 H) 8.16 (d, J=2.19 Hz, 1 H) 8.76 (d, J=2.19 Hz, 1 H) 10.73 (s, 1 H)

309 A N-(3-((1R,S),(5S,R),(6R,S))-3-amino-5- (difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept- 3-en-5-yl)-5-fluoro-4- methylphenyl)-5-cyano- 3-methylpicolinamide

MS m/z = 430.0 [M+H]^+
1H NMR (400 MHz, CHLOROFORM-d) δ 10.03 (s, 1H), 8.69 (s, 1H), 7.94 (s, 1H), 7.79 (d, J=11.54 Hz, 1H), 7.63 (s, 1H), 5.91- 6.42 (m, 1H), 4.45 (br s., 2H), 4.00- 4.10 (m, 1H), 2.87 (s, 3H), 2.48 (d, J=2.74 Hz, 3H), 1.75-1.93 (m, 1H), 1.48 (t, J=5.97 Hz, 1H), 0.97-1.13 (m, 1H)

310 A N-(3-((1R,5S,6R)-3-amino-5- (difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept- 3-en-5-yl)-5-fluoro-4- methylphenyl)-5-cyano- 3-methylpicolinamide

MS m/z = 430.0 [M+H]^+
1H NMR (400 MHz, CHLOROFORM-d) δ 10.04 (s, 1H), 8.69 (d, J=1.56 Hz, 1H), 7.94 (s, 1H), 7.80 (dd, J=1.86, 11.44 Hz, 1H), 7.63 (s, 1H), 7.58-7.68 (m, 1H), 5.92-6.43 (m, 1H), 4.65 (br s., 2H), 4.08 (t, J=5.67 Hz, 1H), 2.86 (s, 3H), 2.78- 2.96 (m, 3H), 2.78-2.96 (m, 3H), 2.48 (d, J=3.13 Hz, 3H), 1.85 (td, J=7.04, 9.78 Hz, 1H), 1.43-1.57 (m, 1H), 0.99- 1.12 (m, 1H)
<table>
<thead>
<tr>
<th>Table Entries</th>
<th>Chemical Structures</th>
<th>MS m/z</th>
<th>NMR Conditions</th>
<th>NMR Data Points</th>
</tr>
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<tr>
<td>311 A</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>430.0 [M+H]^+</td>
<td>1H NMR (400 MHz), CHLOROFORM-d</td>
<td>δ 10.02 (s, 1H), 8.67 (d, J=1.56 Hz, 1H), 7.94 (s, 1H), 7.79 (dd, J=1.96, 11.35 Hz, 1H), 7.61 (s, 1H), 5.99-6.47 (m, 1H), 4.62 (br. s., 2H), 4.07 (t, J=5.48 Hz, 1H), 2.86 (s, 3H), 2.48 (d, J=3.13 Hz, 3H), 1.84 (td, J=7.04, 9.78 Hz, 1H), 1.41-1.58 (m, 1H), 0.95-1.14 (m, 1H).</td>
</tr>
<tr>
<td>312 B</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>442.9 [M+H]^+</td>
<td>1H NMR (300 MHz), CHLOROFORM-d</td>
<td>δ ppm 0.98 - 1.14 (m, 1 H) 1.49 (br. s., 1 H) 1.96 (q, J=8.14 Hz, 1 H) 4.05 (br. s., 1 H) 6.03 - 6.92 (m, 2 H) 7.06 - 7.21 (m, 1 H) 7.66 (d, J=8.18 Hz, 1 H) 7.72 (d, J=6.72 Hz, 1 H) 7.93 - 8.06 (m, 1 H) 8.30 (d, J=8.62 Hz, 1 H) 8.45 (s, 1 H) 9.84 (br. s., 1 H).</td>
</tr>
<tr>
<td>313 B</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>401 [M+H]^+</td>
<td>1H NMR (300 MHz), CHLOROFORM-d</td>
<td>δ ppm 0.92 - 1.10 (m, 1 H) 1.45 (t, J=6.65 Hz, 1 H) 1.91 (dt, J=9.61, 7.11 Hz, 1 H) 3.90 - 4.08 (m, 1 H) 4.84 (br. s., 1 H) 6.01 - 6.48 (m, 1 H) 7.11 (dd, J=11.55, 8.92 Hz, 1 H) 7.69 (dd, J=6.72, 2.78 Hz, 1 H) 7.91 - 8.06 (m, 2 H) 8.24 (dd, J=8.04, 0.73 Hz, 1 H) 8.67 (d, J=1.32 Hz, 1 H) 9.90 (s, 1 H).</td>
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<td>314 B</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>415 [M+H]^+</td>
<td>1H NMR (400 MHz), CHLOROFORM-d</td>
<td>δ ppm 0.92 - 1.07 (m, 1 H) 1.44 (t, J=6.65 Hz, 1 H) 1.83 - 1.96 (m, 1 H) 2.13 (s, 3 H) 3.93 - 4.03 (m, 1 H) 4.67 (br. s., 2 H) 6.05 - 6.46 (m, 1 H) 7.12 (dd, J=11.54, 8.80 Hz, 1 H) 7.69 (dd, J=6.75, 2.64 Hz, 1 H) 7.85 (dd, J=8.12, 1.86 Hz, 1 H) 8.01 (dt, J=8.80, 3.42 Hz, 1 H) 8.19 (d, J=8.02 Hz, 1 H) 8.57 (d, J=1.37 Hz, 1 H) 9.91 (s, 1 H).</td>
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<tr>
<td>315 B</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td>505.9 [M+H]^+</td>
<td>1H NMR (400 MHz, DMSO-d6)</td>
<td>δ ppm 10.78 (s, 1 H) 8.44 (s, 1 H) 8.00 (dd, J=11.15, 2.35 Hz, 1 H) 7.92 (s, 1 H) 5.62 (s, 2 H) 5.14 (q, J=9.00 Hz, 2 H) 4.51 - 4.89 (m, 2 H) 4.00 (m, J=5.67, 5.67 Hz, 1 H) 2.77 (s, 3 H) 1.61 (dt, J=9.83, 7.02 Hz, 1 H) 0.95 (td, J=6.55, 2.74 Hz, 1 H) 0.84 - 0.92 (m, 1 H).</td>
</tr>
</tbody>
</table>
| 316 | B | N-(3-((1S,5R,6S)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chloro-5-fluorophenyl)-5-(prop-2-yn-1-yloxy)pyrazine-2-carboxamide | MS \( m/z = 505.9 \{M+H\}^+ \\
\text{H NMR (400 MHz, DMSO-d6) \( \delta \)} ppm 10.78 (s, 1 H), 8.44 (s, 1 H), 8.00 (dd, J=11.15, 2.35 Hz, 1 H), 7.92 (s, 1 H), 5.62 (s, 2 H), 5.14 (q, J=9.90 Hz, 2 H), 4.51 - 4.89 (m, 2 H), 4.00 (m, J=5.67, 5.67 Hz, 1 H), 2.77 (s, 3 H), 1.61 (dt, J=9.83, 7.02 Hz, 1 H), 0.95 (td, J=6.55, 2.74 Hz, 1 H), 0.84 - 0.92 (m, 1 H) |
| 317 | B | N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chloro-5-fluorophenyl)-5-(prop-2-yn-1-yloxy)pyrazine-2-carboxamide | MS \( m/z = 448 \{M+H\}^+ \\
\text{H NMR (400 MHz, DMSO-d6) \( \delta \)} ppm 0.82 - 1.01 (m, 2 H), 1.57-1.66 (m, 1 H), 3.64 (t, J=2.35 Hz, 1 H), 4.01 (t, J=5.67 Hz, 1 H), 4.53 - 4.88 (m, 2 H), 5.14 (d, J=2.35 Hz, 2 H), 5.62 (br s, 2 H), 8.00 (dd, J=11.15, 2.35 Hz, 1 H), 8.08 (s, 1 H), 8.50 (d, J=1.17 Hz, 1 H), 8.92 (d, J=1.17 Hz, 1 H), 10.80 (s, 1 H) |
| 318 | B | N-(3-((1S,5R,6S)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chloro-5-fluorophenyl)-5-(prop-2-yn-1-yloxy)pyrazine-2-carboxamide | MS \( m/z = 448 \{M+H\}^+ \\
\text{H NMR (400 MHz, DMSO-d6) \( \delta \)} ppm 0.82 - 1.01 (m, 2 H), 1.57-1.66 (m, 1 H), 3.64 (t, J=2.35 Hz, 1 H), 4.01 (t, J=5.67 Hz, 1 H), 4.53 - 4.88 (m, 2 H), 5.14 (d, J=2.35 Hz, 2 H), 5.62 (br s, 2 H), 8.00 (dd, J=11.15, 2.35 Hz, 1 H), 8.08 (s, 1 H), 8.50 (d, J=1.17 Hz, 1 H), 8.92 (d, J=1.17 Hz, 1 H), 10.80 (s, 1 H) |
| 441 | A | N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-chloro-3-(fluoromethyl)picolinamide | MS \( m/z = 441 \{M+H\}^+ \\
\text{H NMR (400 MHz, DMSO-d6) \( \delta \)} ppm 0.81 - 0.90 (m, 1 H), 0.91 - 0.99 (m, 1 H), 1.62 - 1.71 (m, 1 H), 3.29 - 3.32 (m, 2 H), 3.93 - 3.99 (m, 1 H), 4.59 - 4.86 (m, 2 H), 5.54 - 5.65 (m, 2 H), 5.84 - 5.93 (m, 1 H), 5.97 - 6.04 (m, 1 H), 7.36 - 7.50 (m, 1 H), 7.79 - 7.87 (m, 1 H), 8.05 - 8.11 (m, 1 H), 8.13 - 8.19 (m, 1 H), 8.74 - 8.82 (m, 1 H), 10.70 - 10.82 (m, 1 H) |
| 442 | A | N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-chloro-3-fluoropicolinamide | MS \( m/z = 427 \{M+H\}^+ \\
\text{H NMR (300MHz, DMSO) Shift = 10.74 (s, 1 H), 10.82 - 10.63 (m, 1 H), 8.74 - 8.57 (m, 1 H), 8.33 (dd, J=1.9, 10.4 Hz, 1 H), 8.04 (d, J=2.5 Hz, 1 H), 7.82 (dd, J=2.6, 8.6 Hz, 1 H), 7.43 (d, J=8.5 Hz, 1 H), 5.83 - 5.43 (m, 2 H), 4.81 (s, 1 H), 4.65 (s, 1 H), 3.97 (br s., 1 H), 1.67 (td, J=6.9, 9.5 Hz, 1 H), 0.95 (d, J=4.2 Hz, 1 H), 0.86 (td, J=6.3, 9.5 Hz, 1 H) |
| 443 | A | N-(3-(((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-3-methylpicolinamide | **MS m/z = 423 [M]⁺**<br>1H NMR (300MHz, DMSO) Shift = 10.65 (s, 1H), 8.59 (d, J=2.2 Hz, 1H), 8.05 - 8.03 (m, 1H), 8.02 (d, J=2.6 Hz, 1H), 7.85 (dd, J=2.6, 8.7 Hz, 1H), 7.41 (d, J=8.6 Hz, 1H), 5.62 (s, 2H), 4.86 - 4.74 (m, 1H), 4.71 - 4.60 (m, 1H), 3.95 (br. s., 1H), 2.56 (s, 3H), 1.73 - 1.61 (m, 1H), 0.96 - 0.90 (m, 1H), 0.85 (td, J=6.2, 9.4 Hz, 1H) |
| 444 | A | N-(3-(((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluoro-5-methylphenyl)-4-chloro-2-(fluoromethyl)benzamid e | **MS m/z = 457 [M+H]⁺**<br>1H NMR (300MHz, DMSO) Shift = 10.65 (s, 1H), 8.77 (d, J=2.3 Hz, 1H), 8.16 (d, J=2.3 Hz, 1H), 7.85 - 7.75 (m, 1H), 7.70 (dd, J=2.6, 6.4 Hz, 1H), 6.42 - 6.03 (m, 1H), 6.02 (s, 1H), 5.89 - 5.84 (m, 3H), 4.06 - 3.96 (m, 1H), 2.26 (d, J=2.0 Hz, 3H), 1.70 (dd, J=7.2, 16.6 Hz, 1H), 1.14 (d, J=5.8 Hz, 1H), 0.97 - 0.85 (m, 1H) |
| 445 | A | N-(3-(((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-fluoropicolinamide | **MS m/z = 393 [M+H]⁺**<br>1H NMR (300MHz, DMSO) Shift = 10.94 (br. s., 1H), 8.73 (d, J=2.6 Hz, 1H), 8.36 - 8.14 (m, 2H), 8.09 - 7.91 (m, 2H), 7.46 (d, J=8.8 Hz, 1H), 5.10 - 4.72 (m, 2H), 4.22 (br. s., 1H), 1.98 - 1.78 (m, 1H), 1.22 (d, J=13.3 Hz, 1H), 1.01 (d, J=8.0 Hz, 1H) |
Examples 319 and 320

Step 1: N-(3-((1S,5R,6S)-3-benzamido-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-methoxypyrazine-2-carboxamide (319a) and N-(3-((1R,5S,6R)-3-benzamido-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-methoxypyrazine-2-carboxamide (320a)

N-(3-[(1S,R),5(R,S),6(S,R)]-3-benzamido-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-methoxypyrazine-2-carboxamide (3g-rac).

(912 mg, 1.92 mmol) was prepared by a similar procedure to that described in step 1 for the synthesis of 2a rac, but using N-[(1S,R),5(S,R),6(S,R)]-5-(5-amino-2-fluorophenyl)-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl]benzamide (3g-rac). The product was subsequently subjected to chromatography using supercritical CO₂ (additives: 20% iPrOH with 20 mM Ammonia in MeOH) on a OJ-H column (250 x 30 mm, 5 µη) eluting at a flow rate of 120 ml/min (100 bar pressure, 40 °C column temperature). The first peak (retention time = 3.62 min) provided N-(3-((1S,5R,6S)-3-benzamido-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-methoxypyrazine-2-carboxamide (319a) (0.341 g, 0.717 mmol, 39.3% yield; 99% de; 99% ee) as a white solid. The second peak (retention time = 4.38 min) provided N-(3-((1R, 5S, 6R)-3-benzamido-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-methoxypyrazine-2-carboxamide (320a) (0.343 g, 0.722 mmol, 39.5% yield; 99% de; 99% ee) as a white solid. MS m/z = 476 [M+H]⁺ (for both enantiomers). Calculated for C₂₃H₂₂FN₅O₄: 475.47
Step 2a: N-(3-((1S,5R,6S)-3-amino-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-methoxypyrazine-2-carboxamide (Example 319)

A sealed vial was charged with N-(3-((1S,5R,6S)-3-benzamido-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-methoxypyrazine-2-carboxamide (319a, 0.341 g, 0.717 mmol) and ammonia (2.0M solution in methanol; 7.17 ml, 14.34 mmol, Aldrich). The reaction mixture was heated to 80 °C for 24 h. The reaction was concentrated under reduced pressure and purified via silica gel flash chromatography using a gradient of 0-10% (2M ammonia in MeOH)/DCM to afford the title compound as a white solid. (0.129 g, 0.347 mmol, 48.4 % yield).


31'H NMR (300 MHz, CHLOROFORM-J) \( \delta \) ppm 0.87 - 0.96 (m, 1 H) 0.98 - 1.07 (m, 1 H) 1.69 (d, \( J=1.17 \) Hz, 3 H) 1.77 - 1.88 (m, 1 H) 3.96 - 4.04 (m, 1 H) 4.08 (s, 3 H) 7.07 (dd, \( J=1.55 \), 8.77 Hz, 1 H) 7.53 (dd, \( J=7.02 \), 2.78 Hz, 1 H) 7.86 - 7.93 (m, 1 H) 8.15 (d, \( J=1.32 \) Hz, 1 H) 9.01 (d, \( J=1.32 \) Hz, 1 H) 9.46 (br. s., 1 H)


1'H NMR (300 MHz, CHLOROFORM-J) \( \delta \) ppm 0.86 - 0.96 (m, 1 H) 0.98 - 1.07 (m, 1 H) 1.69 (d, \( J=1.17 \) Hz, 3 H) 1.77 - 1.88 (m, 1 H) 3.96 - 4.04 (m, 1 H) 4.08 (s, 3 H) 7.09 (dd, \( J=1.55 \), 8.77 Hz, 1 H) 7.55 (dd, \( J=7.02 \), 2.78 Hz, 1 H) 7.86 - 7.95 (m, 1 H) 8.16 (d, \( J=1.32 \) Hz, 1 H) 9.02 (d, \( J=1.32 \) Hz, 1 H) 9.48 (br. s., 1 H)

General Metal-Catalyzed Amidation Procedures:

The following three (3) methods were used to couple the bromide core intermediates with corresponding amides to prepare compounds of the invention.

Method E: Copper (Cu) Catalyzed Amidation Procedure

Example 321: Synthesis of rac N-(6-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-5-fluoropyridin-2-yl)-5-chloropicolinamide
A sealable tube was charged with mixture of 17d rac (55 mg, 0.164 mmol), 5-chloropicolinamide (38.4 mg, 0.245 mmol), potassium carbonate (90 mg, 0.655 mmol) and copper (I) iodide (9.35 mg, 0.049 mmol). The vial was evacuated and backfilled with nitrogen gas. Dioxane (1 mL) was added, followed by (1R, 2R)-(−)-N,N''-dimethylcyclohexane-1,2-diamine (7.74 µL, 0.049 mmol). The reaction vial was sealed and heated to 100 °C for 2 h. The reaction mixture was cooled and purified by silica gel flash chromatography, eluting with a gradient of DCM/EtOAc = 4:1 to 3:1 to 2:1 to 1:1 to 1:2. The title compound was obtained as an offwhite solid (30 mg, 0.073 mmol, 44.5% yield). MS m/z = 412 [M+H]⁺

1H NMR (400MHz ,CHLOROFORM-d) δ = 10.29 (br. s., 1 H), 8.62 (d, J = 2.0 Hz, 1 H), 8.38 (dd, J = 3.0, 8.9 Hz, 1 H), 8.25 (d, J = 8.4 Hz, 1 H), 7.90 (dd, J = 2.2, 8.3 Hz, 1 H), 7.51 (t, J = 9.7 Hz, 1 H), 6.77 - 6.35 (m, 1 H), 4.24 - 4.06 (m, 1 H), 1.93 - 1.77 (m, 1 H), 1.53 (br. s., 1 H), 1.16 - 0.99 (m, 1 H).

Method F: Palladium (Pd) Catalyzed Amidation Procedure

Examples 322 & 323: Synthesis of N-(6-((1R,5S,6R)-3-amino-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-5-fluoropyridin-2-yl)-5-methoxypyrazine-2-carboxamide (Eg 322) and N-(6-((1S,5R,6S)-3-amino-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-5-fluoropyridin-2-yl)-5-methoxypyrazine-2-carboxamide (eg 323)
A sealable vial was charged with 4 d rac (0.2 g, 0.666 mmol), 5-methoxypyrrole-2-carboxamide (0.148 g, 0.966 mmol), (9,9-dimethyl-9H-xanthene-4,5-diy)bis(diphenylphosphine) (0.116 g, 0.200 mmol), Pd2dba3 (0.046 g, 0.050 mmol), and cesium carbonate (0.543 g, 1.666 mmol). The vial was evacuated and backfilled with N₂ gas. 1,4-Dioxane (2.5 mL) was added and the reaction mixture was stirred in a pre-heated 100 °C oil bath for 15.5 hours. The reaction mixture was cooled to RT and diluted with water and EtOAc. The organic layer was washed with water, brine and dried over magnesium sulfate. The filtrate was concentrated under reduced pressure. The crude residue was triturated with EtOAc and the solid was collected by filtration. The material was taken up in EtOAc and washed with water and brine. The organic layer was dried over magnesium sulfate and the filtrate was concentrated under reduced pressure to afford N-(6-((1R,5S,6R)-3-amino-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-5-fluoropyridin-2-yl)-5-methoxypyrrole-2-carboxamide (0.164 g, 0.440 mmol, 66% yield). This material was subjected to chromatography using supercritical C0₂(additives 20% MeOH with 20 mM NH₃) on a CHIRALPAK AS-H SFC column (21 x 250 mm, 5 μm) eluting at a flow rate 75 ml/min (100 bar pressure, 40 °C column temperature). The first peak (retention time = 1.16 min) provided N-(6-((1R,5S,6R)-3-amino-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-5-fluoropyridin-2-yl)-5-methoxypyrrole-2-carboxamide (Example 322, 32.1 mg, 0.086 mmol, 32.1% yield, 99% de; 99% ee). The second peak (retention time = 3.43 min) provided N-(6-((1 S,5R,6S)-3-amino-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-5-fluoropyridin-2-yl)-5-methoxypyrrole-2-carboxamide (Example 323, 33.4 mg, 0.090 mmol, 33.4% yield; 99% de; 99% ee). MS m/z = 373 [M+H]+. (for both enantiomers)

Peak 1: 1H NMR (300 MHz, DMSO-d6) δ ppm 0.73 (d, J=5.70 Hz, 1 H) 0.82 (dt, J=9.72, 6.18 Hz, 1 H) 1.43 - 1.51 (m, 1 H) 1.54 (s, 3 H) 4.01 - 4.07 (m, 4 H) 5.26 (br. s., 2 H) 7.72 (dd, J=10.96, 8.77 Hz, 1 H) 8.14 (dd, J=8.84, 2.85 Hz, 1 H) 8.47 (d, J=1.32 Hz, 1 H) 8.95 (d, J=1.17 Hz, 1 H) 9.96 (s, 1 H)

Peak 2: 1H NMR (300 MHz, DMSO-d6) δ ppm 0.67 - 0.77 (m, 1 H) 0.77 - 0.87 (m, 1 H)

1.47 (d, J=9.65 Hz, 1 H) 1.53 (s, 3 H) 4.00 - 4.13 (m, 4 H) 5.24 (br. s., 2 H) 7.72 (dd,
The title compounds were synthesized according to procedure F, but using 5-cyanopicolinamide.

**MS** $m/z = 367 [M+H]$\(^+\). (for both enantiomers)

**Eg 324:** 1H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 0.67 - 0.78 (m, 1 H) 0.78 - 0.87 (m, 1 H) 1.43 - 1.52 (m, 1 H) 1.54 (s, 3 H) 4.02 - 4.08 (m, 1 H) 5.25 (br. s., 2 H) 7.74 (dd, $J=10.96$, 8.77 Hz, 1 H) 8.33 - 8.37 (m, 1 H) 8.63 (dd, $J=8.18$, 1.90 Hz, 1 H) 9.22 - 9.27 (m, 1 H) 10.29 (br. s., 1 H)

**Eg 325:** 1H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 0.69 - 0.77 (m, 1 H) 0.78 - 0.90 (m, 1 H) 1.43 - 1.52 (m, 1 H) 1.54 (s, 3 H) 4.01 - 4.09 (m, 1 H) 5.25 (br. s., 2 H) 7.74 (dd, $J=10.89$, 8.84 Hz, 1 H) 8.16 (dd, $J=8.84$, 3.00 Hz, 1 H) 8.32 - 8.37 (m, 1 H) 8.60 - 8.66 (m, 1 H) 9.22 - 9.27 (m, 1 H) 10.30 (br. s., 1 H)

**Method G:** Pd-Catalyzed Amidation followed by deprotection of benzoyl group

**Examples 326 & 327:** Synthesis of N-(6-((IR,5S,6R)-3-amino-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-5-fluoropyridin-2-yl)-5-chloropicolinamide (Eg 326)
Step 1: A sealable vial was charged with N-[(1R,S), (5S,R), (6R,S)]-3-benzamido-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl]-5-bromo-3-fluoropyridin-2-yl)-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl]benzamide 4c rac (0.57 g, 1.410 mmol), 5-chloropicolinamide (0.320 g, 2.045 mmol), (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphine) (0.245 g, 0.423 mmol), Pd2(db)a3 (0.097 g, 0.106 mmol), and cesium carbonate (1.149 g, 3.53 mmol). The vial was evacuated and backfilled with N2 gas. 1,4-Dioxane (5 mL) was added and the reaction mixture was stirred in a pre-heated 100 °C oil bath over for 15.5 hours. The reaction mixture was cooled to RT and diluted with water and EtOAc. The organic layer was washed with water, brine and dried over magnesium sulfate. The filtrate was concentrated under reduced pressure. The crude residue was purified via silica gel chromatography (5-60% EtOAc:Hexanes) to afford N-(6-(((1R,S), (5S,R),(6R,S))-3-benzamido-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-5-bromo-3-fluoropyridin-2-yl)-5-chloropicolinamide (0.554 g, 1.154 mmol, 82% yield). MS m/z = 479.9 [M]+.

Step 2: A microwave vial was charged with N-(6-(((1R,S), (5S,R),(6R,S))-3-benzamido-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-5-bromo-3-fluoropyridin-2-yl)-5-chloropicolinamide (0.554 g, 1.154 mmol), MeOH (4.62 ml) and DBU (0.696 ml, 4.62 mmol). The reaction mixture was heated to 75 °C for 3h in the microwave. The solid was collected by vacuum filtration to afford N-(6-(((1R,S), (5S,R),(6R,S))-3-amino-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-5-bromo-3-fluoropyridin-2-yl)-5-chloropicolinamide (0.309g, 0.822 mmol, 71.2 % yield). This material was subjected to chromatography using supercritical CO2 (additives 20% MeOH with 20 mM NH3) on a CHIRALPAK AS-H SFC column (21 x 250 mm, 5 µm) eluting at a flow rate 75 ml/min (100 bar pressure,
40 °C column temperature). The first peak (retention time = 1.26 min) provided N-(6-((IR,5S,6R)-3-amino-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-5-fluoropyridin-2-yl)-5-chloropicolinamide (Example 326, 115 mg, 0.306 mmol, 38.1% yield, 99% de; 99% ee). The second peak (retention time = 1.95 min) provided N-(6-((lS,5R,6S)-3-amino-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-5-fluoropyridin-2-yl)-5-chloropicolinamide (Example 327, 123.1 mg, 0.328 mmol, 40.8% yield; 99% de; 99% ee) 

MS m/z = 375.9 [M+H]+ (for both enantiomers)

Peak 1: 1H NMR (300 MHz, CHLOROFORM-d) δ ppm 0.97 (dt, J=9.83, 6.70 Hz, 1 H) 1.05 - 1.13 (m, 1 H) 1.67 - 1.74 (m, 1 H) 1.77 (s, 3 H) 4.10 - 4.17 (m, 1 H) 7.46 (dd, J=10.60, 8.84 Hz, 1 H) 7.89 (dd, J=8.33, 2.34 Hz, 1 H) 8.25 (d, J=8.33 Hz, 1 H) 8.31 (dd, J=8.77, 3.07 Hz, 1 H) 8.62 (d, J=1.90 Hz, 1 H) 10.24 (br. s., 1 H)

Peak 2: 1H NMR (300 MHz, CHLOROFORM-d) δ ppm 0.88 - 0.98 (m, 1 H) 1.03 (td, J=6.94, 2.92 Hz, 1 H) 1.66 (dt, J=9.79, 7.23 Hz, 1 H) 1.73 (s, 3 H) 4.06 - 4.14 (m, 1 H) 7.45 (dd, J=10.60, 8.84 Hz, 1 H) 7.89 (dd, J=8.33, 2.34 Hz, 1 H) 8.25 (d, J=8.33 Hz, 1 H) 8.30 (dd, J=8.77, 2.92 Hz, 1 H) 8.61 (d, J=2.19 Hz, 1 H) 10.24 (br. s., 1 H)

Synthesis of N-(6-((IR,5S,6R)-3-amino-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-5-fluoropyridin-2-yl)-3,5-dichloropicolinamide (Example 328)

And N-(6-((lS,5R,6S)-3-amino-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-5-fluoropyridin-2-yl)-3,5-dichloropicolinamide (Example 329)

The title compounds were synthesized according to procedure G, but using 3,5-dichloropicolinamide.
MS \textit{m/z} = 409.9 \,[\text{M+H}]^+. \text{ (for both enantiomers)}

**Peak 1:** 1H NMR (300 MHz, CHLOROFORM-d) \( \delta \) ppm 0.98 - 1.09 (m, 1 H) 1.11 - 1.20 (m, 1 H) 1.72 - 1.85 (m, 4 H) 4.14 - 4.22 (m, 1 H) 7.49 (dd, \( J = 10.45 \), 8.84 Hz, 1 H) 7.92 (d, \( J = 2.05 \) Hz, 1 H) 8.35 (dd, \( J = 8.92 \), 3.07 Hz, 1 H) 8.56 (d, \( J = 2.05 \) Hz, 1 H)

**Peak 2:** 1H NMR (300 MHz, CHLOROFORM-d) \( \delta \) ppm 0.91 - 1.00 (m, 1 H) 1.03 - 1.11 (m, 1 H) 1.65 - 1.73 (m, 1 H) 1.74 (s, 3 H) 4.08 - 4.15 (m, 1 H) 7.46 (dd, \( J = 10.52 \), 8.77 Hz, 1 H) 7.92 (d, \( J = 2.05 \) Hz, 1 H) 8.32 (dd, \( J = 8.84 \), 3.00 Hz, 1 H) 8.54 (d, \( J = 2.05 \) Hz, 1 H)

### Examples 330-336

Using procedures similar to one of the general metal-catalyzed amidation procedures described above, the appropriate bromide and amide were combined to prepare the examples listed in Table 2:

<table>
<thead>
<tr>
<th>Example #</th>
<th>Method</th>
<th>Compound Name</th>
<th>Compound Structure</th>
<th>Analytical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>330</td>
<td>E</td>
<td>N-(6-9((1RS),(5S,R),(6R,S))-3-amino-5-(difuoroxyethyl)-2-oxa-4-azabiclo[4,1.0]hept-3-en-5-yl)-5-fluoropyridin-2-yl)-5-cyanopicolinamide</td>
<td><img src="image" alt="Compound Structure" /></td>
<td>MS \textit{m/z} = 403 ,[\text{M+H}]^+ \text{ 1H NMR (400MHz) } \delta \text{ d = 10.28 (s, 1 H), 8.94 (d, } J = 1.2 \text{ Hz, 1 H), 8.43 (d, } J = 8.2 \text{ Hz, 1 H), 8.37 (dd, } J = 2.9, 8.8 \text{ Hz, 1 H), 8.22 (dd, } J = 2.1, 8.1 \text{ Hz, 1 H), 7.52 (dd, } J = 9.0, 10.2 \text{ Hz, 1 H), 6.72 - 6.32 (m, 1 H), 4.11 (t, } J = 5.3 \text{ Hz, 1 H), 1.89 - 1.74 (m, 1 H), 1.51 (t, } J = 6.5 \text{ Hz, 1 H), 1.13 - 1.00 (m, 1 H)</td>
</tr>
</tbody>
</table>
| 332 | E | N-(5-((1R,5S,6R)-3-(5-((3-5-chloropyridin-2-yl)oxetan-3-yl)amino)-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine | MS \textit{m/z} = 438.8 [M]+  
1H NMR (400MHz) \textit{CHLOROFORM-d} d = 8.65 (d, J = 2.3 Hz, 1H), 7.58 (dd, J = 2.5, 8.4 Hz, 1H), 7.43 (d, J = 8.6 Hz, 1H), 6.82 (dd, J = 8.7, 11.6 Hz, 1H), 6.51 (dd, J = 2.8, 6.4 Hz, 1H), 6.37 - 5.98 (m, 2H), 5.26 (d, J = 6.1 Hz, 1H), 5.15 (d, J = 6.3 Hz, 1H), 4.80 (d, J = 6.1 Hz, 2H), 3.88 (t, J = 5.3 Hz, 1H), 1.86 - 1.75 (m, 1H), 1.38 (t, J = 7.1 Hz, 1H), 1.00 - 0.89 (m, 1H) |
| 333 | E | N-(5-((1R,S,5S,R,6(R,S)-3-amino-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoropyridin-3-yl)-5-chloropicolinamide | MS \textit{m/z} = 376.4 [M+H]+  
1H NMR (MeOH) d: 8.73 (d, J = 2.2 Hz, IH), 8.58 - 8.66 (m, IH), 8.43 (dd, J = 9.0, 2.5 Hz, IH), 8.22 (d, J = 8.4 Hz, IH), 8.09 (dd, J = 8.4, 2.3 Hz, IH), 4.02 - 4.25 (m, IH), 1.76 - 1.89 (m, IH), 1.70 (s, 3H), 1.31 (s, IH), 1.06 (dt, J = 6.8, 3.3 Hz, IH), 0.93 - 1.02 (m, IH) |
| 334 | E | N-(5-((1R,5S,6R)-3-amino-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoropyridin-3-yl)-5-chloropicolinamide | MS \textit{m/z} = 376.4 [M+H]+  
1H NMR (MeOH) d: 8.74 (d, J = 2.0 Hz, IH), 8.63 (s, IH), 8.43 (dd, J = 8.9, 2.4 Hz, IH), 8.23 (d, J = 8.4 Hz, IH), 8.11 (dd, J = 8.4, 2.3 Hz, IH), 4.14 (t, J = 5.3 Hz, IH), 1.82 (d, J = 9.6 Hz, IH), 1.70 (s, 3H), 1.02 - 1.17 (m, IH), 0.98 (dd, J = 9.7, 6.4 Hz, IH) |
Method H:

Examples 337 & 338: Synthesis of \( \text{N}(5-(\{1(\text{R},\text{S}),5(\text{S},\text{R}),6(\text{R},\text{S})\})-\text{amin0-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl})6-\text{fluoropyridin-3-yl})5-
\text{chloropicolinamide} \) (Eg 337)

and \( \text{(IR,5R,6R)}-5-(2-\text{fluoro-5-}(3\text{-methoxy-1,7-naphthyridin-8-yl})\text{amino})\text{phenyl})5-
\text{methyl-2-oxa-4-azabicclo[4.1.0]hept-3-en-3-amine} \) (Eg 338)
A sealable vial was charged with and [(S,R),(S,R),(S,R)]-5-(5-amino-2-fluorophenyl)-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (lrac; 350 mg, 1.488 mmol) and 8-chloro-3-methoxy-1,7-naphthyridine (Intermediate 2; 304 mg, 1.56 mmol). Zro-propanol (6.8 mL) and sulfuric acid (103 µl, 1.93 mmol) were added and the mixture was heated to 55 °C for 20 min. The cooled reaction mixture was diluted with water and extracted with EtOAc. The aqueous phase was neutralized with aqueous saturated sodium bicarbonate solution. The solution was extracted three times with EtOAc. The combined organic phases were separated and dried over MgSO₄. The solvent was removed under reduced pressure. The residue was washed with Et₂O to obtain

[(S,R),(S,R),(S,R)]-5-(2-fluoro-5-((3-methoxy-1,7-naphthyridin-8-yl)amino)phenyl)-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine as a beige solid (290 mg). The solid was subjected to chromatography using supercritical CO₂ (additives 50% MeOH with 20 mM NH₃) on an AD-H column (21 x 250 mm, 5 μm) eluting at a flow rate 50 ml/min (100 bar pressure, 40 °C column temperature). The first peak (retention time = 1.24 min) provided (LR,SR,6R)-5-(2-fluoro-5-((3-methoxy-1,7-naphthyridin-8-yl)amino)phenyl)-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (Example 337, 122 mg, 0.310 mmol, 20.84 % yield; 99% de; 99% ee) as a light-yellow powder.

