Compounds are useful in the treatment of cancer and other diseases wherein mTOR is deregulated.

The present invention provides Pyrazolopyrimidine Compounds of Formula (I): (I) wherein L, T, Z, U, V, W, R^6, R^7, R^8, and m are as defined herein, and pharmaceutically acceptable salts of such Pyrazolopyrimidine Compounds. The Pyrazolopyrimidine Compounds are useful in the treatment of cancer and other diseases or disorders wherein mTOR is deregulated.

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— as to applicant’s entitlement to apply for and be granted a patent (Rule 4.17(II))
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This invention is directed to certain pyrazolo[1,5-a]pyrimidine compounds of Formula (I) as inhibitors of mammalian Target Of Rapamycin (mTOR) kinase, which is also known as FRAP, RAFT, RAPT or SEP. The compounds are useful in the treatment of cancer and other disorders where mTOR is deregulated.

BACKGROUND OF THE INVENTION

The mammalian target of rapamycin (mTOR) is a central regulator of cell growth and proliferation and plays a gatekeeper role in the control of cell cycle progression. The mTOR signaling pathway, which integrates both extracellular and intracellular signals, is activated in certain cellular processes such as tumor formation, angiogenesis, insulin resistance, adipogenesis, and T-lymphocyte activation. In addition, the mTOR signaling pathway is deregulated in diseases such as cancer and type 2 diabetes. See Laplante et al., J. Cell Science 122, pp 3589-3593 (2009).

mTOR mediates mitogenic signals from PI3K/AKT through to the downstream targets S6K1 (ribosomal S6 kinase 1), 4E-BP1 (eukaryotic translation initiation factor 4E-binding protein) and AKT. Recently, it has been shown that mTOR exists in two complexes. Raptor-mTOR complex (mTORC1) is a rapamycin-sensitive complex that phosphorylates S6K1 and 4E-BP1. Rictor-mTOR complex (mTORC2) is a rapamycin-insensitive complex that phosphorylates AKT at Ser473. Although the precise mechanism by which rapamycin inhibits mTOR function is not well understood, rapamycin partially inhibits mTOR function through mTORC1. Since mTORC2 is involved in the regulation of cell survival, metabolism, proliferation, and cytoskeletal organization in a rapamycin-independent manner, complete inhibition of mTOR function through inhibition of both mTORC1 and mTORC2 may lead to a broader spectrum antitumor activity in the treatment of cancer or better efficacy.
addition, inhibition of both mTORC1 and mTORC2 may lead to better efficacy in treating other diseases than through inhibition of mTORC1 alone.

There exists a need in the art for small-molecule compounds having desirable physicochemical properties that are useful for treating cancer and other disorders associated with deregulated mTOR activity. Specifically, there exists a need for small molecule inhibitors of mTOR kinase that block signaling through mTORC1 and mTORC2 for treating cancer and other disorders.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides compounds of Formula (I) (herein referred to as the “Pyrazolopyrimidine Compounds” or “compounds of Formula (I)“):

\[
\begin{array}{c}
\text{R}^8 \backslash T \backslash L \backslash N \backslash U \backslash N \backslash N \\
\text{R}^6 \backslash N \backslash \text{NH} \\
\text{R} \backslash \text{NH}
\end{array}
\]

and pharmaceutically acceptable salts thereof.

In another aspect, the invention provides a pharmaceutical composition comprising a Pyrazolopyrimidine Compound, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.

In yet another aspect, the invention provides a method of treating a cancer, comprising administering a therapeutically effective amount of a Pyrazolopyrimidine Compound or a pharmaceutically acceptable salt thereof to a patient, e.g., a human patient, in need thereof.

In yet another aspect, the invention provides a method of treating a cancer, comprising administering an amount of a Pyrazolopyrimidine Compound or a pharmaceutically acceptable salt thereof, and an amount of one or more of additional anticancer drugs to a patient in need thereof.
In another aspect, the invention provides a method of treating a disease or disorder associated with deregulated mTOR activity, comprising administering a therapeutically effective amount of a Pyrazolopyrimidine Compound or a pharmaceutically acceptable salt thereof to a patient, e.g., a human patient, in need thereof.

**DETAILED DESCRIPTION OF THE INVENTION**

The present invention provides Pyrazolopyrimidine Compounds, pharmaceutical compositions comprising a Pyrazolopyrimidine Compound, and methods of using the Pyrazolopyrimidine Compounds for treating cancer in a patient. In addition, the present invention provides methods of using the Pyrazolopyrimidine Compounds for treating a disease or disorder associated with deregulated mTOR activity in a patient.

**Definitions and Abbreviations**

As used above, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

“Patient” includes both human and animals.

“Mammal” means humans and other mammalian animals.

“Alkyl” means an aliphatic hydrocarbon group which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkyl chain. “Lower alkyl” means a group having about 1 to about 6 carbon atoms in the chain which may be straight or branched. “Alkyl” may be unsubstituted or optionally substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, aryl, cycloalkyl, cyano, hydroxy, alkoxy, alkylthio, amino, oxime (e.g., =N-OH), -NH(alkyl), -NH(cycloalkyl), -N(alkyl)₂, -O-C(0)-alkyl, -O-C(0)-aryl, -0-C(0)-cycloalkyl, -SF₃, carboxy and -C(0)0-alkyl. Non-limiting examples of
suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl and t-butyl. The term "C₁-C₆ alkyl" refers to an alkyl group having from 1 to 6 carbon atoms.

"Alkenyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkenyl chain. "Lower alkenyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. "Alkenyl" may be unsubstituted or optionally substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, aryl, cycloalkyl, cyano, alkoxy and -S(alkyl). Non-limiting examples of suitable alkenyl groups include ethenyl, propenyl, n-butenyl, 3-methylbut-2-enyl, n-pentenyl, octenyl and decenyl.

"Alkylene" means a difunctional group obtained by removal of a hydrogen atom from an alkyl group that is defined above. Non-limiting examples of alkylene include methylene, ethylene and propylene. In one embodiment, an alkylene group has from 1 to 6 carbon atoms. In one embodiment, an alkylene is branched. In another embodiment, the alkylene is linear.

"Alkynyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butylnyl and 3-methylbutynyl. The "alkynyl" may be unsubstituted or optionally substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of aryl and cycloalkyl.

"Aryl" means an aromatic monocyclic or multicyclic ring system comprising about 6 to about 14 carbon atoms, preferably about 6 to about 10 carbon atoms.
The aryl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Non-limiting examples of suitable aryl groups include phenyl and naphthyl.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Preferred heteroaryls contain about 5 to about 6 ring atoms. The "heteroaryl" can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The prefix "aza", "oxa" or "thia" before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur atom respectively, is present as a ring atom. A nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide (indicated herein as "N(O)"). "Heteroaryl" may also include a heteroaryl as defined above fused to an aryl as defined above. Non-limiting examples of suitable heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridine (including N-substituted pyridines), isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, oxindolyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like. The term "heteroaryl" also refers to partially saturated heteroaryl moieties such as, for example, tetrahydroisquinolinyl, tetrahydroquinolinyl and the like. In describing the heteroatoms contained in the heteroaryl group the expressions, "having one to x heteroatoms selected from the group of N, O, and S" or "having one to x heteroatoms selected from the group of N, N(O), O, and S" (wherein x is an a specified integer), for example, mean that each heteroatom in the specified heteroaryl is independently selected from the specified selection of heteroatoms.

"Aralky1" or "aryalkyl" means an aryl-alkyl group in which the aryl and alkyl are as previously described. Preferred aralkyls comprise a lower alkyl group. Non-limiting examples of suitable aralkyl groups include benzyl, 2-phenethyl and naphthalenylmethyl. The bond to the parent moiety is through the alkyl.
"Alkylaryl" means an alkyl-aryl- group in which the alkyl and aryl are as previously described. Preferred alkylaryls comprise a lower alkyl group. A non-limiting example of a suitable alkylaryl group is tolyl. The bond to the parent moiety is through the aryl.

"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 7 ring atoms. The cycloalkyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, cycloheptyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalinyl, norbornyl, adamantyl and the like.

"Cycloalkylalkyl" means a cycloalkyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable cycloalkylalkyls include cyclohexylmethyl, adamantylmethyl and the like.

"Cycloalkenyl" means a non-aromatic mono or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms which ring system contains at least one carbon-carbon double bond. Preferred cycloalkenyl rings contain about 5 to about 7 ring atoms. The cycloalkenyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkenyls include cyclopentenyl, cyclohexenyl, cyclohepta-1,3-dienyl, and the like. A non-limiting example of a suitable multicyclic cycloalkenyl is norbornylenyl.

"Cycloalkenylalkyl" means a cycloalkenyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable cycloalkenylalkyls include cyclopentenylmethyl, cyclohexenylmethyl and the like. The halogen means fluorine, chlorine, bromine, or iodine. Preferred halogens are fluorine, chlorine and bromine.

"Haloalkyl" means an alkyl as defined above wherein one or more hydrogen atoms on the alkyl is replaced by a halogen group as defined above. Non-limiting examples of haloalkyl include trifluoromethyl, 2,2,2-trifluoroethyl, and 2-chloropropyl.
"Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different, each being independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, alkylaryl, heteroarylalkenyl, heteroarylalkynyl, alkylheteroaryl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxy carbonyl, aryloxy carbonyl, aralkoxy carbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkythio, arythio, heteroarythio, aralkythio, heteroarylkylthio, cycloalkyl, heterocyclyl, -SF₅, -OSF₅ (for aryl), -O-C(0)-alkyl, -O-C(0)-aryl, -O-C(0)-cycloalkyl, -C(=N-CN)-NH, -C(=N-NH)₂, -C(=NH)-NH(alkyl), oxime (e.g., =N-OH), -NY₁Y₂, -alkyl-NY₁Y₂, -C(0)NY₁Y₂, -SO₂NY₁Y₂ and -S(Ο)NY₁Y₂, wherein Y₁ and Y₂ can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl, and aralkyl. "Ring system substituent" may also mean a single moiety which simultaneously replaces two available hydrogens on two adjacent carbon atoms (one H on each carbon) on a ring system. Examples of such a moiety are methylene dioxy, ethylenedioxy, -C(CH₃)₂⁻ and the like which form moieties such as, for example:

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"Heteroarylalkyl" means a heteroaryl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable heteroaryls include 2-pyridinylmethyl, quinolinylmethyl and the like.

"Heterocyclyl" means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example, nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom. Respectively, is present as a ring atom. Any -NH in a heterocyclyl ring may exist in protected form such as, for example, as an -N(Boc), -N(CBz), -N(Tos) group.
and the like; such protections are also considered part of this invention. The heterocyclyl can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, lactam, lactone, and the like. "Heterocyclyl" also includes heterocyclyl rings as described above wherein =0 replaces two available hydrogens on the same ring carbon atom. An example of such a moiety is pyrrolidone:

\[ \begin{align*}
\text{H} &\quad \text{(defined as above)}
\end{align*} \]

In describing the heteroatoms contained in a specified heterocyclyl group, the expression, "having one to x heteroatoms selected from the group of N, O, and S" (wherein x is an a specified integer), for example, means that each heteroatom in the specified heterocyclyl is independently selected from the specified selection of heteroatoms.

"Heterocyclylalkyl" means a heterocyclyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable heterocyclylalkyls include piperidinylmethyl, piperazinylmethyl and the like.

"Heterocyclenyl" means a non-aromatic monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur atom, alone or in combination, and which contains at least one carbon-carbon double bond or carbon-nitrogen double bond. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclenyl rings contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclenyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The heterocyclenyl can be optionally substituted by one or more ring system substituents, wherein "ring
system substituent" is as defined above. The nitrogen or sulfur atom of the heterocyclenyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable heterocyclenyl groups include 1,2,3,4-tetrahydropyridinyl, 1,2-dihydropyridinyl, 1,4-dihydropyridinyl, 1,2,3,6-tetrahydropyridinyl, 1,4,5,6-tetrahydropyrimidinyl, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolinyl, 2-pyrazolinyl, dihydroimidazolyl, dihydrooxazolyl, dihydrooxadiazolyl, dihydrothiazolyl, 3,4-dihydro-2H-pyranyl, dihydrofuranyl, fluorodihydrofuranyl, 7-oxabicyclo[2.2.1]heptenyl, dihydrothiophenyl, dihydrothiopyranyl, and the like.

"Heterocyclenyl" also includes heterocyclenyl rings as described above wherein =0 replaces two available hydrogens on the same ring carbon atom. An example of such a moiety is pyrrolidinone:

\[
\text{H} \quad \text{O}
\]

In describing the heteroatoms contained in a specified heterocyclenyl group, the expression, "having one to x heteroatoms selected from the group of N, O, and S" (wherein x is an a specified integer), for example, means that each heteroatom in the specified heterocyclenyl is independently selected from the specified selection of heteroatoms.

"Heterocyclenylalkyl" means a heterocyclenyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core.

It should be noted that in hetero-atom containing ring systems of this invention, there are no hydroxyl groups on carbon atoms adjacent to a N, O or S, as well as there are no N or S groups on carbon adjacent to another heteroatom. Thus, for example, in the ring:

\[
\text{H} \quad \text{O}
\]

there is no -OH attached directly to carbons marked 2 and 5.
It should also be noted that tautomeric forms such as, for example, the moieties:

\[
\begin{array}{c}
\text{NH} \\
\text{N} \\
\text{OH}
\end{array}
\]

are considered equivalent in certain embodiments of this invention.

"Alkynylalkyl" means an alkynyl-alkyl- group in which the alkynyl and alkyl are as previously described. Preferred alkynylalkyls contain a lower alkynyl and a lower alkyl group. The bond to the parent moiety is through the alkyl. Non-limiting examples of suitable alkynylalkyl groups include propargylmethyl.

"Heteroaalkyl" means a heteroaryl-alkyl- group in which the heteroaryl and alkyl are as previously described. Preferred heteroaralkyls contain a lower alkyl group. Non-limiting examples of suitable aralkyi groups include pyridylmethyl, and quinolin-3-ylmethyl. The bond to the parent moiety is through the alkyl.

"Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously defined. Preferred hydroxyalkyls contain a lower alkyl. Non-limiting examples of suitable hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

"Acyl" means an H-C(O)-, alkyl-C(O)- or cycloalkyl-C(O)- group in which the various groups are as previously described. The bond to the parent moiety is through the carbonyl. Preferred acyls contain a lower alkyl. Non-limiting examples of suitable acyl groups include formyl, acetyl and propanoyl.

"Aroyl" means an aryl-C(O)- group in which the aryl group is as previously described. The bond to the parent moiety is through the carbonyl. Non-limiting examples of suitable groups include benzoyl and 1- naphthoyl.

"Alkoxy" means an alkyl-O- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy and n-butoxy. The bond to the parent moiety is through the ether oxygen.

"Aryloxy" means an aryl-O- group in which the aryl group is as previously described. Non-limiting examples of suitable aryloxy groups include phenoxy and naphthoxy. The bond to the parent moiety is through the ether oxygen.

"Aralkyloxy" means an aralkyl-O- group in which the aralkyl group is as previously described. Non-limiting examples of suitable aralkyloxy groups include
benzyloxy and 1- or 2-naphthalenemethoxy. The bond to the parent moiety is through the ether oxygen.

"Alkanoyl" refers to an alkyl-C(O)- group in which the alkyl group is as previously described. Non-limiting examples of alkanoyl groups include methylcarbonyl and ethylcarbonyl. The bond to the parent moiety is through the carbonyl group.

"Alkylthio" means an alkyl-S- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkylthio groups include methylthio and ethylthio. The bond to the parent moiety is through the sulfur.

"Arylthio" means an aryl-S- group in which the aryl group is as previously described. Non-limiting examples of suitable arylthio groups include phenylthio and naphthylthio. The bond to the parent moiety is through the sulfur.

"Aralkylthio" means an aralkyl-S- group in which the aralkyl group is as previously described. A non-limiting example of a suitable aralkylthio group is benzythio. The bond to the parent moiety is through the sulfur.

"Alkoxy carbonyl" means an alkyl-O-C(O)- group. Non-limiting examples of suitable alkoxy carbonyl groups include methoxy carbonyl and ethoxy carbonyl. The bond to the parent moiety is through the carbonyl.

"Aryloxycarbonyl" means an aryl-O-C(O)- group. Non-limiting examples of suitable aryl oxycarbonyl groups include phenoxy carbonyl and naphthoxy carbonyl. The bond to the parent moiety is through the carbonyl.

"Aralkoxycarbonyl" means an aralkyl-O-C(O)- group. Non-limiting example of a suitable aralkoxy carbonyl group is benzyl oxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Alkylsulfonyl" means an alkyl-S(C\textsubscript{2})- group. Preferred groups are those in which the alkyl group is lower alkyl. The bond to the parent moiety is through the sulfonyl.

"Arylsulfonyl" means an aryl-S(0\textsubscript{2})- group. The bond to the parent moiety is through the sulfonyl.

The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents
and/or variables are permissible only if such combinations result in stable compounds. A reference to a "stable compound" or "stable structure" means that the compound is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and to survive formulation into an efficacious therapeutic agent.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

The term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound after being isolated from a synthetic process (e.g., from a reaction mixture), or natural source or combination thereof. Thus, the term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound after being obtained from a purification process or processes described herein or well known to the skilled artisan (e.g., chromatography, recrystallization and the like), in sufficient purity to be characterized by standard analytical techniques described herein or well known to the skilled artisan.

It should also be noted that any carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and Tables herein is assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences. In addition, any one or more of these hydrogen atoms can be deuterium.

When a functional group in a compound is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T. W. Greene et al, Protective Groups in Organic Synthesis (1991), Wiley, New York.

When any variable (e.g., aryl, heterocycle, R², etc.) occurs more than one time in any constituent or in Formula (I), its definition on each occurrence is independent of its definition at every other occurrence.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.
Prodrugs and solvates of the compounds of the invention are also contemplated herein. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) Vol. 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press. The term "prodrug" means a compound (e.g., a drug precursor) that is transformed in vivo to yield a compound of Formula (I) or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms (e.g., by metabolic or chemical processes), such as, for example, through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Prodrugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

For example, if a compound of Formula (I) or a pharmaceutically acceptable salt, hydrate or solvate of the compound contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as, for example, (C₁₋₈alkyl, (C₈₋₁₂alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)ethyl having from 5 to 10 carbon atoms, alkoxy carbonyloxyethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonylamino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C₂-C₃)alkylamino(C₂-C₃)alkyl (such as β-dimethylaminooethyl), carbamoyl-(C₂-C₃)alkyl, N,N-di-(C₁₋₈alkyl)carbamoyl-(C₈₋₁₂alkyl and piperidino-, pyrrolidino- or morpholino(C₂₋₉)alkyl, and the like.

Similarly, if a compound of Formula (I) contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as, for example, (C₈₋₁₂alkanoyloxymethyl, 1-(C₈₋₁₂alkanoyloxymethyl, 1-methyl-1-(C₁₋₈alkanoyloxymethyl, (C₁₋₈alkoxycarbonyloxymethyl, N-(C₁₋₈alkoxycarbonylaminomethyl, succinoyl, (C₁₋₈alkylcarbamoyloxymethyl, N,N-di-(C₁₋₈alkylcarbamoyloxymethyl, and the like.
alkanoyl, a-amino (C1-C4)alkanyl, arylacyl and a-aminoacyl, or a-aminoacyl- a-aminoacyl, where each a-aminoacyl group is independently selected from the naturally occurring L-amino acids, -P(O)(OH)2, -P(O)(O) (C1-C6)alkyl]2 or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate), and the like.

If a compound of Formula (I) incorporates an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as, for example, R-carbonyl, RO-carbonyl, NRR'-carbonyl where R and R' are each independently (C1-C6)alkyl, (C3-C7) cycloalkyl, benzyl, or R-carbonyl is a natural α-aminoacyl or natural α-aminoacyl, —C(OH)C(0)OY where Y1 is H, (C1-C6)alkyl or benzyl, —C(OY)2Y3 wherein Y2 is (C1-C4) alkyl and Y3 is (d-C6)alkyl, carboxy (d-C6)alkyl, amino (C1-C4)alkyl or mono-N— or di-N,N-(CH-C6)alkylaminoalkyl, —C(Y4)Y5 wherein Y4 is H or methyl and Y5 is mono-N— or di-N,N-(CH-C6)alkylamino morpholino, piperidin-1-yl or pyrrolidin-1-yl, and the like.

One or more compounds of the invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. "Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H2O.

One or more compounds of the invention may optionally be converted to a solvate. Preparation of solvates is generally known. Thus, for example, M. Caira et al. J. Pharmaceutical Sci., 93(3), 601-611 (2004) describes the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates, hemisolvate, hydrates and the like are described by E. C. van Tonder et al. AAPS PharmSciTech., 5(1), article 12 (2004); and A. L. Bingham et al. Chem. Commun., 603-604 (2001). A typical, non-limiting, process involves
dissolving the inventive compound in desired amounts of the desired solvent (organic or water or mixtures thereof) at a higher than ambient temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated by standard methods. Analytical techniques such as, for example i. R. spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

"Effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition of the present invention effective in inhibiting the above-noted diseases and thus producing the desired therapeutic, ameliorative, inhibitory or preventative effect.

The compounds of Formula (I) can form salts which are also within the scope of this invention. Reference to a compound of Formula (I) or a Pyrazolopyrimidine Compound herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)" as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of Formula (I) contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein.

Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful. Salts of the compounds of Formula (I) may be formed, for example, by reacting a compound of Formula (I) with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl et al, Camille G. (eds.) Handbook of Pharmaceutical Salts. Properties, Selection and Use. (2002) Zurich: Wiley-VCH; S. Berge et al, Journal of Pharmaceutical Sciences
Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamines, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (e.g., methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g., dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g., decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g., benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Pharmaceutically acceptable esters of the present compounds include the following groups: (1) carboxylic acid esters obtained by esterification of the hydroxy groups, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, acetyl, n-propyl, t-butyl, or n-butyl), alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxyethyl), aryl (for example, phenyl optionally substituted with, for example, halogen, C<sub>1</sub>-alkyl, or C<sub>1</sub>-alkoxy or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyl (for example, methanesulfonyl); (3) amino acid esters (for example, L-valyl or L-isoleucyl); (4) phosphonate esters and (5) mono-, di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a C<sub>1-29</sub> alcohol or reactive derivative thereof, or by a 2,3-di (C<sub>6-24</sub>)acyl glycerol.

The compounds of Formula (I), and salts thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.
The compounds of Formula (I) may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of Formula (I) as well as mixtures thereof, including racemic mixtures, form part of the present invention. In addition, the present invention embraces all geometric and positional isomers. For example, if a compound of Formula (I) incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention. Various stereoisomers are discussed in J. Org. Chem. 35, 2849 (1970).

Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher’s acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Also, some of the compounds of Formula (I) may be atropisomers (e.g., substituted biaryls) and are considered as part of this invention. Enantiomers can also be separated by use of chiral HPLC column.

It is also possible that the compounds of Formula (I) may exist in different tautomeric forms, and all such forms are embraced within the scope of the invention. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates, esters and prodrugs of the compounds as well as the salts, solvates and esters of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention, as are positional isomers (such as, for example, 4-pyridyl and 3-pyridyl). For example, if a compound of Formula (I) incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention. Also, for example, all
keto-enol and imine-enamine forms of the compounds are included in the invention. Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the IUPAC 1974 Recommendations. The use of the terms "salt", "solvate", "ester", "prodrug" and the like, is intended to equally apply to the salt, solvate, ester and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

The present invention also embraces isotopically-labelled compounds of the present invention 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, phosphorus, sulfur, fluorine and chlorine and iodine, such as 2H, 3H, 11C, 12C, 13C, 14C, 15N, 16O, 17O, 18O, 19F, 20F, 31P, 32P, 33S, 34S, 35S, 36S, 38S, 36Cl and 123I, respectively.

Certain isotopically-labelled compounds of Formula (I) (e.g., those labeled with 3H and 14C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., 3H) and carbon-14 (i.e., 14C) isotopes are particularly preferred for their ease of preparation and detectability. Certain isotopically-labelled compounds of Formula (I) can be useful for medical imaging purposes. For instance those compounds labeled with positron-emitting isotopes like 11C or 18F can be useful for application in Positron Emission Tomography (PET) and those labeled with gamma ray emitting isotopes like 123I can be useful for application in Single Photon Emission Computed Tomography (SPECT). Further, substitution of compounds with heavier isotopes such as deuterium (i.e., 2H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances.

Additionally, isotopic substitution of a compound at a site where epimerization occurs may slow or reduce the epimerization process and thereby retain the more active or efficacious form of the compound for a longer period of time. Isotopically labeled compounds of Formula (I), in particular those containing isotopes with longer half
lives (T1/2 > 1 day), can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples herein below, by substituting an appropriate isotopically labeled reagent for a non-isotopically labeled reagent.

Polymorphic forms of the compounds of Formula (I), and of the salts, of the compounds of Formula (I), are intended to be included in the present invention.

The present invention further includes the compounds of Formula (I) in all their isolated forms. For example, the above-identified compounds are intended to encompass all forms of the compounds such as, any solvates, hydrates, stereoisomers, and tautomers thereof.

The following abbreviations are used below and have the following meanings:
BINAP is racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl; CDI is carbonyl dimidazole; CSA is camphorsulfonic acid; DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene; DBN is 1,5-diazabicyclo[4.3.0]non-5-ene; DCC is dicyclohexylcarbodiimide; DCM is dichloromethane; Dibal-H is diisobutylaluminum hydride; DIPEA is N,N-Diisopropylethylamine; DMAP is dimethylaminopyridine; DME is dimethoxyethane; DMF is dimethylformamide; DMPU is N,N,N'-Dimethylpropyleneurea; dppf is diphenylphosphinof errocene; EDCI is 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide; EtOAc is ethyl acetate; FABMS is fast atom bombardment mass spectrometry; HATU is is 0-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate; HOBT is 1-hydroxybenzotriazole; HOOBt is 3-hydroxy-1,2,3-benzotriazin-4(3H)-one; HPLC is high performance liquid chromatography; HRMS is high resolution mass spectrometry; Hunig's base is N,N-disopropylethylamine;

LAH is lithium aluminum hydride; LDA is lithium diisopropylamide; LRMS is low resolution mass spectrometry; m-CPBA is m-chloroperbenzoic acid; MeOH is methanol; NaBH(OAc)₃ is sodium triacetoxyborohydride; NaHMDS is sodium hexamethyldisilazane; NH₂OAc is ammonium acetate; p-TsOH is p-toluenesulfonic acid; p-TsCl is p-toluenesulfonyl chloride; PPTS is pyridinium p-toluenesulfonate; PYBROP is bromotripyrrolidinophosphonium hexafluorophosphate; RT is room temperature; SEM is p-(trimethylsilyl)ethoxy)methyl; SEMCl is β-(trimethylsilyl)ethoxy)methyl chloride; THF is tetrahydrofuran; TLC is thin-layer chromatography; TMAD is N,N,N',N'-tetramethyldiazodicarboxamide; Tr is triphenylmethyl; and Tris is tris(hydroxymethyl)aminomethane.
Compounds of Formula (I)

In one aspect, the present invention provides compounds of Formula (I)

5

or a pharmaceutically acceptable salt thereof, wherein

U is N, CH, or C(R^1);

R^1 is selected from the group consisting of

C_1-C_6 alkyl, hydroxy, -OR, -NR^2(R^3), -N(R^4)-C(O)-R^5, C_3-C_8 cycloalkyl, C_6-C_10 mono or bicyclic aryl, -S(O)_2-R^6, -S(O)-N(R^7)-S(O)-R^8, -S(O)-N(R^7)-S(O)_2-R^9, -S(O)-N(R^7)-S(O)-N(R^8)-S(O)-R^9, -O-C(O)-OR, -O-C(O)-N(R^7)-R^8, -O-C(O)-N(R^7)-S(O)-R^8, -O-C(O)-N(R^7)-S(O)_2-R^9, -O-C(O)-N(R^7)-S(O)-N(R^8)-S(O)-R^9;

C_5-C_10 mono or bicyclic heteroaryl and having one to three heteroatoms selected from the group consisting of N, O, and S;

R^1 and R^1 are independently selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, and phenyl;

R^1 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_8 cycloalkyl, and phenyl;

* a, b, c, and d are independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_10 mono or
bicyclic aryl, 3- to 8-membered monocyclic heterocyclyl, and C5-
C10 mono or bicyclic heteroaryl;
L and Z are bonded to any two carbon atoms of the ring comprising U and are independently selected from the group consisting of CH₂, C(H)(R¹), C(R²)(R³), N(R¹),

5 C(O), O, S, S(O), and S(O)₂;

T is absent such that L is bonded directly to Z, or T is selected from the group consisting of C(O), O, S, N(R¹), S(O), S(O)₂, and C₁-C₄ alkylene, wherein said alkylene of T is unsubstituted or substituted with 1 to 2 moieties, which moieties are independently selected from the group consisting of C₁-C₃ alkyl, halo, hydroxy, C₁-C₃ alkoxy, amino, C₃-C₅ alkylamino and C₁-C₃ dialkylamino;

10 m is 0 or 1;
n is independently 0, 1, 2, 3 or 4;
R¹ and R² are independently selected from the group consisting of H, C₁-C₃ alkyl, halo, hydroxy, C₁-C₃ alkoxy, amino, C₁-C₃ alkylamino and C₁-C₃ dialkylamino;

15 W is absent, or W is selected from the group consisting of C(O), C(N), S(O), S(O)₂, C₁-C₄ alkylene, C₃-C₆ cycloalkyl, phenyl, 5- to 6-membered heteroaryl, and 3-
to 8-membered heterocyclyl;

V is absent, or V is selected from the group consisting of C(O), O, S, N(H), N(C₁-C₃ alkyl), N(C₁-C₅ alkyl), N(C₃-C₆ cycloalkyl), S(O), S(O)₂, and C₁-C₄ alkylene;

20 or W and V together form a C₃-C₆ cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3 to 8-membered heterocyclyl ring;

R³ is selected from the group consisting of

(i) CN, C₁-C₆ alkyl or C₃-C₁₀ cycloalkyl, wherein said alkyl or cycloalkyl of R³ is unsubstituted or substituted with one to three moieties independently selected from the group consisting of hydroxy, C₁-C₆ alkoxy, halo, C₁-C₆ haloalkyl, O-C₁-C₆ haloalkyl, -NR³R⁴, -OR⁴, carboxy, 5- to 6-
membered heteroaryl, -SO₂H, C₁-C₆ alkyl-C(0)-NH-, C₁-C₆ alkyl-SO₂-NH-, and C₁-C₆ alkyl-SO-NH₂;

(ii) 3- to 8-membered heterocyclyl wherein said heterocyclyl of R³ is unsubstituted or substituted with one to three moieties independently selected from the group consisting of halo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, O-
C₁-C₆ haloalkyl, C₁-C₆ alkoxy, cyano, hydroxy, -(CR⁵R⁶)₁OR⁶, -
(CR^R_1)_m NR^R_1 R_2, -(CR^R_1)_m NR^R_1 C(0)R_3, -(CR^R_1)_m C(0)NR^R_1 R_3, amino, C_1-C_6 alkylamino, and C_1-C_6 dialkylamino;  

(iii) C_6-C_{10} aryl or 5- to 10-membered heteroaryl, wherein said aryl or heteroaryl of R^R is unsubstituted or is substituted with one to three moieties independently selected from the group consisting of 5- to 10-membered heterocyclyl, halo, C_1-C_6 haloalkyI, O-C_1-C_6 haloalkyI, C_1-C_6 alkyI, C_1-C_6 alkoxy, cyano, hydroxy, -(CR^R_1)_m OR_4, -(CR^R_1)_m NR^R_1 R_4, -(CR^R_1)_m NR^R_1 C(0)R_4, -(CR^R_1)_m C(0)NR^R_1 R_4, amino, C_1-C_6 alkylamino, and C_1-C_6 dialkylamino,

wherein said heterocyclyl is optionally substituted with one to three moieties independently selected from the group consisting of OH, NH_2 and C_1-C_6 alkoxy; and

(iv) -OH, -OR_5, -OR^R_5 OR_5, -NR_5=OR_5, -NR_5=NR^R_5 R_5, -C(0)NR^R_5 R_5, -NR^R_5 C(0)R_5, C(n-R^R_5)NR^R_5 R_5;  

R^R and R^F are independently selected from H, halogen, OH, CN, C_1-C_6 alkoxy, C_1-C_6 haloalkyl and C_1-C_6 alkyI, wherein the alkyI is optionally substituted with one to three moieties selected from OH, NH_2, C_1-C_3 alkyIamino, and C_1-C_3 dialkylamino and C_1-C_3 alkoxy;

R^3 is selected from the group consisting of H, C_1-C_{10} alkyI, C_1-C_{10} alkenyl, C_1-C_6 alkyI, halo-C_1-C_{10} alkyI, -CF_3, -C(0)R_6, C_1-C_2 arlyI, C_2-C_6 cycloalkyI, C_3-C_8 cycloalkyI, 5- to 10-membered heteroaryl, 5- to 10-membered heterocyclyl, 5- to 10-membered heterocyclyl, C_6-C_10 aryI-C_6 alkyI, C_8-C_10 cycloalkyI-C_6 alkyI, 5- to 10-membered heteroaryl, 5- to 10-membered heterocyclyl and 5- to 10-membered heterocyclyl, wherein each of said alkyI, alkenyl, alkynyl, aryl, cycloalkyI, cycloalkenyl, heteroaryl, heterocyclyl, heterocyclyl, arlyI, cycloalkyI, cycloalkyI, cycloalkenyl, heterocyclyl and heterocyclyl is unsubstituted or substituted with one to three moieties which can be the same or different, each moiety being selected from the group consisting of halogen, C_1-C_{10} alkyI, C_1-C_6 cycloalkyI, C_3-C_10 cycloalkyI, -CF_3, -CN, -CN-R_{10}, C(0)OH, -(CR^R_7)C(0)OH, -(CR^R_7)OR_8, -(CR^R_7)OR_8, -(CR^R_7)C(0)R_8, -(CR^R_7)NR^R_9 R_9, -(CR^R_7)NR^R_9 R_9, -(CR^R_7)NR^R_9 C(0)R_9, -(CR^R_7)C(0)OR_9, -(CR^R_7)C(0)R_9, O-
halod-Csalkyl, -(CR^R_n)C(=N)NR^R_9, -(CR^R_n)C(O)NR^R_9, -(CR^R_n)C(0)OR^9, 
(CR^R_n)S(O)(CR^R_n)_2R^9, -(CR^R_n)NR^0C(O)R^9, -(CR^R_n)NR^0C(O)OR^9, 
(CR^R_n)NR^5C(O)(CR^R_n)_2R^9, -(CR^R_n)S(O)(CR^R_n)_2R^9, -(CR^R_n)S(O)(CR^R_n)_2C(O)R^9, 
(CR^R_n)NR^5S(O)(CR^R_n)_2R^9, -(CR^R_n)S(O)(CR^R_n)_2R^9, Ce-C^6aryl, 5- to 10-membered 
thecyclyl, 5- to 10-membered heterocyclylalkyl, 5- to 10-membered heteroarylalkyl, and 5- to 10-membered heterocyclcyclalkyl. 
wherein each of said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, 
heterocyclcyclalkyl, heterocyclylalkyl, and heterocyclcyclalkyl is unsubstituted or substituted with one to 
five moieties, which can be the same or different, each moiety being selected from the 
group consisting of halogen, C^7-alkyl, C^3-cycloalkyl, -CF3, -CN, -C(0)OH, 
-(CR^R_n)C(0)OH, -OCF3, -O-halod-C^6alkyl, -halod-C^6alkyl, d-C^6hydroxyalkyl, 
-(CR^R_n)OR^9, -(CR^R_n)C(0)OR^9, -(CR^R_n)NR^0R^9, -(CR^R_n)S(O)(CR^R_n)_2C(O)R^9, 
-(CR^R_n)NR^5S(O)(CR^R_n)_2R^9, -(CR^R_n)S(O)(CR^R_n)_2R^9, and -(CR^R_n)S(O)(CR^R_n)_2R^9;

R^6 is selected from the group consisting of H, -CHR^8O^8R^9, -(CR^R_n)OR^10, 
-(CR^R_n)S(O)(CR^R_n)_2R^9, -(CR^R_n)S(O)(CR^R_n)_2R^9, -(CR^R_n)S(O)(CR^R_n)_2R^9, 
(CR^R_n)C(0)d-C^6alkyl, -(CR^R_n)C(0)NR^0R^9, -(CR^R_n)C(0)OR^10, 
-(CR^R_n)R^9S(O)(CR^R_n)_2R^9, -(CR^R_n)NR^0C(O)R^9, -(CR^R_n)NR^0S(O)(CR^R_n)_2R^9, C^6-alkyl, 
halo-d-C^6alkyl, d-C^6alkoxy, halogen, hydroxyl, amino, -(CR^R_n)CN, 5- to 10-membered 
thecyclyl, 5- to 10-membered heterocyclyl, d-C^6cycloalkyl and C^6- 
C^6alkyl, wherein each of said heteroaryl, heterocyclyl, cycloalkyl and aryl can be 
unsubstituted or substituted with one to three moieties selected from the group 
consisting of d-dalkyl, d-dalkenyl, d-C^3alkyl, d-dalkoxy, d-dialkylamino, 
d-dialkylamino, amino, halo or OH;

R^7 is selected from the group consisting of H, OH, OR^10, d-C^6alkyl, C^6-
C^6d-alkyl, C^6d-C^6alkyl, 5- to 10-membered heteroaryl, 5- to 10-membered 
heteroaryl-C^6alkyl, C^6-C^6cycloalkyl, d-C^6cycloalkyl-C^6alkyl, 5- to 10-membered 
heterocyclyl, 5- to 10-membered heterocyclyl-C^6alkyl, 5- to 10-membered heterocyclyl-
C^6alkyl, 5- to 10-membered heterocyclyl-C^6alkyl, d-C^6alkyl, C^6-C^6alkynyl,
C₆-C₁₀aryl-S(0)C₁₋₆alkyl, -S(0₂)C₁₋₆alkyl, -C₁OJd-Cₑalkyl, -C(O)NR₁R₉, -C(O)OR₁ and -S(0₂)NR₀R₉, wherein each of said alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heterocyclenyl, heterocyclenylalkyl, alkenyl and alkylnyl can be unsubstituted or substituted with one to three moieties, which can be the same or different, each moiety being selected from the group consisting of halogen, C₁₋₆alkyl, C₂₋₆cycloalkyl, C₂₋₆cycloalkylalkyl, C₆₋₈cycloalkyl, -CF₃, -CN, -(CR₉R₉)ₚC(0)OH, -OCF₃, -OR₉, -C(O)R₉, -NR₉R₉, -C(0)O-C₁₋₆alkyl, -C(O)NR₀R₉, -SR₉, and -S(0₂)R₉;

ₐ R¹₀ and R⁰ are independently selected from the group consisting of H, OH, C₁₋₆alkyl, C₁₋₆alkenyl, C₁₋₆alkynyl C₂₋₆cycloalkyl, C₆₋₈cycloalkyl, 5- to 10-membered heteroaryl, 5- to 10-membered heterocyclyl, 5- to 10-membered heterocyclylalkyl, and said alkyl, alkenyl, alkylnyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, heterocyclylalkyl, arylalkyl, heteroarylalkyl, heterocyclylalkyl or heterocyclylalkyl is optionally substituted with halogen, C₁₋₆alkyl, C₂₋₆cycloalkyl, -CF₃, -CN, -(CR₉R₉)ₚC(0)OH, -OCF₃, -OR₉, -C(O), amino, -C(0)O-C₁₋₆alkyl, -C(O)NR₀R₉, -SR₉, and -S(0₂)R₉; or R¹₀ and R⁰ together with the nitrogen atom to which they are attached form a 3- to 6-membered heterocyclyl ring;

ₐ R²₀ is independently selected from the group consisting of H, C₂₋₆cycloalkyl, C₁₋₆alkyl, wherein the alkyl or cycloalkyl is optionally substituted with OR₉, OR₀, or OR₀.

The invention also provides compounds of formula I.
and pharmaceutically acceptable salts thereof, wherein

U is N, CH, or C(R₁³);  
R¹⁵ is selected from the group consisting of

- C¹-C₆ alkyl, hydroxy, -OR, -N(R₁⁴)(R₁⁵),
- N(R₁⁴)-C(0)-R¹⁶, -N(R₁⁴)-S(0)-R¹⁶, -N(R₁⁴)-S(0)₂R¹⁶,
- N(R₁⁴)-C(0)-N(R₁⁴)(R₁⁵), C₃-C₈ cycloalkyl, C₆-C₁₀ mono or bicyclic
  aryl, -C(0)R¹⁶, -C(0)OR¹⁶, -C(0)N(R₁⁴)(R₁⁵), -S(0)R¹⁶,
- S(0)₂R¹⁶, -N(R₁⁴)(R₁⁵), -S(0)₂N(R₁⁴)(R₁⁵), -O-C(0)OR¹⁷,
- O-C(0)N(R¹⁷)(R₁⁸),

3- to 8-membered monocyclic heterocyclyl and having one to
three heteroatoms selected from the group consisting of N, O, and
S; and

C₆-C₁₀ mono or bicyclic heteroaryl and having one to three
heteroatoms selected from the group consisting of N, O, and S;

R¹⁴ and R¹⁵ are independently selected from the group
consisting of H, C¹-C₆ alkyl, C₃-C₈ cycloalkyl, and phenyl;
R¹⁶ is independently selected from the group consisting of
C₁-C₆ alkyl, C₃-C₈ cycloalkyl, and phenyl;

R¹⁷ and R¹⁸ are independently selected from the group
consisting of C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₆-C₁₀ mono or
bicyclic aryl, 3- to 8-membered monocyclic heterocyclyl, and C₅-
C₁₀ mono or bicyclic heteroaryl;

L and Z are bonded to any two carbon atoms of the ring comprising U and are

independently selected from the group consisting of CH₂, C(H)(R¹), C(R¹)(R²), N(R¹),
C(O), O, S, S(O), and S(0)₂.
T is absent such that L is bonded directly to Z, or T is selected from the group consisting of C(O), O, S, N(R¹), S(O), S(O)₂, and C₁-C₄ alkylene, wherein said alkylene of T is unsubstituted or substituted with 1 to 2 moieties, which moieties are independently selected from the group consisting of C₁-C₃ alkyl, halo, hydroxy, C₁-C₃ alkoxy, amino, C₁-C₃ alkylamino and C₁-C₃ dialkylamino;

m is 0 or 1;

R¹ and R² are independently selected from the group consisting of H, d-d alkyl, halo, hydroxy, d-d alkoxy, amino, d-d alkylamino and C₁-C₃ dialkylamino;

W is absent, or W is selected from the group consisting of C(O), S(O), S(O)₂;

d-d alkylene, C₃-C₈ cycloalkyl, phenyl, 5- to 6-membered heteroaryl, and 3- to 8-membered heterocyclyl;

V is absent, or V is selected from the group consisting of C(O), O, S, N(H), N(d-d alkyl), N(d-d alkyl), N(C₃-C₈ cycloalkyl), S(O), S(O)₂, and d-d alkylene; or W and V together form a C₃-C₈ cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3 to 8-membered heterocyclyl ring;

R⁰ is selected from the group consisting of

(i) d-d alkyl or d-do cycloalkyl, wherein said alkyl or cycloalkyl of R⁰ is unsubstituted or substituted with one to three moieties independently selected from the group consisting of hydroxy, d-d alkoxy, halo, trifluoromethyl, carboxy, 5- to 6-membered heteroaryl, -SO₂H, d-d alkyl-C(O)-NH-, C₃-C₈ alkyl-SO₂NH₂, and C₃-C₈ alkyl-SO-NH₂;

(ii) 3- to 8-membered heterocyclyl wherein said heterocyclyl of R⁰ is unsubstituted or substituted with one to three moieties independently selected from the group consisting of halo, C₁-C₆ alkyl, C₃-C₈ alkoxy, cyano, hydroxy, amino, C₁-C₆ alkylamino, and C₁-C₆ dialkylamino;

(iii) C₆-C₁₀ aryl or 5- to 10-membered heteroaryl, wherein said aryl or heteroaryl of R⁰ is unsubstituted or is substituted with one to three moieties independently selected from the group consisting of halo, trifluoromethyl, trifluoromethoxy, d-d alkyl, d-C₆ alkoxy, cyano, hydroxy, amino, d-d alkylamino, and d-d dialkylamino; and

(iv) -N(H)OH or -N(H)-C₈ cycloalkoxy;

R³ is H, d-d alkyl, d-C₆ alkenyl, d-C₆ alkynyl, -C(0)R⁰, C₆-d₂ aryl, C₃-C₈ cycloalkyl, d-d cycloalkenyl, 5 to 10-membered heteroaryl, 3- to 8-membered heterocyclyl.
heterocyclyl, 3- to 8-membered heterocyclenyl, (C₆₋C₁₂)aryl( undisclosed)alkyl, (C₃-
C₅)cycloalkyl(C₁₋C₆)alkyl, (C₂₋C₅)cycloalkenyl(C₃₋C₆)alkyl, (5- to 10-membered)
heteroaryl(C₁₋C₆)alkyl, (3- to 8-membered)heterocyclyl (Ci-C₆)alkyl, (3- to 8-
membered)heterocyclenyl (C₁₋C₆)alkyl, wherein said aryl, cycloalkyl, cycloalkenyl,
heteroaryl, heterocyclyl, heterocyclenyl, arylalkyl, cycloalkylalkyl, cycloalkenylalkyl,
heteroarylalkyl, heterocyclylalkyl, and heterocyclenylalkyl of R² is unsubstituted or
substituted with one to three moieties independently selected from the group
consisting of Y, halogen, C₁₋C₆ alkyl, C₃₋C₁₀ cycloalkyl, trifluoromethyl, cyano,
-C(O)OH, -(CH₂)ₓ-C(O)OH, trifluoromethoxy, -OR, -C(0)R⁻, -NR₂R⁻, -C(0)₂alkyl,
-C(0)NR⁻R⁻, -SR⁻, and -S(O)₂R⁻;

Y is C₆₋C₁₀ aryl or 5- to 10-membered heteroaryl, wherein said aryl or
heteroaryl of Y is unsubstituted or substituted with one to five moieties
independently selected from the group consisting of H, halo, cyano,
hydroxy, amino, C₁₋C₆ alkylamino, C₁₋C₆ dialkylamino, trifluoromethyl,
trifluoromethoxy, C₁₋C₆ alkyl, C₁₋C₆ hydroxyalkyl, and C₁₋C₆ alkoxy; and
each occurrence of R² is independently H, C₁₋C₆ alkyl, C₃₋C₁₀
cycloalkyl, phenyl, 5- to 6-membered heteroaryl or 3- to 8-membered
heterocyclyl;

each occurrence of R¹ is independently H, C₁₋C₆ alkyl, C₃₋C₁₀
cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 8-membered
heterocyclyl, or R¹ and R¹₀ together with the nitrogen atom to which they
are attached form a 3- to 6-membered heterocyclyl ring;

each occurrence of R⁻¹ is independently H, C₁₋C₆ alkyl, C₃₋C₁₀
cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 8-membered
heterocyclyl;

each occurrence of R⁻² is independently C₁₋C₆ alkyl, C₃₋C₁₀ cycloalkyl,
phenyl, 5- to 6-membered heteroaryl, or 3- to 8-membered heterocyclyl;

x is an integer from 1 to 4;

R⁷ is selected from the group consisting of H, C₁₋C₆ alkyl, and C₃₋C₈
cycloalkyl, wherein said alkyl or cycloalkyl of R⁷ is unsubstituted or substituted with
one to two moieties selected from the group consisting of halo, C₁₋C₅ alkyl, C₁₋C₅
alkoxy, amino, C₁₋C₃ alkylamino, and C₁₋C₃ dialkylamino; and
R₆ is selected from the group consisting of H, halo, hydroxyl, cyano, C₁-C₆ alkyl, C₁-C₆ alkanoyl, C₁-C₆ alkysulfononyl, C₁-C₆ alkysulfinylnyl, C₁-C₆ haloalkyl, amino, C₁-C₆ alkylamino, C₁-C₆ dialkyamino, C₃-C₈ cycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, and 5- to 10-membered heterocyclyl, wherein each of said aryl, heteroaryl, and heterocyclyl of R₆ is unsubstituted or substituted with one to two moieties selected from the group consisting of halo, C₁-C₃ alkyl, C₁-C₃ alkoxy, amino, C₁-C₃ alkylamino, and C₁-C₃ dialkyamino.

The present invention provides Pyrazolopyrimidine Compounds having the Formula (I), or pharmaceutically acceptable salts thereof:

![Chemical Structure](image)

wherein L, T, Z, U, V, W, R⁶, R⁷, R⁸, and m are as defined above for the compound of Formula (I). The compounds of Formulas (IA) and (IB) as are described in detail below are embodiments of the compound of Formula (I).

In the illustration of the compound of Formula (I) above, ring A is the ring comprising U, ring B is the pyrimidine ring of the pyrazolo[1,5-a]pyrimidine moiety, and ring C is the pyrazole ring of the pyrazolo[1,5-a]pyrimidine moiety. In some embodiments of the compound of Formula (I), m is 1.

In certain embodiments of the compound of Formula (I), L and Z are bonded to any two non-vicinal carbon atoms of the ring comprising U, i.e., ring A. In specific embodiments, the carbon atoms of ring A to which L and Z are bonded have a single ring atom between them.

In some embodiments of the compound of Formula (I), U is N or CH.

In certain embodiments of the compound of Formula (I), U is N.

In other embodiments of the compound of Formula (I), U is CH.
In other embodiments of the compound of Formula (I), U is C(R\(_1^3\)). In some embodiments, R\(_1^3\) is OH, -OC(0)OR\(_{1^7}\), or -OC(0)N(R\(_{1^7}\))(R\(_{1^8}\)). In specific embodiments, R\(_1^3\) is OH.

In certain embodiments of the compound of Formula (I), T is unsubstituted C\(_1\)-C\(_2\) alkyene.

In some embodiments of the compound of Formula (I), the group -L-T-Z- is selected from the group consisting of -CH\(_2\)OCH\(_2\)-, -CH\(_2\)CH\(_2\)OCH\(_2\)-, and C\(_2\)-C\(_4\) alkyene, wherein said alkyene is unsubstituted or substituted with one to two moieties selected from the group consisting of C\(_1\)-C\(_3\) alkyl, fluoro, and hydroxy.

In specific embodiments of the compound of Formula (I), m is 1; and the group -L-T-Z- is selected from the group consisting of -CH\(_2\)OCH\(_2\)-, -CH\(_2\)CH\(_2\)OCH\(_2\)-, and C\(_2\)-C\(_4\) alkyene, wherein said alkyene is unsubstituted or substituted with one to two moieties selected from the group consisting of C\(_1\)-C\(_3\) alkyl, fluoro, and hydroxy.

In certain embodiments of the compound of Formula (I), W is C(O).

In some embodiments of the compound of Formula (I), V is absent.

In other embodiments of the compound of Formula (I), both W and V are absent such that R\(_8^3\) is bonded directly to the nitrogen atom of ring A.

In specific embodiments of the compound of Formula (I), both W and V are absent, and R\(_8^3\) is a 5- to 10-membered mono or bicyclic heteroaryl, wherein said heteroaryl of R\(_8^3\) is unsubstituted or is substituted with one to three moieties independently selected from the group consisting of halo, trifluoromethyl, trifluoromethoxy, C\(_1\)-C\(_6\) alkyl, C\(_1\)-C\(_6\) alkoxy, cyano, hydroxy, amino, C\(_1\)-C\(_6\) alkylamino, and C\(_1\)-C\(_6\) dialkylamino; and wherein said heteroaryl of R\(_8^3\) has from one to five heteroatoms selected from the group consisting of N, O, and S.

In certain embodiments of the compound of Formula (IA), W is C(O), V is absent, and R\(_8^3\) is -N(H)OH or -N(H)-C\(_1\)-C\(_3\) alkoxy.

In specific embodiments of the compound of Formula (I), m is 1;
the group -L-T-Z- is selected from the group consisting of -CH2OCH2-, -CH2CH2OCH2-, and C2-C4 alkylene, wherein said alkylene is unsubstituted or substituted with one to two moieties selected from the group consisting of d -C3 alkyl, fluoro, and hydroxy;

W is C(O); and

V is absent.

In some embodiments of the compound of Formula (I),

R8 is selected from the group consisting of

(i) CN, d-d alkyl or C2-C10 cycloalkyl, wherein said alkyl or cycloalkyl of R8 is unsubstituted or substituted with one to three moieties independently selected from the group consisting of hydroxy, C1-C6 alkoxy, halo, d-d haloalkyl, O-d-d haloalkyl, -NR*R8, -OR8, carboxy, 5- to 6-membered heteroaryl, -SO2H, d-d alkyl-C(0)-NH-, d-d alkyl-SO2-NH-, and d-C6 alkyl-SO-NH2;

(ii) 3- to 8-membered heterocyclyl wherein said heterocyclyl of R8 is unsubstituted or substituted with one to three moieties independently selected from the group consisting of halo, d-C6 alkyl, d-d haloalkyl, O-d-C6 alkoxy, cyano, hydroxy, -(CR*R8)nOR8, -(CR*R8)nNR8C(0)R8, -(CR*R8)nNR8C(0)R8, amino, C1-C6 alkylamino, and d-d dialkylamino;

(iii) C6-C10 aryl or 5- to 10-membered heteroaryl, wherein said aryl or heteroaryl of R8 is unsubstituted or is substituted with one to three moieties independently selected from the group consisting of 5- to 10-membered heterocyclyl, halo, d-d haloalkyl, O-d-d haloalkyl, d-d alkyl, d-d alkoxy, cyano, hydroxy, -(CR*R8)nOR8, -(CR*R8)nNR8R8, -(CR*R8)nNR8C(0)R8, -(CR*R8)nNR8C(0)R8, amino, d-d alkylamino, and d-C6 dialkylamino,

wherein said heterocyclyl is optionally substituted with one to three moieties independently selected from the group consisting of OH, NH2 and d -C6 alkyl; and

(iv) -OH, -OR8, -OR8OR8, -NR8OR8, -NR8OR8, -NR8R8, -C(0)NR8R8, -NR8C(0)R8, C(=N-R8)NR8R8,
and are independently selected from halogen, \( \text{OH}, \text{CN}, \text{C}_1\text{-C}_6 \) alkoxy, \( \text{C}_1\text{-C}_6 \) haloalkyl and \( \text{C}_7\text{-C}_10 \) alkyl, wherein the alkyl is optionally substituted with one to three moieties selected from \( \text{OH}, \text{NH}_2, \text{C}_1\text{-C}_3 \) alkylamino, and \( \text{C}_1\text{-C}_3 \) dialkylamino and \( \text{C}_1\text{-C}_3 \) alkoxy;

In some embodiments of the compound of Formula (I),

\( R^6 \) is selected from the group consisting of

(i) \( \text{C}_1\text{-C}_6 \) alkyl or \( \text{C}_7\text{-C}_{10} \) cycloalkyl, wherein said alkyl or cycloalkyl of \( R^6 \) is unsubstituted or substituted with one to three moieties independently selected from the group consisting of hydroxy, \( \text{C}_1\text{-C}_3 \) alkoxy, fluoro, trifluoromethyl, carboxy, tetrazolyl, \( \text{S}_0 \text{H} \), \( \text{C}_1\text{-C}_6 \) alkyl-C(0)-NH-, \( \text{C}_1\text{-C}_6 \) alkyl-S0 \text{H}, and \( \text{C}_1\text{-C}_6 \) alkyl-SO-NH-

(ii) 5- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from the group consisting of \( \text{N}, \text{O}, \text{S} \), and \( \text{S}(0) \text{H} \) wherein said heterocyclyl of \( R^6 \) is unsubstituted or substituted with one to two moieties independently selected from the group consisting of halo, \( \text{C}_1\text{-C}_6 \) alkyl, \( \text{C}_1\text{-C}_6 \) alkoxy, cyano, hydroxy, amino, \( \text{C}_1\text{-C}_6 \) alkylamino, and \( \text{C}_1\text{-C}_6 \) dialkylamino; and

(iii) phenyl or 5- to 6-membered heteroaryl containing 1 to 3 heteroatoms selected from the group consisting of \( \text{N}, \text{O}, \text{S} \), wherein said phenyl or heteroaryl of \( R^6 \) is unsubstituted or is substituted with one to two moieties independently selected from the group consisting of halo, trifluoromethyl, trifluoromethoxy, \( \text{C}_1\text{-C}_6 \) alkyl, \( \text{C}_1\text{-C}_6 \) alkoxy, cyano, hydroxy, amino, \( \text{C}_1\text{-C}_6 \) alkylamino, and \( \text{C}_1\text{-C}_6 \) dialkylamino;

In some embodiments of the compound of Formula (I),

\( R^6 \) is selected from the group consisting of \( \text{H}, \text{-CHR}^{10} \text{R}^{20}, \text{-}\text{(CR}^{30}\text{R}^{40})_n \text{OR}^{10}, \text{-}\text{(CR}^{30}\text{R}^{40})_n \text{NR}^{10} \text{R}^{10} \text{R}^{20}, \text{-}\text{(CR}^{30}\text{R}^{40})_n \text{SOR}^{10}, \text{-}\text{(CR}^{30}\text{R}^{40})_n \text{S(O)}_2 \text{R}^{10}, \text{-}\text{(CR}^{30}\text{R}^{40})_n \text{C(O)}_2 \text{R}^{10}, \text{-}\text{(CR}^{30}\text{R}^{40})_n \text{C(O)NR}^{10} \text{R}^{20}, \text{-}\text{(CR}^{30}\text{R}^{40})_n \text{C(O)S(O)NR}^{10} \text{R}^{20}, \text{-}\text{(CR}^{30}\text{R}^{40})_n \text{C(O)S(O)NR}^{10} \text{R}^{20}, \text{-}\text{(CR}^{30}\text{R}^{40})_n \text{S(O)NR}^{10} \text{R}^{20}, \text{-}\text{(CR}^{30}\text{R}^{40})_n \text{S(O)NR}^{10} \text{R}^{20}, \text{C}_1\text{-C}_6 \text{alkyl}, \text{-CR}^{10} \text{R}^{20}, \text{C}_1\text{-C}_6 \text{alcohol}, \text{-CR}^{10} \text{R}^{20}, \text{hydroxyl}, \text{amine, -CR}^{10} \text{R}^{20}, \text{CN}, 5- to 10-membered heteroaryl, 5- to 10-membered heterocyclyl, \( \text{C}_2\text{-C}_6 \text{cycloalkyl and C}_6\text{-C}_9 \text{aryl}, \text{wherein each of said heteroaryl, heterocyclyl, cycloalkyl and aryl can be unsubstituted or substituted with one to three moieties selected from the group consisting of C}_1\text{-C}_3 \text{alkyl, C}_1\text{-C}_3 \text{alkenyl,
Ci-C3alkynyI, Ci-C3alkoxy, Ci-C3alkylamino, Ci-C3dialkylamino, amino, halo or OH; wherein all other substituents are as defined above.

In certain embodiments of the compound of Formula (I), R6 is selected from the group consisting of H, C1-C3 alkyl, C1-C6 alkanoyI, cyano, C1-C6 alkylsulfonIy, cyano, halo, hydroxy, amino, C1-C3 alkylamino, and C1-C6 dialkylamino.

In certain embodiments of the compound of Formula (I), R6 is selected from the group consisting of H, C2-C4 alkyl, C1-C6 alkanoyI, cyano, C1-C6 alkylsulfonIy, C3-C4 cycloalkylsulfonIy, C3-C4 cycloalkyI, wherein the C1-C3 alkyl or C3-C4 cycloalkyI is optionally substituted with Ci-C3alkenyl, Ci-C3alkynyl, cyano, halo, hydroxy or amino.

In certain embodiments of the compound of Formula (I), R6 is selected from the group consisting of H, halo, C1-C3 alkyl, C1-C3 alkanoyI, cyano, C1-C3 alkylsulfonIy, cyclopropyl, wherein the C1-C3 alkyl or cyclopropyl is optionally substituted with =CH2 or hydroxy.

In specific embodiments of the compound of Formula (I), R6 is selected from the group consisting of halo, C1-C2 alkanoyI, C1-C3 alkylsulfonIy, and cyano.

In specific embodiments of the compound of Formula (I), R6 is selected from the group consisting of C1-C3 alkanoyI, C1-C3 alkylsulfonIy, and cyclopropyl.

In specific embodiments of the compound of Formula (I), R7 is selected from the group consisting of H, OH, OR10, C1-C6 alkyl, C6-C10 aryl, C6-C10 aryI, cyano, halo, hydroxy, amino, C1-C3 alkylamino, C1-C3 dialkylamino, amino, halo or OH, wherein all other substituents are as defined above.

In specific embodiments of the compound of Formula (I), R7 is selected from the group consisting of H, OH, OR10, C1-C6 alkyl, C6-C10 aryl, C6-C10 aryI, cyano, halo, hydroxy, amino, C1-C3 alkylamino, C1-C3 dialkylamino, amino, halo or OH, wherein all other substituents are as defined above.
to three moieties, which can be the same or different, each moiety being selected from the group consisting of halogen, C-i-Cealkyl, C-3-Cscycloalkyl, -CF3, -CN, -(CR\text{R})_nC(O)OH, -OCF3, -OR\text{R}, -C(O)R\text{R}, -NR\text{R}_nR\text{R}, -C(O)0-C\text{alkyl}, -C(O)NR\text{R}_nR\text{R}, -SR\text{R}, and -S(O\text{R}_2)R\text{R}; wherein all other substituents are as defined above.

In some embodiments of the compound of Formula (I), R\text{T} is H.

In certain embodiments of the compound of Formula (I), R\text{T} is selected from the group consisting of C\text{1}-C\text{8} alkyl, CrC \text{6} alkenyl, CrC \text{6} alkynyl, halo-CrC \text{6} alkyl, -CF3, -C(O)R\text{R} \text{R}, C\text{3}-C\text{8} cycloalkyl, C\text{3}-C\text{8} cycloalkeny1, 5- to 10-membered heteroaryl, 5- to 10-membered heterocyclyl, 5- to 10-membered heterocyclenyl, C\text{6}-C\text{10} ary1/C-C\text{6} alkyl, C3-C8cycloalkeny1CrC \text{6} alkyl, C\text{3}-C8cycloalkeny1CrC \text{6} alkyl, 5- to 10-membered heteroaryl/Ci-Cealkyl, 5- to 10-membered heterocyclyl/Ci-Cealkyl and 5- to 10-membered heterocyclenylalkyi,

wherein each of said alkyl, alkenyl, alkynyl, ary1, cycloalkyl, cycloalkeny1, heteroaryl, heterocyclyl, heterocyclenyl, ary1alkyi, cycloalkylalkyi, cycloalkeny1alkyi heteroarylalkyi, heterocyclylalkyi and heterocyclenylalkyi is unsubstituted or substituted with one to three moieties which can be the same or different, each moiety being selected from the group consisting of halogen, C\text{1}-C\text{8} alkyl, C\text{1}-C\text{8} alkenyl, C\text{3}-C\text{8} cycloalkyl, -CF3, -CN, -CN-R\text{R}_2, -C(O)OH, -

(CR\text{R}_n)\text{R}_nC(O)OH, -(CR\text{R}_n)\text{R}_nOR\text{R}_n, -(CR\text{R}_n)\text{R}_nC(O)R\text{R}_n, -(CR\text{R}_n)\text{R}_nNR\text{R}_nR\text{R}_n, -(CR\text{R}_n)\text{R}_nNR\text{R}_nC(O)R\text{R}_n, -(CR\text{R}_n)\text{R}_nC(O)0-C\text{alkyl, -O-halod-Cealkyl, -(CR\text{R}_n)\text{R}_nC(O)NR\text{R}_nR\text{R}_n, -(CR\text{R}_n)\text{R}_nC(=N)NR\text{R}_nR\text{R}_n, -(CR\text{R}_n)\text{R}_nC(O)NR\text{R}_nS(O)2R\text{R}_n, -(CR\text{R}_n)\text{R}_nNR\text{R}_nC(O)R\text{R}_n, -(CR\text{R}_n)\text{R}_nNR\text{R}_nC(O)NR\text{R}_nR\text{R}_n, -(CR\text{R}_n)\text{R}_nNR\text{R}_nS(O)2NR\text{R}_nR\text{R}_n, -(CR\text{R}_n)\text{R}_nNR\text{R}_nS(O)2C(O)R\text{R}_n, -(CR\text{R}_n)\text{R}_nC\text{alkyl, 5- to 10-membered heteroaryl, 5- to 10-membered heterocycly1, 5- to 10-membered heterocyclenyl, C\text{6}-C\text{10} ary1alkyi, 5- to 10-membered heterocyclylalkyi and 5- to 10-membered heterocyclenylalkyi,

wherein each of said alkyl, alkenyl, alkynyl, cycloalkyl, ary1, heteroaryl, heterocyclylalkyi, heterocyclenylalkyi and heterocyclenylalkyi is unsubstituted or substituted with one to five moieties, which can be the same or different, each moiety being selected from the group consisting of halogen, C-i-Cealkyl, C-3-Cscycloalkyl, -CF3, -CN, -C(O)OH, -
(CR^R)^n_C(0)OH, -OCF_3, -O-halod-Cealkyl, -halod-Cealkyl, d-C hydroxyalkyl, -CR_R^R_n OR, -(CR_R^b)^n CR, ... , C alkanoyl, trifluoromethyl, trifluoromethoxy, hydroxy, C alkoxy, amino, C alkylamino, and C dialkylamino; and 

three and consisting substitued membered C heterocyclenylalkyl, heterocyclenyl, heterocyclenylCi-C heteroarylCi-Cealkyl, heterocyclyl, membered C atom alkyl, amino, C alkylamino, and C dialkylamino; and 

R^a and R^b are independently selected from H, halogen, OH, C, C_6 haloalkyl and C_6 alk oxyl, d - C_6 haloalkyl and C_6 alk oxyl, wherein the alkyl is optionally substituted with one to three moieties selected from OH, NH_2, C_1 C_3 alkylamino, and C_1 C_3 dialkylamino and C_1 C_3 alk oxyl; 

R^{10} and R^9 are independently selected from the group consisting of H, OH, C_1-C_9 alk alkyl, C_1-C_9 alk enyl, C_1-C_9 alky ny l, C_2-C_6 cyclo alk y l, C_6-C_12 ary l, 5- to 10-membered heteroaryl, 5- to 10-membered heterocyclenyl, 5- to 10-membered heterocyclenyl, d-C cyclo alkylid-Cealkyl, C_6-Ci ary l-C_i C_i alk yl, 5- to 10-membered heteroaryl/Ci-Cealkyl, 5- to 10-membered heterocyclenyl/Ci-C_i alk yl, and said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclenyl, heterocyclenyl, cycloalkylalkyl, arylalkyl, heteroaryalkyl, heterocyclenylalkyl or heterocyclenylalkyl is optionally substituted with halogen, d - C_6 alk alkyl, C_2-C_6 cyclo alk y l, -CF_3, -CN, -(CR^R)^n_C(0)OH, -OCF_3, -OR^a, -C(O), amino, -C(0)-C e alky l, -C(0)NR^i, -C(O)NR^i, -SR^i, and -S(O)(0)^i R^i; or R^{10} and R^9 together with the nitrogen atom to which they are attached form a 3- to 6-membered heterocyclenyl ring; 

R^{25} is independently selected from the group consisting of H, C_2-C_6 cyclo alk y l, C_6-C_i alk yl, wherein the alkyl or cycloalkyl is optionally substituted with OR^a, OR^b, OR^c. 

In one embodiment, R^3 is selected from C_6-C_{12} ary l and 5- to 6-membered heteroaryl, optionally substituted as defined above. 

In certain embodiments of the compound of Formula (I), R^3 is 5- to 10-membered mono- or bicyclic aryl or heteroaryl, wherein said heteroaryl of R^3 contains from one to three heteroatoms selected from the group consisting of N, N(O), O, and S, and wherein said aryl or heteroaryl of R^3 is unsubstituted or substituted with one to three moieties independently selected from the group consisting of Y, halogen, C_1-C_6 alk yl, cyano, -C(0)OH, -C(0)NH_2, C_1-C_6 alkanoyl, trifluoromethyl, trifluoromethoxy, hydroxy, C_1-C_6 alkox y, amino, C_1-C_6 alkylamino, and C_1-C_6 dialkylamino; and
Y is phenyl or 5 to 6-membered heteroaryl, wherein said heteroaryl of Y contains 1 to 2 heteroatoms selected from the group consisting of N, N(O), O, and S; wherein Y is unsubstituted or substituted with one to two moieties independently selected from the group consisting of halogen, C1-C6 alkyl, -CN, -C(O)OH, -C(O)NH2, -C(0)-C6 alkyl, trifluoromethyl, trifluoromethoxy, hydroxy, C1-C6 alkoxy, amino, C1-C6 alkylamino, and C1-C6 dialkylamino;

with the proviso that when R3 is bicyclic aryl or heteroaryl, said bicyclic aryl or heteroaryl is not substituted by Y.

In specific embodiments of the compound of Formula (I), R3 is 5 to 10-membered mono- or bicyclic heteroaryl, wherein said heteroaryl of R3 contains from 1 to 2 heteroatoms selected from the group consisting of N and N(O);

Y is phenyl or 5-membered heteroaryl, wherein said heteroaryl of Y contains 1 to 2 heteroatoms selected from the group consisting of N and S; wherein Y is unsubstituted or substituted with one to two moieties independently selected from the group consisting of halo, C1-C3 alkyl, C1-C3 hydroxyalkyl, and C1-C3 alkoxy.

In some embodiments of the compound of Formula (I), R5 and R10 are independently H or C1-C3 alkyl.

In certain embodiments of the compound of Formula (I), R11 is H or C1-C3 alkyl.

In some embodiments of the compound of Formula (I), R13 is C1-C3 alkyl.

In another aspect, the invention provides a compound of the Formula (IA)

\[
\begin{array}{c}
\text{IA}\n\end{array}
\]

wherein

\[U \text{ is } N, \text{ CH, or } C(R^{13});\]
R\textsuperscript{3} is selected from the group consisting of

- C\textsubscript{6} alkyl, hydroxy, -OR, -N(R\textsubscript{1})(R\textsubscript{5}),
-N(R\textsuperscript{14})-C(0)-R\textsubscript{16}, -N(R\textsuperscript{14})S(0)-R\textsubscript{16}, -N(R\textsuperscript{14})S(0)-2R\textsubscript{16},
-N(R\textsuperscript{14})-C(0)-N(R\textsuperscript{15}), C\textsubscript{3}-C\textsubscript{8} cycloalkyl, C\textsubscript{6}-C\textsubscript{10} mono or bicyclic aryl, -C(0)R\textsubscript{16}, -C(0)OR, -C(0)N(R\textsuperscript{16}), -S(0)R\textsubscript{16},
-S(0)2R\textsubscript{16}, -S(0)N(R\textsuperscript{14})(R\textsuperscript{5}), -S(0)2N(R\textsuperscript{14})(R\textsuperscript{5}), -O-C(0)OR, \textsuperscript{5}

3- to 8-membered monocyclic heterocyclyl and having one to three heteroatoms selected from the group consisting of N, O, and S; and

C\textsubscript{6}C\textsubscript{10} mono or bicyclic heteroaryl and having one to three heteroatoms selected from the group consisting of N, O, and S;

R\textsuperscript{14} and R\textsuperscript{15} are independently selected from the group consisting of H, C\textsubscript{1}-C\textsubscript{6} alkyl, C\textsubscript{3}-C\textsubscript{8} cycloalkyl, and phenyl;

R\textsubscript{16} is independently selected from the group consisting of C\textsubscript{1}-C\textsubscript{6} alkyl, C\textsubscript{3}-C\textsubscript{8} cycloalkyl, and phenyl;

R\textsuperscript{17} and R\textsubscript{18} are independently selected from the group consisting of C\textsubscript{r}-C\textsubscript{6} alkyl, C\textsubscript{3}-C\textsubscript{8} cycloalkyl, C\textsubscript{6}-C\textsubscript{10} mono or bicyclic aryl, 3- to 8-membered monocyclic heterocyclyl, and C\textsubscript{6}-

C\textsubscript{10} mono or bicyclic heteroaryl;

L and Z are bonded to any two carbon atoms of the ring comprising U;

T is absent or present;

-L-T-Z- is selected from the group consisting of -CH2OCH2-, -CH2CH2OCH2-, and C\textsubscript{2}-C\textsubscript{4} alkylene, wherein said alkylene is unsubstituted or substituted with one to two moieties selected from the group consisting of C\textsubscript{1}-C\textsubscript{3} alkyl, fluoro, and hydroxy;

W is C(O), S(O), S(0)\textsubscript{2}, and d-d alkyene;

R\textsuperscript{8} is selected from the group consisting of

(i) d-d alkyl or C\textsubscript{3}-C\textsubscript{10} cycloalkyl, wherein said alkyl or cycloalkyl of R\textsuperscript{8} is unsubstituted or substituted with one to three moieties independently selected from the group consisting of hydroxy, d-d alkoxy, fluoro, trifluoromethyl, carboxy, tetrazolyl, -S0\textsubscript{2}H, C\textsubscript{r}-C\textsubscript{6} alkyl-C(0)-NH, d-d alkyl-S0\textsubscript{2}NH, and d-d alkyl-S0\textsubscript{2}NH;
(ii) 5- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from the group consisting of N, O, S, and S(0)2 wherein said heterocyclyl of R6 is unsubstituted or substituted with one to two moieties independently selected from the group consisting of halo, C1-C6 alkyl, C1-C6 alkoxy, cyano, hydroxy, amino, C1-C6 alkylamino, and C1-C6 dialkylamino;

(iii) phenyl or 5- to 6-membered heteroaryl containing 1 to 3 heteroatoms selected from the group consisting of N, O, and S, wherein said phenyl or heteroaryl of R6 is unsubstituted or is substituted with one to two moieties independently selected from the group consisting of halo, trifluoromethyl, trifluoromethoxy, C1-C6 alkyl, C1-C6 alkoxy, cyano, hydroxy, amino, C1-C6 alkylamino, and C1-C6 dialkylamino; and

(iv) -N(H)OH or -N(H)-d-C3 alkoxy;

R3 is 5- to 10-membered mono or bicyclic aryl or heteroaryl, wherein said heteroaryl of R3 contains from one to three heteroatoms selected from the group consisting of N, N(O), O, and S, and wherein said aryl or heteroaryl of R3 is unsubstituted or substituted with one to three moieties independently selected from the group consisting of halogen, C1-C6 alkyl, cyano, -C(0)OH, -C(0)NH2, C1-C6 alkanoyl, trifluoromethyl, trifluoromethoxy, hydroxy, C1-C6 alkoxy, amino, C1-C6 alkylamino, and C1-C6 dialkylamino;

Y is phenyl or 5 to 6-membered heteroaryl, wherein said heteroaryl of Y contains 1 to 2 heteroatoms selected from the group consisting of N, N(O), O, and S; wherein Y is unsubstituted or substituted with one to two moieties independently selected from the group consisting of halogen, C1-C6 alkyl, -CN, -C(0)OH, -C(0)NH2, -C(0)Cl, C1-C6 alkanoyl, trifluoromethyl, trifluoromethoxy, hydroxy, C1-C6 alkoxy, amino, C1-C6 alkylamino, and C1-C6 dialkylamino;

or Y is absent when R3 is bicyclic aryl or heteroaryl; and

R6 is selected from the group consisting of H, C1-C6 alkyl, C1-C6 alkanoyl, cyano, C1-C6 alkylsulfonyl, cyano, halo, hydroxy, amino, C1-C6 alkylamino, and C1-C6 dialkylamino;

or a pharmacologically acceptable salt thereof.
In some embodiments of the compound of Formula (IA), L and Z are bonded to any two non-vicinal carbon atoms.

In certain embodiments of the compound of Formula (IA), -L-T-Z- is selected from the group consisting of -CH2CH2- and -CH2OCH2-;

In some embodiments of the compound of Formula (IA), U is N or CH.
In certain embodiments of the compound of Formula (IA), U is CH.
In other embodiments of the compound of Formula (IA), U is N.
In other embodiments of the compound of Formula (IA), U is C(R13).

In some embodiments, R13 is OH, -OC(0)OR17, or -OC(0)N(R17)(R18). In specific embodiments, R13 is OH.

In certain embodiments of the compound of Formula (IA), the group

\[ \text{\includegraphics[width=0.5\textwidth]{formula.png}} \]

is selected from one of the following moieties:

- \[ \text{\includegraphics[width=0.2\textwidth]{moiety1.png}} \]
- \[ \text{\includegraphics[width=0.2\textwidth]{moiety2.png}} \]
- \[ \text{\includegraphics[width=0.2\textwidth]{moiety3.png}} \]

In some embodiments of the compound of Formula (IA), W is C(O).
In specific embodiments of the compound of Formula (IA), R8 is selected from the group consisting of
In some embodiments of the compound of Formula (IA), the group

\[ R^8 W \]

is selected from one of the following moieties:

- \( R^8 W \)
- \( R^8 W \)
- \( R^8 W \)
- \( R^8 W \)
- \( R^8 W \)
- \( R^8 W \)

\( W \) is C(O); and

\( R^8 \) is selected from the group consisting of

- \( \text{[Chemical structures]} \)
- \( \text{[Chemical structures]} \)
- \( \text{[Chemical structures]} \)

In some embodiments of the compound of Formula (IA), the group
In other embodiments of the compound of Formula (IA), W is C(O) and R is -N(H)OH or -N(H)-d-C_3 alkoxy.

In certain embodiments of the compound of Formula (IA), R^6 is selected from the group consisting of halo, C1-C3 alkanoyl, C1-C3 alkylsulfonyl, and cyano.

In certain embodiments of the compound of Formula (IA), R^6 is selected from the group consisting of halo, C_C3 alkanoyl, C_C3 alkylsulfonyl, cyclopropyl, and cyano.

In specific embodiments of the compound of Formula (IA), R^6 is selected from the group consisting of C_C3 alkanoyl, C_C3 alkylsulfonyl, and cyclopropyl.

In some embodiments of the compound of Formula (IA), R^3 is 5- to 6-membered monocyclic heteroaryl, wherein said heteroaryl of R^3 contains 1 to 2 heteroatoms selected from the group consisting of N and N(O), and is substituted by Y;

wherein Y is phenyl or 5-membered heteroaryl, wherein said heteroaryl of Y contains 1 to 2 heteroatoms selected from the group consisting of N and S; wherein Y is unsubstituted or substituted with one to two moieties independently selected from the group consisting of halo, C_C3 alkyl, C_C3 hydroxyalkyl, and C_C3 alkoxy.

In some embodiments of the compound of Formula (I), (IA), (IB) or (IC), R^3 is pyrazolyl, pyrimidinyl, phenyl or pyridyl, unsubstituted or substituted with one to three moieties as defined above. In another embodiment, R^3 is phenyl or pyridyl, unsubstituted or substituted with one to three moieties as defined above.
In other embodiments of the compound of Formula (IA), R^3 is 9- to 10-membered bicyclic heteroaryl, wherein said heteroaryl of R^3 is unsubstituted or substituted with one to two moieties independently selected from the group consisting of halogen, C_1-C_6 alkyl, cyano, -C(0)OH, -C(0)NH_2, C_1-C_6 alkanoyl, trifluoromethyl, trifluoromethoxy, hydroxy, C_1-C_6 alkoxy, amino, C_1-C_6 alkylamino, and C_1-C_6 dialkylamino. In one embodiment, R^3 is isoquinolinyl optionally substituted.

In another aspect, the invention provides a compound of the Formula (IB)

\[
\begin{align*}
\text{O} & \text{N} & \text{R}^8 \\
\text{Z} & \text{U} & \text{Y} \\
\text{R}^3 & \text{NH}_2 & \\
\text{is} & &
\end{align*}
\]

wherein

- \text{U} is N or CH;
- \text{-L-T-Z-} is selected from the group consisting of \text{-CH}_2\text{CH}_2\text{-} and \text{-CH}_2\text{OCH}_2\text{-};
- \text{R}^8 is selected from the group consisting of

\[
\begin{align*}
\text{HO} & \text{CH}_3 \\
\text{HO} & \text{CH}_3 \\
\text{HO} & \text{CH}_3 \\
\text{H}_3\text{C} & \text{OH} \\
\text{H}_3\text{C} & \text{OH} \\
\text{H}_3\text{C} & \text{OH} \\
\text{HO} & \text{CH}_3 \\
\text{HO} & \text{CH}_3 \\
\text{HO} & \text{CH}_3 \\
\text{H}_3\text{C} & \text{OH} \\
\text{H}_3\text{C} & \text{OH} \\
\text{H}_3\text{C} & \text{OH} \\
\end{align*}
\]

- \text{R}^3 is 5- to 10-membered mono- or bicyclic heteroaryl, wherein said heteroaryl of \text{R}^3 contains from 1 to 2 heteroatoms selected from the group consisting of N and N(O);
- \text{Y} is phenyl or 5-membered heteroaryl, wherein said heteroaryl of \text{Y} contains 1 to 2 heteroatoms selected from the group consisting of N and S; wherein \text{Y} is
unsubstituted or substituted with one to two moieties independently selected from the group consisting of halo, C1-C3 alkyl, C1-C3 hydroxyalkyl, and C1-C3 alkoxy; or Y is absent when R3 is bicyclic heteroaryl; and R6 is selected from the group consisting of halo, C1-C3 alkanoyl, C1-C3 alkylsulfonyl, and cyano; or a pharmaceutically acceptable salt thereof.

In certain embodiments of the compound of Formula (IB), U is N. In other embodiments of the compound of Formula (IB), U is CH.

In specific embodiments of the compound of Formula (IB), the moiety

In other specific embodiments of the compound of Formula (IB), the moiety

In certain embodiments of the compound of Formula (IB), R3 is a 5- to 6-membered monocyclic heteroaryl containing from 1 to 2 heteroatoms selected from the group consisting of N and N(O).

In other embodiments of the compound of Formula (IB), R3 is a 9- to 10-membered bicyclic heteroaryl containing from 1 to 2 nitrogen atoms wherein Y is absent.

The present invention also provides compounds under Formula (IC):
Wherein U is N or CH;

wherein the group -L-T-Z- is selected from the group consisting of -CH2OCH2-, -CH2CH2OCH2-, and C2-C4 alkyene, wherein said alkyene is unsubstituted or substituted with one to two moieties selected from the group consisting of d-d alkyl, fluoro, and hydroxy;

R8 is selected from the group consisting of

(i) CN, d-d alkyl or C2-C10 cycloalkyl, wherein said alkyl or cycloalkyl of R8 is unsubstituted or substituted with one to three moieties independently selected from the group consisting of hydroxy, C1-C6 alkoxy, halo, d-d haloalkyl, O-d-d haloalkyl, -NR*R*, -OR*, carboxy, 5- to 6-membered heteroaryl, -SO2H, d-d alkyl-C(0)-NH-, d-d alkyl-SO2-NH-, and d-C6 alkyl-SO-NH2;

(ii) 3- to 8-membered heterocycl wherein said heterocycl of R8 is unsubstituted or substituted with one to three moieties independently selected from the group consisting of halo, d-C6 alkyl, d-d haloalkyl, O-d-C6 haloalkyl, d-C6 alkoxy, cyano, hydroxy, -(CR*R*)nOR*, -(CR*R*)nNR*R*, -(CR*R*)nNR*C(0)R b, -(CR*R*)nC(0)NR*R*, amino, C1-C6 alkylamino, and d-d dialkylamino;

(iii) C6-C10 aryl or 5- to 10-membered heteroaryl, wherein said aryl or heteroaryl of R8 is unsubstituted or is substituted with one to three moieties independently selected from the group consisting of 5- to 10-membered heterocycl, halo, d-d haloalkyl, O-d-d haloalkyl, d-d alkyl, d-d alkoxy, cyano, hydroxy, -(CR*R*)nOR*, -(CR*R*)nNR*R*, -
(CR*R*R*b)NR*C(0)R, -(CR*R*R*b)NR*C(0)R, amino, d-d alkylamino, and C1-C6 dialkylamino,
wherein said heterocyclyl is optionally substituted with one to three moieties independently selected from the group consisting of OH, NH₂ and d-d alkyl; and
(iv) -OH, -OR a, -OR OR b, -NR R a OR b, -NR R, -C(0)NR R b, -NR C(0)R, C(=N-R)NR R, and
R² is selected from the group consisting of:

Ar¹ is C₆-C₁₀ aryl or a 5- to 6-membered heteroaryl optionally substituted with one to three of R²⁻, which can be the same or different, each R²⁻ being selected from the group consisting of halogen, C₁⁻C₆ alkyl, -CF₃, -CN, -C(0)OH, -(CR*R*R*b)C(0)OH, -OCF₃, -O-haloalkyl, -OR a, -C(0)R, -NR R b, -d-dalkyl, -C(0)NR R b, -NR C(0)R, -S(0₂)NR R b, -NR S(0₂)R, -SR a, and -S(0₂)R b;
R₂ is independently selected from the group consisting of d-C₆ alkyl, -CF₃, -CN, -C(0)OH, -(CR*R*R*b)C(0)OH, -OCF₃, -O-haloalkyl, -OR a, -C(0)R, -NR R b, -C(0) -d-alkyl, -C(0)NR R b, -NR C(0)R, -S(0₂)NR R b, -NR S(0₂)R, -SR a, and -S(0₂)R;
R¹ and R² are independently selected from d-d alkyl and OH;
R³ is selected from d-C₃ hydroxalkyl, C₂-C₆ hydroxyalkyl, -NH(0)C₁⁻C₃ alkyl, -NH(0)OC-r’d alkyl, and -NH(0)NHC-r’d alkyl;
R² and R³ are independently selected from H, halogen, OH, d-d alkoxy, d-C₆ haloalkyl and d-d alkyl, wherein the alkyl is optionally substituted with one to three
moieties selected from OH, NH₂, C₁-C₃ alkylamino, and C₁-C₃ dialkylamino and C₁-C₃ alkoxy;
Z is \(\text{CH}_2\), NH, S or O;
q is 0, 1 or 2;
v is 0, or 1.

R⁶ is selected from the group consisting of H, halo, C₁-C₃ alkyl, C₁-C₃ alkanoyl, cyano, C₁-C₂ alkylsulfonyl, C₂-C₄ cycloalkylsulfonyl, C₂-C₄ cycloalkyl, wherein the C₁-C₃ alkyl or C₂-C₄ cycloalkyl is optionally substituted with C₁-
C₃ alkyl, CrC₃alkynyl, cyano, halo, hydroxy or amino.

All other substituents are as defined above.

In one embodiment, R⁶ is selected from the group consisting of amino, NR⁴R⁵, C₁-C₃ alkyl, C₃-C₄ hydroxycycloalkyl, C₁-C₃ hydroxalkyl, 5-10 membered heteroaryl containing one or two N atoms, wherein said heteroaryl is optionally substituted with one or two R²⁵, which can be the same or different, selected from H, methyl, amino, OH and methylamino;
R⁴ and R⁵ are independently selected from H and C₁-C₃ alkyl;
Z is \(\text{CH}_2\) or O.

In the foregoing embodiments of the compound of Formula (I), (IA) or (IB), R² is selected from the group consisting of C₆-C₁₂aryl or 5-10-membered heteroaryl, wherein each of said aryl or heteroaryl, is unsubstituted or substituted with one to three moieties which can be the same or different, each moiety being selected from the group consisting of halogen, C₁-alkyl, C₁-alkenyl, C₁-C₆alkynyl, C₃-C₄cycloalkyl, -CF₃, -CN, -CN-R²⁵, -C(O)OH, -(CR²⁴R²⁵)nC(O)OH, -OCF₃, -(CR²⁴R²⁵)nOR, -(CR²⁴R²⁵)nC(O)OR, -(CR²⁴R²⁵)nNR¹⁵OR, -(CR²⁴R²⁵)nNR¹⁵R¹⁵, -(CR²⁴R²⁵)nNR¹⁵C(O)R¹⁵, -(CR²⁴R²⁵)nC(O)C(0)OR, -(CR²⁴R²⁵)nC(0)C(0)OR, -(CR²⁴R²⁵)nC(0)OR, -(CR²⁴R²⁵)nC(0)NHOR, -(CR²⁴R²⁵)nC(0)NR¹⁵OR, -(CR²⁴R²⁵)nC(0)NR¹⁵R¹⁵, -(CR²⁴R²⁵)nC(0)NR¹⁵C(O)R¹⁵, -(CR²⁴R²⁵)nC(0)NR¹⁵C(O)OR, -(CR²⁴R²⁵)nC(0)NR¹⁵C(O)OR, -(CR²⁴R²⁵)nC(0)NR¹⁵C(O)OR, -(CR²⁴R²⁵)nC(0)NR¹⁵C(O)OR, -(CR²⁴R²⁵)nC(0)NR¹⁵C(O)OR, -(CR²⁴R²⁵)nC(0)NR¹⁵C(O)OR, -(CR²⁴R²⁵)nC(0)NR¹⁵C(O)OR, -(CR²⁴R²⁵)nC(0)NR¹⁵C(O)OR, -(CR²⁴R²⁵)nC(0)NR¹⁵C(O)OR, -(CR²⁴R²⁵)nC(0)NR¹⁵C(O)OR, -(CR²⁴R²⁵)nC(0)NR¹⁵C(O)OR,
wherein Y is selected from C₆-C₁₀aryl, 5-to-10-membered heteroaryl, 5-to-10-membered heterocyclylalkyl, 5-to-10-membered heteroarylalkyl, 5-to-10-membered heterocyclylalkyl and 5-to-10-membered heterocyclylalkyl,

wherein each of said alkyl, alkenyl, alkynyl, cycloalkyl, arey, heteroaryl, heterocyclyl, heterocyclylalkyl, heterocyclylalkyl and heterocyclylalkyl is unsubstituted or substituted with one to five moieties, which can be the same or different, each moiety being selected from the group consisting of halogen, CrC₆alkyl, C₃-C₆cycloalkyl, -CF₃, -CN, -C(0)OH, -OCF₃, -O-haloC₆alkyl, -C₆hydroxyalkyl, -aryl, -heteroaryl, -heterocyclyl, -heterocyclylalkyl, -heterocyclylalkyl, -heterocyclylalkyl and -heterocyclylalkyl.

In some embodiments of the compound of Formula (I), (IA) or (IB), -R²-Y is

Ar¹ is C₆-C₁₀aryl or a 5-to-6-membered heteroaryl, optionally substituted with one to three of R¹⁹, which can be the same or different, each R¹⁹ being selected from the group consisting of halogen, C₁-C₆alkyl, -CF₃, -CN, -C(0)OH, -OCF₃, -O-haloC₆alkyl, -OR, -C(0)R, -NR²R, -C(0)NR²R, -C(0)S(0₂)NR²R², -NR²C(0)R, -S(0₂)NR²R², -SR², and -S(0₂)R².

R² is independently selected from the group consisting of halogen, CrC₆alkyl, -CF₃, -CN, -C(0)OH, -OCF₃, -O-haloC₆alkyl, -OR, -C(0)R, -NR²R, -C(0)S(0₂)NR²R², -NR²C(0)R, -S(0₂)NR²R², -SR², and -S(0₂)R².
-C(0)0-d-alkyl, -C(0)NR R , -NR C(0)R , -S(0 2 )NR a R , -NR S(0 2 ) R b , -SR , and -S(O 2 ) R ;
R 9 and R 10 are as defined above;
R 21 and R 22 are independently selected from C1-C3 alkyi and OH;
R 23 is selected from d-d hydroxyalkyl, C3-C5 hydroxycycloalkyl, -NHC(0)d-d alkyi, -NHC(0)Od-d alkyi, and -NHC(0)NHd-d alkyi;
R 24 and R 25 are independently selected from H, halogen, OH, d-d alkoxy, C1-C6 haloalkyl and d-C ε alkyi, wherein the alkyi is optionally substituted with one to three moieties selected from OH, NH2,d-C 3 alkylamino, and d-C 3 dialkylamino and d-d alkoxy;
Z 1 is CH2, NH, S or O;
q is 0, 1 or 2;
v is 0, 1 or 2.

In one embodiment, Ar 1 is phenyl or a 5- to 6-membered heteroaryl optionally substituted. In a further embodiment, Ar 1 is phenyl, pyrazolyl, pyrimidinyl, pyridyl, triazolyl, pyrollyl, thienyl, imidazolyl, pyrazinyl or thiazolyl optionally substituted with one to three of R 19. In another embodiment, Ar 1 is phenyl, pyridyl or imidazolyl optionally substituted with one to three of R 19. In another embodiment, Ar 1 is phenyl or imidazolyl optionally substituted.

In one embodiment, in the foregoing embodiments, R 19 and R 20 are independently selected from the group consisting of halogen, CN, d-C 2 alkyl, halod-C 2 alkyl, d-C 2 alkoxy, 0-halod-C 2 alkyl. In one embodiment, in the foregoing embodiments, R 19 and R 20 are independently selected from the group consisting of F, CN, d-C 2 alkyl, fluorod-C 2 alkyl, O-fluorod-alkyi. In one embodiment, R 19 is F or methyl. In another embodiment, R 20 is F or methyl.

In one embodiment, R 23 is .

In one embodiment, R 9 is H and R 10 is cyclopropyl, cyclobutyl or cyclopentyl.
In another embodiment, R 9 and R 10 are independently selected from H and d-d alkyi.
In some embodiments of the compound of Formula (I), (IA), (IB) or (IC), -R^3-Y

(l, IA, IB), or - R^3 (IC) is selected from the group consisting of,

and and R^19, R_po and q are defined above; t is 0, 1 or 2.

In another embodiment, -R^3-Y is selected from the group consisting of,

and t, q, R^18 and R^20 are defined above.
In specific embodiments of the compound of Formula (I), (IA), (IB) or (IC), R₆ is selected from the group consisting of H, -CHR₃R₅, -(CR₃R₅)₉OR₆, -(CR₃R₅)₉NR₇R₈, -(CR₃R₅)₉SR₉, -(CR₃R₅)₉S(O)R₁₀, -(CR₃R₅)₉S(O₂)R₁₀, -(CR₃R₅)₉C(0)C₆alkyl, -(CR₃R₅)₉C(0)NR₉R₁₀, -(CR₃R₅)₉C(0)OR₆, -(CR₃R₅)₉S(O₂)R₁₀, - (CR₃R₅)₉NR₉C(0)R₁₀, - (CR₃R₅)₉NR₉S(O₂)R₁₀, C₆-alkyl, halo-d-C₆alkyl, d-C₆alkoxy, halo, hydroxy, amino, -(CR₃R₅)₉CN. In another embodiment, R₆ is selected from the group consisting of halo, CN, C₁-C₆ alkanoyl, C₁-C₆ alkylsulfonyl, and cyclopropyl.

In certain embodiments of the compound of Formula (I), (IA), (IB) or (IC), R₆ is selected from the group consisting of H, C₁-C₆ alky1, d-C₆ alkanoyl, C₁-C₆ alky1sulfonyl, cyano, d-C₆ alky1sulfonyl, cyano, halo, hydroxy, amino, C₁-C₆ alky1amino, and d-C₆ dialky1amino.

