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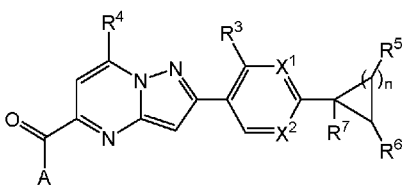
(54) Title: CYCLOALKYL SUBSTITUTED PYRAZOLOPYRIMIDINES HAVING ACTIVITY AGAINST RSV



(I)

(57) Abstract: The invention concerns compounds of formula (I) having antiviral activity, in particular, having an inhibitory activity on the replication of the respiratory syncytial virus (RSV). The invention further concerns pharmaceutical compositions comprising these compounds and the compounds for use in the treatment of respiratory syncytial virus infection. (Formula I)

CYCLOALKYL SUBSTITUTED PYRAZOLOPYRIMIDINES HAVING ACTIVITY AGAINST RSV

Field of the Invention

The invention concerns compounds having antiviral activity, in particular, having an inhibitory activity on the replication of the respiratory syncytial virus (RSV). The invention further concerns pharmaceutical compositions comprising these compounds and the compounds for use in the treatment of respiratory syncytial virus infection.

Background

Human RSV or Respiratory Syncytial Virus is a large RNA virus, member of the family of *Pneumoviridae*, genus *Orthopneumovirus* together with bovine RSV virus. Human RSV is responsible for a spectrum of respiratory tract diseases in people of all ages throughout the world. It is the major cause of lower respiratory tract illness during infancy and childhood. Over half of all infants encounter RSV in their first year of life, and almost all within their first two years. The infection in young children can cause lung damage that persists for years and may contribute to chronic lung disease in later life (chronic wheezing, asthma). Older children and adults often suffer from a (bad) common cold upon RSV infection. In old age, susceptibility again increases, and RSV has been implicated in a number of outbreaks of pneumonia in the aged resulting in significant mortality.

Infection with a virus from a given subgroup does not protect against a subsequent infection with an RSV isolate from the same subgroup in the following winter season. Re-infection with RSV is thus common, despite the existence of only two subtypes, A and B.

Today only three drugs have been approved for use against RSV infection. A first one is ribavirin, a nucleoside analogue that provides an aerosol treatment for serious RSV infection in hospitalized children. The aerosol route of administration, the toxicity (risk of teratogenicity), the cost and the highly variable efficacy limit its use. Synagis® (palivizumab a monoclonal antibody, is used for passive immunoprophylaxis . Athough the benefit of Synagis® has been demonstrated, the treatment is expensive, requires parenteral administration and is restricted to children at risk for developing severe pathology.

Clearly there is a need for an efficacious non-toxic and easy to administer drug against RSV replication. It would be particularly preferred to provide drugs against RSV replication that could be administered perorally.

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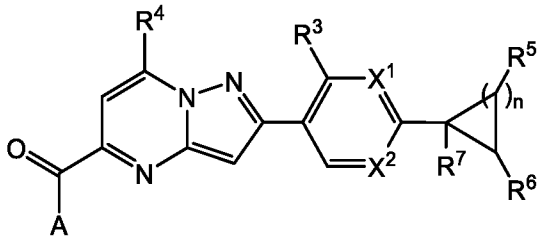
Compounds that exhibit anti-RSV activity are disclosed in WO- 2016/174079.

Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of common general knowledge in the field.

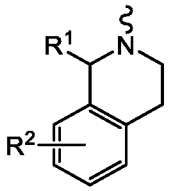
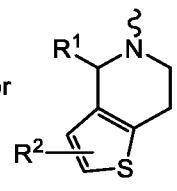
Detailed description of the Invention

The present invention relates to compounds of formula (I)



(I)

including any stereochemically isomeric form thereof, wherein

A is  (a-1) or  (a-2)

n is 1 or 2;

X^1 and X^2 are selected from X^1 is CH and X^2 is CH,
or X^1 is N and X^2 is CH,
or X^1 is CH and X^2 is N;

R^1 is CH_3 or CH_2CH_3;

R^2 is hydrogen, halo or C_{1-4}alkyl;

R^3 is halo;

R^4 is C_{1-6}alkyl; C_{3-6}cycloalkyl; phenyl; phenyl substituted with 1, 2 or 3 substituents each individually selected from halo, C_{1-4}alkyl, C_{1-4}alkyloxy, and hydroxy;

R^5 is hydrogen or C_{1-4}alkyl;

R^6 is hydroxy;
cyano;
C_{1-4}alkyl substituted with hydroxy, -(CO)-$NR^{10}R^{11}$ or -O-(CO)-$NR^{10}R^{11}$;
-(CO)-$NR^{10}R^{11}$;
-(CO)-NR^9-SO_2-R^8;

-(CO)-NR^9-(CO)-SO_2-R^8;
-(CO)-Heterocycle;
-(CO)-NR^9-Heterocycle;
-O-(CO)-$NR^{10}R^{11}$;
-NR^9-(CO)-C_{1-4}alkyl;
-NR^9-(CO)-C_{3-6}cycloalkyl;
-NR^9-(CO)-O-R^8;
-NR^9-(CO)-NR^9-R^8;
-NR^9-SO_2-R^8;
-NR^9-(P=O)-di(C_{1-4}alkyl);
-SO_2-R^8;
-SO_2-$NR^{10}R^{11}$;
-SO_2-NR^9-(CO)-R^8; or
Heteroaryl;

R^7 is hydrogen, halo, C_{1-4}alkyl or -(CO)-$NR^{10}R^{11}$;

R^8 is C_{1-4}alkyl, polyhaloC_{1-4}alkyl, or C_{3-6}cycloalkyl;

each R^9 is independently selected from hydrogen or C_{1-6}alkyl;

R^{10} and R^{11} are each indepently selected from hydrogen; CN; C_{1-4}alkyl; C_{3-6}alkenyl; polyhaloC_{1-4}alkyl; C_{3-6}cycloalkyl; C_{3-6}cycloalkyl substituted with C_{1-4}alkyl; or C_{1-4}alkyl substituted with hydroxy or cyano;

Heterocycle is pyrrolidinyl or oxetanyl; and

Heteroaryl is 3-oxo-2,3-dihydro-1,2-oxazolyl, or tetrazolyl, wherein each Heteroaryl is optionally substituted with one or two substituents each independently selected from C_{1-4}alkyl, halo, amino, and aminocarbonyl;

provided that when R^6 is -NR^9-(CO)-C_{3-6}cycloalkyl then X^1 is CH and X^2 is CH;

or a pharmaceutically acceptable acid addition salt thereof.

As used in the foregoing definitions:

- halo is generic to fluoro, chloro, bromo and iodo;
- C_{1-4}alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, 1-methylethyl, 2-methylpropyl and the like;
- C_{1-6}alkyl is meant to include C_{1-4}alkyl and the higher homologues thereof having 5 or 6 carbon atoms, such as, for example, 2 methylbutyl, pentyl, hexyl and the like;
- C_{3-6}cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl;
- polyhaloC_{1-4}alkyl is defined as polyhalosubstituted C_{1-4}alkyl, in particular C_{1-4}alkyl (as hereinabove defined) substituted with 2 to 6 halogen atoms such as difluoromethyl, trifluoromethyl, trifluoroethyl, and the like;

- -(CO)- or (CO) means carbonyl.

Unless the context clearly requires otherwise, throughout the description and the claims, the words "comprise", "comprising", and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of "including, but not limited to".

The term "compounds of the invention" as used herein, is meant to include the compounds of formula (I), and the salts and solvates thereof.

As used herein, any chemical formula with bonds shown only as solid lines and not as solid wedged or hashed wedged bonds, or otherwise indicated as having a particular configuration (e.g. R, S) around one or more atoms, contemplates each possible stereoisomer, or mixture of two or more stereoisomers.

Hereinbefore and hereinafter, the terms "compound of formula (I)" and "intermediates of synthesis of formula (I)" are meant to include the stereoisomers thereof and the tautomeric forms thereof.

The terms "stereoisomers", "stereoisomeric forms" or "stereochemically isomeric forms" hereinbefore or hereinafter are used interchangeably.

The invention includes all stereoisomers of the compounds of the invention either as a pure stereoisomer or as a mixture of two or more stereoisomers. Enantiomers are stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a racemate or racemic mixture. Diastereomers (or diastereoisomers) are stereoisomers that are not enantiomers, i.e. they are not related as mirror images. If a compound contains a double bond, the substituents may be in the E or the Z configuration. Substituents on bivalent cyclic (partially) saturated radicals may have either the cis- or trans-configuration; for example if a compound contains a disubstituted cycloalkyl group, the substituents may be in the cis or trans configuration.

The term "stereoisomers" also includes any rotamers, also called conformational isomers, the compounds of formula (I) may form.

Therefore, the invention includes enantiomers, diastereomers, racemates, E isomers, Z isomers, cis isomers, trans isomers, rotamers, and mixtures thereof, whenever chemically possible.

The meaning of all those terms, i.e. enantiomers, diastereomers, racemates, E isomers, Z isomers, cis isomers, trans isomers and mixtures thereof are known to the skilled person.

The absolute configuration is specified according to the Cahn-Ingold-Prelog system. The configuration at an asymmetric atom is specified by either R or S. Resolved stereoisomers whose absolute configuration is not known can be designated by (+) or (-) depending on the direction in which they rotate plane polarized light. For instance, resolved enantiomers whose absolute configuration is not known can be designated by (+) or (-) depending on the direction in which they rotate plane polarized light.

When a specific stereoisomer is identified, this means that said stereoisomer is substantially free, i.e. associated with less than 50%, preferably less than 20%, more preferably less than 10%, even more preferably less than 5%, in particular less than 2% and most preferably less than 1%, of the other stereoisomers. Thus, when a compound of formula (I) is for instance specified as (R), this means that the compound is substantially free of the (S) isomer; when a compound of formula (I) is for instance specified as E, this means that the compound is substantially free of the Z isomer; when a compound of formula (I) is for instance specified as cis, this means that the compound is substantially free of the trans isomer.

Some of the compounds according to formula (I) may also exist in their tautomeric form. Such forms in so far as they may exist, although not explicitly indicated in the above formula (I) are intended to be included within the scope of the present invention.

It follows that a single compound may exist in both stereoisomeric and tautomeric form.

Atropisomers (or atropoisomers) are stereoisomers which have a particular spatial configuration, resulting from a restricted rotation about a single bond, due to large steric hindrance. All atropisomeric forms of the compounds of formula (I) are intended to be included within the scope of the present invention.

The pharmaceutically acceptable acid addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms that the compounds of formula (I) are able to form. These pharmaceutically acceptable acid addition salts can conveniently be obtained by treating the base form with such appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, nitric, phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic (i.e. ethanedioic), malonic, succinic (i.e. butanedioic acid), maleic, fumaric, malic, tartaric,

citric, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclamic, salicylic, p-aminosalicylic, pamoic and the like acids.

Conversely said salt forms can be converted by treatment with an appropriate base into the free base form.

The compounds of formula (I) may exist in both unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular association comprising a compound of the invention and one or more pharmaceutically acceptable solvent molecules, e.g. water or ethanol. The term 'hydrate' is used when said solvent is water.

For the avoidance of doubt, compounds of formula (I) may contain the stated atoms in any of their natural or non-natural isotopic forms. In this respect, embodiments of the invention that may be mentioned include those in which (a) the compound of formula (I) is not isotopically enriched or labelled with respect to any atoms of the compound; and (b) the compound of formula (I) is isotopically enriched or labelled with respect to one or more atoms of the compound. Compounds of formula (I) that are isotopically enriched or labelled (with respect to one or more atoms of the compound) with one or more stable isotopes include, for example, compounds of formula (I) that are isotopically enriched or labelled with one or more atoms such as deuterium, ^{13}C, ^{14}C, ^{14}N, ^{15}O or the like.

A first group of compounds are compounds of formula (I) wherein X^1 is CH and X^2 is CH.

A second group of compounds are compounds of formula (I) wherein X^1 is N and X^2 is CH, or X^1 is CH and X^2 is N.

A third group of compounds are compounds of formula (I) wherein wherein radical A is of formula (a-1).

A fourth group of compounds are compounds of formula (I) wherein wherein radical A is of formula (a-2).

A fifth group of compounds are compounds of formula (I) wherein n = 1.

A sixth group of compounds are compounds of formula (I) wherein n = 2.

Another group of compounds are compounds of formula (I) wherein R^6 is hydroxy.

Another group of compounds are compounds of formula (I) wherein R^6 is cyano.

Another group of compounds are compounds of formula (I) wherein R^6 is C_{1-4}alkyl substituted with hydroxy, -(CO)-$NR^{10}R^{11}$ or -O-(CO)-$NR^{10}R^{11}$.

Another group of compounds are compounds of formula (I) wherein R^6 is -(CO)-$NR^{10}R^{11}$.

Another group of compounds are compounds of formula (I) wherein R^6 is -(CO)-NR^9-SO_2-R^8.

Another group of compounds are compounds of formula (I) wherein R^6 is -(CO)-NR^9-(CO)-SO_2-R^8.

Another group of compounds are compounds of formula (I) wherein R^6 is -(CO)-Heterocycle.

Another group of compounds are compounds of formula (I) wherein R^6 is -(CO)-NR^9-Heterocycle.

Another group of compounds are compounds of formula (I) wherein R^6 is -O-(CO)-$NR^{10}R^{11}$.

Another group of compounds are compounds of formula (I) wherein R^6 is -NR^9-(CO)-C_{1-4}alkyl.

Another group of compounds are compounds of formula (I) wherein R^6 is -NR^9-(CO)-C_{3-6}cycloalkyl.

Another group of compounds are compounds of formula (I) wherein R^6 is -NR^9-(CO)-O-R^8.

Another group of compounds are compounds of formula (I) wherein R^6 is -NR^9-(CO)-NR^9-R^8.

Another group of compounds are compounds of formula (I) wherein R^6 is -NR^9-SO_2-R^8.

Another group of compounds are compounds of formula (I) wherein R^6 is -NR^9-(P=O)-di(C_{1-4}alkyl).

Another group of compounds are compounds of formula (I) wherein R^6 is -SO_2-R^8.

Another group of compounds are compounds of formula (I) wherein R^6 is -SO_2-$NR^{10}R^{11}$.

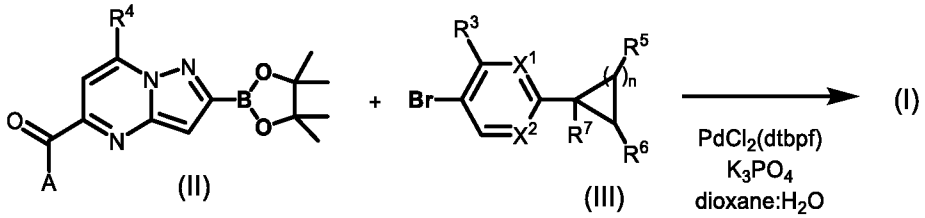
Another group of compounds are compounds of formula (I) wherein R^6 is $-SO_2-NR^9-(CO)-R^8$.

Another group of compounds are compounds of formula (I) wherein R^6 is Heteroaryl.

Interesting compounds of formula (I) are those compounds of formula (I) wherein one or more of the following restrictions apply :

a) A is a radical of formula (a-1); or
b) A is a radical of formula (a-2); or
c) R^1 is methyl; or
d) R^2 is hydrogen; or
e) R^3 is fluoro; or
f) R^4 is cyclopropyl;
g) R^4 is phenyl;
h) n = 1; or
i) n = 2.

Compounds of formula (I) can generally be prepared by reacting an intermediate of formula (II) with an intermediate of formula (III) in a reaction-inert solvent.



Other synthetic pathways for preparing compounds of formula (I) have been described in the experimental party as general methods of preparation and specific working examples.

The compounds of formula (I) may further be prepared by converting compounds of formula (I) into each other according to art-known group transformation reactions.

The starting materials and some of the intermediates are known compounds and are commercially available or may be prepared according to conventional reaction procedures generally known in the art.

The compounds of formula (I) as prepared in the hereinabove described processes may be synthesized in the form of racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. Those compounds of formula (I) that are obtained in racemic form may be converted into the corresponding diastereomeric

salt forms by reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali. An alternative manner of separating the enantiomeric forms of the compounds of formula (I) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

The compounds of formula (I) show antiviral properties. Viral infections treatable using the compounds and methods of the present invention include those infections brought on by ortho- and paramyxoviruses and in particular by human and bovine respiratory syncytial virus (RSV). A number of the compounds of this invention moreover are active against mutated strains of RSV. Additionally, many of the compounds of this invention show a favorable pharmacokinetic profile and have attractive properties in terms of bioavailabilty, including an acceptable half-life, AUC and peak values and lacking unfavourable phenomena such as insufficient quick onset and tissue retention.

The *in vitro* antiviral activity against RSV of the present compounds was tested in a test as described in the experimental part of the description, and may also be demonstrated in a virus yield reduction assay. The *in vivo* antiviral activity against RSV of the present compounds may be demonstrated in a test model using cotton rats as described in Wyde et al. in Antiviral Research, 38, p. 31 - 42(1998).

Additionally the present invention provides pharmaceutical compositions comprising at least one pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of formula (I). Also provided are pharmaceutical compositions comprising a pharmaceutically acceptable carrier, a therapeutically active amount of a compound of formula (I), and another antiviral agent, in particular a RSV inhibiting compound.

In order to prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, in base or acid addition salt form, as the active ingredient is combined in intimate admixture with at least one pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for oral administration, rectal administration, percutaneous administration or parenteral injection.

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For example in preparing the compositions in oral dosage form, any of the usual liquid pharmaceutical carriers may be employed, such as for instance water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid pharmaceutical carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their easy administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral injection compositions, the pharmaceutical carrier will mainly comprise sterile water, although other ingredients may be included in order to improve solubility of the active ingredient. Injectable solutions may be prepared for instance by using a pharmaceutical carrier comprising a saline solution, a glucose solution or a mixture of both. Injectable suspensions may also be prepared by using appropriate liquid carriers, suspending agents and the like. In compositions suitable for percutaneous administration, the pharmaceutical carrier may optionally comprise a penetration enhancing agent and/or a suitable wetting agent, optionally combined with minor proportions of suitable additives which do not cause a significant deleterious effect to the skin. Said additives may be selected in order to facilitate administration of the active ingredient to the skin and/or be helpful for preparing the desired compositions. These topical compositions may be administered in various ways, e.g., as a transdermal patch, a spot-on or an ointment. Addition salts of the compounds of formula (I), due to their increased water solubility over the corresponding base form, are obviously more suitable in the preparation of aqueous compositions.

It is especially advantageous to formulate the pharmaceutical compositions of the invention in dosage unit form for ease of administration and uniformity of dosage. "Dosage unit form" as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined amount of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

For oral administration, the pharmaceutical compositions of the present invention may take the form of solid dose forms, for example, tablets (both swallowable and chewable forms), capsules or gelcaps, prepared by conventional means with pharmaceutically acceptable excipients and carriers such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone, hydroxypropylmethylcellulose and the like), fillers (e.g. lactose,

microcrystalline cellulose, calcium phosphate and the like), lubricants (e.g. magnesium stearate, talc, silica and the like), disintegrating agents (e.g. potato starch, sodium starch glycollate and the like), wetting agents (e.g. sodium laurylsulphate) and the like. Such tablets may also be coated by methods well known in the art.

Liquid preparations for oral administration may take the form of e.g. solutions, syrups or suspensions, or they may be formulated as a dry product for admixture with water and/or another suitable liquid carrier before use. Such liquid preparations may be prepared by conventional means, optionally with other pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, methylcellulose, hydroxypropylmethylcellulose or hydrogenated edible fats), emulsifying agents (e.g. lecithin or acacia), non aqueous carriers (e.g. almond oil, oily esters or ethyl alcohol), sweeteners, flavours, masking agents and preservatives (e.g. methyl or propyl p-hydroxybenzoates or sorbic acid).

Pharmaceutically acceptable sweeteners useful in the pharmaceutical compositions of the invention comprise preferably at least one intense sweetener such as aspartame, acesulfame potassium, sodium cyclamate, alitame, a dihydrochalcone sweetener, monellin, stevioside sucralose (4,1',6'-trichloro-4,1',6'-trideoxygalactosucrose) or, preferably, saccharin, sodium or calcium saccharin, and optionally at least one bulk sweetener such as sorbitol, mannitol, fructose, sucrose, maltose, isomalt, glucose, hydrogenated glucose syrup, xylitol, caramel or honey. Intense sweeteners are conveniently used in low concentrations. For example, in the case of sodium saccharin, the said concentration may range from about 0.04% to 0.1% (weight/volume) of the final formulation. The bulk sweetener can effectively be used in larger concentrations ranging from about 10% to about 35%, preferably from about 10% to 15% (weight/volume).

The pharmaceutically acceptable flavours which can mask the bitter tasting ingredients in the low-dosage formulations are preferably fruit flavours such as cherry, raspberry, black currant or strawberry flavour. A combination of two flavours may yield very good results. In the high-dosage formulations, stronger pharmaceutically acceptable flavours may be required such as Caramel Chocolate, Mint Cool, Fantasy and the like. Each flavour may be present in the final composition in a concentration ranging from about 0.05% to 1% (weight/volume). Combinations of said strong flavours are advantageously used. Preferably a flavour is used that does not undergo any change or loss of taste and/or color under the circumstances of the formulation.

The compounds of formula (I) may be formulated for parenteral administration by injection, conveniently intravenous, intra-muscular or subcutaneous injection, for example by bolus injection or continuous intravenous infusion. Formulations for injection may be

presented in unit dosage form, e.g. in ampoules or multi-dose containers, including an added preservative. They may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating agents such as isotonizing, suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be present in powder form for mixing with a suitable vehicle, e.g. sterile pyrogen free water, before use.

The compounds of formula (I) may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter and/or other glycerides.

In general it is contemplated that an antivirally effective daily amount would be from 0.01 mg/kg to 500 mg/kg body weight, more preferably from 0.1 mg/kg to 50 mg/kg body weight. It may be appropriate to administer the required dose as two, three, four or more sub-doses at appropriate intervals throughout the day. Said sub-doses may be formulated as unit dosage forms, for example, containing 1 to 1000 mg, and in particular 5 to 200 mg of active ingredient per unit dosage form.

The exact dosage and frequency of administration depends on the particular compound of formula (I) used, the particular condition being treated, the severity of the condition being treated, the age, weight, sex, extent of disorder and general physical condition of the particular patient as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that said effective daily amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention. The effective daily amount ranges mentioned hereinabove are therefore only guidelines.

Also, the combination of another antiviral agent and a compound of formula (I) can be used as a medicine. Thus, the present invention also relates to a product containing (a) a compound of formula (I), and (b) another antiviral compound, as a combined preparation for simultaneous, separate or sequential use in antiviral treatment. The different drugs may be combined in a single preparation together with pharmaceutically acceptable carriers. For instance, the compounds of the present invention may be combined with interferon-beta or tumor necrosis factor-alpha in order to treat or prevent RSV infections. Other antiviral compounds (b) to be combined with a compound of formula (I) for use in the treatment of RSV are RSV fusion inhibitors or RSV polymerase inhibitors. Specific antiviral compounds for combination with any of the compounds of formula (I) that are useful in the treatment of RSV are the RSV inhibiting compounds selected from ribavirin,

lumicitabine, presatovir, ALX-0171, MDT-637, BTA-9881, BMS-433771, YM-543403, A-60444, TMC-353121, RFI-641, CL-387626, MBX-300, 3-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-benzimidazol-2-yl}methyl)-1-cyclopropyl-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one, 3-[[7-chloro-3-(2-ethylsulfonyl-ethyl)imidazo[1,2-a]pyridin-2-yl]methyl]-1-cyclopropyl-imidazo[4,5-c]pyridin-2-one, and 3-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-indol-2-yl}methyl)-1-(2,2,2-trifluoroethyl)-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one.

The invention will hereinafter be illlustrated with reference to the following, non-limiting examples.

Experimental part

A. Abbreviations

μw	microwave
AcCl	acetyl chloride
AcOH	acetic acid
aq.	aqueous
br	broad
cataCXium® A	di(1-adamantyl)-*n*-butylphosphine CAS [321921-71-5]
CDI	1,1'-carbonyldiimidazole CAS [530-62-1]
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene CAS [6674-22-2]
DCE	1,2-dichloroethane
DCM	dichloromethane
DIPE	diisopropyl ether
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DPPA	diphenyl phosphoryl azide CAS [26386-88-9]
Et_2O	diethyl ether
Et_3N	triethylamine
EtOAc	ethyl acetate
EtOH	ethanol
h	hour
HATU	1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]-pyridinium 3-oxid hexafluorophosphate CAS [148893-10-1]

HMDS	hexamethyldisilazane CAS [999-97-3]
i-$PrNH_2$	isopropylamine
i-PrOH	isopropyl alcohol
m	multiplet
m/z	mass-to-charge ratio
MeCN	acetonitrile
MeOH	methanol
min	minute(s)
NBS	*N*-bromosuccinimide CAS [128-08-5]
NFSI	*N*-fluorobenzenesulfonimide CAS [133745-75-2]
NMR	nuclear magnetic resonance
o/n	overnight
P(*o*-tol)$_3$	tri(*o*-tolyl)phosphine CAS [6163-58-2]
$Pd(OAc)_2$	palladium (II) acetate CAS [3375-31-3]
$PdCl_2$(dppf).DCM	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane CAS [95464-05-4]
$PdCl_2$(dtbpf)	[1,1'-bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II) CAS [95408-45-0]
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium(0) CAS [51364-51-3]
ppm	parts per million
q	quartet
quin	quintuplet
$Rh_2(OPiv)_4$	rhodium(II) trimethylacetate, dimer CAS [62728-88-5]
rt	room temperature
s	singulet
sext	sextuplet
t	triplet
TBDMS	*tert*-butyldimethylsilyl
TBDMSCl	*tert*-butyldimethylsilyl choride CAS [18162-48-6]
t-BuNO	*tert*-butylnitrite CAS [540-80-7]
t-BuOH	*tert*-butyl alcohol
t-BuOK	potassium *tert*-butoxide
TFA	trifluoroacetic acid CAS [76-05-1]
TFAA	trifluoroacetic anhydride CAS [407-25-0]
THF	tetrahydrofuran
TREAT-HF	triethylamine trihydrofluoride CAS [73602-61-6]
XPhos	2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

	CAS [564483-18-7]
Δ	heat

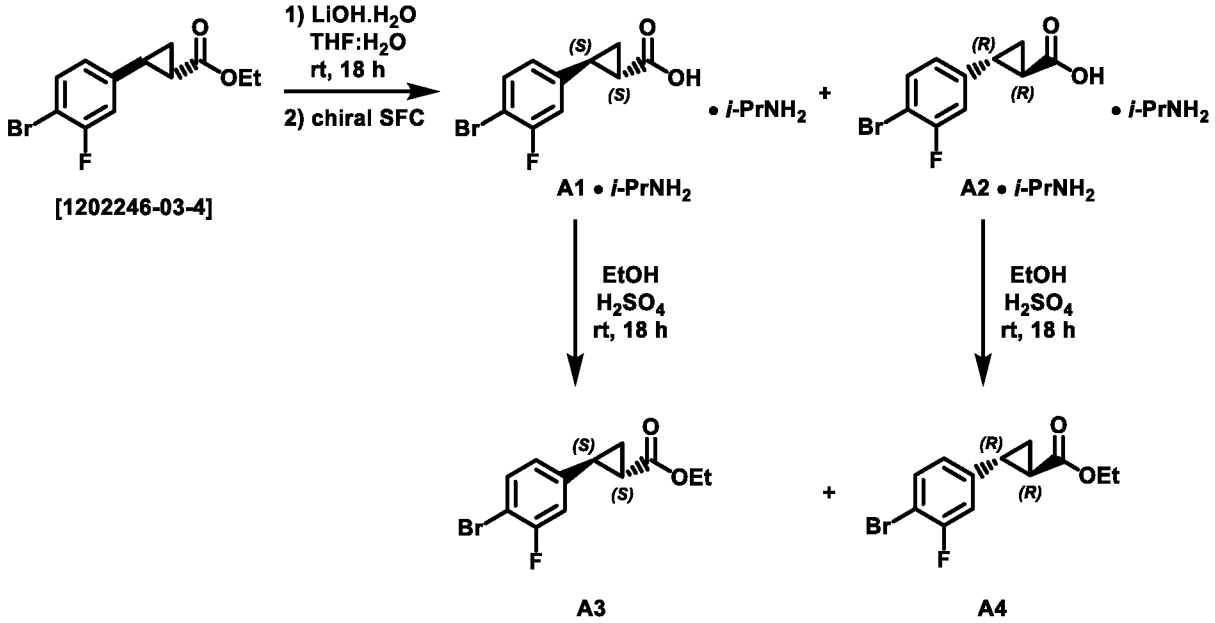
The stereochemical configuration for some compounds has been designated as R^* or S^* (or *R or *S) when the absolute stereochemistry is undetermined although the compound itself has been isolated as a single stereoisomer and is enantiomerically pure.

B. Compound synthesis

B.1. Preparation of Compounds of Formula (I) with n=1

B.1.1. Synthesis of Intermediates

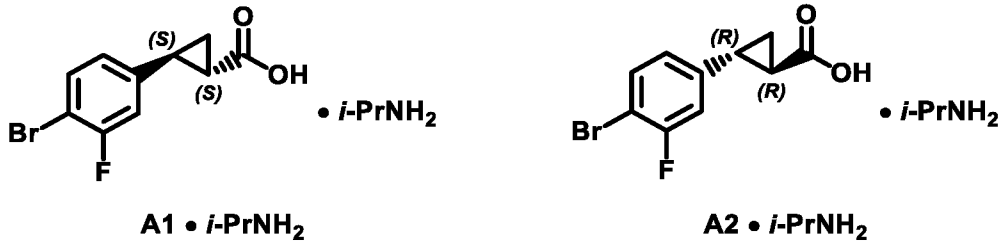
B.1.1.1. Synthesis of Intermediates A3 and A4



Intermediates A1.i-PrNH2 and A2.i-PrNH2

A1.*i*-PrNH2:(1*S*,2*S*)-2-(4-Bromo-3-fluorophenyl)cyclopropane-1-carboxylic acid; propan-2-amine salt

A2.*i*-PrNH2:(1*R*,2*R*)-2-(4-Bromo-3-fluorophenyl)cyclopropane-1-carboxylic acid; propan-2-amine salt

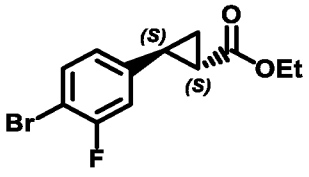


A mixture of ethyl 2-(4-bromo-3-fluorophenyl)cyclopropane-1-carboxylate [1202246-03-4] (184 g, 639 mmol) and lithium hydroxide monohydrate (80.5 g, 1.92 mol) in THF (1.6 L) and H_2O (800 mL) was stirred at rt for 18 h. Brine and a 3M aqueous solution of HCl (~1 L) were added until the pH was acid and the mixture was diluted with EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc (3 times). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated in vacuo. The crude mixture was purified via chiral SFC (Stationary phase: Chiralpack IC 5 µm 250*50

mm, Mobile phase: 85% CO_2, 15% (50:50 MeOH / *i*-PrOH (+1% *i*-$PrNH_2$)) to give intermediates **A2.*i*-PrNH2** (90.2 g, 44%) and **A1.*i*-PrNH2** (96.0 g, 47%).

Intermediate A3

Ethyl (1*S*,2*S*)-2-(4-bromo-3-fluorophenyl)cyclopropane-1-carboxylate

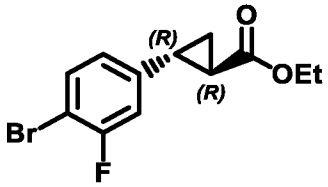


A3

Sulfuric acid (83.0 mL, 1.56 mol) was added to a solution of intermediate **A1.*i*-PrNH2** (96.0 g, 302 mmol) in EtOH (1 L) (exothermic reaction). The reaction mixture was stirred at rt for 18 h. A saturated aqueous solution of $NaHCO_3$, water and EtOAc were added. The layers were separated and the aqueous phase was extracted with EtOAc (twice). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated in vacuo to give intermediate **A3** (91.1 g, 99%) as a yellow oil.

Intermediate A4

Ethyl (1*R*,2*R*)-2-(4-bromo-3-fluorophenyl)cyclopropane-1-carboxylate

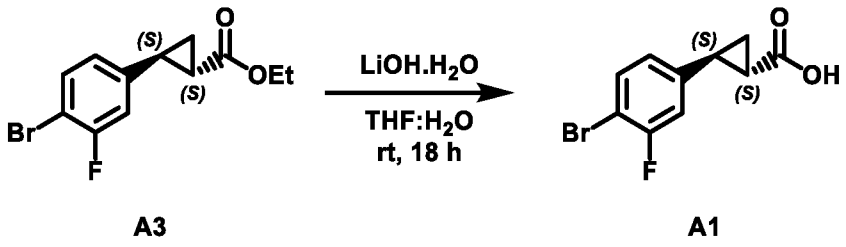


A4

Sulfuric acid (0.86 mL, 16.2 mmol) was added to a solution of intermediate **A2.*i*-PrNH2** (1.00 g, 3.14 mmol) in EtOH (12 mL). The reaction mixture was stirred at rt for 18 h. Water, a saturated aqueous solution of $NaHCO_3$ and EtOAc were added. The layers were separated and the aqueous phase was extracted with EtOAc (3 times). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated in vacuo to give intermediate **A4** (850 mg, 94%) as a yellow oil.

B.1.1.2. Synthesis of Intermediate A1

(1*S*,2*S*)-2-(4-Bromo-3-fluorophenyl)cyclopropane-1-carboxylic acid

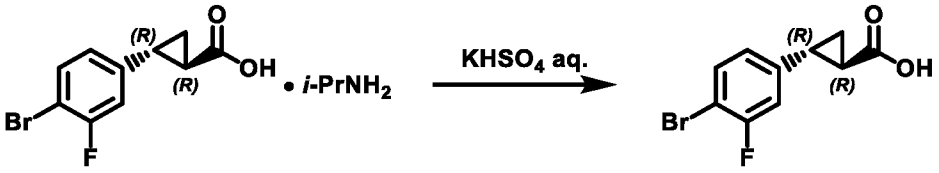


A3 **A1**

Lithium hydroxide monohydrate (833 mg, 19.9 mmol) was added to a solution of intermediate **A3** (1.00 g, 3.31 mmol) in THF (10 mL) and H_2O (5 mL). The reaction mixture was stirred at rt for 18 h. The reaction mixture was diluted with brine and EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc (twice). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated in vacuo to give intermediate **A1** (950 mg, quant., 92% purity).

B.1.1.3. Synthesis of Intermediate A2

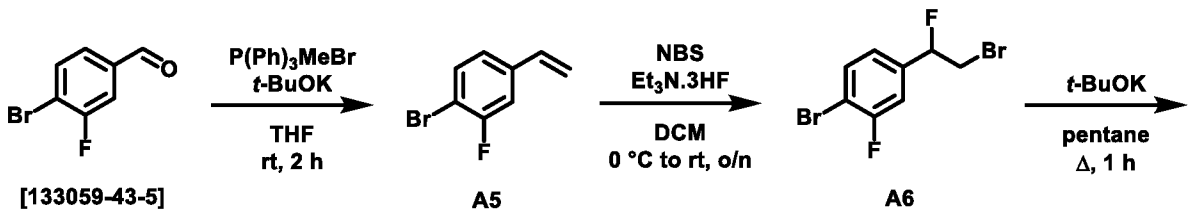
(1*R*,2*R*)-2-(4-Bromo-3-fluorophenyl)cyclopropane-1-carboxylic acid



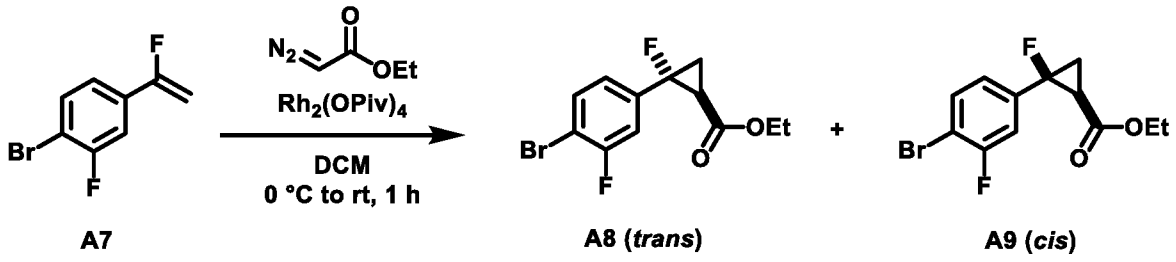
A2 • *i*-PrNH$_2$ **A2**

Intermediate **A2.*i*-PrNH$_2$** was washed with a 10% aqueous solution of $KHSO_4$ to afford intermediate **A2**.

B.1.1.4. Synthesis of Intermediates A8 and A9

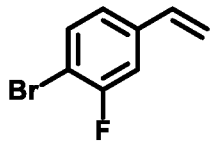


[133059-43-5] A5 A6



Intermediate A5

1-Bromo-4-ethenyl-2-fluorobenzene

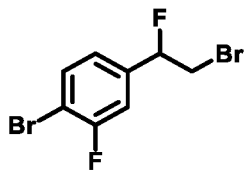


A5

4-Bromo-3-fluorobenzaldehyde [133059-43-5] (1.00 g, 4.93 mmol) was dissolved in anhydrous THF (7 mL) under argon atmosphere. Methyltriphenylphosphonium bromide (1.90 g, 5.32 mmol) and potassium *tert*-butoxide (608 mg, 5.42 mmol) were added and the reaction mixture was stirred at rt for 2 h. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl and concentrated under reduced pressure. The aqueous phase was extracted with DCM. The combined organic extracts were washed with water, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude mixture was purified by flash column chromatography (silica gel, mobile phase: petroleum ether) to afford intermediate **A5** (714 mg, 72%) as a colorless oil.

Intermediate A6

1-Bromo-4-(2-bromo-1-fluoroethyl)-2-fluorobenzene



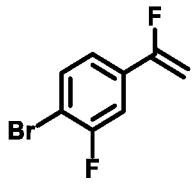
A6

Intermediate **A5** (6.39 g, 31.8 mmol) was dissolved in anhydrous DCM (27 mL) and the solution was cooled to 0°C. NBS (6.22 g, 35.0 mmol) was added and a solution of TREAT-HF (7.8 mL, 47.9 mmol) in DCM (16 mL) was added with a syringe pump over 30 min. The reaction mixture was stirred at 0°C for 15 min and let to warm up to rt. The reaction mixture was stirred overnight. The mixture was poured out into iced water (500 mL) and a 20% aqueous solution of ammonia was added until the pH was slightly basic.

The layers were separated and the aqueous phase was extracted with DCM (4 times). The combined organic extracts were washed with a 0.1N aqueous solution of HCl (twice) and a 5% aqueous solution of $NaHCO_3$ (twice), dried over $MgSO_4$, filtered and evaporated in vacuo. The crude mixture was purified by flash column chromatography (silica gel, mobile phase: pentane) to afford intermediate **A6** (3.61 g, 38%) as a colorless oil.

Intermediate A7

1-Bromo-2-fluoro-4-(1-fluoroethenyl)benzene



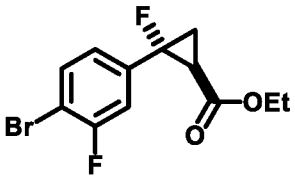
A7

Intermediate **A6** (1.17 g, 3.90 mmol) was dissolved in pentane (24 mL). Potassium *tert*-butoxide (875 mg, 7.80 mmol) was added and the reaction mixture was stirred under reflux for 1 h. The mixture was poured out into an ice / water mixture. The layers were separated and the aqueous phase was extracted with pentane. The combined organic extracts were washed with a 5% aqueous solution of $NaHCO_3$, a 0.05N aqueous solution of HCl and water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The mixture was filtered over silica gel eluting with pentane to afford intermediate **A7** (690 mg, 81%) as a colorless oil.

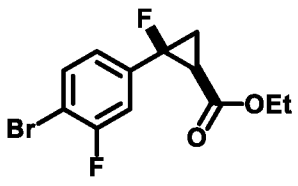
Intermediates A8 and A9

A8: Ethyl *trans*-2-(4-bromo-3-fluorophenyl)-2-fluorocyclopropane-1-carboxylate

A9: Ethyl *cis*-2-(4-bromo-3-fluorophenyl)-2-fluorocyclopropane-1-carboxylate



A8 (*trans*)



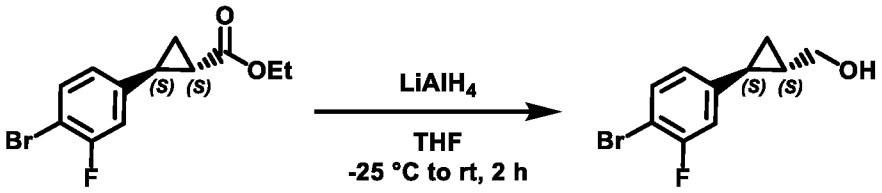
A9 (*cis*)

A solution of intermediate **A7** (82.3 mg, 0.38 mmol) in anhydrous DCM (1 mL) and under an argon atmosphere was cooled to 0°C. Rhodium (II) trimethylacetate, dimer (4.50 mg, 7.50 µmol) was added and a solution of ethyl diazoacetate (solution containing 11 wt. % DCM, 65.2 mg, 0.56 mmol) in anhydrous DCM (1 mL) was added with a syringe pump at a rate of 8 mL/h. Once the addition complete, the reaction mixture was stirred for another 1

h. The reaction mixture was cooled to 0°C and a solution of ethyl diazoacetate (solution containing 11 wt. % DCM, 65.2 mg, 0.56 mmol) in anhydrous DCM (1 mL) was added under the same conditions. Once the addition complete, the reaction mixture was stirred for another 1 h. The reaction mixture was concentrated under reduced pressure. The crude mixture was purified by column chromatography (silica gel, mobile phase gradient: petroleum ether / DCM from 80:20 to 70:30) to give intermediate **A8** (57 mg, 50%) and **A9** (44 mg, 37%) as colorless oils.

B.1.1.5. Synthesis of Intermediate A10

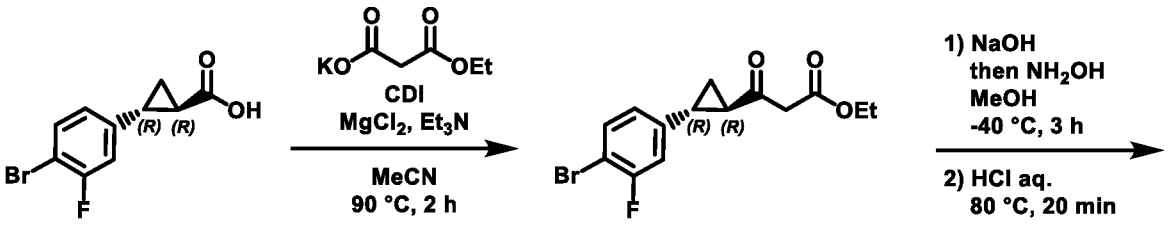
[(1*S*,2*S*)-2-(4-Bromo-3-fluorophenyl)cyclopropyl]methanol



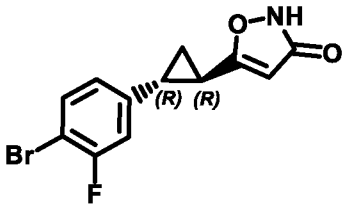
A3 **A10**

Lithium aluminium hydride (1.0 M in THF, 1.59 mL, 1.59 mmol) was added to a solution of intermediate **A3** (400 mg, 1.32 mmol) in anhydrous THF (8 mL) at -25°C and under nitrogen atmosphere. The reaction mixture was gradually warmed to rt and stirred for 2 h. The reaction mixture was cooled to 0°C and a 10% aqueous solution of NaOH was carefully added. The resulting mixture was warmed to rt. The layers were separated and the aqueous phase was extracted with DCM. The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was evaporated in vacuo. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 24 g GraceResolv™, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 90:10 to 80:20) to give intermediate **A10** (167 mg, 51%).

