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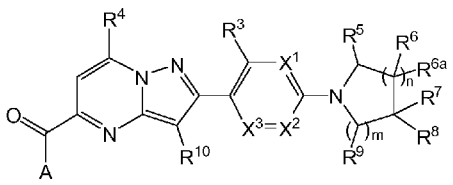
(54) Title: PYRAZOLOPYRIMIDINES HAVING ACTIVITY AGAINST THE RESPIRATORY SYNCYTIAL VIRUS (RSV)



(I)

(57) Abstract: 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. Formula (Ia).

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PYRAZOLOPYRIMIDINES HAVING ACTIVITY AGAINST THE RESPIRATORY SYNCYTIAL VIRUS (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. The other two drugs, RespiGam® (RSV-IG) and Synagis® (palivizumab), polyclonal and monoclonal antibody immunostimulants, are intended to be used in a preventive way. Both are very expensive, and require parenteral administration.

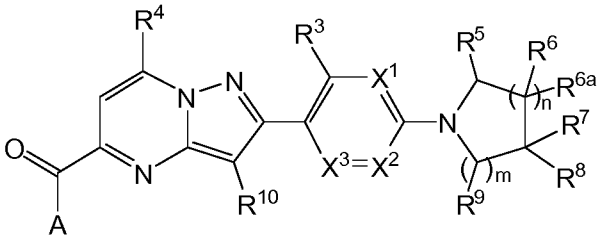
Clearly there is a need for an efficacious non-toxic and easy to administer drug against RSV replication. It would be particularly preferred to provide drugs against RSV replication that could be administered perorally.

Compounds that exhibit anti-RSV activity are disclosed in WO-2016/174079 and WO-2016/091774.

The compounds of the present invention have unexpected better plasma concentration profiles than the pyrazolopyrimidine compounds of WO-2016/174079 bearing a substituted pyrrolidine moiety as demonstrated in Pharmacological Example E.2.

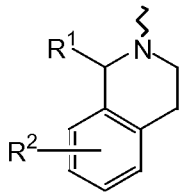
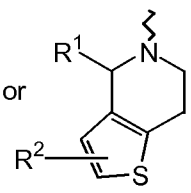
Detailed description of the Invention

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 0, 1, or 2;

m is 1 or 2;

X^1, X^2 and X^3 are selected from X^1 is $CR^{11}$and X^2 is CR^{11} and X^3 is CR^{11},
or X^1 is N and X^2 is CR^{11} and X^3 is CR^{11},
or X^1 is CR^{11} and X^2 is N and X^3 is CR^{11},
or X^1 is CR^{11} and X^2 is CR^{11} and X^3 is N,
or X^1 is N and X^2 is CR^{11} and X^3 is N,
wherein each R^{11} is independently selected from the group consisting of hydrogen, halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkyloxyC_{1-4}alkyloxy, hydroxyC_{1-4}alkyl and hydroxyC_{1-4}alkyloxy;

R^1 is CH_3 or CH_2CH_3;

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

R^3 is halo or CH_3O;

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

R^5 is hydrogen, C_{1-4}alkyl or hydroxyC_{1-4}alkyl;
each R^6 is independently selected from the group consisting of hydrogen, C_{1-4}alkyl, hydroxy, halo and C_{1-4}alkyloxy;
each R^{6a} is independently selected from the group consisting of hydrogen and halo;
R^7 is hydrogen, C_{1-4}alkyl, or hydroxyC_{1-4}alkyl;
R^8 is -OH,
-CN,
-O-(CO)-$NR^{12}R^{13}$,
-C_{1-4}alkyl-(CO)-$NR^{12}R^{13}$,
-(CO)-$NR^{12}R^{13}$,
-(CS)-$NR^{12}R^{13}$,
-(CO)-NR^{12}-CN,
-(CO)-NR^{12}-SO_2-R^{14},
-NR^{12}-(CO)-R^{14},
-NR^{12}-(CO)-O-R^{14},
-NR^{12}-SO_2-R^{14},
-NH_2,
-NR^{12}-R^{15};
-SO_2-R^{14},
-SO_2-$NR^{12}R^{13}$,
-SO_2-NR^{12}-(CO)-R^{14}, or
-SO(=NH)(-R^{14}), or
Heteroaryl[1];
wherein
R^{12} and R^{13} are each independently selected from hydrogen and C_{1-4}alkyl, and;
R^{14} is C_{1-4}alkyl or polyhaloC_{1-4}alkyl;
R^{15} is di(C_{1-4}alkyl)-(P=O)- or polyhaloC_{1-4}alkyl;
or R^7 and R^8 may be taken together to form -CH_2-(SO_2)-CH_2- or -CH_2-O-CH_2- ;
each R^9 is independently selected from the group consisting of hydrogen and C_{1-4}alkyl;
R^{10} is hydrogen, halo or C_{1-6}alkyl;
when n = 1 and m=1, R^8 and R^9 may be taken together to form -CH_2- ;
when n = 1 and m=1, R^5 and R^9 may be taken together to form -CH_2CH_2- ;
when n=1 and m=1, R^8 and R^9 may be taken together to form -CH_2-(CO)-O- ;
Heteroaryl is pyridinyl or pyrimidinyl, wherein each Heteroaryl is optionally substituted with one or two substituents each independently selected from C_{1-4}alkyl, halo, amino, and aminocarbonyl;
Heteroaryl[1] is tetrazolyl, oxadiazolyl or 5-oxo-4,5-dihydro-1,2,4-oxadiazolyl;

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.
- -(CS)- or (CS) means thiocarbonyl.

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.

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

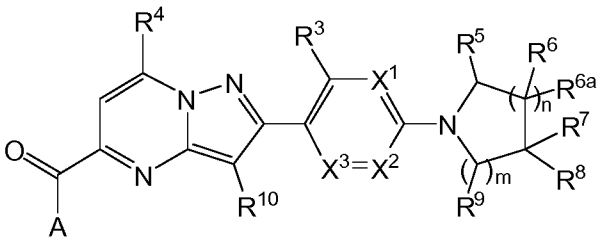
conveniently be obtained by treating the base form with such appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, nitric, phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic (i.e. ethanedioic), malonic, succinic (i.e. butane-dioic 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.

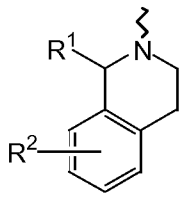
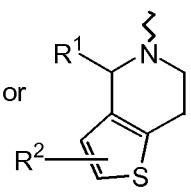
For the avoidance of doubt, compounds of formula (I) may contain the stated atoms in any of their natural or non-natural isotopic forms. In this respect, embodiments of the invention that may be mentioned include those in which (a) the compound of formula (I) is not isotopically enriched or labelled 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.

The present invention also relates to compounds of formula (I)



(I)

including any stereochemically isomeric form thereof, wherein

A is  or 

(a-1) (a-2)

n is 0, 1, or 2;

m is 1 or 2;

X^1, X^2 and X^3 are selected from X^1 is $CR^{11}$and X^2 is CR^{11} and X^3 is CR^{11},
or X^1 is N and X^2 is CR^{11} and X^3 is CR^{11},
or X^1 is CR^{11} and X^2 is N and X^3 is CR^{11},
or X^1 is CR^{11} and X^2 is CR^{11} and X^3 is N,
or X^1 is N and X^2 is CR^{11} and X^3 is N,
wherein each R^{11} is independently selected from the group consisting of hydrogen, halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkyloxyC_{1-4}alkyloxy and hydroxyC_{1-4}alkyl;

R^1 is CH_3 or CH_2CH_3;

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

R^3 is halo or CH_3O;

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

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

each R^6 is independently selected from the group consisting of hydrogen, C_{1-4}alkyl and hydroxy;

each R^{6a} is hydrogen;

R^8 is -OH,
-CN,
-O-(CO)-$NR^{12}R^{13}$,
-C_{1-4}alkyl-(CO)-$NR^{12}R^{13}$,
-(CO)-$NR^{12}R^{13}$,
-(CO)-NR^{12}-CN,
-(CO)-NR^{12}-SO_2-R^{14},
-NR^{12}-(CO)-R^{14},
-NR^{12}-(CO)-O-R^{14},
-NR^{12}-SO_2-R^{14},
-NR^{12}-R^{15};

$-SO_2-R^{14}$,
$-SO_2-NR^{12}R^{13}$,
$-SO_2-NR^{12}-(CO)-R^{14}$, or
$-SO(=NH)(-R^{14})$, or
Heteroaryl^1;
wherein
R^{12} and R^{13} are each independently selected from hydrogen and C_{1-4}alkyl;
R^{14} is C_{1-4}alkyl, or polyhaloC_{1-4}alkyl;
R^{15} is di(C_{1-4}alkyl)-(P=O)-;
or R^7 and R^8 may be taken together to form $-CH_2-(SO_2)-CH_2-$ or $-CH_2-O-CH_2-$;
each R^9 is independently selected from the group consisting of hydrogen and C_{1-4}alkyl;
R^{10} is hydrogen, halo or C_{1-6}alkyl;
when n = 1 and m=1, R^8 and R^9 may be taken together to form $-CH_2-$;
when n = 1 and m=1, R^5 and R^9 may be taken together to form $-CH_2CH_2-$;
when n=1 and m=1, R^8 and R^9 may be taken together to form $-CH_2-(CO)-O-$;
Heteroaryl is pyridinyl or pyrimidinyl, wherein each Heteroaryl is optionally substituted with one or two substituents each independently selected from C_{1-4}alkyl, halo, amino, and aminocarbonyl;
Heteroaryl^1 is tetrazolyl or oxadiazolyl;
or a pharmaceutically acceptable acid addition salt thereof.

In a first embodiment the invention concerns compounds of formula (I), including any stereochemically isomeric form thereof,
wherein
n is 0, 1, or 2;
m is 1 or 2;
X^1, X^2 and X^3 are selected from X^1 is $CR^{11}$and X^2 is CR^{11} and X^3 is CR^{11},
or X^1 is N and X^2 is CR^{11} and X^3 is CR^{11},
or X^1 is CR^{11} and X^2 is N and X^3 is CR^{11},
or X^1 is N and X^2 is CR^{11} and X^3 is N,
wherein each R^{11} is independently selected from the group consisting of hydrogen, halo, C_{1-4}alkyl, C_{1-4}alkyloxy, and C_{1-4}alkyloxyC_{1-4}alkyloxy;
R^1 is CH_3;
R^2 is hydrogen, or halo;
R^3 is halo;
R^4 is C_{3-6}cycloalkyl; phenyl; phenyl substituted with 1 substituent selected from halo, cyano, C_{1-4}alkyl, polyhaloC_{1-4}alkyl, and C_{1-4}alkyloxy; or Heteroaryl;

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

each R^6 is independently selected from the group consisting of hydrogen, C_{1-4}alkyl and hydroxy;

each R^{6a} is hydrogen;

R^7 is hydrogen or C_{1-4}alkyl;

R^8 is -OH,
-CN,
-O-(CO)-$NR^{12}R^{13}$,
-C_{1-4}alkyl-(CO)-$NR^{12}R^{13}$,
-(CO)-$NR^{12}R^{13}$,
-(CO)-NR^{12}-CN,
-(CO)-NR^{12}-SO_2-R^{14},
-NR^{12}-(CO)-R^{14},
-NR^{12}-(CO)-O-R^{14},
-NR^{12}-SO_2-R^{14},
-NR^{12}-R^{15};
-SO_2-R^{14},
-SO_2-$NR^{12}R^{13}$,
-SO_2-NR^{12}-(CO)-R^{14}, or
-SO(=NH)(-R^{14}), or
Heteroaryl^1;
wherein
R^{12} and R^{13} are each independently selected from hydrogen and C_{1-4}alkyl;
R^{14} is C_{1-4}alkyl;
R^{15} is di(C_{1-4}alkyl)-(P=O)-;

or R^7 and R^8 may be taken together to form -CH_2-(SO_2)-CH_2- or -CH_2-O-CH_2- ;

each R^9 is independently selected from the group consisting of hydrogen and C_{1-4}alkyl;

R^{10} is hydrogen, halo or C_{1-6}alkyl;

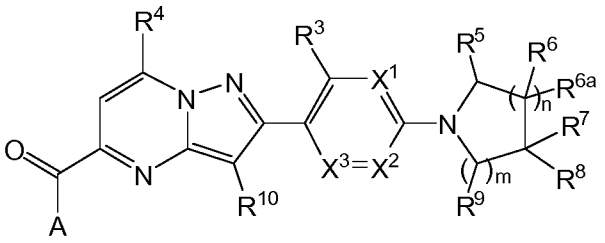
when n=1 and m=1, R^8 and R^9 may be taken together to form -CH_2-(CO)-O- ;

Heteroaryl is pyridinyl or pyrimidinyl, wherein each Heteroaryl is optionally substituted with one substituent selected from halo;

Heteroaryl^1 is tetrazolyl or oxadiazolyl;

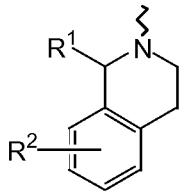
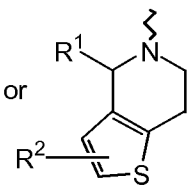
or a pharmaceutically acceptable acid addition salt thereof.

In a second embodiment the invention concerns compounds of formula (I),



(I)

including any stereochemically isomeric form thereof, wherein

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

wherein

n is 0, 1, or 2;

m is 1 or 2;

X^1, X^2 and X^3 are selected from X^1 is $CR^{11}$and X^2 is CR^{11} and X^3 is CR^{11},
or X^1 is N and X^2 is CR^{11} and X^3 is CR^{11},
or X^1 is CR^{11} and X^2 is N and X^3 is CR^{11},
or X^1 is N and X^2 is CR^{11} and X^3 is N,
wherein each R^{11} is independently selected from the group consisting of hydrogen, halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkyloxyC_{1-4}alkyloxy, and hydroxyC_{1-4}alkyloxy;

R^1 is CH_3;

R^2 is hydrogen, or halo;

R^3 is halo;

R^4 is C_{3-6}cycloalkyl; phenyl; phenyl substituted with 1 substituent selected from halo, cyano, C_{1-4}alkyl, polyhaloC_{1-4}alkyl, and C_{1-4}alkyloxy; or Heteroaryl;

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

each R^6 is independently selected from the group consisting of hydrogen, C_{1-4}alkyl, hydroxy, halo and C_{1-4}alkyloxy;

each R^{6a} is independently selected from the group consisting of hydrogen and halo;

R^7 is hydrogen, C_{1-4}alkyl, or hydroxyC_{1-4}alkyl;

R^8 is -OH,
-CN,
-O-(CO)-$NR^{12}R^{13}$,

$-C_{1-4}$alkyl-(CO)-$NR^{12}R^{13}$,
-(CO)-$NR^{12}R^{13}$,
-(CS)-$NR^{12}R^{13}$,
-(CO)-NR^{12}-CN,
-(CO)-NR^{12}-SO_2-R^{14},
-NR^{12}-(CO)-R^{14},
-NR^{12}-(CO)-O-R^{14},
-NR^{12}-SO_2-R^{14},
-NH_2,
-NR^{12}-R^{15};
-SO_2-R^{14},
-SO_2-$NR^{12}R^{13}$,
-SO_2-NR^{12}-(CO)-R^{14}, or
-SO(=NH)(-R^{14}), or
Heteroaryl[1];

wherein

R^{12} and R^{13} are each independently selected from hydrogen and C_{1-4}alkyl, and;

R^{14} is C_{1-4}alkyl or polyhaloC_{1-4}alkyl;

R^{15} is di(C_{1-4}alkyl)-(P=O)- or polyhaloC_{1-4}alkyl;

or R^7 and R^8 may be taken together to form -CH_2-(SO_2)-CH_2- or -CH_2-O-CH_2- ;

each R^9 is independently selected from the group consisting of hydrogen and C_{1-4}alkyl;

R^{10} is hydrogen;

when n=1 and m=1, R^8 and R^9 may be taken together to form -CH_2-(CO)-O- ;

Heteroaryl is pyridinyl or pyrimidinyl, wherein each Heteroaryl is optionally substituted with one substituent selected from halo;

Heteroaryl[1] is tetrazolyl or 5-oxo-4,5-dihydro-1,2,4-oxadiazolyl;

or a pharmaceutically acceptable acid addition salt thereof.

A first group of compounds are compounds of formula (I) wherein X^1 is $CR^{11}$and X^2 is CR^{11} and X^3 is CR^{11}.

A second group of compounds are compounds of formula (I) wherein X^1 is N and X^2 is CR^{11} and X^3 is CR^{11}; or X^1 is CR^{11} and X^2 is N and X^3 is CR^{11}; or X^1 is CR^{11} and X^2 is CR^{11} and X^3 is N; or X^1 is N and X^2 is CR^{11} and X^3 is N.

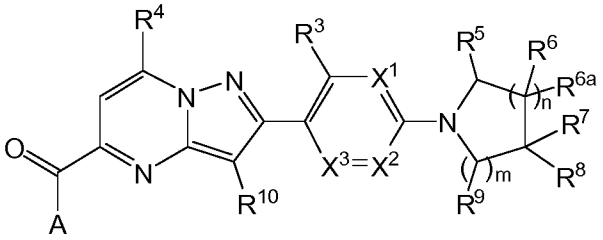
A third group of compounds are compounds of formula (I) wherein X^1 is N and X^2 is CR^{11} and X^3 is CR^{11}.

A third group of compounds are compounds of formula (I) X^1 is CR^{11} and X^2 is N and X^3 is CR^{11}.

A fourth group of compounds are compounds of formula (I) wherein X^1 is CR^{11} and X^2 is CR^{11} and X^3 is N.

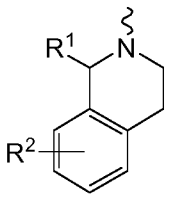
A fifth group of compounds are compounds of formula (I) wherein X^1 is N and X^2 is CR^{11} and X^3 is N.

In a further embodiment the invention concerns compounds of formula (I),



(I)

including any stereochemically isomeric form thereof, wherein

A is 

wherein

n is 0 or 1;

m is 1;

X^1, X^2 and X^3 are selected from X^1 is $CR^{11}$and X^2 is CR^{11} and X^3 is CR^{11}, wherein each R^{11} is hydrogen;

R^1 is CH_3;

R^2 is hydrogen;

R^3 is halo;

R^4 is C_{3-6}cycloalkyl or Heteroaryl;

R^5 is hydrogen;

each R^6 is independently selected from the group consisting of hydrogen, hydroxy, and halo;

each R^{6a} is hydrogen;

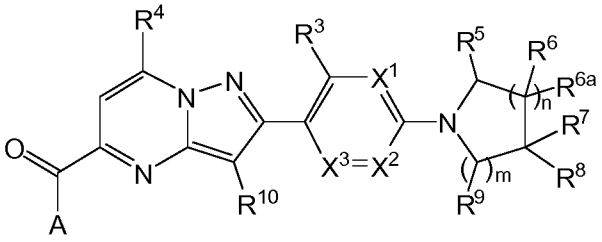
R^7 is hydrogen or hydroxyC_{1-4}alkyl;

R^8 is -OH,

-C_{1-4}alkyl-(CO)-$NR^{12}R^{13}$, or

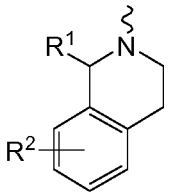
-(CO)-$NR^{12}R^{13}$,
wherein
R^{12} and R^{13} are each independently selected from hydrogen and C_{1-4}alkyl,
R^{10} is hydrogen;
Heteroaryl is pyridinyl;
or a pharmaceutically acceptable acid addition salt thereof.

In another further embodiment the invention concerns compounds of formula (I),



(I)

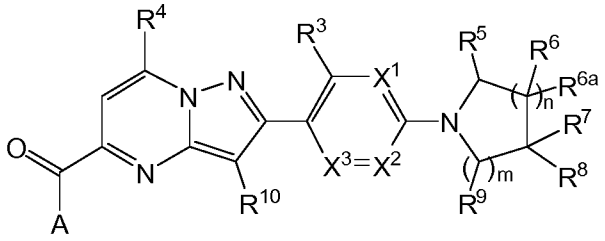
including any stereochemically isomeric form thereof, wherein

A is 

wherein
n is 1;
m is 1;
X^1, X^2 and X^3 are selected from X^1 is $CR^{11}$and X^2 is CR^{11} and X^3 is CR^{11}, wherein each R^{11} is hydrogen;
R^1 is CH_3;
R^2 is hydrogen;
R^3 is halo;
R^4 is C_{3-6}cycloalkyl;
R^5 is hydrogen;
each R^6 is independently selected from the group consisting of hydrogen, hydroxy, and halo;
each R^{6a} is hydrogen;
R^7 is hydrogen or hydroxyC_{1-4}alkyl;
R^8 is -OH, or
-(CO)-$NR^{12}R^{13}$,
wherein
R^{12} and R^{13} are each independently selected from hydrogen and C_{1-4}alkyl,

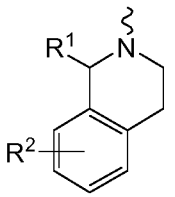
R^{10} is hydrogen;
or a pharmaceutically acceptable acid addition salt thereof.

In yet another further embodiment the invention concerns compounds of formula (I),



(I)

including any stereochemically isomeric form thereof, wherein

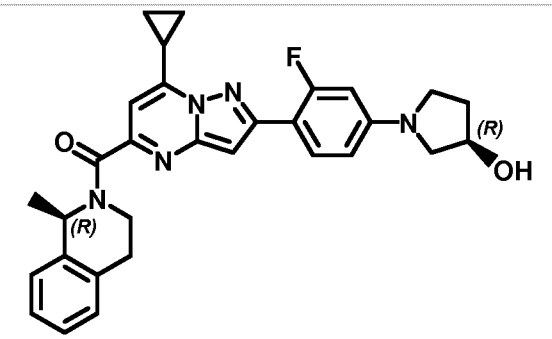
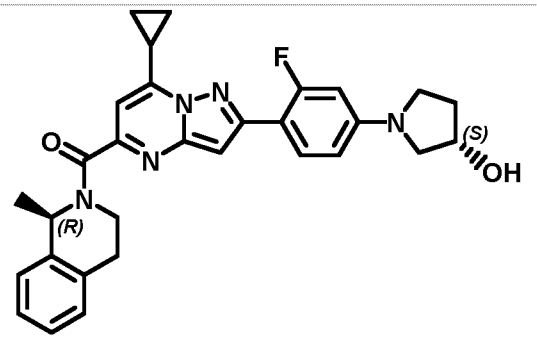
A is 

wherein
n is 1;
m is 1;
X^1, X^2 and X^3 are selected from X^1 is $CR^{11}$and X^2 is CR^{11} and X^3 is CR^{11}, wherein each R^{11} is hydrogen;
R^1 is CH_3;
R^2 is hydrogen;
R^3 is halo;
R^4 is C_{3-6}cycloalkyl;
R^5 is hydrogen;
each R^6 is independently selected from the group consisting of hydrogen and hydroxy;
each R^{6a} is hydrogen;
R^7 is hydrogen;
R^8 is -OH, or
-(CO)-$NR^{12}R^{13}$,
wherein
R^{12} and R^{13} are each independently selected from hydrogen and C_{1-4}alkyl,
R^{10} is hydrogen;
or a pharmaceutically acceptable acid addition salt thereof.

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; or
g) R^4 is phenyl; or
h) R^4 is pyridinyl; or
i) n is 0 and m is 1; or
j) n is 0 and m is 2; or
k) n is 1 and m is 1; or
l) n is 1 and m is 2; and
m) n is 2 and m is 1.

Specific examples of compounds of formula (I) are :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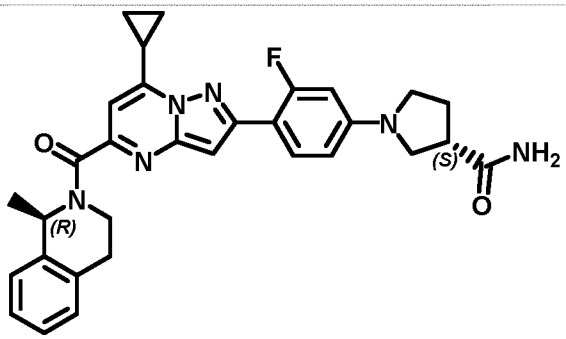	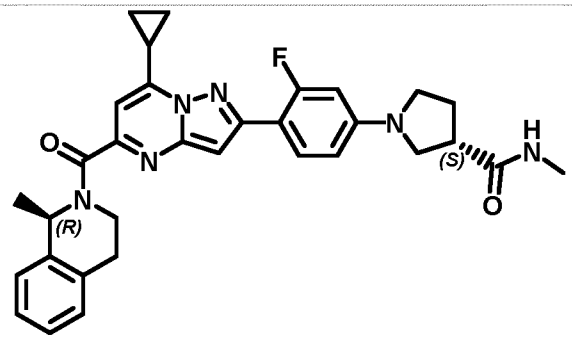
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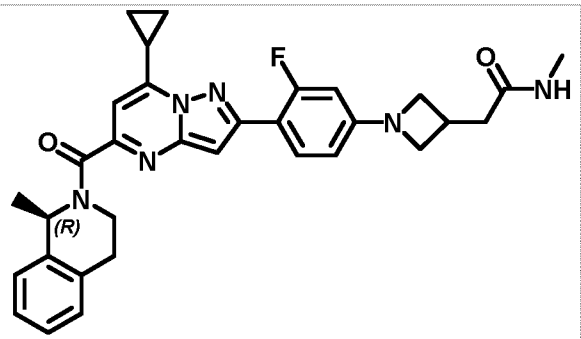	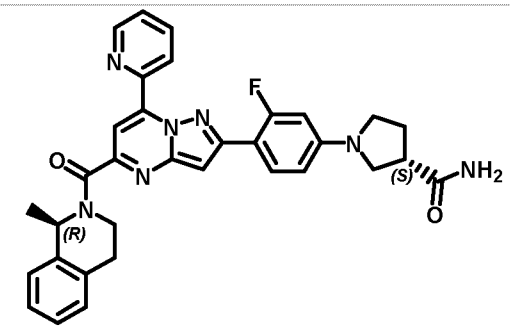
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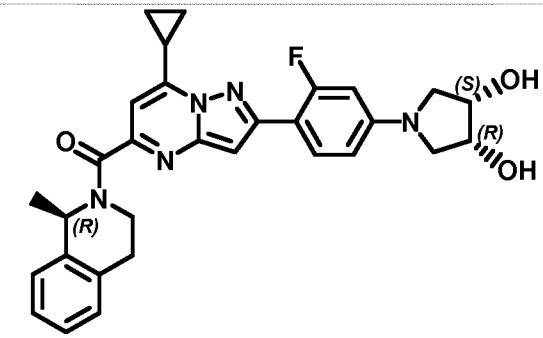	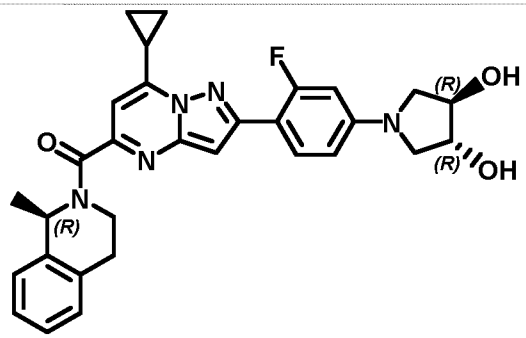
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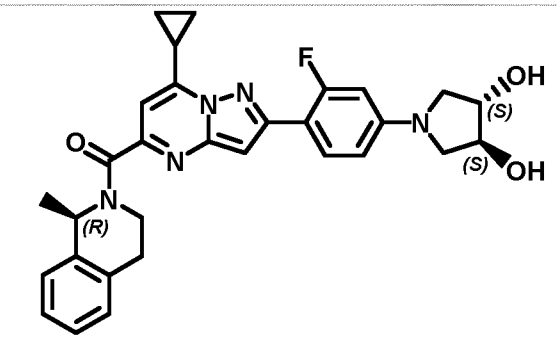	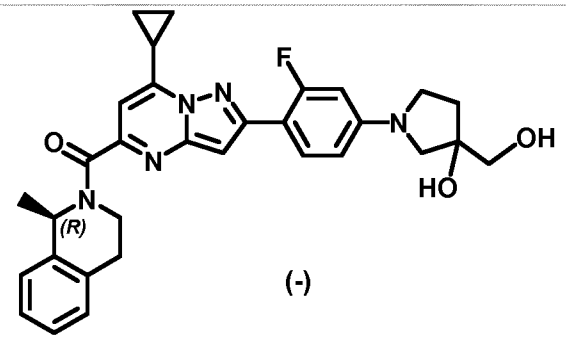
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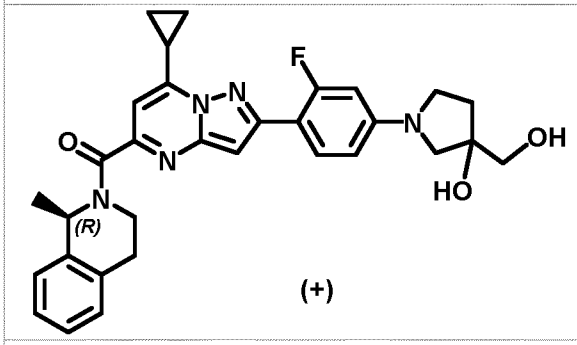
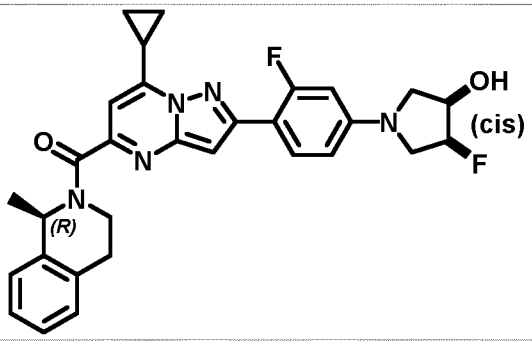
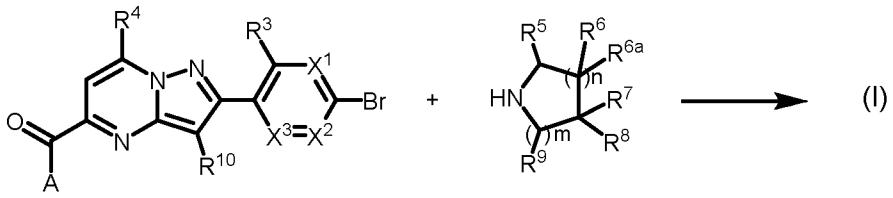
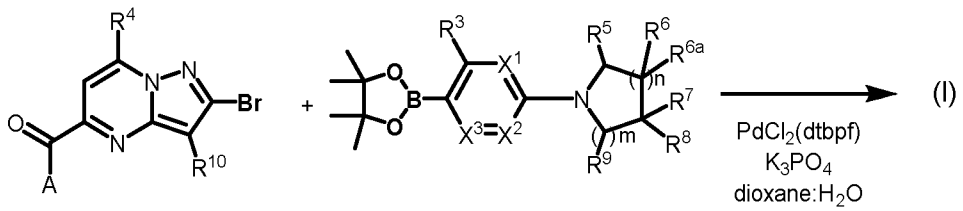
	
Co. No. 104	Co. No. 107

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.



(II) (III)

Compounds of formula (I) can also be prepared by reacting an intermediate of formula (IV) with an intermediate of formula (V) in a reaction-inert solvent.



(IV) (V)

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 *Pneumoviridae* 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.

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-(methyl-sulfonyl)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-(methyl-

sulfonyl)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

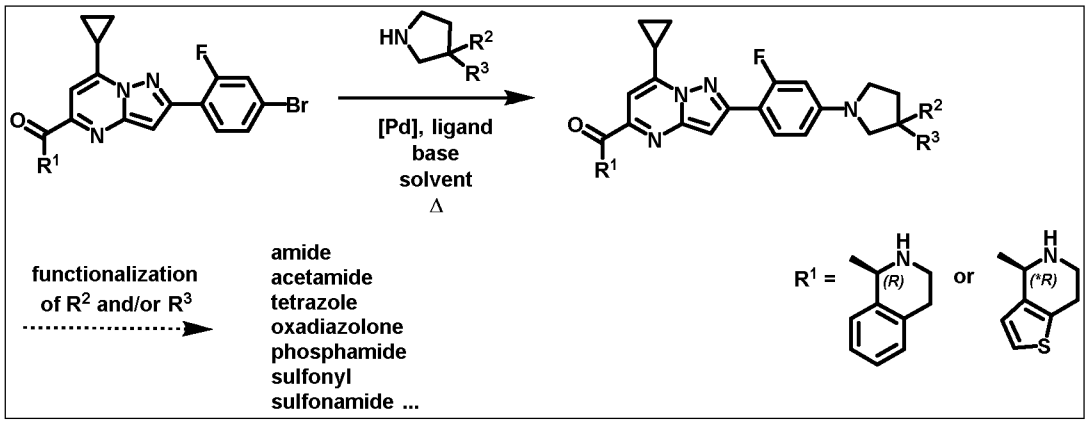
(±)-BINAP	(±)-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene CAS [98327-87-8]
µw	microwave
AcOH	acetic acid
aq.	aqueous
Boc_2O	di-*tert*-butyl dicarbonate - CAS [24424-99-5]
br	broad
CDI	1,1'-carbonyldiimidazole - CAS [530-62-1]
CPME	cyclopentyl methyl ether - CAS [5614-37-9]
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene - CAS [6674-22-2]
DCM	dichloromethane
DIPE	diisopropyl ether
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
Et_2O	diethyl ether
Et_3N	triethylamine
EtOAc	ethyl acetate
EtOH	ethanol
H_2	hydrogen
H	hour
HATU	2-(7-aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate - CAS [148893-10-1]
HMDS	hexamethyldisilazane - CAS [999-97-3]
i-PrOH	isopropyl alcohol
KOAc	potassium actate
LiHMDS	lithium bis(trimethylsilyl)amide - CAS [4039-32-1]
m	multiplet
m/z	mass-to-charge ratio
m-CPBA	3-chloroperbenzoic acid - CAS [937-14-4]
MeCN	acetonitrile
MeOH	methanol
min	minute(s)
N_2	nitrogen
NaO*t*-Bu	sodium *tert*-butoxide
NBS	*N*-bromosuccinimide - CAS [128-08-5]

NMP	methylpyrrolidone - CAS [872-50-4]
NMR	Nuclear Magnetic Resonance
o/n	overnight
$Pd(OAc)_2$	palladium (II) acetate - CAS [3375-31-3]
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium (0) - CAS [14221-01-3]
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium (0) - CAS [51364-51-3]
$PdCl_2$(dtbpf)	[1,1'-bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II) CAS [95408-45-0]
PPACA	propylphosphonic anhydride - CAS [68957-94-8]
ppm	parts per million
Pt/C	platinum on activated charcoal
q	quartet
quin	quintuplet
rt	room temperature
s	singulet
t	triplet
t-BuOK	potassium *tert*-butoxide
TFA	trifluoroacetic acid - CAS [76-05-1]
THF	tetrahydrofuran
TMSCl	chlorotrimethylsilane - CAS [75-77-4]
TTBP.HBF_4	tri-*tert*-butylphosphonium tetrafluoroborate - CAS [131274-22-1]
wt	weight
XantPhos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene CAS [161265-03-8]
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.