The second peak (retention time = 2.33 min) provided (LR,SR,6R)-5-(2-fluoro-5-((3-methoxy-1,7-naphthyridin-8-yl)amino)phenyl)-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (Example 338; 110 mg, 0.280 mmol, 18.79 % yield; 99% de; 99% ee) as a light-yellow powder.

MS m/z = 394.1 [M+H]⁺. Calculated for C₂₁H₂₀FN₄O₂: 393.41 (for both enantiomers)

¹H NMR (312; 300 MHz, DMSO-δ₆) δ ppm 0.38 (td, J = 6.36, 2.92 Hz, 1 H) 0.61 (dt, J = 9.50, 6.21 Hz, 1 H) 1.59 (s, 3 H) 1.64 - 1.80 (m, 1 H) 3.97 (s, 3 H) 3.99 - 4.08 (m, 1 H) 5.40 (s, 2 H) 7.02 - 7.15 (m, 2 H) 7.70 (d, J = 2.78 Hz, 1 H) 7.92 (dd, J = 7.09, 2.85 Hz, 1 H) 8.02 (d, J = 5.70 Hz, 1 H) 8.11 - 8.27 (m, 1 H) 8.61 (d, J = 2.78 Hz, 1 H) 9.19 (s, 1 H) ¹H NMR (313; 300 MHz, DMSO-δ₆) δ ppm 0.39 (td, J = 6.43, 2.92 Hz, 1 H) 0.61 (dt, J = 9.57, 6.25 Hz, 1 H) 1.59 (s, 3 H) 1.64 - 1.77 (m, 1 H) 3.97 (s, 3 H) 4.00 - 4.10 (m, 1 H) 5.41 (s, 2 H) 7.00 - 7.18 (m, 2 H) 7.70 (d, J = 2.78 Hz, 1 H) 7.93 (dd, J = 7.16, 2.92 Hz, 1 H) 8.03 (d, J = 5.70 Hz, 1 H) 8.12 - 8.26 (m, 1 H) 8.61 (d, J = 2.78 Hz, 1 H) 9.19 (s, 1 H)

Examples 339-365

The examples in Table 3 were synthesized following a procedure analogous to Method H

Table 3
<table>
<thead>
<tr>
<th>Exemplar No.</th>
<th>Compound Name</th>
<th>Compound Structure</th>
<th>Analytical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>339</td>
<td>(1S,5R,6S)-5-(2-fluoro-5-((3-methoxy-1,7-naphthyridin-8-yl)amino)phenyl)-5-methyl-2-oxa-4-azabicyclo[4.1.0]hexyl-3-en-3-amine</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>MS ( m/z = 394.0 ) [M+H]⁺. ¹H NMR (300 MHz, CHLOROFORM-d) ( \delta ) ppm 0.81 - 0.92 (m, 1 H), 0.96 - 1.05 (m, 1 H), 1.68 (s, 3 H), 1.78 - 1.88 (m, 1 H), 3.92 - 4.00 (m, 4 H), 6.91 (d, ( J=5.85 ) Hz, 1 H), 7.08 (dd, ( J=11.77 ), 8.84 Hz, 1 H), 7.23 (d, ( J=2.63 ) Hz, 1 H), 7.69 (dd, ( J=7.23 ), 2.56 Hz, 1 H), 8.01 - 8.16 (m, 2 H), 8.50 (d, ( J=2.48 ) Hz, 1 H), 8.86 (s, 1 H)</td>
</tr>
<tr>
<td>340</td>
<td>(1R,5S,6R)-5-(2-fluoro-5-((3-methoxy-1,7-naphthyridin-8-yl)amino)phenyl)-5-methyl-2-oxa-4-azabicyclo[4.1.0]hexyl-3-en-3-amine</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>MS ( m/z = 394.0 ) [M+H]⁺. ¹H NMR (300 MHz, CHLOROFORM-d) ( \delta ) ppm 0.85 (dt, ( J=9.61 ), 6.60 Hz, 1 H), 1.00 (td, ( J=6.91 ), 2.41 Hz, 1 H), 1.67 (s, 3 H), 1.77 - 1.87 (m, 1 H), 3.90 - 4.01 (m, 4 H), 6.90 (d, ( J=5.85 ) Hz, 1 H), 7.07 (dd, ( J=11.69 ), 8.77 Hz, 1 H), 7.22 (d, ( J=2.63 ) Hz, 1 H), 7.67 (dd, ( J=7.16 ), 2.63 Hz, 1 H), 8.02 - 8.12 (m, 2 H), 8.49 (d, ( J=2.63 ) Hz, 1 H), 8.85 (s, 1 H)</td>
</tr>
<tr>
<td>341</td>
<td>(1S,5S,6S)-5-((3-chloro-1,7-naphthyridin-8-yl)amino)-2,3-difluorophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hexyl-3-en-3-amine</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>MS ( m/z = 434.2 ) [M+H]+. ¹H NMR (400 MHz, CHLOROFORM-d) ( \delta ) ppm 8.87 (s, 1 H), 8.60 (s, 1 H), 8.32 (dd, ( J=12.42 ), 6.94, 2.35 Hz, 1 H), 8.07 (d, ( J=5.67 ) Hz, 1 H), 7.96 (d, ( J=2.15 ) Hz, 1 H), 7.32 - 7.45 (m, 1 H), 6.90 (s, 1 H), 4.79 (s, 1 H), 4.67 (s, 1 H), 3.97 (br. s., 1 H), 4.70 - 1.85 (m, 1 H), 1.7 - 1.34 (m, 2 H), 0.77 - 1.01 (m, 2 H)</td>
</tr>
</tbody>
</table>
342 (1R,5S,6R)-5-((3-chloro-1,7-naphthyridin-8-yl)amino)-2,3-difluorophenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine

MS $m/z = 434.2$ [M+H]+
1H NMR (400 MHz, CHLOROFORM-d) $\delta$ ppm 8.86 (br. s., 1 H), 8.59 (s, 1 H), 8.28 - 8.38 (m, 1 H), 8.07 (d, $J=5.67$ Hz, 1 H), 7.96 (s, 1 H), 7.35 (br. s., 1 H), 6.89 (d, $J=5.67$ Hz, 1 H), 4.78 (s, 1 H), 4.66 (s, 1 H), 3.96 (br. s., 1 H), 1.76 (q, $J=7.69$ Hz, 1 H), 1.16 - 1.33 (m, 1 H), 0.92 (q, $J=7.50$ Hz, 1 H). Note NH2 is very broad around 5.5 to 4 ppm.

343 8-((3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)4-fluorophenyl)amino)-5-fluoro-1,7-naphthyridine-3-carbonitrile

MS $m/z = 425.2$ [M+H]+
1H NMR (400 MHz, DMSO-d6) $\delta$ ppm 9.71 (s, 1 H), 9.32 (d, $J=1.96$ Hz, 1 H), 9.13 (d, $J=1.76$ Hz, 1 H), 8.32 (dd, $J=7.34$, 2.64 Hz, 1 H), 8.25 (s, 1 H), 7.93 (dt, $J=8.66$, 3.50 Hz, 1 H), 7.15 (dd, $J=11.83$, 8.90 Hz, 1 H), 5.69 (br. s., 2 H), 4.43 - 4.73 (m, 2 H), 4.01 (t, $J=5.77$ Hz, 1 H), 1.49 - 1.66 (m, 1 H), 1.03 (td, $J=6.21$, 2.25 Hz, 1 H), 0.82 (dt, $J=9.24$, 6.43 Hz, 1 H).

344 (1R,5S,6R)-5-(2-fluoro-5-((5-fluoro-3-methoxy-1,7-naphthyridin-8-yl)amino)phenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine

MS $m/z = 430$ [M+H]+
1H NMR (400 MHz, DMSO-d6) $\delta$ ppm 9.35 (s, 1 H), 8.71 (d, $J=2.93$ Hz, 1 H), 8.22 (dd, $J=7.43$, 2.74 Hz, 1 H), 8.09 (d, $J=1.56$ Hz, 1 H), 7.93 - 8.00 (m, 1 H), 7.71 (d, $J=2.74$ Hz, 1 H), 7.12 (dd, $J=11.74$, 8.80 Hz, 1 H), 5.68 (s, 2 H), 4.43 - 4.73 (m, 2 H), 3.97 - 4.07 (m, 4 H), 1.56 - 1.66 (m, 1 H), 1.02 (td, $J=6.41$, 2.64 Hz, 1 H), 0.81 (dt, $J=9.29$, 6.41 Hz, 1 H).
| 345 | (IR,5S,6R)-5-(5-((3-chloro-1,7-naphthyridin-8-yl)amino)-2-fluoropropieryl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine | MS \( m/z = 416 \) [M+H]+  
1H NMR (400 MHz, DMSO-d6)  
d ppm 9.58 (s, 1 H), 8.90 (d, J=2.35 Hz, 1 H), 8.51 (d, J=2.35 Hz, 1 H), 8.22 (dd, J=7.24, 2.74 Hz, 1 H), 8.14 (d, J=5.67 Hz, 1 H), 8.03 (dt, J=8.36, 3.64 Hz, 1 H), 7.10 - 7.19 (m, 2 H), 5.68 (br. s., 2 H), 4.41 - 4.74 (m, 2 H), 4.02 (t, J=5.58 Hz, 1 H), 1.56 - 1.66 (m, 1 H), 1.02 (td, J=6.16, 2.35 Hz, 1 H). |
| 346 | 8-((3-(IR,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)amino-2-yl)amino)-3-carbonitrile | MS \( m/z = 407 \) [M+H]+  
1H NMR (400 MHz, DMSO-d6)  
d ppm 9.72 (s, 1 H), 9.21 (d, J=1.76 Hz, 1 H), 8.87 - 9.06 (m, 1 H), 8.25 (dd, J=7.34, 2.64 Hz, 1 H), 8.22 (d, J=5.87 Hz, 1 H), 8.02 (dt, J=8.56, 3.55 Hz, 1 H), 7.22 (d, J=5.67 Hz, 1H), 7.16 (dd, J=8.80, 11.74 Hz, 1H), 5.75 (s, 2 H), 4.39 - 4.75 (m, 2 H), 3.90 - 4.10 (m, 1 H), 1.49 - 1.69 (m, 1 H), 1.03 (d, J=1.96 Hz, 1 H), 0.83 (dt, J=9.24, 6.33 Hz, 1 H). |
| 347 | (IR,5S,6R)-5-(5-((7-chloropyrido[3,2-d]pyrimidin-4-yl)amino)-2-fluoropropieryl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine | MS \( m/z = 411 \) [M+H]+  
1H NMR (400 MHz, DMSO-d6)  
d ppm 10.42 (s, 1 H), 8.93 (d, J=2.35 Hz, 1 H), 8.67 (s, 1 H), 8.39 (d, J=2.15 Hz, 1 H), 8.27 (dd, J=7.43, 2.74 Hz, 1 H), 7.90 (dt, J=8.17, 3.64 Hz, 1 H), 7.20 (dd, J=1.83, 8.90 Hz, 1 H), 5.67 (br. s., 2 H), 4.40 - 4.75 (m, 2 H), 4.03 (t, J=5.67 Hz, 1 H), 1.54 - 1.66 (m, 1 H), 1.02 (td, J=6.11, 2.25 Hz, 1 H), 0.83 (dt, J=9.44, 6.43 Hz, 1 H). |
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<td>m/z = 430[M+H]+</td>
<td>δ: 8.57 (s, 1H), 2.04 - 7.02 (m, 1H), 1.13 (br. s., 1H), 0.93 (d, J = 7.4 Hz, 1H).</td>
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<td>m/z = 458.9 [M+H]+</td>
<td>δ: 8.74 (d, J = 8.8 Hz, 1H), 7.95 (ddd, J = 8.8, 4.2, 2.8 Hz, 1H), 7.08 (d, J = 5.9 Hz, 1H), 6.16 - 6.51 (m, 1H), 4.06 - 4.13 (m, 1H), 4.02 (s, 3H), 1.86 - 2.01 (m, 1H), 1.32 - 1.43 (m, 1H), 1.00 (dt, J = 9.3, 6.7 Hz, 1H).</td>
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<td>m/z = 458.9 [M+H]+</td>
<td>δ: 8.74 (d, J = 8.8 Hz, 1H), 7.95 (ddd, J = 8.8, 4.2, 2.8 Hz, 1H), 7.08 (d, J = 5.9 Hz, 1H), 6.16 - 6.51 (m, 1H), 4.06 - 4.13 (m, 1H), 4.02 (s, 3H), 1.86 - 2.01 (m, 1H), 1.32 - 1.43 (m, 1H), 1.00 (dt, J = 9.3, 6.7 Hz, 1H).</td>
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<td>m/z = 458.9 [M+H]+</td>
<td>δ: 8.74 (d, J = 8.8 Hz, 1H), 7.95 (ddd, J = 8.8, 4.2, 2.8 Hz, 1H), 7.08 (d, J = 5.9 Hz, 1H), 6.16 - 6.51 (m, 1H), 4.06 - 4.13 (m, 1H), 4.02 (s, 3H), 1.86 - 2.01 (m, 1H), 1.32 - 1.43 (m, 1H), 1.00 (dt, J = 9.3, 6.7 Hz, 1H).</td>
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<td>8-((3-((IR,5S,6R)-3-amino-5-difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)amino)-5-fluoro-1,7-naphthyridine-3-carbonitrile</td>
<td>m/z = 442.9 [M+H]+</td>
<td>0.87 - 0.94 (m, 1 H) 1.15 - 1.21 (m, 1 H) 1.71 - 1.81 (m, 1 H) 3.97 - 4.06 (m, 1 H) 5.92 (s, 2 H) 6.21 (t, J=56.10 Hz, 1 H) 7.19 (dd, J=1.64, 8.90 Hz, 1 H) 7.94 (dt, J=8.46, 3.59 Hz, 1 H) 8.26 (s, 1 H) 8.43 (dd, J=7.24, 2.74 Hz, 1 H) 9.14 (d, J=1.96 Hz, 1 H) 9.32 (d, J=1.96 Hz, 1 H) 9.75 (s, 1 H)</td>
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<td>353</td>
<td><img src="image2.png" alt="Compound 2" /></td>
<td>(IR,5S,6R)-5-((7-chloropyridin-3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine</td>
<td>m/z = 434.9 [M+H]+</td>
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<td>354</td>
<td><img src="image3.png" alt="Compound 3" /></td>
<td>(1S,5R,6S)-5-(2,6-difluoro-3-((2-methoxypyridin-3-yl)amino)phenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine</td>
<td>m/z = 430.9 [M+H]+</td>
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<td><img src="image4.png" alt="Compound 4" /></td>
<td>(IR,5S,6R)-5-(2,6-difluoro-3-((2-methoxypyridin-3-yl)amino)phenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine</td>
<td>m/z = 430.9 [M+H]+</td>
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356  (IR,SS,6R)-5-(3-chloro-2-fluoro-5-((2-methoxypyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-5-((fluoromethy1)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine  

MS m/z = 446.9 [M+H]+  
1H NMR (300 MHz, DMSO-d6) δ ppm 0.79 - 0.92 (m, 1 H) 0.96 - 1.06 (m, 1 H) 1.51 - 1.65 (m, 1 H) 4.08 (s, 4 H) 4.38 - 4.79 (m, 2 H) 5.70 (s, 2 H) 7.13 (d, J=5.85 Hz, 1 H) 8.17 - 8.26 (m, 1 H) 8.29 (d, J=5.99 Hz, 1 H) 8.33 - 8.41 (m, 1 H) 8.57 (s, 1 H) 9.69 (s, 1 H).

357  (IR,SS,6R)-5-(3-chloro-2-fluoro-5-((2-isopropoxypyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-5-((fluoromethy1)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine  

MS m/z = 474.9 [M+H]+  
1H NMR (300 MHz, DMSO-d6) δ ppm 0.85 - 0.97 (m, 1 H) 1.02 - 1.12 (m, 1 H) 1.48 (d, J=6.14 Hz, 6 H) 1.58 - 1.72 (m, 1 H) 4.08 - 4.17 (m, 1 H) 4.46 - 4.84 (m, 2 H) 5.54 (s, 1 H) 5.76 (s, 2 H) 7.15 (d, J=5.99 Hz, 1 H) 8.28 (d, J=6.58 Hz, 1 H) 8.34 (d, J=5.85 Hz, 1 H) 8.44 (d, J=4.68 Hz, 1 H) 8.55 (s, 1 H) 9.73 (s, 1 H).

358  (IR,SS,6R)-5-(difluoromethyl)-5-(2-fluoro-5-((2-methyl-2H-pyrazolo[3,4-c]pyridin-7-yl)amino)phenyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine  

MS m/z = 403 [M+H]+  
1H NMR (300 MHz, CD3CN) δ ppm 8.21 (s, 1 H) 7.54 - 7.69 (m, 2 H) 7.39 - 7.53 (m, 1 H) 7.10 - 7.26 (m, 2 H) 6.52 (t, J=5.45 Hz, 1 H) 4.48 (td, J=6.80, 2.78 Hz, 1 H) 4.21 (s, 3 H) 2.16 (dt, J=9.83, 7.07 Hz, 1 H) 1.63 (t, J=7.53 Hz, 1 H) 1.30 (td, J=9.03, 6.50 Hz, 1 H).

359  (IR,SS,6R)-5-(2-chloro-5-(3-chloro-1,7-naphthyridin-8-yl)amino)phenyl)-5-((fluoromethy1)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine  

MS m/z = 431.9 [M]+  
1H NMR (300 MHz, MeOD -d4) δ ppm 0.88 - 1.01 (m, 1 H) 1.08 - 1.18 (m, 1 H) 1.96 - 2.10 (m, 1 H) 3.96 - 4.06 (m, 1 H) 4.77 - 4.82 (m, 1 H) 4.92 - 5.04 (m, 1 H) 7.08 (d, J=5.85 Hz, 1 H) 7.40 (d, J=8.77 Hz, 1 H) 7.96 (dd, J=8.62, 2.63 Hz, 1 H) 8.11 (d, J=5.85 Hz, 1 H) 8.23 - 8.30 (m, 2 H) 8.81 (d, J=2.19 Hz, 1 H).
360 (IR,5S,6R)-5-(2-chloro-5-((3-methoxy-1,7-naphthyridin-8-yl)amino)phenyl)-5-((fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine  

$$\text{MS } m/z = 428.0 \ [M+H]^+$$  
$$\text{1H NMR (300 MHz, Solvent) } \delta$$  
ppm 0.93 - 1.01 (m, 1 H) 1.13 - 1.19 (m, 1 H) 1.99 - 2.07 (m, 1 H) 4.01 (s, 3 H) 4.02 - 4.08 (m, 1 H) 4.83 - 4.84 (m, 1 H) 4.95 - 5.02 (m, 1 H) 7.06 - 7.12 (m, 1 H) 7.40 (d, J=8.62 Hz, 1 H) 7.56 (s, 1 H) 7.97 (dd, J=8.62, 2.78 Hz, 1 H) 8.02 (d, J=5.85 Hz, 1 H) 8.22 (d, J=2.78 Hz, 1 H) 8.57 (d, J=2.78 Hz, 1 H) 

361 (IR,5S,6R)-5-((3-chloro-5-fluoro-1,7-naphthyridin-8-yl)amino)-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine  

$$\text{MS } m/z = 452.0 \ [M+H]^+$$  
$$\text{1H NMR (300 MHz, DMSO-d$_6$) }$$  
ppm 0.80 - 0.98 (m, 1 H) 1.17 (br. s., 1 H) 1.66 - 1.86 (m, 1 H) 4.01 (t, J=5.55 Hz, 1 H) 5.91 (s, 2 H) 6.00 - 6.50 (m, 1 H) 7.17 (dd, J=1.77, 8.84 Hz, 1 H) 7.84 - 8.02 (m, 1 H) 8.19 (d, J=1.32 Hz, 1 H) 8.40 (dd, J=7.09, 2.85 Hz, 1 H) 8.59 (d, J=2.34 Hz, 1 H) 9.01 (d, J=2.34 Hz, 1 H) 9.61 (s, 1 H) 

362 (IR,5S,6R)-5-((3-chloro-1,7-naphthyridin-8-yl)amino)-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine  

$$\text{MS } m/z = 434.0 \ [M+H]^+$$  
$$\text{1H NMR (300 MHz, DMSO-d$_6$) }$$  
ppm 0.91 (d, J=9.21 Hz, 1 H) 1.17 (br. s., 1 H) 1.76 (d, J=9.21 Hz, 1 H) 4.03 (t, J=5.19 Hz, 1 H) 5.90 (s, 2 H) 5.99 - 6.43 (m, 1 H) 7.10 - 7.26 (m, 2 H) 7.96 - 8.09 (m, 1 H) 8.15 (d, J=5.70 Hz, 1 H) 8.32 (dd, J=7.02, 2.63 Hz, 1 H) 8.51 (d, J=2.34 Hz, 1 H) 8.90 (d, J=2.34 Hz, 1 H) 9.61 (s, 1 H) 

363 8-((3-((IR,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)amin o)-5-fluoro-1,7-naphthyridine-3-carbonitrile  

$$\text{MS } m/z = 441.0 \ [M+H]^+$$  
$$\text{1H NMR (300 MHz, DMSO-d$_6$) }$$  
ppm 0.84 (dt, J=9.57, 6.39 Hz, 1 H) 1.00 (td, J=6.43, 2.63 Hz, 1 H) 1.78 (dt, J=9.46, 7.03 Hz, 1 H) 3.84 - 4.01 (m, 1 H) 4.70 (d, J=2.48 Hz, 1 H) 4.87 (s, 1 H) 5.69 (s, 2 H) 7.38 (d, J=8.77 Hz, 1 H) 7.96 (dd, J=8.70, 2.70 Hz, 1 H) 8.31 (d, J=1.02 Hz, 1 H) 8.58
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<td>MS m/z = 431.1 [M+H]+</td>
<td>IH NMR (400 MHz, MeOH-d4) δ: 8.59-8.63 (m, 2H), 8.41 (dd, J=7.0, 2.5 Hz, IH), 7.87-7.93 (m, IH), 7.47 (d, J=2.7 Hz, IH), 7.30 (dd, J=1.7, 8.8 Hz, IH), 6.41-6.71 (m, IH), 4.42 (t, J=5.3 Hz, IH), 4.03 (s, 3H), 2.10-2.18 (m, IH), 1.54-1.60 (m, IH), 1.19-1.28 (m, IH)</td>
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<td>365</td>
<td>(IR,5S,6R)-5-(difluoromethyl)-5-(2-fluoro-5-((2-(trifluoromethyl)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine</td>
<td>MS m/z = 469.1 [M+H]+</td>
<td>IH NMR (400 MHz, MeOH-d4) δ: 9.21 (s, IH), 8.38 (d, J=6.1 Hz, IH), 8.21 (dd, J=7.0, 2.7 Hz, IH), 7.90-7.99 (m, IH), 7.31 (d, J=6.1 Hz, IH), 7.18 (dd, J=1.6, 8.9 Hz, IH), 6.16-6.50 (m, IH), 4.07 (t, J=5.5 Hz, IH), 1.88-1.96 (m, IH), 1.36 (br.s., IH), 0.94-1.04 (m, IH)</td>
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<td>446</td>
<td>8-((3-((IR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)amino)-1,7-naphthyridine-3-carbonitrile</td>
<td>MS m/z = 425.1 [M+H]+</td>
<td>IH NMR (MeOH) δ: 9.09 (d, J=2.0 Hz, IH), 8.74 (d, J=2.0 Hz, IH), 8.63 (dd, J=7.0, 2.5 Hz, IH), 8.21 (d, J=5.9 Hz, IH), 7.90 (dt, J=8.9, 3.4 Hz, IH), 7.29-7.37 (m, IH), 7.23 (d, J=5.9 Hz, IH), 6.51-6.87 (m, IH), 4.61 (d, J=6.7, 2.5 Hz, IH), 2.20-2.32 (m, IH), 1.69 (t, J=7.2 Hz, IH), 1.30-1.44 (m, IH)</td>
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<td>447</td>
<td>(IR,5S,6R)-5-(difluoromethyl)-5-(2-fluoro-5-((2-methoxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-2-oxa-4-</td>
<td>MS m/z = 431.1 [M+H]+</td>
<td>IH NMR (MeOH) δ: 8.44 (s, IH), 8.20 (d, J=6.1 Hz, 2H), 7.89 (dt, J=8.8, 3.4 Hz, IH), 7.20 (dd, J=1.7, 8.8 Hz, IH), 7.09 (d, J=5.9 Hz, IH), 6.21-6.61 (m, IH), 1.30-1.44 (m, IH)</td>
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Method I

Example 366: Synthesis of 8-((3-((1S,5R,6S)-3-amino-5-(difluoromethyl)-2-oxa-4-
azabicyclo[4.1.0]hept-3-en-3-amine)-4.5-difluorophenyl)amino)-5-fluoro-1.7-naphthyridine-3-carbonitrile

A sealable vial was charged with (1S,5R,6S)-5-(5-amino-2,3-difluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (20f-A, 0.100 g, 0.346 mmol), chloro[2-(dicyclohexylphosphino)-3,6-dimethoxy-2',4'-6'-triisopropyl-l,1'-

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<td>448 (1R,5S,6R)-5-(difluoromethyl)-5-(2-fluoro-5-((5-fluoro-3-methoxy-1,7-naphthyridin-8-yl)amino)phenyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine</td>
<td>MS m/z = 448.1 [M+H]+ 1H NMR (DMSO-d6) δ: 9.39 (s, 1H), 8.71 (d, J=2.5 Hz, 1H), 8.34 (d, J=4.9 Hz, 1H), 8.10 (s, 1H), 7.98 (d, J=8.6 Hz, 1H), 7.71 (d, J=2.3 Hz, 1H), 7.08-7.21 (m, 1H), 6.05-6.39 (m, 1H), 5.91 (s, 2H), 4.01-4.07 (m, 4H), 1.71-1.81 (m, 1H), 1.17 (br. s., 1H), 0.85-0.94 (m, 1H)</td>
</tr>
<tr>
<td>449 (1R,5S,6R)-5-(difluoromethyl)-5-(2-fluoro-5-((7-(trifluoromethyl)pyridin-3,2-dipyrimidin-4-yl)amino)phenyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine</td>
<td>MS m/z = 469.1 [M+H]+ 1H NMR (DMSO-d6) δ: 10.62 (s, 1H), 9.22 (d, J=2.0 Hz, 1H), 8.77 (s, 1H), 8.66 (s, 1H), 8.40 (dd, J=7.2, 2.7 Hz, 1H), 7.91-7.98 (m, 1H), 7.26 (dd, J=11.7, 8.8 Hz, 1H), 6.04-6.39 (m, 1H), 5.92 (s, 2H), 3.94-4.10 (m, 1H), 1.70-1.85 (m, 1H), 1.18 (br. s., 1H), 0.80-0.99 (m, 1H)</td>
</tr>
</tbody>
</table>
biphenyl[2-(2-aminoethyl)phenyl]palladium(II) (0.025 g, 0.031 mmol), 8-chloro-5-fluoro-1,7-naphthyridine-3-carbonitrile (0.080 g, 0.385 mmol), and potassium bis(trimethylsilyl)amide (0.075 g, 0.376 mmol). The vial was evacuated and backfilled with nitrogen. Dioxane (0.4 mL) was added and the reaction mixture was heated to 70 °C for 1 hour. The reaction mixture was partitioned between water (40 mL), aqueous saturated sodium bicarbonate solution (10 mL) and ethyl acetate (100 mL). The organic phase was separated and was dried over magnesium sulfate. The filtrate was concentrated under reduced pressure and the residue was purified by reverse-phase preparative HPLC using a Phenomenex Gemini column, 10 micron, C18, 100 A, 150 x 30 mm, 0.1% TFA in CH3CN/H2O, gradient 30% to 70% over 15 min to provide the purified product as the TFA salt. The product was partitioned between DCM andaq. 10% Na2CO3. The layers were separated and the aqueous layer was extracted with DCM. The combined organic extracts were washed with brine and dried over sodium sulfate. The filtrate was concentrated in vacuo to afford the title compound as the free base (0.0576 g, 0.125 mmol, 36.2% yield). MS m/z = 461 [M+H]+