B.1.1.6. Synthesis of Intermediate A12



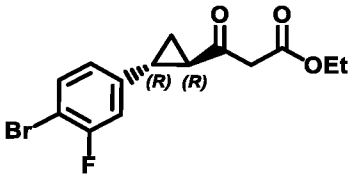
A2 **A11**



A12

Intermediate A11

Ethyl 3-[(1*R*,2*R*)-2-(4-bromo-3-fluorophenyl)cyclopropyl]-3-oxopropanoate

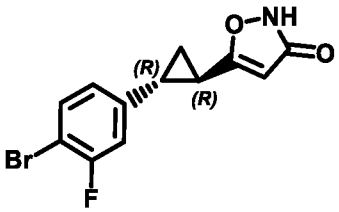


A11

A mixture of intermediate **A2** (1.00 g, 3.86 mmol) and CDI (688 mg, 4.25 mmol) in MeCN (10 mL) was stirred at rt for 1 h. This mixture was added to a mixture of ethyl potassium malonate (1.31 g, 7.72 mmol), magnesium chloride (919 mg, 9.65 mmol) and Et_3N (1.60 mL, 11.5 mmol) in MeCN (10 mL) that was stirred at rt for 1 h. The resulting reaction mixture was stirred at 90°C for 2 h. The reaction mixture was diluted with water and EtOAc and filtered over a pad of Celite®. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated in vacuo. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 120 g Grace®, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 100:0 to 70:30) to afford intermediate **A11** (1 g, 79%) as a white solid.

Intermediate A12

5-[(1*R*,2*R*)-2-(4-Bromo-3-fluorophenyl)cyclopropyl]-2,3-dihydro-1,2-oxazol-3-one



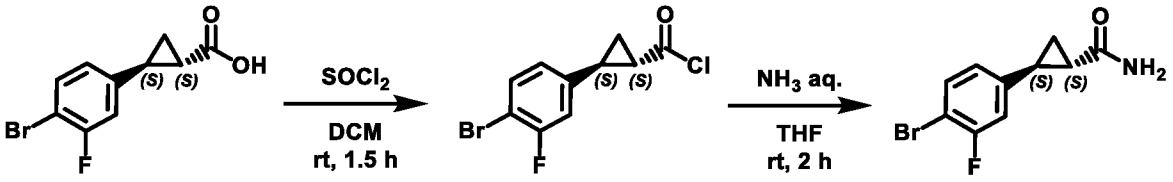
A12

Sodium hydroxide (1.0 M in H_2O, 3.10 mL, 3.10 mmol) was added slowly to a solution of intermediate **A11** (1.00 g, 3.04 mmol) in MeOH (28 mL) at -40°C. The reaction mixture was stirred at this temperature for 20 min. Hydroxylamine (50 wt. % in H_2O, 186 µL, 3.04

mmol) was added slowly and the reaction mixture was stirred at -40°C for 3 h. Hydrochloric acid (37% in H_2O, 7.60 mL, 91.1 mmol) was added and the reaction mixture was stirred at 80°C for 20 min. The solvent (MeOH) was evaporated in vacuo and the residue was diluted with DCM and water. The layers were separated and the aqueous phase was extracted. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 120 g Grace®, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 100:0 to 30:70) to give intermediate **A12** (272 mg, 30%) as a white solid.

B.1.1.7. Synthesis of Intermediate A14

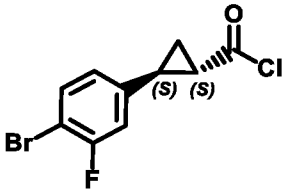
Method A



A1 **A13** **A14**

Intermediate A13

(1*S*,2*S*)-2-(4-Bromo-3-fluorophenyl)cyclopropane-1-carbonyl chloride

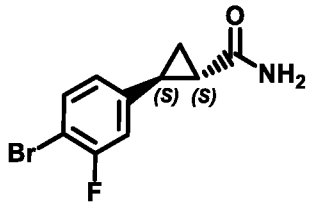


A13

Thionyl chloride (0.27 mL, 3.71 mmol) was added to a solution of intermediate **A1** (533 mg, 1.85 mmol, 90% purity) in DCM (18 mL). The reaction mixture was stirred at rt for 90 min. The mixture was evaporated in vacuo to afford intermediate **A13** (514 mg, quant.).

*Intermediate **A14***

(1*S*,2*S*)-2-(4-Bromo-3-fluorophenyl)cyclopropane-1-carboxamide

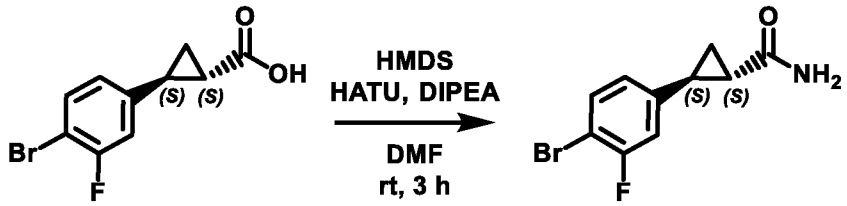


A14

Ammonia (28% in H_2O, 18.0 mL, 266 mmol) was added to a solution of intermediate **A13** (514 mg, 1.85 mmol) in THF (18 mL). The reaction mixture was stirred at rt for 2 h. Brine, a 3.0 M aqueous solution of NaOH and EtOAc were added. The layers were separated and the aqueous phase was extracted with EtOAc (twice). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated in vacuo to afford intermediate **A14** (440 mg, 74%, 80% purity).

Method B

(1*S*,2*S*)-2-(4-Bromo-3-fluorophenyl)cyclopropane-1-carboxamide

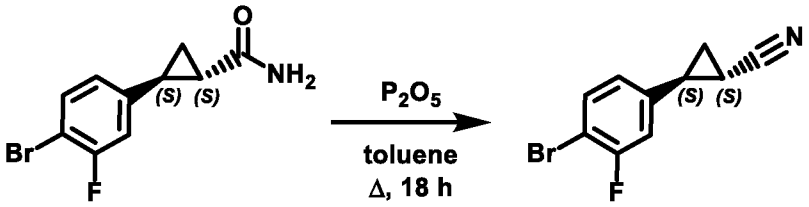


A1 **A14**

HATU (3.74 g, 9.84 mmol) was added portionwise to a mixture of intermediate **A1** (1.70 g, 6.56 mmol), HMDS (13.9 mL, 65.6 mmol) and DIPEA (2.26 mL, 13.1 mmol) in DMF (30 mL). The reaction mixture was stirred at rt for 3 h. The reaction mixture was diluted with brine. The aqueous phase was extracted with EtOAc (twice). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 80 g GraceResolv™, dry loading (SiOH), mobile phase: DCM / MeOH 98:2) to give intermediate **A14** (2.9 g, quant., 59% purity) as a gum.

B.1.1.8. ***Synthesis of Intermediate A15***

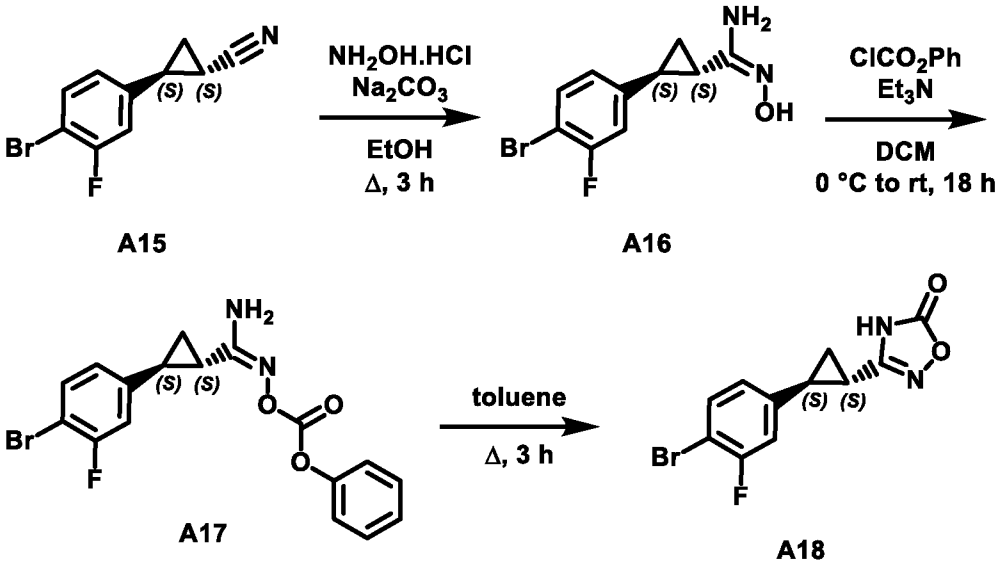
(1*S*,2*S*)-2-(4-Bromo-3-fluorophenyl)cyclopropane-1-carbonitrile



A14 **A15**

A sealed tube was charged with intermediate **A14** (440 mg, 1.36 mmol, 80% purity), anhydrous toluene (13 mL) and phosphorous pentoxide (0.97 g, 6.82 mmol). The reaction mixture was stirred under reflux for 18 h. The reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$, diluted with EtOAc and filtered. The layers were separated and the aqueous phase was extracted with a solution of EtOAc and MeOH (9:1) (twice). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated in vacuo. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 24 g GraceResolv™, dry loading (SiOH), mobile phase gradient: heptane / EtOAc from 90:10 to 70:30) to give intermediate **A15** (185 mg, 55%).

B.1.1.9. ***Synthesis of Intermediate A18***

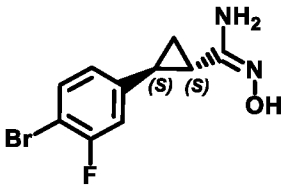


A15 **A16**

A17 **A18**

*Intermediate **A16***

(E)-(1*S*,2*S*)-2-(4-Bromo-3-fluorophenyl)-N'-hydroxycycloprop-1-carboximidamide

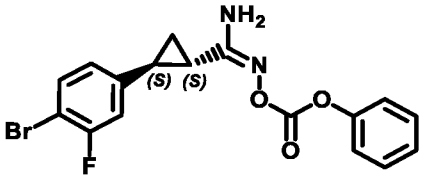


A16

Hydroxylamine hydrochloride (261 mg, 3.75 mmol) was added to a suspension of intermediate **A15** (300 mg, 1.25 mmol) and sodium carbonate (530 mg, 5.00 mmol) in EtOH (15 mL). The reaction mixture was stirred under reflux for 3 h. The mixture was evaporated in vacuo. The residue was diluted with water and DCM. The layers were separated and the aqueous phase was extracted with DCM (twice). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated in vacuo to afford intermediate **A16** (332 mg, 97%).

*Intermediate **A17***

(*E*)-{Amino[(1*S*,2*S*)-2-(4-bromo-3-fluorophenyl)cyclopropyl]methylidene}amino phenyl carbonate

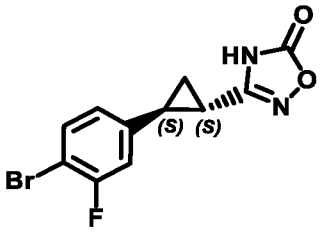


A17

Phenyl chloroformate (228 µL, 1.82 mmol) was added to a mixture of intermediate **A16** (332 mg, 1.22 mmol) and Et_3N (507 µL, 3.65 mmol) in DCM (15 mL) at 0°C. The reaction mixture was stirred at rt for 18 h. The reaction mixture was diluted with water and DCM. The layers were separated and the aqueous phase was extracted with DCM (twice). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated in vacuo. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 40 g GraceResolv™, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 90:10 to 70:30) to afford intermediate **A17** (347 mg, 73%).

*Intermediate **A18***

3-[(1*S*,2*S*)-2-(4-Bromo-3-fluorophenyl)cyclopropyl]-4,5-dihydro-1,2,4-oxadiazol-5-one

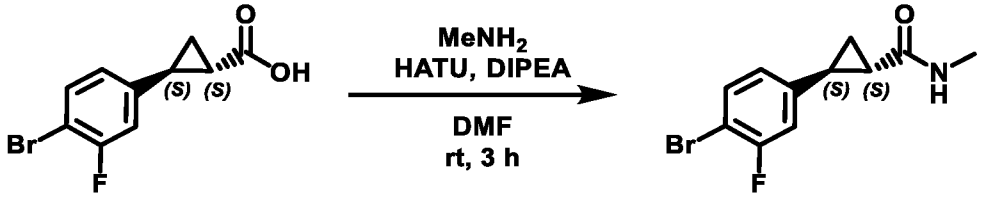


A18

In a sealed tube a solution of intermediate **A17** (347 mg, 0.88 mmol) in anhydrous toluene (10 mL) was stirred under reflux for 3 h. The mixture was evaporated in vacuo. The residue was diluted with DCM. The precipitate was filtered off and dried under vacuum to give intermediate **A18** (140 mg, 53%) as a white solid.

B.1.1.10. Synthesis of Intermediate A19

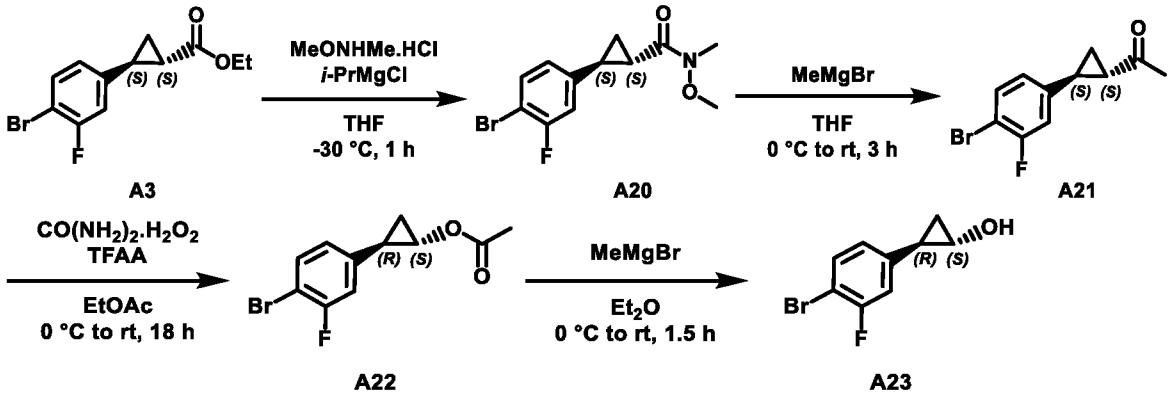
(1*S*,2*S*)-2-(4-Bromo-3-fluorophenyl)-N-methylcyclopropane-1-carboxamide



A1 **A19**

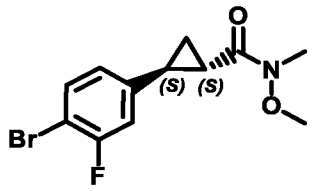
HATU (1.89 g, 4.98 mmol) was added portionwise to a mixture of intermediate **A1** (860 mg, 3.32 mmol), methylamine (2.0 M in THF, 16.6 mL, 33.2 mmol) and DIPEA (1.14 mL, 6.64 mmol) in DMF (15 mL). The reaction mixture was stirred at rt for 3 h. Brine was added and the aqueous phase was extracted with EtOAc (twice). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 80 g GraceResolv™, dry loading (SiOH), mobile phase: DCM / MeOH 98:2) to give intermediate **A19** (1.00 g, quant., 90% purity) as a white solid.

B.1.1.11. Synthesis of Intermediate A23



Intermediate A20

(1*S*,2*S*)-2-(4-Bromo-3-fluorophenyl)-N-methoxy-N-methylcyclopropane-1-carboxamide

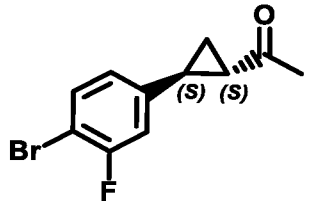


A20

Under nitrogen atmosphere a mixture of intermediate **A3** (60 mg, 0.20 mmol) and N,O-dimethylhydroxylamine hydrochloride (58.1 mg, 0.60 mmol) was stirred at -30°C. Isopropylmagnesium chloride (2.0 M in THF, 0.60 mL, 1.20 mmol) was added. The reaction mixture was stirred at -30°C for 1 h. The reaction was quenched by the addition of a 1N aqueous solution of HCl and diluted with EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated in vacuo to afford intermediate **A20** (58 mg, 97%) as a colorless oil.

Intermediate A21

1-[(1*S*,2*S*)-2-(4-Bromo-3-fluorophenyl)cyclopropyl]ethan-1-one

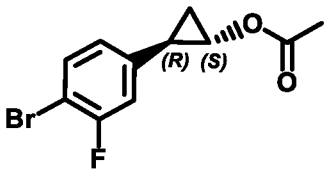


A21

Under nitrogen atmosphere methylmagnesium bromide (3.0 M in Et_2O, 6.62 mL, 19.9 mmol) was added to a solution of intermediate **A20** (3.00 g, 9.93 mmol) in THF (12 mL) at 0°C. The reaction mixture was stirred at rt for 3 h. The reaction was quenched by the addition of an aqueous solution of NH_4Cl and diluted with EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated in vacuo to afford intermediate **A21** (2.55 g, quant.) as a colorless oil.

Intermediate A22

(1*S*,2*R*)-2-(4-Bromo-3-fluorophenyl)cyclopropyl acetate

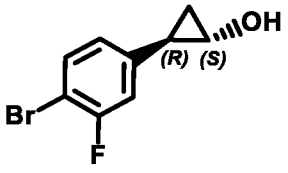


A22

Trifluoroacetic anhydride (5.31 mL, 38.2 mmol) was added dropwise to a mixture of intermediate **A21** (2.55 g, 9.92 mmol) and carbamide peroxide [124-43-6] (3.59 g, 38.2 mmol) in EtOAc (27 mL) at 0°C. The reaction mixture was stirred at rt for 18 h. The reaction was quenched by the addition of an aqueous solution of $NaHCO_3$. The layers were separated and the organic phase was washed with an aqueous solution of $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 80 g GraceResolv™, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 99:1 to 60:40) to afford intermediate **A22** (1.83 g, 67%).

Intermediate A23

(1*S*,2*R*)-2-(4-Bromo-3-fluorophenyl)cyclopropan-1-ol

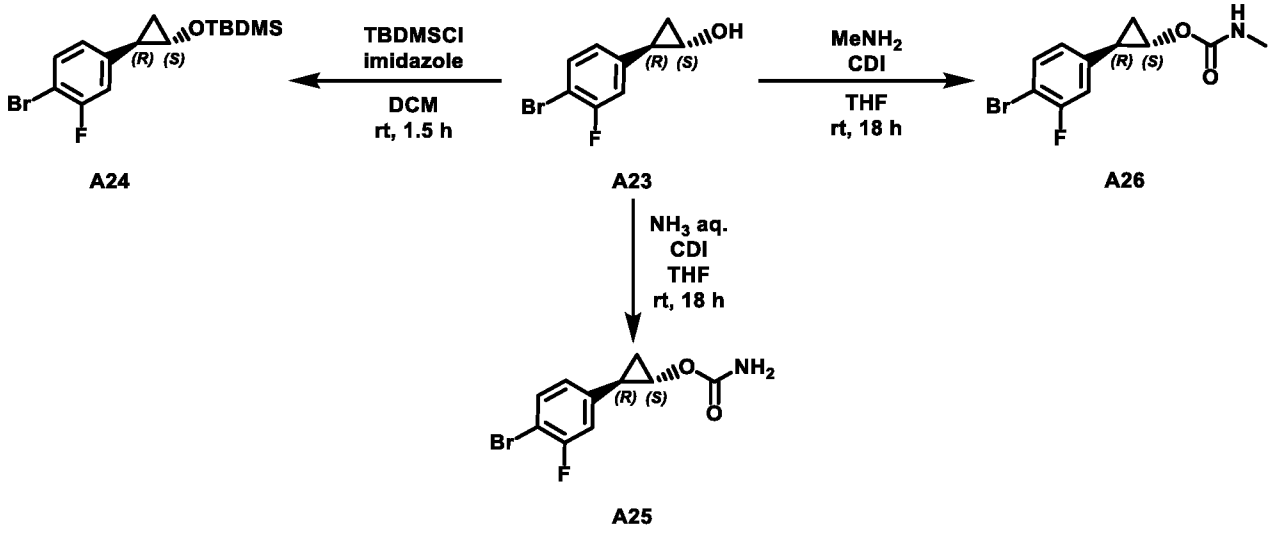


A23

Methylmagnesium bromide (3.0 M in Et_2O, 2.44 mL, 7.32 mmol) was added dropwise to a solution of intermediate **A22** (1.00 g, 3.66 mmol) in Et_2O (20 mL) at 0°C. The reaction mixture was stirred at rt for 1.5 h. The reaction was quenched by the dropwise addition of a 10% aqueous solution of NH_4Cl. The layers were separated and the aqueous phase was

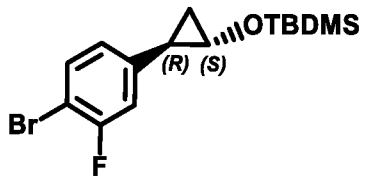
extracted with EtOAc (3 times). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 24 g GraceResolv™, liquid injection, mobile phase gradient: heptane / EtOAc from 99:1 to 50:50) to give intermediate **A23** (600 mg, 71%).

B.1.1.12. Synthesis of Intermediates A24, A25 and A26



Intermediate A24

[(1*S*,2*R*)-2-(4-Bromo-3-fluorophenyl)cyclopropoxy](*tert*-butyl)dimethylsilane

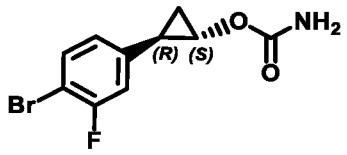


A24

Tert-butyldimethylsilyl chloride (73.1 mg, 0.49 mmol) and imidazole (51.9 mg, 0.76 mmol) were added to a solution of intermediate **A23** (80.0 mg, 0.35 mmol) in DCM (4.3 mL) under nitrogen atmosphere. The reaction mixture was stirred at rt for 1.5 h. The reaction mixture was diluted with DCM and water. The layers were separated and the aqueous phase was extracted with DCM (twice). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford intermediate **A24** (120 mg, quant.).

Intermediate A25

(1*S*,2*R*)-2-(4-Bromo-3-fluorophenyl)cyclopropyl carbamate

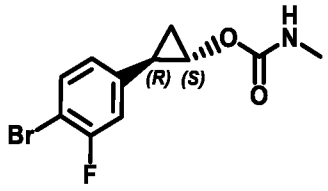


A25

In a sealed tube CDI (140 mg, 0.87 mmol) was added to a solution of intermediate **A23** (100 mg, 433 µmol) in anhydrous THF (1.6 mL). The reaction mixture was stirred at rt for 1 h. Ammonia (28% in H_2O, 1.6 mL, 23.9 mmol) was added and the reaction mixture was stirred at rt for 18 h. The reaction mixture was diluted with water, brine and EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc (twice). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 12 g GraceResolv™, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 99:1 to 50:50) to give intermediate **A25** (78 mg, 66%).

Intermediate A26

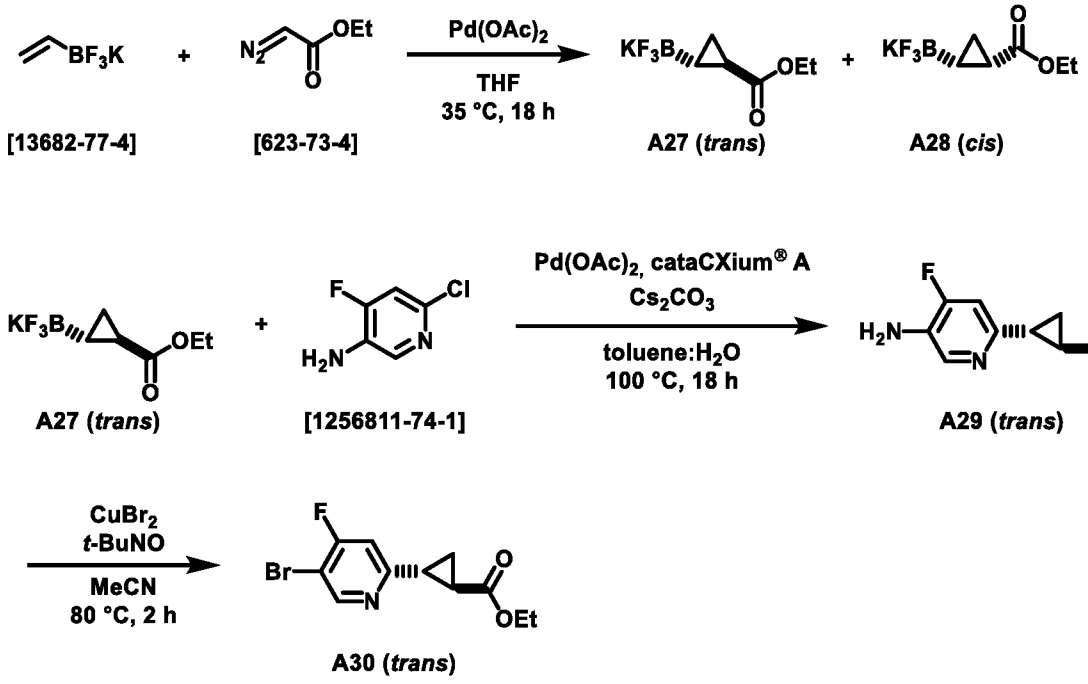
(1*S*,2*R*)-2-(4-Bromo-3-fluorophenyl)cyclopropyl N-methylcarbamate



A26

In a sealed tube CDI (140 mg, 0.87 mmol) was added to a solution of intermediate **A23** (100 mg, 0.43 mmol) in anhydrous THF (1.6 mL). The reaction mixture was stirred at rt for 1 h. Methylamine (2.0 M in THF, 1.10 mL, 2.20 mmol) was added and the reaction mixture was stirred at rt for 18 h. The reaction mixture was diluted with water, brine and EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc (twice). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 12 g GraceResolv™, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 99:1 to 50:50) to afford intermediate **A26** (115 mg, 92%).

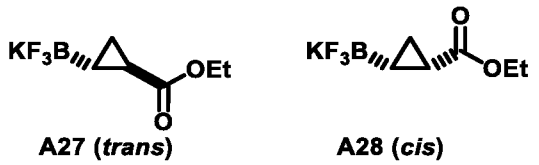
B.1.1.13. ***Synthesis of Intermediate A30***



Intermediates A27 et A28

A27: Ethyl *trans* 2-(trifluoro-λ^4-boranyl)cyclopropane-1-carboxylate potassium

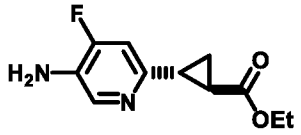
A28: Ethyl *cis* 2-(trifluoro-λ^4-boranyl)cyclopropane-1-carboxylate potassium



Potassium vinyltrifluoroborate [13682-77-4] (2.00 g, 14.9 mmol) was solubilized in THF (20.5 mL). Palladium acetate (33.5 mg, 149 µmol) was added. The mixture was stirred at 35 °C and a solution of ethyl diazoacetate [623-73-4] (2.0 mL, 16.4 mmol) in THF (2 mL) was added with a syringe pump over 4 h. The reaction mixture was stirred at 35 °C for 18 h. The reaction mixture was cooled to rt and diluted with heptane. The mixture was stirred for 30 min and filtered. The gum was crystallized from acetone (20 mL) at -18 °C and the solid was filtered off to afford intermediate **A28** (*cis*:*trans* 80:20) (520 mg, 16%) as a grey solid. The filtrate was treated with activated charcoal, filtered and concentrated to dryness. The product was taken-up in EtOH (20 mL) at 50 °C and the gummy product was filtered to afford intermediate **A27** (*cis*:*trans* 14:86) (1.83 g, 56%) as a white solid.

*Intermediate **A29***

Ethyl *trans*-2-(5-amino-4-fluoropyridin-2-yl)cyclopropane-1-carboxylate

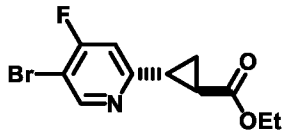


A29 (*trans*)

To a mixture of cataCXium® A (147 mg, 409 µmol), intermediate **A27** (751 mg, 3.41 mmol), 6-chloro-4-fluoropyridin-3-amine [1256811-74-1] (250 mg, 1.71 mmol) and palladium acetate (61.3 mg, 273 µmol) in toluene (19 mL) and H_2O (1.9 mL) under a nitrogen atmosphere was added cesium carbonate (1.67 g, 5.12 mmol). The reaction mixture was stirred at 100 °C for 18 h. The reaction mixture was diluted with water and EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc (twice). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was evaporated in vacuo. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 24 g Grace®, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 100:0 to 20:80) to afford intermediate **A29** (77 mg, 20%).

*Intermediate **A30***

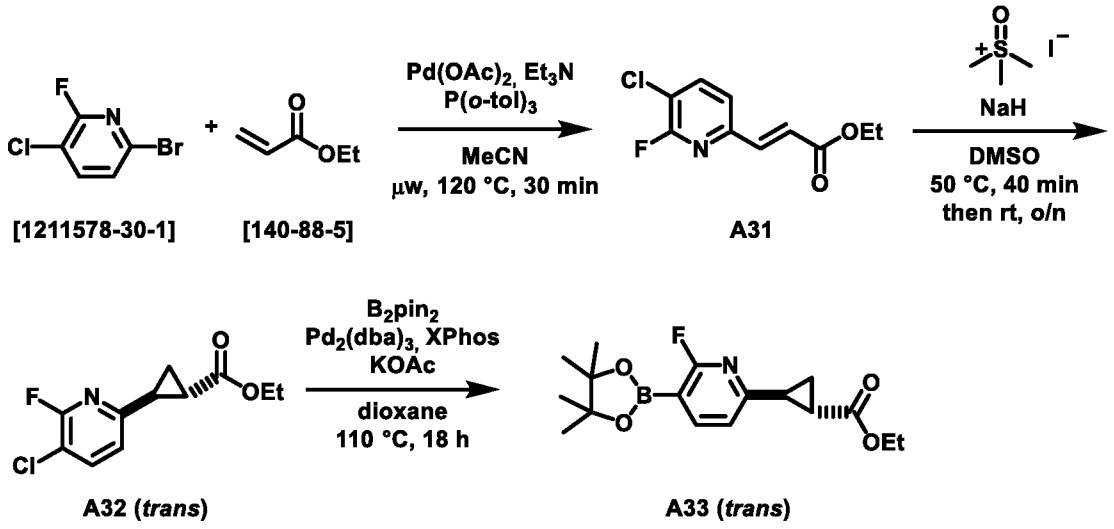
Ethyl *trans*-2-(5-bromo-4-fluoropyridin-2-yl)cyclopropane-1-carboxylate



A30 (*trans*)

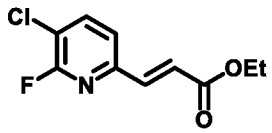
A mixture of intermediate **A29** (103 mg, 459 µmol), copper(II) bromide (123 mg, 0.55 mmol) and *tert*-butyl nitrite (82.0 µL, 689 µmol) in MeCN (6 mL) was stirred at 80 °C for 2 h. The reaction mixture was diluted with water and EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was evaporated in vacuo. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 12 g Grace®, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 100:0 to 50:50) to afford intermediate **A30** (84 mg, 63%).

B.1.1.14. Synthesis of Intermediate A33



Intermediate A31

Ethyl (2*E*)-3-(5-chloro-6-fluoropyridin-2-yl)prop-2-enoate



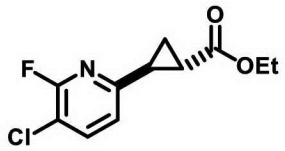
A31

The reaction was performed on two batches of 500 mg of 6-bromo-3-chloro-2-fluoropyridine [1211578-30-1] that were combined for treatment and purification.

A mixture of 6-bromo-3-chloro-2-fluoropyridine [1211578-30-1] (500 mg, 2.38 mmol), ethyl acrylate [140-88-5] (1.55 mL, 14.3 mmol), palladium acetate (53.3 mg, 0.24 mmol), tri(o-tolyl)phosphine (145 mg, 475 µmol) and Et_3N (2.0 mL, 14.3 mmol) in MeCN (8.4 mL) was heated at 120 °C using a single mode microwave (Biotage® Initiator EXP 60) with a power output ranging from 0 to 400 W for 30 min. The two batches were combined and the solvent was evaporated to dryness. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 40 g GraceResolv™, dry loading (Celite®), mobile phase gradient: heptane / EtOAc from 100:0 to 80:20) to afford intermediate **A31** (972 mg, 89%) as a white solid.

*Intermediate **A32***

Ethyl *trans* 2-(5-chloro-6-fluoropyridin-2-yl)cyclopropane-1-carboxylate

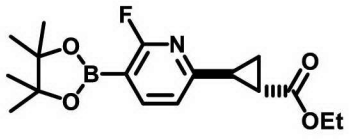


A32 (*trans*)

Under nitrogen atmosphere sodium hydride (60% dispersion in oil, 111 mg, 2.78 mmol) was charged at rt in a round bottom flask. DMSO (10 mL) was added. Trimethylsulfoxonium iodide (706 mg, 3.21 mmol) was added portionwise. The resulting mixture was stirred at 50 °C for 40 min and cooled to rt. A solution of intermediate **A31** (491 mg, 2.14 mmol) in DMSO (7 mL) was added over 30 sec. The reaction mixture was stirred at rt overnight. The reaction was quenched by the dropwise addition of water. The mixture was cooled. Brine, a 1N aqueous solution of HCl and EtOAc were added. The aqueous phase was extracted with EtOAc (twice). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated in vacuo. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 24 g GraceResolv™, dry loading (Celite®), mobile phase gradient: heptane / EtOAc from 100:0 to 90:10). The residue (232 mg) was purified by reverse phase (spherical C18, 25 µm, 40 g YMC-ODS-25, liquid injection (MeCN), mobile phase gradient: (0.2% aq.NH_4HCO_3) / MeCN from 40:60 to 10:90) to afford 143 mg. The residue was purified by achiral SFC (Stationary phase: Whelk-O1 (S,S) 5µm 250*21.2mm, Mobile phase: 96% CO_2, 4% MeOH) to give intermediate **A32** (91 mg, 17%) as a white solid.

*Intermediate **A33***

Ethyl *trans* 2-[6-fluoro-5-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-2-yl]cyclopropane-1-carboxylate



A33 (*trans*)

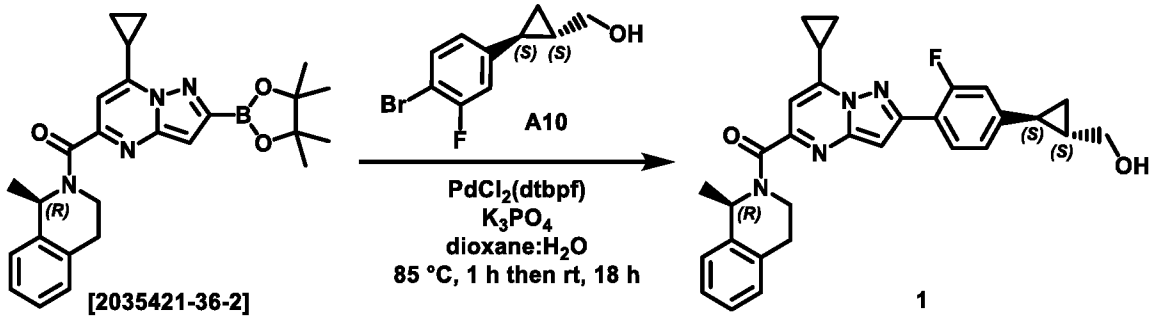
In a sealed tube a mixture of intermediate **A32** (66.0 mg, 271 µmol), bis(pinacolato)diboron (138 mg, 542 µmol) and potassium acetate (53.2 mg, 542 µmol) in 1,4-dioxane (2.7 mL) was purged with nitrogen. Tris(dibenzylideneacetone)dipalladium(0)

(24.8 mg, 27.1 µmol) and XPhos (38.7 mg, 81.3 µmol) were added and the mixture was purged with nitrogen. The reaction mixture was stirred at 110 °C for 18 h. The reaction mixture was diluted with EtOAc and water. The layers were separated and the aqueous phase was extracted with EtOAc (twice). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to afford intermediate **A33** (91 mg, quant.) as a brown oil.

B.1.2. Synthesis of Final Compounds

Compound 1

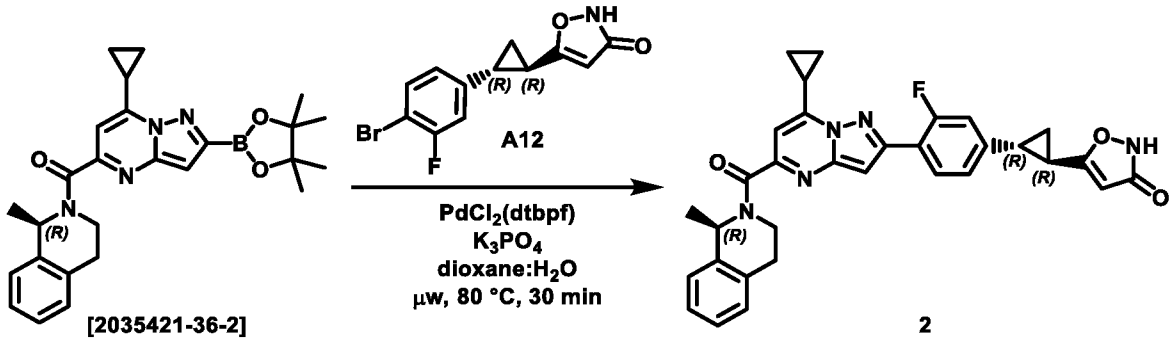
[(1*S*,2*S*)-2-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)cyclopropyl]methanol



A sealed tube was charged with (1*R*)-2-[7-cyclopropyl-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-36-2] (458 mg, 0.62 mmol, 62% purity), intermediate **A10** (167 mg, 0.68 mmol), potassium phosphate tribasic (394 mg, 1.86 mmol), 1,4-dioxane (10 mL) and H_2O (2 mL) and purged with nitrogen for 10 min. [1,1'-Bis(di-*tert*-butylphosphino)ferrocene]dichloro-palladium(II) (40.4 mg, 61.9 µmol) was added and the mixture was purged again with nitrogen for 1 min. The reaction mixture was stirred at 85°C for 1 h and at rt for 18 h. The reaction mixture was filtered over a pad of Celite®, rinsed with EtOAc and brine was added to the filtrate. The layers were separated and the aqueous phase was extracted with EtOAc (twice). The combined organic extracts were washed with a solution of water and brine (1:9) (twice), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 24 g GraceResolv™, liquid injection (DCM), mobile phase gradient: DCM / MeOH from 100:0 to 98:2). The residue was co-evaporated with EtOH (4 times) and dried under high vacuum at 50°C for 18 h to give compound **1** (120 mg, 39%) as an off-white solid.

Compound 2

5-[(1*R*,2*R*)-2-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)cyclopropyl]-2,3-dihydro-1,2-oxazol-3-one

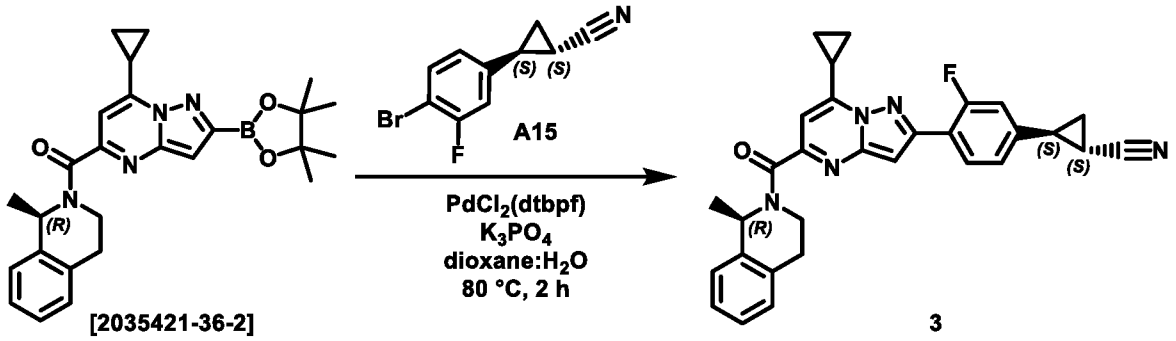


The reaction was performed on two batches of 136 mg.

A sealed tube was charged with a solution of intermediate **A12** (136 mg, 0.46 mmol) in 1,4-dioxane (8.5 mL). (1*R*)-2-[7-Cyclopropyl-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-36-2] (209 mg, 239 µmol, 52% purity), H_2O (2 mL) and potassium phosphate tribasic (329 mg, 1.55 mmol) were added and the mixture was purged with nitrogen. [1,1'-Bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II) (32.7 mg, 50.0 µmol) was added and the mixture was purged again with nitrogen. The reaction mixture was heated at 80°C using a single mode microwave (Biotage® Initiator EXP 60) with a power output ranging from 0 to 400 W for 30 min. The two batches were combined. EtOAc and a 10% aqueous solution of $KHSO_4$ were added. The layers were separated and the organic phase was washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by preparative LC (spherical C18 25 µm, 120 g YMC-ODS-25, dry loading, mobile phase gradient: (0.2% aq.NH_4HCO_3) / MeCN from 65:35 to 25:75). The fractions containing the product were combined and a 10% aqueous solution of $KHSO_4$ and EtOAc were added. The layers were separated and the organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give compound **2** (97 mg, 74%) as a grey solid.

Compound 3

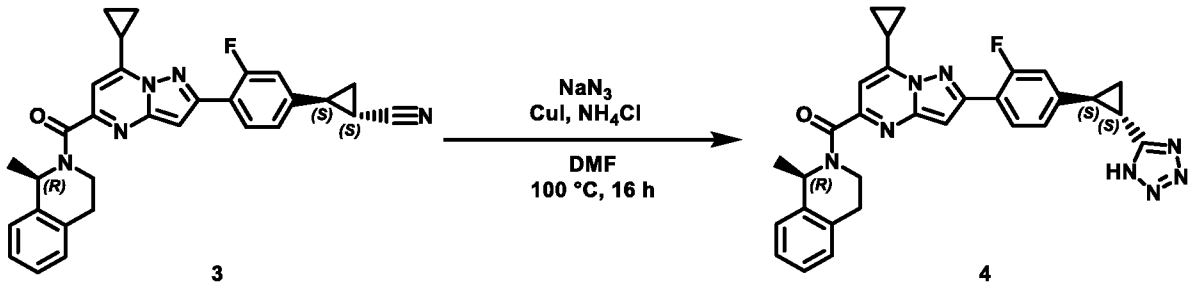
(1*S*,2*S*)-2-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)cyclopropane-1-carbonitrile



A sealed tube was charged with (1*R*)-2-[7-cyclopropyl-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-36-2] (298 mg, 487 µmol, 75% purity), intermediate **A15** (120 mg, 487 µmol, 97% purity), potassium phosphate tribasic (310 mg, 1.46 mmol), 1,4-dioxane (5 mL) and H_2O (1 mL) and purged with nitrogen. [1,1'-Bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II) (31.8 mg, 0.49 mmol) was added and the mixture was purged again with nitrogen. The reaction mixture was stirred at 80°C for 2 h. The reaction mixture was filtered over a pad of Celite®. The filtrate was diluted with EtOAc and brine. The layers were separated and the aqueous phase was extracted with EtOAc (twice). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 24 g GraceResolv™, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 90:10 to 60:40). The residue was co-evaporated with EtOH (twice) and dried under high vacuum at 50°C for 18 h to give compound **3** (225 mg, 94%).