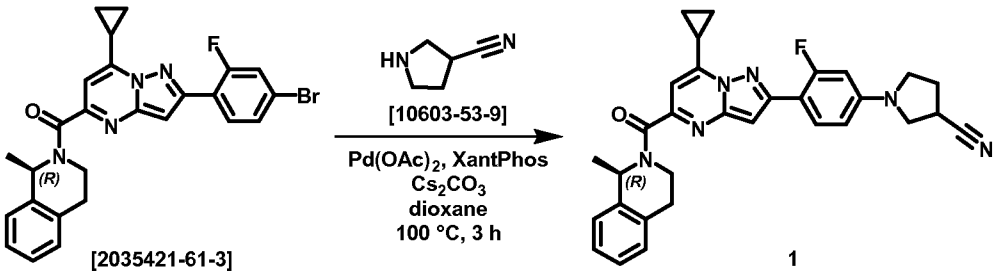
B. Compound synthesis

General scheme



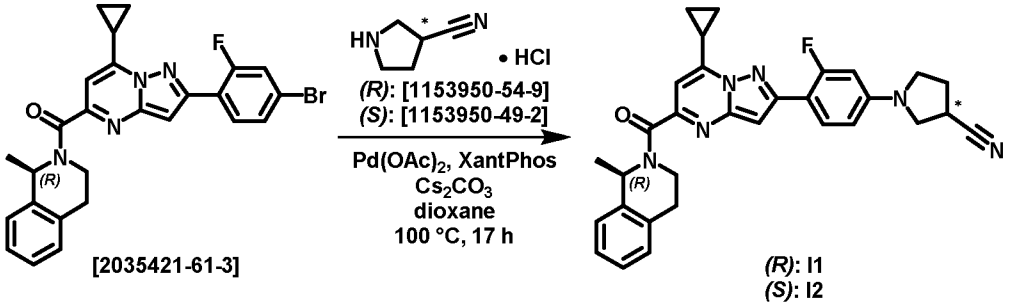
Compound 1

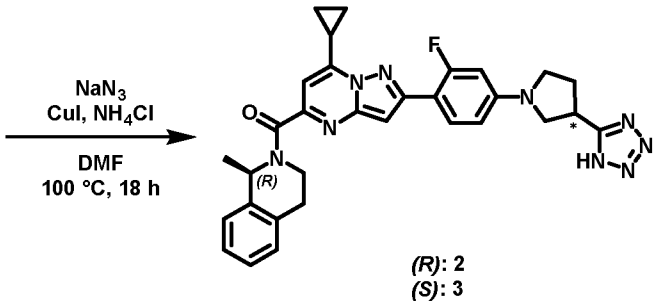
1-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)pyrrolidine-3-carbonitrile



A mixture of (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropylpyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] (0.20 g, 0.39 mmol), pyrrolidine-3-carbonitrile [10603-53-9] (45.7 mg, 475 µmol) and cesium carbonate (387 mg, 1.19 mmol) was purged with nitrogen.1,4-Dioxane (2 mL) was added and the mixture was degassed with nitrogen. Palladium acetate (17.8 mg, 79.1 µmol) and XantPhos (45.8 mg, 79.1 µmol) were added. The reaction mixture was purged with nitrogen and stirred at 100°C for 3 h. The reaction mixture was poured out into water and the aqueous phase was extracted with EtOAc. The mixture was filtered through a pad of Celite® and rinsed 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 the solvent was removed under reduced pressure. The crude mixture was purified by flash chromatography over silica gel (cartridge 24 g, 15-40 µm, mobile phase gradient: heptane / EtOAc from 70:30 to 50:50). The pure fractions were collected and evaporated to dryness. The residue (0.16 g) was taken up in DIPE. The solid was filtered off and dried under vacuum to give compound **1** (127 mg, 62%).

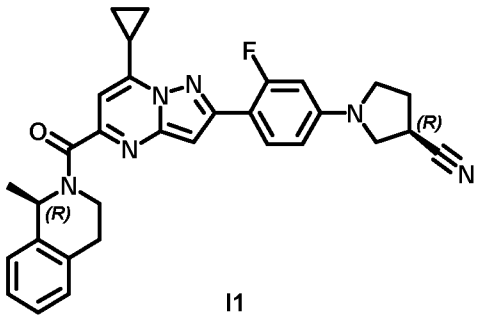
Compound 2 and Compound 3





Intermediate **I1**

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

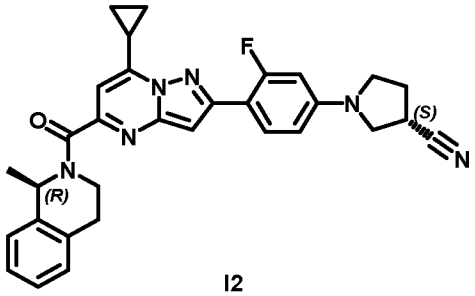


I1

A Schlenk tube was charged with (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] (1.00 g, 1.91 mmol), (*R*)-pyrrolidine-3-carbonitrile hydrochloride [1153950-54-9] (304 mg, 2.29 mmol), cesium carbonate (1.87 g, 5.73 mmol) and XantPhos (111 mg, 191 µmol) and purged with nitrogen. 1,4-Dioxane (20 mL) was added and the mixture was purged again with nitrogen. Palladium acetate (42.9 mg, 191 µmol) was added. The reaction mixture was purged with nitrogen and stirred at 100°C for 17 h. The mixture was diluted with EtOAc and H_2O. 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 the solvent was removed under reduced pressure. 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 90:10 to 50:50) to afford intermediate **I1** (879 mg, 88%) as a pale yellow solid.

Intermediate **I2**

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

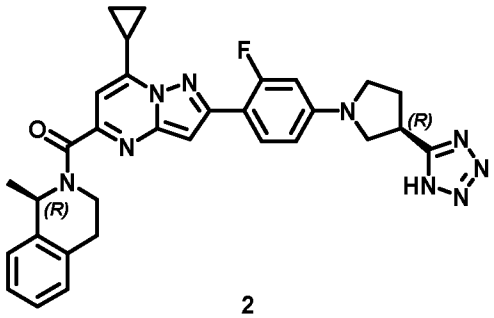


I2

Intermediate **I2** was synthesized from (*S*)-pyrrolidine-3-carbonitrile hydrochloride [1153950-49-2] and (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropylpyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] according to the procedure reported for the synthesis of intermediate **I1**. The purification was carried out by preparative LC (irregular SiOH, 15-40 µm, 40 g Grace®, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 90:10 to 40:60). The residue (997 mg) was taken up in MeCN and concentrated under reduced pressure to afford intermediate **I2** (840 mg, 84%) as a yellow solid.

Compound **2**

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



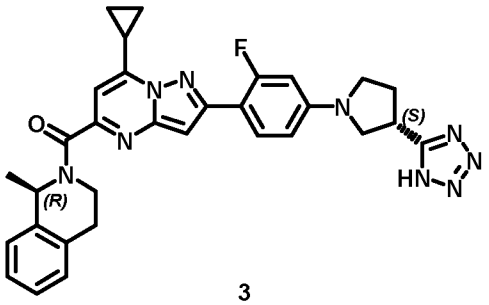
2

In a sealed tube, sodium azide (212 mg, 3.27 mmol) was added to a mixture of intermediate **I1** (170 mg, 327 µmol), copper iodide (93.3 mg, 0.49 mmol) and ammonium chloride (52.4 mg, 0.98 mmol) in DMF (5 mL). The reaction mixture was stirred at 100°C for 18 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 removed 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: DCM / (MeOH/AcOH 9:1) from 100:0 to 94:6). The product was taken up in EtOAc and a 1N aqueous solution of HCl was added. The layers were separated and the organic phase was

washed with 1N aqueous solution of HCl (twice), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The residue (88 mg) was triturated with MeOH. The solid was filtered off and dried under high vacuum at 50°C for 18 h to afford compound **2** (76 mg, 41%) as an orange solid.

Compound **3**

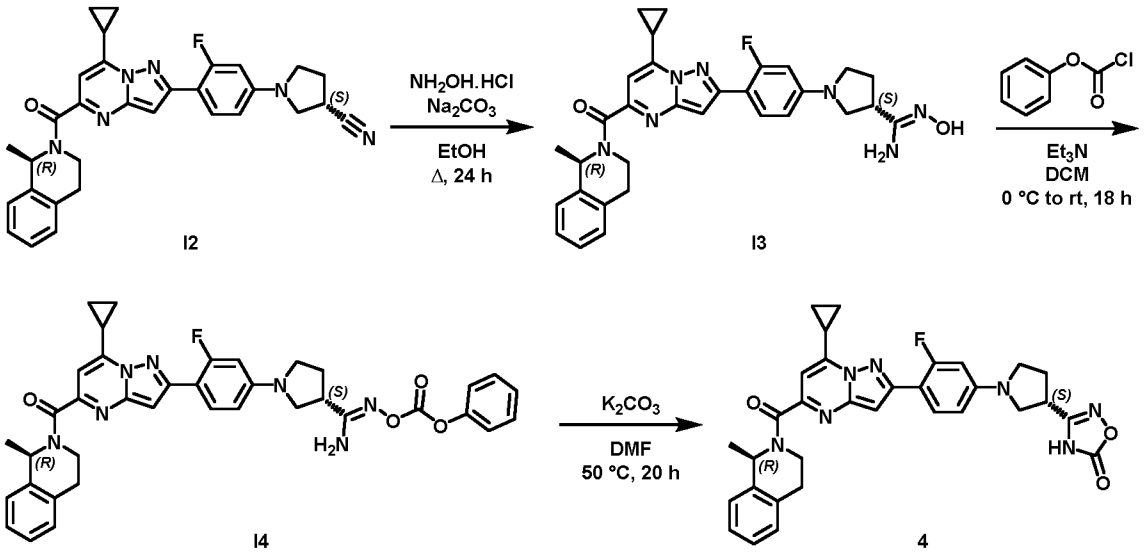
(1*R*)-2-(7-Cyclopropyl-2-{2-fluoro-4-[(3*S*)-3-(1H-1,2,3,4-tetrazol-5-yl)pyrrolidin-1-yl]phenyl}pyrazolo[1,5-a]pyrimidine-5-carbonyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline



3

Compound **3** was synthesized from intermediate **I2** according to the procedure reported for the synthesis of compound **2**. The purification was carried out by preparative LC (irregular SiOH, 15-40 µm, 12 g GraceResolv™, dry loading (Celite®), mobile phase gradient: DCM / (MeOH/AcOH 9:1) from 100:0 to 94:6). The residue was triturated with MeOH. The solid was filtered off and dried under high vacuum at 50°C for 18 h to afford compound **3** (126 mg, 68%) as an orange solid.

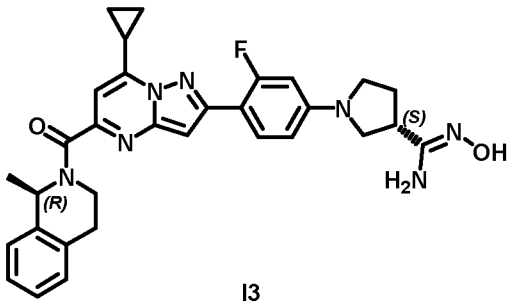
Compound 4



I2 I3 I4 4

Intermediate **I3**

(*Z*,3*S*)-1-(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'-hydroxypyrrolidine-3-carboximidamide

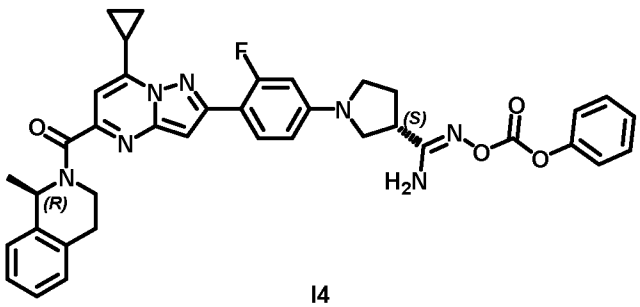


I3

Hydroxylamine hydrochloride (120 mg, 1.73 mmol) was added to a suspension intermediate **I2** (300 mg, 0.58 mmol) and sodium carbonate (244 mg, 2.31 mmol) in EtOH (8 mL). The reaction mixture was stirred under reflux for 24 h and the solvent was evaporated under reduced pressure. DCM and H_2O were added to the residue. 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 under reduced pressure to afford intermediate **I3** (331 mg, 90%, 87% purity) as a yellow gum.

Intermediate **I4**

(*Z*)-{Amino[(3*S*)-1-(4-{7-cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)pyrrolidin-3-yl]methylidene}-amino phenyl carbonate



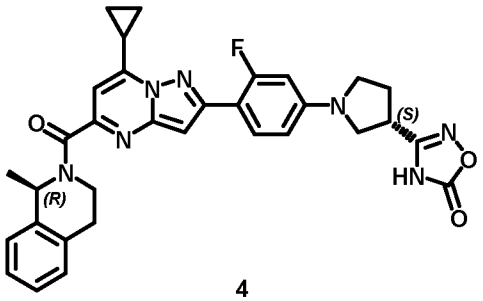
I4

Phenyl chloroformate (98.0 µL, 0.78 mmol) was added to a mixture of intermediate **I3** (331 mg, 0.52 mmol, 87% purity) and triethylamine (220 µL, 1.58 mmol) in DCM (7 mL) at 0°C. The reaction mixture was stirred at rt for 18 h. The reaction mixture was diluted with DCM and H_2O. 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 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 / EtOAc from 100:0 to 90:10). The residue (210 mg) was taken up in MeCN and concentrated under reduced pressure (twice) to give intermediate **I4** (189 mg, 52%) as a yellow gum.

Compound 4

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

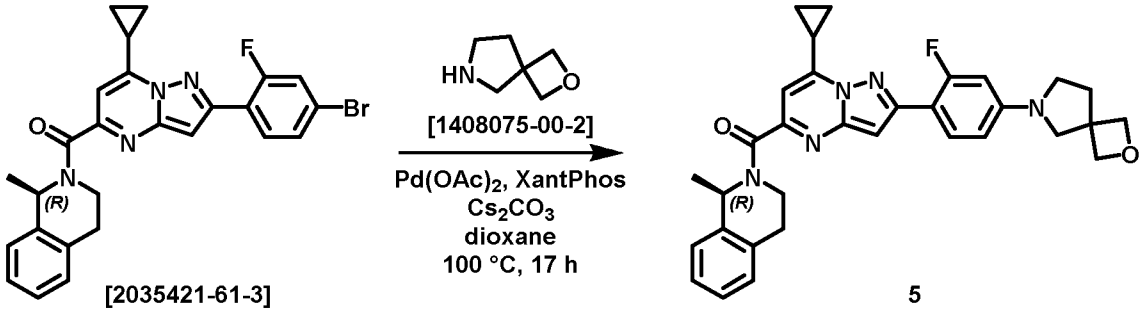


4

In a sealed tube, potassium carbonate (41.1 mg, 0.30 mmol) was added to a solution of intermediate **I4** (172 mg, 0.25 mmol) in DMF (1 mL). The reaction mixture was stirred at 50°C for 20 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 brine (4 times), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude mixture was crystallized from MeOH, and the solid was filtered off and dried under high vacuum at 50°C for 3 h. The solid (110 mg) 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 97:3). The residue was re-crystallized from MeOH, filtered off and dried under high vacuum at 50°C for 3 h to afford compound **4** (81 mg, 56%) as a pale yellowish solid.

Compound 5

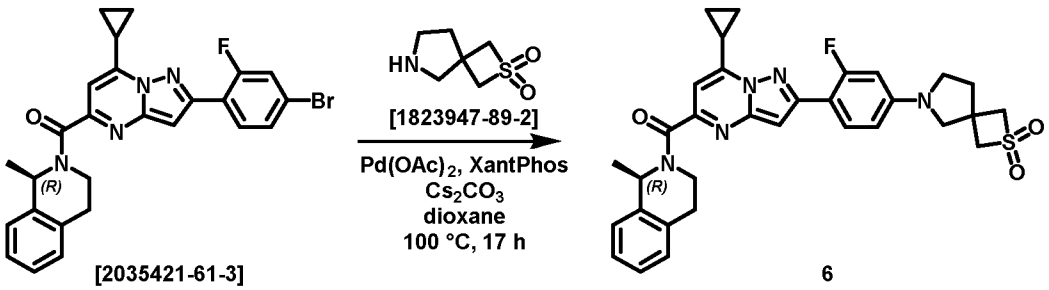
(1*R*)-2-[7-Cyclopropyl-2-(2-fluoro-4-{2-oxa-6-azaspiro[3.4]octan-6-yl}phenyl)pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline



A sealed tube was charged with (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] (150 mg, 0.28 mmol), 2-oxa-6-azaspiro[3.4]octane hemioxalate [1408075-00-2] (89.2 mg, 0.28 mmol), cesium carbonate (276 mg, 0.85 mmol) and XantPhos (16.3 mg, 28.2 µmol) and purged with nitrogen. 1,4-Dioxane (4.5 mL) was added and the mixture was purged again with nitrogen. Palladium acetate (6.33 mg, 28.2 µmol) was added. The reaction mixture was purged with nitrogen and stirred at 100°C for 17 h. The reaction mixture was diluted with EtOAc and H_2O. 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 the solvent was removed under reduced pressure. 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 90:10 to 50:50). The residue was crystallized from MeOH, filtered off and dried under high vacuum at 50°C for 20 h to afford compound **5** (112 mg, 74%) as a yellow solid.

Compound 6

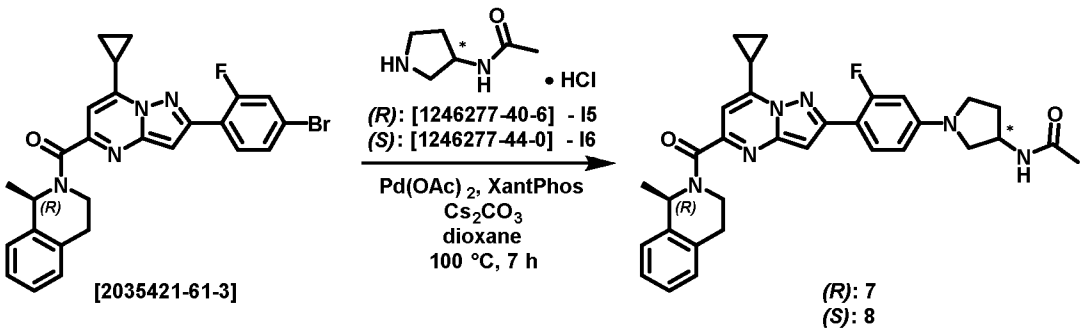
6-[4-(7-Cyclopropyl-5-{[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-pyrazolo[1,5-a]pyrimidin-2-yl]-3-fluorophenyl)-2λ^6-thia-6-azaspiro[3.4]octane-2,2-dione



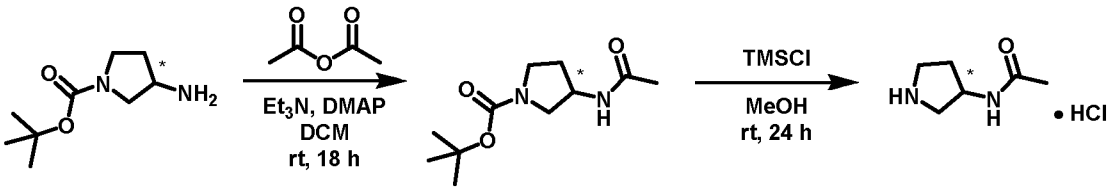
Compound **6** was synthesized from (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] and 2-thia-6-azaspiro[3.4]octane 2,2-dioxide [1823947-89-2] according to the

procedure reported for the synthesis of compound **5**. Compound **6** (86 mg, 58%) was obtained as a yellow solid.

Compound 7 and Compound 8

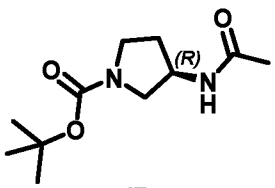


Synthesis of intermediates **I5** and **I6**



Intermediate **I7**

Tert-butyl (3*R*)-3-acetamidopyrrolidine-1-carboxylate

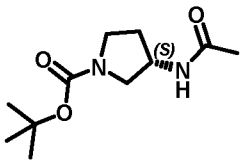


I7

Acetic anhydride (0.56 mL, 5.91 mmol) was added dropwise to a mixture of (*R*)-(+)-1-boc-3-aminopyrrolidine [147081-49-0] (1.00 g, 5.37 mmol), triethylamine (1.12 mL, 8.05 mmol) and DMAP (32.8 mg, 0.27 mmol) in DCM (20 mL). The reaction mixture was stirred at rt for 18 h. The reaction mixture was diluted with DCM and H_2O. 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 under reduced pressure to afford intermediate **I7** (1.64 g) as an oil.

Intermediate **I8**

Tert-butyl (3*S*)-3-acetamidopyrrolidine-1-carboxylate

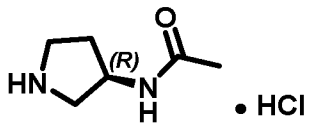


I8

Intermediate **I8** (1.97 g) was synthesized from (*S*)-(-)-1-boc-3-aminopyrrolidine [147081-44-5] according to the procedure reported for the synthesis of intermediate **I7**.

Intermediate **I5**

N-[(3*R*)-Pyrrolidin-3-yl]acetamide hydrochloride

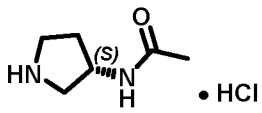


I5

A mixture of intermediate **I7** (1.64 g, 4.53 mmol, 63% purity) and chlorotrimethylsilane (2.30 mL, 18.1 mmol) in MeOH (20 mL) was stirred at rt for 24 h. The mixture was evaporated under reduced pressure to afford intermediate **I5** (1.12 g).

Intermediate **I6**

N-[(3*S*)-Pyrrolidin-3-yl]acetamide hydrochloride



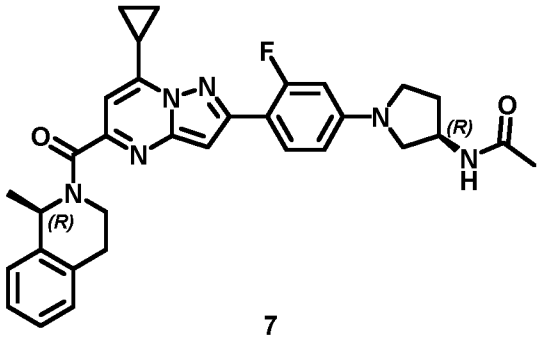
I6

Intermediate **I6** (1.34 g) was synthesized from intermediate **I8** according to the procedure reported for the synthesis of intermediate **I5**.

Synthesis of compounds 7 and 8

Compound 7

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

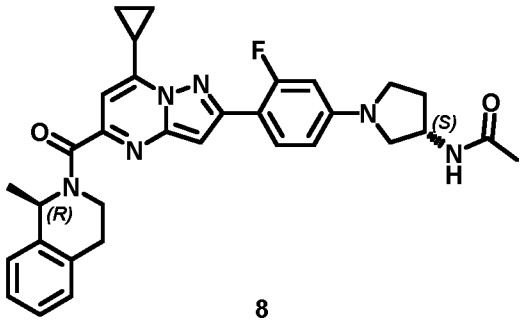


7

A sealed tube was charged with (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] (250 mg, 0.48 mmol), intermediate **I5** (180 mg, 0.72 mmol, 66% purity) and cesium carbonate (782 mg, 2.40 mmol) and purged with nitrogen. 1,4-Dioxane (10 mL) was added and the mixture was degassed with nitrogen. Palladium acetate (16.2 mg, 72.0 µmol) and XantPhos (41.6 mg, 72.0 µmol) were added. The reaction mixture was stirred at 100°C for 7 h. The reaction mixture was poured out into water and the aqueous phase was extracted with EtOAc (twice). 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, 40 g GraceResolv™, liquid injection (DCM), mobile phase gradient: DCM / MeOH / aq.NH_3 from 100:0:0 to 98:2:0.2). The residue (191 mg) was co-evaporated with EtOH (5 times) and triturated with EtOH/Et_2O (1:9). The solid was filtered off and dried under high vacuum at 50°C for 2 h to give compound **7** (140 mg, 53%) as a yellow solid.

Compound 8

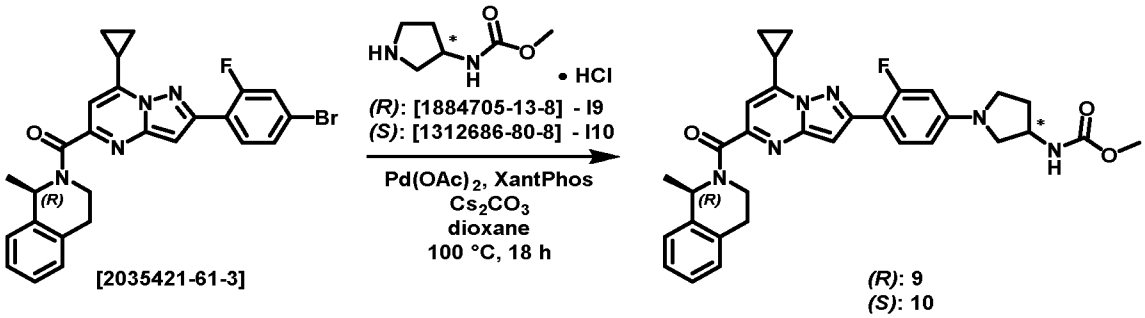
N-[(3*S*)-1-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)pyrrolidin-3-yl]acetamide



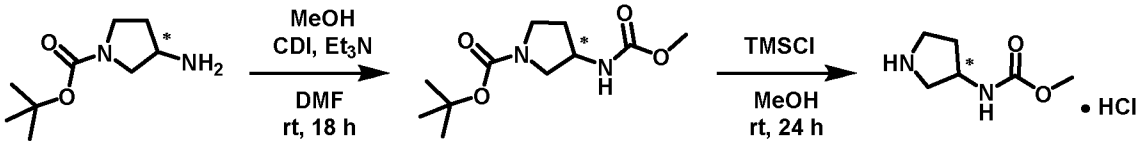
8

Compound **8** (107 mg, 40%) was synthesized from (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropylpyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroiso-quinoline [2035421-61-3] and intermediate **I6** according to the procedure reported for the synthesis of compound **7**.

Compound 9 and Compound 10

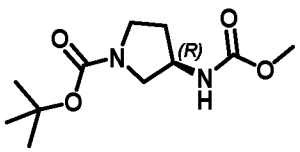


Synthesis of intermediates **I9** and **I10**



Intermediate **I11**

Tert-butyl (3*R*)-3-[(methoxycarbonyl)amino]pyrrolidine-1-carboxylate

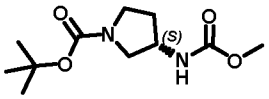


I11

In a sealed tube, CDI (653 mg, 4.03 mmol) was added to a mixture of (*R*)-(+)-1-boc-3-aminopyrrolidine [147081-49-0] (500 mg, 2.69 mmol) and triethylamine (1.49 mL, 10.7 mmol) in DMF (10 mL). The reaction mixture was stirred at rt. MeOH (10 mL, 247 mmol) was added and the reaction mixture was stirred at rt for 18 h. H_2O, brine and EtOAc were 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™, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 90:10 to 70:30) to afford intermediate **I11** (344 mg, 52%).

Intermediate **I12**

Tert-butyl (3*S*)-3-[(methoxycarbonyl)amino]pyrrolidine-1-carboxylate

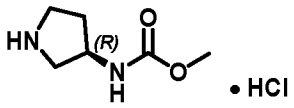


I12

Intermediate **I12** (444 mg, 68%) was synthesized from (*S*)-(-)-1-boc-3-aminopyrrolidine [147081-44-5] according to the procedure reported for the synthesis of intermediate **I11**.

Intermediate **I9**

Methyl N-[(3*R*)-pyrrolidin-3-yl]carbamate hydrochloride

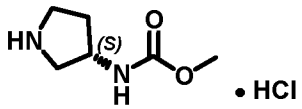


I9

A mixture of intermediate **I11** (344 mg, 1.41 mmol) and chlorotrimethylsilane (0.72 mL, 5.63 mmol) in MeOH (10 mL) was stirred at rt for 24 h. The mixture was evaporated under reduced pressure to afford intermediate **I9** (225 mg, quant.).

Intermediate **I10**

Methyl N-[(3*S*)-pyrrolidin-3-yl]carbamate hydrochloride



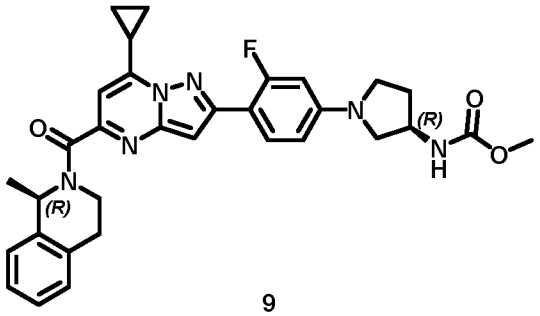
I10

Intermediate **I10** (310 mg, 92%) was synthesized from intermediate **I12** according to the procedure reported for the synthesis of intermediate **I9**.

Synthesis of compounds 9 and 10

Compound 9

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

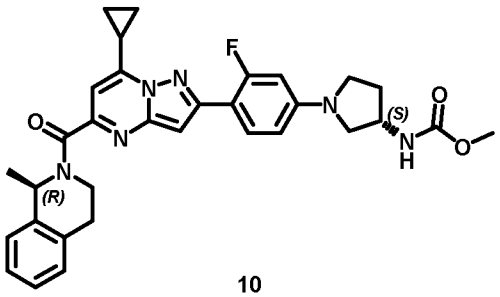


9

A sealed tube was charged with (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] (250 mg, 0.48 mmol), intermediate **I9** (130 mg, 0.72 mmol) and cesium carbonate (782 mg, 2.40 mmol) and purged with nitrogen. 1,4-Dioxane (10 mL) was added and the mixture was degassed with nitrogen. Palladium acetate (10.7 mg, 48.0 µmol) and XantPhos (27.8 mg, 48.0 µmol) were added. The reaction mixture was stirred at 100°C for 18 h. The reaction mixture was poured out into water and the aqueous phase was extracted with EtOAc (twice). 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, 40 g GraceResolv™, liquid injection (DCM), mobile phase gradient: DCM / MeOH / aq.NH_3 from 100:0:0 to 98:2:0.2). The residue (221 mg) was co-evaporated with EtOH (5 times) and triturated with Et_2O. The solid was filtered off and dried under high vacuum at 50°C for 18 h to afford compound **9** (102 mg, 37%) as a yellow solid.

Compound 10

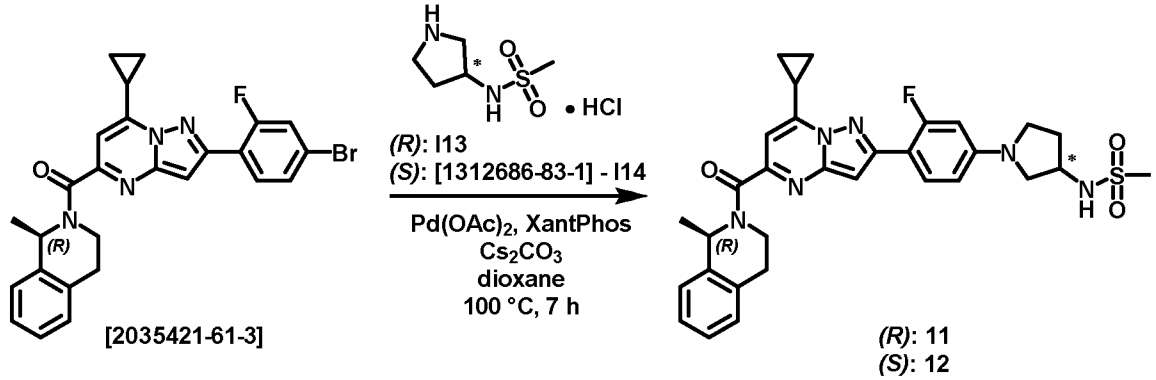
Methyl N-[(3*S*)-1-[4-{7-cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)pyrrolidin-3-yl]carbamate



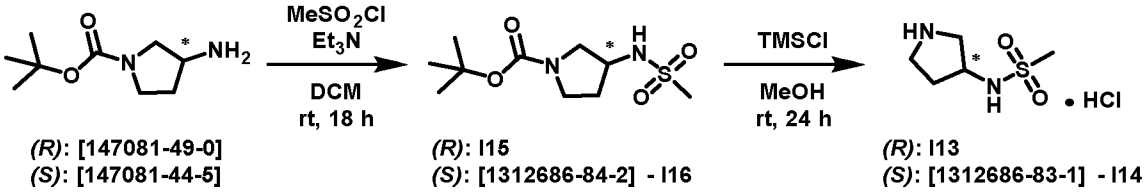
10

Compound **10** (145 mg, 53%) was synthesized from (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropylpyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] and intermediate **I10** according to the procedure reported for the synthesis of compound **9**.

Compound 11 and Compound 12

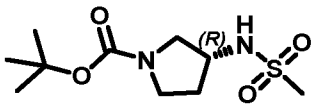


Synthesis of intermediates **I13** and **I14**



Intermediate **I15**

Tert-butyl (3*R*)-3-methanesulfonamidopyrrolidine-1-carboxylate

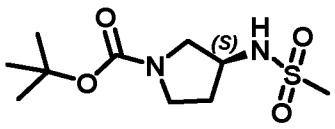


I15

Methanesulfonyl chloride (0.50 mL, 6.44 mmol) was added dropwise to a solution of (*R*)-(+)-1-boc-3-aminopyrrolidine [147081-49-0] (1.00 g, 5.37 mmol) and triethylamine (1.50 mL, 10.7 mmol) in DCM (20 mL). The reaction mixture was stirred at rt for 18 h. The reaction mixture was diluted with DCM and H_2O. 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 under reduced pressure to afford intermediate **I15** (2.00 g) as an oil.

Intermediate **I16**

Tert-butyl (3*S*)-3-methanesulfonamidopyrrolidine-1-carboxylate

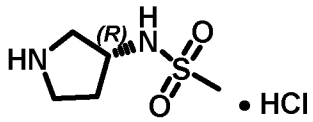


I16

Intermediate **I16** (2.4 g) was synthesized from (*S*)-(-)-1-boc-3-aminopyrrolidine [147081-44-5] according to the procedure reported for the synthesis of intermediate **I15**.

Intermediate **I13**

N-[(3*R*)-pyrrolidin-3-yl]methanesulfonamide hydrochloride

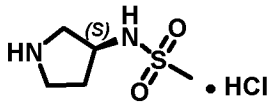


I13

A mixture of intermediate **I15** (2.00 g, 5.37 mmol, 71% purity) and chlorotrimethylsilane (2.73 mL, 21.5 mmol) in DCM (20 mL) was stirred at rt for 24 h. The mixture was evaporated under reduced pressure to give intermediate **I13** (1.20 g).

Intermediate **I14**

N-[(3*S*)-pyrrolidin-3-yl]methanesulfonamide hydrochloride



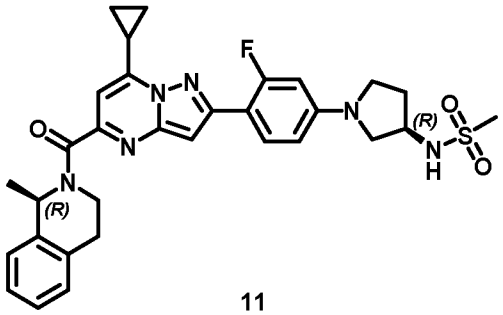
I14

Intermediate **I14** (1.68 g) was synthesized from intermediate **I16** according to the procedure reported for the synthesis of intermediate **I13**.

Synthesis of compounds 11 and 12

Compound 11

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

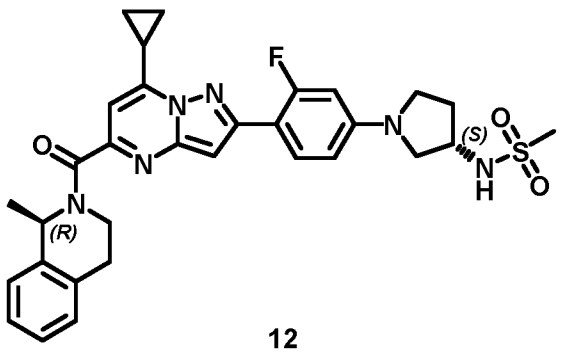


11

A sealed tube was charged with (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] (250 mg, 0.48 mmol), intermediate **I13** (181 mg, 0.72 mmol, 80% purity) and cesium carbonate (782 mg, 2.40 mmol) and purged with nitrogen. 1,4-Dioxane (10 mL) was added and the mixture was degassed with nitrogen. Palladium acetate (16.2 mg, 72.0 µmol) and XantPhos (41.6 mg, 72.0 µmol) were added. The reaction mixture was stirred at 100°C for 7 h. The reaction mixture was poured out into water and the aqueous phase was extracted with EtOAc (twice). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated to dryness. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 40 g GraceResolv™, liquid injection (DCM), mobile phase gradient: DCM / MeOH / aq.NH_3 from 100:0:0 to 98:2:0.2). The residue (256 mg) was co-evaporated with EtOH (5 times) and triturated with EtOH/Et_2O (1:9). The solid was filtered off and dried under high vacuum at 50°C for 2 h to afford compound **11** (148 mg, 52%) as a yellow solid.