1H NMR (CHLOROFORM-d) Shift: 8.92 (d, J=1.9 Hz, 1H), 8.71 (br. s, 1H), 8.66 (d, J=1.9 Hz, 1H), 8.20 (ddd, J=12.4, 6.9, 2.8 Hz, 1H), 8.06 (d, J=1.0 Hz, 1H), 7.34 (dt, J=5.1, 2.6 Hz, 1H), 6.23 (td, J=56.0, 0.9 Hz, 1H), 3.89-3.99 (m, 1H), 1.82-1.93 (m, 1H), 1.60 (br. s, 2H), 1.40-1.48 (m, 1H), 0.94-1.05 (m, 1H)

Example 367: Synthesis of 8-((3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)amino)-5-fluoro-1,7-naphthyridine-3-carbonitrile

The titled compound was synthesized according to Method I, but using (1R,5S,6R)-5 -(5-amino-2,3-difluorophenyl)-5 -(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (20f-B). MS m/z = 461 [M+H]+

1H NMR (CHLOROFORM-d) Shift: 8.91 (d, J=1.9 Hz, 1H), 8.71 (br. s, 1H), 8.65 (d, J=1.9 Hz, 1H), 8.20 (ddd, J=12.4, 6.9, 2.8 Hz, 1H), 8.06 (d, J=1.0 Hz, 1H), 7.34 (dt,
Method K:

Example 368: Synthesis of (lR,5S,6R)-5-(5-(cyclobutylmethyl)amino)-2-fluorophenyl-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine

To a solution of (lR,5S,6R)-5-(5-amino-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (16g-B, 50 mg, 0.184 mmol) in 1,2-dichloroethane (1.2 mL) was added cyclobutanecarbaldehyde (15.51 mg, 0.184 mmol) and sodium triacetoxyborohydride (0.033 mL, 0.221 mmol). After addition, the mixture was then stirred at room temperature for 3h. Additional cyclobutanecarbaldehyde (15.51 mg, 0.184 mmol) was added and the mixture was stirred at room temperature for additional 30 min. The mixture was quenched with saturated NaHCO3 and extracted with DCM (1 x 6 mL). The organic layer was collected, dried over MgSO4, and concentrated. The residue was then dissolved in MeOH and solution mixture was purified by preparative HPLC (0%-100% MeCN 0.1% TFA/H2O 0.1% TFA) to give a desired product, which was dissolved in MeOH. The solution was loaded onto a PL-HCO3 MP SPE 200 mg/6 mL column and eluted with MeOH (2 x 2 mL). The combined eluates were concentrated and dried in vacuo to give 30 mg of the title compound as a light yellow solid. MS m/z = 340.1 [M+H]+

1H NMR (MeOH) δ: 6.91 (t, J=10.3 Hz, 1H), 6.64 (d, J=6.3 Hz, 1H), 6.58 (d, J=7.8 Hz, 1H), 6.16-6.48 (m, 1H), 4.12 (br. s., 1H), 3.05 (d, J=7.0 Hz, 2H), 2.59 (dt, J=15.0, 7.4 Hz, 1H), 2.10 (br. s., 2H), 1.85-1.99 (m, 3H), 1.70-1.81 (m, 2H), 1.36 (br. s., 1H), 1.01 (q, J=7.6 Hz, 1H)

Examples 369-376 listed in Table 4 were synthesized according to Method K using the appropriate aniline and aldehyde or ketone:
<table>
<thead>
<tr>
<th>Example No</th>
<th>Compound Name</th>
<th>Compound Structure</th>
<th>Analytical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>369</td>
<td>(1R,5S,6R)-5-((difluoromethyl)-5-(2-fluoro-5-((3-phenyl)prop-2-yn-1-yl)amino)phenyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>MS m/z = 386.1 [M+H]+ 1H NMR (MeOH) δ: 7.35-7.40 (m, 2H), 7.28-7.33 (m, 3H), 7.05 (dd, J=12.0, 8.7 Hz, 1H), 6.78-6.87 (m, 2H), 6.24-6.55 (m, 1H), 4.17-4.22 (m, 1H), 4.14 (s, 2H), 1.94-2.03 (m, 1H), 1.43 (t, J=6.9 Hz, 1H), 1.05-1.13 (m, 1H)</td>
</tr>
<tr>
<td>370</td>
<td>(1R,5S,6R)-5-((1-(4-chlorophenyl)cyclopropyl)methyl)amino)-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>MS m/z = 436.1 [M+H]+ 1H NMR (MeOH) δ: 7.33-7.38 (m, 2H), 7.25-7.29 (m, 2H), 6.88 (dd, J=11.9, 8.8 Hz, 1H), 6.65 (dd, J=6.7, 2.9 Hz, 1H), 6.54 (dt, J=8.9, 3.4 Hz, 1H), 6.13-6.44 (m, 1H), 4.07 (br. s., 1H), 3.30 (d, J=9.2 Hz, 1H), 1.81-1.90 (m, 1H), 1.33 (d, J=4.3 Hz, 1H), 0.92-1.04 (m, 3H), 0.84-0.90 (m, 2H)</td>
</tr>
<tr>
<td>371</td>
<td>(1R,5S,6R)-5-(difluoromethyl)-5-(2-fluoro-5-(((1(S,R,2(R,S)))-2-phenylcyclopropyl)methyl)amino)phenyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>MS m/z = 402 [M+H]+ 1H NMR (MeOH) δ: 7.20-7.28 (m, 2H), 7.05-7.17 (m, 4H), 6.45-6.83 (m, 3H), 4.58 (dt, J=6.7, 3.6 Hz, 1H), 3.17 (dt, J=6.3, 3.0 Hz, 2H), 2.19 (dt, J=9.8, 7.0 Hz, 1H), 1.84-1.92 (m, 1H), 1.60-1.68 (m, 1H), 1.38-1.47 (m, 1H), 1.31-1.38 (m, 1H), 0.95-1.02 (m, 2H)</td>
</tr>
<tr>
<td>372</td>
<td>(1R,5S,6R)-5-(difluoromethyl)-5-(2-fluoro-5-(((1(S,R,2(R,S)))-2-phenylcyclopropyl)methyl)amino)phenyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>MS m/z = 402 [M+H]+ 1H NMR (MeOH) δ: 7.17-7.33 (m, 5H), 6.98 (dd, J=12.1, 9.0 Hz, 1H), 6.37-6.69 (m, 3H), 4.49 (br. s., 1H), 2.70-2.83 (m, 2H), 2.29-2.36 (m, 1H), 2.05-2.14 (m, 1H), 1.58 (br. s., 1H), 1.45-1.53 (m, 1H), 1.24-1.32 (m, 1H), 1.08-1.15 (m, 1H), 0.95 (q, J=5.7 Hz, 1H)</td>
</tr>
<tr>
<td>Compound</td>
<td>Chemical Structure</td>
<td>Mass Spectrometry</td>
<td>NMR Spectrometry</td>
</tr>
<tr>
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<tr>
<td>373</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>Mass: 418 [M+H]+&lt;br&gt;(300 MHz, CHLOROFORM-d) δ: 0.86 (m, 1 H), 1.18 (m, 1 H), 1.71 (m, 1 H), 3.88 (m, 1 H), 4.20 (m, 1 H), 4.31 (d, J = 5.7 Hz, 2 H), 4.60 (dd, J = 47.1, 10.2 Hz, 1 H), 4.69 (dd, J = 49.1, 10.2 Hz, 1 H), 6.59 (dt, J = 8.7, 3.4, 3.4 Hz, 1 H), 6.83 (dd, J = 6.7, 2.9 Hz, 1 H), 6.91 (dd, J = 11.7, 8.7 Hz, 1 H), 7.09 (t, J = 6.0 Hz, 1 H), 7.78 (s, 1 H).</td>
<td></td>
</tr>
<tr>
<td>374</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>Mass: 435.8 [M+H]+&lt;br&gt;(300 MHz, CHLOROFORM-d) δ: 0.90 (m, 1 H), 1.36 (m, 1 H), 1.80 (m, 1 H), 3.87 (m, 1 H), 4.21 (br, 1 H), 4.30 (d, J = 5.7 Hz, 2 H), 6.21 (t, J = 5.8 Hz, 1 H), 6.62 (m, 1 H), 6.84 (dd, J = 6.5, 2.9 Hz, 1 H), 6.92 (dd, J = 11.7, 8.6 Hz, 1 H), 7.09 (t, J = 6.0 Hz, 1 H), 7.78 (s, 1 H).</td>
<td></td>
</tr>
<tr>
<td>375</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>Mass: 352.1 [M+H]+&lt;br&gt;1H NMR (400 MHz, MeOH-d4) δ: 6.92 (dd, J = 12.0, 8.7 Hz, 1H), 6.71 (dd, J = 6.5, 2.9 Hz, 1H), 6.60 (dt, J = 8.8, 3.4 Hz, 1H), 6.13-6.44 (m, 1H), 4.77 (t, J = 2.3 Hz, 2H), 4.01-4.07 (m, 1H), 3.14 (d, J = 7.2 Hz, 2H), 2.79-2.88 (m, 2H), 2.53-2.64 (m, 1H), 2.40-2.48 (m, 2H), 1.82-1.91 (m, 1H), 1.30-1.36 (m, 1H), 0.96 (dt, J = 9.2, 6.7 Hz, 1H).</td>
<td></td>
</tr>
<tr>
<td>376</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>Mass: 394.1 [M+H]+&lt;br&gt;1H NMR (400 MHz, MeOH-d4) δ: 6.93 (dd, J = 11.9, 8.8 Hz, 1H), 6.71 (dd, J = 6.6, 3.0 Hz, 1H), 6.58 (dt, J = 8.7, 3.4 Hz, 1H), 6.10-6.41 (m, 1H), 3.97-4.03 (m, 1H), 1.80-1.87 (m, 1H), 1.30 (t, J = 6.4 Hz, 3H), 0.91-0.99 (m, 3H), 0.81 (br. s., 2H).</td>
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</table>
Method L:

Example 377: Synthesis of (lR,5S,6R)-5-((5-chloropyridin-2-yl)methyl)amino)-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine

To a solution of tert-butyl ((lR,5S,6R)-5-((5-amino-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)carbamate (16i-B, 0.072 g, 0.194 mmol) and 5-chloropicolinaldehyde (0.028 g, 0.198 mmol) in DCE (1 mL) at RT was added HOAc (0.011 ml, 0.194 mmol) and sodium triacetoxyborohydride (0.050 g, 0.236 mmol). The reaction mixture was stirred at RT for 1.5 h. Trifluoroacetic acid (2.0 ml, 26.9 mmol) was added and after 15 min, and the reaction mixture was diluted with EtOAc and water. The pH was adjusted to 9 with 10 M NaOH. The aqueous phase was extracted with EtOAc and the combined organic extracts were washed with brine and dried over MgSO₄. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (60% to 100% EtOAc in heptane) to give the title compound (0.064 g, 0.161 mmol, 83% yield) as a white solid.

MS m/z = 397.1 [M+H]+

1H NMR (400 MHz, CDC13) δ 0.83-0.92 (m, 1 H), 1.39 (t, J = 6.85 Hz, 1H), 1.66-1.89 (m, 1H), 3.79-3.87 (m, 1H), 4.24 (d, J = 4.50 Hz, 2H), 4.63 (br s, 1H), 4.99 (br s, 2H), 6.23 (t, J = 56.1 Hz, 1H), 6.41 (dt, J = 8.51, 3.37 Hz, 1H), 6.77-6.87 (m, 2H), 7.14 (d, J = 8.41 Hz, 1H), 7.56 (dd, J = 8.41, 2.35 Hz, 1H), 8.48 (d, J = 2.35 Hz, 1H)

Examples 378-385 listed in Table 5 were synthesized according to Method L using the appropriate Boc-protected aniline and aldehyde or ketone:

<table>
<thead>
<tr>
<th>Exam pie No</th>
<th>Compound Name</th>
<th>Compound Structure</th>
<th>Analytical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Table 5
| 378 | (1R,5S,6R)-5-{((R)-1-(5-chloropyridin-2-yl)ethyl)amino)-2-fluorophenyl}-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine and (1R,5S,6R)-5-{((S)-1-(5-chloropyridin-2-yl)ethyl)amino)-2-fluorophenyl}-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine | \[\text{MS } m/z = 411 \text{ [M+H]}^+\]  
1H NMR (400 MHz, CDCl₃)  
\(\delta 0.86-0.95 \text{ (m, 1H), 1.31-1.41} \text{ (m, 1H), 1.44-1.49} \text{ (m, 3H),} 1.72-1.82 \text{ (m, 1H), 3.78-3.89} \text{ (m, 1H), 4.31 (br s, 1H), 4.43-4.54} \text{ (m, 1H), 4.69 (br s, 2H),} 6.19 \text{ (t, } J = 56.14 \text{ Hz, 1H),} 6.30-6.38 \text{ (m, 1H), 6.64 - 6.74} \text{ (m, 1H), 6.81 (ddd, } J = 11.74, 8.61, 3.33 \text{ Hz, 1H), 7.24-7.28} \text{ (m, 1H), 7.56 (ddd, } J = 8.61, 6.46, 2.54 \text{ Hz, 1H), 8.50 (dd, } J = 7.92, 2.05 \text{ Hz, 1H)}\] |
| 379 | (1R,5S,6R)-5-((cyclopropylmethyl)amino)-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine | \[\text{MS } m/z = 326\text{[M+H]}^+\]  
1H NMR (400 MHz, CDCl₃)  
\(\delta 0.15-0.23 \text{ (m, 2H), 0.48-0.55} \text{ (m, 2H), 0.84-0.95} \text{ (m, 1H), 0.97-1.09} \text{ (m, 1H), 1.37 (t, } J = 6.26 \text{ Hz, 1H), 1.76-1.86} \text{ (m, 1H), 2.87 (d, } J = 6.85 \text{ Hz, 2H),} 3.70 \text{ (s br, 1H), 3.84-3.88} \text{ (m, 1H), 4.52 (s br, 2H), 6.22 (t, } J = 56.10 \text{ Hz, 1H),} 6.47 \text{ (dt, } J = 8.61, 3.42 \text{ Hz, 1H), 6.72 (dd, } J = 6.46, 2.93 \text{ Hz, 1H), 6.90 (dd, } J = 11.74, 8.80 \text{ Hz, 1H)}\] |
| 380 | (1R,5S,6R)-5-{((R)-3-bromo-6,7-dihydro-5H-cyclopenta[b]pyridin-7-yl)amino)-2-fluorophenyl}-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine or (1R,5S,6R)-5-{((S)-3-bromo-6,7-dihydro-5H-cyclopenta[b]pyridin-7-yl)amino)-2-fluorophenyl}-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine | \[\text{MS } m/z = 467.0 \text{ [M+H]}^+\].  
\(^1\text{H NMR (400 MHz, CDCl₃) } \delta 0.87-0.94 \text{ (m, 1H), 1.38 (t, } J = 6.70 \text{ Hz, 1H), 1.77-1.83} \text{ (m, 1H), 1.89-1.98} \text{ (m, 1H), 2.71-2.81} \text{ (m, 1H), 2.85-2.93} \text{ (m, 2H), 3.87 (t, } J = 5.48 \text{ Hz, 1H), 4.40 (br s, 1H), 4.48 (s br, 2H), 4.62-4.68} \text{ (m, 1H), 6.24 (t, } J = 55.90 \text{ Hz, 1H),} 6.64 \text{ (dt, } J = 8.61, 3.10 \text{ Hz, 1H), 6.88 (dd, } J = 6.46, 2.93 \text{ Hz, 1H),} 6.93 \text{ (dd, } J = 11.54, 8.61 \text{ Hz, 1H), 7.68} \text{ (s, 1H), 8.47 (s, 1H), or} \] |
| 7-yl]amino)-2-fluorophenyl)-5- (difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine | \( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \)
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0.85-0.94 (m, 1H), 1.38 (t, ( J = 6.75 ) Hz, 1H), 1.72-1.93 (m, 2H), 2.72-2.97 (m, 3H), 3.83-3.88 (m, 1H), 4.41 (s br, 1H), 4.52-4.73 (m, 3H), 6.24 (t, ( J = 55.80 ) Hz, 1H), 6.61 (dt, ( J = 8.61, 3.42 ) Hz, 1H), 6.82 (dd, ( J = 6.46, 2.93 ) Hz, 1H), 6.89 (dd, ( J = 11.54, 8.61 ) Hz, 1H), 7.68 (s, 1H), 8.49 (s, 1H).</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>381</th>
<th>( (1R,5S,6R)-5-(5-(((S)-3-bromo-6,7-dihydro-5H-cyclopenta[b]pyridin-7-yl)amino)-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine ) or ( (1R,5S,6R)-5-(5-(((R)-3-bromo-6,7-dihydro-5H-cyclopenta[b]pyridin-7-yl)amino)-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine )</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS ( m/z = 467.0 ) [M+H]+.</td>
<td></td>
</tr>
</tbody>
</table>
| \( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \)
| 0.85-0.94 (m, 1H), 1.38 (t, \( J = 6.75 \) Hz, 1H), 1.72-1.93 (m, 2H), 2.72-2.97 (m, 3H), 3.83-3.88 (m, 1H), 4.41 (s br, 1H), 4.52-4.73 (m, 3H), 6.24 (t, \( J = 55.80 \) Hz, 1H), 6.61 (dt, \( J = 8.61, 3.42 \) Hz, 1H), 6.82 (dd, \( J = 6.46, 2.93 \) Hz, 1H), 6.89 (dd, \( J = 11.54, 8.61 \) Hz, 1H), 7.68 (s, 1H), 8.49 (s, 1H). |
| or \( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \)
| 0.87-0.94 (m, 1H), 1.38 (t, \( J = 6.70 \) Hz, 1H), 1.77-1.83 (m, 1H), 1.89-1.98 (m, 1H), 2.71-2.81 (m, 1H), 2.85-2.93 (m, 2H), 3.87 (t, \( J = 5.48 \) Hz, 1H), 4.40 (br s, 1H), 4.48 (s br, 2H), 4.62-4.68 (m, 1H), 6.24 (t, \( J = 55.90 \) Hz, 1H), 6.64 (dt, \( J = 8.61, 3.10 \) Hz, 1H), 6.88 (dd, \( J = 6.46, 2.93 \) Hz, 1H), 6.93 (dd, \( J = 11.54, 8.61 \) Hz, 1H), 7.68 (s, 1H), 8.47 (s, 1H). |

<table>
<thead>
<tr>
<th>382</th>
<th>( (1R,5S,6R)-5-(5-(((R)-3-bromo-5,6,7,8-tetrahydroquinolin-8-yl)amino)-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-</th>
<th>MS ( m/z = 483.0 ) [M+H]+.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1H NMR (400 MHz, CHLOROFORM-d) ( \delta ) ppm 0.90 (dd, ( J = 16.24, 8.61 ) Hz, 1H) 1.37 (t, ( J = 7.20 ) Hz, 1H) 1.72 - 1.97 (m, 4H) 2.20 - 2.36 (m, 1H) 2.72 - 2.87 (m, 2H) 3.86 (t, ( J = 5.38 ) Hz, 1H)</td>
<td>and</td>
<td>1H NMR (400 MHz, CHLOROFORM-d) ( \delta ) ppm 0.90 (dd, ( J = 16.24, 8.61 ) Hz, 1H) 1.37 (t, ( J = 7.20 ) Hz, 1H) 1.72 - 1.97 (m, 4H) 2.20 - 2.36 (m, 1H) 2.72 - 2.87 (m, 2H) 3.86 (t, ( J = 5.38 ) Hz, 1H)</td>
</tr>
<tr>
<td>3-en-3-amine and (1R,5S,6R)-5-(5-(((S)-3-bromo-5,6,7,8-tetrahydroquinolin-8-yl)amino)-2-fluorophenyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine</td>
<td>4.24-4.43 (m, 3 H) 4.61 - 4.81 (m, 1 H) 6.24 (t, J=56.50 Hz, 1 H) 6.60 - 6.69 (m, 1 H) 6.78 - 6.96 (m, 2 H) 7.58 (s, 1 H) 8.46 - 8.49 (m, 1 H)</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>383 (R)-4-((3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)amino)cromen-7-carbonitrile and (S)-4-((3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)amino)cromen-7-carbonitrile</td>
<td>MS m/z = 429.0 [M+H]+. 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 0.88 - 0.98 (m, 1 H) 1.37 (br. s., 1 H) 1.76 - 1.86 (m, 1 H) 2.08 - 2.18 (m, 2 H) 3.80 (d, J=7.24 Hz, 1 H) 3.89 (t, J=6.75 Hz, 1 H) 4.17 - 4.36 (m, 4 H) 4.53 - 4.63 (m, 1 H) 6.22 (t, J=57.10 Hz, 1 H) 6.55 - 6.61 (m, 1 H) 6.79 (td, J=5.97, 3.13 Hz, 1 H) 6.96 (dd, J=11.54, 8.80 Hz, 1 H) 7.13 (s, 1 H) 7.16 (d, J=8.02 Hz, 1 H) 7.41 (d, J=7.82 Hz, 1 H)</td>
<td></td>
</tr>
<tr>
<td>384 (1R,5S,6R)-5-(5-(((R)-5-bromo-2,3-dihydro-1H-inden-1-yl)amino)-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine and (1R,5S,6R)-5-(5-(((S)-5-bromo-2,3-dihydro-1H-inden-1-yl)amino)-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine</td>
<td>MS m/z = 467.0 [M+H]+. 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 0.85 - 0.98 (m, 1 H) 1.34 - 1.41 (m, 1 H) 1.77 - 1.95 (m, 2 H) 2.53 (d, J=7.24 Hz, 1 H) 2.80 - 2.90 (m, 1 H) 2.93 - 3.03 (m, 1 H) 3.76 (br. s., 1 H) 3.84 - 3.92 (m, 1 H) 4.35 (br. s., 2 H) 4.83 - 4.91 (m, 1 H) 6.22 (t, J=56.30 Hz, 1 H) 6.54 - 6.61 (m, 1 H) 6.79 (td, J=6.70, 3.10 Hz, 1 H) 6.92 (dd, J=11.74, 8.61 Hz, 1 H) 7.20 (d, J=7.82 Hz, 1 H) 7.31 (br. s., 1 H) 7.39 (s, 1 H)</td>
<td></td>
</tr>
</tbody>
</table>
Method M:

Example 386: Synthesis of N-(3-(((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-6-chlorofuro[3,2-b]pyridin-3-amine

A microwave vial was charged with N-(3-(((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-6-chlorofuro[3,2-b]pyridin-3-amine (Example 128, 0.139 g, 0.307 mmol), tris(dibenzylideneacetone) dipalladium (0) (0.028 g, 0.031 mmol), 2-dicyclohexylphosphino-2′,6′-dimethoxy-1′-t-biphenyl (0.025 g, 0.061 mmol), and zinc cyanide (0.023 g, 0.368 mmol). The vial was evacuated and backfilled with N₂ gas. A solvent mixture of 99:1 DMF: water (1.5 mL) was added and the reaction mixture was heated to 120 °C for 20 minutes in the microwave. The reaction mixture was cooled to rt and diluted with water and EtOAc. The organic layer was separated and sequentially washed with water, 1 M LiCl (aq), and brine before drying over magnesium sulfate. The filtrate was concentrated under reduced pressure. The residue was triturated with DCM : ether ~ 1:1 to afford a
white solid which was collected by filtration, dried under high vacuum and identified as the title compound (0.0931 g, 0.210 mmol, 68.4 % yield). MS m/z = 443.9 [M+H]^+

1H NMR (400 MHz, DMSO-d6) δ ppm 0.88 (dt, J=9.63, 6.33 Hz, 1 H) 0.96 (td, J=6.50, 2.64 Hz, 1 H) 1.69 (dt, J=9.88, 7.09 Hz, 1 H) 3.42 (s, 3 H) 3.94 - 4.01 (m, 1 H) 4.63 - 4.72 (m, 1 H) 4.75 - 4.84 (m, 1 H) 4.86 (s, 2 H) 5.62 (s, 2 H) 7.45 - 7.51 (m, 1 H) 7.75 - 8.02 (m, 2 H) 8.66 (d, J=10.23 Hz, 1 H) 9.04 (s, 1 H)

Table 6 includes compound examples prepared wherein the appropriate halogenated intermediate (also a compound example) was converted into the corresponding cyano-compound (Examples 387-400 in Table 6) according to Method M:

<table>
<thead>
<tr>
<th>Exa mpl eNo</th>
<th>Compound Name</th>
<th>Compound Structure</th>
<th>Analytical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>387</td>
<td>N-(3-((lR,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-cyano-3-(hydroxymethyl)picolinamide</td>
<td><img src="image" alt="Structure" /></td>
<td>MS m/z = 430 [M+H]+ 1H NMR (300 MHz, DMSO-d6) δ ppm 0.77 - 1.00 (m, 2 H) 1.61 - 1.75 (m, 1 H) 3.89 - 4.00 (m, 1 H) 4.55 - 4.71 (m, 1 H) 4.74 - 4.86 (m, 1 H) 4.92 (s, 2 H) 5.60 (s, 2 H) 7.43 (d, J=8.48 Hz, 1 H) 7.85 (d, J=8.77 Hz, 1 H) 8.05 (s, 1 H) 8.54 (s, 1 H) 9.06 (s, 1 H) 10.84 (br. s., 1 H)</td>
</tr>
<tr>
<td>388</td>
<td>N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-cyano-3-fluoropicolinamide</td>
<td><img src="image" alt="Structure" /></td>
<td>MS m/z = 419.9 [M]+ 1H NMR (300 MHz, DMSO-d6) δ ppm 0.82 - 0.98 (m, 1 H) 1.14 (br. s., 1 H) 1.62 - 1.79 (m, 1 H) 3.92 - 4.05 (m, 1 H) 5.88 (s, 2 H) 5.98 - 6.40 (m, 1 H) 7.08 - 7.39 (m, 1 H) 7.70 - 8.02 (m, 2 H) 8.66 (d, J=10.23 Hz, 1 H) 9.04 (s, 1 H) 10.88 (s, 1 H)</td>
</tr>
<tr>
<td>389</td>
<td>N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-cyano-3-(dimethylamino)picolinamide</td>
<td><strong>MS m/z = 445 [M+H]+</strong>&lt;br&gt;1H NMR (300 MHz, DMSO-d6)&lt;br&gt;δ ppm 0.90 (d, J=5.99 Hz, 1 H)&lt;br&gt;1.13 - 1.27 (m, 1 H)&lt;br&gt;1.70 (d, J=4.53 Hz, 1 H)&lt;br&gt;2.92 (br. s., 6 H)&lt;br&gt;3.98 (br. s., 1 H)&lt;br&gt;5.87 (br. s., 2 H)&lt;br&gt;5.97 - 6.46 (m, 1 H)&lt;br&gt;7.19 - 7.34 (m, 1 H)&lt;br&gt;7.72 - 7.90 (m, 3 H)&lt;br&gt;8.35 (br. s., 1 H)&lt;br&gt;10.72 (br. s., 1 H)</td>
<td></td>
</tr>
<tr>
<td>390</td>
<td>N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-cyano-3-(methoxymethyl)picolinamide</td>
<td><strong>MS m/z = 416 [M+H]+</strong>&lt;br&gt;1H NMR (300 MHz, DMSO-d6)&lt;br&gt;δ ppm 0.82 - 1.01 (m, 1 H)&lt;br&gt;1.14 (br. s., 1 H)&lt;br&gt;1.71 (q, J=7.70 Hz, 1 H)&lt;br&gt;2.26 (s, 3 H)&lt;br&gt;4.01 (br. s., 1 H)&lt;br&gt;5.83 (s, 2 H)&lt;br&gt;6.00 - 6.48 (m, 1 H)&lt;br&gt;7.82 (d, J=6.87 Hz, 2 H)&lt;br&gt;8.27 (d, J=8.18 Hz, 1 H)&lt;br&gt;8.58 (d, J=7.89 Hz, 1 H)&lt;br&gt;9.19 (s, 1 H)&lt;br&gt;10.73 (s, 1 H)</td>
<td></td>
</tr>
<tr>
<td>391</td>
<td>N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-cyano-3-(methoxymethyl)picolinamide</td>
<td><strong>MS m/z = 446 [M+H]+</strong>&lt;br&gt;1H NMR (300 MHz, CHLOROFORM-d)&lt;br&gt;δ ppm 9.84 (s, 1 H)&lt;br&gt;8.56 (s, 1 H)&lt;br&gt;8.50 (s, 1 H)&lt;br&gt;7.82 - 7.98 (m, 1 H)&lt;br&gt;7.50 (dd, J=6.50, 2.12 Hz, 1 H)&lt;br&gt;6.91 - 7.04 (m, 1 H)&lt;br&gt;6.03 - 6.46 (m, 1 H)&lt;br&gt;4.97 - 5.28 (m, 4 H)&lt;br&gt;3.91 (t, J=5.70 Hz, 1 H)&lt;br&gt;3.56 (s, 3 H)&lt;br&gt;1.81 - 1.96 (m, 1 H)&lt;br&gt;1.38 - 1.55 (m, 1 H)&lt;br&gt;0.92 - 1.05 (m, 1 H)</td>
<td></td>
</tr>
<tr>
<td>392</td>
<td>8-((3-((lR,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)amino) -1,7-naphthyridine-3-carbonitrile</td>
<td><strong>MS m/z = 407.2 [M+H]+</strong>&lt;br&gt;1H NMR (400 MHz, DMSO-d6)&lt;br&gt;δ ppm 9.72 (s, 1 H)&lt;br&gt;9.21 (d, J=1.76 Hz, 1 H)&lt;br&gt;8.87 - 9.06 (m, 1 H)&lt;br&gt;8.25 (dd, J=7.34, 2.64 Hz, 1 H)&lt;br&gt;8.22 (d, J=5.87 Hz, 1 H)&lt;br&gt;8.02 (dt, J=8.56, 3.55 Hz, 1 H)&lt;br&gt;7.22 (d, J=5.67 Hz, 1 H)&lt;br&gt;7.16 (dd, J=8.80, 11.74 Hz, 1H)&lt;br&gt;5.75 (s, 2 H)&lt;br&gt;4.39 - 4.75 (m, 2 H)&lt;br&gt;3.90 - 4.10 (m, 1 H)&lt;br&gt;1.49 - 1.69 (m, 1 H)&lt;br&gt;1.03 (d, J=1.96 Hz, 1 H)&lt;br&gt;0.83 (dt, J=9.24, 6.33 Hz, 1 H)</td>
<td></td>
</tr>
</tbody>
</table>
| 393 | 4-((3-((1R,5S,6R)-3-methylpyrrolidin-2-yl)-1-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)amino)pyrido[3,2-d]pyrimidine-7-carbonitrile | MS \text{m/z} = 408 \text{[M+H]+} \\
| | | \text{1H NMR (400 MHz, DMSO-d6)} \\
| | | \text{δ ppm: 10.58 (s, 1 H), 9.24 (d, J=1.96 Hz, 1 H), 8.74 (s, 1 H), 8.29 (dd, J=7.43, 2.74 Hz, 1 H), 7.84 - 7.95 (m, 1 H), 7.22 (dd, J=11.74, 8.80 Hz, 1 H), 6.69 (br. s., 2 H), 4.44 - 4.76 (m, 2 H), 4.03 (t, J=5.28 Hz, 1 H), 1.54 - 1.69 (m, 1 H), 0.97 - 1.08 (m, 1 H), 0.78 - 0.89 (m, 1 H).} |
| 394 | N-3-((1R,5S,6R)-3-methylpyrrolidin-2-yl)-4-fluoropropyl-5-cyano-3-isopropylpicolinamide | MS \text{m/z} = 444 \text{[M+H]+} \\
| | | \text{1H NMR (300 MHz, DMSO-}d_6\text{)} \\
| | | \text{δ ppm: 0.83 - 0.98 (m, 1 H), 1.09 - 1.17 (m, 1 H), 1.25 (d, J=6.87 Hz, 6 H), 1.63 - 1.82 (m, 1 H), 3.40 (quin, J=6.83 Hz, 1 H), 3.92 - 4.03 (m, 1 H), 5.88 (s, 2 H), 5.97 - 6.56 (m, 1 H), 7.23 (dd, J=1.77, 8.84 Hz, 1 H), 7.70 - 7.90 (m, 2 H), 8.53 (d, J=1.90 Hz, 1 H), 8.95 (d, J=1.90 Hz, 1 H), 10.78 (s, 1 H)} |
| 395 | N-3-((1R,5S,6R)-3-methylpyrrolidin-2-yl)-4-fluoropropyl-5-cyano-3-(difluoromethyl)picolinamide | MS \text{m/z} = 452.1 \text{[M+H]+} \\
| | | \text{1H NMR (300 MHz, DMSO-}d_6\text{)} \\
<p>| | | \text{δ ppm: 0.77 - 0.96 (m, 4 H), 1.07 - 1.54 (m, 12 H), 1.73 (d, J=9.50 Hz, 2 H), 4.00 (br. s., 1 H), 5.74 - 5.93 (m, 2 H), 5.96 - 6.42 (m, 1 H), 7.14 - 7.31 (m, 1 H), 7.49 - 8.00 (m, 3 H), 8.78 - 8.96 (m, 1 H), 9.28 - 9.42 (m, 1 H), 10.94 - |</p>
<table>
<thead>
<tr>
<th>Linamide</th>
<th>( \text{MS m/z = 432 [M+H]+} )</th>
<th>( \text{1H NMR (300 MHz, DMSO-d}_{6} ) Shift = 10.73 (s, 1H), 8.67 (d, J=1.6 Hz, 1H), 8.22 (d, J=1.5 Hz, 1H), 7.91 (d, J=2.5 Hz, 1H), 7.81 (dd, J=2.5, 8.6 Hz, 1H), 7.42 (d, J=8.6 Hz, 1H), 5.60 (s, 2H), 4.87 - 4.73 (m, 1H), 4.70 - 4.59 (m, 1H), 3.99 - 3.80 (m, 4H), 1.67 (td, J=6.9, 9.7 Hz, 1H), 0.94 (dt, J=2.8, 6.6 Hz, 1H), 0.85 (td, J=6.3, 9.6 Hz, 1H)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-(3-((lR,5S,6R)-3-Methyl-5-oxa-4-fluorophenyl)-5-cyano-3-(hydroxymethyl)picolinamide)</td>
<td>( \text{MS m/z = 430.1 [M+H]+} )</td>
<td>( \text{1H NMR (300MHz, DMSO)} ) Shift = 10.79 (s, 1H), 9.09 - 8.97 (m, 1H), 8.66 (dd, J=1.5, 10.2 Hz, 1H), 7.75 (dd, J=2.6, 6.2 Hz, 1H), 7.65 (dd, J=2.7, 6.4 Hz, 1H), 6.44 - 5.99 (m, 1H), 5.86 (s, 2H), 4.03 - 3.94 (m, 1H), 2.27 (d, J=2.2 Hz, 3H), 1.76 - 1.64 (m, 1H), 1.17 - 1.07 (m, 1H), 0.96 - 0.84 (m, 1H)</td>
</tr>
<tr>
<td>N-(3-((lR,5S,6R)-3-Methyl-5-oxa-4-fluorophenyl)-5-cyano-3-(hydroxymethyl)picolinamide)</td>
<td>( \text{MS m/z = 434.0 [M+H]+} )</td>
<td>( \text{1H NMR (300MHz, DMSO)} ) Shift = 10.79 (s, 1H), 9.09 - 8.97 (m, 1H), 8.66 (dd, J=1.5, 10.2 Hz, 1H), 7.75 (dd, J=2.6, 6.2 Hz, 1H), 7.65 (dd, J=2.7, 6.4 Hz, 1H), 6.44 - 5.99 (m, 1H), 5.86 (s, 2H), 4.03 - 3.94 (m, 1H), 2.27 (d, J=2.2 Hz, 3H), 1.76 - 1.64 (m, 1H), 1.17 - 1.07 (m, 1H), 0.96 - 0.84 (m, 1H)</td>
</tr>
<tr>
<td>Example 401</td>
<td>Synthesis of (R')-7-((3-((17.5 S . 6 R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)amino)-6,7-dihydro-5/\cvclopenta[fclpyridine-3-carbonitrile</td>
<td></td>
</tr>
<tr>
<td>-------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>MS m/z = 446.1 [M+H]+</td>
<td>(^1)H NMR (300 MHz, DMSO-(d_6)) (\delta) ppm 0.80 - 0.95 (m, 1 H) 1.04 - 1.15 (m, 1 H) 1.62 - 1.75 (m, 1 H) 2.26 (s, 3 H) 3.91 (s, 3 H) 3.93 - 4.01 (m, 1 H) 5.85 (s, 2 H) 6.00 - 6.52 (m, 1 H) 7.53 (d, (J=4.97) Hz, 1 H) 7.74 (d, (J=4.68) Hz, 1 H) 8.20 (s, 1 H) 8.66 (s, 1 H) 10.58 (s, 1 H)</td>
<td></td>
</tr>
<tr>
<td>MS m/z = 425.9 [M+H]+</td>
<td>(^1)H NMR (400 MHz, DMSO-d6) (\delta) ppm 0.91 (dt, (J=9.19), 6.55 Hz, 1 H) 1.18 (t, (J=7.14) Hz, 1 H) 1.73 - 1.80 (m, 1 H) 4.00 - 4.06 (m, 1 H) 5.91 (s, 2 H) 6.21 (t, (J=56.10) Hz, 1 H) 7.26 (dd, (J=11.74), 8.80 Hz, 1 H) 7.93 (ddd, (J=8.80), 3.91, 2.93 Hz, 1 H) 8.39 (ddd, (J=4.31) Hz, 1 H) 8.75 (s, 1 H) 8.88 (d, (J=1.96) Hz, 1 H) 9.24 (d, (J=1.96) Hz, 1 H) 10.61 (s, 1 H)</td>
<td></td>
</tr>
<tr>
<td>MS m/z = 418.1 [M+H]+</td>
<td>(^1)H NMR (300MHz, DMSO) (\delta) = 10.95 (s, 1H), 9.05 (s, 1H), 8.68 (dd, (J=1.5), 10.2 Hz, 1H), 8.02 (d, (J=2.5) Hz, 1H), 7.82 (dd, (J=2.6), 8.7 Hz, 1H), 7.45 (d, (J=8.6) Hz, 1H), 5.64 (s, 2H), 4.80 (s, 1H), 4.65 (s, 1H), 4.01 - 3.90 (m, 1H), 1.66 (td, (J=6.9), 9.8 Hz, 1H), 0.94 (dt, (J=2.7), 6.5 Hz, 1H), 0.85 (td, (J=6.2), 9.5 Hz, 1H)</td>
<td></td>
</tr>
</tbody>
</table>
A sealable vial was charged with a mixture of potassium ferrocyanide trihydrate (0.056 g, 0.13 mmol), chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-l,l'-biphenyl)[2-(2'-amino-l,l'-biphenyl)]palladium(II) (0.010 g, 0.013 mmol), 2-(dicyclohexylphosphino)-2',4',6',-tri-isopropyl-l,l'-biphenyl (0.0069 g, 0.014 mmol), and (1P,5S67?)-5-5-((7?)-3-bromo-6,7-dihydro-5i7-cyclopenta[¾]pyridin-7-yl)amino)-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.3.0]non-3-ene (Example 351, 0.115 g, 0.246 mmol). Dioxane (0.65 mL) was added, followed by 0.65 mL of a solution of 30 mg of KOAc in 6.5 mL of water. The reaction mixture was purged with Nitrogen for 5 min. The reaction mixture was heated to 80 °C for 18 h, heated to 100 °C for 2 h and then cooled to room temperature. The reaction mixture was diluted with EtOAc, brine, and water. The aqueous phase was extracted with EtOAc (2 x) and the combined organic extracts were washed with brine and dried over MgSO₄. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (20% to 80% EtOAc in DCM) to give the title compound (0.074 g, 0.18 mmol, 73% yield) as a pale yellow solid.