Compound 4

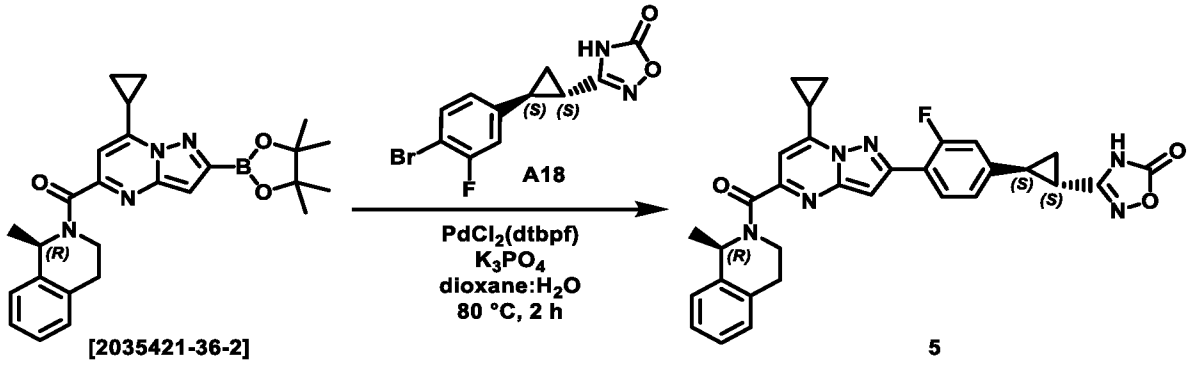
(1*R*)-2-(7-Cyclopropyl-2-{2-fluoro-4-[(1*S*,2*S*)-2-(1H-1,2,3,4-tetrazol-5-yl)cyclopropyl]phenyl}pyrazolo[1,5-a]pyrimidine-5-carbonyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline



In a sealed tube sodium azide (205 mg, 3.15 mmol) was added to a mixture of compound **3** (155 mg, 315 µmol), copper iodide (90.1 mg, 0.47 mmol) and ammonium chloride (50.6 mg, 0.95 mmol) in DMF (5 mL). The reaction mixture was stirred at 100°C for 16 h. EtOAc, 1N aqueous solution of HCl and brine were added. The layers were separated and the aqueous phase was extracted with EtOAc (3 times). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was evaporated in vacuo. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 24 g GraceResolv™, dry loading (SiOH), mobile phase gradient: DCM / MeOH from 100:0 to 93:7). The residue was dissolved in DCM and MeOH (95:5). The organic phase was washed with water (twice), dried over $MgSO_4$, filtered and the solvent was evaporated in vacuo. The residue was co-evaporated with EtOH (4 times) and triturated in EtOH. The solid was filtered off, rinsed with EtOH and dried under high vacuum at 50°C for 18 h to give compound **4** (110 mg, 65%) as a white solid.

Compound 5

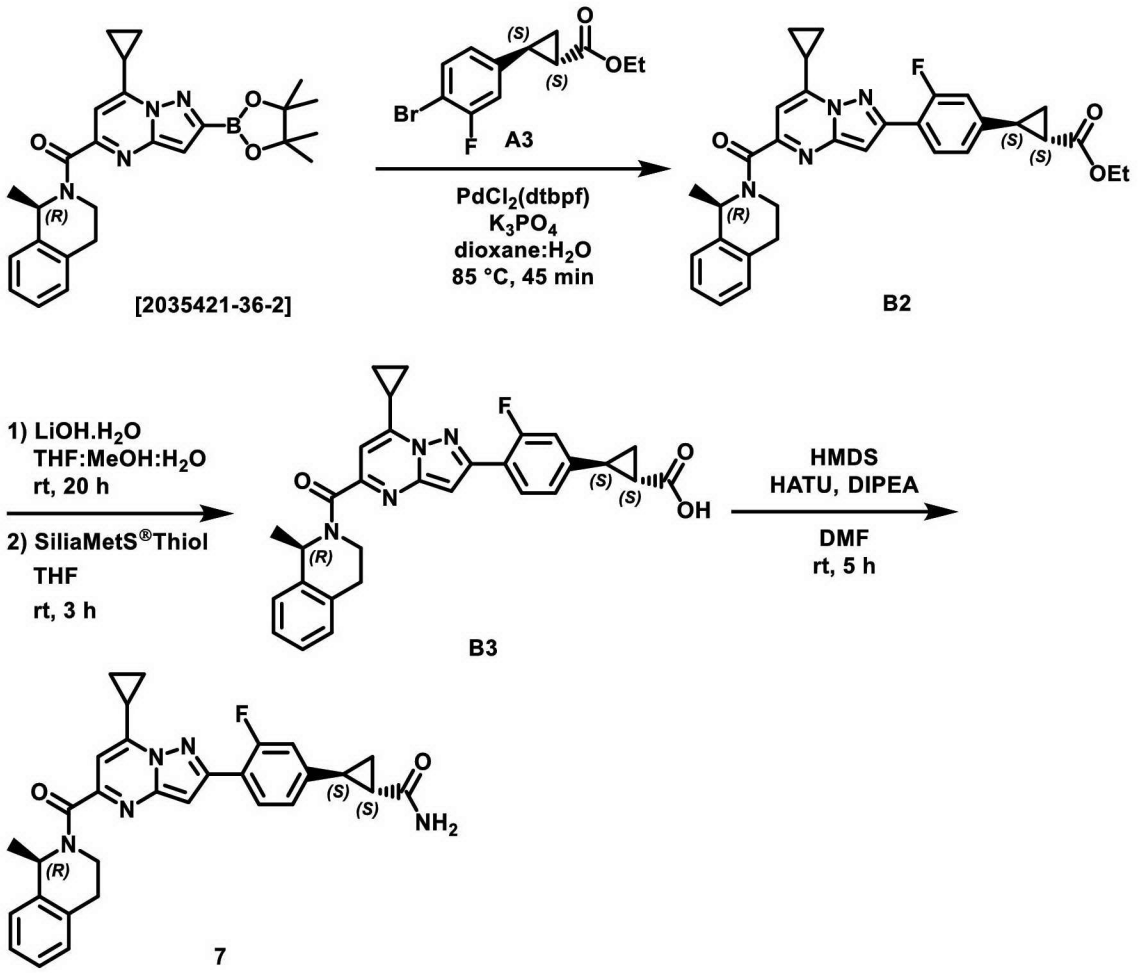
3-[(1*S*,2*S*)-2-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)cyclopropyl]-4,5-dihydro-1,2,4-oxadiazol-5-one



A sealed tube was charged with (1*R*)-2-[7-cyclopropyl-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-36-2] (315 mg, 426 µmol, 62% purity), intermediate **A18** (140 mg, 468 µmol), potassium phosphate tribasic (271 mg, 1.28 mmol), 1,4-dioxane (5 mL) and H_2O (1 mL) and purged with nitrogen for 10 min. [1,1'-Bis(di-*tert*-butylphosphino)ferrocene]dichloro-palladium(II) (27.7 mg, 42.6 µmol) was added and the mixture was purged again with nitrogen for 1 min. The reaction mixture was stirred at 85°C for 1 h. The reaction mixture was filtered over a pad of Celite®, rinsed with EtOAc and brine was added to the filtrate. The layers were separated and the aqueous phase was extracted with EtOAc (twice). The combined organic extracts were washed with water (twice), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by preparative LC

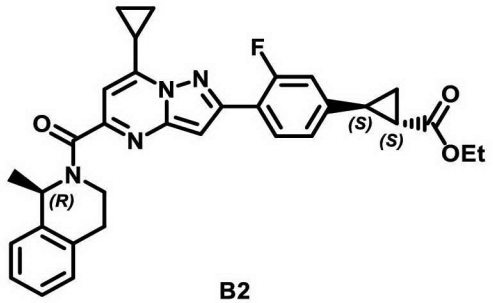
(irregular SiOH, 15-40 µm, 24 g GraceResolv™, dry loading (SiOH), mobile phase gradient: heptane / EtOAc from 90:10 to 60:40). The residue was co-evaporated with EtOH (3 times) and taken up in Et_2O. The resulting solid was filtered off and dried under high vacuum at 50°C for 18 h to give compound **5** (115 mg, 49%) as an off-white solid.

Compound 7



*Intermediate **B2***

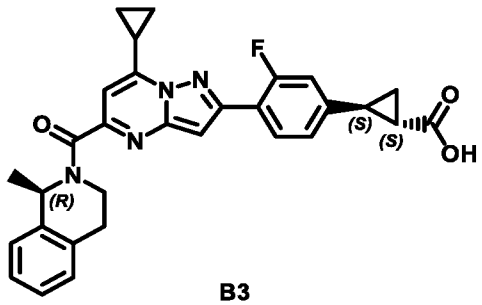
Ethyl (1*S*,2*S*)-2-(4-{7-cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)cyclopropane-1-carboxylate



A mixture of (1*R*)-2-[7-cyclopropyl-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-36-2] (95.0 g, 94.3 mmol, 46% purity), intermediate **A3** (30.7 g, 104 mmol, 97% purity) and potassium phosphate tribasic (60.1 g, 283 mmol) in 1,4-dioxane (800 mL) and H_2O (240 mL) was purged with nitrogen for 20 min. [1,1'-Bis(di-*tert*-butylphosphino)ferrocene]dichloro-palladium(II) (6.15 g, 9.43 mmol) was added and the mixture was purged again with nitrogen for 1 min. The reaction mixture was stirred at 85°C for 45 min. The reaction mixture was cooled down with an ice bath, filtered over a pad of Celite®, rinsed with EtOAc and brine was added to the filtrate. The layers were separated and the aqueous phase was extracted with EtOAc (twice). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 750 g GraceResolv™, dry loading (SiOH), mobile phase gradient: heptane / EtOAc from 90:10 to 80:20) to afford intermediate **B2** (60.7 g, 91%, 76% purity).

*Intermediate **B3***

(1*S*,2*S*)-2-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)cyclopropane-1-carboxylic acid



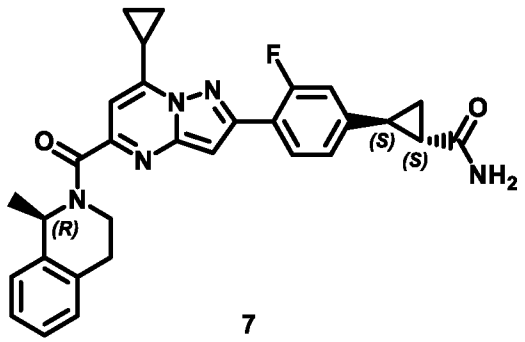
B3

A mixture of intermediate **B2** (52.5 g, 73.1 mmol, 76% purity) and lithium hydroxide monohydrate (9.20 g, 219 mmol) in THF (1 L) and H_2O (0.5 L) was stirred at rt for 20 h. Brine and a 10% aqueous solution of $KHSO_4$ were added until the pH was acid and the mixture was diluted with EtOAc (500 mL). The layers were separated and the aqueous phase was extracted with EtOAc (2 x 500 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated in vacuo. The residue was diluted with THF (450 ml) and SiliaMetS® Thiol (12.2 g, 14.6 mmol, 1.2 mmol/g) was added. The resulting mixture was stirred at rt for 3 h and filtered over a pad of Celite®, rinsed with EtOAc and the filtrate was evaporated to dryness. The product was co-evaporated with MeOH (4 times) and suspended in MeOH (1.69 L). The solution was stirred under reflux until complete solubilization. The suspension was cooled down to -20°C, filtered off, washed with cold

MeOH (-40°C) (4 x 200 mL) and dried under high vacuum at 60°C for 16 h to give compound **B3** (25.8 g, 69%) as a white powder. The filtrate was recrystallized from MeOH to give a second crop of compound **B3** (7 g, 19%).

Compound 7

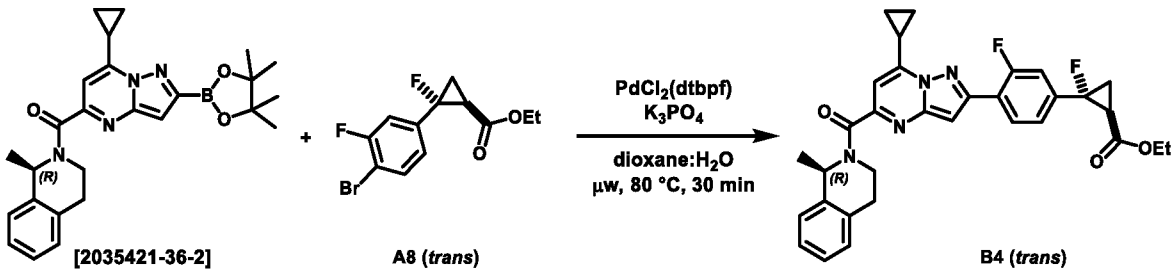
(1*S*,2*S*)-2-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)cyclopropane-1-carboxamide

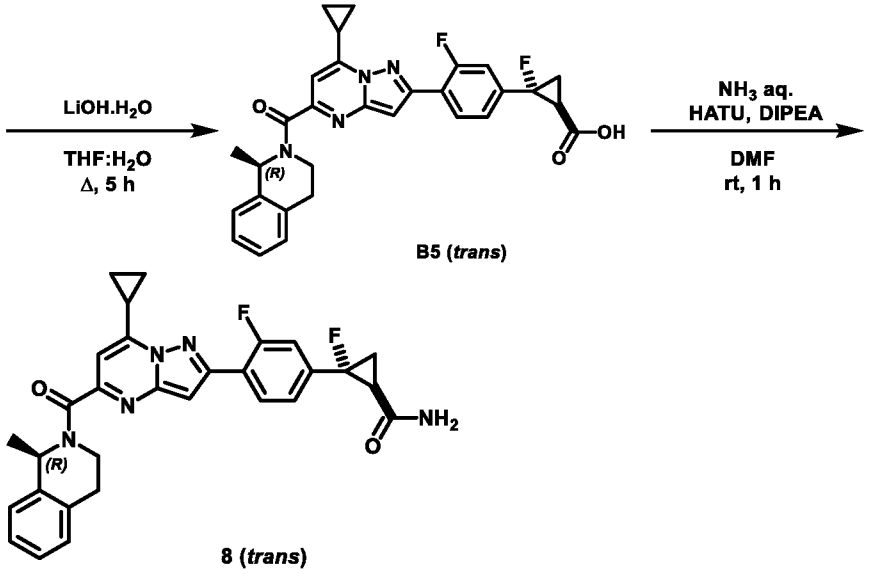


7

HATU (447 mg, 1.18 mmol) was added portionwise to a mixture of intermediate **B3** (200 mg, 0.39 mmol), HMDS (0.83 mL, 3.92 mmol) and DIPEA (0.20 mL, 1.18 mmol) in DMF (5 mL). The reaction mixture was stirred at rt for 5 h. Brine was added and the aqueous phase was extracted with EtOAc (twice). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 24 g GraceResolv™, dry loading (SiOH), mobile phase gradient: DCM / MeOH / aq.NH_3 from 98:2:0.2 to 96:4:0.4). The residue was co-evaporated with MeOH and triturated in MeOH. The solid was filtered off, rinsed with MeOH, and dried under high vacuum at 50°C for 18 h to give compound **7** (140 mg, 70%) as a white solid.

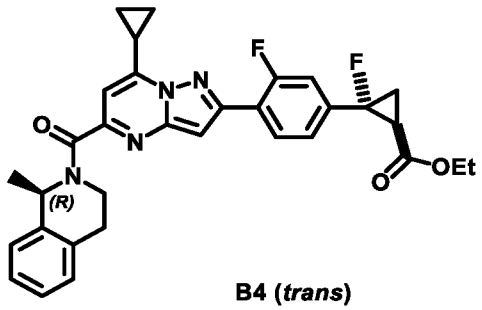
Compound 8





*Intermediate **B4***

Ethyl *trans* -2-{7-cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-2-fluorocyclopropane-1-carboxylate

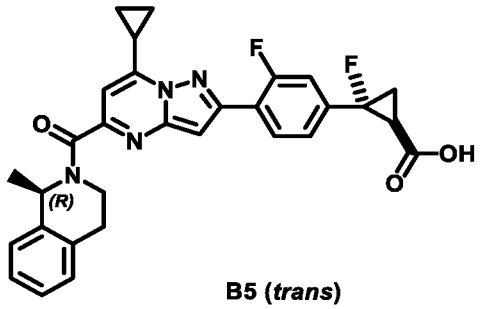


A mixture of (1*R*)-2-[7-cyclopropyl-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-36-2] (0.40 g, 0.54 mmol, 62% purity), intermediate **A8** (182 mg, 0.60 mmol) and potassium phosphate tribasic (345 mg, 1.62 mmol) in 1,4-dioxane (5 mL) and H_2O (1 mL) was purged with nitrogen for 5 min. [1,1'-Bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II) (35.3 mg, 54.1 µmol) was added and the mixture was purged again with nitrogen for 5 min. The reaction mixture was heated at 80°C using a single mode microwave (Anton Paar Monowave 300) with a power output ranging from 0 to 850 W for 30 min. The reaction mixture was diluted with EtOAc and water. The layers were separated and the aqueous phase was extracted with EtOAc (twice). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude mixture was purified by flash chromatography over silica gel (Puriflash Interchim® 25 g, 30 µM, liquid

injection (DCM), mobile phase gradient: heptane / EtOAc from 100:0 to 60:40) to afford intermediate **B4** (0.26 g, 86%) as a beige solid.

*Intermediate **B5***

trans-2-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-2-fluorocyclopropane-1-carboxylic acid

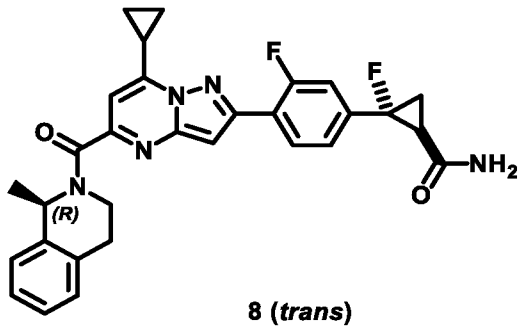


B5 (*trans*)

A mixture of intermediate **B4** (0.25 g, 449 µmol) and lithium hydroxide monohydrate (113 mg, 2.70 mmol) in THF (10 mL) and H_2O (3 mL) was stirred under reflux for 5 h. An aqueous solution of citric acid (518 mg) was added. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness to afford intermediate **B5** (0.21 g, 88%) as a yellow solid.

*Compound **8***

trans-2-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-2-fluorocyclopropane-1-carboxamide

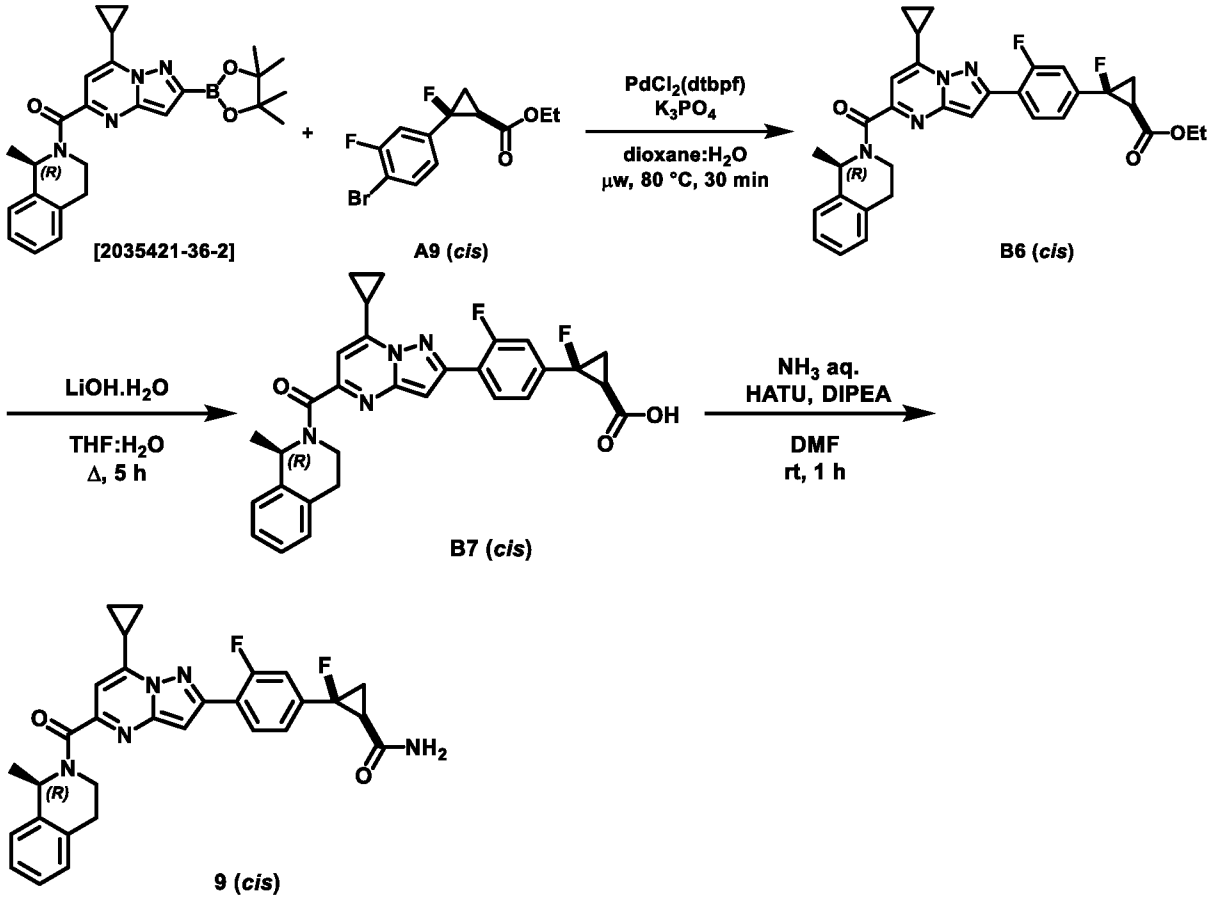


8 (*trans*)

To a solution of intermediate **B5** (0.20 g, 378 µmol) in DMF (5 mL) were added DIPEA (0.2 mL, 1.14 mmol) and HATU (216 mg, 568 µmol). The reaction mixture was stirred at rt for 15 min and ammonia (30% in H_2O, 43 µL, 2.27 mmol) was added dropwise. The reaction mixture was stirred at rt for 1 h. The reaction mixture was diluted with water and EtOAc. The layers were separated and the organic phase was washed with water (3 times)

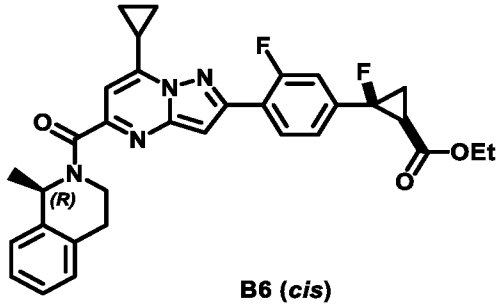
and brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude mixture was purified by flash chromatography over silica gel (Puriflash Interchim® 12 g, 30 µM, liquid injection (DCM), mobile phase gradient: DCM / MeOH from 100:0 to 98:2). The residue (0.12 g) was purified by preparative LC (X-Bridge-C18 5µm, 40 g, mobile phase gradient: (0.5% aq.NH_4HCO_3) / MeCN from 35:65 to 0:100) to give compound **8** (35 mg, 18%) as a white solid.

Compound 9



*Intermediate **B6***

Ethyl *cis*-2-{7-cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-2-fluorocyclopropane-1-carboxylate

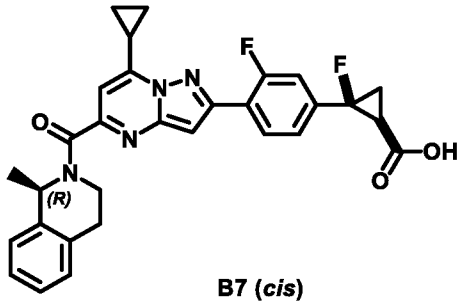


B6 (*cis*)

A mixture of (1*R*)-2-[7-cyclopropyl-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-36-2] (0.4 g, 541 µmol, 62% purity), intermediate **A9** (182 mg, 0.60 mmol) and potassium phosphate tribasic (345 mg, 1.62 mmol) in 1,4-dioxane (9 mL) and H_2O (2.5 mL) was purged with nitrogen for 5 min. [1,1'-Bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II) (35.3 mg, 54.1 µmol) was added and the mixture was purged again with nitrogen for 5 min. The reaction mixture was heated at 80°C using a single mode microwave (Anton Paar Monowave 300) with a power output ranging from 0 to 850 W for 30 min. The reaction mixture was diluted with EtOAc and water. The layers were separated and the aqueous phase was extracted with EtOAc (twice). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude mixture was purified by flash chromatography over silica gel (Puriflash Interchim® 25 g, 30 µM, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 100:0 to 70:30) to afford intermediate **B6** (0.21 g, 70%) as a beige solid.

*Intermediate **B7***

cis-2-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-2-fluorocyclopropane-1-carboxylic acid



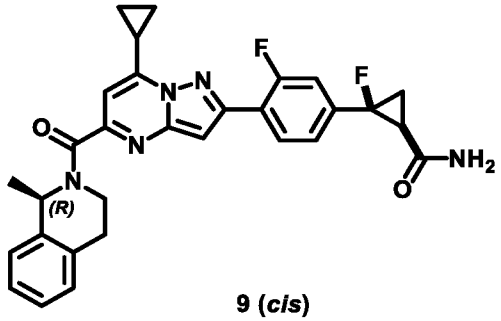
B7 (*cis*)

A mixture of intermediate **B6** (0.21 g, 377 µmol) and lithium hydroxide monohydrate (95 mg, 2.26 mmol) in THF (10 mL) and H_2O (3 mL) was stirred under reflux for 6 h. An aqueous solution of citric acid (435 mg) was added. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed

with brine, dried over $MgSO_4$, filtered and evaporated to dryness to afford intermediate **B7** (0.19 g, quant.) as a yellow solid.

*Compound **9***

cis-2-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-2-fluorocyclopropane-1-carboxamide

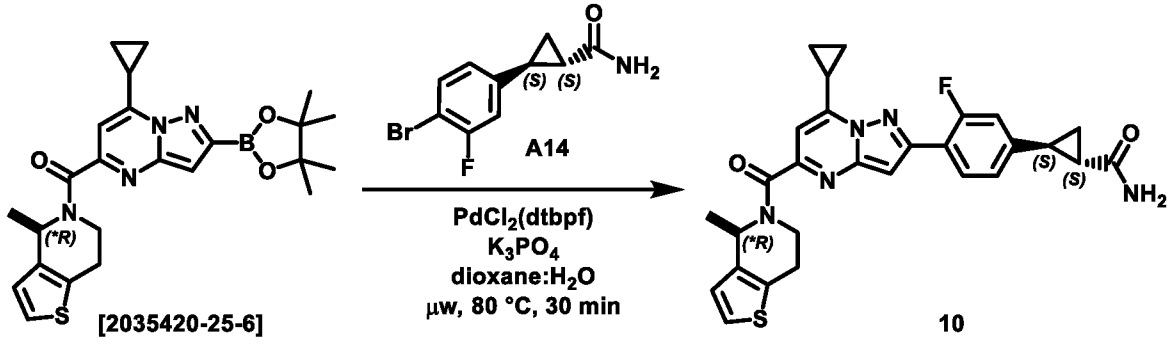


9 (*cis*)

To a solution of intermediate **B7** (0.19 g, 359 µmol) in DMF (5 mL) were added DIPEA (0.19 mL, 1.08 mmol) and HATU (205 mg, 0.54 mmol). The mixture was stirred at rt for 15 min and ammonia (30% in H_2O, 41 µL, 2.16 mmol) was added dropwise. The reaction mixture was stirred at rt for 2 h. The reaction mixture was diluted with water and EtOAc. The layers were separated and the organic phase was washed with water (3 times) and brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude mixture was purified by flash chromatography over silica gel (Puriflash Interchim® 12 g, 30 µM, liquid injection (DCM), mobile phase gradient: DCM / MeOH from 100:0 to 98:2). The residue (0.1 g) was diluted with *i*-PrOH and stirred for 20 min at rt. The solid was filtered off and dried under vacuum to give compound **9** (0.04 g, 21%) as a white solid.

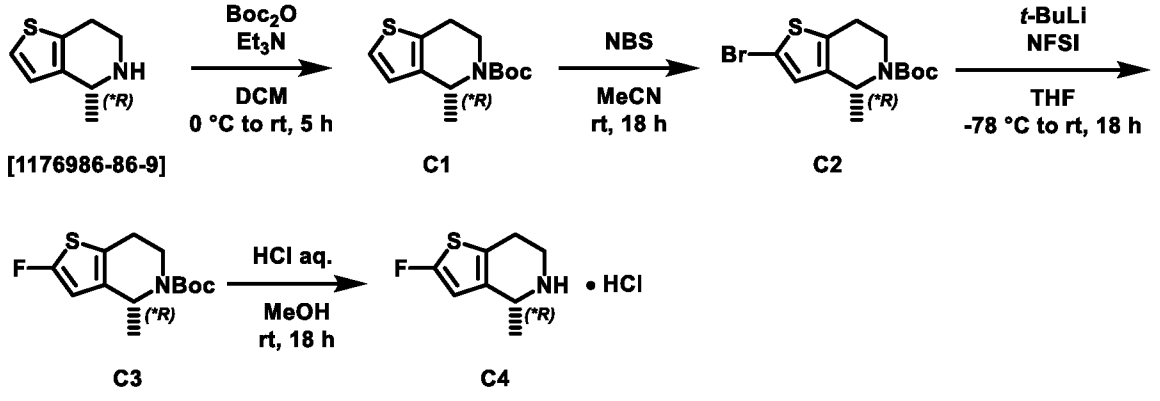
Compound 10

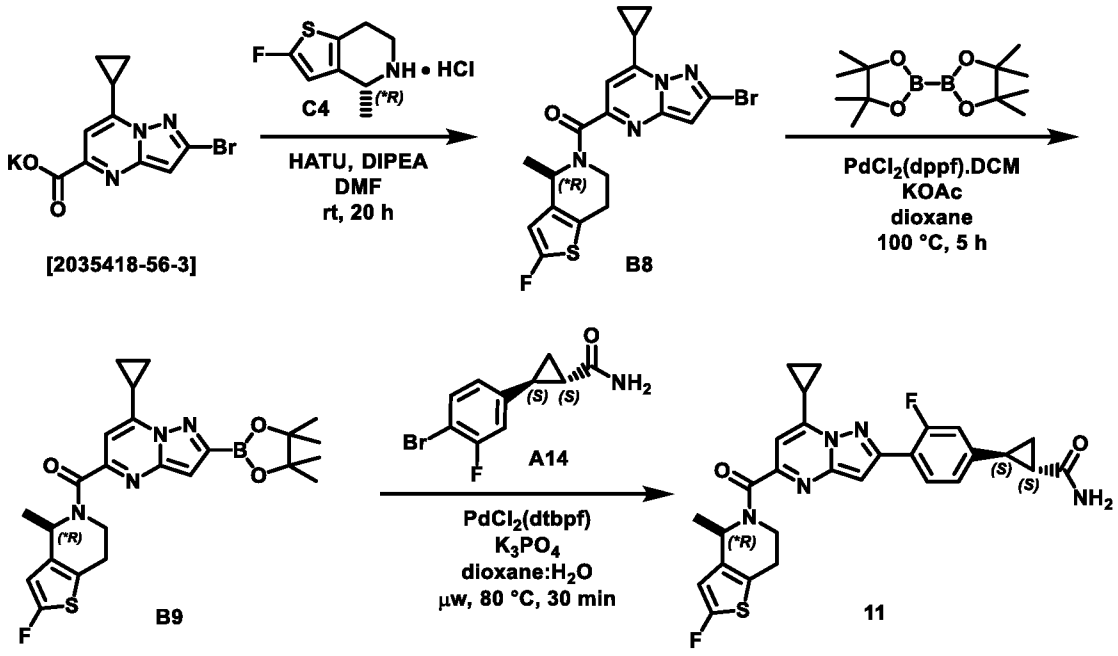
(1*S*,2*S*)-2-(4-{7-Cyclopropyl-5-[(4**R*)-4-methyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine-5-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)cyclopropane-1-carboxamide



A sealed tube was charged with 7-cyclopropyl-5-[(4*R*)-4-methyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine-5-carbonyl]-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyrimidine [2035420-25-6] (288 mg, 409 µmol, 66% purity), intermediate **A14** (116 mg, 450 µmol), potassium phosphate tribasic (296 mg, 1.40 mmol), 1,4-dioxane (7.5 mL) and H_2O (2.5 mL) and purged with nitrogen. [1,1'-Bis(di-*tert*-butylphosphino)ferrocene]-dichloropalladium(II) (29.3 mg, 45.0 µmol) was added and the mixture was purged again with nitrogen. The reaction mixture was heated at 80°C using a single mode microwave (Biotage® Initiator EXP 60) with a power output ranging from 0 to 400 W for 30 min. The reaction mixture was diluted with EtOAc and washed with a saturated aqueous solution of $NaHCO_3$ and brine. The solid was filtered off and washed with EtOAc to give a first crop. The filtrate was decanted and the organic phase was dried over $MgSO_4$, filtered and evaporated in vacuo. The crude mixture was purified by preparative LC (regular SiOH, 15-30 µm, 25 g Interchim®, dry loading (SiOH), mobile phase gradient: heptane / EtOAc from 50:50 to 0:100 then DCM / MeOH from 90:10 to 85:15) to deliver a second crop of compound **10**. The first crop, previously isolated, was diluted in DMF. Insoluble residue was filtered off and discarded. The soluble mixture was purified by preparative LC (regular SiOH, 15-30 µm, 25 g Interchim®, dry loading (SiOH), mobile phase gradient: DCM / MeOH from 90:10 to 85:15). The solid was triturated in Et_2O and filtered off to deliver a third crop of compound **10**. The second and third crops were combined and purified by preparative LC (spherical C18 25 µm, 120 g YMC-ODS-25, dry loading (Celite®), mobile phase gradient (0.2% aq.NH_4HCO_3) / MeCN from 65:35 to 0:100 then MeCN). The fractions containing the product were combined and concentrated to dryness. A second purification was performed by preparative LC (regular SiOH, 15-30 µm, 25 g Interchim®, dry loading (SiOH), mobile phase gradient: DCM / MeOH from 90:10 to 85:15). The solid was triturated in Et_2O, filtered off and washed with Et_2O. The solid was triturated in DCM, filtered off and washed with DCM to give compound **10** (50 mg, 24%) as a white solid.

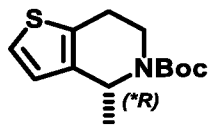
Compound 11





*Intermediate **C1***

Tert-butyl (4**R*)-4-methyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine-5-carboxylate

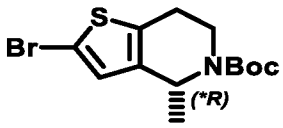


C1

A solution of di-*tert*-butyl dicarbonate (1.42 g, 6.53 mmol) in DCM (5 mL) was added dropwise to a mixture of (4**R*)-4-methyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine [1176986-86-9] (1.00 g, 6.53 mmol) and Et_3N (1.1 mL, 7.91 mmol) in DCM (7 mL) at 0 °C (the internal temperature was maintained between 10 and 20°C). The reaction mixture was stirred at rt for 5 h. The mixture was evaporatedin vacuo. The residue was diluted with water and EtOAc and a saturated aqueous solution of $NaHCO_3$ was added. The layers were separated and the aqueous phase was extracted with EtOAc (twice). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated in vacuo. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 50 g Grace Resolv™, liquid injection (heptane), mobile phase gradient: heptane / EtOAc from 100:0 to 80:20) to afford intermediate **C1** (1.45 g, 88%) as a colorless oil that crystallized on standing.

*Intermediate **C2***

Tert-butyl (4**R*)-2-bromo-4-methyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine-5-carboxylate

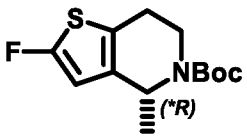


C2

To a solution of intermediate **C1** (1.45 g, 5.72 mmol) in MeCN (31 mL) was added NBS (1.02 g, 5.72 mmol) portionwise. The reaction mixture was stirred at rt for 18 h. The reaction mixture was diluted with EtOAc and brine. The layers were separated and the organic phase was washed with water and brine, dried over $MgSO_4$, filtered and evaporated in vacuo. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 50 g GraceResolv™, dry loading (Celite®), mobile phase gradient: heptane / EtOAc from 100:0 to 90:10 to afford intermediate **C2** (1.66 g, 87%) as a colorless gum.

*Intermediate **C3***

Tert-butyl (4**R*)-2-fluoro-4-methyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine-5-carboxylate

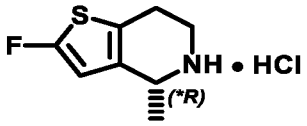


C3

Tert-butyllithium (1.9 M in pentane, 58 mL, 110 mmol) was added dropwise to a solution intermediate **C2** (15.9 g, 47.9 mmol) in anhydrous THF (400 mL) at -78°C. The reaction mixture was stirred at -78°C for 45 min and a solution of NFSI (45.3 g, 144 mmol) in THF (170 mL) was added. The reaction mixture was stirred at -78°C for 30 min and at rt for 18 h. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl and diluted with EtOAc. The layers were separated and the organic phase was evaporated to dryness. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 330 g GraceResolv™, dry loading (Celite®), mobile phase gradient: heptane / EtOAc from 100:0 to 90:10). The residue was purified by reverse phase (spherical C18, 25 µm, 300 g YMC-ODS-25, liquid injection (MeCN, 2-3 mL), mobile phase gradient: (0.2% aq. NH_4HCO_3) / MeCN from 50:50 to 25:75). The pure fractions were combined and evaporated in vacuo to afford intermediate **C3** (6.5 g, 50%) as a colorless oil.

*Intermediate **C4***

(4*R*)-2-Fluoro-4-methyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine hydrochloride

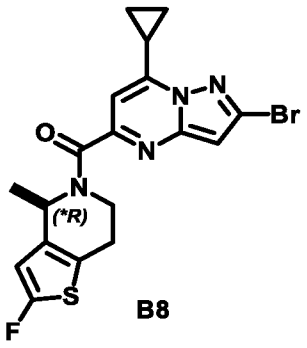


C4

Hydrochloric acid (37% in H_2O, 2.21 mL, 26.4 mmol) was added dropwise to a solution of intermediate **C3** (2.21 g, 8.14 mol) in MeOH (10 mL). The reaction mixture was stirred at rt for 18 h. The mixture was evaporated in vacuo and the residue was co-evaporated with EtOH (twice) and Et_2O to afford intermediate **C4** (1.65 g, 98%) as a white solid.

*Intermediate **B8***

2-Bromo-7-cyclopropyl-5-[(4*R*)-2-fluoro-4-methyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine-5-carbonyl]pyrazolo[1,5-a]pyrimidine

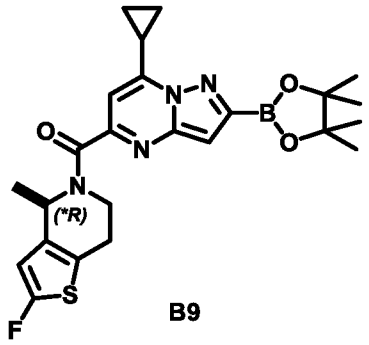


B8

A mixture of potassium 2-bromo-7-cyclopropylpyrazolo[1,5-a]pyrimidine-5-carboxylic acid [2035418-56-3] (2.31 g, 7.22 mmol), intermediate **C4** (1.65 g, 7.94 mmol), HATU (5.49 g, 14.4 mmol) and DIPEA (5.00 mL, 29.0 mmol) in DMF (45 mL) was stirred at rt for 20 h. A saturated aqueous solution of $NaHCO_3$, brine and EtOAc were added. The layers were separated and the aqueous phase was extracted with EtOAc (twice). The combined organic extracts were washed with brine (4 times), dried over $MgSO_4$, filtered and evaporated in vacuo. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 120 g GraceResolv™, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 90:10 to 60:40) to afford intermediate **B8** (3.02 g, 96%) as a white foam.

*Intermediate **B9***

7-Cyclopropyl-5-[(4*R*)-2-fluoro-4-methyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine-5-carbonyl]-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyrimidine

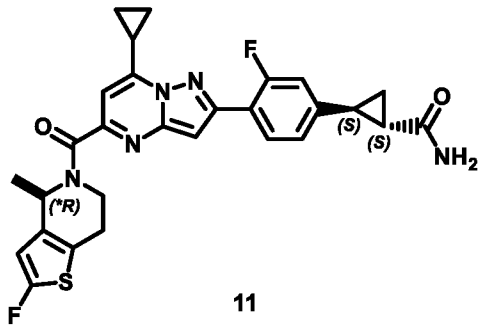


B9

Under nitrogen a sealed tube was charged with a solution of intermediate **B8** (250 mg, 574 µmol) in 1,4-dioxane (2.6 mL). Bis(pinacolato)diboron (219 mg, 861 µmol) and potassium acetate (169 mg, 1.72 mmol) were added. The mixture was purged with nitrogen and [1,1′-bis(diphenylphosphino)ferrocene] dichloropalladium(II), complex with dichloromethane (47.0 mg, 57.4 µmol) was added. The mixture was purged again with nitrogen and the reaction mixture was stirred at 100°C for 5 h. The reaction mixture was diluted with EtOAc, washed with water and brine (twice), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The product **B9** (557 mg, 51% purity) was used in the next step without further purification.

*Compound **11***

(1*S*,2*S*)-2-(4-{7-Cyclopropyl-5-[(4*R*)-2-fluoro-4-methyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine-5-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)cyclopropane-1-carboxamide



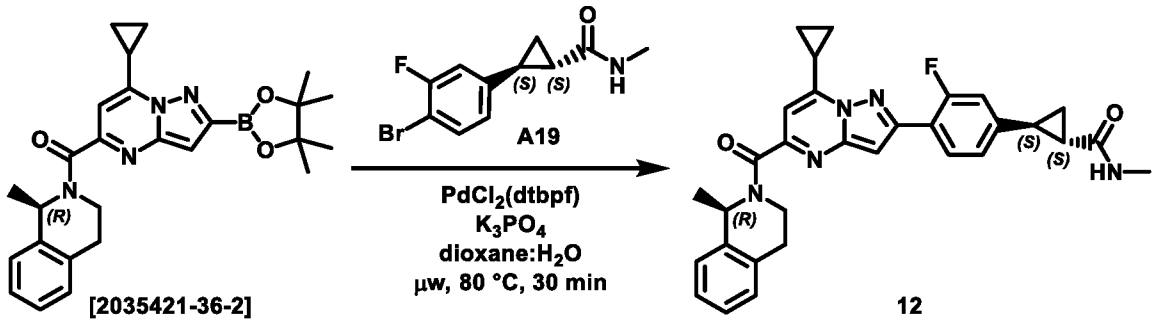
11

A sealed tube was charged with intermediate **A14** (187 mg, 0.42 mmol, 59% purity), intermediate **B9** (480 mg, 0.51 mmol, 51% purity), potassium phosphate tribasic (307 mg, 1.45 mmol), 1,4-dioxane (7.8 mL) and H_2O (2.8 mL) and purged with nitrogen. [1,1'-Bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II) (30.3 mg, 46.6 µmol)

was added and the mixture was purged again with nitrogen. The reaction mixture was heated at 80°C using a single mode microwave (Biotage® Initiator EXP 60) with a power output ranging from 0 to 400 W for 30 min. The reaction mixture was diluted with EtOAc and water. The layers were separated and the organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by preparative LC (regular SiOH, 15-40 µm, 24 g GraceResolv™, dry loading (Celite®), mobile phase gradient: DCM / MeOH / aq.NH_3 from 100:0:0 to 90:10:1). The resulting solid was triturated in MeOH and filtered off. The solid was combined with mother-liquor and purified by reverse phase (spherical C18, 25 µm, 40 g YMC-ODS-25, dry loading (Celite®), mobile phase gradient: (0.2% aq.NH_4HCO_3) / MeCN from 65:35 to 0:100). The solid was triturated in MeOH, filtered off and dried under high vacuum at 50°C for 24 h to afford an off-white solid (79 mg). Another purification was carried out by reverse phase (Stationary phase: YMC-actus Triart-C18 10µm 30*150mm, Mobile phase gradient: (0.2% aq.NH_4HCO_3) / MeCN from 60:40 to 0:100). The solid was triturated in MeOH, filtered off and dried under high vacuum at 50°C for 18 h to give compound **9** (27 mg, 12%) as a white solid.