Compound 12

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



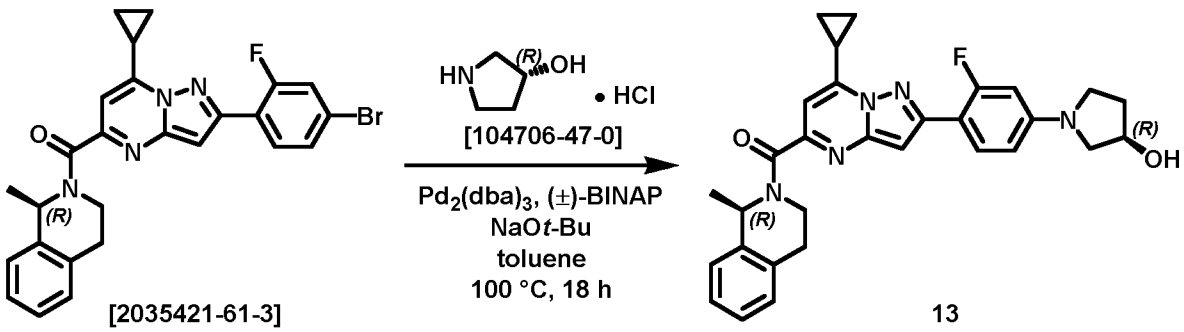
12

A sealed tube was charged with (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-

61-3] (250 mg, 0.48 mmol), intermediate **I14** (226 mg, 0.72 mmol, 64% purity) and cesium carbonate (782 mg, 2.40 mmol) and purged with nitrogen. 1,4-Dioxane (10 mL) was added and the mixture was degassed with nitrogen. Palladium acetate (10.8 mg, 48.0 µmol) and XantPhos (27.8 mg, 48.0 µmol) were added. The reaction mixture was stirred at 100°C for 7 h. The reaction mixture was poured out into water and the aqueous phase was extracted with EtOAc (twice). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated to dryness. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 40 g GraceResolv™, liquid injection (DCM), mobile phase gradient: DCM / MeOH / aq.NH_3 from 100:0:0 to 98:2:0.2). The residue (158 mg) was co-evaporated with EtOH (5 times) and triturated with EtOH/Et_2O (1:9). The solid was filtered off and dried under high vacuum at 50°C for 2 h. The purification sequence was repeated: purification by preparative LC (irregular SiOH, 15-40 µm, 40 g GraceResolv™, liquid injection (DCM), mobile phase gradient: DCM / MeOH / aq.NH_3 from 100:0:0 to 98:2:0.2). The residue was co-evaporated with EtOH (3 times) and triturated with Et_2O. The solid was filtered off and dried under high vacuum at 50°C to afford compound **12** (99 mg, 35%) as a yellow solid.

Compound 13

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

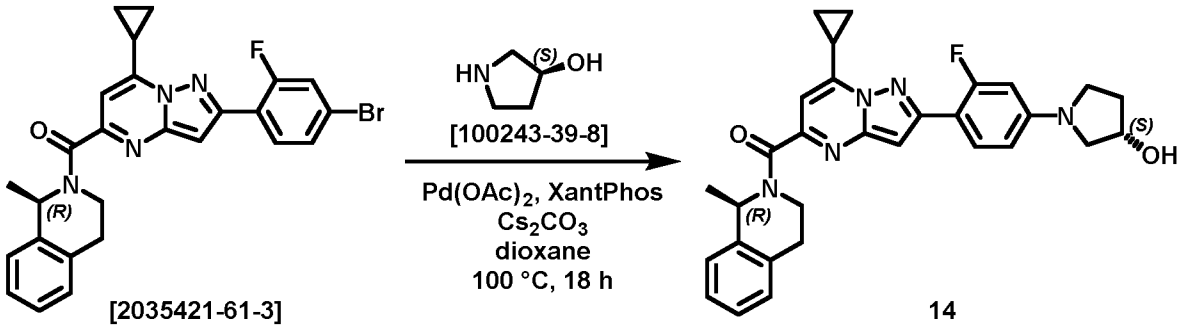


A sealed tube was charged with (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] (250 mg, 0.48 mmol), (*R*)-3-pyrrolidinol hydrochloride [104706-47-0] (77.6 µL, 0.96 mmol) and sodium *tert*-butoxide (138 mg, 1.44 mmol) and purged with nitrogen. Toluene (10 mL) was added and the mixture was degassed with nitrogen. Tris(dibenzylideneacetone)dipalladium (43.9 mg, 48.0 µmol) and (±)-BINAP (59.7 mg, 96.0 µmol) were added. The reaction mixture was stirred at 100°C for 18 h. The reaction mixture was poured out into water and the aqueous phase was extracted with DCM. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and

concentrated to dryness. The crude mixture was purified by preparative LC (regular SiOH, 30 µm, 25 g Interchim®, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 80:20 to 0:100). The residue (65 mg) was taken up in MeCN and DIPE and partially evaporated. The solid was filtered off and dried under high vacuum at 50°C for 16 h and then at 60°C for 24 h to afford compound **13** (45 mg, 18%).

Compound 14

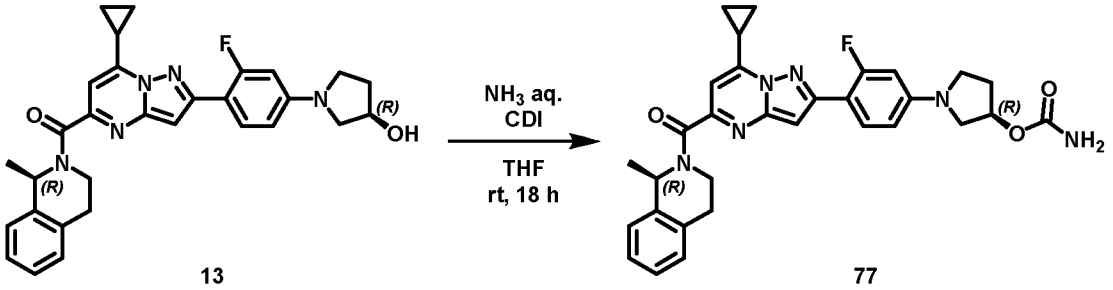
(3*S*)-1-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)pyrrolidin-3-ol



A sealed tube was charged with (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] (200 mg, 0.38 mmol), (*S*)-3-pyrrolidinol [100243-39-8] (167 mg, 1.92 mmol) and cesium carbonate (625 mg, 1.92 mmol) and purged with nitrogen. 1,4-Dioxane (8 mL) was added and the mixture was degassed with nitrogen. Palladium acetate (8.61 mg, 38.4 µmol) and XantPhos (22.2 mg, 38.4 µmol) were added. The reaction mixture was stirred at 100°C for 18 h. The reaction mixture was diluted with H_2O and the aqueous phase was extracted with EtOAc (twice). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude mixture was purified by preparative LC (regular SiOH, 30 µm, 25 g Interchim®, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 80:20 to 0:100). The residue was taken up in MeCN and Et_2O and evaporated to dryness. The solid was triturated with Et_2O, filtered off and dried under high vacuum at 60°C for 18 h to afford compound **14** (64 mg, 33%) as a yellow solid.

Compound 77

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

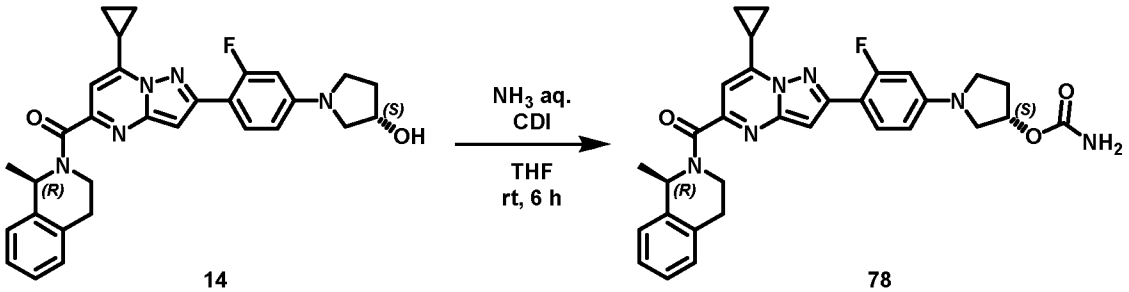


13 77

CDI (2.15 g, 13.3 mmol) was added to a solution of compound **13** (3.39 g, 6.63 mmol) in THF (25 mL). The reaction mixture was stirred at rt for 1 h. Ammonia (28% in H_2O, 24.8 mL, 367 mmol) was added and 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 (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, 330 g GraceResolv™, liquid injection (DCM), mobile phase gradient: DCM / EtOAc from 100:0 to 80:20). The residue (2.8 g) was triturated with MeCN. The solid was filtered off and dried under high vacuum at 50°C for 2 h. The solid (1.87 g) was triturated again with MeCN, filtered off and dried under high vacuum at 50°C overnight. The product (1.32 g) was suspended in MeOH (20 mL) and the solution was stirred at rt for 18 h. The solid was filtered off and dried under high vacuum at 50°C to give compound **77** (951 mg, 26%) as a pale yellow solid.

Compound 78

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

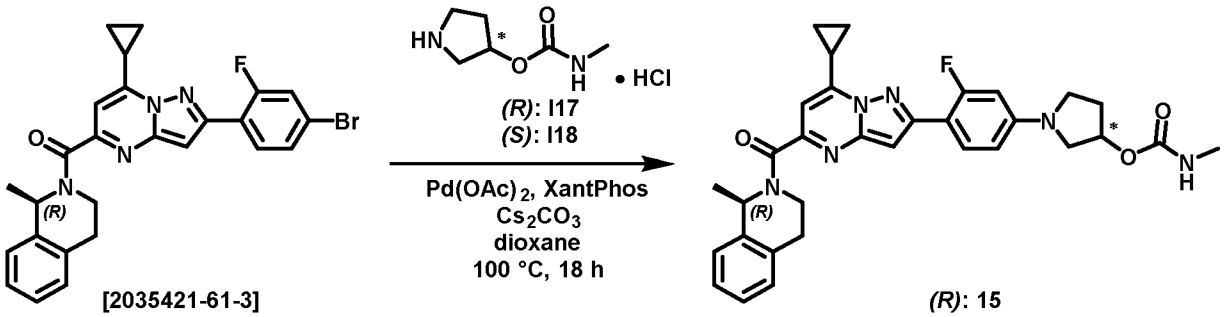


14 78

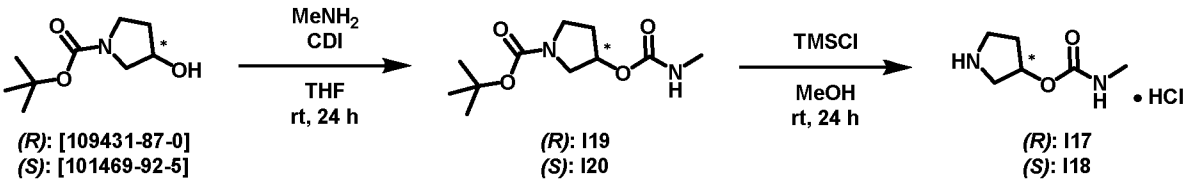
CDI (1.97 g, 12.1 mmol) was added to a solution of compound **14** (3.11 g, 6.07 mmol) in THF (23 mL). The reaction mixture was stirred at rt for 1 h. Ammonia (28% in H_2O, 22.7 mL, 336 mmol) was added and the reaction mixture was stirred at rt for 6 h. The reaction mixture was diluted with H_2O, brine 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 in vacuo. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 330 g GraceResolv™, liquid injection (DCM), mobile phase gradient: DCM / EtOAc from 100:0 to 80:20). The residue (2.4 g) was triturated with MeCN. The solid was filtered off and dried under high vacuum at 50°C. The solid was triturated again with MeCN, filtered off and dried under high vacuum at 50°C overnight. The product (1.03 g) was suspended in MeOH (25 mL) and stirred at rt for 18 h. The solid was filtered off and dried under high vacuum at 50°C to give compound **78** (825 mg, 25%) as a yellow solid.

Compound 15 and Compound 16

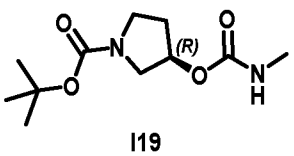


Synthesis of intermediates **I17** and **I18**



Intermediate **I19**

Tert-butyl (3*R*)-3-[(methylcarbamoyl)oxy]pyrrolidine-1-carboxylate

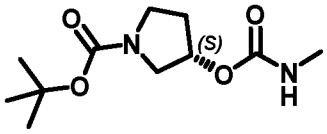


In a sealed tube CDI (871 mg, 5.37 mmol) was added to a solution of (*R*)-(-)-N-boc-3-pyrrolidinol [109431-87-0] (503 mg, 2.69 mmol) in THF (10 mL). The reaction mixture was stirred at rt for 1 h. Methylamine (40% in H_2O, 10 mL, 116 mmol) was added and the reaction mixture was stirred at rt for 2 h. H_2O, brine 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 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 70:30) to give intermediate **I19** (700 mg, quant., 94% purity).

Intermediate **I20**

Tert-butyl (3*S*)-3-[(methylcarbamoyl)oxy]pyrrolidine-1-carboxylate

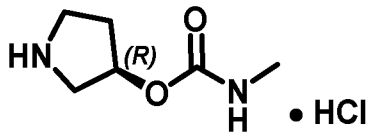


I20

Intermediate **I20** (610 mg, 93%) was synthesized from (*S*)-(+)-N-boc-3-pyrrolidinol [101469-92-5] according to the procedure reported for the synthesis of intermediate **I19**.

Intermediate **I17**

(3*R*)-Pyrrolidin-3-yl N-methylcarbamate hydrochloride

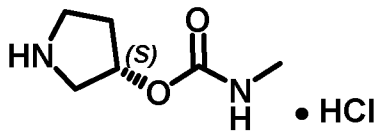


I17

A mixture of intermediate **I19** (700 mg, 2.67 mmol, 93% purity) and chlorotrimethylsilane (1.35 mL, 10.7 mmol) in MeOH (10 mL) was stirred at rt for 24 h. The mixture was evaporated under reduced pressure to afford intermediate **I17** (525 mg).

Intermediate **I18**

(3*S*)-Pyrrolidin-3-yl N-methylcarbamate hydrochloride



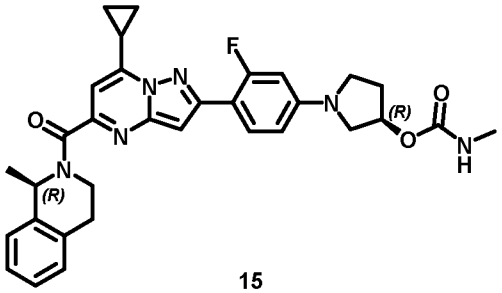
I18

Intermediate **I18** (475 mg) was synthesized from intermediate **I20** according to the procedure reported for the synthesis of intermediate **I17**.

Synthesis of compounds 15 and 16

Compound 15

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

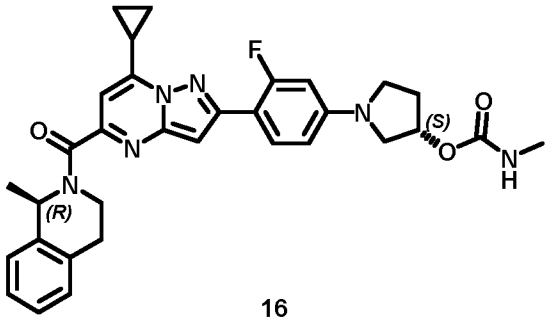


15

A sealed tube was charged with (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] (250 mg, 0.48 mmol), intermediate **I17** (143 mg, 0.72 mmol, 91% purity) and cesium carbonate (782 mg, 2.40 mmol) and purged with nitrogen. 1,4-Dioxane (10 mL) was added and the mixture was degassed with nitrogen. Palladium acetate (10.8 mg, 48.0 µmol) and XantPhos (27.8 mg, 48.0 µmol) were added. The reaction mixture was stirred at 100°C for 18 h. The reaction mixture was poured out into water and the aqueous phase was extracted with EtOAc (twice). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated to dryness. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 40 g GraceResolv™, liquid injection (DCM), mobile phase gradient: DCM / MeOH / aq.NH_3 from 100:0:0 to 98:2:0.2). 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 40:60 to 0:100). The residue was co-evaporated with EtOH (3 times) and triturated with EtOH. The solid was filtered off and dried under high vacuum at 50°C for 18 h to afford compound **15** (75 mg, 27 %) as a yellow solid.

Compound 16

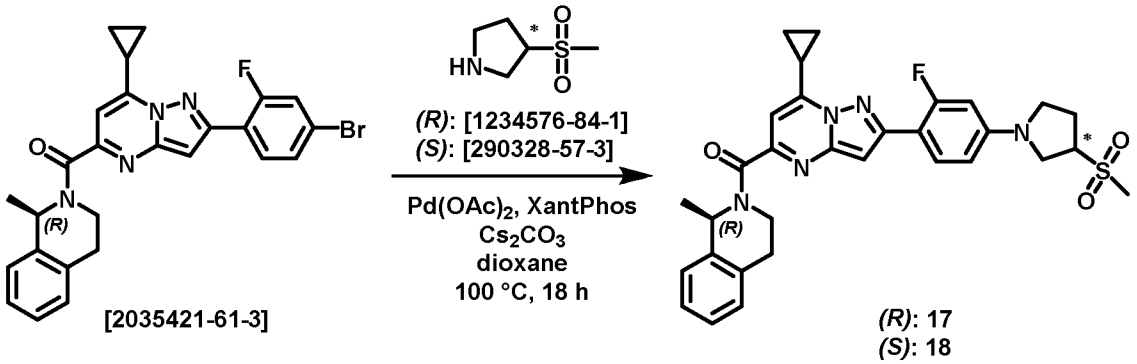
(3*S*)-1-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)pyrrolidin-3-yl N-methylcarbamate



16

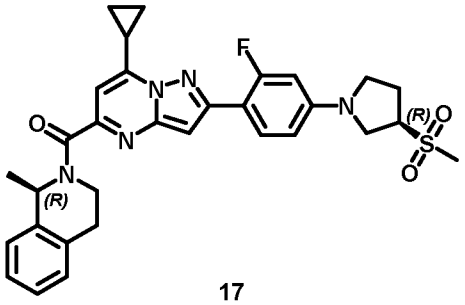
Compound **16** was synthesized from (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] and intermediate **I18** according to the procedure reported for the synthesis of compound **15**. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 40 g GraceResolv™, liquid injection (DCM), mobile phase gradient: DCM / MeOH / aq.NH_3 from 100:0:0 to 98:2:0.2). 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 40:60 to 0:100). The residue was co-evaporated with EtOH (5 times) and triturated with EtOH/Et_2O (1:9). The solid was filtered off and dried under high vacuum at 50°C for 2 h to give compound **16** (54 mg, 20 %) as a white solid.

Compound 17 and Compound 18



Compound 17

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

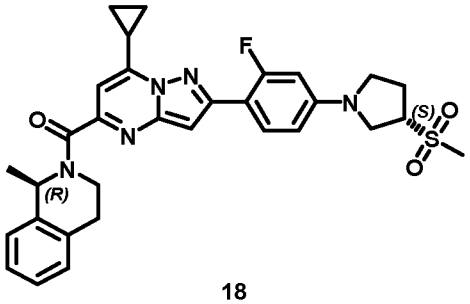


17

A sealed tube was charged with (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] (150 mg, 288 µmol), (*R*)-3-(methylsulfonyl)pyrrolidine [1234576-84-1] (53.4 mg, 288 µmol), cesium carbonate (276 mg, 846 µmol) and XantPhos (19.7 mg, 34.0 µmol) and purged with nitrogen. 1,4-Dioxane (6 mL) was added and the mixture was purged with nitrogen. Palladium acetate (7.88 mg, 35.1 µmol) was added. The reaction mixture was purged with nitrogen and stirred at 100°C for 18 h. The reaction mixture was diluted with EtOAc and brine. The layers were separated and the aqueous phase was extracted. The combined organic extracts were washed with H_2O, dried over $MgSO_4$, filtered and evaporated under reduced pressure. 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 50:50 to 0:100). A second purification was performed by preparative LC (spherical C18 25 µm, 40 g YMC-ODS-25, loading (MeCN, H_2O), mobile phase gradient: (0.2% aq. NH_4HCO_3) / MeCN from 50:50 to 0:100). The fractions containing the product were combined and a 10% aqueous solution of $KHSO_4$ was added. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with H_2O, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue (105 mg) was purified by preparative LC (irregular SiOH, 15-40 µm, 40 g GraceResolv™, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 50:50 to 0:100). The residue was triturated and co-evaporated with Et_2O (twice) and dried under high vacuum at 50°C for 18 h to give compound **17** (54 mg, 32%) as a yellow solid.

Compound 18

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

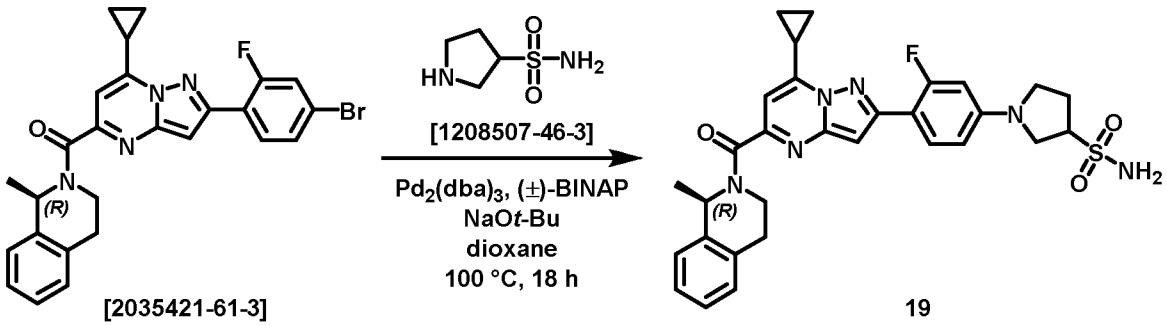


18

Compound **18** was synthesized from (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] and (*S*)-3-(methylsulfonyl)pyrrolidine [290328-57-3] according to the procedure reported for the synthesis of compound **17**. 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 50:50 to 0:100). A second purification was performed by preparative LC (spherical C18 25 µm, 40 g YMC-ODS-25, loading (MeCN, H_2O), mobile phase gradient (0.2% aq.NH_4HCO_3) / MeCN from 50:50 to 0:100). The fractions containing the product were combined and a 10% aqueous solution of $KHSO_4$ was added. The layers were separated and the aqueous phase was extracted with EtOAc. The organic phase was washed with H_2O, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was triturated and co-evaporated with Et_2O (twice) and dried under high vacuum at 50°C for 18 h to give compound **18** (67 mg, 40%) as a pale red solid.

Compound 19

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



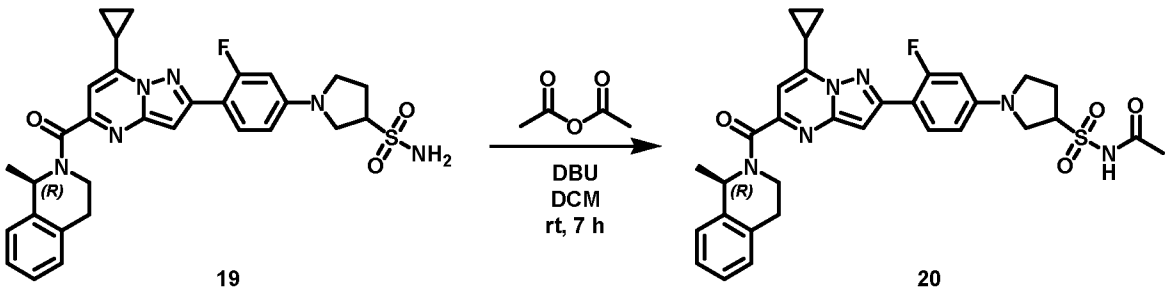
[2035421-61-3] 19

A sealed tube was charged with (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] (400 mg, 768 µmol), pyrrolidine-3-sulfonamide [1208507-46-3] (115 mg, 768 µmol), sodium *tert*-butoxide (105 mg, 1.09 mmol) and (±)-BINAP (100 mg, 161 µmol)

and purged with nitrogen. 1,4-Dioxane (10 mL) was added and the mixture was purged again with nitrogen. Tris(dibenzylideneacetone)dipalladium (140 mg, 153 µmol) was added. The reaction mixture was purged with nitrogen and stirred at 100°C for 18 h. A 10% aqueous solution of $KHSO_4$ was added until pH 6. The aqueous phase was extracted with EtOAc. The combined organic extracts were washed with H_2O, dried over $MgSO_4$, filtered and evaporated 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: DCM / MeOH from 100:0 to 95:5). A second purification was performed by preparative LC (spherical C18 25 µm, 40 g YMC-ODS-25, loading (MeCN, H_2O), mobile phase gradient: (0.2% aq.NH_4HCO_3) / MeCN from 50:50 to 0:100). The product was freeze-dried to give compound **19** (48 mg, 11%) as a yellow solid.

Compound 20

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

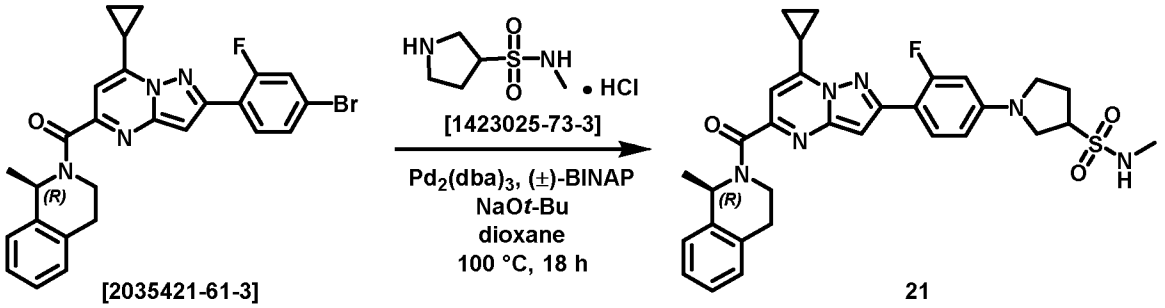


19 20

A mixture of compound **19** (215 mg, 0.37 mmol), acetic anhydride (53.0 µL, 0.56 mmol) and DBU (83.8 µL, 0.56 mmol) in DCM (2 mL) was stirred at rt for 7 h. The reaction mixture was diluted with EtOAc and brine. The layers were separated and the aqueous phase was extracted. The combined organic extracts were washed with H_2O, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude mixture was purified by preparative LC (spherical C18 25 µm, 40 g YMC-ODS-25, loading (MeCN, H_2O), mobile phase gradient: (0.2% aq. NH_4HCO_3) / MeCN from 15:85 to 65:35). The product was freeze-dried to give compound **20** (40 mg, 17%) as a yellow solid.

Compound 21

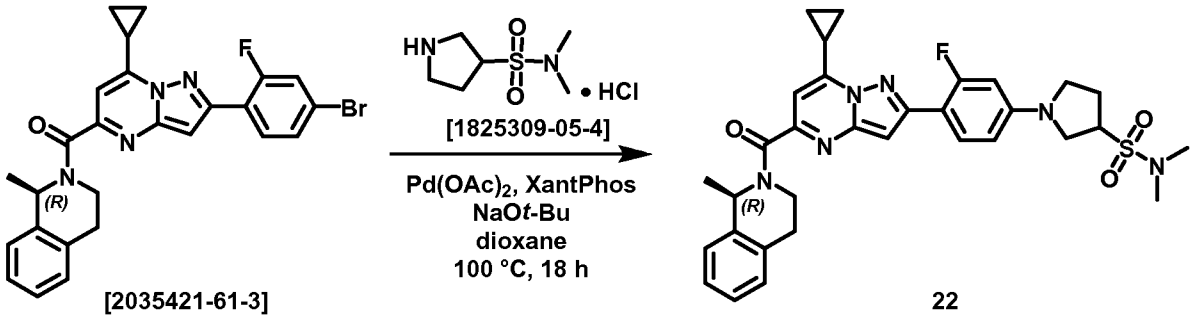
1-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)-N-methylpyrrolidine-3-sulfonamide



A sealed tube was charged with (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] (200 mg, 384 µmol), N-methylpyrrolidine-3-sulfonamide hydrochloride [1423025-73-3] (77.0 mg, 384 µmol), sodium *tert*-butoxide (50.0 mg, 0.52 mmol) and (±)-BINAP (47.8 mg, 76.8 µmol) and purged with nitrogen. 1,4-Dioxane (9 mL) was added and the mixture was purged again with nitrogen. Tris(dibenzylideneacetone)dipalladium (70.3 mg, 76.8 µmol) was added. The reaction mixture was purged with nitrogen and stirred at 100°C for 18 h. The reaction mixture was diluted with EtOAc and brine. The layers were separated and the aqueous phase was extracted. The combined organic extracts were washed with H_2O, dried over $MgSO_4$, filtered and evaporated under reduced pressure. 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 50:50 to 0:100). A second purification was performed by preparative LC (spherical C18 25 µm, 40 g YMC-ODS-25, loading (MeCN, H_2O), mobile phase gradient (0.2% aq.NH_4HCO_3) / MeCN from 50:50 to 0:100). The fractions containing the product were combined and a 10% aqueous solution of $KHSO_4$ was added. The layers were separated and the aqueous phase was extracted with EtOAc. The organic phase was washed with H_2O, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was triturated and co-evaporated with Et_2O (twice) and dried under high vacuum at 50°C for 18 h to give compound **21** (109 mg, 48%) as a pale red solid.

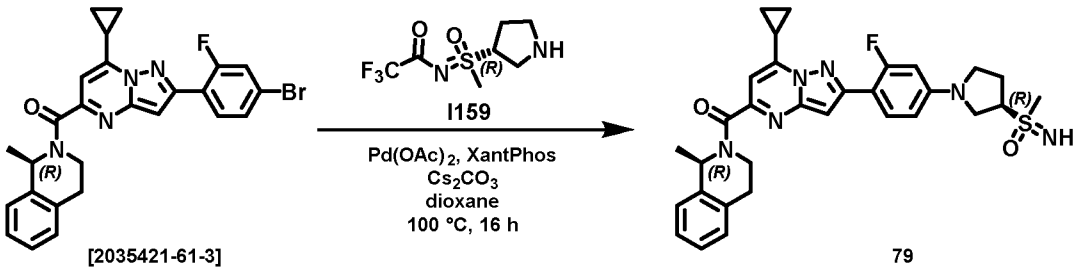
Compound 22

1-(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-dimethylpyrrolidine-3-sulfonamide

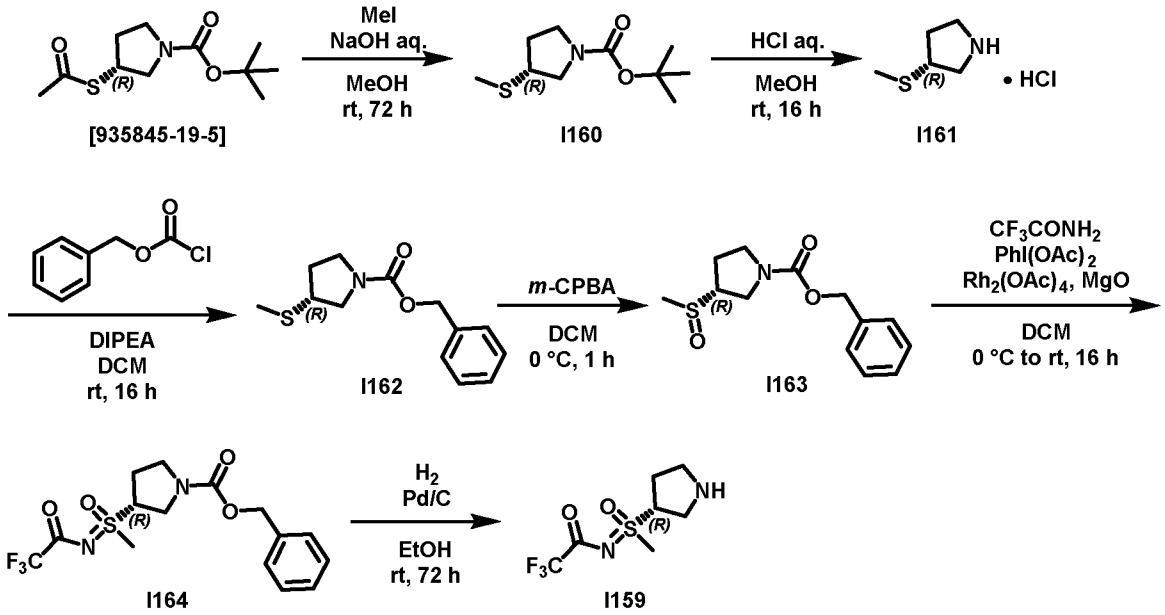


In a sealed tube a mixture of (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] (250 mg, 480 µmol), N,N-dimethyl-3-pyrrolidinesulfonamide hydrochloride [1825309-05-4] (155 mg, 720 µmol) and sodium *tert*-butoxide (231 mg, 2.40 mmol) in 1,4-dioxane (10 mL) was degassed with nitrogen. Palladium acetate (11.0 mg, 72.0 µmol) and XantPhos (27.8 mg, 48.0 µmol) were added. The reaction mixture was stirred at 100°C for 18 h. The reaction mixture was poured out into water and the aqueous phase was extracted with EtOAc (twice). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated to dryness. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 40 g GraceResolv™, liquid injection (DCM), mobile phase gradient: DCM / MeOH from 100:0 to 96:4). The residue was co-evaporated (5 times) and triturated with EtOH. The solid was filtered off and dried under high vacuum at 50°C for 18 h to give compound **22** (150 mg, 52%) as a yellow solid.

Compound 79

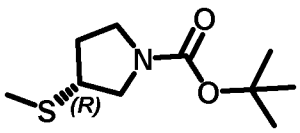


Synthesis of intermediate **I159**



Intermediate **I160**

Tert-butyl (3*R*)-3-(methylsulfanyl)pyrrolidine-1-carboxylate

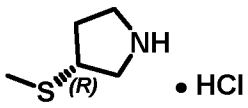


I160

Methyl iodide (3.9 mL, 62.8 mmol) was added to a mixture of (*R*)-*tert*-butyl 3-(acethylthio)pyrrolidine-1-carboxylate [935845-19-5] (7.00 g, 28.5 mmol) and sodium hydroxide (1.0 M in H_2O, 31 mL, 31.0 mmol) in MeOH (140 mL). The reaction mixture was stirred at rt for 72 h. The reaction mixture was diluted with H_2O and 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 the solvent was evaporated in vacuo to afford intermediate **I160** (5.2 g, 84%).

Intermediate **I161**

(3*R*)-3-(Methylsulfanyl)pyrrolidine hydrochloride

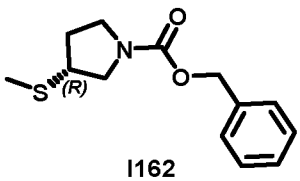


I161

A mixture of intermediate **I160** (5.20 g, 23.9 mmol) and hydrogen chloride (3.0 M in H_2O, 80 mL, 239 mmol) in MeOH (185 mL) was stirred at rt for 16 h. The mixture was evaporated to dryness and co-evaporated with MeOH to afford intermediate **I161** (3.7 g, quant.).

Intermediate **I162**

Benzyl (3*R*)-3-(methylsulfanyl)pyrrolidine-1-carboxylate

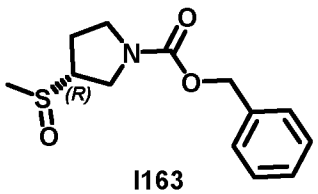


I162

Benzyl chloroformate (3.8 mL, 26.5 mmol) was added to a mixture of intermediate **I161** (3.70 g, 24.1 mmol) and DIPEA (10.3 mL, 60.2 mmol) in DCM (122 mL) at 0°C. The reaction mixture was stirred at rt for 16 h. An aqueous solution of $NaHCO_3$, brine and DCM were added. The layers were separated and the aqueous phase was extracted with DCM (twice). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and the solvent was evaporated in vacuo. The crude mixture was purified by preparative LC (regular SiOH, 30 µm, 220 g Interchim®, liquid injection (DCM / heptane), mobile phase gradient: heptane / EtOAc from 100:0 to 50:50) to afford intermediate **I162** (3.22 g, 53%).

Intermediate **I163**

Benzyl (3*R*)-3-methanesulfinylpyrrolidine-1-carboxylate

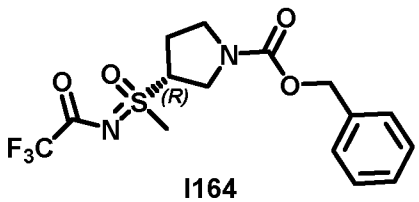


I163

m-CPBA (3.16 g, 14.1 mmol, 77% purity) was added portionwise to a solution of intermediate **I162** (3.22 g, 12.8 mmol) in DCM (128 mL) at 0°C. The reaction mixture was stirred at 0°C for 1 h. A 10% aqueous solution of $NaHCO_3$ and H_2O were added. 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 (regular SiOH, 30 µm, 120 g Interchim®, liquid injection (DCM), mobile phase gradient: DCM / MeOH from 99.8:0.2 to 95:5) to afford intermediate **I163** (1.63 g, 48%).

Intermediate **I164**

Benzyl (3*R*)-3-[methyl(oxo)[(trifluoroacetyl)imino]-λ^6-sulfanyl]pyrrolidine-1-carboxylate

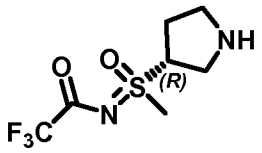


I164

To a mixture of intermediate **I163** (1.63 g, 6.10 mmol), trifluoroacetamide (1.03 g, 9.15 mmol) and magnesium oxide (983 mg, 24.4 mmol) in DCM (85 mL) at 0°C was added rhodium acetate dimer (90.0 mg, 0.41 mmol) and (diacetoxyiodo)benzene (2.95 g, 9.15 mmol). The reaction mixture was stirred at 0°C for 1 h and at rt for 16 h. Celite® was added and the mixture was evaporated to dryness. The crude mixture was purified by preparative LC (regular SiOH, 30 µm, 80 g Interchim®, dry loading (Celite®), mobile phase gradient: DCM / MeOH from 100:0 to 95:5) to afford intermediate **I164** (1.47 g, 64%).