MS m/z = 414.0 [M+H]+. Calculated for C₂H₁₈F₃N₄O 413.1.

¹HNMR (400 MHz, CDCl₃) δ 0.88-0.94 (m, 1H), 1.38 (t, J = 6.80 Hz, 1H), 1.76-1.83 (m, 1H), 1.89-2.00 (m, 1H), 2.77-2.99 (m, 3H), 3.84-3.90 (m, 1H), 4.43 (br, J = 3.33 Hz, 1H), 4.54 (br s, 2H), 4.74 (td, J = 8.00, 2.93 Hz, 1H), 6.24 (t, J = 55.90 Hz, 1H), 6.65 (dt, J = 8.61, 3.50 Hz, 1H), 6.89-6.98 (m, 2H), 7.79 (s, 1H), 8.70 (s, 1H).

The relative stereochemistry at the benzyllic carbon was not determined. The compound may have either R or S stereochemistry at the benzyllic carbon. It was isolated as a single diastereomer.

Table 7 includes compound examples prepared wherein the appropriate halogenated intermediate (also a compound example) was converted into the corresponding cyano-compound (Examples 402-404) according to Method N.
<table>
<thead>
<tr>
<th>mpleNo</th>
<th>Structure</th>
<th>Mass Spectrometry and NMR Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>402</td>
<td>(S)-7-((3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)amino)-6,7-dihydro-5H-cyclopenta[E]pyridine-3-carbonitrile (Example 365)</td>
<td></td>
</tr>
</tbody>
</table>
|        | ![Structure](image1.png) | MS m/z = 414.0 [M+H]+. 
1H NMR (400 MHz, CDCl₃) δ ppm 0.86-0.94 (m, 1H), 1.39 (t, J = 6.70 Hz, 1H), 1.74-1.82 (m, 1H), 1.83-1.96 (m, 1H), 2.76-3.05 (m, 3H), 3.83-3.90 (m, 1H), 4.45 (d br, J = 3.52 Hz, 1H), 4.60-4.82 (m, 3H), 6.24 (t, J = 5.80 Hz, 1H), 6.60 (dt, J = 8.66, 3.30 Hz, 1H), 6.83 (dd, J = 6.46, 2.93 Hz, 1H), 6.88 (dd, J = 11.54, 8.80 Hz, 1H), 7.79 (s, 1H), 8.72 (s, 1H).  
The relative stereochemistry at the benzylic carbon was not determined. The compound may have either R or S stereochemistry at the benzylic carbon. It was isolated as a single diastereomer. |
| 403    | (R)-8-((3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)amino)-5,6,7,8-tetrahydroquinoline-3-carbonitrile and (S)-8-((3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)amino)-5,6,7,8-tetrahydroquinoline-3-carbonitrile |
|        | ![Structure](image2.png) and ![Structure](image3.png) | 1:1 mixture of diastereomers |
| 404    | (R)-1-((3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-| MS m/z = 428.1 [M+H]+.  
1H NMR (400 MHz, CHLOROFORM-d) δ ppm 0.91 (dd, J=15.85, 8.61 Hz, 1H), 1.37 (br, s, 1H), 1.75 - 2.00 (m, 4H), 2.30 - 2.43 (m, 1H) 2.77 - 2.93 (m, 2H) 3.87 (t, J=5.58 Hz, 1H) 4.26 - 4.50 (m, 3H) 4.78 (br, s, 1H) 6.24 (t, J=56.30 Hz, 1H) 6.62 - 6.70 (m, 1H) 6.79 - 6.97 (m, 2H) 7.70 (s, 1H) 8.68 (d, J=6.06 Hz, 1H) |
|        | ![Structure](image4.png) | 3-carbonitrile) |
fluorophenyl)amino)-2,3-dihydro-1H-indene-5-carbonitrile and (S)-1-((3-((IR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-yl)-4-fluorophenyl)amino)-2,3-dihydro-1H-indene-5-carbonitrile

| 2.94 (m, 1H) 2.96 - 3.06 (m, 1H) 3.72 - 3.92 (m, 2H) 4.43 (br. s., 2H) 4.95 (br. s., 1H) 6.21 (t, J=56.10 Hz, 1H) 6.54 - 6.60 (m, 1H) 6.81 (dd, J=1.54, 8.61 Hz, 1H) 7.37 - 7.45 (m, 1H) 7.46 - 7.56 (m, 2H) |

Method O:

Example 405: Synthesis of N-(3-((IR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-yl)-4-fluorophenyl)-5-(cyclopropylethynyl)picolinamide

A sealable vial was evacuated and backfilled with nitrogen and then charged under a positive pressure of nitrogen with N-(3-((IR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-yl)-4-fluorophenyl)-5-chloropicolinamide (Example 76, 200 mg, 0.487 mmol), 2-(dicyclohexylphosphino)-2',4',6',-tri-isopropyl-1',1'-biphenyl (69.6 mg, 0.146 mmol) bis(acetonitrile)palladium(II) dichloride (12.63 mg, 0.049 mmol) and cesium carbonate (555 mg, 1.704 mmol), followed by anhydrous MeCN (1.5 mL). The suspension was stirred for 25 min. Then cyclopropylacetylene (0.083 mL, 0.974 mmol) was added and the reaction mixture was heated to 90 °C for 1.5 h. The reaction mixture was cooled to rt and partitioned between water and EtOAc. The organic extract was washed with brine and dried over MgS04. The filtrate was concentrated in vacuo to give the crude material which was treated with MeOH. A solid precipitated which was filtered off and discarded. The filtrate was absorbed onto a plug of silica gel and purified by silica gel flash chromatography, eluting with a gradient of 15% to 90% EtOAc in hexane, to provide the title compound (116 mg, 0.263 mmol, 54.1 % yield) as light-yellow solid. MS m/z = 441 [M+H]+
Table 8 includes compound examples prepared wherein the appropriate halogenated intermediate was reacted with the corresponding alkyne (Examples 406-410) according to Method O:

<table>
<thead>
<tr>
<th>Exam</th>
<th>Compound Name</th>
<th>Compound Structure</th>
<th>Analytical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>406</td>
<td>(IR,5S,6R)-5-(5-((3-cyclopropylethynyl)-i,7-naphthyridin-8-yl)amino)-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine</td>
<td>MS ( m/z = 464.1 ) [M+H]+</td>
<td>( ^1\text{H NMR (300 MHz, DMSO-d}_6 ) ppm 0.78 - 1.05 (m, 5 H) 1.07 - 1.26 (m, 2 H) 1.58 - 1.82 (m, 2 H) 3.98 - 4.08 (m, 2 H) 5.94 - 6.46 (m, 1 H) 7.21 (dd, ( J=1.84, 8.92 \text{ Hz}, 1 \text{ H} )) 7.75 - 7.94 (m, 1 H) 7.97 - 8.16 (m, 3 H) 8.69 (d, ( J=1.32 \text{ Hz}, 1 \text{ H} )) 10.66 (s, 1 H)</td>
</tr>
<tr>
<td>407</td>
<td>N-((3-(IR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(cyclopropylethynyl)pyrazine-2-carboxamide</td>
<td>MS ( m/z = 442.1 ) [M+H]+</td>
<td>( ^1\text{H NMR (300 MHz, DMSO-d}_6 ) ppm 0.86 - 0.97 (m, 3 H) 0.99 - 1.09 (m, 2 H) 1.15 (br. s., 1 H) 1.58 - 1.83 (m, 2 H) 4.02 (br. s., 1 H) 5.85 (br. s., 2 H) 5.97 - 6.52 (m, 1 H) 7.22 (dd, ( J=1.84, 9.06 \text{ Hz}, 1 \text{ H} )) 7.86 (dd, ( J=7.89, 3.5 \text{ Hz}, 1 \text{ H} )) 8.04 (dd, ( J=7.02, 2.78 \text{ Hz}, 1 \text{ H} )) 8.77 (d, ( J=1.32 \text{ Hz}, 1 \text{ H} )) 9.17 (d, ( J=1.46 \text{ Hz}, 1 \text{ H} )) 10.78 (s, 1 H)</td>
</tr>
<tr>
<td>408</td>
<td>(IR,5S,6R)-5-(5-((3-cyclopropylethynyl)-5-fluoro-1,7-naphthyridin-8-yl)amino)-2-</td>
<td>MS ( m/z = 482.1 ) [M+H]+</td>
<td>( ^1\text{H NMR (300 MHz, DMSO-d}_6 ) ppm 0.84 - 0.94 (m, 3 H) 0.96 - 1.05 (m, 2 H) 1.12 - 1.21 (m, 2 H) 1.63 - 1.84 (m, 3 H) 3.82 - 4.12 (m, 1 H) 5.73 - 6.54</td>
</tr>
</tbody>
</table>
Method P:

Synthesis of N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-
azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-
((3-cyclopropylprop-2-yn-1-yl)oxy)pyrazine-2-carboxamide (Example 411)
To a solution of 3-cyclopropylprop-2-yn-1-ol (205 mg, 2.137 mmol) in DMF (1 mL) was added sodium hydride (60% dispersion in mineral oil; 8.6 mg, 0.214 mmol) at rt. After 15 min N-(3-((IR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloropyrazine-2-carboxamide (Example 261, 88 mg, 0.214 mmol) was added and the reaction mixture was stirred at 60°C for 50 min. Water (1.0 mL) and aqueous, saturated NaHCO₃ solution (1 mL) were added. The resulting mixture was then extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with water and dried over MgSO₄. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel flash column chromatography (0%-20% MeOH/DCM) to give 58 mg of the title compound as an off-white solid. MS m/z = 472 [M+H]+

1H NMR (MeOH) δ: 8.90 (s, 1H), 8.29 (s, 1H), 7.86 (d, J = 5.7 Hz, 2H), 7.17 (t, J = 10.1 Hz, 1H), 6.04 - 6.49 (m, 1H), 5.05 (s, 2H), 4.05 (br. s., 1H), 1.80 - 2.00 (m, 1H), 1.25 - 1.40 (m, 2H), 0.90 - 1.02 (m, 1H), 0.79 (d, J = 7.6 Hz, 2H), 0.63 (br. s., 2H)

Table 9 includes compound examples prepared wherein the appropriate halogenated intermediate was reacted with the corresponding alcohol (Examples 412-418) according to Method P:

<table>
<thead>
<tr>
<th>Example No</th>
<th>Compound Name</th>
<th>Compound Structure</th>
<th>Analytical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>412</td>
<td>N-(3-((IR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-((tetrahydro-2H-pyran-4-yl)methoxy)pyrazine-2-carboxamide</td>
<td>![Structure Image]</td>
<td>MS m/z = 492.1[M+H]+ 1H NMR (MeOH) δ: 8.90 (d, J = 1.2 Hz, 1H), 8.30 (d, J = 1.2 Hz, 1H), 7.79 - 7.92 (m, 2H), 7.06 - 7.28 (m, 1H), 6.04 - 6.54 (m, 1H), 4.34 (d, J = 6.5 Hz, 2H), 4.04 - 4.11 (m, 1H), 4.00 (dd, J = 11.2, 3.9 Hz, 2H), 3.41 - 3.53 (m, 2H), 2.07 - 2.26 (m, 1H), 1.83 - 1.98 (m, 1H), 1.78 (d, J = 12.9 Hz, 2H), 1.40 - 1.57 (m, 2H), 1.33 (br. s., 1H), 0.89 - 1.06 (m, 1H)</td>
</tr>
</tbody>
</table>
| 413 | N-(3-((R,S,6R)-3-amino-5-((3-(((R,S,6R)-3-en-5-yl)-4-fluorophenyl)-5-((R,S)-tetrahydrofuran-3-yl)methoxy)pyrazine-2-carboxamide | MS \( m/z = 478.1[M+H]^+ 
1H NMR (MeOH) \( \delta \): 8.81 - 9.01 (m, IH), 8.20 - 8.37 (m, IH), 7.77 - 7.92 (m, 2H), 7.09 - 7.24 (m, IH), 6.07 - 6.48 (m, IH), 4.44 - 4.50 (m, IH), 4.35 - 4.41 (m, IH), 4.01 - 4.11 (m, IH), 3.87 - 3.96 (m, 2H), 3.67 - 3.82 (m, 2H), 2.75 - 2.91 (m, IH), 2.08 - 2.25 (m, IH), 1.84 - 1.97 (m, IH), 1.73 - 1.84 (m, IH), 1.31 - 1.36 (m, IH), 0.94 - 1.04 (m, IH) |
| 414 | 5-(allyloxy)-N-(3-((R,S,6R)-3-amino-5-(difluoromethyl)-2-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)pyrazine-2-carboxamide | MS \( m/z = 434.1[M+H]^+ 
1H NMR (MeOH) \( \delta \): 8.89 (s, IH), 8.29 (s, 1H), 7.86 (d, \( J = 5.9 \) Hz, 2H), 7.17 (t, \( J = 9.9 \) Hz, IH), 6.00 - 6.48 (m, 2H), 5.44 (d, \( J = 17.2 \) Hz, IH), 5.30 (d, \( J = 11.2 \) Hz, IH), 4.98 (d, \( J = 5.5 \) Hz, 2H), 4.05 (br. s., IH), 1.88 (d, \( J = 7.6 \) Hz, IH), 1.33 (br. s., IH), 0.98 (d, \( J = 8.0 \) Hz, IH) |
| 415 | N-(3-((R,S,6R)-3-amino-5-(difluoromethyl)-2-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(cyclopropylmethyl)pyrazine-2-carboxamide | MS \( m/z = 448.1[M+H]^+ 
1H NMR (MeOH) \( \delta \): 8.87 (s, IH), 8.26 (s, 1H), 7.85 (br. s., IH), 7.04 - 7.30 (m, IH), 6.05 - 6.50 (m, IH), 4.30 (d, \( J = 7.0 \) Hz, 2H), 4.06 (br. s., IH), 1.89 (d, \( J = 6.8 \) Hz, IH), 1.34 (br. s., 2H), 0.99 (d, \( J = 7.4 \) Hz, IH), 0.64 (d, \( J = 8.0 \) Hz, 2H), 0.40 (d, \( J = 3.7 \) Hz, 2H) |
| 416 | N-(3-((R,S,6R)-3-amino-5-(difluoromethyl)-2-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(cyclohexylmethoxy)pyrazine-2-carboxamide | MS \( m/z = 490.1[M+H]^+ 
1H NMR (MeOH) \( \delta \): 8.91 (d, \( J = 1.2 \) Hz, 2H), 8.29 (d, \( J = 1.2 \) Hz, IH), 7.83 - 7.92 (m, 2H), 7.20 (dd, \( J = 11.7, 9.4 \) Hz, IH), 6.09 - 6.48 (m, 1H), 4.29 (d, \( J = 6.1 \) Hz, 2H), 4.04 - 4.13 (m, IH), 1.88 - 1.97 (m, 4H), 1.72 - 1.86 (m, 3H), 1.26 - 1.43 (m, 4H), 1.11 - 1.22 (m, 2H), 0.95 - 1.05 (m, IH) |
Method Q:

Example 4.19: Synthesis of N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-ethoxyprazinamide-2-carboxamide

A solution of N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-3-(methoxymethyl)picolinamide (Example 42, 140 mg, 0.308 mmol) in DCM was cooled to 0 °C. Boron tribromide (0.062 mL, 0.646 mmol) was added dropwise and the reaction mixture was allowed to warm to rt. After 3 hs, the reaction was quenched by the addition of water. The aq. phase was neutralized by the addition of aq. sat bicarbonate solution and extracted with EtOAc. The organic phase was over MgSO4. The filtrate material was absorbed onto
A plug of silica gel and purified by chromatography eluting with a gradient of 15% to 100% EtOAc in hexane, to provide the title compound (62 mg, 0.141 mmol, 45.7% yield) as a white solid. MS m/z = 441 [M+H]+

$^1$H NMR (300 MHz, DMSO-d$_6$) δ ppm 0.79 - 1.02 (m, 1 H) 1.15 (br. s., 1 H) 1.61 - 1.84 (m, 1 H) 4.01 (br. s., 1 H) 4.93 (d, J=5.55 Hz, 2 H) 5.54 (t, J=5.55 Hz, 1 H) 5.87 (br. s., 2 H) 5.98 - 6.46 (m, 1 H) 7.21 (dd, J=11.84, 8.92 Hz, 1 H) 7.78 - 7.97 (m, 2 H) 8.20 (d, J=2.19 Hz, 1 H) 8.64 (d, J=2.34 Hz, 1 H) 10.63 (s, 1 H)

Table 10 includes compound examples prepared wherein the appropriate methoxy compound was converted into the corresponding hydroxy-compound according to Method Q (Examples 420, Table 10):
To a suspension of cesium carbonate (3.76 g, 11.5 mmol) in DMF (20 mL) at room temperature was added 5-chloro-2-fluoropyridine (1.00 mL, 9.96 mmol) and benzylmercaptan (1.15 mL, 9.80 mmol). The reaction mixture was stirred at room temperature for 16 h and heated to 60 °C for 6 h. The reaction mixture was diluted with Et₂O. The organic phase was washed with water (2 x), brine and dried over MgSO₄. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (5% to 10% EtOAc in heptane) to give the title compound (2.33 g, 9.88 mmol, 101% yield) as a colorless oil that was used without further purification in the next step. MS m/z = 236.1 [M+H]+. Calculated for C₁₂H₁₀ClNS 235.0.

Step 2: 5-chloropyridine-2-sulfonyl chloride

Chlorine gas was bubbled through a solution of 2-(benzylthio)-5-chloropyridine (2.33 g, 9.88 mmol) in DCM (65 mL) and water (13 mL) at 0 °C for 20 min, followed by purging with nitrogen for 15 min. The reaction mixture was transferred to a separatory funnel and diluted with water. The aqueous was discarded and the organic phase was washed with brine and dried over MgSO₄. The filtrate was concentrated under reduced pressure to give a colorless oil that was used without further purification in the next step. LC/MS (ESI+) m/z = 211.9 (M+H). Calculated for C₅H₅Cl₂NO₂S 210.9.

Step 3: tert-butyl ((1R,5S,6R)-5-(5-chloropyridine-2-sulfonylido)-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)carbamate

To a solution of tert-butyl ((1R,5S,6R)-5-(5-amino-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)carbamate (16i-B, 0.059 g, 0.16 mmol) in DCM (1.5 mL) at 0 °C were added triethylamine (0.070 mL, 0.50 mmol) and 5-chloropyridine-2-sulfonyl chloride (0.034 g, 0.16 mmol). The reaction mixture was allowed to warm up to room temperature over a period of 2 h and then diluted with EtOAc and water. The aqueous phase was extracted with EtOAc (2 x). The combined organic extracts were washed with brine and dried over MgSO₄. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (10% to 50% EtOAc in heptane) to give the title compound (0.061 g, 0.11 mmol, 70% yield) as a colorless oil. MS m/z = 547.0 [M+H]+. Calculated for C₃₂H₂₅ClF₄N₂O₂S 546.1.

Step 4: -(3-((17S,5S,6S)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloropyridine-2-sulphonamide
To a solution of tert-butyl ((17S,5S,67S)-5-(5-chloropyridine-2-sulfonamido)-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)carbamate (0.061 g, 0.11 mmol) in DCM (2 mL) at room temperature was added trifluoroacetic acid (2.0 mL). The reaction mixture was stirred at room temperature for 30 min and concentrated under reduced pressure. The residue was partitioned between saturated NaHCO₃ and EtOAc. The aqueous phase was extracted with EtOAc (2 x). The combined organic extracts were washed with brine and dried over MgSO₄. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (30% to 70% EtOAc in heptane) to give the title compound (0.045 g, 0.10 mmol, 90% yield) as a white solid. MS m/z = 446.9 [M+H]+. Calculated for C₇H₄ClF₃NO₃S 446.0.

**Example 422**

![Chemical Structure](image)

Synthesis of a 1:1 mixture of (1P,5S,67S)-5-(5-((7S)-l-(5-chloropyridin-2-yl)-2,2,2-trifluoroethyl)amino)-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine and (1P,5S,67S)-V5-r5-r5)-l-(5-chloropyridin-2-yl)2,2,2-trifluoroethyl)amino)-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine

**Step 1**: l-(5-chloropyridin-2-yl)-2,2,2-trifluoroethanol

To a solution of 5-chloropicinaldehyde (0.505 g, 3.57 mmol) in THF (7 mL) at 0 °C were added (trifluoromethyl)trimethylsilane (0.685 mL, 4.63 mmol) and tetra-N-butylammonium fluoride (1 M in THF, 0.036 mL, 0.036 mmol). The reaction mixture was stirred at 0 °C for 15 min and diluted with water (10 mL) and additional tetra-N-butylammonium fluoride (1 M in THF, 2.0 mL, 2.0 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 30 min. The reaction mixture was diluted with EtOAc, the organic phase was separated and washed with water, brine and
dried over MgSO₄. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (5% to 20% EtOAc in heptane) to give the title compound (0.643 g, 3.04 mmol, 85% yield) as a yellow oil. MS m/z = 211.9 [M+H]+. Calculated for C₇H₇ClF₅NO 211.0.

**Step 2:** 1-(5-chloropyridin-2-yl)-2,2,2-trifluoroethanol

To a solution of 1-(5-chloropyridin-2-yl)-2,2,2-trifluoroethanol (0.643 g, 3.04 mmol) in DCM (9 mL) at 0 °C was added 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1H)-one (1.55 g, 3.65 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 20 h before quenching with saturated NaHCO₃ (10 mL) and saturated sodium thiosulfate solution. The reaction mixture was stirred for 20 min and transferred to a separatory funnel. The aqueous phase was discarded and the organic phase was washed with brine and dried over MgSO₄. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (5% to 30% EtOAc in heptane) to afford the title compound (0.545 g, 2.60 mmol, 86% yield) as a pale yellow oil. LC/MS (ESI⁺) m/z = 209.9 (M+H). Calculated for C₇H₇ClF₅NO 209.0.

**Step 3:** tert-butyl ((l,5 S,6 S)-5-(5-amino-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)carbamate and tert-butyl ((l,5 R,6 R)-5-(5-(((I)(I,5 S,6 R)-3-ethyl-4-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)carbamate

To a solution of tert-butyl ((l,5 S,6 S)-5-(5-amino-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)carbamate (161-B, 0.121, 0.326 mmol) and 1-(5-chloropyridin-2-yl)-2,2,2-trifluoroethanolone (0.070 g, 0.33 mmol) in DCM (1.5 mL) at -78 °C were added triethylamine (0.135 mL, 0.969 mmol) and titanium chloride (1 M in DCM, 0.360 mL, 0.360 mmol). The cold bath was removed and the reaction mixture was allowed to stir at room temperature over 10 min. The reaction mixture was again cooled to -78 °C and lithium aluminium hydride (1.0 M in THF, 0.660 mL, 0.660 mmol) was added. The reaction mixture was stirred at -78 °C for 20 min and quenched with EtOAc. Saturated aqueous sodium potassium tartrate (5 mL) was added. The mixture was warmed to room temperature and stirred for 45 min. The mixture was transferred to a separatory funnel. The aqueous phase was extracted with EtOAc (2 x). The combined organic extracts were washed with brine and dried over MgSO₄. The filtrate was concentrated under reduced pressure and the residue was purified by flash
column chromatography on silica gel (10% to 50% EtOAc in heptane) to give a 1:1 mixture of tert-butyl ((1^R,5^S,6^R)-5-((5^)-l-(5-chloropyridin-2-yl)-2,2,2-trifluoroethyl)amino)-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)carbamate and tert-butyl ((1^P,5^S,6^R)-5-((5^-)((5^-)-l-(5-chloropyridin-2-yl)-2,2,2-trifluoroethyl)amino)-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)carbamate (0.070 g, 0.124 mmol, 38% yield combined yield) as a white solid. MS m/z = 565.1 (M+H). Calculated for C_{25}H_{34}ClF_{6}N_{5}O_{4}: 564.1.

**Step 4:** ((1^R,5^S,6^R)-5-(((^)-l-(5-chloropyridin-2-yl)-2,2,2-trifluoroethyl)amino)-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)carbamate (41%). 1.0 mmol, 565.1 (M+H).