In certain embodiments of the compound of Formula (I), (IA), (IB) or (IC), R₆ is selected from the group consisting of H, C₁-C₆ alky1, C₁-C₆ alkanoyl, cyano, C₁-C₆ alky1amino, C₁-C₆ cycloalkylsulfonyl, C₁-C₆ cycloalkyl, cyano, halo, hydroxy, amino, C₁-C₆ alky1amino, and C₁-C₆ dialky1amino.

In certain embodiments of the compound of Formula (I), (IA), (IB) or (IC), R₆ is selected from the group consisting of H, halo, C₁-C₃ alky1, C₁-C₆ alkanoyl, C₁-C₆ alky1sulfonyl, C₂-C₆ cycloalkylsulfonyl, C₃-C₄ cycloalkyl, wherein the C₁-C₃ alky1 or C₃-C₄ cycloalkyl is optionally substituted with C₁-C₆ alkenyl, d-C₃ alky1enyl, cyano, halo, hydroxy or amino.

In certain embodiments of the compound of Formula (I), (IA), (IB) or (IC), R₆ is selected from the group consisting of H, halo, C₁-C₃ alky1, -C(0)Me, -S(C=2)Me, -S(C=2)cyclopropyl, cyano, cyclopropyl, wherein the C₁-C₃ alky1 or cyclopropyl is optionally substituted with =CH₂ or hydroxy.

In specific embodiments of the compound of Formula (I), (IA), (IB) or (IC), R₆ is selected from the group consisting of halo, C₁-C₃ alkanoyl, C₁-C₆ alky1sulfonyl, and cyano.

In specific embodiments of the compound of Formula (I), (IA), (IB) or (IC), R₆ is selected from the group consisting of C₁-C₆ alkanoyl, C₁-C₆ alky1sulfonyl, and cyclopropyl.

In specific embodiments of the compound of Formula (I), (IA), (IB) or (IC), W is C(O). R₆ is selected from the group consisting of amino, NR₇R₈, C₁-C₆ alky1, C₃-C₄...
hydroxycycloalkyi, C₁₋₃ hydroxyalkyi, 5-10 membered heteroaryl containing one or two N atoms, wherein said heteroaryl is optionally substituted with one or two R²⁴, which can be the same or different, selected from H, methyl, amino, OH and methylamino. In one embodiment, the 5-10 membered heteroaryl is pyrazolyl, pyrrolyl, or triazolyl.

In specific embodiments of the compound of Formula (I), (IA), (IB) or (IC), R⁸ is selected from the group consisting of amino, NR²⁴R⁶, C₁₋₃ alkyl, C₅₋₄ hydroxycycloalkyi.

\[
\begin{align*}
\text{HO} & \quad \text{HO} \\
\text{HO} & \quad \text{OH} \\
\text{HO} & \quad \text{CH₃} \\
\text{N} & \quad \text{NH} \\
\text{N} & \quad \text{NH} \\
\text{R²⁴} & \quad \text{N} & \quad \text{NH} \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\end{align*}
\]

wherein R²⁴ is independently selected from the group consisting of H, methyl, amino, OH and methylamino; r is 1 or 2.

In specific embodiments of the compound of Formula (I), (IA), (IB) or (IC), R⁸ is selected from the group consisting of amino,

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{R²⁴} & \quad \text{N} & \quad \text{N} \\
\end{align*}
\]

wherein R²⁴ is independently selected from the group consisting of H, methyl, amino, OH and methylamino; r is 1 or 2. In one
embodiment, \( R_i \) is independently selected from the group consisting of H, methyl, and amino.

In specific embodiments of the compound of Formula (I), (IA), (IB) or (IC), \( R_i \) is selected from the group consisting of

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{and} \quad \text{H}_2\text{C} \quad \text{OH} \quad \text{and} \quad \text{HO} \quad \text{CH}_3 \\
\end{align*}
\]

In specific embodiments of the compound of Formula (I), (IA), (IB) or (IC), \( R_i \) is selected from

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{and} \quad \text{HO} \quad \text{CH}_3 \\
\end{align*}
\]

In specific embodiments of the compound of Formula (I), (IA), (IB) or (IC), \( R^7 \) is selected from the group consisting of H, OH, OR\(^a\), d-alkyl, -\( \text{C}(0)\text{NR} \text{R}^b \), -\( \text{C}(0)\text{OR} \text{R}^a \) and \( \text{S}(\text{O}_2)\text{R}^a \), wherein said alkyl can be unsubstituted or substituted with one to three moieties, which can be the same or different, each moiety being selected from the group consisting of halogen, -\( \text{CF}_3 \), -\( \text{CN} \), -\( \text{C}(\text{R}_a\text{R}_b)\text{C}(0)\text{OH} \), -\( \text{OCF}_3 \), -\( \text{OR}^a \), -\( \text{C}(0)\text{R}^a \), -\( \text{NR}^a \), -\( \text{C}(0)\text{0-C}_{\text{C}_6}\text{alkyl} \), -\( \text{C}(0)\text{NR}^a \text{R}^b \), -\( \text{SR}^a \), and -\( \text{S}(\text{O}_2)\text{R}^a \);

In specific embodiments of the compound of Formula (I), (IA), (IB) or (IC), \( R^9 \) and \( R^9 \) are independently selected from the group consisting of H, OH, \( \text{CrC}_6 \text{alkyl} \), \( \text{C}_3\text{C}_8 \text{cycloalkyl} \), \( \text{C}_6 \text{C}_10 \text{aryl} \), 5- to 10-membered heteroaryl, 5- to 10-membered heterocyclyl, 5- to 10-membered heterocyclylalkyl, 5- to 10-membered heterocyclus alkyl, 5- to 10-membered heterocyclylalkyl, 5- to 10-membered heterocyclylalkyl, and said alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, heterocyclylalkyl, cycloalkylalkyl, arylalkyl, heteroarylalkyl, heterocyclylalkyl or heterocyclylalkyl is optionally substituted with halogen, \( \text{C}(\text{O})\text{alkyl} \), \( \text{C}_3\text{C}_8 \text{cycloalkyl} \), -\( \text{CF}_3 \), -\( \text{CN} \), -\( \text{C}(\text{R}_a\text{R}_b)\text{C}(0)\text{OH} \), -\( \text{OCF}_3 \), -\( \text{OR}^a \), -\( \text{C}(0)\text{NR}^a \text{R}^b \), -\( \text{SR}^a \), and -\( \text{S}(\text{O}_2)\text{R}^a \).

\( \text{C}(\text{O}) \), amino, -\( \text{C}(0)\text{0-C}_{\text{C}_6} \text{alkyl} \), -\( \text{C}(0)\text{NR}^a \text{R}^b \), -\( \text{SR}^a \), and -\( \text{S}(\text{O}_2)\text{R}^a \).
Non-limiting examples of the compounds of Formula (I) include compounds 1-54 as set forth below, and pharmaceutically acceptable salts thereof:
and pharmaceutically acceptable salts thereof.

The present invention also provides a compound selected from the group consisting of:

5
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-3-hydroxy-2-(hydroxymethyl)-2-methylpropan-1-one;

(((R)-1-((1R,3S,5S)-3-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxypropan-1-one;

(R)-1-((1R,3S,5S)-3-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2,3-dihydroxypropan-1-one;

((R)-1-((1R,3S,5S)-3-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxypropan-1-one;

((exo)-3-[6-acetyl-7-amino-3-(6-phenyl-3-pyridinyl)pyrazolo[1,5-a][pyrimidin-5-yl]-8-[(1,1-dioxido-3-isothiazolidinyl)carbonyl]-8-azabicyclo[3.2.1]octane;

1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxypropanone;

1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxypropanone;

1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxypropanone;

1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxypropanone;

1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxypropanone;
1-(5-((1 R,3s,5S)-8-(1 H-1,2,3-triazole-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(7-amino-5-((1 R,3s,5S)-8-(3-methyl-1 H-1,2,4-triazole-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
N-(2-((1 R,3s,5S)-3-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-oxoethyl)methanesulfonamide;
1-(5-((1 R,3s,5S)-8-(1 H-tetrazole-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
5-((1 R,3s,5S)-8-(1 H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(5-(difluoromethyl)thiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1 R,3s,5S)-8-(1 H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(4-(pyrimidin-2-yl)phenyl)pyrazolo[1,5-a]pyrimidin-6-carboxamide;
1-(5-((1 R,3s,5S)-8-(1 H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(5-(difluoromethyl)thiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(7-amino-5-((1 R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-(1-methyl-1 H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1 R,3s,5S)-8-(1 H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(5-hydroxy-6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
5-(5-((1 R,3s,5S)-8-(1 H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)-N-methylpicolinamide;
5-(6-acetyl-7-amino-5-((1 R,3s,5S)-8-(2-hydroxyacetyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-N-methylpicolinamide;
1-(7-amino-5-((1 R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-(1-methyl-1 H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1 R,3s,5S)-8-(1 H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(5-hydroxy-6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-((1 R,3s,5S)-3-(6-acetyl-7-amino-3-(5-hydroxy-6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-(1 R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(thiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
(R)-1-(1 R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(thiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxypropan-1-one;
1-(1 R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(thiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxypropan-1-one;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(3-hydroxymethyl)-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;  
1-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(thiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;  
1-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(7-fluoronaphthalen-2-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;  
(1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(thiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-N-methyl-8-azabicyclo[3.2.1]octane-8-carboxamide;  
1-(7-amino-5-((1R,3s,5S)-8-(5-hydroxy-4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;  
1-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(4-methoxy-3-(methoxymethyl)phenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)-2-hydroxyethanone;  
1-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(4-methoxy-3-(methoxymethyl)phenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;  
1-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;  
1-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2-fluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;  
1-(7-amino-5-((1R,3s,5S)-8-(1-hydroxycyclopropane-1-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)-2-hydroxyethanone;  
(1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-sulfonic acid;
1-(7-amino-5-((1R,3s,5S)-8-(5-hydroxynicotinoyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(7-amino-5-((1R,3s,5S)-8-(4-hydroxynicotinoyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(5-(methoxymethyl)thiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(6-fluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2-methyl-2H-tetrazol-5-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(3,5-difluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2,3-difluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(4-methoxy-3-methylphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(3-chloro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(benzo[d][1,3]dioxol-5-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(4-(difluoromethoxy)phenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(4-fluoro-3-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(4-(2-methoxyethoxy)phenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2-methyl-2H-indazol-5-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(3-(6-(1 H-benzo[d]imidazol-6-yl)pyridin-3-yl)-5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2,5-difluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(4-ethoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-((1R,3s,5S)-3-(6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)-5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-((1R,3s,5S)-3-(3-(6-(1H-pyrazol-3-yl)pyridin-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-(3-(2,4'-bipyridin-5-yl)-5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(4-methoxy-1-(D$_3$)-phenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(1-(fluoromethyl)-1 H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(1-(fluoromethyl)-1 H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(1-methyl-1 H-1,2,4-triazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(1-methyl-1 H-1,2,4-triazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(1-methyl-1 H-1,2,4-triazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(1-methyl-1 H-1,2,4-triazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(3-(6-(1 H-1,2,4-triazol-3-yl)pyridin-3-yl)-5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(4-fluoro-1-methyl-1 H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(1-methyl-1 H-1,2,4-triazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(4-methyl-1 H-1,2,4-triazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(3-(6-(1 H-imidazol-4-yl)pyridin-3-yl)-5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(5-methyl-1 H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(1-methyl-1 H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(5-methyl-1 H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(4-fluoro-1-methyl-1 H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-(3-(6-(1 H-imidazol-4-yl)pyridin-3-yl)-5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(5-methyl-1 H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3r,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(3,5-difluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(1R,3r,5S)-3-(6-acetyl-7-amino-3-(6-(3,5-difluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(3-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(3-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(3-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3r,5S)-3-(6-acetyl-7-amino-3-(6-(trifluoromethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(3-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(3-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(3-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(3-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(3-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(5-methyl-6-(1-methyl-1H-pyrazol-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(1R,3s,5S)-3-(6-acetyl-7-amino-3-(5-methyl-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)pyrazolol[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)pyridin-2(1H)-one;
1-(1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)propane-1,2-dione;
2-(1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-oxoacetamide;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(5-fluoropyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(2-methyl-2H-indazol-6-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(6-(1-methyl- 1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)pyrazolol[1,5-a]pyrimidin-6-yl)ethanone;
1-(7-amino-5-((1R,3s,5S)-8-(morpholine-4-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(1-(4-fluorophenyl)-1H-pyrazol-4-yl)pyrazolol[1,5-a]pyrimidin-6-yl)ethanone;
5-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)-2-methoxybenzonitrile;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-methoxynquinolin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(hydroxymethyl)quinolin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-((4-fluorophenyl)quinolin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(3-(6-(1 H-imidazol-1-yl)pyridin-3-yl)-5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(7-amino-5-((1 R,3s,5S)-8-(5-amino-4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-(4-methyl-1 H-pyrazol-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1 R,3s,5S)-8-(4H-1 H-pyrazole-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(4-methyl-1 H-pyrazol-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(7-amino-5-((1 R,3s,5S)-8-(3-amino-1H-pyrazole-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-(4-methyl-1 H-pyrazol-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-((1 R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(3-methyl-1H-pyrazol-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1 R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(4-methyl-1H-pyrazol-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(4-methyl-1 H-pyrazol-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(3-methyl-1H-pyrazol-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-((1 R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(1-ethyl-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(1-ethyl-1 H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(7-amino-5-((1 R,3s,5S)-8-(5-(dimethylamino)-1 H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(7-amino-5-((1 R,3s,5S)-8-(5-amino-1 H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(7-amino-5-((1R,3s,5S)-8-(5-amino-1H-pyrazole-4-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
N-(3-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-carbonyl)-1H-1,2,4-triazole-5-yl)acetamide;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(1-phenyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(7-amino-5-((1R,3s,5S)-8-(5-amino-4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(3-(2,2'-bipyridin-5-yl)-5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2,6-difluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2,4-difluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(1R,3s,5S)-3-(6-acetyl-7-amino-3-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(1R,3s,5S)-3-(6-acetyl-7-amino-3-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(1R,3s,5S)-3-(6-acetyl-7-amino-3-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(1-(pyridin-2-yl)-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxypropan-1-one;
(1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(2,4-difluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxamide;
(1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(4-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxamide;
1-(1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(2,6-difluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-(1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-(7-amino-3-(6-(2-fluorophenyl)pyridin-3-yl)-5-((1R,3s,5S)-8-(5-methyl-4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
(1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(2-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxamide;
(1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(2,4-difluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-(1R,3s,5S)-3-(6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-(7-amino-5-((1R,3s,5S)-8-(3-amino-1H-pyrazole-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(3-(6-(1H-pyrazol-1-yl)pyridin-3-yl)-5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(1R,3s,5S)-3-(1H-pyrazol-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-(1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(2-phenylpyrimidin-5-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-(1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(5-chloro-6-(2-hydroxypropan-2-yl)pyrimidin-5-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-(1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-fluoro-8-methoxyquinolin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-((1R,3r,5S)-3-(6-acetyl-7-amino-3-(6-fluoro-8-methoxyquinolin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(5-(hydroxymethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(1H-benzo[d]imidazol-5-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
((1R,3s,5S)-3-(7-amino-6-bromo-3-(6-(3-(hydroxymethyl)-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)1H-1,2,4-triazol-3-yl)methanone;
1-((1R,3s,5S)-3-(7-amino-6-bromo-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
((1R,3s,5S)-3-(7-amino-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-(4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-3-(6-(3-(hydroxymethyl)-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)1H-1,2,4-triazol-3-yl)methanone;
1-((1R,3s,5S)-3-(7-amino-3-(6-(1-methyl-1H-1,2,4-triazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(7-amino-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-(4H-1,2,4-triazol-3-yl)methanone;
1-((1R,3s,5S)-3-(7-amino-3-(6-fluoro-8-methoxyquinolin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-(4H-1,2,4-triazol-3-yl)methanone;
(1R,3S,5S)-3-(7-amino-3-(1H-indazol-5-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-1,2,4-triazol-5-yl)methanone;
(1R,3S,5S)-3-(7-amino-3-(1H-indazol-6-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-1,2,4-triazol-5-yl)methanone;
(1R,3S,5S)-3-(7-amino-3-(1H-indazol-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-1,2,4-triazol-5-yl)methanone;
(1R,3S,5S)-3-(7-amino-3-(1H-indazol-5-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-1,2,4-triazol-5-yl)methanone;
(1R,3S,5S)-3-(7-amino-3-(1H-indazol-6-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-1,2,4-triazol-5-yl)methanone;
(1R,3S,5S)-3-(7-amino-3-(1H-indazol-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-1,2,4-triazol-5-yl)methanone;
(1R,3S,5S)-3-(7-amino-3-(6-(2-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
(1R,3S,5S)-3-(7-amino-3-(6-(2-fluoro-4-(trifluoromethyl)phenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
(1R,3S,5S)-3-(7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
(1R,3S,5S)-3-(7-amino-3-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
(1R,3S,5S)-3-(7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
(1R,3S,5S)-3-(7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
(1R,3S,5S)-3-(7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone.
(1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(3-methyl-1H-1,2,4-triazol-5-yl)methanone;
(1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-tetrazol-5-yl)methanone;
5-(5-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-phenylpyridine 1-oxide; (R)-1-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl))-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2,3-dihydroxypropan-1-one;
(1R,3s,5S)-3-(7-amino-6-(methylsulfonyl))-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-N-ethyl-8-azabicyclo[3.2.1]octane-8-carboxamide;
(1R,3s,5S)-3-(7-amino-6-(methylsulfonyl))-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-carboxamide;
(1R,3s,5S)-3-(7-amino-6-(methylsulfonyl))-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-carboxamide;
(1R,3s,5S)-3-(7-amino-6-(methylsulfonyl))-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-carboxamide;
(1R,3s,5S)-3-(7-amino-6-(methylsulfonyl))-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-carboxamide;
(1R,3s,5S)-3-(7-amino-6-(methylsulfonyl))-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-carboxamide;
(1R,3s,5S)-3-(7-amino-6-(methylsulfonyl))-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-carboxamide;
(1R,3s,5S)-3-(7-amino-6-(methylsulfonyl))-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-carboxamide;
(1R,3s,5S)-3-(7-amino-6-(methylsulfonyl))-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-carboxamide;
(1R,3s,5S)-3-(7-amino-6-(methylsulfonyl))-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-carboxamide;
(1R,3s,5S)-3-(7-amino-6-(methylsulfonyl))-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-carboxamide;
(1R,3s,5S)-3-(7-amino-6-(methylsulfonyl))-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-carboxamide;
(1R,3s,5S)-3-(7-amino-6-(methylsulfonyl))-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-carboxamide;
1-(1R,3s,5S)-3-(7-amino-6-(methylsulfonyl))-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-carboxamide;
(1R,3s,5S)-3-(7-amino-6-(methylsulfonyl))-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-carboxamide;
(1R,3s,5S)-3-(7-amino-6-(methylsulfonyl))-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-carboxamide;
(1R,3s,5S)-3-(7-amino-6-(methylsulfonyl))-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-carboxamide;
(1R,3s,5S)-3-(7-amino-6-(methylsulfonyl))-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-carboxamide;
(1R,3s,5S)-3-(7-amino-6-(methylsulfonyl))-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-carboxamide;
(1R,3s,5S)-3-(7-amino-6-(methylsulfonyl))-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-carboxamide;
5-((1R,3S,5S)-8-(5-methyl-4H-1,2,4-triazol-3-yl)-8-azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine;
5-((1R,3S,5S)-8-(4H-1,2,4-triazol-3-yl)-8-azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine;
((1R,3S,5S)-3-(7-amino-3-(5-hydroxy-6-phenylpyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
1-((1R,3S,5S)-3-(7-amino-3-(5-hydroxy-6-phenylpyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
((1R,3S,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-thiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3S,5S)-3-(7-amino-3-(7-fluoronaphthalen-2-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
5-((1R,3S,5S)-8-(4H-1,2,4-triazol-3-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-7-amine;
((1R,3S,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine;
(S)-1-((1R,3S,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxypropan-1-one;
(R)-1-((1R,3S,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxypropan-1-one;
((1R,3S,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-hydroxy-4H-1,2,4-triazol-3-yl)methanone;
(1R,3S,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-N-methyl-8-azabicyclo[3.2.1]octane-8-carboxamide;
((1R,3S,5S)-3-(7-amino-6-(methylsulfonyl)-3-(4-(pyridin-2-yl)phenyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3S,5S)-3-(7-amino-3-(6-(2-fluoro-4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-3-(6-(4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-3-(6-(4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methyl-4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-3-(6-(5-methoxythiophen-2-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
1-((1R,3s,5S)-3-(7-amino-3-(6-(4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
((1R,3s,5S)-3-(7-amino-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
1-((1R,3s,5S)-3-(7-amino-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
((1R,3s,5S)-3-(7-amino-3-(6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
5-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-(1-methyl-1H-pyrazol-3-yl)pyridine 1-oxide;
((1R,3s,5S)-3-(7-amino-3-(6-(2-methyl-2H-tetrazol-5-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
1-((1R,3s,5S)-3-(7-amino-3-(6-(2-methyl-2H-tetrazol-5-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
((1R,3S,5S)-3-(7-amino-3-(6-(3,4-difluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3S,5S)-3-(7-amino-3-(6-(3-fluoro-4-methylphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3S,5S)-3-(7-amino-3-(6-(3-fluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3S,5S)-3-(7-amino-3-(6-(2,3-difluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3S,5S)-3-(7-amino-3-(3′-fluoro-2,2′-bipyridin-5-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3S,5S)-3-(7-amino-3-(6-(3,5-difluoro-4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3S,5S)-3-(7-amino-3-(6-(4-methoxy-3-methylphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3S,5S)-3-(7-amino-3-(6-(3-chloro-4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3S,5S)-3-(7-amino-3-(6-(benzo[d][1,3]dioxol-5-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3S,5S)-3-(7-amino-3-(6-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3S,5S)-3-(7-amino-3-(6-(2,3-difluoro-4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-3-(6-(4-(difluoromethoxy)phenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-3-(6-(4-(2-methoxyethoxy)phenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-3-(6-(2-methyl-2H-indazol-5-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-3-(6-(2-methoxypyrimidin-5-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-3-(6-(2,5-difluoro-4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-3-(6-(4-ethoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-3-(6-(4-cyclopropoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-3-(6-(4-(3H)-phenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-3-(6-(4-(fluoromethoxy)phenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(3-(2,4'-bipyridin-5-yl)-7-amino-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
1-((1R,3s,5S)-3-(3-(2,4'-bipyridin-5-yl)-7-amino-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)2-hydroxyethanone;
((1R,3s,5S)-3-(7-amino-3-(6-butylpyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
1-((1R,3s,5S)-3-(7-amino-3-(6-(4-methoxy-(D3)-phenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;  
((1R,3s,5S)-3-(7-amino-3-(6-methylpyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;  
((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;  
((1R,3s,5S)-3-(7-amino-3-(6-(1-methyl-(D3)-1H-pyrazol-3-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;  
1-((1R,3s,5S)-3-(7-amino-3-(6-(1-methyl-(D3)-1H-pyrazol-3-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;  
1-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-(2-methoxyethoxy)ethanone;  
((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(3-(trifluoromethyl)-1H-pyrazol-5-yl)methanone;  
((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-pyrazol-5-yl)methanone;  
((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-pyrrolo[3,2-c]pyridin-2-yl)methanone;  
((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-pyrrolo[2,3-b]pyridin-2-yl)methanone;  
((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-imidazol-2-yl)methanone;  
((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-benzo[d]imidazol-2-yl)methanone;
((1R,3S,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(3-methyl-1H-pyrazol-4-yl)methanone;
((1R,3S,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(3-methyl-2,4-triazole-5-yl)methanone;
1-((1R,3S,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-(3-methyl-1H,2,4-triazole-5-yl)methanone;
((1R,3S,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(3-(hydroxymethyl)-1H-pyrazol-5-yl)methanone;
((1R,3S,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(3-(aminomethyl)-1H-pyrazol-5-yl)methanone;
((1R,3S,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)((R)-morpholin-3-yl)methanone;
((1R,3R,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)((S)-morpholin-3-yl)methanone;
((1R,3S,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carbonyl)-(4H-1,2,4-triazole-3-yl)methanone;
N-(5-((1R,3S,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carbonyl)-4H-1,2,4-triazole-3-yl)acetamide;
(5-amino-1H-pyrazol-4-yl)((1R,3S,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)methanone;
1-((1R,3S,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2,2,2-trifluoroethanone;
5-((1R,3S,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)-2-methoxybenzonitrile;
((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-(dimethylamino)-4H-1,2,4-triazol-3-yl)methanone;

((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-hydroxy-1H-pyrazol-4-yl)methanone;

((1R,3s,5S)-3-(7-amino-3-(7-(hydroxymethyl)quinolin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

((1R,3s,5S)-3-(7-amino-3-(2-(2-methyl-2H-indazol-5-yl)pyrimidin-5-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(1-phenyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

((1R,3s,5S)-3-(7-amino-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-amino-4H-1,2,4-triazol-3-yl)methanone;

((1R,3s,5S)-3-(7-amino-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-amino-4H-1,2,4-triazol-3-yl)methanone;

((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(2-phenylpyrimidin-5-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(2H-1,2,3-triazol-4-yl)methanone;

((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(2-phenylpyrimidin-5-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(2H-1,2,3-triazol-4-yl)methanone;

((1R,3s,5S)-3-(2,2'-bipyridin-5-yl)-7-amino-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

2-(5-(5-(1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-3-yl)pyridine 1-oxide;

((1R,3s,5S)-3-(7-amino-3-(6-(2-fluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-3-(6-(4-fluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

((1R,3s,5S)-3-(7-amino-3-(6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

((1R,3s,5S)-3-(7-amino-3-(6-(2,6-difluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

((1R,3s,5S)-3-(7-amino-3-(6-(2,4-difluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

((1R,3s,5S)-3-(3-(6-(1H-pyrazol-4-yl)pyridin-3-yl)-7-amino-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

((1R,3s,5S)-3-(7-amino-3-(6-(2-fluoro-4-(trifluoromethyl)phenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

((1R,3s,5S)-3-(7-amino-3-(1-methyl-1H-pyrazol-4-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

1-((1R,3s,5S)-3-(7-amino-3-(1-methyl-1H-pyrazol-4-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;

((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methyl-4H-1,2,4-triazol-3-yl)methanone;

(3-amino-1H-pyrazol-5-yl)((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)methanone;
((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-pyrazol-5-yl)methanone; 1-((1R,3s,5S)-3-(7-amino-3-(6-(4-fluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone; ((1R,3s,5S)-3-(7-amino-3-(6-(4-fluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methyl-4H-1,2,4-triazol-3-yl)methanone; (3-amino-1H-pyrazol-5-yl)1-((1R,3s,5S)-3-(7-amino-3-(6-(4-fluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)methanone; ((1R,3s,5S)-3-(7-amino-3-(6-(4-fluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone; 1-((1R,3s,5S)-3-(7-amino-3-(6-(4-fluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone; ((1R,3s,5S)-3-(7-amino-3-(6-(2,4-difluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-carboxamide; (1R,3s,5S)-3-(7-amino-3-(6-(4-fluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-carboxamide; ((1R,3s,5S)-3-(7-amino-3-(6-(2,4-difluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-carboxamide; ((1R,3s,5S)-3-(7-amino-3-(6-(2,4-difluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methyl-4H-1,2,4-triazol-3-yl)methanone;
1-((1 R,3s,5S)-3-(7-amino-3-(6-(2,4-difluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
(3-amino-1 H-pyrazol-5-yl)((1 R,3s,5S)-3-(7-amino-3-(6-(2,4-difluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)methanone;
((1 R,3s,5S)-3-(7-amino-3-(6-(2-fluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxamide;
1-((1 R,3s,5S)-3-(7-amino-3-(6-(2-fluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
((1 R,3s,5S)-3-(7-amino-3-(6-(2-fluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methyl-4H-1,2,4-triazol-3-yl)methanone;
(3-amino-1 H-pyrazol-5-yl)((1 R,3s,5S)-3-(7-amino-3-(6-(2-fluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)methanone;
((1 R,3s,5S)-3-(7-amino-3-(6-(2-fluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1 H-pyrazol-5-yl)methanone;
((1 R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(2-phenylpyrimidin-5-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(2-amino-4-methylpyrimidin-5-yl)((1 R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)methanone;
4-((1 R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carbonyloxazol-2(3H)-one;
4-((1 R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carbonyl)oxazol-2(3H)-one;
6-((1 R,3S,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carbonyl)pyridin-2(1H)-one;
(S)-4-((1 R,3R,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carbonyloxazolidin-2-one;
(R)-4-((1 R,3S,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carbonyloxazolidin-2-one;
((1 R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(2-aminopyrimidin-4-yl)methanone;
((1 R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(2-aminopyridin-3-yl)methanone;
((1 R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4-aminopyrimidin-5-yl)methanone;
((1 R,3s,5S)-3-(7-amino-3-(2-(3-fluoro-4-methoxyphenyl)pyrimidin-5-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1 R,3s,5S)-3-(7-amino-3-(2-(2,3-difluoro-4-methoxyphenyl)pyrimidin-5-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
1-((1 R,3s,5S)-3-(7-amino-3-(2-(2,3-difluoro-4-methoxyphenyl)pyrimidin-5-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
((1 R,3s,5S)-3-(3-(6-((1 H-pyrazol-1-yl)pyridin-3-yl)-7-amino-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1 R,3s,5S)-3-(7-amino-3-(imidazo[1,2-a]pyrimidin-6-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
(1R,3s,5S)-3-(7-amino-3-(2-(2-hydroxypropan-2-yl)pyrimidin-5-yl)-6-(methylsulfonyl)pyrazolo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
1-((1R,3s,5S)-3-(3-(6-(1H-pyrazol-1-yl)pyridin-3-yl)-7-amino-6-(methylsulfonyl)pyrazolo[3.2.1]octan-8-yl)-7-aminoo-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)pyrazolo[3.2.1]octan-8-yl)-2-hydroxyethanone;
4-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-fluorobenzamide;
4-(7-amino-5-((1R,3s,5S)-8-(2-hydroxyacetyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-fluorobenzamide;
1-((1R,3s,5S)-3-(7-amino-3-(6-(1H-pyrazol-1-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
1-((1R,3s,5S)-3-(7-amino-3-(5-chloro-6-(2-hydroxypropan-2-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
1-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-(pyrimidin-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
1-((1R,3s,5S)-3-(7-amino-6-(cyclopropylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
1-((1R,3s,5S)-3-(7-amino-6-(ethylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
1-((1R,3s,5S)-3-(7-amino-3-(6-phenylpyridin-3-yl)-6-(propylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
1-((1R,3s,5S)-3-(7-amino-6-(isopropylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
1-((1R,3s,5S)-3-(7-amino-6-(propylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
1-((1R,3s,5S)-3-(7-amino-6-(isopropylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
1-((1R,3s,5S)-3-(7-amino-6-(cyclopropylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
1-((1R,3s,5S)-3-(7-amino-6-(ethylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
1-((1R,3s,5S)-3-(7-amino-6-(isopropylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
1-((1R,3s,5S)-3-(7-amino-6-(propylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
1-((1R,3s,5S)-3-(7-amino-6-(isopropylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-3-(6-cyclohexylpyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-3-(6-cyclopentylpyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
1-((1R,3s,5S)-3-(7-amino-3-(6-cyclobutylpyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
((1R,3s,5S)-3-(7-amino-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(2H-1,2,3-triazol-4-yl)methanone;
((1R,3s,5S)-3-(7-amino-3-(6-(2-fluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(2H-1,2,3-triazol-4-yl)methanone;
((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-N-methoxy-8-azabicyclo[3.2.1]octane-8-carboxamide;
((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-N-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxamide;
((1R,3s,5S)-3-(7-amino-3-(6-(2,6-difluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(2H-1,2,3-triazol-4-yl)methanone;
((1R,3s,5S)-3-(7-amino-3-(6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(2H-1,2,3-triazol-4-yl)methanone;
((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(2-phenylpyrimidin-5-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(2H-1,2,3-triazol-4-yl)methanone;
((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(1-phenyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(2H-1,2,3-triazol-4-yl)methanone;
((1R,3s,5S)-3-(7-amino-6-fluoroquinolin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(2H-1,2,3-triazol-4-yl)methanone;
((1R,3s,5S)-3-(7-amino-1-(4-fluorophenyl)-1H-pyrazol-4-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(2H-1,2,3-triazol-4-yl)methanone;
((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-(pyrimidin-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(2H-1,2,3-triazol-4-yl)methanone;
((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-(5-methylthiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-(5-methylthiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(2H-1,2,3-triazol-4-yl)methanone;
1-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-(5-methylthiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methyl-1H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-(5-methylthiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methyl-4H-1,2,4-triazol-3-yl)methanone;
1-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-(5-methylthiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1-hydroxycyclopropyl)methanone;
2-amino-1-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-(5-methylthiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1-hydroxypropan-1-one;
((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-(4-methylthiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(2H-1,2,3-triazol-4-yl)methanone;
1-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-(4-methylthiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)ethanone;
((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-(4-methylthiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methyl-4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-(4-methylthiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-3-(6-(5,6-dihydro-4H-cyclopenta[d]thiazol-2-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-3-(6-(5,6-dihydro-4H-cyclopenta[d]thiazol-2-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-1,2,3-triazol-5-yl)methanone;
((1R,3s,5S)-3-(7-amino-3-(6-(5,6-dihydro-4H-cyclopenta[d]thiazol-2-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methyl-4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-3-(6-(5,6-dihydro-4H-cyclopenta[d]thiazol-2-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-3-(6-(4,5-dimethylthiazol-2-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methyl-1H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-3-(6-(4,5-dimethylthiazol-2-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-1,2,3-triazol-5-yl)methanone;
(3-(7-amino-3-(6-(4,5-dimethylthiazol-2-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methyl-1H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-3-(6-(4,5-dimethylthiazol-2-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-1,2,3-triazol-5-yl)methanone;
((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-(2-methylthiazol-4-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methyl-1H-1,2,4-triazol-3-yl)methanone;
1-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-(2-methylthiazol-4-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methyl-1H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-(2-methylthiazol-4-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(2H-1,2,3-triazol-4-yl)methanone;
5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine;
N-(2-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-oxoethyl)acetamide;
N-(2-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2,2,2-trifluoroacetamide;
((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)((R)-pyrrolidin-2-yl)methanone;
((1R,3R,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-2-yl)methanone;
((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methyl-4H-1,2,4-triazol-3-yl)methanone;
5-((1R,3s,5S)-8-(4H-1,2,4-triazol-3-ylsulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine;
(1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-N-methyl-8-azabicyclo[3.2.1]octane-8-carboxamide;
(1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-N-ethyl-8-azabicyclo[3.2.1]octane-8-carboxamide;
(1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxamide;
(1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-N-(2-methoxyethyl)-8-azabicyclo[3.2.1]octane-8-carboxamide;
(1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-N-(2-hydroxyethyl)-8-azabicyclo[3.2.1]octane-8-carboxamide;
((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-(2,3-difluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
(1R,3S,5S)-3-(7-amino-6-cyclopropyl-3-(6-(4-fluoro-3-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

((1R,3S,5S)-3-(7-amino-6-cyclopropyl-3-(6-(2,5-difluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

((1R,3S,5S)-3-(7-amino-6-cyclopropyl-3-(6-(4-ethoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

((1R,3S,5S)-3-(7-amino-6-cyclopropyl-3-(6-(4-(2-methoxyethoxy)phenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

((1R,3S,5S)-3-(7-amino-6-cyclopropyl-3-(6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

1-((1R,3S,5S)-3-(7-amino-6-cyclopropyl-3-(6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;

((1R,3S,5S)-3-(7-amino-6-cyclopropyl-3-(6-(4-fluoro-5-methyl-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

1-((1R,3S,5S)-3-(7-amino-6-cyclopropyl-3-(6-(4-fluoro-5-methyl-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;

((1R,3S,5S)-3-(7-amino-6-cyclopropyl-3-(6-(3-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

1-((1R,3S,5S)-3-(7-amino-6-cyclopropyl-3-(6-(3-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-(1-methyl-1H-imidazol-4-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-methoxyquinolin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)methanone;
N-(5-((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carbonyl)-4H-1,2,4-triazol-3-yl)acetamide;
((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-(dimethylamino)-4H-1,2,4-triazol-3-yl)methanone;
(3-amino-1H-pyrazol-4-yl)((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-(dimethylamino)-4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-(2-methoxyethylamino)-4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-(2-hydroxyacetyl)-4H-1,2,4-triazol-3-yl)methanone;
7-amino-5-((1R,3s,5S)-8-(2-hydroxyacetyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidine-6-carbonitrile;
5-((1R,3s,5S)-8-(1H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidine-6-carbonitrile;
5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(thiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-6-carbonitrile;
((1R,3S,5S)-3-(7-amino-6-(methoxymethyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
(3-amino-1H-pyrazol-5-yl)((1R,3S,5S)-3-(7-amino-6-(methoxymethyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)methanone;
(3-amino-1H-pyrazol-5-yl)((1R,3S,5S)-3-(7-amino-6-(methoxymethyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)methanone;
((1R,3S,5S)-3-(7-amino-6-(cyclopropyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3S,5S)-3-(7-amino-6-(cyclopropyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3S,5S)-3-(7-amino-6-(cyclopropyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3S,5S)-3-(7-amino-6-(cyclopropyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
1-((1R,3S,5S)-3-(7-amino-6-(cyclopropyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
((1R,3S,5S)-3-(7-amino-6-(cyclopropyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
1-((1R,3S,5S)-3-(7-amino-6-(cyclopropyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
(S)-1 -((1 R,3R,5S)-3-(3-(6-(1 H-imidazol-2-yl)pyridin-3-yl)-6-acetyl-7-
aminopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxypropanone;
2 -((1 R,3s,5S)-3-(3-(6-(1 H-imidazol-2-yl)pyridin-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-oxoethyl acetate;
1 -((1 R,3s,5S)-3-(3-(6-(1 H-imidazol-2-yl)pyridin-3-yl)-7-amino-5-((1 R,3s,5S)-8-(methylsulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolyl)-5(1 R,3s,5S)-8-(1 H-pyrrole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1 -((1 R,3s,5S)-3-(3-(6-(1 H-imidazol-2-yl)pyridin-3-yl)-7-amino-5-((1 R,3s,5S)-8-(1 H-pyrrole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(3-(6-(1 H-imidazol-2-yl)pyridin-3-yl)-7-amino-5-((1 R,3s,5S)-8-(1 H-pyrrole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1 -((1 R,3s,5S)-3-(3-(6-(1 H-imidazol-2-yl)pyridin-3-yl)-7-amino-5-((1 R,3s,5S)-8-(1 H-pyrrole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1 -((1 R,3s,5S)-3-(3-(6-(1 H-imidazol-2-yl)pyridin-3-yl)-7-amino-5-((1 R,3s,5S)-8-(1 H-pyrrole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1 -((1 R,3s,5S)-3-(3-(6-(1 H-imidazol-2-yl)pyridin-3-yl)-7-amino-5-((1 R,3s,5S)-8-(1 H-pyrrole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1 -((1 R,3s,5S)-3-(3-(6-(1 H-imidazol-2-yl)pyridin-3-yl)-7-amino-5-((1 R,3s,5S)-8-(1 H-pyrrole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1 -((1 R,3s,5S)-3-(3-(6-(1 H-imidazol-2-yl)pyridin-3-yl)-7-amino-5-((1 R,3s,5S)-8-(1 H-pyrrole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1 -((1 R,3s,5S)-3-(3-(6-(1 H-imidazol-2-yl)pyridin-3-yl)-7-amino-5-((1 R,3s,5S)-8-(1 H-pyrrole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(3-(6-(1H-imidazol-2-yl)pyridin-3-yl)-7-amino-5-((1R,3s,5S)-8-(5-methyl-4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-((1R,3s,5S)-3-(3-(6-(1H-imidazol-2-yl)pyridin-3-yl)-6-acetyl-7-amino-5-((1R,3s,5S)-8-(5-methyl-4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-fluoroethanone;
1-((1R,3s,5S)-3-(6-(1H-imidazol-2-yl)pyridin-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-fluoropropan-1-one;
1-(3-(3-(6-(1H-imidazol-2-yl)pyridin-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-N-methyl-8-azabicyclo[3.2.1]octane-8-carboxamide;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(5-methyl-1H-imidazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(5-methyl-1H-imidazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-6-cyclopropyl-3-(6-(5-methyl-1H-imidazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-(3-(3-(6-(1H-imidazol-2-yl)pyridin-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-(5-fluoro-1H-imidazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-(5-fluoro-1H-imidazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-(1H-imidazol-2-yl)-5-methylpyridin-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-(3-(6-(1H-imidazol-2-yl)-5-methylpyridin-3-yl)-7-amino-5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-((1R,3s,5S)-3-(3-(4-(1H-imidazol-2-yl)phenyl)-7-amino-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(3-fluoro-4-(1H-imidazol-2-yl)phenyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-(2,4-triazol-3-yl)methanone;
1-((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(3-fluoro-4-(1H-imidazol-2-yl)phenyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(3-fluoro-4-(1H-imidazol-2-yl)phenyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(3-fluoro-4-(1H-imidazol-2-yl)phenyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(3-fluoro-4-(1H-imidazol-2-yl)phenyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(3-(4-(1H-imidazol-2-yl)phenyl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(3-(4-(1H-imidazol-2-yl)phenyl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-(4-fluoro-1H-imidazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-(4-fluoro-1H-imidazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(1-hydroxybutyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;  
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(1-hydroxypropyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;  
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;  
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(1-hydroxypropyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;  
1-(7-amino-3-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-5-((1R,3s,5S)-8-(5-methyl-4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;  
1-(5-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;  
1-(7-amino-5-((1R,3s,5S)-8-(1-hydroxycyclopropanecarbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;  
1-(7-amino-5-((1R,3s,5S)-8-(1-hydroxycyclopropanecarbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;  
1-(5-((1R,3s,5S)-8-(1H-pyrazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;  
1-(7-amino-5-((1R,3s,5S)-8-(1H-pyrazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;  
1-(7-amino-5-((1R,3s,5S)-8-(1H-pyrazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;  
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-((R)-1-hydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(7-amino-5-(1R,3s,5S)-8-(5-amino-1H-pyrazole-4-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-(1R,3s,5S)-8-(1H-pyrrole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(7-amino-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)-5-((1R,3s,5S)-8-(3-methyl-1H-1,2,4-triazole-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(7-amino-3-(6-(1-hydroxybutyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-(4H-1,2,4-triazol-3-yl)methanone;
1-(5-(1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(4-(1-hydroxyethyl)phenyl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(2-hydroxypropan-2-yl)-5-methylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-(5-(1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2-hydroxypropan-2-yl)-5-methylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
(1R,3s,5S)-3-(7-amino-3-(6-(1-hydroxybutyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
(1R,3s,5S)-3-(7-amino-3-(6-(1-hydroxypropyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
(1R,3s,5S)-3-(7-amino-3-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-1,2,4-triazol-5-yl)methanone;
1-((1R,3s,5S)-3-(7-amino-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;

((1R,3s,5S)-3-(7-amino-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(3-methyl-1H-1,2,4-triazol-5-yl)methanone;

((1R,3s,5S)-3-(7-amino-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-1,2,3-triazol-5-yl)methanone;

1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2-methoxyethoxy)methyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;

((1R,3s,5S)-3-(7-amino-3-(6-(2-methoxyethoxy)methyl)pyridin-3-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2-methoxyethoxy)methyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;

((1R,3s,5S)-3-(7-amino-3-(6-(2-methoxyethoxy)methyl)pyridin-3-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2-methoxyethoxy)methyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;

((1R,3s,5S)-3-(7-amino-3-(6-(2-methoxyethoxy)methyl)pyridin-3-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2-methoxyethoxy)methyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;

((1R,3s,5S)-3-(7-amino-3-(6-(2-methoxyethoxy)methyl)pyridin-3-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2-methoxyethoxy)methyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;

((1R,3s,5S)-3-(7-amino-3-(6-(2-methoxyethoxy)methyl)pyridin-3-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
1-((1R,3s,5S)-3-(7-amino-3-(6-(1-hydroxycyclopentyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[3,2,1]octan-8-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl) methanone;

1-((1R,3s,5S)-3-(7-amino-3-(6-(1-hydroxycyclopentyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[3,2,1]octan-8-yl)(4H-1,2,4-triazol-3-yl) methanone;

1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;

1-((1R,3s,5S)-3-(7-amino-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl) methanone;

1-((1R,3s,5S)-3-(7-amino-3-(6-(3-hydroxyoxetan-3-yl)pyridin-3-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl) methanone;

1-((1R,3s,5S)-3-(7-amino-3-(6-(3-hydroxyoxetan-3-yl)pyridin-3-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl) methanone;

1-((1R,3s,5S)-3-(7-amino-3-(6-(3-hydroxyoxetan-3-yl)pyridin-3-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl) methanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(1,2-dihydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
((1R,3s,5S)-3-(7-amino-3-(8-hydroxy-5,6,7,8-tetrahydroquinolin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

Deuterated-(3-exo)-3-

(3-exo)-3-

(3-exo)-3-

(3-exo)-3-

(3-exo)-3-

(3-exo)-3-

(3-exo)-3-

1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(8-hydroxy-5,6,7,8-tetrahydroquinolin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
((1R,3s,5S)-3-(7-amino-3-(8-hydroxy-5,6,7,8-tetrahydroquinolin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(8-hydroxy-5,6,7,8-tetrahydroquinolin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(8-hydroxy-5,6,7,8-tetrahydroquinolin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(8-hydroxy-5,6,7,8-tetrahydroquinolin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
Deuterated-(3-exo)-3-(6-acetyl-7-amino-3-(5,6,7,8-tetrahydro-8-hydroxy-3-quinolinyl-(D))pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
Deuterated-(3-exo)-3-(6-acetyl-7-amino-3-(5,6,7,8-tetrahydro-8-hydroxy-3-quinolinyl-(D))pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(1,2-dihydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(1,2-dihydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(1,2-dihydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(7-hydroxy-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(7-hydroxy-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(7-hydroxy-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(4-hydroxy-3,4-dihydro-2H-pyrano[3,2-b]pyridin-7-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;

(1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(4-hydroxy-3,4-dihydro-2H-pyrano[3,2-b]pyridin-7-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)ethanone;

1-(5-((1R,3s,5S)-8-(1H-pyrazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;

1-(5-((1R,3s,5S)-8-(1H-pyrazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;

1-(5-((1R,3s,5S)-8-(1H-pyrazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;

1-(5-((1R,3s,5S)-8-(1H-pyrazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;

1-(5-((1R,3s,5S)-8-(1H-pyrazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;

1-(5-((1R,3s,5S)-8-(1H-pyrazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(1H,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-(7-amino-3-(6-(1H,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)pyridin-3-yl)-5-((1R,3s,5S)-8-(5-methyl-4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(1H,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)ethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(1H,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
((1 R,3s,5S)-3-(7-amino-3-(6-(2-amino-1,1,1,3,3,3-hexafluoropropan-2-yl)pyridin-3-yl)-6-cyclopropylpyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

1-((1 R,3s,5S)-3-(7-amino-3-(6-(2-amino-1,1,1,3,3,3-hexafluoropropan-2-yl)pyridin-3-yl)-6-cyclopropylpyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;

((1 R,3s,5S)-3-(7-amino-3-(6-(2-amino-1,1,1,3,3,3-hexafluoropropan-2-yl)pyridin-3-yl)-6-cyclopropylpyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methyl-4H-1,2,4-triazol-3-yl)methanone;

(3-amino-1H-pyrazol-5-yl)((1 R,3s,5S)-3-(7-amino-3-(6-(2-amino-1,1,1,3,3,3-hexafluoropropan-2-yl)pyridin-3-yl)-6-cyclopropylpyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)methanone;

15-5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(2-(hydroxymethyl)thiazol-5-yl)pyrazolo[1,5-a]pyrimidin-6-yl)methanone;

5-5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)methyl 4H-1,2,4-triazole-3-carboxylate;

N-((1 R,3s,5S)-3-(7-amino-3-(6-(2-amino-1,1,1,3,3,3-hexafluoropropan-2-yl)pyridin-3-yl)-6-cyclopropylpyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

10-5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)methyl 4H-1,2,4-triazole-3-carboxamide;
((1R,3s,5S)-3-(7-amino-3-(2-(aminomethyl)-4-cyclopropylthiazol-5-yl)-6-cyclopropylpyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
1-(5-((1R,3s,5S)-8-(1H-1,2,4-triazole-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(5-fluoro-6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-(8-(4H-1,2,4-triazole-3-carbonyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
(2R)-1-(3-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-2-hydroxypropan-1-one;
1-(5-(5-(4H-1,2,4-triazole-3-carbonyl)-2,5-diazabicyclo[2.2.2]octan-2-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
(2R)-1-(5-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-2,5-diazabicyclo[2.2.2]octan-2-yl)-2-hydroxypropan-1-one;
1-(5-(3-(4H-1,2,4-triazole-3-carbonyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
(2R)-1-(8-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-2-hydroxypropan-1-one;
1-(8-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-2-hydroxyethanone;
N-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-yl)acetamide;
N-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-yl)acetamide;
N-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-yl)acetamide;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(pyrrolidin-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(1-(1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(pyrrolidin-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-(4H-1,2,4-triazol-3-yl)methanone;
1-((1 R,3s,5S)-3-(7-amino-6-((methylsulfonyl)-3-(6-(pyrrolidin-2-yl)pyridin-3-yl)pyrazolo[3.2.1]octan-8-yl)-2-hydroxyethanone;((1 R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-(pyrrolidin-2-yl)pyridin-3-yl)pyrazolo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
(R)-4-((5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)oxazolidin-2-one;
(S)-4-((5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)oxazolidin-2-one;
(S)-4-((6-acetyl-7-amino-5-((1 R,3s,5S)-8-(2-hydroxyacetyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)oxazolidin-2-one;
(R)-4-((5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)oxazolidin-2-one;
2-((5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)oxazolidin-2-one;
2-((5-((1 R,3s,5S)-8-(2-hydroxyacetyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)oxazolidin-2-one;
1-(7-amino-5-((1 R,3r,5S)-3-hydroxy-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
((1 R,3r,5S)-3-(7-amino-6-((methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1 R,3r,5S)-3-(7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1 R,3r,5S)-3-((6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1 R,3r,5S)-3-((6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
1-(5-((9-(1 H-1,2,4-triazole-3-carbonyl)-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)-7-amino-3-(1-phenyl-1 H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((9-(1 H-1,2,4-triazole-3-carbonyl)-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(7-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3-oxa-i-
azabicyclo[3.3.1]nonan-9-yl)-2-hydroxyethanone;
(7-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl) -
3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)(1 H-1,2,4-triazol-3-yl)methanone;
(mixture of stereoisomer);
(7-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl) -
3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)(1 H-1,2,4-triazol-3-yl)methanone ;
(isomer I);
(7-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl) -
3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)(1 H-1,2,4-triazol-3-yl)methanone;
(isomer II);
(7-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl) -
3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)(1 H-1,2,4-triazol-3-yl)methanone;
(isomer I);
(7-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl) -
3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)(1 H-1,2,4-triazol-3-yl)methanone;
(isomer II);
1-(5-(9-(1 H-1,2,4-triazole-3-carbonyl)-9-azabicyclo[3.3.1]nonan-3-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(7-amino-5-||1S,3R,5R||6-hydroxy-8-(1 H-1,2,4-triazole-3-carbonyl)-8-
azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
((1R,3s,5S)-7-(7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3,9-
diazabicyclo[3.3.1]nonan-9-yl)(1 H-1,2,4-triazol-3-yl)methanone;
endo/exo-7-(6-acetyl-7-amino-3-(6-phenyl-3-pyridinyl)pyrazolo[1,5-a]pyrimidin-5-yl)-
9-(4H-1,2,4-triazol-3-ylcarbonyl)-3-thia-9-azabicyclo[3.3.1]nonane , 3,3-dioxide;
((1R,3s,5S)-3-(7-amino-6-(1-hydroxycyclopropyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1 H-1,2,4-triazol-3-
yl)methanone;
5-((1R,3s,5S)-8-(1 H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-
amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidine-6-carboxamide;
((1 R,3s,5S)-3-(7-(methylamino)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1 R,3s,5S)-3-(7-amino-3-(3-fluoro-(hydroxymethyl)phenyl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
1-((1 R,3s,5S)-3-(7-amino-3-(3-fluoro-4-(hydroxymethyl)phenyl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
((1 R,3s,5S)-3-(7-amino-3-(3-fluoro-4-(1-aminocyclopropyl)-3-fluorophenyl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1 R,3s,5S)-3-(7-amino-3-(4-(2-aminopropan-2-yl)-3-fluorophenyl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1 R,3s,5S)-3-(7-amino-3-(6-(2-fluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carbonyl)-N’-(3-(dimethylamino)propyl)-N-ethyl-2H-1,2,3-triazole-2-carboximidamide;
1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(cyclopropylamino)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-aminopyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(2-(cyclopropylamino)pyrimidin-5-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-((1 R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(cyclobutoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
N’-(5-(6-acetyl-7-amino-5-((1 R,3s,5S)-8-(2-hydroxyacetyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)acetohydrazide;
N’-(5-(6-acetyl-7-amino-5-((1 R,3s,5S)-8-(2-hydroxyacetyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)propionohydrazide;
((1 R,3s,5S)-3-(7-amino-3-(6-cyclobutoxypyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
N-(2-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)pyridin-3-yl)acetamide;
5-(5-(5-(1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)-5-methylimidazolidine-2,4-dione;
5-(5-(6-acetyl-7-amino-5-((1R,3s,5S)-8-(2-hydroxyacetyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-5-methylimidazolidine-2,4-dione;
5-(5-(5-((1R,3s,5S)-8-(1H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)-3-methylurea;
ethy1 5-(5-((1R,3s,5S)-8-(2-hydroxyacetyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl carbamate;
1-(4-(7-amino-5-(1R,3s,5S)-8-(morpholine-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)phenyl)-3-methylurea;
1-(5-(5-(1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)pyridin-2-yl)-3-ethyurea;
1-(4-(5-(1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrimidine-2-carboxamide;
(1R,3S,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-((R)-3-hydroxypyrrolidin-1-yl)-4H-1,2,4-triazol-3-yl)methanone;

(1R,3S,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-((R)-3-hydroxy-4-methyl-4H-1,2,4-triazol-3-yl)methanone;

(1R,3S,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-((4-methylpiperazin-1-yl)-4H-1,2,4-triazol-3-yl)methanone;

(1R,3S,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-(4-methylpiperazin-1-yl)-4H-1,2,4-triazol-3-yl)methanone;

(1R,3S,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-(2-methoxyethoxy)-4H-1,2,4-triazol-3-yl)methanone;

(1R,3S,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-(4-hydroxy-4H-1,2,4-triazol-3-yl)methanone;

(1R,3S,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methoxy-4H-1,2,4-triazol-3-yl)methanone;

(1R,3S,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-(5-methoxy-4H-1,2,4-triazol-3-yl)methanone;

(1R,3S,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-(4-methylpiperazin-1-yl)-4H-1,2,4-triazol-3-yl)methanone;

(1R,3S,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-morpholino-4H-1,2,4-triazol-3-yl)methanone;

1-[(3-Exo)-3-(7-amino-6-fluoro-3-(6-(1H-imidazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]oct-8-yl]-2-hydroxyethanone;

Or a stereoisomer thereof;

Or a pharmaceutically acceptable salt thereof;

Or a pharmaceutically acceptable salt of the stereoisomer thereof.
The compounds according to the invention have pharmacological properties; in particular, the compounds of the present invention can be inhibitors, regulators or modulators of protein kinases, such as mTOR protein kinases. As inhibitors of mTOR, preferred compounds of the present invention can exhibit IC50 values of less than about 5 \( \mu \text{M} \), preferably about 0.001 to about 1.0 \( \mu \text{M} \), and more preferably about 0.001 to about 0.1 \( \mu \text{M} \). The assay methods are described in the Examples set forth below.

**Methods for Making the Compounds of Formula (I)**

The compounds of Formula (I) can be prepared from known or readily prepared starting materials, following methods known to one skilled in the art of organic synthesis. Methods useful for making the compounds of Formula (I) are set forth in the Examples below. Alternative synthetic pathways and analogous structures will be apparent to those skilled in the art of organic synthesis. All stereoisomers and tautomeric forms of the compounds are contemplated.

**EXAMPLES**

Solvents, reagents, and intermediates that are commercially available were used as received. Reagents and intermediates that are not commercially available were prepared in the manner as described below. \(^1\)H NMR spectra were obtained on a Varian spectrometer (400 MHz and 500 MHz) are reported as ppm down field from Me\(_2\)Si with number of protons, multiplicities, and coupling constants, in Hertz indicated parenthetically. Where LC/MS data are presented, analyses was performed using an Agilent 1100 Series LC w/ MicroMass Quattro MS Varian Pursuit XRxs C18, 5micron, 150mm x 4.6mm ID gradient flow (0.1\% TFA or 0.2\% FA): 0 min - 5\% ACN, 7.5 min - 100\% ACN, 8.5 min -100 ACN, 8.51 min - 5\% ACN, 10 min - stop 3 ml/min. The retention time and observed parent ion are given. Where the description indicates the reaction mixture was purified by HPLC, the description refers to using a preparative Agilent 1100 Series LC/MSD SL system: Column Reverse Phase- Varian Pursuit XRxs 10C-18 250 X 2.1mm; elution with gradient Acetonitrile/water with 0.1\%TFA or 0.2\% formic acid. The desired product was detected and collected by a mass-triggered automatic sample collector. Flash
column chromatography was performed using pre-packed normal phase silica from Biotage, Inc.

The following solvents, reagents and reaction conditions may be referred to by their abbreviations:

- Aq: aqueous
- g or gm: grams
- psi: pounds per square inch
- pH: concentration of hydronium ions in a solution
- °C: degrees Celsius
- h: hours
- THF: Tetrahydrofuran
- Et₂O: diethyl ether
- SEM: 2-(trimethylsilyl)ethoxymethyl
- LC-MS: Liquid chromatography mass spectrometry
- DCM: dichloromethane
- N: Normal
- ml: milliliter
- NBS: N-Bromosuccinimide
- NCS: N-Chlorosuccinimide
- NIS: N-Iodosuccinimide
- r.t.: room temperature
- MeOH: methanol
- DIEA: diisopropylethylamine
- EtOAc: ethyl acetate
- EtOH: ethanol
- DMF: dimethylformamide
- wt%: weight percent
- m/z: mass per charge
- LiOH: lithium hydroxide
- DMSO: dimethylsulfoxide
- HPLC: high performance liquid chromatography
- IPA: isopropanol
Ret: retention
F₉: retention time
RP: reverse phase
ACN: acetonitrile
CH₃CN: acetonitrile
MeCN: acetonitrile
Mel: iodomethane
r.t.: room temperature
PTSA: para-toluene sulfonic acid
CDI: N,N'-carbonyldiimidazole
mg: milligram
PMA: phosphomolybdic acid
LiHMDS: Lithium bis(trimethylsilyl)amide
HMDS: hexamethyldisilazane
Pd/C: palladium on carbon
H₂: hydrogen gas
PdCl₂(dppf): [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II)
µmol: micromole
TFA: trifluoroacetic acid
NMP: N-methyl-2-pyrrolidone
min: minute
DME: dimethylethane
AcOH: acetic acid
BBN: 9-borabicyclo[3.3.1]nonane
BOC: tertiary-butylxocarbonyl
M: Molar
mmol: millimolar
DIEA: diisopropylethylamine
Bu₃SnCN: tributyltin cyanide
Pd[P(t-Bu)₃]₂: bis(tributyl)phosphine palladium
Pd[PPh₃]₄: tetrakis(triphenylphosphine) palladium
EDCI: 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide
UV: ultraviolet
LDA: lithium diisopropylamide
Tf: trifluoromethanesulfonyl

In certain instances, where the piperidine moiety attached to the pyrazolo[1,5-]
5
a]pyrimidine core is drawn in the chair conformation (i.e. chair conformation is interchangeable with the flat structure (i.e.
and other conformational isomers including but not limited to the half chair, twist-boat or boat conformation, which can interconvert with each other thermodynamically.

Example 1-1

Scheme 1-1
**Preparation of 1-((5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone**

**Step 1**

**Preparation of pyrazolo[1,5-a]pyrimidine-5,7-diol**

To 1H-pyrazol-3-amine (12.3 g, 148.0 mmol) in EtOH (50 mL) was added diethyl malonate (25.0 mL, 164.7 mmol), 21wt% NaOEt in EtOH (110 mL, 294.6 mmol) and additional EtOH (50 mL). The resulting mixture was then heated at 80 °C under an atmosphere of argon for 16 hours, at which time the reaction was allowed to cool to room temperature. The reaction mixture was then concentrated in vacuo until almost dry, before H2O (500 mL) was added. Vigorous stirring aided the dissolving of solids, at which time cone. HCl was added until pH~2 was attained (solid precipitate formed). The precipitate was collected and dried by vacuum filtration giving pyrazolo[1,5-a]pyrimidine-5,7-diol as a tan solid (17.13 g).

**Step 2**

**Synthesis of 5,7-dichloropyrazolo[1,5-a]pyrimidine**
To pyrazolo[1,5-a]pyrimidine-5,7-diol (9.6 g, 63.5 mmol) in a 500 mL flask was added POCI$_3$ (125 mL, 1341.1 mmol). The flask was then cooled to 0 °C and N,N-dimethylaniline (22 mL, 173.6 mmol) was carefully added. On warming to room temperature, the reaction was then heated at 60 °C under an atmosphere of argon for 16 hours. On cooling, the reaction mixture was concentrated in vacuo to give a brown viscous liquid. This brown viscous liquid was carefully poured onto ice and allowed to warm to room temperature overnight. To the brown solution was carefully added saturated NaHCO$_3$ solution until no further effervescence was observed and pH ~ 8 was attained. Organics were then extracted with CH$_2$Cl$_2$ (4 x 50 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo to give a brown liquid (29.8 g). Gradient column chromatography on silica eluting with 50% CH$_2$Cl$_2$/hexanes (to elute aniline) followed by 75% CH$_2$Cl$_2$/hexanes (to elute product) gave 5,7-dichloropyrazolo[1,5-a]pyrimidine as a white solid (7.7 g).

**Step 3**

**Synthesis of 5-chloropyrazolo[1,5-a]pyrimidin-7-amine**

To 5,7-dichloropyrazolo[1,5-a]pyrimidine (7.6 g, 40.4 mmol) in a sealed vessel was added NH$_3$OH (100 mL). The vessel was then sealed and heated at 85 °C for 2.5 hours, at which time the consistency of the white solid had changed (from foamy white solid to free-flowing white solid). The vessel was removed from the heat source and allowed to cool to room temperature overnight. On cooling, the contents of the vessel were collected and dried by vacuum filtration giving 5-chloropyrazolo[1,5-a]pyrimidin-7-amine as a yellow-tinged white solid (6.8 g).
Step 4

Synthesis of 5-chloro-N,N-bis((2-(trimethylsilyl)ethoxy)methyl)pyrazolo[1,5-a]pyrimidin-7-amine

To 5-chloropyrazolo[1,5-a]pyrimidin-7-amine (6.7 g, 39.7 mmol) in CH$_2$Cl$_2$ (30 mL) was added W/V-diisopropylethylamine (48.0 mL, 275.6 mmol) followed by 2-(Trimethylsilyl)ethoxymethyl chloride (25.0 mL, 141.7 mmol). The reaction was heated at 45 °C for 3 hours before being allowed to cool to room temperature. The reaction mixture was then poured into a separatory funnel containing -100 mL saturated NaHCO$_3$ solution and CH$_2$Cl$_2$ (50 mL). Organics were then extracted with CH$_2$Cl$_2$ (4 x 50 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo to give a thick orange liquid (33.8 g). Gradient column chromatography on silica eluting with 5% to 15% EtOAc/hexanes gave crude 5-chloro-N,N-bis((2-(trimethylsilyl)ethoxy)methyl)pyrazolo[1,5-a]pyrimidin-7-amine as a colorless liquid (18.7 g).

Step 5

Synthesis of tert-butyl 3-(trifluoromethylsulfonyloxy)-8-azabicyclo[3.2.1]oct-3-ene-8-carboxylate

To a solution of N-Boc-nortropinone (6 g, 26.6 mmol) in THF (70 ml) at -78 °C was added LDA (2 M in heptane/THF/ethyl benzene, 20ml, 40 mmol) slowly and the reaction mixture was stirred for 10 min. A solution of N-
phenylbis(trifluoromethanesulfonimide) (10.5 g, 29.3 mmol) in THF (48 ml) was added. The reaction mixture was stirred at -78 °C for 30 min and the cooling bath was removed to warm it up to room temperature for 1.5 h until all N-Boc-nortropinone was utilized. Saturated NH₄Cl solution (10 mL) was added and stirring continued for 5 minutes before the reaction mixture was transferred to a separatory funnel using EtOAc (150 mL). Organics were then extracted with EtOAc (2 x 125 ml), and washed with water (2 x 30 ml), brine (1 x 30 ml), and dried over MgSO₄. Solvent was removed in vacuo and the residue was purified by column chromatography on silica gel. Elution with EtOAc/Hexanes (0-35%) gave desired product, tert-butyl 3-(trifluoromethylsulfonyloxy)-8-azabicyclo[3.2.1]oct-3-ene-8-carboxylate (8.5 g).

**Step 6**

*Synthesis of tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-8-azabicyclo[3.2.1]oct-3-ene-8-carboxylate*

A mixture of tert-butyl 3-(trifluoromethylsulfonyloxy)-8-azabicyclo[3.2.1]oct-3-ene-8-carboxylate (10.1 g, 28.4 mmol), bis(pinacolato)diboron (8.7 g, 34.1 mmol), KOAc (8.4 g, 85.3 mmol), PdCl₂(dppf).CH₂Cl₂ (1.4 g, 1.7 mmol), and dppf (1 g, 1.8 mmol) in dioxane (170 ml) was flushed with Argon and stirred at 80 °C for 16 h. On cooling, the solvent was rotoevaporated, and the crude was redissolved in EtOAc (500 ml), washed with water (1 x 125 ml), brine (1 x 125 ml), and dried over MgSO₄. Solvent was removed in vacuo and the residue was purified by column chromatography on silica gel. Elution with EtOAc/Hexanes (0-40%) gave desired product, tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (8.6 g).

**Step 7**

*Synthesis of tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]oct-3-ene-8-carboxylate*
To 5-chloro-N,N-bis((2-(trimethylsilyl)ethoxy)methyl)pyrazolo[1,5-a]pyrimidin-7-amine (11.1 g, 25.8 mmol) in DME (200 mL) was added tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (9.5 g, 28.4 mmol), PdCl₂(dppf).CH₂Cl₂ (2.1 g, 2.6 mmol) and 2M Na₂CO₃ (100 mL). The reaction was heated at 100 °C for 16 hours, at which time LC/MS analysis confirmed full consumption of starting material. On cooling, H₂O (80 ml) and EtOAc (200 ml) were added and organics were extracted with EtOAc (2 x 250 ml), dried (Na₂SO₄) and concentrated in vacuo to give a crude product. Gradient column chromatography on silica eluting with 10% to 60% EtOAc/hexanes(0-50%) gave tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (13.7 g).

Step 8
Synthesis of tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

A mixture of tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]oct-3-ene-8-carboxylate (12.2 g, 20.3 mmol) and 10% Pd/C (2.1 g) in EtOAc (175 ml) was stirred at 45 °C under hydrogen (balloon pressure) for 16 hours.
After filtration and concentration, the crude mixture of two isomers was purified by gradient column chromatography on silica eluting with EtOAc/Hexanes (0-35%) to give the slightly impure "endo" product (6.24 g, Rf = 0.6 in 25% EtOAc/Hexanes) and the "exo" product (5.44 g, Rf = 0.5 in 25% EtOAc/Hexanes) which was used in the following reaction sequences.

**Step 9**

*Synthesis of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-iodopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate*

To the "exo" tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (6.04 g, 10 mmol) in CH$_3$CN (40 mL) and DCM (40 mL) was added W-iodosuccinimide (2.5 g, 11 mmol) portionwise and the resulting mixture was stirred at room temperature for 1.5 h, at which time LC/MS confirmed full conversion of starting material to product. Solvent was removed in vacuo and the residue was purified by column chromatography on silica gel. Elution with EtOAc/Hexanes (0-50%) gave desired title product (6.4 g).

**Step 10**

*Synthesis of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate*
To tert-butyl 3-((7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-iodopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (2 g, 2.7 mmol) in dioxane (22 mL) and H₂O (5.5 mL) was added the 2-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (1.2 g, 4.1 mmol), PdCl₂(dppf)-CH₂Cl₂ (0.3 g, 0.3 mmol) and K₂CO₃ (1.2 g, 8.2 mmol). The reaction was heated at 100 °C for 15 hours, at which time LC/MS analysis confirmed full consumption of starting material. On cooling, H₂O (40 mL) and EtOAc (100 mL) were added and organics were extracted with EtOAc (2 x 75 mL), dried (Na₂SO₄) and concentrated in vacuo to crude. Gradient column chromatography on silica eluting with 0 to 50% EtOAc/hexanes gave the desired product (1.8 g).

**Step 11**

**Synthesis of (1R,3s,5S)-tert-butyl 3-((7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate**

To a mixture of (1R,3s,5S)-tert-butyl 3-((7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (1.8 g)
5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate in CH$_3$CN (10 mL) and dichloromethane (10 mL) was added W-bromosuccinimide (0.45 g, 2.5 mmol) portionwise and the resulting mixture was stirred at room temperature for 0.5 h, at which time LC/MS confirmed full conversion of starting material to product. Solvent was removed in vacuo and the residue was purified by column chromatography on silica gel. Elution with EtOAc/Hexanes (0-50%) gave the title product (1.7 g).

Step 12

Synthesis of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(1-ethoxyvinyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

A mixture of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (1.2 g, 1.5 mmol), tributyl(1-ethoxyvinyl)tin (1 mL, 2.9 mmol), tetrakis(triphenylphosphine)palladium (0.17 g, 0.15 mmol) in dioxane (12 mL) was degassed with argon for five minutes. It was then heated at 100°C in a sealed tube for 16 h, at which time LC/MS analysis confirmed full consumption of starting material. On cooling, the solvent was rotovaporated, and the crude was redissolved in EtOAc (125 mL), washed with 0.5 M KF solution (1 x 12 mL), water (1 x 25 mL), brine (1 x 25 mL), and dried over MgSO$_4$. Solvent was removed in vacuo and the residue was purified by column chromatography on silica gel. Elution with EtOAc/Hexanes (0-50%) gave the title product (1.2 g).
Step 13

Synthesis of 1-(7-amino-5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-alpyrimidin-6-yl)ethanone

To a mixture of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(1-ethoxyvinyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-alpyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (1.1 g, 1.3 mmol) in dioxane (7 mL) was added 4M HCl in water (2.6 ml) at 0 °C. After stirring for 10 min at 0 °C, 4 M HCl in dioxane (2.6 mL) was added. The reaction mixture was stirred at 0 °C for 30 min. It was then heated at 45 °C for 4 h at which time LC/MS analysis confirmed full consumption of starting material. Solvent was removed in vacuo to get the desired product as an HCl salt.

Step 14

Synthesis of 1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-alpyrimidin-6-yl)ethanone
A mixture of 1H-1,2,4-triazole-3-carboxylic acid (29.4 mg, 0.26 mmol), EDCI (76.7 mg, 0.4 mmol), and 1-hydroxybenzotriazole (27 mg, 0.2 mmol) in DMF (2 ml) was stirred at room temperature for 10 min. Compound 1-(7-amino-5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone hydrochloride (0.2 mmol) was added followed by N,N-diisopropylethylamine (0.17 ml, 1 mmol). It was stirred further for 20 min at room temperature at which time LC/MS analysis confirmed full consumption of starting material. This crude compound was submitted to the analytical group for purification to afford the desired product. LC/MS RT = 2.42 min. Mass calculated for M+H 534.2, observed 534.2.

Example 1-2

Synthesis of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

Step 1
Preparation of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-chloropyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate
2-Chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (5.55 mmol, 1327 mg), $K_2PO_4$ (14.48 mmol, 3070 mg), and $PdCl_2(dppf)$·$CH_2Cl_2$ (0.48 mmol, 394 mg) were added to a solution of tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-iodopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (1.98 mmol, 1101 mg) in dioxane (40 mL) and $H_2O$ (4 mL). The resulting solution was stirred at 70°C under argon overnight. The mixture was diluted with $H_2O$ and then extracted with ethyl acetate (x2). The combined organic layers were washed with brine and dried with $Na_2SO_4$. Evaporation and purification by column chromatography afforded tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-chloropyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate. LCMS $t_R = 3.29$ Min (5 min run, UV 254 nm). Mass calculated for $M+H$ 715.35, observed LC/MS $m/z$ 715.02 ($M+H$).

**Step 2**
Preparation of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate
3-Fluoro-4-methoxyphenylboronic acid (2.79 mmol, 475.7 mg), K$_3$P$_{0}$ (4.20 mmol, 890.4 mg), and PdCl$_2$(dpff)-CH$_2$Cl$_2$ (0.14 mmol, 114.3 mg) were added to a solution of (1R,3S,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-chloropyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (1.40 mmol, 1000 mg) in dioxane (12 mL) and H$_2$O (1.5 mL). The resulting solution was stirred at 150 °C under microwave condition for 1 h. The mixture was diluted with H$_2$O and then extracted with ethyl acetate (x2). The combined organic layers were washed with brine and dried with Na$_2$SO$_4$. Evaporation and purification by column chromatography afforded the title product, LCMS t$_R$ = 3.31 Min (5 min run, UV $254_{nm}$). Mass calculated for, M+ H 805.42, observed LC/MS m/z 805.17 (M+H).

Example 1-3

Preparation of (1R,3S,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-thiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate
To a pressure tube were charged (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-chloropyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (4.17 g, 5.83 mmol), Pd(PPh₃)₄ (350 mg, 0.3 mmol), dioxane (30 mL) and 2-(tri-n-butylstannyl)thiazole (3.8 mL, 12 mmol). The resulting mixture was briefly degassed with Argon; the tube was capped, and heated with stirring under 100 °C overnight. After cooling, solvent was removed. The residue was diluted with EtOAc (30 mL), washed with 0.5 M KF (10 mL) once, brine and dried (MgSO₄). The solution was passed through a short KF pad filled with Celite and concentrated. The residue was purified on silica gel eluting with EtOAc/Hexanes (0-40%) to provide the title compound (3.97 g).

Example 1-4

Preparation of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(6-(3-(hydroxymethyl)-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

Step 1

Preparation of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-(3-formyl-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate
To a pressure tube were charged tert-butyl 3-(7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-3-(6-chloropyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (416 mg, 0.58 mmol), 3-formyl-4-methoxyphenylboronic acid (147 mg, 0.82 mmol), PdCl$_2$(dppf)-CH$_2$Cl$_2$ (40 mg, 0.05 mmol), DME (5 mL) and water (2 mL). The resulting mixture was briefly degassed with Argon; the tube was capped, and heated with stirring under 100°C overnight.

After cooling, solvent was removed. The residue was diluted with water (10 mL) and EtOAc (20 mL). Organic layer was separated, and aqueous layer was extracted with EtOAc (3x). Combined organic layers were dried over (MgSO$_4$). After concentration, the residue was purified on silica gel eluting with EtOAc/Hexanes (0-40%) to provide the title compound (412 mg).

Step 2
Preparation of (1R,3S,5S)-tert-butyl 3-(7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(6-(3-formyl-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-ajpyrimid in-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate
Step 3
Preparation of (1R,3s,5S)-tert-butyl 3-(7-((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(6-(3-(hydroxymethyl)-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

To a mixture of (1R,3s,5S)-tert-butyl 3-(7-((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(6-(3-formyl-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (412 mg, 0.51 mmol) in CH$_3$CN (3 mL) and dichloromethane (3 mL) was added N-bromosuccinimide (90 mg, 2.5 mmol) and the resulting mixture was stirred at room temperature for 20 minutes, at which time LC/MS confirmed full conversion of starting material to product. Solvent was removed in vacuo and the residue was purified by column chromatography on silica gel. Elution with EtOAc/Hexanes (0-40%) gave the title product (371 mg).
To a solution of (1R,3s,5S)-tert-butyl 3-(7-bis((2-trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(6-(3-formyl-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (370 mg, 0.41 mmol) in MeOH (4 ml) was added NaBH₄ (8 mg, 0.21 mmol) and resulting mixture was allowed to stir for 15 minutes. Solvent was removed in vacuo and the residue was purified by column chromatography on silica gel. Elution with EtOAc/Hexanes (0-40%) gave the title product (370 mg).

Example 1-5

Preparation of (1R,3s,5S)-tert-butyl 3-(7-bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-(5-(difluoromethyl)thiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

**Step A. Synthesis of 2-bromo-5-(difluoromethyl)thiazole.**

To 2-bromo-5-hydroxymethylthiazole (1.6 g, 8.1 mmol) in DCM (65 mL) was added dess-martinperiodinane (3.8 g, 8.9 mmol). It was stirred for 12 hour at room temperature, at which time LC/MS analysis confirmed full consumption of starting material. Reaction mixture was diluted with DCM (200 mL), washed with water (1 x 50 mL), brine (1 x 50 mL), and dried over MgSO₄. Gradient column chromatography
on silica gel eluting with 0 to 65% EtOAc/hexanes gave the desired 2-bromothiazole-5-carbaldehyde (1.3 g).

To 2-bromothiazole-5-carbaldehyde (1.1 g, 6 mmol) in dry DCM (80 mL) at -78°C was added DAST (2.4 mL, 18 mmol). The resulting mixture was warmed to room temperature over 16 hour time period, at which time LC/MS analysis confirmed full consumption of starting material. Saturated NaHCO₃ (50 mL) was added slowly and stirring continued for 10 minutes before the reaction mixture was transferred to a separatory funnel using DCM (100 mL). Organics were then extracted with DCM (2 x 50 mL), and washed with water (2 x 50 mL), brine (1 x 50 mL), and dried over MgSO₄. Gradient column chromatography on silica gel eluting with 0 to 40% EtOAc/hexanes gave the desired 2-bromo-5-(difluoro methyl)thiazole (0.8 g).

**Step B. Synthesis of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-(trimethylstanny)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate.**

A mixture of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-chloropyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (1.3 g, 1.8 mmol), hexamethylditin (0.75 mL, 3.6 mmol) and Pd(PPh₃)₄ in dioxane (15 mL) was degassed with argon and heated at 100°C for 16 hour, at which time LC/MS analysis confirmed full consumption of starting material. On cooling, EtOAc (250 mL) was added and washed with brine (1 x 50 mL), and dried over MgSO₄. Solvent was removed in vacuo and the crude product (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-
(trimethylstannyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate was used for the next step without any further purification.

**Step C. Synthesis of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-(5-(difluoromethyl)thiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate.**

A mixture of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-(trimethylstannyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (1 g, 0.8 mmol), 2-bromo-5-(difluoromethyl)thiazole (0.2 g, 0.8 mmol), PdCl$_2$(dpf),CH$_2$Cl$_2$ (0.07 g, 0.08 mmol), Cul (0.015 g, 0.08 mmol) in DMF (6.4 mL) was degassed with argon and heated at 100°C for 2 hour, at which time LC/MS analysis confirmed full consumption of starting material. On cooling, EtOAc (250 mL) was added and washed with water (2 x 25 mL), brine (1 x 25 mL), and dried over MgSO$_4$. Solvent was removed in vacuo and the residue was purified by column chromatography on silica gel. Elution with EtOAc/Hexanes (0-50%) gave desired product, (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-(5-(difluoromethyl)thiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (0.38 g).

Example 1-6
Preparation of (1R,3S,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(4-(pyrimidin-2-yl)phenyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate.

**Step A. Synthesis of (1R,3S,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(4-(pyrimidin-2-yl)phenyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate.**

To (1R,3S,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-iodo pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (4.4 g, 6 mmol) in dioxane (48 mL) and water (12 mL) was added 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrimidine (3 g, 7.9 mmol), PdCl$_2$(dpff).CH$_2$Cl$_2$ (0.5 g, 0.6 mmol) and K$_2$CO$_3$ (2.5 g, 18.1 mmol). The reaction mixture was heated at 100°C for 16 hour, at which time LC/MS analysis confirmed full consumption of starting material. On cooling, the solvent was removed *in vacuo*, and the crude was redissolved in DCM (500 mL), washed with water (1 x 125 mL), brine (1 x 125 mL),...
and dried over MgSO₄. Gradient column chromatography on silica gel eluting with 0
to 40% EtOAc/hexanes gave the desired (1R,3s,5S)-tert-butyl 3-(7-(bis((2-
(trimethylsilyl)ethoxy)methyl) amino)-3-(4-(pyrimidin-2-yl)phenyl)pyrazolo[1,5-
a]pyrimidin-5-yl)-8-azabicyclo[3.2.1] octane -8-carboxylate (1.7 g).

Example 1-7

Preparation of 5-bromo-2-(1-methyl-1H-1, 2, 4-triazol-3-yl)pyridine

5-bromo-2-(1-methyl-1H-1, 2, 4-triazol-3-yl)pyridine was synthesized from 5-
bromopicolinonitrile according to reference procedure (Polyhedron (2004), 23(13),
2141-2151). LCMS 𝑡ᵣ = 0.62 Min (5 min run, UV 254nm). Mass calculated for, M+ 237.9, observed LC/MS m/z 239.0 (M+H).

Example 1-8

Preparation of 5-bromo-2-(1-methyl-(D₃)-1H-pyrazol-3-yl)pyridine

5-bromo-2-(1-methyl-(D₃)-1 H-pyrazol-3-yl)pyridine was prepared from 5-
bromo-2-(1H-pyrazol-3-yl)pyridine according to reference procedure (Bioorganic &
Medicinal Chemistry (2004), 12(22), 5909-5915). LCMS 𝑡ᵣ = 0.92 Min (5 min run,
UV 254nm). Mass calculated for, M+ 240.0, observed LC/MS m/z 241.1 (M+H).
Example 1-9

**Preparation of 2-(4-methoxy-(D$_3$)-phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane**

At 0 °C, 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (189.5 mg, 0.86 mmol) was added to a mixture of NaH (60%, 68.9 mg, 1.72 mmol) in THF (5 ml). After stirring at room temperature for 10 min, the mixture was cooled to 0°C and CD$_3$I (624 mg, 4.30 mmol) was added dropwise. The mixture was stirred at room temperature overnight and then diluted with H$_2$O and then extracted with ethyl acetate (x2). The combined organic layers were washed with brine and dried with Na$_2$SO$_4$. Evaporation and purification by column chromatography afforded 2-(4-methoxy-(D$_3$)-phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane: LCMS t$_R$ = 1.39 Min (5 min run, UV$_{254}$nm). Mass calculated for, M+ 237.1, observed LC/MS m/z 238.2 (M+H).

Example 1-10

**Preparation of 2-(4-(fluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane**

Cs$_2$CO$_3$ (651.6 mg, 2.0 mmol) and then FCH$_2$Br (446.6 mg, 4.0 mmol) were added to a mixture of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (220 mg, 1.0 mmol) in CH$_3$CN (10 ml). After stirring at room temperature overnight, the
mixture was filtered and concentrated. Purification by column chromatography afforded 2-(4-(fluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane: LCMS $t_R = 1.39$ Min (5 min run, $\lambda_{254}$). Mass calculated for, M+ 252.1, observed LC/MS $m/z$ 253.1 (M+H).

Example 1-11

Preparation of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole

At 0 °C, NaH (60%, 160 mg, 4.0 mmol) was added to a mixture of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (388.0 mg, 2 mmol) in THF (12 ml). After stirring at room temperature for 30 min, the mixture was cooled to 0°C and SEMCl (705.7 ul, 4.0 mmol) was added dropwise. The mixture was stirred at room temperature overnight and then diluted with H2O and then extracted with ethyl acetate (x2). The combined organic layers were washed with brine and dried with Na2SO4. Evaporation and purification by column chromatography afforded 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole: LCMS $t_R = 1.47$ Min (5 min run, $\lambda_{254}$). Mass calculated for, M+ 324.2, observed LC/MS $m/z$ 325.0 (M+H).

Example 1-12

Preparation of 3-bromo-4-(2-(trimethylsilyl)ethoxy)methyl)-4H-1,2,4-triazole
By applying the chemistry described in Example 1-1, 3-bromo-4-((2-(trimethylsilyl)ethoxy)methyl)-4H-1,2,4-triazole was prepared from 3-bromo-4H-1,2,4-triazole. LCMS t_R = 1.22 Min (5 min run, UV_254nm). Mass calculated for, M+ 277.0, observed LC/MS m/z 278.0 (M+H).

Example 1-13

Preparation of 4-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole

By applying the chemistry described in Example 1-1, 4-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole was prepared from 4-bromo-1H-imidazole. LCMS t_R = 1.16 Min (5 min run, UV_254nm). Mass calculated for, M+ 276.0, observed LC/MS m/z 277.1 (M+H).

Example 1-14

Preparation of 5-bromo-2-(4-fluoro-1-methyl-1H-pyrazol-3-yl)pyridine

At 0 °C, Selectfluoro (1223.3 mg, 3.45 mmol) was added to 5-bromo-2-(1-methyl-1H-pyrazol-3-yl)pyridine (817.4 mg, 3.45 mmol) in CH_3CN (20 ml). The mixture was slowly warmed up to room temperature. Selectfluoro (2446 mg) was added after stirring at room temperature overnight and more Selectfluoro (1223 mg)
was added after 2 days stirring. The mixture was diluted with sat. NaHCO₃ and then extracted with ethyl acetate (x2). The combined organic layers were washed with brine and dried with Na₂SO₄. Evaporation and purification by column chromatography afforded 5-bromo-2-(4-fluoro-1-methyl-1H-pyrazol-3-yl)pyridine:

$$ t_R = 1.00 \text{ Min (5 min run, UV}_{254nm}) $$
Mass calculated for, M+ 254.98 observed LC/MS m/z 256.0 (M+H).

**Example 1-15**

Preparation of 5-bromo-2-(5-methyl-1H-pyrazol-3-yl)pyridine

5-bromo-2-(5-methyl-1H-pyrazol-3-yl)pyridine was prepared according to reference procedure (Journal of the American Chemical Society (2003), 125(36), 10800-10801) from methyl 5-bromopicolinate. LCMS $t_R = 0.86 \text{ Min (5 min run, UV}_{254nm})$. Mass calculated for, M+ 236.9, observed LC/MS m/z 238.0 (M+H).

**Example 1-16**

Preparation of 5-bromo-2-(5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)pyridine

By applying the chemistry described in Example 1-11, 5-bromo-2-(5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)pyridine was prepared from 5-
bromo-2-(5-methyl-1H-pyrazol-3-yl)pyridine. LCMS $t_R = 1.56$ Min (5 min run, $\text{UV}_{244}$nm). Mass calculated for, M+ 367.0, observed LC/MS m/z 368.0 (M+H).

Example 1-17

Preparation of 5-bromo-2-(4-fluoro-5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)pyridine

By applying the chemistry described in Example 1-14, 5-bromo-2-(4-fluoro-5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)pyridine was synthesized from 5-bromo-2-(5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)pyridine. LCMS $t_R = 1.59$ Min (5 min run, $\text{UV}_{254}$nm). Mass calculated for, M+ 385.0, observed LC/MS m/z 386.2 (M+H).

Example 1-18

Preparation of 2-(2-methyl-2H-tetrazol-5-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine

Pinacol diborane (3047 mg, 12 mmol), KOAc (2944 mg, 30 mmol), and PdCl$_2$(dpdf)$_2$·CH$_2$C$_6$H$_5$ (816 mg, 1 mmol) were added to a mixture of 5-bromo-2-(2-methyl-2H-tetrazol-5-yl)pyridine (2400 mg, 10 mmol) in dioxane (70 mL). The
resulting solution was stirred at 80°C under argon overnight. The mixture was filtered through celite and concentrated to afford crude 2-(2-methyl-2H-tetrazol-5-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine: LCMS $t_R = 0.45$ Min (5 min run, UV$_{254nm}$). Mass calculated for, M+ 287.1, observed LC/MS m/z 282.2 (M+H).

By applying the chemistry above, the following compounds were synthesized.

<table>
<thead>
<tr>
<th>Example No.</th>
<th>Structures</th>
<th>FW</th>
<th>M+H</th>
<th>Retention Time, 5 min method</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-19</td>
<td>![Structure 1-19]</td>
<td>288.1 (boronic ester) 206.1 (boronic acid)</td>
<td>207.1 (observed)</td>
<td>0.38</td>
</tr>
<tr>
<td>1-20</td>
<td>![Structure 1-20]</td>
<td>303.1 (boronic ester) 221.0 (boronic acid)</td>
<td>222.1 (observed)</td>
<td>0.51</td>
</tr>
<tr>
<td>1-21</td>
<td>![Structure 1-21]</td>
<td>208.1 (boronic ester) 126.0 (boronic acid)</td>
<td>127.0 (observed)</td>
<td>0.12</td>
</tr>
<tr>
<td>1-22</td>
<td>![Structure 1-22]</td>
<td>257.0 (boronic ester) 175.0 (boronic acid)</td>
<td>176.1 (observed)</td>
<td>0.73</td>
</tr>
<tr>
<td>1-23</td>
<td>![Structure 1-23]</td>
<td>286.1 (boronic ester) 204.0 (boronic acid)</td>
<td>205.1 (observed)</td>
<td>0.21</td>
</tr>
</tbody>
</table>
Example 1-28

Preparation of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-(methoxycarbonyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

<table>
<thead>
<tr>
<th>1-24</th>
<th>325.2 (boronic ester)</th>
<th>243.1 (boronic acid)</th>
<th>244.2 (observed)</th>
<th>0.86</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-25</td>
<td>324.2 (boronic ester)</td>
<td>242.1 (boronic acid)</td>
<td>243.2 (observed)</td>
<td>0.86</td>
</tr>
<tr>
<td>1-26</td>
<td>415.2 (boronic ester)</td>
<td>333.1 (boronic acid)</td>
<td>334.1 (observed)</td>
<td>0.99</td>
</tr>
<tr>
<td>1-27</td>
<td>433.2 (boronic ester)</td>
<td>351.1 (boronic acid)</td>
<td>352.1 (observed)</td>
<td>1.04</td>
</tr>
</tbody>
</table>

Methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinate (2100 mg, 7.98 mmol), K3PO4 (4230 mg, 19.95 mmol), and PdCl2(dppf)-CH2Cl2 (542.7 mg, 0.66 mmol) were added to a mixture of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-iodopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate.
azabicyclo[3.2.1]octane-8-carboxylate (4848.9 mg, 6.65 mmol) in dioxane (100 mL) and H2O (10 mL). The resulting solution was stirred at 90° C under argon overnight. The mixture was diluted with H2O and then extracted with ethyl acetate (x2). The combined organic layers were washed with brine and dried with Na2SO4. Evaporation and purification by column chromatography afforded (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-(methoxycarbonyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate: LCMS tR = 1.88 Min (5 min run, UV254nm). Mass calculated for, M+ 738.4, observed LC/MS m/z 739.3 (M+H).

Example 1-29

Preparation of methyl 5-(6-acetyl-7-amino-5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)picolinate

By applying the chemistry in example 1-1, methyl 5-(6-acetyl-7-amino-5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)picolinate was prepared: LCMS tR = 0.75 Min (5 min run, UV254nm). Mass calculated for, M+ 420.2, observed LC/MS m/z 421.1 (M+H).

Example 1-30
Preparation of provided 5-(5-((1R, 3s, 5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)picolinic acid

A mixture of methyl 5-(6-acetyl-7-amino-5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)picolinate (99.5 mg, 0.237 mmol), 4H-1,2,4-triazole-3-carboxylic acid (32.2 mg, 0.285 mmol), EDC (90.7 mg, 0.475 mmol), HOBt (64.1 mg, 0.475 mmol) and DIEA (247.6 ul, 1.42 mmol) in DMF (5 mL) was stirred at room temperature for 1h. Concentration provided crude methyl 5-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)picolinate. MeOH (2 ml), THF (1 ml) and 1N NaOH (2 ml) were added and the mixture was stirred at 50°C until LCMS indicated complete conversion. Concentration and Purification with prep-LC provided 5-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)picolinic acid, LCMS t_R = 1.85 Min (10 min run, UV_254nm). Mass calculated for, M+ 501.1, observed LC/MS m/z 501.96 (M+H).

Example 1-31

Preparation of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(1-ethoxyvinyl)-3-(6-(1-hydroxycyclopropyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate
EtMgBr (1.0 M in THF, 1.4 ml, 1.4 mmol) was added dropwise to a mixture of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-(methoxycarbonyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (369.2 mg, 0.5 mmol) and Ti(0;Pr)₄ (205.1 ul, 0.7 mmol) in THF (5 ml) at room temperature. After stirring overnight, the mixture was diluted with H₂O and then extracted with EtOAc (x2). The combined organic layers were washed with brine and dried with Na₂SO₄. Concentration and purification by column chromatography afforded an inseparable mixture: (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-(1-hydroxycyclopropyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate and (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-(3-hydroxypentan-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate, which by applying chemistry in example 1-1 was converted to a mixture of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(1-ethoxyvinyl)-3-(6-(1-hydroxycyclopropyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate and (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(1-ethoxyvinyl)-3-(6-(3-hydroxypentan-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate.
Example 1-32

Preparation of 1-(5-(6-acetyl-7-amino-5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)propan-1-one

Example 1-33

A mixture of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(1-ethoxyvinyl)-3-(6-(1-hydroxycyclopropyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate and (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(1-ethoxyvinyl)-3-(6-(3-hydroxypentan-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (180.1 mg) was treated 4N HCl in H₂O (6 ml) and Dioxane (3 ml) at 50°C for 0.5 h.

Concentration afforded crude mixture of 1-(5-(6-acetyl-7-amino-5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)propan-1-one and 1-(7-amino-5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone.

Example 1-34

Preparation of 1-(5-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)propan-1-one
By applying the chemistry in previous examples, the mixture of 1-(5-(6-acetyl-7-amino-5-((1 R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)propan-1-one and 1-(7-amino-5-((1 R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-(3-hydroxypentan-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone was submitted for EDC-mediated amide coupling reaction. Purification by prep-LC afforded pure 1-(5-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)propan-1-one, LCMS t<sub>R</sub> = 2.47 Min. (10 min run, UV<sub>254nm</sub>). Mass calculated for, M+ 513.2, observed LC/MS m/z 514.08 (M+H) and pure 1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(3-hydroxypentan-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone, LCMS t<sub>R</sub> = 2.10 Min. (10 min run, UV<sub>254nm</sub>). Mass calculated for, M+ 543.2, observed LC/MS m/z 544.03.