Intermediate **I159**

2,2,2-Trifluoro-N-[methyl(oxo)(3*R*)-pyrrolidin-3-yl-λ^6-sulfanylidene]acetamide



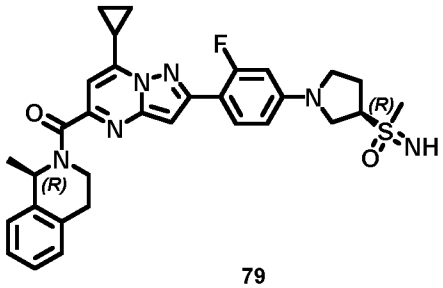
I159

A mixture of intermediate **I164** (1.47 g, 3.89 mmol) and Pd/C (10% wt and in 50% H_2O, 4.13 g, 1.94 mmol) in EtOH (50 mL) was stirred under H_2 atmosphere (20 bars) at rt for 72

h. The reaction mixture was filtered over a pad of Celite® and rinsed with EtOH (twice). The filtrate was evaporated to dryness to give intermediate **I159** (838 mg, 88%).

Compound 79

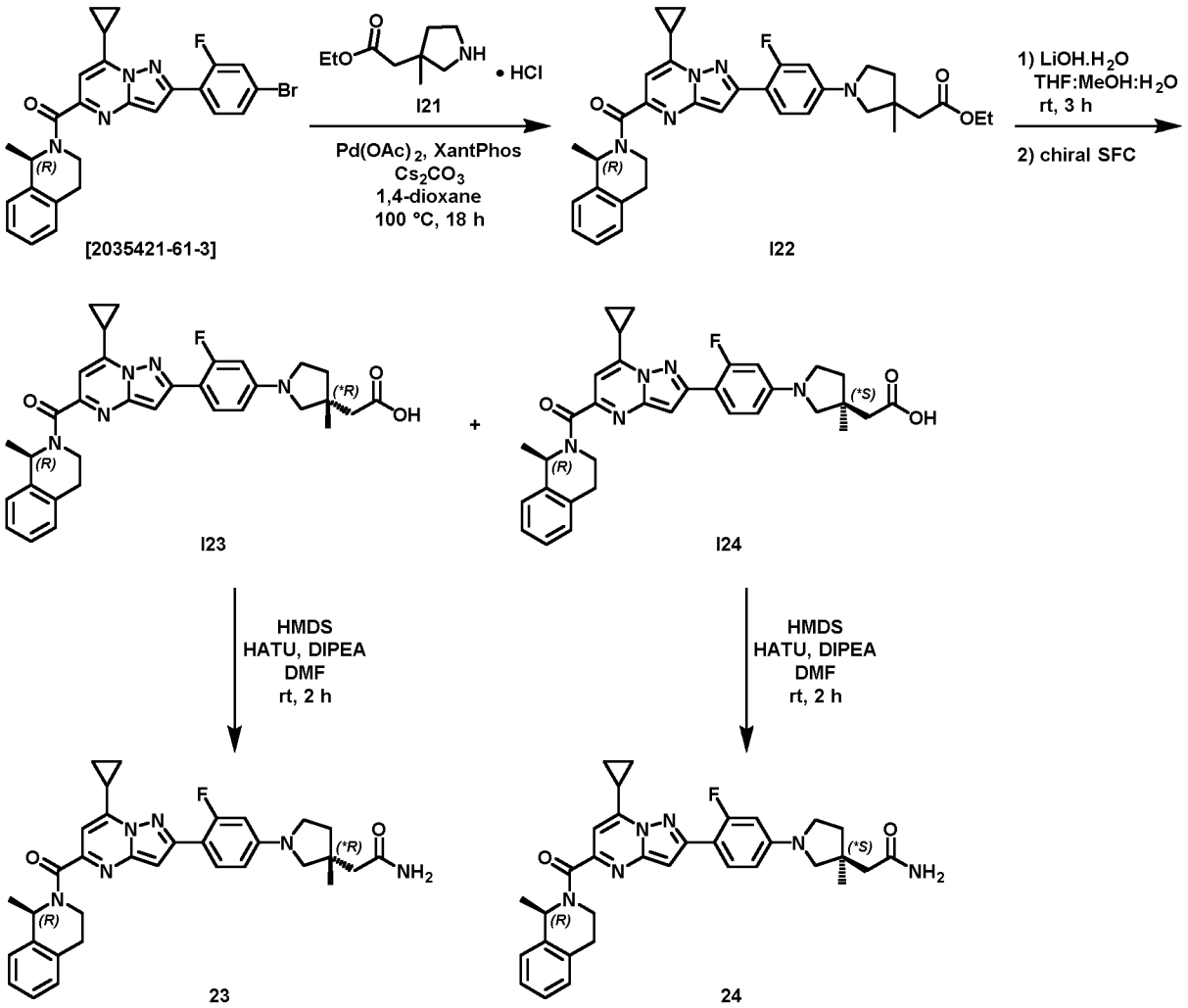
[(3*R*)-1-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)pyrrolidin-3-yl](imino)methyl-λ^6-sulfanone



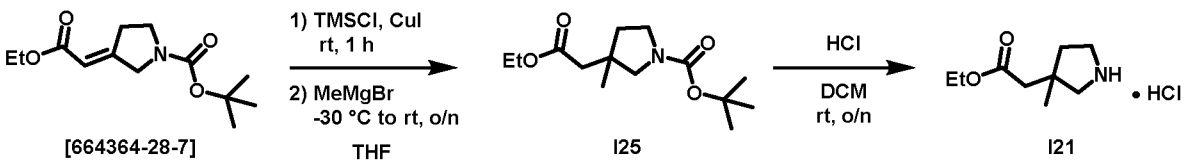
79

In a Schlenk tube were added (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] (300 mg, 0.59 mmol), intermediate **I159** (217 mg, 0.89 mmol), cesium carbonate (580 mg, 1.78 mmol) and 1,4-dioxane (9.5 mL). The mixture was degassed with nitrogen and palladium acetate (13.3 mg, 5.94 µmol) and XantPhos (34.3 mg, 5.94 µmol) were added successively. The reaction mixture was stirred at 100°C for 16 h. H_2O (3.8 mL) was added and the reaction mixture was stirred at rt for 1 h. The reaction mixture was diluted with H_2O and 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 the solvent was evaporated in vacuo. The crude mixture was purified by preparative LC (regular SiOH, 30 µm, 25 g Interchim®, liquid injection (DCM), mobile phase gradient: DCM / MeOH from 99.8:0.2 to 90:10). The residue was solubilized in EtOAc and the mixture was evaporated under vacuum (twice). The residue was dissolved in EtOAc and a precipitate was observed upon the addition of heptane. The solid was filtered off and dried under high vacuum at 40°C for 16 h to give compound **79** (143 mg, 42%).

Compound 23 and Compound 24

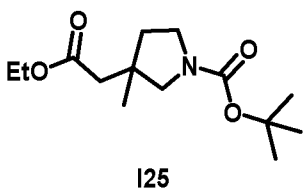


Synthesis of intermediate **I21**



Intermediate **I25**

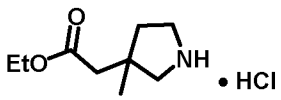
Tert-butyl 3-(2-ethoxy-2-oxoethyl)-3-methylpyrrolidine-1-carboxylate



A mixture of *tert*-butyl (3*E*)-3-(2-ethoxy-2-oxoethylidene)pyrrolidine-1-carboxylate [664364-28-7] (3.50 g, 13.7 mmol), chlorotrimethylsilane (63.8 mL, 54.8 mmol) and cuprous iodide (3.02 g, 15.8 mmol) in THF (150 mL) was stirred at rt for 1 h. The reaction mixture was cooled down to -30°C and methylmagnesium bromide (3.0 M in Et_2O, 27.4 mL, 82.3 mmol) was added dropwise. The reaction mixture was slowly warmed to rt and stirred overnight. EtOAc and 1N aqueous solution of HCl were added. The layers were separated and the organic phase was washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 80 g Grace®, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 90:10 to 70:30) to afford intermediate **I25** (2.0 g, 54%).

Intermediate **I21**

Ethyl 2-(3-methylpyrrolidin-3-yl)acetate hydrochloride



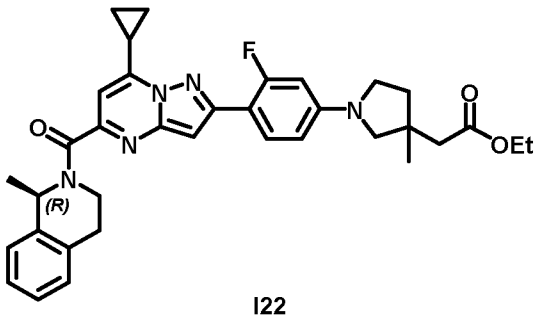
I21

HCl (4.0 M in dioxane, 2.53 mL, 10.1 mmol) was added to a solution of intermediate **I25** (550 mg, 2.03 mmol) in DCM (10 mL). The reaction mixture was stirred at rt overnight and the solvent was evaporated under reduced pressure. The product **I21** was used in the next step without further purification.

Synthesis of compounds 23 and 24

Intermediate **I22**

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



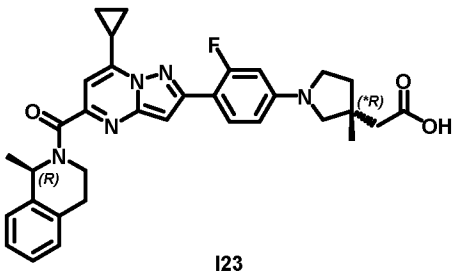
I22

A mixture of (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropylpyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] (474 mg, 0.94 mmol), intermediate **I21** (390 mg, 1.88 mmol), cesium carbonate (0.92 g, 2.82 mmol) and XantPhos (54.3 mg, 93.9 µmol) was purged with nitrogen. 1,4-Dioxane (15 mL) was added and the mixture was purged again with nitrogen. Palladium acetate (21.1 mg, 93.9 µmol) was added. The reaction mixture was purged with nitrogen and stirred at 100°C for 18 h. The reaction mixture was diluted with EtOAc and H_2O. 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 the solvent was removed under reduced pressure. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 40 g Grace®, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 100:0 to 70:30) to afford intermediate **I22** (490 mg, 88%).

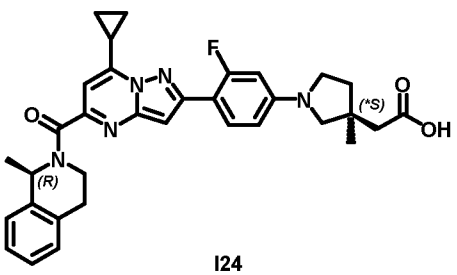
Intermediates **I23** and **I24**

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

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



I23



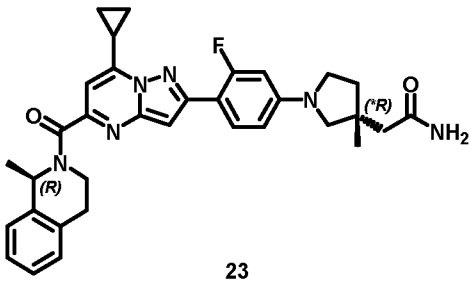
I24

Lithium hydroxide monohydrate (104 mg, 2.45 mmol) was added to a solution of intermediate **I22** (490 mg, 823 µmol) in THF (10 mL), MeOH (3 mL) and H_2O (1.2 mL). The reaction mixture was stirred at rt for 3 h. Few drops of H_2O were added followed by the addition of a 3N aqueous solution of HCl. The layers were separated and the aqueous phase was extracted with DCM (twice). The combined organic extracts were washed with H_2O, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 12 g Grace®, liquid injection (DCM), mobile phase gradient: DCM /MeOH from 100:0 to 97:3) to deliver a mixture of diastereomers (250 mg, 53%). A purification was performed via chiral SFC (Stationary phase: Chiralpak AS-H 5µm 250*20mm, Mobile phase: 65% CO_2, 35% *i*-

PrOH) to afford the diastereomers **I23** (120 mg, 26%) and **I24** (122 mg, 26%). The diastereomers were purified separately by preparative LC (irregular SiOH, 15-40 µm, 12 g Grace®, liquid injection (DCM), mobile phase gradient: DCM / MeOH from 100:0 to 97:3) to give **I23** (95 mg, 20%) and **I24** (92 mg, 20%).

Compound 23

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

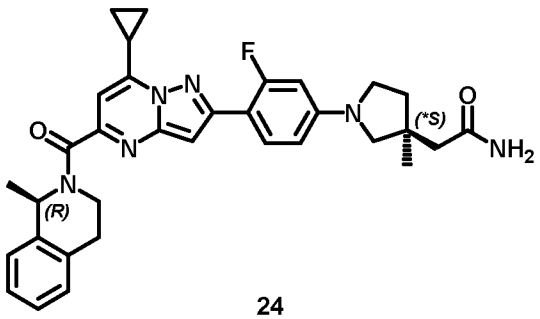


23

A mixture of intermediate **I23** (80.0 mg, 0.14 mmol), HMDS (35.9 µL, 0.17 mmol), HATU (80.4 mg, 0.21 mmol) and DIPEA (36.4 µL, 0.21 mmol) in DMF (2 mL) was stirred at rt for 2 h. H_2O was added and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with H_2O, brine, dried over $MgSO_4$ and concentrated to dryness. The crude mixture was purified by flash chromatography over silica gel (15-40 µm, 12 g Grace®, mobile phase gradient: DCM / MeOH from 100:0 to 97:3). The pure fractions were collected and evaporated to dryness. The residue (53 mg) was crystallized from DIPE to give compound **23** (35.6 mg, 44%).

Compound 24

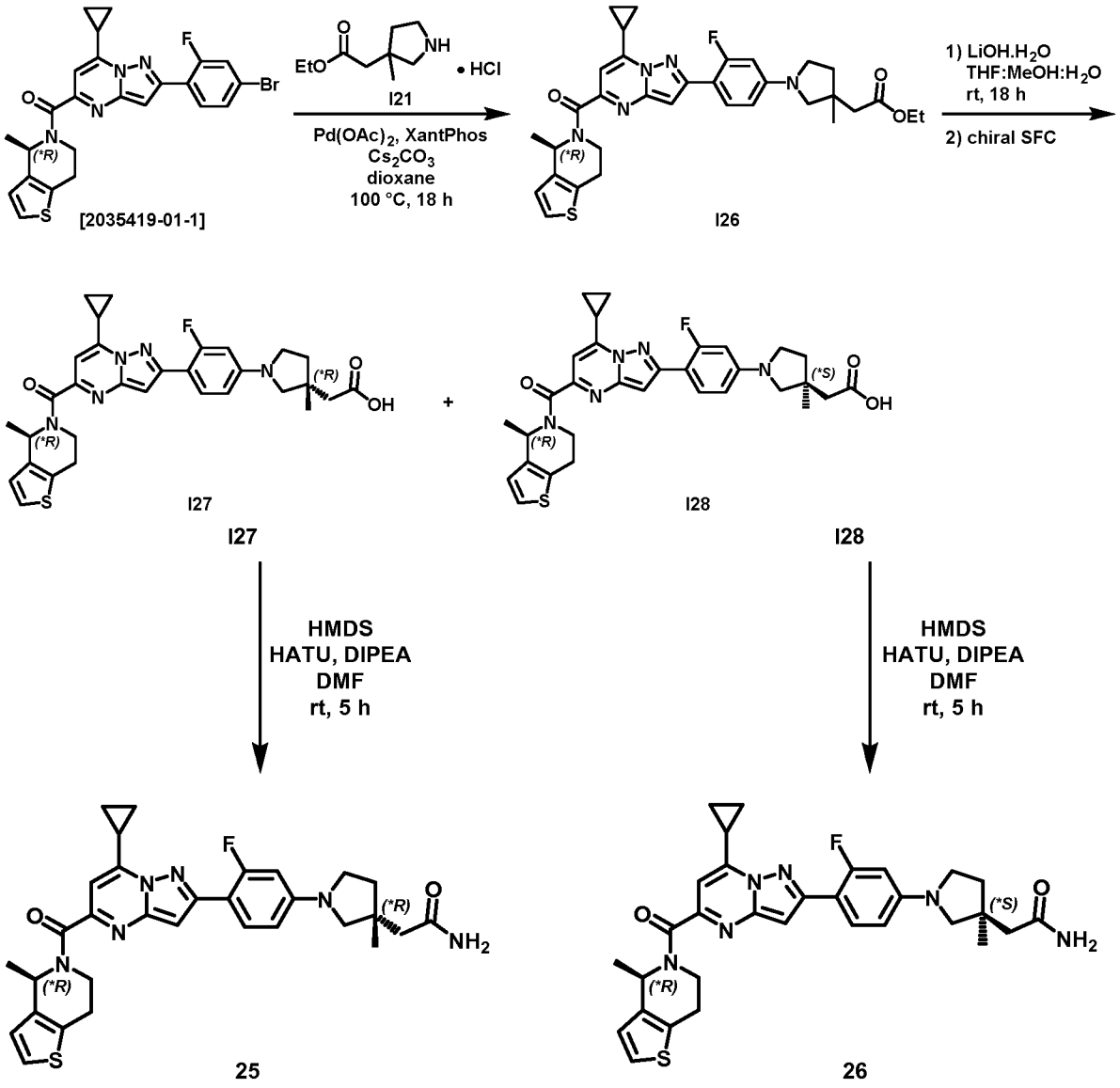
2-[(3*S*)-1-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)-3-methylpyrrolidin-3-yl]acetamide



24

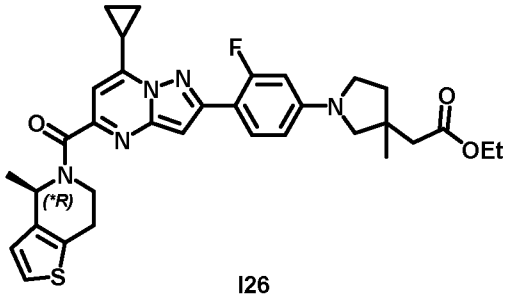
Compound **24** (29 mg, 32%) was synthesized from intermediate **I24** according to the procedure reported for the synthesis of compound **23**.

Compound 25 and Compound 26



Intermediate **I26**

Ethyl 2-[1-(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)-3-methylpyrrolidin-3-yl]acetate



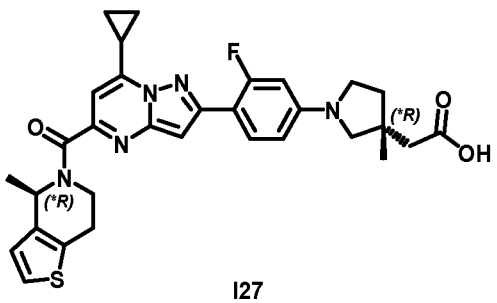
I26

A mixture of 2-(4-bromo-2-fluorophenyl)-7-cyclopropyl-5-[(4*R*)-4-methyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine-5-carbonyl]pyrazolo[1,5-a]pyrimidine [2035419-01-1] (517 mg, 1.01 mmol), intermediate **I21** (420 mg, 2.02 mmol), cesium carbonate (0.99 g, 3.03 mmol) and XantPhos (80.1 mg, 0.14 mmol) was purged with nitrogen. 1,4-Dioxane (12 mL) was added and the mixture was degassed with nitrogen. Palladium acetate (22.7 mg, 0.10 mmol) was added. The reaction mixture was purged with nitrogen and stirred at 100°C for 18 h. The reaction mixture was diluted with EtOAc and H_2O. 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 the solvent was removed under reduced pressure. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 40 g Grace®, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 100:0 to 70:30) to afford intermediate **I26** (440 mg, 72%).

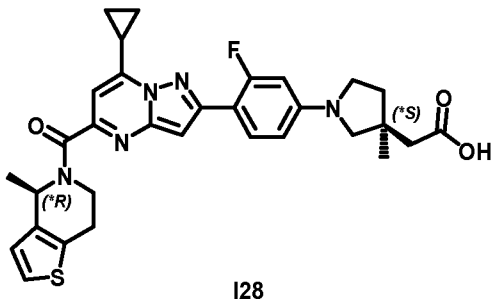
Intermediates **I27** and **I28**

2-[(3**R*)-1-(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)-3-methylpyrrolidin-3-yl]acetic acid

2-[(3**S*)-1-(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)-3-methylpyrrolidin-3-yl]acetic acid



I27



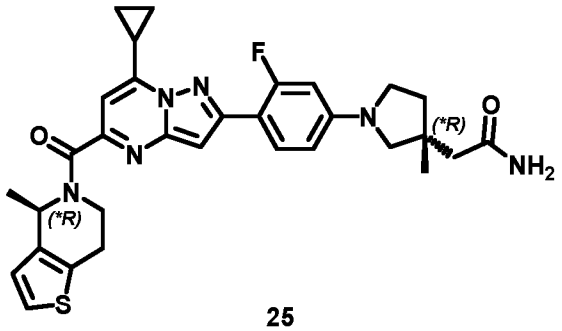
I28

Lithium hydroxide monohydrate (92.1 mg, 2.19 mmol) was added to a solution of intermediate **I26** (440 mg, 0.73 mmol) in THF (10 mL), MeOH (3 mL) and H_2O (1.2 mL). The reaction mixture was stirred at rt for 18 h. Few drops of H_2O were added followed by

the addition of a 3N aqueous solution of HCl. The layers were separated and the aqueous phase was extracted with DCM (twice). The combined organic extracts were washed with H_2O, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 12 g Grace®, liquid injection (DCM), mobile phase gradient: DCM / MeOH from 100:0 to 97:3). The diastereoisomers (220 mg) were separated via chiral SFC (Stationary phase: Chiralpak AS-H 5µm 250*20mm, Mobile phase: 65% CO_2, 35% *i*-PrOH) to give **I27** (94 mg) and **I28** (94 mg). The two separated diastereoisomers were taken up in DIPE and the solids were filtered off and dried under vacuum at 50°C. The diastereoisomers were purified separately by preparative LC (irregular SiOH, 15-40 µm, 12 g Grace®, liquid injection (DCM), mobile phase gradient: DCM / MeOH from 100:0 to 97:3) to afford intermediates **I27** (78 mg, 18%) and **I28** (70 mg, 17%).

Compound 25

2-[(3*R*)-1-(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)-3-methylpyrrolidin-3-yl]acetamide

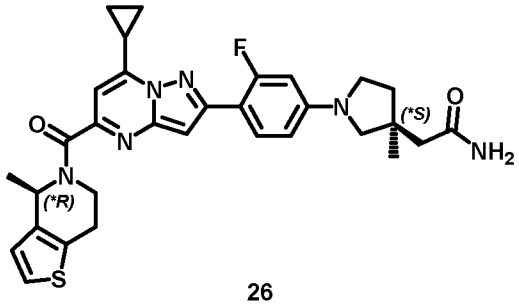


25

A solution of intermediate **I27** (78.0 mg, 0.14 mmol), HMDS (34.6 µL, 0.16 mmol), HATU (77.5 mg, 0.20 mmol) and DIPEA (46.9 µL, 0.27 mmol) in DMF (2 mL) was stirred at rt for 5 h. The reaction mixture was diluted with H_2O and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with H_2O, brine, dried over $MgSO_4$ and concentrated to dryness. The crude mixture was purified by flash chromatography over silica gel (15-40 µm, 12 g Grace®, mobile phase gradient: DCM / MeOH from 100:0 to 97:3). The pure fractions were collected and evaporated to dryness. The residue (32 mg) was crystallized from DIPE to give compound **25** (18 mg, 23%).

Compound 26

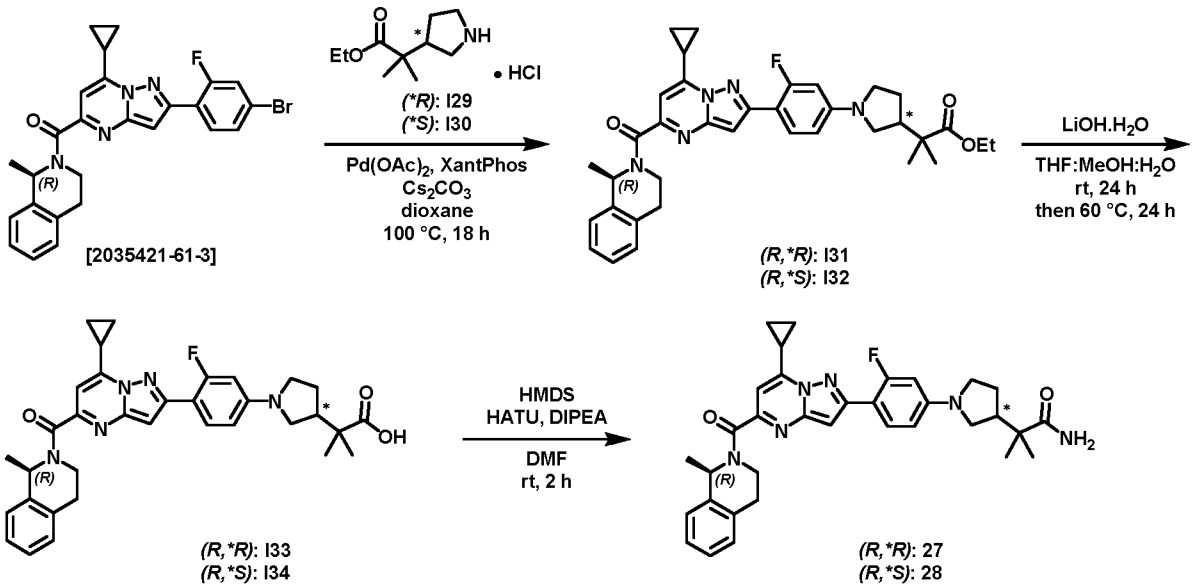
2-[(3*S*)-1-(4-{7-Cyclopropyl-5-[(4*R*)-4-methyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine-5-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)-3-methylpyrrolidin-3-yl]acetamide



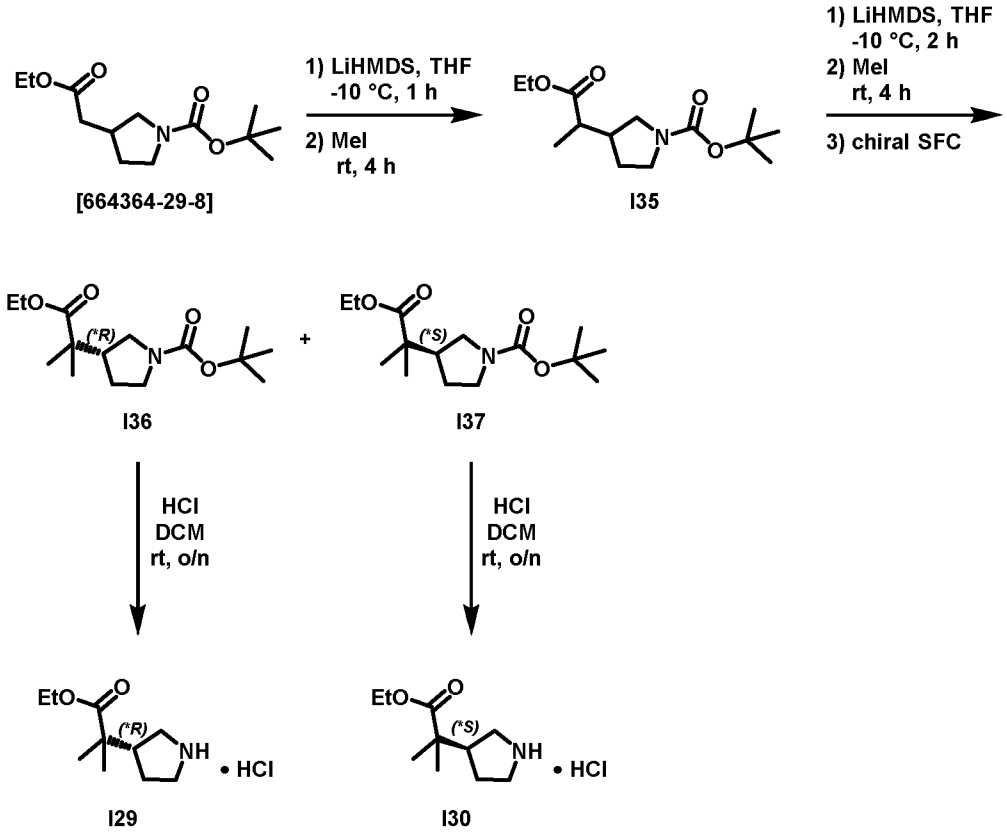
26

Compound **26** (28 mg, 40%) was synthesized from intermediate **I28** according to the procedure reported for the synthesis of compound **25**.

Compound 27 and Compound 28

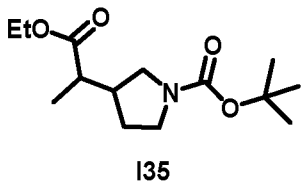


Synthesis of intermediates **I29** and **I30**



Intermediate **I35**

Tert-butyl 3-(1-ethoxy-1-oxopropan-2-yl)pyrrolidine-1-carboxylate



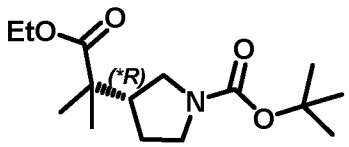
I35

Lithium bis(trimethylsilyl)amide (1.5 M in THF, 10.6 mL, 15.9 mmol) was added to a solution of *tert*-butyl 3-(2-ethoxy-2-oxoethyl)pyrrolidine-1-carboxylate [664364-29-8] (1.7 g, 6.61 mmol) in THF (60 mL) at -10°C for 1 h. Iodomethane (0.98 mL, 15.9 mmol) was added and the reaction mixture was stirred at rt for 4 h. H_2O was added and the aqueous phase was extracted with EtOAc (twice). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Intermediate **I35** was used in the next step without further purification.

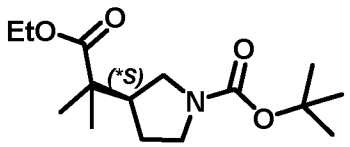
Intermediates **I36** and **I37**

Tert-butyl (3**R*)-3-(1-ethoxy-2-methyl-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

Tert-butyl (3**S*)-3-(1-ethoxy-2-methyl-1-oxopropan-2-yl)pyrrolidine-1-carboxylate



I36

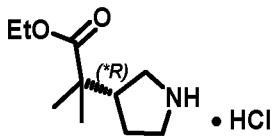


I37

Lithium bis(trimethylsilyl)amide (1.5 M in THF, 18.4 mL, 27.6 mmol) was added to a solution of intermediate **I35** (2.50 g, 9.21 mmol) in THF (37.5 mL) at -10°C under nitrogen. The reaction mixture was stirred at -10°C for 2 h. Iodomethane (1.37 mL, 22.1 mmol) was added and the reaction mixture was stirred at rt for 4 h. The reaction mixture was diluted with EtOAc and the organic phase was washed with H_2O, brine, dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. 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 70:30). The enantiomers were separated via chiral SFC (Stationary phase: Lux amylose 2 5µm 250*21.2mm, Mobile phase: 90% CO_2, 10% *i*-PrOH) to afford intermediates **I36** (850 mg, 32%) and **I37** (850 mg, 32%).

Intermediate **I29**

Ethyl 2-methyl-2-[(3**R*)-pyrrolidin-3-yl]propanoate hydrochloride

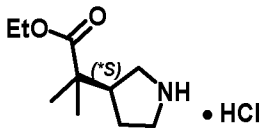


I29

HCl (4.0 M in dioxane, 1.1 mL, 4.40 mmol) was added to a solution of intermediate **I36** (250 mg, 876 µmol) in DCM (5 mL). The reaction mixture was stirred at rt overnight. The solvent was evaporated under reduced pressure and the product **I29** was used in the next step as soon as possible without further purification.

Intermediate **I30**

Ethyl 2-methyl-2-[(3**S*)-pyrrolidin-3-yl]propanoate hydrochloride



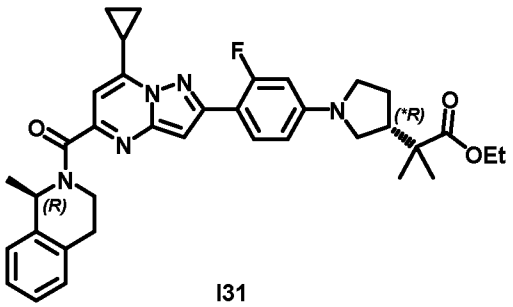
I30

Intermediate **I30** was synthesized from intermediate **I37** according to the procedure reported for the synthesis of intermediate **I29**. The product was used in the next step without further purification.

Synthesis of compounds 27 and 28

Intermediate **I31**

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

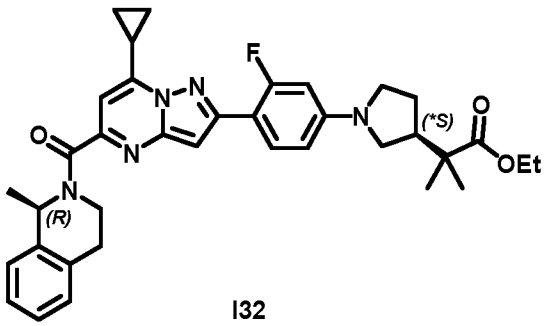


I31

A mixture of (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropylpyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] (228 mg, 0.45 mmol), intermediate **I29** (150 mg, 0.68 mmol), cesium carbonate (441 mg, 1.35 mmol) and XantPhos (26.1 mg, 45.1 µmol) was purged with nitrogen. 1,4-Dioxane (7 mL) was added and the mixture was purged again with nitrogen. Palladium acetate (10.1 mg, 45.1 µmol) was added. The reaction mixture was purged with nitrogen and stirred at 100°C for 18 h. The reaction mixture was diluted with EtOAc and H_2O. 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 the solvent was evaporated under reduced pressure. 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 75:25) to afford intermediate **I31** (190 mg, 69%).

Intermediate **I32**

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

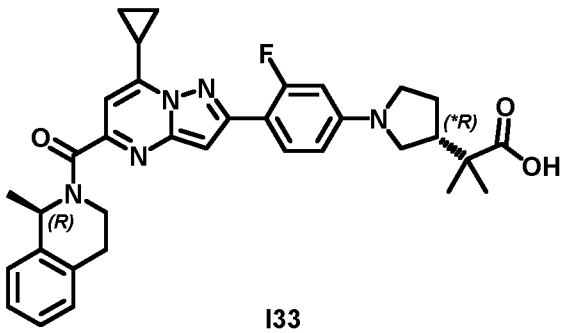


I32

Intermediate **I32** (125 mg, 57%) was synthesized from (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropylpyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] and intermediate **I30** according to the procedure reported for the synthesis of compound **I31** with a shorter reaction time of 3 h.

Intermediate **I33**

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

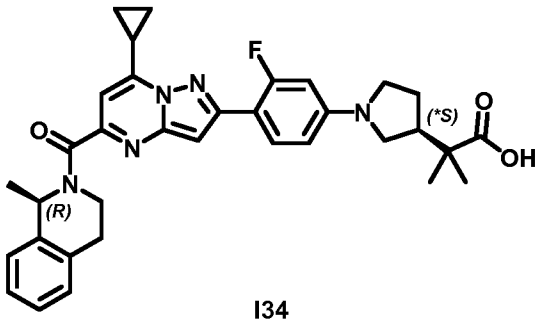


I33

Lithium hydroxide monohydrate (65.4 mg, 1.56 mmol) was added to a solution of intermediate **I31** (0.19 g, 0.31 mmol) in THF (5 mL), MeOH (2 mL) and H_2O (0.4 mL). The reaction mixture was stirred at rt for 24 h and at 60°C for 24 h. Few drops of H_2O were added followed by the addition of a 3N aqueous solution of HCl. The layers were separated and the aqueous phase was extracted with DCM (twice). The combined organic extracts were washed with H_2O, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The product **I33** (210 mg) was used in the next step without further purification.

Intermediate **I34**

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

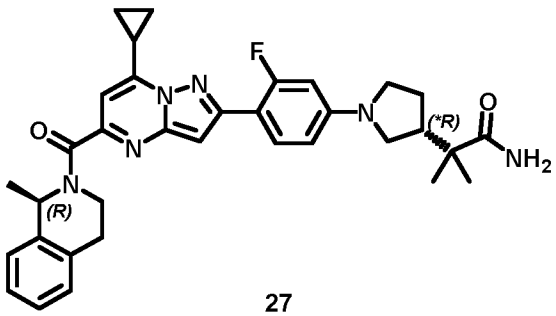


I34

Intermediate **I34** was synthesized from intermediate **I32** according to the procedure reported for the synthesis of intermediate **I33**. The reaction mixture was stirred at 60°C for 24 h. The product **I34** (155 mg) was used in the next step without further purification.