To a solution of tert-butyl ((1^R,5^S,6^R)-5-(5^-(((5^-)-l-(5-chloropyridin-2-yl)-2,2,2-trifluoroethyl)amino)-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)carbamate (1:1 mixture of diastereomers, 0.070 g, 0.12 mmol) in DCM (2 mL) at room temperature was added trifluoroacetic acid (2.00 mL, 0.124 mmol). The reaction mixture was stirred at room temperature for 30 min and concentrated. The concentrate was partitioned between saturated NaHCO₃ and EtOAc. The aqueous phase was discarded. The organic phase was washed with brine and dried over MgSO₄. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (12 g, 20% to 60% EtOAc in heptane) to give (1^A,5^S,6^R)-5-(((^)-l-(5-chloropyridin-2-yl)-2,2,2-trifluoroethyl)amino)-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)carbamate (41% yield) as a white solid. MS m/z = 465.0 [M+H]+. Calculated for C_{10}H_{15}ClF_{5}N_{4}: 464.1. 1.34 NMR (400 MHz, CDCl₃) δ 0.86-0.95 (m, 1H), 1.32-1.41 (m, 1H), 1.73-1.85 (m, 1H), 3.83-3.90 (m, 1H), 4.50 (br s, 2H), 4.87-4.97 (m, 1H), 5.33 (dd, J = 11.93, 7.63 Hz, 1H), 6.02 - 6.34 (m, 1H), 6.60-6.66 (m, 1H), 6.87-6.96 (m, 2H) 7.27-7.35 (m, 1H), 7.65-7.70 (m, 1H), 8.57-8.59 (m, 1H).
Synthesis of N-(3-(((IR.S),(5S.R),(6R.S))-3-amino-5-(fluoromethyl)-2-oxa-4-
azabicclo[4.1.0]hept-3-en-3-yl)phenyl)-5-chloropicolinamide

Step 1: N-(((IR.S),(5S.R),(6R.S))-3-amino-5-(fluoromethyl)-5-chloro-
2-oxa-4-azabicclo[4.1.0]hept-3-en-3-yl)benzamide

The title compound was isolated as a byproduct from the reaction described in
step 4 for the conversion of 6c-rac into 6d-rac. MS m/z = 400.0 [M+H]^+. Calculated for
C_{19}H_{13}ClF_{3}O_{2}: 399.8

Step 2: N-(((IR.S),(5S.R),(6R.S))-5-i3-aminophenviy5-ifluoromethviy2-oxa-4-
azabicclo[4.1.0]hept-3-en-3-yl)benzamide

A sealable vial was charged with N-(((IR.S),(5S.R),(6R.S))-5-(5-azido-2-
chlorophenyl)-5-(fluoromethyl)-2-oxa-4-azabicclo[4.1.0]hept-3-en-3-yl)benzamide
(0.25 g, 0.625 mmol), 1,l-bis[(di-t-butyl-p-methylaminophenyl)palladium(II) chloride
(0.089 g, 0.125 mmol), and sodium formate (0.255 g, 3.75 mmol). The vial was
evacuated and backfilled with N_2 gas. DMF (3 ml) was added and the reaction was stirred
in a pre-heated 90 °C oil bath for 48 hours. The reaction was cooled to ambient
temperature and additional sodium formate (0.255 g, 3.75 mmol) and 1,l-bis[(di-t-butyl-
p-methylaminophenyl)palladium(II) chloride (0.089 g, 0.125 mmol) were added. The
reaction mixture was purged with nitrogen and heated to 130 °C for an additional 72
hours. The reaction was cooled to ambient temperature and diluted with water and
EtOAc. The organic layer was separated and washed sequentially with water, 1M LiCl
aqueous solution, and brine before being dried over magnesium sulfate. The filtrate was
concentrated under reduced pressure and the crude residue was purified via silica gel flash
chromatography using a gradient of 10-70% EtOAc in hexanes to afford the title
compound as a light yellow oil (0.04 g, 0.118 mmol, 18.85 % yield)

MS m/z=340.0 [M+H]^+. Calculated for C_{19}H_{13}F_{3}O_{2}: 339.4
Step 3: N-(3-(((1R.S). (5S.R)i6R.S))-3-amino-5-(fluoromethyl)-2-oxa-4-
azabicvclo[4. 1.0hept-3-en-5-y]phenyl)-5-chloropicolinamide

The title compound was prepared using a procedure similar to that described in step 4 for
the synthesis of 4d rac. but using N-(((1R.S). (5S.R). (6R.S))-5-(3-aminophenyl)-5-
(fluoromethyl)-2-oxa-4-azabicvclo[4.1.0]hept-3-en-5-yl)phenyl)-5-chloropicolinamide

MS m/z=374.9 M+. Calculated for C_{13}H_{16}ClFNO; 374.8

1H NMR (300 MHz, CHLOROFORM-d) δ ppm 0.95 - 1.05 (m, 1 H) 1.27 - 1.31 (m, 1 H)
1.68 - 1.77 (m, 1 H) 4.07 - 4.15 (m, 1 H) 4.40 - 4.59 (m, 1 H) 4.60 - 4.79 (m, 1 H) 7.31 -
7.37 (m, 1 H) 7.38 - 7.46 (m, 1 H) 7.73 - 7.79 (m, 1 H) 7.87 - 7.94 (m, 2 H) 8.24 - 8.29
(m, 1 H) 8.57 - 8.60 (m, 1 H) 9.87 (s, 1 H)

Example 424

Synthesis of N-(3-(((1RS)i 5S.R),(6R.S))-3-amino-5-(fluoromethyl)-2-oxa-4-
azabicvclo[4.1.0]hept-3-en-5-yl)-5-fluoro-(methylsulfonyl)phenyl)-5-
chloropicolinamide

To a solution of N-((3-(((1S,R),(5S,R),(6R,S))-3-amino-5-(fluoromethyl)-2-oxa-4-
azabicvclo[4.1.0]hept-3-en-5-yl)-5-fluoro-(methylthio)phenyl)-5-chloropicolinamide
(0.019 g, 0.043 mmol, Example 141) in MeCN (0.1 mL), water (0.15 mL) and EtAc (0.1
mL) was added sodium (meta)periodate (0.037 g, 0.173 mmol) and ruthenium(III)
chloride (0.5 mg, 2.165 μmol). The reaction mixture was stirred at RT for 30 min, then
diluted with DCM and filtered through a cotton plug. Water was added to the filtrate and
the phases were separated. The aqueous layer was extracted with DCM (3x) times and
the combined organic layers were dried over sodium sulfate. The filtrate was concentrated
under reduced pressure and the crude material was purified by column chromatography,
eluting with 1-10% 2M ammonia in MeOH/DCM, to give the title compound (0.012 g,
0.025 mmol, 58.9% yield).

MS m/z= 471.0 [M+H]^+. Calculated for C_{13}H_{17}ClFNO, 470.9.

1H NMR (400 MHz, DMSO-d6) δ ppm 0.90 - 1.06 (m, 1 H) 1.14 - 1.33 (m, 1 H) 1.75 (m,
1 H) 3.40 (s, 3 H) 3.78 - 3.92 (m, 1 H) 4.55 - 4.76 (m, 1 H) 4.81 (m, 1 H) 5.67 (br. s., 2 H)
8.06 (d, J=14.48 Hz, 1 H) 8.15 - 8.26 (m, 2 H) 8.30 (s, 1 H) 8.82 (s, 1 H) 11.12 (br. s., 1 H)

Example 425

Synthesis of (lS,5R,6S)-5-(5-(6-chlorobenzo[d]oxazol-2-yl)-2-fluorophenyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine

**Step 1:** To a solution of (lS,5R,6S)-5-(5-bromo-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (16f-A, 2.20 g, 6.56 mmol) in DMF (20 mL) under nitrogen was added TEA (1.37 mL, 9.85 mmol) and benzoic anhydride (1.66 g, 7.35 mmol). The reaction mixture was stirred at RT overnight, then diluted with aqueous saturated Na₂CO₃ solution and extracted with EtOAc twice. The organic phase was washed with water, brine and dried over Na₂SO₄. The filtrate was concentrated in vacuo and the crude was purified by silica gel chromatography (0-50% EtOAc-hexane) to obtain N-((lS,5R,6S)-3-benzamido-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorobenzoate as a yellow solid (0.69 g, 69% yield). MS m/z= 419 [M+H]⁺. Calculated for C₂₂H₂₇F₃N₂O₄: 418.4.

**Step 2:** A sealable vial was charged with -(lS,5R,6S)-5-(5-bromo-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)benzamide (16e-A, 1.05 g, 2.39 mmol), (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphine) (0.15 g, 0.26 mmol), palladium (II) acetate (0.029 g, 0.13 mmol), methanol (0.97 ml, 23.86 mmol) and triethylamine (4.99 ml, 35.8 mmol). The vial was evacuated and backfilled with CO gas. The reaction mixture was stirred at 65 °C overnight, then diluted with EtOAc and filtered through a pad of celite. The filtrate was washed with water, brine and dried over Na₂SO₄.

The filtrate was concentrated in vacuo and the crude was purified by silica gel chromatography (0-100% EtOAc-DCM) to obtain methyl 3-((lS,5R,6S)-3-benzamido-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorobenzoate as a yellow solid (0.69 g, 69% yield). MS m/z= 419 [M+H]⁺. Calculated for C₂₂H₂₇F₃N₂O₄: 418.4.
Step 3: A sealable vial was charged with methyl 3-((1S,5R,6S)-3-benzamido-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)-4-fluorobenzoate (0.100 g, 0.24 mmol), 2-amino-5-chlorophenol (0.086 g, 0.60 mmol) and polyphosphoric acid (0.50 mL). The reaction mixture was purged with nitrogen for 1 min and then heated to 170 °C for 1 h. The reaction mixture was allowed to cool to rt, neutralized with aqueous, saturated Na₂CO₃ solution and 1N NaOH. The mixture was extracted three times with a solvent mixture of CHCl₃:i-PrOH (3:1). The combined organic extracts were dried over Na₂SO₄, and concentrated in vacuo. The crude was purified first by silica gel chromatography 0-100% EtOAc-hexane. The collected fractions were further purified by reverse-phase preparative HPLC using a Phenomenex Gemini column, 10 micron, C18, 100 A, 150 x 30 mm, 0.1% TFA in CH₃CN/H₂O , gradient 10% to 100% over 16 min.

The fractions containing the desired product were combined and neutralized with solid Na₂CO₃. The aqueous phase was extracted with DCM and dried over Na₂SO₄. The filtrate was concentrated in vacuo to obtain the title compound as a beige solid (0.5 mg, 11% yield). MS m/z= 408 [M+H]+. Calculated for C₁₀H₁₁ClF₃N₂O₂: 407.8.

¹H NMR (400MHz,CHLOROFORM-d) δ = 8.44 (dd, J = 2.3, 7.4 Hz, 1H), 8.07 (ddd, J = 2.3, 4.6, 8.5 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.36 (d, J = 1.8 Hz, 1H), 7.29 (dd, J = 2.0, 8.4 Hz, 1H), 7.20 (dd, J = 8.4, 11.5 Hz, 1H), 6.41 - 6.07 (m, 1H), 4.90 (br. s., 2H), 4.03 - 3.90 (m, 1H), 1.91 (td, J = 7.1, 9.5 Hz, 1H), 1.51 - 1.43 (m, 1H), 1.07 - 0.95 (m, 1H).

Example 426

Synthesis of (IR,5S,6R)-5-((5-(6-chlorobenzol[d]oxazol-2-yl)-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine

The title compound was synthesized according to procedures and steps analogous to those described for Example 423 above, but using (IR,5S,6R)-5-((5-bromo-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (16f-B) in step 1. MS m/z= 408 [M+H]+. Calculated for C₁₀H₁₁ClF₃N₂O₂: 407.8.
A-1813-WO-PCT

H NMR (400MHz, CHLOROFORM-d) δ = 8.43 (dd, J = 2.2, 7.4 Hz, 1 H), 8.04 (ddd, J = 2.3, 4.7, 8.4 Hz, 1 H), 7.55 (d, J = 8.4 Hz, 1 H), 7.32 (d, J = 1.6 Hz, 1 H), 7.28 (ddd, J = 2.0, 8.4 Hz, 1 H), 7.19 (dd, J = 8.4, 11.5 Hz, 1 H), 6.42 - 6.07 (m, 1 H), 5.01 (br. s., 2 H), 4.03 - 3.91 (m, 1 H), 1.98 - 1.86 (m, 1 H), 1.48 (t, J = 5.9 Hz, 1 H), 1.08 - 0.94 (m, 1 H).

Example 427

Synthesis of 3-((I S,5R,6S)-3-Amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluoro-N-((S)-l-methoxypropan-2-yl)benzamide

Step 1: A sealable vial was charged with N-((I S,5R,6S)-5-(5-bromo-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)benzamide (16e-A, 0.4060 g, 0.924 mmol), palladium acetate (9.34 mg, 0.042 mmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (0.029 g, 0.051 mmol), sodium carbonate (0.058 ml, 1.387 mmol) and toluene (1.849 ml). (S)-(+)-l-Methoxy-2-propylamine (0.195 ml, 1.849 mmol) was added and CO gas was bubbled through the reaction mixture for 10 minutes. The reaction mixture was heated to 80 °C for 3 hours. The reaction mixture was cooled to rt, adsorbed onto a plug of silica gel and purified by flash chromatography, eluting with a gradient of 5% to 80% EtOAc in hexane, to provide 3-((I S,5R,6S)-3-benzamido-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)benzamide (0.3780 g, 0.795 mmol, 86% yield).

MS m/z = 476.0 [M+H]+ Calculated from C24H24F3N3O4: 475.172

31H NMR (300 MHz, CHLOROFORM-J) δ ppm 1.18 (d, J=6.58 Hz, 3 H) 1.73 (br. s., 1 H) 2.18 (dt, J=9.46, 7.03 Hz, 1 H) 3.14 (s, 3 H) 3.26 (dt, J=9.36, J=4.08 Hz, 1 H) 4.24 (br. s., 2 H) 6.10 - 6.57 (m, 1 H) 7.16 - 7.26 (m, 1 H) 7.37 - 7.61 (m, 4 H) 7.88 - 8.05 (m, 1 H) 8.22 (br. s., 1 H)

Step 2: A flask was charged with 3-((I S,5R,6S)-3-benzamido-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluoro-N-((S)-l-methoxypropan-2-yl)benzamide (0.3780 g, 0.795 mmol), 1,8-diazabicyclo-[5.4.0]undec-7-ene (0.143 ml, 0.954 mmol) and MeOH (7.95 ml). The reaction mixture was heated to 65 °C for 4 hours. The crude product was adsorbed onto a plug of silica gel and purified by flash chromatography,
eluting with a gradient of 10% to 100% EtOAc:EtOH (75:25) in hexane, to provide the
title compound (0.0563 g, 0.152 mmol, 19.07 % yield).

M S m/z = 372.0 [M+H]+ Calculated for C17H20F3N3O3: 371.146

1H NMR (400 MHz, DMSO-d6) δ ppm 0.85 - 0.98 (m, 1 H) 1.15 (d, J=6.85 Hz, 4 H)
1.71 - 1.85 (m, 1 H) 3.22 - 3.35 (m, 6 H) 3.42 (dd, J=9.59, 6.46 Hz, 1 H) 4.00 (t, J=5.38 Hz, 1 H) 4.13 - 4.25 (m, 1 H) 5.94 (s, 2 H) 6.00 - 6.36 (m, 1 H) 7.32 (dd, J=11.93, 8.61 Hz, 1 H) 7.86 (ddd, J=8.36, 4.55, 2.35 Hz, 1 H) 8.07 (dd, J=7.82, 2.35 Hz, 1 H) 8.21 (d, J=8.02 Hz, 1 H)

H NMR (400 MHz, CHLOROFORM-d) δ ppm 2.24 (dt, J=9.39, 6.46 Hz, 1 H) 2.44 - 2.55 (m, 3 H) 3.11 (dt, J=3.89, 3.89 Hz, 1 H) 4.58 - 4.68 (m, 5 H) 4.75 (dd, J=9.59, 6.46 Hz, 1 H) 5.28 - 5.36 (m, 1 H) 5.45 - 5.59 (m, 1 H) 7.34 - 7.69 (m, 1 H) 8.64 (dd, J=11.93, 8.41 Hz, 1 H) 9.19 (dd, J=8.41, 4.50, 2.35 Hz, 1 H) 9.40 (dd, J=7.82, 2.35 Hz, 1 H) 9.53 (d, J=8.02 Hz, 1 H)

Synthesis of 3-((lR,5S,6R)-3-Amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluoro-N-((S)-1-methoxypropan-2-yl)benzamide

The title compound was synthesized by procedures and steps analogous to those

described for Example 427 above, but using N-((lR,5S,6R)-5-(5-bromo-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)benzamide (16e-B), in step

1. MS m/z= 372.0 [M+H]+. Calculated for C17H20F3N3O3: 371.146

1H NMR (400 MHz, CHLOROFORM-d) δ ppm 0.92 - 1.06 (m, 1 H) 1.28 (d, J=6.65 Hz, 3 H) 1.42 (br. s., 1 H) 1.85 (q, J=7.76 Hz, 1 H) 3.38 (s, 3 H) 3.45 (br. s., 2 H) 3.50 (s, 1 H) 3.94 (br. s., 1 H) 4.35 (br. s., 1 H) 6.02 - 6.36 (m, 1 H) 6.39 (d, J=6.64 Hz, 1 H) 7.16 (t, J=9.98 Hz, 1 H) 7.81 (br. s., 1 H) 7.94 (d, J=7.24 Hz, 1 H)

Example 429
Synthesis of (lR,5S,6R)-5-(difluoromethyl)-5-(2-fluoro-5-(5-(prop-1-yn-1-yl)pyridin-3-yl)phenyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine

A microwave vial was charged with mixture of potassium phosphate (0.19 g, 0.90 mmol), (IR,5S,6R)-5-(5-bromo-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (16f-B, 0.10 g, 0.30 mmol), (5-(prop-1-yn-1-yl)pyridin-3-yl)boronic acid (0.12 g, 0.75 mmol) and 1,1-bis[(di-t-butyl-p-methylaminophenyl)palladium(II)] chloride (10.56 mg, 0.015 mmol) in dioxane/water (2.0/0.5 mL). The reaction mixture was heated to 110 °C for 30 min in the microwave. The reaction mixture was then diluted with water and extracted with DCM three times. The combined organic extracts were washed with brine and dried over sodium sulfate. The filtrate was concentrated in vacuo and the crude material was purified by silica gel chromatography (0-100% EtOAc-DCM) to obtain the title compound as a white solid (82.3 mg, 74% yield). MS m/z= 372 [M+H]+. Calculated for C20H17F3N3O: 371.4.

1H NMR (400MHz, CHLOROFORM-d) δ = 8.65 (d, J = 2.3 Hz, 1 H), 8.55 (d, J = 1.8 Hz, 1 H), 7.80 (t, J = 2.1 Hz, 1 H), 7.73 (dd, J = 2.3, 7.4 Hz, 1 H), 7.49 (dd, J = 2.4, 4.6, 8.4 Hz, 1 H), 7.19 (dd, J = 8.4, 11.7 Hz, 1 H), 6.40 - 6.04 (m, 1 H), 4.44 (br. s., 2 H), 3.99 - 3.88 (m, 1 H), 2.08 (s, 3 H), 1.93 - 1.82 (m, 1 H), 1.48 - 1.38 (m, 1 H), 1.03 - 0.93 (m, 1 H).

Example 430

Synthesis of (lS,5R,6S)-5-(difluoromethyl)-5-(2-fluoro-5-(5-(prop-1-yn-1-yl)pyridin-3-yl)phenyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine

The title compound was synthesized according to the procedure described for Example 429 above, but using (lS,5R,6S)-5-(5-bromo-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (16f-A). MS m/z= 372 [M+H]+. Calculated for C20H17F3N3O: 371.4.
$^1$H NMR (400MHz, CHLOROFORM-d) = 8.64 (d, $J = 2.2$ Hz, 1 H), 8.53 (d, $J = 1.8$ Hz, 1 H), 7.78 (t, $J = 2.1$ Hz, 1 H), 7.73 (dd, $J = 2.4$, 7.3 Hz, 1 H), 7.49 (ddd, $J = 2.5$, 4.5, 8.4 Hz, 1 H), 7.19 (dd, $J = 8.5$, 11.6 Hz, 1 H), 6.41 - 6.02 (m, 1 H), 4.53 (br. s., 2 H), 4.01 - 3.86 (m, 1 H), 2.06 (s, 3 H), 1.87 (td, $J = 7.0$, 9.5 Hz, 1 H), 1.48 - 1.37 (m, 1 H), 0.97 (td, $J = 6.7$, 9.2 Hz, 1 H).

Example 431

Synthesis of 2946458 (5R,S)-5-(2-fluoro-5-(pyridin-3-yl)phenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine

Step 1: N-(((IR,S),(5R,S),(5R,S))-5-(2-fluoro-5-(5-(prop-1-yn-1-yl)pyridin-3-yl)phenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)benzamide was synthesized according to the procedure described for Example 429 above, but using (6f-rac). MS $m/z= 458$ [M+H]$^+$. Step 2: A solution of N-(((IR,S),(5R,S),(5R,S))-5-(2-fluoro-5-(5-(prop-1-yn-1-yl)pyridin-3-yl)phenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-yl)benzamide (0.253 g, 0.277 mmol) in MeOH (3.5 mL) under argon atmosphere was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (0.4 ml, 2.68 mmol). The reaction mixture was heated at 60 °C for 3 h. The reaction mixture was cooled to room temperature, and the suspension was filtered. The solid was rinsed with MeOH to give the title compound (0.0944 g) as a white solid. MS $m/z= 354.3$ [M]$^+$. $^1$H NMR (400 MHz, DMSO-d6) δ ppm 8.75 (d, $J=2.15$ Hz, 1 H), 8.58 (d, $J=1.57$ Hz, 1 H), 7.99 (s, 1 H), 7.78 (dd, $J=7.53$, 2.25 Hz, 1 H), 7.69 - 7.75 (m, 1 H), 7.32 (dd, $J=1.93$, 8.41 Hz, 1 H), 5.77 (s, 2 H), 4.46 - 4.75 (m, 2 H), 4.01 (t, $J=5.67$ Hz, 1 H), 2.11 (s, 3 H), 1.51 - 1.75 (m, 1 H), 1.03 (td, $J=6.26$, 2.35 Hz, 1 H), 0.82 (dt, $J=9.39$, 6.46 Hz, 1 H).

Example 432
Synthesis of (4-((1S,R), (5R,S), i6S,R)y3-amino-5-fluoromethyl-2-oxa-4-
azabicclo[4. 1.01hept-3-en-5-yl]-5-fluoro-2-(5-(prop-1-yn-1-yl))piperidin-3-
yDphenDmethanol

Step 1: To a solution of 1-bromo-4-fluoro-5-iodo-2-(((4-
methoxybenzyl)oxy)methyl)benzene (intermediate 60, 0.766 g, 1.291 mmol) in Et$_2$O (3.7 mL) at -78 °C was added a solution of n-butyllithium (2.5M in hexanes, 0.516 mL, 1.291 mmol) dropwise. The solution was stirred at -78 °C for 15 min. In a separate flask, a solution of 4-(fluoromethyl)-2-oxa-3-azabicyclo[3. 1.0]hex-3-ene (6c rac, 0.114 g, 0.993 mmol) in toluene (4.5 mL) was treated with boron fluoride diethyl etherate at -78 °C. This solution was added via cannula to the aryl lithium solution and the resulting reaction mixture was stirred at -78 °C for 1 h. The reaction was quenched with saturated aqueous ammonium chloride at -78 °C and diluted with water and EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with water, brine, and dried over sodium sulfate. The filtrate was concentrated in vacuo and the crude material was purified by silica gel chromatography, eluting with 1:9 EtOAc in hexane, to provide [(1S,R), (4R,S), (5S,R)]-4-(5-bromo-2-fluoro-4-(((4-methoxybenzyl)oxy)methyl)phenyl)-4-(fluoromethyl)-2-oxa-3-
azabicclo[3. 1.0]hexane. MS m/z = 440.2/442.0 (M+H).

Steps 2-4: [(1R,S), (5S,R), r6R,S)y5-(5-bromo-2-fluoro-4-rr4-
methoxybenzyl]oxy)methyl[phenyl]-5-(fluoromethyl)-2-oxa-4-azabicclo[4. 1.01hept-3-
en-3-amine

The title compound was synthesized using procedures similar to those described in steps 2-4 for the synthesis of 4d rac, but using [(1S,R), (4R,S), (5S,R)]-4-(5-bromo-2-fluoro-4-
(((4-methoxybenzyl)oxy)methyl)phenyl)-4-(fluoromethyl)-2-oxa-3-azabicyclo[3.1.0]hexane. MS m/z = 467.0/469.0 (M+H).

**Step 5:** [(1R,S),(5S,R), (6R,S)]-5-(2-fluoro-4-(((4-methoxybenzyl)oxy)methyl)-5-(5-(prop-1-yn-1-yl)pyridin-3-yl)phenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine was synthesized in an analogous manner as Example 390, but using [(1R,S), (5S,R), (6R,S)]-5-(5-bromo-2-fluoro-4-(((4-methoxybenzyl)oxy)methyl)phenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine and (5-(prop-1-yn-1-yl)pyridin-3-yl)boronic acid. MS m/z = 504.2 (M+H).

**Step 6:** 2,3-Dichloro-5,6-dicyano-p-benzoquinone (0.040 g, 0.178 mmol) was added in one portion to a solution of [(1R,S),(5S,R), (6R,S)]-5-(2-fluoro-4-(((4-methoxybenzyl)oxy)methyl)phenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (0.069 g, 0.137 mmol) in DCM (1.3 ml) and water (0.065 ml) at room temperature. After 40 minutes, an additional amount of 2,3-dichloro-5,6-dicyano-p-benzoquinone (0.040 g, 0.178 mmol) was added. After 40 minutes, the reaction was partitioned between EtOAc and IN NaOH. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with IN NaOH, brine, and dried over sodium sulfate. The filtrate was concentrated *in vacuo* to give the crude material which was purified by silica gel chromatography, eluting with 1:20 2M NH₃·MeOH in CH₂Cl₂, to afford the title compound. MS m/z = 384.0 (M+H).

**1H NMR** (400 MHz, METHANOL-^δ^)  δ ppm 0.84 - 0.96 (m, 1 H) 1.12 - 1.22 (m, 1 H) 1.24 - 1.38 (m, 1 H) 1.72 - 1.84 (m, 1 H) 2.08 (s, 3 H) 3.97 - 4.08 (m, 1 H) 4.46 (s, 2 H) 4.69 (d, J=47.30 Hz, 2 H) 7.31 (d, J=7.63 Hz, 1 H) 7.38 (d, J=13.1 Hz, 1 H) 7.80 (s, 1 H) 8.41 (s, 1 H) 8.52 (s, 1 H)

**Example 433**

![Synthesis diagram]

**Synthesis of i5-fluoro-4-(T(1R.S),(5S.R), (6R.S))]-5-(fluoromethyl)-3-imino-2-oxa-4-azabicyclo[4.1.0]heptan-5-yl)-2-(5-fluoropyridin-3-yl)phenyl)methanol**

**Step 1:** A glass microwave reaction vessel was charged with the [(1R,S), (5S,R), (6R,S)]-5-(5-bromo-2-fluoro-4-(((4-methoxybenzyl)oxy)methyl)phenyl)-5-(fluoromethyl)-2-oxa-
4-azabicyclo[4.1.0]hept-3-en-3-amine (step 4 in Example 393, 0.0709 g, 0.152 mmol), sodium carbonate (0.096 g, 0.910 mmol), and 5-fluoropyridine-3-boronic acid (0.034 g, 0.243 mmol) in 1,4-dioxane (1.2 ml) and water (0.4 ml). The vessel was capped and the solution was degassed by bubbling nitrogen gas through the solution for 10 minutes. Next, Aposh-PdCl₂ (10.74 mg, 0.015 mmol) was added and the vessel was sealed. The reaction mixture was stirred and heated in a Initiator microwave reactor (Personal Chemistry, Biotage AB, Inc., Uppsala, Sweden) at 120°C for 20 minutes. The reaction was poured into water and the mixture was extracted with EtOAc. The combined organic extracts were washed with water, saturated aqueous sodium chloride, and dried over sodium sulfate. The solution was filtered and concentrated in vacuo to give the crude material. The crude material was taken up in MeCN (1.6 mL) and 4-(dimethylamino)pyridine (0.037 g, 0.303 mmol) and di-tert-butyl dicarbonate (0.073 g, 0.334 mmol) were added. After 2.5 hours, the reaction was concentrated and purified by silica gel chromatography by eluting with 1:2 EtOAc/Heptanes, to provide [(1R,S), (5S,R), (6R,S),Z]-tert-butyl 3-((tert-butoxycarbonyl)imino)-5-(2-fluoro-5-(5-fluoropyridin-3-yl)-4-(((4-methoxybenzyl)oxy)methyl)phenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]heptane-4-carboxylate. MS m/z = 684.2 (M+H).

Step 2: 2,3-Dichloro-5,6-dicyano-p-benzoquinone (0.027 g, 0.121 mmol) was added in one portion to a solution of [(1R,S), (5S,R), (6R,S),Z]-tert-butyl 3-((tert-butoxycarbonyl)imino)-5-(2-fluoro-5-(5-fluoropyridin-3-yl)-4-(((4-methoxybenzyl)oxy)methyl)phenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]heptane-4-carboxylate in DCM (0.9 ml) and water (0.045 ml) at room temperature. After 2 hours, the reaction is filtered through a plug of aluminum oxide (activated, neutral, Brockmann I) with 1:9 MeOH/DCM. Removal of the solvents in vacuo to afford [(1R,S), (5S,R), (6R,S),Z]-tert-butyl 3-((tert-butoxycarbonyl)imino)-5-(2-fluoro-5-(5-fluoropyridin-3-yl)-4-((4-hydroxymethyl)phenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]heptane-4-carboxylate which is used directly in the next step without further purification. LC/MS (EST) m/z = 586 (M+Na), 564.2 (M+H).

Step 3: Trifluoroacetic acid (1 mL, 13.46 mmol) was added in one portion to a solution of [(1R,S), (5S,R), (6R,S),Z]-tert-butyl 3-((tert-butoxycarbonyl)imino)-5-(2-fluoro-5-(5-fluoropyridin-3-yl)-4-((4-hydroxymethyl)phenyl)-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]heptane-4-carboxylate (0.052 g, 0.092 mmol) in DCM (2 mL) at RT. After 45 minutes, the reaction was concentrated and the crude material was partitioned between DCM and 10% Na₂CO₃. The layers were separated and the aqueous layer was
extracted with DCM. The combined organic extracts were washed with saturated aqueous sodium chloride and dried over sodium sulfate. The solution was filtered and concentrated in vacuo to give the crude material. The crude material was purified by silica gel chromatography by eluting with 1:20 2M NH₃-MeOH in CH₂Cl₂, to provide the title compound. LC/MS (EST) m/z = 364.1 (M+H).