Compound 12

(1*S*,2*S*)-2-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)-N-methylcyclopropane-1-carboxamide

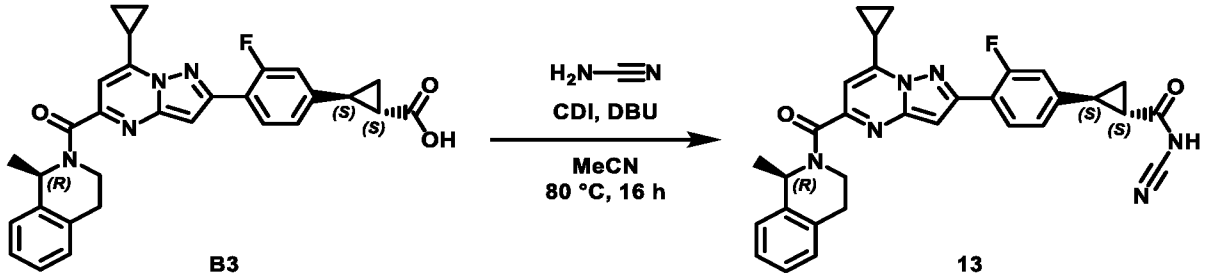


A sealed tube was charged with (1*R*)-2-[7-cyclopropyl-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-36-2] (448 mg, 655 µmol, 67% purity), intermediate **A19** (198 mg, 656 µmol), potassium phosphate tribasic (475 mg, 2.24 mmol), 1,4-dioxane (10 mL) and H_2O (3 mL) and purged with nitrogen. [1,1'-Bis(di-*tert*-butylphosphino)ferrocene]dichloro-palladium(II) (47.0 mg, 72.1 µmol) was added and the mixture was purged again with nitrogen. The reaction mixture was heated at 80°C using a single mode microwave (Biotage® Initiator EXP 60) with a power output ranging from 0 to 400 W for 30 min. The reaction mixture was diluted with EtOAc and water. The layers were separated and the

aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated in vacuo. The crude mixture was purified by preparative LC (irregular SiOH, 40 g Grace®, liquid injection (DCM), mobile phase gradient: DCM / MeOH from 100:0 to 90:10). The solid was triturated in MeOH, filtered off and dried under vacuum at 50°C to give compound **12** (160 mg, 47%) as an off-white solid.

Compound 13

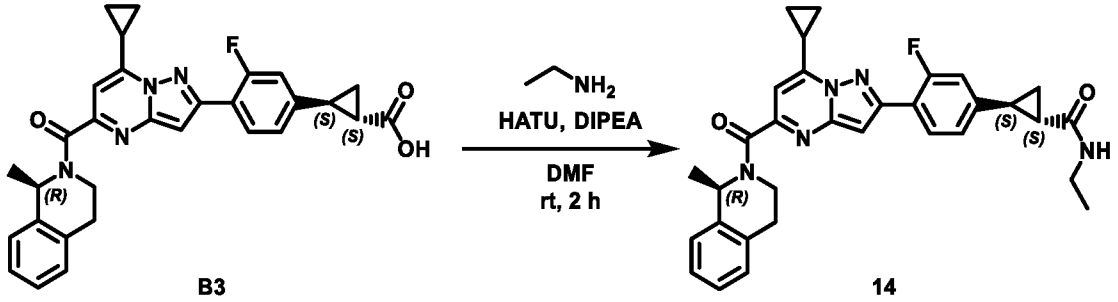
(1*S*,2*S*)-N-Cyano-2-(4-{7-cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)cyclopropane-1-carboxamide



A mixture of intermediate **B3** (200 mg, 0.39 mmol) and CDI (95.3 mg, 0.59 mmol) in MeCN (4.0 mL) was stirred at rt for 2 h. DBU (117 µL, 0.78 mmol) and cyanamide [420-04-2] (32.9 mg, 0.78 mmol) were added. The reaction mixture was stirred at 80°C for 16 h. The solvent was evaporated in vacuo. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 24 g GraceResolv™, liquid injection (DCM), mobile phase gradient: DCM / MeOH / AcOH from 100:0:0 to 95:4.5:0.5). The residue was crystallized from MeCN and dried under vacuum at 50°C for 16 h. The solid was purified by reverse phase (Stationary phase: YMC-actus Triart C18 10µm 30*150mm, Mobile phase gradient: (0.2% aq.NH_4HCO_3) / MeCN from 75:25 to 35:65) to give compound **13** (70 mg, 33%).

Compound 14

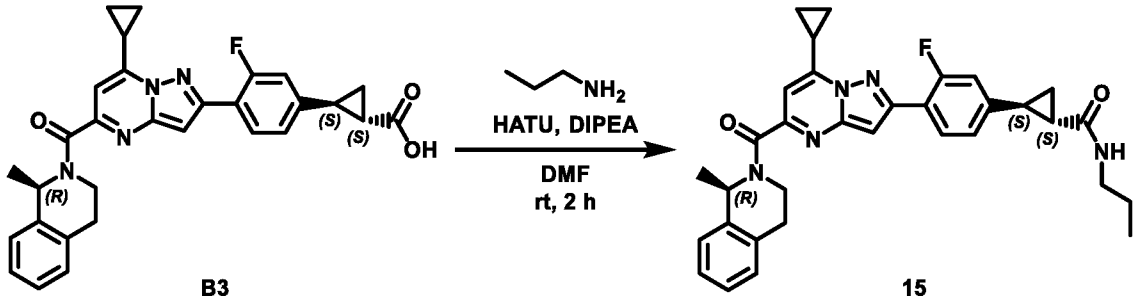
(1*S*,2*S*)-2-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)-N-ethylcyclopropane-1-carboxamide



To a mixture of intermediate **B3** (0.2 g, 0.39 mmol) in DMF (5 mL) were added DIPEA (0.20 mL, 1.18 mmol) and HATU (0.22 g, 0.59 mmol). The reaction mixture was stirred at rt for 15 min and ethylamine (2.0 M in MeOH, 1.18 mL, 2.35 mmol) was added dropwise. The reaction mixture was stirred at rt for 2 h. The reaction mixture was diluted with water and EtOAc. The layers were separated and the organic phase was washed with water and brine (3 times), dried over $MgSO_4$, filtered and evaporated to dryness. The residue was taken up in Et_2O. The solid was filtered off and dried under vacuum to give compound **14** (75 mg, 36%).

Compound 15

(1*S*,2*S*)-2-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)-N-propylcyclopropane-1-carboxamide

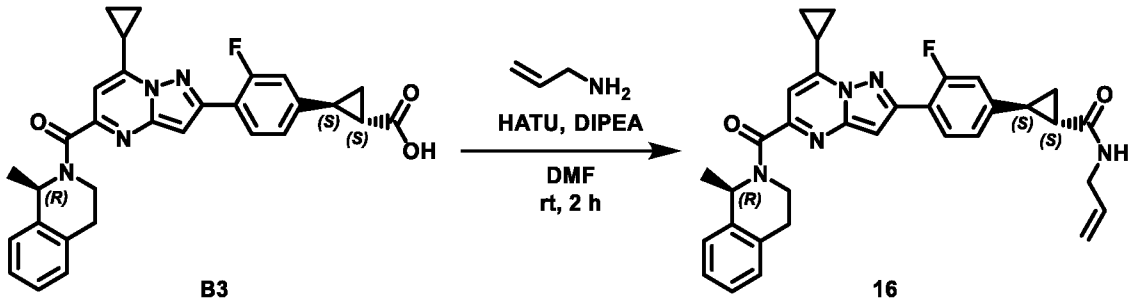


B3 15

Compound **15** was synthesized from intermediate **B3** and propylamine [107-10-8] according to the procedure reported for the synthesis of compound **14**. The residue was taken up in DIPE. The solid was filtered off and dried under vacuum to give compound **15** (0.15 g, 69%) as a beige solid.

Compound 16

(1*S*,2*S*)-2-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)-N-(prop-2-en-1-yl)cyclopropane-1-carboxamide

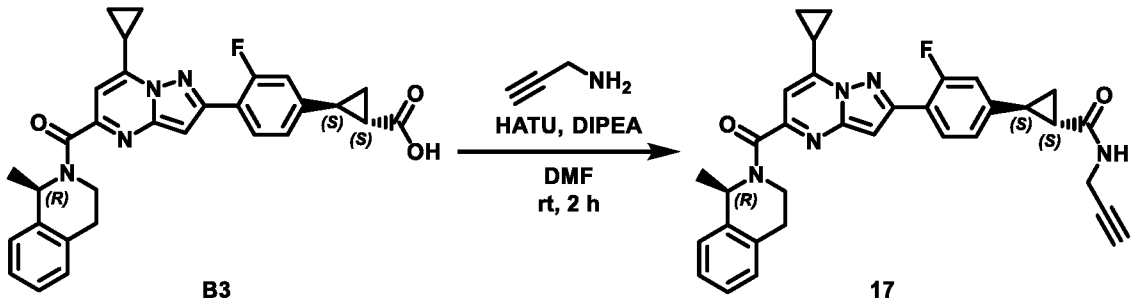


B3 16

Compound **16** was synthesized from intermediate **B3** and allylamine [107-11-9] according to the procedure reported for the synthesis of compound **14**. Compound **16** (98 mg, 46%) was obtained as a beige solid.

Compound 17

(1*S*,2*S*)-2-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)-N-(prop-2-yn-1-yl)cyclopropane-1-carboxamide

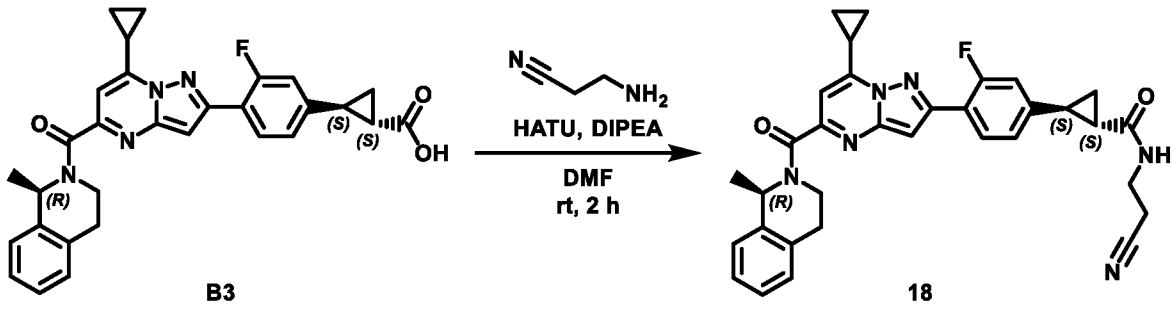


B3 17

Compound **17** was synthesized from intermediate **B3** and propargylamine [2450-71-7] according to the procedure reported for the synthesis of compound **14**. Compound **17** (0.2 g, 93%) was obtained as a beige solid.

Compound 18

(1*S*,2*S*)-N-(2-Cyanoethyl)-2-(4-{7-cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydro-isoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)cyclopropane-1-carboxamide

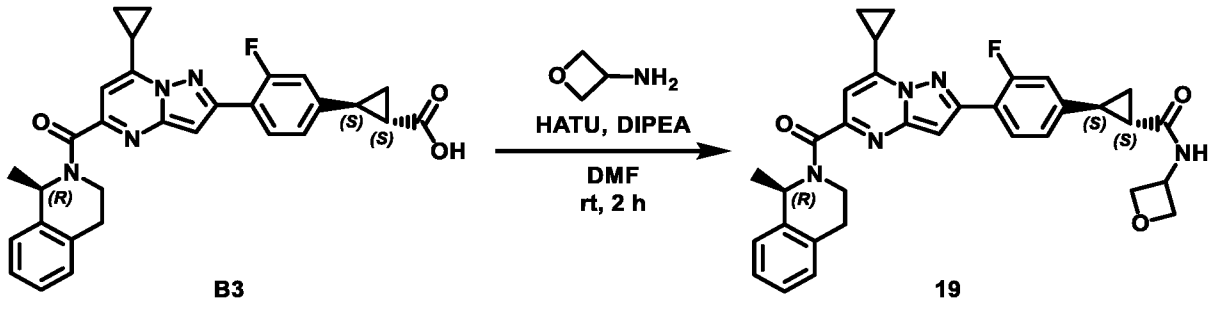


B3 18

Compound **18** was synthesized from intermediate **B3** and 3-aminopropionitrile according to the procedure reported for the synthesis of compound **14**. Compound **18** (187 mg, 85%) was obtained as a beige solid.

Compound 19

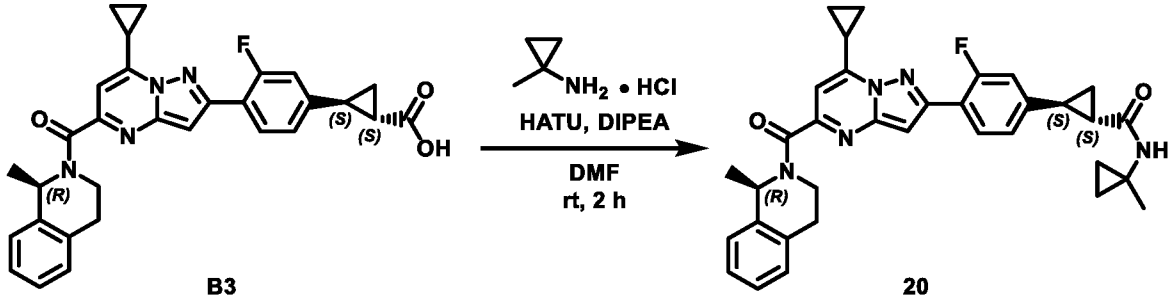
(1*S*,2*S*)-2-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)-N-(oxetan-3-yl)cyclopropane-1-carboxamide



Compound **19** was synthesized from intermediate **B3** and 3-oxetamine [21635-88-1] according to the procedure reported for the synthesis of compound **14**. Compound **19** (182 mg, 82%) was obtained as a white solid.

Compound 20

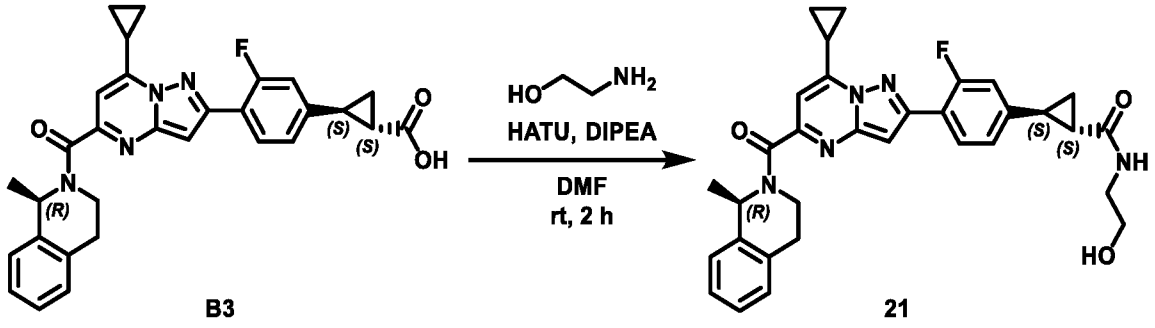
(1*S*,2*S*)-2-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)-N-(1-methylcyclopropyl)cyclopropane-1-carboxamide



To a solution of intermediate **B3** (0.15 g, 0.29 mmol) in DMF (5 mL) were added DIPEA (0.30 mL, 1.76 mmol) and HATU (0.17 g, 0.44 mmol). The reaction mixture was stirred at rt for 15 min and 1-methylcyclopropylamine hydrochloride [88887-87-0] (0.13 g, 1.18 mmol) was added. The reaction mixture was stirred at rt for 2 h. The reaction mixture was diluted with water and EtOAc. A precipitate was formed and filtered off to give compound **20** (100 mg, 60%) as a white solid.

Compound 21

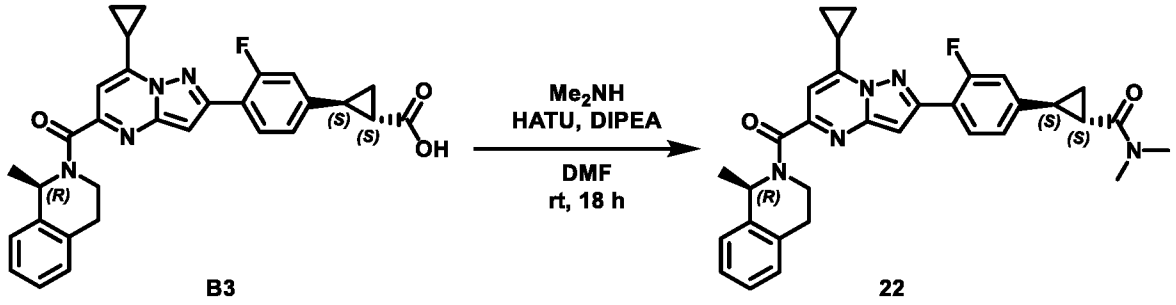
(1*S*,2*S*)-2-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)-N-(2-hydroxyethyl)-cyclopropane-1-carboxamide



Compound **21** was synthesized from intermediate **B3** and ethanolamine [141-43-5] according to the procedure reported for the synthesis of compound **20**. Compound **21** (145 mg, 67%) was obtained as a white solid.

Compound 22

(1*S*,2*S*)-2-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)-N,N-dimethylcyclopropane-1-carboxamide

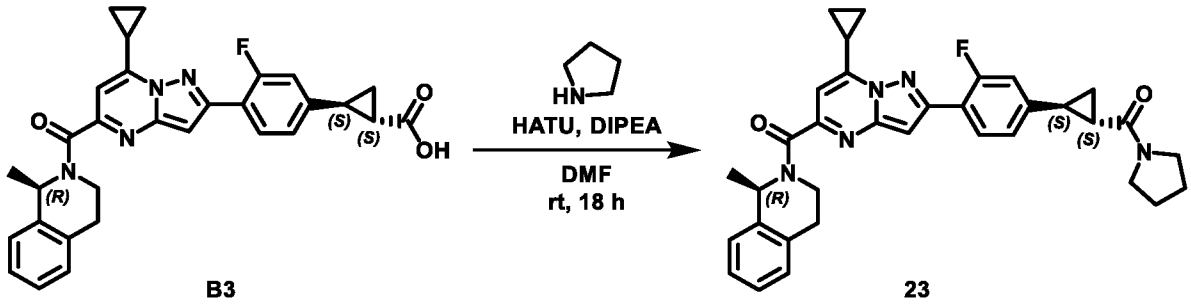


HATU (168 mg, 0.44 mmol) was added to a suspension of intermediate **B3** (150 mg, 0.29 mmol), dimethylamine (2.0 M in THF, 740 µL, 1.48 mmol) and DIPEA (152 µL, 0.881 mmol) in DMF (2 mL). The reaction mixture was stirred at rt for 18 h. The reaction mixture was diluted with H_2O, brine and EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine (3 times), dried over $MgSO_4$, filtered and evaporated in vacuo. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 12 g GraceResolv™, liquid injection (DCM), mobile phase gradient: heptane / (EtOAc/MeOH, 90:10) from

80:20 to 60:40). The residue was taken up in Et_2O and evaporated in vacuo (twice) to give compound **22** (117 mg, 74%) as an off-white solid.

Compound 23

(1*R*)-2-(7-Cyclopropyl-2-{2-fluoro-4-[(1*S*,2*S*)-2-(pyrrolidine-1-carbonyl)cyclopropyl]-phenyl}pyrazolo[1,5-a]pyrimidine-5-carbonyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline

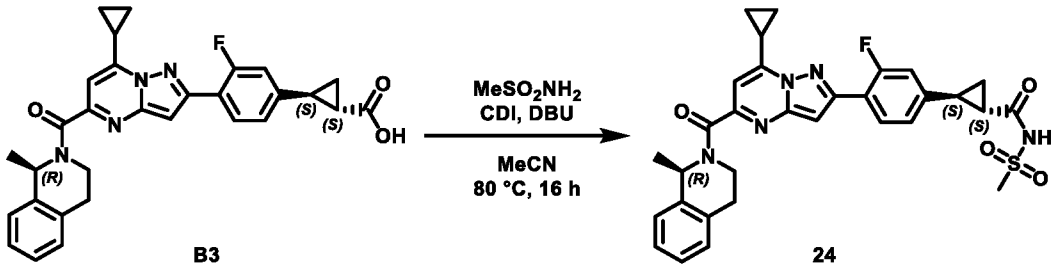


B3 23

Compound **23** was synthesized from intermediate **B3** and pyrrolidine [123-75-1] according to the procedure reported for the synthesis of compound **22**. Compound **23** (112 mg, 68%) was obtained as an off-white solid.

Compound 24

(1*S*,2*S*)-2-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)-N-methanesulfonyl-cyclopropane-1-carboxamide



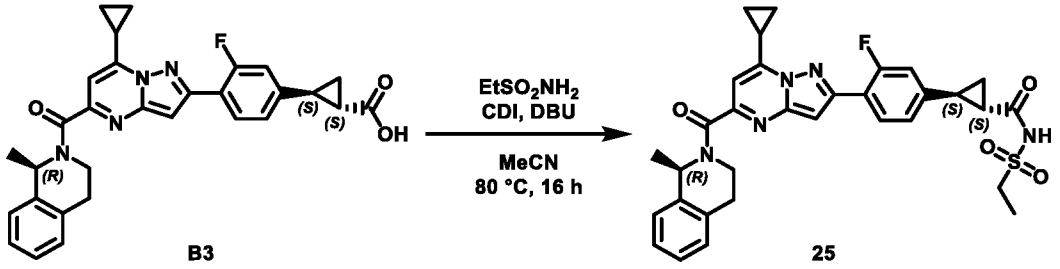
B3 24

A mixture of intermediate **B3** (200 mg, 0.39 mmol) and CDI (63.5 mg, 0.39 mmol) in MeCN (4 mL) was stirred at rt for 2 h. DBU (87.8 µL, 0.59 mmol) and methanesulfonamide [3144-09-0] (55.9 mg, 0.59 mmol) were added. The reaction mixture was stirred at 80°C for 16 h. Brine, a 1N aqueous solution of HCl and EtOAc were added. The layers were separated and the aqueous phase was extracted with EtOAc (twice). The combined organic extracts were washed with a solution of water and brine (1:1), dried over $MgSO_4$, filtered and evaporated in vacuo. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 12 g GraceResolv™, liquid injection (DCM), mobile phase

gradient: DCM / MeOH from 100:0 to 98:2). The residue (206 mg) was crystallized from MeOH, filtered off and dried under high vacuum at 50°C for 24 h to give compound **24** (192 mg, 83%) as a white solid.

Compound 25

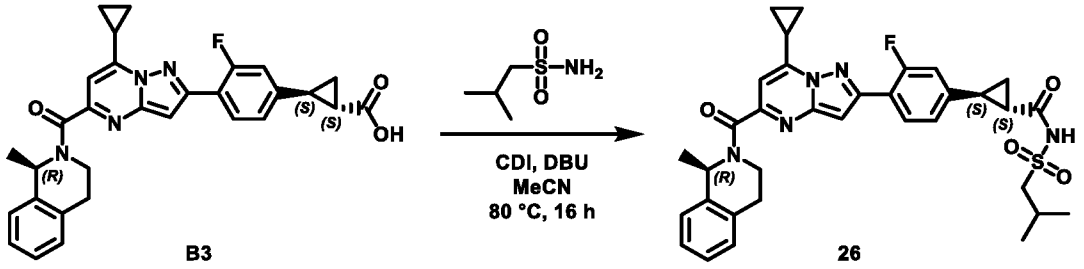
(1*S*,2*S*)-2-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)-N-(ethanesulfonyl)-cyclopropane-1-carboxamide



Compound **25** was synthesized from intermediate **B3** and ethanesulfonamide [1520-70-3] according to the procedure reported for the synthesis of compound **24**. Compound **25** (117 mg, 66%) was obtained as an off-white solid.

Compound 26

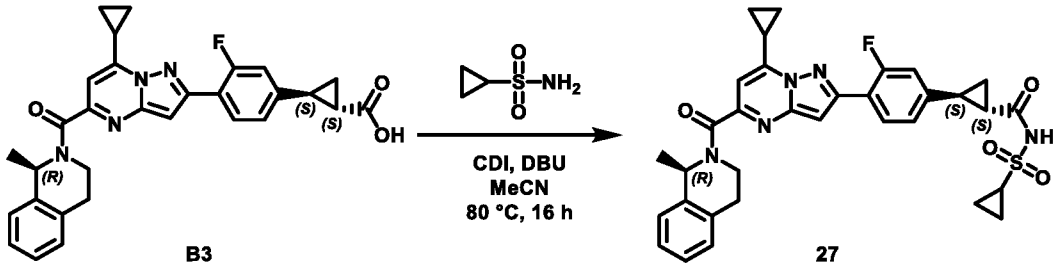
(1*S*,2*S*)-2-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)-N-(2-methylpropanesulfonyl)-cyclopropane-1-carboxamide



Compound **26** was synthesized from intermediate **B3** and 2-methylpropane-1-sulfonamide [60199-80-6] according to the procedure reported for the synthesis of compound **24**. Compound **26** (87 mg, 47%) was obtained as an off-white solid.

Compound 27

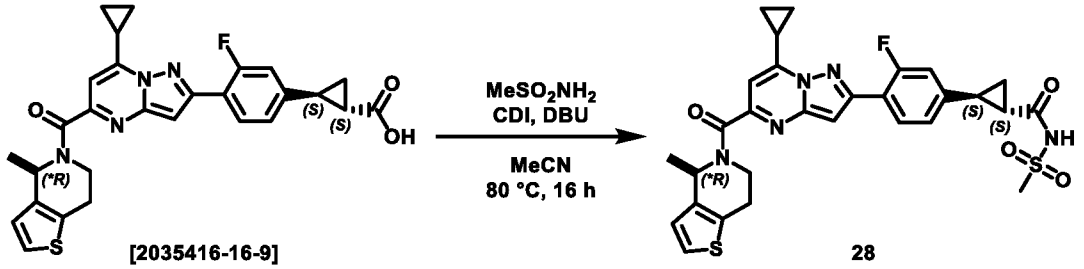
(1*S*,2*S*)-N-(Cyclopropanesulfonyl)-2-(4-{7-cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)-cyclopropane-1-carboxamide



Compound **27** was synthesized from intermediate **B3** and cyclopropanesulfonamide [154350-28-4] according to the procedure reported for the synthesis of compound **24**. Compound **27** (106 mg, 59%) was obtained as an off-white solid.

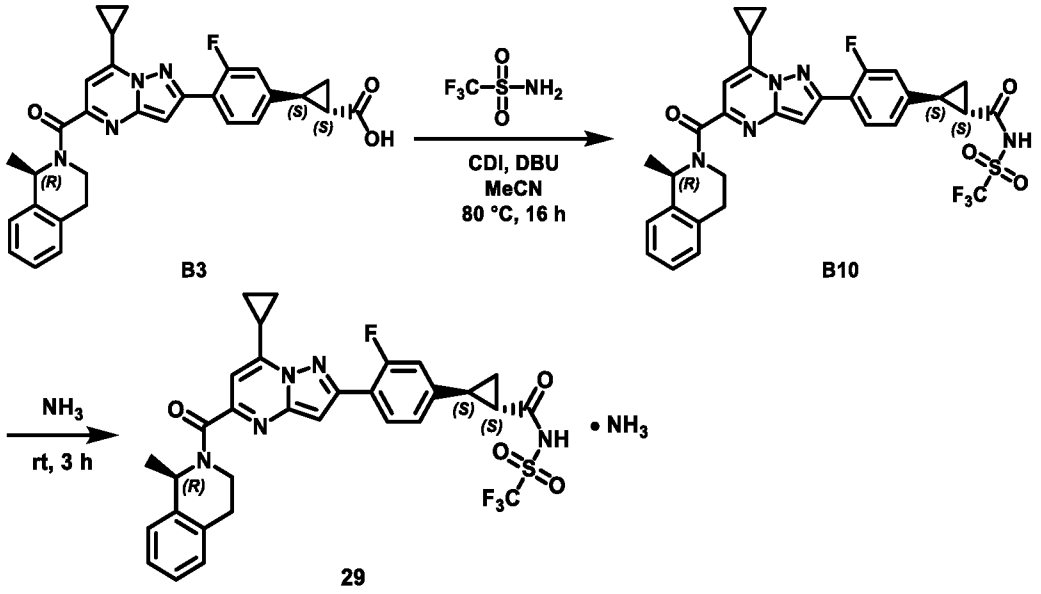
Compound 28

(1*S*,2*S*)-2-(4-{7-Cyclopropyl-5-[(4**R*)-4-methyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine-5-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)-N-methanesulfonyl-cyclopropane-1-carboxamide



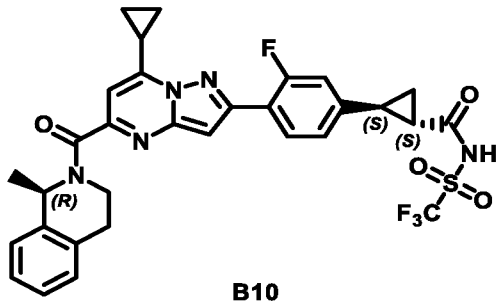
Compound **28** was synthesized from (1*S*,2*S*)-2-(4-{7-cyclopropyl-5-[(4**R*)-4-methyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine-5-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)cyclopropane-1-carboxylic acid [2035416-16-9] and methanesulfonamide [3144-09-0] according to the procedure reported for the synthesis of compound **24**. Compound **28** (128 mg, 74%) was obtained as an off-white solid.

Compound 29



*Intermediate **B10***

(1*S*,2*S*)-2-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)-*N*-trifluoromethanesulfonylcyclopropane-1-carboxamide

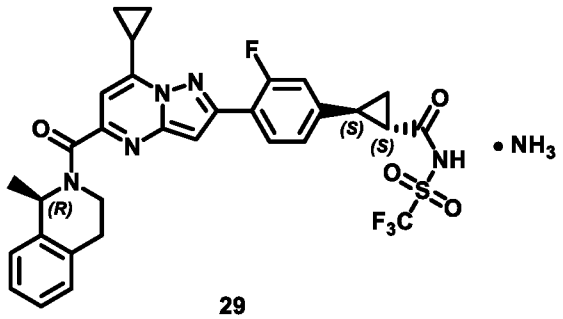


A mixture of intermediate **B3** (150 mg, 0.29 mmol) and CDI (57.2 mg, 0.35 mmol) in MeCN (3 mL) was stirred at rt for 2 h. DBU (65.8 µL, 0.44 mmol) and trifluoromethanesulfonamide [421-85-2] (65.7 mg, 0.44 mmol) were added. The reaction mixture was stirred at 80°C for 16 h. Brine, a 1N aqueous solution of HCl and DCM were added. The layers were separated and the aqueous phase was extracted with DCM (twice). The combined organic extracts were washed with a solution of water and brine (1:1), dried over $MgSO_4$, filtered and evaporated in vacuo. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 12 g GraceResolv™, liquid injection (DCM), mobile phase gradient: DCM / (MeOH/AcOH 90:10) from 100:0 to 95:5). A second purification was performed by reverse phase (spherical C18, 25 µm, 40 g YMC-ODS-25, dry loading

(Celite®), mobile phase gradient: (0.2% aq.NH_4HCO_3) / MeCN from 75:25 to 35:65). The fractions containing the product were combined and a 1N aqueous solution of HCl was added until pH 1. The layers were separated and the aqueous phase was extracted with DCM (3 times). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford intermediate **B10** (113 mg, 60%) as a white solid.

*Compound **29***

(1*S*,2*S*)-2-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)-N-trifluoromethanesulfonylcyclopropane-1-carboxamide amine salt

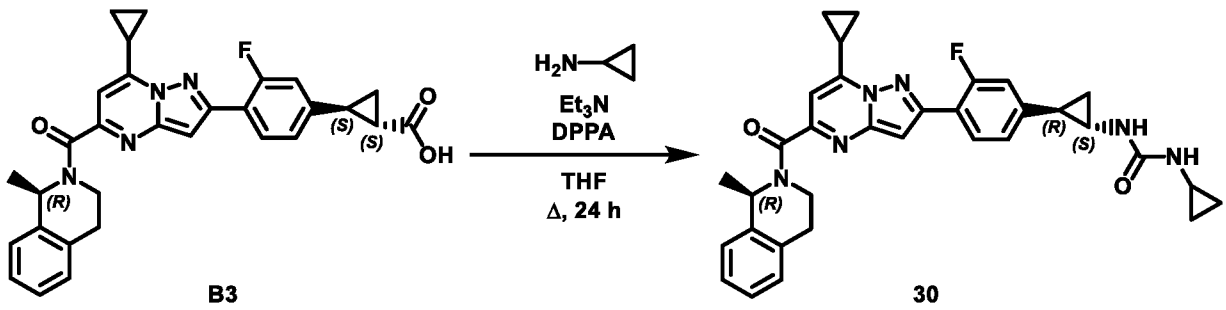


29

A solution of intermediate **B10** (113 mg, 176 µmol) in ammonia (2.0 M in *i*-PrOH, 2 mL, 4.0 mmol) was stirred at rt for 3 h. The mixture was concentrated under reduced pressure. The residue was solubilized in MeOH (2 mL), extended with water (10 mL) and freeze-dried to give compound **29** (100 mg, 86%) as a white solid.

Compound 30

1-Cyclopropyl-3-[(1*S*,2*R*)-2-(4-{7-cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydro-isoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)cyclopropyl]urea

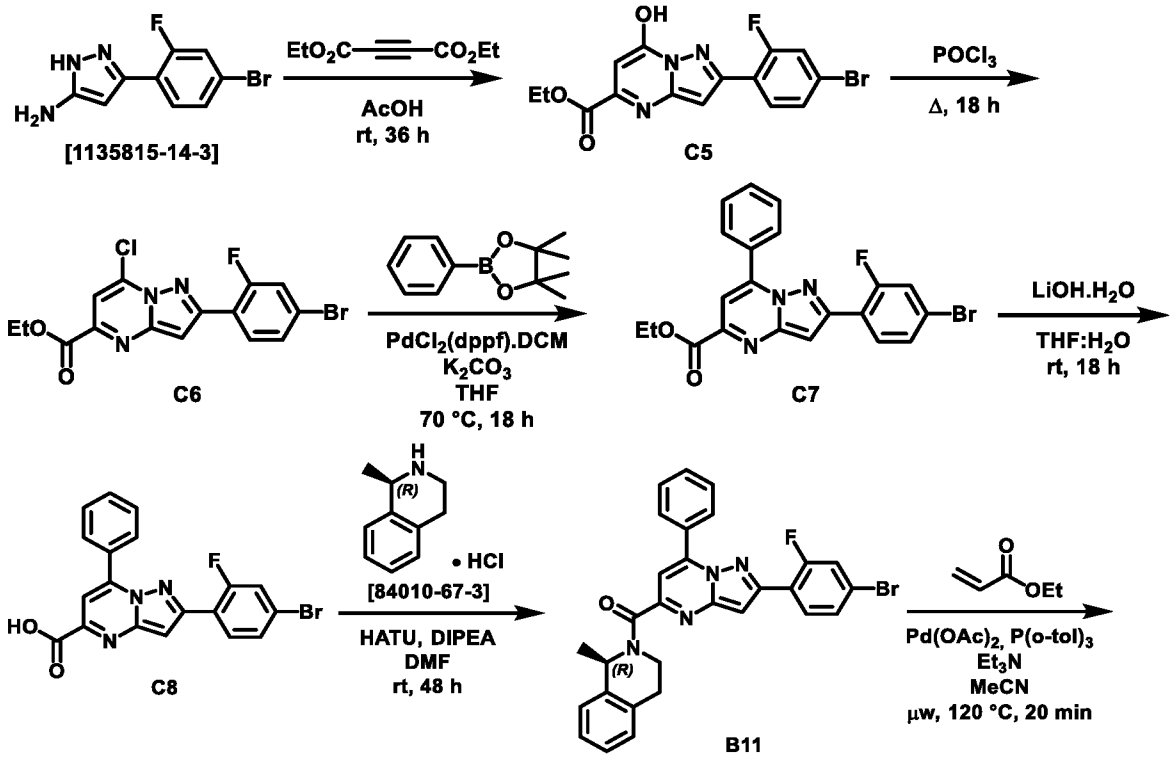


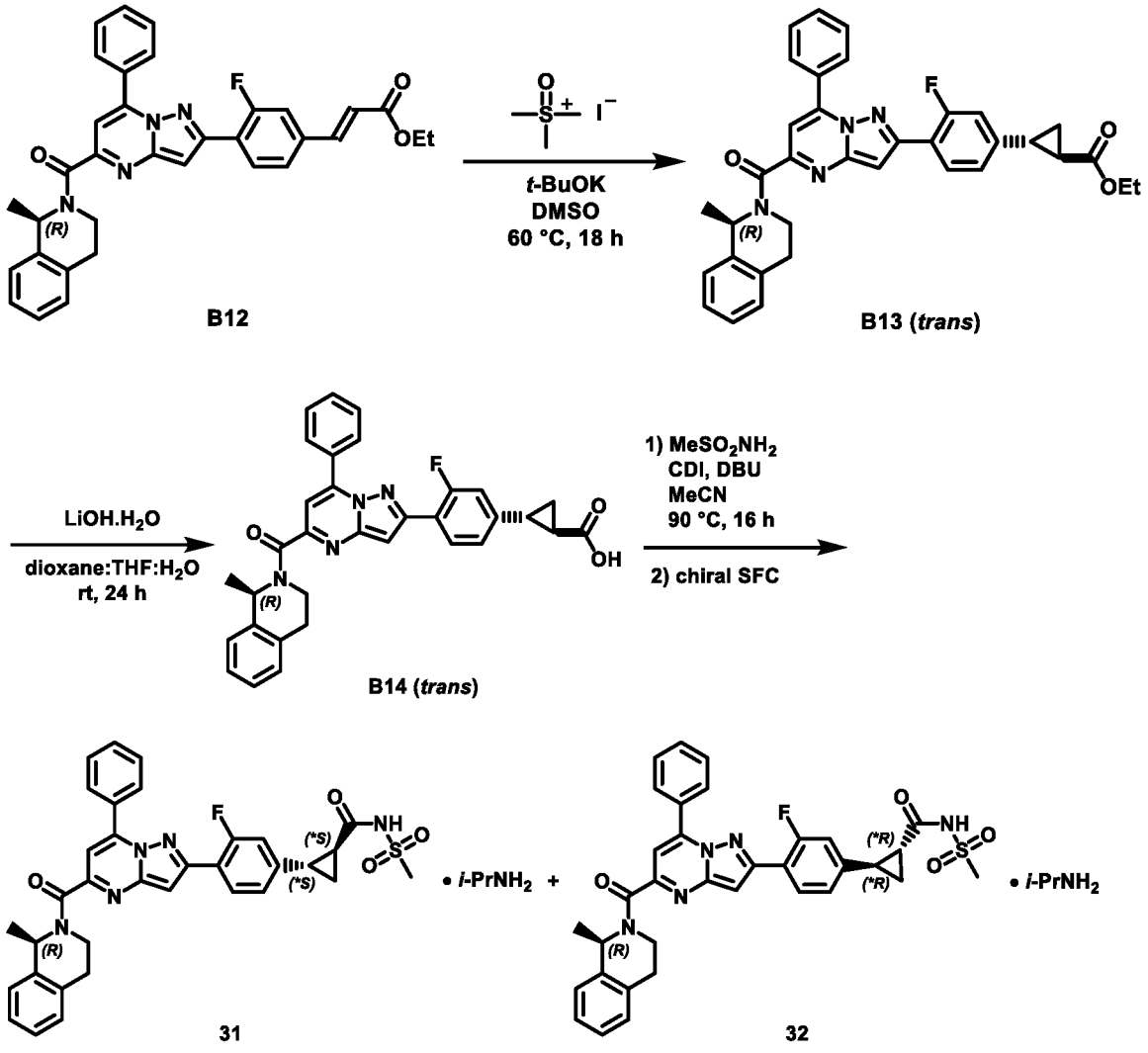
B3 **30**

To a mixture of intermediate **B3** (200 mg, 0.39 mmol) and Et_3N (55 µL, 0.40 mmol) in THF (3.2 mL) was added DPPA (127 µL, 0.59 mmol) dropwise. The reaction mixture was

stirred under reflux for 2 h. After cooling down to rt, cyclopropylamine [765-30-0] (81 µL, 1.18 mmol) was added and the reaction mixture was stirred under reflux for an additional hour. Extra amount of cyclopropylamine (41 µL, 0.59 mmol) was added and the reaction mixture was stirred under reflux for 16 h. Et_3N (27 µL, 0.20 mmol) was added and the reaction mixture was stirred under reflux for 5 h. The reaction mixture was diluted with EtOAc, washed with a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 12 g GraceResolv™, liquid injection (DCM), mobile phase gradient: heptane / (EtOAc/MeOH, 90:10) from 70:30 to 60:40). A second purification was carried out by reverse phase (spherical C18, 25 µm, 40 g YMC-ODS-25, dry loading (Celite®), mobile phase gradient: (0.2% aq.NH_4HCO_3) / MeCN from 60:40 to 0:100). The residue was taken up in Et_2O and evaporated in vacuo to give compound **30** (97 mg, 44%) as an off-white foam.

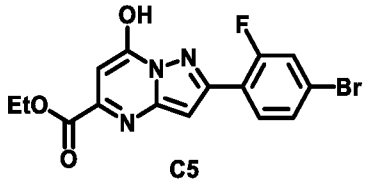
Compounds 31 and 32





Intermediate ***C5***

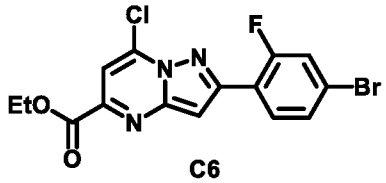
Ethyl 2-(4-bromo-2-fluorophenyl)-7-hydroxypyrazolo[1,5-a]pyrimidine-5-carboxylate



A mixture of 3-(4-bromo-2-fluorophenyl)-1H-pyrazol-5-amine [1135815-14-3] (15.0 g, 58.6 mmol) and diethyl acetylenedicarboxylate [762-21-0] (9.40 mL, 58. 6 mmol) in acetic acid (110 mL) was stirred at rt for 36 h. The reaction mixture was diluted with EtOAc and heptane (30:60) (150 mL) and the mixture was stirred at rt for 30 min. The precipitate was filtered off and dried under vacuum to afford intermediate **C5** (18.6 g, 84%).

*Intermediate **C6***

Ethyl 2-(4-bromo-2-fluorophenyl)-7-chloropyrazolo[1,5-a]pyrimidine-5-carboxylate

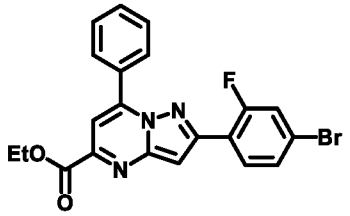


C6

A mixture of intermediate **C5** (15.0 g, 39.5 mmol) in phosphorous (V) oxychloride [10025-87-3] (147 mL) was stirred under reflux for 18 h. The solvent was evaporated to dryness. Water was added slowly and the mixture was stirred at 0°C for 30 min. The precipitate was filtered off and dried under vacuum to afford intermediate **C6** (15.3 g, 97%).

*Intermediate **C7***

Ethyl 2-(4-bromo-2-fluorophenyl)-7-phenylpyrazolo[1,5-a]pyrimidine-5-carboxylate

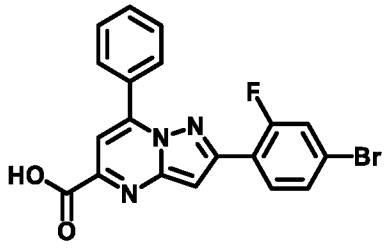


C7

A mixture of intermediate **C6** (1.00 g, 2.51 mmol) and 2-phenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [24388-23-6] (461 mg, 2.26 mmol) in THF (30 mL) was degassed with nitrogen for 10 min. [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (205 mg, 0.25 mmol) and potassium carbonate (2.0 M in H_2O, 3.8 mL, 7.53 mmol) were added and the reaction mixture was stirred at 70°C for 18 h. The reaction mixture was diluted with water. The precipitate was filtered off and dried under vacuum at 60°C to afford intermediate **C7** (1.2 g, quant.).

*Intermediate **C8***

Ethyl 2-(4-bromo-2-fluorophenyl)-7-phenylpyrazolo[1,5-a]pyrimidine-5-carboxylic acid

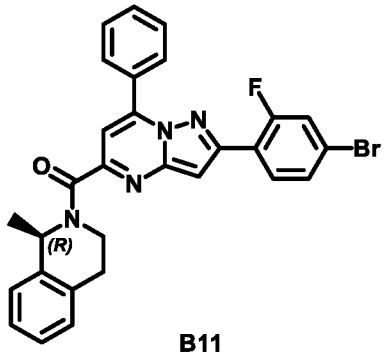


C8

A mixture of intermediate **C7** (1.2 g, 2.73 mmol) and lithium hydroxide monohydrate (229 mg, 5.45 mmol) in THF (29 mL) and H_2O (0.7 mL) was stirred at rt for 18 h. The reaction mixture was diluted with water and acidified with a 3N aqueous solution of HCl. The mixture was extracted with DCM (twice). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was evaporated to afford intermediate **C8** (1.0 g, 89%).