Example 1-35

Preparation of (1R,3s,5S)-tert-butyl 3-((7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-hydroxymethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

\[
\text{BocN} \quad \text{LiAlH}_4 \quad \text{THF} \quad \text{BocN} \\
\text{NSEM}_2 \quad \text{NSEM}_2
\]
At 0°C, UAIH₄ (55.3 mg, 1.46 mmol) was added to (1R,3s,5S)-tert-butyl 3-(7-(bis(2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-(methoxycarbonyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (537.9 mg, 0.73 mmol) in THF (10 ml). The mixture was slowly warmed up to room temperature, and stirred for 2 h. EtOAc (10 ml), followed by H₂O (80 ul), 15% NaOH (80 ul) and H₂O (240 ul) were added to reaction mixture and the mixture was further stirred for 2h. Filtration, concentration and purification by column chromatography afforded (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-(hydroxymethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate: LCMS tᵣᵣ = 1.50 Min (5 min run, UV/254nm). Mass calculated for, M+ 710.4, observed LC/MS m/z 711.2 (M+H).

Example 1-36

Preparation of (1R,3s,5S)-tert-butyl 3-(7-(bis(2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-(fluoromethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

At 0 °C, DAST (112.5 mg, 0.69 mmol) was added to (1R,3s,5S)-tert-butyl 3-(7-(bis(2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-(hydroxymethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (309.9 mg, 0.43 mmol) in DCM (10 ml). The mixture was slowly warmed up to room temperature and stirred for 2h. More DAST (309.9 mg, 0.43 mmol) was added. Once LCMS indicated complete conversion, the mixture was diluted with sat. NaHCO₃ and then extracted with DCM (x2). The combined organic layers were washed with brine and dried with Na₂SO₄. Concentration and purification by column chromatography afforded (1R,3s,5S)-tert-butyl 3-(7-(bis(2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-
(fluoromethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate: LCMS \( t_R = 1.79 \) Min (5 min run, \( \text{UV}_{254} \)). Mass calculated for, M+ 712.4, observed LC/MS m/z 713.3 (M+H).

**Example 1-37**

**Preparation of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-(2-oxopyridin-1(2H)-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate**

A degassed mixture of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-chloropyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (357 mg, 0.50 mmol), \( \text{Cs}_2\text{CO}_3 \) (244.4 mg, 0.75 mmol), pyridin-2(1H)-one (95 mg, 1.0 mmol), Xanphos (43.4 mg, 0.075 mmol), \( \text{Pd}_2(\text{dba})_3 \) (22.9 mg, 0.025 mmol) in Dioxane (6 ml) was heated at 110°C overnight. The mixture was cooled to room temperature, filtered and evaporated. Purification by column chromatography afforded (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-(2-oxopyridin-1(2H)-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate: LCMS \( t_R = 1.88 \) Min (5 min run \( \text{UV}_{254} \)). Mass calculated for, M+ 774.4, observed LC/MS m/z 774.3 (M+H).

**Example 1-38**

**Preparation of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-chloro-5-methylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate**
6-chloro-5-methylpyridin-3-ylboronic acid (347.2 mg, 2.02 mmol), K$_3$P$_4$O$_4$ (117.15 mg, 5.52 mmol), and PdCl$_2$(dpdf)-CH$_2$Cl$_2$ (150.3 mg, 0.18 mmol) were added to a mixture of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-iodopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (1342.8 mg, 1.84 mmol) in dioxane (20 mL) and H$_2$O (2 mL). The resulting solution was stirred at 65°C under argon overnight. The mixture was diluted with H$_2$O and then extracted with ethyl acetate (x2). The combined organic layers were washed with brine and dried with Na$_2$SO$_4$. Evaporation and purification by column chromatography afforded (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-chloro-5-methylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate: LCMS $t_R = 1.56$ Min (5 min run UV$_{254nm}$). Mass calculated for, M+ 774.4, observed LC/MS m/z 775.3 (M+H).

Example 1-39

Preparation of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-chloro-5-fluoropyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

By applying the chemistry described in Example 36, (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-chloro-5-fluoropyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate...
Example 1-40

Preparation of (1R,3S,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(3'-fluoro-2,2'-bipyridin-5-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

A degassed mixture of (1R,3S,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-chloropyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (1000 mg, 1.40 mmol), Pd(PPh₃)₄ (161.9 mg, 0.14 mmol), 3-fluoro-2-(tributylstannyl)pyridine (1080 mg, 2.80 mmol) in Dioxane (6 mL) and CH₂CN (6 mL) was heated at 180°C for 60 min under microwave condition. The reaction mixture was cooled to room temperature, filtered through 9:1 SiO₂:KF plug and concentrated in vacuo. Purification by column chromatography afforded (1R,3S,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(3'-fluoro-2,2'-bipyridin-5-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate, LCMS t<sub>R</sub> = 1.62 Min (5 min run, UV<sub>254nm</sub>). Mass calculated for, M+ 775.4, observed LC/MS m/z 776.3 (M+H) and (1R,3S,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-butylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate was prepared from (1R,3S,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-iodopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate: LCMS t<sub>R</sub> = 2.02 Min (5 min run UV<sub>254nm</sub>). Mass calculated for, M+ 732.3, observed LC/MS m/z 733.3 (M+H).
Example 1-41

Preparation of 1-(5-((1R,3S,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(hydroxymethyl)quinolin-3-yl)pyrazolo[1,5-alpyrimidin-6-yl)ethanone

Step 1: Preparation of 3-bromoquinoline-6-carboxylic acid

To a suspension of quinoline-6-carboxylic acid (2.77 g, 16.0 mmol) in CCl₄ (20 ml) in a flask wrapped with Al foil was added bromine (987 uL, 19.2 mmol) dropwise. The resulting mixture was stirred at rt for 30 min, then heated under reflux for 30 min. A solution of pyridine (1.55 mL, 19.2 mmol) in CCl₄ (4 mL) was added dropwise at refluxing temperature. Then the reaction mixture was heated under reflux for 4 h. The reaction mixture was treated with 3 N NaOH until all the precipitates were dissolved. The aqueous layer was separated and washed with DCM once more, then acidified with 3 N HCl. The resulting orange precipitates were filtered, and washed with H₂O, and a small amount of MeOH to afford the titled compound as an off-white solid (3.36 g).

Step 2: Preparation of (3-bromoquinolin-6-yl)methanol
To a mixture of 3-bromoquinoline-6-carboxylic acid (1.32 g, 5.24 mmol) and TEA (876 µL, 6.29 mmol) in THF (30 mL) was added EtOCl (599 µL, 6.29 mmol) at 0 °C and stirred for 30 min. Then, a solution of NaBH₄ (793 mg, 21.0 mmol) in H₂O (6 mL) was added at the same temperature. The resulting reaction mixture was stirred at 0 °C for 30 min before being warmed to rt and stirred overnight. THF was removed. The residue was diluted with H₂O, acidified with 4 N HCl, then neutralized with NaHCO₃, extracted with EtOAc, and purified by a SiO₂ column (0-50% EtOAc/Hexanes, Rf = 0.35 in 50% EtOAc) to afford the titled compound as a colorless oil (220 mg).

Step 3: Preparation of 1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(hydroxymethyl)quinolin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone

This compound was prepared from (3-bromoquinolin-6-yl)methanol, following essentially the same procedures given previously.

Following Scheme 1-1 and using procedures similar to the preparation of above examples, the following compounds listed in Table 1-1 were prepared.

| Compound ID | Structures | Compound Name | M+H (calculated) | M+H (observed) | pAKT | p4E-1
<table>
<thead>
<tr>
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</thead>
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<tr>
<td>1.1.1</td>
<td><img src="image" alt="Structure" /></td>
<td>1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-3-hydroxy-2-(hydroxymethyl)-2-methylpropan-1-one</td>
<td>555.2/555.2</td>
<td>B</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>1.1.2</td>
<td>((R)-1-(((1R,3S,5S)-3-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxypropan-1-one</td>
<td>511.2/511.7</td>
<td>A</td>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1.3</td>
<td>((R)-1-(((1R,3S,5S)-3-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2,3-dihydroxypropan-1-one</td>
<td>527.2/527.6</td>
<td>B</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1.4</td>
<td>3-(β-Acetyl-7-amino-3-(6-phenylpyridinyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-(1,1-dioxido-3-isothiazolidiny1)-2-carbonyl-8-azabicyclo[3.2.1]octan-1-one (mix of 2 diastereomers)</td>
<td>586.2/586.0</td>
<td>B</td>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1.5</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone</td>
<td>497.2/497.1</td>
<td>A</td>
<td>A</td>
<td></td>
</tr>
</tbody>
</table>

| 1.1.6 | ![Chemical Structure](image2) | 1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxy-2-methylpropan-1-one | 525.2/525.2 | B | ND |

| 1.1.7 | ![Chemical Structure](image3) | 1-((1R,3s,5S)-8-((1H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone | 534.2/534.2 | A | A |

| 1.1.8 | ![Chemical Structure](image4) | (5S)-1-((1R,3R,5S)-3-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxypropan-1-one | 511.2/510.9 | A | B |
| 1.1.9 | ![](image) | 1-((1R,3r,5s)-3-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-
| | | a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone |
| 1.1.20 | ![](image) | 1-((1R,3s,5s)-3-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-
| | | a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-(1H-tetrazol-5-
| | | yl)ethanone |
| 1.1.21 | ![](image) | 1-((1R,3s,5s)-8-(1H-1,2,3-triazole-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-
| | | a]pyrimidin-6-yl)ethanone |

| | | 497.2/496.9 | B | B |
| | | 549.2/549.1 | B | C |
| | | 534.2/534.0 | A | A |
| 1.1.22 | \[
\text{1-[(7-amino-5-}
\text{\((1R,3S,5S)-5-\text{[methyl-1H-1,2,4-
\text{triazole-5-carbonyl]-8-
\text{azabicyc[3.2.1]octan-3-yl]-3-(6-
\text{phenylpyridin-3-y1)pyrazolo[1,5-
\text{a]pyrimidin-8-
\text{yl}ethanone}}
\]
\] | 548.2/547.9 | A | A |

| 1.1.23 | \[
\text{N-[(2-[(1R,3S,5S)-3-
\text{[6-acetyl-7-amino-
\text{3-(6-phenylpyridin-
\text{3-y1)pyrazolo[1,5-
\text{a]pyrimidin-5-y1]b-
\text{azabicyc[3.2.1]octan-8-y1)-2-
\text{oxoethyl]methanesulfonamide}}
\]
\] | 574.2/573.9 | B | B |

| 1.1.24 | \[
\text{1-[(5-[(1R,3S,5S)-8-
\text{[1H-tetrazole-5-
\text{carbonyl]-8-
\text{azabicyc[3.2.1]octan-3-yl]-7-amino-
\text{3-(6-phenylpyridin-
\text{3-y1)pyrazolo[1,5-
\text{a]pyrimidin-6-
\text{yl}ethanone}}
\]
\] | 535.2/535.2 | C | C |

| 1.1.25 | \[
\text{5-[(1R,3S,5S)-8-
\text{[1H-1,2,4-triazole-
\text{3-carbonyl]-8-
\text{azabicyc[3.2.1]octan-3-yl]-7-amino-
\text{3-(6-phenylpyridin-
\text{3-y1)pyrazolo[1,5-
\text{a]pyrimidine-6-
\text{carboxamide}}
\]
\] | 535.2/534.9 | A | A |
| 1.1.26 | ![Chemical Structure](image1.png) | 1-[(5-[(1R,3S,5S)-8-(1H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl]-7-amino-3-(6-((difluoromethyl)thiazol-2-yl)pyridin-3-yl)pyrazol-1,5-yl)pyrimidin-6-yl]ethanone | 591.1/590.9 | B | B |
| 1.1.27 | ![Chemical Structure](image2.png) | 1-[(5-[(1R,3S,5S)-8-(1H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl]-7-amino-3-(4-(pyrimidin-2-yl)phenyl)pyrazol-1,5-yl)pyrimidin-6-yl]ethanone | 535.2/534.9 | ND | ND |
| 1.1.28 | ![Chemical Structure](image3.png) | 5-[(5-[(1R,3S,5S)-8-(1H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl]-6-acetyl-7-amino(pyrazol-1,5-yl)pyrimidin-3-yl)-N-methylpicolinamide | 515.2/515.0 | C | C |
| 1.1.29 | ![Chemical Structure](image4.png) | 3-(6-acetyl-7-amino-5-((1R,3S,5S)-8-(2-hydroxyacetetyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazol-1,5-yl)pyrimidin-3-yl)-N-methylpicolinamide | 478.2/477.9 | ND | ND |
| 1.1.30 | ![Chemical Structure](image5.png) | 1-[(7-amino-5-[(1R,3S,5S)-8-azabicyclo[3.2.1]octan-3-yl]-3-(6-((1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)pyrazol-1,5-yl)pyrimidin-6-yl]ethanone | 443.2/443.0 | ND | ND |
| 1.1.31 | ![Chemical Structure](image6.png) | 1-[(5-[(1R,3S,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl]-7-amino-3-(5-hydroxy-6-phenyl)pyridin-3-yl)pyrazol-1,5-yl]pyrimidin-6-yl]ethanone | 550.2/549.9 | C | C |
1.132 1-((1R,3S,5S)-3-((6-acetyl-7-amino-3-(5-hydroxy-6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone

513.2/512.9  C  C

1.133 1-((1R,3S,5S)-3-((6-acetyl-7-amino-3-(6-thiaziol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone

504.2/503.9  A  B

1.134 (R)-1-((1R,3S,5S)-3-((6-acetyl-7-amino-3-(6-thiaziol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxypropan-1-one

518.2/517.9  B  ND

1.135 1-((1R,3S,5S)-3-((6-acetyl-7-amino-3-(6-thiaziol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxy-2-methylpropan-1-one

532.2/532.0  B  ND
<p>| 1.1.36 | <img src="image1" alt="Chemical Structure" /> | 1-((1R,3s,5S)-3-((6-acetyl-7-amino-3-(6-(3-(hydroxymethyl)-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone | 557.2/557.0 | A | A |
| 1.1.37 | <img src="image2" alt="Chemical Structure" /> | 1-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-thiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-8-yl)ethanone | 541.2/540.8 | A | A |
| 1.1.38 | <img src="image3" alt="Chemical Structure" /> | 1-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(7-fluoronaphthalen-2-yl)pyrazolo[1,5-a]pyrimidin-8-yl)ethanone | 525.2/526.0 | B | A |
| 1.1.39 | <img src="image4" alt="Chemical Structure" /> | (1R,3s,5S)-3-((6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-N-methyl-8-azabicyclo[3.2.1]octan-8-carboxamide | 496.2/496.0 | A | A |
| 1.1.40 | <img src="structure1.png" alt="Chemical Structure" /> | 1-(7-amino-5-((1R,3s,5S)-8-(5-hydroxy-4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-alpyrimidin-6-yl)ethanone | 550.2/550.0 | B | B |
| 1.1.41 | <img src="structure2.png" alt="Chemical Structure" /> | 1-(5-((1R,3s,5S)-8-(1H-pyrrole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-alpyrimidin-6-yl)ethanone | 532.2/532.0 | A | A |
| 1.1.42 | <img src="structure3.png" alt="Chemical Structure" /> | 1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-ylsulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-alpyrimidin-6-yl)ethanone | 570.2/569.9 | B | B |
| 1.1.43 | <img src="structure4.png" alt="Chemical Structure" /> | 1-(5-((1R,3s,5S)-8-(1H-pyrrole-2-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-alpyrimidin-6-yl)ethanone | 532.2/532.0 | B | B |
| 1.1.44 | <img src="structure5.png" alt="Chemical Structure" /> | 1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(4-methoxy-3-(methoxymethyl)phenyl)pyridin-3-yl)pyrazolo[1,5-alpyrimidin-5-y)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone | 571.3/571.0 | A | B |
| 1.1.45 | <img src="structure6.png" alt="Chemical Structure" /> | 1-(5-((1R,3s,5S)-8-(1H-pyrrole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(4-methoxy-3-(methoxymethyl)phenyl)pyridin-3-yl)pyrazolo[1,5-alpyrimidin-6-yl)ethanone | 608.3/608.0 | A | A |
| 1.1.46 | <img src="image" alt="Molecule 1" /> | 1-((5-((1R,3S,5R)-8-(4H-1,2,4-triazole-3-carbonyl)-3H-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-methoxyphenylimidazol-5-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone) | 564.2/564.0 | A | A |
| 1.1.47 | <img src="image" alt="Molecule 2" /> | 1-((5-((1R,3S,5R)-8-(4H-1,2,4-triazole-3-carbonyl)-3H-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2-fluoro-4-methoxyphenylimidazol-5-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone) | 582.2/582.0 | A | A |
| 1.1.48 | <img src="image" alt="Molecule 3" /> | 1-((7-amino-5-(1H-tetrahydroisoquinolin-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone) | 523.2/523.0 | B | B |
| 1.1.49 | <img src="image" alt="Molecule 4" /> | (1R,3S,5S)-3-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-sulfonic acid | 519.2/518.9 | C | D |
| 1.1.50 | <img src="image" alt="Molecule 5" /> | 1-((7-amino-5-((1R,3S,5S)-8-(5-hydroxynicotinoyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone) | 560.2/560.0 | B | B |
| 1.1.51 | <img src="image" alt="Molecule 6" /> | 1-((7-amino-5-((1R,3S,5S)-8-(4-hydroxynicotinoyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone) | 560.2/560.0 | B | B |
| 1.1.52 | ( \text{pyrazolo}[1,5-\alpha]pyrimidin-6-yl} ) | 1-(5-((1R,3a,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(5-(methoxymethyl)thiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-\alpha]pyrimidin-6-yl}ethanone | 585.2/585.0 | B | B |
| 1.1.53 | | 1-(5-((1R,3a,5S)-8-(1H-imidazole-4-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-\alpha]pyrimidin-6-yl}ethanone | 533.2/533.0 | ND | ND |
| 1.1.54 | | 1-(5-((1R,3a,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-\alpha]pyrimidin-6-yl}ethanone | 582.23/581.92 | B | B |
| 1.1.55 | | 1-(5-((1R,3a,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-\alpha]pyrimidin-6-yl}ethanone | 538.23/538.01 | A | A |</p>
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<th>Structure</th>
<th>Formula</th>
<th>MW</th>
<th>DB</th>
<th>Note</th>
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<tbody>
<tr>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>1-[(1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-3-hydroxy-2-(hydroxyethyl)-2-methylpropan-1-one</td>
<td>559.3/558.88</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone</td>
<td>582.23/581.90</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>1-[(1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone</td>
<td>545.22/545.20</td>
<td>B</td>
<td>B</td>
</tr>
</tbody>
</table>
1.1.59

1-((1R,3S,5S)\text{-}3-(6-acetyl-7-amino-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)azabicyclo[3.2.1]octan-8-yl)-3-hydroxy-2-(hydroxymethyl)-2-methylpropan-1-one

603.26/602.95

A

A

1.1.60

1-((1R,3S,5S)\text{-}3-(6-acetyl-7-amino-3-(6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone

501.22/500.97

B

B

1.1.61

1-((1R,3S,5S)\text{-}8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)7-amino-3-(6-(2,3-difluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-8-yl)ethanone

570.21/569.92

A

A
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<td>1-(5-((1R,3a,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(2-fluoro-2,3-bipyridin-5-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone</td>
<td>553.21/553.0</td>
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<td>1-(5-((1R,3a,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2-methyl-2H-tetrazolo-5-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone</td>
<td>540.22/539.94</td>
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<td>1-(5-((1R,3a,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(3,5-difluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone</td>
<td>600 22/599.97</td>
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<td><img src="image4" alt="Chemical Structure 1.1.65" /></td>
<td>1-(5-((1R,3a,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2,3-difluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone</td>
<td>600 22/599.99</td>
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<td>1-(5-((1R,3a,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(4-methoxy-3-methylphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone</td>
<td>578.25/577.88</td>
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<td>1.1.67</td>
<td>1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(3-chloro-4-methoxyphenyl)pyrimidin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone</td>
<td>598.20/597.88</td>
<td>B</td>
<td>B</td>
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<tr>
<td>1.1.66</td>
<td>1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(3-benzo[d][1,3]dioxol-5-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone</td>
<td>578.21/577.90</td>
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<td>1.1.67</td>
<td>1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(4-(difluoromethoxy)phenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone</td>
<td>600.22/600.04</td>
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<td>1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(4-fluoro-3-methoxyphenyl)pyrimidin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone</td>
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<td>1-(5-(((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-3-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2-methyl-2H-indazol-5-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-y1)ethanone</td>
<td>588.25/588.04</td>
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<td>574.23/574.00</td>
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<td><img src="image3" alt="Structure" /></td>
<td>1-(5-(((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-3-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2,5-difluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-y1)ethanone</td>
<td>600.22/600.00</td>
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<td>1-(5-(((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-3-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(4-ethoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-y1)ethanone</td>
<td>578.25/578.01</td>
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<td>1-(3-(6-(1H-pyrazol-3-yl)pyridin-3-yl)-5- ((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-3-azabicyclo[3.2.1]octan-3-yl)-7-amino[1,5-a]pyrimidin-6-y1)ethanone</td>
<td>524.21/523.97</td>
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1-((1R,3s,5S)-3-(3-((6-(1H-pyrazol-3-yl)pyridin-3-yl)-6-acetyl-7-amino)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone

1-((1R,3s,5S)-3-(3-(2,4'-bipyridin-5-yl))-5-(((1R,3s,5R)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-8-yl)-7-amino)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone

1-((1R,3s,5S)-3-(3-(6-acetyl-7-amino)-3-(6-(4-methoxy-(D)-phenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone

1-((1R,3s,5S)-3-(3-(6-acetyl-7-amino)-3-(6-(4-methoxy-(D)-phenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone

1-((1R,3s,5S)-3-(6-acetyl-7-amino)-3-(6-(4-methoxy-(D)-phenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone

1-((1R,3s,5S)-3-(6-acetyl-7-amino)-3-(6-(4-methoxy-(D)-phenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone

1-((1R,3s,5S)-3-(6-acetyl-7-amino)-3-(6-(4-methoxy-(D)-phenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone

1-((1R,3s,5S)-3-(6-acetyl-7-amino)-3-(6-(4-methoxy-(D)-phenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone

1-((1R,3s,5S)-3-(6-acetyl-7-amino)-3-(6-(4-methoxy-(D)-phenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone
<p>| 1.1.81 | <img src="image1.png" alt="Structure" /> | 5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]oct-3-yl)-6-acetyl-7-aminopyrazolo[1,5-alpyrimidin-3-yl]picolinic acid | 502.18/501.96 | ND | ND |
| 1.1.82 | <img src="image2.png" alt="Structure" /> | 1-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]oct-3-yl)-7-amino-3-(6-(1-methyl-(D3)-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-alpyrimidin-6-yl]ethanone | 541.25/541.05 | B | B |
| 1.1.83 | <img src="image3.png" alt="Structure" /> | 1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(1-methyl-(D3)-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-alpyrimidin-5-yl]-8-azabicyclo[3.2.1]oct-8-yl)-2-hydroxyethanone | 514.22/514.08 | B | B |
| 1.1.84 | <img src="image4.png" alt="Structure" /> | 1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(1-methyl-(D3)-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-alpyrimidin-5-yl]-8-azabicyclo[3.2.1]oct-8-yl)-2-hydroxyethanone | 504.24/504.2 | A | A |
| 1.1.85 | <img src="image5.png" alt="Structure" /> | 1-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]oct-3-yl)-7-amino-3-(6-(3-hydroxypentan-3-yl)pyridin-3-yl)pyrazolo[1,5-alpyrimidin-6-yl]ethanone | 544.27/544.03 | C | C |</p>
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<td>556.22/556.09</td>
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<td><img src="image2" alt="Structure" /></td>
<td>1-((1R,3a,5S)-3-(6-acetyl-7-amino-3-(6-(1-fluoromethyl)-1H-pyrazol-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone</td>
<td>519.21/519.04</td>
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<td>1.1.88</td>
<td><img src="image3" alt="Structure" /></td>
<td>1-((1R,3a,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(1-methyl-1H-1,2,4-triazol-3-yl)pyrazidin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone</td>
<td>539.23/539.03</td>
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<td>1-((1R,3a,5S)-3-(6-acetyl-7-amino-3-(6-(1-methyl-1H-1,2,4-triazol-3-yl)pyrazidin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone</td>
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<td>aminopyrazolo[1,5-a]pyrimidin-6-y1ethanone</td>
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<td>556.22/556.2</td>
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<td>1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(4-fluoro-1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone</td>
<td>519.21/519.1</td>
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<td>1.1.95</td>
<td><img src="image4.png" alt="Chemical Structure" /></td>
<td>1-((1R,3s,5S)-3-(6-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(5-methyl-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone</td>
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<td>524.21/523.9</td>
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<td>1-((5-((1R,3a,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(3,5-difluorophenyl)pyridin-3-yl)pyrazolo[1,5-alpyrimidin-8-yl)ethanone</td>
<td>570.21/570.2</td>
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<td><img src="https://example.com/structure5.png" alt="Chemical Structure" /></td>
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<td>533.20/533.1</td>
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<td><img src="image7" alt="Chemical Structure 7" /></td>
<td>1-(5-((1R,3s,5S)-8-(3-(1H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]oct-3-yl)-7-amino-3-(6-(1-methyl-1H-imidazol-4-yl)pyridin-3-yl)pyrazolo[1,5-alpyrimidin-6-y]ethanone)</td>
<td></td>
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<tr>
<td><img src="image8" alt="Chemical Structure 8" /></td>
<td>505.20/50.96</td>
<td></td>
<td></td>
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<tr>
<td><img src="image9" alt="Chemical Structure 9" /></td>
<td>1-(5-((1R,3s,5S)-8-(3-(1H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]oct-3-yl)-7-amino-3-(6-(1-methyl-1H-imidazol-4-yl)pyridin-3-yl)pyrazolo[1,5-alpyrimidin-6-y]ethanone)</td>
<td></td>
<td></td>
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<tr>
<td><img src="image10" alt="Chemical Structure 10" /></td>
<td>556.22/555.95</td>
<td></td>
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<td>Table 1</td>
<td>Compound Structure</td>
<td>Chemical Formula</td>
<td>Molar Mass</td>
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<tr>
<td>1.1.113</td>
<td><img src="image1.png" alt="Chemical Structure" /></td>
<td>1-((1R,3s,5S))-3-(6-acetyl-7-amino-3-(5-fluoro-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone</td>
<td>519.21/518.95</td>
</tr>
<tr>
<td>1.1.114</td>
<td><img src="image2.png" alt="Chemical Structure" /></td>
<td>1-((1R,3s,5S))-3-(4H-1,2,4-triazole-3-carbonyl)pyrimidin-5-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone</td>
<td>552.25/551.97</td>
</tr>
<tr>
<td>1.1.115</td>
<td><img src="image3.png" alt="Chemical Structure" /></td>
<td>1-((1R,3s,5S))-3-(6-acetyl-7-amino-3-(5-methyl-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone</td>
<td>515.24/514.96</td>
</tr>
<tr>
<td>1.1.116</td>
<td><img src="image4.png" alt="Chemical Structure" /></td>
<td>1-((1R,3s,5S))-3-(4H-1,2,4-triazole-3-carbonyl)pyrimidin-6-yl)pyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2(1H)-one</td>
<td>551.21/550.96</td>
</tr>
<tr>
<td>1.1.117</td>
<td><img src="image5.png" alt="Chemical Structure" /></td>
<td>1-((1R,3s,5S))-3-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)propane-1,2-dione</td>
<td>509.22/509.1</td>
</tr>
<tr>
<td>1.1.124</td>
<td>5-(5-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-7-amino-pyrazolo[1,5-alpyrimidin-3-yl]pyridin-2-yl)-2-methoxy-benzonitrile</td>
<td>589.2/589.2</td>
<td>B</td>
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<td>1.1.125</td>
<td>1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-methoxyquinolin-3-yl)pyrazolo[1,5-alpyrimidin-6-yl]ethanone</td>
<td>538.2/538.2</td>
<td>C</td>
</tr>
<tr>
<td>1.1.126</td>
<td>1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(hydroxymethyl)quinolin-3-yl)pyrazolo[1,5-alpyrimidin-6-yl]ethanone</td>
<td>538.2/538.2</td>
<td>C</td>
</tr>
<tr>
<td>1.1.127</td>
<td>1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(5-methyl-1H-imidazol-2-yl)pyridin-3-yl)pyrazolo[1,5-alpyrimidin-5-yl]-8-azabicyclo[3.2.1]octan-8-yl)ethanone</td>
<td>501.23/500.89</td>
<td>D</td>
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<tr>
<td>1.1.128</td>
<td>1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(4-methyl-1H-imidazol-1-yl)pyridin-3-yl)pyrazolo[1,5-alpyrimidin-6-yl]ethanone</td>
<td>538.23/538.00</td>
<td>D</td>
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<tr>
<td>1.1.129</td>
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</tr>
<tr>
<td><img src="image1.png" alt="Chemical Structure" /></td>
<td>1-(3-(6-((1H-imidazol-1-yl)pyridin-3-yl)-5-(1R,3a,5S)-6-(4H-1,2,4-triazole-3-carbonyl)azoazabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-6-yl)ethanone</td>
<td>524.22/523.90</td>
<td>D</td>
</tr>
</tbody>
</table>

| 1.1.130 | 
|---|---|---|---|
| ![Chemical Structure](image2.png) | 1-(7-amino-5-((1R,3a,5S)-8-(5-amino-4H-1,2,4-triazole-3-carbonyl)azoazabicyclo[3.2.1]octan-3-yl)-3-(6-(4-methyl-1H-pyrazol-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone | 553.25/552.96 | A | A |

| 1.1.131 | 
|---|---|---|---|
| ![Chemical Structure](image3.png) | 1-(5-((1R,3a,5S)-8-(1H-pyrazolo-5-carbonyl)azoazabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(4-methyl-1H-pyrazol-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone | 537.24/536.93 | B | B |

| 1.1.132 | 
|---|---|---|---|
| ![Chemical Structure](image4.png) | 1-(7-amino-5-((1R,3a,5S)-8-(3-amino-1H-pyrazolo-5-carbonyl)azoazabicyclo[3.2.1]octan-3-yl)-3-(6-(4-methyl-1H-pyrazol-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone | 552.25/552.00 | A | A |

| 1.1.133 | 
|---|---|---|---|
| ![Chemical Structure](image5.png) | 1-((1R,3a,5S)-3-(6-acetyl-7-amino-3-(6-(3-methyl-1H-pyrazol-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)azoazabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone | 501.23/501.00 | B | C |
| 1.1.134 | 1-(1R,3s,5S)-3-(6-acetyl-7-amino-3-azabicyclo[3.2.1]octan-8-yl)-1H-pyrazol-1-yl)pyridin-3-yl| 501 23/501.00 | A | B |
| 1.1.135 | 1-(5-(1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-3-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(4-methyl-1H-pyrazol-1-yl)pyridin-3-yl)pyrazolato[1,5-a]pyrimidin-8-yl| 538 23/538.20 | A | A |
| 1.1.136 | 1-(5-(1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-3-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(3-methyl-1H-pyrazol-1-yl)pyridin-3-yl)pyrazolato[1,5-a]pyrimidin-8-yl| 538 23/538.00 | A | B |
| 1.1.137 | 1-(1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(1-ethyl-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolato[1,5-a]pyrimidin-8-yl)-3-azabicyclo[3.2.1]octan-8-yl| 515.24/515.06 | A | B |
| 1.1.138 | 1-(5-(1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(1-ethyl-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolato[1,5-a]pyrimidin-8-yl| 552.25/552.07 | A | A |
| 1.1.139 | 1-(7-amino-5-\{(1R,3a,5S)-8-(5-dimethylamino-1H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl\}-3-(8-phenylpyridin-3-yl)pyrazolo[1,5-aj]pyrimidin-6-yl)ethanone | 577.2/577.2 | C | C |
| 1.1.140 | 1-(7-amino-5-\{(1R,3a,5S)-8-(5-amino-1H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl\}-3-(8-phenylpyridin-3-yl)pyrazolo[1,5-aj]pyrimidin-6-yl)ethanone | 549.2/549.3 | A | A |
| 1.1.141 | 1-(7-amino-5-\{(1R,3a,5S)-8-(5-amino-1H-pyrazole-4-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl\}-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-aj]pyrimidin-6-yl)ethanone | 548.2/548.2 | A | A |
| 1.1.142 | N-3-\{(1R,3a,5S)-3-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-aj]pyrimidin-6-yl)-8-azabicyclo[3.2.1]octane-6-carbonyl\}-1H-1,2,4-triazole-5-yl)acetamide | 591.2/591.2 | B | B |
| 1.1.143 | 1-(5-\{(1R,3a,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl\}-7-amino-3-(1-phenyl-1H-pyrazol-4-yl)pyrazolo[1,5-aj]pyrimidin-6-yl)ethanone | 523.2/523.2 | A | A |
| 1.1.144 | 1-((7-amino-5-((1R,3S,5S)-8-(5-amino-4H-1,2,4-triazolo-3-carbonyl)8-azabicyclo[3.2.1]octan-3-yl)-3-((6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone | 597.2/597.2 | A | A |
| 1.1.145 | 1-((5-((1R,3S,5S)-8-(4H-1,2,4-triazolo-3-carbonyl)8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone | 552.2/552.1 | A | A |
| 1.1.146 | 1-((3-(2,2-bipyridin-5-yl)-5-((1R,3S,5S)-8-(4H-1,2,4-triazolo-3-carbonyl)8-azabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-6-yl)ethanone | 535.2/535.2 | A | A |
| 1.1.147 | 1-((5-((1R,3S,5S)-8-(4H-1,2,4-triazolo-3-carbonyl)8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2,6-difluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone | 570.2/570.2 | A | A |
| 1.1.148 | 1-((5-((1R,3S,5S)-8-(4H-1,2,4-triazolo-3-carbonyl)8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2,4-difluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone | 570.2/570.2 | A | A |
1.1.149
1-((5-(((1R,3a,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone

538.2/538.2 A A

1.1.150
1-((1R,3a,5S)-3-(6-acetyl-7-amino-3-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone

424.2/424.0 ND ND

1.1.151
1-((5-(((1R,3a,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone

461.2/460.9 B B

1.1.152
1-((1R,3a,5S)-3-(6-acetyl-7-amino-3-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone

482.2/482.2 ND ND

1.1.153
1-((5-(((1R,3a,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone

519.3/519.2 ND ND

1.1.154
1-((1R,3a,5S)-3-(6-acetyl-7-amino-3-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone

454.2/454.1 ND ND
1.1.155 1-((5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-((1H-hydroxyethyl)-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone

1.1.156 1-((7-amino-5-((1R,3s,5S)-8-(3-amino-1H-pyrazole-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-(4-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone

1.1.157 1-((5-((1R,3s,5S)-8-(1H-pyrazole-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(4-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone

1.1.158 (R)-1-((1R,3s,5S)-3-(8-acetyl-7-amino-3-(6-(4-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxypropan-1-one

1.1.159 1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(4-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-6-yl)-2-hydroxyethanone

1.1.160 1-((7-amino-3-(6-(4-fluorophenyl)pyridin-3-yl)-8-(1R,3s,5S)-8-(5-methyl-4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)ethanone
| 1.1.161 | 1-((1R,3α,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone | 524.2/524.2 | B | B |
| 1.1.162 | 1-((1R,3α,5S)-3-(6-acetyl-7-amino-3-(1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-6-yl)-2-hydroxyethanone | 487.2/487.1 | B | B |
| 1.1.163 | 1-((1R,3α,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(4-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone | 552.2/552.1 | A | B |
| 1.1.164 | 1-((1R,3α,5S)-3-(6-acetyl-7-amino-3-(6-(2,4-difluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-6-yl)-2-hydroxyethanone | 533.2/533.2 | A | B |
| 1.1.165 | 1-((7-amino-3-(6-(2,4-difluorophenyl)pyridin-3-yl)-5-(1R,3α,5S)-8-(5-methyl-4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone | 584.2/584.2 | A | A |
1.1.172

\[
1\text{-}((1\text{R},3\text{e},5\text{S})\text{-}3\text{-(6\text{-}acetyl}-7\text{-amino}-3\text{-}(6\text{-}(2\text{-fluorophenyl})pyridin}-3\text{-yl})pyrazolo[1,5\text{a}]pyrimidin}-5\text{-yl})\text{-8-azabicyclo[3.2.1]octan}-8\text{-yl})\text{-2-hydroxyethanone}
\]

515.2/515.2

A

A

1.1.173

\[
1\text{-}((7\text{-amino}-3\text{-}(6\text{-}(2\text{-fluorophenyl})pyridin}-3\text{-yl})\text{-5-}((1\text{R},3\text{e},5\text{S})\text{-}8\text{-}(5\text{-methyl}-4\text{H}-1,2,4\text{-triazole}-3\text{-carbonyl})\text{-8-azabicyclo[3.2.1]\text{octan}-3-yl})\text{-pyrazolo[1,5-a]pyrimidin}-6\text{-yl})\text{ethanone}
\]

566.2/566.2

A

A

1.1.174

\[
(1\text{R},3\text{e},5\text{S})\text{-}3\text{-}(6\text{-acetyl}-7\text{-amino}-3\text{-}(6\text{-}(2\text{-fluorophenyl})pyridin}-3\text{-yl})\text{-pyrazolo[1,5-a]pyrimidin}-5\text{-yl})\text{-8-azabicyclo[3.2.1]\text{octane-8-carboxamidine}}
\]

500.2/500.2

A

A

1.1.175

\[
(1\text{R},3\text{e},5\text{S})\text{-}3\text{-}(6\text{-acetyl}-7\text{-amino}-3\text{-}(6\text{-}(1\text{-methyl}-1\text{H-pyrazol}-4\text{-yl})\text{-pyridin}-3\text{-yl})\text{-pyrazolo[1,5-a]pyrimidin}-5\text{-yl})\text{-8-azabicyclo[3.2.1]\text{octane-8-carboxamidine}}
\]

486.2/486.2

A

B

1.1.176

\[
1\text{-}(7\text{-amino}-5\text{-}((1\text{R},3\text{e},5\text{S})\text{-}8\text{-}(3\text{-amino}-1\text{H-pyrazole}-5\text{-carbonyl})\text{-8-azabicyclo[3.2.1]\text{octan}-3-yl})\text{-3-(6\text{-}(1\text{-methyl}-1\text{H-pyrazol}-4\text{-yl})\text{-pyridin}-3-yl})\text{-pyrazolo[1,5-a]pyrimidin}-6\text{-yl})\text{ethanone}
\]

552.3/552.2

B

B
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<th>Chemical Formula</th>
<th>MW</th>
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<td><img src="image1" alt="Molecule 1" /></td>
<td>1-(3-(6-(1H-pyrazol-1-yl)pyridin-3-yl)-5-(3R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-8-y</td>
<td>524.22/524.3</td>
<td>A</td>
<td>A</td>
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<tr>
<td>1.1.178</td>
<td><img src="image2" alt="Molecule 2" /></td>
<td>1-(5-(1R,3s,5S)-3-(3-(6-(1H-pyrazol-1-yl)pyridin-3-yl)acetyl)-7-aminopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone</td>
<td>487.21/487.1</td>
<td>A</td>
<td>B</td>
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<tr>
<td>1.1.179</td>
<td><img src="image3" alt="Molecule 3" /></td>
<td>1-(5-(1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-6-y</td>
<td>535.22/535.3</td>
<td>A</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>1.1.180</td>
<td><img src="image4" alt="Molecule 4" /></td>
<td>1-(5-(1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-6-y</td>
<td>517.23/517.3</td>
<td>B</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>1.1.181</td>
<td><img src="image5" alt="Molecule 5" /></td>
<td>1-(5-(1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-6-y</td>
<td>550.2/550.4</td>
<td>A</td>
<td>A</td>
<td></td>
</tr>
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<td>1.1.182</td>
<td><img src="image1.png" alt="Chemical Structure" /></td>
<td>1-((5-((1R,3S,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-fluoro-8-methoxyquinolin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone)</td>
<td>555.2/556.2</td>
<td>A</td>
<td>A</td>
<td></td>
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<tr>
<td>1.1.183</td>
<td><img src="image2.png" alt="Chemical Structure" /></td>
<td>1-((1R,3S,5S)-3-(6-acetyl-7-amino-3-(6-fluoro-8-methoxyquinolin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone</td>
<td>518.2/519.2</td>
<td>A</td>
<td>B</td>
<td></td>
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<tr>
<td>1.1.184</td>
<td><img src="image3.png" alt="Chemical Structure" /></td>
<td>1-((1R,3S,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(5-(hydroxymethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone)</td>
<td>487.21/488.2</td>
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<td>B</td>
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<td>1.1.185</td>
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<td>459.20/460.1</td>
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Example 1-42

Preparation of 1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone

Step 1: Preparation of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

To tert-butyl 3-(7-bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-iodopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (9.96 g, 13.67 mmol) in dioxane (100 mL) and H2O (10 mL) was added 2-(1-methyl-1H-pyrazol-3-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (5.84 g, 20.50 mmol), PdCl2(dppe)CH2Cl2 (1.15 g, 1.36 mmol) and K3PO4 (8.69 g, 40.9 mmol). The reaction was heated at 80°C overnight. On cooling, filtration and concentration afforded crude product. Gradient column chromatography on silica gave (1R,3s,5S)-tert-butyl 3-(7-bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone.
Step 2: Preparation of (1R,3S,5S)-tert-butyl 3-(7-bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate.

At 0°C, to a mixture of (1R,3S,5S)-tert-butyl 3-(7-bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (10.92 g, 14.4 mmol) in dichloromethane (40 mL) was added W-bromosuccinimide (2.33 g, 13.07 mmol) portionwise and the resulting mixture was warmed up to room temperature slowly. The mixture was purified by column chromatography on silica gel to give (1R,3S,5S)-tert-butyl 3-(7-bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(6-(1-ethoxyvinyl)-1H-pyrazol-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate.

Step 3: Preparation of (1R,3S,5S)-tert-butyl 3-(7-bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-((1-ethoxyvinyl)-3-(6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate.
A mixture of compound (1R,3s,5S)-tert-butyl 3-[(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)pyrazolo[3,2,1]octane-8-carboxylate (9900 mg, 11.81 mmol), tributyl(1-ethoxyvinyl)tin (8529.7 mg, 23.63 mmol), tetrakis(triphenylphosphine)palladium (1365.6 mg, 1.18 mmol) in dioxane (100 mL) was degassed with argon for five minutes. It was then heated at 100°C in a sealed tube for 16 h, at which time LC/MS analysis confirmed full consumption of starting material. On cooling, the solvent was rotoevaporated, and the crude residue was redissolved in EtOAc, washed with 0.5 M KF solution, brine (1 x 25 mL), and dried over MgSO₄. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel to give (1R,3s,5S)-tert-butyl 3-[(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(1-ethoxyvinyl)-3-(6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)pyrazolo[3,2,1]octane-8-carboxylate.

Step 4: Preparation of 1-(7-amino-5-(1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone
To a mixture of 1R,3s,5S)-tert-butyl 3-(7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-6-(1-ethoxyvinyl)-3-(6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone (6058.3 mg, 7.30 mmol) in dioxane (50 mL) was added 4 M HCl in water (60 mL) slowly. After stirring for 30 min at 50°C, the solvent was removed in vacuo to get 1-(7-amino-5-(1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone as a HCl salt.

Step 5: Preparation of 1-(5-((1R,3s,5S)-8-4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone

1H-1,2,4-triazole-3-carboxylic acid (58.0 mg, 0.51 mmol), EDC (133.7 mg, 0.70 mmol), HOBT (94.5 mg, 0.70 mmol) and DIEA (730 uL, 4.20 mmol) were added to a mixture of 1-(7-amino-5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone (207.7 mg, 0.47 mmol) in DMF (5 mL) and the mixture was stirred at room temperature for 1 h. Purification with prep-LC provided 1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone.

Example 2-1
Preparation of \(((1R,3s,5S)-3-(7-amino-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-yl)(4H-1,2,4-triazol-3-yl)methanone

Step A - Synthesis of tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-chloropyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

2-Chloro-5-(4,4,5,5-tetramethyl-1,2-dioxaborolan-2-yl)pyridine (5.55 mmol, 1327 mg), K$_3$PO$_4$ (14.48 mmol, 3070 mg), and PdCl$_2$(dpdpf)-CH$_2$Cl$_2$ (0.48 mmol, 394 mg) were added to a solution of tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-iodopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (1.98 mmol, 1101 mg) in dioxane (40 mL) and H$_2$O (4 mL). The resulting solution was stirred at 70°C under argon overnight. The mixture was diluted with H$_2$O and then extracted with ethyl acetate (x2). The combined organic layers were washed with brine and dried with Na$_2$SO$_4$.

Evaporation and purification by column chromatography afforded tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-chloropyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate, LCMS $t_R = 3.29$ Min (5
min run, UV (254 nm). Mass calculated for M+H 715.35, observed LC/MS m/z 715.02 (M+H).

Step B - Synthesis of Tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

3-Fluoro-4-methoxyphenylboronic acid (2.79 mmol, 475.7 mg), K_3PO_4 (4.20 mmol, 890.4 mg), and PdCl_2(dppf)-CH_2Cl_2 (0.14 mmol, 114.3 mg) were added to a solution of tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-chloropyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (1.40 mmol, 1000 mg) in dioxane (12 mL) and H_2O (1.5 mL). The resulting solution was stirred at 150 °C under microwave condition for 1 h. The mixture was diluted with H_2O and then extracted with ethyl acetate (x2). The combined organic layers were washed with brine and dried with Na_2SO_4. Evaporation and purification by column chromatography afforded tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate, LCMS t_R = 3.31 Min (5 min run, UV 254 nm). Mass calculated for, M+H 805.42, observed LC/MS m/z 805.17 (M+H).

Example 2-2

Scheme 2-1
Preparation of 1-(3-(7-Amino-6-bromo-3-(6-(3-(hydroxymethyl)-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone

Step A - Synthesis of 5-(5-(7-Amino-5-(8-azabicyclo[3.2.1]octan-3-yl)-6-bromopyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)-2-methoxyphenyl)methanol

Terf-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(6-(3-(hydroxymethyl)-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (219 mg) was treated with 4 N HCl in dioxane (4 mL) and water (1 mL) and the resulting mixture was stirred for 40 minutes, concentrated and lyophilized to provide the title compound.

Step B - Synthesis of 1-(3-(7-Amino-6-bromo-3-(6-(3-(hydroxymethyl)-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone
The preparation is similar to that described in Example 1-1 except using glycolic acid to replace 1/7-1,2,4-triazole-3-carboxylic acid. LC/MS Retention time = 3.34 min. Mass calculated for M+H 593.1, observed 592.9.

Following the procedures similar to preparation of \(((1\,R,3s,5S)-3-(7\text{-}amino\text{-}3\text{-} (6\text{-}(3\text{-}fluoro\text{-}4\text{-}methoxyphenyl)\text{pyridin}-3\text{-}y)\text{pyrazolo}[1\,5\text{-}a]\text{pyrimidin}-5\text{-}y)\text{8}- \text{azabicyclo}[3.2.1]\text{oc tan}-8\text{-}y)(4\text{H}-1\,2,4\text{-}triazol-3\text{-}y)\text{methanone}, the following compounds (Table 2-1) can be prepared:

**Table 2-1**

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<th>Structures</th>
<th>Compound Name</th>
<th>M+H (calculated) / M+H (observed)</th>
<th>pAKT S473 IC50</th>
<th>pE5- BPI Thr374 IC50</th>
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<td>(((1,R,3s,5S)-3-(7\text{-}amino\text{-}8\text{-}bromo\text{-}3\text{-} (6\text{-}phenyl\text{pyridin}-3\text{-} y)\text{pyrazolo}[1,5\text{-}a]\text{pyrimidin}-5\text{-}y)\text{8}- \text{azabicyclo}[3.2.1]\text{oct an}-8\text{-}y)(1\text{H}-1,2,4\text{-}triazol-3\text{-}y)\text{methanone}</td>
<td>570.1/569.7</td>
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<td>(R)-1-((1R,3S,5S)-3-(7-amino-6-bromo-3-(6-(3-(hydroxymethyl)-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxypropan-1-one</td>
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<td>618.1/617.9</td>
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<td>((1R,3s,5S)-3-(7-amino-3-(6-(3-(hydroxymethyl)-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone</td>
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<tr>
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<td>((1R,3a,5S)-3-(7-amino-3-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-alpyrimidin-5-yl]-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone</td>
<td>419.2/419.2</td>
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<td>ND</td>
<td></td>
</tr>
<tr>
<td>2.19</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>((1R,3S,5S)-3-(7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-alpyrimidin-5-yl]-8-azabicyclo[3.2.1]octan-8-yl)((R)-pyrrolidin-2-yl)methanone</td>
<td>493.3/494.2</td>
<td>B</td>
<td>C</td>
<td></td>
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<tr>
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<td><img src="image3.png" alt="Structure" /></td>
<td>((1R,3R,5S)-3-(7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-alpyrimidin-5-yl]-8-azabicyclo[3.2.1]octan-8-yl)((S)-pyrrolidin-2-yl)methanone</td>
<td>493.3/494.2</td>
<td>C</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>2.21</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>((1R,3a,5S)-3-(7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-alpyrimidin-5-yl]-8-azabicyclo[3.2.1]octan-8-yl)(morpholin-3-yl)methanone</td>
<td>509.3/510.2</td>
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<tr>
<td>2.22</td>
<td><img src="image5.png" alt="Structure" /></td>
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<td>507.3/508.0</td>
<td>ND</td>
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<td></td>
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</tbody>
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Example 3-1

Preparation of ((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-1,2,4-triazol-3-yl)methanone

Method A:

Scheme 3-1
Step A - Synthesis of Tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(methylthio)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

A mixture of tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (417 mg, 0.5 mmol), Al2O3 (510 mg, 5 mmol) and NaSCH3 (70 mg, 1 mmol) in DMF (4 mL) was heated at 80 °C for 15 h, at which time LC/MS confirmed full conversion of starting material to product (i.e., no starting material was present). The reaction mixture was cooled to room temperature and diluted with EtOAc (25 mL). It was then filtered and the filtrate was washed with water (2 x 3 mL), brine (1 x 3 mL) and dried over MgSO4. The solvent was removed to give the crude product which was purified by column chromatography on silica gel eluting with 25% EtOAc/Hexanes to give the desired product (301 mg).

Step B - Synthesis of Tert-butyl 3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate
A mixture of compound tert-butyl 3-(7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-6-(methythio)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (319 mg, 0.4 mmol), Oxone (1.2 g, 2 mmol) and NaHCO₃ (336 mg, 4 mmol) in MeOH (12 mL) and Water (3 mL) was heated at 65 °C for 15 h, at which time LC/MS analysis confirmed full consumption of starting material. After cooling, it was diluted with DCM: MeOH (1:1, 100 mL) and filtered. The filtrate was concentrated to afford the crude title product which was used for the next step without further purification.

**Step C - Preparation of 5-(8-Azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine**

To the crude tert-butyl 3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate in MeOH (5 mL) was added 4M HCl in 1,4-dioxane at r.t. It was stirred further at room temperature for 2 h, at which time LC/MS analysis confirmed full consumption of the
starting material. The solvent was removed in vacuo to afford the desired product as an HCl salt.

Step D - Synthesis: 

\[(1R,3S,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-1,2,4-triazol-3-yl)methanone\]

A mixture of 1H-1,2,4-triazole-3-carboxylic acid (29.4 mg, 0.26 mmol), EDCI (76.7 mg, 0.4 mmol), and 1-hydroxybenzotriazole (27 mg, 0.2 mmol) in DMF (2 mL) was stirred at room temperature for 10 min. The 5-(8-azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine HCl (0.2 mmol) was added, followed by N,N-diisopropylethylamine (0.17 mL, 1 mmol). It was stirred further for 20 min at room temperature at which time LC/MS analysis confirmed full consumption of starting material. This crude compound was purification by HPLC to afford the desired title product.

**Method 2:**

**Scheme 3-2**
Step 1. Synthesis of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-iodo-1,5-a[pyrimidin-5-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate.

To (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-iodo pyrazolo[1,5-a][pyrimidin-5-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate (10.1 g, 13.9 mmol) in dioxane (100 mL) and water (25 mL) was added 2-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (5.9 g, 20.8 mmol), PdCl₂(dppf),CH₂Cl₂ (1.4 g, 1.7 mmol) and K₂CO₃ (5.8 g, 41.6 mmol). The reaction mixture was heated at 100°C for 16 hour, at which time LC/MS analysis confirmed full consumption of
starting material. On cooling, the solvent was removed \textit{in vacuo}, and the crude was redissolved in EtOAc (500 mL), washed with water (1 x 125 mL), brine (1 x 125 mL), and dried over MgSO$_4$. Gradient column chromatography on silica gel eluting with 0 to 50\% EtOAc/hexanes gave the desired (1R,3s,5S)-3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (8.6 g).

**Step 2.** *Synthesis of (1R,3s,5S)-3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-iodo-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate* 

\begin{figure}
\centering
\includegraphics[width=\textwidth]{reaction_scheme}
\caption{Synthesis of (1R,3s,5S)-3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-iodo-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate.}
\end{figure}

To (1R,3s,5S)-3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-phenyl pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (16.9 g, 22.4 mmol) in CH$_3$CN (75 mL) and DCM (75 mL) was added AcOH (15.4 mL, 268.6 mmol) followed by N-iodosuccinimide (10.1 g, 44.8 mmol) portionwise and the resulting mixture was stirred at room temperature for 16 hour, at which time LC/MS confirmed full conversion of starting material to product. Solvent was removed \textit{in vacuo} and the residue was dissolved in EtOAc (500 mL). To this solution was added 28 g of NaHCO$_3$ in 200 mL of water. It was then stirred at room temperature for 20 min. Organics were extracted and washed with water (1 x 200 mL), brine (1 x 200 mL), and dried over MgSO$_4$. Solvent was removed \textit{in vacuo} and the residue was purified by column chromatography on silica gel. Elution with EtOAc/Hexanes (0-40\%) gave desired product, (1R,3s,5S)-3-(7-(bis((2-
(trimethylsilyl)ethoxy)methyl)amino)-6-iodo-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (18.2 g).

**Step 3.** Synthesis of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

A mixture of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-iodo-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (21.5 g, 24.4 mmol), CuI (27.9 g, 146.3 mmol) and sodiummethane sulfinate (7.5 g, 73.2 mmol) in DMSO (195 mL) was degassed with argon for five minutes. It was then heated at 90°C in a sealed tube for 2.5 hour, at which time LC/MS analysis confirmed full consumption of starting material to product. On cooling, EtOAc (1000 mL) were added and solids were filtered off on a celite pad. Filtrate was washed with sat. NH₄Cl (1 x 200 mL), water (3 x 200 mL), brine (1 x 200 mL), and dried over MgSO₄. Solvent was removed in vacuo and the crude was subjected to iodination condition one more time in order to purify it by column chromatography on silica gel.
To the above crude mixture in CH$_3$CN (90 mL) and DCM (90 mL) was added AcOH (16.8 mL, 292.7 mmol) followed by N-iodosuccinimide (2.7 g, 12.2 mmol) portionwise and the resulting mixture was stirred at room temperature for 16 hour, at which time LC/MS confirmed full conversion of starting material to product. Solvent was removed in vacuo and the residue was dissolved in EtOAc (500 mL). To this solution was added 28 g of NaHCO$_3$ in 200 mL of water. It was then stirred at room temperature for 20 minutes. Organics were extracted and washed with water (1 x 200 mL), brine (1 x 200 mL), and dried over MgSO$_4$. Solvent was removed in vacuo and the residue was purified by column chromatography on silica gel. Elution with EtOAc/Hexanes (0-40%) gave desired product, (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-aza bicyclo[3.2.1]octane-8-carboxylate (12.6 g, 62%) and starting material (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-iodo-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (5.8 g).

**Step 4. Synthesis of 5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-(methyl sulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine**

$$\text{(1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(methyl sulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (12.3 g, 14.8 mmol) was dissolved in a mixture of TFA (60 mL) and water (6 mL) at room temperature. Stirring continued for 45 min at room temperature. LC/MS analysis confirmed full consumption of starting material to product. TFA along with water was rotoevaporated, and the crude product 5-}$$
Step 5. Synthesis of ((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-1,2,4-triazol-3-yl) methanone

A mixture of 1H-1,2,4-triazole-3-carboxylic acid (2.8 g, 24.4 mmol), EDCI (4.7 g, 24.4 mmol), and 1-hydroxybenzotriazole (2.2 g, 16.3 mmol) in DMF (100 mL) was stirred at room temperature for 10 min. To this mixture 5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine (12.2 g, 14.8 mmol) was added followed by N,N-diisopropylethylamine (12.9 mL, 73.9 mmol). It was stirred further for 20 min at room temperature, at which time LC/MS analysis confirmed full consumption of starting material. Solvent was removed in vacuo to complete dryness. To this crude was added water (200 mL) and solids were filtered and washed with additional water (200 mL). It was then washed with MeOH (125 mL), a 1:1 mixture of ACN and water (200 mL), ACN (100 mL) and diethyl ether (100 mL) successively to afford ((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-1,2,4-triazol-3-yl) methanone hydrochloride (7.5 g).

Step 6. Synthesis of ((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-1,2,4-triazol-3-yl) methanone hydrochloride
To a suspension of ((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-1,2,4-triazol-3-yl)methanone (8g, 14.1 mmol) in DCM (350 mL) and MeOH (100 mL) was added 4M HCl in 1,4-dioxane (14.1 mL, 56.2 mmol). It was stirred further for 10 min at room temperature during which time solution became clear. Solvent was removed in vacuo until solids were precipitate out. To this crude was added diethyl ether (200 mL) and solids were filtered and washed with additional diethyl ether (800 mL). Solids were redissolved in a 1:1 mixture of ACN and water and lyophilized to get the desired ((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-1,2,4-triazol-3-yl)methanone as an HCl salt (8.5 g).

EXAMPLE 3-2

Synthesis of (1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-carboxamide
A mixture of potassium cyanate (0.24 g, 3 mmol) and AcOH (0.17 mL, 3 mmol) in DMF (2 mL) was stirred at room temperature for 10 minutes. To this solution was added 5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl) pyrazolo[1,5-a]pyrimidin-7-amine (0.17 g, 0.2 mmol) followed by N,N-diisopropyl ethylamine (0.5 mL, 3 mmol). It was stirred further for 30 min at room temperature, at which time LC/MS analysis confirmed full consumption of starting material. Pure compound (1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl) pyrazolo[1,5-a]pyrimidin-5-yl)-N-ethyl-8-azabicyclo[3.2.1]octane-8-carboxamide was isolated by preparative HPLC.

EXAMPLE 3-3

Synthesis of (1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl) pyrazolo[1,5-a]pyrimidin-5-yl)-N-ethyl-8-azabicyclo[3.2.1]octane-8-carboxamide

To 5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)-3-(6-phenyl pyridin-3-yl) pyrazolo[1,5-a]pyrimidin-7-amine (0.17 g, 0.2 mmol) in DMF (2 mL) was added N,N-diisopropylethylamine (0.18 mL, 1 mmol) followed by ethyl isocyanate (16 μL, 0.2 mmol). The reaction mixture was stirred at room temperature for 1 hour, at which time LC/MS analysis confirmed full consumption of starting material. Pure compound (1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-N-ethyl-8-azabicyclo[3.2.1]octane-8-carboxamide was isolated by preparative HPLC.
Example 3-4

Preparation of (1R,3s,5S)-tert-butyl 3-(7-(bis(2-(trimethylsilyl)ethoxy)methyl) amino)-3-(6-(methylcarbamoyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate.

Step A. Synthesis of (1R,3s,5S)-tert-butyl 3-(7-(bis(2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-(methylcarbamoyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

To (1R,3s,5S)-tert-butyl 3-(7-(bis(2-(trimethylsilyl)ethoxy)methyl)amino)-3-iodopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (3.5 g, 4.8 mmol) in dioxane (40 mL) and water (10 mL) was added N-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinamide (2.5 g, 9.5 mmol), PdCl₂(dppf).CH₂Cl₂ (0.5 g, 0.6 mmol) and K₂CO₃ (2 g, 14.3 mmol). The reaction mixture was heated at 100°C for 16 hour, at which time LC/MS analysis confirmed full consumption of starting material. On cooling, the solvent was removed in vacuo, and the crude was redissolved in DCM (500 mL), washed with water (1 x 125 mL).
brine (1 x 125 mL), and dried over MgSO₄. Gradient column chromatography on silica gel eluting with 0 to 100% EtOAc/hexanes gave the desired (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-(methylcarbamoyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimdin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (3.2 g).

Example 3-5

Preparation of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(5-(methoxymethoxy)-6-phenylpyrazolo[1,5-a]pyrimdin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

![Chemical Structure]

Step A. Synthesis of 5-bromo-2-chloro-3-(methoxymethoxy) pyridine

To 5-bromo-2-chloropyridin-3-ol (2.3 g, 11 mmol) in DCM (88 mL) was added N,N-diisopropylethylamine (9.6 mL, 55 mmol) at 0°C followed by MOMCl (4.2 mL, 55 mmol). Reaction mixture was warmed up to room temperature and stirred further for one hour at which time LC/MS analysis confirmed full consumption of starting material. Organics were then extracted with DCM (1 x 500 mL), and washed with water (1 x 125), brine (1 x 125 mL), and dried over MgSO₄. Solvent was removed in
vacuo and the residue was purified by column chromatography on silica gel. Elution with EtOAc/hexanes (0-30%) gave desired product, 5-bromo-2-chloro-3-(methoxymethoxy) pyridine (2.5 g).

**Step B. Synthesis of 2-chloro-3-(methoxymethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine**

To 5-bromo-2-chloro-3-(methoxymethoxy) pyridine (2.5 g, 10.1 mmol) in dioxane (80 mL) was added bis(pinacolato)diboron (3.3 g, 13.1 mmol), PdCl$_2$(dpdf), CH$_2$Cl$_2$ (0.8 g, 1 mmol) and KOAc (3 g, 30.1 mmol). It was then degassed with Argon for five minutes before heating at 100°C for 16 hours, at which time LC/MS analysis confirmed full consumption of starting material. On cooling, the solvent was rotovaporated, and the crude was redissolved in DCM (500 mL), washed with water (1 x 125 mL), brine (1 x 125 mL), and dried over MgSO$_4$. Solvent was removed in vacuo to get the crude compound 2-chloro-3-(methoxymethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine, which was used for the next step without any further purification.

**Step C. Synthesis of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-chloro-5-(methoxymethoxy) pyridine-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate**
To 2-chloro-3-(methoxymethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (6.5 g, 10.52 mmol) in dioxane (28 mL) and water (7 mL) was added (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-iodopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (2.4 g, 3.3 mmol), PdCl₂(dppf), CH₂Cl₂ (0.3 g, 0.4 mmol) and K₂CO₃ (1.4 g, 10 mmol). The reaction was heated at 100 °C for 16 hours, at which time LC/MS analysis confirmed full consumption of starting material. On cooling, the solvent was rotoevaporated, and the crude was redissolved in DCM (500 mL), washed with water (1 x 125 mL), brine (1 x 125 mL), dried (MgSO₄) and concentrated in vacuo to crude. Gradient column chromatography on silica gel eluting with 0 to 45% EtOAc/hexanes gave the desired (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-chloro-5-(methoxymethoxy)pyridine-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (2.4 g).

**Step D.Synthesis of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(5-(methoxymethoxy)-6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate**
To (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-chloro-5-(methoxymethoxy) pyridine-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (2.1 g, 2.6 mmol) in dioxane (21 mL) and water (5.2 mL) was added phenylboronic acid (0.6 g, 5.2 mmol), PdCl₂(dpdpf)CH₂Cl₂ (0.26 g, 0.3 mmol) and K₂Pd₄ηH₂O (1.4 g, 6.5 mmol). The reaction was heated at 100 °C for 16 hours, at which time LC/MS analysis confirmed full consumption of starting material. On cooling, the solvent was rotoevaporated, and the crude was redissolved in DCM (250 mL), washed with water (1 x 50 mL), brine (1 x 50 mL), dried (MgSO₄) and concentrated in vacuo to crude. Gradient column chromatography on silica gel eluting with 0 to 50% EtOAc/hexanes gave the desired (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl) ethoxy)methyl)amino)-3-(5-(methoxymethoxy)-6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (1.7 g).

Example 3-6

Preparation of 5-((1R,3s,5S)-8-(1H-tetrazol-5-yl)-8-azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine

Step A. Synthesis of (1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenyl pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-carbonitrile
5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine (0.8 g, 0.97 mmol) in EtOH (18 mL) and DMF (4 mL) was treated with NaHCO₃ (0.5 g, 5.9 mmol) for 10 minutes at room temperature. Cyanic bromide (3M in DCM, 1 mL, 2.9 mmol) was added and the resulting mixture was stirred at room temperature for 16 hours, at which time LC/MS confirmed full conversion of starting material to product. Solvent was removed in vacuo to complete dryness. To this crude was added water (30 mL) and solids were filtered and washed with additional water (30 mL) to afford (1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carbonitrile (0.4 g).

**Step B. Synthesis of 5-((1R,3s,5S)-8-(1H-tetrazol-5-yl)-8-azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine**

A mixture of (1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carbonitrile (29.4 mg, 0.05 mmol), NH₄Cl (4 mg, 0.08 mmol) and sodium azide (4.9 mg, 0.08 mmol) in DMF (0.5
mL) was heated at 100°C for 19 hours, at which time LC/MS analysis confirmed full consumption of starting material. Pure compound 5-((1 R,3s,5S)-8-(1 H-tetrazol-5-yl)-8-azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)-3-(6-phenyl pyridin-3-yl)pyrazolo[1,5-a] pyrimidin-7-amine was isolated by preparative HPLC.

Example 3-7

Preparation of 5-((1 R,3s,5S)-8-(5-methyl-4H-1,2,4-triazol-3-yl)-8-aza bicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine

A mixture of (1 R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carbonitrile (0.12 g, 0.21 mmol), acetamidine hydrochloride (49.6 mg, 0.53 mmol), Cs₂CO₃ (0.34 g, 1.1 mmol) and CuBr (1.5 mg, 0.01 mmol) in DMSO (1.5 mL) was degassed with argon and heated at 120°C for 16 hours, at which time LC/MS analysis confirmed full consumption of starting material. Pure compound 5-((1 R,3s,5S)-8-(5-methyl-4H-1,2,4-triazol-3-yl)-8-aza bicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine was isolated by preparative HPLC.

Example 3-8

Preparation of 5-((1 R,3s,5S)-8-(4H-1,2,4-triazol-3-yl)-8-azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine
A mixture of (1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carbonitrile (23.5 mg, 0.04 mmol) and hydrazine (0.01 mL) in EtOH (0.3 mL) was heated at 75°C for 16 hours, at which time LC/MS analysis confirmed full consumption of starting material. After cooling, formic acid (0.32 mL) was added and it was heated further at 80°C for 1 hour. Pure compound 5-((1R,3s,5S)-8-(4H-1,2,4-triazol-3-yl)-8-azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl) pyrazolo[1,5-a]pyrimidin-7-amine was isolated by preparative HPLC.

Example 3-9

Preparation of (1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carbaldehyde

A mixture of 5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine (0.3 g, 0.35 mmol), formic acid
acid (0.71 mL) and acetic anhydride (0.71 mL) in DMF (3 mL) was degassed with argon and heated at 100°C for one hour, at which time LC/MS analysis confirmed full consumption of starting material. Pure compound (1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carbaldehyde was isolated by preparative HPLC.

Example 3-10

Preparation of N-(5-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carbonyl)-4H-1,2,4-triazol-3-yl)acetamide

Step 1: Preparation of methyl 5-acetamido-4H-1,2,4-triazole-3-carboxylate

A suspension of methyl 5-amino-4H-1,2,4-triazole-3-carboxylate (1.42 g, 10.0 mmol) in acetic anhydride (30 mL) was refluxed for 30 min until a clear solution was formed. The solution was evaporated to dryness and H₂O (40 mL) was added. The resulting suspension was stirred at rt overnight. H₂O was evaporated to afford the titled compound as a white powder (1.85 g), which was used without further purification.

Step 2: Preparation of 5-acetamido-4H-1,2,4-triazole-3-carboxylic acid

A mixture of methyl 5-acetamido-4H-1,2,4-triazole-3-carboxylate (500 mg, 2.72 mmol) and LiOH (2.1 eq) in THF/MeOH/H₂O (8/4/2 mL) was stirred at 50°C for
1 h (precipitates formed). All the volatiles were removed and the white solid residue was acidified with 7 mL of HCl (1 N), filtered and washed with H2O to afford the titled compound as a white solid (413 mg), which was used without further purification.

Step 3: Preparation of N-(5-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carbonyl)-4H-1,2,4-triazol-3-yl)acetamide

A mixture of 5-acetamido-4H-1,2,4-triazole-3-carboxylic acid (31.3 mg, 0.184 mmol), HOBT (16.5 mg, 0.122 mmol), EDCI-HCl (30.5 mg, 0.159 mmol) in DMF (2 mL) was stirred at rt for 10 min. Then a slurry of 5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine TFA salt (100 mg, 0.122 mmol, preparation described previously) in DMF (2 mL) was added, followed by DIEA (6 eq). The resulting solution was stirred at rt for 1 h. The reaction mixture was concentrated to half volume, diluted with DMSO and purified by a reverse phase HPLC to afford the titled compound as a pale yellow solid (57 mg).

Example 3-11

Preparation of ((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-hydroxy-1H-pyrazol-4-yl)methanone

Step 1: Preparation of ethyl 3-hydroxy-1'H-pyrazole-4-carboxylate
To a solution of NaOEt in EtOH (60 mL, 21 w%) were added diethyl 2-(ethoxymethylene)malonate (10.4 mL, 52.0 mmol) and hydrazine monohydrate (5.04 mL, 104 mmol) with cooling in an ice-water bath. The resulting mixture was then heated at 80 °C for 4 h. After cooling to rt, HCl (1 N, 180 mL) was added to the reaction mixture and then extracted with EtOAc three times. The combined organic layers were washed with brine and dried over Na₂SO₄. A solid obtained after evaporation was washed with ether and dried under high vacuum to afford the titled compound as an off-white solid (4.42 g), which was used without further purification.

Step 2: Preparation of 3-hydroxy-1H-pyrazole-4-carboxylic acid

A solution of ethyl 3-hydroxy-1H-pyrazole-4-carboxylate (625 mg, 4.00 mmol) in 10% NaOH (aq) (20 mL) and EtOH (10 mL) was heated under reflux for 20 h. EtOH was removed under reduced pressure. The residue was diluted with 10 mL of H₂O and acidified with 4 N HCl. The precipitates were filtered to afford the titled compound as a white solid (460 mg), which was used without further purification.

Step 3: Preparation of ((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-hydroxy-1H-pyrazol-4-yl)methanone
A mixture of 5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine HCl salt (58.4 mg, 0.100 mmol, preparation described previously), 3-hydroxy-1H-pyrazole-4-carboxylic acid (16.7 mg, 0.130 mmol), and DIEA (5 eq) was stirred in NMP (2 mL) until completely dissolved. Then HATU (49.4 mg, 0.130 mmol) was added. The resulting mixture was stirred at 50 °C for 4 h. The reaction mixture was concentrated to half volume, diluted with DMSO and purified by a reverse phase HPLC to afford the titled compound as a pale yellow solid (8.4 mg).

Example 3-12

Preparation of 2-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine

Step A - Synthesis of 5-bromo-2-phenylpyrimidine

A mixture of 5-bromo-2-iodopyrimidine (285 mg, 1.0 mmol), potassium phosphate (637 mg, 3.0 mmol), phenylboronic acid (134 mg, 1.1 mmol) and
dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (73 mg, 0.1 mmol) in dioxane (5 mL) was heated to 120 °C for 20 minutes in a microwave. LC/MS analysis of the reaction indicated that the reaction was complete. DCM (10 mL) was added, and the precipitates removed by passing through a plug of celite. The filtrate was concentrated, and the crude residue purified by flash column chromatography, gradient elution (0 to 100 %) hexane / ethyl acetate, to afford compound Int-1a as a white solid (201 mg, 86 % yield). HPLC-MS tR = 1.39 min (UV254 nm); mass calculated for formula C10H7BrN4 233.98, observed LCMS m/z 235.0 (M+H).

Step B - Synthesis of 2-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine

A mixture of 5-bromo-2-phenylpyridine (1.17 g, 5.0 mmol), bis(pinacolato)diboron (2.54 g, 10.0 mmol), potassium acetate (1.47 g, 15.0 mmol), dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (408 mg, 0.5 mmol) in dioxane (20 mL) was flushed with argon and stirred at 80 °C for 16 h. On cooling, the solvent was evaporated in vacuo, the crude residue redissolved in EtOAc (50 mL), washed with water (1 x 50 mL), brine (1 x 50 mL), and dried over MgSO4. The solvent was concentrated to yield crude residue (Int-1b) which was taken forward as is in the next step. HPLC-MS tR = 0.72 min (UV254 nm); mass calculated for formula C16H19BN202 282.15, observed LCMS m/z 201.0 (M+H).
Example 3-13

Preparation of 2-(5-(4, 4, 5, 5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-yl)propan-2-ol

Step A - Synthesis of 1-(5-bromopyrimidin-2-yl)ethanone

To a stirred solution of 5-bromo-2-cyanopyrimidine (600 mg, 3.26 mmol) in THF (40 mL) at -78 °C was added methylmagnesium bromide (1.4M solution, 7 mL, 9.78 mmol). The reaction mixture was stirred for an additional 20 minutes until LC/MS analysis indicated that the reaction was complete. Quenching with saturated NH₄Cl, extraction with EtOAc and drying over MgSO₄, afforded the crude residue which was purified by flash column chromatography, gradient elution (0 to 50 %) hexane / ethyl acetate, to afford compound Int-2a as a white solid (170 mg, 26 % yield). HPLC-MS tR = 0.54 min (UV254 nm); mass calculated for formula C₆H₅BrN₂O₁₉₉.96, observed LCMS m/z 201.0 (M+H).

Step B - Synthesis of 2-(5-bromopyrimidin-2-yl)propan-2-ol
To a stirred solution of 1-(5-bromopyrimidin-2-yl)ethanone (100 mg, 0.5 mmol) in THF (10 mL) at -78 °C was added methylmagnesium bromide (1.4M solution, 3.6 mL, 5 mmol). The reaction mixture was stirred for an additional 20 minutes until LC/MS analysis indicated that the reaction was complete. Quenching with saturated NH₄Cl, extraction with EtOAc and drying over MgSO₄, afforded the crude residue which was taken forward as is in the next step.

**Step C - Synthesis of 2-(5-(4AA5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-yl)propan-2-ol**

A mixture of 2-(5-bromopyrimidin-2-yl)propan-2-ol (0.5 mmol), bis(pinacolato)diboron (254 mg, 1.0 mmol), potassium acetate (150 mg, 1.5 mmol), dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (41 mg, 0.05 mmol) in dioxane (3 mL) was flushed with argon and stirred at 80 °C for 16 h. On cooling, the solvent was evaporated in vacuo, the crude residue redissolved in EtOAc (10 mL), washed with water (1 x 10 mL), brine (1 x 10 mL), and dried over MgSO₄. The solvent was concentrated to yield crude residue which was taken forward as is in the next step. HPLC-MS tR = 0.33 min (UV254 nm); mass calculated for formula C₁₃H₂₁BN₂O₂ 2642.135, observed LCMS m/z 183.0 (M+H).

Example 3-14
Preparation of 5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-(cyclopropylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine

Step A - Preparation of 5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-iodo-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine

To (1R,3s,5S)-tert-butyl 3-(7-bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-iodo-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (2.6 g, 2.95 mmol) was added TFA / water (15:1, 16 mL) at r.t. It was stirred further at room temperature for 30 min at which time LC/MS analysis confirmed full consumption of the starting material. The solvent was removed in vacuo, the resulting residue re-dissolved in MeCN/water (2 mL) and lyophilized overnight to afford the desired product as a TFA salt. HPLC-MS tR = 0.82 min (UV254 nm); mass calculated for formula C24H23IN6 522.10, observed LCMS m/z 523.0 (M+H).

Step B - Synthesis of 5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-(cyclopropylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine
A mixture of compound 5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-iodo-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine (200 mg, 0.38 mmol), bis[copper(I)trifluoromethanesulfonate]benzene complex (96 mg, 0.38 mmol) and sodium cyclopropanesulfinate (197 mg, 1.15 mmol) in DMF (3 mL) was heated at 90 °C for 1 h, at which time LC/MS analysis confirmed full consumption of starting material. After cooling, the volatiles were removed in vacuo. The residue was redissolved in DCM/iPrOH (9:1, 20 mL), washed with a mixture of NH₄Cl(aq)/NH₄OH (7:3, 20 mL) and dried with Na₂SO₄. The organics were removed in vacuo, the resulting residue re-dissolved in MeCN/water (2 mL) and lyophilized overnight to afford the desired product. HPLC-MS tR = 0.68 min (UV254 nm); mass calculated for formula C₂₅H₂₆N₆O₂S 474.20, observed LCMS m/z 475.1 (M+H).

Example 3-15

Preparation of (1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-N-methoxy-8-azabicyclo[3.2.1]octane-8-carboxamide

Step 1: Preparation of 4-nitrophenyl methoxycarbamate
Methoxylamine hydrochloride (1.00 g, 12.0 mmol) was suspended in a mixture of dry pyridine (0.97 mL, 12.0 mmol) and dichloromethane (24 mL), and a solution of 4-nitrophenyl chlorocarbonate (2.41 g, 12.0 mmol) in dichloromethane (12 mL) was added over 30 min with stirring. The resulting heavy white suspension was warmed to reflux, refluxed for 6 h, and cooled to room temperature. The suspension was diluted with dichloromethane and washed with 1M HCl, keeping the emulsion with the aqueous layer, and the aqueous layer was re-extracted with dichloromethane. The combined organic phase was washed with water, saturated aqueous sodium bicarbonate and brine, keeping any emulsions with the aqueous layer, and then dried over magnesium sulfate and concentrated under reduced pressure. The crude product was purified by chromatography (90 g silica gel, 20-40% EtOAc/hexanes) to give the title compound (0.92 g) as a white crystalline solid.

A second set of less pure product fractions was isolated to give additional product (0.21 g) as a white solid.

**Step 2: Preparation of (1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-N-methoxy-8-azabicyclo[3.2.1]octane-8-carboxamide**

5-[(3-exo)-8-azabicyclo[3.2.1]oct-3-yl]-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine (56.5 mg, 0.119 mmol) was dissolved in a solution of N,N-Diisopropylethylamine (108 mg, 0.833 mmol) and dry DMF (1.5 mL). To the reaction was added a solution of 4-nitrophenyl methoxycarbamate (30.3 mg, 0.143 mmol) and dry DMF (1.5 mL). The yellow reaction appeared to become a little darker yellow. After stirring for 40 min at room temperature additional 4-nitrophenyl
methoxycarbamate (approx. 5 mg, 0.023 mmol) was added to the reaction. After another 20 min of stirring the reaction was complete. The homogeneous reaction was filtered through a syringe filter and purified by preparative chromatography. Like fractions of pure product were combined and lyophilized to give 59.3 mg of free base as a flocculent yellow powder. The free base was dissolved in a minimum amount of methanol, and 1M HCl (1 mL) was added, and the resultant solution was concentrated in vacuo. The wet residue was suspended in methanol, again treated with 1M HCl (1 mL), and concentrated in vacuo. The residue was suspended in methanol and concentrated in vacuo, and dried under vacuum. The title compound (49 mg, 66%) was obtained as a tan solid as its dihydrochloride salt.

Example 3-16

Preparation of (1R,3S,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-(2,6-difluorophenyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

Step 1: Preparation of 5-bromo-2-(2,6-difluorophenyl)pyridine

n-Butyllithium in hexane(2.50 M, 9.02 mL, 22.5 mmol) was added dropwise to a solution of 1,3-difluorobenzene (2.03 mL, 20.6 mmol) in anhydrous tetrahydrofuran (30 mL) at -78 °C and the resulting solution was stirred at the same temperature for 30 min, then warmed to -50 °C and zinc dichloride in tetrahydrofuran(0.50 M, 45.1 mL, 22.5 mmol) was added slowly. After 20 min, 5-bromo-2-iodopyridine (7.0 g, 25 mmol) in tetrahydrofuran (20 mL) and
tetrakis(triphenylphosphine)palladium(0) (1.19 g, 1.03 mmol) were added sequentially. The vessel was partially evacuated and back filled with nitrogen three times, sparged with a gentle stream of nitrogen for 5 minutes, and warmed to ambient temperature. The bright yellow, transuscent reaction solution was stirred for 15 minutes at ambient temperature, then heated at 40 °C for 16 hr. The reaction mixture as then cooled to ambient temperature, concentrated, and purified by flash chromatography (90 g silica gel, 0 to 10% ethyl acetate in hexanes) to afford the title compound (14 g) as a tan solid.

**Step 2: Preparation of 2-(2,6-difluorophenyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine**

![Reaction Scheme](image)

5-bromo-2-(2,6-difluorophenyl)pyridine (0.89 g, 3.3), potassium acetate (0.970 g, 9.89 mmol), bis(pinacolato)diboron (1.26 g, 4.94 mmol), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (1:1) (0.269 g, 0.330 mmol) were placed in a 3-neck 50 mL round bottom flask equipped with a reflux condensor and rubber septum. The vessel was evacuated and filled with nitrogen (x3) and 1,4-dioxane (1.3 mL) was added. The mixture was sparged with nitrogen for 5-10 minutes and then maintained under nitrogen with a balloon at 95 °C for 3 h. The reaction was then cooled to ambient temperature then filtered through a short plug of magnesol (about 50 mL), and the filtrate was concentrated. The residue was taken up in 250 mL of 1:1 ethenhexanes and filtered through a short plug of magnesol (about 50 mL), and the clear filtrate was concentrated to dryness to afford 1.1 g of product that was -56% (by weight) the desired product. This material was used without further purification.
Step 3 : Preparation of tert-butyl 3-{7-(bis[2-(trimethylsilyl)ethoxy]methyl)amino}-3-[6-(2,6-difluorophenyl)pyridin-3-yl]pyrazolo[1,5-a]pyrimidin-5-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate

tert-Butyl 3-[7-(bis[2-(trimethylsilyl)ethoxy]methyl)amino]-3-iodopyrazolo[1,5-a]pyrimidin-5-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate (1.26 g, 1.73 mmol), 2-(2,6-difluorophenyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (0.88 g, 2.1 mmol), [1,1’-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (1:1) (141 mg, 0.173 mmol), and potassium carbonate (0.716 g, 5.18 mmol) were placed in a 100-mL round bottom flask equipped with a reflux condenser and rubber septa. Then, the reaction vessel was evacuated and back filled with nitrogen 3 times before adding 1,4-dioxane (3.50 mL) and water (0.933 mL). Then, the reaction was sparged with nitrogen for 8 minutes, then maintained under nitrogen with a balloon and heated at 95 °C for 6 hr. The reaction mixture was then cooled to ambient temperature, diluted with dichloromethane (100 mL), filtered through a plug of Magnesol (ca. 60 mL), and the filtrate was concentrated. The crude product was purified by flash chromatography, (0 to 10% ethyl acetate/dichloromethane) to afford the title compound (690 mg, 50%) as an ivory foam.

Example 3-17
Preparation of (1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-(5-methylthiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(2H-1,2,3-triazol-4-yl)methanone

Step 1: Preparation of 2-(5-bromopyridin-2-yl)-5-methylthiazole

A solution of 5-methyl-2-(tributylstannyl)thiazole (2.87 g, 6.65 mmol), 5-bromo-2-iodopyridine (1.97 g, 6.73 mmol), and Pd(PPh₃)₄ (0.38 g, 0.33 mmol) in toluene (35 mL) was degassed and heated to 100 °C for 12 hours. Solvent was removed under vacuum and the residue was partitioned between diethyl ether and 0.5 M aqueous potassium fluoride. The ether layer was washed with brine, dried with Na₂SO₄, and the solvent was removed under vacuum. The resulting residue was purified by flash chromatography (1-10%, EtOAc/Hexanes) to afford the title compound as an orange solid (1.39 g).

Step 2: Preparation of 5-methyl-2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)thiazole

A mixture of 2-(5-bromopyridin-2-yl)-5-methylthiazole (2.00 g, 7.84 mmol), bis(pinacolato)diboron (2.08 g, 8.18 mmol), PdCl₂(dppf)-DCM (320 mg, 0.390 mmol), and KOAc (2.30 g, 24.0 mmol) in dioxane (20 mL) and DMSO (2.0 mL) was degassed and then heated at 90 °C for 16 hours. It was then partitioned between
ethyl acetate and water and the organic layer was washed twice with water, and then 0.5 M aqueous NaOH. The combined aqueous layers were neutralized with 2 M aqueous HCl, and extracted twice with ethyl acetate. The resulting organic layers were washed with brine and the solvent was removed under vacuum to afford the title compound (1.72 g) as a yellow solid which was used without further purification.

Step 3: Preparation of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-(5-methylthiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

A mixture of 5-methyl-2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-2-yl)thiazole (338 mg, 1.12 mmol), (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-iodopyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (627 mg, 0.859 mmol), PdCl₂(dppf)·DCM (70.2 mg, 0.086 mmol), and K₂CO₃ (356 mg, 2.58 mmol) in dioxane (6.3 mL) and water (1.6 mL) was degassed and then heated at 90°C for 5 hours. It was then partitioned between EtOAc and water and the organic layer was washed with brine, dried with Na₂SO₄, and the solvent was removed under vacuum. The resulting residue was purified by flash chromatography (10-25%, EtOAc/Hexanes) to afford the title compound as a yellow solid (579 mg).

Step 4: Preparation of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(6-(5-methylthiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate
NBS (108 mg, 0.606 mmol) was added to a solution of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-(5-methylthiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (472 mg, 0.606 mmol) in HOAc (5.0 mL). After 20 minutes it was quenched with 20% aqueous Na2S2O3 and saturated aqueous sodium bicarbonate was added. The mixture was partitioned between EtOAc and water and the organic layer was washed with saturated aqueous bicarbonate and brine, dried with Na2SO4, and the solvent was removed under vacuum. The resulting residue was purified by flash chromatography (25%, EtOAc/Hexanes) to afford the title compound as a yellow solid (548 mg).

**Step 5: Preparation of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-(5-methylthiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate**

Degassed DMF (8 mL) was used to dissolve (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(6-(5-methylthiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (425 mg,
0.496 mmol), and Al₂O₃ (505.6 mg) and sodium methyl mercaptide (115.8 mg, 1.49 mmol) were added. The mixture was heated at 80°C for 16 hours and then cooled to room temperature. EtOAc (42 mL) was added and after stirring, the mixture was filtered and the solid was washed with EtOAc. The filtrate was washed with water and brine, dried with Na₂SO₄, and the solvent was removed under vacuum. The resulting residue was purified by flash chromatography (20-25%, EtOAc/Hexanes) to afford the title compound as a yellow solid (130 mg).

**Step 6: Preparation of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-\(\text{trimethylsilyl})\text{ethoxy})\text{methyl})\text{amino})-6-(\text{methylsulfonyl})-3-(6-(5-\text{methylthiazol-2-yl})\text{pyridin-3-yl})\text{pyrazolo}[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate**

A mixture of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-\(\text{trimethylsilyl})\text{ethoxy})\text{methyl})\text{amino})-6-(\text{methylthio})\text{pyrazolo}[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (82.4 mg, 0.100 mmol), NaHCO₃ (84.0 mg, 1.00 mmol), Ozone® (307.4 mg, 0.500 mmol), methanol (3.0 mL), and water (0.80 mL) was rapidly stirred while heated at 65°C for 15 hours and then cooled to room temperature. DCIW MeOH (1:1, 30 mL) was added and the mixture was filtered and solvent was removed from the filtrate under vacuum to afford the title compound as an orange solid (97.2 mg) that was used as is in the next reaction.

**Step 7: Preparation of 5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-(\text{methylsulfonyl})-3-(6-(5-\text{methylthiazol-2-yl})\text{pyridin-3-yl})\text{pyrazolo}[1,5-a]pyrimidin-7-amine hydrochloride**
A mixture of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(methylsulfonyl)-3-(6-(5-methylthiazol-2-yl)pyridin-3-yl)pyrazolo[3,2,1]octane-8-carboxylate from the previous step was partially dissolved in methanol (2.0 mL), 4M HCl in 1,4-dioxane (2.0 mL) was added, and the solution was stirred for 2 hours. Solvent was removed under vacuum to afford the title compound as an orange solid (95.0 mg) that was used as is in the next reaction.

Step 8: Preparation of 5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)-3-(6-(5-methylthiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-]pyrimidin-7-amine

5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)-3-(6-(5-methylthiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-]pyrimidin-7-amine hydrochloride from the previous step was dissolved in DMF (2.0 mL), 2H-1,2,3-Triazole-4-carboxylic acid (15.0 mg, 0.132 mmol), EDC (48.8 mg, 0.254 mmol), HOBt (35.1 mg, 0.229 mmol), and DIPEA (88.7 uL, 0.509 mmol) were added and stirred for 22 hours. The solution
was purified by preparative reversed-phase liquid chromatography and converted to the dihydrochloride salt to afford the desired compound as a yellow solid (9.3 mg).

**Example 3-18**

Preparation of 5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-(5,6-dihydro-4H-cyclopenta[d]thiazol-2-yl)pyridin-3-yl)-6-(methylsulfonyl) pyrazolo[1,5-a]pyrimidin-7-amine

**Step 1:** Preparation of 5,6-dihydro-4H-cyclopenta[d]thiazol-2-amine

\[
\begin{align*}
\text{O} & \quad \text{H}_2\text{N} \quad \text{NH}_2 \\
\text{Cl} & \quad \rightarrow \\
\text{dioxane} & \quad \rightarrow \\
\text{NaHCO}_3 & \quad \rightarrow \\
\text{H}_2\text{N} & \quad \rightarrow \\
\text{N} & \quad \text{H}_2\text{N}
\end{align*}
\]

2-Chlorocyclopentanone (9.01 g, 74.4 mmol) was added slowly to a 95°C stirred mixture of thiourea (5.77 g, 75.0 mmol) in 1,4-dioxane (150 mL). After full addition, the temperature was maintained for an hour then the mixture was cooled to room temperature. It was then filtered and washed with 1,4-dioxane and diethyl ether, and dried under air suction to afford 11.15 g white solid. This was partitioned between diethyl ether and saturated aqueous sodium carbonate. The ether layer was washed with brine, dried with Na$_2$SO$_4$, and solvent removed by rotoevaporation to afford 9.8 g beige solid. (Modified procedure from US Patent application 64699, 2008, Florjancic, A.S.; et al).

**Step 2:** Preparation of 2-bromo-5,6-dihydro-4H-cyclopenta[d]thiazole
Copper (II) bromide (13.5 g, 60.0 mmol) was added to a mixture of 5,6-dihydro-4/7-cyclopental[d]thiazol-2-amine (7.01 g, 50.0 mmol) and fert-butyl nitrite (9.91 mL, 75.0 mmol) in anhydrous acetonitrile (50 mL) creating an exotherm. After an hour, it was poured into a solution of saturated aqueous NH₄Cl (140 mL) and concentrated NH₃OH (60 mL) diluted with water (to 800 mL) and stirred for 30 minutes. It was extracted with 20% dichloromethane in diethyl ether and the ether layer was washed with water, 20% aqueous Na₂S₂O₇, and brine. It was dried with Na₂S₂O₇ and solvent removed by rotoevaporation. The brown residue was purified by flash chromatography (25-50%, DCM/Hexanes) to afford the title compound as a white solid (3.53 g). (Modified procedure from Caleta, I.; et. al. J. Med. Chem. 2009, 52, 1744.).

Step 2: Preparation of 2-(tributylstannyl)-5,6-dihydro-4H-cyclopental[d]thiazole

n-Butyllithium (2.5M, 8.2 mL, 21 mmol) was added dropwise to a slurry of 2-bromo-5,6-dihydro-4/7-cyclopental[d]thiazole (3.5 g, 17 mmol) in diethyl ether (34 mL) at -75°C. After stirring an hour, tributylchlorostannane (5.3 mL, 19 mmol) was added in bolus and the cold bath was removed. After 2 hours, it was quenched with saturated aqueous sodium bicarbonate and extracted with more diethyl ether. The ether layer was washed with brine and dried with Na₂S₂O₇, and solvent was removed by rotoevaporation to afford red oil (8.3 g) that was used as is.

Step 3: Preparation of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-(5,6-dihydro-4H-cyclopental[d]thiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate
A mixture of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-chloropyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (1.97 g, 2.75 mmol), copper(I) iodide (0.11 g, 0.55 mmol), PdCl₂(dppf)DCM (0.45 g, 0.55 mmol), and DMF (30 mL) was degassed and heated at 95°C with rapid stirring for 30 minutes. It was cooled to room temperature and poured into a rapidly stirring mixture of concentrated NH₄OH and saturated aqueous NH₄Cl (3:7, 200 mL) and diethyl ether with enough DCM to dissolve the suspended solids. After 10 minutes the layers were partitioned, the organic layer was washed with water and brine, dried with Na₂SO₄, and solvent was removed by rotoevaporation. The brown residue was purified by flash chromatography (10-20%, DCM/Hexanes) to afford the title compound as a beige solid (2.09 g). (Modified procedure from Nyffenegger, C.; et al. Tetrahedron 2008, 64, 9567.).

Step 4: Preparation of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-(5H-dihydro-4H-cyclopenta[d]azol-2-yl)pyridin-3-yl)-6-iodopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate
DCM (5 mL) was added to a mixture of \((1R,3s,5S)\)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-(5,6-dihydro-4H-cyclopenta[d]thiazol-2-yl)pyridin-3-yl)pyrazolo[3,2,1]octane-8-carboxylate (0.42 g, 0.53 mmol) in HOAc (4 mL) to make a solution and W-iodosuccinimide (0.13 g, 0.55 mmol) was added at room temperature. After 45 minutes 20% aqueous Na2S2C3 was added and the mixture was basified with NaHCO3. The mixture was then partitioned between water and EtOAc. The organic layer was washed with water and brine, dried with Na2SO4, and solvent was removed by rotoevaporation to afford the title compound as a yellow solid (0.57 g) that was used as is in the next reaction.

**Step 5: Preparation of 5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-(5,6-dihydro-4H-cyclopenta[d]thiazol-2-yl)pyridin-3-yl)-6-iodopyrazolo[1,5-a]pyrimid-7-amine tris(2,2,2-trifluoroacetate)**

Water (4 mL) and TFA (8 mL) were premixed then added to \((1R,3s,5S)\)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-(5,6-dihydro-4H-cyclopenta[d]thiazol-2-yl)pyridin-3-yl)pyrazolo[3,2,1]octane-8-carboxylate (0.49 g, 0.53 mmol) to form a solution. After 15 minutes, solvent was removed by rotoevaporation to afford the title compound as a red solid (0.54 g) that was used as is in the next reaction.