Compound 27

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



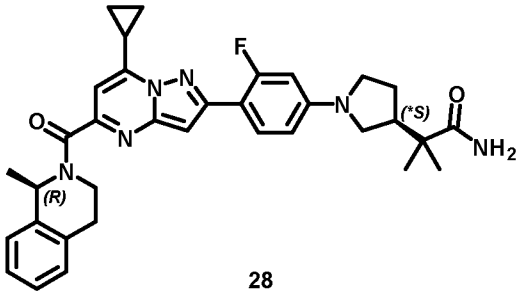
27

A mixture of intermediate **I33** (190 mg, 327 µmol), HMDS (83.2 µL, 392 µmol), HATU (186 mg, 0.49 mmol) and DIPEA (112 µL, 0.65 mmol) in DMF (5 mL) was stirred at rt for 2 h. H_2O was added and the aqueous phase was extracted with EtOAc. The organic phase was washed with H_2O, brine, dried over $MgSO_4$ and concentrated to dryness. The crude mixture was purified by flash chromatography over silica gel (Grace® 12 g, 15-40 µm, mobile phase gradient: DCM / MeOH from 100:0 to 97:3). The pure fractions were

collected and evaporated to dryness. The residue (85 mg) was taken up in DIPE and the solid was filtered off and dried under vacuum to give compound **27** (50 mg, 26%).

Compound 28

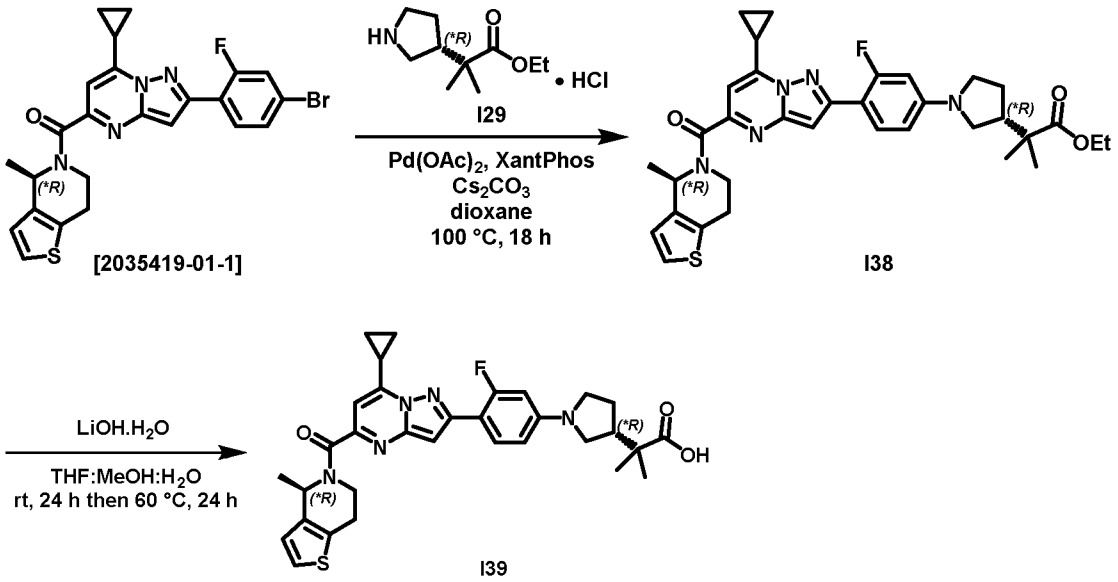
2-[(3*S*)-1-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)pyrrolidin-3-yl]-2-methylpropanamide

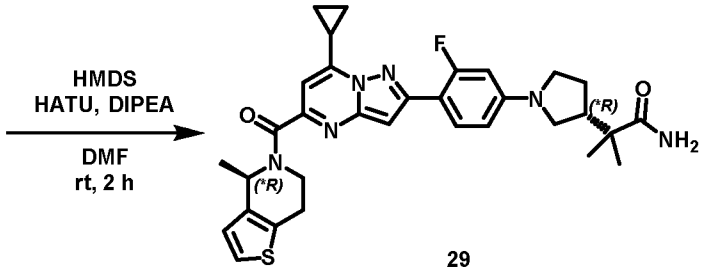


28

Compound **28** was synthesized from intermediate **I34** according to the procedure reported for the synthesis of compound **27**. The crude mixture was purified by flash chromatography over silica gel (15-40 µm, 12 g Grace®, mobile phase gradient: DCM / MeOH from 100:0 to 97:3). The pure fractions were collected and evaporated to dryness. The product was lyophilized with MeCN / H_2O (80:20) to give compound **28** (56 mg, 36%).

Compound 29

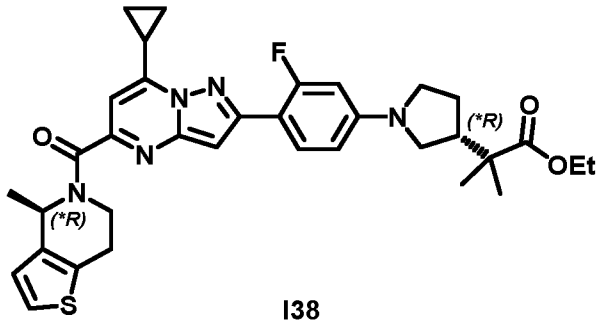




29

Intermediate **I38**

Ethyl 2-[(3*R*)-1-(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)pyrrolidin-3-yl]-2-methylpropanoate

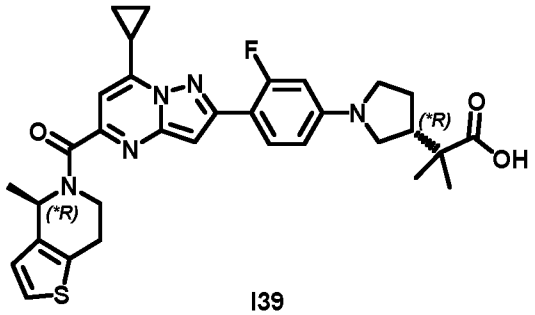


I38

A mixture of 2-(4-bromo-2-fluorophenyl)-7-cyclopropyl-5-[(4*R*)-4-methyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine-5-carbonyl]pyrazolo[1,5-a]pyrimidine [2035419-01-1] (300 mg, 0.59 mmol), intermediate **I29** (195 mg, 0.88 mmol), cesium carbonate (573 mg, 1.76 mmol) and XantPhos (33.9 mg, 58.6 µmol) was purged with nitrogen. 1,4-Dioxane (7 mL) was added and the mixture was degassed with nitrogen. Palladium acetate (13.2 mg, 58.6 µmol) was added. The reaction mixture was purged with nitrogen and stirred at 100°C for 18 h. The reaction mixture was diluted with EtOAc and H_2O. 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 the solvent was removed under reduced pressure. 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 75:25) to give intermediate **I38** (120 mg, 33%).

Intermediate **I39**

2-[(3*R*)-1-(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)pyrrolidin-3-yl]-2-methyl-propanoic acid

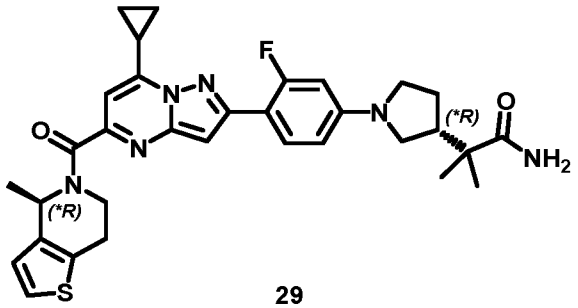


I39

Lithium hydroxide monohydrate (24.5 mg, 0.59 mmol) was added to a solution of intermediate **I38** (0.12 g, 195 µmol) in THF (5 mL), MeOH (1 mL) and H_2O (0.6 mL). The reaction mixture was stirred at rt for 24 h and at 60°C for another 24 h. Few drops of H_2O 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 washed with H_2O, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 4 g Grace®, liquid injection (DCM), mobile phase gradient: DCM / MeOH from 100:0 to 97:3) to afford intermediate **I39** (75 mg, 65%).

Compound 29

2-[(3*R*)-1-(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)pyrrolidin-3-yl]-2-methyl-propanamide

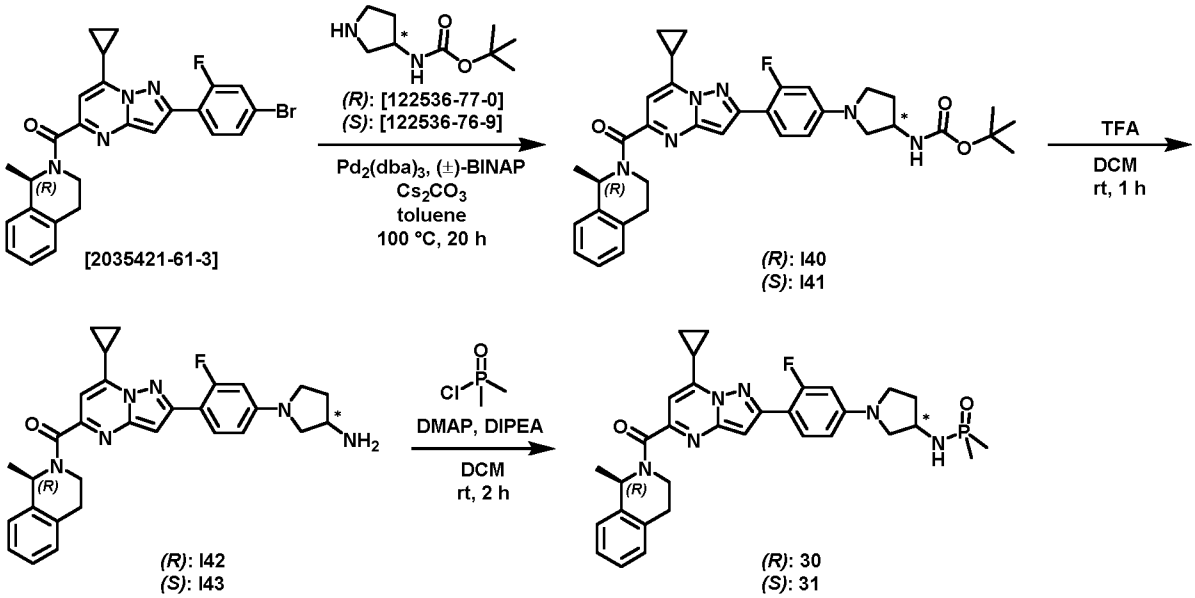


29

A solution of intermediate **I39** (75.0 mg, 0.13 mmol), HMDS (32.5 µL, 0.15 mmol), HATU (72.8 mg, 0.19 mmol) and DIPEA (44.0 µL, 0.26 mmol) in DMF (2 mL) was stirred at rt for 2 h. The reaction mixture was diluted with H_2O and EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc. The organic phase was washed with H_2O, brine, dried over $MgSO_4$ and concentrated to dryness. The crude compound was purified by flash chromatography over silica gel (15-40µm, 4 g Grace®, mobile phase gradient: DCM / MeOH from 100:0 to 97:3). The pure fractions were

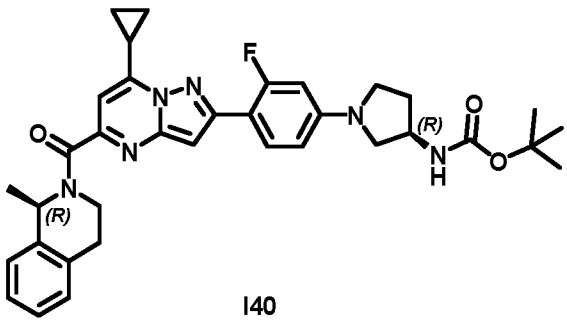
collected and evaporated to dryness. The product was lyophilized (MeCN / H_2O, 80:20) to give compound **29** (41 mg, 55%).

Compound 30 and Compound 31



Intermediate **I40**

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



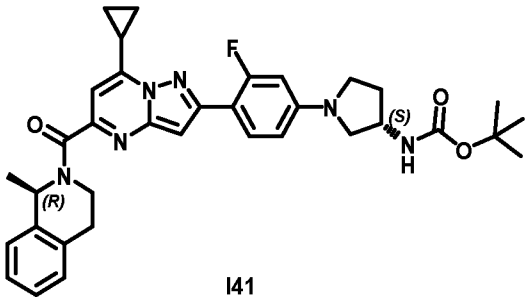
I40

A Schenlk tube was charged with (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] (500 mg, 0.95 mmol), (*R*)-3-(boc-amino)pyrrolidine [122536-77-0] (355 mg, 1.91 mmol), cesium carbonate (1.09 g, 3.34 mmol) and toluene (20 mL). The mixture was purged with nitrogen. (±)-BINAP (59.3 mg, 95.3 µmol) and tris(dibenzylideneacetone)dipalladium (87.2 mg, 95.3 µmol) were added. The reaction mixture was purged with nitrogen and stirred at 100°C for 20 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 under reduced pressure. 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 60:40) to afford intermediate **I40** (542 mg, 93%) as a yellow foam.

Intermediate **I41**

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

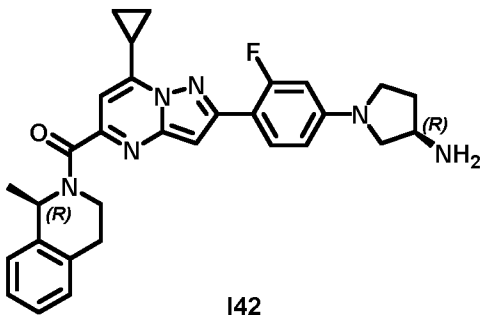


I41

Intermediate **I41** was synthesized from (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropylpyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] and (*S*)-3-(boc-amino)pyrrolidine [122536-76-9] according to the procedure reported for the synthesis of intermediate **I40**. Intermediate **I41** (570 mg, 98%) was obtained as a yellow foam.

Intermediate **I42**

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



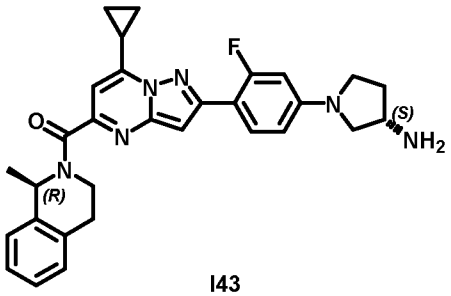
I42

TFA (1.60 mL, 20.9 mmol) was added to a solution of intermediate **I40** (401 mg, 65.7 µmol) in DCM (8 mL). The reaction mixture was stirred at rt for 1 h. DCM and a saturated

aqueous solution of $NaHCO_3$ were added. The layers were separated and the organic phase was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to afford intermediate **I42** (358 mg) as a yellow gum. The product was engaged in the next step without further purification.

Intermediate **I43**

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

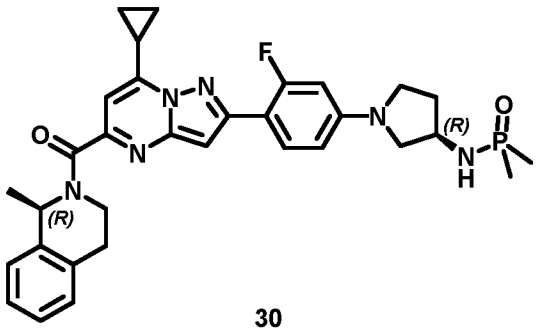


I43

Intermediate **I43** was synthesized from intermediate **I41** according to the procedure reported for the synthesis of intermediate **I42**. Intermediate **I43** (450 mg) was obtained as a yellow gum and engaged in the next step without further purification.

Compound 30

(1*R*)-2-(7-Cyclopropyl-2-{4-[(3*R*)-3-[(dimethylphosphoryl)amino]pyrrolidin-1-yl]-2-fluorophenyl}pyrazolo[1,5-a]pyrimidine-5-carbonyl)-1-methyl-1,2,3,4-tetrahydro-isoquinoline



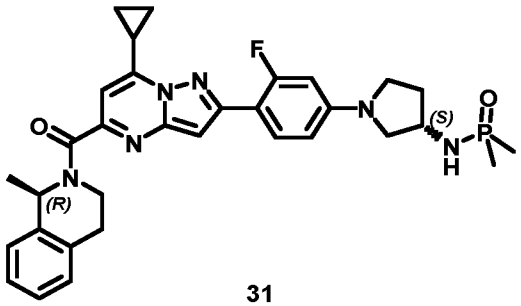
30

Dimethylphosphinic chloride (360 µL, 0.72 mmol) was added to a mixture of intermediate **I42** (354 mg, 638 µmol, 92% purity), DIPEA (242 µL, 1.40 mmol) and DMAP (7.79 mg, 63.8 µmol) in DCM (5.6 mL). The reaction mixture was stirred at rt for 2 h. The reaction mixture was diluted with DCM and washed with a 10% aqueous solution of $NaHCO_3$. The

organic phase was dried over $MgSO_4$, filtered and evaporated 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 96:4). The residue was taken up in MeOH, evaporated and triturated with Et_2O. The solid was filtered off and dried under high vacuum at 50°C for 2 h to give compound **30** (199 mg, 53%) as a yellowish solid.

Compound 31

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

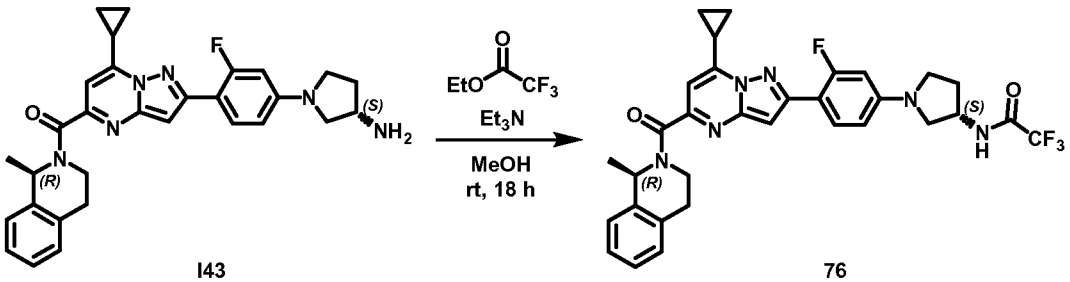


31

Compound **31** was synthesized from intermediate **I43** according to the procedure reported for the synthesis of compound **30**. The product was dried under high vacuum at 50°C for 20 h to give compound **31** (233 mg, 58%) as a yellowish solid.

Compound 76

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

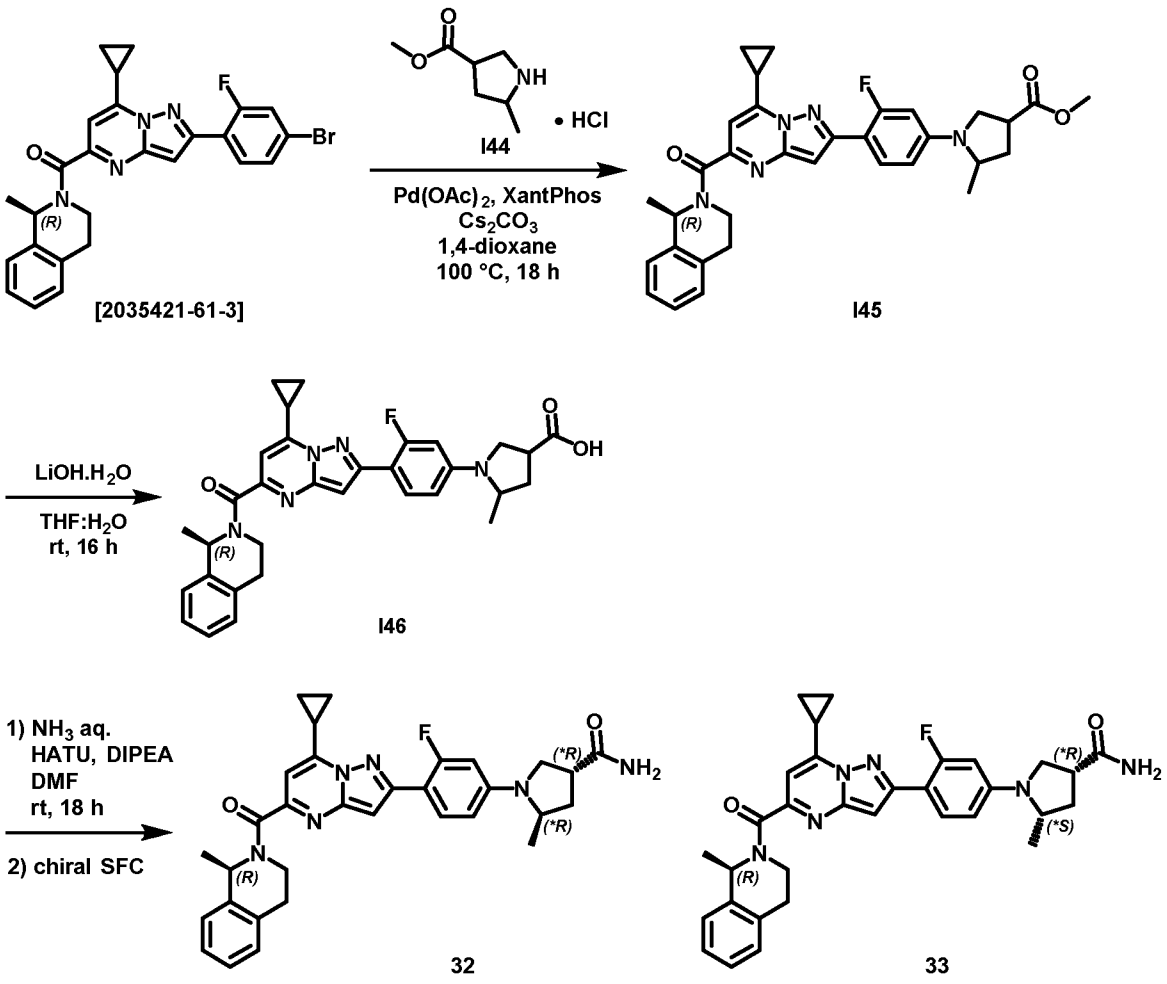


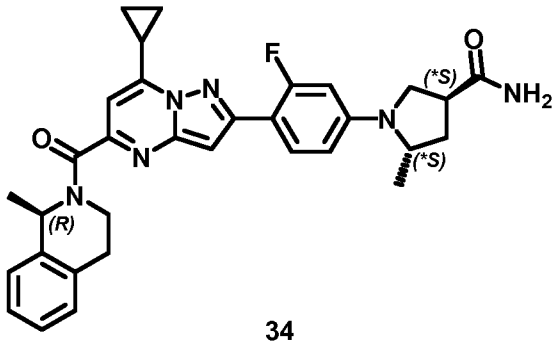
I43 76

In a sealed tube Et_3N (32 µL, 0.23 mmol) and ethyl trifluoroacetate (30 µL, 0.25 mmol) were added to a solution of intermediate **I43** (100 mg, 196 µmol) in MeOH (0.8 mL). The reaction mixture was stirred at rt for 18 h. The reaction mixture was diluted with H_2O and

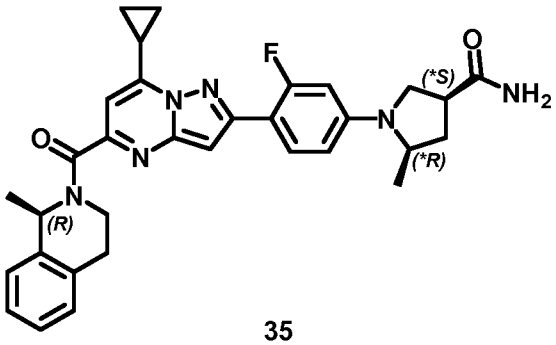
EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc (twice). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 24 g GraceResolv™, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 90:10 to 60:40). The residue was crystallized from MeOH. The solid was filtered off and dried under high vacuum at 50°C for 20 h to give compound **76** (53 mg, 45%) as a yellow solid.

Compounds 32, Compound 33, Compound 34 and Compound 35



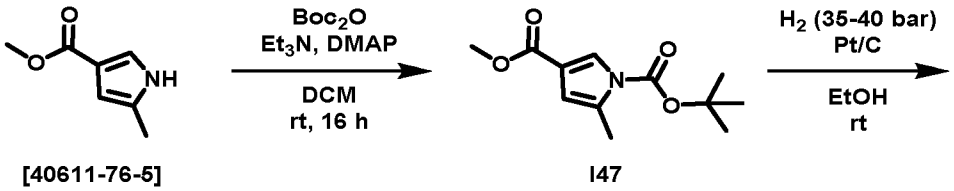


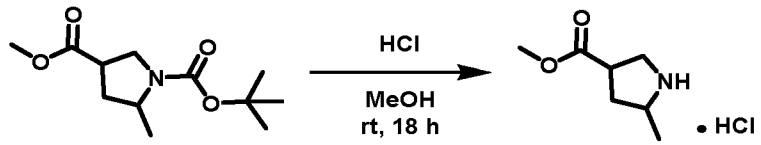
34



35

Synthesis of intermediate **I44**

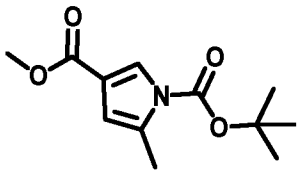




I48 I44

Intermediate **I47**

1-*Tert*-butyl 3-methyl 5-methyl-1H-pyrrole-1,3-dicarboxylate

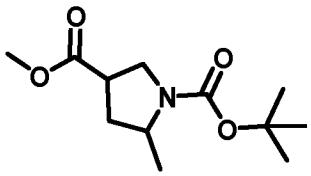


I47

A sealed tube was charged with DMAP (8.78 mg, 71.8 µmol), 5-methyl-1H-pyrrole-3-carboxylic acid methyl ester [40611-76-5] (100 mg, 0.72 mmol), Boc_2O (154 µL, 0.72 mmol), triethylamine (0.30 mL, 2.16 mmol) and anhydrous DCM (2 mL). The reaction mixture was stirred at rt for 18 h. H_2O, a saturated aqueous solution of $NaHCO_3$ 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 under reduced pressure to afford intermediate **I47** (170 mg, 99%).

Intermediate **I48**

1-*Tert*-butyl 3-methyl 5-methylpyrrolidine-1,3-dicarboxylate

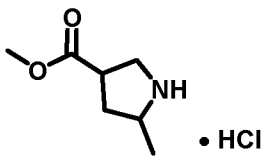


I48

In an autoclave, a mixture of intermediate **I47** (1.25 g, 5.22 mmol) and platinium on carbon (1 wt%, 4.1 g, 209 µmol) in EtOH (38 mL) was stirred at rt under 35 bar of H_2 for 16 h. Platinium on carbon (1 wt%, 1.02 g, 52 µmol) was added and the reaction mixture was stirred at rt under 40 bar of H_2. Platinium on carbon (1 wt%, 1.02 g, 52 µmol) was added and the reaction mixture was stirred at rt under 40 bar of H_2. The reaction mixture was filtered over Celite® and the filtrate was concentrated under reduced pressure. 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 80:20 to 0:100) to afford intermediate **I48** (850 mg, 67%) as a colorless oil.

Intermediate **I44**

Methyl 5-methylpyrrolidine-3-carboxylate hydrochloride



I44

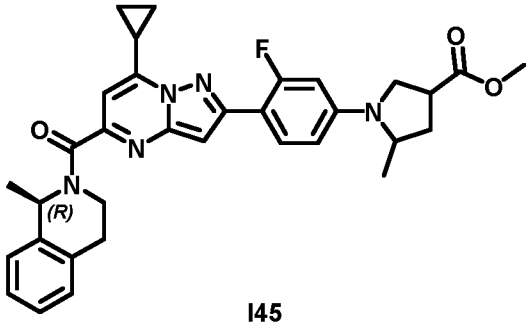
Hydrochloric acid (3.0 M in CPME, 12.5 mL, 37.5 mmol) was added dropwise to a solution of intermediate **I48** (850 mg, 3.49 mmol) in MeOH (5.0 mL). The reaction mixture was stirred at rt for 18 h and the solvent was removed under reduced pressure. The residue was co-evaporated with toluene to give intermediate **I44** (627 mg, quant.) as a colorless oil.

Synthesis of compounds 32, 33, 34 and 35

Intermediate **I45**

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

carboxylate

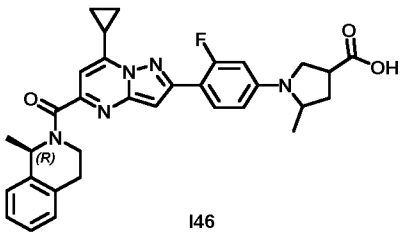


I45

A sealed tube was charged with (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] (703 mg, 1.39 mmol), intermediate **I44** (250 mg, 1.39 mmol) and cesium carbonate (1.36 g, 4.18 mmol) and purged with nitrogen. 1,4-Dioxane (11 mL) was added and the mixture was degassed with nitrogen. Palladium acetate (31.2 mg, 0.14 mmol) and XantPhos (80.5 mg, 0.14 mmol) were added. The reaction mixture was stirred at 100°C for 18 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 $MgSO_4$ and concentrated to dryness. 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 50:50) to afford intermediate **I45** (260 mg, 33%) as a yellowish solid.

Intermediate **I46**

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



I46

Lithium hydroxide monohydrate (151 mg, 3.59 mmol) was added to a solution of intermediate **I45** (680 mg, 1.20 mmol) in THF (27 mL) and H_2O (6.8 mL). The reaction mixture was stirred at rt for 16 h. A 10% aqueous solution of $KHSO_4$ was added until pH 6. The aqueous phase was extracted with EtOAc. The combined organic extracts were washed with H_2O, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The

crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 40 g GraceResolv™, liquid injection (DCM), mobile phase gradient: heptane / EtOAc / AcOH from 80:19.5:0.5 to 40:58.5:1.5) to afford intermediate **I46** (660 mg, quant.).

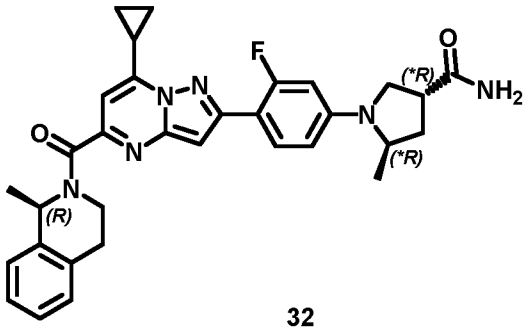
Compounds 32, 33, 34 and 35

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

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

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

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



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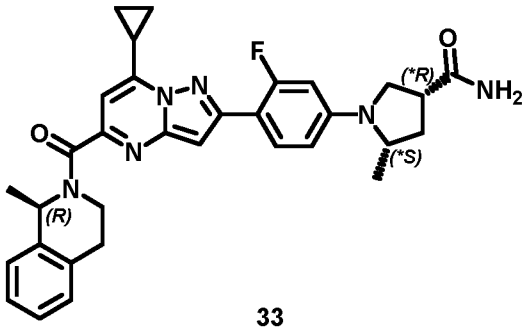
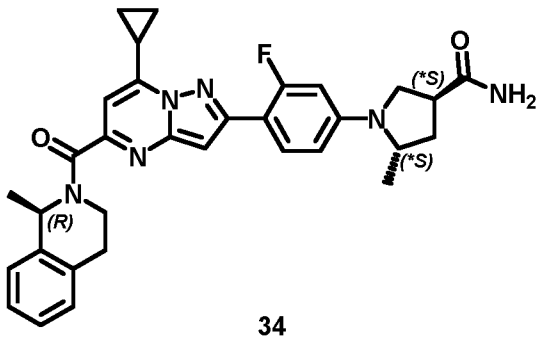
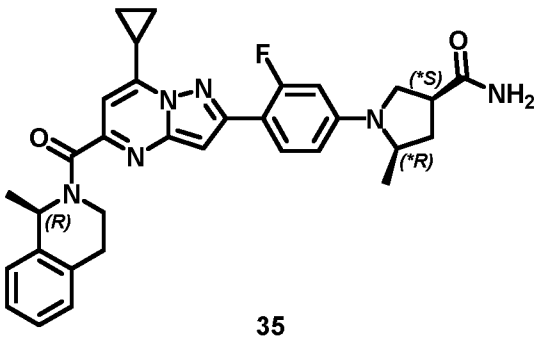


33



34



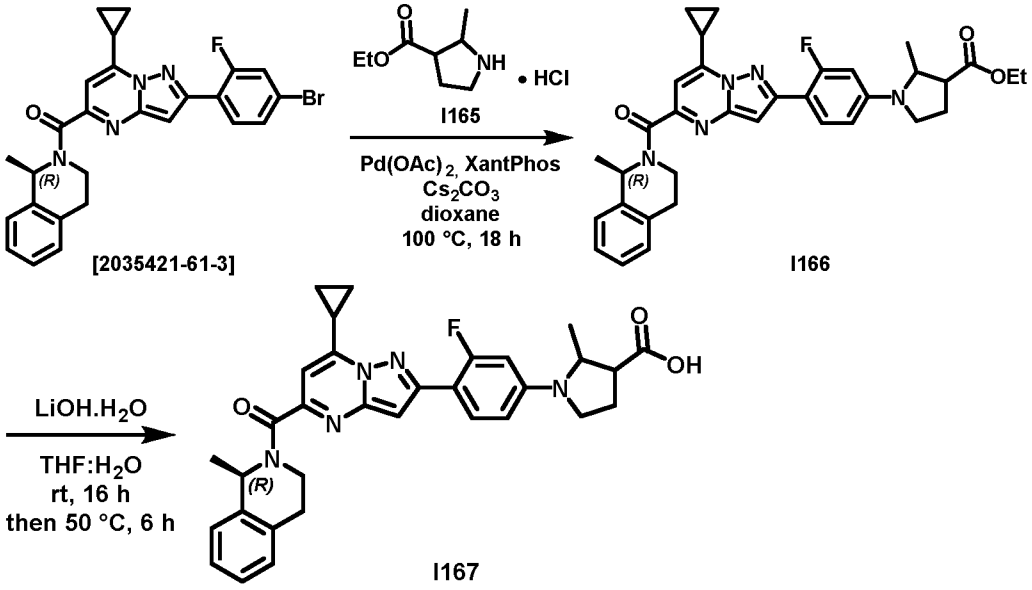
35

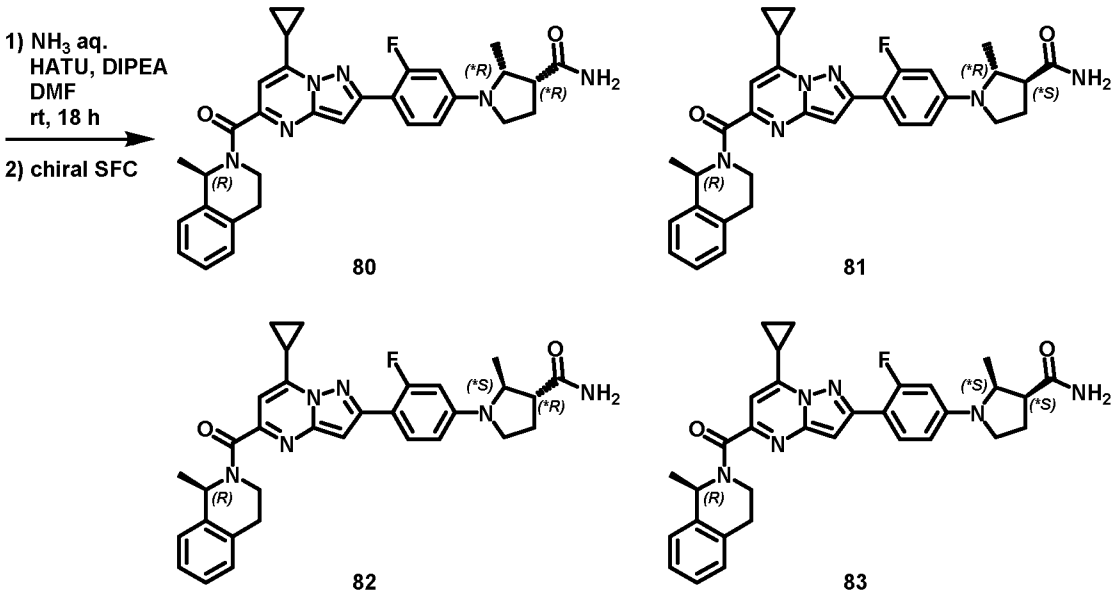
A mixture of intermediate **I46** (660 mg, 1.19 mmol), HATU (680 mg, 1.79 mmol) and DIPEA (616 µL, 3.58 mmol) in DMF (20 mL) was stirred at rt for 1 h. Ammonia (28% in H_2O, 403 µL, 5.96 mmol) was added and the reaction mixture was stirred at rt for 18 h. The reaction mixture was diluted with H_2O and EtOAc. The layers were separated and the

organic phase was washed with a 1% aqueous solution of $NaHCO_3$ (twice), dried over $MgSO_4$, filtered and evaporated 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: DCM / *i*-PrOH from 100:0 to 80:20) to afford a mixture of diasteroisomers (550 mg, 83%) as a yellow oil.