*Intermediate **B11***

(1*R*)-2-[2-(4-Bromo-2-fluorophenyl)-7-phenylpyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline

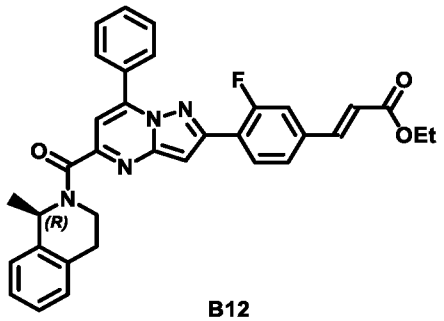


B11

DIPEA (1.27 mL, 7.29 mmol) and HATU (1.20 g, 3.15 mmol) were added to a mixture of (1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride [84010-67-3] (535 mg, 2.91 mmol) and intermediate **C8** (1.00 g, 2.43 mmol) in DMF (30 mL). The reaction mixture was stirred at rt for 48 h. The reaction mixture was poured out into water and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude mixture was purified by flash chromatography over silica gel (40 g GraceResolv™, 15-40 µm, mobile phase gradient: heptane / EtOAc from 100:0 to 70:30). The pure fractions were collected and evaporated to dryness to afford intermediate **B11** (680 mg, 52%).

*Intermediate **B12***

Ethyl (2*E*)-3-(3-fluoro-4-{5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-7-phenylpyrazolo[1,5-a]pyrimidin-2-yl}phenyl)prop-2-enoate

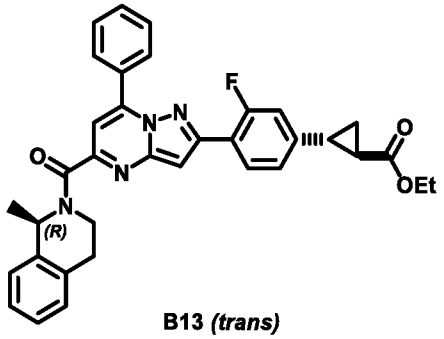


B12

A solution of intermediate **B11** (0.36 g, 665 µmol) in MeCN (12 mL) was degassed with nitrogen for 10 min. Ethyl acrylate (0.36 mL, 3.33 mmol), palladium acetate (14.9 mg, 66.5 µmol), tri(*o*-tolyl)phosphine (30.4 mg, 99.7 µmol) and Et_3N (0.14 mL, 997 µmol) were added. The reaction mixture was heated at 120°C using a single mode microwave (Biotage® Initiator EXP 60) with a power output ranging from 0 to 400 W for 20 min. The reaction mixture was poured out into a solution of water and DCM. The organic phase was separated (hydrophobic frit) and evaporated to dryness. The crude mixture was purified by flash chromatography over silica gel (cartridge 24 g, 15-40 µm, mobile phase gradient: heptane / EtOAc from 100:0 to 70:30). The pure fractions were collected and evaporated to dryness to afford intermediate **B12** (240 mg, 64 %).

*Intermediate **B13***

Ethyl 2-(3-fluoro-4-{5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-7-phenylpyrazolo[1,5-a]pyrimidin-2-yl}phenyl)cyclopropane-1-carboxylate



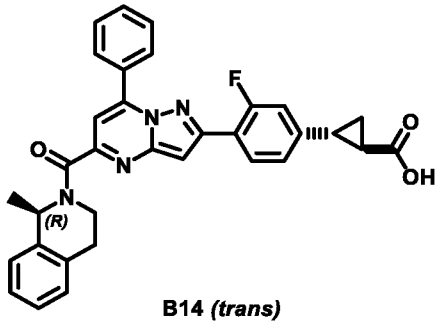
B13 *(trans)*

Trimethylsulfoxonium iodide [1774-47-6] (104 mg, 0.47 mmol) was added to a solution of potassium *tert*-butoxide (52.8 mg, 0.47 mmol) in DMSO (6 mL). The reaction mixture was stirred at rt for 30 min. A solution of intermediate **B12** (240 mg, 428 µmol) in DMSO (2

mL) was added and the reaction mixture was stirred at 60°C for 18 h. The reaction mixture was poured out into water. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with water and brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude mixture was purified by flash chromatography over silica gel (cartridge 24 g, 15-40 µm, mobile phase gradient: heptane / EtOAc from 100:0 to 70:30). The pure fractions were collected and evaporated to dryness to afford intermediate **B13** (160 mg, 65%).

*Intermediate **B14***

2-(3-Fluoro-4-{5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-7-phenylpyrazolo[1,5-a]pyrimidin-2-yl}phenyl)cyclopropane-1-carboxylic acid



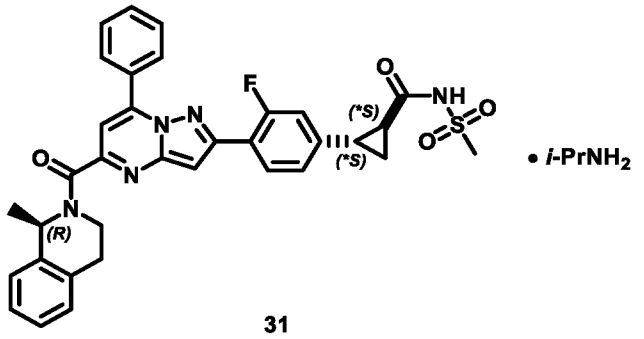
B14 ***(trans)***

Lithium hydroxide monohydrate (109 mg, 2.61 mmol) was added to a solution of intermediate **B13** (300 mg, 522 µmol) in THF (4.3 mL) and H_2O (1.4 mL). The reaction mixture was stirred at rt for 24 h. Few drops of water were added followed by a 3N aqueous solution of HCl. The layers were separated and the aqueous phase was extracted with DCM (twice). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated in vacuo to afford intermediate **B14** (300 mg, quant).

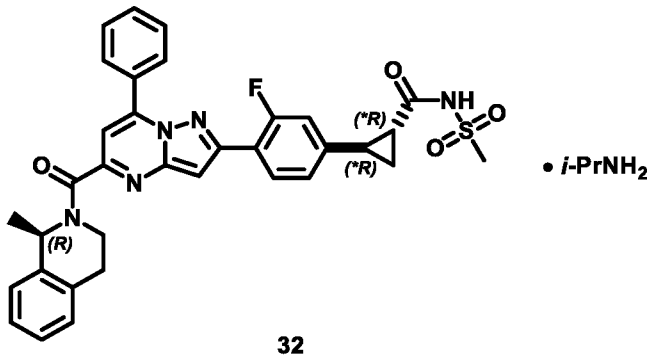
*Compounds **31** and **32***

31 : (1**S*,2**S*)-2-(3-Fluoro-4-{5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-7-phenylpyrazolo[1,5-a]pyrimidin-2-yl}phenyl)-N-methanesulfonyl-cyclopropane-1-carboxamide; propan-2-amine salt

32 : (1**R*,2**R*)-2-(3-Fluoro-4-{5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-7-phenylpyrazolo[1,5-a]pyrimidin-2-yl}phenyl)-N-methanesulfonyl-cyclopropane-1-carboxamide; propan-2-amine salt



31

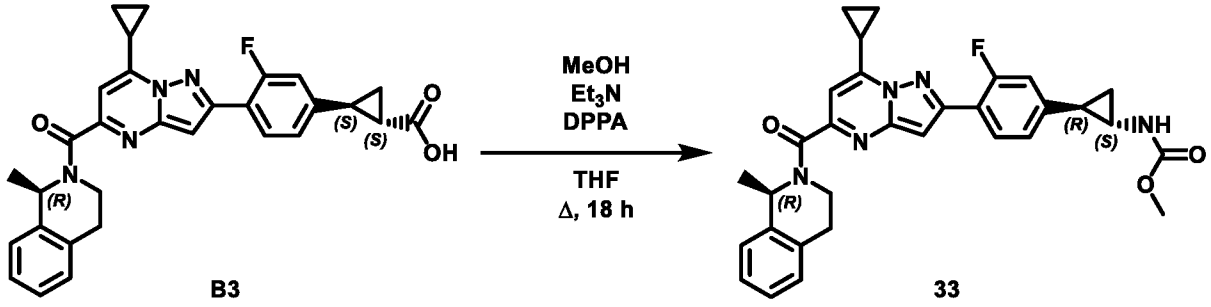


32

A mixture of intermediate **B14** (300 mg, 0.55 mmol) and CDI (107 mg, 659 µmol) in MeCN (6 mL) was stirred at rt for 2 h. DBU (123 µL, 0.82 mmol) and methanesulfonamide [3144-09-0] (78.3 mg, 0.82 mmol) were added. The reaction mixture was stirred at 80°C for 16 h. Brine, a 1N aqueous solution of HCl and DCM were added. The layers were separated and the aqueous phase was extracted with DCM (twice). The combined organic extracts were washed with a solution of water and brine (1:1), dried over $MgSO_4$, filtered and evaporated in vacuo (280 mg, 82%). The diastereoisomers were separated via chiral SFC (Stationary phase: Whelk-O1 (S,S) 5µm 250*21.2mm, Mobile phase: 40% CO_2, 60% (EtOH:DCM 80:20), 0.3% *i*-$PrNH_2$) to give compound **32** (114 mg, 37%) and compound **31** (115 mg, 38%) as yellow solids.

Compound 33

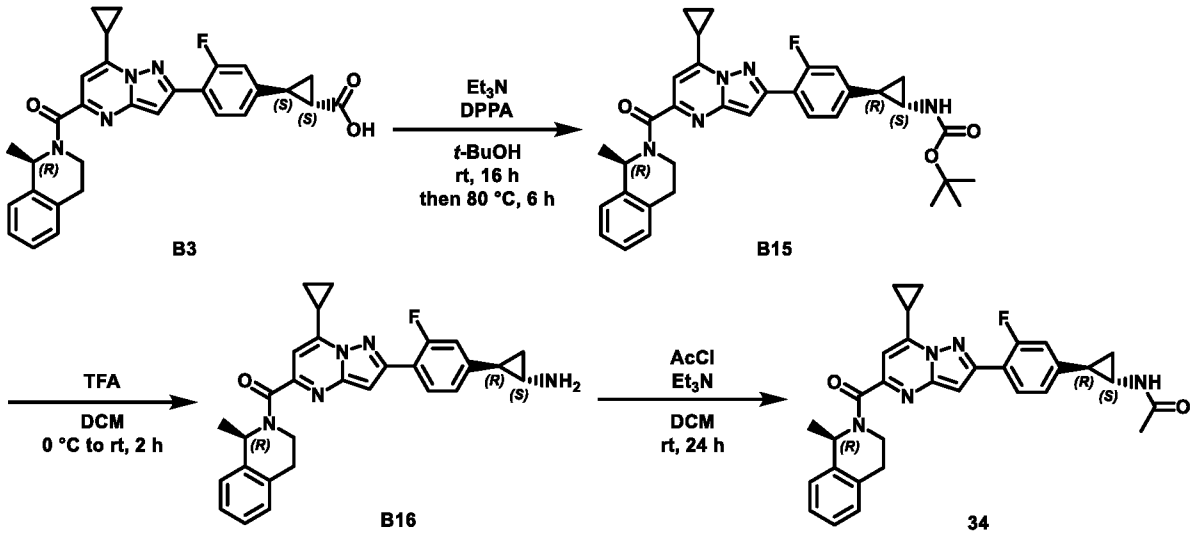
Methyl N-[(1*S*,2*R*)-2-(4-{7-cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)cyclopropyl]carbamate



B3 33

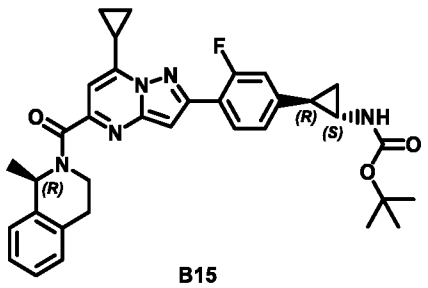
In a sealed tube DPPA (63.3 µL, 0.29 mmol) was added to a mixture of intermediate **B3** (150 mg, 0.29 mmol) and Et_3N (53.1 µL, 0.38 mmol) in THF (3.5 mL) at rt. The reaction mixture was stirred under reflux for 1 h. MeOH (350 µL, 8.64 mmol) was added and the reaction mixture was stirred under reflux for 18 h. The reaction mixture was diluted with EtOAc, washed with a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 12 g GraceResolv™, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 90:10 to 60:40). The residue was taken up in Et_2O, evaporated in vacuo (twice) and dried under high vacuum at 50°C for 4 h to give compound **33** (69 mg, 44%) as a white solid.

Compound 34



*Intermediate **B15***

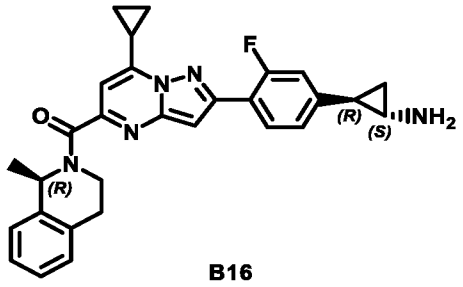
Tert-butyl N-[(1*S*,2*R*)-2-(4-{7-cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)cyclopropyl]-carbamate



A mixture of intermediate **B3** (500 mg, 979 µmol), DPPA (232 µL, 1.08 mmol) and Et_3N (136 µL, 979 µmol) in *t*-BuOH (10 mL) was stirred at rt for 16 h and at 80°C for 6 h. The reaction mixture was diluted with EtOAc, washed with a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 12 g GraceResolv™, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 90:10 to 70:30) to afford intermediate **B15** (331 mg, 58%) as a white solid.

*Intermediate **B16***

(1*S*,2*R*)-2-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)cyclopropan-1-amine

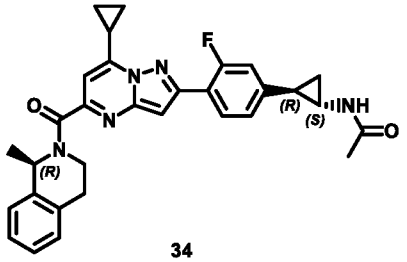


B16

To a solution of intermediate **B15** (321 mg, 0.55 mmol) in DCM (7.4 mL) was added TFA (3.0 mL, 39.2 mmol) dropwise at 0°C. The reaction mixture was stirred at rt for 2 h. The reaction mixture was diluted with DCM and a 10% aqueous solution of K_2CO_3 was added. The mixture was filtered. The layers were separated and the aqueous phase was extracted with DCM (twice). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford intermediate **B16** (242 mg, 91 %) as a white solid.

*Compound **34***

N-[(1*S*,2*R*)-2-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)cyclopropyl]acetamide

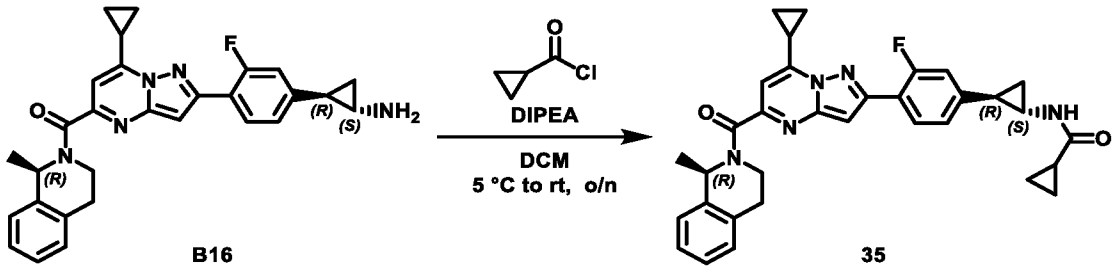


34

Acetyl chloride (39.3 µL, 0.55 mmol) was added to a mixture of intermediate **B16** (242 mg, 0.50 mmol) and Et_3N (167 µL, 1.21 mmol) in DCM (1.3 mL). The reaction mixture was stirred at rt for 24 h. The reaction was quenched by the addition of an aqueous solution of $NaHCO_3$. The layers were separated and the aqueous phase was extracted with DCM. The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was evaporated in vacuo. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 12 g GraceResolv™, liquid injection (DCM), mobile phase gradient: DCM / MeOH from 100:0 to 98:2). The residue was crystallized from MeOH, filtered off and dried to give compound **34** (104 mg, 40%) as a white solid.

Compound 35

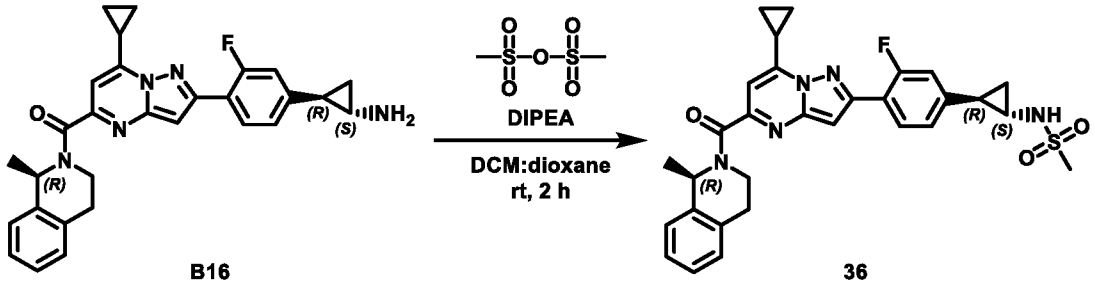
N-[(1*S*,2*R*)-2-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)cyclopropyl]cyclopropane-carboxamide



In a sealed tube DIPEA (178 µL, 1.02 mmol) was added to a solution of intermediate **B16** (158 mg, 0.31 mmol) in DCM (4 mL) at 5°C. The mixture was stirred for 15 min and cyclopropanecarbonyl chloride [4023-34-1] (30.8 µL, 339 µmol) was added. The reaction mixture was stirred at rt overnight. The reaction mixture was poured out into cold water. The layers were separated and the aqueous phase was extracted with DCM. The combined organic extracts were dried over $MgSO_4$, filtered and evaporated to dryness. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 12 g GraceResolv™, liquid injection (DCM), mobile phase gradient: DCM / EtOAc from 100:0 to 70:30). The residue was crystallized from MeOH, filtered off and dried under high vacuum at 50°C for 3 h to give compound **35** (87 mg, 51%) as an off-white solid.

Compound 36

N-[(1*S*,2*R*)-2-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)cyclopropyl]methanesulfonamide

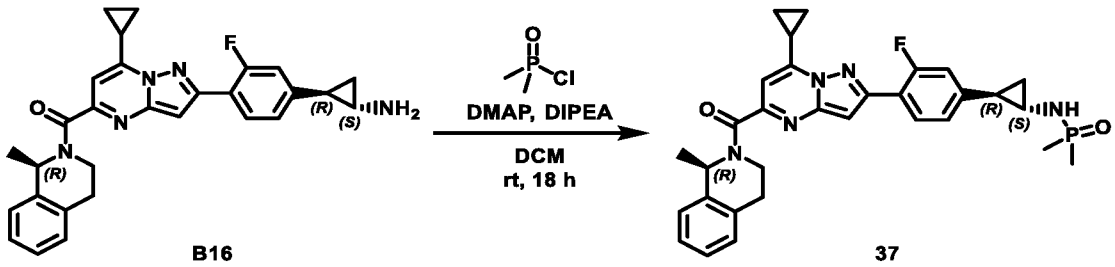


B16 36

To a mixture of intermediate **B16** (134 mg, 267 µmol) and DIPEA (55.2 µL, 0.32 mmol) in 1,4-dioxane (1 mL) under nitrogen was added a solution of methanesulfonic anhydride [7143-01-3] (51.2 mg, 0.29 mmol) in DCM (1 mL) dropwise. The reaction mixture was stirred at rt for 2 h. The reaction mixture was diluted with DCM and washed with a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$, filtered and evaporated in vacuo. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 12 g Grace®, dry loading (Celite®), mobile phase gradient: DCM / EtOAc from 100:0 to 95:5). The residue was crystallized from MeOH, filtered off and dried under high vacuum at 50°C for 20 h to give compound **36** (68 mg, 45%) as a white solid.

Compound 37

(1*R*)-2-(7-Cyclopropyl-2-{4-[(1*R*,2*S*)-2-[(dimethylphosphoryl)amino]cyclopropyl]-2-fluorophenyl}pyrazolo[1,5-a]pyrimidine-5-carbonyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline

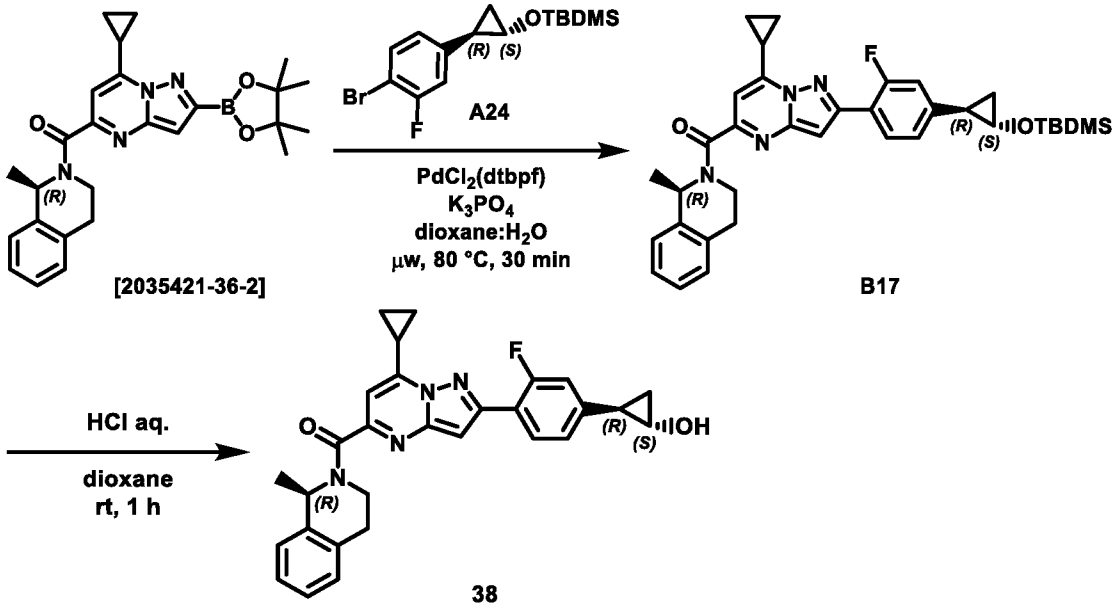


B16 37

Dimethylphosphinic chloride [1111-92-8] (41.0 mg, 0.36 mmol) was added to a mixture of intermediate **B16** (158 mg, 0.33 mmol), DIPEA (113 µL, 0.66 mmol) and DMAP (4.0 mg, 33.0 µmol) in anhydrous DCM (3.2 mL). The reaction mixture was stirred at rt for 2 h. An additional amount of dimethylphosphinic chloride (18.0 mg, 0.16 mmol) and DIPEA (57.0 µL, 0.33 mmol) were added and the reaction mixture was stirred for another 18 h. The reaction mixture was diluted with DCM, washed with a 10% aqueous solution of $NaHCO_3$,

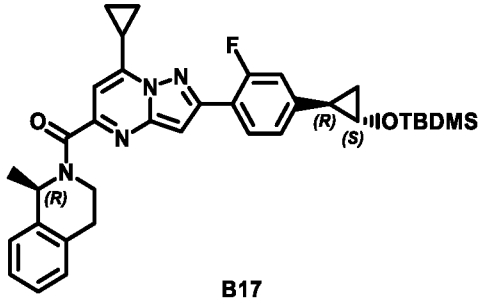
dried over $MgSO_4$, filtered and evaporated in vacuo. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 12 g GraceResolv™, liquid injection (DCM), mobile phase gradient: DCM / MeOH from 100:0 to 96:4). The product was solubilized in MeCN (2 mL), extended with water (10 mL) and freeze-dried to give compound **37** (30 mg, 16%) as a white solid.

Compound 38



*Intermediate **B17***

(1*R*)-2-(2-{4-[(1*R*,2*S*)-2-[(*Tert*-butyldimethylsilyl)oxy]cyclopropyl]-2-fluorophenyl}-7-cyclopropylpyrazolo[1,5-a]pyrimidine-5-carbonyl)-1-methyl-1,2,3,4-tetrahydro-isoquinoline

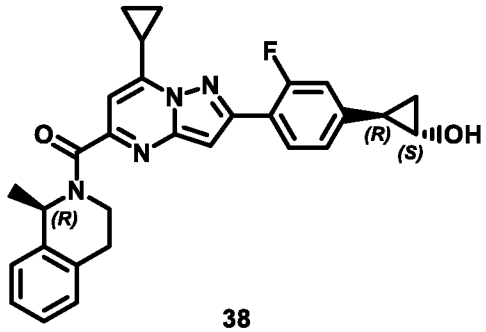


A sealed tube was charged with intermediate **A24** (120 mg, 347 µmol), (1*R*)-2-[7-cyclopropyl-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-36-2] (253 mg, 347 µmol, 63% purity), potassium phosphate tribasic (225 mg 1.06 mmol), 1,4-dioxane (3.5 mL) and

H_2O (1.0 mL) and purged with nitrogen. [1,1'-Bis(di-*tert*-butylphosphino)ferrocene]-dichloropalladium(II) (11.3 mg, 17.4 µmol) was added and the mixture was purged again with nitrogen. The reaction mixture was heated at 80°C using a single mode microwave (Biotage® Initiator EXP 60) with a power output ranging from 0 to 400 W for 30 min. The reaction mixture was diluted with water and EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc (twice). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was evaporated in vacuo. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 24 g GraceResolv™, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 99:1 to 40:60) to give intermediate **B17** (170 mg, 82%).

*Compound **38***

(1*S*,2*R*)-2-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)cyclopropan-1-ol

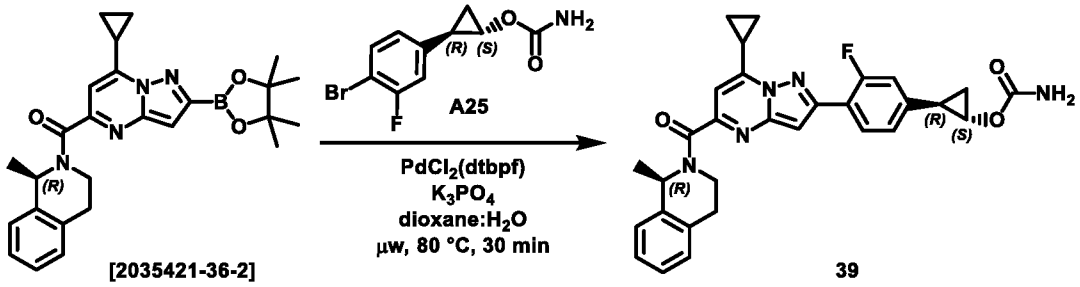


38

Hydrochloric acid (1.0 M in H_2O, 2.00 mL, 2.00 mmol) was added dropwise to a solution of intermediate **B17** (140 mg, 235 µmol) in 1,4-dioxane (2 mL). The reaction mixture was stirred at rt for 1 h. The reaction mixture was concentrated under reduced pressure. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 24 g GraceResolv™, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 99:1 to 40:60). The residue was taken up in acetone, evaporated in vacuo and dried under vacuum at 50°C for 16 h to give compound **38** (88 mg, 88%) as a white solid.

Compound 39

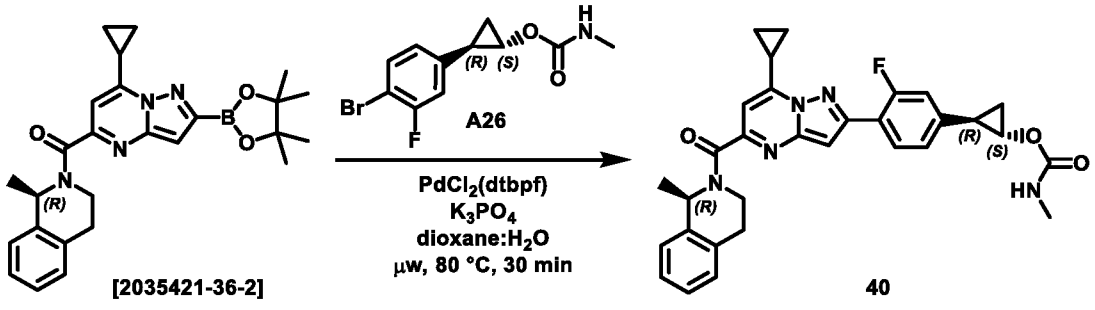
(1*S*,2*R*)-2-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)cyclopropyl carbamate



A sealed tube was charged with intermediate **A25** (78.0 mg, 285 µmol), (1*R*)-2-[7-cyclopropyl-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-36-2] (207 mg, 285 µmol, 63% purity), potassium phosphate tribasic (184 mg, 0.87 mmol), 1,4-dioxane (2.9 mL) and H_2O (0.8 mL) and purged with nitrogen. [1,1'-Bis(di-*tert*-butylphosphino)ferrocene]-dichloropalladium(II) (9.27 mg, 14.2 µmol) was added and the mixture was purged again with nitrogen. The reaction mixture was heated at 80°C using a single mode microwave (Biotage® Initiator EXP 60) with a power output ranging from 0 to 400 W for 30 min. The reaction mixture was diluted with water and EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc (twice). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was evaporated in vacuo. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 12 g GraceResolv™, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 80:20 to 40:60). A second purification was carried out by preparative LC (spherical C18 25 µm, 40 g YMC-ODS-25, dry loading (Celite®), mobile phase gradient (0.2% aq.NH_4HCO_3) / MeCN from 60:40 to 0:100). The residue was taken up in EtOH, evaporated in vacuo and dried under vacuum at 50°C for 16 h to give compound **39** (75 mg, 50%) as a white solid.

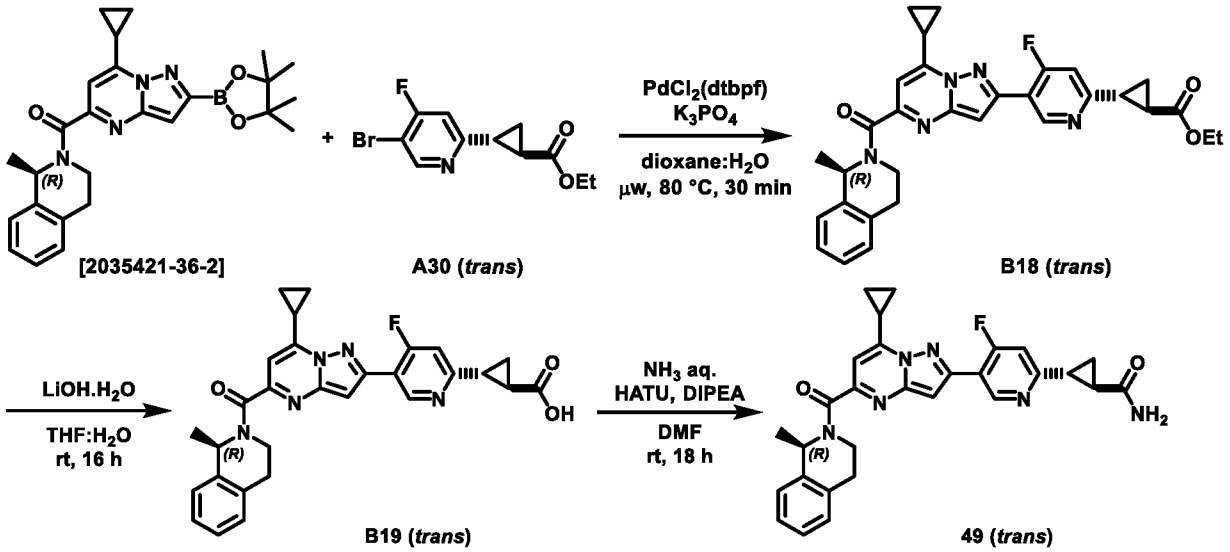
Compound 40

(1*S*,2*R*)-2-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)cyclopropyl N-methylcarbamate



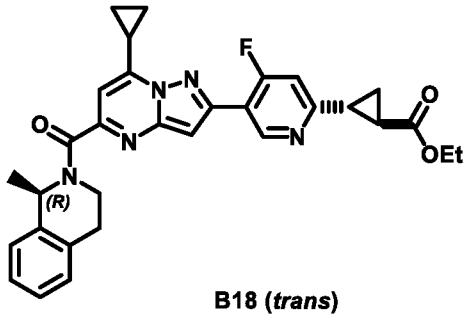
Compound **40** was synthesized from intermediate **A26** and (1*R*)-2-[7-cyclopropyl-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-36-2] according to the procedure reported for the synthesis of compound **39**. Compound **40** (120 mg, 56%) was obtained as a white solid.

Compound 49



*Intermediate **B18***

Ethyl *trans*-2-(5-{7-cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-4-fluoropyridin-2-yl)cyclopropane-1-carboxylate

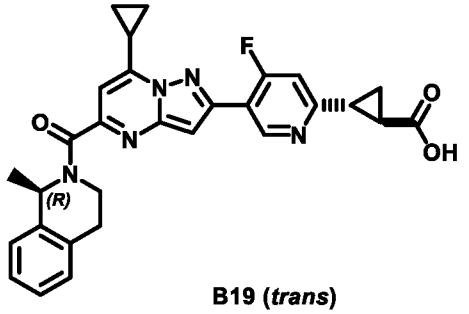


B18 (*trans*)

A sealed tube was charged with intermediate **A30** (111 mg, 385 µmol), (1*R*)-2-[7-cyclopropyl-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-36-2] (285 mg, 385 µmol, 62% purity), potassium phosphate tribasic (245 mg, 1.16 mmol), 1,4-dioxane (2.7 mL) and H_2O (0.7 mL) and purged with nitrogen. [1,1'-Bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II) (25.1 mg, 38.5 µmol) was added. The mixture was purged again with nitrogen and heated at 80 °C using a single mode microwave (Biotage® Initiator EXP 60) with a power output ranging from 0 to 400 W for 30 min. The reaction mixture was diluted with EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, filtered and evaporated in vacuo. The crude mixture was purified by preparative LC (irregular SiOH, 30 µm, 24 g GraceResolv™, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 80:20 to 20:80) to afford intermediate **B18** (182 mg, 88%).

*Intermediate **B19***

Trans-2-(5-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-4-fluoropyridin-2-yl)cyclopropane-1-carboxylic acid

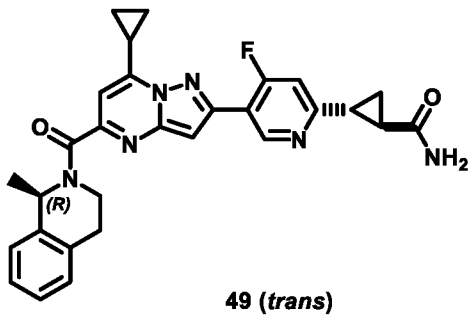


B19 (*trans*)

Lithium hydroxide monohydrate (42.0 mg, 1.00 mmol) was added to a solution of intermediate **B18** (180 mg, 334 µmol) in THF (2.9 mL) and H_2O (0.9 mL). The reaction mixture was stirred at rt for 16 h. A 10% aqueous solution of $KHSO_4$ was added until pH 6 and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with water, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 24 g GraceResolv™, liquid injection (DCM), mobile phase gradient: heptane / EtOAc / AcOH from 50:48.75:1.25 to 0:97.5:2.5). The residue was taken up in MeCN and the product was dried under vacuum at 50 °C for 16 h to afford intermediate **B19** (140 mg, 82%).

*Compound **49***

Trans-2-(5-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-4-fluoropyridin-2-yl)cyclopropane-1-carboxamide

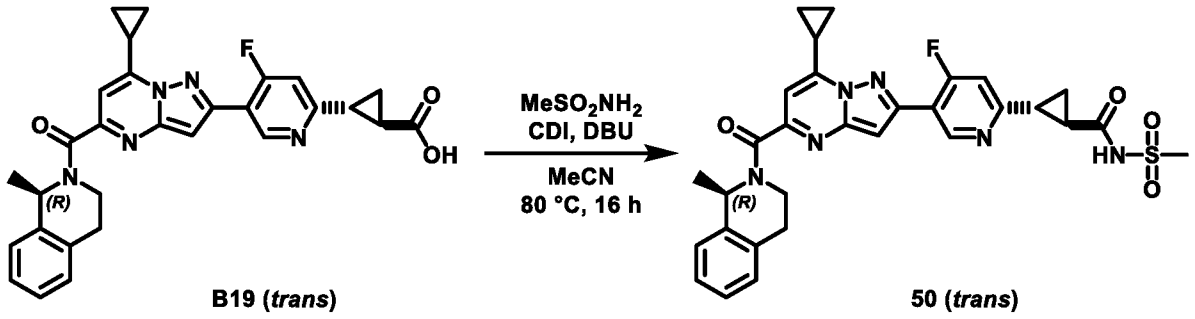


49 (*trans*)

A mixture of intermediate **B19** (66.0 mg, 129 µmol), HATU (73.6 mg, 194 µmol) and DIPEA (66.7 µL, 387 µmol) in DMF (3.5 mL) was stirred at rt for 1 h. Ammonia (28% in H_2O, 43.6 µL, 645 µmol) was added and the reaction mixture was stirred at rt for 18 h. The reaction mixture was diluted with water and EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered and evaporated in vacuo. The crude mixture was purified by reverse phase (spherical C18 25 µm, 40 g YMC-ODS-25, dry loading (Celite®), mobile phase gradient: (0.2% aq.NH_4HCO_3) / MeCN from 65:35 to 25:75) to give after freeze-drying (MeCN/H_2O) compound **49** (52 mg, 79%) as a white solid.

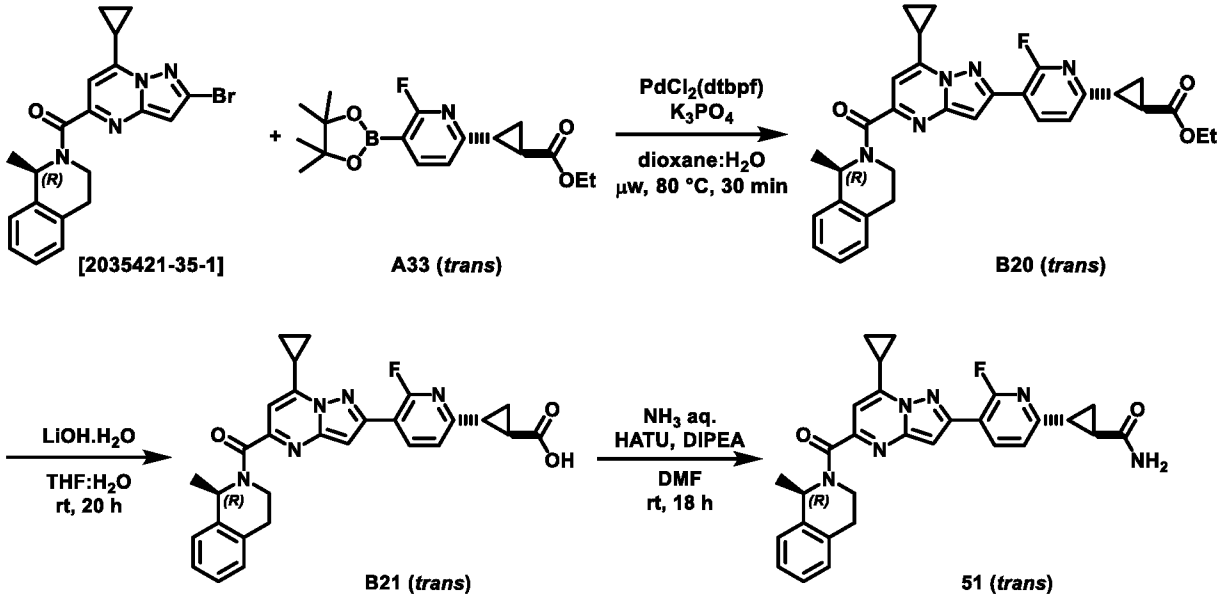
Compound 50

Trans-2-(5-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-4-fluoropyridin-2-yl)-N-methanesulfonylcyclopropane-1-carboxamide



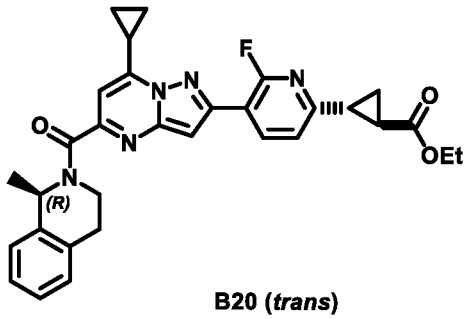
A mixture of intermediate **B19** (63.0 mg, 123 µmol) and CDI (30.0 mg, 185 µmol) in MeCN (1.2 mL) was stirred at rt for 2 h. DBU (36.8 µL, 246 µmol) and methanesulfonamide (23.4 mg, 246 µmol) were added. The reaction mixture was stirred at 80 °C for 16 h. Brine, a 1N aqueous solution of HCl and EtOAc were added. The layers were separated and the aqueous phase was extracted with EtOAc (twice). The combined organic extracts were washed with a solution of water and brine (1:1), dried over $MgSO_4$, filtered and evaporated in vacuo. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 12 g GraceResolv™, liquid injection (DCM), mobile phase gradient: DCM / *i*-PrOH from 99:1 to 80:20) to give after freeze drying ($MeCN/H_2O$) compound **50** (55 mg, 76%).

Compound 51



*Intermediate **B20***

Ethyl *trans*-2-(5-{7-cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-6-fluoropyridin-2-yl)cyclopropane-1-carboxylate

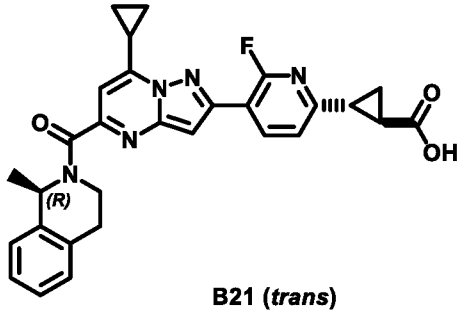


B20 (*trans*)

A sealed tube was charged with (1*R*)-2-{2-bromo-7-cyclopropylpyrazolo[1,5-a]pyrimidine-5-carbonyl}-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-35-1] (95.6 mg, 226 µmol), intermediate **A33** (91.0 mg, 271 µmol), potassium phosphate tribasic (164 mg, 773 µmol), 1,4-dioxane (3.5 mL) and H_2O (1.2 mL) and purged with nitrogen. [1,1'-Bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II) (16.2 mg, 24.9 µmol) was added and the mixture was purged again with nitrogen. The reaction mixture was heated at 80 °C using a single mode microwave (Biotage® Initiator EXP 60) with a power output ranging from 0 to 400 W for 30 min. The reaction mixture was diluted with EtOAc and water. The layers were separated and the organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 12 g GraceResolv™, dry loading (Celite®), mobile phase gradient: heptane / EtOAc from 80:20 to 50:50) to afford intermediate **B20** (128 mg, 98%) as an off-white solid.

*Intermediate **B21***

Trans-2-(5-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-6-fluoropyridin-2-yl)cyclopropane-1-carboxylic acid

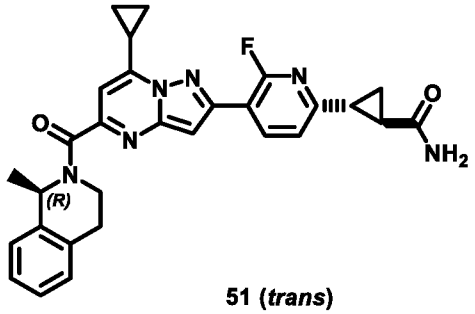


B21 (*trans*)

Lithium hydroxide monohydrate (24.6 mg, 587 µmol) was added to a solution of intermediate **B20** (113 mg, 195 µmol) in H_2O (1.5 mL) and THF (3.2 mL). The reaction mixture was stirred at rt for 20 h. A 10% aqueous solution of $KHSO_4$ was added and the mixture was diluted with DCM. The layers were separated and the aqueous phase was extracted with DCM (twice). The combined organic extracts were washed with a solution of water and brine (1:1), dried over $MgSO_4$, filtered and evaporated in vacuo. The residue (102 mg) was taken up in toluene and evaporated (twice) to afford intermediate **B21** (111 mg, 95%, 85% purity) as a yellowish gum.