1H NMR (400 MHz, METHANOL-δ) δ ppm 0.86 - 0.96 (m, 1H) 1.13 - 1.21 (m, 1H) 1.72 - 1.84 (m, 1H) 3.97 - 4.07 (m, 1H) 4.48 (s, 2H) 4.69 (d, J=48.12 Hz, 2H) 5.49 (s, 1H) 7.29 - 7.46 (m, 2H) 7.71 (d, J=9.59 Hz, 1H) 8.40 (s, 1H) 8.49 (s, 1H)

Example 434

Synthesis of (IR,5S,6R)-5-(difluoromethy)n-5-(2-fluoro-5-(4-(prop-1-yn-1-yl)-1H-pyrazol-1-yl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine

A sealable vial was charged with potassium carbonate, (0.095 g, 0.686 mmol), (IR,5S,6R)-5-(5-bromo-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (16f-B, 0.100 g, 0.298 mmol), and 4-(prop-1-yn-1-yl)-1H-pyrazole (intermediate 61, 0.041 g, 0.388 mmol). The vial was evacuated and backfilled with nitrogen twice before adding toluene (3 ml) and 0.1 mL of a premixed stock solution of of copper(I) iodide (55 mg) and trans-N,N'-dimethylcyclohexane-1,2-diamine (0.2 mL) in toluene (1 mL). The reaction mixture was heated at 110 °C overnight. The reaction was poured into a 9:1 mixture of aqueous saturated ammonium chloride/ammonium hydroxide and the mixture was extracted with EtOAc. The combined organic extracts were washed with a 9:1 mixture of aqueous saturated ammonium chloride/ammonium hydroxide, brine, and dried over sodium sulfate. The filtrate was concentrated in vacuo to give the crude material which was purified by reverse-phase preparative HPLC using a Phenomenex Gemini column, 10 micron, C18, 100 A, 150 x 30 mm, 0.1% TFA in CH₃CN/H₂O , gradient 10% to 95% over 15 min to provide the purified product as the TFA salt. The product was partitioned between DCM and aq. 10%
A-1813-WO-PCT

The layers were separated and the aqueous layer was extracted with DCM. The combined organic extracts were washed with brine and dried over sodium sulfate. The filtrate was concentrated *in vacuo* to afford the title compound as the free base.

$\text{MS } m/z = 361.1 \ [\text{M+H}^+]$. 

$^1\text{H NMR } (400 \text{ MHz, CHLOROFORM-}d) \ \delta \text{ ppm } 0.96 - 1.05 \ (m, 1 \text{ H}) 1.36 - 1.48 \ (m, 1 \text{ H}) 1.80 - 1.93 \ (m, 1 \text{ H}) 2.03 \ (s, 3 \text{ H}) 3.86 - 4.01 \ (m, 1 \text{ H}) 6.20 \ (t, J=56.34 \ Hz, 1 \text{ H}) 7.10 - 7.23 \ (m, 1 \text{ H}) 7.26 \ (s, 1 \text{ H}) 7.66 \ (s, 1 \text{ H}) 7.76 \ (m, 1 \text{ H}) 7.88 \ (s, 1 \text{ H})$ 

**Example 435**

![Chemical Structure](image1)

**Synthesis of (lR.5S.6R)-5-(difluoromethyl)-2-fluoro-5-(4-(prop-1-yn-1-yl)-1H-pyrazol-1-yl)phenyl)-2-oxa-4-azabicclo[4.1.0]hept-3-en-3-amine**

The title compound was synthesized according to the procedure described for Example 432, above, but using 4-(cyclopropylethynyl)-1H-pyrazole (Intermediate 62). 

$\text{MS } m/z = 387.0 \ [\text{M+H}^+]$. 

$^1\text{H NMR } (400 \text{ MHz, METHANOL-}d) \ \delta \text{ ppm } 0.64 - 0.75 \ (m, 2 \text{ H}) 0.79 - 0.91 \ (m, 2 \text{ H}) 0.91 - 1.02 \ (m, 1 \text{ H}) 1.20 - 1.37 \ (m, 1 \text{ H}) 1.38 - 1.48 \ (m, 1 \text{ H}) 1.87 - 1.96 \ (m, 1 \text{ H}) 3.35 \ (s, 1 \text{ H}) 4.01 - 4.09 \ (m, 1 \text{ H}) 6.17 \ (t, J=56.14 \ Hz, 1 \text{ H}) 7.27 \ (dd, J=1.35, 9.00 \ Hz, 1 \text{ H}) 7.66 \ (s, 1 \text{ H}) 7.67 - 7.74 \ (m, 1 \text{ H}) 7.84 \ (dd, J=6.46, 2.74 \ Hz, 1 \text{ H}) 8.20 \ (s, 1 \text{ H})$. 

**Example 436**

![Chemical Structure](image2)

**Synthesis of methyl 6-(((lS.5R.6S)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)carbamoyl)nicotinate**
Step 1: Methyl 6-((3-((1S,5R,6S)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)carbamoyl)nicotinimidate was isolated as a by-product in the coupling of (1S,5R,6S)-5-(5-amino-2,3-difluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (20f-A) with 5-cyano-2-pyridinecarboxylic acid according to method B.

Step 2: Methyl 6-((3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)carbamoyl)nicotinimidate (0.050 g, 0.11 mmol) was dissolved in hydrochloric acid (2N, 5 mL, 10.00 mmol) and stirred at room temperature. After 15 minutes, the reaction mixture was neutralized with 1N sodium hydroxide (10 mL). A solution of aqueous saturated sodium bicarbonate (5 mL) was added and the mixture stirred for 10 minutes. The suspension was filtered and the solid was washed with water (10 mL). The solid was further purified by silica gel chromatography [10-90% (2% NH₄OH in 3:1 ethyl acetate: ethanol) in hexane] to give the title compound (0.0298 g, 0.066 mmol, 59.5% yield). MS m/z = 452.9 [M+H]+.

1H NMR (CHLOROFORM-d) Shift: 9.75 (s, 1H), 9.04 (dd, J=2.0, 0.7 Hz, 1H), 8.48 (dd, J=8.0, 2.0 Hz, 1H), 8.26 (dd, J=8.1, 0.7 Hz, 1H), 7.99 (ddd, J=11.7, 7.0, 2.8 Hz, 1H), 7.22-7.28 (m, 1H), 6.23 (td, J=55.8, 0.9 Hz, 1H), 5.17 (br. s., 2H), 4.01 (s, 3H), 3.92 (td, J=6.8, 2.6 Hz, 1H), 1.80-1.92 (m, 1H), 1.40-1.49 (m, 1H), 0.90-1.03 (m, 1H)

Example 437

Synthesis of 6-((3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-chloro-5H-pyrrolo[3.4-b]pyridin-7(6H)one

A solution of N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-3-hydroxymethyl)picolinamide (Example 420, 60 mg, 0.136 mmol) in DCM (2 mL) was cooled 0°C under nitrogen atmosphere. A solution of Deoxo-fluor, (50w% in THF, 0.150 mL, 0.408 mmol) was added dropwise and the reaction mixture was allowed to stir at rt for 25 min. The reaction mixture was poured into aqueous saturated bicarbonate solution and extracted with EtOAc. The crude material was absorbed onto a plug of silica
gel and purified by chromatography, eluting with a gradient of 20% to 100% EtOAc in hexane, to provide the title compound as white solid. MS m/z = 423 [M+H]+.

'H NMR (300 MHz, DMSO-d6) δ ppm 0.80 - 0.98 (m, 1 H) 1.16 (br. s., 1 H) 1.66 - 1.88 (m, 1 H) 3.99 (t, J=5.41 Hz, 1 H) 5.52 (s, 2 H) 5.84 - 6.47 (m, 3 H) 7.19 (dd, J=1.84, 8.62 Hz, 1 H) 7.33 (ddd, J=8.62, 4.38, 2.78 Hz, 1 H) 7.47 (dd, J=7.31, 2.63 Hz, 1 H) 8.27 (d, J=2.19 Hz, 1 H) 8.82 (d, J=2.19 Hz, 1 H)

Example 439

Synthesis of N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicvclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(methylamino)pyrimidine-2-carboxamide dihydro chloride

Step 1: Tert-butyl (2-((3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicvclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl) carbamoyl)pyrimidin-5-yl)(methyl)carbamate
The title compound was prepared using the procedure described in Method A above but using 5-((tert-butoxycarbonyl)(methyl)amino)pyrimidine-2-carboxylate, Intermediate 81. MS m/z = 507.0 [M+H]+.

Step 2: N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(methylamino)pyrimidine-2-carboxamide dihydrochloride

A solution of tert-butyl (2-(((IR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)(methyl)carbamate (0.06 g, 0.1 mmol) in 1,4-dioxane (2 mL) was treated with HCl (4.0M in 1,4-dioxane; 1 mL). The resulting suspension was treated with water (0.1 mL) resulting in a pale-yellow biphasic solution. The solution was stirred for 2 h, concentrated, and lyophilized from 1,4-dioxane to give N-(3-((IR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(methylamino)pyrimidine-2-carboxamide dihydrochloride (0.05 g, 0.105 mmol, 93 % yield) as a pale-yellow solid.

1H NMR (400 MHz, DMSO-d6): δ 10.61-10.78 (m, 2H), 9.54 (br. s, 1H), 8.37 (br. s, 1H), 8.25 (s, 2H), 8.14 (dd, J=2.54, 7.24 Hz, 1H), 7.98-8.05 (m, 1H), 7.41 (dd, J=9.00, 11.93 Hz, 1H), 6.76 (t, J=53 Hz, 1H), 4.83-5.56 (br. s, 2H), 4.69 (dt, J=2.74, 6.65 Hz, 1H), 2.86 (s, 3H), 2.12 (td, J=7.09, 9.49 Hz, 1H), 1.63 (t, J=6.26 Hz, 1H), 1.25-1.38 (m, 1H). MS m/z = 407.0 [M+H]+.

Example 440

Step 1: (IR,5S,6R)-5-(difluoromethyl)-5-(2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine

A glass microwave reaction vessel was charged with (IR,5S,6R)-5-(5-bromo-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine (0.1 g, 0.32 mmol), potassium acetate (0.095 g, 0.967 mmol), (I,1’-bis(diphenylphosphino)ferrocene)dichloropalladium(II) (0.024 g, 0.032 mmol), and bis(pinacolato) diboron (0.098 g, 0.387 mmol). The vessel was evacuated and flushed with nitrogen twice. Next, degassed DMSO (1.5 ml) was added and the reaction mixture
was heated in an oil bath at 80 °C. After two hours, the reaction was poured into water and the mixture was extracted with EtOAc. The combined organic extracts were washed with water, saturated aqueous sodium chloride, and dried over sodium sulfate. The solution was filtered and concentrated in vacuo to give the intermediate \((\text{IR,5S,6R})-5-(\text{difluoromethyl})-5-(2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-3-amine\) which was used without further purification.

**Step 2.** A glass microwave reaction vessel was charged with sodium carbonate (0.171 g, 1.609 mmol), 3-bromo-5-(4-fluorophenyl)-4H-1,2,4-triazole (0.078 g, 0.322 mmol), \(\text{EtOAc}\) (2.5 ml) and water (0.83 ml). The vessel was capped and the solution was degassed by bubbling nitrogen gas through the solution for 10 minutes. Next, 1,1-bis[(di-t-butyl-p-methlyaminophenyl]palladium(II) chloride (0.023 g, 0.032 mmol) was added and the vessel was sealed. The reaction mixture was stirred and heated in a Initiator microwave reactor (Personal Chemistry, Biotage AB, Inc., Upssala, Sweden) at 120 °C for 20 minutes. The reaction was poured into water and the mixture was extracted with EtOAc. The combined organic extracts were washed with a 9:1 mixture of aqueous saturated ammonium chloride/ammonium hydroxide, saturated aqueous sodium chloride, and then stirred with activated carbon. The solution was filtered through a pad of celite and concentrated in vacuo to give the crude material. The crude material was purified by silica gel chromatography by eluting with 1:40 2M \(\text{NH}_2\cdot\text{MeOH}\) in \(\text{CH}_2\text{Cl}_2\), and then repurified by preparative TLC by eluting with 1:30 2M \(\text{NH}_2\cdot\text{MeOH}\) in \(\text{CH}_2\text{Cl}_2\) to provide the titled compound as a white solid after concentration with MeOH.

**LC/MS (EST) \(m/z = 418.1 (\text{M}+\text{H})^+\).**

**1H NMR (400 MHz, MeOH-d4) \(\delta\) ppm:**
- 0.95 - 1.04 (m, 1 H)
- 1.36 (m, 1 H)
- 1.90 - 1.99 (m, 1 H)
- 4.05-4.13 (m, 1 H)
- 6.28 (t, \(J=56.34\) Hz, 1 H)
- 7.23 - 7.29 (m, 2 H)
- 7.27 - 7.34 (m, 1 H)
- 8.03 - 8.16 (m, 3 H) 8.28 (dd, \(J=7.53, 1.86\) Hz, 1 H)
Example 4

Synthesis of N-(3-((lR,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-
azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2,4,6-trifluorobenzamide

To a solution of 2,4,6-trifluorobenzoic acid (120 mg, 0.681 mmol, Aldrich) in
dichloromethane (2 mL) was added oxalyl chloride (0.242 mL, 2.73 mmol, Aldrich),
followed by catalytic amounts of DMF (20 µL). The reaction mixture was stirred at room
temperature for 3h. The reaction mixture was concentrated under reduced pressure and
the residue was dissolved in DCM (2 mL). This solution was added dropwise to a
separate solution of (lR,5S,6R)-5-(5-amino-2-fluorophenyl)-5-(difluoromethyl)-2-oxa-4-
azabicyclo[4.1.0]hept-3-en-3-amine (185 mg, 0.682 mmol) and diisopropylethylamine
(0.12 mL, 0.682 mmol) in dichloromethane (2.5 mL) cooled to 0 °C. After completed
addition, the reaction mixture was stirred for 20 min at 0 °C. The reaction mixture was
quenched with aqueous saturated sodium bicarbonate solution and extracted with DCM (2
× 3 mL). The combined organic extracts were dried over MgSO4 and concentrated under
reduced pressure. The residue was dissolved in MeOH (1.5 mL) and cooled to 0 °C. H2O
(4 mL) was added to the solution and the mixture was stirred at 0 °C for 1h. The white
solid was filtered off, washed with H2O and dried in under reduced pressure to give 203
mg of the title compound as a white solid.

LC/MS (ESI-) m/z = 430.1 [M+H]+.
1H NMR (MeOH) δ: 7.80-7.88 (m, 1H), 7.75 (dd, J=6.9, 2.6 Hz, 1H), 7.20 (dd, J=1 1.7,
8.8 Hz, 1H), 7.04 (t, J=8.4 Hz, 2H), 6.12-6.48 (m, 1H), 4.07 (t, J=5.5 Hz, 1H), 1.83-1.94
(m, 1H), 1.34 (br. s., 1H), 0.96-1.05 (m, 1H)

Table 11 contains representative compounds of the invention (the examples
presented herein) and their mass observed and associated biological data, including
BACE enzyme assay, BACE cell assay and Cathepsin D (Cat D) assay, inhibitory data
expressed as µM IC50's. The assays procedures and data measurements are described
hereinbelow.
Table 1

<table>
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<th>Example No</th>
<th>Observed Mass</th>
<th>BACE1 Enzyme assay IC₅₀ (μM)</th>
<th>BACE cell assay IC₅₀ (μM)</th>
<th>CatD IC₅₀ (μM)</th>
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<td>0.109</td>
<td>81.3</td>
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<td>372</td>
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<td>0.059</td>
<td>&gt; 400.0</td>
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<td>&gt; 10.0</td>
<td>42.8</td>
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<td>0.0765</td>
<td>907.85</td>
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The present invention also provides methods for making compounds of Formulas I-III, and sub-formulas therein. For example, the compounds of the present invention and additional examples may be made by the following methods, as similarly described in the literature references mentioned below.

In one embodiment of the invention, there is provided a method of making a compound of Formula I-A having a general structure of

![Chemical Structure](image)

the method comprising the step of reacting a compound 20

![Chemical Structure](image)

wherein $A^4, A^5, A^6, A^8$, each $R^1$, each $R^2$ and $R^3$ of Formula I-A are as defined herein, with a compound having the structure $R^9\text{-COOH}$, wherein $R^9$ is as defined herein, to make a compound of Formula I-A.

In one embodiment of the invention, there is provided a method of making a compound of Formula I-B having a general structure of
the method comprising the step of reacting a compound 20

wherein \( A_4, A_5, A_6, A_8, \) each \( R, \) each \( R^2, \) and \( R^3 \) of Formula I-B are as defined herein,

with a compound having the structure , wherein each \( W \) and each \( R^{10} \) are, independently, as defined herein, in the presence of acid to make a compound of Formula I-B.

In one embodiment of the invention, there is provided a method of making a compound of Formula I-C

the method comprising the step of reacting a compound 20
wherein \( A_4, A_5, A_6, A_8, \) each \( R, \) each \( R_2 \) and \( R_0 \) of Formula I-C are as defined herein,

with a compound having the structure \( R^{10} \), wherein each \( W \) and each \( R^{10} \) are, independently, as defined herein, to make a compound of Formula I-C.

In another embodiment of the invention, there is provided a method of making a compound of Formula II having a general formula of

wherein \( A_4, A_5, A_6, A_8, \) each \( R_2, R_3 \) and \( R^7 \) of Formula II are as defined herein, with a compound having either structure of \( R^6\text{-COOH} \) in the presence of a base or \( R^3\text{-Cl} \) in the presence of an acid, wherein \( R^9 \) is as defined herein, to make a compound of Formula II.
As can be appreciated by the skilled artisan, the above synthetic schemes and representative examples are not intended to comprise a comprehensive list of all means by which the compounds described and claimed in this application may be synthesized. Further methods will be evident to those of ordinary skill in the art. Additionally, the various synthetic steps described above may be performed in an alternate sequence or order to give the desired compounds.

For example, in these procedures, the steps may be preceded, or followed, by additional protection/deprotection steps as necessary. Particularly, if one or more functional groups, for example carboxy, hydroxy, amino, or mercapto groups, are or need to be protected in preparing the compounds of the invention, because they are not intended to take part in a specific reaction or chemical transformation, various known conventional protecting groups may be used. For example, protecting groups typically utilized in the synthesis of natural and synthetic compounds, including peptides, nucleic acids, derivatives thereof and sugars, having multiple reactive centers, chiral centers and other sites potentially susceptible to the reaction reagents and/or conditions, may be used.


Salts, including pharmaceutically acceptable salts, of a compound of the invention having a salt-forming group may be prepared in a conventional manner or manner known to persons skilled in the art. For example, acid addition salts of compounds of the invention may be obtained by treatment with an acid or with a suitable anion exchange reagent. A salt with two acid molecules (for example a dihalogenide) may also be converted into a salt with one acid molecule per compound (for example a monohalogenide); this may be done by heating to a melt, or for example by heating as a
solid under a high vacuum at elevated temperature, for example from 50 °C to 170 °C, one molecule of the acid being expelled per molecule of the compound.

Acid salts can usually be converted to free-base compounds, e.g. by treating the salt with suitable basic agents, for example with alkali metal carbonates, alkali metal hydrogen carbonates, or alkali metal hydroxides, typically potassium carbonate or sodium hydroxide. Exemplary and suitable salts, and their preparation, are described herein in the Definition section of the application.

All synthetic procedures described herein can be carried out under known reaction conditions, advantageously under those described herein, either in the absence or in the presence (usually) of solvents or diluents. As appreciated by those of ordinary skill in the art, the solvents should be inert with respect to, and should be able to dissolve, the starting materials and other reagents used. Solvents should be able to partially or wholly solubilize the reactants in the absence or presence of catalysts, condensing agents or neutralizing agents, for example ion exchangers, typically cation exchangers for example in the H⁺ form. The ability of the solvent to allow and/or influence the progress or rate of the reaction is generally dependant on the type and properties of the solvent(s), the reaction conditions including temperature, pressure, atmospheric conditions such as in an inert atmosphere under argon or nitrogen, and concentration, and of the reactants themselves.

Suitable solvents for conducting reactions to synthesize compounds of the invention include, without limitation, water; esters, including lower alkyl-lower alkanoates, e.g., EtOAc; ethers including aliphatic ethers, e.g., Et₂O and ethylene glycol dimethylether or cyclic ethers, e.g., THF; liquid aromatic hydrocarbons, including benzene, toluene and xylene; alcohols, including MeOH, EtOH, 1-propanol, IPOH, n- and t-butanol; nitriles including CH₃CN; halogenated hydrocarbons, including CH₂Cl₂, CHCl₃ and CCl₄; acid amides including DMF; sulfoxides, including DMSO; bases, including heterocyclic nitrogen bases, e.g. pyridine; carboxylic acids, including lower alkanecarboxylic acids, e.g., AcOH; inorganic acids including HCl, HBr, HF, H₂SO₄ and the like; carboxylic acid anhydrides, including lower alkane acid anhydrides, e.g., acetic anhydride; cyclic, linear, or branched hydrocarbons, including cyclohexane, hexane, pentane, isopentane and the like, and mixtures of these solvents, such as purely organic solvent combinations, or water-containing solvent combinations e.g., aqueous solutions. These solvents and solvent mixtures may also be used in "working-up" the reaction as
well as in processing the reaction and/or isolating the reaction product(s), such as in chromatography.

Purification methods are known in the art and include, for example, crystallization, chromatography (liquid and gas phase, and the like), extraction, distillation, trituration, reverse phase HPLC and the like. Reactions conditions such as temperature, duration, pressure, and atmosphere (inert gas, ambient) are known in the art and may be adjusted as appropriate for the reaction.

The invention further encompasses "intermediate" compounds, including structures produced from the synthetic procedures described, whether isolated or generated in-situ and not isolated, prior to obtaining the finally desired compound. Structures resulting from carrying out steps from a transient starting material, structures resulting from divergence from the described method(s) at any stage, and structures forming starting materials under the reaction conditions are all "intermediates" included in the invention. Further, structures produced by using starting materials in the form of a reactive derivative or salt, or produced by a compound obtainable by means of the process according to the invention and structures resulting from processing the compounds of the invention in situ are also within the scope of the invention.

The invention also provides new starting materials and/or intermediates, as well as processes for the preparation thereof. In select embodiments, such starting materials are used and reaction conditions so selected as to obtain the desired compound(s). Starting materials of the invention, are either known, commercially available, or can be synthesized in analogy to or according to methods that are known in the art. Many starting materials may be prepared according to known processes and, in particular, can be prepared using processes described in the examples. In synthesizing starting materials, functional groups may be protected with suitable protecting groups when necessary. Protecting groups, their introduction and removal are described above.

Compounds of the present invention can possess, in general, one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers as well as in the form of racemic or non-racemic mixtures thereof. While shown without respect to stereochemistry in Formulas I-III, the present invention includes such optical isomers and diastereomers, as well as the racemic and resolved, enantiomerically pure R and S stereoisomers, as well as other mixtures of R and S stereoisomers and pharmaceutically acceptable salts thereof.
The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, e.g., by formation of diastereoisomeric salts, by treatment with an optically active acid or base. Examples of appropriate acids are tartaric, diacetyl tartaric, dibenzoyl tartaric, ditoluoyltartaric, and camphorsulfonic acid and then separation of the mixture of diastereoisomers by crystallization followed by liberation of the optically active bases from these salts. A different process for separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize the separation of the enantiomers. Still another available method involves synthesis of covalent diastereoisomeric molecules by reacting compounds of the invention with an optically pure acid in an activated form or an optically pure isocyanate. The synthesized diastereoisomers can be separated by conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure compound. The optically active compounds of the invention can likewise be obtained by using optically active starting materials. These isomers may be in the form of a free acid, a free base, an ester or a salt. All such isomeric forms of such compounds are expressly included in the present invention.

The compounds of the invention may also be represented in multiple tautomeric forms. Tautomers often exist in equilibrium with each other, and interconvert under environmental and physiological conditions. The compounds of the invention may also occur in cis- or trans- or E- or Z- double bond isomeric forms. The invention expressly includes all tautomeric forms of the compounds described herein.

All crystal forms of the compounds described herein are expressly included in the present invention.

The present invention also includes isotopically-labeled compounds, which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as $^{2}$H (deuterium), $^{3}$H (tritium), $^{13}$C, $^{14}$C, $^{15}$N, $^{16}$O, $^{17}$O, $^{31}$P, $^{32}$P, $^{35}$S, $^{18}$F, and $^{35}$Cl.

Compounds of the present invention that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labeled compounds of the present invention, for example those into which radioactive isotopes such as $^{3}$H and $^{14}$C are incorporated, are useful in drug and/or
substrate tissue distribution assays. Deuterated ($\text{^2H}$), Tritiated ($\text{^3H}$) and carbon-14, i.e., $^{14}$C, isotopes are particularly preferred for their ease of preparation and detection. Further, substitution with heavier isotopes such as deuterium, i.e., $\text{^2H}$, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds of this invention can generally be prepared by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

BIOLOGICAL EVALUATION

The compounds of the invention may be modified by appending appropriate functionalities to enhance selective biological properties. The pharmacokinetic and pharmacodynamic properties of a compound relate, directly and indirectly, to the ability of the compound to be effective for its intended use.

Although the pharmacological properties of the compounds of the invention (Formulas I-III) vary with structural change, in general, activity possessed by compounds of Formulas I-III may be demonstrated both in vitro as well as in vivo. The following exemplified pharmacological assays have been carried out with the compounds according to the invention, to assess and characterize the compound's ability to modulate BACE activity and to regulate the cleavage of amyloid beta precursor protein, thereby reducing or inhibiting the production of amyloid beta.

In Vitro Enzymatic BACE FRET (fluorescence resonance energy transfer) Assay

(Enzyme Assay data in the Example Table I)

The assay buffer used in this screen is 0.05 M acetate, pH 4.2, 10% DMSO final, 100 uM genapol (which is a nonionic detergent, below its Critical Micelle Concentration). The Beta Secretase enzyme (0.2nM) is pre-incubated for one hour with inhibitors, typically in about 1uL of DMSO according to a serial dilution, are added thereto. This assay is effectively started by the addition of FRET substrate (50nM) and the combination is incubated for one hour. The FRET assay is terminated with by addition of Tris buffer, which raises the pH to neutrality, and the fluorescence is determined. The FRET substrate is a peptide with commercially available fluorophore and quencher, on opposite sides of the BACE cleavage site. Proteolytic cleavage of the FRET substrate releases quenching of fluorescence (excitation 488 nm and emission 425 nm).
Where available, the in-vitro BACE FRET enzyme data for each of the Examples is provided in Table 1.

**In Vitro BACE cell-based assay**

The cell-based assay measures inhibition or reduction of Aβ40 in conditioned medium of test compound treated cells expressing amyloid precursor protein.

Cells stably expressing Amyloid Precursor Protein (APP) were plated at a density of 40K cells/well in 96 well plates (Costar). The cells were cultivated for 24 hours at 37 °C and 5% CO₂ in DMEM supplemented with 10% FBS. The test compounds were then added to cells in 10-point dose response concentrations with the starting concentration being either 100 µM or 10 µM. The compounds were diluted from stock solutions in DMSO and the final DMSO concentration of the test compounds on cells was 0.1%. After 24 h of incubation with the test compounds the supernatant conditioned media was collected and the Aβ 40 levels were determined using a sandwich ELISA. The IC₅₀ of the compound was calculated from the percent of control or percent inhibition of Aβ 40 as a function of the concentration of the test compound.

The sandwich ELISA to detect Aβ 40 was performed in 96 well microtiter plates, which were pre-treated with goat anti-rabbit IgG (Pierce). The capture and detecting antibody pair that were used to detect Aβ 40 from cell supematants were affinity purified pAb40 ( Biosource) and biotinylated 6E10 (Signet Labs Inc.), respectively. The optimal concentration for the pAb40 antibody was 3 µg/ml in Superblock/TBS (Pierce) that was supplemented with 0.05% Tween 20 (Sigma). Optimal concentration for the detection antibody 6E10-biotinylated was 0.5 µg/ml in Superblock/TBS (Pierce) that had been supplemented with 2% normal goat serum and 2 % normal mouse serum.

Cellular supematants were incubated with the capture antibody for 3 h at 4 °C, followed by 3 wash steps in TBS-tween (0.05%). The detecting antibody incubation was for 2 h at 4 °C, again followed by the wash steps as described previously. The final readout of the ELISA is Time-Resolved Fluorescence (counts per minute) using Delfia reagents Streptavidin-Europium and Enhancement solutions (Perkin Elmer) and the Victor 2 multilabel counter (Perkin Elmer).

Where available, the in-vitro BACE cell based data for each of the Examples is provided in Table 1.
In Vitro Enzymatic Cathepsin D (Cat D) FRET (fluorescence resonance energy transfer) Assay

Recombinant Cat D was expressed in CHO cells. The assay buffer for CathepsinD is 0.05 M citrate pH 3.5, 10% DMSO final, 5 mM CHAPS. The Cat D enzyme (9 nM) is pre-incubated for one hour with inhibitors, typically in about 1 uL of DMSO according to a serial dilution, is added thereto. The assays are effectively started by the addition of different FRET substrates (20 nM for Cat D) and the combination is incubated for one hour. The FRET assay is terminated with by addition of Tris buffer, which raises the pH to neutrality, and the fluorescence is determined. The FRET substrate is a peptide with commercially available fluorophore and quencher, on opposite sides of the BACE cleavage site. The Cat D substrate peptide sequence is based on sequence #1 of Table 1 from Gulnik et al. FEBS Letters v413 p379-384 1997. Proteolytic cleavage of the FRET substrate releases quenching of fluorescence (Cat D excitation 500 nm and emission 580 nm).

Alternatively, a Cat D assay may also be run according to the procedure described in the article, Characterization of new fluorogenic substrates for the rapid and sensitive assay of cathepsin E and cathepsin D, J. Biochem., 125:1 137, 1999. In addition, the cathepsin D and cathepsin E assays are described in PCT publication WO2011069934. This WIPO publication describes BACE inhibitor compounds having an amide linker connecting two aromatic groups with extremely poor cathepsin D and/or cathepsin E inhibitory activity (see Table 2 (?)).

Where available, the in-vitro Cat D FRET assay data for each of the Examples, conducted by the first procedure, is provided. For example, the compound of example 43 has a Cat D IC_{50} value of >400 uM. As shown by the high micromolar Cat D data (very poorly active or inactive against cat D), the compounds of the present invention possess the unexpected property of little to no ability to inhibit the activity of Cat D. It was surprisingly found that incorporation of an amino- or amido-linker between the core of the compounds and the R^1 and R^2 groups, respectively, has conferred a significantly reduced, poor or no potency on the protein Cat D. Thus, with this surprising selectivity profile, the compounds of the present invention are believed to minimize, reduce or completely eliminate any risk of retinal atrophy and abnormal development of the eye and of the retinal pigmented epithelium as it relates to the normal function and activity of Cat D.
In vivo Inhibition of Beta-Secretase

Several animal models, including mouse, rat, dog, and monkey, may be used to screen for inhibition of beta-secretase activity in vivo following administration of a test compound sample. Animals used in this invention can be wild type, transgenic, or gene knockout animals. For example, the Tg2576 mouse model, prepared and conducted as described in Hsiao et al., 1996, Science 271A, 99-102, and other non-transgenic or gene knockout animals are useful to analyze in vivo inhibition of Amyloid beta peptide (Abeta) production in the presence of inhibitory test compounds. Generally, 2 to 18 month old Tg2576 mice, gene knockout mice or non-transgenic animals are administered test compounds formulated in vehicles, such as cyclodextran, phosphate buffers, hydroxypropyl methylcellulose or other suitable vehicles. One to twenty-four hours following the administration of compound, animals are sacrificed, and brains as well as cerebrospinal fluid (CSF) and plasma are removed for analysis of A-beta levels and drug or test compound concentrations (Dovey et al., 2001, Journal of Neurochemistry, 76,173-181) Beginning at time 0, animals are administered by oral gavage, or other means of delivery such as intravenous injection, an inhibitory test compound of up to 100 mg/kg in a standard, conventional formulation, such as 2% hydroxypropyl methylcellulose, 1% Tween80. A separate group of animals receive 2% hydroxypropyl methylcellulose, 1% Tween80 alone, containing no test compound, and serve as a vehicle-control group. At the end of the test period, animals are sacrificed and brain tissues, plasma or cerebrospinal fluid are collected. Brains are either homogenized in 10 volumes (w/v) of 0.2% diethylamine (DEA) in 50 mM NaCl (Best et al., 2005, Journal of Pharmacology and Experimental Therapeutics, 313, 902-908), or in 10 volumes of 0.5% TritonX-100 in Tris-buffered saline (pH at about 7.6). Homogenates are centrifuged at 355,000g, 4°C for 30 minutes. CSF or brain supernatants are then analyzed for the presence of A-beta peptide by specific sandwich ELISA assays based on ECL (Electrochemiluminescence) technology. For example, rat Abeta40 is measured using biotinylated-4G8 (Signet) as a capture antibody and Fab40 (an in-house antibody specific to the C-terminal of Abeta40) as a detection antibody. For example, 4 hours after administration of 30 mg/kg oral dose of the test compound in 2% hydroxypropyl methylcellulose, 1% Tween80 (pH2.2) to 200g male Sprague Dawley rats, amyloid beta peptide levels are measured for reduction by X% and Y% in cerebrospinal fluid and brain, respectively, when compared to the levels measured in the vehicle-treated or control mice.