The sample was combined with another sample (123 mg) and the diastereoisomers were separated via chiral SFC (Stationary phase: CHIRACEL OJ-H 5µm 250*30mm, Mobile phase: 58% CO_2, 42% MeOH(0.3% *i*-$PrNH_2$)). Four fractions (A, B, C and D) were isolated. After evaporation of the solvent, the residue of fraction A was taken up in EtOH, the solid was filtered off and dried under vacuum at 50°C for 16 h to give compound **32** (94 mg, 11%). The residue of fraction B was crystallized from EtOAc, filtered off and dried under vacuum at 50°C for 16 h to give compound **35** (168 mg, 20%). The residue of fraction C was crystallized from EtOAc. The solid was filtered off and dried under vacuum at 50°C for 16 h to give compound **34** (94 mg, 11%). The residue of fraction D was taken-up in EtOH, the solid was filtered off and dried under vacuum at 50°C for 16 h to give compound **33** (164 mg, 20 %).

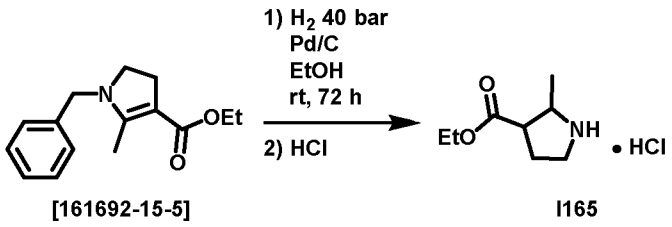
Compounds 80, 81, 82 and 83





Synthesis of intermediate **I165**

Ethyl 2-methylpyrrolidine-3-carboxylate hydrochloride

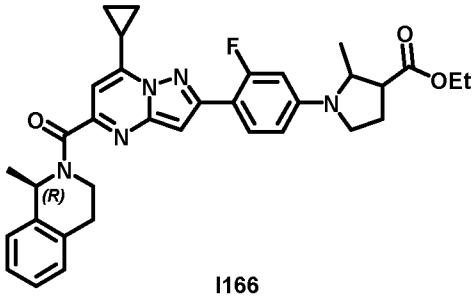


A mixture of ethyl 1-benzyl-2-methyl-4,5-dihydro-1H-pyrrole-3-carboxylate [161692-15-5] (3.60 g, 14.7 mmol) and Pd/C (10%, 1.56 g, 1.47 mmol) in EtOH (73 mL) was stirred at rt under hydrogen atmosphere (40 bars) for 72 h. The reaction mixture was filtered over a pad of Celite® and hydrogen chloride (3.0 M in CPME, 5.9 mL, 18 mmol) was added to the filtrate. The solvent was evaporated under vacuum to afford intermediate **I165** (2.6 g, 91%). The product was engaged in the next step as such.

Synthesis of compounds 80, 81, 82 and 83

Intermediate **I166**

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

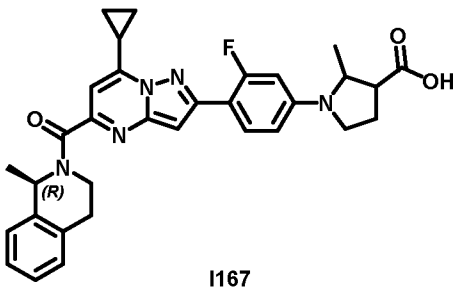


I166

In a sealed tube were added (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] (2.81 g, 5.56 mmol), intermediate **I165** (1.40 g, 7.23 mmol) and cesium carbonate (5.44 g, 16.7 mmol). The mixture was purged with nitrogen. 1,4-Dioxane (45 mL) was added and the mixture was degassed with nitrogen. Palladium acetate (125 mg, 556 µmol) and XantPhos (322 mg, 556 µmol) were added. The reaction mixture was stirred at 100°C for 18 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 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 **I166** (1.93 g, 60%) as a yellowish solid.

Intermediate **I167**

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



I167

Lithium hydroxide monohydrate (995 mg, 23.7 mmol) was added to a solution of intermediate **I166** (1.93 g, 3.32 mmol) in THF (34 mL) and H_2O (11 mL). The reaction mixture was stirred at rt for 16 h and at 50°C for 6 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 H_2O, 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™, liquid injection (DCM), mobile phase gradient: heptane / EtOAc / AcOH from 80:19.5:0.5 to 30:68:2 to afford intermediate **I167** (1.59 g, 87%).

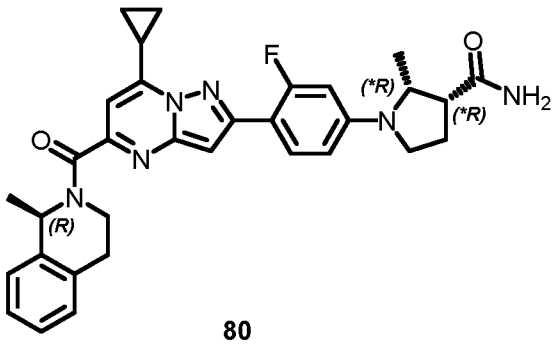
Compounds 80, 81, 82 and 83

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

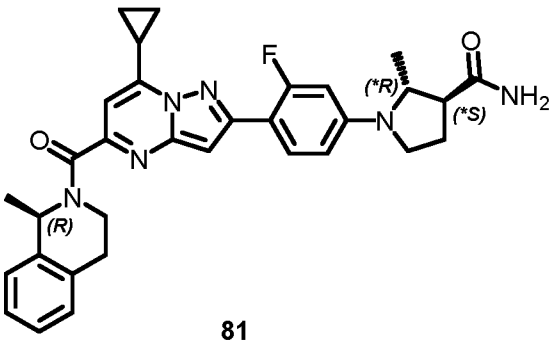
(2*R*,3*S*)-1-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)-2-methylpyrrolidine-3-carboxamide

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

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



80



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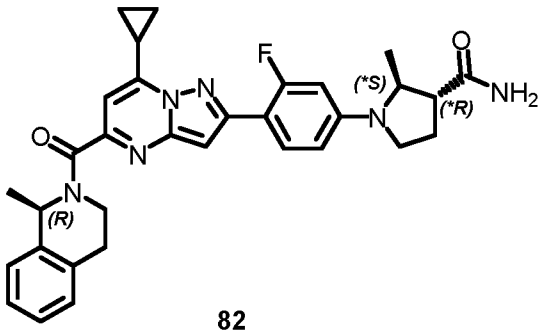
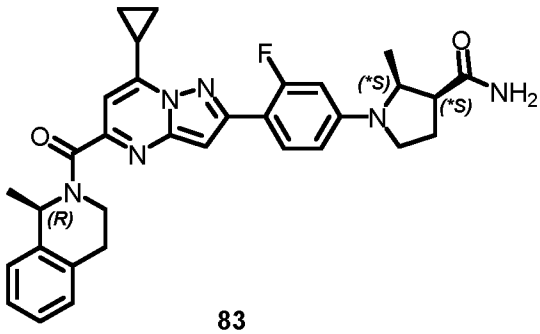


82

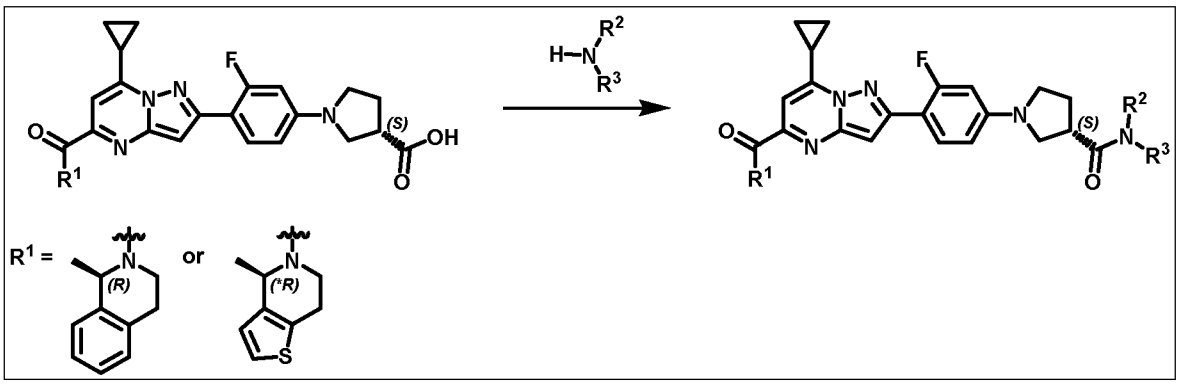


83

A mixture of intermediate **I167** (1.59 g, 2.87 mmol), HATU (1.64 g, 4.31 mmol) and DIPEA (1.49 mL, 8.62 mmol) in DMF (48 mL) was stirred at rt for 1 h. Ammonia (28% in H_2O, 1.0 mL, 14.4 mmol) was added and the reaction mixture was stirred at rt for 18 h. The reaction mixture was diluted with H_2O and EtOAc. The layers were separated and the organic phase was washed with 1% aqueous solution of $NaHCO_3$ (twice), dried over $MgSO_4$, filtered and evaporated in vacuo. The crude mixture was purified by preparative

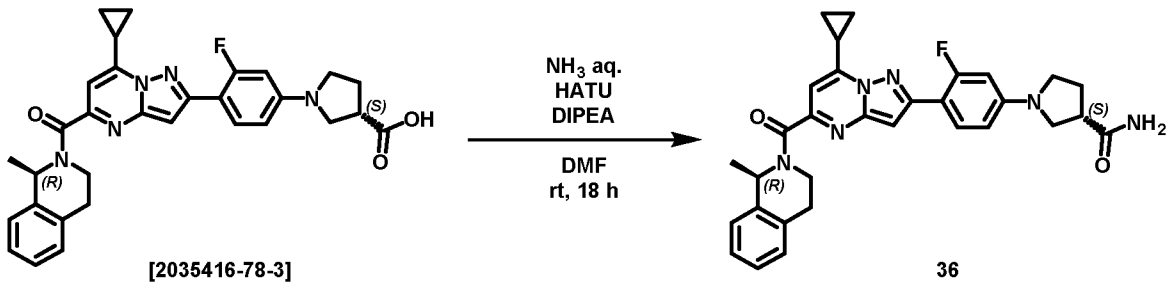
LC (irregular SiOH, 15-40 µm, 80 g GraceResolv™, liquid injection (DCM), mobile phase gradient: DCM / *i*-PrOH from 100:0 to 80:20) to deliver a mixture of diastereoisomers (1.3 g, 82%). The diastereoisomers (700 mg) were separated by chiral SFC (Stationary phase: CHIRALPAK AS-H 5µm 250*20mm, Mobile phase: 60% CO_2, 40% MeOH (0.3% *i*-$PrNH_2$)). The separated diastereoisomers were taken up in Et_2O. The solid was filtered off and dried under vacuum at 50°C for 16 h to give compound **81** (60 mg, 4%), compound **80** (180 mg, 11%) and compound **82** (65 mg, 4%). The last residue was taken up in EtOH. The solid was filtered off and dried under vacuum at 50°C for 16 h to give compound **83** (215 mg, 14%).

General Scheme



Compound 36

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

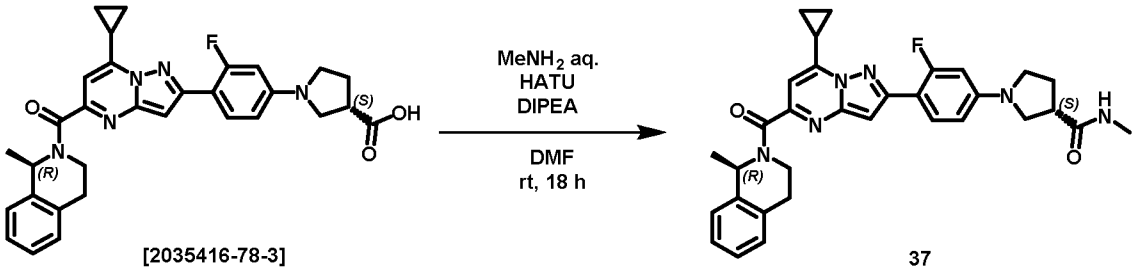


A mixture of (3*S*)-1-(4-{7-cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)pyrrolidine-3-carboxylic acid [2035416-78-3] (10.5 g, 18.4 mmol), HATU (10.5 g, 27.6 mmol) and DIPEA (10 mL, 58.0 mmol) in DMF (180 ml) was stirred at rt for 1 h. Ammonia (28% in H_2O, 15 mL, 222 mmol) was added and the reaction mixture was stirred at rt for 18 h. H_2O, 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 (3 times), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 330 g GraceResolv™, liquid injection (DCM), mobile phase gradient: DCM / MeOH from 100:0 to 98:2). The residue was crystallized from MeCN, filtered off and dried under vacuum at 50°C for 2 h to give compound **36** (6.47 g, 65%) as a yellow solid.

Compound 37

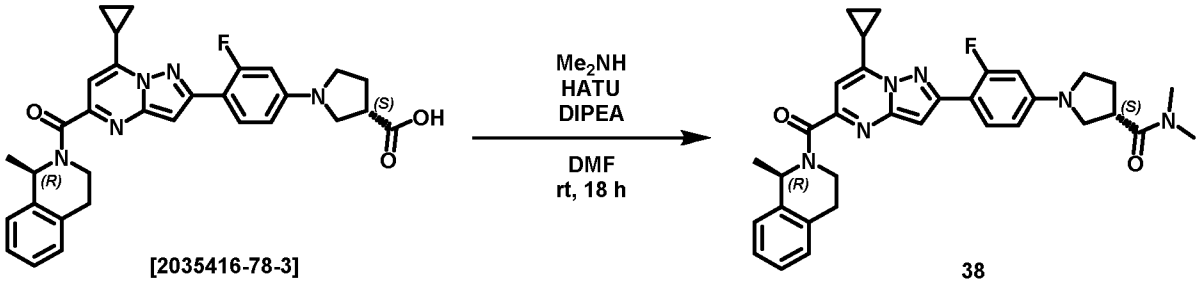
(3*S*)-1-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)-N-methylpyrrolidine-3-carboxamide



A mixture of (3*S*)-1-(4-{7-cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)pyrrolidine-3-carboxylic acid [2035416-78-3] (180 mg, 333 µmol), HATU (190 mg, 500 µmol) and DIPEA (172 µL, 1.00 mmol) in DMF (9 mL) was stirred at rt for 1 h. Methylamine (40% in H_2O, 144 µL, 1.67 mmol) was added and the reaction mixture was stirred at rt for 18 h. The reaction mixture was diluted with H_2O and EtOAc. The layers were separated and the organic phase was washed with a 1% aqueous solution of $NaHCO_3$ (twice), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 40 g GraceResolv™, liquid injection (DCM), mobile phase gradient: DCM / *i*-PrOH from 100:0 to 80:20) to give compound **37** (135 mg, 73%) as a yellow oil.

Compound 38

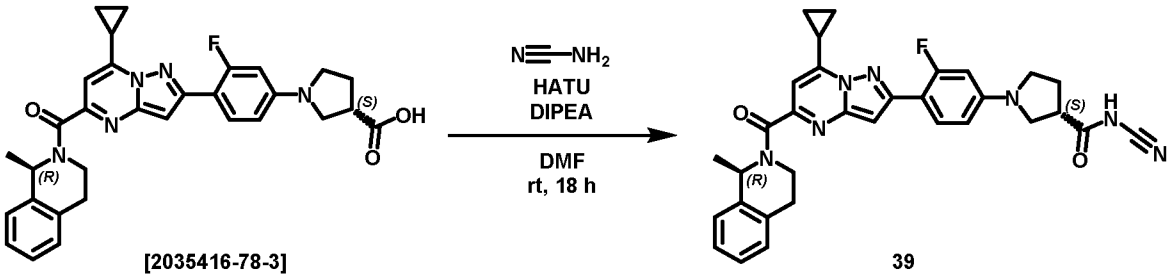
(3*S*)-1-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)-N,N-dimethylpyrrolidine-3-carboxamide



Compound **38** was synthesized from (3*S*)-1-(4-{7-cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)pyrrolidine-3-carboxylic acid [2035416-78-3] and dimethylamine (2.0 M in THF) [124-40-3] according to the procedure reported for the synthesis of compound **37**. 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 40:60 to 0:100) to give compound **38** (102 mg, 54%) as a yellow oil.

Compound 39

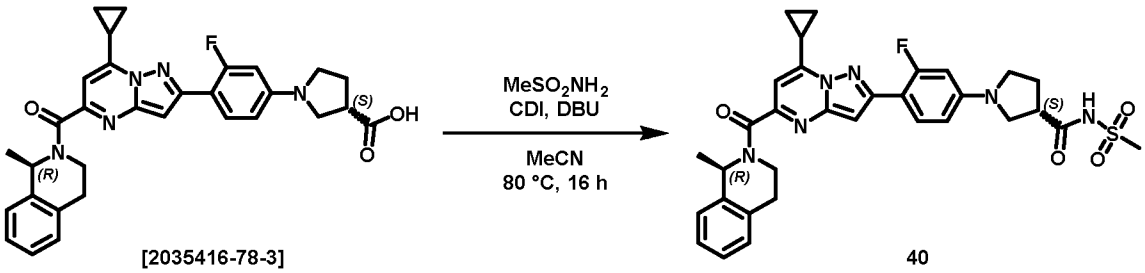
(3*S*)-N-Cyano-1-(4-{7-cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)pyrrolidine-3-carboxamide



Compound **39** was synthesized from (3*S*)-1-(4-{7-cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)-pyrrolidine-3-carboxylic acid [2035416-78-3] and cyanamide [420-04-2] according to the procedure reported for the synthesis of compound **37**. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 24 g GraceResolv™, liquid injection (DCM), mobile phase gradient: DCM / *i*-PrOH from 100:0 to 50:50) to give a yellow oil (90 mg). A second purification was performed 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 85:15 to 45:55) to give after freeze-drying compound **39** (70.0 mg, 27%) as a yellow solid.

Compound 40

(3*S*)-1-(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-methanesulfonylpyrrolidine-3-carboxamide

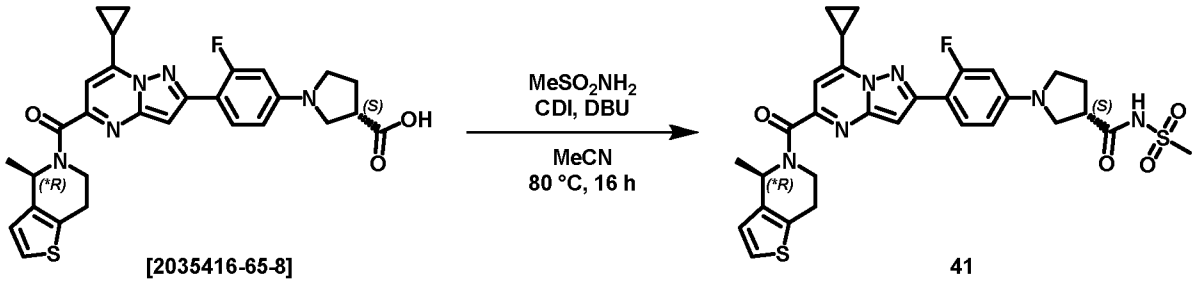


[2035416-78-3] 40

A mixture of (3*S*)-1-(4-{7-cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)pyrrolidine-3-carboxylic acid [2035416-78-3] (200 mg, 371 µmol) and CDI (180 mg, 1.11 mmol) in MeCN (5 mL) was stirred at rt for 2 h. DBU (221 µL, 1.48 mmol) and methanesulfonamide [3144-09-0] (141 mg, 1.48 mmol) were added and the reaction mixture was stirred at 80°C for 16 h. Brine, 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 under reduced pressure. The crude mixture was purified 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 85:15 to 45:55). The fractions containing the product were combined and 1N aqueous solution of HCl and EtOAc were added. The layers were separated and the aqueous phase was extracted. The organic phase was washed with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The mixture was purified 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 75:25 to 50:50). The residue (182 mg) was dissolved in MeCN (5 mL) and CDI (180 mg, 1.11 mmol) was added. The mixture was stirred at rt for 2 h and DBU (221 µL, 1.48 mmol) and methanesulfonamide (141 mg, 1.48 mmol) were added. The reaction mixture was stirred at 80°C for 16 h. Brine, an aqueous solution of 1N 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 under reduced pressure. The crude mixture was purified 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 85:15 to 45:55) to give after freeze-drying compound **40** (131 mg, 57%) as a yellow solid.

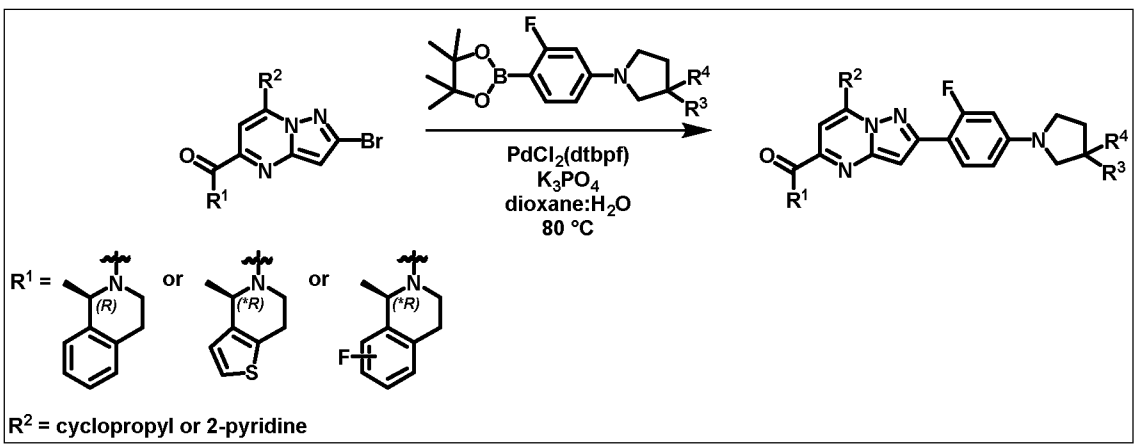
Compound 41

(3*S*)-1-(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-methanesulfonylpyrrolidine-3-carboxamide

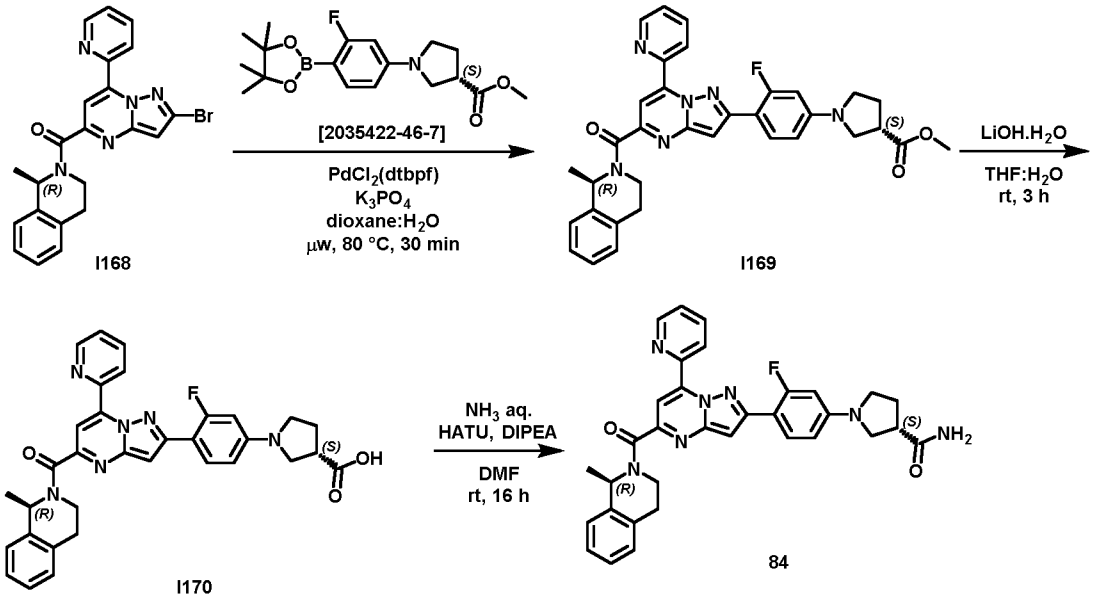


A mixture of (3*S*)-1-(4-{7-cyclopropyl-5-[(4**R*)-4-methyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine-5-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)pyrrolidine-3-carboxylic acid [2035416-65-8] (153 mg, 0.28 mmol) and CDI (54.6 mg, 0.34 mmol) in MeCN (3 mL) was stirred at rt for 2 h. DBU (62.8 µL, 0.42 mmol) and methanesulfonamide [3144-09-0] (40.0 mg, 0.42 mmol) were added. The resulting mixture was stirred at 80°C for 16 h. Brine, 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 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: DCM / MeOH from 100:0 to 99:1). The residue was crystallized from MeOH, filtered off and dried under high vacuum at 50°C for 18 h to give compound **41** (93 mg, 53%) as a yellow solid.

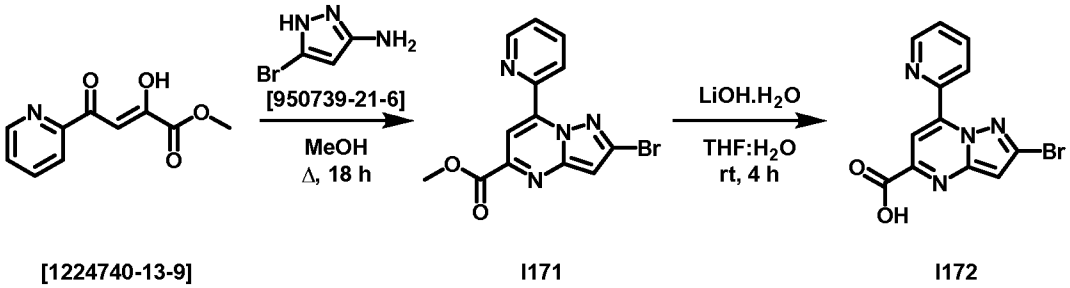
General Scheme

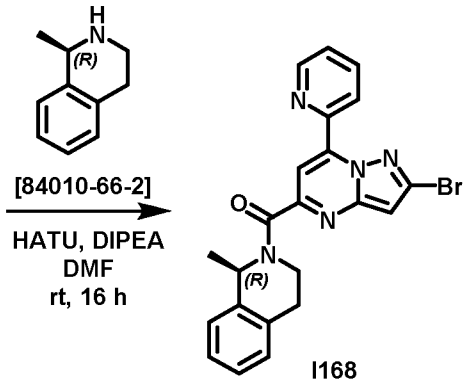


Compound 84



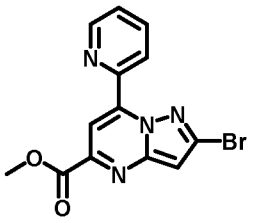
Synthesis of intermediate **I168**





Intermediate **I171**

Methyl 2-bromo-7-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidine-5-carboxylate

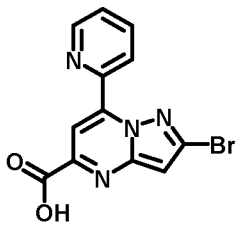


I171

A mixture of methyl 2-hydroxy-4-oxo-4-(pyridin-2-yl)but-2-enoate [1224740-13-9] (730 mg, 3.52 mmol) and 3-bromo-1H-pyrazol-5-amine [950739-21-6] (628 mg, 3.88 mmol) in MeOH (17 mL) was stirred under reflux for 18 h. The reaction mixture was cooled to rt and the precipitate was filtered off, rinsed with MeOH and dried. The residue (546 mg) was purified via achiral SFC (Stationary phase: Lux Cellulose-2 5µm 250*30mm, mobile phase: 60% CO_2, 40% MeOH) to afford intermediate **I171** (147 mg, 13%) as a yellow solid.

Intermediate **I172**

Methyl 2-bromo-7-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidine-5-carboxylic acid

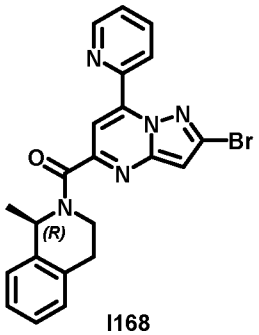


I172

Lithium hydroxide monohydrate (21.1 mg, 883 µmol) was added to a solution of intermediate **I171** (147 mg, 0.44 mmol) in THF (5 mL) and H_2O (2.5 mL). The reaction mixture was stirred at rt for 4 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 H_2O (twice), dried over $MgSO_4$, filtered and concentrated to dryness to afford intermediate **I172** (134 mg, 95%) as a yellow solid.

Intermediate **I168**

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



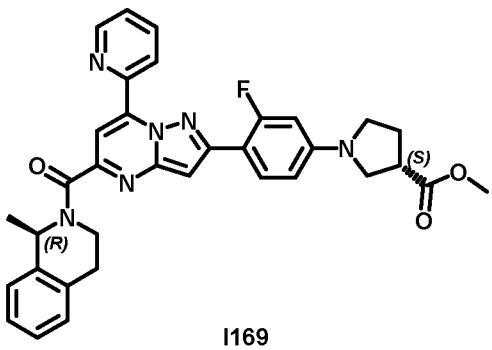
I168

HATU (207 mg, 546 µmol) was added to a mixture of intermediate **I172** (134 mg, 420 µmol), (1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline [84010-66-2] (68.0 mg, 462 µmol) and DIPEA (220 µL, 1.26 mmol) in DMF (3.8 mL). The reaction mixture was stirred at rt for 16 h. The reaction mixture was diluted with H_2O. 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 to dryness. The crude mixture was purified by flash chromatography (irregular SiOH, 15-40 µm, 12 g GraceResolv™, dry loading (SiOH), mobile phase gradient: heptane / EtOAc from 90:10 to 60:40) to afford intermediate **I168** (113 mg, 60%) as a yellow solid.

Synthesis of compound 84

Intermediate **I169**

Methyl (3*S*)-1-(3-fluoro-4-{5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-7-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidin-2-yl}phenyl)pyrrolidine-3-carboxylate



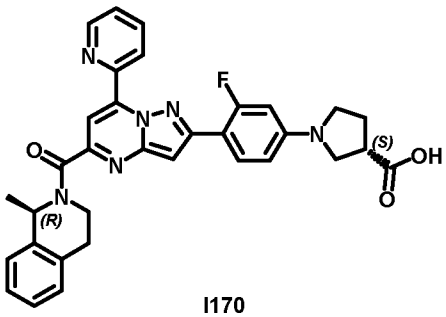
I169

A sealed tube was charged with intermediate **I168** (98.0 mg, 219 µmol), methyl (3*S*)-1-[3-fluoro-4-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrrolidine-3-carboxylate [2035422-46-7] (84.0 mg, 0.24 mmol), potassium phosphate tribasic (141 mg, 0.67 mmol), 1,4-dioxane (3.2 mL) and H_2O (0.6 mL) and purged with nitrogen. [1,1'-Bis(di-*tert*-butylphosphino)ferrocene] palladium dichloride (14.5 mg, 22.3 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 combined with another fraction (15 mg, 33.5 μmol) and diluted with H_2O and EtOAc. The layers were separated and the organic phase was washed with brine (twice), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude mixture was purified by flash chromatography (irregular SiOH, 15-40 μm, 12 g GraceResolv™, dry loading (SiOH), mobile phase gradient: heptane / EtOAc from 70:30 to 0:100) to afford intermediate **I169** (113 mg, 75%) as an orange foam.

Intermediate **I170**

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

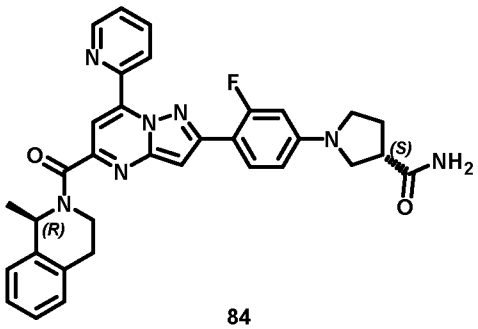


I170

Lithium hydroxide monohydrate (13.7 mg, 574 μmol) was added to a solution of intermediate **I169** (113 mg, 191 μmol) in THF (1.2 mL) and H_2O (0.6 mL). The reaction mixture was stirred at rt for 3 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 H_2O (twice), dried over $MgSO_4$, filtered and concentrated to dryness to afford intermediate **I170** (117 mg, quant., 95% purity) as an orange solid.

Compound 84

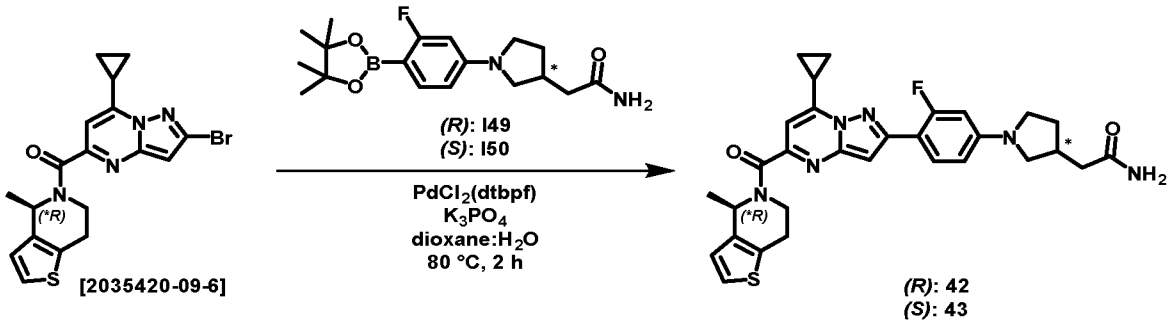
(3*S*)-1-(3-Fluoro-4-{5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-7-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidin-2-yl}phenyl)pyrrolidine-3-carboxamide



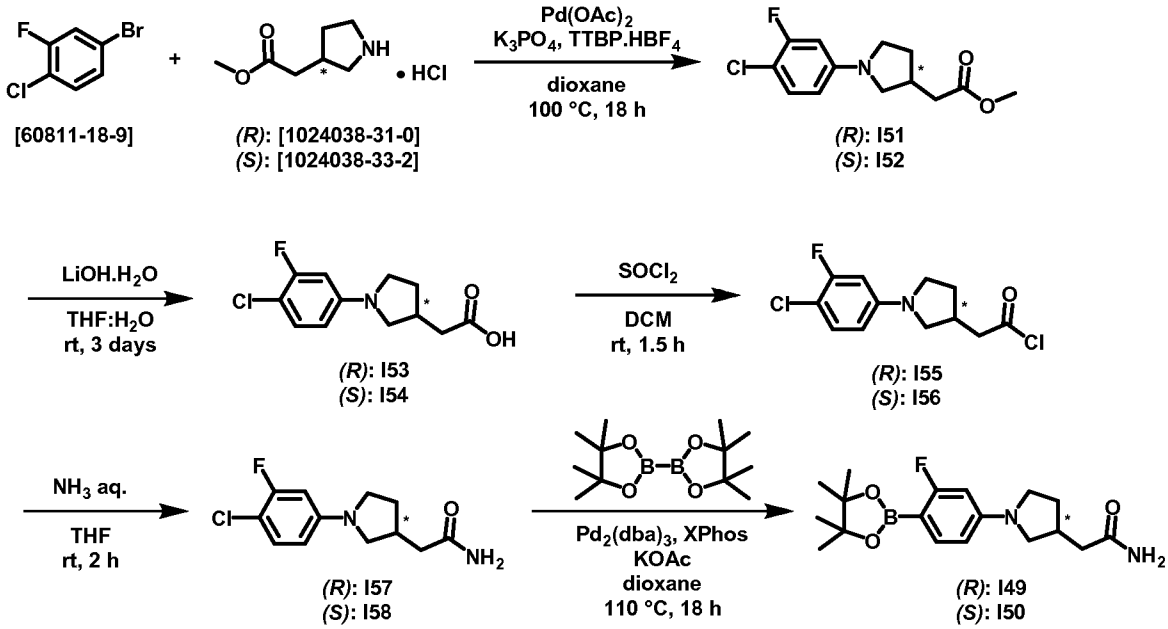
84

A mixture of intermediate **I170** (117 mg, 193 µmol, 95% purity), HATU (110 mg, 289 µmol) and DIPEA (100 µL, 578 µmol) in DMF (1.9 mL) was stirred at rt for 10 min. Ammonia (30% in H_2O, 365 µL, 5.78 mmol) was added and the reaction mixture was stirred at rt for 16 h. The reaction mixture was diluted with EtOAc and H_2O. The layers were separated and the organic phase was washed with H_2O and brine (twice), dried over $MgSO_4$, filtered and concentrated in vacuo. 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 (88 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 65:35 to 0:100). The fractions containing the product were combined, concentrated to dryness and co-evaporated with MeOH and MeCN (twice). The solid was dried under high vacuum at 60°C for 16 h to give compound **84** (58 mg, 52%) as an orange solid.