**Step 6: Preparation of 5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-(5,6-dihydro-4H-cyclopenta[d]thiazol-2-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimid-7-amine**

243
A mixture of sodium methanesulfonate (0.42 g, 3.49 mmol), copper (I)
trifluoromethanesulfonate benzene complex (0.65 g, 1.16 mmol), and DMSO (4 mL)
were degassed and then heated at 90°C for 5 minutes. A solution of 5-((1R,3S,5S)-
8-azabicyclo[3.2.1]octan-3-yl)-3-(6-(5,6-dihydro-4H-cyclopenta[d]thiazol-2-yl)pyridin-
3-yl)-6-iodopyrazolo[1,5-a]pyrimidin-7-amine tris(2,2,2-trifluoroacetate) (0.53 g, 0.58
mmol) in DMSO (7.2 mL) was added and after 30 minutes, solvent was removed
under vacuum. The residue was partitioned between 10% isopropyl alcohol/ DCM
and (7:3) saturated aqueous NH₄Cl/ concentrated aqueous NH₄OH. The organic
layer was washed with water and brine, dried with sodium sulfate, and solvent was
removed by rotoevaporation. The orange residue was purified by flash
chromatography [5-10%, (10% NH₄OH/ Methanol)/ DCM] to afford the title
compound as a yellow solid (0.12 g).

Example 3-19

Preparation of 4-(5-bromopyridin-2-yl)-2-methylthiazole

Step 1: Preparation of 2-bromo-1-(5-bromopyridin-2-yl) ethanone

This compound was prepared by the method of Reck, F.; Zhou, F.;

1-(5-bromopyridin-2-yl)ethanone (200 mg, 1.0 mmol) was dissolved in Acetic
acid (50 mL) and HBr in Acetic acid (48% solution, 280 uL) was added along with
water (100 uL). Warmed to 70C and added Bromine (51.5 uL, 1.0 mmol) and stirred
for 1 hour. The reaction was concentrated to give the desired product (280 mg)
containing a small amount of dibrominated product. This material was used as is.

*Step 2: Preparation of 5-bromo-2-(2-methyl-1,3-thiazol-4-yl)pyridine*

2-bromo-1-(5-bromopyridin-2-yl)ethanone (3.77 g, 13.5 mmol) was dissolved
in ethanol (32 mL) and ethanethioamide (1.12 g, 14.8 mmol) was added and the
reaction stirred for 18 h at 75 °C. The mixture was concentrated; the residual solid
was dispersed in ethyl acetate (100 mL), and treated with saturated sodium
bicarbonate solution (100 mL) until no further gas evolution was noted. The
combined organics were washed with water (50 mL) and brine (50 mL). The
aqueous washes were back-extracted with ethyl acetate (100 mL) and the combined
organic layers were dried over magnesium sulfate, treated with Darco, filtered
through a paper filter, and concentrated to give a yellow solid. The crude product
was purified by flash chromatography (90 g silica gel, 1-5% methanol in ethyl
acetate). The major product was further purified by flash chromatography (40 g silica
gel, 10% ethyl acetate in hexane) to give the title compound (1.94 g) as a colorless
crystalline solid.

Following the Scheme 3-1 and Scheme 3-2 and the examples listed above,
the following compounds (Table 3-1) can be prepared:
<table>
<thead>
<tr>
<th>Compound ID</th>
<th>Structures</th>
<th>Compound Name</th>
<th>N/H (calculated)</th>
<th>N/H (observed)</th>
<th>pAKT</th>
<th>pE-BPI</th>
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<tr>
<td>3.1</td>
<td><img src="image" alt="Structure 3.1" /></td>
<td>1-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone</td>
<td>533.1/532.9</td>
<td></td>
<td>A</td>
<td>B</td>
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<td>3.2</td>
<td><img src="image" alt="Structure 3.2" /></td>
<td>1-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-1,2,4-triazol-3-yl)methanone</td>
<td>570.1/569.8</td>
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<td>A</td>
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<td>570.1/570.1</td>
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<td>B</td>
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<td>3.4</td>
<td>((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-alpyrimidin-5-yl]-8-azabicyclo[3.2.1]octan-8-yl)(3-methyl-1H-1,2,4-triazol-5-yl)methanone</td>
<td>584.2/584.0</td>
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<td>A</td>
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<td>3.5</td>
<td>((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-alpyrimidin-5-yl]-8-azabicyclo[3.2.1]octan-8-yl)(1H-tetrazol-5-yl)methanone</td>
<td>571.1/570.9</td>
<td>C</td>
<td>D</td>
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<td>3.6</td>
<td>5-(5-((1R,3s,5S)-8-(1H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-6-(methylsulfonyl)pyrazolo[1,5-alpyrimidin-3-yl]-2-phenylypyridine 1-oxide</td>
<td>586.1/586.2</td>
<td>B</td>
<td>B</td>
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<td>3.7</td>
<td>(R)-1-((1R,3S,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-alpyrimidin-5-yl]-8-azabicyclo[3.2.1]octan-8-yl)-2,3-dihydroxypropan-1-one</td>
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<td>C</td>
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(1R,3s,5S)-3-(7-amino-6-((methylsulfonyl)-3-(6-phenylpyridin-3-y)pyrazolo[1,5-a]pyrimidin-5-yl)-N-ethyl-8-azabicyclo[3.2.1]octan-8-carboxamide

546.2/546.0

A A

(1R,3s,5S)-3-(7-amino-6-((methylsulfonyl)-3-(6-phenylpyridin-3-y)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-carboxamide

518.1/517.9

C

(1R,3s,5S)-3-(7-amino-6-((methylsulfonyl)-3-(6-phenylpyridin-3-y)pyrazolo[1,5-a]pyrimidin-5-yl)-N-cyclopropyl-8-azabicyclo[3.2.1]octan-8-carboxamide

558.2/557.9

B C

(1R,3s,5S)-3-(7-amino-6-((methylsulfonyl)-3-(6-phenylpyridin-3-y)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-y(1-hydroxycyclopropyl)methanone

559.2/558.9

B C

(1R,3s,5S)-3-(7-amino-6-((methylsulfonyl)-3-(6-phenylpyridin-3-y)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-y(3-hydroxyphenyl)methanone

596.2/596.0

B B

(1R,3s,5S)-3-(7-amino-6-((methylsulfonyl)-3-(6-phenylpyridin-3-y)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-y(4-hydroxyphenyl)methanone

596.2/595.9

B C
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<th>Significance</th>
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<td>C ((\text{1R,3s,SS}))-3-(\text{7}-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl))-8-azabicyclo[3.2.1]octan-8-yl-3,3,3-trifluoro-2-hydroxypropan-1-one</td>
<td>601.1/601.2</td>
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<td>3.16</td>
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<td>C ((\text{1R,3s,SS}))-3-(\text{7}-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl))-8-azabicyclo[3.2.1]octan-8-yl(\text{5-hydroxy})pyridin-2-yl)methanone</td>
<td>596.2/595.9</td>
<td>A B</td>
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<tr>
<td>3.17</td>
<td><img src="image3.png" alt="Chemical Structure" /></td>
<td>C ((\text{5-(1R,3s,SS)}))-8-(1H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-3-yl)-N-methylpicolinamide</td>
<td>551.1/550.9</td>
<td>D C</td>
</tr>
<tr>
<td>3.18</td>
<td><img src="image4.png" alt="Chemical Structure" /></td>
<td>C ((\text{5-(1R,3s,SS)}))-8-(1H-tetrazol-5-yl)-8-azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine</td>
<td>543.1/542.9</td>
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<tr>
<td>3.19</td>
<td><img src="image5.png" alt="Chemical Structure" /></td>
<td>C ((\text{1R,3s,SS}))-3-(\text{7}-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl))-8-azabicyclo[3.2.1]octan-8-carboxaldehyde</td>
<td>503.1/502.8</td>
<td>B B</td>
</tr>
<tr>
<td>3.20</td>
<td><img src="image6.png" alt="Chemical Structure" /></td>
<td>C ((\text{5-(1R,3s,SS)}))-8-(5-methyl-1H-1,2,4-triazol-3-yl)-8-azabicyclo[3.2.1]octan-3-yl)-8-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine</td>
<td>556.2/555.9</td>
<td>ND ND</td>
</tr>
<tr>
<td>3.26</td>
<td>5-(((1R,3S,5S)-3-(4H-1,2,4-triazol-3-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-(methyl)sulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine</td>
<td>606.2/606.1</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>3.27</td>
<td>(S)-1-((1R,3S,5S)-3-(7-amino-6-(methyl)sulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-3-yl)-2-hydroxypropan-1-one</td>
<td>547.2/547.0</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>3.28</td>
<td>(R)-1-((1R,3S,5S)-3-(7-amino-6-(methyl)sulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-3-yl)-2-hydroxypropan-1-one</td>
<td>547.2/547.0</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>3.29</td>
<td>(((1R,3S,5S)-3-(7-amino-6-(methyl)sulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-3-yl)-8-hydroxy-4H-1,2,4-triazol-3-yl)methanone</td>
<td>586.2/586.0</td>
<td>B</td>
<td>B</td>
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<td>3.30</td>
<td>(1R,3S,5S)-3-(7-amino-6-(methyl)sulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-N-methyl-8-azabicyclo[3.2.1]octan-3-yl)carbamate</td>
<td>532.2/532.0</td>
<td>B</td>
<td>B</td>
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<td>3.31</td>
<td>(((1R,3S,5S)-3-(7-amino-6-(methyl)sulfonyl)-3-(4-(pyridin-2-yl)phenyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-3-yl)-8-hydroxy-4H-1,2,4-triazol-3-yl)methanone</td>
<td>570.2/570.0</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Structure</td>
<td>Chemical Formula</td>
<td>CAS Number</td>
<td>Color</td>
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<tr>
<td>3.32</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>(((1R,3a,5S)-3-(7-amino-3-(6-(2-fluoro-4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfanyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone</td>
<td>618.2/618.0</td>
<td>A</td>
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<tr>
<td>3.33</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>(((1R,3a,5S)-3-(7-amino-3-(6-(4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfanyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone</td>
<td>600.2/600.0</td>
<td>A</td>
</tr>
<tr>
<td>3.34</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>(((1R,3a,5S)-3-(7-amino-3-(6-(4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfanyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methyl-4H-1,2,4-triazol-3-yl)methanone</td>
<td>614.2/614.0</td>
<td>A</td>
</tr>
<tr>
<td>3.35</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>(((1R,3a,5S)-3-(7-amino-3-(6-(5-methoxythiophen-2-yl)pyridin-3-yl)-6-(methylsulfanyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone</td>
<td>606.2/605.9</td>
<td>A</td>
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<tr>
<td>3.36</td>
<td><img src="image5.png" alt="Structure" /></td>
<td>1-(1R,3a,5S)-3-(7-amino-3-(6-(4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfanyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone</td>
<td>563.2/563.0</td>
<td>A</td>
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<tr>
<td>Number</td>
<td>Structure</td>
<td>Chemical Formula</td>
<td>Molecular Weight</td>
<td>Solubility</td>
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<tr>
<td>3.37</td>
<td><img src="image1" alt="" /></td>
<td>((1R,3s,5S)-3-(7-amino-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)-5-((methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone</td>
<td>618.2/618.0</td>
<td>A</td>
</tr>
<tr>
<td>3.38</td>
<td><img src="image2" alt="" /></td>
<td>1-((1R,3s,5S)-3-(7-amino-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)-5-((methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone</td>
<td>581.2/580.7</td>
<td>A</td>
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<tr>
<td>3.39</td>
<td><img src="image3" alt="" /></td>
<td>((1R,3s,5S)-3-(7-amino-3-(6-(3,4-dimethoxyphenyl)pyridin-3-yl)-5-((methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone</td>
<td>630.2/630.0</td>
<td>B</td>
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<tr>
<td>3.40</td>
<td><img src="image4" alt="" /></td>
<td>((1R,3s,5S)-3-(7-amino-3-(6-(1H-pyrazol-3-yl)pyridin-3-yl)-5-((methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone</td>
<td>574.2/574.2</td>
<td>A</td>
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<tr>
<td>3.47</td>
<td>Azabicyclo[3.2.1]octan-8-yl(4H-1,2,4-triazol-3-yl)methanone</td>
<td>((1R,3S,5S)-3-(7-amino-3-(6-(2,3-difluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl(4H-1,2,4-triazol-3-yl)methanone)</td>
<td>606.2/605.9</td>
<td>A</td>
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<tr>
<td>3.48</td>
<td></td>
<td>((1R,3S,5S)-3-(7-amino-3-(3′-fluoro-2,2′-bipyridin-5-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl(4H-1,2,4-triazol-3-yl)methanone)</td>
<td>589.2/588.9</td>
<td>A</td>
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<td>3.49</td>
<td></td>
<td>((1R,3S,5S)-3-(7-amino-3-(6-(3,5-difluoro-4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl(4H-1,2,4-triazol-3-yl)methanone)</td>
<td>636.2/635.9</td>
<td>B</td>
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<td>3.50</td>
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<td>((1R,3S,5S)-3-(7-amino-3-(6-(4-methoxy-3-methylphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl(4H-1,2,4-triazol-3-yl)methanone)</td>
<td>614.2/613.9</td>
<td>A</td>
</tr>
<tr>
<td>3.51</td>
<td></td>
<td>((1R,3S,5S)-3-(7-amino-3-(6-(3-chloro-4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl(4H-1,2,4-triazol-3-yl)methanone)</td>
<td>634.2/633.9</td>
<td>A</td>
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<tr>
<td>3.52</td>
<td>(((1 \text{R},3\text{s},5\text{S})-3-(7\text{-amino}-3-(6-(benzo}[d][1,3\text{]dioxol-5-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazol(1,5\text{-a})pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone</td>
<td>614.2/613.9</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>3.53</td>
<td>(((1 \text{R},3\text{s},5\text{S})-3-(7\text{-amino}-3-(6-(2,2\text{-difluorobenzo}[d][1,3\text{]dioxol-5-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazol(1,5\text{-a})pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone</td>
<td>650.2/650.1</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>3.54</td>
<td>(((1 \text{R},3\text{s},5\text{S})-3-(7\text{-amino}-3-(6-(2,3\text{-difluoro-4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazol(1,5\text{-a})pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone</td>
<td>636.2/635.9</td>
<td>A</td>
<td>A</td>
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<tr>
<td>3.55</td>
<td>(((1 \text{R},3\text{s},5\text{S})-3-(7\text{-amino}-3-(6-(4-(difluoromethoxy)phenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazol(1,5\text{-a})pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone</td>
<td>636.2/636.0</td>
<td>A</td>
<td>A</td>
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<tr>
<td>3.56</td>
<td>(((1 \text{R},3\text{s},5\text{S})-3-(7\text{-amino}-3-(6-(4-(2-methoxyethoxy)phenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazol(1,5\text{-a})pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone</td>
<td>644.2/644.5</td>
<td>B</td>
<td>B</td>
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</table>
| 3.57 | \(((1R,3s,5S)-3-(7-
    \text{amino-3}(8-(2-methyl-
    2H-indazol-5-y1)(pyridin-3-yl)-8-
    (methylsulfonyl)pyrazol
    olo[1,5-\text{a}]pyrimdin-5-y1)-8-
    azabicyclo[3.2.1]octan-
    8-y1)(4H-1,2,4-triazol-3-y1)methanone\) | 624.2/624.5 | A | A |
| 3.58 | \(((1R,3s,5S)-3-(7-
    \text{amino-3}(6-(2-
    methoxy)pyrimdin-5-
    y1)(pyridin-3-yl)-8-
    (methylsulfonyl)pyrazol
    olo[1,5-\text{a}]pyrimdin-5-
    y1)-8-
    azabicyclo[3.2.1]octan-
    8-y1)(4H-1,2,4-triazol-3-y1)methanone\) | 602.2/602.3 | C | C |
| 3.59 | \(((1R,3s,5S)-3-(7-
    \text{amino-3}(6-(2,5-
    difluoro-4-
    methoxypheynyl)pyridin-
    n-3-y1)-8-
    (methylsulfonyl)pyrazol
    olo[1,5-\text{a}]pyrimdin-5-
    y1)-8-
    azabicyclo[3.2.1]octan-
    8-y1)(4H-1,2,4-triazol-3-
    y1)methanone\) | 636.18/635.9 | 5 | A | A |
| 3.60 | \(((1R,3s,5S)-3-(7-
    \text{amino-3}(6-(4-
    ethoxyphenyl)pyridin-
    n-3-y1)-8-
    (methylsulfonyl)pyrazol
    olo[1,5-\text{a}]pyrimdin-5-
    y1)-8-
    azabicyclo[3.2.1]octan-
    8-y1)(4H-1,2,4-triazol-3-
    y1)methanone\) | 614.2/614.0 | A | A |
| 3.61 | \(((1R,3s,5S)-3-(7-
    \text{amino-3}(6-(4-
    cyclopropoxphenyyl)py-
    ridin-3-y1)-8-
    (methylsulfonyl)pyrazol
    olo[1,5-\text{a}]pyrimdin-5-
    y1)-8-
    azabicyclo[3.2.1]octan-
    8-y1)(4H-1,2,4-triazol-3-
    y1)methanone\) | 626.2/626.0 | B | B |
<p>| 3.62 | <img src="image" alt="Chemical Structure" /> | ((1R,3s,5S)-3-((7-amino-3-(6-(4-methoxy-3-phenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone | 603.2/603.0 | A | A |
| 3.63 | <img src="image" alt="Chemical Structure" /> | ((1R,3s,5S)-3-((7-amino-3-(6-(4-(fluoromethoxy)phenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone | 618.2/618.0 | A | A |
| 3.64 | <img src="image" alt="Chemical Structure" /> | ((1R,3s,5S)-3-((3-(2,4-bipyridin-5-yl)-7-amino-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone | 571.2/571.0 | C | C |
| 3.65 | <img src="image" alt="Chemical Structure" /> | 1-(1R,3s,5S)-3-((3-(2,4-bipyridin-5-yl)-7-amino-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone | 534.2/533.9 | C | C |
| 3.66 | <img src="image" alt="Chemical Structure" /> | ((1R,3s,5S)-3-((7-amino-3-(6-(butoxy)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone | 550.2/550.0 | ND | ND |
| 3.67 | <img src="image" alt="Chemical Structure" /> | 1-(1R,3s,5S)-3-((7-amino-3-(6-((4-methoxy-3-phenoxy)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone | 566.2/566.2 | A | B |</p>
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<td>((1R,3s,5S)-3-(7-amino-3-(6-methylpyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone</td>
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<td>3.74</td>
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| 3.98| \((3\text{-amino}\cdot 1\text{H}\cdot 1,2,4\text{-triazol-3-yl})\cdot (1\text{R,3s,5s}-3\text{-}(7\text{-amino-6-}
|methylsulfonfonyl)-3\text{-}(6\text{-phenylpyridin-3-yl})\cdot \text{pyrazolo}[1,5-
|     | \text{a}pyrimidin-5-yl)\cdot 8\text{-azabicyclo}[3.2.1]\text{pocan-6-y}l)methanone     | 585.2/585.1|    |    |
| 3.99| \(((1\text{R,3s,5s})\text{-3-(7}\text{-amino-6-}
|methylsulfonfonyl)-3\text{-}(6\text{-phenylpyridin-3-}
|     | yl)\cdot \text{pyrazolo}[1,5-
|     | \text{a}pyrimidin-5-yl)\cdot 8\text{-azabicyclo}[3.2.1]\text{pocan-6-y}l)(3-
|     | \text{trifluoromethyl})\cdot 1\text{H}-1,2,4\text{-triazol-3-yl)methanone}               | 638.2/638.0|    |    |
| 3.100| \(((1\text{R,3s,5s})\text{-3-(7}\text{-amino-3-}(6\text{-3-fluoro-4-}
|     | \text{methoxyphenyl)pyridin-3-yl})\cdot 6-
|     | \text{methylsulfonfonyl)\cdot \text{pyrazolo}[1,5-
|     | \text{a}pyrimidin-5-yl)\cdot 8\text{-azabicyclo}[3.2.1]\text{pocan-6-y}l(5\text{-amino-4-
|     | 1,2,4\text{-triazol-3-yl)methanone}                                                    | 633.2/633.1|    |    |
| 3.101| \(((1\text{R,3s,5s})\text{-3-(7}\text{-amino-6-}
|     | \text{methylsulfonfonyl})\cdot 3\text{-}(2-
|     | \text{phenylpyrimidin-5-yl)\cdot \text{pyrazolo}[1,5-
|     | \text{a}pyrimidin-5-yl)\cdot 8\text{-azabicyclo}[3.2.1]\text{pocan-6-y}l(2\text{H}-1,2,3-
|     | \text{triazol-4-yl)methanone}                                                          | 571.2/571.0| N/A| N/A|
| 3.102| \(((1\text{R,3s,5s})\text{-3-(2,2-
|     | \text{bipyridin-5-yl)\cdot 7-
|     | \text{amino-6-}
|     | \text{methylsulfonfonyl)\cdot \text{pyrazolo}[1,5-
|     | \text{a}pyrimidin-5-yl)\cdot 8-
<p>|     | \text{azabicyclo}[3.2.1]\text{pocan-6-y}l(4\text{H}-1,2,4\text{-triazol-3-yl)methanone}} | 571.2/571.2| A  | A  |
| 3.103 | 2-{5-[5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yi)-7-amino-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-3-yi)pyridin-2-yl]pyridine 1-oxide | 587.2/587.1 | ND | ND |
| 3.104 | ([1R,3s,5S]-3-{7-amino-3-[(2-fluorophenyl)pyridin-3-yl]-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yi)-8-azabicyclo[3.2.1]octan-3-yi)(4H-1,2,4-triazol-3-yl) methanone | 588.2/588.1 | A | A |
| 3.105 | ([1R,3s,5S]-3-{7-amino-3-[(2-fluorophenyl)pyridin-3-yl]-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yi)-8-azabicyclo[3.2.1]octan-3-yi)(4H-1,2,4-triazol-3-yl) methanone | 588.2/588.1 | A | A |
| 3.106 | ([1R,3s,5S]-3-{7-amino-3-[(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl]-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yi)-8-azabicyclo[3.2.1]octan-3-yi)(4H-1,2,4-triazol-3-yl) methanone | 574.2/574.2 | A | A |
| 3.107 | ([1R,3s,5S]-3-{7-amino-3-[(2,6-difluorophenyl)pyridin-3-yl]-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yi)-8-azabicyclo[3.2.1]octan-3-yi)(4H-1,2,4-triazol-3-yl) methanone | 606.2/606.1 | A | A |
| 3.108 | ([1R,3s,5S]-3-{7-amino-3-[(2,4-difluorophenyl)pyridin-3-yl]-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yi)-8-azabicyclo[3.2.1]octan-3-yi)(4H-1,2,4-triazol-3-yl) methanone | 606.2/606.1 | A | A |</p>
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591.2/591.1

B

ND
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<td>((1R,3s,5S)-3-(7-amino-3-(6-cyclohexylpyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-al]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)4H-1,2,4-triazol-3-yl)methanone</td>
<td>576.3/576.5</td>
<td>B</td>
</tr>
<tr>
<td>3.166</td>
<td><img src="image6" alt="Structure" /></td>
<td>((1R,3s,5S)-3-(7-amino-3-(6-cyclopentylpyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-al]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)4H-1,2,4-triazol-3-yl)methanone</td>
<td>562.2/562.4</td>
<td>B</td>
</tr>
<tr>
<td>ID</td>
<td>Formula</td>
<td>MW (g/mol)</td>
<td>Crystal form</td>
<td>Analysis</td>
</tr>
<tr>
<td>-----</td>
<td>-------------------------------------------------------------------------</td>
<td>------------</td>
<td>--------------</td>
<td>----------</td>
</tr>
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<td>3.167</td>
<td>((1R,3S,5S)-3-(7-amino-3-(6-cyclobutylpyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-y)-1H-1,2,4-triazole-5-yl)methanone</td>
<td>548.2/548.1</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>3.168</td>
<td>1-(((1R,3S,5S)-3-(7-amino-3-(6-cyclobutylpyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-yl)-2-hydroxyethanone</td>
<td>511.2/511.3</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>3.169</td>
<td>((1R,3S,5S)-3-(7-amino-3-(6-(3-fluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-yl)-2H-1,2,4-triazole-4-yl)methanone</td>
<td>618.2/618.7</td>
<td>A</td>
<td>B</td>
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<td>3.170</td>
<td>((1R,3S,5S)-3-(7-amino-3-(6-(3-fluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-yl)-2H-1,2,3-triazole-4-yl)methanone</td>
<td>588.20/588.2</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>3.171</td>
<td>((1R,3S,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-N-methoxy-8-azabicyclo[3.2.1]octane-8-carboxamide</td>
<td>548.2/548.5</td>
<td>B</td>
<td>B</td>
</tr>
</tbody>
</table>
(1R,3e,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-N-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxamide

((1R,3e,5S)-3-(7-amino-3-(6-(2,5-difluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-1,2,3-triazol-5-yl)methanone

((1R,3e,5S)-3-(7-amino-3-(6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(2H-1,2,3-triazol-4-yl)methanone

((1R,3e,5S)-3-(7-amino-6-(methylsulfonyl)-3-(2-phenylpyridin-5-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-8-azabicyclo[3.2.1]octan-8-yl)(2H-1,2,3-triazol-4-yl)methanone

((1R,3e,5S)-3-(7-amino-6-(methylsulfonyl)-3-(1-phenyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(2H-1,2,3-triazol-4-yl)methanone

((1R,3e,5S)-3-(7-amino-3-(6-fluoroquinolin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(2H-1,2,3-triazol-4-yl)methanone
<p>| 3.178 | ((1R,3s,5S)-3)-(7-amino-3-(1-(4-fluorophenyl)-1H-pyrazol-4-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)((1H-1,2,3-triazol-4-yl)methanone | 577.2/577.1 | C | C |
| 3.179 | ((1R,3s,5S)-3)-(7-amino-6-(methylsulfonyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)((1H-1,2,3-triazol-4-yl)methanone | 572.2/572.2 | ND | ND |
| 3.180 | ((1R,3s,5S)-3)-(7-amino-6-(methylsulfonyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)((4H-1,2,4-triazol-3-yl)methanone | 591.2/591.2 | A | A |
| 3.181 | ((1R,3s,5S)-3)-(7-amino-6-(methylsulfonyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)((1H-1,2,3-triazol-4-yl)methanone | 591.2/591.2 | B | A |
| 3.182 | ((1R,3s,5S)-3)-(7-amino-6-(methylsulfonyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)ethanone | 538.2/538.4 | B | B |
| 3.183 | ((1R,3a,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-(5-methylthiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-alpyrimidin-5-yl])-8-azabicyclo[3.2.1]octan-8-yl)(5-methyl-4H-1,2,4-triazol-3-yl)methanone | 526.2/526.3 | B | B |
| 3.184 | ((1R,3a,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-(5-methylthiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-alpyrimidin-5-yl])-8-azabicyclo[3.2.1]octan-8-yl)(5-methyl-4H-1,2,4-triazol-3-yl)methanone | 605.2/605.2 | A | A |
| 3.185 | 1-((1R,3a,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-(5-methylthiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-alpyrimidin-5-yl])-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone | 554.2/554.2 | B | B |
| 3.186 | ((1R,3a,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-(5-methylthiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-alpyrimidin-5-yl])-8-azabicyclo[3.2.1]octan-8-yl)(1-hydroxycyclopropyl)m ethanone | 580.2/580.2 | C | C |
| 3.187 | 1-((1R,3a,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-(5-methylthiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-alpyrimidin-5-yl])-8-azabicyclo[3.2.1]octan-8-yl)-3,3,3-trifluoro-2-hydroxypropan-1-one | 622.2/621.9 | C | C |</p>
<table>
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<tr>
<th></th>
<th>Structure</th>
<th>Chemical Formula</th>
<th>Molecular Weight (g/mol)</th>
<th>Column 1</th>
<th>Column 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.188</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>2-amino-1-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-(5-methylthiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-alpyrimidin-5-yl]-8-azabicyclo[3.2.1]octan-8-yl)-3,3,3-trifluoropropan-1-one</td>
<td>621.2/621.3</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>3.189</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-(4-methylthiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-alpyrimidin-5-yl]-8-azabicyclo[3.2.1]octan-8-yl)(2H-1,2,3-triazol-4-yl)methanone</td>
<td>591.2/591.0</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>3.190</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>1-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-(4-methylthiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-alpyrimidin-5-yl]-8-azabicyclo[3.2.1]octan-8-yl)ethanone</td>
<td>538.2/538.2</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>3.191</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-(4-methylthiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-alpyrimidin-5-yl]-8-azabicyclo[3.2.1]octan-8-yl)(3-methyl-1H-1,2,3-triazol-3-yl)methanone</td>
<td>605.2/605.2</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>3.192</td>
<td><img src="image5.png" alt="Structure" /></td>
<td>((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-(4-methylthiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-alpyrimidin-5-yl]-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone</td>
<td>591.2/591.0</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>3.193</td>
<td>((1R,3s,5S)-3-(7-amino-3-6-(5,6-dihydro-4H-cyclopenta[d]thiazol-2-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-3-yl)4H-1,2,4-triazol-3-yl)methanone</td>
<td>617.2/617.1</td>
<td>B</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>3.194</td>
<td>((1R,3s,5S)-3-(7-amino-3-6-(5,6-dihydro-4H-cyclopenta[d]thiazol-2-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-3-yl)(1H-1,2,3-triazol-5-yl)methanone</td>
<td>617.2 / 617.5</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>3.195</td>
<td>((1R,3s,5S)-3-(7-amino-3-6-(5,6-dihydro-4H-cyclopenta[d]thiazol-2-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-3-yl)(5-methyl-4H-1,2,4-triazol-3-yl)methanone</td>
<td>631.2 / 631.2</td>
<td>C</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>3.196</td>
<td>((1R,3s,5S)-3-(7-amino-3-6-(4,5-dimethylthiazol-2-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-3-yl)(5-methyl-4H-1,2,4-triazol-3-yl)methanone</td>
<td>605.2 / 605.0</td>
<td>B</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>3.197</td>
<td>((1R,3s,5S)-3-(7-amino-3-6-(4,5-dimethylthiazol-2-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-3-yl)(5-methyl-4H-1,2,4-triazol-3-yl)methanone</td>
<td>619.2 / 619.4</td>
<td>B</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>3.198</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>((1R,3s,5S)-3-(7-amino-3-(6-(4,5-dimethylthiazol-2-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazololo[1,5-alpyrimdin-5-yl]8-azabicyclo[3.2.1]octan-8-yl)1H-1,2,3-triazol-5-yl)methanone</td>
<td>605.2 / 605.3</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>3.199</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-(2-methylthiazol-4-yl)pyridin-3-yl)pyrazololo[1,5-alpyrimdin-5-yl]8-azabicyclo[3.2.1]octan-8-yl)(5-methyl-1H-1,2,4-triazol-3-yl)methanone</td>
<td>605.2 / 605.2</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>3.200</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>1-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-(2-methylthiazol-4-yl)pyridin-3-yl)pyrazololo[1,5-alpyrimdin-5-yl]8-azabicyclo[3.2.1]octan-8-yl)ethanone</td>
<td>538.2 / 538.2</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>3.201</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-(2-methylthiazol-4-yl)pyridin-3-yl)pyrazololo[1,5-alpyrimdin-5-yl]8-azabicyclo[3.2.1]octan-8-yl)(2H-1,2,3-triazol-4-yl)methanone</td>
<td>591.2 / 591.1</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>3.202</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td>5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazololo[1,5-alpyrimdin-7-amino</td>
<td>474.18/475.0</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>3.203</td>
<td><img src="image6" alt="Chemical Structure" /></td>
<td>N-(2-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazololo[1,5-alpyrimdin-5-yl]8-azabicyclo[3.2.1]octan-8-yl)-2-oxoethyl)acetamide</td>
<td>573.22/574.0</td>
<td>A</td>
<td>A</td>
</tr>
</tbody>
</table>
| 3.204 | ![Chemical Structure](image1.png) | N-(2-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-3.204 4627.19/628.0 ND ND

| 3.205 | ![Chemical Structure](image2.png) | ((1R,3S,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-571.24/572.2 B B

| 3.206 | ![Chemical Structure](image3.png) | ((1R,3R,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-571.24/572.2 C C


EXAMPLE 4-1

SCHEME 4-1

Preparation of ((1R, 3s, 5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone

Step A · Synthesis of (1R,3s,5S)-tert-butyl 3-(7-bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate
To a solution of (1R,3s,5S)-ferf-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (0.200 g, 0.240 mmols) in Dioxane (2 mL) was added cyclopropyl boronic acid (0.102 g, 1.2 mmols), K$_3$PO$_4$ (0.153 g, 0.720 mmols), PdCl$_2$ (dpff) (0.020 g, 10% eq) and water (0.200 mL). Reaction mixture was degassed and heated at 100 °C for 15 h. The reaction was passed through celite, diluted with EtOAc and washed with sat. NaHCO$_3$ and water. The organic layer dried with MgSO$_4$ and concentrated. ISCO purification (20% EtOAc in Hexane) gave the title compound as yellow oil (0.102 g).

Step B - Synthesis of ((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone

Intermediate (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)octane-8-carboxylate was treated with TFA/water (9:1, 1 mL) for 5 minutes, concentrated and lyophilized to provide the
corresponding amine which was converted to the title product following standard amide coupling reaction described before.

Example 4-2

Preparation of ((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-methoxyquinolin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone

Step 1: Preparation of (1R,3s,5S)-tert-butyl 3-((R)-7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(7-methoxynaphthalen-2-yl)-4,5-dihydropyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

![Chemical structure]

To a solution of (1R,3s,5S)-tert-butyl 3-((7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-3-(7-methoxynaphthalen-2-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (773 mg, 1.02 mmol) in CH$_2$CN (20 mL) was added NBS (1.1 eq) at rt and stirred for 15 min. All the volatiles were removed under reduced pressure and the residue was purified by a SiO$_2$ column (0-40%, EtOAc/Hexanes, $R_f = 0.7$ in 50% EtOAc) to afford the titled compound as a yellow forming solid (354 mg).

Step 2: Preparation of (1R,3s,5S)-tert-butyl 3-((R)-7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-6-cyclopropyl-3-(7-methoxynaphthalen-2-yl)-4,5-dihydropyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

286
A mixture of (1R,3s,5S)-tert-butyl 3-((R)-7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(7-methoxynaphthalen-2-yl)-4,5-dihydropyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (177 mg, 0.211 mmol), cyclopropylboronic acid (181 mg, 2.11 mmol), PdCl₂(dpff)DCM (34.5 mg, 0.042 mmol), and K₃PO₄ (134 mg, 0.633 mmol) in dioxane/H₂O (2/0.2 mL) was degassed and then heated at 150 °C under microwave radiation for 3 h. The reaction mixture was diluted with EtOAc, filtered through a short pad of celite, washed with H₂O and brine, dried over Na₂SO₄, and concentrated. The crude product was purified by a SiO₂ column (0-30% EtOAc/Hexanes, Rf = 0.75 in 50% EtOAc) to afford the titled compound as a pale yellow forming solid (71.2 mg).

Step 3: Preparation of ((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-methoxyquinolin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone

This compound was prepared from (1R,3s,5S)-tert-butyl 3-((R)-7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-cyclopropyl-3-(7-methoxynaphthalen-2-yl)-4,5-dihydropyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate and 4H-1,2,4-triazole-3-carboxylic acid, following essentially the similar procedures given in Preparative Example 4-1.
Example 4-3

Preparation of 4-nitrophenyl [[tert-butyl(dimethyl)silyl]oxy]carbamate

(Aminoxy)(tert-butyl)dimethylsilane \((1.00 \, \text{g}, \, 6.79 \, \text{mmol})\) was dissolved in a mixture of dry pyridine \((0.549 \, \text{mL}, \, 6.79 \, \text{mmol})\) and dichloroethane \((15 \, \text{mL}; \, \text{dichloromethane could also be used}), \) and a solution of 4-nitrophenyl chlorocarbonate \((1.37 \, \text{g}, \, 6.79 \, \text{mmol})\) in dichloroethane \((7 \, \text{mL})\) was added over 5 min. The resulting mixture was stirred at room temperature overnight and was then diluted with dichloromethane, washed twice with water, twice with saturated aqueous sodium bicarbonate, and brine, dried over magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by chromatography \((90 \, \text{g silica gel, 20\% EtOAc/hexanes eluent})\) to give the title compound \((1.73 \, \text{g}, \, 8.1\%)\) as a white solid.

Following Scheme 4-1 and using procedures similar to the preparation of example 4-1, the following compounds listed in Table 4-1 were prepared:

Table 4-1

<p>| 4.1 | ((1,1,R,3,S,5,S):3,(7)-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazol[1,5-al]pyrimidin-5-y)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methane | 532.3/532.0 | A | A |
| 4.2 | <img src="image" alt="Chemical Structure" /> | (1R,3a,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methyl-4H-1,2,4-triazol-3-yl)methanone | 546.3/546.0 | A | A |
| 4.3 | <img src="image" alt="Chemical Structure" /> | 5-(1R,3a,5S)-8-(4H-1,2,4-triazol-3-ylsulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine | 568.2/568.2 | C | C |
| 4.4 | <img src="image" alt="Chemical Structure" /> | (1R,3a,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-N-methyl-8-azabicyclo[3.2.1]octane-8-carboxamide | 494.3/494.0 | A | B |
| 4.5 | <img src="image" alt="Chemical Structure" /> | (1R,3a,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-N-ethyl-8-azabicyclo[3.2.1]octane-8-carboxamide | 508.3/508.0 | B | B |
| 4.6 | <img src="image" alt="Chemical Structure" /> | (1R,3a,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxamide | 480.2/480.0 | A | A |
| 4.7 | <img src="image" alt="Chemical Structure" /> | (1R,3a,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-N-(2-methoxyethyl)-8-azabicyclo[3.2.1]octane-8-carboxamide | 538.3/538.1 | B | B |
| 4.8 | <img src="image" alt="Chemical Structure" /> | (1R,3a,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-N-(2-hydroxyethyl)-8-azabicyclo[3.2.1]octane-8-carboxamide | 524.3/524.0 | A | B |
| 4.9 | <img src="image" alt="Chemical Structure" /> | ((1R,3a,5S)-3-(7-amino-6-cyclopropyl-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone | 580.25/580.0 | A | B |
| 4.10 | (1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-(2,3-difluoro-4-methoxyphenyl)pyridin-3-yl)pyrazol[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone | 598.24/598.0 | A | A |
| 4.11 | (1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-(4-fluoro-3-methoxyphenyl)pyridin-3-yl)pyrazol[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone | 580.25/580.0 | ND | D |
| 4.12 | (1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-(2,5-difluoro-4-methoxyphenyl)pyridin-3-yl)pyrazol[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone | 598.24/598.0 | A | A |
| 4.13 | (1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-(4-ethoxyphenyl)pyridin-3-yl)pyrazol[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone | 576.27/576.1 | B | B |
| 4.14 | (1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-(4-(2-methoxyethoxy)phenyl)pyridin-3-yl)pyrazol[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone | 606.28/606.1 | B | B |
| 4.15 | (1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-(difluoromethoxy)phenyl)pyridin-3-yl)pyrazol[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone | 598.24/598.0 | B | B |
| 4.16 | (1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-methylpyridin-3-yl)pyrazol[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone | 470.23/470.0 | B | ND |</p>
<table>
<thead>
<tr>
<th>No.</th>
<th>Structure</th>
<th>Chemical Formula</th>
<th>Molecular Weight</th>
<th>Isomer A</th>
<th>Isomer B</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.17</td>
<td><img src="image" alt="Structure" /></td>
<td>((1R,3S,5S)-3-(7\text{-amino-6-cyclopropyl-3-yl}))(4H-1,2,4-triazol-3-yl)methanone</td>
<td>536.25/536.0</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>4.18</td>
<td><img src="image" alt="Structure" /></td>
<td>((1R,3S,5S)-3-(7\text{-amino-6-cyclopropyl-3-yl}))(4H-1,2,4-triazol-3-yl)methanone</td>
<td>497.25/499.0</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>4.19</td>
<td><img src="image" alt="Structure" /></td>
<td>((1R,3S,5S)-3-(7\text{-amino-6-cyclopropyl-3-yl}))(4H-1,2,4-triazol-3-yl)methanone</td>
<td>554.24/554.0</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>4.20</td>
<td><img src="image" alt="Structure" /></td>
<td>((1R,3S,5S)-3-(7\text{-amino-6-cyclopropyl-3-yl}))(4H-1,2,4-triazol-3-yl)methanone</td>
<td>517.24/517.0</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>4.21</td>
<td><img src="image" alt="Structure" /></td>
<td>((1R,3S,5S)-3-(7\text{-amino-6-cyclopropyl-3-yl}))(4H-1,2,4-triazol-3-yl)methanone</td>
<td>550.24/550.0</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>4.22</td>
<td><img src="image" alt="Structure" /></td>
<td>((1R,3S,5S)-3-(7\text{-amino-6-cyclopropyl-3-yl}))(4H-1,2,4-triazol-3-yl)methanone</td>
<td>513.23/513.0</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>4.23</td>
<td><img src="image" alt="Structure" /></td>
<td>((1R,3S,5S)-3-(7\text{-amino-6-cyclopropyl-3-yl}))(4H-1,2,4-triazol-3-yl)methanone</td>
<td>536.25/536.0</td>
<td>C</td>
<td>ND</td>
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<tr>
<td>No.</td>
<td>Chemical Structure</td>
<td>Molecular Formula</td>
<td>Molecular Weight</td>
<td>Retention Time</td>
<td>Phase</td>
</tr>
<tr>
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<tr>
<td>4.24</td>
<td><img src="image1.png" alt="Chemical Structure" /></td>
<td>((\text{R},3s,5S)-3-(7\text{-amino-6-cyclopropyl-3-(6-methoxyquinolin-3-yl)}\text{pyrazolo[1,5-a]pyrimidin-5-yl})-8\text{-azabicyclo[3.2.1]octan-8-yl})\text{methanone})</td>
<td>536.2</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>4.25</td>
<td><img src="image2.png" alt="Chemical Structure" /></td>
<td>((\text{R},3s,5S)-3-(7\text{-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)}\text{pyrazolo[1,5-a]pyrimidin-5-yl})-8\text{-azabicyclo[3.2.1]octan-8-yl})\text{methanone})</td>
<td>575.22</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>4.26</td>
<td><img src="image3.png" alt="Chemical Structure" /></td>
<td>((\text{R},3s,5S)-3-(7\text{-amino-6-cyclopropyl-3-(1-phenyl-1H-pyrazol-4-yl)}\text{pyrazolo[1,5-a]pyrimidin-5-yl})-8\text{-azabicyclo[3.2.1]octan-8-yl})\text{methanone})</td>
<td>521.2</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>4.27</td>
<td><img src="image4.png" alt="Chemical Structure" /></td>
<td>((5\text{-amino-4H-1,2,4-triazol-3-yl})\text{(1 R,3s,5S)-3-(7\text{-amino-6-cyclopropyl-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)}\text{pyrazolo[1,5-a]pyrimidin-5-yl})-8\text{-azabicyclo[3.2.1]octan-8-yl})\text{methanone})</td>
<td>595.3</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>4.28</td>
<td><img src="image5.png" alt="Chemical Structure" /></td>
<td>(N\text{-(5-((1 R,3s,5S)-3-(7\text{-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)}\text{pyrazolo[1,5-a]pyrimidin-5-yl})-8\text{-azabicyclo[3.2.1]octan-8-carbonyl})-4H-1,2,4-triazol-3-yl)acetamide})</td>
<td>58.93</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>4.29</td>
<td><img src="image6.png" alt="Chemical Structure" /></td>
<td>((\text{R},3s,5S)-3-(7\text{-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)}\text{pyrazolo[1,5-a]pyrimidin-5-yl})-8\text{-azabicyclo[3.2.1]octan-8-yl})\text{acetamide})</td>
<td>575.3</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>4.30</td>
<td><img src="image7.png" alt="Chemical Structure" /></td>
<td>((3\text{-amino-1 H-pyrazol-4-yl})\text{(1 R,3s,5S)-3-(7\text{-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)}\text{pyrazolo[1,5-a]pyrimidin-5-yl})-8\text{-azabicyclo[3.2.1]octan-8-yl})\text{methanone})</td>
<td>546.3</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>4.31</td>
<td><img src="image8.png" alt="Chemical Structure" /></td>
<td>((\text{R},3s,5S)-3-(7\text{-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)}\text{pyrazolo[1,5-a]pyrimidin-5-yl})-8\text{-azabicyclo[3.2.1]octan-8-yl})\text{(5-(2-methoxyethylamino)-4H-1,2,4-triazol-3-yl)methanone})</td>
<td>605.3</td>
<td>C</td>
<td>C</td>
</tr>
</tbody>
</table>
### EXAMPLE 5-1

**Scheme 5-1**

**Preparation of 5-((1R,3s,5S)-8-(1H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidine-6-carbonitrile**

*Step 1*
Synthesis of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-cyano-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

To a Schlenk tube were charged (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (83 mg, 0.1 mmol), Bu3SnCN (47 mg, 0.15 mmol), Pd(PPh3)4 (23 mg, 0.02 mmol), Bis(tri-f-butylphosphine)palladium (10 mg, 0.02 mmol). The tube was evacuated and charged with Ar for three cycles. Dioxane (3 ml) was added; the tube was capped and heated at 150 °C with stirring for 16 h. After cooling, the mixture was diluted with EtOAc and washed with brine once. Organic layer separated, dried over MgSO4 and concentrated. The residue was purified on silica gel. Elution with EtOAc/hexane (0-25%) gave the desired product (59 mg).

Step 2
Preparation of 7-amino-5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidine-6-carbonitrile
To a solution of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-6-cyano-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (59 mg, 0.08 mmol) in TFA (2 ml) was added few drops of water and stirring continued for 2 h at room temperature. LC/MS showed no starting material remaining. TFA along with water was rotoevaporated, and the crude was dried under the high vacuum for 4 h, which was used without further purification for the next step.

Step 3

Synthesis of 5-((1R,3s,5S)-8-(1H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octane-3-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidine-6-carbonitrile

A mixture of 1H-1,2,4-triazole-3-carboxylic acid (29.4 mg, 0.26 mmol), EDCI (76.7 mg, 0.4 mmol), and 1-hydroxybenzotriazole (27 mg, 0.2 mmol) in DMF (2 mL) was stirred at room temperature for 10 min. Substrate 7-amino-5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidine-6-carbonitrile (0.2 mmol) was added followed by W.W-diisopropylethylamine (0.17 ml, 1
mmol). It was stirred further for 20 min at room temperature at which time LC/MS analysis confirmed full consumption of starting material. This crude compound was submitted to the analytical group for purification to afford the desired product.

Following the Scheme 5-1 and the procedures similar to preparation of (5-(8-(1H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidine-6-carbonitrile, the following compounds (Table 5-1) can be prepared:

Table 5-1

<table>
<thead>
<tr>
<th>Compound ID</th>
<th>Structures</th>
<th>Compound Name</th>
<th>M+H(calculated)</th>
<th>M+H(observed)</th>
<th>pAKT S473 I50</th>
<th>pE681 Thr37/46 I50</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.1</td>
<td><img src="image" alt="Structure 5.1" /></td>
<td>7-amino-5-((1R,3S,5S)-8-(2-hydroxyacetyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidine-6-carbonitrile</td>
<td>480.2/479.9</td>
<td>A</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>5.2</td>
<td><img src="image" alt="Structure 5.2" /></td>
<td>5-((1R,3S,5S)-8-(1H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidine-6-carbonitrile</td>
<td>517.2/516.9</td>
<td>A</td>
<td>A</td>
<td></td>
</tr>
</tbody>
</table>
Example 5-2

Preparation of \(((1R,3s,5S)-3-(7-amino-6-methyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)\((4H-1,2,4-triazol-3-yl)methanone\)

A degassed mixture of \((1R,3s,5S)-\)tert-butyl 3-(7-(bis(2-(trimethylsilyl)ethoxy)methyl)amino)-6-iodo-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (65 mg, 0.74 mmol), Pd(PPh₃)₄ (8.5 mg, 0.0074 mmol), trimethylboroxine (20.5 ul, 0.15 mmol), and K₂CO₃ (30.5 mg, 0.22 mmol) in DMF (3 ml) was heated at 120°C for 30 min under
microwave condition. The mixture was diluted with H₂O and then extracted with ethyl acetate (x2). The combined organic layers were washed with brine and dried with Na₂SC₂O₄ and concentrated to provide crude (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-methyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate. LCMS tᵣ = 1.75 Min (5 min run, UV₂₅₄nm). Mass calculated for, M+ 770.4, observed LC/MS m/z 771.4 (M+H).

By applying the chemistry described in Example 5-1, the crude (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-methyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate was first treated with 50% TFA in H₂O to remove the BOC and SEM protecting group and then followed by EDCI-mediated amide coupling reaction to afford ((1R,3s,5S)-3-(7-amino-6-methyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone: LCMS tᵣ = 2.26 Min (10 min run, UV₂₅₄nm). Mass calculated for, M+ 505.2, observed LC/MS m/z 505.97 (M+H).

Example 5-3

Preparation of ((1R,3s,5S)-3-(7-amino-6-fluoro-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone
At 0°C, Selectfluor® (25.3 mg, 0.071 mmol) was added to (1R,3S,5S)-tert-butyl 3-(7-(bis(2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (18.0 mg, 0.023 mmol) in CH₂CN (3 ml). The mixture was slowly warmed up to room temperature. Once LCMS indicated complete conversion, the mixture was diluted with sat. NaHCO₃ and then extracted with ethyl acetate (x2). The combined organic layers were washed with brine and dried with Na₂SO₄ and concentrated to provide crude (1R,3S,5S)-tert-butyl 3-(7-(bis(2-(trimethylsilyl)ethoxy)methyl)amino)-6-fluoro-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate. LCMS t<sub>R</sub> = 2.01 Min (5 min run, UV<sub>254nm</sub>). Mass calculated for, M+ 774.4, observed LC/MS m/z 775.3 (M+H). By applying the chemistry described in Example 5-1, the crude (1R,3S,5S)-tert-butyl 3-(7-(bis(2-(trimethylsilyl)ethoxy)methyl)amino)-6-fluoro-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate was first treated with 50% TFA in H₂O to remove the BOC and SEM protecting group and then followed by EDCI-mediated amide coupling reaction to afford [(1R,3S,5S)-3-(7-amino-6-fluoro-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl][4H-1,2,4-triazol-3-yl]methanone: LCMS t<sub>R</sub> = 2.23 Min (10 min run, UV<sub>254nm</sub>). Mass calculated for, M+ 509.2, observed LC/MS m/z 509.97 (M+H).

Example 5-4

Preparation of 5-((1R,3S,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-isopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine
A degassed mixture of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-iodo-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (315 mg, 0.35 mmol), Pd(PPh_3)_4 (41.3 mg, 0.035 mmol), tributyl(prop-1-en-2-yl)stannane (354.7 mg, 1.07 mmol) in Dioxane (6 mL) was heated at 80°C overnight. The reaction mixture was cooled to room temperature, filtered through 9:1 SiC>2:KF plug and concentrated in vacuo to afford crude (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-phenylpyridin-3-yl)-6-(prop-1-en-2-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate, LCMS t_R = 1.89 Min (5 min run, UV_254nm). Mass calculated for, M+ 796.4, observed LC/MS m/z 797.4 (M+H).

At 0°C, TFA (3 ml) and then Et_3SiH (1 ml) were added to the crude (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-phenylpyridin-3-yl)-6-(prop-1-en-2-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate. The mixture was stirred at room temperature for 2h and then concentrated. Purification by prep-LC provided 5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-isopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine: LCMS t_R = 1.94 Min (10 min run, UV_254nm). Mass calculated for, M+ 438.2, observed LC/MS m/z 439.0 (M+H).

Example 5-5

Preparation of (1R,3s,5S)-3-(7-amino-6-isopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone

![Chemical Structure](image.png)
A mixture of 5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-isopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine (30 mg, 0.068 mmol), 41-1-1,2,4-triazole-3-carboxylic acid (10.1 mg, 0.085 mmol), EDC (26.0 mg, 0.14 mmol), HOBr (18.4 mg, 0.14 mmol) and DIEA (70.9 ul, 0.41 mmol) in DMF (2 mL) was stirred at room temperature. Purification with prep-LC provided (1 R,3s,5S)-3-(7-amino-6-isopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone, LCMS t_R = 2.25 Min (10 min run, UV, 254nm). Mass calculated for, M+ 533.2, observed LC/MS m/z 533.99 (M+H).

Scheme 5-2
Preparation of 2-(5-((1R, 3s, 5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-aj]pyrimidin-6-yl)acetonitrile

Step A - Synthesis of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-3-(6-phenylpyridin-3-yl)-6-vinylpyrazolo[1,5-aj]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate
To a pressure tube were charged (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (834 mg, 1 mmol), vinylboronic pinacol ester (170 mmol, 1 mmol), Pd(PPh₃)₃ (230 mg, 0.2 mmol), Pd(PBu₃)₂ (100 mg, 0.2 mmol), 2 M Na₂CO₃ (5 mL) and dioxane (15 mL). The mixture was degassed with Ar and stirred at 100 °C for 16 hours. On cooling, EtOAc (50 mL) was added, and resulting mixture was washed with water (1 x 20 mL), brine, and dried over MgSO₄. After filtration and concentration the residue was purified on silica gel. Gradient elution with EtOAc/hexanes (0 to 30%) gave the desired product (630 mg).

Step B - Synthesis of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-formyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

To a solution of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(6-phenylpyridin-3-yl)-6-vinylpyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (128 mg, 0.16 mmol) in dioxane (3 mL) and water (250 mL) was added OsO₄ (2.5% in f-BuOH, 154 µL, 0.012 mmol). After stirring for 20 minutes, NaI₀₄ (103 mg, 0.48 mmol) was added followed by addition of more water (0.25 mL) and dioxane (1 mL). After stirring for 16 hours, the reaction was quenched with saturated Na₂S₂O₃ (5 mL), and stirred for 20 minutes. The reaction mixture was extracted with dichloromethane (3 x 20 mL), washed with brine and dried over MgSO₄. After filtration and concentration the residue was purified on silica gel. Gradient elution with EtOAc/hexanes (0 to 30%) gave the desired product (107 mg).
Step C - Synthesis of \((1R,3s,5S)\)-tert-butyl 3-\((\text{7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-6-(hydroxymethyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl})\)-8-azabicyclo[3.2.1]octane-8-carboxylate

To a solution of \((1R,3s,5S)\)-tert-butyl 3-\((\text{7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-6-formyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl})\)-8-azabicyclo[3.2.1]octane-8-carboxylate \((477 \text{ mg, 0.61 mmol})\) in MeOH \((4 \text{ mL})\) was added NaBH\(_4\) \((23 \text{ mg, 0.61 mmol})\) and the resulting mixture was stirred for 10 minutes. After concentration the residue was purified on silica gel. Gradient elution with EtOAc/hexanes \((0 \text{ to } 40\%)\) gave the title product \((420 \text{ mg})\).

Step D - Synthesis of \((1R,3s,5S)\)-tert-butyl 3-\((\text{7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-6-(cyanomethyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl})\)-8-azabicyclo[3.2.1]octane-8-carboxylate

After concentration the residue was purified on silica gel. Gradient elution with EtOAc/hexanes \((0 \text{ to } 40\%)\) gave the title product \((420 \text{ mg})\).
To a solution of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-6-(cyanomethyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (140 mg, 0.18 mmol) in triethylamine (74 uL, 0.56 mmol) and dichloromethane (1 mL) was added mesyl chloride (14 uL, 0.18 mmol) and the resulting mixture was stirred for 10 minutes, diluted with dichloromethane (10 mL), washed with water (2x 5 mL), brine and dried (MgSO$_4$). After concentration, the residue was taken into a solution of DMSO (1 mL) and acetonitrile (1 mL), and 18-crown-6 (6 mg) was added followed by addition of KCN (11 mg, 0.17 mmol). The reaction mixture was allowed to stir for 2 days, diluted with dichloromethane (10 mL), washed with water (3 x 5 mL), brine and dried (MgSO$_4$). After concentration the residue was purified on silica gel. Gradient elution with EtOAc/hexanes (0 to 40%) gave the title product (50 mg).

Step E - Synthesis of 2-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)acetonitrile

![Chemical Structure](image)

Compound (1R,3s,5S)-tert-butyl 3-(7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-6-(cyanomethyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (50 mg) was treated with TFA/water (9:1, 1 mL) for 5 minutes, concentrated and lyophilized to provide the corresponding amine which was converted to the title product following standard amide coupling reaction.
Scheme 5-3

Preparation of ((1R,3s,5S)-3-(7-amino-6-(methoxymethyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

Step A - Synthesis of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(methoxymethyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate
To a 0 °C solution of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(hydroxymethyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (0.83 g, 1.1 mmol) in DMF (8.5 mL) was added NaH (0.05 g, 1.3 mmol, 60% in mineral oil). It was then warmed up to room temperature. After 30 minutes at room temperature, iodomethane (0.09 mL, 1.4 mmol) was added and stirring was continued for 25 minutes, at which time LC/MS analysis confirmed full consumption of starting material. Reaction mixture was diluted with EtOAc (125 mL), washed with water (3 x 25 mL), brine (1 x 25 mL), and dried over MgSO₄. Gradient column chromatography on silica gel eluting with 0 to 50% EtOAc/hexanes gave the desired (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(methoxymethyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (0.7 g).

Step B - Synthesis of 5-(1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl-6-(methoxymethyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine

Intermediate (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(methoxymethyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (74 mg) was treated with TFA/water (9:1, 20 uL) and mixture was stirred for 2 minutes, and diluted with water (1 mL) and acetonitrile (0.2 mL). The crude reaction mixture was directly purified by HPLC to afford the title product.
Step C - Synthesis of \(((1R,3s,5S)-3-(7\text{-amino}-6-(\text{methoxymethyl})-3-(6\text{-phenylpyridin}-3\text{-yl})\text{pyrazolo}[1,5-a]\text{pyrimidin}-5\text{-yl})\text{8-azabicyclo}[3.2.1]\text{octan}-8\text{-yl})(4H-1,2,4\text{-triazol}-3\text{-yl})\text{methanone}

The title compound was prepared by following standard amide coupling procedure described before.

Following and using procedures similar to the preparation of example 5-3, the following compounds listed in Table 5-2 were prepared:

Table 5-2
5.4

\[ \text{((1R,3S,5S)-3-(7-amino-6-(methoxymethyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone} \]

536.2/536.0 A A

5.5

\[ \text{(3-amino-1H-pyrazol-5-yl)((1R,3S,5S)-3-(7-amino-6-(methoxymethyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)methanone} \]

550.3/550.0 B C

5.6

\[ \text{((1R,3S,5S)-3-(7-amino-6-(methoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone} \]

566.3/566.0 A A

5.7

\[ \text{((1R,3S,5S)-3-(7-amino-6-(hydroxymethyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone} \]

522.2/522.0 A A
Example 5-4

Scheme 5-4

Preparation of ((1R,3s,5S)-3-(7-amino-6-ethyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone

Intermediate (1R,3s,5S)-tert-butyl 3-(7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-3-(6-phenylpyridin-3-yl)-6-vinylpyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (313 mg, 0.4 mmol) was treated with TFA (1 mL) and Et3SiH (256 µL, 0.6 mmol) and the reaction was stirred for 1 hr. After concentration, the residue was purified by HPLC to provide intermediate 5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-ethyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine (10 mg) which was further converted to the title product by standard amide coupling reaction.

Following Scheme 5-4 the following compounds (Table 5-3) were made:

Table 5-3

<table>
<thead>
<tr>
<th>Compound ID</th>
<th>Structures</th>
<th>Compound Name</th>
<th>M+H (calculate)</th>
<th>M+H (observed)</th>
<th>pAKT S473 IC50</th>
<th>p4E-BP1 Thr3 7/46 IC50</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.8</td>
<td><img src="image" alt="Structure" /></td>
<td>((1R,3s,5S)-3-(7-amino-6-ethyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone</td>
<td>520.3</td>
<td>520.0</td>
<td>A</td>
<td>A</td>
</tr>
</tbody>
</table>
Example 6-1

Preparation of 1-((1R,3s,5S)-3-(3-(6-(1H-imidazol-2-yl)pyridin-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone

Step A - Synthesis of (1R,3s,5S)-tert-butyl 3-(7-bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-formylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

To a pressure tube were charged (1R,3s,5S)-ferf-butyl 3-(7-bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-iodopyrazolo[1,5-a]pyrimidin-5-yl)-8-
azabicyclo[3.2.1]octane-8-carboxylate (9.4 g, 12.9 mmol), 2-formylpyridinyl-5-boronic acid pinacol ester (6 g, 25.75 mmol), Pd(II)(dpdf) (2.1 g, 2.57 mmol), Pd[PdBu3]2 (80 mg, 0.16 mmol) and K2CO3 (5.3 g, 38.4 mmol), DME (80 mL) and water (40 mL). The mixture was degassed with Ar and stirred at 100 °C for 5 hours. On cooling, EtOAc (100 mL) was added, and resulting mixture was washed with water (1 x 60 mL), brine (1 x 125 mL), and dried over MgSO4. After filtration and concentration the residue was purified on silica gel. Gradient elution with EtOAc/hexanes (0 to 40%) gave the desired product (2.84 g).

**Step B - Synthesis of (1R,3S,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(6-formylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate**

To a suspension of (1R,3S,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(6-formylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (708 mg, 1 mmol) in DCM and acetonitrile (1:1, 4 mL) was added NBS (178 mg, 1 mmol) and the mixture was stirred for 5 minutes. After concentration, the residue was purified on silica gel. Gradient elution with EtOAc/hexanes (0 to 40%) gave the desired product (670 mg).

**Step C - Synthesis of (1R,3S,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(1-ethoxyvinyl)-3-(6-formylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate**
A mixture of compound \((1R,3s,5S)-\text{ferf-butyl}~3-(7-(\text{bis}(2-(\text{trimethylsilyl})\text{ethoxy})\text{methyl})\text{amino})-6\text{-bromo-3-(6-formylpyridin-3-yl)}\text{pyrazolo}[1,5-a]\text{pyrimidin-5-yl})-8\text{-azabicyclo[3.2.1]octane-8-carboxylate}\) (394 mg, 0.5 mmol), tributyl(1-ethoxyvinyl)tin (338 \(\mu\)L, 1 mmol), tetrakis(triphenylphosphine)palladium (29 mg, 0.025 mmol) in dioxane (6 mL) was degassed with argon for 1 minute. It was then heated at 100 °C in a sealed tube for 16 h. On cooling, the reaction mixture was diluted with EtOAc (30 mL), washed with 0.5 M KF solution (1 x 10 mL), brine (1 x 25 mL), and dried over MgSO\(_4\). The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel. Elution with EtOAc/Hexanes (0-25%) gave the title product 454 mg as yellow oil.

**Step D - Synthesis of \((1R,3s,5S)-\text{tert-butyl}~3-(3-(6-(1H-imidazol-2-yl)pyridin-3-yl)-7-(\text{bis}(2-(\text{trimethylsilyl})\text{ethoxy})\text{methyl})\text{amino})-6-(1-ethoxyvinyl)\text{pyrazolo}[1,5-a]\text{pyrimidin-5-yl})-8\text{-azabicyclo[3.2.1]octane-8-carboxylate}\)**

To a pressure tube were charged \((1R,3s,5S)-\text{ferf-butyl}~3-(7-(\text{bis}(2-(\text{trimethylsilyl})\text{ethoxy})\text{methyl})\text{amino})-6-(1-ethoxyvinyl)-3-(6-formylpyridin-3-yl)\text{pyrazolo}[1,5-a]\text{pyrimidin-5-yl})-8\text{-azabicyclo[3.2.1]octane-8-carboxylate}\) (450 mg) and EtOH (2 mL) and the solution was cooled to 0 - 5 °C by an ice bath. To the
solution was added NH₄OH (28%, 0.55 mL), followed by glyoxal (40%, 85 µL). The tube was sealed and the reaction mixture was heated at 90 °C with stirring for 1 hour. After concentration under reduced pressure, the residue was re-taken into EtOAc (20 mL), washed with water (5 mL), brine (10 mL) and dried over MgSO₄.

The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel. Elution with EtOAc gave the title product (340 mg).

Step E - Synthesis of 1-(3-(6-(1H-imidazol-2-yl)pyridin-3-yl)-7-amino-5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone

To a solution of (1R,3s,5S)-3-(3-(6-(1H-imidazol-2-yl)pyridin-3-yl)-7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(1-ethoxyvinyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate in dioxane (2 mL) was added 4 M HCl in water (2 mL) at 0 °C. After stirring for 5 minutes at 0 °C, 4 M HCl in dioxane (3 mL) was added. The reaction mixture was warmed to 50 °C for 40 minutes. The LC-MS indicated that reaction was almost complete. Additional 4 M HCl in dioxane (2 mL) was added and the mixture was heated to boiling for 2 minutes to complete the reaction. After cooling, the dioxane supernatant was taken out by a glass pipette and aqueous layer was lyophilized to furnish the title product as HCl salt.

Step F - Synthesis of 1-((1R,3s,5S)-3-(3-(6-(1H-imidazol-2-yl)pyridin-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone
A mixture of glycolic acid (25 mg, 0.3 mmol), EDCI (72 mg, 0.38 mmol), and 1-hydroxybenzotriazole (34 mg, 0.25 mmol) in DMF (1 ml) was warmed up to a homogeneous solution. This mixture was added into a solution of 1-(3-(3-((1H-imidazol-2-yl)pyridin-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-6-yl)-2-ethoxyethyl)amine (0.25 mmol) and N,N-diisopropylethylamine (130 µL, 0.75 mmol) in DMF (2 mL). It was stirred further for 10 min and the crude compound was directly purified by HPLC to afford the desired product.

**EXAMPLE 6-2**

Preparation of 1-((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-(4,5-dimethyl-1H-imidazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone

**Step A. Synthesis of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-cyclopropyl-3-(6-formylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-aza bicyclo[3.2.1]octan-8-carboxylate**
A mixture of ((1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(6-formylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (0.47 g, 0.6 mmol), cyclopropylboronic acid (0.31 g, 3.6 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (0.11 g, 0.24 mmol), Pd2(dba)3 (0.11 g, 0.12 mmol) and K3PO4 (0.38 g, 1.8 mmol) in toluene (5 mL) was degassed with argon and heated at 100°C for 16 hours, at which time LC/MS analysis confirmed full consumption of starting material. On cooling, EtOAc (100 mL) was added and washed with water (2 x 20 mL), brine (1 x 20 mL), and dried over MgSO4. Solvent was removed in vacuo and the residue was purified by column chromatography on silica gel. Elution with EtOAc/hexanes (0-45%) gave desired product, ((1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-cyclopropyl-3-(6-(4,5-dimethyl-1H-imidazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (0.14 g).

**Step B.** (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-cyclopropyl-3-(6-(4,5-dimethyl-1H-imidazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate
A mixture of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-cyclopropyl-3-(6-formylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (0.14 g, 0.19 mmol), 2,3-butanedione (25 µL, 0.28 mmol) and NH₂OH (28% by weight, 0.2 mL, 1.7 mmol) in ethenol (2 mL) was heated at 90°C for 3 hours, at which time LC/MS analysis confirmed full consumption of starting material. On cooling, DCM (50 mL) was added and washed with water (1 x 10 mL), brine (1 x 10 mL), and dried over MgSO₄. Solvent was removed in vacuo and the residue was purified by column chromatography on silica gel. Elution with EthAc/Hexanes (25%-100%) gave desired product, (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-cyclopropyl-3-(6-(4,5-dimethyl-1H-imidazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (0.11 g).

Step C. Synthesis of 5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-cyclopropyl-3-(6-(4,5-dimethyl-1H-imidazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine

(1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-cyclopropyl-3-(6-(4,5-dimethyl-1H-imidazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-aza bicyclo[3.2.1]octane-8-carboxylate (0.11 g, 0.14 mmol) was dissolved in a mixture of TFA (2 mL) and water (0.2 mL) at room temperature. Stirring continued for 45 min at room temperature. LC/MS analysis confirmed full consumption of starting material to product. TFA along with water was rotoevaporated, and the crude product 5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-cyclopropyl-3-(6-(4,5-
dimethyl-1H-imidazol-2-yl) pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine was dried under the high vacuum for 24 hour, which was used without further purification for the next step.

**Step D. Synthesis of 1-((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-(4,5-dimethyl-1H-imidazol-2-yl) pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3,2.1]octan-8-yl)-2-hydroxy ethanone**

A mixture of glycolic acid (3.8 mg, 0.05 mmol), EDCI (19.2 mg, 0.1 mmol), and 1-hydroxybenzotriazole (6.8 mg, 0.05 mmol) in DMF (1 mL) was stirred at room temperature for 10 minutes. Compound 5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-cyclopropyl-3-(6-(4,5-dimethyl-1H-imidazol-2-yl) pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine (0.05 mmol) was added followed by W/V-diisopropylethylamine (0.04 mL, 0.25 mmol). It was stirred further for 20 minutes at room temperature at which time LC/MS analysis confirmed full consumption of starting material. Pure compound 1-((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-(4,5-dimethyl-1H-imidazol-2-yl) pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone was isolated by preparative HPLC.

**EXAMPLE 6-3**

*Preparation of 1-((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-(4-fluoro-1H-imidazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone*
Step 1: Preparation of (1R,3s,5S)-tert-butyl 3-(7-bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-cyclopropyl-3-(6-(1H-imidazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

The compound (1R,3s,5S)-tert-butyl 3-(7-bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-cyclopropyl-3-(6-(1H-imidazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (Previously made, 210 mg, 0.229 mmol) was mixed with SelectFluor® in dry ACN (3 mL) and stirred overnight. The mixture was diluted with EtOAc and washed with NaHCO$_3$ (aq.) and water, brine. After concentration, the crude was used in the next step directly without further purification.

Step 2: Preparation of 5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-cyclopropyl-3-(6-(4-fluoro-1H-imidazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine
The compound 5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-cyclopropyl-3-(6-(4-fluoro-1H-imidazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine was prepared with the same condition described previously.

Step 3: Preparation of 1-((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-(4-fluoro-1H-imidazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone

The compound 1-((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-(4-fluoro-1H-imidazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone was made with the same condition described previously.

Following the examples, the following compounds (Table 6-1) were prepared.
Table 6-1

<table>
<thead>
<tr>
<th>Compound ID</th>
<th>Structures</th>
<th>Compound Name</th>
<th>M+H (calculated)</th>
<th>M+H (observed)</th>
<th>pAKT S473 IC50</th>
<th>p4E-BP1 Thr37/46 IC50</th>
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<tbody>
<tr>
<td>6.1</td>
<td><img src="image1" alt="Structure 1" /></td>
<td>1-((1R,3a,5S)-3-((3-(6-(1H-imidazol-2-yl)pyridin-3-yl)-7-amino-6-cyclopropylpyrazolo[1,5-a]pyrimdin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone</td>
<td>485.2/485.1</td>
<td>A</td>
<td></td>
<td>A</td>
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<td>6.2</td>
<td><img src="image2" alt="Structure 2" /></td>
<td>1-((1R,3a,5S)-3-((3-(6-(1H-imidazol-2-yl)pyridin-3-yl)-7-amino-6-cyclopropylpyrazolo[1,5-a]pyrimdin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-4H-1,2,4-triazol-3-yl)methanone</td>
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<td>A</td>
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<td>6.3</td>
<td><img src="image3" alt="Structure 3" /></td>
<td>1-((1R,3a,5S)-3-((3-(6-(1H-imidazol-2-yl)pyridin-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimdin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone</td>
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<td>1-((3-(6-(1H-imidazol-2-yl)pyridin-3-yl)-5-((1R,3a,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimdin-5-yl)ethanone</td>
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<td>A</td>
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<td>6.5</td>
<td><img src="image5" alt="Structure 5" /></td>
<td>1-((1R,3a,5S)-3-((3-(6-(1H-imidazol-2-yl)pyridin-3-yl)-7-amino-6-ethylpyrazolo[1,5-a]pyrimdin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone</td>
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<td>1-((1R,3a,5S)-3-(3-(6-(1H-imidazol-2-yl)pyridin-3-yl)7-amino-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethane</td>
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<td>(R)-1-((1R,3S,5S)-3-(3-(6-(1H-imidazol-2-yl)pyridin-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxypropan-1-one</td>
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<td>A</td>
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<td>487.2 / 487.0</td>
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<td>1-((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-(5-methyl-1H-imidazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-y1)-2-hydroxyethanone</td>
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<td>1-((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(5-fluoro-6-(1H-imidazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-y1)-2-hydroxyethanone</td>
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<td>6.32</td>
<td>1-((1R,3S,5S)-3-(7-amino-6-cyclopropyl-3-(6-(4,5-dimethyl-1H-imidazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone</td>
<td>513.2/513.3</td>
<td>A</td>
<td>B</td>
<td></td>
<td></td>
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<tr>
<td>6.33</td>
<td>1-((1R,3S,5S)-3-(3-(6-(1H-imidazol-2-yl)5-methylpyridin-3-yl)6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone</td>
<td>501.23/501.1</td>
<td>C</td>
<td>ND</td>
<td></td>
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<tr>
<td>6.34</td>
<td>1-(3-(6-(1H-imidazol-2-yl)5-methylpyridin-3-yl)-5-(1R,3S,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-8-yI)ethanone</td>
<td>538.23/538.3</td>
<td>ND</td>
<td>ND</td>
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<td>522.18/522.0</td>
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<td>6.36</td>
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<td>(1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(3-fluoro-4-(1H-imidazol-2-yl)phenyl)pyrazolo[1,5-d]pyrimidin-5-y) octan-8-yl)4H-1,2,4-triazol-3-yl)methanone</td>
<td>539.24/539.1</td>
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<td></td>
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<tr>
<td>6.37</td>
<td><img src="image2.png" alt="Image" /></td>
<td>1-(1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(3-fluoro-4-(1H-imidazol-2-yl)phenyl)pyrazolo[1,5-d]pyrimidin-5-y) octan-8-yl)2-hydroxyethanone</td>
<td>502.23/502.1</td>
<td>A</td>
<td>A</td>
<td></td>
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<tr>
<td>6.38</td>
<td><img src="image3.png" alt="Image" /></td>
<td>1-(1R,3s,5S)-3-(6-acetyl-7-amino-3-(3-fluoro-4-(5-methyl-1H-imidazol-2-yl)phenyl)pyrazolo[1,5-d]pyrimidin-5-y) octan-8-yl)2-hydroxyethanone</td>
<td>518.22/518.1</td>
<td>A</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>6.39</td>
<td><img src="image4.png" alt="Image" /></td>
<td>1-(5-(1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(3-fluoro-4-(5-methyl-1H-imidazol-2-yl)phenyl)pyrazolo[1,5-d]pyrimidin-6-y)ethanone</td>
<td>555.23/555.0</td>
<td>A</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>6.40</td>
<td><img src="image5.png" alt="Image" /></td>
<td>1-(1R,3s,5S)-3-(6-acetyl-7-amino-3-(3-fluoro-4-(1H-imidazol-2-yl)phenyl)pyrazolo[1,5-d]pyrimidin-5-y) octan-8-yl)2-hydroxyethanone</td>
<td>504.21/504.0</td>
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<td>A</td>
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<tr>
<td>6.41</td>
<td><img src="image6.png" alt="Image" /></td>
<td>1-(5-(1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(3-fluoro-4-(1H-imidazol-2-yl)phenyl)pyrazolo[1,5-d]pyrimidin-6-y)ethanone</td>
<td>541.21/541.0</td>
<td>A</td>
<td>A</td>
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</tr>
</tbody>
</table>
Example 7-1

Preparation of 1-{5-[[1R,3s,5S]-3-[(3-(1H-imidazol-2-yl)phenyl)6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-5-yl]-8-azabicyclo[3.2.1]octan-8-yl]-2-hydroxyethanone

| 6.42 | 1-((1R,3s,5S)-3-(3-(4-(1H-imidazol-2-yl)phenyl)6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone | 486.22/486.1 | A | A |
| 6.43 | 1-((3-(4-(1H-imidazol-2-yl)phenyl)-5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-6-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone | 523.22/523.1 | A | A |
| 6.44 | 1-((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-(4-fluoro-1H-imidazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-3-hydroxy-2,2-dimethylpropan-1-one | 503.2/503.3 | ND | ND |
| 6.45 | 1-((1R,3s,5S)-3-(3-(6-(1H-imidazol-2-yl)pyridin-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-3-hydroxy-2,2-dimethylpropan-1-one | 528.26/529.2 | B | ND |
| 6.46 | 1-((1R,3s,5S)-3-(3-(6-(1H-imidazol-2-yl)pyridin-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-3-hydroxy-2-(hydroxymethyl)-2-methylpropan-1-one | 544.25/545.0 | B | B |

328
Step 1: Preparation of 2-(5-bromopyridin-2-yl)propan-2-ol

The title compound was prepared analogously to the procedure reported in (substituting acetone for dimethylformamide): Simone, F.; Kodanko J.; Morys, A.; Hayashi, T.; Moenne-Loccoz, P.; Lippard, S. J. Am. Chem. Soc. 2009, 131, 14508-14520. All achiral compounds and racemic precursors reported in Table 7-1 were made by substituting the appropriate ketone or aldehyde during the alkylation.

Step 2: Preparation of tert-butyl 3-[7-(bis[2-(trimethylsilyl)ethoxy]methyl)amino]-3-[6-(1-hydroxy-1-methylethyl)pyridin-3-yl]pyrazolo[1,5-a]pyrimidin-5-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate

Potassium acetate (1.383 g, 14.09 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (168 mg, 0.230 mmol), bis(pinacolato)diboron (1.40 g, 5.49 mmol), and 2-(5-bromopyridin-2-yl)propan-2-ol (1.099 g, 5.086 mmol) were combined in a microwave tube equipped with a stir bar.
The headspace was exchanged for dry nitrogen (x3), and 1,4-dioxane (10 mL) was added. The vessel was lowered into a 90 °C oil bath, and stirred rapidly for 2.5 h. The mixture was cooled to room temperature and tert-butyl 3-[7-(bis[2-(trimethylsilyl)ethoxy]methyl)amino]-6-bromo-3-[6-(1-hydroxy-1-methylethyl)pyridin-3-yl]pyrazolo[1,5-a]pyrimidin-5-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate (1.774 g, 2.431 mmol) in 1,4-dioxane (6 mL, 80 mmol), and aqueous sodium carbonate (2.0 M, 3.3 mL, 6.6 mmol) were added. The organic layer became homogeneous, and the aq. becomes milky. The reaction was again lowered into the 90 °C bath, and stirred vigorously for 16 h, at which point HPLC shows the reaction to be complete. The mixture was cooled and partitioned between ethyl acetate (200 mL) and water (50 mL). The organics were washed with water (50 mL), brine (50 mL), dried with MgSO₄, filtered through celite, and concentrated. The crude material was purified by flash chromatography (20-100% ethyl acetate in hexanes). The title compound (1.01 g) was isolated as a brown oil.

Step 3: Preparation of tert-butyl 3-[7-(bis[2-(trimethylsilyl)ethoxy]methyl)amino]-6-bromo-3-[6-(1-hydroxy-1-methylethyl)pyridin-3-yl]pyrazolo[1,5-a]pyrimidin-5-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate

fert-butyl 3-[7-(bis[2-(trimethylsilyl)ethoxy]methyl)amino]-3-[6-(1-hydroxy-1-methylethyl)pyridin-3-yl]pyrazolo[1,5-a]pyrimidin-5-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate (0.500 g, 0.676 mmol) was dissolved in acetic acid (3.5 mL, 62 mmol) and W-bromosuccinimide (144.2 mg, 0.8105 mmol) was added in a single portion, and the reaction was monitored by HPLC. The reaction was complete in less than 10 min and the mixture was diluted with ethyl acetate and poured into a 1:1 mixture of saturated aq. sodium bicarbonate and aq. sodium thiosulfate (20%). The layers

were separated and the organics washed several times with sodium bicarbonate solution then brine. The organics were dried with magnesium sulfate, filtered and concentrated to provide 550 mg of the desired material.

tert-butyl 3-{7-(bis[2-(trimethylsilyl)ethoxy]methyl)amino}-6-bromo-3-[6-(1-hydroxy-1-methylethyl)pyridin-3-yl]pyrazolo[1,5-a]pyrimidin-5-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate (0.550 g, 0.672 mmol), tributyl[1-(ethyloxy)ethenyl]stannane (681 μL, 2.02 mmol) and tetrakis(triphenylphosphine)palladium(0) (78 mg, 0.067 mmol) were placed in a 3-neck 25-mL round bottom flask equipped with a reflux condenser and rubber septa. Then, the flask was evacuated and back-filled with nitrogen three times before adding 1,4-dioxane (20 mL). The resulting solution was sparged with nitrogen for 15 minutes and then lowered into an oil bath that was heated at 100 °C and the resulting solution stirred overnight at the same temperature. Another portion of tetrakis(triphenylphosphine)palladium(0) (78 mg, 0.067 mmol) was added after 14 h, and the reaction allowed to progress for another 24 h, at which point, analysis showed consumption of the starting material and formation of the desired product. The reaction was cooled to ambient temperature and concentrated in vacuo. The crude dark oil was purified by flash chromatography (40 g silica gel, 0 to 8% methanol in chloroform) to afford the title compound (476 mg).
Step 5: Preparation of 1-{7-amino-5-[3-(exo)-8-azabicyclo[3.2.1]oct-3-yl]-3-[6-(1-hydroxy-1-methylethyl)pyridin-3-yl][pyrazolo[1,5-a]pyrimidin-6-yl]ethanone tris(trifluoroacetate)

To a vial containing tert-butyl (3-exo)-3-[7-(bis[2-(trimethylsilyl)ethoxy]methyl)amino]-6-(1-ethoxyvinyl)-3-[6-(1-hydroxy-1-methylethyl)pyridin-3-yl][pyrazolo[1,5-a]pyrimidin-5-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate (0.476 g, 0.588 mmol) was added a preformed solution of trifluoroacetic acid (8 mL) and water (4 mL). The mixture was stirred to dissolve the solids. After 30 min, HPLC samples show the complete consumption of starting material. The reaction was concentrated, dissolved in methanol and concentrated, and twice dissolved with toluene and concentrated to provide a yellow oil. The oil was treated with diethyl ether and sonicated to provide the title compound (271 mg) as a yellow solid which was collected by filtration.

Step 6: Preparation of 1-{5-[(1R,3S,5S)-8-(1H-1,2,4-triazole-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl]-7-amino-3-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)[pyrazolo[1,5-a]pyrimidin-6-yl]ethanone
To a round bottom flask under nitrogen was added 1-(7-amino-5-(8-azabicyclo[3.2.1]oct-3-yl)-3-[6-(1-hydroxy-1-methylethyl)pyridin-3-yl]pyrazolo[1,5-a]pyrimidin-6-yl)ethanone tris(trifluoroacetate) (0.270 g, 0.354 mmol), N,N-dimethylformamide (6 mL), and N,N-diisopropylethylamine (0.370 mL, 2.12 mmol). In a separate oven dried flask under nitrogen was added N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.102 g, 0.531 mmol), 1-hydroxybenzotriazole hydrate (0.0868 g, 0.566 mmol), N,N-dimethylformamide (6 mL) and 1H-1,2,4-triazole-5-carboxylic acid (0.0600 g, 0.531 mmol). This flask went from cloudy to homogeneous over the course of 5-10 min and was stirred an additional 20 min before adding to the other flask via syringe. The mixture was stirred for 15 min before checking by HPLC and shown to be complete at this time. LCMS had a mass consistent with the desired product. The mixture was partitioned between sat’d NaHCO₃ and 10% IPA in dichloromethane. The layers were separated and the aqueous extracted with dichloromethane. The combined organics were washed twice with water, and brine, dried with MgSO₄, filtered and evaporated. The residue was purified by flash chromatography (0-15% (10% NH₃OH in MeOH) in CHCl₃) to provide a yellow solid. Methanol and 2 mL of 1M HCl were added to the solids. The solution was concentrated, and this process repeated 4 times to give a yellow solid which was not of the desired purity. The solids were dissolved in 0.1 N HCl (2ml) and aq. NaHCO₃ was added (6ml). The resulting white solid was filtered and washed with water, and the residue was again submitted to aq. methanolic HCl as described above to provide the title compound (103mg) as a colorless solid.

The following compounds listed in Table 7-1 were prepared following procedures similar to the preparation of 1-(5-((1R,3s,5S)-8-(1H-1,2,4-triazole-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone.
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<th>Compound Name</th>
<th>M+H (calculated)</th>
<th>pAKT S473 IC50</th>
<th>pE-BPI Thr271 IC50</th>
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<td>1-(S)-(1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl-7-amino-3-(6-(hydroxymethyl)pyridin-3-yl)pyrazolo[1,5-alpyrimidin-6-yl]ethanone</td>
<td>488.2 / 488.3</td>
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<td>530.3 / 530.4</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>7.3</td>
<td><img src="image3" alt="Structure" /></td>
<td>1-(S)-(1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl-7-amino-3-(6-(1-hydroxypropyl)pyridin-3-yl)pyrazolo[1,5-alpyrimidin-6-yl]ethanone</td>
<td>516.2 / 516.5</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>7.4</td>
<td><img src="image4" alt="Structure" /></td>
<td>1-(S)-(1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl-7-amino-3-(6-(1-hydroxyethyl)pyridin-3-yl)pyrazolo[1,5-alpyrimidin-6-yl]ethanone</td>
<td>502.2 / 502.4</td>
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<td>A</td>
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<td><img src="image5" alt="Structure" /></td>
<td>1-(S)-(1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl-7-amino-3-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-alpyrimidin-6-yl]ethanone</td>
<td>516.25 / 516.2</td>
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7.6
1-(5-(((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(1-hydroxy-3-methylbutyl)pyridin-3-yl)pyrazolo[1,5-α]pyrimidin-6-ylylethanone

544.3 / 544.4 C B

7.7
1-((7-amino-5-((1R,3s,5S)-8-(1-hydroxycyclopropane carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-α]pyrimidin-6-ylylethanone

505.3 / 505.4 ND ND

7.8
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-α]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone

479.2 / 479.5 B B

7.9
1-(7-amino-3-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-5-((1R,3s,5S)-8-(5-methyl-4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-α]pyrimidin-6-ylylethanone

530.3 / 530.4 B B

7.10
1-(5-((1R,3s,5S)-8-(1H-1,2,3-triazole-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-α]pyrimidin-6-ylylethanone

516.25 / 516.5 B B

7.11
1-(5-((1R,3s,5S)-8-(1H-pyrazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-α]pyrimidin-6-ylylethanone

515.2 / 515.3 A B
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<td>515.3 / 515.4</td>
<td>B, B</td>
</tr>
<tr>
<td>7.13</td>
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<td><img src="image" alt="Chemical Structure" /></td>
<td>1-(7-amino-5-((1R,3a,5S)-8-(5-amino-4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-(2-hydroxypropan-2-y)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-y)ethanone</td>
<td>531.3 / 531.3</td>
<td>B, B</td>
</tr>
<tr>
<td>7.14</td>
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<td><img src="image" alt="Chemical Structure" /></td>
<td>1-(6-((1R,3a,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-((R)-1-hydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-y)ethanone</td>
<td>502.2 / 502.4</td>
<td>B, B</td>
</tr>
<tr>
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<td>1-(7-amino-5-((1R,3a,5S)-8-(5-amino-1H-pyrazole-4-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-(2-hydroxypropan-2-y)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-y)ethanone</td>
<td>530.3 / 530.5</td>
<td>B, B</td>
</tr>
<tr>
<td>7.16</td>
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<td>1-(6-((1R,3a,5S)-8-(1H-pyrazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2-hydroxypropan-2-y)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-y)ethanone</td>
<td>514.26 / 514.5</td>
<td>A, B</td>
</tr>
</tbody>
</table>
Example 7-2

5 Preparation of (1R,3s,5S)-3-(7-amino-3-(6-(2-hydroxypropan-2-yl)pyridin-2-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)methanone

10 Step 1: Preparation of 2-(5-(7-amino-3-(6-(2-hydroxypropan-2-yl)pyridin-2-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-6-methylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)pyridin-3-yl)propan-2-ol
tert-butyl 3-[7-(bis[2-(trimethylsilyl)ethoxy]methyl)amino]-3-[6-(1-hydroxy-1-methylethyl)pyridin-3-yl]pyrazolo[1,5-a]pyrimidin-5-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate (1.01 g, 1.37 mmol) was dissolved in acetic acid (7.1 mL, 120 mmol) and W-lodosuccinimide (368.3 mg, 1.637 mmol) was added in a single portion, and the reaction was monitored by HPLC. The reaction was complete in less than 10 minutes and the mixture was diluted with ethyl acetate and poured into a 1:1 mixture of sodium bicarbonate (sat'd) and sodium thiosulfate (20%). The layers were separated and the organics washed several times with sodium bicarbonate solution, then brine. The organics were dried with magnesium sulfate, filtered and concentrated to provide the desired material (860 mg) which was subsequently treated with aqueous TFA to afford the desired product as TFA salt following procedure described previously.

Step 2: preparation of 2-{5-[7-amino-5-(8-azabicyclo[3.2.1]oct-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-3-yl]pyridin-2-yl}propan-2-ol tris(trifluoroacetate) (salt) (0.720 g, 0.851 mmol), sodium
methanesulfinate (306 mg, 2.55 mmol), and Copper(I) iodide (486 mg, 2.55 mmol) were dissolved / suspended in dry dimethyl sulfoxide (18 mL, 250 mmol) under a nitrogen atmosphere. The reaction was placed in an oil bath at 90 °C. After mixing 15 min, HPLC showed the starting material to have been consumed and a mixture of the desired material:des-iodo material was observed. The reaction mixture was poured into a 7:3 mixture of sat'd NH₄Cl:20%NH₄OH (200 ml) and extracted 3X75 ml with 10% IPA in DCM. The combined organics were washed with brine, dried, filtered and evaporated to provide a yellow oil, which was purified by silica gel chromatography, eluted with 0-15% (10% NH₄OH in MeOH) in chloroform to provide the desired material as a yellow solid (319 mg).

**Step 3: Synthesis of** \((1R,3s,5S)-3-(7\text{-amino-3-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-}6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-1,2,4-triazol-5-yl)methanone

\[
\text{HN} \quad \text{OH}
\]

\[
\text{O} \quad \text{S} \quad \text{NH}_2
\]

The title compound was prepared following standard amide coupling procedure described before.

The following compounds listed in Table 7-2 were prepared following procedures similar to the preparation of 1-((1R,3s,5S)-8-(1H-1,2,4-triazole-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone.
<table>
<thead>
<tr>
<th>Compound ID</th>
<th>Structure</th>
<th>Compound Name</th>
<th>M+H (calculated)</th>
<th>pAKT S473 IC50</th>
<th>p4E-BP1 Thr37/46 IC50</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.25</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>(((1R,3s,5s)-3-(7-amino-3-(6-(1-hydroxybutyl)pyridin-3-yl)-8-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone</td>
<td>566.2 / 566.5</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>7.26</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>(((1R,3s,5s)-3-(7-amino-3-(6-(1-hydroxypropyl)pyridin-3-yl)-8-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone</td>
<td>552.2 / 552.2</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>7.27</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>(((1R,3s,5s)-3-(7-amino-3-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-8-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-1,2,4-triazol-5-yl)methanone</td>
<td>552.23 / 552.2</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>7.28</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>1-(((1R,3s,5s)-3-(7-amino-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)-8-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone</td>
<td>527.2 / 527.3</td>
<td>B</td>
<td>ND</td>
</tr>
<tr>
<td>7.29</td>
<td><img src="image5.png" alt="Structure" /></td>
<td>(((1R,3s,5s)-3-(7-amino-3-(6-(1-hydroxypropan-2-yl)pyridin-3-yl)-8-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(3-methyl-1H-1,2,4-triazol-5-yl)methanone</td>
<td>576.3 / 578.4</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>7.30</td>
<td><img src="image6.png" alt="Structure" /></td>
<td>(((1R,3s,5s)-3-(7-amino-3-(6-(1-hydroxypropan-2-yl)pyridin-3-yl)-8-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-1,2,3-triazol-5-yl)methanone</td>
<td>563.2 / 564.4</td>
<td>B</td>
<td>B</td>
</tr>
</tbody>
</table>
Example 7-3

Preparation of 5-bromo-2-[(2-methoxyethoxy)methyl]pyridine

The title compound was prepared following the method for the preparation of 3-bromo-6-[(R)-2-ethoxy-propoxymethyl]-2-propyl-pyridine reported by Herold, P.; Mah, R.; Tschinke, V.; Jelakovic, S.; Stutz, S.; and Marti, C. International Patent Application WO 2009/056617 A2, May 7, 2009. The following two compounds (Table 7-3) were prepared following similar procedures described before.

Table 7-3

<table>
<thead>
<tr>
<th>Compound ID</th>
<th>Structure</th>
<th>Compound Name</th>
<th>M+H (calculated)/M+H (observed)</th>
<th>pAKT S473 IC50</th>
<th>p4E-BP1 Thr37/46 IC50</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.31</td>
<td><img src="image" alt="Image" /></td>
<td>1-((1R,3a,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-((2-methoxyethoxy)methyl) pyridin-3-yl)pyrazolo[1,5-alpyrimidin-6-yl]ethanone</td>
<td>546.3 / 546.3</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>7.32</td>
<td><img src="image" alt="Image" /></td>
<td>((1R,3a,5S)-3-(7-amino-3-(6-((2-methoxyethoxy)methyl) pyridin-3-yl)-8-(methyl)sulfonyl)pyrazolo[1,5-alpyrimidin-5-yl]-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone</td>
<td>582.23 / 582.4</td>
<td>D</td>
<td>C</td>
</tr>
</tbody>
</table>

Example 7-4

Preparation of (1S)-1-(5-bromopyridin-2-yl)ethanol
The (R)-(+)-2-Methyl-CBS-oxazaborolidine (2.08 g, 7.5 mmol) was dissolved in THF (10 mL), cooled to 0 °C and borane-dimethyl sulfide complex (2 M solution in THF, 7.50 mL, 15.0 mmol, 2.0 equiv.) was added dropwise. The resulting solution was stirred for 1 hour, then cooled to -40 °C and a solution of 1-(5-bromopyridin-2-yl)ethanone in THF (8.0 mL) was added dropwise over 5 min. A white precipitate formed toward the end of the addition. The slurry was stirred for 1 hour, warmed to -10 °C, and stirred for another 60 min at this temperature. Analysis of the solution (HPLC) showed >95% conversion to the desired product. The reaction was poured into ethyl acetate (100 mL), washed with saturated ammonium chloride, water, and brine (50 ml each), dried over magnesium sulfate, filtered, and concentrated by rotary evaporation. The residual oil was purified by flash chromatography over silica gel (90 g), eluting with 40% ethyl acetate in hexanes to give the title compound (1.34 g) as a colorless oil.