Actual vehicles used: Oral: 2% HPMC, 1% Tween80, pH 2.2
IV: 5%EtOH, 45%Propylene glycol in 5% Dextrose

The compounds of the invention may be shown to reduce the formation and/or deposition of amyloid beta peptide in the cerebrospinal fluid (CSF) as well as in the brain of a mouse or rat at either 3mpk, 10 mpk or 30 mpk (mpk = mg compound per kg weight of the animal) dosing concentrations after 4hrs. The following examples exhibited the following percent Abeta 40 reductions at 10 mpk (unless otherwise noted) in the CSF and brain of the rat, respectively.

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<thead>
<tr>
<th>Ex. No.</th>
<th>% reduction of rat CSF levels at 10mpk</th>
<th>% reduction of rat brain levels at 10mpk</th>
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<tr>
<td>127</td>
<td>67</td>
<td>50</td>
</tr>
<tr>
<td>320</td>
<td>82 (at 30 mpk)</td>
<td>62 (at 30 mpk)</td>
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<tr>
<td>117</td>
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INDICATIONS

According to the amyloid cascade hypothesis, cerebral deposition of amyloid-beta peptide (Aβ) is critical for Alzheimer’s disease (AD) pathogenesis. Aβ generation is initiated when β-secretase (BACE1) cleaves the amyloid precursor protein. De Meyer et al re-affirm the believed role which the accumulation of beta-amyloid protein (A-beta) in cerebral spinal fluid (CSF) in a subject plays in the progression of symptoms, initially revealed as mild cognitive impairment, which ultimately leads to AD. Arch Neurol. 67(8):949-956, 2010. Amyloid-beta (Ab) peptides generated from amyloid precursor protein (APP) by proteolytic cleavage, such as by aspartyl protease enzymes including beta-secretase (BACE) and gamma-secretase, likely play a causal role in AD pathogenesis (Tanzi and Bertram, Cell, (120): 545-555, 2005; Walsh and Selkoe, Neuron, (44): 181-193, 2004). Although the precise mechanisms of Ab toxicity are unclear, oligomeric forms of Ab may contribute to cognitive decline by altering synaptic structure and function (Palop and Mucke, Nat. Neuroscience, (13): 812-818, 2010; Selkoe, Behavioral Brain Res., (192): 106-113, 2008; Shankar et al., Nat. Medicine (14): 837-842, 2008). Transgenic mouse models that overexpress mutant APP and produce high levels of Ab show amyloid plaque deposition, synaptic deficits, learning and memory impairments, and other behavioral abnormalities (Games et al., Nature, (373): 523-527, 1995; Gotz et al., Molecular Psychiatry (9): 664-683, 2004; Hsia et al., Proc. Natl. Academy of Science

<table>
<thead>
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<th>Ex. No.</th>
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<th>% reduction of rat brain levels at 10npk</th>
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For more than a decade, BACE1 has been a prime target for designing drugs to prevent or treat AD. However, development of such agents has turned out to be extremely challenging, with major hurdles in cell penetration, oral bioavailability/metabolic clearance, and brain access.

MK-8931, a small molecule inhibitor of BACE (structure unknown) was tested in a two-part randomised, double-blind, placebo-controlled phase I clinical trial in 88 healthy individuals (18–45 years old). MK-8931 seemed to be generally well tolerated (66 patients), and no serious adverse events were reported. A major goal of the trial was to determine whether MK-8931 was able to enter the brain and block β-secretase. To monitor this, biomarkers of BACE1 activity in the CSF were measured, including Aβ40 and Aβ42, as well as soluble peptide APP (βAPPβ), a direct product of BACE1 cleavage of APP. MK-8931 significantly reduced CSF Aβ concentrations in a sustained and dose-dependent manner. At 36 h post-dose, a single dose of 100 mg reduced CSF Aβ40 concentrations by 75% and a single dose of 550 mg by 92%. Similar reductions of CSF concentrations of Aβ42 and βAPPβ, the BACE1-cleaved ectodomain of APP, were also observed. Vassar & Yan, *Lancet Neurology*, 13:319-329 (2014). Currently, MK-8931 is enrolling mild-to-moderate Alzheimer's disease patients in a Ph 2/3 trial; and enrolling participants with prodromal Alzheimer's disease in a Ph III safety and efficacy trial. (US clinical trials; Merck Newsroom, 2014).


Dementia, Down's Syndrome to APP over-production, are all believed to be linked to the deposition of A-beta on the brain. With methods for identifying brain amyloid deposition, positron emission scanning (PET) and CSF measurements of Ab42, identification of AD suffering individuals needing treatment is becoming easier and more common. It is firmly believed that by reducing the formation of A-beta, one can begin to pre-treat AD.


The US biotech company CoMentis is developing an orally bioavailable small molecule CTS-21 166, a highly potent, highly selective and efficacious brain-penetrating
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beta-secretase inhibitor. CoMentis successfully completed a Phase I study of CTS-21166 in healthy volunteers in 2008. Results indicated that CTS-21166 was safe, well-tolerated and pharmacodynamically active at all dose levels. All clinical subjects administered CTS-21166 showed area-under-curve (AUC) reduction in plasma A-Beta40 reductions ranging from 40-75%. Because of the urgent need for AD treatment, Phase II studies for CTS-21166 are planned, or ongoing, for AD patients. In preclinical studies, CTS-21166 exhibits excellent efficacy, selectivity, brain penetration and pharmacologic activity.

Using a fragment-based chemistry strategy, Eli Lilly and company generated LY2811376 [(5)-4-(2,4-difluoro-5-pyrimidin-5-yl-phenyl)-4-methyl-5,6-dihydro-4//-[1,3]thiazin-2-ylamine], an orally available non-peptidic BACE1 inhibitor that produces profound Aβ-lowering effects in animals. The biomarker changes obtained in preclinical animal models translate into man at doses of LY281 1376 that were safe and well tolerated in healthy volunteers (US Ph I Clinical trial - www.clinicaltrials.gov). Prominent and long-lasting Aβ reductions in lumbar CSF were measured after oral dosing of 30 or 90 mg of LY281 1376. This represents the first translation of BACE1-driven biomarker changes in CNS from preclinical animal models to man. Because of toxicology findings identified in longer-term preclinical studies, this compound is no longer progressing in clinical development. However, BACE1 remains a viable target because the adverse effects reported here were recapitulated in LY281 1376-treated BACE1 KO mice and thus are unrelated to BACE1 inhibition. The magnitude and duration of central Aβ reduction obtainable with BACE1 inhibition positions this protease as a tractable small-molecule target through which to test the amyloid hypothesis in man. *Neuroscience*, 31(46):16507-16515, 2011

The compounds of the invention have been shown to modulate, and specifically inhibit the activity of the beta-secretase enzyme, thereby reducing the A-beta peptide fragments. Accordingly, compounds of the invention are useful for, but not limited to, the prevention or treatment of beta-secretase related diseases, including Alzheimer's disease. The compounds of the invention have the ability to modulate the activity of beta secretase enzyme, thereby regulating the production of amyloid beta (Abeta peptide) and reducing the formation and deposition of Abeta peptide in both the cerebral spinal fluid as well as in the brain, resulting in a decrease of amyloid plaque on the brain. In one embodiment of the invention, there is provided a method of treating a disorder related to a beta-secretase enzyme in a subject, the method comprising administering to the subject an effective dosage amount of a compound of Formulas I, II, III, and sub-formulae thereof. In another
embodiment, there is provided a method of reducing production of amyloid beta, and of reducing plaque formation on the brain. In another embodiment, there is provided a method for the treatment, prevention or amelioration of a disease or disorder characterized by the elevated beta-amyloid deposits or beta-amyloid levels in a subject, the method comprising administering to the subject a therapeutically effective amount of a compound according to any of Formulas I - III. In yet another embodiment, the invention provides a method of treating Alzheimer's disease, cognitive impairment including mild, moderate and/or severe, Down's Syndrome, cognitive decline, senile dementia, cerebral amyloid angiopathy or a neurodegenerative disorder.

Accordingly, the compounds of the invention would be useful in therapy as CNS agents in treating neurological disorders and related conditions in subjects.

In one embodiment, the compounds of the invention are provided for the manufacture of a medicament, or a pharmaceutical composition, for the therapeutic and/or prophylactic treatment of diseases and disorders characterized by elevated levels of β-amyloid and/or β-amyloid oligomers and/or b-amyloid plaques and further deposits, including Alzheimer's Disease. In another embodiment, the invention provides compounds, in effective dosage amounts, for the therapeutic and/or prophylactic treatment of AD. Thus, the compounds of the invention may be used to treat prodromol patients, i.e., subjects exhibiting the biomarkers and/or hallmarks of developing AD.

Besides being useful for human treatment, the compounds of the invention may be useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. For example, animals including horses, dogs, and cats may be treated with compounds provided herein.

FORMULATIONS AND METHOD OF USE

Treatment of diseases and disorders herein is intended to also include therapeutic administration of a compound of the invention, or a pharmaceutical salt thereof, or a pharmaceutical composition of either to a subject (i.e., an animal, preferably a mammal, most preferably a human) which may be in need of preventative treatment, such as, for example, for pain, inflammation and the like. Treatment also encompasses prophylactic administration of a compound of the invention, or a pharmaceutical salt thereof, or a pharmaceutical composition of either to a subject (i.e., an animal, preferably a mammal, most preferably a human). Generally, the subject is initially diagnosed by a licensed physician and/or authorized medical practitioner, and a regimen for prophylactic and/or
therapeutic treatment via administration of the compound(s) or compositions of the invention is suggested, recommended or prescribed.

The amount of compound(s) which is/are administered and the dosage regimen for treating neurological disorders and beta-secretase mediated diseases with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the type of disease, the severity of the disease, the route and frequency of administration, and the particular compound employed. Thus, the dosage regimen may vary widely, but can be determined routinely using standard methods. A daily dose of about 0.01 to 500 mg/kg, advantageously between about 0.01 and about 50 mg/kg, more advantageously about 0.01 and about 30 mg/kg, and even more advantageously between about 0.1 and about 10 mg/kg body weight may be appropriate, and should be useful for all methods of use disclosed herein. The daily dose can be administered in one to four doses per day.

While it may be possible to administer a compound of the invention alone, in the methods described, the compound administered normally will be present as an active ingredient in a pharmaceutical composition. Thus, in another embodiment of the invention, there is provided a pharmaceutical composition comprising a compound of this invention in combination with a pharmaceutically acceptable excipient, which includes diluents, carriers, adjuvants and the like (collectively referred to herein as "excipient" materials) as described herein, and, if desired, other active ingredients. A pharmaceutical composition of the invention may comprise an "effective amount" of a compound of the invention or an "effective dosage amount" of a compound of the invention. An "effective dosage amount" of a compound of the invention includes an amount less than, equal to or greater than an effective amount of the compound. For example, a pharmaceutical composition in which two or more unit dosages, such as in tablets, capsules and the like, are required to administer an effective amount of the compound, or alternatively, a multidose pharmaceutical composition, such as powders, liquids and the like, in which an effective amount of the compound is administered by administering a portion of the composition.

The compound(s) of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The compounds and compositions of the present invention may, for example, be administered orally, mucosally, topically, rectally, pulmonarily such as by inhalation spray, or parentally including intravascularly,
intravenously, intraperitoneally, subcutaneously, intramuscularly intrasternally and infusion techniques, in dosage unit formulations containing conventional pharmaceutically acceptable carriers, adjuvants, and vehicles.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. For example, these may contain an amount of active ingredient from about 1 to 2000 mg, advantageously from about 1 to 500 mg, and typically from about 5 to 150 mg. A suitable daily dose for a human or other mammal may vary widely depending on the condition of the patient and other factors, but, once again, can be determined using routine methods and practices.

For therapeutic purposes, the active compounds of this invention are ordinarily combined with one or more adjuvants or other "excipients" appropriate to the indicated route of administration. If orally administered on a per dose basis, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, to form the final formulation. For example, the active compound(s) and excipient(s) may be tableted or encapsulated by known and accepted methods for convenient administration. Examples of suitable formulations include, without limitation, pills, tablets, soft and hard-shell gel capsules, troches, orally-dissolvable forms and delayed or controlled-release formulations thereof. Particularly, capsule or tablet formulations may contain one or more controlled-release agents, such as hydroxypropylmethyl cellulose, as a dispersion with the active compound(s).

Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules using one or more of the carriers or diluents mentioned for use in the formulations for oral administration or by using other suitable dispersing or wetting agents and suspending agents. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, tragacanth gum, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art. The active ingredient may also be administered by
injection as a composition with suitable carriers including saline, dextrose, or water, or with cyclodextrin (ie. Captisol), cosolvent solubilization (ie. propylene glycol) or micellar solubilization (ie. Tween 80).

The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The active ingredient may also be administered by injection as a composition with suitable carriers including saline, dextrose, or water. The daily parenteral dosage regimen will be from about 0.1 to about 30 mg/kg of total body weight, and preferably from about 0.1 to about 10 mg/kg.

For pulmonary administration, the pharmaceutical composition may be administered in the form of an aerosol or with an inhaler including dry powder aerosol.

The pharmaceutical compositions may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers, buffers etc. Tablets and pills can additionally be prepared with enteric coatings. Such compositions may also comprise adjuvants, such as wetting, sweetening, flavoring, and perfuming agents. Accordingly, in yet another embodiment of the present invention, there is provided a method of manufacturing a medicament, the method comprising combining an amount of a compound according to Formulas I-III with a pharmaceutically acceptable carrier to manufacture the medicament.

In yet another embodiment, the invention provides a method of manufacturing a medicament for the treatment of Alzheimer's disease, the method comprising combining an amount of a compound according to Formulas I-III with a pharmaceutically acceptable carrier to manufacture the medicament.

COMBINATIONS

While the compounds of the invention can be dosed or administered as the sole active pharmaceutical agent, they can also be used in combination with one or more
compounds of the invention or in conjunction with other agents. When administered as a combination, the therapeutic agents can be formulated as separate compositions that are administered simultaneously or sequentially at different times, or the therapeutic agents can be given as a single composition.

The phrase "co-therapy" (or "combination-therapy"), in defining use of a compound of the present invention and another pharmaceutical agent, is intended to embrace administration of each agent in a sequential manner in a regimen that will provide beneficial effects of the drug combination, and is intended as well to embrace co-administration of these agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of these active agents or in multiple, separate capsules for each agent.

Specifically, the administration of compounds of the present invention may be in conjunction with additional therapies known to those skilled in the art in the prevention or treatment of beta-secretase, gamma-secretase and/or other reagents known in influence the formation and/or deposition of amyloid beta, otherwise responsible for the formation of plaque on the brain.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the accepted dosage ranges. Compounds of Formulas I, II and III may also be administered sequentially with other known medicinal agents. The invention is not limited in the sequence of administration; compounds of the invention may be administered either prior to, simultaneous with or after administration of the known anti-inflammatory agent.

The foregoing description is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds, compositions and methods. Variations and changes, which are obvious to one skilled in the art, are intended to be within the scope and nature of the invention, as defined in the appended claims. From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions. All patents and other publications recited herein are hereby incorporated by reference in their entireties.
What is claimed is:

1. A compound of Formula I

\[
\begin{align*}
&\text{A-1 8 1 3-WO-PCT - 357 -} \\
&\text{claimed is:} \\
&\text{A compound of Formula I} \\
&\text{or a stereoisomer, tautomer, hydrate, solvate or pharmaceutically acceptable salt thereof,} \\
&\text{wherein} \\
&A^4 \text{ is CR}^4 \text{ or N;} \\
&A^5 \text{ is CR}^5 \text{ or N;} \\
&A^6 \text{ is CR}^6 \text{ or N;} \\
&A^8 \text{ is CR}^8 \text{ or N, provided that no more than two of A}^4, A^5, A^6 \text{ and A}^8 \text{ is N;} \\
&\text{each of R}^4 \text{ and R}^6, \text{ independently, is H, F, Cl, C}^6\text{-alkyl, C}^2\text{-alkenyl,} \\
&C_2\text{alkynyl, CN, -CH}_2\text{OCi}_2\text{-alkyl, -OCl}_2\text{-alkyl, -S(0)}_0\text{C}^1\text{-alkyl, -NHCl}_2\text{-alkyl or -} \\
&C(0)\text{C}_i\text{-alkyl, wherein each of the C}^2\text{-alkenyl, C}_2\text{-alkynyl, and C}^6\text{-alkyl} \\
&\text{portion of -CH}_2\text{OCi}_2\text{-alkyl, -OCl}_2\text{-alkyl, -S(0)}_0\text{C}^1\text{-alkyl, -NHCl}_2\text{-alkyl and -C(0)C}_i\text{-alkyl} \\
&\text{alkyl are optionally substituted with 1-4 substituents of F, oxo or OH;} \\
&\text{each of R}^1 \text{ and R}^2, \text{ independently, is H, F, Cl, C}^i\text{-alkyl, C}_2\text{-alkenyl,} \\
&C_2\text{alkynyl, CN, -CH}_2\text{OCi}_2\text{-alkyl, -OCl}_2\text{-alkyl, -S(0)}_0\text{C}^1\text{-alkyl, -NHCl}_2\text{-alkyl or -} \\
&C(0)\text{C}_i\text{-alkyl, wherein each of the C}^2\text{-alkenyl, C}_2\text{-alkynyl, and C}^6\text{-alkyl} \\
&\text{portion of -CH}_2\text{OCi}_2\text{-alkyl, -OCl}_2\text{-alkyl, -S(0)}_0\text{C}^1\text{-alkyl, -NHCl}_2\text{-alkyl and -C(0)C}_i\text{-alkyl} \\
&\text{alkyl are optionally substituted with 1-4 substituents of F, oxo or OH;} \\
&R^3 \text{ is C}_i\text{-alkyl, CH}_2\text{OCi}_2\text{-alkyl, CH}_2\text{OH, C}_i\text{-haloalkyl or cyclopropyl, wherein} \\
&\text{each of the C}_i\text{-alkyl, CH}_2\text{OCi}_2\text{-alkyl, C}_i\text{-haloalkyl and cyclopropyl is optionally} \\
&\text{substituted with 1-4 F atoms;} \\
&\text{each of R}^4, R^5, R^6 \text{ and R}^8, \text{ independently, is H, halo, haloalkyl, haloalkoxyl,} \\
&C_i\text{-4-alkyl, CN, OH, OCl}_2\text{-alkyl, S(0)}_0\text{C}_4\text{-alkyl, NHCl}_2\text{-alkyl or C(0)C}_4\text{-alkyl;} \\
&R^7 \text{ is -NH-R}^9, -NH-C(=0)-R^9, -C(=0)NH-R^9, -O-R^9 \text{ or -S-R}^9; \\
&R^9 \text{ is acetyl, C}_i\text{-alkyl, C}_2\text{alkynyl, C}_2\text{alkynyl or a fully or partially unsaturated} \\
&\text{3-, 4-, 5-, 6- or 7-membered monocyclic or 8-, 9- or 10-membered bicyclic ring formed of} \\
&\text{carbon atoms, said ring optionally including 1-4 heteroatoms if monocyclic or 1-5}
heteroatoms if bicyclic, said heteroatoms selected from O, N or S, wherein the C$_6$-alkyl, C$_2$-alkenyl, C$_2$-alkynyl and ring are optionally substituted, independently, with 1-5 substituents of R$^{10}$; and each R$^{10}$, independently, is H, halo, haloalkyl, CN, OH, N0$_2$, NH$_2$, SF$_5$, acetyl, C(0)NHCH$_3$, oxo, cyclopropylmethoxy, 2-butylnyloxy, C$_1$-$\alpha$-alkyl, C$_2$-$\alpha$-alkynyl, C$_3$-$\alpha$-alkynyl, C$_3$-$\alpha$-cycloalkyl, C$_1$-$\alpha$-alkylamino-, C$_1$-$\alpha$-dialkylamino-, C$_1$-$\alpha$-alkoxy-, C$_1$-$\alpha$-thioalkoxy-, morpholiny, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolidinyl, tetrahydropyrrolyl, piperazinyl, oxetan-3-yl, imidazo-pyridinyl or dioxolyl, wherein each of the cyclopropylmethoxy, 2-butylnyloxy, C$_1$-$\alpha$-alkenyl, C$_2$-$\alpha$-alkynyl, C$_3$-$\alpha$-alkynyl, C$_3$-$\alpha$-cycloalkyl, C$_1$-$\alpha$-alkylamino-, C$_1$-$\alpha$-dialkylamino-, C$_1$-$\alpha$-alkoxy-, C$_1$-$\alpha$-thioalkoxy-, morpholiny, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolidinyl, oxetan-3-yl or dioxolyl, is optionally substituted independently with 1-5 substituents of F, CI, CN, N0$_2$, NH$_2$, OH, oxo, CF$_3$, CHF$_2$, CH$_2$F, methyl, methoxy, ethyl, ethoxy, CH$_2$CF$_3$, CH$_3$CHF$_2$, propyl, propoxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxy, cyclobutyl, isobutoxy, tert-butoxy, isobutyl, sec-butyl, tert-butyl, cyclopentyl, cyclohexyl, C$_1$-$\alpha$-alkylamino-, C$_1$-$\alpha$-dialkylamino-, C$_1$-$\alpha$-alkoxy-, C$_1$-$\alpha$-thioalkoxy-, tetrahydropyrrolyl, or oxetan-3-yl, provided the compound is not N-(3-((1R,5R,6R)-3-amino-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methoxy-1,7-naphthyridin-8-amine; or

N-(3-((1R,5R,6R)-3-amino-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-methoxy-2-pyrazinecarboxamide.

2. The compound according to Claim 1, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each of R$^1$ and R$^2$, independently, is H, F, CH$_3$, CH$_2$F, CHF$_2$ or CF$_3$.

3. The compound according to any one of Claims 1 and 2, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each of R$^5$ and R$^6$, independently, is H, F, CH$_3$, CH$_2$F, CHF$_2$ or CF$_3$.

4. The compound according to any one of Claims 1, 2 and 3, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each of R$^1$ and R$^2$, independently, is H, F or CF$_3$. 


5. The compound according to any one of Claims 1-4, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each of $R^a$ and $R^b$, independently, is H or F.

6. The compound according to any one of Claims 1-5, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each of $R^1$ and $R^2$, independently, is H, F or CF$_3$; and each of $R^8$ and $R^b$, independently, is H or F.

7. The compound according to any one of Claims 1-6, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each of $R^1$, $R^2$, $R^a$ and $R^b$, independently, is H.

8. The compound according to any one of Claims 1-7, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein $R^3$ is CH$_3$, CF$_3$, CH$_2$F or CHF$_2$.

9. The compound according to any one of Claims 1-8, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein $R^7$ is -NH-CH$_2$-R$^9$ or -NH-C(=0)-R$^9$; or $R^7$ is

$$
\begin{align*}
\text{R}^{10} & \text{\textbullet} \text{\textbullet} \text{\textbullet} \text{\textbullet} \\
\text{V} & \text{\textbullet} \text{\textbullet} \text{\textbullet} \text{\textbullet} \\
\text{W} & \text{\textbullet} \text{\textbullet} \text{\textbullet} \text{\textbullet} \\
\text{R}^{10} & \text{\textbullet} \text{\textbullet} \text{\textbullet} \text{\textbullet}
\end{align*}
$$

wherein $V$ is NR$_2$, O or S; and each $W$, independently, is CH, CF, CCl, CCH$_3$ or N.

10. The compound according to any one of Claims 1 and 9, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein
A-1813-WO-PCT

A\(^4\) is CR\(^4\) or N;
A\(^5\) is CR\(^5\) or N;
A\(^6\) is CR\(^6\) or N;
A\(^8\) is CR\(^8\) or N, provided that no more than one of A\(^4\), A\(^5\), A\(^6\) and A\(^8\) is N;
each of R\(^4\) and R\(^5\), independently, is H, F, Cl, CF\(_3\), OCF\(_3\), methyl, ethyl, CN, OH,
OCH\(_3\), SCH\(_3\), NHCH\(_3\), C(0)CH\(_3\) or CH\(_2\)OCHF\(_2\);
each of R\(^1\) and R\(^2\), independently, is H, F, Cl, CF\(_3\), OCF\(_3\), methyl, ethyl, CN, OH,
OCH\(_3\), SCH\(_3\), NHCH\(_3\), C(0)CH\(_3\) or CH\(_2\)OCHF\(_2\);
R\(^3\) is C\(_4\)alkyl, C\(_4\)haloalkyl, CH\(_2\)OH, CH\(_2\)OCHF\(_2\) or cyclopropyl; and
each of R\(^4\), R\(^5\), R\(^6\) and R\(^8\), independently, is H, F, Cl, CF\(_3\), CH\(_2\)F, CF\(_3\), OCF\(_3\),
methyl, ethyl, CN, OH, OCH\(_3\), SCH\(_3\), NHCH\(_3\) or C(0)CH\(_3\).

11. The compound according to any one of claims 1-9, or a stereoisomer or
pharmaceutically acceptable salt thereof, wherein
each of R\(^1\) and R\(^2\), independently, is H, F or CF\(_3\);
each of R\(^4\) and R\(^5\), independently, is H or F;
R\(^3\) is CH\(_3\), CF\(_3\), CH\(_2\)F or CHF\(_2\); and
R\(^7\) is -NH-R\(^9\), -NH-C(=0)-R\(^9\) or
\[\text{wherein } V \text{ is NR}^{10}, O \text{ or S; and}
\text{each } W, \text{ independently, is CH, CF, CC} \text{I, CCH} \text{3 or N.}\]

12. The compound according to any one of claims 1-11, or a stereoisomer or
pharmaceutically acceptable salt thereof, wherein R\(^7\) is -NH-C(=0)-R\(^9\).
13. The compound according to any one of claims 1-11, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein $R_7$ is

\[ \text{Diagram}\]

wherein $V$ is $NR^{10}$, $O$ or $S$; and each $W$, independently, is $\text{CH}$, $\text{CF}$, $\text{CCl}$, $\text{CCH}_3$ or $\text{N}$.

14. The compound according to any one of claims 1-13, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein

- $A^4$ is $\text{CR}^4$;
- $A^5$ is $\text{CR}^5$ or $\text{N}$;
- $A^6$ is $\text{CR}^6$; and
- $A^8$ is $\text{CR}^8$ or $\text{N}$, provided only one of $A^5$ and $A^8$ is $\text{N}$, and wherein each of $R^4$, $R^5$, $R^6$ and $R^8$, independently, is $\text{H}$, $\text{F}$, $\text{Cl}$, $\text{CF}_3$, $\text{CF}_2\text{H}$, $\text{CH}_2\text{F}$ or $\text{CH}_3$.

15. A compound according to Claim 1, or a stereoisomer, tautomer, hydrate, solvate or pharmaceutically acceptable salt thereof, having a Formula II:

\[ \text{Diagram}\]

wherein

- $A^4$ is $\text{CR}^4$ or $\text{N}$;
- $A^5$ is $\text{CR}^5$ or $\text{N}$;
- $A^6$ is $\text{CR}^6$ or $\text{N}$;
- $A^8$ is $\text{CR}^8$ or $\text{N}$, provided that no more than two of $A^4$, $A^5$, $A^6$ and $A^8$ is $\text{N}$; each of $R^4$ and $R^8$, independently, is $\text{H}$, $\text{F}$, $\text{Cl}$, $\text{C}_{1-6}$-alkyl, $\text{C}_2$-alkenyl,
$C_{2-4}$alkynyl, CN, $\text{-CH}_2\text{O}_{\text{C}_i\text{-alkyl}}$, $\text{-OCi}_i\text{-alkyl}$, $\text{-S(O)}_i\text{C}_i\text{-alkyl}$, $\text{-NH}_\text{C}_i\text{-alkyl}$ or $\text{-C(O)}_i\text{C}_i\text{-alkyl}$, wherein each of the $\text{C}_i\text{-alkyl}$, $C_{2-4}$alkenyl, $C_{2-4}$alkynyl, and $\text{C}_i\text{-alkyl}$ portion of $\text{-CH}_2\text{O}_{\text{C}_i\text{-alkyl}}$, $\text{-OCi}_i\text{-alkyl}$, $\text{-S(O)}_i\text{C}_i\text{-alkyl}$, $\text{-NH}_\text{C}_i\text{-alkyl}$ and $\text{-C(O)}_i\text{C}_i\text{-alkyl}$ are optionally substituted with 1-4 substituents of F, oxo or OH;

each of $R^1$ and $R^2$, independently, is H, F, Cl, $\text{C}_i\text{-alkyl}$, $C_{2-4}$alkenyl, $C_{2-4}$alkynyl, CN, $\text{-CH}_2\text{O}_{\text{C}_i\text{-alkyl}}$, $\text{-OCi}_i\text{-alkyl}$, $\text{-S(O)}_i\text{C}_i\text{-alkyl}$, $\text{-NH}_\text{C}_i\text{-alkyl}$ or $\text{-C(O)}_i\text{C}_i\text{-alkyl}$, wherein each of the $\text{C}_i\text{-alkyl}$, $C_{2-4}$alkenyl, $C_{2-4}$alkynyl, and $\text{C}_i\text{-alkyl}$ portion of $\text{-CH}_2\text{O}_{\text{C}_i\text{-alkyl}}$, $\text{-OCi}_i\text{-alkyl}$, $\text{-S(O)}_i\text{C}_i\text{-alkyl}$, $\text{-NH}_\text{C}_i\text{-alkyl}$ and $\text{-C(O)}_i\text{C}_i\text{-alkyl}$ are optionally substituted with 1-4 substituents of F, oxo or OH;

$R^3$ is $\text{Ci}_i\text{-alkyl}$, $\text{CH}_2\text{O}_{\text{C}_i\text{-alkyl}}$, $\text{CH}_2\text{OH}$, $\text{Ci}_i\text{-haloalkyl}$ or cyclopropyl, wherein each of the $\text{C}_i\text{-alkyl}$, $\text{CH}_2\text{O}_{\text{C}_i\text{-alkyl}}$, $\text{Ci}_i\text{-haloalkyl}$ and cyclopropyl is optionally substituted with 1-4 F atoms;

each of $R^4$, $R^5$, $R^6$ and $R^8$, independently, is H, halo, haloalkyl, haloalkoxy, $\text{Ci}_4\text{-alkyl}$, CN, OH, $\text{OCi}_i\text{-alkyl}$, $\text{S(O)}_i\text{Ci}_i\text{-alkyl}$, $\text{NH}_\text{Ci}_4\text{-alkyl}$ or $\text{C(O)}_i\text{Ci}_4\text{-alkyl}$;

$R^7$ is $\text{-NH-R}_9$, $\text{-NH-C(=0)-R}_9$, $\text{-C(=0)-NH-R}_9$;

or $R^7$ is

\[
\begin{align*}
\text{R}_10 & \quad \text{W} \\
\text{V} & \quad \text{N} \\
\text{R}_10 & \quad \text{W} \\
\end{align*}
\]

wherein V is NR$_{10}$, O or S; and

each W, independently, is CH, CF, CCl, CCH$_3$ or N;

$R^9$ is acetyl, $\text{Ci}_6\text{-alkyl}$, $C_{2-4}$alkenyl, $C_{2-4}$alkynyl or a fully or partially unsaturated 3-, 4-, 5-, 6- or 7-membered monocyclic or 8-, 9- or 10-membered bicyclic ring formed of carbon atoms, said ring optionally including 1-4 heteroatoms if monocyclic or 1-5 heteroatoms if bicyclic, said heteroatoms selected from O, N or S, wherein the $\text{Ci}_6$-alkyl,
C_{2,3}alkenyl, C_{2,3}alkynyl and ring are optionally substituted, independently, with 1-5 substituents of R; and each R, independently, is H, halo, haloalkyl, CN, OH, N\text{O}_2, NH_2, SF_5, acetyl, -C(0)NHCH_3, oxo, cyclopropylm ethoxy, 2-butynyloxy, C_alkyl, C_{2,3}alkenyl, C_2-

alkynyl, C_alkyl, C_alkylamino-, C_alkoxyl, C_{dialkylamino}-, C_{thioalkoxyl}, morpholinyl, pyrazolyl, isoxazolyl, dihydroprynyl, pyrrolyl, pyrrolidinyl, tetrahydroprpyrrolyl, piperazinyl, oxetan-3-yl, imidazo-pyridinyl or dioxyolyl, wherein each of the cyclopropylmethoxy, 2-butynyloxy, C_alkyl, C_{2,3}alkenyl, C_{2,3}alkynyl, C_3-

cycloalkyl, C_6alkylamino-, C_6alkoxyl, C_{6dialkylamino}-, C_{6thioalkoxyl}, morpholinyl, pyrazolyl, isoxazolyl, dihydroprynyl, pyrrolidinyl, oxetan-3-yl or dioxyolyl, is optionally substituted independently with 1-5 substituents of F, Cl, CN, N\text{O}_2, NH_2, OH, oxo, CF_3, CHF_2, CH_2F, methyl, methoxy, ethyl, ethoxy, CH_2CF_3, CH_2CHF_2, propyl, propoxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxy, cyclobutyl, isobutoxy, tert-butoxy, isobutyl, sec-buty1, tert-buty1, cyclopentyl, cyclohexyl, C_{alkylamino}-, C_{dialkylamino}-, C_{thioalkoxyl}.

dialkylamino, C_{dthioalkoxyl} tetrahydroprynyl, tetrahydroprpyrrolyl or oxetan-3yl.