Compound 42 and Compound 43

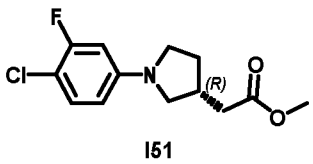


Synthesis of the intermediates **I49** and **I50**



Intermediate **I51**

Methyl 2-[(3*R*)-1-(4-chloro-3-fluorophenyl)pyrrolidin-3-yl]acetate

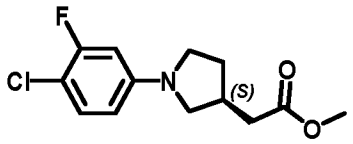


I51

A Schlenk tube was charged with 4-bromo-1-chloro-2-fluorobenzene [60811-18-9] (1.02 mL, 8.35 mmol), potassium phosphate tribasic (4.73 g, 22.3 mmol), methyl (3*R*)-3-pyrrolidinylacetate hydrochloride [1024038-31-0] (1.00 g, 5.57 mmol) and 1,4-dioxane (45 mL) and purged with nitrogen for 5 min. Tri-*tert*-butylphosphonium tetrafluoroborate (0.16 g, 0.56 mmol) and palladium acetate (62.5 mg, 0.28 mmol) were added and the reaction mixture was purged with nitrogen for 2 min. The reaction mixture was stirred at 100°C for 18 h. The reaction mixture was diluted with EtOAc and H_2O. 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 removed under reduced pressure. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 40 g GraceResolv™, liquid injection (DCM / heptane), mobile phase gradient: heptane / EtOAc from 80:20 to 60:40) to afford intermediate **I51** (880 mg, 58%) as a colorless oil.

Intermediate **I52**

Methyl 2-[(3*S*)-1-(4-chloro-3-fluorophenyl)pyrrolidin-3-yl]acetate

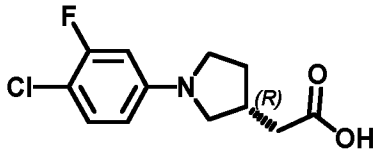


I52

Intermediate **I52** was synthesized from 4-bromo-1-chloro-2-fluorobenzene [60811-18-9] and methyl (3*S*)-3-pyrrolidinylacetate hydrochloride [1024038-33-2] according to the procedure reported for the synthesis of intermediate **I51**. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 40 g GraceResolv™, dry loading (SiOH), mobile phase: heptane / EtOAc 80:20) to afford intermediate **I52** (830 mg, 55%) as a colorless oil.

Intermediate **I53**

2-[(3*R*)-1-(4-Chloro-3-fluorophenyl)pyrrolidin-3-yl]acetic acid

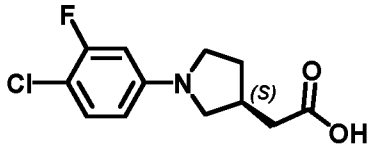


I53

Intermediate **I51** (880 mg, 3.24 mmol) was solubilized in THF (10 mL) and a solution of lithium hydroxide monohydrate (680 mg, 16.2 mmol) in H_2O (5 mL) was added. The reaction mixture was stirred at rt for 3 days. A 10% aqueous solution of $KHSO_4$ 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 under reduced pressure to afford intermediate **I53** (840 mg, quant.) as a white solid.

Intermediate **I54**

2-[(3*S*)-1-(4-Chloro-3-fluorophenyl)pyrrolidin-3-yl]acetic acid

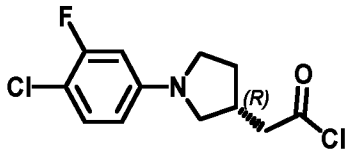


I54

Intermediate **I54** was synthesized from intermediate **I52** according to the procedure reported for the synthesis of intermediate **I53**. Intermediate **I54** (800 mg, quant.) was obtained as a white solid.

Intermediate **I55**

2-[(3*R*)-1-(4-Chloro-3-fluorophenyl)pyrrolidin-3-yl]acetyl chloride

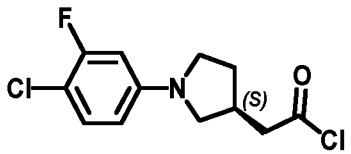


I55

Thionyl chloride (307 µL, 4.24 mmol) was added to a solution of intermediate **I53** (840 mg, 3.26 mmol) in DCM (30 mL). The reaction mixture was stirred at rt for 90 min. The mixture was evaporated under reduced pressure to afford intermediate **I55** (900 mg, quant.). The product was used in the next step without any purification.

Intermediate **I56**

2-[(3*S*)-1-(4-Chloro-3-fluorophenyl)pyrrolidin-3-yl]acetyl chloride

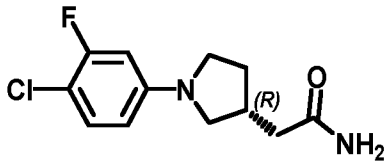


I56

Intermediate **I56** (856 mg, quant.) was synthesized from intermediate **I54** according to the procedure reported for the synthesis of intermediate **I55**.

Intermediate **I57**

2-[(3*R*)-1-(4-Chloro-3-fluorophenyl)pyrrolidin-3-yl]acetamide

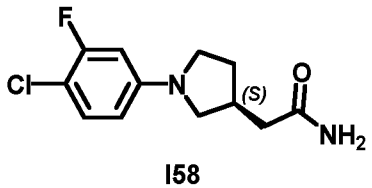


I57

Ammonia (28% in H_2O, 30 mL, 444 mmol) was added to a solution of intermediate **I55** (900 mg, 3.26 mmol) in THF (30 mL). The reaction mixture was stirred at rt for 2 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 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 / aq.NH_3 from 100:0:0 to 90:10:1) to afford intermediate **I57** (588 mg, 63%, 90% purity) as a white solid.

Intermediate **I58**

2-[(3*S*)-1-(4-Chloro-3-fluorophenyl)pyrrolidin-3-yl]acetamide

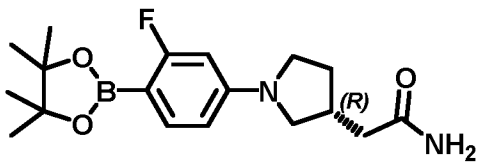


I58

Intermediate **I58** was synthesized from intermediate **I56** according to the procedure reported for the synthesis of intermediate **I57**. Intermediate **I58** (741 mg, 85%, 91% purity) was obtained as a white solid.

Intermediate **I49**

2-[(3*R*)-1-[3-Fluoro-4-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrrolidin-3-yl]acetamide

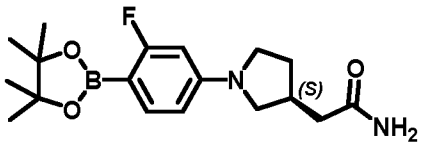


I49

A sealed tube was charged with intermediate **I57** (541 mg, 2.11 mmol), bis(pinacolato)diboron (0.64 g, 2.53 mmol), acetic acid potassium salt (0.41 g, 4.22 mmol) and 1,4-dioxane (14 mL) and purged with nitrogen for 10 min. XPhos (301 mg, 0.63 mmol) and tris(dibenzylideneacetone)dipalladium (193 mg, 0.21 mmol) were added and the reaction mixture was purged with nitrogen. The reaction mixture was stirred at 110°C for 18 h. The reaction mixture was filtered over Celite®. EtOAc and brine were 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 evaporated 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 100:0:0 to 90:10:1) to afford intermediate **I49** (587 mg, 67%, 84% purity) as a grey solid.

Intermediate **I50**

2-[(3*S*)-1-[3-Fluoro-4-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrrolidin-3-yl]acetamide



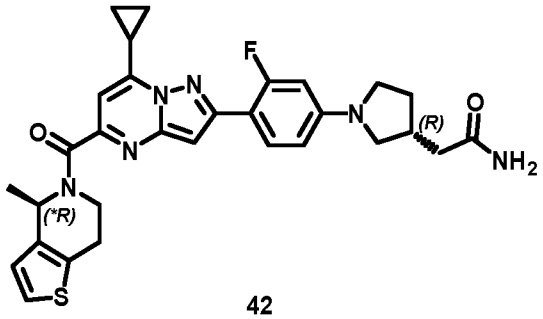
I50

Intermediate **I50** was synthesized from intermediate **I58** according to the procedure reported for the synthesis of intermediate **I49**. Intermediate **I50** (935 mg, 77%, 83% purity) was obtained as a grey solid.

Synthesis of compounds 42 and 43

Compound **42**

2-[(3*R*)-1-(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)pyrrolidin-3-yl]acetamide

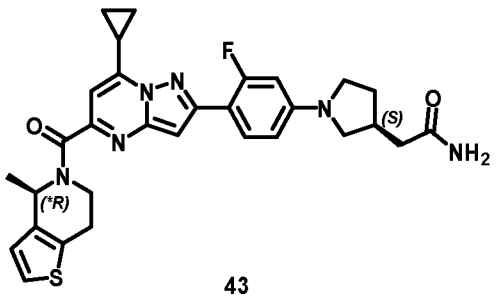


42

A sealed tube was charge with 2-bromo-7-cyclopropyl-5-[(4*R*)-4-methyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine-5-carbonyl]pyrazolo[1,5-a]pyrimidine [2035420-09-6] (200 mg, 0.479 mmol), intermediate **I49** (278 mg, 0.67 mmol, 84% purity), potassium phosphate tribasic (305 mg, 1.44 mmol), 1,4-dioxane (6 mL) and H_2O (2 mL) and purged with nitrogen. [1,1′-Bis(di-*tert*-butylphosphino)ferrocene] dichloropalladium (31.2 mg, 47.9 µmol) was added and the reaction mixture was purged with nitrogen. The reaction mixture was stirred at 80°C for 2 h. The reaction mixture was filtered over Celite®. EtOAc and brine were 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 evaporated 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 / aq.NH_3 from 100:0:0 to 96:4:0.4). The residue was co-evaporated with MeOH and triturated with MeOH. The solid was filtered off and dried under high vacuum at 50°C for 24 h to give compound **42** (115 mg, 43%) as a yellow solid.

Compound 43

2-[(3*S*)-1-(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)pyrrolidin-3-yl]acetamide

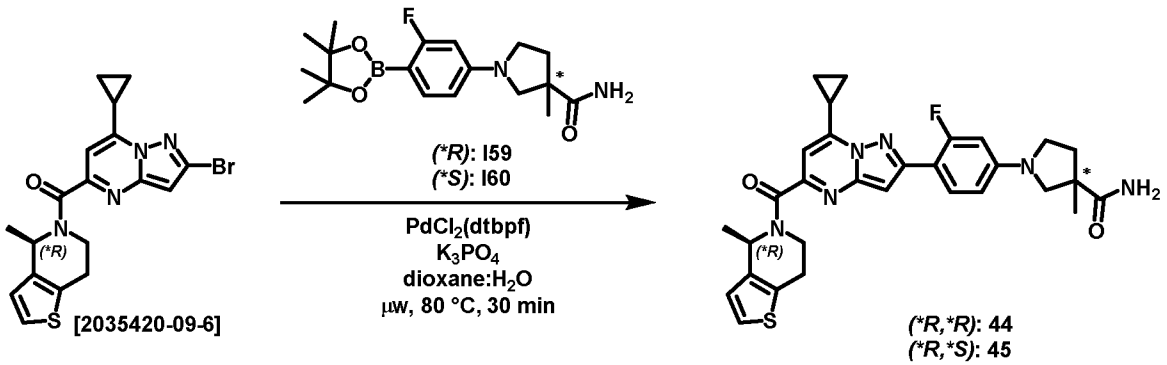


43

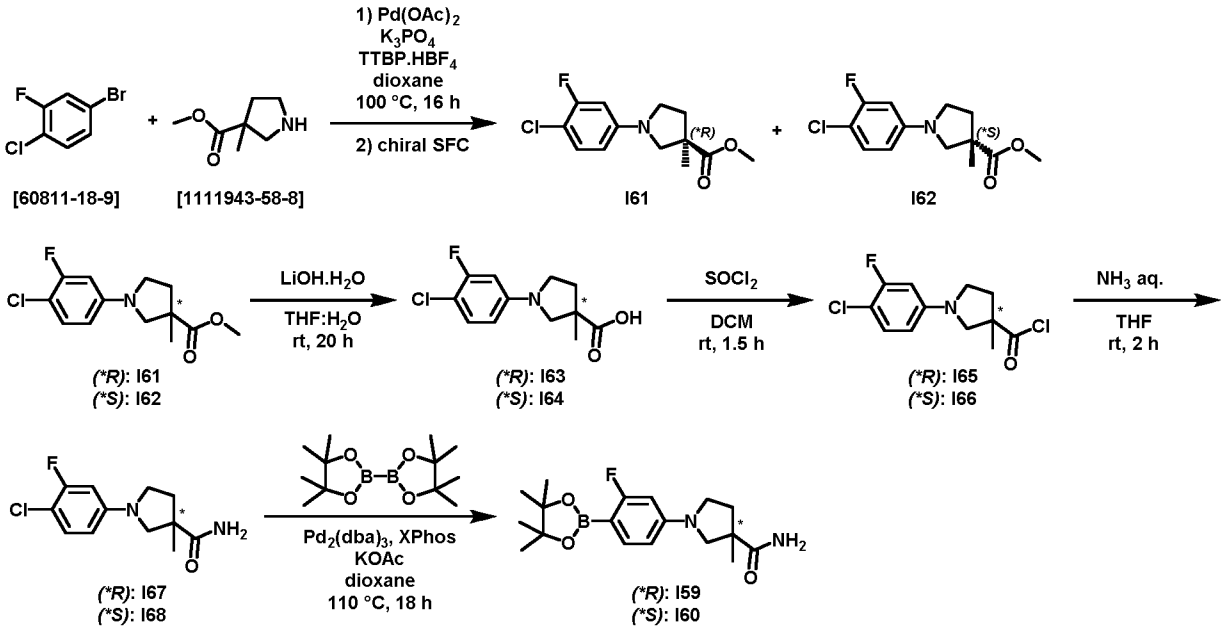
Compound **43** was synthesized from 2-bromo-7-cyclopropyl-5-[(4*R*)-4-methyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine-5-carbonyl]pyrazolo[1,5-a]pyrimidine [2035420-09-6]

and intermediate **I50** according to the procedure reported for the synthesis of compound **42**. Compound **43** (161 mg, 60%) was obtained as a yellow solid.

Compound 44 and Compound 45



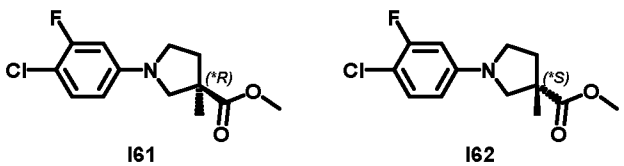
Synthesis of intermediates **I59** and **I60**



Intermediates **I61** and **I62**

(*R*)-Methyl 1-(4-chloro-3-fluorophenyl)-3-methylpyrrolidine-3-carboxylate

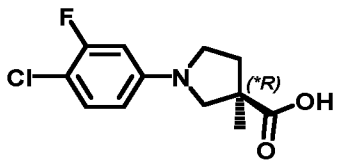
(*S*)-methyl 1-(4-chloro-3-fluorophenyl)-3-methylpyrrolidine-3-carboxylate



A sealed tube was charged with 4-bromo-1-chloro-2-fluorobenzene [60811-18-9] (4.0 mL, 32.8 mmol), potassium phosphate tribasic (15.3 g, 72.3 mmol), methyl 3-methylpyrrolidine-3-carboxylate [1111943-58-8] (3.45 g, 24.1 mmol), tri-*tert*-butylphosphonium tetrafluoroborate (638 mg, 2.20 mmol) and 1,4 dioxane (163 mL) and purged with nitrogen (3 times). Palladium acetate (247 mg, 1.10 mmol) was added and the reaction mixture was stirred at 100°C for 16 h. The reaction mixture was diluted with EtOAc and H_2O. 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 under reduced pressure. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 120 g GraceResolv™, liquid injection (heptane), mobile phase gradient: heptane / EtOAc from 100:0 to 70:30). The enantiomers (3.81 g) were separated via chiral SFC (Stationary phase: Whelk O1 (S,S) 5µm 250*21.1mm, Mobile phase: 90% CO_2, 10% MeOH) to afford **I61** (1.7 g, 26%) as a colorless oil and **I62** (1.67 g, 26%) as a colorless oil.

Intermediate **I63**

(3*R*)-1-(4-Chloro-3-fluorophenyl)-3-methylpyrrolidine-3-carboxylic acid

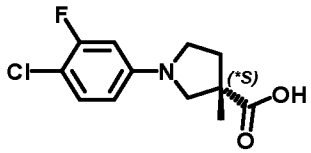


I63

In a sealed tube lithium hydroxide monohydrate (344 mg, 8.19 mmol) was added to a solution of intermediate **I61** (445 mg, 1.64 mmol) in THF (13 mL) and H_2O (6.5 mL). The reaction mixture was stirred at rt for 20 h. A 10% aqueous solution of $KHSO_4$ 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 under reduced pressure. The residue (465 mg) was taken up in Et_2O and evaporated under reduced pressure to afford intermediate **I63** (415 mg, 98%).

Intermediate **I64**

(3*S*)-1-(4-Chloro-3-fluorophenyl)-3-methylpyrrolidine-3-carboxylic acid

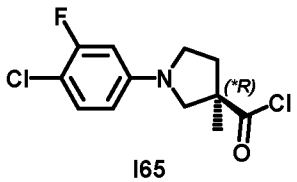


I64

Intermediate **I64** was synthesized from intermediate **I62** according to the procedure reported for the synthesis of intermediate **I63**. Intermediate **I64** (395 mg, 99%) was obtained as a yellow solid.

Intermediate **I65**

(3*R*)-1-(4-Chloro-3-fluorophenyl)-3-methylpyrrolidine-3-carbonyl chloride

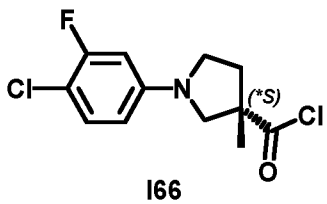


I65

Thionyl chloride (145 µL, 2.00 mmol) was added to a solution of intermediate **I63** (395 mg, 1.53 mmol) in DCM (14 mL). The reaction mixture was stirred at rt for 1.5 h. The mixture was evaporated under reduced pressure to afford intermediate **I65** (423 mg, quant.). The product was used in the next step without any purification.

Intermediate **I66**

(3*S*)-1-(4-Chloro-3-fluorophenyl)-3-methylpyrrolidine-3-carbonyl chloride

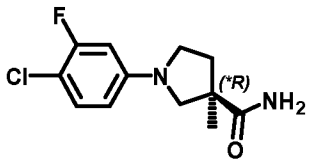


I66

Intermediate **I66** was synthesized from intermediate **I64** according to the procedure reported for the synthesis of intermediate **I65**. Intermediate **I66** (401 mg, quant.) was used in the next step without any purification.

Intermediate **I67**

(3*R*)-1-(4-Chloro-3-fluorophenyl)-3-methylpyrrolidine-3-carboxamide

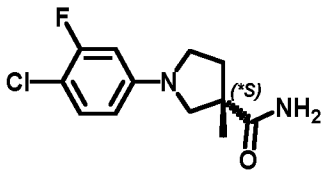


I67

Ammonia (28% in H_2O, 14 mL, 207 mmol) was added to a solution of intermediate **I65** (423 mg, 1.53 mmol) in THF (14 mL). The reaction mixture was stirred at rt for 2 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 under reduced pressure. The crude product was purified by preparative LC (irregular SiOH, 15-40 µm, 12 g GraceResolv™, liquid injection (DCM), mobile phase gradient: DCM / MeOH / aq.NH_3 from 100:0:0 to 90:10:1) to afford intermediate **I67** (286 mg, 73%) as a yellowish solid.

Intermediate **I68**

(3*S*)-1-(4-Chloro-3-fluorophenyl)-3-methylpyrrolidine-3-carboxamide

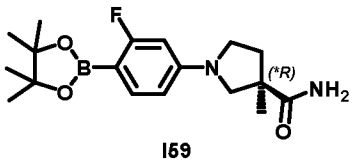


I68

Intermediate **I68** was synthesized from intermediate **I66** according to the procedure reported for the synthesis of intermediate **I67**. Intermediate **I68** (259 mg, 69%) was obtained as a yellowish solid.

Intermediate **I59**

(3*R*)-1-[3-Fluoro-4-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-3-methylpyrrolidine-3-carboxamide



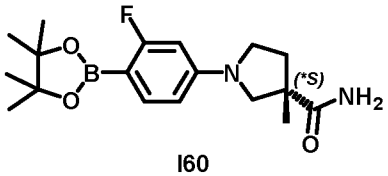
I69

A sealed tube was charged with intermediate **I67** (286 mg, 1.11 mmol), bis(pinacolato)diboron (567 mg, 2.23 mmol), acetic acid potassium salt (219 mg, 2.23

mmol) and 1,4-dioxane (10 mL) and was purged with nitrogen. Tris(dibenzylideneacetone)dipalladium (102 mg, 0.11 mmol) and XPhos (159 mg, 0.33 mmol) 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 H_2O. 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 under reduced pressure. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 24 g Grace®, dry loading (Celite®), mobile phase gradient: DCM / MeOH from 100:0 to 95:5) to afford intermediate **I59** (393 mg, 73%, 72% purity) as a yellowish oil that crystallized on standing.

Intermediate **I60**

(3*S)-1-[3-Fluoro-4-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-3-methylpyrrolidine-3-carboxamide



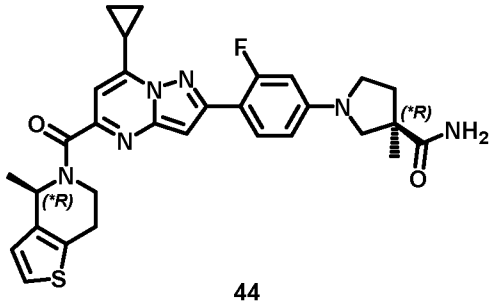
I60

Intermediate **I60** was synthesized from intermediate **I68** according to the procedure reported for the synthesis of intermediate **I59**. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 24 g Grace®, liquid injection (DCM), mobile phase gradient: DCM / MeOH from 100:0 to 95:5) to afford intermediate **I60** (449 mg, 89%, 70% purity) as a yellowish oil that crystallized on standing.

Synthesis of compounds 44 and 45

Compound 44

(3*R)-1-(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)-3-methylpyrrolidine-3-carboxamide

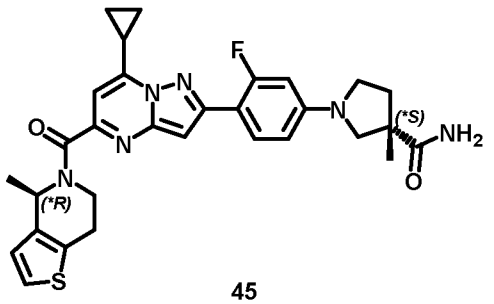


44

A sealed tube was charged with 2-bromo-7-cyclopropyl-5-[(4*R*)-4-methyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine-5-carbonyl]pyrazolo[1,5-a]pyrimidine [2035420-09-6] (248 mg, 0.59 mmol), intermediate **I59** (345 mg, 0.71 mmol, 72% purity), potassium phosphate tribasic (431 mg, 2.03 mmol), 1,4-dioxane (11 mL) and H_2O (4 mL) and purged with nitrogen. [1,1'-Bis(di-*tert*-butylphosphino)ferrocene] dichloropalladium (42.7 mg, 65.4 µmol) was added and the mixture was purged 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 H_2O. 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, 24 g GraceResolv™, mobile phase gradient: heptane / (EtOAc/MeOH 9:1) from 70:30 to 50:50). The residue was triturated with pentane and the solid was filtered off and dried under high vacuum at 50°C for 30 h to give compound **44** (193 mg, 58%) as a yellow solid.

Compound 45

(3*S*)-1-(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)-3-methylpyrrolidine-3-carboxamide

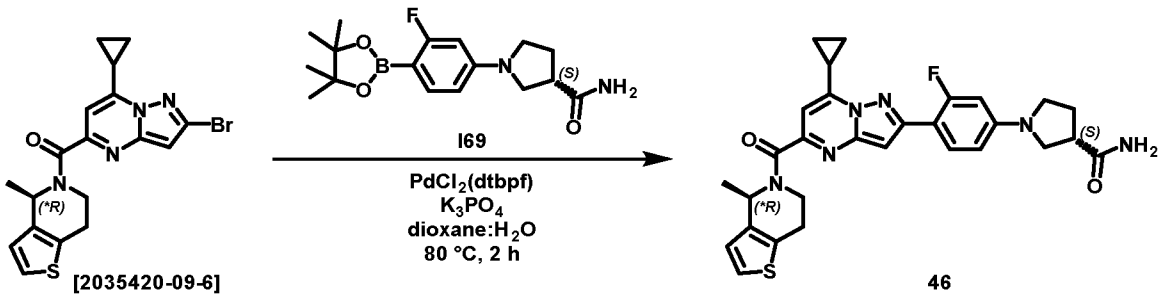


45

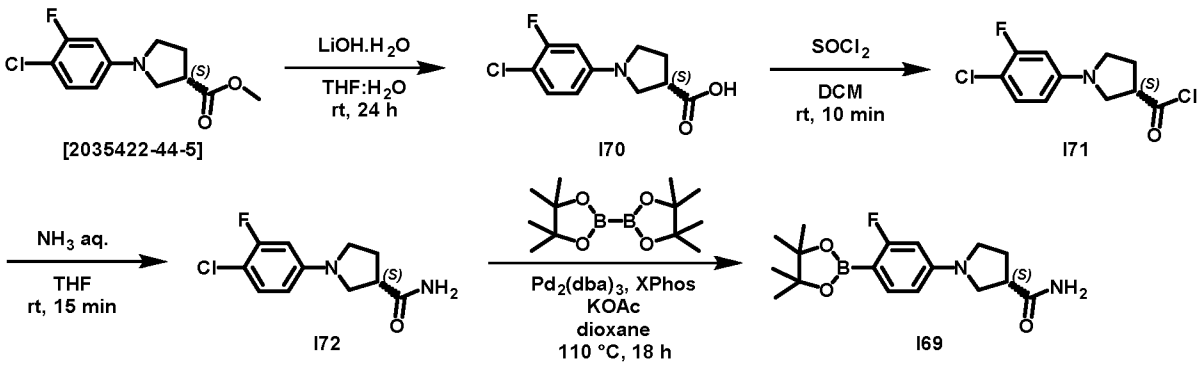
Compound **45** was synthesized from 2-bromo-7-cyclopropyl-5-[(4*R*)-4-methyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine-5-carbonyl]pyrazolo[1,5-a]pyrimidine [2035420-09-6]

and intermediate **I60** according to the procedure reported for the synthesis of compound **44**. Compound **45** (275 mg, 71%) was obtained as a yellow solid.

Compound 46

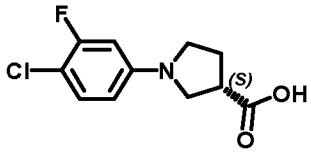


Synthesis of intermediate **I69**



Intermediate **I70**

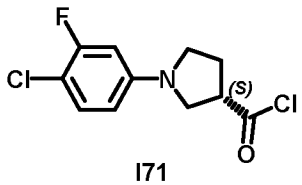
(3*S*)-1-(4-Chloro-3-fluorophenyl)pyrrolidine-3-carboxylic acid



Lithium hydroxide monohydrate (3.34 g, 79.6 mmol) was added to a solution of methyl (3*S*)-1-(4-chloro-3-fluorophenyl)pyrrolidine-3-carboxylate [2035422-44-5] (4.10 g, 15.9 mmol) in THF (100 mL) and H_2O (50 mL). The reaction mixture was stirred at rt for 24 h. A 10% aqueous solution of $KHSO_4$ 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 concentrated under reduced pressure to afford intermediate **I70** (3.8 g, 98%) as an orange solid.

Intermediate **I71**

(3*S*)-1-(4-Chloro-3-fluorophenyl)pyrrolidine-3-carbonyl chloride

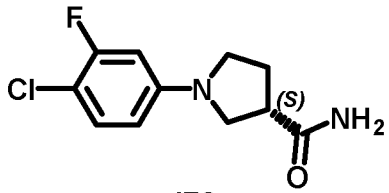


I71

Thionyl chloride (77.4 µL, 1.0.7 mmol) was added to a solution of intermediate **I70** (200 mg, 0.82 mmol) in DCM (8 mL). The reaction mixture was stirred at rt for 10 min and evaporated under reduced pressure to afford intermediate **I71** (215 mg, quant.).

Intermediate **I72**

(3*S*)-1-(4-Chloro-3-fluorophenyl)pyrrolidine-3-carboxamide

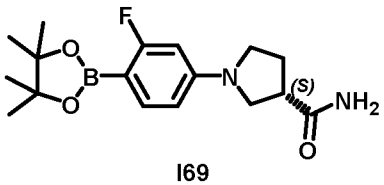


I72

Ammonia (28% in H_2O, 120 mL, 1.77 mol) was added to a solution of intermediate **I71** (3.23 g, 12.3 mmol) in THF (120 mL). The reaction mixture was stirred at rt for 15 min. 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 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: DCM / MeOH from 100:0 to 96:4) to afford intermediate **I72** (2.38 g, 80%) as a white solid.

Intermediate **I69**

(3*S*)-1-[3-Fluoro-4-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrrolidine-3-carboxamide

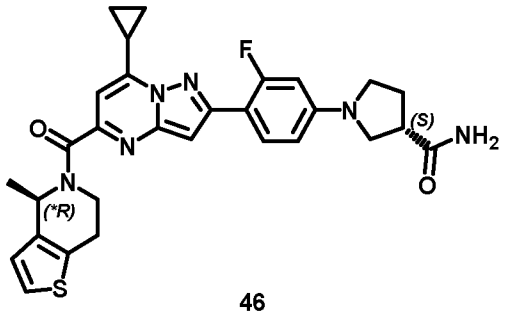


I69

A sealed tube was charged with intermediate **I72** (3.22 g, 13.3 mmol), bis(pinacolato)-dibroron (6.75 g, 26.6 mmol) and potassium acetate (2.61 g, 26.6 mmol) in 1,4-dioxane (115 mL) and purged with nitrogen. Tris(dibenzylideneacetone)dipalladium (1.22 g, 1.33 mmol) and XPhos (1.90 g, 3.98 mmol) were added and the mixture was purged with nitrogen. The reaction mixture was stirred at 110°C for 18 h. The reaction mixture was filtered over Celite®. EtOAc, brine and H_2O were added to the filtrate. 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 under reduced pressure. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 80 g Grace®, liquid injection (DCM), mobile phase gradient: DCM / MeOH from 100:0 to 96:4) to give intermediate **I69** (5.24 g, 78%, 66% purity) as a colorless oil.

Synthesis of compound **46**

(3*S*)-1-(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)pyrrolidine-3-carboxamide

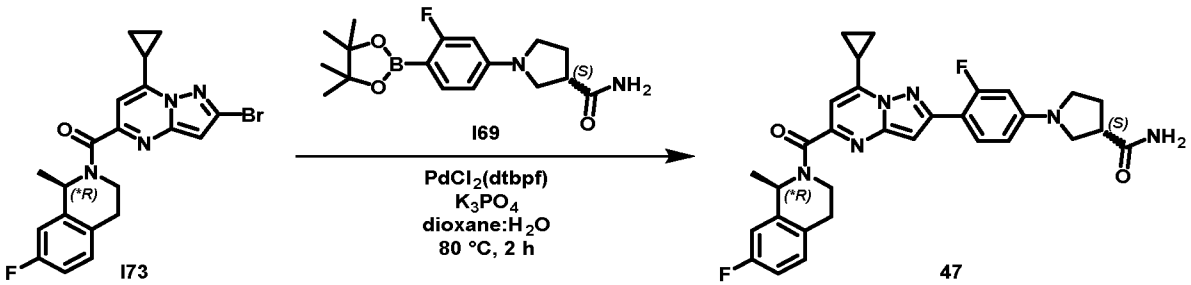


46

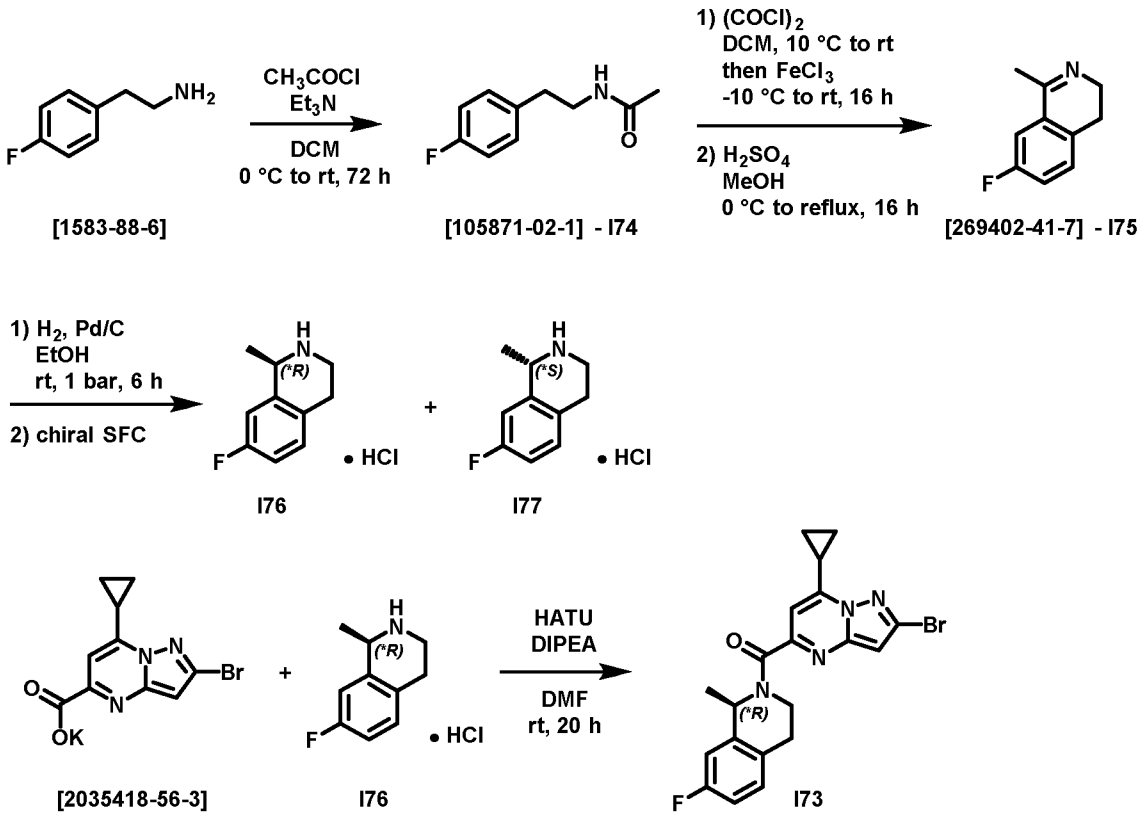
A sealed tube was charged with 2-bromo-7-cyclopropyl-5-[(4**R*)-4-methyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine-5-carbonyl]pyrazolo[1,5-a]pyrimidine [2035420-09-6] (200 mg, 0.48 mmol), intermediate **I69** (291 mg, 0.58 mmol, 66% purity), potassium phosphate (0.31 g, 1.44 mmol), 1,4-dioxane (5 mL) and H_2O (1.5 mL) and purged with nitrogen. [1,1′-Bis(di-*tert*-butylphosphino)ferrocene] dichloropalladium (23.4 mg, 35.9 µmol) was added and the mixture was purged with nitrogen. The reaction mixture was stirred at 80°C for 2 h. The reaction mixture was filtered over Celite®. EtOAc and brine were 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 under reduced pressure. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 80 g Grace®, liquid injection (DCM), mobile phase gradient: DCM / MeOH from 100:0 to 96:4). 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 24 h to give compound **46** (210 mg, 80%) as a yellow solid.

Compound 47

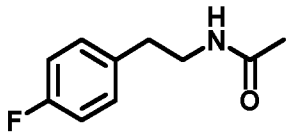


Synthesis of intermediate **I73**



Intermediate **I74**

N-[2-(4-Fluorophenyl)ethyl]acetamide

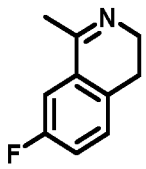


I74

Acetyl chloride (0.27 mmol, 20.0 mL) was added dropwise to a mixture of 2-(4-fluoro-phenyl)ethylamine [1583-88-6] (34.6 g, 249 mmol) and Et_3N (52.0 mL, 373 mmol) in DCM (200 mL) at 0°C. The resulting mixture was stirred at rt for 72 h. The reaction mixture was diluted with DCM. The mixture was washed with a 10 % aqueous solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered and the solvent was removed in vacuo to afford intermediate **I74** (48.2 g, quant.).