The following two compounds (Table 7-4) were prepared following similar procedures described before.
**Preparation of (5-bromopyridin-2-yl)methanol**

The commercially available 5-bromopyridine-2-carbaldehyde (2.0g, 10.8 mmol) was dissolved in methanol (60 mL) and solid sodium borohydride (407 mg, 10.8 mmol) was added at 20 °C. The reaction was stirred 30 minutes then the solvent was removed and 25 mL of saturated ammonium chloride solution was added and the reaction was extracted with 200 mL EtOAc which was washed with water and brine, 30 mL each. The organic phase was dried over magnesium sulfate

---

**Table 7-4**

<table>
<thead>
<tr>
<th>Compound ID</th>
<th>Structure</th>
<th>Compound Name</th>
<th>M+H (calculated)</th>
<th>M+H (observed)</th>
<th>pAKT S473</th>
<th>pS9 BP1 Thr37/46</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.33</td>
<td><img src="image1" alt="Structure" /></td>
<td>1-(5-((1R,3s,5S)-5-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(1R)-1-hydroxyethyl(pyridin-3-yl)pyrazolo[1,5-apyrimidin-6-yl)ethanone</td>
<td>502.2 / 502.4</td>
<td>B</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>7.34</td>
<td><img src="image2" alt="Structure" /></td>
<td>1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(1S)-1-hydroxyethyl(pyridin-3-yl)pyrazolo[1,5-apyrimidin-6-yl)ethanone</td>
<td>502.3 / 502.4</td>
<td>A</td>
<td>A</td>
<td></td>
</tr>
</tbody>
</table>
and filtered through a 2 cm silica gel pad. The clear filtrate was concentrated by rotary evaporation to give a white solid, 1.99g which was used as is.

The following compound (Table 7-5) was prepared following similar procedures described before.

Table 7-5

<table>
<thead>
<tr>
<th>Compound ID</th>
<th>Structures</th>
<th>Compound Name</th>
<th>IM+H (calculated)</th>
<th>IM+H (observed)</th>
<th>pAKT S473 IC50</th>
<th>p*E-BP1 Thr37/46 IC50</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.35</td>
<td><img src="image" alt="Structure" /></td>
<td>((1R,3s,5S)-3-(7-amino-3-(6-(hydroxymethyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone</td>
<td>524.2</td>
<td>524.3</td>
<td>B</td>
<td>B</td>
</tr>
</tbody>
</table>

Example 7-6

Preparation of 1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octane-8-carboxylate-10-(7-tert-butyl 3-(7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-3-(thiazol-5-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

Step 1: Preparation of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-3-(thiazol-5-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

345
A mixture of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-iodopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (2.95 g, 4.04 mmol, preparation described previously), 5-(tributylstannyl)thiazole (3.02 g, 8.08 mmol), Pd(PPh₃)₄ (934 mg, 0.81 mmol) in dioxane (40 mL) was stirred at 100 °C under Argon for 2 h. The reaction mixture was concentrated and purified by a SiO₂ column (0-40% EtOAc/Hexanes, Rf = 0.5 in 50% EtOAc) to afford the titled compound as a brownish oil (514 mg).

Step 2: Preparation of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(2-(1-hydroxyethyl)thiazol-5-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

To a solution of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(thiazol-5-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (290 mg, 0.422 mmol) in THF (3 mL) was added n-BuLi (1.1 eq) dropwise at -78 °C. The mixture was warmed to -50 °C and kept for 30 min before recooling to -78 °C. A solution of acetaldehyde (71 μL, 1.27 mmol) in THF (2 mL) was added dropwise. The reaction mixture was slowly warmed to rt and stirred for 30 min. The reaction was quenched with H₂O and extracted with EtOAc, washed with brine, dried over Na₂SO₄ and concentrated. The crude product
was purified by a SiO₂ column (0-50% EtOAc/Hexanes, Rₜ = 0.3 in 50% EtOAc) to afford the titled compound as a yellow solid (210 mg).

**Step 3: Preparation of 1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(2-(1-hydroxyethyl)thiazol-5-yl)pyrazolo[1,5-ajpyrimidin-6-yl)ethanone**

1. NBS, CH₃CN, rt
2. CH₃=C(OEt)SnBu₃ Pd(PPPh₃)₄ (10%)
   dioxane, 100 °C
3. TFA/H₂O, rt
4. EDCI, HOBT, DIEA
   DMF, rt

This compound was prepared from (1R,3s,5S)-tert-butyl 3-(7-((bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(2-(1-hydroxyethyl)thiazol-5-yl)pyrazolo[1,5-ajpyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate, following essentially the same procedures given in previous examples.

**Table 7-6**

| 7.36 | 1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(2-(1-hydroxyethyl)thiazol-5-yl)pyrazolo[1,5-ajpyrimidin-6-yl)ethanone | 508.2/508.1 | C | C |

347
Preparation of \((1\text{R},3\text{s},5\text{S})\)-3-(7-amino-3-(2-(1-hydroxyethyl)thiazol-5-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone

Step 1: Preparation of \((1\text{R},3\text{s},5\text{S})\)-tert-butyl 3-(7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-3-(2-(1-hydroxyethyl)thiazol-5-yl)-6-iodopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

To a solution of \((1\text{R},3\text{s},5\text{S})\)-tert-butyl 3-(7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-3-(2-(1-hydroxyethyl)thiazol-5-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (131 mg, 0.179 mmol) in HOAc (3 mL) was added NIS (48.4 mg, 0.215 mmol) and stirred at rt for 30 min. HOAc was removed under reduced pressure and the residue was purified by a SiO₂ column (0-40% EtOAc/Hexanes, \(R_f = 0.7 \) in 50% EtOAc) to afford the titled compound as a pale yellow oil (116 mg).

Step 2: Preparation of \((1\text{R},3\text{s},5\text{S})\)-tert-butyl 3-(7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-3-(2-(1-hydroxyethyl)thiazol-5-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate
A mixture of (1R,3S,5S)-tert-butyl 3-(7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-3-(2-(1-hydroxyethyl)thiazol-5-yl)-6-iodopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (116 mg, 0.135 mmol), MeSO₂Na (41.5 mg, 0.406 mmol), and Cul (154 mg, 0.810 mmol) in DMSO (1.3 mL) was heated at 90 °C for 2 h. The reaction mixture was diluted with 15 mL of EtOAc and filtered through a short pad of celite and washed with extra EtOAc. The combined filtrate was washed with NH₄Cl and then brine, dried over Na₂SO₄, and concentrated. The crude product was purified by a SiO₂ column (0-40% EtOAc/Hexanes, Rf = 0.4 in 50% EtOAc) to afford the titled product as a colorless oil (90.0 mg).

Step 3: Preparation of ((1R,3S,5S)-3-(7-amino-3-(2-(1-hydroxyethyl)thiazol-5-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-3-yl)quinolin-7-yl)methanol TFA salt

This compound was prepared from (3-(7-amino-5-((1R,3S,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-3-yl)quinolin-7-yl)methanol TFA salt following essentially the same procedure given previously.
Table 7-7

| 7.37 | \((1R,3s,5S)-3-(7-amino-3-(2-(1-hydroxyethyl)thiazol-5-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)ethanone | 544.2 | ND | ND |

Example 7-8

Preparation of \((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-8-yl)7-amino-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone

Step 1: Preparation of 1-(5-bromopyridin-2-yl)cyclobutanol

To a solution of 2,5-dibromopyridine (4.74 g, 20.0 mmol) in toluene (200 mL) was added n-BuLi (1.2 eq) dropwise at -50 °C. The mixture was stirred at that temperature for 40 min, then cooled to -78 °C before cyclobutanone (1.82 g, 26.0 mmol) was added dropwise. The reaction mixture was stirred at -78 °C for 1 h, then warmed to 0 °C and quenched with 40 mL of NH₄Cl (sat.). The organic layer was separated and concentrated. The crude product was purified by a silica gel column (0-40% EtOAc/Hexanes, Rₜ = 0.7 in 50% EtOAc) to afford the titled compound as a red oil (3.11 g).
Step 2: Preparation of 1-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-((1-hydroxycyclobutyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone

This compound was prepared from 1-(5-bromopyridin-2-yl)cyclobutanol, following essentially the same procedures given previously. Compounds in Table 7-8 were made in a similar way.

<table>
<thead>
<tr>
<th>Compound ID</th>
<th>Structures</th>
<th>Compound Name</th>
<th>MHH (calculated)</th>
<th>MHH (observed)</th>
<th>p&lt;sub&gt;AKT&lt;/sub&gt; S473 IC&lt;sub&gt;50&lt;/sub&gt;</th>
<th>p&lt;sub&gt;MEK&lt;/sub&gt; ERK1/2 IC&lt;sub&gt;50&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.38</td>
<td><img src="image" alt="Structure 1" /></td>
<td>1-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-((1-hydroxycyclobutyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone</td>
<td>528.2/528.3</td>
<td>A</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>7.39</td>
<td><img src="image" alt="Structure 2" /></td>
<td>1-((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-((6-((1-hydroxycyclobutyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone</td>
<td>514.3/514.2</td>
<td>A</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>7.45</td>
<td><img src="image1.png" alt="Chemical Structure" /></td>
<td>1-(6-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azaazabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(3-hydroxyxetan-3-y1)pyridin-3-y1)pyrazolo[1,5-alpyrimidin-6-y1]ethanone</td>
<td>530.2/530.2</td>
<td>B</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>7.46</td>
<td><img src="image2.png" alt="Chemical Structure" /></td>
<td>((1R,3s,5S)-3-(7-amino-3-(6-(1-hydroxyclopylyl)pyridin-3-y1)-6-(methylsulfonyl)pyrazolo[1,5-alpyrimidin-5-y1]-8-azaazabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-y1)methanone</td>
<td>578.2/578.2</td>
<td>A</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>7.47</td>
<td><img src="image3.png" alt="Chemical Structure" /></td>
<td>1-(6-((1R,3s,5S)-3-(7-amino-3-(6-(1-hydroxyclopylyl)pyridin-3-y1)-6-(methylsulfonyl)pyrazolo[1,5-alpyrimidin-5-y1]-8-azaazabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone</td>
<td>541.2/541.2</td>
<td>B</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>7.48</td>
<td><img src="image4.png" alt="Chemical Structure" /></td>
<td>((1R,3s,5S)-3-(7-amino-3-(6-(3-hydroxyxetan-3-y1)pyridin-3-y1)-6-(methylsulfonyl)pyrazolo[1,5-alpyrimidin-5-y1]-8-azaazabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-y1)methanone</td>
<td>566.2/566.0</td>
<td>C</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>7.49</td>
<td><img src="image5.png" alt="Chemical Structure" /></td>
<td>1-(6-((1R,3s,5S)-3-(7-amino-3-(6-(3-hydroxyxetan-3-y1)pyridin-3-y1)-6-(methylsulfonyl)pyrazolo[1,5-alpyrimidin-5-y1]-8-azaazabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone</td>
<td>529.2/529.2</td>
<td>C</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>7.50</td>
<td><img src="image6.png" alt="Chemical Structure" /></td>
<td>1-(6-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azaazabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(1-</td>
<td>542.3/542.2</td>
<td>A</td>
<td>A</td>
<td></td>
</tr>
</tbody>
</table>
Example 7-9

Preparation of 1-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octane-8-carboxylate

Step 1: Preparation of (1R,3s,5S)-3-(7-amino-3-(6-(1,2-dihydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

A mixture of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-vinylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (1.63 g, 2.28 mmol, preparation described previously), tributyl(vinyl)stannane (1.33 mL, 4.56 mmol), Pd(PPh₃)₄ (263 mg, 0.228 mmol) in dioxane (20 mL) was stirred at 100 °C under Argon for 16 h. The
reaction mixture was concentrated and purified by a SiO₂ column (0-40% EtOAc/Hexanes, R_f = 0.75 in 50% EtOAc) to afford the titled compound as pale yellow solid (1.48 g).

Step 2: Preparation of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-(1,2-dihydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

To a slurry of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-vinylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (1.48 g, 2.09 mmol) in Acetone/H₂O/MeCN (12/4/4 mL) was added NMO (50 wt. % in H₂O, 0.867 mL, 4.18 mmol), followed by OsO₄ (2.5 wt. % in t-BuOH, 1.31 mL, 0.105 mmol) at rt. The resulting reaction mixture was stirred at rt overnight. The organic solvents were evaporated and the aqueous residue was extracted with EtOAc (x 3). The combined organic layers were dried over Na₂SO₄, concentrated, and purified by a SiO₂ column (0-100% EtOAc/Hexanes, R_f = 0.1 in 50% EtOAc) to afford the titled compound as a brownish oil (176 mg).

Step 3: Preparation of 1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(1,2-dihydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone
This compound was prepared from (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-(1,2-dihydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate, following essentially the same procedures given in previous examples.

**Table 7-9**

<table>
<thead>
<tr>
<th>Example 7-10</th>
<th>Preparation of 8-(tert-butyldimethylsilyloxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6,7,8-tetrahydroquinoline</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.52</td>
<td>1-(5-(1R,3s,5S)-8-(4H-1,2,4-triazolo-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(1,2-dihydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone</td>
</tr>
</tbody>
</table>

Step 1: Synthesis of 8-(tert-butyldimethylsilyloxy)-5,6,7,8-tetrahydroquinoline
To a cooled (0 °C) solution of tetrahydro-quinolin-8-ol (1.0 g, 6.7 mmol) and imidazole (1.0 g, 14.74 mmol) in anhydrous DMF was added TBS-Cl (1.1 g, 7.4 mmol). The reaction mixture was stirred at room temperature for 12h. Added ethylacetate (20 mL). The organic layer was washed with H2O (3 x 10 mL). Dried over sodium sulfate and filtered. The organic layer was concentrated in vacuo and purification of the crude material via Isco (10-20% ethyl acetate/hexanes) gave rise to the desired tetrahydro-quinolin-8-OTBS (1.76 g) in quantitative yield.

Step 2: Synthesis of 8-(tert-butyldimethylsilyloxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6,7,8-tetrahydroquinoline

To a solution of 8-(tert-butyldimethylsilyloxy)-5,6,7,8-tetrahydroquinoline (1.0g, 3.8 mmol), bispinacolatodiboron (1.4g, 5.32 mmol), 4,4'-di-tert-butyl-2-2' dipryridyl (126 mg, 0.19 mmol) in MTBE (10 mL) was added 1.5 cyclooctadiene(methoxy) Iridium(i)dimer (51 mg, 0.19 mmol). The reaction mixture was degassed before heating at 90 °C in a sealed tube for 8h. The mixture was cooled to room temperature and was concentrated in vacuo. Purification of the crude material via Isco (20-30-50% ethyl acetate/hexanes) gave rise to the desired boronic ester (1.08g).

Example 7-11

Synthesis of tetrahydro-quinolin-8-D-8-ol

357
To a cooled (0 °C) solution of 6,7-dihydroquinolin-8(5H)-one (1.0 g, 6.8 mmol) in anhydrous THF:MeOH (10 mL, 1:4) was added NaBD₄ (342 mg, 8.16 mmol). The reaction mixture was stirred at 0 °C for 20 minutes and stirring was continued at room temperature for 2h. The reaction mixture was quenched with saturated ammonium chloride (2 mL). The mixture was extracted with ethylacetate (3 x 10 mL). Dried over sodium sulfate and filtered. The organic layer was concentrated in vacuo and purification of the crude material via Isco (50% ethyl acetate/hexanes) gave rise to the desired alcohol (1.02 g).

Example 7-12

**Synthesis of 8-(tert-butyldimethylsilyloxy)-8-methyl-5,6,7,8-tetrahydroquinoline**

**Step 1: Synthesis of 8-methyl-5,6,7,8-tetrahydroquinolin-8-ol**

To a cooled (0 °C) solution of the ketone (1.4 g, 9.52 mmol) in anhydrous THF (50 mL) was added 1.4M of MeMgBr (10.2 mL, 14.3 mmol). The reaction mixture was stirred at 0 °C for 10 minutes and stirring was continued at room temperature for 2h. The reaction mixture was cooled to 0 °C and CH₂Cl₂ (5 mL) was added. The reaction was quenched with H₂O (2.5 mL) and extracted with ethylacetate (3 x 10 mL). Dried over sodium sulfate and filtered. The organic layer was concentrated in vacuo and purification of the crude material via Isco (30% ethyl acetate/hexanes) gave rise to the desired alcohol (477 mg).
Step 2: Synthesis of 8-(tert-butyldimethylsilyloxy)-8-methyl-5,6,7,8-
tetrahydroquinoline

To a cooled (0 °C) solution of the alcohol (477 g, 2.92 mmol) and 2,6-lutidine
(0.75 mL, 6.4 mmol) in anhydrous CH₂Cl₂ was added TBSOTf (0.81 mL, 3.51 mmol).
The reaction mixture was stirred at room temperature for 12h. Ethyl acetate (10 mL)
was added. The organic layer was washed with H₂O (3 x 10 mL). Dried over
sodium sulfate and filtered. The organic layer was concentrated in vacuo and
purification of the crude material via Isco (10-20% ethyl acetate/hexanes) gave rise
to the desired product (736.5 mg).

Example 7-13

Preparation of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6,7-dihydro-5H-
cyclopenta[b]pyridin-7-yl acetate

Step 1: Synthesis of 6,7-dihydro-5H-cyclopenta[b]pyridine 1-oxide

3-Chloroperoxybenzoic acid (11.6 g, 67.1 mmol) was dissolved in EtOAc (70
mL, 6 ml/g). The reaction mixture was stirred for 10 minutes at room temperature,
and then cooled to 0 °C. 2,3-cyclopentenopyridine was dissolved in EtoAc (25 mL, 5
mL/g) which was added dropwise to reaction mixture over 15 minutes keeping the
temperature constant below 10 °C. The reaction mixture was stirred overnight at
ambient temperature. The reaction mixture was quenched with Sat. NaHCO₃ (50
The organic layer was dried over sodium sulfate and filtered. Acqu layer was extracted with DCM (40 mL) twice. The organic layer was dried over sodium sulfate and filtered. Combined organic layer was concentrated in vacuo and purification of the crude material via isco (0-5% Methanol/DCM) gave rise to the desired 6,7-dihydro-5,7-cyclopenta[b]pyridine 1-oxide (1.4 g).

Step 2: Synthesis of 6,7-dihydro-5H-cyclopenta[b]pyridine-7-yl acetate

![Chemical structure]

A mixture of 6,7-dihydro-5H-cyclopenta[b]pyridine 1-oxide and acetic anhydride was stirred for 30 minutes at 100 °C. Concentrated and added DCM (30 mL). The organic layer was washed with Sat. NaHCO₃. The organic layer was dried over sodium sulfate and filtered. The organic layer was concentrated in vacuo and purification of the crude material via isco (3-5% Methanol/DCM) gave rise to the desired 6,7-dihydro-5,7-cyclopenta[b]pyridine-7-yl acetate (900 mg).

Step 2: Synthesis of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6,7-dihydro-5H-cyclopenta[b]pyridin-7-yl acetate

![Chemical structure]

A solution of bispinacolatodiboron (246.0 mg, 2.54 mmol), 4,4′-di-tert-butyl-2,2′ dipyridyl (23 mg, 0.085 mmol) and 1,5 cyclooctadiene(methoxy) Iridium(I)dimer (56 mg, 0.085 mmol) in MTBE (10 mL) was degassed with Ar three time and then stirred at room temperature 10 minutes until the solution became read and then added compound 6,7-dihydro-5H-cyclopenta[b]pyridine-7-yl acetate (300.0 mg, 1.7 mmol). The reaction mixture heated at 90 °C in a sealed tube for 2h. The mixture
was cooled to room temperature and was concentrated in vacuo. Purification of the crude material via Isco (30-50% ethyl acetate/hexanes) gave rise to the desired boronic ester (169 mg).

Following previous examples, the following compounds in Table 7-10 were prepared:

<table>
<thead>
<tr>
<th>Compound ID</th>
<th>Structures</th>
<th>Compound Name</th>
<th>MH+ (calculated)/ MH+ (observed)</th>
<th>pAKT S473</th>
<th>IC50</th>
<th>pME-BP1</th>
<th>The117/46</th>
<th>IC50</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.53</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>((1R,3s,5S)-3-(7-amino-3-(8-hydroxy-9,6,7,8-tetrahydroquinolin-3-yl)-8-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone</td>
<td>564.21/ 564.0</td>
<td>B</td>
<td>B</td>
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<tr>
<td>7.54</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(8-hydroxy-9,6,7,8-tetrahydroquinolin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone</td>
<td>526.26/ 526.1</td>
<td>A</td>
<td>A</td>
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<tr>
<td>7.55</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(8-hydroxy-8-methyl-5,6,7,8-tetrahydroquinolin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone</td>
<td>540.28/ 540.1</td>
<td>B</td>
<td>B</td>
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<tr>
<td>7.56</td>
<td>DEUTERATED-(3-EXO)-3-[7-AMINO-6-CYCLOPROPYL-3-(5,6,7,8-TETRAHYDRO-8-HYDROXY-3-QUINOLINYL-(D)]PYRAZOL[1,5-a]PYRIMIDIN-5-YL]-8-(4H-1,2,4-TRIAZOL-3-YLCARBONYL)-8-AZABICYCLO[3.2.1]OCTANE</td>
<td>527.27/527.0 A A</td>
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<tr>
<td>7.57</td>
<td>DEUTERATED-(3-EXO)-3-[6-ACETYL-7-AMINO-3-(5,6,7,8-TETRAHYDRO-8-HYDROXY-3-QUINOLINYL-(D)]PYRAZOL[1,5-a]PYRIMIDIN-5-YL]-8-(4H-1,2,4-TRIAZOL-3-YLCARBONYL)-8-AZABICYCLO[3.2.1]OCTANE</td>
<td>529.25/529.1 B A</td>
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<td>7.58</td>
<td>1-(5-((1R,3a,5S)-8-(4H-1,2,4-triazole-3-carboxyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(8-hydroxy-5,6,7,8-tetrahydroquinolin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone</td>
<td>528.24 528.1 A A</td>
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<td>7.59</td>
<td>1-(5-((1R,3a,5S)-8-(4H-1,2,4-triazole-3-carboxyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(8-hydroxy-5,6,7,8-tetrahydroquinolin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone</td>
<td>528.24/528.1 B A</td>
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<td>7.60</td>
<td>1-(5-((1R,3a,5S)-8-(4H-1,2,4-triazole-3-carboxyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(8-hydroxy-5,6,7-dihydro-5H-cyclopent[a]pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone</td>
<td>514.2/514.2 B ND</td>
<td></td>
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<tr>
<td>Example 7-14</td>
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</tr>
<tr>
<td><strong>Preparation of</strong> 1-((1R,3s,5R)-3-(7-amino-6-cyclopenty</td>
<td>3-(7-hydroxy-6,7-dihydro-8H-cyclopenta[b]pyridin-3-yl)pyrazolo[1,5-alpyrimidin-5-yl]-8-azabicyclo[3.2.1]octan-8-yl)pyridin-3-yl)pyrazolo[1,5-alpyrimidin-6-yl]ethanone</td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Step 1:</strong> Preparation of 1-(5-bromopyridin-2-yl)-2,2,2-trifluoroethane</td>
<td>528.2/528.0</td>
<td>B</td>
<td>B</td>
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<tr>
<td><strong>Step 2:</strong></td>
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<tr>
<td><strong>Step 3:</strong></td>
<td>550.2/550.1</td>
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<tr>
<td><strong>Step 4:</strong></td>
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<td>A</td>
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</tbody>
</table>

*Preparation of 1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-8-yl)(1H,1,2,4-triazol-3-yl)ethanone)*
2,5-Dibromopyridine (7.11 g, 30 mmol) was dissolved in dry toluene (200 mL) and cooled to -78 °C. n-BuLi (14.4 mL, 2.5 M in THF, 36 mmol) was added dropwise. The mixture was stirred at -78 °C for 2 hours and ethyl trifluoroacetate (6.39 g, 45 mmol) was added. The resulting mixture was allowed to warm to room temperature slowly and stirred at room temperature for 30 min. The reaction was quenched with NH₄Cl (aq.) and extracted with EtOAc. The organics were dried and concentrated and the resulting residue was purified by column chromatography (silica gel, 0-30% EtOAc/Hexane) to give the product 1-(5-bromopyridin-2-yl)-2,2,2-trifluoroethanone (5.87 g).

**Step 2: Preparation of 1-(5-bromopyridin-2-yl)-2,2,2-trifluoroethanol**

To a suspension of 1-(5-bromopyridin-2-yl)-2, 2,2-trifluoroethanol (3.81 g, 15.0 mmol) MeOH (20 mL) was added sodium borohydride (1.70 g, 45.0 mmol). The solution was stirred at rt for 1 h. The reaction solution was quenched by water, extracted by ethyl acetate and dried over sodium sulfate. After concentration the crude product was purified by column (silica gel, EtOAc/Hexane 0-40%) to give the product 1-(5-bromopyridin-2-yl)-2, 2,2-trifluoroethanol (3.57 g).

**Step 3: Preparation of 2,2,2-trifluoro-1-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)ethanol**
A mixture of 1-(5-bromopyridin-2-yl)-2,2,2-trifluoroethanol (1.28 g, 5.00 mmol),
bis(pinacolato)diboron (1.52 g, 6.00 mmol), PdCb(dpff) (408 mg, 0.500 mmol), and
KOAc (1.47 g, 15.0 mmol) in dioxane (20 mL) was degassed and then heated at 80 °C and stirred overnight. The reaction mixture was filtered and concentrated to afford the crude titled compound, which was used without further purification.

Step 4: Preparation of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

A mixture of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-iodopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (2.43 g, 3.3 mmol, preparation described previously), 2,2,2-trifluoro-1-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)ethanol (crude product from step 3, 5.0 mmol), PdCb(dpff) (243 mg, 0.3 mmol), and K3PO4 (2.12 g, 10 mmol) in dioxane/H2O (20/2 mL) was degassed and then heated at 90 °C for overnight. The reaction mixture was diluted with EtOAc, filtered through a short pad of celite, washed with H2O and brine, dried over Na2SO4, and
concentrated. The crude product was purified by column (silica gel, 0-50% EtOAc/Hexanes) to afford the titled compound as brownish oil (2.62 g).

Step 5: Preparation of \((1R,3s,5S)\)-tert-butyl 3-(7-(bis(2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

The compound of \((1R,3s,5S)\)-fert-butyl 3-(7-(bis(2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate was made following procedure described previously.

Step 6: Preparation of \((1R,3s,5S)\)-tert-butyl 3-(7-(bis(2-(trimethylsilyl)ethoxy)methyl)amino)-6-(1-ethoxyvinyl)-3-(6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

\[
\text{CH}_2=\text{C(OEt)}\text{SnBu}_3 \rightarrow \text{Pd}>(\text{PPH}_3)_3 \rightarrow \text{dioxane, 100 °C}
\]
The compound of (1R,3S,5S)-tert-butyl 3-(7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-6-(1-ethoxyvinyl)-3-(6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate was made following procedure described previously.

Step 7: Preparation of 1-(7-amino-5-((1R,3S,5S)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone

The compound of 1-(7-amino-5-((1R,3S,5S)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone was prepared following procedure described previously.

Step 8: Preparation of 1-(5-((1R,3S,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone

The compound of 1-(5-((1R,3S,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone was made following procedure described previously.
Example 7-15

Preparation of benzyl 1-(5-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)pyridin-2-yl)cyclopropylcarbamate

Step 1: 1-(5-bromopyridin-2-yl)cyclopropanamine

To a mixture of 5-bromopicolinonitrile (1.82g, 10.0 mmol), tetrapropoxytitanium (3.26 ml, 11.0 mmol) and boron trifluoride diethyl etherate (2.51 ml 20.0 mmol) at 0 °C was added ethylmagnesium bromide (1.0 M in ether, 22 ml, 22.0 mmol). The resulting solution was allowed to stir at rt for 3h. Ammonium chloride solution was added and the solution was extracted with ethyl acetate for three times. The organic layers were collected and washed with brine and dried over sodium sulfate. After concentration the crude product was purified by SI02 column.

Step 2: benzyl 1-(5-bromopyridin-2-yl)cyclopropylcarbamate

At 0 °C, to the mixture of 1-(5-bromopyridin-2-yl)cyclopropanamine (1.07g, 5.0 mmol), triethylamine (766ul, 5.5 mmol) was added benzyl chloroformate (785ul,
5.5 mmol). The resulting mixture was allowed to stir at rt for 1 h. After work up, the crude product was purified by column chromatography on SiO2.

**Step 3: benzyl 1-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)cyclopropylcarbamate**

This compound was prepared from benzyl 1-(5-bromopyridin-2-yl)cyclopropylcarbamate, following essentially the same procedures given previously.

Following these examples, compounds in Table 7-1 were made similarly:

<table>
<thead>
<tr>
<th>Compound ID</th>
<th>Structures</th>
<th>Compound Name</th>
<th>MHH (calculated)</th>
<th>MHH (observed)</th>
<th>pAKTS473 IC50</th>
<th>pME-BP1 IC50</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.65</td>
<td><img src="image.png" alt="Image" /></td>
<td>1-[5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-5-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethane</td>
<td>556.2</td>
<td>556.2</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>7.66</td>
<td>1-(5-((1R,3s,5S)-8-(1H-pyrazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone</td>
<td>555.2/555.1</td>
<td>C</td>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.67</td>
<td>1-(1(R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)3-hydroxyethanone</td>
<td>519.2/519.1</td>
<td>C</td>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.68</td>
<td>(5-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl))-3-(6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)1H-1,2,4-triazol-3-yl)methanone</td>
<td>592.2/591.8</td>
<td>ND</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.69</td>
<td>(5-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl))-3-(6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)1H-pyrazol-3-yl)methanone</td>
<td>591.2/590.8</td>
<td>C</td>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.70</td>
<td>1-(1(R,3s,5S)-3-(7-amino-6-(methylsulfonyl))-3-(6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)2-hydroxyethanone</td>
<td>555.2/555.0</td>
<td>C</td>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.71</td>
<td>(5-((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)2-hydroxyethanone</td>
<td>540.3/540.3</td>
<td>B</td>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>Chemical Structure</td>
<td>Molecular Formula</td>
<td>Exact Mass</td>
<td>Retention Time</td>
<td>Peak Area</td>
<td>Peak Height</td>
</tr>
<tr>
<td>-----</td>
<td>--------------------</td>
<td>-------------------</td>
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<td>---------------</td>
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<tr>
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<td><img src="image1.png" alt="Chemical Structure" /></td>
<td>C&lt;sub&gt;68&lt;/sub&gt;H&lt;sub&gt;77&lt;/sub&gt;N&lt;sub&gt;19&lt;/sub&gt;O&lt;sub&gt;16&lt;/sub&gt;S&lt;sub&gt;2&lt;/sub&gt;F&lt;sub&gt;2&lt;/sub&gt;</td>
<td>941.3/941.2</td>
<td>B B</td>
<td>489.3/489.2</td>
<td>489.3/489.2</td>
</tr>
<tr>
<td>7.73</td>
<td><img src="image2.png" alt="Chemical Structure" /></td>
<td>C&lt;sub&gt;69&lt;/sub&gt;H&lt;sub&gt;79&lt;/sub&gt;N&lt;sub&gt;20&lt;/sub&gt;O&lt;sub&gt;17&lt;/sub&gt;S&lt;sub&gt;2&lt;/sub&gt;F&lt;sub&gt;2&lt;/sub&gt;</td>
<td>953.4/953.3</td>
<td>B B</td>
<td>556.2/556.2</td>
<td>556.2/556.2</td>
</tr>
<tr>
<td>7.74</td>
<td><img src="image3.png" alt="Chemical Structure" /></td>
<td>C&lt;sub&gt;69&lt;/sub&gt;H&lt;sub&gt;79&lt;/sub&gt;N&lt;sub&gt;20&lt;/sub&gt;O&lt;sub&gt;17&lt;/sub&gt;S&lt;sub&gt;2&lt;/sub&gt;F&lt;sub&gt;2&lt;/sub&gt;</td>
<td>953.4/953.3</td>
<td>B B</td>
<td>556.2/556.2</td>
<td>556.2/556.2</td>
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<tr>
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<td>C&lt;sub&gt;69&lt;/sub&gt;H&lt;sub&gt;79&lt;/sub&gt;N&lt;sub&gt;20&lt;/sub&gt;O&lt;sub&gt;17&lt;/sub&gt;S&lt;sub&gt;2&lt;/sub&gt;F&lt;sub&gt;2&lt;/sub&gt;</td>
<td>953.4/953.3</td>
<td>ND ND</td>
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<td>624.2/624.0</td>
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<tr>
<td>7.76</td>
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<td>C&lt;sub&gt;68&lt;/sub&gt;H&lt;sub&gt;77&lt;/sub&gt;N&lt;sub&gt;19&lt;/sub&gt;O&lt;sub&gt;16&lt;/sub&gt;S&lt;sub&gt;2&lt;/sub&gt;F&lt;sub&gt;2&lt;/sub&gt;</td>
<td>941.3/941.2</td>
<td>ND ND</td>
<td>587.2/587.0</td>
<td>587.2/587.0</td>
</tr>
<tr>
<td>7.82</td>
<td>1-(7-amino-3-(6-(2-amino-1,1,1,3,3,3-hexafluoropropan-2-yl)pyridin-3-yl)-5-((1R,3s,5S)-8-(3-methyl-4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octa-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone</td>
<td>637.2/637.2</td>
<td>C</td>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.83</td>
<td>1-(1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octa-3-yl)pyrazol[1,5-a]pyrimidin-6-yl)ethanone</td>
<td>638.2/638.2</td>
<td>C</td>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.84</td>
<td>1-(7-amino-3-(6-(2-amino-1,1,1,3,3,3-hexafluoropropan-2-yl)pyridin-3-yl)-3-(1H-pyrazole-5-carbonyl)-8-azabicyclo[3.2.1]octa-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone</td>
<td>637.2/637.2</td>
<td>C</td>
<td>C</td>
<td></td>
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<tr>
<td>7.85</td>
<td>((1R,3s,5S)-3-(7-amino-3-(6-(2-amino-1,1,1,3,3,3-hexafluoropropan-2-yl)pyridin-3-yl)-6-cyclopropylpyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octa-3-yl)methanone</td>
<td>621.2/621.2</td>
<td>C</td>
<td>C</td>
<td></td>
<td></td>
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<tr>
<td>7.86</td>
<td>1-(1R,3s,5S)-3-(7-amino-3-(6-(2-amino-1,1,1,3,3,3-hexafluoropropan-2-yl)pyridin-3-yl)-6-cyclopropylpyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octa-3-yl)methanone</td>
<td>584.2/584.1</td>
<td>ND</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step</td>
<td>Reaction/Comment</td>
<td>Mass (mass spectra)</td>
<td>ND</td>
<td>ND</td>
<td></td>
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</tr>
<tr>
<td>------</td>
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</tr>
<tr>
<td>7.87</td>
<td>n-8-yl)-2-hydroxyethanone ((1R,3s,5S)-3-(7-amino-3-(6-(2-amino-1,1,3,3,3-hexafluoropropan-2-yl)pyridin-3-yl)-6-cyclopropylpyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl](5-methyl-1,2,4-triazol-3-yl)methanone</td>
<td>635.2/635.3</td>
<td>ND</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.88</td>
<td>2-((tert-butyldimethylsilyloxy)methyl)-5-(tributylstannyl)thiazole</td>
<td>636.2/636.2</td>
<td>C</td>
<td>C</td>
<td></td>
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<tr>
<td>7.89</td>
<td>(3-amino-1H-pyrazol-5-yl)(1R,3s,5S)-3-(7-amino-3-(6-(2-amino-1,1,3,3,3-hexafluoropropan-2-yl)pyridin-3-yl)-6-cyclopropylpyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)methanone</td>
<td>635.2/635.3</td>
<td>ND</td>
<td>ND</td>
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<td></td>
</tr>
</tbody>
</table>

**Example 7-15**

5 Preparation of 1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(2-(hydroxymethyl)thiazol-5-yl)pyrazol[1,5-a]pyrimidin-6-yl)ethanone

Step 1: Preparation of 2-((tert-butyldimethylsilyloxy)methyl)-5-(tributylstannyl)thiazole
2-((tert-butyldimethylsilyloxy)methyl)thiazole (8.0 g, 35 mmol) was dissolved in dry THF (350 mL) and the solution was cooled to -78 °C. To this solution, t-BuLi (1.7 M, 25 mL, 42 mmol) was added dropwise. The reaction was warmed to -40 °C and stirred for 2 hours. Then, Bu₃SnCl (14.6 g, 45 mmol) was added and the resulting mixture was allowed to warm to room temperature slowly and stirred for another 30 min. NH₄Cl (aq.) was added to quench the reaction and extracted with EtOAc. The organics was dried and concentrated. The residue was purified with column (silica gel, 0:30 EtOAc/hexane) to give the product 2-((tert-butyldimethylsilyloxy)methyl)-5-(tributylstannyl)thiazole (14.1 g).

Step 2: Preparation of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(2-((tert-butyldimethylsilyloxy)methyl)thiazol-5-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

A mixture of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-iodopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (1.46 g, 2.0 mmol), 2-((tert-butyldimethylsilyloxy)methyl)-5-(tributylstannyl)thiazole (2.08 g, 4.0 mmol), Pd(PPh₃)₄ (230 mg, 0.2 mmol) in dioxane (10 mL) was stirred at 100 °C under Argon for 4 h. The reaction mixture was passed through a short plug filled with silica gel (9:1) to remove majority of the Sn species (eluting with EtOAc). The filtrate was concentrated and purified by a silica column to afford the titled compound as a brownish oil (580 mg).
Step 3: Preparation of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(2-((tert-butyldimethylsilyloxy)methyl)thiazol-5-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

To a solution of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(2-((tert-butyldimethylsilyloxy)methyl)thiazol-5-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (250 mg, 0.3 mmol) in CH$_3$CN (10 mL) was added NBS (54 mg, 0.3 mmol) at rt and the reaction was stirred for 1 hour. All the volatiles were removed under reduced pressure and the residue was purified by a SiO$_2$ column to afford the titled compound as brownish oil (240 mg).

Step 4: Preparation of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(1-ethoxyvinyl)-3-(2-((tert-butyldimethylsilyloxy)methyl)thiazol-5-yl)-6-(1-ethoxyvinyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

A mixture of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(2-((tert-
butyldimethylsilyloxy)methyl)thiazol-5-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (240 mg, 0.26 mmol), tributyl(1-ethoxyvinyl)tin (250 μL, 0.75 mmol), Pd(PPh_3)_4 (29.0 mg, 0.025 mmol) in dioxane (2 mL) was stirred at 100 °C under Argon for 16 h. The reaction mixture was passed through a short plug filled with SiO_2/KF (9:1) to remove majority of the Sn species (eluting with EtOAc). The filtrate was concentrated and purified by a SiO_2 column to afford the titled compound as brownish oil (177 mg).

Step 5: Preparation of 1-(7-amino-5-((1R,3S,5S)-8-azabicyclo[3.2.1]octan-3-yl)-3-(2-(hydroxymethyl)thiazol-5-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone

![Chemical structure]

\[(1R,3S,5S)\text{-tert-butyl 3-\text{-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(2-((tert-butyldimethylsilyloxy)methyl)thiazol-5-yl)-6-(1-ethoxyvinyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(2-(hydroxymethyl)thiazol-5-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone}\]

(1R, 3S,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(2-((tert-butyldimethylsilyloxy)methyl)thiazol-5-yl)-6-(1-ethoxyvinyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-carboxylate (177 mg) was treated with a mixture of TFA/H_2O (50%, 5 mL) at rt for 3 h and 50 °C for another hour. All the volatiles were removed to afford the titled compound as pale yellow oil, which was used in the next step without further purification.

Step 6: Preparation of 1-(5-((1R,3S,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(2-(hydroxymethyl)thiazol-5-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone

![Chemical structure]
A mixture of 4H-1,2,4-triazole-3-carboxylic acid (34 mg, 0.3 mmol), HOBT (41 mg, 0.3 mmol), EDCI.HCl (57 mg, 0.3 mmol), DIEA (157 µL, 1.0 mmol) and 1-(7-amino-5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-3-(2-(hydroxymethyl)thiazol-5-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone (around 0.3 mmol) in DMF (2 mL) was stirred at rt for 6 h. The reaction mixture was concentrated to half volume, diluted with DMSO and purified by a reverse phase HPLC to afford the titled compound (Table 7-12).

Table 7-12

| 7.90 | 1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(2-(hydroxymethyl)thiazol-5-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone | 494.2/494.3 | ND | ND |

Example 7-16

Preparation of ((1R,3s,5S)-3-(7-amino-3-(2-(hydroxymethyl)thiazol-5-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

Step 1: Preparation of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-6-iodo-3-(2-(tert-butyldimethylsilyloxy)methyl)thiazol-5-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate
To a solution of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-3-(2-((tert-butyldimethylsilyloxy)methyl)thiazol-5-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (330 mg, 0.398 mmol) in HOAc (3 mL) was added NIS (90 mg, 0.4 mmol) at rt and the reaction was stirred for 30 min. All the volatiles were removed under reduced pressure and the residue was purified by a SiO₂ column to afford the titled compound as brownish oil (253 mg).

Step 2: Preparation of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-3-(2-((tert-butyldimethylsilyl)oxy)methyl)thiazol-5-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

A mixture of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-3-(2-((tert-butyldimethylsilyloxy)methyl)thiazol-5-yl)-6-iodopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (253 mg, 0.26 mmol), MeSO₃Na (83 mg, 0.78 mmol), and Cul (301 mg, 1.59 mmol) in DMSO (2 mL) was heated at 90 °C for 2.5 h. The reaction mixture was cooled to room temperature and diluted with EtOAc. The mixture was washed with ammonia (1N), water and brine and dried over Na₂SO₄. After concentration, the crude was used in the next step directly without further purification.
**Step 3**: Preparation of (5-(7-amino-5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)methanol

The title compound was prepared with the same conditions described previously.

**Step 4**: Preparation of ((1R,3s,5S)-3-(7-amino-3-(2-(hydroxymethyl)thiazol-5-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone and (5-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)methyl 4H-1,2,4-triazole-3-carboxylate

The compounds ((1R,3s,5S)-3-(7-amino-3-(2-(hydroxymethyl)thiazol-5-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone and (5-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)methyl 4H-1,2,4-triazole-3-carboxylate
yl)thiazol-2-yl)methyl 4H-1,2,4-triazole-3-carboxylate were prepared with the same conditions described previously.

Similarly compounds in Table 7-13 were made.

<table>
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<th>Compound ID</th>
<th>Structures</th>
<th>Compound Name</th>
<th>M+H (calculated)/ M+H (observed)</th>
<th>pAKT S473 IC50</th>
<th>pE-BP1 Thr37/46 IC50</th>
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<tbody>
<tr>
<td>7.91</td>
<td><img src="structure1.png" alt="Structure" /></td>
<td>((1R,3s,5S)-3-((7-amino-3-(2-hydroxymethyl)thiazol-5-yl)-6-(methylsulfonfyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone</td>
<td>530.1/530.2</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>7.92</td>
<td><img src="structure2.png" alt="Structure" /></td>
<td>((5-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-6-(methylsulfonfyl)pyrazolo[1,5-a]pyrimidin-3-yl)(thiazol-2-yl)methyl 4H-1,2,4-triazole-3-carboxylate</td>
<td>625.1/625.3</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>7.93</td>
<td><img src="structure3.png" alt="Structure" /></td>
<td>((1R,3s,5S)-3-((7-amino-3-(aminomethyl)thiazol-5-yl)-6-(methylsulfonfyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone</td>
<td>529.1/529.2</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>7.94</td>
<td><img src="structure4.png" alt="Structure" /></td>
<td>N-((5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-6-</td>
<td>624.2/624.3</td>
<td>ND</td>
<td>ND</td>
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</tbody>
</table>
Example 7-17

Preparation of ((1R,3s,5S)-3-(7-amino-3-(6-(hydroxymethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-1,2,4-triazol-5-yl)methanone

![Chemical Structure](image-url)
Scheme 7-1

Step A - Synthesis of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-iodopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

To tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-iodopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (1.0 g, 1.37 mmol) in dioxane (10 mL) and H2O (1.5 mL) was added methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinate (0.61 g, 2.33 mmol).
PdCl₂(dppf)-CH₂C₁₂ (0.48g, 0.58 mmol) and K₂CO₃ (0.97 g, 6.99 mmol). The reaction was heated at 100 °C for 15 hours, at which time LC/MS analysis confirmed full consumption of starting material. On cooling, H₂O (5 mL) and EtOAc (25 mL) were added and separated the layers. The aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layer was dried (Na₂SO₄) and concentrated in vacuo to afford crude product. Gradient column chromatography on silica eluting with 30 to 90% EtOAc/hexanes gave the desired product (607 mg).

Step B - Synthesis of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-3-(6-(hydroxymethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

To a solution of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-3-(6-(methoxycarbonyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (Int-4a) (570 mg, 0.77 mmol) in anh tetrahydrofuran (6 mL) was added ethanol (9 mL). To the resulting solution was added calcium chloride powder (257 mg, 2.31 mmol) followed by sodium borohydride (117 mg, 3.09 mmol). Stirred reaction mixture at room temperature for 1.5 hours at which point LC-MS analysis confirmed full consumption of starting material. The reaction was diluted with dichloromethane and then quenched by slowly adding 2N HCl (aq) slowly until reaction mixture stopped bubbling. The mixture was further diluted with water (100 mL). Separated the layers, the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with saturated sodium bicarbonate, brine, dried over anhydrous sodium
sulfate and concentrated in vacuo to give a thick brown oil (560 mg) which was used without further purification in the next step.

**Step C - Synthesis of (5-(7-amino-5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)methanol**

To (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-(hydroxymethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-carboxylate (Int-4b) (549 mg, 0.77 mmol) was added 1,4-dioxane (10 mL) followed by 4N HCl in dioxane (10 mL) and water (5 mL). The resulting solution was stirred at 50 °C for 30 minutes at which point LC-MS analysis indicated that the reaction was complete. The solvent was removed in vacuo to get the desired product as an HCl salt. This HCl product was lyophilized to afford the desired product (5-(7-amino-5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)methano as a brown solid.

**Step C - Synthesis of ((1R,3s,5S)-3-(7-amino-3-(6-(hydroxymethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-1,2,4-triazol-5-yl)methanone**


A mixture of 1H-1,2,4-triazole-3-carboxylic acid (56 mg, 0.50 mmol), EDCI (147 mg, 0.77 mmol), and 1-hydroxybenzotriazole (52 mg, 0.38 mmol) in DMF (5 ml) was stirred at room temperature for 10 min. (5-(7-amino-5-((1 R,3S,5S)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)methanol hydrochloride (0.38 mmol) was added followed by N,N-diisopropylethylamine (0.33 ml, 1.92 mmol). It was stirred further for 20 min at room temperature at which time LC/MS analysis confirmed full consumption of starting material. This crude compound was purified by HPLC to afford the desired product (Table 7-14). LC/MS RT = 1.59 min.

Table 7-14

<table>
<thead>
<tr>
<th>Compound ID</th>
<th>Structures</th>
<th>Compound Name</th>
<th>m/z (calculated)</th>
<th>m/z (observed)</th>
<th>pAKT</th>
<th>pIV-BPI</th>
<th>IC50</th>
</tr>
</thead>
<tbody>
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<td><img src="image" alt="Structure" /></td>
<td>((1R,3S,5S)-3-(7-amino-3-(6-(hydroxymethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-1,2,4-triazol-5-yl)methanone</td>
<td>446.2/445.9</td>
<td>446.2/445.9</td>
<td>D</td>
<td>C</td>
<td></td>
</tr>
</tbody>
</table>

Example 7-18

Preparation of 1-(5-((1R,3S,5S)-8-(1H-1,2,4-triazole-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(5-fluoro-6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone

386
Step A - Synthesis of 2-(5-bromo-3-fluoropyridin-2-yl)propan-2-ol

To 2,5-dibromo-3-fluoropyridine in toluene at -78 °C was added n-butyllithium drop wise. The resulting solution was stirred at -78 °C for 1.5 hours. Then at -78 °C, added acetone drop wise to the reaction mixture and continue to stir reaction at -78 °C for 2 hours at which point LC-MS and TLC indicated the reaction was complete. The reaction was warmed to 0 °C and quenched with saturated ammonium chloride solution (aq.) and then diluted with water (50 mL) and extracted with ethyl acetate (2 x 100 mL). The organic layer was dried (Na2SO4) and concentrated in vacuo to afford crude product. Gradient column chromatography on silica eluting with 0 to 30% EtOAc/hexanes gave the desired product (1.04 g).
Step B - Synthesis of 2-(3-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)propan-2-ol

A 50 mL round-bottomed flask was charged with 2-(5-bromo-3-fluoropyridin-2-yl)propan-2-ol (Int-5a) (0.5 g, 2.15 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.1 g, 4.29 mmol), potassium acetate (0.63 g, 6.44 mmol), PdCl₂(dpff)-CH₂Cl₂ (0.17 g, 0.22 mmol). The reaction vessel was sealed with a rubber septum, flushed with Argon and 1,4-dioxane (10 mL) added to the reaction. The reaction mixture was stirred at 80 °C for 2 hours at which point TLC and LC-MS indicated full consumption of the starting material. The solvent was removed in vacuo and the residue was partitioned between dichloromethane and water. The organic layer was dried (Na₂SO₄) and concentrated in vacuo to afford crude product 2-(3-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)propan-2-ol which was used in the next reaction without further purification.

Step C - Synthesis of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(5-fluoro-6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

388
To tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-iodopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (0.46 g, 0.63 mmol) in dioxane (10 mL) and H$_2$O (1.5 mL) was added 2-(3-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)propan-2-ol (0.30 g, 1.07 mmol), PdCl$_2$(dpf)-CH$_2$Cl$_2$ (0.13 g, 0.16 mmol) and K$_2$CO$_3$ (0.26 g, 1.88 mmol). The reaction was heated at 85 °C for 15 hours, at which time LC/MS analysis confirmed full consumption of starting material. On cooling, H$_2$O (5 ml) and EtOAc (25 mL) were added and separated the layers. The aqueous layer was extracted with EtOAc (2 x 10 ml). The combined organic layer was dried (Na$_2$SO$_4$) and concentrated in vacuo to afford crude product. Gradient column chromatography on silica eluting with 30 to 90% EtOAc/hexanes gave the desired product (0.25 g).

**Step D - Synthesis of (1R,3s,5S)-tert-butyl 3-(7-(bis(2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(5-fluoro-6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate**

To a mixture of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(5-fluoro-6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (1.1 g, 1.45 mmol) in CH$_2$CN (15 mL) and dichloromethane (15 mL) was added N-bromosuccinimide (0.28 g, 1.59 mmol) in one portion and the resulting mixture was stirred at room temperature for 0.5 h, at which time LC/MS confirmed reaction was not complete. Added more N-bromosuccinimide (0.28 g, 1.59 mmol) in one portion and the resulting mixture was stirred at room temperature for 1.5 h at which time LC/MS confirmed full conversion of starting material to product. The solvent was
removed in vacuo and the residue was purified by column chromatography on silica gel. Elution with EtOAc/Hexanes (0-30%) gave the title product (0.87 g).

Step E - Synthesis of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-6-(1-ethoxyvinyl)-3-(5-fluoro-6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

A mixture of compound (1R,3s,5S)-tert-butyl 3-(7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(5-fluoro-6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (0.86 g, 1.03 mmol), tributyl(1-ethoxyvinyl)tin (0.75 g, 2.06 mmol), tetrakis(triphenylphosphine)palladium (0.12 g, 0.103 mmol) in dioxane (20 mL) was degassed with argon for five minutes. It was then heated at 100 °C in a sealed tube for 16 h, at which time LC/MS analysis confirmed full consumption of starting material. On cooling, the solvent was concentrated in vacuo, and the crude residue was dissolved in EtOAc (125 mL), washed with 0.5 M KF solution (1 x 20 mL), water (1 x 25 mL), brine (1 x 25 mL), and dried over MgSO₄. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel. Elution with EtOAc/Hexanes (20-50%) gave the title product (0.78 g).

Step F - Synthesis of 1-(7-amino-5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-3-(5-fluoro-6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone
To a mixture of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(1-ethoxyvinyl)-3-(5-fluoro-6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (0.85 g, 0.103 mmol) in dioxane (2 mL) was added 4 M HCl in water (1 ml) at 0 °C. After stirring for 10 min at 0 °C, 4 M HCl in dioxane (1 mL) was added. The reaction mixture was stirred at 0 °C for 30 min and the cooling bath was removed to warm it up to room temperature for 30 minutes, and then heated at 50 °C for 1 hour at which time LC/MS analysis confirmed full consumption of starting material. The solvent was removed in vacuo to get the desired product as an HCl salt. This HCl product was lyophilized to afford the desired product as a yellow solid (51 mg).

**Step G - Synthesis of 1-(5-((1R,3s,5S)-8-(1H-1,2,4-triazole-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(5-fluoro-6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone**
A mixture of 1H-1,2,4-triazole-3-carboxylic acid (15.4 mg, 0.14 mmol), EDCI (41.3 mg, 0.22 mmol), and 1-hydroxybenzotriazole (14.2 mg, 0.11 mmol) in DMF (2 ml) was stirred at room temperature for 10 minutes. 1-(7-amino-5-((1R,3S,5S)-8-azabicyclo[3.2.1]octan-3-yl)-3-(5-fluoro-6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone hydrochloride (50 mg, 0.11 mmol) was added followed by N,N-diisopropylethylamine (0.57 ml, 0.33 mmol). It was stirred further for 20 min at room temperature at which time LC/MS analysis confirmed full consumption of starting material. This crude compound was purified by HPLC to afford the desired product (Table 7-15).

Table 7-15

<table>
<thead>
<tr>
<th>Compound ID</th>
<th>Structures</th>
<th>Compound Name</th>
<th>NH + (calculated)</th>
<th>NH + (observed)</th>
<th>pAKT IC50</th>
<th>pME-2 BP4 TNFα IC50</th>
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<tbody>
<tr>
<td>7.98</td>
<td><img src="image.png" alt="Structure" /></td>
<td>1-(5-((1R,3S,5S)-8-(1H-1,2,4-triazole-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(5-fluoro-6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone</td>
<td>534.2/534.0</td>
<td>A</td>
<td>A</td>
<td></td>
</tr>
</tbody>
</table>

Example 8-1

Scheme 8-1
Preparation of 1-(5-(8-(4H-1,2,4-triazole-3-carbonyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-yl)ethanone

Step 1

Preparation of 5-chloro-3-(6-phenylpyridin-3-yl)-N,N-bis((2-(trimethylsilyl)ethoxy)methyl)pyrazolo[1,5-a]pyrimidin-7-amine
Substrate 2-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (2.38 mmol, 675 mg), K$_3$P$_4$O$_4$ (5.96 mmol, 1264 mg), and PdCl$_2$(dpdf)-CH$_2$Cl$_2$ (0.20 mmol, 162 mg) were added to a solution of 5-chloro-3-ido-N,N-bis((2-(trimethylsilyl)ethoxy)methyl)pyrazolo[1,5-a]pyrimidin-7-amine (1.98 mmol, 1101 mg) in dioxane (18 mL) and H$_2$O (3 mL). The resulting solution was stirred at 70°C under argon overnight. The mixture was diluted with H$_2$O and then extracted with ethyl acetate (×2). The combined organic layers were washed with brine and dried with Na$_2$SO$_4$. Evaporation and purification by column chromatography afforded 5-chloro-3-(6-phenylpyridin-3-yl)-N,N-bis((2-(trimethylsilyl)ethoxy)methyl)pyrazolo[1,5-a]pyrimidin-7-amine: LCMS $t_R = 3.36$ Min (5 min run, UV 254nm). Mass calculated for M+H 582.2, observed LC/MS m/z 582.2 (M+H).

**Step 2**

Preparation of tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

![Diagram of the preparation process](image-url)
A mixture of 5-chloro-3-(6-phenylpyridin-3-yl)-N,N-bis((2-(trimethylsilyl)ethoxy)methyl)pyrazolo[1,5-a]pyrimidin-7-amine (226 mg, 0.39 mmol), tert-butyl 3,8-diazabicyclo[3.2.1]octane-8-carboxylate (330 mg, 1.56 mmol), NaHCO₃ (196 mg, 2.33 mmol) in NMP (4 mL) was heated at 130°C overnight. The mixture was cooled to room temperature and diluted with H₂O and then extracted with ethyl acetate (x2). The combined organic layers were washed with brine and dried with Na₂SO₄. Evaporation of solvent afforded the crude displacement compound.

Purification by column chromatography afforded tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate: LCMS tᵣ = 3.38 Min (5 min run, UV 254 nm). Mass calculated for, M+H 758.4, observed m/z 758.3 (M+H).

Step 3

Preparation of tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

NBS (64 mg, 0.36 mmol) was added to a solution of tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (249 mg, 0.33 mmol) in DMF (6 mL). After stirring at room temperature for 1 h, the mixture was diluted with H₂O and then extracted with ethyl acetate (x2). The combined organic layers were washed with brine and dried with Na₂SO₄. Evaporation and purification by column chromatography afforded tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3,8-
Step 4

Preparation of tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(1-ethoxyvinyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

A degassed mixture of tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (256 mg, 0.31 mmol), Pd(PPh$_3$)$_4$ (35 mg, 0.031 mmol), tributyl(1-ethoxyvinyl)stannane (221 mg, 0.61 mmol) in dioxane (6 mL) was heated at 100 °C overnight. The reaction mixture was cooled to room temperature, filtered through a 9:1 SiC>2-KF plug and concentrated in vacuo. Purification by column chromatography afforded tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(1-ethoxyvinyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate, LCMS $t_R$ = 3.58 Min (10 min run, UV 254 nm). Mass calculated for M+H 828.45, observed LC/MS m/z 828.07 (M+H).

Step 5

Preparation of 1-(5-(8-(4H-1,2,4-triazole-3-carbonyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone
The tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(1-ethoxyvinyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (31 mg) was treated with 4N HCl in H₂O (2 mL) and Dixoane (2 mL) until the disappearance of starting material in LCMS. Concentration afforded crude 1-(7-amino-5-(3,8-diazabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone, which was used for next step without further purification, LCMS tᵣₑₜ = 1.08 Min (10 min run, UV 254nm). Mass calculated for, M+ H 440.2, observed LC/MS m/z 440.2 (M+H).

A mixture of 1-(7-amino-5-(3,8-diazabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone (1 mg, 0.025 mmol), 4/7-1,2,4-triazole-3-carboxylic acid (3.1 mg, 0.027 mmol), EDCI (9.5 mg, 0.05 mmol), HOBt (6.75 mg, 0.05 mmol) and DIEA (26 ul, 0.15 mmol) in DMF (1 ml) was stirred at room temperature overnight. Purification with prep-LC provided 1-(5-(8-(4/7-1,2,4-triazole-3-carbonyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone, LCMS tᵣₑₜ = 3.31 Min (10 min run, UV 254nm). Mass calculated for M+ H 535.2, observed LC/MS m/z 534.95 (M+H).

Following the Scheme 8-1 and the procedures similar to preparation of 1-(5-(8-(4/7-1,2,4-triazole-3-carbonyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone, the following compounds (Table 8-1) can be prepared:
Table 8-1

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<tr>
<th>Compound ID</th>
<th>Structures</th>
<th>Compound Name</th>
<th>M+H (calculated)</th>
<th>M+H (observed)</th>
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<th>IC50 46</th>
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<td><img src="structure1.png" alt="Structure Image" /></td>
<td>1-((5-((4H-1,2,4-triazole-3-carbonyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone</td>
<td>535.2/535.0</td>
<td>B</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>8.2</td>
<td><img src="structure2.png" alt="Structure Image" /></td>
<td>(2R)-1-((3-6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-2-hydroxypropan-1-one</td>
<td>512.2/512.0</td>
<td>B</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>8.3</td>
<td><img src="structure3.png" alt="Structure Image" /></td>
<td>1-((5-((4H-1,2,4-triazole-3-carbonyl)-2,5-diazabicyclo[2.2.2]octan-2-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone</td>
<td>535.2/535.2</td>
<td>B</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>8.4</td>
<td><img src="structure4.png" alt="Structure Image" /></td>
<td>(2R)-1-((5-6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-2,5-diazabicyclo[2.2.2]octan-2-yl)-2-hydroxypropan-1-one</td>
<td>512.2/512.0</td>
<td>C</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>8.5</td>
<td><img src="structure5.png" alt="Structure Image" /></td>
<td>1-((3-(4H-1,2,4-triazole-3-carbonyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone</td>
<td>535.2/535.0</td>
<td>B</td>
<td>C</td>
<td></td>
</tr>
</tbody>
</table>
Example 8-2

Preparation of N-(5-((1R, 3s, 5S)-8-(4H-1,2, 4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)acetamide

Step 1: Preparation of (1R,3s,5S)-tert-butyl 3-(7-acetamido-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate
To a slurry of 5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine TFA salt (204 mg, 0.262 mmol, preparation described previously) in DCM (3 mL) was added TEA (5 eq), followed by (Boc)_2O (1.0 eq) in DCM (3 mL) at 0 °C. The resulting reaction mixture was warmed to rt and stirred for 1 h. All the volatiles were removed. The residue was dissolved in a mixture of pyridine/ACO_2 (1:2) and DMAP (1:1 eq) was added. The resulting mixture was heated at 60 °C for 4 h. After an aqueous workup, the crude mixture was purified by a SiO_2 column (0-100% EtOAc/Hexanes, R_f = 0.1 in 50% EtOAc) to afford the titled compound as a pale yellow oil (22 mg).

Step 2: Preparation of N-(5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-yl)acetamide TFA salt

(1R,3s,5S)-ferf-Butyl 3-(7-acetamido-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (22.0 mg, 0.0354 mmol) was treated with a mixture of TFA/H_2O (1:2 mL, 5/1) at rt for 2 h. All the volatiles were removed to afford the titled compound as a pale yellow oil, which was used without further purification.

Step 3: Preparation of N-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-3-azabicyclo[3.2.1]octan-3-yl)-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-yl)acetamide

400
This compound was prepared from N-(5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-yl)acetamide TFA salt and 4H-1,2,4-triazole-3-carboxylic acid, following essentially the same amide coupling procedure described above (Scheme 8-1, step 5).

Table 8-2

| 8.8 | N-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-yl)acetamide | 574.3/574.2 | ND | ND |

Example 8-3

Preparation of N-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-yl)acetamide

Step 1: Preparation of (1R,3s,5S)-tert-butyl 3-(7-acetamido-6-acetyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-carboxylate
To a slurry of 1-(7-amino-5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone HCl salt (565 mg, 1.03 mmol, preparation described previously) in DCM (5 mL) was added TEA (5 eq), followed by (Boc)₂O (1.0 eq) in DCM (5 mL) at 0 °C. The resulting reaction mixture was warmed to rt and stirred for 1 h. To this solution was added 3.0 eq of AcCl, followed by 3.0 eq of TEA and 1.5 eq of DMAP at rt. The resulting reaction mixture was stirred at 50 °C overnight. After an aqueous workup, the crude mixture was purified by a SiO₂ column (0-100% EtOAc/Hexanes, R_f = 0.4 in 100% EtOAc) to afford the titled compound as an orange solid (320 mg).

Step 2: Preparation of N-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-yl)acetamide

This compound was prepared from (1R,3s,5S)-tert-butyl 3-(7-acetamido-6-acetyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-
azabicyclo[3.2.1]octane-8-carboxylate and 4H-1,2,4-triazole-3-carboxylic acid, following standard amide coupling procedure described previously (Scheme 8-1, step 5).

### Table 8-3

| 8.9 | N-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-yl)acetamide | 576.2/576.2 | ND | ND |

#### Example 8-4

Preparation of N-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-yl)acetamide

**Step 1:** Preparation of (1R,3s,5S)-tert-butyl 3-(7-acetamido-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

To a slurry of 5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine TFA salt (198 mg, 0.268 mmol, preparation described previously) in DCM (3 mL) was added TEA (5 eq), followed by (Boc)$_2$O.
(1.0 eq) in DCM (3 mL) at 0 °C. The resulting reaction mixture was warmed to rt and stirred for 1 h. To this solution was added 3.0 eq of AcCl, followed by 3.0 eq of TEA and 1.5 eq of DMAP at rt. The resulting reaction mixture was stirred at rt for overnight. After an aqueous workup, the crude mixture was purified by a silica column (0-60% EtOAc/Hexanes, Rf = 0.3 in 50% EtOAc) to afford the titled compound as pale yellow forming solid (190 mg).

Step 2: Preparation of N-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenyl/pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-yl)acetamide

This compound was prepared from (1R,3s,5S)-tert-butyl 3-(7-acetamido-3-(6-phenyl/pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate and 4H-1,2,4-triazole-3-carboxylic acid, following similar amide coupling procedure described (Scheme 8-1 , step 5).

<table>
<thead>
<tr>
<th>Table 8-4</th>
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</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>8.10</td>
</tr>
</tbody>
</table>

404
Example 8-5

Preparation of 1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(pyrrolidin-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone

Step 1: Preparation of benzyl 2-(5-bromopyridin-2-yl)pyrrolidine-1-carboxylate

To a suspension of 5-bromo-2-(pyrrolidin-2-yl)pyridine (2.67 g, 11.8 mmol) in DCM (20 mL) at 0 °C was added DIEA (1.5 eq), followed by CbzCl (1.1 eq). The resulting clear solution was warmed to rt and stirred for 2 h. The reaction mixture was washed with brine, dried over Na₂SO₄, and concentrated. The crude product was purified by a SiO₂ column (0-50% EtOAc/Hexanes, R₄ = 0.35 in 50% EtOAc) to afford the titled compound as a brownish oil (3.63 g).

Step 2: Preparation of benzyl 2-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)pyrrolidine-1-carboxylate
This compound was prepared from benzyl 2-(5-bromopyridin-2-y1)pyrrolidine-1-carboxylate, following essentially the similar procedures given in Preparative Example 1-1.

Step 3: Preparation of 1-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(pyrrolidin-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone

A mixture of benzyl 2-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)pyrrolidine-1-carboxylate (48.0 mg, 0.0726 mmol) and Pd/C (cat.) in MeOH (5 mL) was stirred at rt under a hydrogen atmosphere for 3 h. The reaction mixture was filtered, converted to HCl salt by adding HCl in MeOH (1.25 M), and concentrated to afford the titled compound as a pale yellow solid (34.5 mg).

The following compounds listed in Table 8-5 were prepared following procedures similar to the preparation of 1-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(pyrrolidin-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone
### Table 8-5

<table>
<thead>
<tr>
<th>Compound ID</th>
<th>Structures</th>
<th>Compound Name</th>
<th>MH+ (calculated)/MH+ (observed)</th>
<th>pAKT S473 IC50</th>
<th>pE-BPI Trk270IC50</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>8.11</strong></td>
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<td>1-((5-((1R,3s,5s)-8-(4H-1,2,4-triazole-3-carbonyl)8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(pyrrolidin-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone</td>
<td>527.3/527.2</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td><strong>8.12</strong></td>
<td><img src="image2" alt="Structure" /></td>
<td>1-((1R,3s,5s)-3-(6-acetyl-7-amino-3-(6-(pyrrolidin-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone</td>
<td>490.3/490.1</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td><strong>8.13</strong></td>
<td><img src="image3" alt="Structure" /></td>
<td>((1R,3s,5s)-3-(7-amino-6-(methylsulfonyl))-3-(6-(pyrrolidin-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone</td>
<td>563.2/563.2</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td><strong>8.14</strong></td>
<td><img src="image4" alt="Structure" /></td>
<td>1-((1R,3s,5s)-3-(7-amino-6-(methylsulfonyl))-3-(6-(pyrrolidin-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone</td>
<td>526.2/526.0</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td><strong>8.15</strong></td>
<td><img src="image5" alt="Structure" /></td>
<td>((1R,3s,5s)-3-(7-amino-6-cyclopropyl)-3-(6-(pyrrolidin-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone</td>
<td>525.3/525.3</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

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**Example 8-6**
Preparation of (R)-4-(5-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)oxazolidin-2-one

Step 1: Preparation of (R)-4-(5-bromopyridin-2-yl)oxazolidin-2-one

To a suspension of (R)-2-amino-2-(5-bromopyridin-2-yl)ethanol hydrogen chloride (4.97 g, 19.6 mmol) and TEA (9.02 mL, 64.7 mmol) in DCM (60 mL) at 0 °C was added a solution of triphosgene (2.91 g, 9.80 mmol) in DCM (20 mL) during 45 min. The resulting mixture was stirred at 0 °C for 15 min, then warmed to rt and stirred for 1 h. The reaction was quenched with NH₄Cl (15 mL) and stirred for 15 min. The aqueous layer was separated, basicified with Na₂CO₃, and extracted with DCM (x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated. The crude product was purified by a S1O2 column (0-80% EtOAc/Hexanes, Rf = 0.15 in 50% EtOAc) to afford the titled compound as an off-white solid (3.60 g).

Step 2: Preparation of (R)-4-(5-bromopyridin-2-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)oxazolidin-2-one

To a solution of (R)-4-(5-bromopyridin-2-yl)oxazolidin-2-one (1.66 g, 6.83 mmol) in THF (28 mL) at 0 °C was added NaH (1.3 eq) and stirred for 10 min, and then, SEMCl (1.81 mL, 10.2 mmol) was added dropwise. The resulting reaction
mixture was warmed to rt and stirred for 2 h. THF was removed under reduced pressure. The residue was diluted with EtOAc, washed with H2O and brine, dried over Na2SO4, and concentrated. The crude product was purified by a SiO2 column (0-40% EtOAc/Hexanes, Rf = 0.6 in 50% EtOAc) to afford the titled compound as a pale yellow oil (1.91 g).

Step 3: Preparation of (R)-4-(5-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)oxazolidin-2-one

This compound was prepared from (R)-4-(5-bromopyridin-2-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)oxazolidin-2-one, following essentially the similar procedures given in Preparative Example 1-1.

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
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</tbody>
</table>

8.16

(R)-4-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)oxazolidin-2-one

543.2/543.1 ND ND
The following compounds listed in Table 8-6 were prepared following procedures similar to the preparation of (R)-4-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)oxazolidin-2-one.

Table 8-6

<table>
<thead>
<tr>
<th>Compound ID</th>
<th>Structures</th>
<th>Compound Name</th>
<th>M+H (calculated)</th>
<th>M+H (observed)</th>
<th>pAKT S473 IC50</th>
<th>pMEK1/2 Thr202/204 IC50</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.17</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>(S)-4-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)oxazolidin-2-one</td>
<td>543.2/543.1</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>8.18</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>(S)-4-(5-(6-acetyl-7-amino-5-((1R,3s,5S)-8-(2-hydroxyacetyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)oxazolidin-2-one</td>
<td>506.2/506.2</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
</tbody>
</table>

Example 8-7

Preparation of 2-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)pyrazolidin-3-one

Step 1: Preparation of benzyl 3-oxopyrazolidine-1-carboxylate

\[
\text{HN-NH} \xrightarrow{\text{CbzCl, DIEA DCM, rt}} \text{HN-N Cbz}
\]
To a suspension of pyrazolidin-3-one hydrogen chloride (5.00 g, 40.8 mmol) in DCM (120 mL) at 0 °C was added DIEA (2.5 eq), followed by CbzCl (1.15 eq). The resulting clear solution was warmed to rt and stirred 3 h. The reaction mixture was washed with brine. The aqueous layer was separated and back-extracted with DCM (x 2). The combined organic layers were dried over Na2SO4, and concentrated. The crude product was purified by a SiO2 column (0-100% EtOAc/Hexanes, Rf = 0.35 in 100% EtOAc) to afford the desired product as a white solid (5.31 g).

Step 2: Preparation of (1R,3s,5S)-tert-butyl 3-(3-(6-(2-(benzyloxycarbonyl)-5-oxopyrazolidin-1-yl)pyridin-3-yl)-7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

A mixture of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-chloropyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (1.50 g, 2.10 mmol, preparation described previously), benzyl 3-oxopyrazolidine-1-carboxylate (925 mg, 4.20 mmol), Pd2(dba)3 (96.1 mg, 0.105 mmol), XantPhos (182 mg, 0.315 mmol) and Cs2CO3 (1.03 g, 3.15 mmol) in dioxane (20 mL) was stirred at 110 °C under Argon for 16 h. After cooling to rt, the reaction mixture was filtered and purified by a SiO2 column (0-50% EtOAc/Hexanes, Rf = 0.5 in 50% EtOAc) to afford the titled compound as a light brown forming solid (1.23 g).

Step 3: Preparation of 2-(5-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)pyrazolidin-3-one
This compound was prepared from (1R,3s,5S)-tert-butyl 3-((6-((2-(benzyloxy carbonyl))-5-oxopyrazolidin-1-yl)pyridin-3-yl)-7-(bis((2-(trimethylsilyl))ethoxy)methyl)amino)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate, following essentially the similar procedures given in Preparative Example 1-1.

Table 8-7

| 8.19 | 2-(5-((1R,3s,5S)-8-(6H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)pyrazolidin-3-one | 542.2/542.2 | B | B |
| 8.20 | 2-(3-((6-acetyl-7-amino-5-((1R,3s,5S)-8-(2-hydroxyacetyl))-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)pyrazolidin-3-one | 505.2/505.1 | ND | ND |
Example 8-8

Preparation of 1-(7-amino-5-((1R,3r,5S)-3-hydroxy-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidine-6-yl)ethanone

Step 1: Preparation of (1R,5S)-tert-butyl 3-(7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-3-iodopyrazolo[1,5-a]pyrimidine-5-yl)8-azabicyclo[3.2.1]oct-3-ene-8-carboxylate

To a solution of (1R,5S)-tert-butyl 3-(7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)pyrazolo[1,5-a]pyrimidine-5-yl)8-azabicyclo[3.2.1]oct-3-ene-8-carboxylate (6.32 g, 10.5 mmol, preparation described previously) in CH$_3$CN (50 mL) was added NIS (2.60 g, 11.5 mmol). The resulting solution was stirred at rt for 1 h. The reaction was quenched with Na$_2$S$_2$O$_4$ and CH$_3$CN was evaporated. The aqueous residue was extracted with EtOAc, washed with brine, dried over Na$_2$S$_2$O$_4$ and concentrated. The crude product was purified by a SiO$_2$ column (0-15% EtOAc/Hexanes, $R_f = 0.4$ in 20% EtOAc) to afford the titled compound as a pale yellow oil (6.94 g).

Step 2: Preparation of (1R,5S)-tert-butyl 3-(7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidine-5-yl)8-azabicyclo[3.2.1]oct-3-ene-8-carboxylate

413
This compound was prepared from (1R,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-iodopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]oct-3-ene-8-carboxylate and 2-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine, following essentially the similar procedures given in Preparative Example 1-1.

**Step 3: Preparation of (1R,3r,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate and (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate**

To solution of (1R,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]oct-3-ene-8-carboxylate (251 mg, 0.332 mmol) and Mn(dpdpm)_3 (5.0 mg, 0.0083 mmol) in a mixed solvent of IPA/DCM (1.4/0.2 mL) under an oxygen atmosphere was added PhSiH_3 (82.5 μL, 0.664 mmol). The resulting mixture was stirred at 0 °C for 3 h. The reaction was quenched with sat. Na_2S_2O_3 and stirred at rt for 1 h. Brine was added and the mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SC_4 and concentrated. The crude
product was purified by a S1O2 column (0-30% EtOAc/Hexanes) to afford the major product ($R_f = 0.65$ in 50% EtOAc/Hexanes) as a pale yellow oil (164 mg), and the minor isomer ($R_f = 0.75$ in 50% EtOAc/Hexanes) as a pale yellow solid (46 mg).

**Step 4: Preparation of 1-(7-amino-5-((1R,3r,5S)-3-hydroxy-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone**

This compound was prepared from (1R,3r,5S)-tert-butyl 3-(7-((bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate, following essentially the similar procedures given in Preparative Example 1-1. Following similar procedures the following compounds were prepared (Table 8-8):

<table>
<thead>
<tr>
<th>Compound ID</th>
<th>Structures</th>
<th>Compound Name</th>
<th>N-H (calculated/observed)</th>
<th>pAKT S473 IC50</th>
<th>pMEK1/2 Thr202/204 IC50</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.21</td>
<td><img src="image" alt="Structure" /></td>
<td>1-(7-amino-5-((1R,3r,5S)-3-hydroxy-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone</td>
<td>S50.2/S50.2</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>No.</td>
<td>Scheme</td>
<td>Molecular Structure</td>
<td>Formula</td>
<td>Molecular Weight</td>
<td>Stereoisomers</td>
</tr>
<tr>
<td>-----</td>
<td>---------</td>
<td>---------------------</td>
<td>---------</td>
<td>------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>8.22</td>
<td><img src="image1" alt="Molecular Structure" /></td>
<td>( (1R,3r,5S)-3-(7\text{amino-6-(methylsulfonyl)}-3-(6-phenylpyridin-3-yl)pyrazol[1,5-a]pyrimidin-5-yl)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone )</td>
<td>586.2/586.2 B C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.23</td>
<td><img src="image2" alt="Molecular Structure" /></td>
<td>( (1R,3r,5S)-3-(7\text{amino-3-(6-phenylpyridin-3-yl)pyrazol[1,5-a]pyrimidin-5-yl)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone )</td>
<td>508.2/508.1 C C</td>
<td></td>
<td></td>
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<tr>
<td>8.24</td>
<td><img src="image3" alt="Molecular Structure" /></td>
<td>( (1R,3r,5S)-3-(7\text{amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazol[1,5-a]pyrimidin-5-yl)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone )</td>
<td>548.2/548.2 B C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.25</td>
<td><img src="image4" alt="Molecular Structure" /></td>
<td>( (1R,3s,5S)-3-(7\text{amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazol[1,5-a]pyrimidin-5-yl)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone )</td>
<td>548.2/548.2 B C</td>
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</tr>
</tbody>
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Scheme 8-2
Example 8-9

Preparation of 1-(5-(9-(1H-1,2,4-triazole-3-carbonyl)-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone
Step 1
Preparation of tert-butyl 7-(4, 4, 5, 5-tetramethyl-1,3, 2-dioxaborolan-2-yl)-3-oxa-9-azabicyclo[3.3. 1]non-6-ene-9-carboxylate (C)

Compound A was prepared following literature procedures (US2008080462).

Preparation of B: Substrate A (500 mg, 2.07 mmol) was dissolved in THF (6 mL) and cooled to -78 °C and treated with LDA (1.55 mL, 3.11 mmol, 2M solution). After 5 min., W-phenylbis(trifluoromethanesulfonimide) (81.71 mg, 2.28 mmol) in THF (6 mL) was added dropwise. The mixture was stirred at -78 °C for 30 min. and then gradually warmed to rt and continued to stir until starting material completely disappeared (-1.5 h). The reaction was quenched with saturated aqueous ammonium chloride (20 mL) followed by addition of ethyl acetate (50 mL). Two layers were separated and organic layer was collected. The aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic layer was washed with water (1 x 100 mL), brine (1 x 100 mL) and dried (Na₂SO₄), filtered and evaporated under reduced pressure to provide crude material which was purified by column chromatography (0-40% hexane-ethyl acetate) to give desired product B (701 mg).

Preparation of C: A mixture of substrate B (701 mg, 1.879 mmol), bis(pinacolato)diboron (573.1 mg, 2.256 mmol), Pd(dppf)Cl₂.C₂H₂Cl₂ (87.1 mg, 0.112 mmol), dppf (65.4 mg, 0.118 mmol) and KOAc (554 mg, 5.64 mmol) in dioxane (11
was heated under argon at 80 °C for 16 h. Upon cooling, the solvent was evaporated off under reduced pressure and the residue was dissolved in ethyl acetate (50 mL). The organic layer was washed with water (1 x 50 ml), brine (1 x 50 ml), dried (Na$_2$SO$_4$) and evaporated under reduced pressure to give crude material which was purified by column chromatography (0-40% hexane-ethyl acetate) to provide the desired product C (390 mg) as a white solid.

Step 2
Preparation of tert-butyl 7-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)pyrazolo[1,5-a]pyrimidin-5-yl)-3-oxa-9-azabicyclo[3.3.1]non-6-ene-9-carboxylate (E)

A solution of D (1.01 g, 2.35 mmol) in DME (18 mL) was treated with boronate C (910 mg, 2.59 mmol), Pd(dppf)Cl$_2$.CH$_2$Cl$_2$ (191 mg, 0.24 mmol), 2M aqueous Na$_2$CO$_3$ (9.1 mL) under argon and heated at 100 °C for 16 h. Upon cooling, water (50 mL) and ethyl acetate (70 mL) was added. Two layers were separated and organic layer was collected. Aqueous layer was then extracted with ethyl acetate (2 x 70 mL). Combined organic layer was washed with brine (1 x 150 mL), dried (Na$_2$SO$_4$) and evaporated under reduced pressure to give crude material which was purified by column chromatography (0-40% hexane-ethyl acetate) to provide the desired product E (1.27 g). HPLC-MS $t_R=3.09$ min (UV 254 nm). Mass calculated for formula C$_{30}$H$_{51}$N$_{10}$S$_{17}$O$_7$: 618.2 (m/z). Observed M+H$^+$ (LCMS) 618.2 (m/z).

Step 3
Preparation of tert-butyl 7-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)pyrazolo[1,5-a]pyrimidin-5-yl)-3-oxa-9-azabicyclo[3.3.1]non-6-ene-9-carboxylate (F)
Substrate E (1.27 g, 2.06 mmol) in EtOAc (50 mL) was hydrogenated at 50 °C using 10 % Pd/C catalyst (200 mg) and 1 atmospheric hydrogen pressure for 16 h. After filtering off the catalyst, the solvent was evaporated off under reduced pressure and crude material was purified by column chromatography (0-40% hexane-ethyl acetate) to give desired product F (1.1 g). HPLC-MS t_R = 3.15 min (UV 254 nm). Mass calculated for formula C_9H_25N_5O_5Si_2 619.3; observed M+H^+ (LCMS) 620.2 (m/z).

Step 4
Preparation of tert-butyl 7-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-iodopyrazolo[1,5-a]pyrimidin-5-yl)-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate (G)

Substrate F (1.1 g, 1.77 mmol) was suspended in acetonitrile (20 mL) and treated with NIS (396.4 mg, 1.77 mmol) at room temperature. The mixture was stirred for 30 min. Then solvent was evaporated off under reduced pressure, and the crude material was purified by column chromatography (S102, 0-40% hexane-EtOAc) to provide desired compound G (1.37 g). HPLC-MS t_R = 3.37 min (UV 254 nm). Mass calculated for formula C_23H_27I_2N_5O_5Si_2 745.2; observed M+H^+ (LCMS) 746.0 (m/z).

Step 5
Preparation of tert-butyl 7-(7-((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate (H)

The iodide G (1.37 g, 1.84 mmol) in dioxane (10 mL) and water (2.5 mL) was treated with boronate (1.22 g, 3.2 mmol), Pd(dppf)Cl₂·CH₂Cl₂ (182.6 mg, 0.22 mmol) and K₂CO₃ (763 mg, 5.52 mmol) under argon and heated at 100 °C for 16 h. Upon cooling, the mixture was filtered through Celite and the filtrate was evaporated off under reduced pressure to give crude residue which was purified by column chromatography (SiO₂, 0-40% hexane-EtOAc) to provide desired product H (1.14 g). HPLC-MS \( t_R = 3.49 \text{ min (UV } \lambda_{254 \text{ nm})} \). Mass calculated for formula \( \text{C}_{41}\text{H}_{60}\text{N}_{10}\text{O}_{2}\text{Si}_2 \) 772.4; observed \( \text{M}+\text{H}^+ \) (LCMS) 773.2 (m/z).

Step 6
Preparation of tert-butyl 7-((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate (I)

Substrate H (1.14 g, 1.47 mmol) was suspended in acetonitrile (15 mL) and treated with NBS (263.1 mg, 1.47 mmol) at room temperature. The mixture was
stirred for 30 min. Then solvent was evaporated off under reduced pressure, and the crude material was purified by column chromatography \( \text{S102, 0-40% hexane-EtOAc} \) to provide desired compound I (1.13 g). HPLC-MS \( t_R=3.58 \text{ min (UV } 254 \text{ nm)} \). Mass calculated for formula \( \text{C}_{41}\text{H}_{92}\text{BrN}_{8}\text{O}_{2} \text{Si}_{2} 850.3 \); observed \( \text{M}^+ \) (LCMS) 851.2 (m/z).

**Step 7**

Preparation of tert-butyl 7-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(1-ethoxyvinyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate (J)

Substrate I (1.13 g, 1.33 mmol) in dioxane (20 mL) was treated with \( \text{Pd(PPh}_3)_4 \) (307.2 mg, 0.26 mmol) and tributyl(1-ethoxyvinyl)tin (1.35 mL, 3.99 mmol) under argon and the mixture was heated at 100 °C for 16 h. Upon cooling, the mixture was filtered through a pad of 10%KF-SiC\(_3\) and the filtrate was evaporated off under reduced pressure to give a residue which was purified by column chromatography \( \text{S102, 0-40% hexane-EtOAc} \) to provide desired compound J (1.08 g). HPLC-MS \( t_R=3.65 \text{ min (UV } 254 \text{ nm)} \). Mass calculated for formula \( \text{C}_{45}\text{H}_{66}\text{N}_{8}\text{O}_{6}\text{Si}_{2} 842.4 \); observed \( \text{M}^+ \) (LCMS) 843.2 (m/z).

**Step 8**

Preparation of 1-(7-amino-5-(3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone (K)
Substrate \( J \) (1.08 g, 1.28 mmol) was treated with TFA-H\(_2\)O (1:1, 24 mL) at rt and the mixture was stirred for 16 h. Then the solvent was evaporated off under reduced pressure and the material was lyophilized from acetonitrile:water (3:1) to give yellow solid \( K \) (612 mg) which was used without further purification. HPLC-MS \( t_R = 1.16 \) min (UV 204 nm). Mass calculated for formula C\(_{26}\)H\(_{30}\)N\(_6\)O\(_2\) 454.2; observed \( M^{+} \) (LCMS) 455.2 (m/z).

**Step 9**

Preparation of 1-((5-(9-(1H-1,2,4-triazole-3-carbonyl)-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone (L)

Carboxylic acid (0.44 mmol) in DMF (2 mL) was treated with EDCI (0.68 mmol) and HOBr (0.34 mmol). Then substrate \( K \) (0.33 mmol) followed by DIEA (1.69 mmol) was added. After 30 min, the reaction mixture was treated with water (0.4 mL) and DMSO-MeCN (3:1, 3 mL). Pure compound L was isolated by preparative HPLC.
HPLC-MS $t_R = 3.18$ min (UV 254 nm). Mass calculated for formula $C_{29}H_{27}N_{9}O_{3}$ 549.2; observed $M+H^+$ (LCMS) 549.9 (m/z).

Following the Scheme 8-2 and the procedures similar to preparation of 1-(5-(9-(1H-1,2,4-triazole-3-carbonyl)-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone, the following compounds (Table 8-9) can be prepared:

<table>
<thead>
<tr>
<th>Table 8-9</th>
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<tbody>
<tr>
<td>Example 8-10</td>
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<tr>
<td>Preparation of 1-(5-(9-(1H-1,2,4-triazole-3-carbonyl)-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone</td>
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<td>1-(5-(9-(1H-1,2,4-triazole-3-carbonyl)-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone</td>
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<tr>
<td>539.2</td>
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<td>1-(7-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)-2-hydroxyethanone</td>
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<tr>
<td>513.2</td>
</tr>
<tr>
<td>B</td>
</tr>
<tr>
<td>B</td>
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</table>

Example 8-10

Preparation of 1-(7-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)-2-hydroxyethanone
Step 1

Synthesis of tert-butyl 7-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(methylthio)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate

Substrate (303 mg, 0.35 mmol) in DMF (6 mL) was treated with Al₂O₃ (537.7 mg, 5.3 mmol) and NaSMe (73.54 mg, 1.05 mmol) under argon and the mixture was heated at 80 °C for 16 h. Upon cooling, the mixture was filtered through a pad of Celite and the filtrate was evaporated off under reduced pressure to give a residue which was purified by column chromatography (S1O2, 0-80% hexane-EtOAc) to provide desired compound tert-butyl 7-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(methylthio)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate.

Step 2
Preparation of tert-butyl 7-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate

Method A

Substrate (234 mg, 0.28 mmol) was dissolved in MeOH (12 mL) and water (3 mL) and treated with NaHCO$_3$ (237.3 mg, 2.86 mmol) followed by oxone (878 mg, 1.43 mmol). The mixture was stirred for 12 h and treated with CH$_2$Cl$_2$ and filtered. The filtrate was washed with water and the organic layer was dried (Na$_2$SO$_4$), filtered and evaporated under reduced pressure to give crude product tert-butyl 7-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate.

Method B

Step A: Preparation of tert-butyl 7-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-iodo-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate
Substrate (300 mg, 0.38 mmol) (isomer I was separated from isomer II by chiral HPLC) was dissolved in MeCN (10 mL) and treated with AcOH (0.44 mL, 7.76 mmol) and NIS (174.86 mg, 0.77 mmol). The mixture was stirred overnight and the solvent was evaporated off. The residue was then purified by the column chromatography. Isomer II was also processed similarly to obtaining corresponding iodide.

**Step B: Preparation of tert-butyl 7-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate**

Substrate (220 mg, isomer I, 0.24 mmol) was dissolved in DMSO (2.5 mL) under argon and treated with Cul (278.8 mg, 1.46 mmol) and MeSO_2Na (74.66 mg, 0.732 mmol). The mixture was heated at 90 °C for 4 h and the cooled to room temperature and diluted with EtOAc (10 mL). It was filtered and the filtrate was washed with water (15 ml) and saturated NH_4Cl (15 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated under reduced pressure to provide crude material which was purified by column chromatography (0-80% hexane-ethyl acetate) to give desired product tert-butyl 7-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate. Similarly isomer 2 was also processed.

**Step 3**
Preparation of 5-(3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine

Crude substrate was treated with TFA-H2O (1:1, 6 mL) at room temperature and the mixture was stirred for 16 h. Then the solvent was evaporated off under reduced pressure and the material was lyophilized from acetonitrile:water (3:1) to give a yellow solid which was used without further purification.

Step 4
Preparation of (7-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)(1H-1,2,4-triazol-3-yl)methanone

Carboxylic acid (120 mg) in DMF (2 mL) was treated with EDCI (122 mg) and HOBt (61.2 mg). Then substrate (122 mg) was added followed by DIEA (0.3 mL).
After the reaction was complete, the reaction mixture was treated with water (0.4 mL) and DMSO-MeCN (3:1, 3 mL). Pure compound was isolated by preparative HPLC.

Final stereochemical\textsuperscript{a} pure isomer was prepared following similar procedures.

Example 8-11

Preparation of endo/exo-7-[6-acetyl-7-amino-3-(6-phenyl-3-pyridinyl)pyrazolo[1,5-a]pyrimidin-5-yl]-9-(4h-1,2,4-triazol-3-ylcarbonyl)-3-thia-9-azabicyclo[3.3.1]nonane, 3,3-dioxide

\begin{align*}
\text{Step1} \\
\text{Synthesis of tert-butyl 7-oxo-3-thia-9-azabicyclo[3.3.1]nonane-9-carboxylate}
\end{align*}

The substrate 3-thia-9-azabicyclo[3.3.1]nonan-7-one (Bowers, Simeon; Probst, Gary D.; Truong, Anh P.; Horn, Roy K.; Konradi, Andrei W.; Sham, Hing L.; Garofalo, Albert W.; Wong, Karina; Goldbach, Erich; Quinn, Kevin P.; Sauer, John-Michael; Wallace, William; Nguyen, Lan; Hemphill, Susanna S.; Bova, Michael P.; Basi, Guriqbal S. Bioorganic & Medicinal Chemistry Letters 2009, 19, 6952-6956) (1.068 g, 5.63 mmol) was dissolved in EtOH (50 ml) and treated with Et\textsubscript{3}N (1.17 mL, 8.44 mmol) and BOC\textsubscript{2}O (1.35 g, 6.14 mmol). The mixture was stirred at room
temperature and then the solvent was evaporated off to provide a residue which was purified by column chromatography.

**Step 2**

Preparation of tert-butyl 7-(trifluoromethylsulfonyloxy)-3-thia-9-azabicyclo[3.3.1]non-6-ene-9-carboxylate

Substrate (400 mg, 1.55 mmol) was dissolved in THF (15 mL) and cooled to -78 °C and treated with LDA (1.29 mL, 2.33 mmol, 2M solution). After 5 min., N-phenylbis(trifluoromethanesulfonimide) (606.9 mg, 1.7 mmol) in THF (15 mL) was added dropwise. The mixture was stirred at -78 °C for 30 min. and then gradually warmed to rt and continued to stir until starting material completely disappeared (~1.5 h). The reaction was quenched with saturated aqueous ammonium chloride (20 mL) followed by addition of ethyl acetate (50 mL). Two layers were separated and organic layer was collected. The aqueous layer was extracted with ethyl acetate (2 × 50 mL). The combined organic layer was washed with water (1 × 100 mL), brine (1 × 100 mL) and dried (Na₂SO₄), filtered and evaporated under reduced pressure to provide crude material which was purified by column chromatography (0-40% hexane-ethyl acetate) to give desired product tert-butyl 7-(trifluoromethylsulfonyloxy)-3-thia-9-azabicyclo[3.3.1]non-6-ene-9-carboxylate (704 mg).

**Step 3**

Preparation of tert-butyl 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-thia-9-azabicyclo[3.3.1]non-6-ene-9-carboxylate
A mixture of substrate (704 mg, 1.81 mmol), bis(pinacolato)diboron (551.8 mg, 2.17 mmol), Pd(dppf)Cl₂·CH₂Cl₂ (88.2 mg, 0.133 mmol), dpff (63.4 mg, 0.114 mmol) and KOAc (548 mg, 5.57 mmol) in dioxane (10 ml) was heated under argon at 80 °C for 16 h. Upon cooling, the solvent was evaporated off under reduced pressure and the residue was dissolved in ethyl acetate (50 mL). The organic layer was washed with water (1 x 50 ml), brine (1 x 50 mL), dried (Na₂SO₄) and evaporated under reduced pressure to give crude material which was purified by column chromatography (0-40% hexane-ethyl acetate) to provide the desired product tert-butyl 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-thia-9-azabicyclo[3.3.1]non-6-ene-9-carboxylate.