*Compound **51***

Trans-2-(5-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-6-fluoropyridin-2-yl)cyclopropane-1-carboxamide

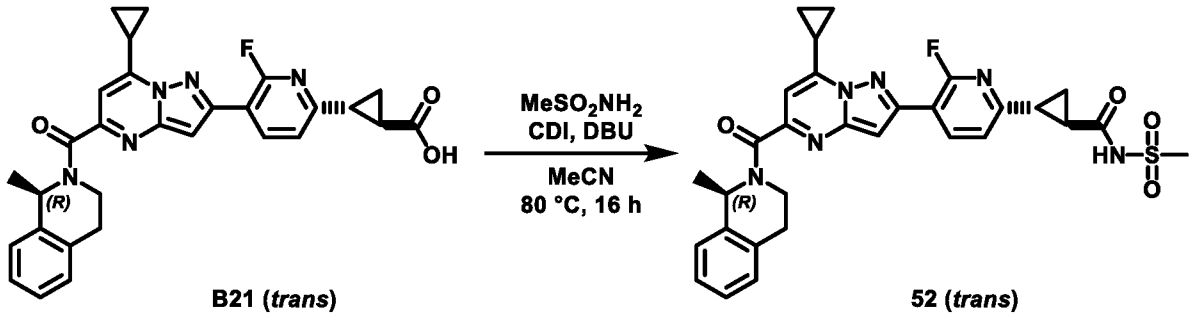


51 (*trans*)

A mixture of intermediate **B21** (55.0 mg, 91.4 µmol, 85% purity), HATU (52.1 mg, 137 µmol) and DIPEA (50 µL, 0.29 mmol) in DMF (2.5 mL) was stirred at rt for 1 h. Ammonia (28% in H_2O, 32 µL, 474 µmol) was added and the reaction mixture was stirred at rt for 18 h. The reaction mixture was diluted with water and EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc (twice). The combined organic extracts were washed with brine (3 times), dried over $MgSO_4$, filtered and evaporated in vacuo. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 12 g GraceResolv™, liquid injection (DCM), mobile phase gradient: DCM / MeOH from 100:0 to 98:2). The residue (34 mg) was solubilized in MeOH (2 mL), extended with water (10 mL) and freeze-dried to give compound **51** (29 mg, 62%) as a white solid.

Compound 52

Trans-2-(5-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-6-fluoropyridin-2-yl)-N-methanesulfonylcyclopropane-1-carboxamide



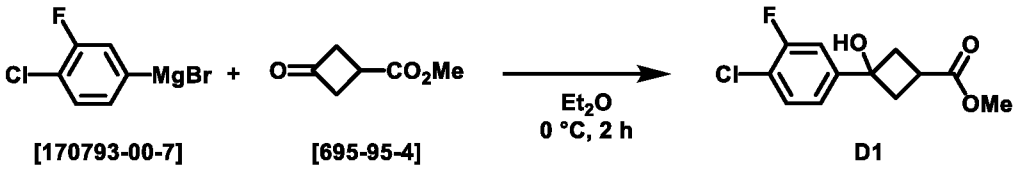
B21 (*trans*) 52 (*trans*)

A mixture of intermediate **B21** (55.0 mg, 91.4 µmol, 85% purity) and CDI (17.8 mg, 0.11 mmol) in MeCN (1 mL) was stirred at rt for 2 h. DBU (20.5 µL, 137 µmol) and methanesulfonamide (13.0 mg, 137 µmol) were added. The reaction mixture was stirred at 80 °C for 16 h. Brine, a 1N aqueous solution of HCl and DCM were added. The layers were separated and the aqueous phase was extracted with DCM (twice). The combined organic extracts were washed with a solution of water and brine (1:1), dried over $MgSO_4$, filtered and evaporated in vacuo. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 12 g GraceResolv™, liquid injection (DCM), mobile phase gradient: DCM / MeOH from 100:0 to 99:1). The residue was crystallized from MeOH. The solid was filtered off and dried under high vacuum at 50 °C for 18 h. The product (40 mg) was solubilized in MeCN (2 mL), extended with water (10 mL) and freeze-dried. The residue (36 mg) was purified by reverse phase (spherical C18, 25 µm, 40 g YMC-ODS-25, dry loading (Celite®), mobile phase gradient: (0.2% aq.NH_4HCO_3) / MeCN from 85:15 to 55:45) and freeze-dried to give compound **52** (26 mg, 48%) as a white solid.

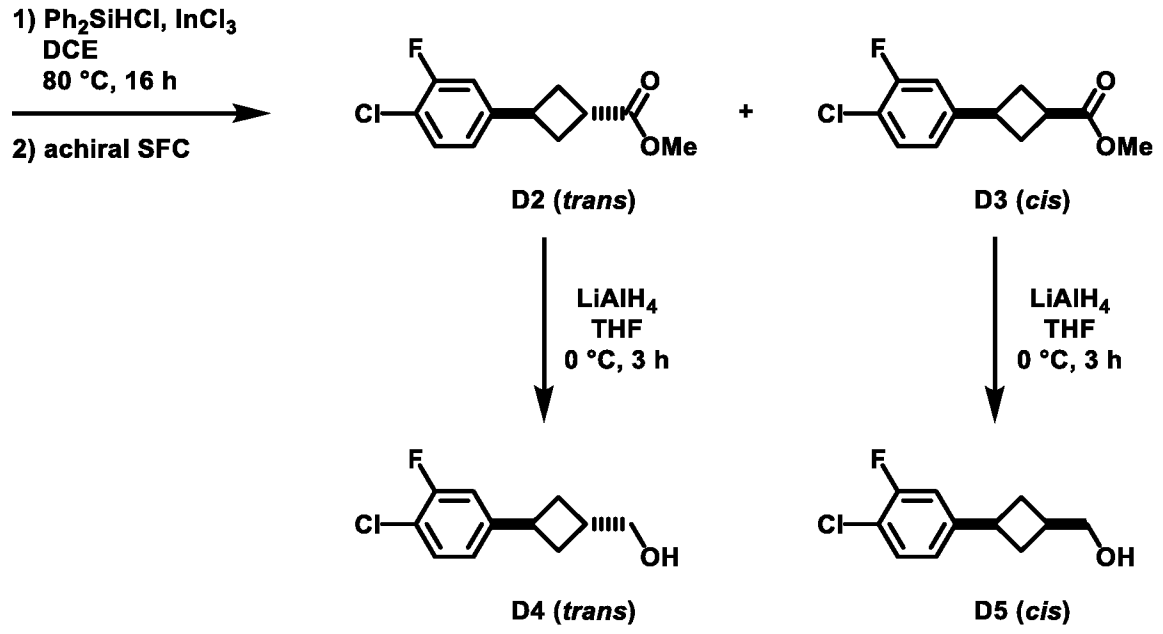
B.2. Preparation of Compounds of Formula (I) with n=2

B.2.1. Synthesis of Intermediates

B.2.1.1. Synthesis of Intermediates D4 and D5

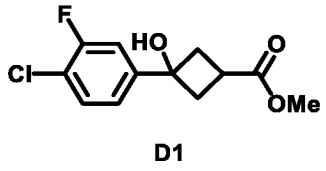


[170793-00-7] [695-95-4] D1



*Intermediate **D1***

Methyl 3-(4-chloro-3-fluorophenyl)-3-hydroxycyclobutane-1-carboxylate



D1

4-Chloro-3-fluorophenylmagnesium bromide [170793-00-7] (0.5 M in THF, 13.6 mL, 6.83 mmol) was added to a solution of methyl 3-oxocyclobutanecarboxylate [695-95-4] (0.74 mL, 7.04 mmol) in Et_2O (70 mL) at 0°C. The reaction mixture was stirred at 0°C for 2 h. A saturated aqueous solution of NH_4Cl was added and the mixture was diluted with EtOAc. The layers were separated and the organic phase was washed with water, dried over $MgSO_4$ and concentrated in vacuo to afford intermediate **D1** (1.47 g, 83%) as a yellow oil.

*Intermediates **D2** and **D3***

D2: Methyl *trans*-3-(4-chloro-3-fluorophenyl)cyclobutane-1-carboxylate

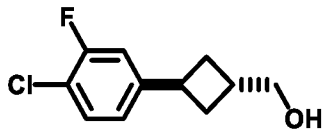
D3: Methyl *cis*-3-(4-chloro-3-fluorophenyl)cyclobutane-1-carboxylate

D2 (*trans*) D3 (*cis*)

Diphenylchlorosilane (2.30 mL, 11.7 mmol) was added to a mixture of intermediate **D1** (1.47 g, 5.68 mmol) and indium chloride (65.2 mg, 295 µmol) in DCE (8 mL). The reaction mixture was stirred at 80°C for 16 h. The mixture was poured out into a solution of EtOAc and water. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered and evaporated in vacuo. The crude mixture was purified by preparative LC (regular SiOH, 15-30 µm, 40 g Interchim®, dry loading (SiOH), mobile phase gradient: heptane / EtOAc from 100:0 to 50:50) to afford intermediate **D3** (266 mg, 19%) and two fractions A (268 mg) and B (536 mg) as a mixture of diastereoisomers. Fraction B was purified by preparative LC (Stationary phase: irregular bare silica 150 g, mobile phase: heptane / EtOAc 95:5) to afford a mixture of diastereoisomers (210 mg). The residue was combined with fraction A and the mixture was purified via achiral SFC (Stationary phase: Chiralpak IG 5µm 250*20mm, Mobile phase: 95% CO_2, 5% MeOH) to give intermediate **D2** (300 mg, 22%) and intermediate **D3** (67 mg, 5%) as colorless oils.

*Intermediate **D4***

[*trans*-3-(4-Chloro-3-fluorophenyl)cyclobutyl]methanol

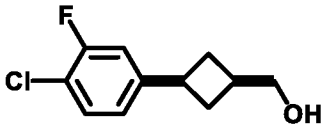


D4 (*trans*)

Lithium aluminium hydride (1.0 M in THF, 0.95 mL, 0.95 mmol) was added dropwise to a solution of intermediate **D2** (225 mg, 927 µmol) in THF (9 mL) at 0°C. The reaction mixture was stirred at 0°C for 3 h. The reaction was quenched by the careful addition of water (32 µL) at 0°C followed by a 3M aqueous solution of NaOH (32 µL) and water (64 µL). The mixture was subsequently diluted with EtOAc. A solution of Rochelle salt was added and the layers were separated. The organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated to dryness to afford intermediate **D4** (286 mg, quant. 70% purity) as a colorless oil.

*Intermediate **D5***

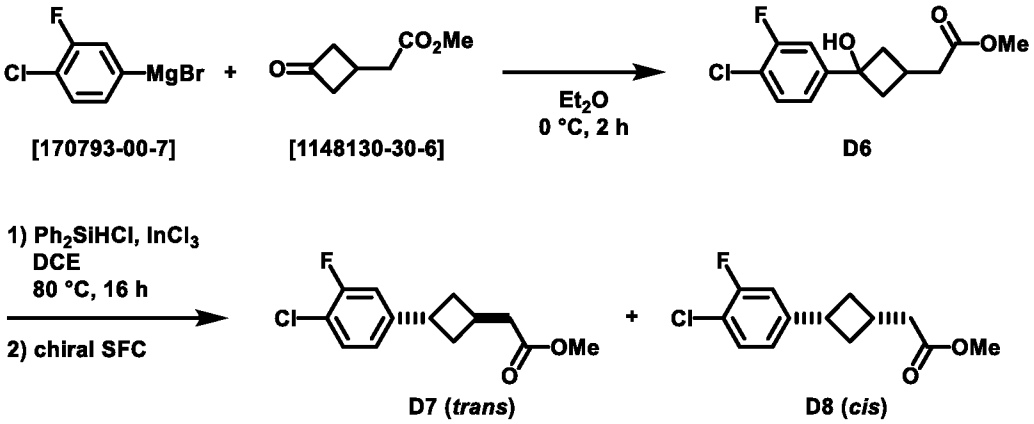
[*cis*-3-(4-Chloro-3-fluorophenyl)cyclobutyl]methanol



D5 (*cis*)

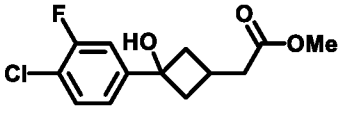
Intermediate **D5** was synthesized from intermediate **D3** according to the procedure reported for the synthesis of intermediate **D4**. Intermediate **D5** (221 mg, quant.) was obtained as a colorless oil.

B.2.1.2. Synthesis of Intermediates D7 and D8



*Intermediate **D6***

Methyl 2-[3-(4-chloro-3-fluorophenyl)-3-hydroxycyclobutyl]acetate



D6

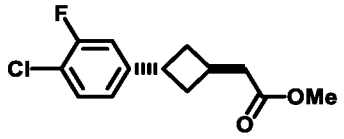
4-Chloro-3-fluorophenylmagnesium bromide [170793-00-7] (13.7 mL, 6.83 mmol) was added to a solution of methyl 2-(3-oxocyclobutyl)acetate [1148130-30-6] (1.00 g, 7.04 mmol) in Et_2O (70 mL) at 0°C. The reaction mixture was stirred at 0°C for 2 h. A saturated aqueous solution of NH_4Cl was added and the mixture was diluted with EtOAc. The layers were separated and the organic phase was washed with water, dried over $MgSO_4$ and concentrated in vacuo. The crude mixture was purified by preparative LC (regular SiOH,

15-30 µm, 40 g GraceResolv™, dry loading (SiOH), mobile phase gradient: heptane / EtOAc from 90:10 to 50:50) to afford intermediate **D6** (1.15 g, 61%) as a colorless oil.

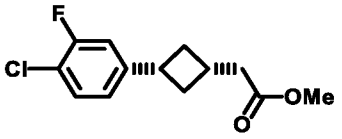
*Intermediates **D7** and **D8***

D7: Methyl 2-[*trans*-3-(4-chloro-3-fluorophenyl)cyclobutyl]acetate

D8: Methyl 2-[*cis*-3-(4-chloro-3-fluorophenyl)cyclobutyl]acetate



D7 (*trans*)



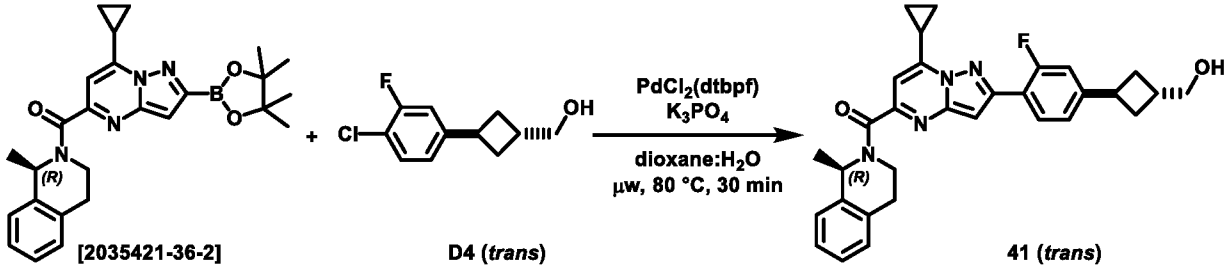
D8 (*cis*)

Diphenylchlorosilane (1.70 mL, 8.65 mmol) was added to a mixture of intermediate **D6** (1.15 g, 4.22 mmol) and indium chloride (48.4 mg, 219 µmol) in DCE (6 mL). The reaction mixture was stirred at 80°C for 16 h. The resulting mixture was poured out into a solution of EtOAc and water. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered and evaporated in vacuo. The crude mixture was purified by preparative LC (regular SiOH, 15-30 µm, 80 g Interchim®, dry loading (SiOH), mobile phase gradient: heptane / EtOAc from 100:0 to 50:50). The diastereoisomers (684 mg) were separated by chiral SFC (Stationary phase: Lux Cellulose-2 5µm 250*30mm, Mobile phase: 96% CO_2, 4% *i*-PrOH) to afford intermediate **D8** (313 mg, 29%) and intermediate **D7** (158 mg, 15%).

B.2.2. Synthesis of Final Compounds

Compound 41

[*trans*-3-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)cyclobutyl]methanol



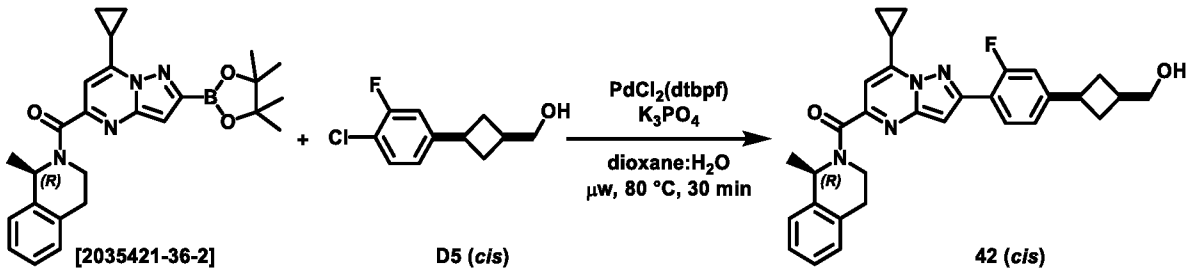
[2035421-36-2] D4 (*trans*) 41 (*trans*)

A sealed tube was charged with (1*R*)-2-[7-cyclopropyl-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-36-2] (392 mg, 582 µmol, 68% purity), intermediate **D4** (200 mg, 932 µmol), potassium phosphate tribasic (551 mg, 2.60 mmol), 1,4-dioxane (7 mL) and H_2O (3 mL)

and purged with nitrogen. [1,1'-Bis(di-*tert*-butylphosphino)ferrocene]dichloro-palladium(II) (84.7 mg, 130 µmol) was added and the mixture was purged again with nitrogen. The reaction mixture was heated at 80°C using a single mode microwave (Biotage® Initiator EXP 60) with a power output ranging from 0 to 400 W for 30 min. The reaction mixture was diluted with EtOAc and water and filtered over a pad of Celite®. The filtrate was decanted and the organic phase was washed with brine (twice), dried over $MgSO_4$, filtered and concentrated to dryness. The crude mixture was purified by flash chromatography (irregular SiOH, 15-40 µm, 25 g GraceResolv™, dry loading (SiOH), mobile phase gradient: heptane / EtOAc from 90:10 to 20:80). The residue was purified by reverse phase (spherical C18, 25 µm, 40 g YMC-ODS-25, liquid injection (MeCN), mobile phase gradient: (0.2% aq.NH_4HCO_3) / MeCN, from 60:40 to 0:100). The fractions containing pure product were combined, concentrated to dryness and co-evaporated with MeCN to give compound **41** (116 mg, 39%) as a white foam.

Compound 42

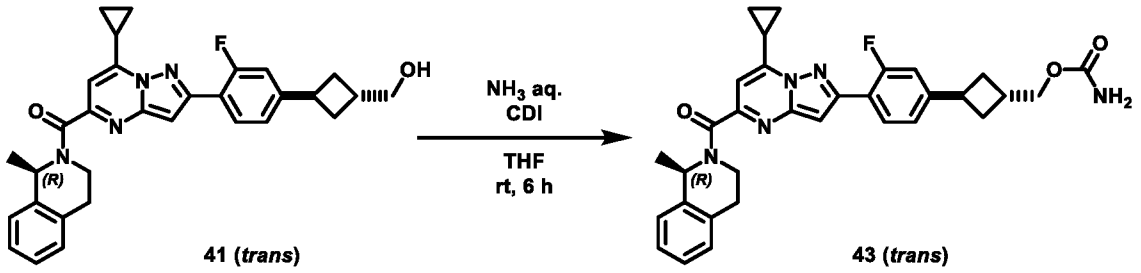
[*cis*-3-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)cyclobutyl]methanol



Compound **42** was synthesized from intermediate **D5** and (1*R*)-2-[7-cyclopropyl-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-36-2] according to the procedure reported for the synthesis of compound **41**. The crude mixture was purified by flash chromatography (irregular SiOH, 15-40 µm, 25 g GraceResolv™, dry loading (SiOH), mobile phase gradient: heptane / EtOAc from 90:10 to 20:80). The residue was purified by reverse phase (spherical C18, 25 µm, 40 g YMC-ODS-25, liquid injection (MeCN), mobile phase gradient: (0.2% aq.NH_4HCO_3) / MeCN from 60:40 to 0:100). The fractions containing pure product were combined, concentrated to dryness, co-evaporated with MeCN and dried under high vacuum at 60°C for 16 h to give compound **42** (154 mg, 52%) as a white solid.

Compound 43

[*trans*-3-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)cyclobutyl]methyl carbamate

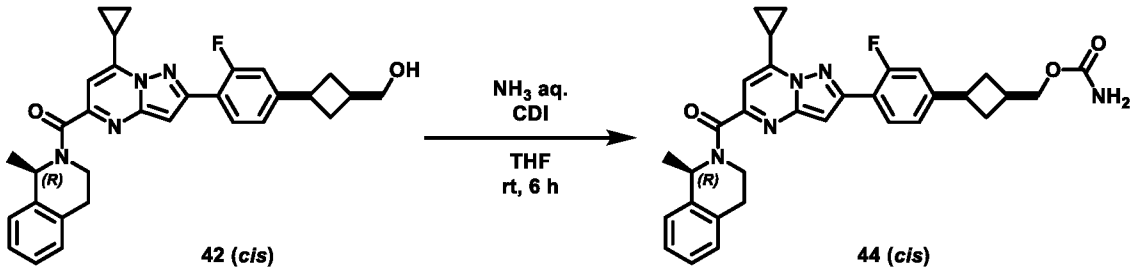


41 (*trans*) 43 (*trans*)

CDI (41.9 mg, 259 µmol) was added to a solution of compound **41** (66.0 mg, 129 µmol) in THF (0.8 mL) and the reaction mixture was stirred at rt for 4 h. Ammonia (28% in H_2O, 484 µL, 7.16 mmol) was added and the reaction mixture was stirred at rt for 2 h. The reaction mixture was diluted with EtOAc. The layers were separated and the organic phase was washed with a saturated aqueous solution of NH_4Cl (twice), water and brine (twice), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was dried under high vacuum at 60°C for 16 h to give compound **43** (42 mg, 59%) as a white solid.

Compound 44

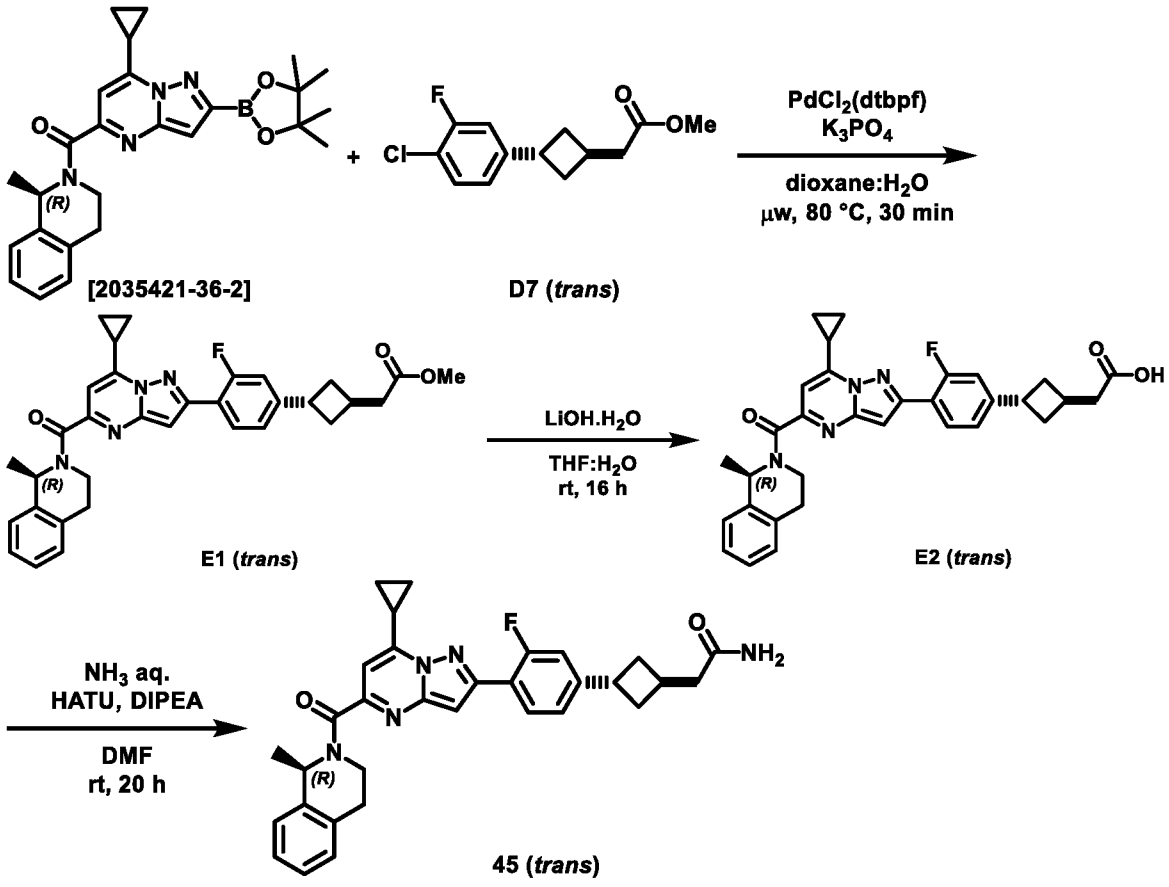
[*cis*-3-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)cyclobutyl]methyl carbamate



42 (*cis*) 44 (*cis*)

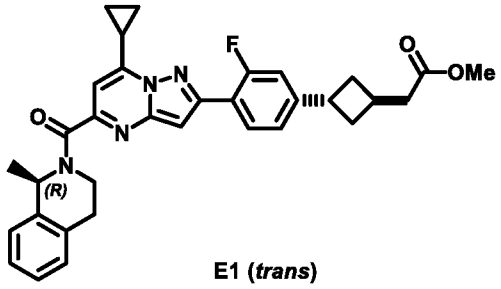
CDI (46.4 mg, 286 µmol) was added to a solution of compound **42** (73.0 mg, 143 µmol) in THF (0.9 mL) and the reaction mixture was stirred at rt for 4 h. Ammonia (28% in H_2O, 535 µL, 7.92 mmol) was added and the reaction mixture was stirred at rt for 2 h. The reaction mixture was combined with another sample (20.0 mg, 39.2 µmol) and diluted with EtOAc, water and brine. The layers were separated and the organic phase was washed with a saturated aqueous solution of NH_4Cl (twice) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was taken up in MeCN (twice) and concentrated to dryness. The product was dried under high vacuum at 60°C for 16 h to give compound **44** (52 mg, 52%) as a white solid.

Compound 45



*Intermediate **E1***

Methyl 2-[*trans*-3-(4-{7-cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)cyclobutyl]acetate

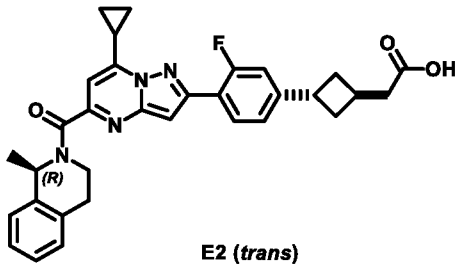


A sealed tube was charged with (1*R*)-2-[7-cyclopropyl-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-36-2] (284 mg, 385 mmol, 62% purity), intermediate **D7** (158 mg, 615 µmol), potassium phosphate tribasic (364 mg, 1.71 mmol), 1,4-dioxane (3.5 mL) and H_2O (1.4 mL) and purged with nitrogen. [1,1'-Bis(di-*tert*-butylphosphino)ferrocene]dichloro-

palladium(II) (56.0 mg, 85.9 µmol) was added and the mixture was purged again with nitrogen. The reaction mixture was heated at 80°C using a single mode microwave (Biotage® Initiator EXP 60) with a power output ranging from 0 to 400 W for 30 min. The reaction mixture was diluted with EtOAc. The organic layer was washed with an aqueous solution of $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and evaporated in vacuo. The crude mixture was purified by preparative LC (regular SiOH, 30 µm, 25 g Interchim®, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 90:10 to 30:70) to afford intermediate **E1** (138 mg, 65%) as a yellow foam.

*Intermediate **E2***

2-[*trans*-3-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)cyclobutyl]acetic acid

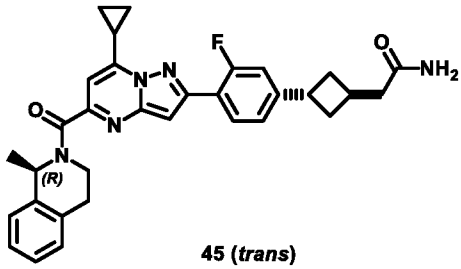


E2 (*trans*)

Lithium hydroxide monohydrate (32.3 mg, 0.77 mmol) was added to a solution of intermediate **E1** (138 mg, 0.25 mmol) in THF (2.2 mL) and H_2O (0.77 mL). The reaction mixture was stirred at rt for 16 h. A 10% aqueous solution of $KHSO_4$ was added until pH 3 and the mixture was diluted with EtOAc. The layers were separated and the organic phase was washed with brine and water (twice), dried over $MgSO_4$, filtered and concentrated to dryness to afford intermediate **E2** (140 mg, 94%) as a yellow solid.

*Compound **45***

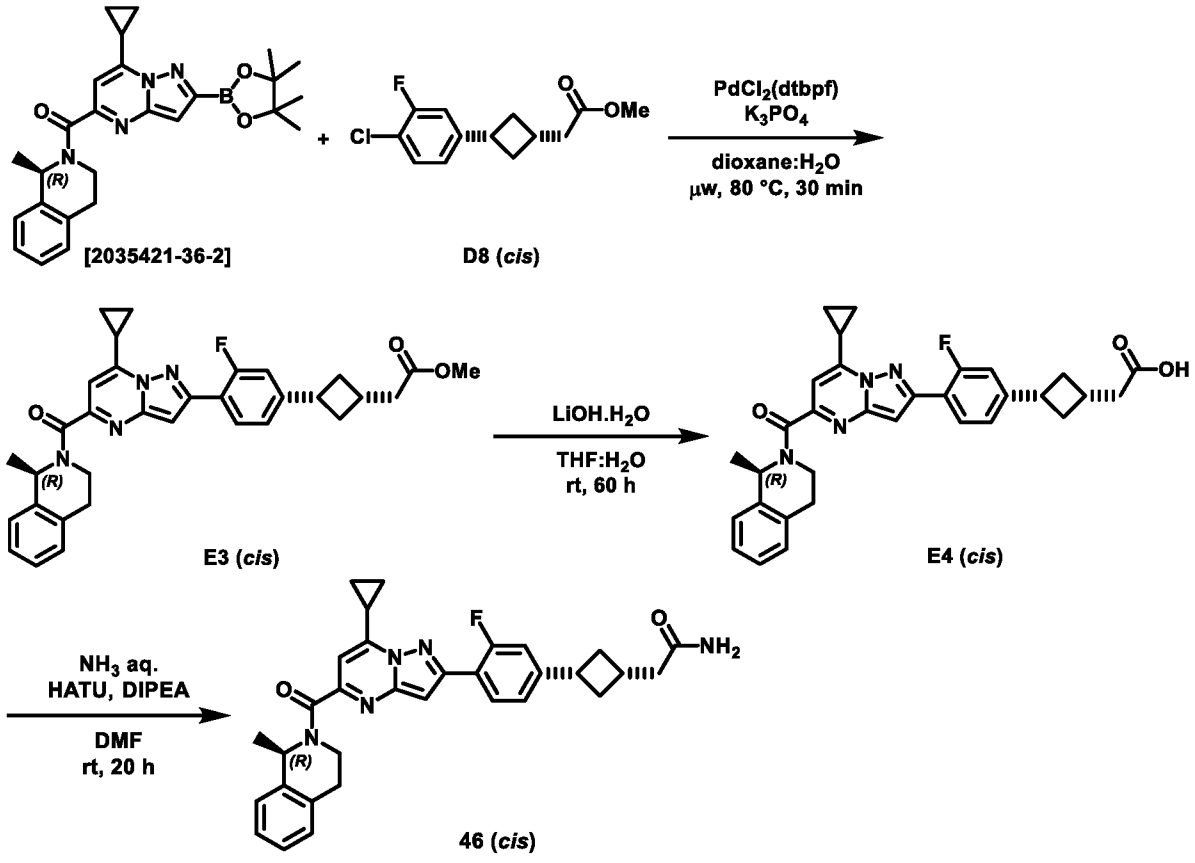
2-[*trans*-3-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)cyclobutyl]acetamide



45 (*trans*)

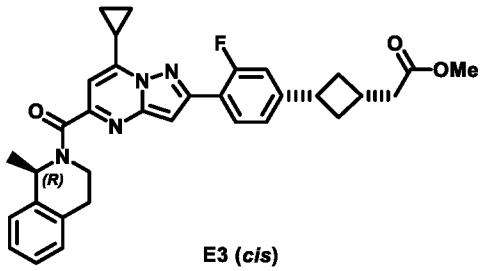
In a screw cap vial HATU (66.7 mg, 175 µmol) was added to a mixture of intermediate **E2** (70.0 mg, 117 µmol) and DIPEA (60.5 µL, 0.35 mmol) in DMF (1.1 mL). The reaction mixture was stirred at rt for 10 min. Ammonia (30% in H_2O, 221 µL, 3.51 mmol) was added and the reaction mixture was stirred at rt for 20 h. The reaction mixture was diluted with water, brine and EtOAc. The layers were separated and the organic phase was washed with brine (3 times), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (irregular SiOH, 15-40 µm, 12 g GraceResolv™, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 50:50 to 0:100). The residue (30 mg) was diluted with EtOAc and sonicated. A precipitate was observed. The suspension was concentrated to dryness and dried under high vacuum at 60°C for 16 h to give compound **45** (28 mg, 45%) as a white solid.

Compound 46



*Intermediate **E3***

Methyl 2-[*cis*-3-(4-{7-cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)cyclobutyl]acetate

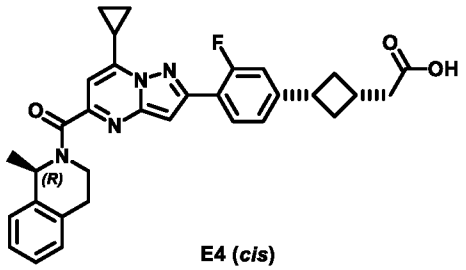


E3 (*cis*)

A sealed tube was charged with (1*R*)-2-[7-cyclopropyl-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-36-2] (563 mg, 762 µmol, 62% purity), intermediate **D8** (313 mg, 1.22 mmol), potassium phosphate tribasic (721 mg, 3.40 mmol), 1,4-dioxane (10.4 mL) and H_2O (2.7 mL) and purged with nitrogen. [1,1'Bis(di-*tert*-butylphosphino)ferrocene]dichloro-palladium(II) (111 mg, 170 µmol) was added and the mixture was purged again with nitrogen. The reaction mixture was heated at 80°C using a single mode microwave (Biotage® Initiator EXP 60) with a power output ranging from 0 to 400 W for 30 min. The reaction mixture was diluted with EtOAc and the organic phase was washed with an aqueous solution of $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and evaporated in vacuo. The crude mixture was purified by preparative LC (regular SiOH, 30 µm, 25 g Interchim®, dry loading (SiOH), mobile phase gradient: heptane / EtOAc from 90:10 to 30:70) to afford intermediate **E3** (227 mg, 54%) as a beige foam.

*Intermediate **E4***

2-[*cis*-3-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)cyclobutyl]acetic acid



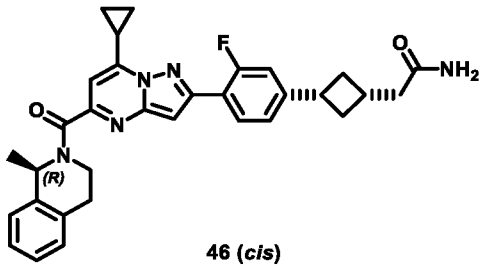
E4 (*cis*)

Lithium hydroxide monohydrate (52.7 mg, 1.26 mmol) was added to a solution of intermediate **E3** (225 mg, 407 µmol) in THF (3.6 mL) and H_2O (1.2 mL). The reaction mixture was stirred at rt for 60 h. A 10% aqueous solution of $KHSO_4$ was added until pH 3

and the mixture was diluted with EtOAc. The layers were separated and the organic phase was washed with brine and water (twice), dried over $MgSO_4$, filtered and concentrated to dryness to afford intermediate **E4** (221 mg, 93%) as a yellow solid.

*Compound **46***

2-[*cis*-3-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)cyclobutyl]acetamide

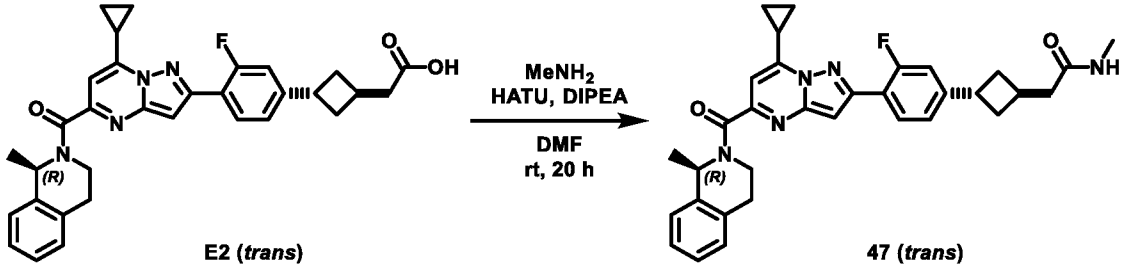


46 (*cis*)

In a screw cap vial HATU (107 mg, 282 µmol) was added to a mixture of intermediate **E4** (110 mg, 188 µmol, 92% purity) and DIPEA (97.1 µL, 564 µmol) in DMF (1.8 mL). The reaction mixture was stirred at rt for 10 min. Ammonia (30% in H_2O, 356 µL, 5.64 mmol) was added and the reaction mixture was stirred at rt for 20 h. The reaction mixture was diluted with water, brine and EtOAc. The layers were separated and the organic phase was washed with brine (3 times), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (irregular SiOH, 15-40 µm, 12 g GraceResolv™, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 50:50 to 0:100). The residue (61 mg) was diluted with Et_2O and the solution was sonicated. A precipitate was formed. The suspension was concentrated to dryness and dried under high vacuum at 60°C for 16 h to give compound **46** (58 mg, 57%) as a white solid.

Compound 47

N-methyl-2-[*trans*-3-(4-{7-cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)cyclobutyl]acetamide



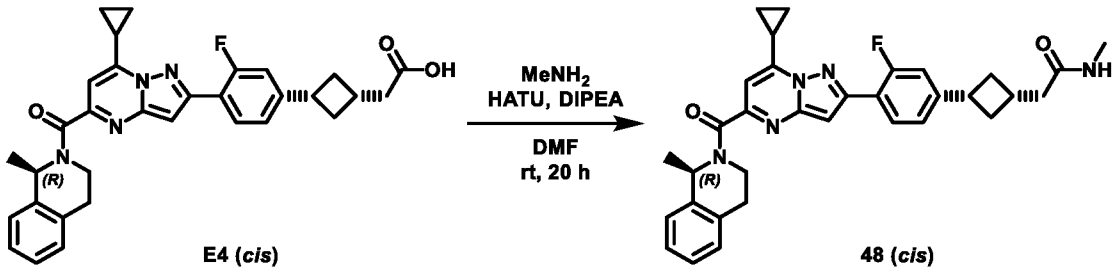
E2 (*trans*) **47 (*trans*)**

In a screw cap vial HATU (66.7 mg, 175 µmol) was added to a mixture of intermediate **E2** (70.0 mg, 117 µmol) and DIPEA (70.5 µL, 409 µmol) in DMF (1.1 mL). The reaction

mixture was stirred at rt for 10 min. Methylamine (2.0 M in THF, 409 µL, 818 µmol) was added and the reaction mixture was stirred at rt for 20 h. The reaction mixture was diluted with water, brine and EtOAc. The layers were separated and the organic phase was washed with brine (3 times), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (irregular SiOH, 15-40 µm, 12 g GraceResolv™, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 50:50 to 0:100). Et_2O was added to the residue (37 mg). The mixture was sonicated. A precipitate was formed and the suspension was concentrated to dryness. The product was dried under high vacuum at 60°C for 16 h to give compound **47** (36 mg, 56%) as a white solid.

Compound 48

N-methyl-2-[*cis*-3-(4-{7-cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)cyclobutyl]acetamide



Compound **48** was synthesized from intermediate **E4** according to the procedure reported for the synthesis of compound **47**. The crude mixture was purified by flash chromatography (irregular SiOH, 15-40 µm, 12 g GraceResolv™, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 50:50 to 0:100). Et_2O was added to the residue (80 mg) and sonicated. A precipitate was formed. The suspension was concentrated to dryness and dried under high vacuum at 60°C for 16 h to give compound **48** (75 mg, 72%) as a white solid.

C. Compound identification

^{1}H-NMR

^{1}H-NMR spectra were recorded on a Bruker Avance DRX 400 spectrometer using internal deuterium lock and equipped with reverse double-resonance (^{1}H, ^{13}C, SEI) probe head with z gradients and operating at 400 MHz for proton and 100 MHz for carbon and a Bruker Avance 500 MHz spectrometer equipped with a Bruker 5mm BBFO probe head with z gradients and operating at 500 MHz for proton and 125 MHz for carbon.
NMR spectra were recorded at ambient temperature unless otherwise stated.

Data are reported as follow: chemical shift in parts per million (ppm) relative to TMS (δ = 0 ppm) which was used as internal standard, integration, multiplicity (s = singulet, d = doublet, t = triplet, q = quartet, quin = quintuplet, sex = sextuplet, m = multiplet, b = broad, or a combination of these), coupling constant(s) J in Hertz (Hz).

Compound 1

Major rotamer (65%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.06 (t, J=8.2 Hz, 1H), 7.32 (d, J=7.3 Hz, 1H), 7.05 - 7.25 (m, 6H), 6.89 (s, 1H), 5.59 (q, J=6.6 Hz, 1H), 4.67 (t, J=5.7 Hz, 1H), 3.81 (br dd, J=13.4, 4.3 Hz, 1H), 3.42 - 3.54 (m, 2H), 3.34 - 3.41 (m, 1H), 2.83 - 3.05 (m, 2H), 2.71 (br d, J=16.4 Hz, 1H), 1.88 - 1.93 (m, 1H), 1.52 (d, J=6.6 Hz, 3H), 1.22 - 1.44 (m, 5H), 0.98 (t, J=6.9 Hz, 2H).

Minor rotamer (35%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.06 (t, J=8.2 Hz, 1H), 7.05 - 7.25 (m, 7H), 6.85 (s, 1H), 4.96 (q, J=6.9 Hz, 1H), 4.67 (t, J=5.7 Hz, 1H), 4.55 (br d, J=12.0 Hz, 1H), 3.42 - 3.54 (m, 1H), 3.34 - 3.41 (m, 1H), 3.23 - 3.30 (m, 1H), 2.83 - 3.05 (m, 3H), 1.88 - 1.93 (m, 1H), 1.55 (d, J=6.6 Hz, 3H), 1.22 - 1.44 (m, 5H), 0.98 (t, J=6.9 Hz, 2H).

Compound 2

Major rotamer (65%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 11.13 (br s, 1H), 8.11 (br t, J=7.4 Hz, 1H), 7.06 - 7.36 (m, 7H), 6.90 (s, 1H), 5.88 (s, 1H), 5.59 (q, J=6.6 Hz, 1H), 3.81 (br d, J=10.1 Hz, 1H), 3.47 (br t, J=11.8 Hz, 1H), 2.82 - 3.07 (m, 2H), 2.72 (br d, J=16.4 Hz, 1H), 1.63 (br t, J=6.9 Hz, 2H), 1.53 (br d, J=6.3 Hz, 3H), 1.21 - 1.39 (m, 4H), 1.11 - 1.20 (m, 2H).

Minor rotamer (35%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 11.13 (br s, 1H), 8.11 (br t, J=7.4 Hz, 1H), 7.06 - 7.36 (m, 7H), 6.87 (s, 1H), 5.88 (s, 1H), 4.96 (q, J=6.3 Hz, 1H), 4.56 (br d, J=11.3 Hz, 1H), 3.19 - 3.28 (m, 1H), 2.82 - 3.07 (m, 3H), 1.63 (br t, J=6.9 Hz, 2H), 1.55 (br d, J=6.6 Hz, 3H), 1.21 - 1.39 (m, 4H), 1.11 - 1.20 (m, 2H).