16. The compound according to any one of Claims 1 and 15, or a stereoisomer, tautomer or pharmaceutically acceptable salt thereof, wherein

A_4 is CR_4 or N;

A_5 is CR_5 or N;

A_6 is CR_6 or N;

A_8 is CR_8 or N, provided no more than one of A_4, A_5, A_6 and A_8 is N;

each of R, independently, is H, F, CH_3, CH_2F, CHF_2 or CF_3;

each of R_1 and R_2, independently, is H, F, CH_3, CH_2F, CHF_2 or CF_3;

R_3 is C_{dalkyl}, C_{dhaloalkyl}, CH_2OH, CH_2OCHF_2 or cyclopropyl; and each of R, R_3, R_5 and R_8, independently, is H, F, Cl, CF_3H, CH_2F, CF_3, OCF_3, methyl, ethyl, CN, OH, OCH_3, SCH_3, NHCH_3 or C(0)CH_3.

17. The compound according to any one of Claims 1-6, 7 and 15-16, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein

A_4 is CR_4;

A_5 is CR_5;

A_6 is CR_6; and
A $^8$ is CR$^8$; wherein each of $R^4$, $R^5$, $R^6$ and $R^8$, independently, is H, F, CF$_3$, CF$_2$H, CH$_2$F or CH$_3$;

$R^3$ is CH$_3$, CF$_3$, CH$_2$F or CHF$_2$; and

$R^7$ is -NH-C(=0)-$R^9$ or

![Chemical structure]

wherein $V$ is NR$_{10}$, O or S; and
each $W$, independently, is CH, CF, CC1 or N.

18. The compound according to any one of Claims 14-16, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein $R^7$ is -NH-C(=0)-$R^9$.

19. The compound according to any one of Claims 15-17, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein $R^7$ is

![Chemical structure]

wherein $V$ is NR$_{10}$, O or S; and
each $W$, independently, is CH, CF, CC1, CCH$_3$ or N.

20. The compound according to any one of Claims 15-19, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each of $R^1$ and $R^2$, independently, is H, F or CF$_3$; and each of $R^a$ and $R^b$, independently, is H or F.

21. The compound according to any one of Claims 1-12 and 15-18, or a stereoisomer or pharmaceutically acceptable salt thereof, having a Formula II-A
wherein

A\(^4\) is CR\(^4\) or N;

A\(^5\) is CR\(^5\) or N;

A\(^6\) is CR\(^6\) or N;

A\(^8\) is CR\(^8\) or N, provided that no more than one of A\(^4\), A\(^5\), A\(^6\) and A\(^8\) is N;

each of R\(^4\) and R\(^6\), independently, is H, F, Cl, C\(_6\)-alkyl, C\(_2\)-alkenyl, C\(_2\)-alkynyl, C\(_{23}\)alkynyl, CN, -CH\(_2\)OCi\(_\delta\)-alkyl, -OCi\(_\delta\)-alkyl, -S(0)\(_\delta\)Ci\(_\delta\)-alkyl, -NHCl\(_\delta\)-alkyl or -

C(0)Cl, wherein each of the Cl\(_\delta\)-alkyl, C\(_2\)-alkenyl, C\(_2\)-alkynyl, and Cl\(_\delta\)-alkyl portion of -CH\(_2\)OCi\(_\delta\)-alkyl, -OCi\(_\delta\)-alkyl, -S(0)\(_\delta\)Ci\(_\delta\)-alkyl, -NHCl\(_\delta\)-alkyl and -C(0)Ci\(_\delta\)-alkyl are optionally substituted with 1-4 substituents of F, oxo or OH;

each of R\(^1\) and R\(^2\), independently, is H, F, Cl, C\(_6\)-alkyl, C\(_2\)-alkenyl, C\(_2\)-alkynyl, CN, -CH\(_2\)OCi\(_\delta\)-alkyl, -OCi\(_\delta\)-alkyl, -S(0)\(_\delta\)Ci\(_\delta\)-alkyl, -NHCl\(_\delta\)-alkyl or -

C(0)Cl, wherein each of the Cl\(_\delta\)-alkyl, C\(_2\)-alkenyl, C\(_2\)-alkynyl, and Cl\(_\delta\)-alkyl portion of -CH\(_2\)OCi\(_\delta\)-alkyl, -OCi\(_\delta\)-alkyl, -S(0)\(_\delta\)Ci\(_\delta\)-alkyl, -NHCl\(_\delta\)-alkyl and -C(0)Ci\(_\delta\)-alkyl are optionally substituted with 1-4 substituents of F, oxo or OH;

R\(^3\) is Cl\(_\delta\)-alkyl, CH\(_2\)OCi\(_\delta\)-alkyl, CH\(_2\)OH, Ci\(_\delta\)-haloalkyl or cyclopropyl, wherein each of the Cl\(_\delta\)-alkyl, CH\(_2\)OCi\(_\delta\)-alkyl, Cl\(_\delta\)-haloalkyl and cyclopropyl is optionally

substituted with 1-4 F atoms;

each of R\(^4\), R\(^5\), R\(^6\) and R\(^8\), independently, is H, F, Cl or CH\(_3\);

R\(^9\) is acetyl, Cl\(_6\)-alkyl, C\(_2\)-alkenyl. C\(_2\)-alkynyl or a fully or partially unsaturated 3-, 4-, 5-, 6- or 7-membered monocyclic or 8-, 9- or 10-membered bicyclic ring formed of carbon atoms, said ring optionally including 1-4 heteroatoms if monocyclic or 1-5 heteroatoms if bicyclic, said heteroatoms selected from O, N or S, wherein the Cl\(_6\)-alkyl, C\(_2\)-alkenyl, C\(_2\)-alkynyl and ring are optionally substituted, independently, with 1-5 substituents of R\(^{10}\);

and each R\(^{10}\), independently, is H, halo, haloalkyl, CN, OH, NO\(_2\), NH\(_2\), SF\(_3\), acetyl,
-C(0)NHCH₃, oxo, cyclopropylmethoxy, 2-butylnyloxy, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₆₋₁₀alkycycloalkyl, C₁₋₆alkylamino-, C₁₋₆dialkylamino-, C₁₋₆alkoxyl, C₁₋₆thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolyl, pyrrolidinyl, tetrahydropyryl, piperazinyl, oxetan-3-yl, imidazo-pyridinyl or dioxolyl, wherein each
tetrahydropyrrolyl, morpholinyl, heteroatoms
butoxy, tetrahydropyrrolyl, A-1
oxo, stereoisomer, tautomer or pharmaceutically acceptable salt thereof, wherein
22. The compound according to any one of Claims 1-3, 8-19 and 21, or a
stereoisomer, tautomer or pharmaceutically acceptable salt thereof, wherein
A₄ is CR₄;
A₅ is CR₅;
A₆ is CR₆;
A₈ is CR₈, wherein each of R₄, R₅, R₆ and R₈, independently, is H, F, Cl, CF₂H,
CH₃F, CF₃, OCF₃, methyl, ethyl, CN, OH, OCH₃, SCH₃, NHCH₃ or C(0)CH₃;
each of R₁ and R₂, independently, is H, F, CH₃, CH₂F, CHF₂ or CF₃;
each of R₃ and R₄, independently, is H, F, CH₃, CH₂F, CHF₂ or CF₃;
R₃ is CH₃, C₂H₅, CF₃H or CH₂F;
R₅ is acetyl, C₁₋₆-alkyl, C₆₋₁₀alkenyl. C₆₋₁₀alkynyl or a fully or partially unsaturated
3-₄, ₅-₆- or 7-membered monocyclic or 8-, 9- or 10-membered bicyclic ring formed of
carbon atoms, said ring optionally including 1-4 heteroatoms if monocyclic or 1-5
heteroatoms if bicyclic, said heteroatoms selected from O, N or S, wherein the C₁₋₆-alkyl,
C₆₋₁₀alkenyl, C₆₋₁₀alkynyl and ring are optionally substituted, independently, with 1-5
substituents of R₉;
and
each R₉, independently, is H, halo, haloalkyl, CN, OH, N⁰₂, NH₂, SF₃, acetyl,
-C(0)NHCH₃, oxo, cyclopropylmethoxy, 2-butylnyloxy, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₆₋₁₀alkycycloalkyl, C₁₋₆alkylamino-, C₁₋₆dialkylamino-, C₁₋₆alkoxyl, C₁₋₆thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolyl, pyrrolidinyl, tetrahydropyryl, piperazinyl, oxetan-3-yl, imidazo-pyridinyl or dioxolyl, wherein each
of the cyclopropylmethoxy, 2-butynyloxy, C\textsubscript{1-6}alkyl, C\textsubscript{2-6}alkenyl, C\textsubscript{2-6}alkynyl, C\textsubscript{3-6}cycloalkyl, C\textsubscript{1-6}alkylamino-, C\textsubscript{1-6}dialkylamino-, C\textsubscript{1-6}alkoxy, C\textsubscript{1-6}thioalkoxy, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolidinyl, oxetan-3-yl or dioxolyl, is optionally substituted independently with 1-5 substituents of F, Cl, CN, N\textsubscript{2}, NH\textsubscript{2}, OH, oxo, CF\textsubscript{3}, CHF\textsubscript{2}, CH\textsubscript{3}F, methyl, methoxy, ethyl, ethoxy, CH\textsubscript{2}CF\textsubscript{3}, CH\textsubscript{3}CHF\textsubscript{2}, propyl, propoxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxy, cyclobutyl, isobutoxy, tert-butoxy, isobutyl, sec-butyl, tert-butyl, cyclopentyl, cyclohexyl, C\textsubscript{1-6}alkylamino-, C\textsubscript{1-6}dialkylamino, C\textsubscript{1-6}thioalkoxyl, tetrahydropyranyl, tetrahydropyrrolyl or oxetan-3yl.

23. The compound according to any one of Claims 1-18 and 21-22, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein

A\textsubscript{4} is CR\textsubscript{4} or N;
A\textsubscript{5} is CR\textsubscript{5} or N;
A\textsubscript{6} is CR\textsubscript{6} or N;

A\textsubscript{8} is CR\textsubscript{8} or N, wherein each of R\textsubscript{4}, R\textsubscript{5}, R\textsubscript{6} and R\textsubscript{8}, independently, is H, F, Cl or CH\textsubscript{3}, provided no more than one of A\textsubscript{4}, A\textsubscript{5}, A\textsubscript{6} and A\textsubscript{8} is N;

each of R\textsubscript{1}, R\textsubscript{2}, R\textsubscript{6} and R\textsubscript{8}, independently, is H; and
R\textsubscript{3} is CF\textsubscript{3}, CH\textsubscript{3}, CF\textsubscript{2}H or CH\textsubscript{2}F.

24. The compound according to any one of Claims 1-12, 15-18 and 21-23, or a stereoisomer or pharmaceutically acceptable salt thereof, having a Formula II-A

![formula II-A](image)

wherein

A\textsubscript{4} is CR\textsubscript{4}, wherein R\textsubscript{4} is H, F or Cl;
A\textsubscript{5} is CR\textsubscript{5} or N, wherein R\textsubscript{5} is H, F, Cl or CH\textsubscript{3};
A\textsubscript{6} is CH;
A\textsubscript{8} is CR\textsubscript{8} or N, wherein R\textsubscript{8} is H or F,
provided that no more than one of A₅ and A₈ is N;
each of R and R', independently, is H or F;
each of R¹ and R², independently, is H or F;
R³ is CH₃, CF₃, CH₃F or CHF₂;
R⁹ is a fully unsaturated 5- or 6-membered monocyclic or 8-, 9- or 10-membered
bicyclic ring formed of carbon atoms, said ring optionally including 1-4 heteroatoms if
monocyclic or 1-5 heteroatoms if bicyclic, said heteroatoms selected from O, N or S,
wherein the ring is optionally substituted, independently, with 1-5 substituents of R¹⁰;
and
each R¹⁰, independently, is H, halo, haloalkyl, CN, OH, NO₂, NH₂, SF₅, acetyl.

-C(0)NHCH₂, oxo, cyclopropylmephtoxy, 2-butylnoxy, Ci₆alkyl, C₂alkenyl, C₂-
alkynyl, C₃₋₄cycloalkyl, Ci₆alkylamino-, Ci₆dialkylamino-, Ci₆alkoxyl, Ci₆thioalkoxyl,
morpholinyl, pyrazolyl, isoxazolyl, dihydropryanyl, pyrrolyl, pyrrolidinyi,
tetrahydropyrrollyl, piperaiznyl, oxetan-3-yl, imidazo-pyridinyi or dioxolyl, wherein each
of the cyclopropylmethoxy, 2-butylnoxy, Ci₆alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, C₅-
C₆cycloalkyl, Ci₆alkylamino-, Ci₆dialkylamino-, C₁₋₄alkoxyl, C₁₋₄thioalkoxyl,
morpholinyl, pyrazolyl, isoxazolyl, dihydropryanyl, pyrrolidinyi, oxetan-3-yl or dioxolyl,
is optionally substituted independently with 1-5 substituents of F, CI, CN, N0₂, NH₂, OH,
oxo, CF₃, CHF₂, CH₂F, methyl, methoxy, ethyl, ethoxy, CH₂CF₃, CH₂CHF₂, propyl,
prooxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxy, cyclobutyl, isobutoxy, tert-
butoxy, isobutyl, sec-buty, tert-buty, cyclopentyl, cyclohexyl, Ci₆alkylamino-, C₁-
dsalkylamino, Ci₆thioalkoxyl tetrahydropyranyl, tetrahydropyrrollyl or oxetan-3yl.

25. The compound according Claim 24, or a stereoisomer or pharmaceutically
acceptable salt thereof, wherein each of R⁸, R¹°, R¹¹ and R², independently, is H.
26. The compound according any one of Claims 24 and 25, or a stereoisomer or
pharmaceutically acceptable salt thereof, wherein R³ is CH₃, CH₂F or CHF₂.
27. The compound according to any one of Claims 24-26, or a stereoisomer or
pharmacologically acceptable salt thereof, wherein R³ is CHF₂ or CHF₂.
28. The compound according to any one of Claims 24-27, or a stereoisomer or
pharmacologically acceptable salt thereof, wherein R³ is CH₂F.
29. The compound according to any one of Claims 24-27, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein \( R^3 \) is \( \text{CHF}_2 \).

30. The compound according to any one of Claims 24-29, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein 
   \( A^5 \) is \( \text{CH}, \text{CF}, \text{CH}_3 \) or \( \text{N} \);
   \( A^6 \) is \( \text{CH} \); and
   \( A^8 \) is \( \text{CH} \).

31. The compound according to any one of Claims 24-30, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein 
   \( A^4 \) is \( \text{CF} \);
   \( A^5 \) is \( \text{CH}, \text{CF} \) or \( \text{N} \);
   \( A^6 \) is \( \text{CH} \); and
   \( A^8 \) is \( \text{CH} \).

32. The compound according to any one of Claims 24-30, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein 
   \( A^4 \) is \( \text{CCl} \);
   \( A^5 \) is \( \text{CH}, \text{CF} \) or \( \text{N} \);
   \( A^6 \) is \( \text{CH} \); and
   \( A^8 \) is \( \text{CH} \).

33. The compound according to any one of Claims 24-32, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein
   \( R^9 \) is a ring selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrazolyl, pyrazolo[3,4-c]pyridinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl or thienyl, wherein the ring is optionally substituted with 1-5 substituents of \( R^{10} \); and
   each \( R^{10} \), independently, is halo, haloalkyl, \( \text{CN}, \text{OH} \), \( \text{NO}_2 \), \( \text{NH}_2 \), \( \text{SF}_3 \), acetyl, \( -\text{C}(\text{=O})\text{NHCH}_3 \), oxo, cyclopropylmethoxy, 2-butylnoxyl, \( \text{Cl}_n\text{alkyl} \), \( \text{C}_2\text{alkenyl} \), \( \text{C}_3\text{alkynyl} \), \( \text{C}_4\text{cycloalkyl} \), \( \text{C}_6\text{alkylamino} \), \( \text{C}_6\text{dialkylamino} \), \( \text{C}_6\text{alkoxyl} \), \( \text{C}_6\text{thioalkoxyl} \), morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolyl, pyrrolidinyl, tetrahydropyrrolyl, piperazinyl, oxetan-3-y1, imidazo-pyridinyl or dioxyol, wherein each of the cyclopropylmethoxy, 2-butylnoxyl, \( \text{Cl}_n\text{alkyl} \), \( \text{C}_2\text{alkenyl} \), \( \text{C}_2\text{alkynyl} \), \( \text{C}_3\text{cycloalkyl} \), \( \text{C}_6\text{alkylamino} \), \( \text{C}_6\text{dialkylamino} \), \( \text{C}_6\text{alkoxyl} \), \( \text{C}_6\text{thioalkoxyl} \), morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolidinyl, oxetan-3-y1 or dioxyol,
is optionally substituted independently with 1-5 substituents of F, Cl, CN, NO₂, NH₂, OH, oxo, CF₃, CHF₂, CH₂F, methyl, methoxy, ethyl, ethoxy, CH₂CF₃, CH₂CHF₂, propyl, proproxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxy, cyclobutyl, isobutyl, tert-butoxy, isobutyl, sec-buty1, tert-buty1, cyclopentyl, cyclohexyl, C₃₋₆ alkylamino-, C₃₋₆ dialkylamino, C₃₋₆ thioalkoxy tetrahydropyranyl, tetrahydropryrolyl or oxetan-3yl.

34. The compound according to any one of Claims 24-32, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R⁹ is a ring selected from pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrazolyl, pyrazolo[3,4-c]pyridinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl or thienyl, wherein the ring is optionally substituted with 1-5 substituents of R₁⁰.

35. The compound according to any one of Claims 24-34 or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R⁹ is

![Chemical structure]

; and

each R₁⁰, independently, is H, F, Cl, Br, CF₃, CHF₂, CH₂F, CN, OH, -C(0)NHCH₃, cyclopropylmethoxy, 2-propynyloxy, 2-butylnyloxy, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, C₁₋₆ alkoxyl or C₁₋₆ thioalkoxyl, wherein each of the cyclopropylmethoxy, 2-propynyloxy, 2-butylnyloxy, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, C₁₋₆ alkoxyl and C₁₋₆ thioalkoxyl is optionally substituted independently with 1-5 substituents of F, Cl, CN, NO₂, NH₂, OH, oxo, CF₃, CHF₂, CH₂F, methyl, methoxy, ethyl, ethoxy, CH₂CF₃, CH₂CHF₂, propyl, proproxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxy, cyclobutyl, isobutyl, tert-butoxy, isobutyl, sec-buty1, tert-buty1, C₁₋₆ alkylamino-, C₁₋₆ dialkylamino, C₁₋₆ thioalkoxyl, oxazolyl or thiazolyl.

36. The compound according to any one of Claims 24-35, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R¹ is CHF₂; and R⁹ is
each $R^{10}$, independently, is H, F, Cl, Br, CH$_3$, CHF$_2$, CH$_2$F, CN, 2-propynoxy, 2-butynoxy or Ci$_2$alkoxyl, wherein the Ci$_2$alkoxyl is optionally substituted independently with 1-5 substituents of F, Cl, methyl, methoxy, ethyl, ethoxy, oxazolyl or thiazolyl.

37. The compound according to any one of Claims 24-35, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein $R^3$ is CH$_2$F; and $R^9$ is

$$
\begin{array}{c}
\text{N} \\
\text{R}^{10} \\
\text{R}^{10}
\end{array}
$$

; and

each $R^{10}$, independently, is H, F, Cl, Br, CH$_3$, CHF$_2$, CH$_2$F, CN, 2-propynoxy, 2-butynoxy or Ci$_2$alkoxyl, wherein the Ci$_2$alkoxyl is optionally substituted independently with 1-5 substituents of F, Cl, methyl, methoxy, ethyl, ethoxy, oxazolyl or thiazolyl.

38. The compound according to any one of Claims 24-35, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein $R^3$ is CHF$_2$; and $R^9$ is

$$
\begin{array}{c}
\text{N} \\
\text{R}^{10} \\
\text{R}^{10}
\end{array}
$$

; and

each $R^{10}$, independently, is H, F, Cl, Br, CH$_3$, CHF$_2$, CH$_2$F, CN, 2-propynoxy, 2-butynoxy or Ci$_2$alkoxyl, wherein the Ci$_2$alkoxyl is optionally substituted independently with 1-5 substituents of F, Cl, methyl, methoxy, ethyl, ethoxy, oxazolyl or thiazolyl.

39. The compound according to any one of Claims 24-35, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein $R^3$ is CH$_2$F; and $R^9$ is

$$
\begin{array}{c}
\text{N} \\
\text{R}^{10} \\
\text{R}^{10}
\end{array}
$$

; and

each $R^{10}$, independently, is H, F, Cl, Br, CH$_3$, CHF$_2$, CH$_2$F, CN, 2-propynoxy, 2-butynoxy or Ci$_2$alkoxyl, wherein the Ci$_2$alkoxyl is optionally substituted
independently with 1-5 substituents of F, Cl, methyl, methoxy, ethyl, ethoxy, oxazolyl or thiazolyl.

40. The compound according to any one of Claims 1-11, 13-17 and 19-20, or a stereoisomer, tautomer, hydrate, solvate or pharmaceutically acceptable salt thereof, having a Formula II-B:

\[
\text{II-B}
\]

wherein

10

\[ A^4 \text{ is } CR^4, \text{ wherein } R^4 \text{ is } H, \text{ F or Cl;} \]
\[ A^5 \text{ is } CR^5 \text{ or N, wherein } R^5 \text{ is } H, \text{ F or CH}_3; \]
\[ A^6 \text{ is } \text{CH;} \]
\[ A^8 \text{ is } CR^8 \text{ or N, wherein } R^8 \text{ is } H \text{ or F,} \]

provided that no more than one of \( A^3 \) and \( A^8 \) is N;

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each of \( R^4 \) and \( R^9 \), independently, is \( H \) or \( F \);

each of \( R^1 \) and \( R^2 \), independently, is \( H \) or \( F \);

\[ R^3 \text{ is } \text{CH}_3, \text{ CF}_3, \text{CH}_2F \text{ or CHF}_2; \]

\[ R^9 \text{ is a fully unsaturated 5- or 6-membered monocyclic or 8-, 9- or 10-membered bicyclic ring formed of carbon atoms, said ring optionally including 1-4 heteroatoms if monocyclic or 1-5 heteroatoms if bicyclic, said heteroatoms selected from O, N or S, wherein the ring is optionally substituted, independently, with 1-5 substituents of } R^{10}; \]

and each \( R^{10} \), independently, is \( H \), halo, haloalkyl, CN, OH, NO\(_2\), NH\(_2\), SF\(_3\), acetyl, -C(0)NHCH\(_3\), oxo, cyclopropylmethoxy, 2-butynylxy, Cl\(_{4}\)alkyl, C\(_{2}\)-alkenyl, C\(_{2}\)-alkynyl, C\(_{3}\)-Cycloalkyl, Cl\(_{4}\)alkylamino-, Cl\(_{4}\)dialkylamino-, Cl\(_{4}\)alkoxyl, Cl\(_{4}\)thioalkoxyl, morpholinyl, pyrazolyl, isoaxazolyl, dihydropyranyl, pyrrolyl, pyrrolidinyl, tetrahydropryrol, piperaziny, oxetan-3-yl, imidazo-pyridinyl or dioxolyl, wherein each of the cyclopropylmethoxy, 2-butynlyoxy, Cl\(_{4}\)alkyl, C\(_{2}\)-alkenyl, C\(_{2}\)-alkynyl, C\(_{3}\)-Cycloalkyl, Cl\(_{4}\)alkylamino-, Cl\(_{4}\)dialkylamino-, Cl\(_{4}\)alkoxyl, Cl\(_{4}\)thioalkoxyl, morpholinyl, pyrazolyl, isoaxazolyl, dihydropyranyl, pyrrolidinyl, oxetan-3-yl or dioxolyl,
is optionally substituted independently with 1-5 substituents of F, Cl, CN, NO₂, NH₂, OH, oxo, CF₃, CHF₂, CH₂F, methyl, methoxy, ethyl, ethoxy, CH₂CF₃, CH₂CHF₂, propyl, propoxy, isopropyl, isoproxy, cyclopropyl, butyl, butoxy, cyclobutyl, isobutoxy, tert-butoxy, isobutyl, sec-butyl, tert-butyl, cyclopentyl, cyclohexyl, C₃alkylamino-, C₃dialkylamino, C₃thioalkoxy tetrahydropyranyl, tetrahydropyrrolyl or oxetan-3yl; and each W, independently, is CH, CF, CC1, CCH₃ or N.

41. The compound according Claim 40, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each of R¹, R², R³ and R⁴, independently, is H.

42. The compound according any one of Claims 40 and 41, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R³ is CH₃, CH₂F or CHF₂.

43. The compound according to any one of Claims 40-42, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R³ is CH₂F or CHF₂.

44. The compound according to any one of Claims 40-43, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R³ is CH₂F.

45. The compound according to any one of Claims 40-43, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R³ is CHF₂.

46. The compound according to any one of Claims 40-45, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein A₄ is CF or CCl₁;

A⁵ is CH, CF, CH₃ or N;
A⁶ is CH; and
A⁸ is CH.

47. The compound according to any one of Claims 40-46, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein A₄ is CF;

A⁵ is CH, CF or N;
A⁶ is CH; and
A⁸ is CH.

48. The compound according to any one of Claims 40-46, or a stereoisomer or
pharmaceutically acceptable salt thereof, wherein $A^4$ is CC1;
$A^5$ is CH or CF;
$A^6$ is CH; and $A^8$ is CH.

49. The compound according to any one of Claims 40-48 or a stereoisomer or pharmaceutically acceptable salt thereof, wherein

$$
\begin{align*}
\text{is} & \\
\end{align*}
$$

10 each $R^{10}$, independently, is H, F, Cl, Br, CH$_3$, CHF$_2$, CH$_2$F, CN, 2-propynoxy, 2-butylnoxy or C$^\text{alkoxyl}$, wherein the C$^\text{alkoxyl}$ is optionally substituted independently with 1-5 substituents of F, Cl, methyl, methoxy, ethyl, ethoxy, oxazolyl or thiazolyl.

50. The compound of Claim 1, or a stereoisomer or pharmaceutically acceptable salt thereof, selected from

$$
\begin{align*}
\end{align*}
$$
51. The compound of Claim 1, or a tautomer or pharmaceutically acceptable salt thereof, selected from:

- N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-3-methylpicolinamide;
- N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-cyano-3-methylpicolinamide;
- N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-chloro-5-cyanopicolinamide;
- N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-chloro-5-methoxypicolinamide;
- N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3,5-dichloropicolinamide;
- N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-bromopicolinamide;
N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloropicolinamide;
N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-cyanopicolinamide;
N-(3-((1R,5S,6S)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-2,4-difluorophenyl)-5-methoxylicolinamide;
N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-cyanopicolinamide;
N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(prop-2-yn-1-yloxy)pyrazine-2-carboxamide trifluoroacetate;
N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-(oxazol-4-ylmethoxy)pyrazine-2-carboxamide;
N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-cryptropicolinamide;
N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloropicolinamide;
N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-cyano-3-methylpicolinamide;
N-(3-((1R,5S,6R)-3-amino-5-(difluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-cyano-3-methylpicolinamide;
A-1813-WO-PCT

N-(3-((1R,5S,6R)-3-benzamido-5-methyl-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-methoxypyrazine-2-carboxamide; and
N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-2-oxa-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-chlorophenyl)-5-cyano-3-(methoxymethyl)picolinamide.

52. A pharmaceutical composition comprising a compound according to any of Claims 1-51 and a pharmaceutically acceptable excipient.

53. Use of a compound according to any one of Claims 1-51 for reducing beta amyloid peptide levels in the cerebral spinal fluid of a subject.

54. Use of a compound according to any one of Claims 1-51 for treating Alzheimer's disease, cognitive impairment or a combination thereof in a subject.

55. Use of a compound according to any one of Claims 1-51 for the treatment of a neurological disorder selected from the group consisting of mild cognitive impairment, Down's syndrome, Hereditary cerebral hemorrhage with dutch-type amyloidosis, cerebral amyloid angiopathy, degenerative dementia, dementia associated with Parkinson's disease, dementia associated with supranuclear palsy, dementia associated with cortical basal degeneration, diffuse lewy body type of Alzheimer's disease or a combination thereof in a subject.

56. Use of a compound according to any one of Claims 1-51 for the reduction of formation of plaque on the brain of a subject.

57. A process for preparing a compound of Formula I according to Claim 1, the process comprising the step of reacting a protected compound 20
wherein each $R^1$ and each $R^2, R^3, A^4, A^5, A^6$ and $A^8$ of compound 20 are as defined in claim 1, with a compound having the structure or $R^9-C(=O)OH$ in the presence of an acid activating agent or $R^9-CI$ in the presence of a base, wherein $R^9$ is as defined in claim 1 to prepare the compound according to claim 1.

58. A process for preparing a compound of Formula I-A according to any one of Claims 1-20, the process comprising the step of reacting a compound 20

wherein each $R^1$ and each $R^2, R^3, A^4, A^5, A^6$ and $A^8$ of compound 20 are as defined in each of claims 1-20, with a compound having the structure $R^9-COOH$, wherein $R^9$ is as defined in each of claims 1-20 to prepare the compound according to any one of claims 1-20.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/14 C07D413/10 C07D413/12 C07D417/12 C07D417/14
C07D471/04 C07D265/12 C07D491/048 A61P25/00 A61K31/536

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, EMBASE, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>EP 2 511 268 A1 (SHIONOGI &amp; CO [JP]) 17 October 2012 (2012-10-17) claims 1, 11, 13; tables 1-3, 1-4</td>
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X See patent family annex.

Date of the actual completion of the international search
5 May 2014

Date of mailing of the international search report
13/05/2014

Name and mailing address of the ISA/
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016

Authorized officer
Moriggi, J
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