Step 4

Preparation of tert-butyl 7-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)pyrazolo[1,5-a]pyrimidin-5-yl)-3-thia-9-azabicyclo[3.3.1]non-6-ene-9-carboxylate

A solution of 5-chloro-N,N-bis((2-(trimethylsilyl)ethoxy)methyl)pyrazolo[1,5-a]pyrimidin-7-amine (239.6 mg, 0.56 mmol) in DME (7.4 mL) was treated with boronate (206 mg, 0.56 mmol), Pd(dppf)Cl₂·CH₂Cl₂ (78.3 mg, 0.098 mmol), 2M aqueous Na₂CO₃ (3.68 ml) under argon and heated at 100 °C for 16 h. Upon cooling, water (50 mL) and ethyl acetate (70 mL) was added. Two layers were separated and the organic layer was collected. Aqueous layer was then extracted with ethyl acetate (2 x 70 mL). Combined organic layer was washed with brine (1 x
150 mL), dried (Na2SC4) and evaporated under reduced pressure to give crude material which was purified by column chromatography (0-40% hexane-ethyl acetate) to provide the desired product tert-butyl 7-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)pyrazolo[1,5-a]pyrimidin-5-yl)-3-thia-9-azabicyclo[3.3.1]nonane-9-carboxylate (262 mg).

Step 5
Preparation of tert-butyl 7-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)pyrazolo[1,5-a]pyrimidin-5-yl)-3-thia-9-azabicyclo[3.3.1]nonane-9-carboxylate

Substrate (744 mg, 1.17 mmol) in EtOAc (25 mL) was hydrogenated at 50 °C using 10% Pd/C catalyst (520 mg) and 1 atmospheric hydrogen pressure for 16 h. After filtering off the catalyst, the solvent was evaporated off under reduced pressure and the crude material was purified by column chromatography (0-40% hexane-ethyl acetate) to give the desired product tert-butyl 7-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)pyrazolo[1,5-a]pyrimidin-5-yl)-3-thia-9-azabicyclo[3.3.1]nonane-9-carboxylate as a mixture of stereoisomers.

Step 6
Preparation of tert-butyl 7-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-iodopyrazolo[1,5-a]pyrimidin-5-yl)-3-thia-9-azabicyclo[3.3.1]nonane-9-carboxylate

NIS, MeCN, rt, 30 min
Substrate (61 mg, 0.096 mmol) was suspended in acetonitrile (2 mL) and treated with NIS (23.77 mg, 0.105 mmol) at room temperature. The mixture was stirred for 30 min. Then solvent was evaporated off under reduced pressure, and the crude material was purified by column chromatography (SiO₂, 0-40% hexane-EtOAc) to provide the desired product tert-butyl 7-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-iodopyrazolo[1,5-a]pyrimidin-5-yl)-3-thia-9-azabicyclo[3.3.1]nonane-9-carboxylate.

**Step 7**

*Preparation of tert-butyl 7-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3-thia-9-azabicyclo[3.3.1]nonane-9-carboxylate*

The substrate (279 mg, 0.366 mmol) in dioxane (14 mL) and water (3.5 mL) was treated with boronate (162.6 mg, 0.55 mmol), Pd(dppf)Cl₂·CH₂Cl₂ (40.66 mg, 0.048 mmol) and K₂CO₃ (162.6 mg, 1.11 mmol) under argon and heated at 100 °C for 16 h. Upon cooling, the mixture was filtered through Celite and the filtrate was evaporated off under reduced pressure to give crude residue which was purified by column chromatography (SiO₂, 0-40% hexane-EtOAc) to provide desired product tert-butyl 7-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3-thia-9-azabicyclo[3.3.1]nonane-9-carboxylate.

**Step 8**

*Preparation of intermediate sulfone*
The substrate (157 mg, 0.199 mmol) was dissolved in MeOH (5 mL) and CH₂Cl₂ (10 mL) at room temperature and treated with oxone (269 mg, 0.478 mmol) in water (4 mL). After reaction was complete, solvent was evaporated and the residue was taken up in EtOAc (20 mL). Washing with saturated aqueous NaHCO₃ (20 mL), brine (20 mL), drying (Na₂SO₄), filtration and evaporation under reduced pressure gave the crude product which as purified by column chromatography.

Step 9
Preparation of intermediate bromide

Substrate (66 mg, 0.08 mmol) was suspended in acetonitrile (2 mL) and treated with NBS (15.73 mg, 0.088 mmol) at room temperature. The mixture was stirred for 30 min. Then solvent was evaporated off under reduced pressure, and the crude material was purified by column chromatography (SiO₂, 0-40% hexane-EtOAc) to provide desired compound.

Step 10
Preparation of intermediate vinyl ether
Substrate (64 mg, 0.071 mmol) in dioxane (4 mL) was treated with Pd(PPh₃)₄ (7.92 mg, 0.006 mmol) and tributyl(1-ethoxyvinyl)tin (46.6 µL, 0.13 mmol) under argon and the mixture was heated at 100 °C for 16 h. Upon cooling, the mixture was filtered through a pad of 10%KF-SiO₂ and the filtrate was evaporated off under reduced pressure to give a residue which was purified by column chromatography (SiO₂, 0-40% hexane-EtOAc) to provide desired product.

**Step 11**

*Preparation of intermediate ketone*

Substrate (45 mg, 0.05 mmol) was treated with TFA-H₂O (10 mL, 1:1) at room temperature and the mixture was stirred for 16 h. Then the solvent was evaporated off under reduced pressure and the material was lyophilized from acetonitrile:water (3:1) to give the desired product which was used without further purification.
Step 12

Preparation of endo/exo-7-[6-acetyl-7-amino-3-(6-phenyl-3-pyridinyl)pyrazolo[1,5-a]pyrimidin-5-yl]-9-(4h-1,2,4-triazol-3-ylcarbonyl)-3-thia-9-azabicyclo[3.3.1]nonane, 3,3-dioxide

Carboxylic acid (60 mg) in DMF (1 mL) was treated with EDCI (270 mg) and HOBt (122 mg). Then substrate (26 mg) followed by DIEA (0.48) was added. Then the reaction mixture was treated with water (0.1 mL) and DMSO-MeCN (3:1, 3 mL). Pure product was isolated by preparative HPLC.

Example 8-12

Preparation of 1-(5-((1R,5S)-9-(1H-1,2,4-triazole-3-carbonyl)-9-azabicyclo[3.3.1]nonan-3-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone
Step 1
Preparation of tert-butyl 3-(trifluoromethylsulfonyloxy)-9-azabicyclo[3.3.1]non-3-ene-9-carboxylate

Substrate (1.0 g, 4.18 mmol) was dissolved in THF (50 mL) and cooled to -78 °C and treated with LDA (3.15 mL, 6.27 mmol, 2M solution). After 5 min., N-phenylbis(trifluoromethanesulfonimide) (1.64 g, 4.59 mmol) in THF (15 mL) was added dropwise. The mixture was stirred at -78 °C for 30 min. and then gradually warmed to rt and continued to stir until starting material completely disappeared (-1.5 h). The reaction was quenched with saturated aqueous ammonium chloride (80 mL) followed by addition of ethyl acetate (100 mL). Two layers were separated and the organic layer was collected. The aqueous layer was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with water (1 × 100 mL), brine (1 × 100 mL) and dried (Na2SO4), filtered and evaporated under reduced pressure to provide crude material which was purified by column chromatography (0-40% hexane-ethyl acetate) to give the desired product tert-butyl 3-(trifluoromethylsulfonyloxy)-9-azabicyclo[3.3.1]non-3-ene-9-carboxylate.

Step 2
Preparation of tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-9-azabicyclo[3.3.1]non-3-ene-9-carboxylate

Substrate (1.0 g, 4.18 mmol) was dissolved in THF (50 mL) and cooled to -78 °C and treated with LDA (3.15 mL, 6.27 mmol, 2M solution). After 5 min., N-phenylbis(trifluoromethanesulfonimide) (1.64 g, 4.59 mmol) in THF (15 mL) was added dropwise. The mixture was stirred at -78 °C for 30 min. and then gradually warmed to rt and continued to stir until starting material completely disappeared (-1.5 h). The reaction was quenched with saturated aqueous ammonium chloride (80 mL) followed by addition of ethyl acetate (100 mL). Two layers were separated and the organic layer was collected. The aqueous layer was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with water (1 × 100 mL), brine (1 × 100 mL) and dried (Na2SO4), filtered and evaporated under reduced pressure to provide crude material which was purified by column chromatography (0-40% hexane-ethyl acetate) to give the desired product tert-butyl 3-(trifluoromethylsulfonyloxy)-9-azabicyclo[3.3.1]non-3-ene-9-carboxylate.
A mixture of substrate (1.46 g, 3.95 mmol), bis(pinacolato)diboron (1.2 g, 4.75 mmol), Pd(dppf)Cl$_2$.CH$_2$Cl$_2$ (184 mg, 0.236 mmol), dppf (138 mg, 0.249 mmol) and KOAc (1.16 g, 11.85 mmol) in dioxane (80 ml) was heated under argon at 80 °C for 16 h. Upon cooling, the solvent was evaporated off under reduced pressure and the residue was dissolved in ethyl acetate (100 mL). The organic layer was washed with water (1 x 100 ml), brine (1 x 50 mL), dried (Na$_2$SO$_4$) and evaporated under reduced pressure to give crude material which was purified by column chromatography (0-40% hexane-ethyl acetate) to provide the desired product tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)pyrazolo[1,5-a]pyrimidin-5-yl)-9-azabicyclo[3.3.1]non-3-ene-9-carboxylate.

**Step 3**

Preparation of tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)pyrazolo[1,5-a]pyrimidin-5-yl)-9-azabicyclo[3.3.1]non-3-ene-9-carboxylate

A solution of 5-chloro-N,N-bis((2-(trimethylsilyl)ethoxy)methyl)pyrazolo[1,5-a]pyrimidin-7-amine (1.42 g, 3.31 mmol) in DME (20 mL) was treated with boronate (1.28 g, 3.68 mmol), Pd(dppf)Cl$_2$.CH$_2$Cl$_2$ (268 mg, 0.335 mmol), 2M aqueous Na$_2$CO$_3$ (12.79 mL) under argon and heated at 100 °C for 16 h. Upon cooling, water (50 mL) and ethyl acetate (70 mL) was added. Two layers were separated and organic layer was collected. The aqueous layer was then extracted with ethyl acetate (2 x 70 mL). Combined organic layers were washed with brine (1 x 150 mL), dried (Na$_2$SO$_4$) and evaporated under reduced pressure to give crude material which was purified by column chromatography (0-40% hexane-ethyl acetate) to provide the desired product tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)pyrazolo[1,5-a]pyrimidin-5-yl)-9-azabicyclo[3.3.1]non-3-ene-9-carboxylate.
Step 4
Preparation of tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)pyrazolo[1,5-a]pyrimidin-5-yl)-9-azabicyclo[3.3.1]nonane-9-carboxylate

Substrate (1.25 g, 2.03 mmol) in EtOAc (100 mL) was hydrogenated at 50 °C using 10% Pd/C catalyst (159 mg) and 1 atmospheric hydrogen pressure for 16 h. After filtering off the catalyst, the solvent was evaporated off under reduced pressure and crude material was purified by column chromatography (0-40% hexane-ethyl acetate) to give the desired product tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)pyrazolo[1,5-a]pyrimidin-5-yl)-9-azabicyclo[3.3.1]nonane-9-carboxylate as a mixture of stereoisomers.

Step 5
Preparation of tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-iodopyrazolo[1,5-a]pyrimidin-5-yl)-9-azabicyclo[3.3.1]nonane-9-carboxylate

Substrate (611 g, 0.99 mmol) was suspended in acetonitrile (10 mL) and treated with NIS (221.8 mg, 0.99 mmol) at room temperature. The mixture was stirred for 30 min. Then solvent was evaporated off under reduced pressure, and the crude material was purified by column chromatography (SiO2, 0-40% hexane-EtOAc) to provide desired compound tert-butyl 3-(7-(bis((2-
Step 6

Preparation of tert-butyl \(3-(7\text{-}(\text{bis}(2\text{-}(\text{trimethylsilyl})\text{ethoxy})\text{methyl})\text{amino})\text{-}3\text{-}(6\text{-}\text{phenylpyridin-3-yl})\text{pyrazolo}[1,5\text{-}a]\text{pyrimidin-5-yl})\text{-}9\text{-}\text{azabicyclo}[3.3.1]\text{nonane-9-carboxylate}\).

The substrate (695 mg, 0.93 mmol) in dioxane (10 mL) and water (2.5 mL) was treated with boronate (615 mg, 1.62 mmol), \(\text{Pd(dppf)}\text{Cl}_2\cdot\text{CH}_2\text{Cl}_2\) (90.3 mg, 0.106 mmol) and \(\text{K}_2\text{CO}_3\) (385 mg, 2.63 mmol) under argon and heated at 100 °C for 16 h. Upon cooling, the mixture was filtered through Celite and the filtrate was evaporated off under reduced pressure to give crude residue which was purified by column chromatography (SiO\(_2\), 0-40% hexane-ETOAc) to provide the desired product tert-butyl \(3-(7\text{-}(\text{bis}(2\text{-}(\text{trimethylsilyl})\text{ethoxy})\text{methyl})\text{amino})\text{-}3\text{-}(6\text{-}\text{phenylpyridin-3-yl})\text{pyrazolo}[1,5\text{-}a]\text{pyrimidin-5-yl})\text{-}9\text{-}\text{azabicyclo}[3.3.1]\text{nonane-9-carboxylate}.

Step 7

Preparation of tert-butyl \(3-(7\text{-}(\text{bis}(2\text{-}(\text{trimethylsilyl})\text{ethoxy})\text{methyl})\text{amino})\text{-}6\text{-}\text{bromo}-3\text{-}(6\text{-}\text{phenylpyridin-3-yl})\text{pyrazolo}[1,5\text{-}a]\text{pyrimidin-5-yl})\text{-}9\text{-}\text{azabicyclo}[3.3.1]\text{nonane-9-carboxylate}.
Substrate (500 mg, 0.649 mmol) was suspended in acetonitrile (10 mL) and treated with NBS (127.13 mg, 0.71 mmol) at room temperature. The mixture was stirred for 30 min. Then solvent was evaporated off under reduced pressure, and the crude material was purified by column chromatography (S1O2, 0-40% hexane-EtOAc) to provide the desired compound tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-9-azabicyclo[3.3.1]nonane-9-carboxylate.

Step 8
Preparation of tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(1-ethoxyvinyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-9-azabicyclo[3.3.1]nonane-9-carboxylate

Substrate (499 mg, 0.588 mmol) in dioxane (6 mL) was treated with Pd(PPh3)4 (67.93 mg, 0.0588 mmol) and tributyl(1-ethoxyvinyl)tin (0.59 mL, 0.176 mmol) under argon and the mixture was heated at 100 °C for 16 h. Upon cooling, the mixture was filtered through a pad of 10%KF-SiC4 and the filtrate was evaporated off under reduced pressure to give a residue which was purified by column
chromatography (S1O2, 0-40% hexane-EtOAc) to provide the desired product tert-buty 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(1-ethoxyvinyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-9-azabicyclo[3.3.1]nonane-9-carboxylate.

Step 9
Preparation of 1-(7-amino-5-(9-azabicyclo[3.3.1]nonan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone

Substrate (45 mg, 0.05 mmol) was treated with TFA-H2O (10 mL, 1:1) at room temperature and the mixture was stirred for 16 h. Then the solvent was evaporated off under reduced pressure and the material was lyophilized from acetonitrile:water (3:1) to give compound which was used without further purification.

Step 10
Preparation of 1-(5-((1R,5S)-9-(1H-1,2,4-triazole-3-carbonyl)-9-azabicyclo[3.3.1]nonan-3-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone
Carboxylic acid (63.1 mg) in DMF (2 mL) was treated with EDCI (170 mg) and 
HOBt (56.3 mg). Then substrate (136 mg) followed by DIEA (0.36) was added. Once 
the reaction was complete, the reaction mixture was treated with water (0.1 mL) and 
DMSO-MeCN (3:1, 3 mL). Pure compound was isolated by preparative HPLC.

Example 8-13

Preparation of ((1R,5S)-7-(7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-
5-yl)-3,9-diazabicyclo[3.3.1]nonan-9-yl) (1H-1,2,4-triazol-3-yl)methanone

Step 1
Preparation of 3-benzyl 9-tert-butyl 7-(trifluoromethyl)sulfonyloxy)-3,9-
diazabicyclo[3.3.1]non-6-ene-3, 9-dicarboxylate
Substrate (110 mg, 0.29 mmol) was dissolved in THF (5 mL) and cooled to -78 °C and treated with LDA (0.24 mL, 0.44 mmol, 2M solution). After 5 min., N-phenylbis(trifluoromethanesulfonylimide) (114.2 g, 0.32 mmol) in THF (5 mL) was added dropwise. The mixture was stirred at -78 °C for 30 min. and then gradually warmed to rt and continued to stir until starting material completely disappeared (-1.5 h). The reaction was quenched with saturated aqueous ammonium chloride (20 mL) followed by addition of ethyl acetate (50 mL). Two layers were separated and the organic layer was collected. The aqueous layer was extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed with water (1 × 100 mL), brine (1 × 50 mL) and dried (Na₂SO₄), filtered and evaporated under reduced pressure to provide crude material which was purified by column chromatography (0-40% hexane-ethyl acetate) to give the desired product 3-benzyl 9-tert-butyl 7-(trifluoromethylsulfonyloxy)-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylate.

**Step 2**

**Preparation of 3-benzyl 9-tert-butyl 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylate**

A mixture of substrate (52 mg, 0.10 mmol), bis(pinacolato)diboron (31.1 mg, 0.122 mmol), Pd(dpff)Cl₂·CH₂Cl₂ (5 mg, 0.006 mmol), dpff (3.59 mg, 0.006 mmol) and KOAc (30.1 mg, 0.30 mmol) in dioxane (80 mL) was heated under argon at 80 °C for 16 h. Upon cooling, the solvent was evaporated off under reduced pressure and the residue was dissolved in ethyl acetate (10 mL). The organic layer was washed with water (1 × 10 mL), brine (1 × 10 mL), dried (Na₂SO₄) and evaporated under...
reduced pressure to give crude material which was purified by column chromatography (0-40% hexane-ethyl acetate) to provide the desired product 3-benzyl 9-tert-butyl 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylate.

Step 3
Preparation of 3-benzyl 9-tert-butyl 7-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylate

A solution of chloride (24.01 mg, 0.041 mmol) in DME (2 mL) was treated with boronate (30 mg, 0.062 mmol), Pd(dppf)Cl₂·CH₂Cl₂ (5.73 mg, 0.007 mmol), 2M aqueous Na₂CO₃ (0.27 mL) under argon and heated at 100 °C for 16 h. Upon cooling, water (5 mL) and ethyl acetate (10 mL) was added. Two layers were separated and the organic layer was collected. The aqueous layer was then extracted with ethyl acetate (2 x 20 mL). Combined organic layers were washed with brine (1 x 15 mL), dried (Na₂SO₄) and evaporated under reduced pressure to give crude material which was purified by column chromatography (0-40% hexane-ethyl acetate) to provide the desired product 3-benzyl 9-tert-butyl 7-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylate.

Step 4
Preparation of tert-butyl 7-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3,9-diazabicyclo[3.3.1]nonane-9-carboxylate

Substrate (3.6 g, 0.39 mmol) in EtOAc (5 mL) was hydrogenated at 50 °C using 10% Pd/C catalyst (25 mg) and at 1 atmospheric hydrogen pressure for 16 h. After filtering off the catalyst, the solvent was evaporated off under reduced pressure and crude material was purified by column chromatography (0-40% hexane-ethyl acetate) to give the desired product as a mixture of stereoisomers.

Step 5
Preparation of (1R,5S)-tert-butyl 7-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-9-(1H-1,2,4-triazole-3-carbonyl)-3,9-diazabicyclo[3.3.1]nonane-9-carboxylate

Carboxylic acid (25 mg) in DMF (2 mL) was treated with EDCI (108.8 mg) and HOBt (49.1 mg). Then substrate (32 mg) followed by DIEA (0.19) was added. Once the reaction was complete the reaction mixture was treated with water (0.1 mL) and DMSO-MeCN (3:1, 3 mL). Pure compound (1R,5S)-tert-butyl 7-(7-(bis((2-
(trimethylsilyl)ethoxy)methyl)amino)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-9-(1 H-1,2,4-triazole-3-carbonyl)-3,9-diazabicyclo[3.3.1]nonane-3-carboxylate was isolated by preparative HPLC.

Step 6
Preparation of \(((1R,5S)-7-(7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3,9-diazabicyclo[3.3.1]nonan-9-yl)(1H-1,2,4-triazol-3-yl)ethanone

Substrate (45 mg, 0.05 mmol) was treated with TFA-H$_2$O (10 mL, 1:1) at room temperature and the mixture was stirred for 16 h. Then the solvent was evaporated off under reduced pressure and the material was purified by preparative HPLC to give the desired product.

Example 8-14
Preparation of 1-(7-amino-5-(1S,3R,5R)-6-hydroxy-8-(1 H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone
Step 1
Preparation of (1R,5R)-tert-butyl 6-(tert-butyldimethylsilyloxy)-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate

Substrate (918 mg, 3.79 mmol) was dissolved in DMF (50 mL) and treated with imidazole (515.4 mg, 7.58 mmol) and TBSCI (625.5 mg, 4.17 mmol). The mixture was stirred at room temperature for 12 h. The reaction was diluted with EtOAc (200 mL) and washed with water (200 mL), saturated aqueous NaHCO$_3$ (200 mL) and brine (200 mL). The organic layer was then dried (Na$_2$SO$_4$), filtered and evaporated under reduced pressure to provide crude material which was purified by column chromatography (SiO$_2$, 0-10% EtOAc-hexane).

Step 2
Preparation of (1R,5R)-tert-butyl 6-(tert-butyldimethylsilyloxy)-3-(trifluoromethylsulfonyloxy)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate

Substrate (334 mg, 0.94 mmol) was dissolved in THF (10 mL) and cooled to -78 °C and treated with LDA (0.83 mL, 1.41 mmol, 2M solution). After 5 min., N-phenylbis(trifluoromethanesulfonimide) (370 mg, 1.03 mmol) in THF (10 mL) was added dropwise. The mixture was stirred at -78 °C for 30 min. and then gradually warmed to rt and continued to stir until starting material completely disappeared (-1.5 h). The reaction was quenched with saturated aqueous ammonium chloride (20 mL) followed by addition of ethyl acetate (50 mL). Two layers were separated.
and the organic layer was collected. The aqueous layer was extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed with water (1 × 100 mL), brine (1 × 100 mL) and dried (Na₂SO₄), filtered and evaporated under reduced pressure to provide crude material which was purified by column chromatography (0-40% hexane-ethyl acetate) to give the desired product (1R,5R)-tert-butyl 6-(tert-butyldimethylsilyloxy)-3-(trifluoromethylsulfonyloxy)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate.

Step 3
Preparation of (1R,5R)-tert-butyl 6-(tert-butyldimethylsilyloxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate

A mixture of substrate (386 mg, 0.79 mmol), bis(pinacolato)diboron (240.8 mg, 0.94 mmol), Pd(dpdpf)Cl₂.CH₂Cl₂ (38.5 mg, 0.049 mmol), dpdp (27.65 mg, 0.0.048 mmol) and KOAc (239.5 mg, 2.43 mmol) in dioxane (5 ml) was heated under argon at 80 °C for 16 h. Upon cooling, the solvent was evaporated off under reduced pressure and the residue was dissolved in ethyl acetate (50 mL). The organic layer was washed with water (1 × 50 mL), brine (1 × 50 mL), dried (Na₂SO₄) and evaporated under reduced pressure to give crude material which was purified by column chromatography (0-40% hexane-ethyl acetate) to provide the desired product (1R,5R)-tert-butyl 6-(tert-butyldimethylsilyloxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate.

Step 4
Preparation of (1R,5R)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-phenyopyridin-3-yl)pyrazolo[1,5-alpyrimidin-5-yl)-6-(tert-butyldimethylsilyloxy)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate
A solution of chloride (600 mg, 1.03 mmol) in DME (7.4 mL) was treated with boronate (303 mg, 0.65 mmol), Pd(dppf)Cl$_2$, CH$_2$C$_2$I$_2$ (78.3 mg, 0.098 mmol), 2M aqueous Na$_2$CO$_3$ (3.5 mL) under argon and heated at 100 °C for 16 h. Upon cooling, water (50 mL) and ethyl acetate (70 mL) was added. Two layers were separated and the organic layer was collected. The aqueous layer was then extracted with ethyl acetate (2 x 70 mL). The combined organic layers were washed with brine (1 x 150 mL), dried (Na$_2$SO$_4$) and evaporated under reduced pressure to give crude material which was purified by column chromatography (0-40% hexane-ethyl acetate) to provide the desired product (1R,5R)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-6-(tert-butyl(dimethyl)silyloxy)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate.

Step 5
Preparation of (IS)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-6-(tert-butyl(dimethyl)silyloxy)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate
Substrate (490 mg, 0.67 mmol) in EtOAc (25 mL) was hydrogenated at 60 °C using 10 % Pd/C catalyst (150 mg) under 1 atmospheric hydrogen pressure for 16 h. After filtering off the catalyst, the solvent was evaporated off under reduced pressure and crude material was purified by column chromatography (0-40% hexane-ethyl acetate) to give the desired product (IS)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-6-(tert-butyldimethylsilyloxy)-8-azabicyclo[3.2.1]octane-8-carboxylate as a mixture of stereoisomers.

Step 6
Preparation of (1S,3R,5R)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-6-(tert-butyldimethylsilyloxy)-8-azabicyclo[3.2.1]octane-8-carboxylate

Substrate (387 mg, 0.43 mmol) was dissolved in THF (5 mL) and cooled to 0 °C and treated with t-BuOK (1.3 mmol, 1.3 mL, 1 M solution). The reaction mixture was warmed to room temperature and stirred for 30 min. Then the reaction was quenched with saturated NH₄Cl (10 mL) and EtOAc (30 mL) was added. The two layers were separated and the organic layer was collected. The organic layer was washed with brine (50 mL), dried (Na₂SO₄), and evaporated under reduced pressure to give a residue which was purified by column chromatography (SiO₂, 0-30% EtOAc-hexane).
Step 7
Preparation of (1S,3R,5R)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-6-(tert-butyldimethylsilyloxy)-8-azabicyclo[3.2.1]octane-8-carboxylate

Substrate (54 mg, 0.061 mmol) was suspended in acetonitrile (2 mL) and treated with NBS (12 mg, 0.067 mmol) at room temperature. The mixture was stirred for 30 min. Then solvent was evaporated off under reduced pressure, and the crude material was purified by column chromatography (SiO₂, 0-40% hexane-EtOAc) to provide the desired compound (1S,3R,5R)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-6-(tert-butyldimethylsilyloxy)-8-azabicyclo[3.2.1]octane-8-carboxylate.

Step 8
Preparation of (1S,3R,5R)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(1-ethoxyvinyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-6-(tert-butyldimethylsilyloxy)-8-azabicyclo[3.2.1]octane-8-carboxylate
Substrate (61 mg, 0.063 mmol) in dioxane (4 mL) was treated with Pd(PPh₃)₄ (7.92 mg, 0.006 mmol) and tributyl(1-ethoxyvinyl)tin (47.6 µL, 0.13 mmol) under argon and the mixture was heated at 100 °C for 16 h. Upon cooling, the mixture was filtered through a pad of 10%KF·SiO₂ and the filtrate was evaporated off under reduced pressure to give a residue which was purified by column chromatography (SiO₂, 0-40% hexane-EtOAc) to provide the desired product (1S,3R,5R)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(1-ethoxviny l)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-6-(tert-butyldimethylsilyloxy)-8-azabicyclo[3.2.1]octane-8-carboxylate.

Step 9
Preparation of 1-(7-amino-5-((1S,3R,5R)-6-hydroxy-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone

Substrate (45 mg, 0.05 mmol) was treated with TFA-H₂O (10 mL, 1:1) at room temperature and the mixture was stirred for 16 h. Then the solvent was evaporated off under reduced pressure and the material was lyophilized from acetonitrile:water (3:1) to give the desired compound which was used without further purification.
**Step 10**

*Preparation of 1-(7-amino-5-((1S,3R,5R)-6-hydroxy-8-(1H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone*

Carboxylic acid (49.2 mg, 0.145 mmol) in DMF (2 mL) was treated with EDCI (138.3 mg, 0.725 mmol) and HOBt (62.44 mg, 0.47 mmol). Then substrate (66.3 mg, 0.145 mmol) followed by DIEA (0.48) was added. Once the reaction was complete the reaction mixture was treated with water (0.1 mL) and DMSO-MeCN (3:1, 3 mL). Pure compound 1-(7-amino-5-((1S,3R,5R)-6-hydroxy-8-(1H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone was isolated by preparative HPLC.

**Example 8-15**

*Preparation of 1-(5-(7-(1H-1,2,4-triazole-3-carbonyl)-7-azabicyclo[2.2.1]heptan-2-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone*
Step 1
Preparation of tert-butyl 2-(2-cyanoacetyl)-7-azabicyclo[2.2.1]heptane-7-carboxylate

\[
\text{CH}_3\text{CN (0.40 mL, 7.67 mmol) was added dropwise to a solution of nBuLi (3.06 mL, 7.67 mmol) in THF (30 mL) at -78 °C. After stirring for 1 h at -78 °C, a solution of ester (892 mg, 3.49 mmol) in THF (10 mL) was added dropwise and the resulting reaction mixture was stirred at -78 °C for 1 h, then slowly warmed to 0 °C before being quenched with saturated NH}_4\text{Cl (30 mL). THF was removed and the residue was diluted with EtOAc. The organic layer was separated and washed with brine, dried over Na}_2\text{SC}_4\text{ , and concentrated. The crude product was purified by column chromatography (SiO}_2\text{, 0-30% EtOAc/Hexanes) to afford the desired product tert-butyl 2-(2-cyanoacetyl)-7-azabicyclo[2.2.1]heptane-7-carboxylate.}
\]

Step 2
Preparation of tert-butyl 2-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)pyrazolo[1,5-a]pyrimidin-5-yl)-7-azabicyclo[2.2.1]heptane-7-carboxylate

A mixture of 3-aminopyrazole (261 mg, 3.14 mmol) and ketonitrile (756 mg, 2.86 mmol) in HOAc (10 mL) was heated at 100 °C in a sealed tube overnight. After cooling to room temperature, all the volatiles were removed under reduced pressure to afford crude material, which was used without further purification.
To a slurry of above crude material in CH₂Cl₂ (10 mL) was added SEMCI (2.01 mL, 11.45 mmol), followed by DIPEA (3.98 mL, 22.85 mmol). The resulting reaction mixture was stirred at 45 °C for 1 h. After cooling to rt, all the volatiles were removed under reduced pressure. The residue was diluted with EtOAc, washed with H₂O and brine, and concentrated. The crude product was purified by column chromatography (S102, 0-15% EtOAc/Hexane) to afford the desired product tert-butyl 2-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)pyrazolo[1,5-a]pyrimidin-5-yl)-7-azabicyclo[2.2.1]heptane-7-carboxylate.

Step 3
Preparation of tert-butyl 2-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-iodopyrazolo[1,5-a]pyrimidin-5-yl)-7-azabicyclo[2.2.1]heptane-7-carboxylate

To a solution of substrate (257 mg, 0.43 mmol) in CH₃CN (10 mL) was added NIS (97.66 mg, 0.436 mmol). The resulting solution was stirred at room temperature for 1 h. TLC showed complete consumption of SM. The reaction mixture was evaporated and purified by column chromatography (S102, 0-40% EtOAc/Hexanes) to afford desired product tert-butyl 2-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-iodopyrazolo[1,5-a]pyrimidin-5-yl)-7-azabicyclo[2.2.1]heptane-7-carboxylate.

Step 4
Preparation of tert-butyl 2-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-7-azabicyclo[2.2.1]heptane-7-carboxylate
The substrate (241 mg, 0.34 mmol) in dioxane (10 mL) and water (2.5 mL) was treated with boronate (231.8 mg, 0.61 mmol), Pd(dppf)Cl₂.CH₂Cl₂ (34 mg, 0.039 mmol) and K₂CO₃ (145. mg, 0.99 mmol) under argon and heated at 100 °C for 16 h. Upon cooling, the mixture was filtered through Celite and the filtrate was evaporated off under reduced pressure to give crude residue which was purified by column chromatography (SiO₂, 0-40% hexane-EtOAc) to provide the desired product tert-butyl 2-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-7-azabicyclo[2.2.1]heptane-7-carboxylate.

Step 5
Preparation of tert-butyl 2-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(6'-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-7-azabicyclo[2.2.1]heptane-7-carboxylate

Substrate (286 mg, 0.0.35 mmol) was suspended in acetonitrile (5 mL) and treated with NBS (68.8 mg, 0.38 mmol) at room temperature. The mixture was stirred for 30 min. Then solvent was evaporated off under reduced pressure, and the crude
material was purified by column chromatography (S1O2, 0-40% hexane-EtOAc) to provide the desired compound tert-butyl 2-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-7-azabicyclo[2.2.1]heptane-7-carboxylate.

**Step 6**
Preparation of tert-butyl 2-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(1-ethoxyvinyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-7-azabicyclo[2.2.1]heptane-7-carboxylate

Substrate (212 mg, 0.258 mmol) in dioxane (3 mL) was treated with Pd(PPh₃)₄ (29.8 mg, 0.025 mmol) and tributyl(1-ethoxyvinyl)tin (0.77 mL, 0.26 mmol) under argon and the mixture was heated at 100 °C for 16 h. Upon cooling, the mixture was filtered through a pad of 10%KF-SiC₄ and the filtrate was evaporated off under reduced pressure to give a residue which was purified by column chromatography (S1O2, 0-40% hexane-EtOAc) to provide the desired compound tert-butyl 2-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(1-ethoxyvinyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-7-azabicyclo[2.2.1]heptane-7-carboxylate.

**Step 7**
Preparation of 1-(7-amino-5-(7-azabicyclo[2.2.1]heptan-2-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone
Substrate (188 mg, 0.23 mmol) was treated with TFA-H2O (10 mL, 1:1) at room temperature and the mixture was stirred for 16 h. Then the solvent was evaporated off under reduced pressure and the material was lyophilized from acetonitrile:water (3:1) to give the desired compound which was used without further purification.

**Step 8**

*Preparation of 1-(5-(7-(1H-1,2,4-triazole-3-carbonyl)-7-azabicyclo[2.2.1]heptan-2-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone*

Carboxylic acid (49.78 mg) in DMF (2 mL) was treated with EDCI (129 mg) and HOBt (45.6 mg). Then substrate (97.8 mg) followed by DIEA (0.29) was added. Once the reaction was complete the reaction mixture was treated with water (0.1 mL) and DMSO-MeCN (3:1, 3 mL). Pure compound 1-(5-(7-(1H-1,2,4-triazole-3-carbonyl)-7-azabicyclo[2.2.1]heptan-2-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone was isolated by preparative HPLC.
Following these examples, the following compounds were prepared (Table 8-10)

<table>
<thead>
<tr>
<th>Compound ID</th>
<th>Structures</th>
<th>Compound Name</th>
<th>M_{HH} (calculated) / M_{HH} (observed)</th>
<th>pAKT S273 K20</th>
<th>pERK BP1 Thr37/46 K20</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.29</td>
<td></td>
<td>(7-((7-amino-6-(methylsulfanyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)-1(1H-1,2,4-triazol-3-yl)methanone (mixture of stereoisomers)</td>
<td>586.1/585.2</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>8.30</td>
<td></td>
<td>(7-((7-amino-6-(methylsulfanyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)-1(1H-1,2,4-triazol-3-yl)methanone (isomer 1)</td>
<td>586.1/586.2</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>8.31</td>
<td></td>
<td>(7-((7-amino-6-(methylsulfanyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)-1(1H-1,2,4-triazol-3-yl)methanone (isomer II)</td>
<td>586.1/586.2</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>8.32</td>
<td></td>
<td>(7-((7-amino-6-(methylsulfanyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)(1- hydroxycyclopropyl)methanone (isomer II)</td>
<td>575.2/575.2</td>
<td>A</td>
<td>B</td>
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<td>8.33</td>
<td></td>
<td>1-(5-((1H-1,2,4-triazole-3-carbonyl)-9-azabicyclo[3.3.1]nonan-3-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)methanone</td>
<td>548.2/548.2</td>
<td>B</td>
<td>B</td>
</tr>
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Example 8-16

Preparation of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(1-hydroxycyclopropyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate
Step A. Synthesis of methyl 7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-5-((1R,3s,5S)-8-(tert-butoxycarbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl) pyrazolo[1,5-a]pyrimidine-6-carboxylate

A mixture of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-iodo-3-(6-phenylpyridin-3-yl)pyrazolo[3.2.1]octane-8-carboxylate (0.23 g, 0.3 mmol), bis(triphenylphosphine)palladium chloride (0.04 g, 0.05 mmol), DMSO (0.06 mL), triethylamine (0.08 mL, 0.6 mmol) and molybdenumhexacarbonyl (0.27 g, 1 mmol) in methanol (7 mL) were heated at 105°C for 18 hour, at which time LC/MS analysis confirmed full consumption of starting material. On cooling, solids were filtered on a celite pad and washed with ETOAc (25 mL). Filtrate was washed with sat. NaHCO₃ (1 x 5 mL), water (3 x 5 mL), brine (1 x 5 mL), and dried over MgSO₄. Gradient column chromatography on silica gel eluting with 0 to 50% ETOAc/hexanes gave the desired methyl 7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-5-((1R,3s,5S)-8-(tert-butoxycarbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl) pyrazolo[1,5-a]pyrimidine-6-carboxylate (0.1 g).
Step B. Synthesis of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(1-hydroxycyclopropyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-aza bicyclo[3.2.1]octane-8-carboxylate

Samarium powder was placed in a 10 mL two necked flask and covered with 2 mL of dry THF. It was then warmed up to 50°C followed by addition of methyl 7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-5-((1R,3s,5S)-8-(tert-butoxycarbonyl)-8-aza bicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-carboxylate (48 mg, 0.06 mmol), diiodomethane (15 µL) in THF (1 mL) over a 30 min period. After stirring for 12 hour at 50°C, it was cooled to 0°C and quenched with sat. NH₄Cl (0.5 mL). Stirring continued for 5 minutes before the reaction mixture was transferred to a separatory funnel using DCM (15 mL). Organics were then extracted with DCM (2 x 15 mL), and washed with brine (1 x 20 mL), and dried over MgSO₄. Solvent was removed in vacuo and the crude product (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(1-hydroxycyclopropyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-aza bicyclo[3.2.1]octane-8-carboxylate was used for the next step without any further purification.

Procedures similar to those described for the preparation of (1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-aza bicyclo[3.2.1]octan-8-yl)(1H-1,2,4-triazol-3-yl)methanone, the following compound listed in Table 8-1 was prepared:
Table 8-1 1

| 8.39 | ((1R,3s,5S)-3-(7-amino-8-(1-hydroxycyclopentyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate | 548.2547.9 | C | C |

**Example 8-1 7**

Preparation of 7-amino-5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidine-6-carboxamide

![Chemical structure](image)

\[(1R,5S)-\text{tert-butyl 3-(7-\text{bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-cyano-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate} \]

(0.27 g, 0.35 mmol) in H\textsubscript{2}SO\textsubscript{4} (3 mL) was heated at 70°C for four hours, at which time LC/MS analysis confirmed full consumption of starting material. On cooling to 0°C in an icebath, 7N NH\textsubscript{3} in MeOH (15 mL) was added slowly to neutralize the reaction mixture. Solids were filtered off and washed with additional DCM (200 mL). Solvent was removed from the filtrate in vacuo and the pure compound 7-amino-5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidine-6-carboxamide was isolated by preparative HPLC.

Procedure similar to that described for the preparation of ((1 R,3s,5S)-3-(7-amino-6-bromo-3-((2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-
yl)-8-azabicyclo[3.2.1]octan-8-yl)(1 H-1,2,4-triazol-3-yl)methanone, the following compound listed in Table 8-12 was prepared:

Table 8-12

| 8.40 | 5-((1R,3s,5S)-3-(7-(methylamino)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone | 535.2/534.9 | A | A |

Example 8-18

Preparation of ((1 R,3s,5S)-3-(7-(methylamino)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1 H-1,2,4-triazol-3-yl)methanone

Step 1

Synthesis of ((R,3s,5S)-tert-butyl 3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)carboxylate
To a solution of 5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine TFA salt (434 mg, 0.62 mmol) in DMF (2 mL) was added DIEA (261 μL, 1.47 mmol) was added Boc₂O (140 mg, 0.64 mmol), and the resulting solution was stirred for 10 minutes. EtOAc (20 mL) was added, and resulting solution was washed with water (3x), brine and dried (MgSO₄). After evaporation, a crude product (340 mg) was obtained and used in the next step without further purification.

Step 2
Synthesis of (1R,3s,5S)-tert-butyl 3-(7-(methylamino)-6-(methylsulfanyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

To a solution of (1R,3s,5S)-tert-butyl 3-(7-amino-6-(methylsulfanyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (215 mg, 0.37 mmol) in DMF (2 mL) was added NaH (60%, 19 mg, 0.48
After stirring 20 minutes, Mel (30 µL, 0.48 mmol) was added. The resulting solution was stirred for 2 hours, diluted with EtOAc (20 mL), washed with water (3x), brine and dried (MgSCU). After concentration, the residue was purified by gradient column chromatography on silica gel. Eluting with 0 to 50% EtOAc/hexanes gave a relatively pure product (100 mg).

Step 3

Synthesis \(((1R,3s,5S)-3-(7-(methylamino)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)\)methanone

\[
\begin{align*}
\text{BocN} & \quad \text{H} \quad \text{N} \quad \text{OH} \\
\text{SO} & \quad \text{NH} \quad \text{N} \quad \text{O} \\
\text{H} & \quad \text{N} \quad \text{N} \quad \text{SO} \\
\end{align*}
\]

1. TFA/water
2. EDCI, HOBr, DIEA, DMF

The synthesis of the title compound from \((1R,3s,5S)-\)tert-butyl 3-(7-(methylamino)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate using TFA to remove Boc group and amide coupling was achieved by similar procedures described in previous examples.
Table 8-13

| 8.41 | ((1R,3s,5S)-3-(7-(methylamino)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone | 584.2/583.9 | A | B |

Example 8-19

Preparation of ((1R,3s,5S)-3-(7-amino-3-(3-fluoro-4-(hydroxymethyl)phenyl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone
Scheme 8-3

Step A - Synthesis of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(3-fluoro-4-formylphenyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

5
(1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(3-fluoro-4-formylphenyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate was prepared using the protocol described previously. HPLC-MS tR = 2.11 min (UV254 nm); mass calculated for formula C37H56FN5O5Si2 725.38, observed LCMS m/z 726.3 (M+H).

Step B - Synthesis of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(3-fluoro-4-(hydroxymethyl)phenyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

To an ice-cooled solution of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(3-fluoro-4-formylphenyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (400 mg, 0.55 mmol) in MeOH (5.5 mL) and THF (5.5 mL) was added sodium borohydride (84 mg, 2.2 mmol). The reaction mixture was warmed to rt over 1 h until LC/MS analysis confirmed the reaction was complete. DCM (10 mL) was added and the reaction mixture quenched with the addition of 1N HCl. Extraction into DCM, drying over MgSO4 and concentration afforded crude product. HPLC-MS tR = 1.76 min (UV254 nm); mass calculated for formula C37H58FN5O5Si2 727.40, observed LCMS m/z 728.0 (M+H).

Step C - Synthesis of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(4-((tert-butyl(dimethyl)silyloxy)methyl)-3-fluorophenyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate
To a mixture of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-3-(3-fluoro-4-
(hydroxymethyl)phenyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-
carboxylate (0.55 mmol) and imidazole (75 mg, 1.1 mmol) in DMF (5.5 mL) was added tert-butyldimethylchlorosilane (100 mg, 0.66 mmol). The reaction mixture was stirred at rt for 16 h until LC/MS analysis confirmed the reaction was complete. The volatiles were removed in vacuo, the resulting residue redissolved in EtOAc (10 mL) and washed with saturated NaHCO₃ (2 x 20 mL). Drying over MgSO₄ and purification by column chromatography on silica gel, gradient EtOAc/Hexanes (0-50%), yielded the title product as a white solid (320 mg, 69 %). HPLC-MS tR = 2.2 min (UV254 nm); mass calculated for formula C₄₃H₇₂FN₅O₅Si₃ 841.48, observed LC/MS m/z 742.0 (M+H).

Step C - Synthesis of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(4-((tert-butyldimethylsilyloxy)methyl)-3-fluorophenyl)-6-iodopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

(1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(4-((tert-butyldimethylsilyloxy)methyl)-3-fluorophenyl)-6-iodopyrazolo[1,5-a]pyrimidin-5-
yl)-8-azabicyclo[3.2.1]octane-8-carboxylate was prepared using the protocol described in previous example.

**Step D - Synthesis of (4-(7-amino-5-((1R,3S,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-iodopyrazolo[1,5-a]pyrimidin-3-yl)-2-fluorophenyl)methanol**

![Chemical structure](image)

(4-(7-amino-5-((1R,3S,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-iodopyrazolo[1,5-a]pyrimidin-3-yl)-2-fluorophenyl)methanol was prepared using the protocol described in Scheme 5, Step B. HPLC-MS tR = 0.86 min (UV254 nm); mass calculated for formula C20H21FN5O4 493.08, observed LCMS m/z 494.0 (M+H).

**Step E - Synthesis of (4-(7-amino-5-((1R,3S,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-fluorophenyl)methanol**

![Chemical structure](image)

(4-(7-amino-5-((1R,3S,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-fluorophenyl)methanol was prepared using the protocol described previously. HPLC-MS tR = 0.62 min (UV254 nm); mass calculated for formula C21H23FN6O3S 458.158, observed LCMS m/z 459.0 (M+H).
**Step F - Synthesis of** \(((1R,3s,5S)-3-(7-amino-3-(3-fluoro-4-(hydroxymethyl)phenyl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone\)

\(((1R,3s,5S)-3-(7-amino-3-(3-fluoro-4-(hydroxymethyl)phenyl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone\) was prepared using the protocol described previously.

HPLC-MS tR = 0.96 min (UV254 nm); mass calculated for formula C23H26FN5O5S 503.16, observed LCMS m/z 504.1 (M+H).

Following Scheme 8 and procedures similar to those described above for the preparation of \(((1R,3s,5S)-3-(7-amino-3-(3-fluoro-4-(hydroxymethyl)phenyl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone\) the following compounds listed in Table 8-14 were prepared:

<table>
<thead>
<tr>
<th>Table 8-14</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.42</td>
</tr>
</tbody>
</table>

\(((1R,3s,5S)-3-(7-amino-3-(3-fluoro-4-(hydroxymethyl)phenyl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone\) | 541.17/541.3 | A | A |
Preparation of benzyl 1-(2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropylcarbamate

Scheme 8-4

Step A - Synthesis of 1-(4-bromo-2-fluorophenyl)cyclopropanamine
To a cooled solution of 4-bromo-2-fluorobenzonitrile (432 mg, 2.16 mmol) in THF (10 mL) at -78 °C, was added titanium (IV) isopropoxide (0.7 mL, 2.4 mmol).

After stirring for 10 minutes, ethylmagnesium bromide (1M, 4.75 mL, 4.75 mmol) was added and the reaction mixture warmed to 0 °C and then to rt. BFs.OEt (0.53 mL, 4.32 mmol) was then added and the reaction mixture stirred for an additional 1h at rt. The reaction was quenched with saturated NH₄Cl and NaOH (1N). Extraction with EtOAc, and drying over MgSO₄ yielded crude product which was taken forward as crude in the next step. HPLC-MS tR = 0.34 min (UV254 nm); mass calculated for formula C9H9BrFN2 228.99, observed LCMS m/z 230.0 (M+H).

Step B - Synthesis of benzyl 1-(4-bromo-2-fluorophenyl)cyclopropylcarbamate

To a cooled solution of 1-(4-bromo-2-fluorophenyl)cyclopropanamine (2.16 mmol) in DCM (10 mL) at 0 °C, was added DIEA (0.75 mL, 4.32 mmol) and benzyl chloroformate (0.37 mL, 2.59 mmol). The reaction mixture was warmed to rt and stirred for 1h until LC/MS analysis indicated the reaction was complete. The reaction was quenched with HCl (1N) and extracted with DCM. Drying over MgSO₄ yielded crude product which was purified by flash chromatography (gradient EtOAc/Hexanes 0-50%). HPLC-MS tR = 1.31 min (UV254 nm); mass calculated for formula C17H15BrFNO2 363.02, observed LCMS m/z 363.9 (M+H)

Step C - Synthesis of benzyl benzyl 1-(2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropylcarbamate
benzyl benzyl 1-(2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropylcarbamate was prepared using the protocol described previously.

Following procedures similar to those described above, the following compounds listed in Table 8-15 were prepared:

<table>
<thead>
<tr>
<th>Table 8-15</th>
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<tr>
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<td>((1R,3s,5S)-3-(7-amino-3-(4-(1-amino-3,4-phenyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carbonyl)-N'-(3-(dimethylamino)propyl)-N-ethyl-2H-1,2,3-triazole-2-carboximidamide</td>
</tr>
<tr>
<td>8.45</td>
</tr>
<tr>
<td>((1R,3s,5S)-3-(7-amino-3-(4-(2-aminopropan-2-yl)-3-fluorophenyl)-6-(methylsulfonyl)pyrazol[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carbonyl)-N'-(3-(dimethylamino)propyl)-N-ethyl-2H-1,2,3-triazole-2-carboximidamide</td>
</tr>
</tbody>
</table>

Example 8-21

Preparation of (E)-4-((1R,3s,5S)-3-(7-amino-3-(6-(2-fluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazol[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carbonyl)-N'-(3-(dimethylamino)propyl)-N-ethyl-2H-1,2,3-triazole-2-carboximidamide
5-[(3-exo)-8-azabicyclo[3.2.1]oct-3-yl]-3-[6-(2-fluorophenyl)pyridin-3-yl]-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-7-amine (50.0 mg, 0.102 mmol) was slurried in dry N,N-Dimethylformamide (3.9 mL, 50 mmol). 1,2,3-triazole-4-carboxylic acid (14.9 mg, 0.132 mmol), [C] N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (48.6 mg, 0.254 mmol), 1-Hydroxybenzotriazole hydrate (35.0 mg, 0.228 mmol), and W,W-Diisopropylethylamine (88.4 uL, 0.508 mmol) were then added sequentially. The brown mixture was stirred under an atmosphere of Nitrogen. After 16 hours, the mixture was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The aqueous layer was re-extracted with EtOAc and the organic layers were washed with aqueous sodium bicarbonate and brine, dried with sodium sulfate, filtered, and rotoevaporated. The residue was purified via Prep HPLC to provide 10mg of TFA salt. The TFA salt was then dissolved in methanol and 5ml of 0.1 M HCl was added and the solvent removed on the rotovap. this procedure was repeated 3X to provide the HCl salt (10mg) as a yellow solid (Table 8-16).
Example 8-22

**Step 1: Preparation of 5-Bromo-pyridin-2-yl-cyclopropylamine**

To a sealed tube was added 5-bromo-2-fluoropyridine (1.25 g, 7.10 mmol) and cyclopropylamine (5.0 mL, 72 mmol). Upon heating at 80°C for 48 hours the reaction was complete. The contents of the tube were transferred to a round bottom flask and concentrated in vacuo. The remaining residue was dissolved in dichromethane and washed twice with saturated sodium bicarbonate and twice with brine. The organics were dried over sodium sulfate, filtered and concentrated in vacuo to afford the title compound (1.13 g, 75%) as a tan solid.
Step 2: Preparation of tert-butyl (5-bromopyridin-2-yl)cyclopropylcarbamate

5-Bromo-pyridin-2-yl-cyclopropylamine (3.91 g, 16.5 mmol) was suspended in triethylamine (15.0 mL, 110 mmol). Di-tert-butyldicarbonate (10.8 g, 49.6 mmol) was then added followed by 4-dimethylaminopyridine (252 mg, 2.1 mmol). Upon heating at 70°C for 2.5 hours the reaction was complete. The contents of the flask were concentrated in vacuo and the remaining residue partitioned between dichloromethane and saturated sodium bicarbonate. The dichloromethane layer was washed twice more with saturated sodium bicarbonate and twice with brine before drying the organics over magnesium sulfate, filtering and concentrating in vacuo. This residue was purified by flash chromatography (120 g of silica gel) using 0-20% ethyl acetate in hexanes to afford the title compound (4.97 g,) as a colorless oil.

Step 3: Preparation of ((1R,3S,5S)-3-(7-amino-3-(6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(2H-1,2,3-triazol-4-yl)methanone

To a mixture of potassium acetate (868 mg, 8.85 mmol), Bis(pinacolato)diboron (876 mg, 3.45 mmol) and [1,1’-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (105 mg, 0.14 mmol) under an atmosphere of nitrogen was added (5-Bromo-pyridin-2-yl)-cyclopropyl-carbamic acid (1.08 g, 4.72 mmol) dissolved in dry dichloromethane (15 mL) and K2CO3 (0.35 g, 2.60 mmol). The mixture was stirred at 90°C for 4 hours. The reaction was quenched by pouring into water and extracted with dichloromethane. The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography (100 g of silica gel) using 0-20% ethyl acetate in hexanes to afford the title compound (1.20 g, 87% yield) as a light yellow solid.
acid tert-butyl ester (1.00 g, 3.19 mmol) as a solution in dioxane (20 mL). The flask was evacuated and charged with nitrogen three times and then lowered into a bath at 90°C. Upon stirring for 3 hours the starting material was consumed (by LC-MS) so the flask was removed from the oil bath and allowed to cool to room temperature.

Upon cooling to room temperature (1R,3S,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)-methyl)amino)-3-iodopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (1.11 g, 1.52 mmol) was added as a solution in dioxane (10 mL) to the reaction mixture along with 2.1 mL (4.14 mmol) of a 2.0M solution of sodium carbonate and [1,1’-Bis(diphenylphosphino)ferrocene]-dichloropalladium(II) (70 mg, 0.09 mmol). The flask was evacuated and charged with nitrogen three times and then lowered back into the bath at 90°C. Upon stirring overnight the starting iodide had been consumed. The reaction mixture was cooled to room temperature and the crude mixture was partitioned between EtOAc and water. The organics were washed twice more with water and twice with brine before drying over sodium sulfate, filtering and concentrating in vacuo. This residue was purified by flash chromatography (125 g of silica gel) using 0-30% ethyl acetate in hexane to afford the title compound (425 mg) as a tan solid.

**Step 4: Preparation of (1R,3S,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)-methyl)amino)-6-bromo-3-(6-((tert-butoxycarbonyl)(cyclopropyl)amino)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate**

To a round bottom flask containing ((1R,3S,5S)-3-(7-amino-3-(6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(2H-1,2,3-triazol-4-yl)methanone (400 mg, 0.48 mmol), acetonitrile (15 mL) and acetic acid (680 µL, 12.0 mmol) was added N-
bromosuccinimide (85 mg, 0.48 mmol). After stirring for 20 minutes at room temperature starting material was consumed. The contents of the flask were transferred to a separatory funnel using 40 mL of ethyl acetate and 20 mL of water before neutralizing with saturated sodium bicarbonate. Washed the organics three additional times with saturated sodium bicarbonate and then twice with brine. Dried the organics over sodium sulfate, filtered and concentrated in vacuo to afford the title compound (425 mg) as a yellow-brown foam.

Step 5: Preparation of (1R,3s,5S)-tert-butyl 3-((7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-((tert-butoxycarbonyl)(cyclopropyl)amino)pyridin-3-yl)ethoxyvinyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

To a flask containing (1R,3s,5S)-tert-butyl 3-((7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(6-((tert-butoxycarbonyl)(cyclopropyl)amino)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (425 mg, 0.46 mmol) and dioxane (10 mL) was added tributyl[(1-ethoxy)ethenyl]stannane. The system was evacuated and charged with nitrogen three times before adding tetrakis (54 mg, 0.05 mmol). The process of evacuating and charging with nitrogen was repeated three times and then the flask lowered into a bath at 90°C. Upon stirring overnight starting material was consumed (by LC-MS). Removed the solvent in vacuo and purified the remaining residue by flash chromatography (50 g silica gel) using 0.5% methanol in chloroform to afford the title compound (400 mg) as a yellow oil that still contained a small amount of triphenylphosphine. Used as is for the next reaction.
Step 6: Preparation of 1-(7-amino-5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-(cyclopropylamino)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone

To a round bottom flask containing (1R,3s,5S)-ferf-butyl 3-(7-((2-(dimethylsilyl)-ethoxy)-methyl)amino)-3-(6-((ferf-butoxycarbonyl)(cyclopropyl)amino)pyridin-3-yl)-6-(1-ethoxyvinyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (360 mg, 0.40 mmol) was added a premixed solution of TFA (10 mL) and water (4 mL). Upon stirring for 6 hours the reaction was complete. The TFA and water were removed in vacuo. To the residue that remained was added 100 mL of ether. This led to the formation of a yellow precipitate that was then sonicated for approximately 5 minutes to break up all the solids. The solids were filtered onto a glass frit (with two 50 mL ether washes) and then dried under high vacuum to afford the title compound (186 mg, 73%) as a yellow solid (bis TFA salt).

Step 7: Preparation of 1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(cyclopropylamino)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone
To a round bottom flask was added 1-(7-amino-5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-(cyclopropylamino)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone (180 mg, 0.28 mmol), DMF (5 mL) and N,N-diisopropylethylamine (0.24 mL, 1.39 mmol). In a separate flask was added EDC (107 mg, 0.56 mmol), HOBT monohydrate (94 mg, 0.61 mmol), 1H-1,2,4-triazole-5-carboxylic acid (63 mg, 0.56 mmol) and DMF (5 mL). Stirred the contents of the second flask for 15 minutes and then added the solution to the flask containing 1-(7-amino-5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-(cyclopropylamino)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone. After 50 minutes at room temperature the starting material was consumed. The contents of the flask were therefore transferred to a separatory funnel and partitioned between ethyl acetate and water. Washed the organics twice with saturated sodium bicarbonate, water and brine before drying over sodium sulfate, filtering and concentrating in vacuo. Purified the remaining solids by flash chromatography using 0-10% methanol (containing 1% NH₄OH) in chloroform to afford the title compound as a yellow solid. The following compounds (Table 8-17) were made similarly.
Table 8-17

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<td>513.2 / 513.4</td>
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<td>1-[(5-((1R,3S,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(8-aminopyridin-3-yl)pyrazol[1,5-a]pyrimidin-6-yl]ethanone</td>
<td>473.2 / 473.4</td>
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<tr>
<td>8.49</td>
<td><img src="image" alt="Structure" /></td>
<td>1-[(5-((1R,3S,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(2-cyclopropylamino)pyrimidin-5-yl)pyrazol[1,5-a]pyrimidin-6-yl]ethanone</td>
<td>514.3/514.0</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>8.50</td>
<td><img src="image" alt="Structure" /></td>
<td>1-[(1R,3S,5S)-3-(6-acetyl-7-amino-3-(6-cyclopropylamino)pyridin-3-yl)pyrazol[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl]-2-hydroxyethanone</td>
<td>477.3/477.0</td>
<td>B</td>
<td>B</td>
</tr>
</tbody>
</table>

5 Example 8-23

Preparation of di-tert-butyl 1-acetyl-2-(5-((4, 4, 5, 5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)hydrazine-1,2-dicarboxylate

Step 1: Preparation of N'-(5-bromopyridin-2-yl)acetohydrazide
Acetic anhydride (1.13 mL, 12.0 mmol) was added to a solution of 5-bromo-2-hydrazinylpyridine (1.90 g, 10.0 mmol) and TEA (2.09 mL, 15.0 mmol) in DCM (200 mL). After 16 hours, the reaction mixture was concentrated by rotoevaporation and the residue was partitioned between EtOAc and saturated aqueous NaHCO₃. The organic layer was washed with water and brine, dried with Na₂SO₄, and the solvent was removed under vacuum. The resulting residue was triturated with DCM to afford the title compound as a white solid (1.86 g).

**Step 2: Preparation of di-tert-butyl 1-acetyl-2-(5-bromopyridin-2-yl)hydrazine-1,2-dicarboxylate**

(Boc)₂O (8.29 mL, 36.8 mmol) was added to a slurry of N’-(5-bromopyridin-2-yl)acetohydrazide (2.65 g, 11.5 mmol) and DMAP (35.5 mg, 0.288 mmol) in CH₂CN (18 mL). After an hour, the solution was diluted with Et₂O and sequentially washed with 1M KHSO₄, saturated aqueous NaHCO₃, and brine. The organic layer was dried with Na₂SO₄, and the solvent was removed under vacuum. The resulting residue was purified by a SiO₂ column (5-10% Et₂O/hexane) to afford the titled compound as clear syrup (4.80 g). (Modified synthesis of O. Loog, et al., *Synthesis*, 2000, 11, 1591-1597).

**Step 3: Preparation of di-tert-butyl 1-acetyl-2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)hydrazine-1,2-dicarboxylate**
A mixture of di-tert-butyl 1-acetyl-2-(5-bromopyridin-2-yl)hydrazine-1,2-dicarboxylate (4.80 g, 11.2 mmol), bis(pinacolato)diboron (5.66 g, 22.3 mmol), PdCl$_2$(dpdf)-DCM (683 mg, 0.837 mmol), and KOAc (6.57 g, 66.9 mmol) in dioxane (43.5 mL) was degassed and then heated at 90°C for 15 hours. It was then partitioned between 20% i-PrOH/ DCM and (3:7) saturated aqueous NH$_4$Cl/ concentrated aqueous NH$_4$OH. The organic layer was washed with brine, dried with Na$_2$SO$_4$, and the solvent was removed under vacuum. The resulting residue was purified by a SiO$_2$ column (15-25% EtOAc/hexane) to afford the titled compound as yellow glass (3.54 g).

Example 8-24

Preparation of di-tert-butyl 1-(5-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-5-(1R,3s,5S)-8-(tert-butoxycarbonyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)-2-propionylhydrazine-1,2-dicarboxylate

Step 1: Preparation of di-tert-butyl 1-(5-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-5-(1R,3s,5S)-8-(tert-butoxycarbonyl)nyl)8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)hydrazine-1,2-dicarboxylate
Di-tert-butyl 1-acetyl-2-(5-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-5-((1R,3s,5S)-8-(tert-butoxycarbonyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)hydrazine-1,2-dicarboxylate (0.33 g, 1.48 mmol) and K$_2$CO$_3$ (0.03 g, 0.22 mmol) were dissolved in MeOH (3.2 mL). After 16 hours, the solution was partitioned between Et$_2$O/DCM and water. The organic layer was washed with brine, dried with Na$_2$SO$_4$, and the solvent was removed under vacuum to afford the title compound as yellow solid (0.30 g) that was used as is in the next reaction.

**Step 2: Preparation of di-tert-butyl 1-(5-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-5-((1R,3s,5S)-8-(tert-butoxycarbonyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)-2-propionylhydrazine-1,2-dicarboxylate**

Propionic anhydride (0.08 mL, 0.60 mmol) was added to a solution of di-tert-butyl 1-(5-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-5-((1R,3s,5S)-8-(tert-butoxycarbonyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)-2-propionylhydrazine-1,2-dicarboxylate in MeCN.
yl)pyridin-2-yl)hydrazine-1,2-dicarboxylate (0.30 g, 0.30 mmol) and DMAP (0.02 g, 0.12 mmol) in MeCN (3 mL) and the reaction was heated at 50°C. More propionic anhydride was added in portions (0.77 mL total) until no more conversion was seen, monitored by HPLC. The reaction partitioned between Et₂O and 1N aqueous HCl. The organic layer was washed with water, saturated aqueous NaHCO₃, and brine. It was dried with Na₂SO₄ and solvent was removed under vacuum. The resulting residue was purified by a SiO₂ column (20-25% Et₂O/hexane) to afford the titled compound as yellow glass (0.25 g).

Following previously procedures and examples, the following two compounds were prepared (Table 8-18):

<table>
<thead>
<tr>
<th>Compound ID</th>
<th>Structures</th>
<th>Compound Name</th>
<th>NMH (calculated) / NMH (observed)</th>
<th>pAKT5473</th>
<th>I330</th>
<th>ME-EBP1 Thr37/46 IC50</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.51</td>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>N’-(5-(6-acetyl-7-amino-5-((1R,3S,5S)-8-(2-hydroxyacetyl)-6-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidine-3-yl)pyridin-2-yl)acetohydrazide</td>
<td>493.2 / 493.4</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>8.52</td>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>N’-(5-(6-acetyl-7-amino-5-((1R,3S,5S)-8-(2-hydroxyacetyl)-6-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidine-3-yl)pyridin-2-yl)propionohydrazide</td>
<td>507.2 / 507.4</td>
<td>C</td>
<td>D</td>
<td></td>
</tr>
</tbody>
</table>
Example 8-25

Preparation of (1R,3s,5S)-tert-butyl 3-(7-[(2-(trimethylsilyl)ethoxy)methyl]amino)-3-(6-(cyclopropylmethoxy)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

Step 1: Preparation of tert-butyl (3-exo)-3-[7-[bis[[2-(trimethylsilyl)ethoxy]methyl]amino]-3-[6-(cyclopropylmethoxy)pyridin-3-yl]-6-iodopyrazolo[1,5-a]pyrimidin-5-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate

868 mg, 1.16 mmol was dissolved in acetonitrile (10 mL), and N-iodosuccinimide (274 mg, 1.16 mmol) was added. No reaction had occurred after 1h. The solvent was removed, and the residue was dissolved in acetic acid (10 mL). The reaction was complete after stirring 1h at room temperature. The reaction was added to a mixture of dichloromethane and saturated aqueous sodium bicarbonate. The pH of the reaction was adjusted to 7 with sodium bicarbonate, and the layers were separated. The aqueous layer was extracted three more times with dichloromethane, and the combine organics were dried over sodium sulfate and concentrated to give a dark oil (1.18 g). The crude product was purified by flash chromatography (45 g silica gel, 10% ElOAc in hexane). Like fractions of the major product were combined and concentrated to give desired product (0.7086 g) as an orange foam.
Step 2: Preparation of tert-butyl (3-exo)-3-[7-(bis[2-(trimethylsilyl)ethoxy)methyl]amino)-3-[6-(cyclopropylmethoxy)pyridin-3-yl]-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate

Sodium methanesulfinate (289 mg, 2.41 mmol), and copper iodide (837 mg, 4.40 mmol) were weighed into a 100 mL RBF. The flask was flushed with nitrogen for 5 min, and dry DMSO (5 ml) was added to the solids. The suspension with purged with nitrogen for 5 min, and the reaction was placed in an oil bath at 90 °C. After stirring for approx. 5 min, a solution of tert-butyl (3-exo)-3-[7-(bis[2-(trimethylsilyl)ethoxy)methyl]amino)-3-[6-(cyclopropylmethoxy)pyridin-3-yl]-6-iodopyrazolo[1,5-a]pyrimidin-5-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate (705 mg, 0.803 mmol) and dry DMSO (8 mL) were added to the reaction. After heating to 90 °C for 70 min, the reaction was cooled to room temperature and partitioned between EtOAc and saturated aqueous ammonium chloride. The organic layer was washed two more times with saturated aqueous ammonium chloride and then twice with saturated aqueous LiCl. The organic layers were dried with sodium sulfate and concentrated in vacuo to give crude product (776 mg) as an orange oil. The crude oil was dissolved in 20% EtOAc in hexane and loaded onto a 90 g silica gel column that had been pre-equilibrated with 10% EtOAC in hexane. The column was eluted sequentially with 10% EtOAc in hexane (500 mL), 12% EtOAc in hexane (500 mL), 15% EtOAc in hexane (500 mL) and 20% EtOAc in hexane (approx. 700 mL). Like fractions of pure product were combined and concentrated in vacuo. Like fractions of impure product were combined, concentrated in vacuo and purified by radial
chromatography using 20% EtOAC in hexane. Pure product fractions were combined with those above and concentrated in vacuo to give desired product (375 mg).

Following previously procedures and examples, the following two compounds were prepared (Table 8-19):

### Table 8-19

<table>
<thead>
<tr>
<th>Compound ID</th>
<th>Structure</th>
<th>Compound Name</th>
<th>M+H (calculated)</th>
<th>M+H (observed)</th>
<th>pAKT S473 IC50</th>
<th>p4E-BP1 Thr705/Thr706 IC50</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.53</td>
<td><img src="image" alt="Structure" /></td>
<td>((1R,3S,5S)-3-(7-amino-3-(6-cylohexyl)methylene)pyridin-3-yl)-8-(methylsulfonyl)pyrazol-4(1H,1,2,4-triazole-3-yl)methanone</td>
<td>564.2 / 564.3</td>
<td>C</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>8.54</td>
<td><img src="image" alt="Structure" /></td>
<td>((1R,3S,5S)-3-(7-amino-3-((3-cyclopropylmethylene)pyridin-3-yl)-6-(methylsulfonyl)pyrazol-4(1H,1,2,4-triazole-3-yl)methanone</td>
<td>564.2 / 564.2</td>
<td>D</td>
<td>D</td>
<td></td>
</tr>
</tbody>
</table>

Example 8-26

*Synthesis of tert-butyl 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[4,3-h]pyrano[3,2-b]pyridin-7-yl)-2-carboxylate (1D)*

491
2,3-Dihydro-4H-pyrano[3,2-b]pyridin-4-one (1.2 g, 8.04 mmol) was dissolved in DMF (10 mL) and dimethylformaldehyde dimethylacetal (20 mL). The solution was allowed to stir at 80°C for 1 h and concentrated to dryness through rotary evaporation in vacuo. The residue was dissolved in dichloromethane (50 mL); the resulting solution was washed with water (30 mL x 2), dried over Na₂SO₄, and concentrated to get intermediate 1A. HPLC-MS t_R=0.321 min (UV/MS). Mass calculated for formula C₉H₇N₃O₂ 173.1; observed M⁺ (LCMS) 174.1 (m/z).

The above solid was dissolved in MeOH, and the solution was allowed to cool to 0°C in a ice/water bath. Hydrazine monohydrate (1.2 mL) was added dropwise, followed by acetic acid (0.92 mL). The reaction mixture was then allowed to stir at room temperature overnight and concentrated to dryness. The residue was taken up with ethyl acetate (80 mL), washed with saturated NaHCO₃, brine, dried over Na₂SO₄, and concentrated to dryness to afford a brown solid (~700 mg) as intermediate 1B. HPLC-MS t_R=0.431 min (UV). Mass calculated for formula C₉H₇N₃O₂ 173.1; observed M⁺ (LCMS) 174.1 (m/z).

The brown solid was suspended in dichloromethane (20 mL), a piece of DMAP (~20 mg) was added. Then, di-tert-butyl dicarbonate (1.32 g, 6.06 mmol) in dichloromethane (5 mL) was added dropwise via syringe. After stirring for 1 h, the reaction mixture was washed with water (30 mL x 2), dried over Na₂SO₄, and concentrated. Flask column chromatography over silica (EtOAc/hexanes 40% to 55%) gave rise to a white solid (1.0 g) as intermediate 1C. HPLC-MS t_R=0.431 min
Mass calculated for formula $C_{14}H_{16}N_{3}O_{3}$ 273.1; observed $MH^+$ (LCMS) 274.2 (m/z).

Intermediate 1C. (500 mg, 1.83 mmol), bis(pinacolate)bidboron (511 mg), Ir catalyst [Ir(COD)(OMe)]2 (61 mg, 0.082 mmol) and ligand 4,4'-di-tert-butyl-2,2'-bipyridine (49 mg, 0.18 mmol) were charged in a microwave reaction tube, after flushing with Argone, tert-butyl methyl ether (10 mL) was added. The tube was capped and heated at 90°C for 40 min under microwave irradiation. After cooling to room temperature and standing overnight, some crystals were formed, which was filtered, washed with cold TBME and dried in vacuo, giving rise to a pale brown solid (150 mg) as intermediate 1D. HPLC-MS $t_{R}=0.772$ min (UV 254 nm). Observed $MH^+$ (LCMS) 318.0 (m/z), Mass calculated for the corresponding boronic acid formula $C_{14}H_{16}BN_{3}O_{5}$ 317.1.

Following similar procedures described previously, the following compound (Table 8-20) was made.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structures</th>
<th>CompoundName</th>
<th>M(calculated)</th>
<th>pAKT</th>
<th>pIE-8P1</th>
</tr>
</thead>
</table>
| 8.55     |            | ((1R,3r,5S)-3-(7-amino-6-cyclopent-3-(2H-pyrrozol)[4,3-]
|          |            | 6]pyrazolo[3,2-
|          |            | bipyridine-7-
|          |            | 8]pyrazolo[1,5-
|          |            | a]pyrimidin-5-yl]8-
|          |            | azabicyclo[3.2.1]oct-
|          |            | an-8-yl)[4H-1,2,4-
|          |            | triazol-3-
|          |            | yl]methanone | 550.0/549.2 | C | C |

Table 8-20

Example 8-27
Preparation of 1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(3-hydroxyprop-1-ynyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)

Step 1: Preparation of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-3-(6-(3-hydroxyprop-1-ynyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

A mixture of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-3-(6-chloropyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (358 mg, 0.500 mmol, preparation described previously), propargyl alcohol (59.0 μL, 1.00 mmol), allylpalladium(II) chloride dimer (4.6 mg, 0.013 mmol), triphenylphosphine (26.2 mg, 0.100 mmol), Cul (4.8 mg, 0.025 mmol), and K₂CO₃ (138 mg, 1.00 mmol) in DMF (2 mL) was heated at 100 °C under Argon for 20 h. The reaction mixture was diluted with EtOAc, washed with H₂O and brine, dried over Na₂SO₄, and concentrated. The crude product was purified by a SiO₂ column (0-60% EtOAc/Hexanes, Rf = 0.25 in 50% EtOAc) to afford the titled compound as a brownish solid (295 mg).

Step 2: Preparation of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(6-(3-hydroxyprop-1-ynyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate
To a solution of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-
(trimethylsilyl)ethoxy)methyl)amino)-3-(6-(3-hydroxyprop-1-ynyl)pyridin-3-
yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (499 mg,
0.679 mmol) in CH₂CN (15 mL) was added NBS (1.1 eq) at 0 °C and stirred at 0 °C
for 30 min, then at rt for 15 min. All the volatiles were removed under reduced
pressure and the residue was purified by a silica column (0-50%, EtOAc/Hexanes, Rₚ
= 0.35 in 50% EtOAc) to afford the titled compound as a brownish oil (312 mg).

Step 3: Preparation of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-
(trimethylsilyl)ethoxy)methyl)amino)-6-(1-ethoxyvinyl)-3-(6-(3-hydroxyprop-1-
yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-
carboxylate

A mixture of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-
(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(6-(3-hydroxyprop-1-ynyl)pyridin-3-
yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (67.9 mg,
0.0835 mmol), tributyl(1-ethoxyvinyl)tin (84.6 uL, 0.251 mmol), Pd(PPh₃)₄ (29.0 mg, 0.025 mmol) in dioxane (2 mL) was stirred at 100 °C under Argon for 2 h. The reaction mixture was passed through a short plug filled with SiO₂/KF (9:1) to remove majority of the Sn species (eluting with EtOAc). The filtrate was concentrated and purified by a SiO₂ column (0-50% EtOAc/Hexanes, Rf = 0.4 in 50% EtOAc) to afford the titled compound as a brownish oil (28.3 mg).

Step 4: Preparation of 1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(3-hydroxyprop-1-ynyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone

![Chemical structure](image)

This title compound was prepared from (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(1-ethoxyvinyl)-3-(6-(3-hydroxyprop-1-ylnyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate and 4H-1,2,4-triazole-3-carboxylic acid, following essentially the same procedures given previously.

Similarly compounds in Table 8-21 were made:
<table>
<thead>
<tr>
<th>Compound ID</th>
<th>Structures</th>
<th>Compound Name</th>
<th>MHH (calculated)</th>
<th>MHH (observed)</th>
<th>pAKT S473 IC50</th>
<th>pEBP1 Thy172 IC50</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.56</td>
<td><img src="image1" alt="Structure" /></td>
<td>1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(3-hydroxyprop-1-ynyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-y)ethanone</td>
<td>512.2/512.2</td>
<td>B</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>8.57</td>
<td><img src="image2" alt="Structure" /></td>
<td>1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(3-methoxyprop-1-ynyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-y)ethanone</td>
<td>526.2/526.3</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>8.58</td>
<td><img src="image3" alt="Structure" /></td>
<td>1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(3-(2-hydroxyethoxy)prop-1-ynyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-y)ethanone</td>
<td>556.2/556.2</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>8.59</td>
<td><img src="image4" alt="Structure" /></td>
<td>1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(3-(2-methoxyethoxy)prop-1-ynyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-y)ethanone</td>
<td>570.3/570.2</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>8.60</td>
<td><img src="image5" alt="Structure" /></td>
<td>1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(cyclopropylthienyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-y)ethanone</td>
<td>522.2/522.0</td>
<td>B</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>Example 8-28</td>
<td></td>
<td></td>
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<tr>
<td>--------------</td>
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<td></td>
</tr>
</tbody>
</table>

**Preparation of 5-((1R,3s,5S)-8-(4-aminopyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine**

A suspension of 5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine (66 mg, 0.1 mmol), 4-amino-2-chloropyrimidine (26 mg, 0.2 mmol) and K$_2$CO$_3$ (28 mg, 0.2 mmol) in DMF (2 mL) was heated up to 170 °C with MW reactor and stirred for 1 hour. The solution was evaporated to dryness and H$_2$O (4 mL) was added. The resulting suspension was collected and purified with HPLC to give the desired product 5-((1R,3s,5S)-8-(4-aminopyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine.
Similarly compounds in Table 8-22 were made:

<table>
<thead>
<tr>
<th>CompoundID</th>
<th>Structures</th>
<th>Compound Name</th>
<th>MH1 (calculated)</th>
<th>MH1 (observed)</th>
<th>pAKT S473</th>
<th>p4E-BP1 Thr37/46</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.63</td>
<td><img src="image" alt="Structure" /></td>
<td>5-((1R,3a,5S)-8-(4-aminopyrimidin-2-yl)-8-azabicyclo[3.2.1]octa-3-yl)-6-[(methylsulfonfyl)-3-[(6-phenylpyrimidin-3-yl)pyrazol][1.5-alpyrimidin-7-amine]</td>
<td>568.2/568.3</td>
<td>C</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>8.64</td>
<td><img src="image" alt="Structure" /></td>
<td>5-((1R,3a,5S)-8-(5-aminopyrimidin-4-yl)-8-azabicyclo[3.2.1]octa-3-yl)-6-[(methylsulfonfyl)-3-[(6-phenylpyrimidin-3-yl)pyrazol][1.5-alpyrimidin-7-amine]</td>
<td>568.2/568.3</td>
<td>B</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>8.65</td>
<td><img src="image" alt="Structure" /></td>
<td>5-((1R,3a,5S)-8-((3-aminopyrimidin-2-yl)-8-azabicyclo[3.2.1]octa-3-yl)-6-[(methylsulfonfyl)-3-[(6-phenylpyrimidin-3-yl)pyrazol][1.5-alpyrimidin-7-amine]</td>
<td>567.2/567.3</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>8.66</td>
<td><img src="image" alt="Structure" /></td>
<td>N-4-((1R,3a,5S)-3-{(7-amino-6-(methylsulfonfyl)-3-(6-phenylpyrimidin-3-yl)pyrazol][1.5-alpyrimidin-5-yl)-8-azabicyclo[3.2.1]octa-3-yl)pyrimidin-5-yl)acetamide</td>
<td>610.2/610.2</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>8.67</td>
<td><img src="image" alt="Structure" /></td>
<td>N-2-((1R,3a,5S)-3-{(7-amino-6-(methylsulfonfyl)-3-(6-phenylpyrimidin-3-yl)pyrazol][1.5-alpyrimidin-5-yl)-8-azabicyclo[3.2.1]octa-3-yl)pyrimidin-3-yl)acetamide</td>
<td>609.2/609.3</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
</tbody>
</table>
Example 8-29

Preparation of 5-(5-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)-5-methylimidazolidine-2,4-dione

Step 1: Preparation of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(6-(4-methyl-2,5-dioxoimidazolidin-4-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

The compound (1R,3s,5S)-tert-butyl 3-(3-(6-acetylpyridin-3-yl)-7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (previously made. 401 mg, 0.5 mmol) was mixed with KCN (36 mg, 0.55 mmol) and (NH₄)₂CO₃ (216 mg, 4.5 mmol) in EtOH/H₂O (5 mL/5 mL) and the resulting mixture was heated up to 80 °C and stirred overnight. After cooling to room temperature, the reaction was diluted with EtOAc and washed with water and brine. After concentration, the crude was purified with column chromatography (silica gel, 0-60% EtOAc/hexane) gave the product (428 mg).

Step 2: Preparation of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(1-ethoxyvinyl)-3-(6-(4-methyl-2,5-dioxoimidazolidin-4-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate
The compound of \((1R,3s,5S)\)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(1-ethoxyvinyl)-3-(6-(4-methyl-2,5-dioxoimidazolidin-4-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate was made following similar examples described previously.

**Step 3: Preparation of 5-(5-(6-acetyl-7-amino-5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)-5-methylimidazolidine-2,4-dione**

The compound of 5-(5-(6-acetyl-7-amino-5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)-5-methylimidazolidine-2,4-dione was made with the same condition described previously.
Step 4: Preparation of 5-(5-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)-5-methylimidazolidine-2,4-dione

The compound of 5-(5-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)-5-methylimidazolidine-2,4-dione was made with the same condition described previously.

Similarly compounds in Table 8-23 were made:

<table>
<thead>
<tr>
<th>Compound ID</th>
<th>Structures</th>
<th>Compound Name</th>
<th>MHH (calculated/ MHH (observed))</th>
<th>pAKT S473 I535</th>
<th>pAEBP1 Thr308/410 I535</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.68</td>
<td><img src="image" alt="Structure" /></td>
<td>5-(5-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)-5-methylimidazolidine-2,4-dione</td>
<td>570.2/570.3</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>8.69</td>
<td><img src="image" alt="Structure" /></td>
<td>5-(6-((8-acetyl-7-amino-6-((1R,3s,5S)-8-(2-hydroxyacetyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)-5-methylimidazolidine-2,4-dione</td>
<td>533.2/533.3</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>
Example 8-30

Preparation of (1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carbonitrile

Step 1: Preparation of (1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carbonitrile

The compound 5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine TFA salt (329 mg, 0.49 mmol) was mixed with NaHCO₃ (126 mg, 1.5 mmol) and NCBr (52 mg, 0.49 mmol) in EtOH (8 mL) and DMF (2 mL). The mixture was stirred at room temperature overnight and the solvent was removed under reduced pressure. The residue was taken up with water and the solid was collected through filtration and washed with water. The product was dried under air to give yellowish solid (213 mg).

Similarly compounds in Table 8-24 were made:
Preparation of (1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carbonitrile-N-hydroxy-8-azabicyclo[3.2.1]octane-8-carbonitrile

The compound (1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carbonitrile (213 mg, 0.426 mmol) was mixed with NH₂OH.HCl salt (148 mg, 2.13 mmol) and Et₃N (326 µL mg, 2.34 mmol) in DMSO (2 mL). The mixture was heated up to 75 ºC and stirred

Table 8-24

<table>
<thead>
<tr>
<th>Compound ID</th>
<th>Structures</th>
<th>Compound Name</th>
<th>MHH (calculated)</th>
<th>MHH (observed)</th>
<th>pAKT S473</th>
<th>pEBP1 Thr7946</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.70</td>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>(1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carbonitrile</td>
<td>500.2</td>
<td>500.3</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>8.71</td>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>(1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carbonitrile</td>
<td>464.2</td>
<td>464.2</td>
<td>B</td>
<td>B</td>
</tr>
</tbody>
</table>
overnight. The solution was filtered and purified with HPLC to give the desired product (Table 8-25).

**Table 8-25**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Purity</th>
<th>C</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboximidamide</td>
<td>8.72</td>
<td>533.2/533.3</td>
<td></td>
</tr>
</tbody>
</table>

Example 8-32

Preparation of (1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboximidamide and 3-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-1,2,4-oxadiazol-5(4H)-one

Step 1: Preparation of (1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboximidamide and 3-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-1,2,4-oxadiazol-5(4H)-one

The compound (1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-N-hydroxy-8-azabicyclo[3.2.1]octane-8-carboximidamide (100 mg, 0.188 mmol) was mixed with CDI (31 mg, 0.19 mmol) in
dry DMF (2 mL). The mixture was heated up to 75 °C and stirred for 1 hour. The mixture was diluted with more DMSO and purified with HPLC to give the product (1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboximidamide and 3-(1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-1,2,4-oxadiazol-5(4H)-one (Table 8-26).

Table 8-26

| 8.73 | (1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboximidamide | 517.2/517.2 | C | C |
| 8.74 | 3-(1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-1,2,4-oxadiazol-5(4H)-one | 559.2/559.3 | C | D |

Example 8-33

Preparation of 1-(5-(5-((1R,3s,5S)-8-(1H-1,2,4-triazole-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)-3-methylurea
Step A - Synthesis of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(6-(methoxycarbonyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

Scheme 8-5

Step A - Synthesis of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(6-(methoxycarbonyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate
To a mixture of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-3-(6-(methoxycarbonyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (3.7 g, 5.01 mmol) in CH$_3$CN (25 mL) and dichloromethane (25 mL) was added W-bromosuccinimide (0.98 g, 5.5 mmol) in one portion and the resulting mixture was stirred at room temperature for 0.5 h, at which time LC/MS confirmed reaction was not complete. Added more N-bromosuccinimide (0.98 g, 5.5 mmol) in one portion and the resulting mixture was stirred at room temperature for 1.5 h at which time LC/MS confirmed full conversion of starting material to product. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel. Elution with EtOAc/Hexanes (20-50%) gave the title product (3.2 g).

**Step B - Synthesis of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-6-(1-ethoxyvinyl)-3-(6-(methoxycarbonyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate**

![Chemical structure](image)
A mixture of compound (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-bromo-3-(6-(methoxycarbonyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (2.6 g, 3.18 mmol), tributyl(1-ethoxyvinyl)tin (2.30 g, 6.37 mmol), tetrakis(triphenylphosphine)palladium (0.73 g, 0.64 mmol) in dioxane (30 mL) was degassed with argon for five minutes. It was then heated at 100 °C in a sealed tube for 16 h, at which time LC/MS analysis confirmed full consumption of starting material. On cooling, the solvent was concentrated in vacuo, and the crude residue was dissolved in EtOAc (150 mL), washed with 0.5 M KF solution (1 x 50 mL), water (1 x 50 mL), brine (1 x 50 mL), and dried over MgSO₄. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel. Elution with EtOAc/Hexanes (20-70%) gave the title product (1.9 g).

**Step C - Synthesis of potassium 5-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-5-((1R,3s,5S)-8-(tert-butoxy carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-(1-ethoxyvinyl)pyrazolo[1,5-a]pyrimidin-3-yl)picolinate**

To (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-((1-ethoxyvinyl)-3-(6-(methoxycarbonyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (1.5 g, 1.85 mmol) in ethanol (60 mL) was added 2N potassium hydroxide solution (1.1 mL, 2.2 mmol). The resulting solution was stirred at room temperature for 16 h at which time LC-MS analysis indicated full conversion of starting material to product. The solvent was removed in vacuo to afford desired product 1.51 g.
Step D - Synthesis of (1R,3s,5S)-tert-butyl 3-(3-(6-aminopyridin-3-yl)-7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(1-ethoxyvinyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

To potassium 5-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-8-(tert-butoxycarbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-(1-ethoxyvinyl)pyrazolo[1,5-a]pyrimidin-5-yl)picolinate (0.5 g, 0.63 mmol) in 1,4-dioxane (20 mL) was added followed by potassium hydroxide (0.7 mg, 0.13 mmol), diphenylphosphoryl azide (0.2 mL, 0.94 mmol) and triethylamine (0.18 mL, 1.26 mmol). The resulting solution was stirred at 80 °C for 2 hours at which time LC-MS analysis indicated reaction was complete. The reaction mixture was cooled to room temperature, poured into water (30 mL) and then extracted with ethyl acetate (3 x 50 mL). The combined organic extract was washed with brine (50 mL), and dried over MgSO₄. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel. Elution with EtOAc/Hexanes (20-70%) gave the title product (202 mg).

Step E - Synthesis of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(1-ethoxyvinyl)-3-(6-(3-methylureido)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate
To (1R,3s,5S)-tert-butyl 3-((3-(6-aminopyridin-3-yl)-7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-6-(1-ethoxyvinyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (150 mg, 0.195 mmol) in 1,2-dichloroethane (3 mL) was added methyl isocyanate (12.7 µL, 0.205 mmol) and the resulting solution stirred at 75 °C for 16 hours, at which time LC-MS analysis indicated the reaction was complete. The solvent was removed in vacuo to afford desired product which was used without further purification in the next reaction step in the synthetic sequence.

Step F - Synthesis of 1-(5-(6-acetyl-7-amino-5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)-3-methylurea

To a mixture of (1R,3s,5S)-tert-butyl 3-((7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-6-(1-ethoxyvinyl)-3-(6-(3-methylureido)pyrimidin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (0.13 g, 0.156 mmol) in dioxane (2 mL) was added 4 M HCl in water (1 ml) at 0 °C. After stirring for 10 min at 0 °C, 4 M HCl in dioxane (1 mL) was added. The reaction mixture was stirred at 0 °C for 30 min and the cooling bath was removed to warm up to room temperature for 30 minutes, and then heated at 50 °C for 1 hour at which time LC/MS analysis confirmed full consumption of starting material. The solvent was removed in vacuo to get the desired product as an HCl salt. This HCl product was lyophilized to afford the desired product as a yellow solid (70 mg).
Step G - Synthesis of 1-(5-(6-acetyl-7-amino-5-((1R,3s,5S)-8-((2-(trimethylsilyl)ethoxy)methyl)-1H-1,2,4-triazole-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)-3-methylurea

A mixture of potassium 1-((2-(trimethylsilyl)ethoxy)methyl)-1H-1,2,4-triazole-5-carboxylate (41.0 mg, 0.145 mmol), 1-(5-(6-acetyl-7-amino-5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)-3-methylurea (68 mg, 0.145 mmol), W,W-diisopropylethylamine (0.051 mL, 0.289 mmol in NMP (2 ml) was stirred at room temperature for 10 min. 2-(7-Aza-1 H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) (55 mg, 0.145 mmol) was added to the reaction mixture at room temperature in one portion. The reaction was stirred for 30 min at room temperature at which time LC/MS analysis confirmed full consumption of starting material. The reaction was diluted with ethyl acetate (10 mL) and extracted with water (2 x 5 mL) and brine (1 x 5 mL). The organic layer was dried using anhydrous sodium sulfate, filtered, and concentrated in vacuo and the residue was purified by column chromatography on silica gel. Elution with EtOAc/Hexanes (75-100%) gave the title product (67 mg).

Step H - Synthesis of 1-(5-(5-((1R,3s,5S)-8-(1H-1,2,4-triazole-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)-3-methylurea

512
To a mixture of 1-(5-(6-acetyl-7-amino-5-((1R,3s,5S)-8-(1-((2-
trimethylsilyl)ethoxy)methyl)-1H-1,2,4-triazole-5-carbonyl)-8-azabicyclo[3.2.1]octan-
3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)-3-methylurea (67 mg, 0.102 mmol) in
dioxane (2 mL) and water (1 mL) was added 4 M HCl in dioxane (2 ml) at room temperature. The reaction mixture was heated at 50 °C for 1 hour at which time LC/MS analysis confirmed full consumption of starting material. The solvent was removed in vacuo. This crude compound was purified by HPLC to afford the desired product. LC/MS RT = 2.01 min. Mass calculated for M+H 530.2, observed 530.0.

Following Scheme 8-5 and procedures similar to the preparation of 1-(5-(5-
((1R,3s,5S)-8-(1H-1,2,4-triazole-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-
7-aminopyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)-3-methylurea, the following
compounds listed in Table 8-26 below were prepared:

Table 8-26

<table>
<thead>
<tr>
<th>Compound ID</th>
<th>Structures</th>
<th>Compound Name</th>
<th>M+H(calculated)/M+H(observed)</th>
<th>pAKT 5470 IC50</th>
<th>p4EBP1 71k IC50</th>
</tr>
</thead>
</table>
| 8.75        | ![Image](image.png) | 1-(5-((1R,3s,5S)-8-(1H-1,2,4-triazole-5-carbonyl)-8-
azabicyclo[3.2.1]octan-3-yl)-6-acetyl-7-
aminopyrazolo[1,5-a]pyrimidin-3-
yl)pyridin-2-yl)-3-methylurea | 530.2 / 530.0 | A | B |
<table>
<thead>
<tr>
<th>Page</th>
<th>Chemical Structure</th>
<th>Molecular Formula</th>
<th>Mass (Da)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.76</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>N-(5-((5-((1R,3S,5S)-8-((1H-1,2,4-triazole-5-carbonyl)-8-azabicyclo[3.2.1]octa-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)acetamide)</td>
<td>515.2 / 514.9</td>
<td>A A</td>
</tr>
<tr>
<td>8.77</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>ethyl 5-(6-acetyl-7-amino-5-((1R,3S,5S)-8-(2-hydroxyacetyl)-8-azabicyclo[3.2.1]octa-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-ylcarbamate</td>
<td>508.2 / 508.0</td>
<td>B ND</td>
</tr>
<tr>
<td>8.78</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>ethyl 5-((5-((1R,3S,5S)-8-(1H-1,2,4-triazole-5-carbonyl)-8-azabicyclo[3.2.1]octa-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-ylcarbamate</td>
<td>545.2 / 544.9</td>
<td>A A</td>
</tr>
<tr>
<td>8.79</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>1-((4-((7-aminomethyl-3-((1R,3S,5S)-8-azabicyclo[3.2.1]octa-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)iphenyl)-3-methylurea)</td>
<td>391.2 / 392.0</td>
<td>ND ND</td>
</tr>
<tr>
<td>8.80</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td>1-((4-((5-((1R,3S,5S)-8-(dih-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octa-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)phenyl)-3-methylurea)</td>
<td>486.22 / 487.0</td>
<td>D D</td>
</tr>
<tr>
<td>8.81</td>
<td><img src="image6" alt="Chemical Structure" /></td>
<td>1-((4-((5-((1R,3S,5S)-8-(dih-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octa-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)phenyl)-3-methylurea)</td>
<td>530.25 / 531.0</td>
<td>ND ND</td>
</tr>
<tr>
<td>8.82</td>
<td>1-(4-(7-amino-5-((1R,3s,5S)-8-(2-hydroxyacetyl)-8-azabicyclo[3.2.1]octa-4-yl)phenyl)-3-methylurea</td>
<td>449.22/450.0</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>8.83</td>
<td>1-(4-(7-amino-5-((1R,3s,5S)-8-(morpholine-3-carbonyl)-8-azabicyclo[3.2.1]octa-4-yl)phenyl)-3-methylurea</td>
<td>504.26/505.0</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>8.84</td>
<td>1-(5-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octa-4-yl)phenyl)-3-methylurea</td>
<td>501.23/502.0</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>8.85</td>
<td>1-(4-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octa-4-yl)phenyl)-3-methylurea</td>
<td>528.23/529.0</td>
<td>A</td>
<td>B</td>
</tr>
</tbody>
</table>

Example 8-34

Preparation of (1R,3s,5S,E)-3-(7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-N'-cyano-8-azabicyclo[3.2.1]octane-8-carboximidamide
To 5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine (142 mg, 0.299 mmol, 1.00 equiv) and DIEA (0.16 mL, 0.90 mmol, 3.0 equiv) in DCM (3 mL) was added diphenyl cyanocarbonimidate (71 mg, 0.30 mmol, 1.0 equiv). The resulting solution was allowed to stir at rt for 18 hr and then was concentrated. The residue was dissolved in DMF (3 mL) and then was heated in a sealed vessel at 100 °C for 24 hr. Concentration and purification of the residue by preparative chromatography afforded the title compound (1R,3s,5S,E)-3-(7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-N'-cyano-8-azabicyclo[3.2.1]octane-8-carboximidamide (11.1 mg).