Compound 3

Major rotamer (65%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.12 (t, J=7.9 Hz, 1H), 7.32 (d, J=7.3 Hz, 1H), 7.10 - 7.29 (m, 6H), 6.91 (s, 1H), 5.59 (q, J=6.4 Hz, 1H), 3.81 (br dd, J=13.6, 3.8 Hz, 1H), 3.41 - 3.51 (m, 1H), 2.87 - 3.05 (m, 2H), 2.80 - 2.86 (m, 1H), 2.71 (br d, J=16.1 Hz, 1H), 2.17 - 2.23 (m, 1H), 1.71 (dt, J=9.3, 5.4 Hz, 1H), 1.58 - 1.65 (m, 1H), 1.52 (d, J=6.6 Hz, 3H), 1.32 - 1.38 (m, 2H), 1.24 - 1.31 (m, 2H).

Minor rotamer (35%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.12 (t, J=7.9 Hz, 1H), 7.10 - 7.29 (m, 6H), 7.07 (d, J=7.6 Hz, 1H), 6.87 (s, 1H), 4.96 (q, J=6.8 Hz, 1H), 4.52 - 4.59 (m, 1H), 3.23 - 3.30 (m, 1H), 2.87 - 3.05 (m, 3H), 2.80 - 2.86 (m, 1H), 2.17 - 2.23 (m, 1H), 1.71 (dt, J=9.3, 5.4 Hz, 1H), 1.58 - 1.65 (m, 1H), 1.55 (d, J=6.6 Hz, 3H), 1.32 - 1.38 (m, 2H), 1.24 - 1.31 (m, 2H).

Compound 4

Major rotamer (65%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 8.13 (br s, 1H), 7.05 - 7.38 (m, 7H), 6.90 (s, 1H), 5.59 (q, J=6.4 Hz, 1H), 3.81 (br dd, J=12.6, 3.5 Hz, 1H), 3.40 - 3.52 (m, 2H), 2.85 - 3.08 (m, 2H), 2.68 - 2.76 (m, 1H), 2.57 - 2.65 (m, 1H), 1.78 (br s, 2H), 1.52 (d, J=6.6 Hz, 3H), 1.22 - 1.40 (m, 4H).

Minor rotamer (35%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 8.13 (br s, 1H), 7.05 - 7.38 (m, 7H), 6.86 (s, 1H), 4.96 (q, J=6.7 Hz, 1H), 4.56 (br d, J=13.1 Hz, 1H), 3.40 - 3.52 (m, 2H), 2.85 - 3.08 (m, 3H), 2.57 - 2.65 (m, 1H), 1.78 (br s, 2H), 1.55 (br d, J=6.6 Hz, 3H), 1.22 - 1.40 (m, 4H).

Compound 5

Major rotamer (65%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 12.28 (br s, 1H), 8.12 (t, J=8.1 Hz, 1H), 7.04 - 7.35 (m, 7H), 6.90 (s, 1H), 5.59 (q, J=6.6 Hz, 1H), 4.34 (br t, J=5.1 Hz, 1H), 3.81 (br dd, J=13.4, 4.6 Hz, 1H), 2.82 - 3.08 (m, 2H), 2.71 (br d, J=16.2 Hz, 1H), 2.56 - 2.64 (m, 1H), 2.25 - 2.34 (m, 1H), 1.66 (t, J=7.3 Hz, 2H), 1.52 (d, J=6.6 Hz, 3H), 1.22 - 1.40 (m, 4H).

Minor rotamer (35%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 12.28 (br s, 1H), 8.12 (t, J=8.1 Hz, 1H), 7.04 - 7.35 (m, 7H), 6.87 (s, 1H), 4.96 (q, J=6.9 Hz, 1H), 4.51 - 4.60 (m, 1H), 3.22 - 3.29 (m, 1H), 2.82 - 3.08 (m, 3H), 2.56 - 2.64 (m, 1H), 2.25 - 2.34 (m, 1H), 1.66 (t, J=7.3 Hz, 2H), 1.55 (br d, J=7.1 Hz, 3H), 1.22 - 1.40 (m, 4H).

Compound 7

Major rotamer (65%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 8.09 (t, J=8.1 Hz, 1H), 7.61 (br s, 1H), 7.32 (d, J=7.6 Hz, 1H), 7.05 - 7.26 (m, 6H), 6.95 (br s, 1H), 6.89 (s, 1H), 5.59 (q, J=6.9 Hz, 1H), 3.81 (br dd, J=13.4, 3.8 Hz, 1H), 3.41 - 3.52 (m, 1H), 2.82 - 3.07 (m, 2H), 2.72 (br d, J=16.2 Hz, 1H), 2.29 - 2.35 (m, 1H), 1.90 - 1.98 (m, 1H), 1.52 (d, J=7.1 Hz, 3H), 1.23 - 1.44 (m, 6H).

Minor rotamer (35%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 8.09 (t, J=8.1 Hz, 1H), 7.61 (br s, 1H), 7.05 - 7.26 (m, 7H), 6.95 (br s, 1H), 6.85 (s, 1H), 4.96 (q, J=6.6 Hz, 1H), 4.52 - 4.60 (m, 1H), 3.22 - 3.29 (m, 1H), 2.82 - 3.07 (m, 3H), 2.29 - 2.35 (m, 1H), 1.90 - 1.98 (m, 1H), 1.55 (d, J=7.1 Hz, 3H), 1.23 - 1.44 (m, 6H).

Compound 8

Major rotamer (65%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.19 (br t, J=7.9 Hz, 1H), 7.74 (br s, 1H), 7.45 (br d, J=8.2 Hz, 1H), 7.41 (br d, J=12.0 Hz, 1H), 7.32 (br d, J=7.3 Hz, 1H), 7.06 - 7.27 (m, 4H), 6.98 (br s, 1H), 6.93 (s, 1H), 5.59 (q, J=6.6 Hz, 1H), 3.82 (dd, J=13.4, 3.9 Hz, 1H), 3.42 - 3.54 (m, 1H), 2.83 - 3.07 (m, 2H), 2.72 (br d, J=16.1 Hz, 1H), 2.56 - 2.66 (m, 1H), 1.90 - 1.97 (m, 1H), 1.73 - 1.85 (m, 1H), 1.53 (br d, J=6.9 Hz, 3H), 1.26 - 1.40 (m, 4H).

Minor rotamer (35%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.19 (br t, J=7.9 Hz, 1H), 7.74 (br s, 1H), 7.45 (br d, J=8.2 Hz, 1H), 7.41 (br d, J=12.0 Hz, 1H), 7.06 - 7.27 (m, 5H), 6.98 (br s, 1H), 6.89 (s, 1H), 4.98 (q, J=6.6 Hz, 1H), 4.56 (br dd, J=12.3, 3.8 Hz, 1H), 3.23 - 3.31 (m, 1H), 2.83 - 3.07 (m, 2H), 2.56 - 2.66 (m, 2H), 1.90 - 1.97 (m, 1H), 1.73 - 1.85 (m, 1H), 1.56 (br d, J=6.6 Hz, 3H), 1.26 - 1.40 (m, 4H).

Compound 9

Major rotamer (65%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.17 (br t, J=7.6 Hz, 1H), 7.60 (br s, 1H), 7.22 - 7.33 (m, 3H), 6.98 - 7.20 (m, 5H), 6.85 (s, 1H), 5.53 (q, J=6.6 Hz, 1H), 3.75 (br d, J=9.8 Hz, 1H), 3.40 (br t, J=11.2 Hz, 1H), 2.76 - 3.01 (m, 2H), 2.65 (br d, J=16.1 Hz, 1H), 2.23 - 2.29 (m, 1H), 2.06 (dt, J=20.8, 7.3 Hz, 1H), 1.61 - 1.72 (m, 1H), 1.46 (br d, J=6.6 Hz, 3H), 1.26 - 1.34 (m, 2H), 1.14 - 1.25 (m, 2H).

Minor rotamer (35%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.17 (br t, J=7.6 Hz, 1H), 7.60 (br s, 1H), 7.22 - 7.33 (m, 2H), 6.98 - 7.20 (m, 6H), 6.81 (s, 1H), 4.91 (q, J=6.3 Hz, 1H), 4.49 (br d, J=10.4 Hz, 1H), 3.15 - 3.22 (m, 1H), 2.76 - 3.01 (m, 3H), 2.23 - 2.29 (m, 1H), 2.06 (dt, J=20.8, 7.3 Hz, 1H), 1.61 - 1.72 (m, 1H), 1.49 (br d, J=6.9 Hz, 3H), 1.26 - 1.34 (m, 2H), 1.14 - 1.25 (m, 2H).

Compound 10

Major rotamer (65%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.09 (br t, J=8.0 Hz, 1H), 7.63 (br s, 1H), 7.38 (d, J=5.4 Hz, 1H), 7.15 - 7.21 (m, 2H), 7.08 - 7.12 (m, 1H), 7.02 (d, J=5.0 Hz, 1H), 6.97 (br s, 1H), 6.89 (s, 1H), 5.54 (q, J=6.8 Hz, 1H), 3.92 (br dd, J=13.7, 5.2 Hz, 1H), 3.37 - 3.46 (m, 1H), 2.91 - 3.00 (m, 2H), 2.72 - 2.77 (m, 1H), 2.29 - 2.35 (m, 1H), 1.91 - 1.97 (m, 1H), 1.46 (d, J=6.9 Hz, 3H), 1.40 (br dt, J=9.4, 4.6 Hz, 1H), 1.25 - 1.38 (m, 5H).

Minor rotamer (35%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.08 (br t, J=8.0 Hz, 1H), 7.63 (br s, 1H), 7.29 (d, J=5.0 Hz, 1H), 7.15 - 7.21 (m, 2H), 7.08 - 7.12 (m, 1H), 6.97 (br s, 1H), 6.87 (s, 1H), 6.79 (d, J=5.4 Hz, 1H), 4.90 (q, J=6.2 Hz, 1H), 4.71 (br dd, J=13.2, 5.0 Hz, 1H), 3.18 - 3.25 (m, 1H), 2.91 - 3.00 (m, 3H), 2.29 - 2.35 (m, 1H), 1.91 - 1.97 (m, 1H), 1.50 (d, J=6.6 Hz, 3H), 1.40 (br dt, J=9.4, 4.6 Hz, 1H), 1.25 - 1.38 (m, 5H).

Compound 11

Major rotamer (65%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.09 (br t, J=8.0 Hz, 1H), 7.63 (br s, 1H), 7.14 - 7.22 (m, 2H), 7.10 (d, J=3.5 Hz, 1H), 6.97 (br s, 1H), 6.89 (s, 1H), 6.68 (d, J=1.6 Hz, 1H), 5.38 (q, J=6.4 Hz, 1H), 3.91 (br dd, J=13.7, 4.9 Hz, 1H), 3.39 - 3.49 (m, 1H), 2.92 - 3.00 (m, 1H), 2.72 - 2.92 (m, 1H), 2.59 (br dd, J=15.9, 1.7 Hz, 1H), 2.30 - 2.35 (m, 1H), 1.91 - 1.97 (m, 1H), 1.43 (d, J=6.9 Hz, 3H), 1.23 - 1.41 (m, 6H).

Minor rotamer (35%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.08 (br t, J=7.9 Hz, 1H), 7.63 (br s, 1H), 7.14 - 7.22 (m, 2H), 7.10 (d, J=3.5 Hz, 1H), 6.97 (br s, 1H), 6.88 (s, 1H), 6.43 (d, J=1.6 Hz, 1H), 4.76 (q, J=4.8 Hz, 1H), 4.65 - 4.71 (m, 1H), 3.20 - 3.28 (m, 1H), 2.92 - 3.00 (m, 1H), 2.72 - 2.92 (m, 2H), 2.30 - 2.35 (m, 1H), 1.91 - 1.97 (m, 1H), 1.47 (d, J=6.6 Hz, 3H), 1.23 - 1.41 (m, 6H).

Compound 12

Major rotamer (65%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 8.04 - 8.13 (m, 2H), 7.32 (d, J=7.6 Hz, 1H), 7.05 - 7.26 (m, 6H), 6.89 (s, 1H), 5.59 (q, J=6.6 Hz, 1H), 3.81 (ddd, J=13.6, 5.1, 1.3 Hz, 1H), 3.41 - 3.52 (m, 1H), 2.85 - 3.06 (m, 2H), 2.65 - 2.76 (m, 1H), 2.63 (d, J=4.6 Hz, 3H), 2.30 - 2.38 (m, 1H), 1.88 - 1.96 (m, 1H), 1.52 (d, J=7.1 Hz, 3H), 1.42 (dt, J=9.1, 4.6 Hz, 1H), 1.19 - 1.39 (m, 5H).

Minor rotamer (35%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 8.04 - 8.13 (m, 2H), 7.05 - 7.26 (m, 7H), 6.86 (s, 1H), 4.96 (q, J=6.6 Hz, 1H), 4.51 - 4.59 (m, 1H), 3.22 - 3.29 (m, 1H), 2.85 - 3.06 (m, 3H), 2.63 (d, J=4.6 Hz, 3H), 2.30 - 2.38 (m, 1H), 1.88 - 1.96 (m, 1H), 1.54 (d, J=7.1 Hz, 3H), 1.42 (dt, J=9.1, 4.6 Hz, 1H), 1.19 - 1.39 (m, 5H).

Compound 13

Major rotamer (65%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.08 (t, J=8.0 Hz, 1H), 7.32 (d, J=7.6 Hz, 1H), 7.05 - 7.26 (m, 6H), 6.97 (br s, 1H), 6.89 (s, 1H), 5.59 (q, J=6.5 Hz, 1H), 3.82 (br dd, J=13.6, 3.8 Hz, 1H), 3.42 - 3.51 (m, 1H), 2.83 - 3.06 (m, 2H), 2.72 (br d, J=16.1 Hz, 1H), 2.42 (br s, 1H), 1.88 (br s, 1H), 1.52 (d, J=6.9 Hz, 3H), 1.47 (dt, J=9.2, 4.7 Hz, 1H), 1.32 - 1.42 (m, 3H), 1.23 - 1.31 (m, 2H).

Minor rotamer (35%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.08 (t, J=8.0 Hz, 1H), 7.05 - 7.26 (m, 7H), 6.97 (br s, 1H), 6.85 (s, 1H), 4.96 (q, J=6.6 Hz, 1H), 4.52 - 4.59 (m, 1H), 3.42 - 3.51 (m, 1H), 2.83 - 3.06 (m, 3H), 2.42 (br s, 1H), 1.88 (br s, 1H), 1.55 (d, J=6.9 Hz, 3H), 1.47 (dt, J=9.2, 4.7 Hz, 1H), 1.32 - 1.42 (m, 3H), 1.23 - 1.31 (m, 2H).

Compound 14

Major rotamer (65%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 8.14 (br t, J=5.1 Hz, 1H), 8.09 (br t, J=8.1 Hz, 1H), 7.32 (br d, J=7.1 Hz, 1H), 7.05 - 7.26 (m, 6H), 6.89 (s, 1H), 5.59 (q, J=6.2 Hz, 1H), 3.81 (br dd, J=13.9, 4.3 Hz, 1H), 3.41 - 3.52 (m, 1H), 3.07 - 3.16 (m, 2H), 2.82 - 3.07 (m, 2H), 2.71 (br d, J=15.7 Hz, 1H), 2.29 - 2.37 (m, 1H), 1.88 - 1.97 (m, 1H), 1.52 (d, J=7.1 Hz, 3H), 1.41 (dt, J=8.8, 4.7 Hz, 1H), 1.22 - 1.38 (m, 5H), 1.03 (t, J=7.3 Hz, 3H).

Minor rotamer (35%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 8.14 (br t, J=5.1 Hz, 1H), 8.09 (br t, J=8.1 Hz, 1H), 7.05 - 7.26 (m, 7H), 6.86 (s, 1H), 4.96 (q, J=7.1 Hz, 1H), 4.55 (d, J=12.1 Hz, 1H), 3.21 - 3.30 (m, 1H), 3.07 - 3.16 (m, 2H), 2.82 - 3.07 (m, 3H), 2.29 - 2.37 (m, 1H), 1.88 - 1.97 (m, 1H), 1.55 (d, J=7.1 Hz, 3H), 1.41 (dt, J=8.8, 4.7 Hz, 1H), 1.22 - 1.38 (m, 5H), 1.03 (t, J=7.3 Hz, 3H).

Compound 15

Major rotamer (65%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 8.14 (br t, J=5.1 Hz, 1H), 8.09 (br t, J=7.8 Hz, 1H), 7.32 (br d, J=7.1 Hz, 1H), 7.04 - 7.26 (m, 6H), 6.89 (s, 1H), 5.59 (q, J=7.1 Hz, 1H),

3.81 (br dd, J=13.1, 3.0 Hz, 1H), 3.42 - 3.52 (m, 1H), 2.82 - 3.14 (m, 4H), 2.71 (br d, J=16.7 Hz, 1H), 2.29 - 2.38 (m, 1H), 1.92 - 2.01 (m, 1H), 1.48 - 1.58 (m, 3H), 1.38 - 1.47 (m, 3H), 1.23 - 1.38 (m, 5H), 0.86 (t, J=7.3 Hz, 3H).

Minor rotamer (35%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 8.14 (br t, J=5.1 Hz, 1H), 8.09 (br t, J=7.8 Hz, 1H), 7.04 - 7.26 (m, 7H), 6.86 (s, 1H), 4.96 (q, J=6.1 Hz, 1H), 4.55 (br d, J=11.6 Hz, 1H), 3.22 - 3.30 (m, 1H), 2.82 - 3.14 (m, 5H), 2.29 - 2.38 (m, 1H), 1.92 - 2.01 (m, 1H), 1.48 - 1.58 (m, 3H), 1.38 - 1.47 (m, 3H), 1.23 - 1.38 (m, 5H), 0.86 (t, J=7.3 Hz, 3H).

Compound 16

Major rotamer (70%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.31 (br s, 1 H), 8.09 (br t, J=7.7 Hz, 1H), 7.32 (br d, J=7.3 Hz, 1H), 7.13 - 7.26 (m, 5H), 7.05 - 7.13 (m, 1H), 6.89 (s, 1H), 5.75 - 5.89 (m, 1H), 5.54 - 5.65 (m, 1H), 5.16 (br d, J=17.0 Hz, 1H), 5.07 (br d, J=10.4 Hz, 1H), 3.70 - 3.85 (m, 3H), 3.43 - 3.52 (m, 1H), 2.83 - 3.06 (m, 2H), 2.72 (br d, J=16.7 Hz, 1H), 2.36 (s, 1H), 2.00 - 2.05 (m, 1H), 1.53 (d, J=6.6 Hz, 3H), 1.41 - 1.47 (m, 1H), 1.23 - 1.39 (m, 5H).

Minor rotamer (30%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.31 (br s, 1H), 8.09 (br t, J=7.7 Hz, 1H), 7.13 - 7.26 (m, 5H), 7.05 - 7.13 (m, 2H), 6.85 (s, 1H), 5.75 - 5.89 (m, 1H), 5.16 (br d, J=17.0 Hz, 1H), 5.07 (br d, J=10.4 Hz, 1H), 4.94 - 5.00 (m, 1H), 4.55 (br d, J=10.7 Hz, 1H), 3.70 - 3.85 (m, 2H), 3.43 - 3.52 (m, 1H), 2.83 - 3.06 (m, 3H), 2.36 (s, 1H), 2.00 - 2.05 (m, 1H), 1.55 (d, J=6.9 Hz, 3H), 1.41 - 1.47 (m, 1H), 1.23 - 1.39 (m, 5H).

Compound 17

Major rotamer (65%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 8.64 (br t, J=5.1 Hz, 1H), 8.09 (br t, J=8.1 Hz, 1H), 7.32 (br d, J=7.6 Hz, 1H), 7.04 - 7.26 (m, 6H), 6.89 (s, 1H), 5.59 (q, J=6.6 Hz, 1H), 3.88 - 3.96 (m, 2H), 3.81 (br dd, J=13.6, 3.5 Hz, 1H), 3.42 - 3.51 (m, 1H), 3.13 (t, J=2.3 Hz, 1H), 2.82 - 3.06 (m, 2H), 2.71 (br d, J=16.2 Hz, 1H), 2.34 - 2.41 (m, 1H), 1.96 - 2.03 (m, 1H), 1.52 (d, J=7.1 Hz, 3H), 1.44 (dt, J=9.1, 4.6 Hz, 1H), 1.31 - 1.41 (m, 3H), 1.22 - 1.31 (m, 2H).

Minor rotamer (35%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 8.64 (br t, J=5.1 Hz, 1H), 8.09 (br t, J=8.1 Hz, 1H), 7.04 - 7.26 (m, 7H), 6.86 (s, 1H), 4.96 (q, J=6.4 Hz, 1H), 4.55 (br d, J=12.1 Hz, 1H), 3.88 - 3.96 (m, 2H), 3.21 - 3.30 (m, 1H), 3.13 (t, J=2.3 Hz, 1H), 2.82 - 3.06 (m, 3H), 2.34 -

2.41 (m, 1H), 1.96 - 2.03 (m, 1H), 1.52 (d, J=7.1 Hz, 3H), 1.44 (dt, J=9.1, 4.6 Hz, 1H), 1.31 - 1.41 (m, 3H), 1.22 - 1.31 (m, 2H).

Compound 18

Major rotamer (65%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 8.56 (br t, J=5.3 Hz, 1H), 8.10 (br t, J=7.8 Hz, 1H), 7.32 (br d, J=7.6 Hz, 1H), 7.04 - 7.26 (m, 6H), 6.89 (s, 1H), 5.59 (q, J=6.6 Hz, 1H), 3.81 (br dd, J=14.1, 4.0 Hz, 1H), 3.42 - 3.52 (m, 1H), 3.28 - 3.41 (m, 2H partially obscured by H2O peak), 2.82 - 3.07 (m, 2H), 2.68 - 2.76 (m, 1H), 2.67 (br t, J=6.6 Hz, 2H), 2.34 - 2.41 (m, 1H), 1.96 - 2.04 (m, 1H), 1.49 - 1.58 (m, 3H), 1.45 (dt, J=9.1, 4.6 Hz, 1H), 1.31 - 1.41 (m, 3H), 1.23 - 1.31 (m, 2H).

Minor rotamer (35%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 8.56 (br t, J=5.3 Hz, 1H), 8.10 (br t, J=7.8 Hz, 1H), 7.04 - 7.26 (m, 7H), 6.86 (s, 1H), 4.96 (q, J=6.6 Hz, 1H), 4.55 (br d, J=11.6 Hz, 1H), 3.28 - 3.41 (m, 2H partially obscured by H2O peak), 3.21 - 3.30 (m, 1H), 2.82 - 3.07 (m, 3H), 2.67 (br t, J=6.6 Hz, 2H), 2.34 - 2.41 (m, 1H), 1.96 - 2.04 (m, 1H), 1.49 - 1.58 (m, 3H), 1.45 (dt, J=9.1, 4.6 Hz, 1H), 1.31 - 1.41 (m, 3H), 1.23 - 1.31 (m, 2H).

Compound 19

Major rotamer (65%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.94 (br d, J=6.9 Hz, 1H), 8.10 (br t, J=8.0 Hz, 1H), 7.32 (d, J=7.6 Hz, 1H), 7.05 - 7.26 (m, 6H), 6.90 (s, 1H), 5.60 (q, J=6.6 Hz, 1H), 4.85 (sxt, J=6.9 Hz, 1H), 4.68 - 4.77 (m, 2H), 4.43 (t, J=6.1 Hz, 2H), 3.82 (br dd, J=13.9, 4.1 Hz, 1H), 3.43 - 3.52 (m, 1H), 2.83 - 3.06 (m, 2H), 2.72 (br d, J=15.8 Hz, 1H), 2.33 - 2.39 (m, 1H), 1.93 - 2.01 (m, 1H), 1.53 (d, J=6.6 Hz, 3H), 1.44 (dt, J=9.0, 4.7 Hz, 1H), 1.32 - 1.41 (m, 3H), 1.24 - 1.31 (m, 2H).

Minor rotamer (35%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.94 (br d, J=6.9 Hz, 1H), 8.10 (br t, J=8.0 Hz, 1H), 7.05 - 7.26 (m, 7H), 6.86 (s, 1H), 4.97 (q, J=6.5 Hz, 1H), 4.85 (sxt, J=6.9 Hz, 1H), 4.68 - 4.77 (m, 2H), 4.56 (br d, J=12.6 Hz, 1H), 4.43 (t, J=6.1 Hz, 2H), 3.23 - 3.31 (m, 1H), 2.83 - 3.06 (m, 3H), 2.33 - 2.39 (m, 1H), 1.93 - 2.01 (m, 1H), 1.55 (br d, J=6.6 Hz, 3H), 1.44 (dt, J=9.0, 4.7 Hz, 1H), 1.32 - 1.41 (m, 3H), 1.24 - 1.31 (m, 2H).

Compound 20

Major rotamer (65%)

^{1}H-NMR (500 MHz, DMSO-d6, 77°C) δ ppm 8.01 - 8.17 (m, 2H), 7.00 - 7.33 (m, 7H), 6.76 - 6.87 (m, 1H), 5.60 (br d, J=2.8 Hz, 1H), 3.85 (br dd , J=8.8, 2.2 Hz, 1H), 3.44 - 3.55

(m, 1H), 2.87 - 2.97 (m, 2H), 2.70 - 2.79 (m, 1H), 2.33 (br d, J=3.5 Hz, 1H), 1.89 (br s, 1H), 1.53 (br d, J=5.0 Hz, 3H), 1.17 - 1.45 (m, 9H), 0.65 (br s, 2H), 0.51 (br s, 2H).

Minor rotamer (35%)

^{1}H-NMR (500 MHz, DMSO-d6, 77°C) δ ppm 8.01 - 8.17 (m, 2H), 7.00 - 7.33 (m, 7H), 6.76 - 6.87 (m, 1H), 4.98 - 5.10 (m, 1H), 4.48 - 4.61 (m, 1H), 3.24 - 3.36 (m, 1H), 2.87 - 2.97 (m, 3H), 2.33 (br d, J=3.5 Hz, 1H), 1.89 (br s, 1H), 1.53 (br d, J=5.0 Hz, 3H), 1.17 - 1.45 (m, 9H), 0.65 (br s, 2H), 0.51 (br s, 2H).

Compound 21

Major rotamer (65%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.17 (br t, J=4.9 Hz, 1H), 8.09 (br t, J=7.7 Hz, 1H), 7.32 (br d, J=7.3 Hz, 1H), 7.05 - 7.26 (m, 6H), 6.89 (s, 1H), 5.59 (q, J=6.6 Hz, 1H), 4.68 (br t, J=5.0 Hz, 1H), 3.82 (br dd, J=12.9, 3.8 Hz, 1H), 3.45 - 3.51 (m, 1H), 3.42 (q, J=5.4 Hz, 2H), 3.17 (q, J=5.5 Hz, 2H), 2.90 - 3.06 (m, 2H), 2.72 (br d, J=16.4 Hz, 1H), 2.32 - 2.38 (m, 1H), 2.00 - 2.06 (m, 1H), 1.53 (br d, J=6.6 Hz, 3H), 1.42 (dt, J=8.7, 4.5 Hz, 1H), 1.24 - 1.39 (m, 5H).

Minor rotamer (35%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.17 (br t, J=4.9 Hz, 1H), 8.09 (br t, J=7.7 Hz, 1H), 7.05 - 7.26 (m, 7H), 6.85 (s, 1H), 4.97 (q, J=6.6 Hz, 1H), 4.68 (br t, J=5.0 Hz, 1H), 4.55 (br d, J=14.8 Hz, 1H), 3.42 (q, J=5.4 Hz, 2H), 3.24 - 3.29 (m, 1H), 3.17 (q, J=5.5 Hz, 2H), 2.90 - 3.06 (m, 2H), 2.83 - 2.90 (m, 1H), 2.32 - 2.38 (m, 1H), 2.00 - 2.06 (m, 1H), 1.55 (br d, J=6.9 Hz, 3H), 1.42 (dt, J=8.7, 4.5 Hz, 1H), 1.24 - 1.39 (m, 5H).

Compound 22

Major rotamer (65%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 8.07 (br t, J=7.8 Hz, 1H), 7.32 (br d, J=7.1 Hz, 1H), 7.06 - 7.28 (m, 6H), 6.90 (s, 1H), 5.59 (q, J=7.1 Hz, 1H), 3.77 - 3.86 (m, 1H), 3.42 - 3.53 (m, 1H), 3.12 (s, 3H), 2.90 - 3.06 (m, 2H), 2.87 (s, 3H), 2.71 (br d, J=16.7 Hz, 1H), 2.39 (t, J=6.6 Hz, 2H), 1.52 (br d, J=7.1 Hz, 3H), 1.41 - 1.49 (m, 1H), 1.20 - 1.39 (m, 5H).

Minor rotamer (35%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 8.07 (br t, J=7.8 Hz, 1H), 7.06 - 7.28 (m, 7H), 6.86 (s, 1H), 4.96 (q, J=6.6 Hz, 1H), 4.51 - 4.60 (m, 1H), 3.20 - 3.30 (m, 1H), 3.12 (s, 3H), 2.90 - 3.06 (m, 2H), 2.83 - 2.90 (m, 1H), 2.87 (s, 3H), 2.39 (t, J=6.6 Hz, 2H), 1.55 (br d, J=7.1 Hz, 3H), 1.41 - 1.49 (m, 1H), 1.20 - 1.39 (m, 5H).

Compound 23

Major rotamer (65%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 8.07 (t, J=8.3 Hz, 1H), 7.32 (d, J=7.1 Hz, 1H), 7.05 - 7.27 (m, 6H), 6.90 (s, 1H), 5.59 (q, J=6.6 Hz, 1H), 3.81 (br dd, J=13.6, 4.0 Hz, 1H), 3.59 - 3.68 (m, 1H), 3.42 - 3.55 (m, 2H), 3.28 - 3.34 (m, 2H partially obscured by H2O peak), 2.86 - 3.06 (m, 2H), 2.71 (br d, J=16.7 Hz, 1H), 2.36 - 2.43 (m, 1H), 2.21 (dt, J=8.5, 4.6 Hz, 1H), 1.84 - 1.93 (m, 2H), 1.74 - 1.83 (m, 2H), 1.52 (d, J=6.6 Hz, 3H), 1.43 - 1.49 (m, 1H), 1.21 - 1.39 (m, 5H).

Minor rotamer (35%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 8.07 (t, J=8.3 Hz, 1H), 7.05 - 7.27 (m, 7H), 6.86 (s, 1H), 4.96 (q, J=6.4 Hz, 1H), 4.55 (br d, J=12.1 Hz, 1H), 3.59 - 3.68 (m, 1H), 3.42 - 3.55 (m, 1H), 3.28 - 3.34 (m, 2H partially obscured by H2O peak), 3.22 - 3.29 (m, 1H), 2.86 - 3.06 (m, 3H), 2.36 - 2.43 (m, 1H), 2.21 (dt, J=8.5, 4.6 Hz, 1H), 1.84 - 1.93 (m, 2H), 1.74 - 1.83 (m, 2H), 1.55 (br d, J=6.6 Hz, 3H), 1.43 - 1.49 (m, 1H), 1.21 - 1.39 (m, 5H).

Compound 24

Major rotamer (35%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 12.06 (s, 1H), 8.12 (t, J=8.0 Hz, 1H), 7.32 (d, J=7.3 Hz, 1H), 7.10 - 7.29 (m, 6H), 6.91 (s, 1H), 5.59 (q, J=6.6 Hz, 1H), 3.81 (br dd, J=13.9, 4.4 Hz, 1H), 3.43 - 3.51 (m, 1H), 3.29 (s, 3H), 2.83 - 3.06 (m, 2H), 2.72 (br d, J=16.1 Hz, 1H), 2.53 - 2.59 (m, 1H), 2.11 - 2.18 (m, 1H), 1.56 - 1.62 (m, 2H), 1.52 (d, J=6.9 Hz, 3H), 1.32 - 1.38 (m, 2H), 1.22 - 1.31 (m, 2H).

Minor rotamer (65%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 12.06 (s, 1H), 8.12 (t, J=8.0 Hz, 1H), 7.10 - 7.29 (m, 6H), 7.07 (br d, J=7.1 Hz, 1H), 6.87 (s, 1H), 4.96 (q, J=6.6 Hz, 1H), 4.55 (br dd, J=12.3, 3.8 Hz, 1H), 3.29 (s, 3H), 3.24 - 3.28 (m, 1H), 2.83 - 3.06 (m, 3H), 2.53 - 2.59 (m, 1H), 2.11 - 2.18 (m, 1H), 1.56 - 1.62 (m, 2H), 1.55 (d, J=6.6 Hz, 3H), 1.32 - 1.38 (m, 2H), 1.22 - 1.31 (m, 2H).

Compound 25

Major rotamer (65%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 11.96 (s, 1H), 8.12 (t, J=7.8 Hz, 1H), 7.32 (d, J=7.6 Hz, 1H), 7.05 - 7.29 (m, 6H), 6.90 (s, 1H), 5.59 (q, J=6.6 Hz, 1H), 3.81 (br dd, J=12.6, 4.0 Hz, 1H), 3.43 - 3.51 (m, 1H), 3.40 (q, J=7.1 Hz, 2H), 2.82 - 3.06 (m, 2H), 2.71 (br d, J=16.2 Hz, 1H), 2.53 - 2.58 (m, 1H partially obscured by DMSO peak), 2.12 - 2.19 (m, 1H), 1.50 - 1.63 (m, 2H), 1.52 (d, J=7.1 Hz, 3H), 1.25 - 1.39 (m, 4H), 1.23 (t, J=7.3 Hz, 3H).

Minor rotamer (35%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 11.96 (s, 1H), 8.12 (t, J=7.8 Hz, 1H), 7.05 - 7.29 (m, 7H), 6.87 (s, 1H), 4.96 (q, J=7.1 Hz, 1H), 4.51 - 4.59 (m, 1H), 3.40 (q, J=7.1 Hz, 2H), 3.22 - 3.30 (m, 1H), 2.82 - 3.06 (m, 3H), 2.53 - 2.58 (m, 1H partially obscured by DMSO peak), 2.12 - 2.19 (m, 1H), 1.50 - 1.63 (m, 2H), 1.55 (br d, J=7.1 Hz, 3H), 1.25 - 1.39 (m, 4H), 1.23 (t, J=7.3 Hz, 3H).

Compound 26

Major rotamer (65%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 12.01 (s, 1H), 8.11 (t, J=8.1 Hz, 1H), 7.32 (d, J=7.6 Hz, 1H), 7.05 - 7.28 (m, 6H), 6.90 (s, 1H), 5.59 (q, J=6.7 Hz, 1H), 3.81 (br dd, J=13.9, 3.8 Hz, 1H), 3.42 - 3.51 (m, 1H), 3.33 (s, 1H), 2.83 - 3.06 (m, 2H), 2.71 (br d, J=16.7 Hz, 1H), 2.53 - 2.57 (m, 1H partially obscured by DMSO peak), 2.06 - 2.18 (m, 2H), 1.50 - 1.63 (m, 2H), 1.52 (d, J=6.6 Hz, 3H), 1.21 - 1.39 (m, 5H), 1.03 (d, J=6.6 Hz, 6H).

Minor rotamer (35%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 12.01 (s, 1H), 8.11 (t, J=8.1 Hz, 1H), 7.05 - 7.28 (m, 7H), 6.87 (s, 1H), 4.96 (q, J=6.2 Hz, 1H), 4.52 - 4.59 (m, 1H), 3.33 (s, 1H), 3.22 - 3.30 (m, 1H), 2.83 - 3.06 (m, 3H), 2.53 - 2.57 (m, 1H partially obscured by DMSO peak), 2.06 - 2.18 (m, 2H), 1.50 - 1.63 (m, 2H), 1.55 (d, J=6.6 Hz, 3H), 1.21 - 1.39 (m, 5H), 1.03 (d, J=6.6 Hz, 6H).

Compound 27

Major rotamer (65%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 12.02 (s, 1H), 8.12 (br t, J=8.1 Hz, 1H), 7.04 - 7.34 (m, 7H), 6.90 (s, 1H), 5.59 (q, J=6.2 Hz, 1H), 3.77 - 3.84 (m, 1H), 3.41 - 3.51 (m, 1H), 2.85 - 3.06 (m, 3H), 2.68 - 2.76 (m, 1H), 2.11 - 2.18 (m, 1H), 1.49 - 1.62 (m, 2H), 1.52 (d, J=7.1 Hz, 3H), 1.21 - 1.39 (m, 5H), 1.05 - 1.13 (m, 4H).

Minor rotamer (35%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 12.02 (s, 1H), 8.12 (br t, J=8.1 Hz, 1H), 7.04 - 7.34 (m, 7H), 6.87 (s, 1H), 4.96 (q, J=6.7 Hz, 1H), 4.51 - 4.59 (m, 1H), 3.22 - 3.31 (m, 1H), 2.85 - 3.06 (m, 4H), 2.11 - 2.18 (m, 1H), 1.49 - 1.62 (m, 2H), 1.55 (d, J=6.6 Hz, 3H), 1.21 - 1.39 (m, 5H), 1.05 - 1.13 (m, 4H).

Compound 28

Major rotamer (65%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 12.07 (s, 1H), 8.12 (t, J=8.1 Hz, 1H), 7.38 (d, J=5.6 Hz, 1H), 7.26 (br d, J=12.6 Hz, 1H), 7.20 (d, J=9.1 Hz, 1H), 7.09 - 7.13 (m, 1H), 7.02 (d, J=5.6 Hz, 1H), 6.90 (s, 1H), 5.53 (q, J=6.6 Hz, 1H), 3.92 (br dd, J=13.9, 4.8 Hz, 1H), 3.36 - 3.46 (m, 1H), 3.28 (s, 3H), 2.82 - 3.01 (m, 2H), 2.74 (br dd, J=15.9, 2.8 Hz, 1H), 2.53 - 2.59 (m, 1H partially obscured by DMSO peak), 2.10 - 2.18 (m, 1H), 1.53 - 1.62 (m, 2H), 1.46 (d, J=6.6 Hz, 3H), 1.32 - 1.39 (m, 2H), 1.21 - 1.31 (m, 2H).

Minor rotamer (35%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 12.07 (s, 1H), 8.11 (t, J=8.1 Hz, 1H), 7.29 (d, J=5.6 Hz, 1H), 7.26 (br d, J=12.6 Hz, 1H), 7.20 (d, J=9.1 Hz, 1H), 7.09 - 7.13 (m, 1H), 6.88 (s, 1H), 6.79 (d, J=5.1 Hz, 1H), 4.89 (q, J=6.1 Hz, 1H), 4.71 (br dd, J=12.6, 4.5 Hz, 1H), 3.28 (s, 3H), 3.15 - 3.26 (m, 1H), 2.82 - 3.01 (m, 3H), 2.53 - 2.59 (m, 1H partially obscured by DMSO peak), 2.10 - 2.18 (m, 1H), 1.53 - 1.62 (m, 2H), 1.50 (d, J=6.6 Hz, 3H), 1.32 - 1.39 (m, 2H), 1.21 - 1.31 (m, 2H).

Compound 29

Major rotamer (65%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 8.07 (t, J=8.1 Hz, 1H), 7.32 (d, J=7.1 Hz, 1H), 7.05 - 7.25 (m, 6H), 6.94 (s, 1H), 6.88 (s, 1H), 5.59 (q, J=7.1 Hz, 1H), 3.82 (br dd, J=13.1, 4.5 Hz, 1H), 3.41 - 3.48 (m, 1H partially obscured by H2O peak), 2.85 - 3.06 (m, 2H), 2.71 (br d, J=17.7 Hz, 1H), 2.26 - 2.32 (m, 1H), 1.85 - 1.92 (m, 1H), 1.52 (d, J=7.1 Hz, 3H), 1.31 - 1.42 (m, 3H), 1.19 - 1.30 (m, 3H).

Minor rotamer (35%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 8.07 (t, J=8.1 Hz, 1H), 7.05 - 7.25 (m, 7H), 6.94 (s, 1H), 6.84 (s, 1H), 4.96 (q, J=6.6 Hz, 1H), 4.52 - 4.59 (m, 1H), 3.22 - 3.32 (m, 1H), 2.85 - 3.06 (m, 3H), 2.26 - 2.32 (m, 1H), 1.85 - 1.92 (m, 1H), 1.54 (br d, J=6.6 Hz, 3H), 1.31 - 1.42 (m, 3H), 1.19 - 1.30 (m, 3H).

Compound 30

Major rotamer (65%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 8.07 (t, J=8.1 Hz, 1H), 7.32 (d, J=7.1 Hz, 1H), 7.06 - 7.25 (m, 6H), 6.89 (s, 1H), 6.33 (d, J=3.0 Hz, 1H), 6.14 (d, J=2.0 Hz, 1H), 5.59 (q, J=6.6 Hz, 1H), 3.81 (br dd, J=12.6, 5.1 Hz, 1H), 3.41 - 3.51 (m, 1H), 2.85 - 3.06 (m, 2H), 2.71 - 2.79 (m, 1H), 2.67 - 2.71 (m, 1H), 2.37 - 2.44 (m, 1H), 1.94 - 2.02 (m, 1H), 1.52 (d, J=6.6 Hz, 3H), 1.18 - 1.40 (m, 6H), 0.53 - 0.59 (m, 2H), 0.31 - 0.36 (m, 2H).

Minor rotamer (35%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 8.07 (t, J=8.1 Hz, 1H), 7.06 - 7.25 (m, 7H), 6.85 (s, 1H), 6.33 (d, J=3.0 Hz, 1H), 6.14 (d, J=2.0 Hz, 1H), 4.96 (q, J=6.9 Hz, 1H), 4.55 (br d, J=10.5 Hz, 1H), 3.22 - 3.31 (m, 1H), 2.85 - 3.06 (m, 2H), 2.71 - 2.79 (m, 2H), 2.37 - 2.44 (m, 1H), 1.94 - 2.02 (m, 1H), 1.55 (d, J=6.6 Hz, 3H), 1.18 - 1.40 (m, 6H), 0.53 - 0.59 (m, 2H), 0.31 - 0.36 (m, 2H).

Compound 31

Major rotamer (65%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.29 (dd, J=6.6, 3.2 Hz, 2H), 7.98 (t, J=8.0 Hz, 1H), 7.61 - 7.71 (m, 4H), 7.45 (s, 1H), 7.34 (d, J=7.6 Hz, 1H), 7.08 - 7.27 (m, 6H), 5.64 (q, J=6.6 Hz, 1H), 4.00 (br dd, J=13.9, 3.8 Hz, 1H), 3.50 - 3.58 (m, 1H), 3.03 - 3.11 (m, 1H), 2.77 (s, 3H), 2.73 - 2.77 (m, 1H), 2.25 (dt, J=8.8, 4.7 Hz, 1H), 1.74 - 1.80 (m, 1H), 1.56 (d, J=6.6 Hz, 3H), 1.32 - 1.38 (m, 1H), 1.10 - 1.15 (m, 1H).

Minor rotamer (35%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.26 (dd, J=6.6, 2.8 Hz, 2H), 7.98 (t, J=8.0 Hz, 1H), 7.61 - 7.71 (m, 4H), 7.41 (s, 1H), 7.08 - 7.27 (m, 7H), 5.14 (q, J=6.6 Hz, 1H), 4.60 (br dd, J=12.9, 4.1 Hz, 1H), 3.50 - 3.58 (m, 1H), 2.92 - 3.00 (m, 1H), 2.85 - 2.91 (m, 1H), 2.77 (s, 3H), 2.25 (dt, J=8.8, 4.7 Hz, 1H), 1.74 - 1.80 (m, 1H), 1.61 (d, J=6.6 Hz, 3H), 1.32 - 1.38 (m, 1H), 1.10 - 1.15 (m, 1H).