Following this example and previous procedures, compounds (Table 8-27) were made:

<table>
<thead>
<tr>
<th>Compound ID</th>
<th>Structures</th>
<th>Compound Name</th>
<th>MHH (calculated)</th>
<th>MHH (observed)</th>
<th>pAKT S473 IC50</th>
<th>pERK1/2 Thr37/46 IC50</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.86</td>
<td><img src="image" alt="Structure" /></td>
<td>(1R,3s,5S,E)-3-(7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-N'-cyano-8-azabicyclo[3.2.1]octane-8-carboximidamide</td>
<td>463.22/464.0</td>
<td>C</td>
<td>C</td>
<td></td>
</tr>
</tbody>
</table>
**Example 8-35**

**Preparation of (((1R,3s,5S)-3-(7-amino-3-(2-aminopyrimidin-5-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone**

**Step A:** A suspension of ((1R,3S,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-iodopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (500 mg, 0.686 mmol, 1.00 equiv), 2-amino-pyrimidin-5-yl)boronic acid (143 mg, 1.03 mmol, 1.50 equiv), PdCl₂(dppf) (56 mg, 0.069 mmol, 0.1 mmol) in dioxane/water (7/0.7 mL) was allowed to stir at 85 °C for 18 hr. After cooling to rt, the crude reaction mixture was filtered, concentrated affording the title compound that was used directly in Step B.
Step B: The crude residue was treated with 4 N HCl dioxane/water (5/1) for 30 min. Lyophilization afforded the crude residue which was converted to the final product ((1R,3s,5S)-tert-butyl 3-(3-(2-aminopyrimidin-5-yl)-7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate with an EDCI-mediated coupling.

<table>
<thead>
<tr>
<th>Compound ID</th>
<th>Structures</th>
<th>Compound Name</th>
<th>M+H (calculated) / M+H (observed)</th>
<th>pAKT S473IC50</th>
<th>pIE-BP1 Thr37/46 IC50</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.88</td>
<td><img src="structure_image.png" alt="Structure" /></td>
<td>((1R,3s,5S)-3-(7-aminoo-3(2-aminopyrimidin-5-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone</td>
<td>431.19/432.0</td>
<td>D</td>
<td>ND</td>
</tr>
</tbody>
</table>

Example 8-36

Preparation of 6-(methylsulfonyl)-3-(3-phenylpyridin-3-yl)-5-((1R,3s,5S)-8-(2,2,2-trifluoroethyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine
To a solution of 5-((1 R,3S,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-
(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine (0.22 g, 0.051 mmol, 1.00 equiv) and DIEA (0.44 mL, 2.6 mmol, 5.0 equiv) in DMF (2 mL) at rt was added 2,2,2-trifluoroethyl trifluoromethanesulfonate (0.12 mL, 0.51 mmol, 1.0 equiv). The resulting solution was stirred at rt for 24 hr, concentrated and preparative chromatography afforded the title compound 6-(methylsulfonyl)-3-(6-
phenylpyridin-3-yl)-5-((1 R,3S,5S)-8-(2,2,2-trifluoroethyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine.

Similarly, compounds (Table 8-29) were prepared:

Table 8-29

<table>
<thead>
<tr>
<th>Compound ID</th>
<th>Structures</th>
<th>Compound Name</th>
<th>MHH (calculated)</th>
<th>MHH (observed)</th>
<th>pPICT</th>
<th>pHE-BP1 Thr27/Ala</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.89</td>
<td><img src="image1" alt="Structure" /></td>
<td>6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)-5-((1R,3S,5S)-8-((2,2,2-trifluoroethyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine</td>
<td>556.19/55</td>
<td>6.2</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>8.90</td>
<td><img src="image2" alt="Structure" /></td>
<td>1-((1R,3S,5S)-8-((2,2,2-trifluoroethyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)phenyl)-3-methylurea</td>
<td>473.22/47</td>
<td>4.0</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>8.91</td>
<td><img src="image3" alt="Structure" /></td>
<td>5-((1R,3S,5S)-8-((4H-1,2,4-triazol-3-yl)methyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine</td>
<td>555.22/55</td>
<td>6.2</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>
Preparation of 1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(1-amino-2,2,2-trifluoroethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-5-yl)acetamide

**Example 8-37**

Step A: To a solution of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-6-(1-ethoxyvinyl)-3-(6-formylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-5-yl)acetamide (0.25 g, 0.32 mmol, 1.00 equiv) in 1,2-DCE (3 mL) was added Dess-Martin periodinane (0.271 mg, 0.640 mmol, 2.00 equiv) in one portion. The resulting heterogeneous reaction mixture was allowed to stir at rt for 2 hr. The reaction was quenched with the addition of ethyl acetate (10 mL) and saturated 1/1 NaHCO₃/Na₂S₂O₃ (10 mL). After stirring for 30 min at rt, the mixture was partitioned between ethyl acetate and water (2x). The organic phase was washed with brine and dried (magnesium sulfate). Filtration and concentration afforded (1R,3s,5S)-tert-butyl 3-(7-(bis((2-trimethylsilyl)ethoxy)methyl)amino)-6-(1-ethoxyvinyl)-3-(6-formylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-5-yl)acetamide.
yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate as a yellow compound (246 mg) that was used without additional purification.

Step B: A suspension of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-(1-ethoxyvinyl)-3-(6-formylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (0.246 g, 0.316 mmol, 1.00 equiv) from Step A, 2-methylpropane-2-sulfinamide (46 mg, 0.38 mmol, 1.2 equiv) and CuSO₄ (0.10 g, 0.63 mmol, 2.0 equiv) in DCM (3 mL) was heated at 45 °C for 2 hr. After cooling to rt and filtering through Celite and concentration, the residue was purified by Biotage (15% ethyl acetate in hexanes to 100% ethyl acetate gradient) affording the title compound as a yellow oil (218 mg).

Step C: To a solution of (1R,3s,5S)-tert-butyl 3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-6-((E)-(tert-butylsulfinylimino)methyl)pyridin-3-yl)-6-(1-ethoxyvinyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (120 mg, 0.136 mmol, 1.0 equiv) and KOAc (13 mg) in DMF (4 mL) at -40 °C was added trimethyl(trifluoromethyl)silane (2.0 M in THF, 0.28 mL, 0.28 mmol) dropwise. After warming to rt, the reaction mixture was stirred for 6 hr, partitioned between ethyl acetate and water, dried.

Step D: The residue from Step C was dissolved in THF and treated with HCl. After 5 hr, the mixture was concentrated and lyophilized. EDCI mediated coupling afforded the title compound.

Preparation of 4-((2-(trimethylsilyl)ethoxy)methyl)-4H-1,2,4-triazole-3-carboxylic acid
Step A: To a solution of methyl 4H-1,2,4-triazole-3-carboxylate (5.00 g, 39.4 mmol, 1.00 equiv) in DMF (200 mL) at 0 °C was added dropwise LiHMDS (1.0 M solution in toluene, 43 mL, 43 mmol, 1.1 equiv). The resulting solution was aged 15 minutes, then SEMCl (7.3 mL, 41 mmol, 1.0 equiv) was added dropwise over 5 minutes. After stirring for 5 min at 0 °C, the ice bath was removed and the yellow solution was allowed to warm to rt, and then stirred for 1 hr. The mixture was quenched by the addition of water, partitioned between ethyl acetate and water, washed with brine and dried over magnesium sulfate. Concentration and final purification by Biotage (15% to 70% ethyl acetate in hexanes) afforded the title compound as pale oil (5.13 g).

Step B: To a solution of methyl 4-((2-(trimethylsilyl)ethoxy)methyl)-4H-1,2,4-triazole-3-carboxylate (225 mg, 0.874 mmol, 1.00 equiv) in EtOH (1.5 mL) was added aq. KOH (2N, 0.9 mL, 0.87 mmol, 1.0 equiv). After stirring at rt for 1 hr, the reaction mixture was concentrated affording the title compound as a colorless solid (271 mg) (Table 8-30).

Table 8-30

<table>
<thead>
<tr>
<th>Compound ID</th>
<th>Structures</th>
<th>Compound Name</th>
<th>MH+ (calculated)/MH+ (observed)</th>
<th>pAKT 50</th>
<th>pE-BP1 Thc2746 IC50</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.93</td>
<td><img src="image" alt="Structure" /></td>
<td>1-(5-(1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo(3.2.1)octan-3-yl)-7-amino-3-(6-(1-amino-2,2,2-trifluoroethyl)pyridin-3-yl)pyrazol[1,5-a]pyrimidin-6-yl)ethanone</td>
<td>554.21/555.1</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

Example 8-38
Preparation of ((1R,3S,5S)-3-(7-amino-3-(2-(aminomethyl)pyrimidin-5-yl)-6-bromopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone.

Step A, B and C: preparation of the boronic acid, the Suzuki reaction and bromination were realized following similar examples described previously.

Step D: To a solution of 5-(5-((1R,3S,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-6-bromopyrazolo[1,5-a]pyrimidin-3-yl)pyrimidine-2-carbonitrile (0.020g, 0.385 mmol) in EtOAc (1 mL) was added Pd/C (catalytic) and AcOH (1 mL). The reaction was stirred under H2 for 15 h. The reaction was passed through celite, washed with EtOAc and concentrated. HPLC purification gave ((1R,3S,5S)-3-(7-amino-3-(2-(aminomethyl)pyrimidin-5-yl)-6-bromopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone (0.003g) as a light yellow solid.

Following previous examples, compounds in Table 8-31 were made:
<table>
<thead>
<tr>
<th>Compound ID</th>
<th>Structures</th>
<th>Compound Name</th>
<th>MHH (calculated)</th>
<th>pAKT S473</th>
<th>Thr3740</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.94</td>
<td><img src="image" alt="Structure" /></td>
<td>5-(1R,3s,5s)-3-(7-amino-3-(2-(aminomethyl)pyrimidin-5-yl)-6-bromopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)4H-1,2,4-triazolo-3-yl)methanone</td>
<td>524.12/523.84</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>8.95</td>
<td><img src="image" alt="Structure" /></td>
<td>5-(1R,3s,5s)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-pyrazolo[1,5-a]pyrimidin-3-yl)pyrimidine-2-carbonitrile</td>
<td>442.18/441.95</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>8.96</td>
<td><img src="image" alt="Structure" /></td>
<td>5-(1R,3s,5s)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-6-cyclopropylpyrazolo[1,5-a]pyrimidin-3-yl)pyrimidine-2-carbonitrile</td>
<td>482.21/482.00</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>8.97</td>
<td><img src="image" alt="Structure" /></td>
<td>5-(1R,3s,5s)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-7-amino-pyrazolo[1,5-a]pyrimidin-3-yl)pyrimidine-2-carboxamide</td>
<td>502.20/501.97</td>
<td>C</td>
<td>ND</td>
</tr>
</tbody>
</table>

Example 8-39
Preparation of \(((1R, 3s, 5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-morpholino-4H-1,2,4-triazol-3-yl)methanone

Step-A: Synthesis of methyl hydrazinecarbimidothioate hydroiodide

To a solution of hydrazinecarbimidothioic acid (1.0 g, 10.97 mmols) in EtOH (10 mL) was added Methyl iodide (0.700 mL, 11.34 mmol) and heated to 60 °C for 30 minutes. The reaction mixture was cooled to rt and the solid was filtered out. The solid was washed with ether, to get methyl hydrazinecarbimidothioate hydroiodide as a white solid (2.25g).

Step-B: Synthesis of morpholine-4-carboximidyrazide
To a solution of methyl hydrazinecarbimidothioate hydroiodide (0.100 g, 0.429 mmol) in MeOH (2 mL) was added morpholine (0.075 mL, 0.858 mmol) and refluxed overnight. Reaction was cool to RT and concentrated to get morpholine-4-carboximidhydrazide as a white solid in quantitative yield.

**Step-C: Synthesis of methyl 5-morpholino-4H-1,2,4-triazole-3-carboxylate**

To a solution of 4, morpholine-4-carboximidhydrazide (0.100 g, 0.429 mmol) in ACOH (1 mL) was added 5, diethyl oxalate (0.582 mL, 4.29 mmol) and refluxed for 2 h. Reaction was concentrated, diluted with EtOAc and washed with water. The organic layer dried and concentrated. ISCO purification (0-1% MeOH in DCM) to obtain 6, methyl 5-morpholino-4H-1,2,4-triazole-3-carboxylate (0.213 g).

**Step-D: Synthesis of 5-morpholino-4H-1,2,4-triazole-3-carboxylic acid**
To a solution of methyl 5-morpholino-4H-1,2,4-triazole-3-carboxylate (0.090g, 0.398 mmol) in THF (1 mL) was added 1 N LiOH (0.800 mL, 0.80 mmol) and H₂O (1 mL). The reaction was stirred at rt for 12 h. The reaction mixture was concentrated and lyophilized to get 5-morpholino-4/7-1,2,4-triazole-3-carboxylic acid quantative yield and used as it is in next step.

**Step-E: Synthesis of ((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(5-morpholino-4H-4H-1,2,4-triazol-3-yl)methanone)

The title compound was made following the standard coupling conditions described before.
Example 8-40

**Preparation of building block tert-butyl 4-(5-(methoxycarbonyl)-4H-1,2,4-triazol-3-yl)piperazine-1-carboxylate**

To a solution of methyl 5-(piperazin-1-yl)-4H-1,2,4-triazole-3-carboxylate (1.0 g, 4.44 mmols) in DCM (10 mL) was added (BOC)_2O (0.970 g, 4.44 mmol), DMAP (0.050 g, 0.41 mmol), DIEA (3.9 mL, 22.4 mmol). The reaction was stirred at RT overnight. Reaction concentrated and ISCO purification (0-5% MeOH in DCM) to obtain tert-butyl 4-(5-(methoxycarbonyl)-4H-1,2,4-triazol-3-yl)piperazine-1-carboxylate (0.580 g).

Example 8-41

**Preparation of building block 5-(2-methoxethyl)-4H-1,2,4-triazole-3-carboxylic acid**

*Step A: synthesis of 4-tert-butyl 3-methyl 5-hydroxy-4H-1,2,4-triazole-3,4-dicarboxylate*
Use the same reaction conditions described above.

5

Step B: Synthesis of methyl 5-(2-methoxyethoxy)-4H-1,2,4-triazole-3-carboxylate

To a solution of 4-tert-butyl 3-methyl 5-hydroxy-4H-1,2,4-triazole-3,4-dicarboxylate (0.170 g, 0.453 mmol) in THF (4 mL) was added 2-methoxyethanol (0.053 mL, 0.672 mmol), DEAD (0.107 mL, 0.682 mmol), PPh₃ (0.142 g, 0.542 mmol) and stirred at rt for 15 h. Reaction concentrated and ISCO purification (0-5% MeOH in DCM) to get methyl 5-(2-methoxyethoxy)-4H-1,2,4-triazole-3-carboxylate (0.050 g) as a colorless oil.

20 Step C: Synthesis of 5-(2-methoxyethoxy)-4H-1,2,4-triazole-3-carboxylic acid

Standard hydrolysis condition described previously gave the title compound.
Example 8-42

Preparation of building block 5-methoxy-4H-1,2,4-triazole-3-carboxylic acid and 5-methoxy-4-methyl-4H-1,2,4-triazole-3-carboxylic acid

Step-A: Synthesis of methyl 5-methoxy-4H-1,2,4-triazole-3-carboxylate and methyl 5-methoxy-4-methyl-4H-1,2,4-triazole-3-carboxylate

To a solution of 5-hydroxy-4H-1,2,4-triazole-3-carboxylic acid (0.033g, 0.250 mmol) was added ACN:MeOH (1 mL: 1 mL) and diazomethane (0.500 mL, 1 mmols). The reaction was stirred for 20 min. and was concentrated to give a mixture of methyl 5-methoxy-4H-1,2,4-triazole-3-carboxylate and methyl 5-methoxy-4-methyl-4H-1,2,4-triazole-3-carboxylate. The crude was used in next step.

Step-B: Synthesis of 5-methoxy-4H-1,2,4-triazole-3-carboxylic acid and 5-methoxy-4-methyl-4H-1,2,4-triazole-3-carboxylic acid.
Use the same reaction conditions as above section to provide mixture of two compounds.

Following similar procedures describe above, the following compounds (Table 8-32) were made:

<table>
<thead>
<tr>
<th>Compound ID</th>
<th>Structures</th>
<th>Compound Name</th>
<th>pAKT S473 IC50</th>
<th>pE-BP1 Thr37/46 IC50</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.98</td>
<td></td>
<td>(((1R,3S,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-aj]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-(piperazin-1-yl)-4H-1,2,4-triazol-3-yl)methanone</td>
<td>616.32/616.1</td>
<td>C</td>
</tr>
<tr>
<td>8.99</td>
<td></td>
<td>(((1R,3S,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-aj]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-((R)-3-hydroxypropynilin-1-yl)-4H-1,2,4-triazol-3-yl)methanone</td>
<td>617.30/617.1</td>
<td>ND</td>
</tr>
<tr>
<td>8.100</td>
<td></td>
<td>(((1R,3S,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-aj]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-(2-methoxyethoxy)-4H-1,2,4-triazol-3-yl)methanone</td>
<td>606.29/606.1</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Molecular Structure</td>
<td>Formula</td>
<td>PMR Value</td>
<td>N.O.</td>
</tr>
<tr>
<td>---</td>
<td>---------------------</td>
<td>---------</td>
<td>-----------</td>
<td>------</td>
</tr>
<tr>
<td>8.101</td>
<td><img src="image1.png" alt="Molecular Structure" /></td>
<td>((1R,3a,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methoxy-4-methyl-4H-1,2,4-triazol-3-yl)methanone</td>
<td>576.28/576.0</td>
<td>ND</td>
</tr>
<tr>
<td>8.102</td>
<td><img src="image2.png" alt="Molecular Structure" /></td>
<td>((1R,3a,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-(4-methylpiperazin-1-yl)-4H-1,2,4-triazol-3-yl)methanone</td>
<td>630.33/630.1</td>
<td>C</td>
</tr>
<tr>
<td>8.103</td>
<td><img src="image3.png" alt="Molecular Structure" /></td>
<td>((1R,3a,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methoxy-4H-1,2,4-triazol-3-yl)methanone</td>
<td>562.26/562.0</td>
<td>B</td>
</tr>
<tr>
<td>8.104</td>
<td><img src="image4.png" alt="Molecular Structure" /></td>
<td>(5-amino-4H-1,2,4-triazol-3-yl)((1R,3a,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)methanone</td>
<td>547.26/547.1</td>
<td>A</td>
</tr>
<tr>
<td>8.105</td>
<td><img src="image5.png" alt="Molecular Structure" /></td>
<td>((1R,3a,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-morpholino-4H-1,2,4-triazol-3-yl)methanone</td>
<td>617.30/617.3</td>
<td>C</td>
</tr>
</tbody>
</table>
Example 8A

Step 1. **Fert-Butyl (3-exo)-3-[(3-Exo)-3-{7-amino-6-fluoro-3-[6-(1H-imidazol-2-yl)pyridin-3-yl]pyrazolo[1,5-a]pyrimidin-5-yl]-8-azabicyclo[3.2.1]oct-8-yl]-2-hydroxyethanone**

An oven-dried, nitrogen cooled round bottom flask was charged with fert-butyl (3-exo)-3-[7-(bis{[2-(trimethylsilyl)ethoxy]methyl}amino)pyrazol-5-yl]-8-azabicyclo[3.2.1]oct-8-yl-2-hydroxyethanone (2.20 g, 3.01 mmol), sodium formate (2.20 g, 32.3 mmol) and Pd/Cb(dppf)-dichloromethane adduct (0.13 g, 0.16 mmol), dioxane (10 mL) and water (5 mL), sparged with a stream of nitrogen.
Step 2. **Ferf-Butyl (3-exo)-3-[7-(bis[2-(trimethylsilyl)ethoxy]methyl)amino]-3-bromopyrazol[1,5-a]pyrimidin-5-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate**

A stirring solution of ferf-butyl (3-exo)-3-[7-(bis[2-(trimethylsilyl)ethoxy]methyl)amino]pyrazol[1,5-a]pyrimidin-5-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate (1.58 g, 2.62 mmol) in MeCN (20 mL) was charged with NBS (0.49 g, 2.75 mmol) and stirred at room temperature for 1 hour. The reaction mixture was concentrated under vacuum and purified by flash chromatography (Biotage, 0-50% EtOAc/hexanes) to obtain ferf-butyl (3-exo)-3-[7-(bis[2-(trimethylsilyl)ethoxy]methyl)amino]-3-bromopyrazol[1,5-a]pyrimidin-5-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate.

Step 3. ferf-Butyl (3-exo)-3-[7-(bis[2-(trimethylsilyl)ethoxy]methyl)amino]-3-bromo-6-fluoropyrazolon-5-yl-8-azabicyclo[3.2.1]octane-8-carboxylate

A 5 mL microwave vial was charged with ferf-butyl (3-exo)-3-[7-(bis[2-(trimethylsilyl)ethoxy]methyl)amino]-3-bromo-6-fluoropyrazolon-5-yl-8-azabicyclo[3.2.1]octane-8-carboxylate (1.11 g, 1.63 mmol) and MeCN (10 mL), cooled to 0°C and charged dropwise with a solution of Selectfluor® (0.61 g, 1.7 mmol) in MeCN (15 mL). The reaction mixture was stirred at 0°C for a total of 2.5 hours, including addition time then poured into 10:1 hexanes:DCM, filtered through celite, eluted with EtOAc, concentrated in vacuo and purified by flash chromatography (Biotage, 0-20% EtOAc/Hex) to obtain ferf-butyl (3-exo)-3-[7-(bis[2-(trimethylsilyl)ethoxy]methyl)amino]-3-bromo-6-fluoropyrazolon-5-yl-8-azabicyclo[3.2.1]octane-8-carboxylate.

LRMS (ESI) calc’d for C30H52BrFN5O4Si2 [M+H]+: 700, Found: 700.

Step 4. ferf-Butyl (3-exo)-3-[7-(bis[2-(trimethylsilyl)ethoxy]methyl)amino]-6-fluoro-3-[r6-(1-[2-(trimethylsilyl)ethoxy]methyl]imidazol-2-
An oven-dried, nitrogen cooled 5 mL microwave vial was charged with PdCl2(dppf)-dichloromethane adduct (28 mg, 0.034 mmol) and cesium carbonate (0.34 g, 1.044 mmol), sealed under a nitrogen atmosphere, charged with a degassed solution of ferf-butyl (3-exo)-3-[7-(bis[2-(trimethylsilyl)ethoxy]methyl)amino]-3-bromo-6-fluoropyrazolo[1,5-a]pyrimidin-5-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate (243 mg, 0.347 mmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(1-[2-(trimethylsilyl)ethoxy]methyl)-1/7-imidazol-2-yl)pyridine (0.28 g, 0.70 mmol) in dioxane (2.0 mL) and water (0.5 mL) and heated to 100°C for 18 hours. The reaction mixture was cooled to room temperature, filtered through celite, eluted with EtOAc, concentrated under vacuum and purified by flash chromatography (Biotage, 0-50% EtOAc/hexanes) to obtain ferf-butyl (3-exo)-3-{7-(bis[2-(trimethylsilyl)ethoxy]methyl)amino]-6-fluoro-3-[6-(1-[2-(trimethylsilyl)ethoxy]methyl)-1/7-imidazol-2-yl)pyrazolo[1,5-a]pyrimidin-5-yl}-8-azabicyclo[3.2.1]octane-8-carboxylate.


Step 5. 5-(3-Exo)-8-azabicyclo[3.2.1]oct-3-yl-6-fluoro-3-1H-imidazol-2-yl)pyridin-3-yl)pyrazolo[1,5-alpyrimidin-7-amine

A solution of ferf-butyl (3-exo)-3-[7-(bis[2-(trimethylsilyl)ethoxy]methyl)amino]-6-fluoro-3-[6-(1-[2-(trimethylsilyl)ethoxy]methyl)-1/7-imidazol-2-yl)pyrazolo[1,5-a]pyrimidin-5-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate (188.5 mg, 0.211 mmol) in TFA (2.0 mL) and water (2.0 mL) was stirred at room temperature for 72.5 hours and then heated to 50°C for 24 hours. The reaction mixture was cooled to room temperature,
concentrated *in vacuo*, dissolved in DMSO and purified by mass-triggered reverse-phase HPLC to provide 5-{(3-Exo)-8-azabicyclo[3.2.1]oct-3-yl}-6-fluoro-3-[6-\(1\)H-imidazol-2-yl]pyridin-3-yl]pyrazolo[1,5-a]pyrimidin-7-amine as the tris TFA salt. LRMS (ESI) calc’d for C21H22FN8 [M+H]⁺: 405, Found: 405.

1-{(3-Exo)-3-[7-amino-6-fluoro-3-[6-(1H-imidazol-2-yl)pyridin-3-yl]pyrazolo[1,5-a]pyrimidin-5-yl]-8-azabicyclo[3.2.1]oct-8-yl}-2-hydroxyethanone

10 Step 6. 

A stirring solution of 5-{(3-exo)-8-azabicyclo[3.2.1]oct-3-yl]-6-fluoro-3-[6-(1H-imidazol-2-yl)pyridin-3-yl]pyrazolo[1,5-a]pyrimidin-7-amine (27 mg, 0.036 mmol), glycolic acid (10 mg, 0.131 mmol), EDC HCl (20 mg, 0.104 mmol), HOBT (15 mg, 0.098 mmol) and DIPEA (0.07 mL, 0.401 mmol) in DMF (0.5 mL) was heated to 60°C for 14 hours. The reaction mixture was cooled to room temperature, diluted with DMSO and purified by mass-triggered reverse-phase HPLC to provide 1-{(3-exo)-3-[7-amino-6-fluoro-3-[6-(1H-imidazol-2-yl)pyridin-3-yl]pyrazolo[1,5-a]pyrimidin-5-yl]-8-azabicyclo[3.2.1]oct-8-yl]-2-hydroxyethanone as the bis TFA salt.


The final compound had an Mtor IC₅₀ of 2 nM, pAKT473 IC₅₀ of 101 nM, pAKT473 IC₅₀ of 374 nM.

Example 8 B
Step 1. **4-{7-Amino-5-[3-exo)-8-azabicyclo[3.2.1]oct-3-yl]pyrazolo[1,5-a]pyrimidin-3-yl}pyridin-2(1H)-one**

An oven-dried, nitrogen cooled 5 mL microwave vial was charged with fert-butyl (3-exo)-3-[7-(bis[2-(trimethylsilyl)ethoxy]methyl)amino)-3-iodopyrazolo[1,5-a]pyrimidin-5-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate (0.20 g, 0.27 mmol), PdCl₂(dppf)-dichloromethane adduct (22 mg, 0.027 mmol) and cesium carbonate (0.27 g, 0.83 mmol), sealed under a nitrogen atmosphere, charged with a degassed mixture of 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (214 mg, 0.565 mmol), dioxane (1.0 mL) and water (0.2 mL) and heated to 100°C for 17.5 hours. The reaction mixture was cooled to room temperature, filtered through celite, eluted with EtOAc, concentrated under vacuum and purified by flash chromatography (Biotage, 0-50% EtOAc/hexanes) to obtain fert-butyl (3-exo)-3-[7-(bis[2-(trimethylsilyl)ethoxy]methyl)amino]-3-(2-methoxypyridin-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate.

Step 2. 4-[7-Amino-5-(3-exo)-8-azabicyclo[3.2.1]oct-3-yl]pyrazolon-5-alpyrimidin-3-yl]pyridin-2(1H)-one

A solution of tert-butyl (3-exo)-3-[7-(bis[(2-trimethylsilyl)ethoxy]methyl)amino]-3-(2-methoxypyridin-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl]-8-azabicyclo[3.2.1]octane-8-carboxylate (21.0 mg, 0.0300 mmol) and HBr (0.03 mL, 0.3 mmol) in acetic acid (0.5 mL) was stirred for 1.5 hours at 100°C, diluted with DMSO and purified by mass-triggered reverse-phase HPLC to provide 4-[7-amino-5-(3-exo)-8-azabicyclo[3.2.1]oct-3-yl]pyrazolon-5-alpyrimidin-3-yl]pyridin-2(1H)-one.


Mtor IC50 of the final compound was 489 nM.

Example 9

Compounds of Formula (I), wherein m is 0; L and Z are CH2; and T is absent in ring A can be prepared according to Scheme 7 below.
Compound I can be prepared from the propargylic acid intermediate Int-10a through the steps depicted in Scheme 8-2 above. Briefly, bromination of Int-10a using N-bromosuccinimide and silver nitrate provides the bromo intermediate Int-10b. Diels-Alder cycloaddition with N-Boc-protected pyrrole provides the diene intermediate Int-10c. Catalytic reduction of Int-10c affords the reduced intermediate Int-10d. Treatment of Int-10d with sodium methoxide and TMSCHN$_2$ provides Int-10e. Treatment of Int-10e with the lithium salt of acetonitrile affords the cyano-keto intermediate Int-10f. Cycloaddition of Int-10f with 3-aminopyrazole followed by protection of the amino moiety with SEM-CI provides the pyrazolo[1,5-a]pyrimidine.
Iodination of \textbf{Int-10g} using a procedure similar to the one describing in step 9 of Example 1 affords the iodo intermediate \textbf{Int-10h}. Coupling of the iodo intermediate \textbf{Int-10h}, such as by using Suzuki coupling conditions described in Step 10 of Example 1, affords the 3-substituted intermediate \textbf{Int-10i}. Treatment of \textbf{Int-10i} with W-bromosuccinimide such as by using the procedure described in Step 11 of Example 1 provide the 6-bromo intermediate \textbf{Int-10j}. Depending on the desired 6-substituent, the 6-bromo intermediate \textbf{Int-10j} can be converted to the 6-substituted \textbf{Int-10k} using a variety of procedures. For instance, alkanoyl substitution of the 6-position can be accomplished by using procedures similar to those described in Step 12 of Example 1. Sulfonyl substitution of the 6-position can be performed either using procedures similar to those described in scheme-3-1 (Steps A and B) or scheme-3-2 (step 3) of Example 3-1. Nitrile substitution of the 6-position can be accomplished using a procedure similar to that described in Step 1 of Example 5. Acylation of the amino moiety of ring A of \textbf{Int-10k} can be performed using a procedure similar to that described in Step 14 of Example 1.
**Example 10**

Compounds of Formula (I), wherein \( m \) is 1; and \( L, Z \), and \( T \) are \( CH_2 \) in ring A can be prepared according to Scheme 8 below.

Scheme 8

![Scheme 8 Diagram](image)

Compound ii can be prepared from keto intermediate \( \text{Int-1a} \) using the sequence summarized in Scheme 8 above. \( \text{Int-1a} \) is converted to the N Boc-protected intermediate \( \text{Int-1b} \) by a three step sequence. \( \text{Int-1a} \) is treated with 1-chloroethyl chloroformate, followed by treatment with refluxing methanol. The nitrogen atom is Boc protected using Boc₂O to provide the N Boc-protected intermediate \( \text{Int-1b} \). The triflate is formed by treating \( \text{Int-1b} \) under conditions similar to those described in Step 5 of Example 1-1. The triflate is then converted to the boronate ester such as by using the procedure described in Step 6 of Example 1-1. The boronate ester is then combined with \( \text{Int-1d} \) (prepared as described in Steps 1-4 of Example 1-1, scheme-1-1) under Suzuki coupling conditions, such as those described in Step 7 of Example 1-1 to afford \( \text{Int-1c} \). \( \text{Int-1c} \) is then reduced using palladium on charcoal such as by using a procedure similar to that described in Step 8 of Example 1-1. The \( R^3 \), \( R^6 \) and the \( R^8 \) substituents can be installed using procedures similar to those described in steps 9 through 14 as in Examples 1-1 above. Sulfonyl substitution of the 6-position can be performed either using procedures similar to those described in scheme-3-1 (Steps A and B) or scheme-3-2.
(step 3) of Example 3-1. Nitrile substitution of the 6-position can be accomplished using a procedure similar to that described in Step 1 of Example 5.

**Example 11**

Compounds of the of Formula (I) that incorporate deuterium atoms can be prepared from commercially available or known deuterium-containing reagents using modifications of the procedures described above in Examples 1-10. For instance, a deuterated compound of Formula (I) wherein R3 is pyridyl substituted by Y, wherein Y is phenyl substituted by five $^2$H, i.e., compound 54, can be prepared as shown in Scheme 8 below. Compound 54 is a deuterated analog of compound 7.

![Scheme 9](image)

**Scheme 9**

*Step A - Synthesis of tert-butyl 3-(7-bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-phenyl-$^5$-pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)8-azabicyclo[3.2.1]octane-8-carboxylate (Int-12a)*

Phenyl-$^5$-boronic acid (2.79 mmol, 354.3 mg), K$_3$PO$_4$ (4.20 mmol, 890.4 mg), and PdCl$_2$(dpdf)-C$_2$H$_4$I$_2$ (0.14 mmol, 114.3 mg) are added to a solution of fert-butyl
3-(7-(bis((2-(trimethylsilyl)ethoxy)methyl)amino)-3-(6-chloropyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (which can be prepared as described in Step 2 of Example 1-2) (1.40 mmol, 1000 mg) in dioxane (12 mL) and H2O (1.5 mL). The resulting solution is stirred at 150 °C under microwave condition for 1 h. The mixture is diluted with H2O and then extracted with ethyl acetate (x2). The combined organic layers are washed with brine and dried with Na2SO4. Evaporation and purification by column chromatography affords the desired compound Int-12a.

Step B - Synthesis of Compound 54

Compound 1-(5-(8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-phenyl-d5-pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone (54) can be prepared using methods similar to those described in Steps 13 & 14 of Example 1-1 from Int-12a.

EXAMPLE 12

mTOR Kinase Assay

Methods: An HTRF mTOR enzyme assay was developed to assess the compounds’ inhibitory activity. The mTOR assay buffer contained 10 mM Hepes (pH 7.4), 50 mM NaCl, 100 µg/ml BSA, 50 mM B-glycerophosphate, 10 mM MnCl2 and 0.5 mM DTT. An active truncated mTOR enzyme was prepared similarly to that reported by Toral-Barza et al., Biochemical and Biophysical Research Communications 332, pp 304-310 (2005). 20 ng of human mTOR enzyme (< 5 % pure was preincubated with the compound for 10 minutes followed by the addition of 5 µM ATP and 0.2 µM GST-S6K (Zhang et al., Protein Expression and Purification 48, pp 414-420 (2006)). The reaction was incubated for one hour at 30 °C. Anti phospho p70-S6K(Thr389) (1:1 ng/well, anti-phospho-p70S6K-cryptate (Phosp70S6-Kin-K cat# 64CUSKAY, from Cisbio)) and anti GST-XL665 (1:1 Ratio with the substrate GST-S6K, anti GST-XL665, cat# 61GSTXLB) Cisbio) were added after the reaction was stopped. The plates were read (PHERAstar, BMG) at least 2 hours after adding the anti phospho p70-S6K and the anti GST-XL665.
**IC50 DETERMINATIONS:** Dose-response curves were plotted from the inhibition data generated, each in duplicate, from 8 point serial dilutions of inhibitory compounds. Concentration of compound was plotted against the HTRF em665/em590 ratio signal. To generate IC50 values, the dose-response curves were fitted to a standard sigmoidal curve and IC50 values were derived by nonlinear regression analysis.

**Results:** All Compounds were tested in the mTOR assay to determine their IC50 values. All compounds had an mTor IC50 value between 0.5-2000 nM. For example, compound 1.1.93 had an mTor IC50 value of 2.3 nM. Compounds 1-46, 48, 49, and 51-54 had an IC50 value in the range of 1-10 nM. Compounds 47 and 50 had an IC50 value in the range of 10 nM to 25 nM.

**EXAMPLE 13**

**mTOR Target Engagement Assay**

The target engagement of mTOR kinase inhibitors was evaluated using an immunofluorescent cell-based assay. In this assay, inhibition of mTORC1 activity was measured by the reduction in the level of phosphorylated 4E-BP1 Thr37/46, and inhibition of mTORC2 activity was measured by the reduction of phosphorylated AKT Ser473 (pAKT S473).

PC3 cells (prostate tumor cell-line that contains a mutation in the tumor suppressor PTEN, that promotes the phosphorylation and activation of AKT and 4E-BP1) were used in the immunofluorescence assay. PC3 cells were seeded on 384 well plates (black clear bottom, Matrix #4332) overnight. PC3 cells were then treated with 40 µl of the serially diluted test compounds (in 5% fetal bovine serum, F12 medium containing 0.25% DMSO) for ninety minutes at 37 °C. The test compound solution was removed, and the plates were washed gently two times with 25 µl phosphate buffered saline (PBS). The cells were fixed by adding 25 µl of Prefer reagent (from Anatech LTD, Cat#414, a glyoxal fixative for fixing proteins within a cell) for sixty minutes followed by three washes with PBS. 5% Goat serum in PBS/0.3% Triton was used to block non-specific binding (60 minutes).

The primary antibodies targeting pAKT S473 and p4E-BP1 Thr37/46 were diluted into PBS/0.3% Triton and incubated with the cells overnight at 4 °C. The antibodies targeting pAKTS473 (Cat# 4085, Cell signaling) and p4E-BP1 Thr37/46...
(Cat#2855, Cell signaling) were used at a 1:100 dilution. Plates were washed three times with PBS/0.1% Tween 20 before adding the secondary antibody at a 1:200 dilution, (goat anti-rabbit containing a fluorescent label, Alexa Fluor 488, Cat# A11008, Invitrogen) in PBS/0.3% Triton for 60 minutes.

Finally, the plates were washed three times with PBS/0.1% Tween 20 and the fluorescent intensity was read using an Analyst HT from Molecular Devices. The fluorescent intensity values from the serially diluted compound treatment group were analyzed using the Xfit 4 program (Microsoft) (Formula 205: Y = Bottom + (Top-Bottom) / (1 + (IC50/X)^Hillslope) to generate the IC50 value. Where Top is the maximum signal without Compound (+ DMSO only) and Bottom represents maximum inhibition. Y is the fluorescence at some compound concentration. The control used to determine the fluorescent intensities for 100% pAKT S473 or 100% phosphorylated p4E-BP1 Thr37/46 were measured from untreated wells that contained only DMSO, instead of test compound.

The above tables lists representative compounds of the invention with activity data whereby the IC50 values are rated "A," "B," "C," or "D." The IC50 values are rated "A" for IC50 values in the range of 1 nM to 100 nM, "B" for IC50 values in the range from 100 nM to 1000 nM, "C" for IC50 values in the range from 1000 nM to 10 μM, and "D" for IC50 values greater than 10 μM. The designation "ND" or "NA" means that the IC50 was not determined.

**Uses of the Pyrazolopyrimidine Compounds**

The Pyrazolopyrimidine Compounds are useful in human and veterinary medicine in the therapy of proliferative diseases such as cancer, autoimmune diseases, viral diseases, fungal diseases, neurological/neurodegenerative disorders, arthritis, inflammation, anti-proliferative (e.g., ocular retinopathy), neuronal, alopecia and cardiovascular disease. Many of these diseases and disorders are listed in U.S. 6,413,974.

While not being bound by any specific theory it believed that the Pyrazolopyrimidine Compounds are useful in the treatment of proliferative diseases such as cancer, autoimmune diseases, viral diseases, fungal diseases, neurological/neurodegenerative disorders, arthritis, inflammation, anti-proliferative
(e.g., ocular retinopathy), neuronal, alopecia and cardiovascular disease because of their mTOR inhibitory activity.

The general value of the compounds of the invention in inhibiting mTOR can be determined, for example, using the assay described above in Example 12. In addition, the general value in inhibiting mTORC1 or mTORC2 function can be evaluated using the assays described above in Example 13.

More specifically, the Pyrazolopyrimidine Compounds can be useful in the treatment of a variety of cancers, including (but not limited to) the following: tumor of the bladder, breast (including BRCA-mutated breast cancer), colorectal, colon, kidney, liver, lung, small cell lung cancer, non-small cell lung cancer, head and neck, esophagus, bladder, gall bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma;


chronic lymphocytic leukemia ("CLL"), acute and chronic myelogenous leukemia, myelodysplasia syndrome and promyelocytic leukemia;

fibrosarcoma, rhabdomyosarcoma;

head and neck, mantle cell lymphoma, myeloma;

astrocytoma, neuroblastoma, glioma, glioblastoma, malignant glial tumors, astrocytoma, hepatocellular carcinoma, gastrointestinal stromal tumors ("GIST") and schwannomas;

melanoma, multiple myeloma, seminoma, teratocarcinoma, osteosarcoma,

xenoderma pigmentosum, keratocanthoma, thyroid follicular cancer, endometrial cancer, gastrointestinal tract cancer and Kaposi's sarcoma.

While not being bound by any specific theory, due to the key role of kinases in the regulation of cellular proliferation in general, inhibitors of kinases could act as reversible cytostatic agents which may be useful in the treatment of any disease process which features abnormal cellular proliferation, e.g., benign prostate hyperplasia, familial adenomatosis polyposis, neuro-fibromatosis, atherosclerosis, pulmonary fibrosis, arthritis, psoriasis, glomerulonephritis, restenosis following
angioplasty or vascular surgery, hypertrophic scar formation, inflammatory bowel disease, transplantation rejection, endotoxic shock, and fungal infections.

The Pyrazolopyrimidine Compounds may induce or inhibit apoptosis. The apoptotic response is aberrant in a variety of human diseases. The

Pyrazolopyrimidine Compounds, as modulators of apoptosis, can be useful in the treatment of cancer (including but not limited to those types mentioned hereinabove), viral infections (including, but not limited to, herpevirus, poxvirus, Epstein- Barr virus, Sindbis virus and adenovirus), prevention of AIDS development in HIV-infected individuals, autoimmune diseases (including but not limited to systemic lupus, erythematous, autoimmune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel disease, and autoimmune diabetes mellitus), neurodegenerative disorders (including but not limited to Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, spinal muscular atrophy and cerebellar degeneration), myelodysplasia syndromes, aplastic anemia, ischemic injury associated with myocardial infarctions, stroke and reperfusion injury, arrhythmia, atherosclerosis, toxin-induced or alcohol related liver diseases, hematological diseases (including but not limited to chronic anemia and aplastic anemia), degenerative diseases of the musculoskeletal system (including but not limited to osteoporosis and arthritis) aspirin-sensitive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases and cancer pain.

While not being bound by any specific theory, the Pyrazolopyrimidine Compounds, as inhibitors of kinases, can modulate the level of cellular RNA and DNA synthesis. These compounds can therefore be useful in the treatment of viral infections (including but not limited to HIV, human papilloma virus, herpesvirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus).

In particular embodiments of the invention, Pyrazolopyrimidine Compounds, as inhibitors of mTOR kinase could act in diseases or disorders other than cancer that are associated with dysregulated mTOR activity such as viral infections (including, but not limited to, herpevirus, poxvirus, Epstein- Barr virus, Sindbis virus and adenovirus), prevention of AIDS development in HIV-infected individuals, autoimmune diseases (including but not limited to systemic lupus, erythematous, autoimmune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel disease, and autoimmune diabetes mellitus), neurodegenerative
disorders (including but not limited to Alzheimer’s disease, AIDS-related dementia, Parkinson’s disease, amyotrophic lateral sclerosis, retinitis pigmentosa, spinal muscular atrophy and cerebellar degeneration), myelodysplastic syndromes, aplastic anemia, ischemic injury associated with myocardial infarctions, stroke and reperfusion injury, arrhythmia, atherosclerosis, toxin-induced or alcohol related liver diseases, hematological diseases (including but not limited to chronic anemia and aplastic anemia), degenerative diseases of the musculoskeletal system (including but not limited to osteoporosis and arthritis) aspirin-sensitive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases and cancer pain.

The Pyrazolopyrimidine Compounds may also be useful in the chemoprevention of cancer. Chemoprevention is defined as inhibiting the development of invasive cancer by either blocking the initiating mutagenic event or by blocking the progression of pre-malignant cells that have already suffered an insult or inhibiting tumor relapse.

The Pyrazolopyrimidine Compounds may also be useful in inhibiting tumor angiogenesis and metastasis.

Another aspect of this invention is a method of treating a patient (e.g., human) having a disease or condition associated with mTOR kinases by administering a therapeutically effective amount of a Pyrazolopyrimidine Compound, or a pharmaceutically acceptable salt of said compound to the patient. Another aspect of the invention is the use of the Pyrazolopyrimidine Compound for the preparation of a medicament for the treatment of cancer. In another embodiment, the Pyrazolopyrimidine Compound is for use in method of treating cancer. In the therapies described above, a preferred dosage for administration to a patient is about 0.001 to 1000 mg/kg of body weight/day of the Pyrazolopyrimidine Compound. An especially preferred dosage is about 0.01 to 25 mg/kg of body weight/day of the Pyrazolopyrimidine Compound, or a pharmaceutically acceptable salt of said compound.

**COMBINATION THERAPY**

The compounds of the present invention can be administered alone or in combination with other therapies suitable for the disease or disorder being treated. Where separate dosage formulations are used, the compound and the other therapeutic agent can be administered at essentially the same time (concurrently) or
at separately staggered times (sequentially). The pharmaceutical combination is understood to include all these regimens. Administration in these various ways are suitable for the present invention as long as the beneficial therapeutic effect of the compound and the other therapeutic agent are realized by the patient at substantially the same time. In an embodiment, such beneficial effect is achieved when the target blood level concentrations of each active drug are maintained at substantially the same time.

The instant compounds are also useful in combination with known therapeutic agents and anti-cancer agents. For example, instant compounds are useful in combination with known anti-cancer agents. Combinations of the presently disclosed compounds with other anti-cancer or chemotherapeutic agents are within the scope of the invention. Therefore, the present invention encompasses pharmaceutical compositions comprising a therapeutically effective amount of the compound of the invention and a pharmaceutically acceptable carrier and optionally other therapeutic ingredients, such as an anti-cancer agent. Examples of such agents can be found in Cancer Principles and Practice of Oncology by V.T. Devita and S. Hellman (editors), 6th edition (February 15, 2001), Lippincott Williams & Wilkins Publishers. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the cancer involved. Such anti-cancer agents include, but are not limited to, the following: estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic/cytostatic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors and other angiogenesis inhibitors, inhibitors of cell proliferation and survival signaling, apoptosis inducing agents, agents that interfere with cell cycle checkpoints, agents that interfere with receptor tyrosine kinases (RTKs) and cancer vaccines. The instant compounds are particularly useful when co-administered with radiation therapy.

In an embodiment, the instant compounds are also useful in combination with known anti-cancer agents including the following: estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-
CoA reductase inhibitors, HIV protease inhibitors, reverse transcriptase inhibitors, and other angiogenesis inhibitors.

“Estrogen receptor modulators” refers to compounds that interfere with or inhibit the binding of estrogen to the receptor, regardless of mechanism. Examples of estrogen receptor modulators include, but are not limited to, diethylstibestral, tamoxifen, raloxifene, idoxifene, LY353381, LY117081, toremifene, fluoxymesteron, 4-[7-(2,2-dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2H-1-benzopyran-3-yl]-phenyl-2,2-dimethylpropanoate, 4,4′-dihydroxybenzophenone-2,4-dinitrophenyl-hydrazone, and SH646.

Other hormonal agents include: aromatase inhibitors (e.g., aminogluthethimide, anastrozole and tetrazole), luteinizing hormone release hormone (LHRH) analogues, ketoconazole, goserelin acetate, leuprolide, megestrol acetate and mifepristone.

“Androgen receptor modulators” refers to compounds which interfere or inhibit the binding of androgens to the receptor, regardless of mechanism. Examples of androgen receptor modulators include finasteride and other 5α-reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole, and abiraterone acetate.

“Retinoid receptor modulators” refers to compounds which interfere or inhibit the binding of retinoids to the receptor, regardless of mechanism. Examples of such retinoid receptor modulators include bexarotene, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid, a-difluoromethylornithine, ILX23-7553, trans-N-(4′-hydroxyphenyl) retinamide, and N-4-carboxyphenyl retinamide.

“Cytotoxic/cytostatic agents” refer to compounds which cause cell death or inhibit cell proliferation primarily by interfering directly with the cell’s functioning or inhibit or interfere with cell mytosis, including alkylating agents, tumor necrosis factors, intercalators, hypoxia activatable compounds, microtubule inhibitors/microtubule-stabilizing agents, inhibitors of mitotic kinesins, inhibitors of histone deacetylase, inhibitors of kinases involved in mitotic progression, nитетметаболиты; biological response modifiers; hormonal/anti-hormonal therapeutic agents, haematopoietic growth factors, monoclonal antibody targeted therapeutic agents, topoisomerase inhibitors, proteasome inhibitors and ubiquitin ligase inhibitors.
Examples of cytotoxic agents include, but are not limited to, sertenef, cachectin, chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine, melphalan, uracil mustard, thiotepa, busulfan, carmustine, lomustine, streptozocin, tasonermin, lonidamine, carboplatin, altretamine, dacarbazine, procarbazine, prednimustine, dibromodulcitol, ranimustine, fotemustine, nedaplatin, oxaliplatin, temozolomide, heptaplatin, estramustine, imposulfan tosilate, trofosfamide, nimustine, dibospididum chloride, pumitepa, lobaplatin, satraplatin, proflomycin, cisplatin, irofulven, dexifosfamide, cis-aminedichloro(2-methyl-pyridine)platinum, benzylguanine, glufosfamide, GPX100, (trans, trans, trans)-bis-mu-(hexane-1,6-diamine)-mu-[diamine-platinum(ll)]bis[diamine(chloro)platinum (ll)]tetrachloride, diarizidinylspermine, arsenic trioxide, 1-(11-dodecylamino-10-hydroxyundecyl)-3,7-dimethylxanthine, zorubicin, doxorubicin, daunorubicin, idarubicin, anthracenedione, bleomycin, mitomycin C, dactinomycin, plicatomycin, bisantrene, mitoxantrone, pirarubicin, pinafide, valrubicin, amrubucin, antineoplaston, 3’-deamino-3’-

An example of a hypoxia activatable compound is tirapazamine.

Examples of proteasome inhibitors include but are not limited to lactacystin and bortezomib.

Examples of microtubule inhibitors/microtubule-stabilising agents include vincristine, vinblastine, vindesine, vinzolidine, vinorelbine, vindesine sulfate, 3’,4’-didehydro-4’-deoxy-8’-norvincaleukoblastine, podophyllotoxins (e.g., etoposide (VP-16) and teniposide (VM-26)), paclitaxel, docetaxel, rhizoxin, dolastatin, mivobulin istethionate, auristatin, cemadotin, RPR109881, BMS184476, vinflunine, cryptophycin, 2,3,4,5,6-pentafluoro-N-(3-fluoro-4-methoxyphenyl) benzene sulfonamide, anhydrovinblastine, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline-t-butylamide, TDX258, the epothilones (see for example U.S. Pat. Nos. 6,284,781 and 6,288,237) and BMS188797.

Some examples of topoisomerase inhibitors are topotecan, hycaptamine, irinotecan, rubitecan, 6-ethoxypropionyl-3’,4’-0-exo-benzylidene-chartreusin, 9-methoxy-N,N-dimethyl-5-nitropyrazolo[3,4,5-kl]acridine-2-(6H) propanamine, 1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1 H,12H-
benzo[de]pyrano[3',4':b,7]-indolizino[1,2b]quinoline-10,13(9H,15H)dione, lurtotecan, 7-[2-(N-isopropylamino)ethyl]-(20S)camptothecin, BNP1350, BNP1 100, BN80915, BN80942, etoposide phosphate, teniposide, sobuzoxane, 2'-dimethylamino-2'-deoxy-etoposide, GL331, N-[2-(dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide, asulacrine, (5a,5aB,8aa,9b)-9-[2-[N-[2-(dimethylamino)ethyl]-N-methylamino]ethyl]-5-[4-hydroxy-3,5-dimethoxyphenyl]-5,5a,6,8,8a,9-hexahydrofuro(3',4':6,7)naphtho(2,3-d)-1,3-dioxol-6-one, 2,3-(methylenedioxy)-5-methyl-7-hydroxy-8-methoxybenzo[c]-phenanthridinium, 6,9-bis[[2-aminooethyl]amino]benzo[g]isouquinoline-5, 10-dione, 5-(3-amino propylamino)-7;10-dihydroxy-2-(2-hydroxyethylaminomethyl)-6H-pyrazolo[4,5, 1-de]acidin-6-one, N-[1-[2(diethylamino)ethyl]amino]-7-methoxy-9-oxo-9H-thioxanthen-4-ylmethyl]formamide, N-(2-(dimethylamino)ethyl)acridine-4-carboxamide, 6-[[2-(dimethylamino)ethyl]amino]-3-hydroxy-7H-indeno[2,1-c] quinolin-7-one, and dimesna.

Examples of inhibitors of mitotic kinesins, and in particular the human mitotic kinesis KSP, are described in PCT Publications WO 01/30768, WO 01/98278, WO 03/050,064, WO 03/050,122, WO 03/049,679, WO 03/049,678, WO 03/39460 and WO2003/09921 1, WO2004/039774, WO2003/10641 7. In an embodiment inhibitors of mitotic kinesins include, but are not limited to inhibitors of KSP, inhibitors of MKLP1, inhibitors of CENP-E, inhibitors of MCAK, inhibitors of Kif14, inhibitors of Mphosphl and inhibitors of Rab6-KIFL.

Examples of "histone deacetylase inhibitors" include, but are not limited to, SAHA, TSA, oxamfatin, PXD101, MG98, valproic acid and scriptaid.

Further reference to other histone deacetylase inhibitors may be found in the following manuscript; Miller, T.A. et al. J. Med. Chem. 46(24):5097-51 16 (2003).

"Inhibitors of kinases involved in mitotic progression" include, but are not limited to, inhibitors of aurora kinase, inhibitors of Polo-like kinases (PLK; in particular inhibitors of PLK-1), inhibitors of bub-1 and inhibitors of bub-R1. An example of an "aurora kinase inhibitor" is VX-680.

"Antiproliferative agents" includes antisense RNA and DNA oligonucleotides such as G3139, ODN698, RVASKRAS, GEM231, and INX3001, and antimetabolites such as enocitabine, carmofur, tegafur, pentostatin,
doxifluridine, trimetrexate, fludarabine, galocitabine, cytarabine
ocfosfate, fosteabine sodium hydrate, raltitrexed, paltitrexid, emitefur, tiazofurin,
decitabine, nolatrexed, pemetrexed, nelzarabine, 2'-deoxy-2'-methyldenecytidine,
2'-fluoromethylene-2'-deoxycytidine, N-[5-(2,3-dihydro-benzofuryl)sulfonyl]-N'-(3,4-
dichlorophenyl)urea, N6-[4-deoxy-4-[N2-[2(E),4(E)-tetradecadienoyl]glycylamino]-L-
glycero-B-L-manno-heptopyranosyl]adenine, aplidine, eteinscadin, troxacitabine, 4-
[2-amino-4-oxo-4,6,7,8-tetrahydro-3H-pyrimidino[5,4-b][1.4]thiazin-6-y1-(S)-ethyl]-
2,5-thienoyl-L-glutamic acid, aminopterin, 5-flurouracil, floxuridine, methotrexate,
leucovarin, hydroxyurea, thioguanine (6-TG), mercaptopurine (6-MP), cytarabine,
pentostatin, fludarabine phosphate, cladribine (2-CDA), asparaginase, gencitabine,
alanosine, 11-acetyl-8-[(carbamoyloxymethyl)-4-formyl-6-methoxy-14-oxa-1.1-
diazatetracyclo(7.4.1.0.0)-tetraeca-2,4,6-trien-9-yl acetic acid ester, swainsonine,
lometrexol, dexrazoxane, methioninase, 2'-cyano-2'-deoxy-N4-palmitoyl-1-B-D-
arabino furanosyl cytosine and 3-aminopyridine-2-carboxaldehyde
thiosemicarbazone.

Examples of monoclonal antibody targeted therapeutic agents include those therapeutic agents which have cytotoxic agents or radioisotopes attached to a cancer cell specific or target cell specific monoclonal antibody. Examples include Bexxar.

"HMG-CoA reductase inhibitors" refers to inhibitors of 3-hydroxy-3-
methylglutaryl-CoA reductase. Examples of HMG-CoA reductase inhibitors that may be used include but are not limited to lovastatin (MEVACOR®; see U.S. Pat. Nos. 4,231,938, 4,294,926 and 4,319,039), simvastatin (ZOCOR®; see U.S. Pat. Nos. 4,444,784, 4,820,850 and 4,916,239), pravastatin (PRAVACHOL®; see U.S. Pat. Nos. 4,346,227, 4,537,859, 4,410,629, 5,030,447 and 5,180,589), fluvastatin (LESCOL®; see U.S. Pat. Nos. 5,354,772, 4,911,165, 4,929,437, 5,189,164, 5,118,853, 5,290,946 and 5,356,896) and atorvastatin (LIPITOR®; see U.S. Pat. Nos. 5,273,995, 4,681,893, 5,489,691 and 5,342,952). The structural formulas of these and additional HMG-CoA reductase inhibitors that may be used in the instant methods are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", Chemistry & Industry, pp. 85-89 (5 February 1996) and US Patent Nos. 4,782,084 and 4,885,314. The term HMG-CoA reductase inhibitor as used herein includes all
pharmaceutically acceptable lactone and open-acid forms (i.e., where the lactone ring is opened to form the free acid) as well as salt and ester forms of compounds which have HMG-CoA reductase inhibitory activity, and therefore the use of such salts, esters, open-acid and lactone forms is included within the scope of this invention.

“Prenyl-protein transferase inhibitor” refers to a compound which inhibits any one or any combination of the prenyl-protein transferase enzymes, including farnesyl-protein transferase (FPTase), geranylgeranyl-protein transferase type I (GGPTase-I), and geranylgeranyl-protein transferase type-II (GGPTase-II, also called Rab GGPTase).


“Angiogenesis inhibitors” refers to compounds that inhibit the formation of new blood vessels, regardless of mechanism. Examples of angiogenesis inhibitors include, but are not limited to, tyrosine kinase inhibitors, such as inhibitors of the tyrosine kinase receptors Flt-1 (VEGFR1) and Flk-1/KDR (VEGFR2), inhibitors of epidermal-derived, fibroblast-derived, or platelet derived growth factors, MMP...

Other therapeutic agents that modulate or inhibit angiogenesis and may also be used in combination with the compounds of the instant invention include agents that modulate or inhibit the coagulation and fibrinolysis systems (see review in Clin. Chem. La. Med. 38:679-692 (2000)). Examples of such agents that modulate or inhibit the coagulation and fibrinolysis pathways include, but are not limited to, heparin (see Thromb. Haemost. 80:10-23 (1998)), low molecular weight heparins and carboxypeptidase U inhibitors (also known as inhibitors of active thrombin activatable fibrinolysis inhibitor [TAFIa]) (see Thrombosis Res. 101:329-354 (2001)). TAFIa inhibitors have been described in PCT Publication WO 03/013,526 and U.S. Ser. No. 60/349,925 (filed January 18, 2002).

"Agents that interfere with cell cycle checkpoints" refer to compounds that inhibit protein kinases that transduce cell cycle checkpoint signals, thereby sensitizing the cancer cell to DNA damaging agents. Such agents include inhibitors of ATR, ATM, the Chk1 and Chk2 kinases and cdk and cdc kinase inhibitors and are specifically exemplified by 7-hydroxystaurosporin, flavopiridol, CYC202 (Cyclacel) and BMS-387032.
"Agents that interfere with receptor tyrosine kinases (RTKs)" refer to compounds that inhibit RTKs and therefore mechanisms involved in oncogenesis and tumor progression. Such agents include inhibitors of c-Kit, Eph, PDGF, Flt3 and c-Met. Further agents include inhibitors of RTKs shown as described by Bume-Jensen and Hunter, Nature, 411:355-365, 2001.

"Inhibitors of cell proliferation and survival signaling pathway" refer to pharmaceutical agents that inhibit cell surface receptors and signal transduction cascades downstream of those surface receptors. Such agents include inhibitors of inhibitors of EGFR (for example gefitinib and erlotinib), inhibitors of ERB-2 (for example trastuzumab), inhibitors of IGFR, inhibitors of CD20 (rituximab), inhibitors of cytokine receptors, inhibitors of MET, inhibitors of PI3K kinase family (for example LY294002), serine/threonine kinases (including but not limited to inhibitors of Akt such as described in (WO 03/086404, WO 03/086403, WO 03/086394, WO 03/086279, WO 02/083675, WO 02/083139, WO 02/083140 and WO 02/083138), inhibitors of Raf kinase (for example BAY-43-9006), inhibitors of MEK (for example CI-1040 and PD-098059) and inhibitors of mTOR (for example Wyeth CCI-779 and Ariad AP23573). Such agents include small molecule inhibitor compounds and antibody antagonists.

Examples of mTOR inhibitors include ridaforolimus, temsirolimus, everolimus, a rapamycin-analog. Ridaforolimus, also known as AP 23573, MK-8669 and deforolimus, is a unique, non-prodrug analog of rapmycin that has antiproliferative activity in a broad range of human tumor cell lines in vitro and in murine tumor xenograft models utilizing human tumor cell lines. Ridaforolimus has been administered to patients with advanced cancer and is currently in clinical development for various advanced malignancies, including studies in patients with advanced soft tissue or bone sarcomas. Thus far, these trials have demonstrated that ridaforolimus is generally well-tolerated with a predictable and manageable adverse even profile, and possess anti-tumor activity in a broad range of cancers. A description and preparation of ridaforolimus is described in U.S. Patent No. 7,091,213 to Ariad Gene Therapeutics, Inc. Temsirolimus, also known as Torisel®, is currently marketed for the treatment of renal cell carcinoma. A description and preparation of temsirolimus is described in U.S. Patent No. 5,362,718 to American Home Products Corporation. Everolimus, also known as Certican® or RAD001,
marketed by Novartis, has greater stability and enhanced solubility in organic solvents, as well as more favorable pharmokinetics with fewer side effects than rapamycin (sirolimus). Everolimus has been used in conjunction with microemulsion cyclosporin (Neoral®, Novartis) to increase the efficacy of the immunosuppressive regime.

"Apoptosis inducing agents" include activators of TNF receptor family members (including the TRAIL receptors).

The invention also encompasses combinations with NSAID's which are selective COX-2 inhibitors. For purposes of this specification NSAID's which are selective inhibitors of COX-2 are defined as those which possess a specificity for inhibiting COX-2 over COX-1 of at least 100 fold as measured by the ratio of IC50 for COX-2 over IC50 for COX-1 evaluated by cell or microsomal assays. Such compounds include, but are not limited to those disclosed in U.S. Pat. 5,474,995, U.S. Pat. 5,861,419, U.S. Pat. 6,001,843, U.S. Pat. 6,020,343, U.S. Pat. 5,409,944, U.S. Pat. 5,436,265, U.S. Pat. 5,536,752, U.S. Pat. 5,550,142, U.S. Pat. 5,604,260, U.S. 5,698,584, U.S. Pat. 5,710,140, WO 94/15932, U.S. Pat. 5,344,991, U.S. Pat. 5,134,142, U.S. Pat. 5,380,738, U.S. Pat. 5,393,790, U.S. Pat. 5,466,823, U.S. Pat. 5,633,272, and U.S. Pat. 5,932,598.

Inhibitors of COX-2 that are particularly useful in the instant method of treatment are: 3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(5/7)-furanone; and 5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine; or a pharmaceutically acceptable salt thereof.

Compounds that have been described as specific inhibitors of COX-2 and are therefore useful in the present invention include, but are not limited to: parecoxib, CELEBREX® and BEXTRA® or a pharmaceutically acceptable salt thereof.

Other examples of angiogenesis inhibitors include, but are not limited to, endostatin, ukrain, ranpirnase, IM862, 5-methoxy-4-{2-methyl-3-[3-methyl-2-butenyl]oxiranyl}-1-oxaspiro[2,5]oct-6-yl(chloroacetyl)carbamate, acetyldinanaline, 5-amino-1-[[3,5-dichloro-4-(4-chlorobenzoyl)phenyl][methyl]-1 H,1,2,3-triazole-4-carboxamide, CM101, squalamine, combretastatin, RPI4610, NX31838, sulfated mannopentaose phosphate, 7,7-(carbonyl-bis[imino-N-methyl-4,2-
pyrrolocarbonylimino[N-methyl-4,2-pyrrole]-carbonylimino]-bis-(1,3-naphthalene
disulfonate), and 3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone (SU5416).

As used above, "integrin blockers" refers to compounds which selectively
antagonize, inhibit or counteract binding of a physiological ligand to the
\( \alpha_\nu \beta_3 \) integrin, to compounds which selectively antagonize, inhibit or counteract
binding of a physiological ligand to the \( \alpha_\nu \beta_3 \) integrin, to compounds which
antagonize, inhibit or counteract binding of a physiological ligand to both the \( \alpha_\nu \beta_3 \)
integrin and the \( \alpha_\nu \beta_3 \) integrin, and to compounds which antagonize, inhibit or
counteract the activity of the particular integrin(s) expressed on capillary endothelial
cells. The term also refers to antagonists of the \( \alpha_\nu \beta_3 , \alpha_\nu \beta_4 , \alpha_\nu \beta_6 , \alpha_\alpha \beta_2 , \alpha_\alpha \beta_3 , \alpha_\alpha \beta_5 \)
and \( \alpha_\nu \beta_4 \) integrins. The term also refers to antagonists of any combination of \( \alpha_\nu \beta_3 ,
\alpha_\nu \beta_4 , \alpha_\nu \beta_6 , \alpha_\alpha \beta_2 , \alpha_\alpha \beta_3 , \alpha_\alpha \beta_5 \) and \( \alpha_\nu \beta_4 \) integrins.

Some specific examples of tyrosine kinase inhibitors include N-(trifluoromethylphenyl)-5-methylisoxazol-4-carboxamide, 3-[(2,4-dimethylpyrrol-5-yl)methylenyl]indolin-2-one, 17-(allylamino)-17-demethoxygeldanamycin, 4-(3-chloro-4-fluorophenylamino)-7-methoxy-6-[3-(4-morpholinyloxy)propoxy]quinazoline, N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, BIBX1382, 2,3,9,10,11,12-hexahydro-1-0-(hydroxymethyl)-1-0-hydroxy-9-methyl-9, 12-epoxy-1H-dindolo[1,2,3-f:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazoquinol-1-one, SH268, genistein, imatinib (STI571), CEP2563, 4-(3-chlorophenylamino)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidinemethane sulfonate, 4-(3-bromo-4-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, 4-(4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, SU6668, STI571A, N-4-chlorophenyl-4-(4-pyridylmethyl)-1-pthalazinamine, and EMD121974.

Combinations with compounds other than anti-cancer compounds are
also encompassed in the instant methods. For example, combinations of the
instantly claimed compounds with PPAR-\( \gamma \) (i.e., PPAR-gamma) agonists and PPAR-
\( \delta \) (i.e., PPAR-delta) agonists are useful in the treatment of certain malignances.
PPAR-\( \gamma \) and PPAR-\( \delta \) are the nuclear peroxisome proliferator-activated receptors \( \gamma \)
and \( \delta \). The expression of PPAR-\( \gamma \) on endothelial cells and its involvement in
angiogenesis has been reported in the literature (see J. Cardiovasc. Pharmacol.
More recently, PPAR-γ agonists have been shown to inhibit the angiogenic response to VEGF in vitro; both troglitazone and rosiglitazone maleate inhibit the development of retinal neovascularization in mice. (Arch. Ophthalmol. 2001; 119:709-717). Examples of PPAR-γ agonists and PPAR-γ/α agonists include, but are not limited to, thiazolidinediones (such as DRF2725, CS-011, troglitazone, rosiglitazone, and pioglitazone), fenofibrate, gemfibrozil, clofibrate, GW2570, SB219994, AR-H039242, JTT-501, MCC-555, GW2331, GW409544, NN2344, KRP297, NP0110, DRF4158, NN622, GI262570, PNU182716,

DRF552926, 2-[(5,7-dipropyl-3-trifluoromethyl-1-[2-(5,7-dipropyl-3-trifluoromethyl-1-(4-methylpropionic acid (disclosed in USSN 09/782,856), and 2(R)-7-(3-(2-chloro-4-(4-fluorophenox) phenoxy)propoxy)-2-ethylchromane-2-carboxylic acid (disclosed in USSN 60/235,708 and 60/244,697).

Another embodiment of the instant invention is the use of the presently disclosed compounds in combination with gene therapy for the treatment of cancer. For an overview of genetic strategies to treating cancer see Hall et al (Am J Hum Genet 61:785-789, 1997) and Kufe et al (Cancer Medicine, 5th Ed, pp 876-889, BC Decker, Hamilton 2000). Gene therapy can be used to deliver any tumor suppressing gene. Examples of such genes include, but are not limited to, p53, which can be delivered via recombinant virus-mediated gene transfer (see U.S. Pat. No. 6,069,134, for example), Duc-4, NF-1, NF-2, RB, WT1, BRCA1, BRCA2, a uPA/uPAR antagonist ("Adenovirus-Mediated Delivery of a uPA/uPAR Antagonist Suppresses Angiogenesis-Dependent Tumor Growth and Dissemination in Mice," Gene Therapy, August 1998; 5(8):1105-13), and interferon gamma (J. Immunol. 2000; 164:217-222).

The compounds of the instant invention may also be administered in combination with an inhibitor of inherent multidrug resistance (MDR), in particular MDR associated with high levels of expression of transporter proteins. Such MDR inhibitors include inhibitors of p-glycoprotein (P-gp), such as LY335979, XR9576, OC144-093, R101922, VX853 and PSC833 (valspodar).

A compound of the present invention may be employed in conjunction with anti-emetic agents to treat nausea or emesis, including acute, delayed, late-phase, and anticipatory emesis, which may result from the use of a compound of the
present invention, alone or with radiation therapy. For the prevention or treatment of emesis, a compound of the present invention may be used in conjunction with other anti-emetic agents, especially neurokinin-1 receptor antagonists, 5HT3 receptor antagonists, such as ondansetron, granisetron, tropisetron, and zatisetron, GABAB receptor agonists, such as baclofen, a corticosteroid such as Decadron (dexamethasone), Kenalog, Aristocort, Nasalide, Preferid, Benecorten or others such as disclosed in U.S. Patent Nos. 2,789,118, 2,990,401, 3,048,581, 3,126,375, 3,929,768, 3,996,359, 3,928,326 and 3,749,712, an antidopaminergic, such as the phenothiazines (for example prochlorperazine, fluphenazine, thioridazine and mesoridazine), metoclopramide or dronabinol. In an embodiment, an anti-emesis agent selected from a neurokinin-1 receptor antagonist, a 5HT3 receptor antagonist and a corticosteroid is administered as an adjuvant for the treatment or prevention of emesis that may result upon administration of the instant compounds.

Neurokinin-1 receptor antagonists of use in conjunction with the compounds of the present invention are fully described, for example, in U.S. Pat. Nos. 5,162,339, 5,232,929, 5,242,930, 5,373,003, 5,387,595, 5,459,270, 5,494,926, 5,496,833, 5,637,699, 5,719,147; European Patent Publication Nos. EP 0 360 390, 0 394 989, 0 428 434, 0 429 366, 0 430 771, 0 436 334, 0 443 132, 0 482 539, 0 498 069, 0 499 313, 0 512 901, 0 512 902, 0 514 273, 0 514 274, 0 514 275, 0 514 276, 0 515 681, 0 517 589, 0 520 555, 0 522 808, 0 528 495, 0 532 456, 0 533 280, 0 536 817, 0 545 478, 0 558 156, 0 577 394, 0 585 913, 0 590 152, 0 599 538, 0 610 793, 0 634 402, 0 686 629, 0 693 489, 0 694 535, 0 699 655, 0 699 674, 0 707 006, 0 708 101, 0 709 375, 0 709 376, 0 714 891, 0 723 959, 0 733 632 and 0 776 893; PCT International Patent Publication Nos. WO 90/05525, 90/05729, 91/09844, 91/18899, 92/01688, 92/06079, 92/12151, 92/15585, 92/17449, 92/20661, 92/20676, 92/21677, 92/22569, 93/00330, 93/00331, 93/01 159, 93/01 165, 93/01 169, 93/01 170, 93/06099, 93/091 16, 93/10073, 93/14084, 93/141 13, 93/18023, 93/19064, 93/21 155, 93/21 181, 93/23380, 93/24465, 94/00440, 94/01402, 94/02461, 94/02595, 94/03429, 94/03445, 94/04494, 94/04496, 94/05625, 94/07843, 94/08997, 94/10165, 94/10167, 94/10168, 94/10170, 94/11 138, 94/13639, 94/13663, 94/14767, 94/15903, 94/19320, 94/19332, 94/20500, 94/26735, 94/26740, 94/29309, 95/02595, 95/04040, 95/04042, 95/06645, 95/07886, 95/07908, 95/08549, 95/1 180, 95/1401 7, 95/1531 1, 95/16679, 95/17382, 95/18124, 95/18129, 95/19344, 95/20575, 95/21819, 95/22525, 95/23798,
In an embodiment, the neurokinin-1 receptor antagonist for use in conjunction with the compounds of the present invention is selected from: 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine, or a pharmaceutically acceptable salt thereof, which is described in U.S. Pat. No. 5,719,147.

A compound of the instant invention may also be administered with an agent useful in the treatment of anemia. Such an anemia treatment agent is, for example, a continuous erythropoiesis receptor activator (such as epoetin alfa).

A compound of the instant invention may also be administered with an agent useful in the treatment of neutropenia. Such a neutropenia treatment agent is, for example, a hematopoietic growth factor which regulates the production and function of neutrophils such as a human granulocyte colony stimulating factor, (G-CSF). Examples of a G-CSF include filgrastim.

A compound of the instant invention may also be administered with an immunologic-enhancing drug, such as levamisole, bacillus Calmette-Guerin, octreotide, isoprinosine and Zadaxin.

A compound of the instant invention may also be useful for treating or preventing cancer, including bone cancer, in combination with bisphosphonates (understood to include bisphosphonates, diphosphonates, bisphosphonic acids and diphosphonic acids). Examples of bisphosphonates include but are not limited to: etidronate (Didronel), pamidronate (Aredia), alendronate (Fosamax), risedronate (Actonel), zoledronate (Zometa), ibandronate (Boniva), incadronate or cimadronate, clodronate, EB-1053, minodronate, neridronate, pireidronate and tiludronate including any and all pharmaceutically acceptable salts, derivatives, hydrates and mixtures thereof.
A compound of the instant invention may also be useful for treating or preventing breast cancer in combination with aromatase inhibitors. Examples of aromatase inhibitors include but are not limited to anastrozole, letrozole and exemestane.

A compound of the instant invention may also be useful for treating or preventing cancer in combination with siRNA therapeutics.

A compound of the instant invention may also be useful for treating or preventing cancer in combination with compounds which induce terminal differentiation of the neoplastic cells. Suitable differentiation agents include the compounds disclosed in any one or more of the following references.


c) Steroid hormones (Lotem, J. and Sachs, L. (1975) Int. J. Cancer 15: 731-740);


g) Inhibitors of DNA or RNA synthesis (Schwartz, E. L. and Sartorelli, A. C. (1982) Cancer Res. 42: 2651-2655, Terada, M., Epner, E., Nudel, U., Salmon,

A compound of the instant invention may also be useful for treating or preventing cancer in combination with γ-secretase inhibitors.

Also included in the scope of the claims is a method of treating cancer that comprises administering a therapeutically effective amount of a compound of Formula I in combination with radiation therapy and/or in combination with a second compound selected from: an estrogen receptor modulator, an androgen receptor modulator, a retinoid receptor modulator, a cytotoxic cytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an HIV protease inhibitor, a reverse transcriptase inhibitor, an angiogenesis inhibitor, PPAR-γ agonists, PPAR-δ agonists, an inhibitor of inherent multidrug resistance, an anti-emetic agent, an agent useful in the treatment of anemia, an agent useful in the treatment of neutropenia, an immunologic-enhancing drug, an inhibitor of cell proliferation and survival signaling, a bisphosphonate, an aromatase inhibitor, an siRNA therapeutic, γ-secretase inhibitors, agents that interfere with receptor tyrosine kinases (RTKs) and an agent that interferes with a cell cycle checkpoint.

The compounds of the instant invention are useful in combination with the following therapeutic agents: abarelix (Plenaxis depot®); aldesleukin (Prokine®); Aldesleukin (Proleukin®); Alemtuzumabb (Campath®); altretinoin (Panretin®); allopurinol (Zyloprim®); altretamine (Hexalen®); amifostine (Ethyo®); anastrozole (Arimidex®); arsenic trioxide (Trisenox®); asparaginase (Elspar®); azacitidine (Vidaza®); bendamustine hydrochloride (Treanda®); bevacuzimab (Avastin®); bexarotene capsules (Targetretin®); bexarotene gel (Targetretin®); bleomycin (Blenoxane®); bortezomib (Velcade®); busulfan intravenous (Busulfex®); busulfan oral (Myleran®); calusterone (Methosarb®); capecitabine (Xeloda®); carboplatin (Blenoxane®); bortezomib (Velcade®); busulfan intravenous (Busulfex®); busulfan oral (Myleran®); calusterone (Methosarb®); capecitabine (Xeloda®); carboplatin
(Paraplatin®); carmustine (BCNU®, BiCNU®); carmustine (Gliadel®); carmustine with Polifeprosan 20 Implant (Gliadel Wafer®); celecoxib (Celebrex®); cetuximab (Erbilux®); chlorambucil (Leukeran®); cisplatin (Platinol®); cladribine (Leustatin®, 2-CdA®); clofarabine (Clolar®); cyclophosphamide (Cytoxan, Neosar®);

cyclophosphamide (Cytoxan Injection®); cyclophosphamide (Cytoxan Tablet®);
cytarabine (Cytosar-U®); cytarabine liposomal (DepoCyt®); dacarbazine (DTIC-Dome®); dactinomycin, actinomycin D (Cosmegen®); dalteparin sodium injection (Fragmin®); Darbepoetin alfa (Aranesp®); dasatinib (Sprycel®); daunorubicin liposomal (DanuoXome®); daunorubicin, daunomycin (Daunorubicin®);
daunorubicin, daunomycin (Cerubidine®); degarelix (Firmagon®); Denileukin difitox (Ontak®); dextrazoxane (Zinacef®); dextrazoxane hydrochloride (Totect®); docetaxel (Taxotere®); doxorubicin (Adriamycin PFS®); doxorubicin (Adriamycin®, Rubex®); doxorubicin liposomal (Doxil®);
dromostanolone propionate (Dromostanolone ®); dromostanolone propionate (Masterone Injection®); eculizumab injection (Soliris®); Elliott’s B Solution (Elliott’s B Solution®); eltrombopag (Promacta®); epirubicin (Ellence®); Epoeitin alfa (epogen®); ertoutabin (Tarceva®); estramustine (Emcyt®); etoposide phosphate (Etopophos®); etoposide, VP-16 (Vepesid®); everolimus tablets (Afinitor®);
exemestane (Aromasin®); ferumoxytol (Feraheme Injection®); Filgrastim (Neupogen®); floxuridine (intraarterial) (FUDR®); fludarabine (Fludara®);
fluorouracil, 5-FU (Adrucil®); fulvestrant (Faslodex®); gefitinib (Iressa®); gemcitabine (Gemzar®); gemtuzumab ozogamicin (Mylotarg®); goserecin acetate (Zoladex Implant®); goserecin acetate (Zoladex®); histrelin acetate (Histrelin implant®); hydroxyurea (Hydrea®); ibritumomab Tiuxetan (Zevalin®); idarubicin (Idamycin®); ifosfamide (IFEX®); imatinib mesylate (Gleevec®); interferon alfa 2a (Roferon A®); Interferon alfa-2b (Intron A®); iobenguaine I 123 injection (AdreView®); irinotecan (Camptosar®); ixabepilone (Ixempra®); lapatinib tablets (Tykerb®); lenalidomide (Revlimid®); letrozole (Femara®); leucovorin (Wellcovorin®, Leucovorin®); Leuprolide Acetate (Eligard®); levamisole (Ergamisol®); lomustine, CCNU (CeeBU®); meclorethamine, nitrogen mustard (Mustargen®); megestrol
acetate (Megace®); melphalan, L-PAM (Alkeran®); mercaptopurine, 6-MP (Purinethol®); mesna (Mesnex®); mesna (Mesnex tabs®); methotrexate (Methotrexate®); methoxsalen (Uvadex®); mitomycin C (Mutamycin®); mitotane (Lysodren®); mitoxantrone (Novantrone®); nandrolone phenpropionate (Durabolin-50®); nelarabine (Arranon®); nilotinib (Tasigna®); Nofetumomab (Verluma®); ofatumumab (Arzerra®); Oprelvekin (Neumega®); oxaliplatin (Eloxatin®); paclitaxel (Taxol®); paclitaxel protein-bound particles (Abraxane®); palifermin (Kepivance®); pamidronate (Aredia®); panitumumab (Vectibix®); pazopanib tablets (Votrient®); pegademase (Adagen®); pemetrexed disodium (Alimta®); pentostatin (Nipent®); pipobroman (Vercyte®); plerixafor (Mozobil®); plicamycin, mithramycin (Mithracin®); porfimer sodium (Photofrin®); pralatrexate injection (Folotyn®); procarbazine (Matulane®); quinacrine (Atabrine®); Rasburicase (Elitek®); raloxifene hydrochloride (Evista®); Rituximab (Rituxan®); romiplostim (Nplate®); sargramostim (Leukine®); Sargramostim (Prokine®); sorafenib (Nexavar®); streptozocin (Zanosar®); sunitinib maleate (Sutent®); talc (Sclerosol®); tamoxifen (Nolvadex®); temozolomide (Temodar®); temsirolimus (Torisel®); teniposide, VM-26 (VM-26®); testolactone (Teslac®); thioguanine, 6-TG (Thioguanine®); thiotepa (Thiotepa®); toremifene (Fareston®); Tositumomab (Bexxar®); Tositumomab-131 tositumomab (Bexxar®); Trastuzumab (Herceptin®); tretonoin, ATRA (Vesanoid®); Uracil Mustard (Uracil Mustard Capsules®); valrubicin (Valstar®); vinblastine (Velban®); vincristine (Oncovin®); vinorelbine (Navelbine®); vorinostat (Zolinza®); and zoledronate (Zometa®).

Non-limiting examples of other suitable anti-cancer agents for combination with the instant compounds are selected from the group consisting of a Cytostatic agent, Cisplatin, Deforolimus (described in PCT publication No. 2003/064383), Doxorubicin, liposomal doxorubicin (e.g., Caelyx®, Myocet®, Doxil®), Taxotere, Taxol, Etoposide, Irinotecan, Camptostar, Topotecan, Paclitaxel, Docetaxel, Epothilones, Tamoxifen, 5-Fluorouracil, Methotrexate, Temozolomide.
cyclophosphamide, SCH 66336, R 1 15777®, L778,123®, BMS 214662®, Iressa®,
Tarceva®, Antibodies to EGFR, antibodies to IGFR (including, for example, those
published in US 2005/0136063 published June 23, 2005), ESK inhibitors, KSP
inhibitors (such as, for example, those published in WO 2006/098962 and WO
2006/098961; ispinesib, SB-743921 from Cytokinetics), Centrosome associated
protein E ("CENP-E") inhibitors (e.g., GSK-923295), Gleevec®, Intron, Ara-C,
Adriamycin, Cytoxan, Gemcitabine, Uracil mustard, Chloromethine, Ifosfamide,
Melphalan, Chlorambucil, Pipobroman, Triethylenemelamine,
Triethylenethiophosphoramide, Busulfan, Carmustine, Lomustine, Streptozocin,
Docarbazine, Flouxuridine, Cytarabine, 6 Mercaptopurine, 6 Thioguanine,
Fludarabine phosphate, Oxaliplatin, Leucovirin, ELOXATINTM, Vinblastine, Vincristine,
Vindesine, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin,
Idarubicin, Mitramycin, Deoxycoformycin, Mitomycin C, L Asparaginase, Teniposide
17a-Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone,
Dromostanolone propionate, Testolactone, Megestrolacetate, Methylprednisolone,
Methyltestosterone, Prednisolone, Triamcinolone, Chlorotrianisene,
Hydroxyprogesterone, Aminoglutethimide, Estramustine,
Medroxyprogesteroneacetate, Leuprolide, Flutamide, Toremifene, Goserelin,
Cisplatin, Carboplatin, Hydroxyurea, Amsacrine, Procarbazine, Mitotane,
Mitoxantrone, Levamisole, Navelbene, Anastrazole, Letrazole, Capecitabine,
Relexafine, Droloxafine, Hexamethylmelamine, Avastin, herceptin, Bexxar,
bortezombi ("Velcade"), Zevalin, Trisenox, Xeloda, Vinorelbine, Porfimer, Erbitux,
Liposomal, Thiotepa, Altretamine, Melphalan, Trastuzumab, Lerozole, Fulvestrant,
Exemestane, Fulvestrant, Ifosfamide, Rituximab, C225®, Satriplatin, mylotarg,
Avastin, Rituxan, Panitumibam, Sutent, Sorafinib, Sprycel (dastinib), Nilotinib, Tykerb
(Lapatinib) and Campath.

In one embodiment, the invention provides a method of treating cancer, the
method comprising administering an amount of a Pyrazolopyrimidine Compound or a
pharmaceutically acceptable salt thereof, and an amount of one additional anticancer
agent selected from the group consisting of Adriamycin, Altretamine, Amidox,
Aminoglutethimide, Amsacrine, Anastrazole, Antibodies to EGFR, 3-AP, Aphidicolon,
Ara-C, Arsenic trioxide, L Asparaginase, Bevacizumab, Bleomycin, BMS 214662,
Bortezomib, Busulfan, Campath, Camptostar, Capecitabine, Carboplatin,
in one embodiment, the invention provides a method of treating cancer, the method comprising administering an amount of a Pyrazolopyrimidine Compound or a pharmaceutically acceptable salt thereof, and an amount of one or more of a MAP Kinase pathway inhibitor such as bRaf, MEK, or ERK inhibitors to a patient in need thereof.

In another embodiment, the invention provides a method of treating cancer, the method comprising administering an amount of a Pyrazolopyrimidine Compound or a pharmaceutically acceptable salt thereof, and an amount of one or more of ERK inhibitors (for example, compounds described in WO2008/156739, WO2007/070398, WO 2008/156739 and US publication 2007/0232610) to a patient in need thereof.
In one embodiment, the invention provides a method of treating cancer, the method comprising administering an amount of a Pyrazolopyrimidine Compound or a pharmaceutically acceptable salt thereof, and an amount of one or more of an anti-IGF-1 R antibody. Specific anti-IGF-1 R antibodies include, but are not limited to, dalotuzumab, figitumumab, cixutumumab, SHC 717454, Roche R1507, EM164 or Amgen AMG479.

The instant invention also includes a pharmaceutical composition useful for treating or preventing cancer that comprises a therapeutically effective amount of a compound of Formula I and a second compound selected from: an estrogen receptor modulator, an androgen receptor modulator, a retinoid receptor modulator, a cytotoxic/cytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an HIV protease inhibitor, a reverse transcriptase inhibitor, an angiogenesis inhibitor, a PPAR-γ agonist, an inhibitor of cell proliferation and survival signaling, a bisphosphonate, an aromatase inhibitor, an siRNA therapeutic, γ-secretase inhibitors, agents that interfere with receptor tyrosine kinases (RTKs) and an agent that interferes with a cell cycle checkpoint.

The use of all of these approaches in combination with the instant compounds described herein are within the scope of the present invention.

Compositions and Administration

This invention is also directed to pharmaceutical compositions which comprise at least one Pyrazolopyrimidine Compound, or a pharmaceutically acceptable salt of said compound and at least one pharmaceutically acceptable carrier.

When administered to a patient, the Pyrazolopyrimidine Compounds can be administered as a component of a composition that comprises a pharmaceutically acceptable carrier or vehicle. The present invention provides pharmaceutical compositions comprising an effective amount of at least one Pyrazolopyrimidine Compound and a pharmaceutically acceptable carrier. In the pharmaceutical compositions and methods of the present invention, the active ingredients will typically be administered in admixture with suitable carrier materials suitably selected with respect to the intended form of administration, i.e., oral tablets, capsules (either
solid-filled, semi-solid filled or liquid filled), powders for constitution, oral gels, elixirs, dispersible granules, syrups, suspensions, and the like, and consistent with conventional pharmaceutical practices. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), Remington's Pharmaceutical Sciences, 18th Edition, (1990), Mack Publishing Co., Easton, Pennsylvania. For example, for oral administration in the form of tablets or capsules, the active drug component may be combined with any oral non-toxic pharmaceutically acceptable inert carrier, such as lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, talc, mannitol, ethyl alcohol (liquid forms) and the like. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. Powders and tablets may be comprised of from about 0.5 to about 95 percent inventive composition. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

9 Moreover, when desired or needed, suitable binders, lubricants, disintegrating agents and coloring agents may also be incorporated in the mixture. Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes. Among the lubricants there may be mentioned for use in these dosage forms, boric acid, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrants include starch, methylcellulose, guar gum, and the like. Sweetening and flavoring agents and preservatives may also be included where appropriate.

14 Liquid form preparations include solutions, suspensions and emulsions and may include water or water-propylene glycol solutions for parenteral injection. Liquid form preparations may also include solutions for intranasal administration.

20 Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas.

25 Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.
For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

The Pyrazolopyrimidine Compounds of the present invention may also be delivered transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Additionally, the compositions of the present invention may be formulated in sustained release form to provide the rate controlled release of any one or more of the components or active ingredients to optimize therapeutic effects, i.e., anti-cancer activity and the like. Suitable dosage forms for sustained release include layered tablets containing layers of varying disintegration rates or controlled release polymeric matrices impregnated with the active components and shaped in tablet form or capsules containing such impregnated or encapsulated porous polymeric matrices.

In one embodiment, the Pyrazolopyrimidine Compound is administered orally.

In another embodiment, the Pyrazolopyrimidine Compound is administered intravenously.

In another embodiment, the Pyrazolopyrimidine Compound is administered topically.

In still another embodiment, the Pyrazolopyrimidine Compounds is administered sublingually.

In one embodiment, a pharmaceutical preparation comprising at least one Pyrazolopyrimidine Compound is in unit dosage form. In such form, the preparation is subdivided into unit doses containing effective amounts of the active components.

Compositions can be prepared according to conventional mixing, granulating or coating methods, respectively, and the present compositions can contain, in one embodiment, from about 0.1% to about 99% of the Pyrazolopyrimidine Compound(s) by weight or volume. In various embodiments, the present compositions can contain, in one embodiment, from about 1% to about 70% or from about 5% to about 60% of the Pyrazolopyrimidine Compound(s) by weight or volume.
The quantity of Pyrazolopyrimidine Compound in a unit dose of preparation may be varied or adjusted from about 0.1 mg to about 5000 mg. In various embodiments, the quantity is from about 10 mg to about 5000 mg, about 10 mg to about 1000 mg, 1 mg to about 500 mg, 1 mg to about 100 mg, and 1 mg to about 50 mg.

For convenience, the total daily dosage may be divided and administered in portions during the day if desired. In one embodiment, the daily dosage is administered in one portion. In another embodiment, the total daily dosage is administered in two divided doses over a 24 hour period. In another embodiment, the total daily dosage is administered in three divided doses over a 24 hour period. In still another embodiment, the total daily dosage is administered in four divided doses over a 24 hour period.

For administration to human patients, the amount and frequency of administration of the Pyrazolopyrimidine Compounds will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. Generally, a total daily dosage of the Pyrazolopyrimidine Compounds range from about 0.1 to about 5000 mg per day, although variations will necessarily occur depending on the target of therapy, the patient and the route of administration. In one embodiment, the dosage is from about 1 to about 200 mg/day, administered in a single dose or in 2-4 divided doses. In another embodiment, the dosage is from about 10 to about 5000 mg/day, administered in a single dose or in 2-4 divided doses. In another embodiment, the dosage is from about 100 to about 5000 mg/day, administered in a single dose or in 2-4 divided doses. In still another embodiment, the dosage is from about 500 to about 5000 mg/day, administered in a single dose or in 2-4 divided doses.

The compositions of the invention can further comprise one or more additional therapeutic agents, selected from those listed above herein. Accordingly, in one embodiment, the present invention provides compositions comprising: (i) at least one Pyrazolopyrimidine Compound or a pharmaceutically acceptable salt thereof; (ii) one or more additional therapeutic agents that are not a Pyrazolopyrimidine Compound; and (iii) a pharmaceutically acceptable carrier, wherein the amounts in the
composition are together effective to treat disease or disorder associated with dysregulated mTOR activity, such as a cancer.

**Kits**

Another aspect of this invention is a kit comprising a therapeutically effective amount of at least one Pyrazolopyrimidine Compound, or a pharmaceutically acceptable salt of said compound, and a pharmaceutically acceptable carrier, vehicle or diluent.

Yet another aspect of this invention is a kit comprising an amount of at least one Pyrazolopyrimidine Compound, or a pharmaceutically acceptable salt of said compound and an amount of at least one additional anti-cancer agent listed above, wherein the amounts of the two or more active ingredients result in a desired therapeutic effect. In one embodiment, the at least one Pyrazolopyrimidine Compound and the at least one additional anti-cancer agent are provided in the same container. In one embodiment, the at least one Pyrazolopyrimidine Compound and the at least one additional anti-cancer agent are provided in separate containers.

While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and other variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.
What is claimed is:

1. A compound in the Formula (I):

   \[
   R^8_V\cdot W_N(U\cdot T\cdot Z)\cdot R^6\cdot R^3
   \]

   or a pharmaceutically acceptable salt thereof, wherein

   U is N, CH, or C(R\textsuperscript{13});

   R\textsuperscript{13} is selected from the group consisting of

   \begin{align*}
   & \text{Cl-C}_6 \text{ alkyl, hydroxy, } -\text{OR}^\text{16}, -\text{N}(\text{R}^\text{14})(\text{R}^\text{15}), \\
   & -\text{N}(\text{R}^\text{14})\cdot \text{C}(\text{O})\cdot \text{R}^\text{16}, -\text{N}(\text{R}^\text{14})\cdot \text{S}(\text{O})\cdot \text{R}^\text{16}, -\text{N}(\text{R}^\text{14})\cdot \text{S}(\text{O})\cdot \text{R}^\text{16}, \\
   & -\text{N}(\text{R}^\text{14})\cdot \text{C}(\text{O})\cdot \text{N}(\text{R}^\text{14})\cdot (\text{R}^\text{15})\cdot \text{C}_3\cdot \text{C}_8 \text{ cycloalkyl, } \text{C}_6\cdot \text{C}_10 \text{ mono or bicyclic aryI, } -\text{C}(\text{O})\cdot \text{R}^\text{16}, -\text{C}(\text{O})\cdot \text{OR}^\text{16}, -\text{C}(\text{O})\cdot \text{N}(\text{R}^\text{14})\cdot (\text{R}^\text{15})\cdot -\text{S}(\text{O})\cdot \text{R}^\text{16}, \\
   & -\text{S}(\text{O})\cdot \text{R}^\text{16}, -\text{S}(\text{O})\cdot \text{N}(\text{R}^\text{14})\cdot (\text{R}^\text{15})\cdot -\text{S}(\text{O})\cdot \text{N}(\text{R}^\text{14})\cdot (\text{R}^\text{15})\cdot -\text{O}\cdot \text{C}(\text{O})\cdot \text{OR}^\text{17}, \\
   & -\text{O}\cdot \text{C}(\text{O})\cdot \text{N}(\text{R}^\text{17})\cdot (\text{R}^\text{18}).
   \end{align*}

   3- to 8-membered monocyclic heterocyclyl and having one to three heteroatoms selected from the group consisting of N, O, and S; and

   \begin{align*}
   & \text{C}_5\cdot \text{C}_10 \text{ mono or bicyclic heteroaryl and having one to three heteroatoms selected from the group consisting of N, O, and S;}
   \end{align*}

   R\textsuperscript{14} and R\textsuperscript{15} are independently selected from the group consisting of H, C1-C6 alkyl, C3-C8 cycloalkyl, and phenyl;

   R\textsuperscript{16} is independently selected from the group consisting of Cl-C6 alkyl, C3-C8 cycloalkyl, and phenyl;

   R\textsuperscript{17} and R\textsuperscript{18} are independently selected from the group consisting of C1-C6 alkyl, C3-C8 cycloalkyl, C6-C10 mono or
bicyclic aryl, 3- to 8-membered monocyclic heterocyclyl, and C₅- C₉ mono or bicyclic heteroaryl;

L is ded to any two carbon atoms of the ring comprising U and are independent selected from the group consisting of CH₂, C(H)(R¹), C(R¹)(R²), N(R¹), C(O), O, S, S(O), and S(O)₂;

T is absent such that L is bonded directly to Z, or T is selected from the group consisting of C(O), O, S, N(R¹), S(O), S(O)₂, and C₅₋₄ alkylene, wherein said alkylene of T is unsubstituted or substituted with 1 to 2 moieties, which moieties are independently selected from the group consisting of C1-C3 alkyl, halo, hydroxy, C1-C3 alkoxy, amino, C1-C3 alkylamino and C1-C3 dialkylamino;

m is 0 or 1;

n is independently 0, 1, 2, 3 or 4;

R¹ and R² are independently selected from the group consisting of H, C1-C3 alkyl, halo, hydroxy, C1-C3 alkoxy, amino, C1-C3 alkylamino and C1-C3 dialkylamino;

W is absent, or W is selected from the group consisting of C(O), C(N), S(O), S(O)₂, C₅₋₄ alkylene, C3-C8 cycloalkyl, phenyl, 5- to 6-membered heteroaryl, and 3- to 8-membered heterocyclyl;

V is absent, or V is selected from the group consisting of C(O), O, S, N(H), N(C₁₋₃ alkyl), N(C₁₋₃ alkyl), N(C₅₋₆ cycloalkyl), S(O), S(O)₂, and C₅₋₄ alkylene; or W and V together form a C3-C8 cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3 to 8-membered heterocyclyl ring;

R⁸ is selected from the group consisting of

(i) CN, C1-C6 alkyl or C3-C10 cycloalkyl, wherein said alkyl or cycloalkyl of R⁸ is unsubstituted or substituted with one to three moieties independently selected from the group consisting of hydroxy, C1-C6 alkoxy, halo, C1-C₆ haloalkyl, O-C1-C₆ haloalkyl, -NRₐRₐ, -ORₐ, carboxy, 5- to 6-membered heteroaryl, -SO₂H, C₁₋₆ alkyl-C(O)-NH-, C₁₋₆ alkyl-SO₂-NH-, and C₁₋₆ alkyl-SO-NH₂;

(ii) 3- to 8-membered heterocyclyl wherein said heterocyclyl of R⁸ is unsubstituted or substituted with one to three moieties independently selected from the group consisting of halo, C1-C6 alkyl, C1-C6 haloalkyl, O-C1-C₆ haloalkyl, C1-C₆ alkoxy, cyano, hydroxy, -(CRₐRₐ)ₙORₐ, -
haloC₆alkyl, -(CRᵃRᵇ)ₙC(O)NR¹⁰R⁹, -(CRᵃRᵇ)ₙC≡N(NR¹⁰R⁹, -(CRᵃRᵇ)ₙC(=N)NR¹⁰R⁹, -(CRᵃRᵇ)ₙC l ° )₂R⁹, -(CRᵃRᵇ)ₙC(=O)NR¹⁰R⁹, -(CRᵃRᵇ)ₙC(O)OH, -(CRᵃRᵇ)ₙS(O₂)NR¹⁰R⁹, -(CRᵃRᵇ)ₙS(O₂)NR¹⁰C(O)R⁹, -(CRᵃRᵇ)ₙS(O₂)S(O₂)R⁹, C₆-C₈arylamino, 5- to 10-membered heteroaryl, 5- to 10-membered heterocyclenyl, 5- to 10-membered heterocyclenylalkyl, 5- to 10-membered heterocyclenylalkyl, and 5- to 10-membered heterocyclenylalkyl, wherein each of said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclylalkyl, heterocyclylalkyl and heterocyclenylalkyl is unsubstituted or substituted with one to five moieties, which can be the same or different, each moiety being selected from the group consisting of halogen, C₆alkyl, C₆C₈cycloalkyl, -CF₃, -CN, -C(O)OH, -(CRᵃRᵇ)ₙC(O)OH, -OCF₃, -O-haloCroC₆alkyl, -haloC₆alkyl, C₆hydroxyalkyl, -(CRᵃRᵇ)ₙOR⁹, -(CRᵃRᵇ)ₙC(O)R⁹, -(NR¹⁰R⁹, -(CRᵃRᵇ)ₙC(O)O-Cr⁹, -(CRᵃRᵇ)ₙS(O₂)NR¹⁰R⁹, -(CRᵃRᵇ)ₙS(O₂)SR⁹, -(CRᵃRᵇ)ₙS(O₂)R⁹; R⁶ is selected from the group consisting of H, -CHR¹⁰R⁹, -(CRᵃRᵇ)ₙOR¹⁰, -(CRᵃRᵇ)ₙONR¹⁰R⁹, -(CRᵃRᵇ)ₙONR¹⁰R⁹, -(CRᵃRᵇ)ₙS(O)R¹⁰, -(CRᵃRᵇ)ₙS(O₂)R¹⁰, -(CRᵃRᵇ)ₙS(O₂)R¹⁰, -(CRᵃRᵇ)ₙC(O)C₆alkyl, -(CRᵃRᵇ)ₙC(O)NR¹⁰R⁹, -(CRᵃRᵇ)ₙC(O)OR¹⁰, -(CRᵃRᵇ)ₙS(O₂)NR¹⁰R⁹, -(CRᵃRᵇ)ₙNR¹⁰C(O)R⁹, -(CRᵃRᵇ)ₙNR¹⁰S(O₂)R⁹, -(CRᵃRᵇ)ₙCN, 5- to 10-membered heteroaryl, 5- to 10 membered heterocyclyl, C₃-C₈cycloalkyl and C₆-C₈arylamino, wherein each of said heteroaryl, heterocyclyl and aryl can be unsubstituted or substituted with one to three moieties selected from the group consisting of C₆alkyl, C₆C₈alkenyl, C₆C₈alkylamino, C₆C₈dialkylamino, amino, halo or OH; R⁷ is selected from the group consisting of H, OH, OR¹⁰, d-Cealkyl, C₁₀arylamino, C₆-C₈arylamino, C₆-C₈alkyl, 5- to 10-membered heteroaryl, 5- to 10-membered heteroarylalkyl, C₆C₈cycloalkyl, C₆C₈cycloalkylalkyl, C₆C₈alkyl, 5- to 10 membered heterocyclyl, 5- to 10 membered heterocyclenyl, 5- to 10 membered heterocyclenylalkyl, C₆C₈alkyl, C₆C₈alkyl, C₆C₈alkyl.
C6-Cioaryl-S(O)C6alkyl, -S(O2)C6alkyl, -C(O)C1-C6alkyl, -C(O)NR10R9, -C(O)OR10 and -S(O2)NR10R9, wherein each of said alkyl, aryl, aryalkyl, heteroaryl, heterocycle, cycloalkylalkyl, heterocycloalkyl, heterocyclylalkyl, alkenyl and alkynyl can be unsubstituted or substituted with one to three moieties, which can be the same or different, each moiety being selected from the group consisting of halogen, CrC6alkyl, C3-Cscycloalkyl, -CF3, -CN, -(CRaRb)nC(O)OH, -OCF3, -OR9, -C(O)R9, -NR10R9, -C(O)O-Ci-C6alkyl, -C(O)NR10R9, -SR9, and -S(O2)R9;

R10 and R9 are independently selected from the group consisting of H, OH, Ci-C6alkyl, CrC6alkenyl, Ci-C6alkynyl, C3-C8cycloalkyl, C6-Ciaryl, 5- to 10-membered heteroaryl, 5- to 10-membered heterocyclyl, 5- to 10-membered heterocycloalkyl, C3-C8cycloalkyl-Ci-C6alkyl, Ci-Cioaryl-C6alkyl, 5- to 10-membered heteroaryl-Ci-C6alkyl, 5- to 10-membered heterocyclyl-Ci-C6alkyl, 5- to 10-membered heterocycloalkyl-Ci-C6alkyl, and said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, heterocyclylalkyl, aryalkyl, heteroaryalkyl, heterocyclylalkyl or heterocyclylalkyl is optionally substituted with halogen, Ci-C6alkyl, C3-C8cycloalkyl, -CF3, -CN, -(CRaRb)nC(O)OH, -OCF3, -ORa, -C(O), amino, -C(O)O-Ci-C6alkyl, -C(O)NRaRb, -SRa, and -S(O2)Ra; or R10 and R9 together with the nitrogen atom to which they are attached form a 3- to 6-membered heterocyclyl ring;

R25 is independently selected from the group consisting of H, C3-C8cycloalkyl, Ci-C6alkyl, wherein the alkyl or cycloalkyl is optionally substituted with ORa, ORb, ORa,

2. The compound of claim 1 having the Formula (I):
or a pharmaceutically acceptable salt thereof, wherein

U is N, CH, or C(R^13);

R^{13} is selected from the group consisting of

- Cl-C_6 alkyl, hydroxy, -OR^{16}, -N(R^{14})(R^{15}),
- N(R^{14})-C(O)-R^{16}, -N(R^{14})-S(O)-R^{16}, -N(R^{14})-S(O)_2R^{16},
- N(R^{14})-C(O)-N(R^{14})(R^{15}), C_3-C_8 cycloalkyl, C_6-C_10 mono or bicyclic aryl,
- C(O)R^{16}, -C(O)OR^{16}, -C(O)N(R^{14})(R^{15}), -S(O)R^{16},
- S(O)_2R^{16}, -S(O)-N(R^{14})(R^{15}), -S(O)_2-N(R^{14})(R^{15}), -O-C(O)OR^{17},
- O-C(O)N(R^{17})(R^{18}),
- C_5-C_10 mono or bicyclic heteroaryl

3- to 8-membered monocyclic heterocyclyl and having one to three heteroatoms selected from the group consisting of N, O, and S; and

C_5-C_10 mono or bicyclic heteroaryl and having one to three heteroatoms selected from the group consisting of N, O, and S;

R^{14} and R^{15} are independently selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, and phenyl;

R^{16} is independently selected from the group consisting of Cl-C_6 alkyl, C_3-C_8 cycloalkyl, and phenyl;

R^{17} and R^{18} are independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_10 mono or bicyclic aryl, 3- to 8-membered monocyclic heterocyclyl, and C_5-C_10 mono or bicyclic heteroaryl;
L and Z are bonded to any two carbon atoms of the ring comprising U and are independent of the group consisting of CH₂, C(H)(R¹), C(R¹)(R²), N(R¹), C(O), O, S, N(R¹), S(O), S(O)₂, and -C₃-C₆ alkyl, -C₃-C₆ alkoxy, cyano, hydroxy, C₁-C₆ alkylamino, and C₁-C₆ dialkylamino; and

T is absent or T is selected from the group consisting of C(O), O, S, N(R¹), S(O), S(O)₂, and -C₃-C₆ alkylene, wherein said alkylene of T is unsubstituted or substituted with one to two moieties, which moieties are independently selected from the group consisting of C₁-C₆ alkyl, halo, hydroxy, C₁-C₆ alkoxy, amino, C₁-C₆ alkylamino and C₁-C₆ dialkylamino;

m is 0 or 1;

R¹ and R² are independently selected from the group consisting of H, C₁-C₃ alkyl, halo, hydroxy, C₁-C₃ alkoxy, amino, C₁-C₆ alkylamino and C₁-C₆ dialkylamino;

W is absent, or W is selected from the group consisting of C(O), S(O), S(O)₂, -C₃-C₆ alkoxy, C₃-C₈ cycloalkyl, phenyl, 5- to 6-membered heteroaryl, and 3- to 8-membered heterocyclyl;

V is absent, or V is selected from the group consisting of C(O), O, S, N(H), N(Ci-C₃ alkyl), N(Ci-C₃ alkyl), N(C₃-C₈ cycloalkyl), S(O), S(O)₂, and -C₆ alkylene;

or W and V together form a C₃-C₈ cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3 to 8-membered heterocyclyl ring;

R⁸ is selected from the group consisting of

(i) C₁-C₆ alkyl or C₃-C₁₀ cycloalkyl, wherein said alkyl or cycloalkyl of R⁸ is unsubstituted or substituted with one to three moieties independently selected from the group consisting of hydroxy, -C₆ alkxy, halo, trifluoromethyl, carboxy, 5- to 6-membered heteroaryl, -SO₂H, C₁-C₆ alkyl-C(O)-NH-, -C₆ alkyl-SO₂-NH-, and -C₆ alkyl-SO-NH-

(ii) 3- to 8-membered heterocyclyl wherein said heterocyclyl of R⁸ is unsubstituted or substituted with one to three moieties independently selected from the group consisting of halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, amino, C₁-C₆ alkylamino, and C₁-C₆ dialkylamino;

(iii) C₆-C₁₀ aryl or 5- to 10-membered heteroaryl, wherein said aryl or heteroaryl of R⁸ is unsubstituted or is substituted with one to three moieties independently selected from the group consisting of halo, trifluoromethyl, trifluoromethoxy, C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, amino, C₁-C₆ alkylamino, and C₁-C₆ dialkylamino; and
(iv) -N(H)OH or -N(H)-C_x-C_y alkoxy;
\[ R^3 = \text{H or alkyl, C}_1-C_6 \text{ aikeny}, C_1-C_6 \text{ alkylnyl, -C(O)R}^{10}, C_6-CI_2 \text{ aryl, C}_3-C_8 \text{ cydoalkyi aikeny}, 5- to 10-membered heteroaryl, 3- to 8-membered heterocyclyl, 5- to 10-membered heteroarylalkyi, (C_6-CI_2)aryl(CrC6)alkyl, (C_3-C_8)cyloalkyi(Cr-C_6)alkyi, (C_3-C_8)cycloalkenyl(Cr-C_6)alkyi, (C_3-C_6)cycloalkenyl(Cr-C_6)alkyi, (3- to 8-membered)heterocyclyl(Cr-C_6)alkyi, (3- to 8-membered)heterocyclyl(Cr-C_6)alkyi, wherein said aryl, cydoalkyi, cydoalkenyl, heteroaryl, heterocycydi, heterocyclyd, arylalkyi, cydoalkylalkyi, cydoalkenylalkyi, heteroarylalkyi, heterocyclyldalkyi, and heterocyclydenalkyi of R^3 is unsubstituted or substituted with one to three moieties independently selected from the group consisting of Y, halogen, C_1-C_6 alkyl, C_3-C_10 cydoalkyi, trifluoromethyl, cyano, -C(O)OH, -(CH_2)_x-C(O)OH, trifluoromethoxy, -OR^{11}, -C(O)R^{10}, -NR^9R^9, -C(O)R^{12}-alkyi, -C(O)NR^9R^{10}, -SR^{11}, and -S(O)R^{12};

Y is C_6-CI_6 aryl or 5- to 10-membered heteroaryl, wherein said aryl or heteroaryl of Y is unsubstituted or substituted with one to five moieties independently selected from the group consisting of 2H, halo, cyano, hydroxy, amino, C_1-C_6 alkylamino, C_1-C_6 dialkylamino, trifluoromethyl, trifluoromethoxy, C_3-C_6 alkyl, C_3-C_6 hydroxyalkyi, and CrC_6 alkoxy; and each occurrence of R^9 is independently H, C_1-C_6 alkyl, C_3-C_10 cydoalkyi, phenyl, 5- to 6-membered heteroaryl or 3- to 8-membered heterocycydi;

each occurrence of R^{10} is independently H, C_3-C_6 alkyl, C_3-C_10 cydoalkyi, phenyl, 5- to 6-membered heteroaryl, or 3- to 8-membered heterocycydi, or R^9 and R^{10} together with the nitrogen atom to which they are attached form a 3- to 6-membered heterocycydi ring;

each occurrence of R^{11} is independently H, C_3-C_6 alkyl, C_3-C_10 cydoalkyi, phenyl, 5- to 6-membered heteroaryl, or 3- to 8-membered heterocycydi;

each occurrence of R^{12} is independently C_1-C_6 alkyl, C_3-C_10 cydoalkyi, phenyl, 5- to 6-membered heteroaryl, or 3- to 8-membered heterocycydi; and

x is an integer from 1 to 4;
R7 is selected from the group consisting of H, C6alkyl, and C3-C8 cycloalkyl. R in said alkyl or cycloalkyl of R7 is unsubstituted or substituted with one to two moieties selected from the group consisting of halo, C1-C3 alkoxy, amino, C1-C3 alkylamino, and C1-C3 dialkylamino; and

R6 is selected from the group consisting of H, halo, hydroxyl, cyano, C1-C6 alkyl, C6alkanoyl, C6alkylsulfonyl, C1-C6 alkylsulfinyl, C1-C6 alkoxy, C6haloalkyl, amino, C1-C6 alkylamino, C1-C6 dialkylamino, C3-C8 cycloalkyl, C6-C10 aryl, 5- to 10-membered heteroaryl, and 5- to 10-membered heterocyclyl, wherein each of said aryl, heteroaryl, and heterocyclyl of R6 is unsubstituted or substituted with one to two moieties selected from the group consisting of halo, C1-C3 alkyl, C1-C3 alkoxy, amino, C1-C3 alkylamino, and C1-C3 dialkylamino.

3. The compound of claim 2 or a pharmaceutically acceptable salt thereof, wherein m is 1.

4. The compound of claim 2 or a pharmaceutically acceptable salt thereof, wherein the group -L-T-Z- is selected from the group consisting of -CH2OCH2-, -CH2CH2OCH2-, and C2-C4 alkylene, wherein said alkylene is unsubstituted or substituted with one to two moieties selected from the group consisting of C1-C3 alkyl, fluoro, and hydroxy.

5. The compound of claim 2 or a pharmaceutically acceptable salt thereof, wherein W is C(O).

6. The compound of claim 2 or a pharmaceutically acceptable salt thereof, wherein V is absent.

7. The compound of claim 2 or a pharmaceutically acceptable salt thereof, wherein R8 is selected from the group consisting of (i) C1-C6 alkyl or C3-C10 cycloalkyl, wherein said alkyl or cycloalkyl of R8 is unsubstituted or substituted with one to three moieties independently selected from the group consisting of hydroxy, C1-C6 alkoxy, fluoro, trifluoromethyl, carboxy,
tetrazolyl, \(-\text{SO}_2\text{H}\), \(\text{C}_1\text{C}_6\text{alkyl}-\text{c(O)}-\text{NH}\), \(\text{c}_1\text{C}_6\text{alkyl-}\text{SO}_2\text{-NH}\), and \(\text{c}_1\text{-C}_6\text{alkyl-SO}_2\text{-NH}\).

(ii) 3-8) heterocyclyl containing 1 to 3 heteroatoms selected from the group consisting of \(\text{N}, \text{O}, \text{S}\), and \(\text{S(O)}2\) wherein said heterocycle of \(\text{R}_8\) is unsubstituted or substituted with one to two moieties independently selected from the group consisting of halo, \(\text{C}_2\text{C}_6\text{alkyl}, \text{c}_1\text{-C}_6\text{alkoxy}, \text{cyano}, \text{hydroxy}, \text{amino}, \text{C}_1\text{-C}_6\text{alkylamino}, \text{and C}_1\text{-C}_6\text{dialkylamino}; \text{and}

(iii) phenyl or 5- to 6-membered heteroaryl containing 1 to 3 heteroatoms selected from the group consisting of \(\text{N}, \text{O}, \text{and S}\), wherein said phenyl or heteroaryl of \(\text{R}_8\) is unsubstituted or is substituted with one to two moieties independently selected from the group consisting of halo, trifluoromethyl, trifluoromethoxy, \(\text{C}_1\text{-C}_6\text{alkyl}, \text{c}_1\text{-C}_6\text{alkoxy}, \text{cyano}, \text{hydroxy}, \text{amino}, \text{c}_1\text{-C}_6\text{alkylamino}, \text{and c}_1\text{-C}_6\text{dialkylamino}; \text{and}

The compound of claim 2 or a pharmaceutically acceptable salt thereof, wherein \(\text{R}_6\) is selected from the group consisting of \(\text{H}, \text{C}_1\text{-C}_6\text{alkyl}, \text{c}_1\text{-C}_6\text{alkanoyl}, \text{cyano}, \text{c}_1\text{-C}_6\text{alkylsulfonyl}, \text{cyano}, \text{halo}, \text{hydroxy}, \text{amino}, \text{c}_1\text{-C}_6\text{alkylamino}, \text{and c}_1\text{-C}_6\text{dialkylamino}; \text{and}

The compound of claim 2 or a pharmaceutically acceptable salt thereof, wherein \(\text{R}_7\) is \(\text{H}\).

The compound of claim 2 or a pharmaceutically acceptable salt thereof, wherein \(\text{R}_3\) is 5- to 10-membered mono- or bicyclic aryl or heteroaryl, wherein said heteroaryl of \(\text{R}_3\) contains from one to three heteroatoms selected from the group consisting of \(\text{N}, \text{N(O)}, \text{O}, \text{and S}\), wherein said aryl or heteroaryl of \(\text{R}_3\) is unsubstituted or substituted with one to three moieties independently selected from the group consisting of \(\gamma, \text{halogen, c}_1\text{-C}_6\text{alkyl, cyano, c}_1\text{-C}_6\text{alkanoyl, trifluoromethyl, trifluoromethoxy, hydroxy, c}_1\text{-C}_6\text{alkoxy, amino, c}_1\text{-C}_6\text{alkylamino, and c}_1\text{-C}_6\text{dialkylamino}; \text{and}

\(\gamma\) is phenyl or 5 to 6-membered heteroaryl, wherein said heteroaryl of \(\gamma\) contains 1 to 2 heteroatoms selected from the group consisting of \(\text{N}, \text{N(O)}, \text{O}, \text{and S}\); wherein \(\gamma\) is unsubstituted or substituted with one to two moieties independently
selected from the group consisting of halogen, \( \text{Cl-C}_6 \) alkyl, \(-\text{CN}, \ -\text{C(O)OH}, \ -\text{C(O)NH}_2, \ -\text{C(O)-Ci-C-} \) trifl, \(-\text{o}r\text{omethyl}, \ -\text{trifluoromethoxy, \ hydroxy, \ C1-C6 alkoxy, \ amino, \ C1-C6 alkyl, \ -\text{C(O)-Ci-C-} \) dialkylamino; and

with the proviso that when \( R^3 \) is bicyclic aryl or heteroaryl, said bicyclic aryl or heteroaryl is not substituted by \( Y \).

11. The compound of claim 2 or a pharmaceutically acceptable salt thereof, wherein the compound has the Formula (IA)

\[
\text{(IA)}
\]

wherein

\( U \) is \( N, \text{CH}, \text{oR} \); \( R^3 \) is selected from the group consisting of

\( \text{Ci-C}_6 \) alkyl, hydroxy, \(-\text{OR}, \ -\text{N(R}_{14})(\text{R}_{15}), \)

\(-\text{N(R}_{14})\text{-C(O)-R}_{16}, \ -\text{N(R}_{14})\text{-S(O)-R}_{16}, \ -\text{N(R}_{14})\text{-S(O)R}_{16}, \)

\(-\text{N(R}_{14})\text{-C(O)-N(R}_{14})(\text{R}_{15}), \ C_3\text{-C}_8 \text{ cycloalkyl, \ C}_6\text{-Cl}_0 \text{ mono or bicyclic aryl, \ -C(O)R}_{16}, \ -\text{C(O)OR}_{16}, \ -\text{C(O)N(R}_{14})(\text{R}_{15}), \ -\text{S(O)R}_{16}, \)

\(-\text{S(O)}_2\text{R}_{16}, \ -\text{S(O)-N(R}_{14})(\text{R}_{15}), \ -\text{S(O)}_2\text{-N(R}_{14})(\text{R}_{15}), \ -\text{O-C(O)}\text{OR}_{17}, \ -\text{O-C(O)N(R}_{17})(\text{R}_{18}), \)

3- to 8-membered monocyclic heterocyclyl and having one to three heteroatoms selected from the group consisting of \( N, \text{O}, \) and \( S; \) and

\( \text{C}_5\text{-C}_10 \text{ mono or bicyclic heteroaryl and having one to three heteroatoms selected from the group consisting of } N, \text{O}, \text{and } S; \)

\( R^4 \) and \( R^5 \) are independently selected from the group consisting of \( H, \text{C}1\text{-C}6 \text{ alkyl, C}_3\text{-C}_8 \text{ cycloalkyl, and phenyl;} \)
R^{16} is independently selected from the group consisting of Calkyl, C3-C8 cycloalkyl, and phenyl;
R^{17} and R^{18} are independently selected from the group insisting of C1-C6 alkyl, C3-C8 cycloalkyl, C6-C10 mono or bicyclic aryl, 3- to 8-membered monocyclic heterocyclyl, and C5-C10 mono or bicyclic heteroaryl;
L and Z are bonded to any two carbon atoms of the ring comprising U;
T is absent, or present;
-L-T-Z- is selected from the group consisting of \(-\text{CH}_2\text{OCH}_2\), \(-\text{CH2CH2OCH}_2\), and C2-C4 alkyene, wherein said alkyene is unsubstituted or substituted with one to two moieties selected from the group consisting of C1-C3 alkyl, fluoro, and hydroxy;
W is C(O), S(O), S(O)₂, and C₁₋₄ alkyene;
R^{8} is selected from the group consisting of
(i) C1-C₆ alkyl or C3-C10 cycloalkyl, wherein said alkyl or cycloalkyl
of R^{8} is unsubstituted or substituted with one to three moieties independently selected from the group consisting of hydroxy, C1-C6 alkoxy, fluoro, trifluoromethyl, carboxy, tetrazolyl, -SO₂H, C1-C6 alkyl-C(O)-NH⁻, C1-C₆ alkyl-SO₂-NH⁻, and C₁₋₄ alkyene;
(ii) 5- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from the group consisting of N, O, S, and S(O)₂ wherein said heterocyclyl of R^{8} is unsubstituted or substituted with one to two moieties independently selected from the group consisting of halo, CrC₆ alkyl, C1-C6 alkoxy, cyano, hydroxy, amino, C1-C6 alkylamino, and C1-C6 dialkylamino; and
(iii) phenyl or 5- to 6-membered heteroaryl containing 1 to 3 heteroatoms selected from the group consisting of N, O, and S, wherein said phenyl or heteroaryl of R^{8} is unsubstituted or is substituted with one to two moieties independently selected from the group consisting of halo, trifluoromethyl, trifluoromethoxy, C1-C6 alkyl, C1-C6 alkoxy, cyano, hydroxy, amino, C1-C₆ alkylamino, and C1-C₆ dialkylamino; and
(iv) -N(H)OH or -N(H)-Cl-C₃ alkoxy;
R^{3} is 5- to 10-membered mono or bicyclic aryl or heteroaryl, wherein said heteroaryl of R^{3} contains from one to three heteroatoms selected from the group
consisting of N, N(O), O, and S, and wherein said aryl or heteroaryl of R^3 is unsubstituted or substituted with one to three moieties independently selected from the group halogen, C_1-C_6 alkyl, cyano, -C(O)OH, -C(O)NH$_2$, C_1-C_6 alkanoyl, trifluoromethyl, trifluoromethoxy, hydroxy, C_1-C_6 alkoxy, amino, C_1-C_6 alkylamino, and C_1-C_6 dialkylamino;

Y is phenyl or 5 to 6-membered heteroaryl, wherein said heteroaryl of Y contains 1 to 2 heteroatoms selected from the group consisting of N, N(O), O, and S; wherein Y is unsubstituted or substituted with one to two moieties independently selected from the group consisting of halogen, C_1-C_6 alkyl, -CN, -C(O)OH, -C(O)NH$_2$, C_1-C_6 alkyloxy, -C(O)-C_6 alkyl, trifluoromethyl, trifluoromethoxy, hydroxy, C_1-C_6 alkoxy, amino, C_1-C_6 alkylamino, and C_1-C_6 dialkylamino;

or Y is absent when R^3 is bicyclic aryl or heteroaryl; and

R^6 is selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_6 alkanoyl, cyano, C_1-C_6 alkylsulfonyl, cyano, halo, hydroxy, amino, C_1-C_6 alkylamino, and C_1-C_6 dialkylamino.

12. The compound of claim 11 or a pharmaceutically acceptable salt thereof, wherein -L-T-Z- is selected from the group consisting of -CH$_2$C$_2$H$_2$- and -CH$_2$OCH$_2$-;

13. The compound of claim 11 or a pharmaceutically acceptable salt thereof, wherein R^8 is selected from the group consisting of

![Chemical structures](attachment:image.png)
14. The compound of claim 11 or a pharmaceutically acceptable salt thereof, wherein R⁶ is selected from the group consisting of halo, C₁-C₃ alkanoyl, C₁-C₃ alkylsulfuric acid.

15. The compound of claim 11 or a pharmaceutically acceptable salt thereof, wherein R³ is 5- to 6-membered monocyclic heteroaryl, wherein said heteroaryl of R³ contains from 1 to 2 heteroatoms selected from the group consisting of N and N(O), and is substituted by Y;

   wherein Y is phenyl or 5-membered heteroaryl, wherein said heteroaryl of Y contains 1 to 2 heteroatoms selected from the group consisting of N and S; wherein Y is unsubstituted or substituted with one to two moieties independently selected from the group consisting of halo, C₁-C₃ alkyl, C₁-C₃ hydroxyalkyl, and C₁-C₃ alkoxy.

16. The compound under claim 1, or a pharmaceutically acceptable salt thereof, under Formula (IC):

   \[ \text{IC} \]

   Wherein U is N or CH;

   wherein the group -L-T-Z- is selected from the group consisting of -CH₂OCH₂-, -CH₂CH₂OCH₂-, and C₂-C₄ alkyiene, wherein said alkyiene is unsubstituted or substituted with one to two moieties selected from the group consisting of C₁-C₃ alkyl, fluoro, and hydroxy;

   R⁸ is selected from the group consisting of

   (i) CN, C₁-C₆ alkyl or C₃-C₁₀ cycloalkyl, wherein said alkyl or cycloalkyl of R⁸ is unsubstituted or substituted with one to three moieties.
independently selected from the group consisting of hydroxy, \( \text{Ci-C}_6 \) alkoxy, halo, \( \text{Ci-C}_6 \) haloalkyi, 0-\( \text{Ci-C}_6 \) haloalkyi, -NR\( ^a \)R\( ^b \), -OR\( ^a \), carboxy, 5- to 6-eteroaryl, -SO\( _2 \)H, \( \text{Ci-C}_6 \) alkyl-\( \text{C} (\text{O}) \)-NH-, \( \text{Ci-C}_6 \) alkyl-SO\( _2 \)-NH-, and \( \text{Ci-C}_6 \) alkyl-SO-NH-;

(ii) 3- to 8-membered heterocycl wherein said heterocycl of \( R^8 \) is unsubstituted or substituted with one to three moieties independently selected from the group consisting of halo, \( \text{C}_1-\text{C}_8 \) alkyl, \( \text{C}_1-\text{C}_6 \) haloalkyi, O-\( \text{Ci-C}_6 \) haloalkyi, \( \text{Ci-C}_6 \) alkoxy, cyano, hydroxy, -(CR\( ^a \)R\( ^b \))\( _n \)OR\( ^a \), -(CR\( ^a \)R\( ^b \))\( _n \)NR\( ^a \)R\( ^b \), -(CR\( ^a \)R\( ^b \))\( _n \)C(O)NR\( ^a \)R\( ^b \), amino, \( \text{Ci-C}_6 \) alkylamino, and \( \text{Ci-C}_6 \) dialkylamino;

(iii) \( \text{C}_6-\text{C}_{10} \) aryl or 5- to 10-membered heteroaryl, wherein said aryl or heteroaryl of \( R^8 \) is unsubstituted or is substituted with one to three moieties independently selected from the group consisting of 5- to 10-membered heterocycl, halo, \( \text{CrC}_6 \) haloalkyi, O-\( \text{CrC}_6 \) haloalkyi, \( \text{CrC}_6 \) alkyl, \( \text{C}_1-\text{C}_6 \) alkoxy, cyano, hydroxy, -(CR\( ^a \)R\( ^b \))\( _n \)OR\( ^a \), -(CR\( ^a \)R\( ^b \))\( _n \)NR\( ^a \)R\( ^b \), -(CR\( ^a \)R\( ^b \))\( _n \)NR\( ^a \)C(O)R\( ^b \), -(CR\( ^a \)R\( ^b \))\( _n \)C(O)NR\( ^a \)R\( ^b \), amino, \( \text{C}_1-\text{C}_6 \) alkylamino, and \( \text{C}_1-\text{C}_6 \) dialkylamino,

wherein said heterocycl is optionally substituted with one to three moieties independently selected from the group consisting of OH, NH\(_2\) and \( \text{C}_1-\text{C}_6 \) alkyl ; and

(iv) \(-\text{OH}, -\text{OR}^a, -\text{OR}^a\text{OR}^b, -\text{NR}^a\text{OR}^b, -\text{NR}^a\text{R}^b, -\text{C(O)NR}^a\text{R}^b, -\text{NR}^a\text{C(O)R}^b, \text{C(=N-R}^a\text{)}\text{NR}^a\text{R}^b;\)

\( R^3 \) is selected from the group consisting of:

588
Ar¹ is C₆-C₁₀aryl or a 5- to 6-membered heteroaryl optionally substituted with
one to three of R¹⁹, which can be the same or different, each R¹⁹ being selected from
the group consisting of halogen, C₁-C₆ alkyl, -CF₃, -CN, -C(Ø)OH, -(CRᵃRᵇ)ₙC(Ø)OH,
-OCF₃, -O-haloC₆ alkyl, -ORᵃ, -C(Ø)Rᵃ, -NRᵃRᵇ, -C(Ø)O-C₁-C₆ alkyl, -C(Ø)NRᵃRᵇ,
-NRᵃC(Ø)Rᵇ, -S(O₂)NRᵃRᵇ, -NRᵃS(O₂)Rᵇ, -SRᵃ, and -S(S₂)Rᵃ;
R²₀ is independently selected from the group consisting of halogen, C₁-C₆ alkyl, -CF₃,
-CN, -C(Ø)OH, -(CRᵃRᵇ)ₙC(Ø)OH, -OCF₃, -O-haloC₆ alkyl, -ORᵃ, -C(Ø)Rᵃ, -NRᵃRᵇ,
-C(Ø)O-C₆ alkyl, -C(Ø)NRᵃRᵇ, -NRᵃC(Ø)Rᵇ, -S(O₂)NRᵃRᵇ, -NRᵃS(O₂)Rᵇ, -SRᵃ, and
-S(S₂)Rᵃ;
R²¹ and R²² are independently selected from C₁-C₃ alkyi and OH;
R²₃ is selected from C₁-C₃ hydroxyalkyl, C₃-C₅ hydroxycycloalkyl, -NHC(Ø)C₁-
C₃ alkyi, -NHC(Ø)OC₁-C₃ alkyi, and -NHC(Ø)NHC(Ø)C₁-C₃ alkyi;
Rᵃ and Rᵇ are independently selected from H, halogen, OH, C₁-C₆ alkoxy, C₁-
C₆ haloalkyi and C₁-C₆ alkyi, wherein the alkyi is optionally substituted with one to
three moieties selected from OH, NH₂, C₁-C₃ alkylamino, and C₁-C₃ dialkylamino and
C₁-C₃ alkoxy;
Z¹ is CH₂, NH, S or O;
q is 0, 1 or 2;
v is 0, or 1.

R⁶ is selected from the group consisting of H, halo, C₁-C₃ alkyi, C₁-C₃ alkanoyl, cyano, C₁-C₃ alkylsulfonyl, C₃-C₄ cycloalkylsulfonyl, C₃-C₄ cycloalkyl,
wherein the C1-C3 alkyl or C3-C4 cycloalkyl is optionally substituted with C1-C5 alkyl, C1-C3 alkenyl, cyano, halo, hydroxy or amino.

All other substituents are as defined above in claim 1.

17. The compound of claim 16, or a pharmaceutically acceptable salt thereof, wherein

R^8 is selected from the group consisting of amino, NR^aR^b, C1-C3 alkyl, C3-C5 hydroxycycloalkyl, C1-C3 hydroxyalkyl, 5-10 membered heteroaryl containing one or two N atoms, wherein said heteroaryl is optionally substituted with one or two R^24, which can be the same or different, selected from H, methyl, amino, OH and methylamino;

R^a and R^b are independently selected from H and C1-C3 alkyl;

Z^1 is CH₂ or O;

All other substituents are as defined in claim 16.

18. The compound of claim 2, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:
A compound selected from the group consisting of:

1-((1 R,3s,5S)-3-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-3-hydroxy-2-(hydroxymethyl)-2-methylpropan-1-one;

((R)-1-((1 R,3S,5S)-3-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxypropan-1-one;

(R)-1-((1 R,3S,5S)-3-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2,3-dihydroxypropan-1-one;

(exo)-3-[6-acetyl-7-amino-3-(6-phenyl-3-pyridinyl)pyrazolo[1,5-a][pyrimidin-5-yl]-8-[[1,1-dioxido-3-isothiazolidinyl]carbonyl]-8-azabicyclo[3.2.1]octane;

1-((1 R,3s,5S)-3-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxypropan-1-one;

1-((1 R,3s,5S)-3-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxy-2-methylpropan-1-one;

1-(5-((1 R,3s,5S)-8-((1 H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;

(S)-1-((1 R,3R,5S)-3-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxypropan-1-one;

1-((1 R,3r,5S)-3-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;

1-((1 R,3s,5S)-3-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-(1 H-tetrazol-5-yl)ethanone;

1-(5-((1 R,3s,5S)-8-((1 H-1,2,3-triazole-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(7-amino-5-((1 R,3s,5S)-8-(3-methyl-1 H-1,2,4-triazole-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone
N-(2-((1 R,3s,5S)-uc-del-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-oxoethyl)methanesulfonamide;
1-((1 R,3s,5S)-8-(1 H-tetrazole-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-((1 R,3s,5S)-8-(1 H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
5-((1 R,3s,5S)-8-(1 H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-((1 R,3s,5S)-8-(1 H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(5-difluoromethyl)thiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-((1 R,3s,5S)-8-(1 H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(5-hydroxy-6-phenylpyrimidin-3-yl)-N-methylpicolinamide;
5-((1 R,3s,5S)-8-(1 H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)-N-methylpicolinamide;
1-((1 R,3s,5S)-8-(1 H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)-N-nitroso-picolinamide;
1-((1 R,3s,5S)-8-(1 H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)-N-nitroso-picolinamide;
1-((1 R,3s,5S)-8-(1 H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)-N-nitroso-picolinamide;
1-((1 R,3s,5S)-8-(1 H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)-N-nitroso-picolinamide;
1-((1 R,3s,5S)-8-(1 H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)-N-nitroso-picolinamide;
1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-phenylpyridin-5-yl)-N-methyl-8-azabicyclo[3.2.1]octane-8-carboxamide;  
1-(7-amino-5-((1 R,3s,5S)-8-(5-hydroxy-4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;  
1-((1 R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(4-methoxy-3-(methoxymethyl)phenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-sulfonic acid;  
1-(7-amino-5-((1 R,3s,5S)-8-(5-hydroxy-4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;  
1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2-methyl-2H-tetrazol-5-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2,3-difluoro-4-nitro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;

1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(4-methoxy-3-methylphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;

1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(3-chloro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;

1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(4-(difluoromethoxy)phenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;

1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(4-fluoro-3-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;

1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(4-(2-nitroethoxy)phenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;

1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2-nitroethyld-2H-indazol-5-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;

1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2-nitroethyld-2H-indazol-5-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;

1-(3-(6-(1 H-benzo[d]imidazol-6-yl)pyridin-3-yl)-5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-6-yl)ethanone;

1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2-nitroethyld-2H-indazol-5-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;

1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2,5-difluoro-4-nitro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(phenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrinnidin-6-yl)ethanone; 
1-(3-(6-(1 H-pyrazol-3-yl)pyridin-3-yl)-5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-6-yl)ethanone; 
1-(3-(3,6-(1 H-pyrazol-3-yl)pyridin-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-6-yl)ethanone; 
5-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-6-yl)ethanone; 
1-(3-(6-acetyl-7-amino-3-(6-(1 H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone; 
5-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-((1 R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(1-(fluoromethyl)-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1 R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(1-methyl-1H-1,2,4-triazole-3-carbonyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1 R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(1-methyl-1H-1,2,4-triazole-3-carbonyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1 R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(4-fluoro-1H-1,2,4-triazole-3-carbonyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1 R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(4-fluoro-1H-1,2,4-triazole-3-carbonyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1 R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(4-fluoro-1H-1,2,4-triazole-3-carbonyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1 R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(4-fluoro-1H-1,2,4-triazole-3-carbonyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1 R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(4-fluoro-1H-1,2,4-triazole-3-carbonyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3r,5S)-3-(6-acetyl-7-amino-3-(6-(3,5-difluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(3-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(trifluoronmethy)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3r,5S)-3-(6-acetyl-7-amino-3-(6-(4-fluoro-1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(5-fluoro-6-(1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(5-fluoro-6-(1-methyl-1H-imidazol-4-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(5-fluoro-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(5-fluoro-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(5-fluoro-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-(5-((1R,3s,5S)-8-(4H-1H,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(5-fluoropyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone
1-(1R,3s,5S)-Z-amino-S-is-methyl-G-ilpyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)propene-1,2-dione;
1-(5-((1R,3s,5S)-8-(4H-1H,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-fluoropyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-oxoacetamide;
1-(5-((1R,3s,5S)-8-(4H-1H,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(7-amino-5-((1R,3s,5S)-8-(morpholine-4-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(4H-1H,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(1H-pyrazol-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(5-methyl-1H-imidazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(4H-1H,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(4-methyl-1H-imidazol-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(5-methyl-1H-imidazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(3-(6-(1H-imidazol-1-yl)pyridin-3-yl)-5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(7-amino-5-((1R,3s,5S)-8-(3-aminopyrazolo[1,5-a]pyrimidin-3-yl)-3-(6-(4-methyl-1H-pyrazol-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(1H-pyrazole-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(7-amino-5-((1R,3s,5S)-8-(3-aminopyrazolo[1,5-a]pyrimidin-3-yl)-3-(6-(4-methyl-1H-pyrazol-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(1H-pyrazole-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(7-amino-5-((1R,3s,5S)-8-(3-aminopyrazolo[1,5-a]pyrimidin-3-yl)-3-(6-(4-methyl-1H-pyrazol-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(1H-pyrazole-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(7-amino-5-((1R,3s,5S)-8-(3-aminopyrazolo[1,5-a]pyrimidin-3-yl)-3-(6-(4-methyl-1H-pyrazol-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(1H-pyrazole-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(7-amino-5-((1R,3s,5S)-8-(3-aminopyrazolo[1,5-a]pyrimidin-3-yl)-3-(6-(4-methyl-1H-pyrazol-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(7-amino-5-((1R,3s,5S)-8-(5-amino-1H-pyrazole-4-carbonyl)-8-azabicycl[3.2.1]octane-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone
N-(3-((1R,3s,5S)-8-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carbonyl)-1H-1,2,4-triazol-5-yl)acetamide;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octane-3-yl)-7-amino-3-(1-phenyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(7-amino-5-((1R,3s,5S)-8-(5-amino-4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octane-3-yl)-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octane-3-yl)-7-amino-3-(6-(2-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octane-3-yl)-7-amino-3-(6-(2,6-difluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octane-3-yl)-7-amino-3-(6-(2,4-difluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octane-3-yl)-7-amino-3-(6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octane-3-yl)-7-amino-3-(6-acetyl-7-amino-3-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carbonyl)-2-hydroxyethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octane-3-yl)-7-amino-3-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octane-3-yl)-7-amino-3-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carbonyl)-2-hydroxyethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octane-3-yl)-7-amino-3-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octane-3-yl)-7-amino-3-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carbonyl)-2-hydroxyethanone;
1-(5-((1R,3S,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-((1R)-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone,
1-(7-amino-3-((1R,3s,5S)-8-(3-amino-1H-pyrazole-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-(4-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(4-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxypropan-1-one;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(4-fluorophenyl)pyridin-3-yl)pyridin-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(4-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(4-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(4-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(4-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(4-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(4-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(4-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(4-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(4-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(4-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(4-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(4-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(4-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(4-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(4-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(4-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(4-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
(1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(2,4-difluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxamide;
1-((1R,3r,5S)-3-(6-acetyl-7-annino-3-(6-fluoro-8-nnethoxyquinolin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)bicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;

1-((1R,3s,5S)-3-(7-amino-6-bromo-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;

1-((1R,3s,5S)-3-(7-amino-6-bromo-3-(6-(3-hydroxymethyl)-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;

1-((1R,3s,5S)-3-(7-amino-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;

1-((1R,3s,5S)-3-(7-amino-3-(6-(3-(hydroxymethyl)-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;

1-((1R,3s,5S)-3-(7-amino-6-bromo-3-(6-(3-(hydroxymethyl)-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;

1-((1R,3s,5S)-3-(7-amino-3-(6-(3-(hydroxymethyl)-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;

1-((1R,3s,5S)-3-(7-amino-3-(6-(1-methyl-1H-1,2,4-triazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;

1-((1R,3s,5S)-3-(7-amino-3-(6-(1-methyl-1H-1,2,4-triazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
((1R,3s,5S)-3-(7-amino-3-(1H-indazol-5-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-1,2,4-triazol-5-yl)methanone;
((1R,3s,5S)-3-(7-amino-3-(1H-pyrrolo[2,3-b]pyridin-5-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-1,2,4-triazol-5-yl)methanone;
((1R,3s,5S)-3-(7-amino-3-(1H-indazol-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-1,2,4-triazol-5-yl)methanone;
((1R,3s,5S)-3-(7-amino-3-(6-(2-fluorophenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-3-(6-(2-fluoro-4-(trifluoromethyl)phenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-3-(1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-1,2,4-triazol-3-yl)methanone;
5-((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-annine;
1-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-1,2,3-triazol-5-yl)methanone;
((1R,3S,5S)-3-(7-amino-6-(methylsulfonfyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methyl-1H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-6-(methylsulfonfyl)pyrazolo[1,5-a]pyrimidin-5-yl)-N-methylpicolinamide;
((1R,3S,5S)-3-(7-amino-6-(methylsulfonfyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-6-(methylsulfonfyl)pyrazolo[1,5-a]pyrimidin-5-yl)-N-methylpicolinamide;
((1R,3S,5S)-3-(7-amino-6-(methylsulfonfyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-6-(methylsulfonfyl)pyrazolo[1,5-a]pyrimidin-5-yl)-N-methylpicolinamide;
5-((1 R,3s,5S)-8-(5-methyl-4H-1,2,4-triazol-3-yl)-8-azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonylethyl)-3-(7-amino-3-(5-hydroxy-6-phenylpyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-7-amine;  
5-((1 R,3s,5S)-2,4-triazol-3-yl)-8-azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonylmethyl)-3-(7-amino-3-(5-hydroxy-6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine;  
((1 R,3s,5S)-3-(7-amino-3-(5-hydroxy-6-phenylpyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;  
1-((1 R,3s,5S)-3-(7-amino-3-(5-hydroxy-6-phenylpyridin-3-yl)-6-(methylsulfonylethyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;  
((1 R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-(thiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;  
((1 R,3s,5S)-3-(7-amino-3-(7-fluoronaphthalen-2-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;  
((1 R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-amine;  
(S)-1 -((1 R,3R,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxypropan-1-one;  
(R)-1 -((1 R,3S,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxypropan-1-one;  
((1 R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-hydroxy-4H-1,2,4-triazol-3-yl)methanone;  
((1 R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-N-methyl-8-azabicyclo[3.2.1]octane-8-carboxamide;  
((1 R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(4-(pyridin-2-yl)phenyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;  
((1 R,3s,5S)-3-(7-amino-3-(6-(2-fluoro-4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3S,5S)-3-(7-amino-3-(6-(4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)none;
((1R,3S,5S)-3-(7-amino-3-(6-(4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)none;
((1R,3S,5S)-3-(7-amino-3-(6-(4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)none;
((1R,3S,5S)-3-(7-amino-3-(6-(4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)none;
((1R,3S,5S)-3-(7-amino-3-(6-(4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)none;
((1R,3S,5S)-3-(7-amino-3-(6-(4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)none;
((1R,3S,5S)-3-(7-amino-3-(6-(4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)none;
((1R,3S,5S)-3-(7-amino-3-(6-(4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)none;
((1R,3S,5S)-3-(7-amino-3-(6-(4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)none;
((1R,3S,5S)-3-(7-amino-3-(6-(4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)none;
((1R,3s,5S)-3-(7-amino-3-(6-(3,4-difluorophenyl)pyridin-3-yl)-6-
(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-
1,2,4-triazol-3-yl)methanone;  
((1R,3s,5S)-3-(7-amino-3-(6-(3-fluoro-4-methylphenyl)pyridin-3-yl)-6-
(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-
1,2,4-triazol-3-yl)methanone;  
((1R,3s,5S)-3-(7-amino-3-(6-(3-fluorophenyl)pyridin-3-yl)-6-
(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-
1,2,4-triazol-3-yl)methanone;  
((1R,3s,5S)-3-(7-amino-3-(6-(2,3-difluorophenyl)pyridin-3-yl)-6-
(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-
1,2,4-triazol-3-yl)methanone;  
((1R,3s,5S)-3-(7-amino-3-(6-(3'-fluoro-2,2'-bipyridin-5-yl)-6-
(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-
1,2,4-triazol-3-yl)methanone;  
((1R,3s,5S)-3-(7-amino-3-(6-(3,5-difluoro-4-methoxyphenyl)pyridin-3-yl)-6-
(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-
1,2,4-triazol-3-yl)methanone;  
((1R,3s,5S)-3-(7-amino-3-(6-(4-methoxy-3-methylphenyl)pyridin-3-yl)-6-
(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-
1,2,4-triazol-3-yl)methanone;  
((1R,3s,5S)-3-(7-amino-3-(6-(4-methoxy-3-methylphenyl)pyridin-3-yl)-6-
(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-
1,2,4-triazol-3-yl)methanone;  
((1R,3s,5S)-3-(7-amino-3-(6-(4-methoxy-3-methylphenyl)pyridin-3-yl)-6-
(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-
1,2,4-triazol-3-yl)methanone;  
((1R,3s,5S)-3-(7-amino-3-(6-(benzo[d][1,3]dioxol-5-yl)pyridin-3-yl)-6-
(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-
1,2,4-triazol-3-yl)methanone;  
((1R,3s,5S)-3-(7-amino-3-(6-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)pyridin-3-yl)-6-
(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-
1,2,4-triazol-3-yl)methanone;  
((1R,3s,5S)-3-(7-amino-3-(6-(3,4-difluorophenyl)pyridin-3-yl)-6-
(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-
1,2,4-triazol-3-yl)methanone;
((1R,3S,5S)-3-(7-amino-3-(6-(4-(difluoromethoxy)phenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrinnidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)ethanone;
((1R,3S,5S)-3-(7-amino-3-(6-(4-(2-methoxyethoxy)phenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrinnidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)ethanone;
((1R,3S,5S)-3-(7-amino-3-(6-(2-methyl-2H-indazol-5-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrinnidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)ethanone;
((1R,3S,5S)-3-(7-amino-3-(6-(2-methoxypyrimidin-5-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrinnidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)ethanone;
((1R,3S,5S)-3-(7-amino-3-(6-(2,5-difluoro-4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrinnidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)ethanone;
((1R,3S,5S)-3-(7-amino-3-(6-(4-ethoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrinnidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)ethanone;
((1R,3S,5S)-3-(7-amino-3-(6-(4-cyclopropoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrinnidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)ethanone;
((1R,3S,5S)-3-(7-amino-3-(6-(4-(difluoromethoxy)phenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrinnidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)ethanone;
1-((1R,3s,5S)-3-(7-amino-3-(6-(4-methoxy-(D$_3$)-phenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone

1-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

1-((1R,3s,5S)-3-(7-amino-3-(6-(1-methyl-(D$_3$)-1H-pyrazol-3-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

1-((1R,3s,5S)-3-(7-amino-3-(6-(1-methyl-(D$_3$)-1H-pyrazol-3-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;

1-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-(2-methoxyethoxy)ethanone;

1-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(3-(trifluoromethyl)-1H-pyrazol-5-yl)methanone;

1-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-pyrazol-5-yl)methanone;

1-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-pyrrolo[3,2-c]pyridin-2-yl)methanone;

1-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-pyrrolo[2,3-b]pyridin-2-yl)methanone;

1-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-imidazol-2-yl)methanone;

1-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-benzo[d]imidazol-2-yl)methanone;
(1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)methanone;
(1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)8-azabicyclo[3.2.1]octan-8-yl)2-(3-methyl-1H,2,4-triazol-5-yl)ethanone;
(1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(3-methyl-1H-pyrazol-4-yl)methanone;
(1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(3-(hydroxymethyl)-1H-pyrazol-5-yl)methanone;
(1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(3-(aminomethyl)-1H-pyrazol-5-yl)methanone;
(1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)((R)-morpholin-3-yl)methanone;
(1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)((S)-morpholin-3-yl)methanone;
(1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)((1R,2,4-triazol-3-yl)nnmethanone;
N-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carbonyl)-4H-1,2,4-triazol-3-yl)acetamide;
(5-amino-1H-pyrazol-4-yl)((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyndin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)methanone;
N-(5-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)nnmethanone;
N-(5-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)nnmethanone;
(1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)methanone
(1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)methanone
(1 R,3s,5S)-3-(7-amino-3-(6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-hydroxy-1 H-pyrazol-4-yl)methanone;
(1 R,3s,5S)-3-(7-amino-3-(7-(hydroxymethyl)quinolin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
(1 R,3s,5S)-3-(7-amino-3-(2-(2-methyl-2H-indazol-5-yl)pyrimidin-5-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
(1 R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(1-phenyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(3-(trifluoromethyl)-1 H-pyrazol-4-yl)methanone;
(1 R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-amino-4H-1,2,4-triazol-3-yl)methanone;
(1 R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(5-aminopyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(2H-1,2,3-triazol-4-yl)methanone;
(1 R,3s,5S)-3-(7-amino-3-(2,2'-bipyridin-5-yl)-7-amino-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
(1 R,3s,5S)-3-(7-amino-3-(2-phenylpyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(2H-1,2,3-triazol-4-yl)methanone;
(1 R,3s,5S)-3-(7-amino-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-aminopyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)methanone;
(1 R,3s,5S)-3-(7-amino-3-(6-(2-fluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3S,5S)-3-(7-amino-3-(6-(4-fluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3S,5S)-3-(7-amino-3-(6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3S,5S)-3-(7-amino-3-(6-(2,6-difluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3S,5S)-3-(7-amino-3-(6-(2,4-difluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3S,5S)-3-(7-amino-3-(6-(1H-pyrazol-4-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3S,5S)-3-(7-amino-3-(6-(1H-pyrazol-4-yl)pyridin-3-yl)-7-amino-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3S,5S)-3-(7-amino-3-(6-(1H-pyrazol-4-yl)pyridin-3-yl)-7-amino-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)methanone;

1-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;

((1R,3s,5S)-3-(7-amino-3-(6-(4-fluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methyl-4H-1,2,4-triazol-3-yl)methanone;

1-((1R,3s,5S)-3-(7-amino-3-(6-(4-fluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxypropan-1-one;

((1R,3s,5S)-3-(7-amino-3-(6-(4-fluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

1-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

(R)-1-((1R,3s,5S)-3-(7-amino-3-(6-(4-fluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxypropan-1-one;

((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(1H-pyrazol-2-yl)-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

1-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(1H-pyrazol-2-yl)-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;

((1R,3s,5S)-3-(7-amino-3-(6-(2,4-difluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methyl-4H-1,2,4-triazol-3-yl)methanone;

((1R,3s,5S)-3-(7-amino-3-(6-(2,4-difluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methyl-4H-1,2,4-triazol-3-yl)methanone;
1-((1 R,3S,5S)-3-(7-amino-3-(6-(2,4-difluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
(3-amino-1H-pyrazol-5-yl)((1 R,3S,5S)-3-(7-amino-3-(6-(2,4-difluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)methanone;
(1 R,3S,5S)-3-(7-amino-3-(6-(2-fluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-N-ethyl-8-azabicyclo[3.2.1]octane-8-carboxamide;
((1 R,3S,5S)-3-(7-amino-3-(6-(2-fluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)methanone;
1-((1 R,3S,5S)-3-(7-amino-3-(6-(2-fluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
((1 R,3S,5S)-3-(7-amino-3-(6-(2-fluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methyl-4H-1,2,4-triazol-3-yl)methanone;
(3-amino-1H-pyrazol-5-yl)((1 R,3S,5S)-3-(7-amino-3-(6-(2-fluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)methanone;
((1 R,3S,5S)-3-(7-amino-3-(6-(2-fluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-pyrazol-5-yl)methanone;
((1 R,3S,5S)-3-(7-amino-3-(6-(2-fluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-pyrazol-5-yl)methanone;
((1 R,3S,5S)-3-(7-amino-3-(6-(2-fluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1H-pyrazol-5-yl)methanone;
4-((1 R,3S,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyrimidin-5-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)oxazol-2(3H)-one;
4-((1 R,3S,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyrimidin-5-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)methanone;
6-((1 R,3S,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carbonyl)pyridin-2(1 H)-one;
(S)-4-((1 R)-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carbonyl)oxazolidin-2-one;
(R)-4-((1 R,3S,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carbonyl)oxazolidin-2-one;
((1 R,3S,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(2-aminopyrimidin-4-yl)methanone;
((1 R,3S,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(2-aminopyrimidin-3-yl)methanone;
((1 R,3S,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4-aminopyrimidin-5-yl)methanone;
((1 R,3S,5S)-3-(7-amino-3-(2-(3-fluoro-4-methoxyphenyl)pyrimidin-5-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-thiazol-3-yl)methanone;
((1 R,3S,5S)-3-(7-amino-3-(imidazo[1,2-a]pyrimidin-6-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-thiazol-3-yl)methanone;
((1 R,3S,5S)-3-(7-amino-3-(2-(3-fluoro-4-methoxyphenyl)pyrimidin-5-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-thiazol-3-yl)methanone;
((1 R,3S,5S)-3-(7-amino-3-(2-(3-fluoro-4-methoxyphenyl)pyrimidin-5-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-thiazol-3-yl)methanone;
((1 R,3S,5S)-3-(7-amino-3-(2-(3-fluoro-4-methoxyphenyl)pyrimidin-5-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-thiazol-3-yl)methanone;
((1 R,3S,5S)-3-(7-amino-3-(2-(3-fluoro-4-methoxyphenyl)pyrimidin-5-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-thiazol-3-yl)methanone;
((1 R,3S,5S)-3-(7-amino-3-(2-(3-fluoro-4-methoxyphenyl)pyrimidin-5-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-thiazol-3-yl)methanone;
((1R,3s,5S)-3-(7-amino-3-(2-(2-hydroxypropan-2-yl)pyrimidin-5-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

1-((1R,3s,5S)-3-(7-amino-3-(5-chloro-6-(2-hydroxypropan-2-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;

((1R,3s,5S)-3-(7-amino-3-(7-amino-6-(methylsulfonyl)-3-(tetrahydro-2H-pyran-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;

4-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-fluorobenzannide;

4-((1R,3s,5S)-8-(2-hydroxyacetyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-fluorobenzannide;

((1R,3s,5S)-3-(7-amino-3-(6-(2-hydroxypropan-2-yl)-5-methylpyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

((1R,3s,5S)-3-(7-amino-3-(5-chloro-6-(2-hydroxypropan-2-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

((1R,3s,5S)-3-(7-amino-6-(cyclopropylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

((1R,3s,5S)-3-(7-amino-6-(ethylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

((1R,3s,5S)-3-(7-amino-6-(propylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

((1R,3s,5S)-3-(7-amino-3-(6'-methoxy-2,3'-bipyridin-5-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3S,5S)-3-(7-amino-3-(6-cyclohexylpyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl) (2H-1,2,3-triazol-4-yl)nethanone;

((1R,3S,5S)-3-(7-amino-3-(6-cyclopentylpyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl) (2H-1,2,3-triazol-4-yl)nethanone;

1-((1R,3S,5S)-3-(7-amino-3-(6-cyclobutylpyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;

((1R,3S,5S)-3-(7-amino-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl) (2H-1,2,3-triazol-4-yl)nethanone;

((1R,3S,5S)-3-(7-amino-3-(6-(2-fluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl) (2H-1,2,3-triazol-4-yl)nethanone;

((1R,3S,5S)-3-(7-amino-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl) (2H-1,2,3-triazol-4-yl)nethanone;

((1R,3S,5S)-3-(7-amino-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl) (2H-1,2,3-triazol-4-yl)nethanone;

((1R,3S,5S)-3-(7-amino-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl) (2H-1,2,3-triazol-4-yl)nethanone;

((1R,3S,5S)-3-(7-amino-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl) (2H-1,2,3-triazol-4-yl)nethanone;

((1R,3S,5S)-3-(7-amino-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl) (2H-1,2,3-triazol-4-yl)nethanone;

((1R,3S,5S)-3-(7-amino-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl) (2H-1,2,3-triazol-4-yl)nethanone;

((1R,3S,5S)-3-(7-amino-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl) (2H-1,2,3-triazol-4-yl)nethanone;
((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-(pyrimidin-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(2H-1,2,3-triazol-4-yl)methanone;
((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-(5-methylthiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
1-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-(5-methylthiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methyl-1H-1,2,4-triazol-3-yl)methanone;
1-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-(5-methylthiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methyl-4H-1,2,4-triazol-3-yl)methanone;
1-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-(5-methylthiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methyl-1H-1,2,4-triazol-3-yl)methanone;
((1R,3S,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-(4-methylthiazol-2-yl)pyridin-3-yl)pyrazol-1-Y,5-imidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methyl-4H-1,2,4-triazol-3-yl)methanone;

((1R,3S,5S)-3-(7-amino-3-(6-(5,6-dihydro-4H-cyclopenta[d]thiazol-2-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

((1R,3S,5S)-3-(7-amino-3-(6-(4,5-dimethylthiazol-2-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methyl-4H-1,2,4-triazol-3-yl)methanone;

((1R,3S,5S)-3-(7-amino-3-(6-(5,6-dihydro-4H-cyclopenta[d]thiazol-2-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

(3-(7-amino-3-(6-(4,5-dimethylthiazol-2-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methyl-1H-1,2,4-triazol-3-yl)methanone;

((1R,3S,5S)-3-(7-amino-3-(6-(4,5-dimethylthiazol-2-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,3-triazol-5-yl)methanone;

((1R,3S,5S)-3-(7-amino-3-(6-(4,5-dimethylthiazol-2-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methyl-4H-1,2,4-triazol-3-yl)methanone;

((1R,3S,5S)-3-(7-amino-3-(6-(2-methylthiazol-4-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methyl-1H-1,2,4-triazol-3-yl)methanone;

((1R,3S,5S)-3-(7-amino-3-(6-(2-methylthiazol-4-yl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(2H-1,2,3-triazol-4-yl)methanone;

1-((1R,3S,5S)-3-(7-amino-3-(6-(2-methylthiazol-4-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methyl-1H-1,2,4-triazol-3-yl)methanone;

1-((1R,3S,5S)-3-(7-amino-3-(6-(2-methylthiazol-4-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)ethanone;

((1R,3S,5S)-3-(7-amino-3-(6-(2-methylthiazol-4-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(2H-1,2,3-triazol-4-yl)methanone;
5-((1 R,3S,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidine-7-amine;
N-(2-((1 R,3S,5S)-8-azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidine-7-yl)-2-oxoethylacetamide;
N-(2-((1 R,3S,5S)-3-(7-azaino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidine-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-oxoethyl)-2,2,2-trifluoroacetamide;
N-(2-((1 R,3S,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidine-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)((R)-pyrrolidin-2-yl)methanone;
((1 R,3S,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidine-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)((S)-pyrrolidin-2-yl)methanone;
((1 R,3S,5S)-3-(7-amino-6-((4H-1,2,4-triazol-3-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidine-7-amine;
((1 R,3S,5S)-3-(7-amino-6-cyclopropyl-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-annino-6-cyclopropyl-3-(6-(4-fluoro-3-nmethoxyphenyl)pyridin-3-yl)pyrazol[1,5a]imidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone

1-((1R,3s,5S)-3-(7-annino-6-cyclopropyl-3-(6-(2,5-difluoro-4-nmethoxyphenyl)pyridin-3-yl)pyrazol[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
(1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-(1-methyl-1H-imidazol-4-yl)pyridin-3-yl)pyrazolyl) pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone; 

(1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-methoxyquinolin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone; 

(1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(3-chlorophenyl)methanone; 

((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-amino-4H-1,2,4-triazol-3-yl)((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)methanone; 

N-(5-((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carbonyl)-4H-1,2,4-triazol-3-yl)acetamide; 

((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-((dimethylamino)-4H-1,2,4-triazol-3-yl)methanone; 

(3-amino-1H-pyrazol-4-yl)((1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)methanone; 

(1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolyl) pyrazolo[1,5-a]pyrimidin-5-yl)-N-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxamide; 

(1R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolyl) pyrazolo[1,5-a]pyrimidin-5-yl)-N-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxamide; 

7-amino-5-((1 R,3s,5S)-8-(2-hydroxyethylamino)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidine-6-carbonitrile; 

5-((1 R,3s,5S)-8-(1H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidine-6-carbonitrile; 

5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-thiazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-6-carbonitrile;
(1R,3s,5S)-3-(7-amino-6-(methoxymethyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)methanone;

(3-amino-yl)((1R,3s,5S)-3-(7-amino-6-(methoxymethyl)-3-(6-phenylpyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)methanone;

((1R,3s,5S)-3-(7-amino-6-(4-methoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)methanone;

((1R,3s,5S)-3-(7-amino-6-(hydroxymethyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)methanone;

(3-amino-yl)((1R,3s,5S)-3-(7-amino-6-ethyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)methanone;

(1R,3s,5S)-3-(3-(6-(1H-imidazol-2-yl)pyridin-3-yl)-7-amino-6-cyclopropylpyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;

(1R,3s,5S)-3-(3-(6-(1H-imidazol-2-yl)pyridin-3-yl)-7-amino-6-cyclopropylpyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

1-((1R,3s,5S)-3-(3-(6-(1H-imidazol-2-yl)pyridin-3-yl)-7-amino-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;

1-((1R,3s,5S)-3-(3-(6-(1H-imidazol-2-yl)pyridin-3-yl)-7-amino-6-(prop-1-en-2-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
(S)-1-((1 R,3R,5S)-3-(3-(6-(1 H-imidazol-2-yl)pyridin-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]imidazin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxypropan-1-one;  
2-((1 R,3S,5S)-3-(3-(6-(1 H-imidazol-2-yl)pyridin-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]imidazin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-oxoethyl acetate;  
1-((3-(6-(1 H-imidazol-2-yl)pyridin-3-yl)-7-amino-5-((1 R,3s,5S)-8-(methylsulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;  
1-((3-(6-(1 H-imidazol-2-yl)pyridin-3-yl)-7-amino-5-((1 R,3s,5S)-8-(1 H-pyrrole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;  
(R)-1-((1 R,3S,5S)-3-(3-(6-(1 H-imidazol-2-yl)pyridin-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]imidazin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxypropan-1-one;  
1-((1 R,3s,5S)-3-(3-(6-(1 H-imidazol-2-yl)pyridin-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]imidazin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-(2-methoxyethoxy)ethanone;  
((1 R,3s,5S)-3-(3-(6-(1 H-imidazol-2-yl)pyridin-3-yl)-7-amino-6-cyclopropylpyrazolo[1,5-a]imidazin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1 H-pyrrol-3-yl)methanone;  
((1 R,3s,5S)-3-(3-(6-(1 H-imidazol-2-yl)pyridin-3-yl)-7-amino-6-cyclopropylpyrazolo[1,5-a]imidazin-5-yl)-8-azabicyclo[3.2.1]octane-8-carbaldehyde;  
1-((1 R,3s,5S)-3-(3-(6-(1 H-imidazol-2-yl)pyridin-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]imidazin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-methoxyethanone;  
1-((3-(6-(1 H-imidazol-2-yl)pyridin-3-yl)-7-amino-5-((1 R,3s,5S)-8-(3-amino-1 H-pyrazole-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;  
1-((3-(6-(1 H-imidazol-2-yl)pyridin-3-yl)-7-amino-5-((1 R,3s,5S)-8-(tetrahydrofuran-2-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;  
1-((3-(6-(1 H-imidazol-2-yl)pyridin-3-yl)-7-amino-5-((1 R,3s,5S)-8-(5-amino-4H-1,2,4-triazole-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-((3-(6-(1 H-imidazol-2-yl)pyridin-3-yl)-7-amino-5-((1 R,3s,5S)-8-(5-methyl-4H-1,2,4-triazole-3-carboxylate)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone
1-((1 R,3s,5S)-3-(3-(6-(1 H-imidazol-2-yl)pyridin-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-fluoroethanone;
1-((1 R,3s,5S)-3-(3-(6-(1 H-imidazol-2-yl)pyridin-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-fluoropropan-1-one;
(1 R,3s,5S)-3-(3-(6-(1 H-imidazol-2-yl)pyridin-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-5-yl)-N-methyl-8-azabicyclo[3.2.1]octane-8-carboxamide;
(1 R,3s,5S)-methyl 3-((3-(6-(1 H-imidazol-2-yl)pyridin-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate;
1-((1 R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(5-methyl-1 H-imidazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1 R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(6-(5-methyl-1 H-imidazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1 R,3s,5S)-3-(6-acetyl-7-amino-3-(5-fluoro-6-(1 H-imidazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1 R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(5-fluoro-6-(1 H-imidazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
(1 R,3s,5S)-3-(3-(6-(1 H-imidazol-2-yl)pyridin-3-yl)-5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-((1 R,3s,5S)-3-(3-(4-(1 H-imidazol-2-yl)phenyl)-7-amino-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1 R,3s,5S)-3-(7-amino-6-cyclopropyl-3-(3-fluoro-4-(1 H-imidazol-2-yl)phenyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1 R,3s,5S)-3-(6-acetyl-7-amino-3-(3-fluoro-4-(1 H-imidazol-2-yl)phenyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1 R,3s,5S)-3-(6-acetyl-7-amino-3-(3-fluoro-4-(5-methyl-1H-imidazol-2-yl)phenyl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-((1 R,3s,5S)-3-(6-acetyl-7-amino-3-(3-fluoro-4-(1H-imidazol-2-yl)phenyl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-((1 R,3s,5S)-3-(3-(4-(1 H-imidazol-2-yl)phenyl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
1-((1 R,3s,5S)-3-(3-(4-(1 H-imidazol-2-yl)phenyl)-5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(P-(1H-hydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(L-1-hydroxypropyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(1-hydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2-hydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(7-amino-5-((1 R,3s,5S)-8-(1-hydroxycyclopropanecarbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-((1 R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-((1 R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-((1 R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-((1 R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-((1 R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
WO 2011/090935

1-(7-amino-5-((1 R,3s,5S)-8-(5-annino-1 H-pyrazole-4-carbonyl)-8-
azabicyclo[3.2.1]octan-3-yl)-3-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1 ,5-
a]pyrimidin-6-yl)ethanone;
1-(5-((1 R,3s,5S)-8-(3-methyl-1 H-pyrrole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-
(6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1 ,5-a]pyrimidin-6-yl)ethanone;
1-(7-amino-3-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1 ,5-a]pyrimidin-6-
yl)ethanone;
1-((1 R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(1-hydroxycyclobutyl)pyridin-3-
yl)pyrazolo[1 ,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1 R,3s,5S)-8-(1 H-1,2,3-triazole-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-
amino-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)pyrazolo[1 ,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1 R,3s,5S)-8-(1 H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-
amino-3-(6-(2-hydroxypropan-2-yl)-5-nnethylpyridin-3-yl)pyrazolo[1 ,5-a]pyrimidin-6-
yl)ethanone;
1-((1 R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(1-hydroxycyclobutyl)pyridin-3-
yl)pyrazolo[1 ,5-a]pyrimidin-6-yl)ethanone;
((1 R,3s,5S)-3-(7-amino-3-(6-(1-hydroxybutyl)pyridin-3-yl)-6-
(methylsulfonyl)pyrazolo[1 ,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1 H-
1,2,4-thazol-5-yl)ethanone;
((1 R,3s,5S)-3-(7-amino-3-(6-(1-hydroxypropyl)pyridin-3-yl)-6-
(methylsulfonyl)pyrazolo[1 ,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1 H-
1,2,4-thazol-5-yl)ethanone;
((1 R,3s,5S)-3-(7-amino-3-(6-(1-hydroxypropyl)pyridin-3-yl)-6-
(methylsulfonyl)pyrazolo[1 ,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1 H-
1,2,4-thazol-5-yl)ethanone;
1-((1R,3S,5S)-3-(7-amino-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxytet

1-((1R,3S,5S)-3-(7-amino-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(3-methyl-1H-2,4-triazol-5-yl)tnethanone;

1-((1R,3S,5S)-3-(7-amino-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(3-methyl-1H-2,4-triazol-5-yl)tnethanone;

1-((1R,3S,5S)-3-(7-amino-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(3-methyl-1H-2,4-triazol-5-yl)tnethanone;

1-((1R,3S,5S)-3-(7-amino-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(3-methyl-1H-2,4-triazol-5-yl)tnethanone;

1-((1R,3S,5S)-3-(7-amino-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(3-methyl-1H-2,4-triazol-5-yl)tnethanone;

1-((1R,3S,5S)-3-(7-amino-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(3-methyl-1H-2,4-triazol-5-yl)tnethanone;

1-((1R,3S,5S)-3-(7-amino-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(3-methyl-1H-2,4-triazol-5-yl)tnethanone;

1-((1R,3S,5S)-3-(7-amino-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(3-methyl-1H-2,4-triazol-5-yl)tnethanone;

1-((1R,3S,5S)-3-(7-amino-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(3-methyl-1H-2,4-triazol-5-yl)tnethanone;

1-((1R,3S,5S)-3-(7-amino-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(3-methyl-1H-2,4-triazol-5-yl)tnethanone;

1-((1R,3S,5S)-3-(7-amino-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(3-methyl-1H-2,4-triazol-5-yl)tnethanone;

1-((1R,3S,5S)-3-(7-amino-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(3-methyl-1H-2,4-triazol-5-yl)tnethanone;

1-((1R,3S,5S)-3-(7-amino-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(3-methyl-1H-2,4-triazol-5-yl)tnethanone;

1-((1R,3S,5S)-3-(7-amino-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(3-methyl-1H-2,4-triazol-5-yl)tnethanone;

1-((1R,3S,5S)-3-(7-amino-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(3-methyl-1H-2,4-triazol-5-yl)tnethanone;

1-((1R,3S,5S)-3-(7-amino-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(3-methyl-1H-2,4-triazol-5-yl)tnethanone;

1-((1R,3S,5S)-3-(7-amino-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(3-methyl-1H-2,4-triazol-5-yl)tnethanone;
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(P-1,4-hydrtmcyclobutyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;  
((1R,3s,5S)-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)ethanone;  
((1R,3s,5S)-3-(7-annino-6-bronno-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)ethanone;  
((1R,3s,5S)-3-(7-annino-6-cyclopropyl-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)ethanone;  
((1R,3s,5S)-3-(7-annino-6-cyclopropyl-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)ethanone;  
((1R,3s,5S)-3-(7-annino-6-cyclopropyl-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)ethanone;  
((1R,3s,5S)-3-(7-annino-6-cyclopropyl-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)ethanone;  
((1R,3s,5S)-3-(7-annino-6-cyclopropyl-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)ethanone;  
((1R,3s,5S)-3-(7-annino-6-cyclopropyl-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)ethanone;  
((1R,3s,5S)-3-(7-annino-6-cyclopropyl-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)ethanone;  
((1R,3s,5S)-3-(7-annino-6-cyclopropyl-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)ethanone;  
((1R,3s,5S)-3-(7-annino-6-cyclopropyl-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)ethanone;  
((1R,3s,5S)-3-(7-annino-6-cyclopropyl-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)ethanone;  
((1R,3s,5S)-3-(7-annino-6-cyclopropyl-3-(6-(1-hydroxycyclobutyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)ethanone;
1-(5-((1 R,3S,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(8-hydroxy-5,6,7,8-tetrahydroquinolin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
((1 R,3S,5i)-3-(8-hydroxy-5,6,7,8-tetrahydroquinolin-3-yl)-6-(methylsulfonfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)ethanone;
((1 R,3S,5S)-3-(7-aminoo-6-cyclopropyl-3-(8-hydroxy-5,6,7,8-tetrahydroquinolin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)ethanone;
((1 R,3S,5S)-3-(7-aminoo-6-cyclopropyl-3-(8-hydroxy-5,6,7,8-tetrahydroquinolin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)ethanone;
Deuterated-(3-exo)-3-[7-aminoo-6-cyclopropyl-3-(5,6,7,8-tetrahydro-8-hydroxy-3-quinolinyl-D)]pyrazolo[1,5-a]pyrimidin-5-yl]-8-(4H-1,2,4-triazol-3-ylcarbonyl)-8-azabicyclo[3.2.1]octane;
1-(5-((1 R,3S,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(8-hydroxy-5,6,7,8-tetrahydroquinolin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1 R,3S,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(8-hydroxy-5,6,7,8-tetrahydroquinolin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1 R,3S,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(8-hydroxy-5,6,7,8-tetrahydroquinolin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
((1 R,3S,5S)-3-(7-aminoo-6-cyclopropyl-3-(7-hydroxy-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
((1 R,3S,5S)-3-(7-aminoo-6-cyclopropyl-3-(7-hydroxy-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)ethanone;
((1 R,3S,5S)-3-(7-aminoo-6-cyclopropyl-3-(7-hydroxy-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl)-6-(methylsulfonfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)ethanone;
1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(1H-pyrazol-3-yl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidine;

((1 R,3s,5S)-3-(6-cyclopropyl-3-(4-hydroxy-3,4-dihydro-2H-pyran-3,2-b)pyridin-7-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;

1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;

1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;

1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;

1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;

1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;

1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;

1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-
amino-3-(6-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-
amino-3-(6-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-
amino-3-(6-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-
amino-3-(6-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-
amino-3-(6-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
((1 R,3s,5S)-3-(7-amino-3-(6-(2-aminoo-1,1,1,3,3,3-hexafluoropropan-2-yl)pyridin-3-yl)-6-cyclopropylpyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazole-3-yl)ethanone;  
1-((1 R,3s,5S)-3-(7-amino-3-(6-(2-aminoo-1,1,1,3,3,3-hexafluoropropan-2-yl)pyridin-3-yl)-6-cyclopropylpyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;  
((1 R,3s,5S)-3-(7-amino-3-(6-(2-aminoo-1,1,1,3,3,3-hexafluoropropan-2-yl)pyridin-3-yl)-6-cyclopropylpyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methyl-4H-1,2,4-triazol-3-yl)ethanone;  
((1 R,3s,5S)-3-(7-amino-3-(6-(2-aminoo-1,1,1,3,3,3-hexafluoropropan-2-yl)pyridin-3-yl)-6-cyclopropylpyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-amino-4H-1,2,4-triazol-3-yl)ethanone;  
((3-amino-1H-pyrazol-5-yl)((1 R,3s,5S)-3-(7-amino-3-(6-(2-aminoo-1,1,1,3,3,3-hexafluoropropan-2-yl)pyridin-3-yl)-6-cyclopropylpyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)methanone;  
1-((5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(2-(hydroxynethyl)thiazol-5-yl)pyrazolo[1,5-a]pyrinnidin-3-yl)thiazol-2-yl)methyl 4H-1,2,4-triazole-3-carboxylate;  
((1 R,3s,5S)-3-(7-amino-3-(2-(aminomethyl)thiazol-5-yl)-6-cyclopropylpyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)ethanone;  
(5-(5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)methyl 4H-1,2,4-triazole-3-carboxylate;  
((1 R,3s,5S)-3-(7-amino-3-(2-(aminomethyl)thiazol-5-yl)-6-cyclopropylpyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)ethanone;  
N-((5-((1 R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)methyl 4H-1,2,4-triazole-3-carboxamide;  
((1 R,3s,5S)-3-(7-amino-3-(2-(aminomethyl)thiazol-5-yl)-6-cyclopropylpyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)ethanone;
(1R,3s,5S)-3-(7-amino-3-(2-(aminomethyl)-4-cyclopropylthiazol-5-yl)-6-cyclopropyl-3-(6-(phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone; 
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(5-fluoro-6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)ethanone; 
1-(5-(8-(4H-1,2,4-triazole-3-carbonyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone; 
(2R)-1-(3-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-2-hydroxypropan-1-one; 
1-(5-(5-(4H-1,2,4-triazole-3-carbonyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone; 
(2R)-1-(5-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-2,5-diazabicyclo[2.2.2]ocatan-2-yl)-2-hydroxypropan-1-one; 
1-(5-(3-(4H-1,2,4-triazole-3-carbonyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone; 
(2R)-1-(8-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-2-hydroxypropan-1-one; 
1-(8-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-2-hydroxyethanone; 
N-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-y)acetamide; 
N-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-yl)acetamide; 
N-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-yl)acetamide; 
1-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(pyrrolidin-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone; 
1-((1R,3s,5S)-3-(6-acetyl-7-amino-3-(6-(pyrrolidin-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazole-3-y)methanone;
1-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-(pyrrolidin-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
((1R,3s,5i)-6-cyclopropyl-3-(6-(pyrrolidin-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidinii-3-oxoazabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)ethanone;
(R)-4-(5-((1R,3s,5S)-8-H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)pyndin-2-yl)oxazolidin-2-one;
(S)-4-(5-((1R,3s,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)pyndin-2-yl)oxazolidin-2-one;
((1R,3r,5S)-3-(7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
((1R,3r,5S)-3-(7-amino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
1-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-(pyrrolidin-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;
1-(7-(6-acetyl-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)^_oxa-9-azabicyclo[3.3.1]nonan-9-yl)-2-hydroxyethanone;
(7-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)(1 H-1,2,4-triazol-3-yl)methanone;
(mixture of stereoisomer);
(7-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)(1 H-1,2,4-triazol-3-yl)methanone;
(isomer I);
(7-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)(1 H-1,2,4-triazol-3-yl)methanone;
(isomer II);
(7-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)(1 H-1,2,4-triazol-3-yl)methanone;
(isomer II);
1-(5-(9-(1 H-1,2,4-triazole-3-carbonyl)-9-azabicyclo[3.3.1]nonan-3-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
1-(7-amino-5-((1 S,3R,5R)-6-hydroxy-8-(1 H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;
(((1 S,3R,5S)-7-(7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3,9-diazabicyclo[3.3.1]nonan-9-yl)(1 H-1,2,4-triazol-3-yl)methanone;
endo/exo-7-(6-acetyl-7-amino-3-(6-phenyl-3-pyridinyl)pyrazolo[1,5-a]pyrimidin-5-yl)-9-(4H-1,2,4-triazole-3-ylcarbonyl)-3-thia-9-azabicyclo[3.3.1]nonane, 3,3-dioxide;
(((1 R,3S,5S)-3-(7-amino-6-(1-hydroxycyclopropyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(1 H-1,2,4-triazol-3-yl)methanone;
5-((1 R,3S,5S)-8-(1 H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidine-6-carboxamide;
((R,3S,5S)-3-(7-(methylamino)-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazol-1-yl)imidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

1-((R,3S,5S)-3-(7-amino-3-(3-fluoro-4-(hydroxymethyl)phenyl)-6-(methylsulfonyl)pyrazolo[1,5-a]imidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

1-((R,3S,5S)-3-(7-amino-3-(4-(1-aminocyclopropyl)-3-fluorophenyl)-6-(methylsulfonyl)pyrazolo[1,5-a]imidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

1-((R,3S,5S)-3-(7-amino-3-(4-(2-aminopropan-2-yl)-3-fluorophenyl)-6-(methylsulfonyl)pyrazolo[1,5-a]imidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4-triazol-3-yl)methanone;

(E)-4-((R,3S,5S)-3-(7-amino-3-(6-(2-fluorophenyl)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]imidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carbonyl)N’-(3-(dimethylamino)propyl)-N-ethyl-2H-1,2,3-triazole-2-carboximidamide;

1-((R,3S,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-cyclobutoxyphenyl)pyridin-2-yl)acetohydrazide;

1-((R,3S,5S)-8-(4H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-propionohydrazide;

N’-(5-(6-acetyl-7-amino-3-(6-(cyclobutoxyphenyl)pyridin-3-yl)pyrazolo[1,5-a]imidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-hydroxyethanone;
\((1R,3s,5S)-3-(7\text{-}\text{amino}-3-(6-(cyclopropylmethoxy)pyridin-3-yl)-6-(methylsulfonyl)pyrazolo[1,5-a]pyrimidin-5-yl)-8\text{-}azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4\text{-}\text{triazole})\text{none;}

\((1\text{R},5\text{S})-3-(6\text{-}cyclopropyl-3-(2H-pyrazolo[4,3\text{-}h]pyrano[3,2\text{-}b]pyridin-7-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8\text{-}azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4\text{-}\text{triazole})\text{methanone;}

1\text{-(5}\text{-(1R,3s,5S)-8-(4H-1,2,4\text{-}\text{triazole}-3\text{-}carbonyl)-8\text{-}azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(3\text{-}hydroxyprop-1\text{-}ynyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;}

1\text{-(5-(1R,3s,5S)-8-(4H-1,2,4\text{-}triazole}-3\text{-}carbonyl)-8\text{-}azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(3\text{-}methoxyprop-1\text{-}ynyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;}

1\text{-(5-(1R,3s,5S)-8-(4H-1,2,4\text{-}triazole}-3\text{-}carbonyl)-8\text{-}azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(3\text{-}methoxyethoxy)prop-1\text{-}ynyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;}

1\text{-(5-(1R,3s,5S)-8-(4H-1,2,4\text{-}triazole}-3\text{-}carbonyl)-8\text{-}azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(3\text{-}methoxyethoxy)prop-1\text{-}ynyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;}

1\text{-(5-(1R,3s,5S)-8-(4H-1,2,4\text{-}triazole}-3\text{-}carbonyl)-8\text{-}azabicyclo[3.2.1]octan-3-yl)-7-amino-3-(6-(6-(cyclopropylethynyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-6-yl)ethanone;}

5\text{-((1R,3s,5S)-3-(7\text{-}\text{amino}-6-(methylsulfonyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8\text{-}azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4\text{-}\text{triazole})\text{ethanone;}

5\text{-((1R,3s,5S)-3-(7\text{-}\text{amino}-6-(methylsulfonyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8\text{-}azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4\text{-}\text{triazole})\text{methanone;}

5\text{-((1R,3s,5S)-3-(7\text{-}\text{amino}-6-(methylsulfonyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8\text{-}azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4\text{-}\text{triazole})\text{methanone;}

5\text{-((1R,3s,5S)-3-(7\text{-}\text{amino}-6-(methylsulfonyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8\text{-}azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4\text{-}\text{triazole})\text{methanone;}

5\text{-((1R,3s,5S)-3-(7\text{-}\text{amino}-6-(methylsulfonyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8\text{-}azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4\text{-}\text{triazole})\text{methanone;}

5\text{-((1R,3s,5S)-3-(7\text{-}\text{amino}-6-(methylsulfonyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8\text{-}azabicyclo[3.2.1]octan-8-yl)(4H-1,2,4\text{-}\text{triazole})\text{methanone;}

N\text{-(4-(1R,3s,5S)-3-(7\text{-}a}minolo[1,5-a]pyrimidin-5-yl)-8\text{-}azabicyclo[3.2.1]octan-8-yl)(4H-1,2,

648
N-(2-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)8-azabicyclo[3.2.1]octan-8-yl)pyridin-3-yl)acetanilide;
5-(5-(5-(1H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)6-acetyl-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)5-methylimidazolidine-2,4-dione;
5-(5-(6-acetyl-7-amino-5-((1R,3s,5S)-8-(1H-1,2,4-triazole-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carbonitrile;
5-(5-(5-((1R,3s,5S)-8-(1H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboximidamide;
3-((1R,3s,5S)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octane-8-carboximidamide;
N-(5-(5-((1R,3s,5S)-8-(1H-1,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-yl)-3-methylurea;
ethyl 5-(6-acetyl-7-amino-5-((1R,3s,5S)-8-(2-hydroxyacetyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-ylcarbamate;
ethyl 5-(5-(5-((1R,3s,5S)-8-(1H-1,2,4-triazole-5-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-aminopyrazolo[1,5-a]pyrimidin-3-yl)pyridin-2-ylcarbamate;
1-(4-(7-amino-5-((1R,3s,5S)-8-(morpholine-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-o]pyrimidin-3-yl)phenyl)-3-n-nethylurea;
1-(5-(5-((1H,2,4-triazole-3-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-7-amino-3-n-pyridin-2-yl)pyrazolo[1,5-o]pyrimidin-3-yl)phenyl)-3-n-nethylurea;
1-(4-(5-((1R,3s,5S)-8-(2,2,2-trifluoroethyl)-8-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-o]pyrimidin-3-yl)phenyl)-3-n-nethylurea;
\((1R,3s,5S,E)-3-(7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-o]pyrimidin-5-yl)N'-cyano-8-azabicyclo[3.2.1]octane-8-carboximidamide;\)
\((1R,3s,5S,E)-3-(7-amino-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-o]pyrimidin-5-yl)^{-}\)N'-cyano-8-azabicyclo[3.2.1]octane-8-carboximidamide;
\((1R,3s,5S,E)-3-(7-amino-3-(2-aminopyrimidin-5-yl)pyrazolo[1,5-o]pyrimidin-5-yl)^{-}\)N'-cyano-8-azabicyclo[3.2.1]octane-8-carboximidamide;
\((1R,3s,5S,E)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-o]pyrimidin-5-yl)^{-}\)N'-cyano-8-azabicyclo[3.2.1]octane-8-carboximidamide;
\((1R,3s,5S,E)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-o]pyrimidin-5-yl)^{-}\)N'-cyano-8-azabicyclo[3.2.1]octane-8-carboximidamide;
\((1R,3s,5S,E)-3-(7-amino-6-(methylsulfonyl)-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-o]pyrimidin-5-yl)^{-}\)N'-cyano-8-azabicyclo[3.2.1]octane-8-carboximidamide;
((1R,3s,5S)-3-(7-annino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-(piperazin-1-yl)-4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-annino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-(2-methoxyethoxy)-4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-annino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methoxy-4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-annino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-(4-methylpiperazin-1-yl)-4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-annino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-morpholino-4H-1,2,4-triazol-3-yl)methanone;
((1R,3s,5S)-3-(7-annino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-hydroxy-4H-1,2,4-triazol-3-yl)methanone; and
(5-amino-4H-1,2,4-triazol-3-yl)((1R,3s,5S)-3-(7-annino-6-cyclopropyl-3-(6-phenylpyridin-3-y1)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)methanone;
((1R,3s,5S)-3-(7-annino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-morpholino-4H-1,2,4-triazol-3-yl)methanone; and
((1R,3s,5S)-3-(7-annino-6-cyclopropyl-3-(6-phenylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-8-yl)(5-hydroxy-4H-1,2,4-triazol-3-yl)methanone;
Or a stereoisomer thereof;
Or a pharmaceutically acceptable salt thereof;
Or a pharmaceutically acceptable salt of the stereoisomer thereof.
20. A compound that is 1-[(3-Exo)-3-{7-amino-6-fluoro-3-[6-(1H-imidazol-2-yl)pyridin-4-yl]pyrazolo[1,5-a]pyrimidin-5-yl}-8-azabicyclo[3.2.1]oct-8-yl]-2-hydroxyethyl
Or a stereoisomer thereof;
Or a pharmaceutically acceptable salt thereof;
Or a pharmaceutically acceptable salt of the stereoisomer thereof.

21. A pharmaceutical composition comprising the compound of any one of claims 1 to 20 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

22. A method of treating a cancer, comprising administering a therapeutically effective amount of the compound any one of claims 1 to 20 or a pharmaceutically acceptable salt thereof to a patient in need thereof.
### INTERNATIONAL SEARCH REPORT

**INTERNATIONAL SEARCH REPORT**

**International application No.**

**PCT/US 11/21534**

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**A. CLASSIFICATION OF SUBJECT MATTER**

**IPC(6)** × **A01N 43/90 (201 1.01)**

**USPC** × **514/259.1**

According to International Patent Classification (IPC) or to both national classification and IPC

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**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

USPC: 514/259.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

USPC: 514/166, 210.18, 210.21, 233.2, 259.3; 544/1 17 (text search) Find search terms below

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PubMed, USPTO, EPAB, JPAB, Google Scholar, Patentscope, SureChem, C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
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<tbody>
<tr>
<td>Y</td>
<td>US 7,605,155 B2 (GUZI et al.) 20 October 2009 (20.10.2009) col 3, ln 24 to col 6, ln 20, col 7-8, Table 1; col 59, ln 60-67; col 61, ln 1-14; col 62, ln 58-62; col 234, Table 2</td>
<td>1-22</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C.

* Special categories of cited documents:
  * A* document defining the general state of the art which is not considered to be of particular relevance
  * E* earlier application of a patent but published on or after the international filing date
  * L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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**Name and mailing address of the ISA/US**

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-3201

**Authorized officer:**

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

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