Compound 32

Major rotamer (65%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.29 (dd, J=6.5, 3.0 Hz, 2H), 7.98 (t, J=8.0 Hz, 1H), 7.62 - 7.73 (m, 4H), 7.45 (s, 1H), 7.34 (d, J=7.6 Hz, 1H), 7.09 - 7.27 (m, 6H), 5.64 (q, J=6.8 Hz, 1H), 4.00 (br dd, J=13.9, 3.8 Hz, 1H), 3.50 - 3.58 (m, 1H), 3.02 - 3.12 (m, 1H), 2.79 (s, 3H), 2.73 - 2.78 (m, 1H), 2.23 - 2.29 (m, 1H), 1.76 - 1.83 (m, 1H), 1.56 (d, J=6.9 Hz, 3H), 1.33 - 1.40 (m, 1H), 1.10 - 1.16 (m, 1H).

Minor rotamer (35%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.26 (dd, J=6.6, 2.8 Hz, 2H), 7.98 (t, J=8.0 Hz, 1H), 7.62 - 7.73 (m, 4H), 7.41 (s, 1H), 7.09 - 7.27 (m, 7H), 5.15 (q, J=6.6 Hz, 1H), 4.60 (br dd, J=12.8, 4.3 Hz, 1H), 3.50 - 3.58 (m, 1H), 2.85 - 3.12 (m, 2H), 2.79 (s, 3H), 2.23 - 2.29 (m, 1H), 1.76 - 1.83 (m, 1H), 1.61 (d, J=6.9 Hz, 3H), 1.33 - 1.40 (m, 1H), 1.10 - 1.16 (m, 1H).

Compound 33

Major rotamer (65%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 8.07 (t, J=8.1 Hz, 1H), 7.62 (br s, 1H), 7.32 (br d, J=7.1 Hz, 1H), 7.06 - 7.26 (m, 6H), 6.89 (s, 1H), 5.59 (q, J=6.6 Hz, 1H), 3.81 (br dd, J=13.9, 3.8 Hz, 1H), 3.55 (s, 3H), 3.41 - 3.51 (m, 1H), 2.86 - 3.06 (m, 2H), 2.71 - 2.80 (m, 1H), 2.66 - 2.71 (m, 1H), 1.99 - 2.09 (m, 1H), 1.52 (d, J=7.1 Hz, 3H), 1.20 - 1.39 (m, 6H).

Minor rotamer (35%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 8.07 (t, J=8.1 Hz, 1H), 7.62 (br s, 1H), 7.06 - 7.26 (m, 7H), 6.85 (s, 1H), 4.96 (q, J=6.6 Hz, 1H), 4.51 - 4.60 (m, 1H), 3.55 (s, 3H), 3.23 - 3.31 (m, 1H), 2.86 - 3.06 (m, 3H), 2.71 - 2.80 (m, 1H), 1.99 - 2.09 (m, 1H), 1.55 (br d, J=7.1 Hz, 3H), 1.20 - 1.39 (m, 6H).

Compound 34

Major rotamer (65%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.22 (d, J=4.4 Hz, 1H), 8.08 (t, J=8.2 Hz, 1H), 7.32 (d, J=7.3 Hz, 1H), 7.05 - 7.25 (m, 6H), 6.89 (s, 1H), 5.59 (q, J=6.5 Hz, 1H), 3.82 (br dd, J=13.7, 3.9 Hz, 1H), 3.42 - 3.51 (m, 1H), 2.83 - 3.05 (m, 3H), 2.71 (br d, J=16.1 Hz, 1H), 1.97 - 2.03 (m, 1H), 1.81 (s, 3H), 1.52 (d, J=6.9 Hz, 3H), 1.31 - 1.39 (m, 2H), 1.22 - 1.31 (m, 4H).

Minor rotamer (35%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.22 (d, J=4.4 Hz, 1H), 8.08 (t, J=8.2 Hz, 1H), 7.05 - 7.25 (m, 7H), 6.86 (s, 1H), 4.96 (q, J=6.8 Hz, 1H), 4.55 (br dd, J=12.6, 3.5 Hz, 1H), 3.23 - 3.31 (m, 1H), 2.83 - 3.05 (m, 4H), 1.97 - 2.03 (m, 1H), 1.81 (s, 3H), 1.55 (d, J=6.6 Hz, 3H), 1.31 - 1.39 (m, 2H), 1.22 - 1.31 (m, 4H).

Compound 35

Major rotamer (65%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 8.45 (d, J=4.0 Hz, 1H), 8.07 (t, J=8.3 Hz, 1H), 7.32 (d, J=7.1 Hz, 1H), 7.05 - 7.26 (m, 6H), 6.89 (s, 1H), 5.59 (q, J=7.1 Hz, 1H), 3.81 (br dd, J=13.9, 3.8 Hz, 1H), 3.41 - 3.51 (m, 1H), 2.82 - 3.07 (m, 3H), 2.71 (br d, J=16.7 Hz, 1H), 1.99 - 2.06 (m, 1H), 1.52 (d, J=7.1 Hz, 3H), 1.46 - 1.51 (m, 1H), 1.31 - 1.39 (m, 2H), 1.21 - 1.31 (m, 4H), 0.62 - 0.72 (m, 4H).

Minor rotamer (35%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 8.45 (d, J=4.0 Hz, 1H), 8.07 (t, J=8.3 Hz, 1H), 7.05 - 7.26 (m, 7H), 6.85 (s, 1H), 4.96 (q, J=6.7 Hz, 1H), 4.51 - 4.59 (m, 1H), 3.21 - 3.31

(m, 1H), 2.82 - 3.07 (m, 4H), 1.99 - 2.06 (m, 1H), 1.54 (d, J=6.6 Hz, 3H), 1.46 - 1.51 (m, 1H), 1.31 - 1.39 (m, 2H), 1.21 - 1.31 (m, 4H), 0.62 - 0.72 (m, 4H).

Compound 36

Major rotamer (65%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 8.08 (t, J=7.8 Hz, 1H), 7.68 (d, J=3.0 Hz, 1H), 7.32 (d, J=7.1 Hz, 1H), 7.05 - 7.25 (m, 6H), 6.90 (s, 1H), 5.59 (q, J=6.7 Hz, 1H), 3.81 (br dd, J=14.1, 4.0 Hz, 1H), 3.41 - 3.52 (m, 1H), 2.85 - 3.07 (m, 2H), 2.98 (s, 3H), 2.75 - 2.81 (m, 1H), 2.71 (br d, J=16.2 Hz, 1H), 2.19 - 2.26 (m, 1H), 1.52 (d, J=6.6 Hz, 3H), 1.24 - 1.39 (m, 6H).

Minor rotamer (65%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 8.08 (t, J=7.8 Hz, 1H), 7.68 (d, J=3.0 Hz, 1H), 7.05 - 7.25 (m, 7H), 6.86 (s, 1H), 4.96 (q, J=7.1 Hz, 1H), 4.55 (br d, J=12.1 Hz, 1H), 3.22 - 3.30 (m, 1H), 2.85 - 3.07 (m, 3H), 2.98 (s, 3H), 2.75 - 2.81 (m, 1H), 2.19 - 2.26 (m, 1H), 1.55 (d, J=7.1 Hz, 3H), 1.24 - 1.39 (m, 6H).

Compound 37

Major rotamer (65%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 8.07 (t, J=8.1 Hz, 1H), 7.32 (d, J=7.6 Hz, 1H), 7.04 - 7.26 (m, 6H), 6.89 (s, 1H), 5.59 (q, J=6.6 Hz, 1H), 5.05 (dd, J=7.6, 2.5 Hz, 1H), 3.81 (br dd, J=13.6, 4.0 Hz, 1H), 3.41 - 3.52 (m, 1H), 2.82 - 3.06 (m, 2H), 2.71 (br d, J=16.2 Hz, 1H), 2.52 - 2.59 (m, 1H partially obscured by DMSO peak), 2.02 - 2.10 (m, 1H), 1.52 (d, J=6.6 Hz, 3H), 1.21 - 1.41 (m, 12H).

Minor rotamer (35%)

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 8.07 (t, J=8.1 Hz, 1H), 7.04 - 7.26 (m, 7H), 6.85 (s, 1H), 5.05 (dd, J=7.6, 2.5 Hz, 1H), 4.96 (q, J=6.6 Hz, 1H), 4.55 (br d, J=12.1 Hz, 1H), 3.22 - 3.30 (m, 1H), 2.82 - 3.06 (m, 3H), 2.52 - 2.59 (m, 1H partially obscured by DMSO peak), 2.02 - 2.10 (m, 1H), 1.55 (d, J=7.1 Hz, 3H), 1.21 - 1.41 (m, 12H).

Compound 38

Major rotamer (65%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.05 (t, J=8.0 Hz, 1H), 7.32 (d, J=7.6 Hz, 1H), 7.15 - 7.25 (m, 3H), 6.99 - 7.14 (m, 3H), 6.88 (s, 1H), 5.78 (s, 1H), 5.59 (q, J=6.6 Hz, 1H), 3.81 (br dd, J=13.7, 3.6 Hz, 1H), 3.43 - 3.51 (m, 2H), 2.83 - 3.06 (m, 2H), 2.72 (br d, J=16.1 Hz, 1H), 2.00 - 2.06 (m, 1H), 1.52 (d, J=6.9 Hz, 3H), 1.23 - 1.38 (m, 4H), 1.17 - 1.22 (m, 1H), 1.08 (q, J=6.3 Hz, 1H).

Minor rotamer (35%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.05 (t, J=8.0 Hz, 1H), 7.15 - 7.25 (m, 3H), 6.99 - 7.14 (m, 4H), 6.85 (s, 1H), 5.79 (s, 1H), 4.96 (q, J=6.7 Hz, 1H), 4.55 (br d, J=12.3 Hz, 1 H), 3.43 - 3.51 (m, 1H), 3.23 - 3.29 (m, 1H), 2.83 - 3.06 (m, 3H), 2.00 - 2.06 (m, 1H), 1.55 (d, J=6.6 Hz, 3H), 1.23 - 1.38 (m, 4H), 1.17 - 1.22 (m, 1H), 1.08 (q, J=6.3 Hz, 1H).

Compound 39

Major rotamer (65%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.08 (t, J=8.0 Hz, 1H), 7.32 (d, J=7.3 Hz, 1H), 7.06 - 7.26 (m, 6H), 6.89 (s, 1H), 6.52 - 6.79 (m, 2H), 5.59 (q, J=6.5 Hz, 1H), 4.06 - 4.11 (m, 1H), 3.82 (br dd, J=13.4, 3.6 Hz, 1H), 3.42 - 3.51 (m, 1H), 2.83 - 3.06 (m, 2H), 2.71 (br d, J=16.4 Hz, 1 H), 2.22 - 2.28 (m, 1H), 1.52 (d, J=6.9 Hz, 3H), 1.32 - 1.40 (m, 3H), 1.24 - 1.32 (m, 3H).

Minor rotamer (35%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.08 (t, J=8.0 Hz, 1H), 7.06 - 7.26 (m, 7H), 6.86 (s, 1H), 6.70 (br s, 1H), 6.61 (br s, 1H), 4.96 (q, J=6.8 Hz, 1H), 4.55 (br dd, J=12.6, 3.5 Hz, 1H), 4.06 - 4.11 (m, 1H), 3.23 - 3.30 (m, 1H), 2.83 - 3.06 (m, 3H), 2.22 - 2.28 (m, 1H), 1.55 (d, J=6.9 Hz, 3H), 1.32 - 1.40 (m, 3H), 1.24 - 1.32 (m, 3H).

Compound 40

Major rotamer (65%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.08 (t, J=8.0 Hz, 1H), 7.32 (d, J=7.3 Hz, 1H), 7.06 - 7.25 (m, 7H), 6.89 (s, 1H), 5.59 (q, J=6.6 Hz, 1H), 4.10 (dt, J=6.3, 3.5 Hz, 1H), 3.82 (br dd, J=13.6, 3.8 Hz, 1H), 3.42 - 3.50 (m, 1H), 2.83 - 3.05 (m, 2H), 2.71 (br d, J=16.4 Hz, 1H), 2.58 (d, J=4.7 Hz, 3H), 2.22 - 2.28 (m, 1H), 1.52 (d, J=6.6 Hz, 3H), 1.23 - 1.39 (m, 6H).

Minor rotamer (35%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.08 (t, J=8.0 Hz, 1H), 7.06 - 7.25 (m, 8H), 6.86 (s, 1H), 4.96 (q, J=6.4 Hz, 1H), 4.55 (br dd, J=12.3, 3.5 Hz, 1H), 4.10 (dt, J=6.3, 3.5 Hz, 1H), 3.24 - 3.31 (m, 1H), 2.83 - 3.05 (m, 3H), 2.58 (d, J=4.7 Hz, 3H), 2.22 - 2.28 (m, 1H), 1.55 (d, J=6.9 Hz, 3H), 1.23 - 1.39 (m, 6H).

Compound 41

Major rotamer (65%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.12 (t, J=8.2 Hz, 1H), 7.32 (d, J=7.6 Hz, 1H), 7.06 - 7.30 (m, 6H), 6.90 (s, 1H), 5.59 (q, J=6.4 Hz, 1H), 4.61 (t, J=5.4 Hz, 1H), 3.82 (br dd, J=13.7, 3.9 Hz, 1H), 3.63 (quin, J=8.4 Hz, 1H), 3.57 (dd, J=6.8, 5.5 Hz, 2H), 3.43 -

3.51 (m, 1H), 2.83 - 3.06 (m, 2H), 2.72 (br d, J=15.8 Hz, 1H), 2.37 - 2.42 (m, 1H), 2.19 (dd, J=8.4, 6.8 Hz, 4H), 1.53 (d, J=6.9 Hz, 3H), 1.32 - 1.39 (m, 2H), 1.25 - 1.32 (m, 2H).

Minor rotamer (35%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.12 (t, J=8.2 Hz, 1H), 7.06 - 7.30 (m, 7H), 6.86 (s, 1H), 4.97 (q, J=6.9 Hz, 1H), 4.61 (t, J=5.4 Hz, 1H), 4.55 (br dd, J=13.1, 3.0 Hz, 1H), 3.63 (quin, J=8.4 Hz, 1H), 3.57 (dd, J=6.8, 5.5 Hz, 2H), 3.24 - 3.31 (m, 1H), 2.83 - 3.06 (m, 3H), 2.37 - 2.42 (m, 1H), 2.19 (dd, J=8.4, 6.8 Hz, 4H), 1.55 (d, J=6.6 Hz, 3H), 1.32 - 1.39 (m, 2H), 1.25 - 1.32 (m, 2H).

Compound 42

Major rotamer (65%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.11 (br t, J=8.0 Hz, 1H), 7.32 (br d, J=7.6 Hz, 1H), 7.05 - 7.26 (m, 6H), 6.90 (s, 1H), 5.59 (q, J=6.6 Hz, 1H), 4.51 (t, J=5.2 Hz, 1H), 3.82 (br dd, J=13.4, 3.3 Hz, 1H), 3.42 - 3.52 (m, 2H), 3.40 (t, J=5.2 Hz, 2H), 2.83 - 3.06 (m, 2H), 2.72 (br d, J=16.1 Hz, 1H), 2.31 - 2.45 (m, 3H), 1.85 - 1.95 (m, 2H), 1.53 (br d, J=6.9 Hz, 3H), 1.32 - 1.40 (m, 2H), 1.21 - 1.31 (m, 2H).

Minor rotamer (35%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.11 (br t, J=8.0 Hz, 1H), 7.05 - 7.26 (m, 7H), 6.86 (s, 1H), 4.97 (q, J=6.7 Hz, 1H), 4.53 - 4.59 (m, 1H), 4.51 (t, J=5.2 Hz, 1H), 3.42 - 3.52 (m, 1H), 3.40 (t, J=5.2 Hz, 2H), 3.23 - 3.31 (m, 1H), 2.83 - 3.06 (m, 3H), 2.31 - 2.45 (m, 3H), 1.85 - 1.95 (m, 2H), 1.55 (br d, J=6.6 Hz, 3H), 1.32 - 1.40 (m, 2H), 1.21 - 1.31 (m, 2H).

Compound 43

Major rotamer (65%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.13 (t, J=8.0 Hz, 1H), 7.06 - 7.35 (m, 7H), 6.90 (s, 1H), 6.35 - 6.70 (br s, 2H), 5.59 (q, J=6.8 Hz, 1H), 4.11 (d, J=7.3 Hz, 2H), 3.82 (br dd, J=13.9, 3.8 Hz, 1H), 3.73 (quin, J=8.6 Hz, 1H), 3.43 - 3.52 (m, 1H), 2.86 - 3.06 (m, 2H), 2.72 (br d, J=16.1 Hz, 1H), 2.54 - 2.60 (m, 1H), 2.24 - 2.32 (m, 2H), 2.16 - 2.23 (m, 2H), 1.53 (d, J=6.6 Hz, 3H), 1.32 - 1.39 (m, 2H), 1.25 - 1.32 (m, 2H).

Minor rotamer (35%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.13 (t, J=8.0 Hz, 1H), 7.06 - 7.35 (m, 7H), 6.86 (s, 1H), 6.35 - 6.70 (br s, 2H), 4.97 (q, J=6.6 Hz, 1H), 4.53 - 4.59 (m, 1H), 4.11 (d, J=7.3 Hz, 2H), 3.73 (quin, J=8.6 Hz, 1H), 3.24 - 3.31 (m, 1H), 2.86 - 3.06 (m, 3H), 2.54 - 2.60 (m, 1H), 2.24 - 2.32 (m, 2H), 2.16 - 2.23 (m, 2H), 1.55 (d, J=6.6 Hz, 3H), 1.32 - 1.39 (m, 2H), 1.25 - 1.32 (m, 2H).

Compound 44

Major rotamer (65%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.12 (br t, J=8.0 Hz, 1H), 7.32 (br d, J=7.6 Hz, 1H), 7.06 - 7.29 (m, 6H), 6.90 (s, 1H), 6.32 - 6.69 (br s, 2H), 5.59 (q, J=6.9 Hz, 1H), 3.94 (d, J=6.0 Hz, 2H), 3.78 - 3.86 (m, 1H), 3.41 - 3.51 (m, 2H), 2.83 - 3.06 (m, 2H), 2.72 (br d, J=16.7 Hz, 1H), 2.37 - 2.46 (m, 2H), 1.91 (q, J=10.2 Hz, 2H), 1.53 (br d, J=6.9 Hz, 3H), 1.32 - 1.40 (m, 2H), 1.19 - 1.31 (m, 2H).

Minor rotamer (35%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.12 (br t, J=8.0 Hz, 1H), 7.06 - 7.29 (m, 7H), 6.86 (s, 1H), 6.32 - 6.69 (br s, 2H), 4.97 (q, J=6.5 Hz, 1H), 4.52 - 4.59 (m, 1H), 3.94 (d, J=6.0 Hz, 2H), 3.41 - 3.51 (m, 1H), 3.23 - 3.31 (m, 1H), 2.83 - 3.06 (m, 3H), 2.37 - 2.46 (m, 2H), 1.91 (q, J=10.2 Hz, 2H), 1.55 (br d, J=6.6 Hz, 3H), 1.32 - 1.40 (m, 2H), 1.19 - 1.31 (m, 2H).

Compound 45

Major rotamer (65%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.12 (t, J=7.9 Hz, 1H), 7.07 - 7.34 (m, 8H), 6.90 (s, 1H), 6.76 (br s, 1H), 5.59 (q, J=6.7 Hz, 1H), 3.79 - 3.85 (m, 1H), 3.67 (quin, J=8.4 Hz, 1H), 3.43 - 3.51 (m, 1H), 2.87 - 3.06 (m, 2H), 2.72 (br d, J=16.4 Hz, 1H), 2.36 (s, 2H), 2.25 - 2.33 (m, 2H), 2.11 - 2.19 (m, 2H), 1.53 (d, J=6.9 Hz, 3H), 1.32 - 1.40 (m, 2H), 1.25 - 1.31 (m, 2H).

Minor rotamer (35%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.12 (t, J=7.9 Hz, 1H), 7.07 - 7.34 (m, 8H), 6.86 (s, 1H), 6.76 (br s, 1H), 4.97 (q, J=6.6 Hz, 1H), 4.52 - 4.59 (m, 1H), 3.67 (quin, J=8.4 Hz, 1H), 3.24 - 3.31 (m, 1H), 2.87 - 3.06 (m, 3H), 2.36 (s, 2H), 2.25 - 2.33 (m, 2H), 2.11 - 2.19 (m, 2H), 1.55 (d, J=6.6 Hz, 3H), 1.32 - 1.40 (m, 2H), 1.25 - 1.31 (m, 2H).

Compound 46

Major rotamer (65%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.11 (br t, J=7.9 Hz, 1H), 7.32 (d, J=7.6 Hz, 1H), 7.05 - 7.27 (m, 7H), 6.90 (s, 1H), 6.72 (br s, 1H), 5.59 (q, J=6.6 Hz, 1H), 3.81 (br dd, J=13.4, 3.6 Hz, 1H), 3.38 - 3.52 (m, 2H), 2.83 - 3.07 (m, 2H), 2.72 (br d, J=16.4 Hz, 1H), 2.54 - 2.62 (m, 2H), 2.21 (d, J=6.9 Hz, 2H), 1.83 (q, J=10.2 Hz, 2H), 1.52 (d, J=6.9 Hz, 3H), 1.32 - 1.39 (m, 2H), 1.22 - 1.31 (m, 2H).

Minor rotamer (35%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.11 (br t, J=7.9 Hz, 1H), 7.05 - 7.27 (m, 8H), 6.86

(s, 1H), 6.72 (br s, 1H), 4.97 (q, J=6.8 Hz, 1H), 4.52 - 4.60 (m, 1H), 3.38 - 3.52 (m, 1H), 3.23 - 3.30 (m, 1H), 2.83 - 3.07 (m, 3H), 2.54 - 2.62 (m, 2H), 2.21 (d, J=6.9 Hz, 2H), 1.83 (q, J=10.2 Hz, 2H), 1.55 (d, J=6.9 Hz, 3H), 1.32 - 1.39 (m, 2H), 1.22 - 1.31 (m, 2H).

Compound 47

Major rotamer (65%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.12 (t, J=7.9 Hz, 1H), 7.77 (br d, J=4.1 Hz, 1H), 7.32 (d, J=7.3 Hz, 1H), 7.06 - 7.30 (m, 6H), 6.90 (s, 1H), 5.59 (q, J=6.7 Hz, 1H), 3.82 (br dd, J=13.4, 3.6 Hz, 1H), 3.67 (quin, J=8.2 Hz, 1H), 3.43 - 3.51 (m, 1H), 2.82 - 3.06 (m, 2H), 2.72 (br d, J=16.4 Hz, 1H), 2.59 - 2.63 (m, 1H), 2.57 (d, J=4.7 Hz, 3H), 2.38 (d, J=8.2 Hz, 2H), 2.25 - 2.33 (m, 2H), 2.10 - 2.17 (m, 2H), 1.52 (d, J=6.9 Hz, 3H), 1.32 - 1.38 (m, 2H), 1.25 - 1.32 (m, 2H).

Minor rotamer (35%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.12 (t, J=7.9 Hz, 1H), 7.77 (br d, J=4.1 Hz, 1H), 7.06 - 7.30 (m, 7H), 6.86 (s, 1H), 4.97 (q, J=6.6 Hz, 1H), 4.52 - 4.59 (m, 1H), 3.67 (quin, J=8.2 Hz, 1H), 3.23 - 3.31 (m, 1H), 2.82 - 3.06 (m, 3H), 2.59 - 2.63 (m, 1H), 2.57 (d, J=4.7 Hz, 3H), 2.38 (d, J=8.2 Hz, 2H), 2.25 - 2.33 (m, 2H), 2.10 - 2.17 (m, 2H), 1.55 (d, J=6.6 Hz, 3H), 1.32 - 1.38 (m, 2H), 1.25 - 1.32 (m, 2H).

Compound 48

Major rotamer (65%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.11 (t, J=8.0 Hz, 1H), 7.69 (br d, J=3.8 Hz, 1H), 7.32 (d, J=7.6 Hz, 1H), 7.05 - 7.26 (m, 6H), 6.90 (s, 1H), 5.59 (q, J=6.5 Hz, 1H), 3.81 (br dd, J=13.9, 4.1 Hz, 1H), 3.39 - 3.51 (m, 2H), 2.83 - 3.06 (m, 2H), 2.72 (br d, J=16.4 Hz, 1H), 2.56 (d, J=4.7 Hz, 3H), 2.54 - 2.55 (m, 1H), 2.43 - 2.48 (m, 2H), 2.22 (d, J=7.3 Hz, 2H), 1.78 - 1.86 (m, 2H), 1.52 (d, J=6.6 Hz, 3H), 1.32 - 1.39 (m, 2H), 1.25 - 1.31 (m, 2H).

Minor rotamer (35%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.11 (t, J=8.0 Hz, 1H), 7.69 (br d, J=3.8 Hz, 1H), 7.05 - 7.26 (m, 7H), 6.86 (s, 1H), 4.97 (q, J=6.6 Hz, 1H), 4.55 (br dd, J=13.2, 3.5 Hz, 1H), 3.39 - 3.51 (m, 1H), 3.23 - 3.31 (m, 1H), 2.83 - 3.06 (m, 3H), 2.56 (d, J=4.7 Hz, 3H), 2.54 - 2.55 (m, 1H), 2.43 - 2.48 (m, 2H), 2.22 (d, J=7.3 Hz, 2H), 1.78 - 1.86 (m, 2H), 1.55 (d, J=6.6 Hz, 3H), 1.32 - 1.39 (m, 2H), 1.25 - 1.31 (m, 2H).

Compound 49

Major rotamer (65%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 9.15 (d, J=10.4 Hz, 1H), 7.70 (br s, 1H), 7.61 (d, J=12.0 Hz, 1H), 7.32 (d, J=7.3 Hz, 1H), 7.21 - 7.26 (m, 1H), 7.15 - 7.21 (m, 3H), 6.99 (br

s, 1H), 6.94 (s, 1H), 5.59 (q, J=6.9 Hz, 1H), 3.80 (br ddd, J=13.6, 4.7, 1.3 Hz, 1H), 3.42 - 3.51 (m, 1H), 2.83 - 3.05 (m, 2H), 2.71 (br d, J=16.1 Hz, 1H), 2.54 - 2.57 (m, 1H), 2.20 - 2.26 (m, 1H), 1.52 (d, J=6.6 Hz, 3H), 1.39 - 1.47 (m, 2H), 1.25 - 1.38 (m, 4H).

Minor rotamer (35%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 9.15 (d, J=10.4 Hz, 1H), 7.70 (br s, 1H), 7.61 (d, J=12.0 Hz, 1H), 7.15 - 7.21 (m, 3H), 7.10 - 7.15 (m, 1H), 7.07 (d, J=7.3 Hz, 1H), 6.99 (br s, 1H), 6.90 (s, 1H), 4.95 (q, J=6.1 Hz, 1H), 4.55 (br dd, J=12.9, 3.2 Hz, 1H), 3.23 - 3.30 (m, 1H), 2.83 - 3.05 (m, 3H), 2.54 - 2.57 (m, 1H), 2.20 - 2.26 (m, 1H), 1.55 (br d, J=6.9 Hz, 3H), 1.39 - 1.47 (m, 2H), 1.25 - 1.38 (m, 4H).

Compound 50

Major rotamer (65%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 12.11 (br s, 1H), 9.17 (d, J=10.4 Hz, 1H), 7.68 (d, J=11.7 Hz, 1H), 7.32 (d, J=7.6 Hz, 1H), 7.21 - 7.26 (m, 1H), 7.15 - 7.21 (m, 3H), 6.94 (s, 1H), 5.59 (q, J=6.6 Hz, 1H), 3.80 (br dd, J=13.6, 4.1 Hz, 1H), 3.43 - 3.51 (m, 1H), 3.27 (s, 3H), 2.84 - 3.05 (m, 2H), 2.74 - 2.79 (m, 1H), 2.71 (br d, J=16.4 Hz, 1H), 2.40 - 2.46 (m, 1H), 1.60 - 1.67 (m, 1H), 1.56 - 1.60 (m, 1H), 1.53 (d, J=6.6 Hz, 3H), 1.25 - 1.40 (m, 4H).

Minor rotamer (35%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 12.11 (br s, 1H), 9.17 (d, J=10.4 Hz, 1H), 7.68 (d, J=11.7 Hz, 1H), 7.15 - 7.21 (m, 3H), 7.10 - 7.15 (m, 1H), 7.07 (d, J=7.9 Hz, 1H), 6.91 (s, 1H), 4.95 (q, J=6.6 Hz, 1H), 4.55 (br dd, J=11.8, 4.3 Hz, 1H), 3.27 (s, 3H), 3.24 - 3.29 (m, 1H), 2.84 - 3.05 (m, 3H), 2.74 - 2.79 (m, 1H), 2.40 - 2.46 (m, 1H), 1.60 - 1.67 (m, 1H), 1.56 - 1.60 (m, 1H), 1.55 (br d, J=7.3 Hz, 3H), 1.25 - 1.40 (m, 4H).

Compound 51

Major rotamer (65%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.56 (br t, J=8.8 Hz, 1H), 7.71 (br s, 1H), 7.59 (br d, J=7.6 Hz, 1H), 7.32 (br d, J=7.6 Hz, 1H), 7.10 - 7.26 (m, 4H), 7.01 (br s, 1H), 6.93 (s, 1H), 5.59 (q, J=6.8 Hz, 1H), 3.80 (br d, J=13.9 Hz, 1H), 3.42 - 3.51 (m, 1H), 2.83 - 3.06 (m, 2H), 2.71 (br d, J=16.7 Hz, 1H), 2.17 - 2.23 (m, 1H), 1.52 (d, J=6.9 Hz, 3H), 1.39 - 1.44 (m, 1H), 1.32 - 1.39 (m, 3H), 1.22 - 1.32 (m, 3H).

Minor rotamer (35%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 8.56 (br t, J=8.8 Hz, 1H), 7.71 (br s, 1H), 7.59 (br d, J=7.6 Hz, 1H), 7.10 - 7.26 (m, 4H), 7.05 - 7.09 (d, J=7.6 Hz, 1H), 7.01 (br s, 1H), 6.90 (s, 1H), 4.92 - 4.99 (m, 1H), 4.55 (br d, J=10.1 Hz, 1H), 3.24 - 3.31 (m, 1H), 2.83 - 3.06

(m, 3H), 2.17 - 2.23 (m, 1H), 1.55 (br d, J=6.6 Hz, 3H), 1.39 - 1.44 (m, 1H), 1.32 - 1.39 (m, 3H), 1.22 - 1.32 (m, 3H).

Compound 52

Major rotamer (65%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 12.09 (s, 1H), 8.57 - 8.63 (m, 1H), 7.64 (d, J=7.9 Hz, 1H), 7.32 (d, J=7.6 Hz, 1H), 7.21 - 7.25 (m, 1H), 7.14 - 7.21 (m, 3H), 6.94 (s, 1H), 5.59 (q, J=6.6 Hz, 1H), 3.80 (br dd, J=13.2, 4.7 Hz, 1H), 3.43 - 3.50 (m, 1H), 3.24 (s, 3H), 2.84 - 3.06 (m, 2H), 2.69 - 2.76 (m, 2H), 1.53 (d, J=6.9 Hz, 3H), 1.50 - 1.59 (m, 3H), 1.25 - 1.39 (m, 4H).

Minor rotamer (35%)

^{1}H-NMR (500 MHz, DMSO-d6) δ ppm 12.09 (s, 1H), 8.57 - 8.63 (m, 1H), 7.64 (d, J=7.9 Hz, 1H), 7.14 - 7.21 (m, 3H), 7.10 - 7.14 (m, 1H), 7.07 (d, J=7.3 Hz, 1H), 6.90 (s, 1H), 4.96 (q, J=6.7 Hz, 1H), 4.55 (br dd, J=13.1, 3.0 Hz, 1H), 3.27 - 3.31 (m, 1H), 3.24 (s, 3H), 2.84 - 3.06 (m, 3H), 2.69 - 2.76 (m, 1H), 1.54 (d, J=6.6 Hz, 3H), 1.50 - 1.59 (m, 3H), 1.25 - 1.39 (m, 4H).

Melting points

For a number of compounds, melting points (m.p.) were determined with a differential scanning calorimeter DSC 1 (Mettler Toledo). Melting points were measured with a temperature gradient of 10°C/minute from 25°C to 350°C. The reported values are peak values. Values are obtained with experimental uncertainties that are commonly associated with this analytical method.

Co. No.	m.p.	Co. No.	m.p.
4	254.07°C	27	177.21°C
7	280.69°C	28	286.12°C
10	302.90°C	30	213.73°C
11	300.14°C	32	186.79°C
12	258.18°C	34	232.53°C
15	238.10°C	35	255.06°C
16	240.35°C	36	196.25°C
18	212.72°C	39	297.87°C
19	248.97°C	40	274.46°C
24	166.75°C	42	129.63°C
25	171.93°C	44	300.97°C
26	160.53°C	48	143.95°C

Optical rotation

The optical rotation was measured using a polarimeter with light at the wavelength of the D-line of sodium (589 nm) at a temperature of 20°C in DMF as solvent.

Co. No.	$[\alpha]_D^{20}$	c (w/v %)	Co. No.	$[\alpha]_D^{20}$	c (w/v %)
1	+19.62°	0.2549	27	+151.72°	0.29
2	-276.67°	0.3	28	+142.07°	0.29
3	+117.96°	0.284	29	+169.63°	0.27
4	+148.62°	0.29	30	+77.04°	0.27
5	+154.43°	0.2655	31	+143.73°	0.295
7	+126.59°	0.267	32	-193.46°	0.306
10	+129.96°	0.1385	33	+56.12°	0.2566
11	+115.17°	0.29	34	+65°	0.26
12	+122.67°	0.3	35	+77.78°	0.27
13	+171.58°	0.285	36	+35.2°	0.25
14	+124.77°	0.1619	37	+44.33°	0.2301
15	+129.22°	0.2221	38	+16.25°	0.277
16	+119.88°	0.2319	39	+41.57°	0.267
17	+106.21°	0.177	40	+53.79°	0.264
18	+122.99°	0.1805	41	-35.1°	0.302
19	+116.64°	0.1929	42	-35.5°	0.262
20	+130.23°	0.215	43	-32.18°	0.289
21	+129.71°	0.1673	44	-31.44°	0.299
22	+129.62°	0.26	45	-28.97°	0.252
23	+140.37°	0.27	46	-29.6°	0.277
24	+164.07°	0.27	47	-31.34°	0.268
25	+156.3°	0.27	48	-27.94°	0.272
26	+167.31°	0.26			

E. Pharmacological examples

E.1 Antiviral activity

Black 384-well clear-bottom microtiter plates (Corning, Amsterdam, The Netherlands) were filled via acoustic drop ejection using the echo liquid handler (Labcyte, Sunnyvale, California). 200 nL of compound stock solutions (100% DMSO) were transferred to the assay plates. 9 serial 4-fold dilutions of compound were made, creating per quadrant the same compound concentration. The assay was initiated by adding 10 µL of culture medium to each well (RPMI medium without phenol red, 10% FBS-heat inactivated, 0.04% gentamycin (50 mg/mL). All addition steps are done by using a multidrop dispenser (Thermo Scientific, Erembodegem, Belgium). Next, rgRSV224 virus (MOI = 1) diluted in

culture medium was added to the plates. rgRSV224 virus is an engineered virus that includes an additional GFP gene (Hallak LK, Spillmann D, Collins PL, Peeples ME. Glycosaminoglycan sulfation requirements for respiratory syncytial virus infection; Journal of virology (2000), 74(22), 10508-13) and was in-licensed from the NIH (Bethesda, MD, USA). Finally, 20 µL of a HeLa cell suspension (3,000 cells/well) were plated. Medium, virus- and mock-infected controls were included in each test. The wells contain 0.05% DMSO per volume. Cells were incubated at 37°C in a 5% CO2 atmosphere. Three days post-virus exposure, viral replication was quantified by measuring GFP expression in the cells by an in house developed MSM laser microscope (Tibotec, Beerse, Belgium). The EC_{50} was defined as the 50% inhibitory concentration for GFP expression. In parallel, compounds were incubated for three days in a set of white 384-well microtiter plates (Corning) and the cytotoxicity of compounds in HeLa cells was determined by measuring the ATP content of the cells using the ATPlite kit (Perkin Elmer, Zaventem, Belgium) according to the manufacturer's instructions. The CC_{50} was defined as the 50% concentration for cytotoxicity.

Table : antiviral data

Co. No.	RSV HELA EC_{50} (µm)	TOX HELA CC_{50} (µm)	Co. No.	RSV HELA EC_{50} (µm)	TOX HELA CC_{50} (µm)
1	0.062	41.832	28	0.037	53.433
2	0.084	42.528	29	2.359	>100
3	0.319	>100	30	0.049	40.842
4	0.120	44.004	31	0.040	35.201
5	0.098	41.824	32	0.061	37.273
7	0.030	>100	33	0.155	>100
8	0.332	34.366	34	0.022	>100
9	0.098	20.115	35	0.057	>100
10	0.014	>25	36	0.110	>100
11	0.044	N.A.	37	0.063	41.604
12	0.024	>100	38	0.159	50.384
13	0.731	49.807	39	0.082	12.488
14	0.170	>50	40	0.138	>100
15	0.408	>100	41	0.152	49.770
16	0.263	>100	42	0.263	69.225
17	0.182	>100	43	0.307	>100
18	0.076	>100	44	0.332	>100
19	0.095	>100	45	0.146	29.549
20	0.287	>10	46	0.145	30.407

Co. No.	RSV HELA EC_{50} (µm)	TOX HELA CC_{50} (µm)	Co. No.	RSV HELA EC_{50} (µm)	TOX HELA CC_{50} (µm)
21	0.062	>100	47	0.148	25.758
22	0.427	51.798	48	0.151	23.933
23	0.427	16.892	49	0.150	10.760
24	0.020	44.874	50	0.389	53.276
25	0.034	51.898	51	0.047	25.857
26	0.138	52.099	52	0.117	65.298
27	0.040	55.763			

N.A. : not available

F. Prophetic composition examples

"Active ingredient" as used throughout these examples relates to a final compound of Formula (I), the pharmaceutically acceptable salts thereof, the solvates and the stereochemically isomeric forms and the tautomers thereof.

Typical examples of recipes for the formulation of the invention are as follows:

F.1. Tablets

Active ingredient	5 to 50 mg
Di calcium phosphate	20 mg
Lactose	30 mg
Talcum	10 mg
Magnesium stearate	5 mg
Potato starch	ad 200 mg

In this Example, active ingredient can be replaced with the same amount of any of the compounds according to the present invention, in particular by the same amount of any of the exemplified compounds.

F.2. Suspension

An aqueous suspension is prepared for oral administration so that each 1 milliliter contains 1 to 5 mg of one of the active compounds, 50 mg of sodium carboxymethyl cellulose, 1 mg of sodium benzoate, 500 mg of sorbitol and water ad 1 ml.

F.3. Injectable

A parenteral composition is prepared by stirring 1.5 % by weight of active ingredient of the invention in 10% by volume propylene glycol in water.

F.4. Ointment

Active ingredient	5 to 1000 mg
Stearyl alcohol	3 g

Lanoline	5 g
White petroleum	15 g
Water	ad 100 g

In this Example, active ingredient can be replaced with the same amount of any of the compounds according to the present invention, in particular by the same amount of any of the exemplified compounds.

Reasonable variations are not to be regarded as a departure from the scope of the invention. It will be obvious that the thus described invention may be varied in many ways by those skilled in the art.

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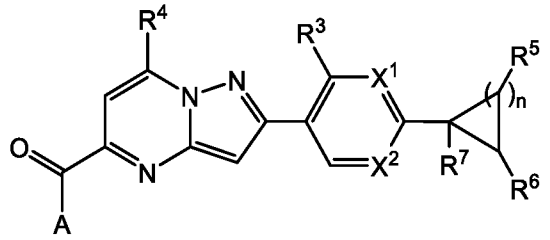
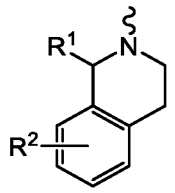
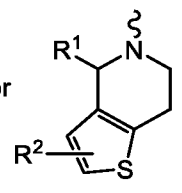
Claims

1. A compound of formula (I), including any stereochemically isomeric form thereof, wherein



(I)

including any stereochemically isomeric form thereof, wherein

A is  (a-1) or  (a-2)

n is 1 or 2;

X^1 and X^2 are selected from X^1 is CH and X^2 is CH,
or X^1 is N and X^2 is CH,
or X^1 is CH and X^2 is N;

R^1 is CH_3 or CH_2CH_3;

R^2 is hydrogen, halo or C_{1-4}alkyl;

R^3 is halo;

R^4 is C_{1-6}alkyl; C_{3-6}cycloalkyl; phenyl; phenyl substituted with 1, 2 or 3 substituents each individually selected from halo, C_{1-4}alkyl, C_{1-4}alkyloxy, and hydroxy;

R^5 is hydrogen or C_{1-4}alkyl;

R^6 is hydroxy;
cyano;
C_{1-4}alkyl substituted with hydroxy, -(CO)-$NR^{10}R^{11}$ or -O-(CO)-$NR^{10}R^{11}$;
-(CO)-$NR^{10}R^{11}$;
-(CO)-NR^9-SO_2-R^8;
-(CO)-NR^9-(CO)-SO_2-R^8;
-(CO)-Heterocycle;
-(CO)-NR^9-Heterocycle;
-O-(CO)-$NR^{10}R^{11}$;
-NR^9-(CO)-C_{1-4}alkyl;

$-NR^9-(CO)-C_{3-6}$cycloalkyl;
$-NR^9-(CO)-O-R^8$;
$-NR^9-(CO)-NR^9-R^8$;
$-NR^9-SO_2-R^8$;
$-NR^9-(P=O)$-di(C_{1-4}alkyl);
$-SO_2-R^8$;
$-SO_2-NR^{10}R^{11}$;
$-SO_2-NR^9-(CO)-R^8$; or
Heteroaryl;

R^7 is hydrogen, halo, C_{1-4}alkyl or $-(CO)-NR^{10}R^{11}$;

R^8 is C_{1-4}alkyl, polyhaloC_{1-4}alkyl, or C_{3-6}cycloalkyl;

each R^9 is independently selected from hydrogen or C_{1-6}alkyl;

R^{10} and R^{11} are each indepently selected from hydrogen; CN; C_{1-4}alkyl; C_{3-6}alkenyl; polyhaloC_{1-4}alkyl; C_{3-6}cycloalkyl; C_{3-6}cycloalkyl substituted with C_{1-4}alkyl; or C_{1-4}alkyl substituted with hydroxy or cyano;

Heterocycle is pyrrolidinyl or oxetanyl; and

Heteroaryl is 3-oxo-2,3-dihydro-1,2-oxazolyl, or tetrazolyl, wherein each Heteroaryl is optionally substituted with one or two substituents each independently selected from C_{1-4}alkyl, halo, amino, and aminocarbonyl;

provided that when R^6 is $-NR^9-(CO)-C_{3-6}$cycloalkyl then X^1 is CH and X^2 is CH;

or a pharmaceutically acceptable acid addition salt thereof.

2. The compound as claimed in claim 1 wherein X^1 is CH and X^2 is CH.

3. The compound as claimed in claim 1 wherein wherein X^1 is N and X^2 is CH, or X^1 is CH and X^2 is N.

4. The compound as claimed in any one of claims 1 to 3 wherein radical A is of formula (a-1).

5. The compound as claimed in any one of claims 1 to 3 wherein radical A is of formula (a-2).

6. The compound as claimed in any one of claims 1 to 5 wherein n is 1.

7. The compound as claimed in any one of claims 1 to 5 wherein n is 2.

8. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically active amount of a compound as claimed in any of claims 1 to 7.

9. The pharmaceutical composition according to claim 8, which further comprises another antiviral agent.

10. The pharmaceutical composition according to claim 9, wherein the other antiviral agent is a RSV inhibiting compound.

11. A process for preparing a pharmaceutical composition as claimed in any one of claims 8 to 10 wherein a therapeutically active amount of a compound as claimed in any one of claims 1 to 7 is intimately mixed with a pharmaceutically acceptable carrier.

12. A compound as claimed in any one of claims 1 to 7 for use as a medicine.

13. A compound as claimed in any one of claims 1 to 7, or a pharmaceutical composition as claimed in any one of claims 8 to 10, for use in the treatment of a respiratory syncytial virus infection.

14. A method of treating a respiratory syncytial virus (RSV) infection comprising administering to a subject in need thereof an anti-virally effective amount of a compound of formula (I) as defined in any one of claims 1 to 7.

15. The use of a compound as defined in any one of claims 1 to 7 in the manufacture of a medicament for the treatment of a respiratory syncytial virus (RSV) infection.