Intermediate **I75**

7-Fluoro-1-methyl-3,4-dihydroisoquinoline



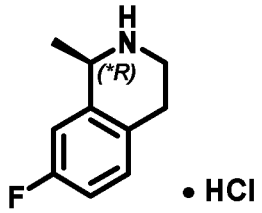
I75

Oxalyl chloride (2.0 M in DCM, 67.5 mL, 135 mmol) and oxalyl chloride neat (11.5 mL, 136 mmol) were added dropwise to a solution of intermediate **I74** (48.2 g, 266 mmol) in DCM (2.7 L) at 10°C. The resulting mixture was stirred at rt for 30 min and cooled down to -10°C. Iron chloride (III) [7705-08-0] (52.0 g, 0.32 mol) was added portionwise. The reaction mixture was stirred at rt for 16 h. The reaction mixture was quenched by the addition of a 3N aqueous solution of HCl and diluted with 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 the solvent was removed in vacuo. The residue (59.2 g) was dissolved in MeOH (2.4 L) and sulfuric acid (2.26 mol, 120 mL) was added dropwise carefully at 0°C. The resulting mixture was stirred under reflux for 16 h. The solvent was removed in vacuo. The residue was dissolved in DCM and a 3N aqueous solution of HCl was added. The layers were separated and the organic phase was washed with a 3N aqueous solution of HCl (once). The combined aqueous extracts were basified with ammonia (28% in H_2O) and extracted with DCM (twice). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was removed in vacuo to afford intermediate **I75** (34.3 g, 63%, 80% purity).

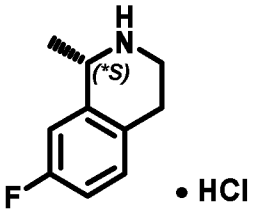
Intermediates **I76** and **I77**

(1*R*)-7-Fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride

(1*S*)-7-Fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride



I76



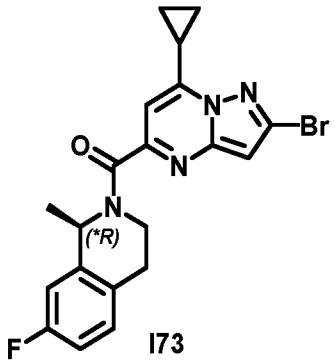
I77

The reaction was performed on 2 batches of 84 mmol of **I75**.

To a solution of intermediate **I75** (17.2 g, 84.0 mmol, 80%purity) in EtOH (500 mL) was added Pd/C (10 wt. %, 1.80 g, 1.70 mmol). The reaction mixture was stirred at rt under H_2 atmosphere (1 bar) for 6 h. The two batches were combined. The reaction mixture was filtered over Celite® and HCl (3.0 M in CPME, 67.2 mL, 0.20 mol) was added to the filtrate at 0°C. The resulting mixture was stirred at rt for 5 min and evaporated to dryness. The residue was triturated in Et_2O and the solid was filtered off to give a mixture of enantiomers (33 g) as a white solid. The enantiomers were separated via chiral SFC (Stationary phase: Chiralpak AD-H 5µm 250*30mm, Mobile phase: 78% CO_2, 22% *i*-PrOH (1.0% *i*-$PrNH_2$)) to give **I76** (11.5 g) and **I77** (15.5 g). Intermediate **I76** was taken up in HCl (3.0 M in CPME, 25 mL) and EtOH (10 mL). The resulting suspension was stirred for 5 min and Et_2O was added (200 mL). The solid was filtered off and dried to give intermediate **I76** (10.5 g, 31%). Intermediate **I77** was taken up in DCM and 1M aqueous solution of NaOH. The layers were separated and the aqueous phase was extracted with DCM (once). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed in vacuo. The residue (11.1 g) was dissolved in EtOH (100 mL) and HCl (3.0 M in CPME, 25 mL) was added at 0°C. The mixture was evaporated to dryness. The solid was triturated with Et_2O, filtered off and dried to give intermediate **I77** (11.6 g, 34%).

Intermediate **I73**

(1*R*)-2-{2-Bromo-7-cyclopropylpyrazolo[1,5-a]pyrimidine-5-carbonyl}-7-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline

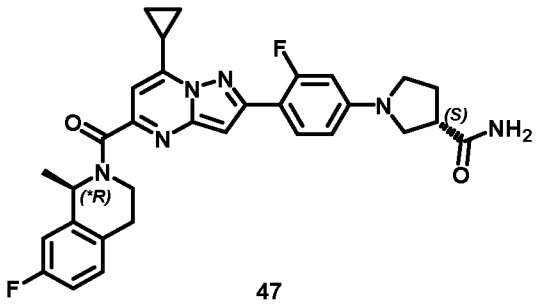


I73

To a mixture of potassium 2-bromo-7-cyclopropylpyrazolo[1,5-a]pyrimidine-5-carboxylate [2035418-56-3], intermediate **I76** (2.46 g, 12.3 mmol) and DIPEA (4.90 mL, 28.4 mmol) in DMF (54 mL) was added HATU (5.34 g, 14.1 mmol). The reaction mixture 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 under reduced pressure. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 220 g GraceResolv™, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 100:0 to 60:40). A first fraction of pure intermediate **I73** (1.20 g, 30%) was obtained, while the second fraction containing impurities was purified again by preparative LC (irregular SiOH, 40 µm 120 g, mobile phase: 100% DCM). A second crop of intermediate **I73** (1.3 g, 32%) was isolated. Intermediate **I73** (2.50 g, 62%) was obtained as a white foam.

Synthesis of compound 47

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

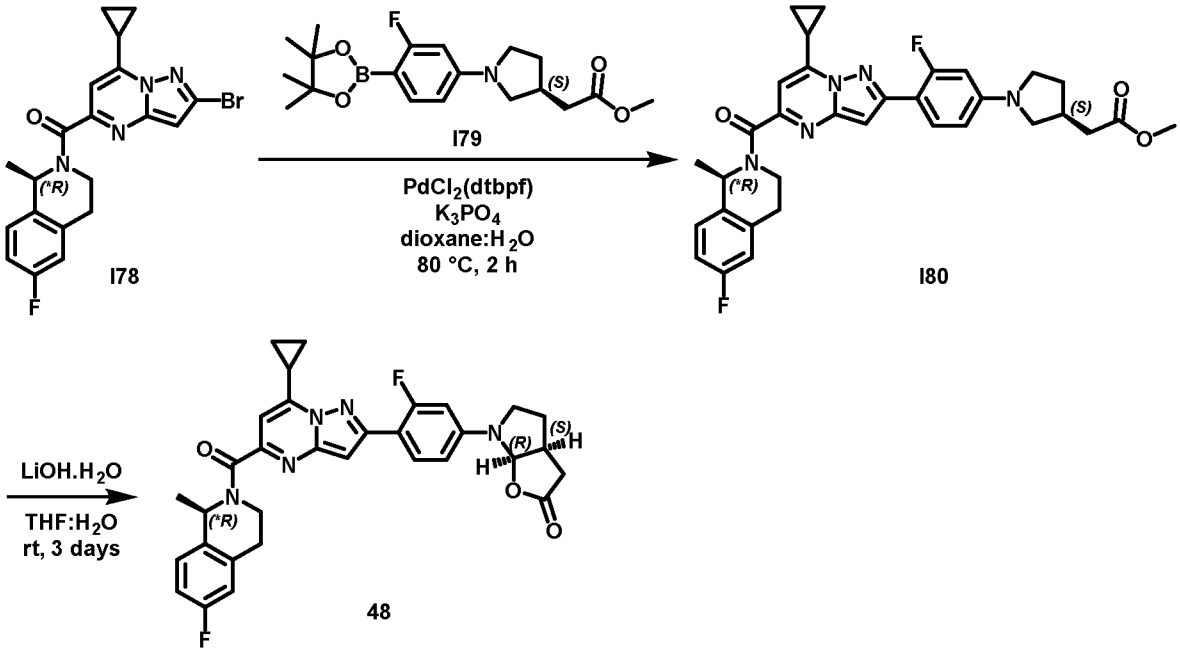


47

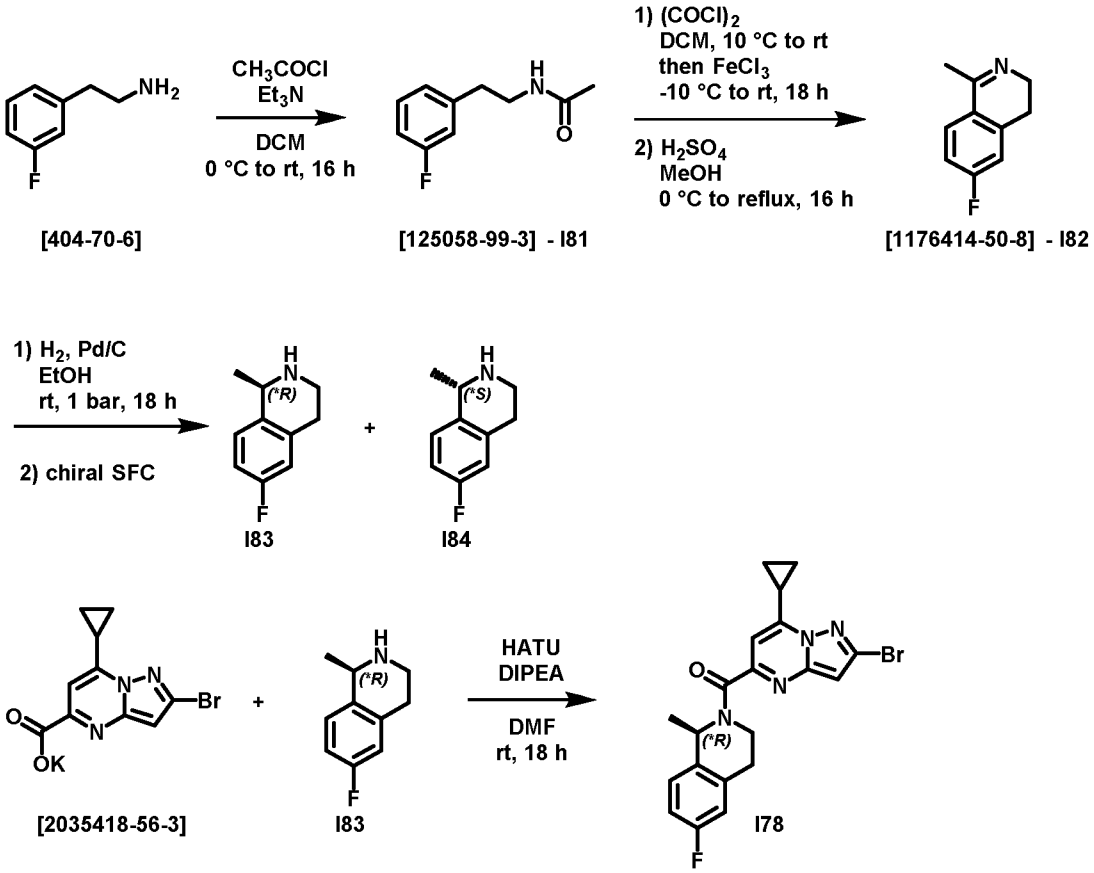
A sealed tube was charged with (1**R*)-2-{2-bromo-7-cyclopropylpyrazolo[1,5-a]pyrimidine-5-carbonyl}-7-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline **I73** (200 mg, 0.47 mmol), intermediate **I69** (283 mg, 0.56 mmol), potassium phosphate tribasic (297 mg, 1.40 mmol), 1,4-dioxane (5 mL) and H_2O (1.5 mL) and purged with nitrogen. [1,1′-Bis(di-

tert-butylphosphino)ferrocene] dichloropalladium (22.8 mg, 34.9 µmol) 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 Celite®. EtOAc and brine were 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 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: DCM / MeOH from 100:0 to 96:4). The pure fractions were combined while fractions containing impurities were subjected to a second purification by preparative LC (irregular SiOH, 15-40 µm, 80 g GraceResolv™, liquid injection (DCM), mobile phase gradient: DCM / MeOH from 100:0 to 98:2). 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 24 h to give compound **47** (185 mg, 71%) as a yellow solid.

Compound 48

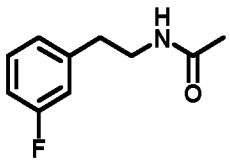


Synthesis of intermediate **I78**



Intermediate **I81**

N-[2-(3-Fluorophenyl)ethyl]acetamide

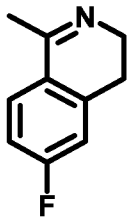


I81

Acetyl chloride (16.0 mL, 225 mmol) was added dropwise at 0°C to a mixture of 3-fluorophenethylamine [404-70-6] (25.0 g, 180 mmol) and Et_3N (38.5 mL, 270 mmol) in DCM (500 mL). The reaction mixture was stirred at rt for 16 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 washed with brine, dried over $MgSO_4$, filtered and the solvent was removed in vacuo to afford intermediate **I81** (35.3 g, quant.) as a yellow oil.

Intermediate **I82**

6-Fluoro-1-methyl-3,4-dihydroisoquinoline

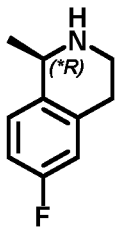


I82

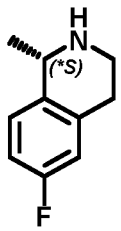
In a 5 L jacketed reactor equiped with a thermoregulator and mechanical stirring, oxalyl chloride (2.0 M in DCM, 108 mL, 216 mmol) was added dropwise to a solution intermediate **I81** (35.3 g, 180 mmol) in DCM (1.7 L) at 10°C. The resulting mixture was stirred at rt for 30 min and cooled down to -10°C. Iron chloride [7705-08-0] (35.0 g, 216 mmol) was added portionwise. The reaction mixture was stirred at rt for 18 h. The reaction mixture was quenched by the addition of a 3N aqueous solution of HCl and diluted with 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 the solvent was removed in vacuo. The residue (43.6 g) was dissolved in MeOH (1.6 L) in a 5 L jacketed reactor equiped with thermoregulator and mechanical stirring. Sulfuric acid (1.54 mol, 82.0 mL) was added dropwise carefully at 0°C. The resulting mixture was stirred under reflux for 16 h. The solvent was removed in vacuo. The residue was dissolved in DCM and a 3N aqueous solution of HCl was added. The layers were separated and the organic phase was washed with a 3N aqueous solution of HCl (twice). The combined aqueous extracts were basified with ammonia (28% in H_2O) and extracted with DCM (twice). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was removed in vacuo to afford intermediate **I82** (28.9 g, 90% purity).

Intermediates **I83** and **I84**

(1**R*)-6-Fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline (I83) and (1**S*)-6-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline (I84)



I83

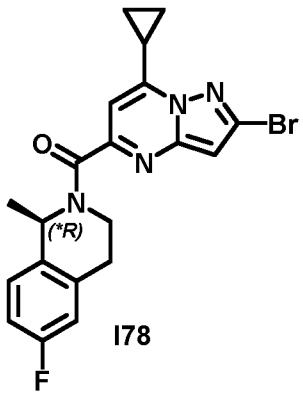


I84

EtOH (400 mL) and Pd/C (10%, 3.39 g, 3.19 mmol) were charged in a Parr flask. A solution of intermediate **I82** (28.9 g, 159 mmol, 90% purity) in EtOH (500 mL) was added. The reaction was pressurized with H_2 at 1 bar and stirred at rt for 18 h. The reaction mixture was filtered through a pad of Celite® and rinsed with MeOH. The filtrate was treated with HCl (3.0 M in CPME, 63.8 mL, 191 mmol) at 0°C. The resulting mixture was stirred at rt for 5 min and evaporated to dryness. The residue was triturated in Et_2O and the solid was filtered off. The solid was purified by preparative LC (irregular SiOH, 15-40 µm, 330 g Grace®, dry loading (Celite®), mobile phase gradient: DCM / MeOH / aq.NH_3 from 98:2:0.2 to 96:4:0.4) to afford a mixture of enantiomers (20.3 g). The enantiomers were separated via chiral SFC (Stationary phase: Chiralpak AD-H 5 µm 250*30 mm, Mobile phase: 80% CO_2, 20% *i*-PrOH (0.3% *i*-$PrNH_2$)) to give **I83** (9.73 g) and **I84** (9.68 g). The enantiomers were treated separately. Intermediates **I83** and **I84** were dissolved in EtOAc and an aqueous solution of $NaHCO_3$ was added. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were dired over MgSO4, filtered and the solvent was removed in vacuo to give intermediates **I83** (8.74 g, 32%) and **I84** (8.34 g, 30%) as colorless oils.

Intermediate **I78**

(1**R*)-2-{2-Bromo-7-cyclopropylpyrazolo[1,5-a]pyrimidine-5-carbonyl}-6-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline



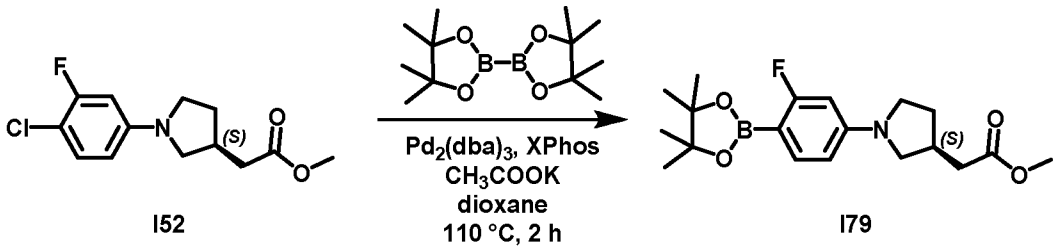
I78

HATU (6.91 g, 18.2 mmol) was added to a mixture of potassium 2-bromo-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-5-carboxylate [2035418-56-3] (3.23 g, 10.1 mmol), intermediate **I83** (2.00 g, 12.1 mmol) and DIPEA (4.35 mL, 25.2 mmol) in DMF (50 mL). The reaction mixture was stirred at rt for 18 h. A saturated aqueous solution of $NaHCO_3$, brine, H_2O and EtOAc were added. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with a solution of brine

and water (9:1) (3 times), dried over $MgSO_4$, filtered, rinsed with EtOAc and evaporated 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 90:10 to 70:30) to give intermediate **I78** (4.5 g, quant.) as a white gum.

Synthesis of intermediate **I79**

Methyl 2-[(3*S*)-1-[3-fluoro-4-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrrolidin-3-yl]acetate



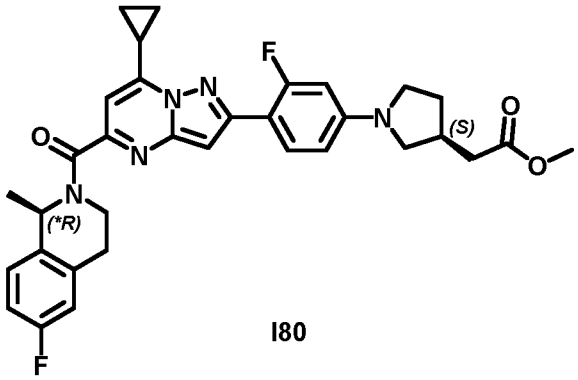
I52 I79

A sealed tube was charged with intermediate **I52** (1.40 g, 5.15 mmol), bis(pinacolato)-diboron (1.57 g, 6.18 mmol), acetic acid potassium salt (1.01 g, 10.3 mmol) and 1,4-dioxane (35 mL) and purged with nitrogen. XPhos (737 mg, 1.55 mmol) and tris(dibenzylideneacetone)dipalladium (472 mg, 0.52 mmol) were added and the mixture was purged with nitrogen. The reaction mixture was stirred at 100°C for 18 h and then at 110°C for 2 h. The reaction mixture was filtered over a pad of Celite®. EtOAc and brine were 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 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 95:5 to 80:20) to give intermediate **I79** (1.1 g, 59%) as a grey solid.

Synthesis of compound **48**

Intermediate **I80**

Methyl 2-[(3*S*)-1-(4-{7-cyclopropyl-5-[(1**R*)-6-fluoro-1-methyl-1,2,3,4-tetrahydro-isoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)pyrrolidin-3-yl]acetate

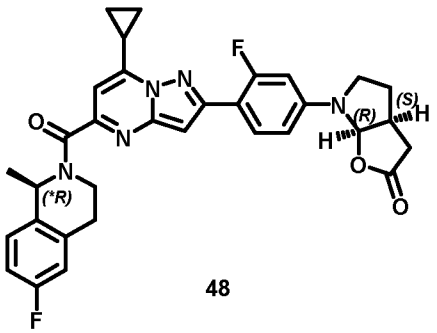


I80

A sealed tube was charged with intermediate **I78** (253 mg, 0.59 mmol), intermediate **I79** (300 mg, 0.83 mmol), potassium phosphate tribasic (376 mg, 1.77 mmol), 1,4-dioxane (7 mL) and H_2O (2.5 mL) and purged with nitrogen. [1,1'-bis(di-*tert*-butylphosphino)-ferrocene] palladium dichloride (38.4 mg, 59.0 µmol) was added. The reaction mixture was purged with nitrogen and stirred at 80°C for 2 h. The reaction mixture was filtered over Celite®. EtOAc and brine were 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 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) to afford intermediate **I80** (271 mg, 75%, 95% purity) as a yellow solid.

Compound 48

(3a*S*,6a*R*)-6-(4-{7-Cyclopropyl-5-[(1**R*)-6-fluoro-1-methyl-1,2,3,4-tetrahydro-isoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)-hexahydro-2H-furo[2,3-b]pyrrol-2-one

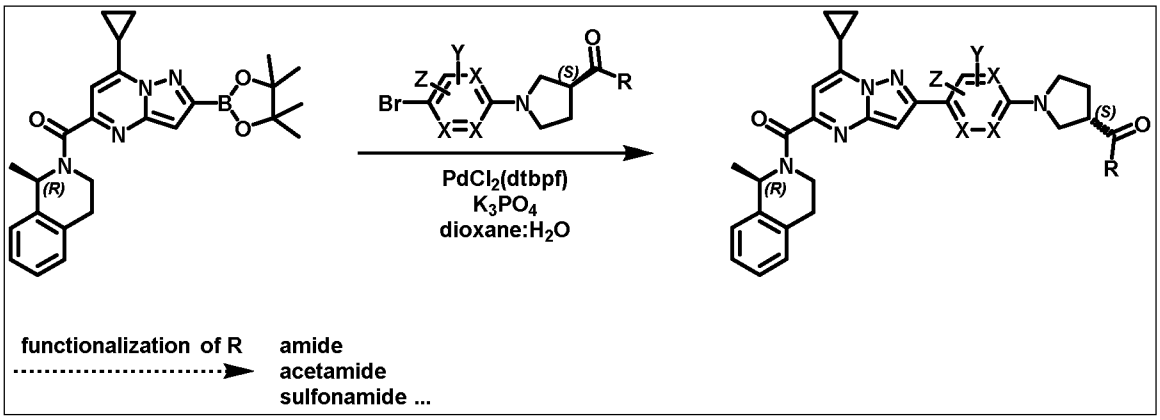


48

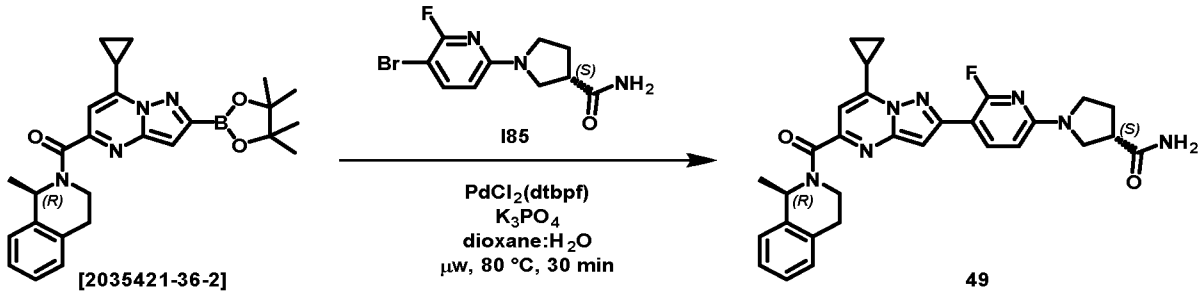
Intermediate **I80** (271 mg, 0.44 mmol, 95% purity) was solubilized in THF (5 mL) and a solution of lithium hydroxide monohydrate (92.2 mg, 2.19 mmol) in H_2O (2.5 mL) was added. The reaction mixture was stirred at rt for 3 days. Brine, a 10% aqueous solution of $KHSO_4$ and EtOAc were added. The layers were separated and the aqueous phase was

extracted with EtOAc (twice). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude mixture was purified by preparative LC (regular SiOH, 30 µm, 25 g Interchim®, liquid injection (DCM), mobile phase gradient: heptane / EtOAc / AcOH from 90:10:0.25 to 60:40:1). 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 2 days to afford a white solid (250 mg). The batch was split in two samples A and B that were purified independently by preparative LC (Stationary phase: irregular SiOH 40 g, Mobile phase: 98% DCM, 2% MeOH). Compound **48** was dried under high vacuum to give a yellow solid (50 mg, 20%).

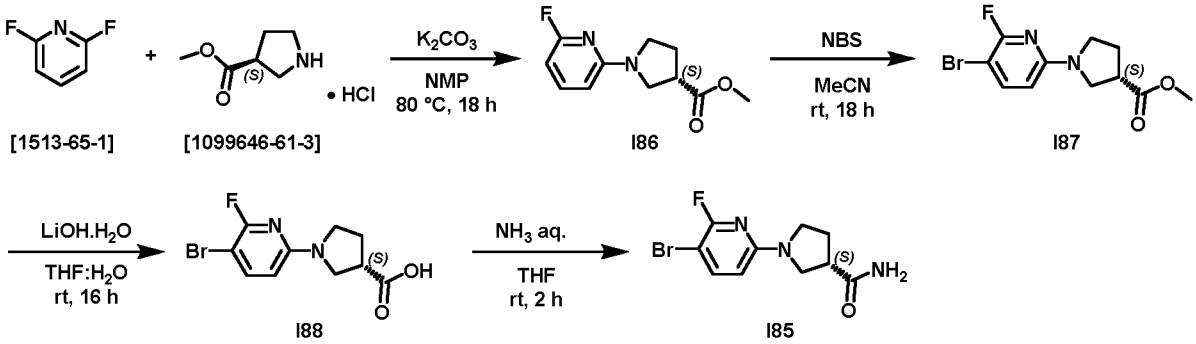
General Scheme



Compound 49

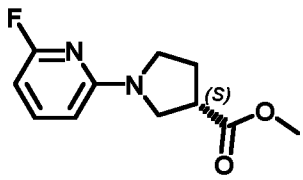


Synthesis of intermediate **I85**



Intermediate **I86**

Methyl (3*S*)-1-(6-fluoropyridin-2-yl)pyrrolidine-3-carboxylate

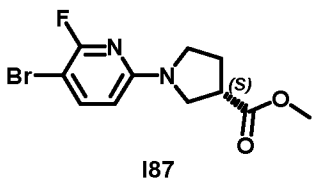


I86

A mixture of 2,6-difluoropyridine [1513-65-1] (1.00 g, 8.69 mmol), (*S*)-3-methyl pyrrolidine-3-carboxylate hydrochloride [1099646-61-3] (1.58 g, 9.56 mmol) and potassium carbonate (3.60 g, 26.1 mmol) in NMP (65 mL) was stirred at 80°C for 18 h. The reaction mixture was diluted with EtOAc and H_2O. The layers were separated and the aqueous phase was extracted with EtOAc (5 times). The organic extracts were combined and the solvent was removed under reduced pressure. 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 100:0 to 50:50) to afford intermediate **I86** (1.6 g, 82%) as a colorless oil.

Intermediate **I87**

Methyl (3*S*)-1-(5-bromo-6-fluoropyridin-2-yl)pyrrolidine-3-carboxylate

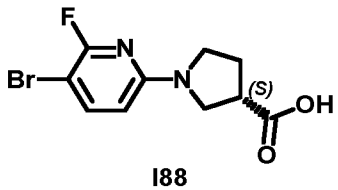


I87

Intermediate **I86** (1.60 g, 7.14 mmol) and NBS [128-08-5] (1.65 g, 9.28 mmol) in MeCN (36 mL) were stirred at rt for 18 h. The mixture was evaporated 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 100:0 to 50:50) to afford intermediate **I87** (1.58 g, 61%, 84% purity) as a colorless oil.

Intermediate **I88**

(3*S*)-1-(5-Bromo-6-fluoropyridin-2-yl)pyrrolidine-3-carboxylic acid

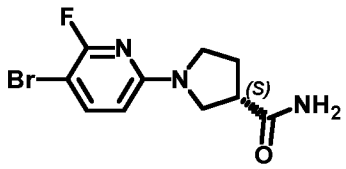


I88

Lithium hydroxide monohydrate (41.9 mg, 1.00 mmol) was added to a solution of intermediate **I87** (120 mg, 0.33 mmol, 84% purity) 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 H_2O, 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 / AcOH from 60:39:1 to 20:80:2) to afford intermediate **I88** (96 mg, quant.).

Intermediate **I85**

(3*S*)-1-(5-Bromo-6-fluoropyridin-2-yl)pyrrolidine-3-carboxamide



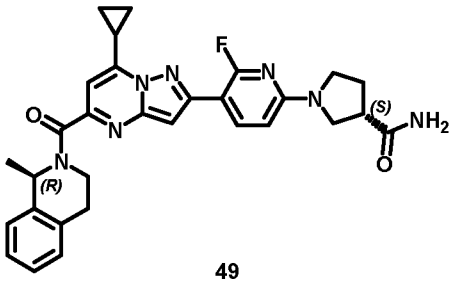
I85

A mixture of intermediate **I88** (96.3 mg, 0.33 mmol), HATU (165 mg, 0.43 mmol) and DIPEA (172 µL, 1.0 mmol) in DCM (1.9 mL) was stirred at rt for 1 h. Ammonia (28% in H_2O, 0.11 mL, 1.67 mmol) was added and the reaction mixture was stirred at rt for 18 h. The reaction mixture was diluted with H_2O and EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc (twice), dried over $MgSO_4$ and evaporated under reduced pressure. The crude mixture was purified by preparative LC (regular SiOH, 30 µm, 12 g GraceResolv™, dry loading (Celite®), mobile phase gradient: DCM / MeOH /

aq.NH_3 from 99:1:0.1 to 90:10:1). The residue was suspended in DCM and filtered off to afford intermediate **I85** (62 mg, 65%) as a yellow solid.

Synthesis of compound **49**

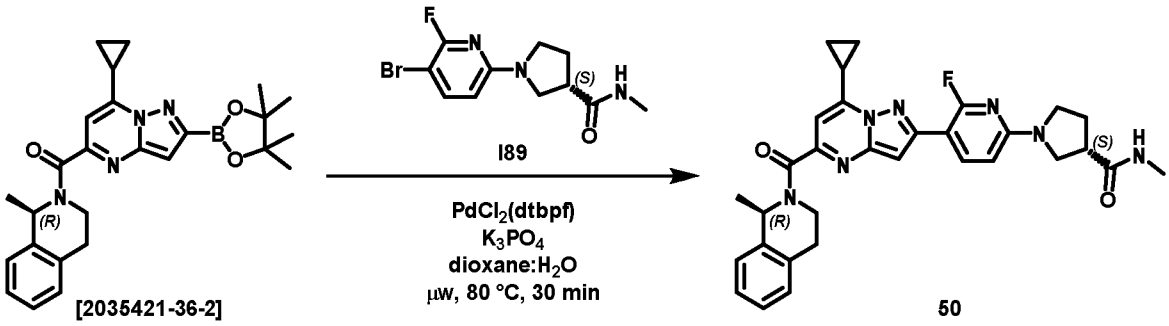
(3*S*)-1-(5-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-pyrazolo[1,5-a]pyrimidin-2-yl}-6-fluoropyridin-2-yl)pyrrolidine-3-carboxamide



49

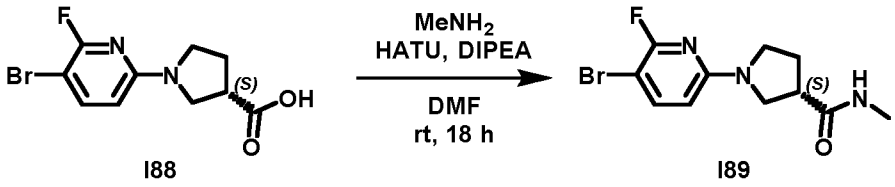
A sealed tube was charged with intermediate **I85** (62.0 mg, 0.22 mmol), (1*R*)-2-[7-cyclopropyl-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-36-2] (190 mg, 0.22 mmol, 52% purity), potassium phosphate tribasic (137 mg, 0.65 mmol), 1,4-dioxane (2.2 mL) and H_2O (0.5 mL) and purged with nitrogen. [1,1'-Bis(di-*tert*-butylphosphino)ferrocene] palladium dichloride (14.0 mg, 21.5 µmol) was added and the mixture was purged 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 layers were separated and the organic phase was washed with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude mixture was purified by preparative LC (regular SiOH, 30 µm, 24 g Interchim®, liquid injection (DCM), mobile phase gradient: DCM / *i*-PrOH from 100:0 to 80:20). A second purification was performed by preparative LC (regular SiOH, 30 µm, 24 g Interchim®, liquid injection (DCM), mobile phase gradient: DCM / *i*-PrOH from 100:0 to 80:20). The mixture (79 mg) was purified 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 65:35 to 25:75). The residue was taken up in MeCN and DIPE, concentrated under reduced pressure and dried under high vacuum at 50°C for 16 h to give compound **49** (70 mg, 60%) as a white solid.

Compound 50



Synthesis of intermediate **I89**

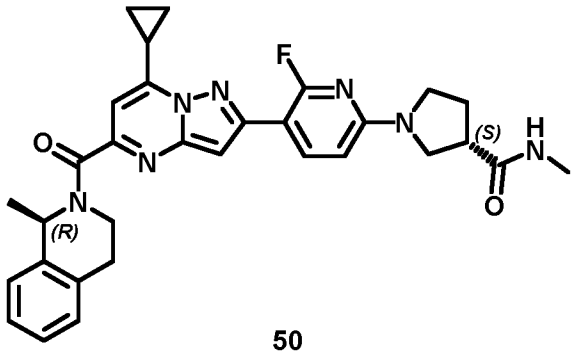
(3*S*)-1-(5-Bromo-6-fluoropyridin-2-yl)-*N*-methylpyrrolidine-3-carboxamide



A mixture of intermediate **I88** (220 mg, 761 µmol), HATU (434 mg, 1.14 mmol) and DIPEA (393 µL, 2.28 mmol) in DMF (21 mL) was stirred at rt for 1 h. Methylamine (2.0 M in THF, 1.9 mL, 3.81 mmol) was added and the reaction mixture was stirred at rt for 18 h. The reaction mixture was diluted with H_2O and EtOAc. The layers were separated and the organic phase was washed with a 1% aqueous solution of $NaHCO_3$ (twice), dried over $MgSO_4$, filtered and evaporated 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: DCM / *i*-PrOH from 100:0 to 80:20) to afford intermediate **I89** (220 mg, 96%) as a yellow oil.

Synthesis of compound 50

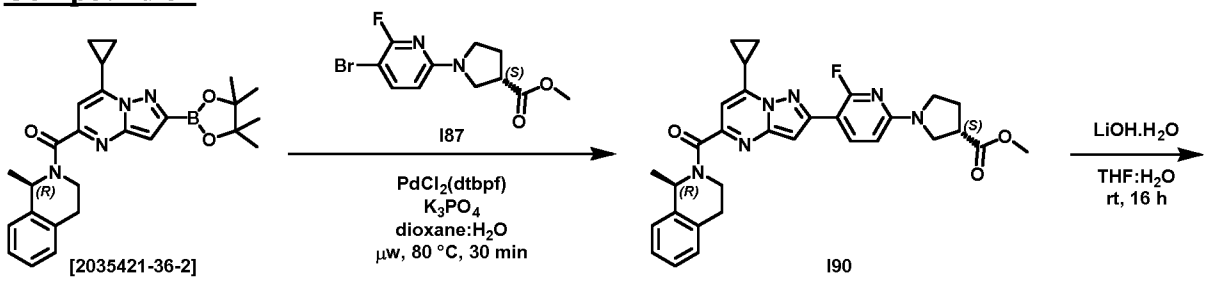
(3*S*)-1-(5-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-pyrazolo[1,5-a]pyrimidin-2-yl}-6-fluoropyridin-2-yl)-*N*-methylpyrrolidine-3-carboxamide

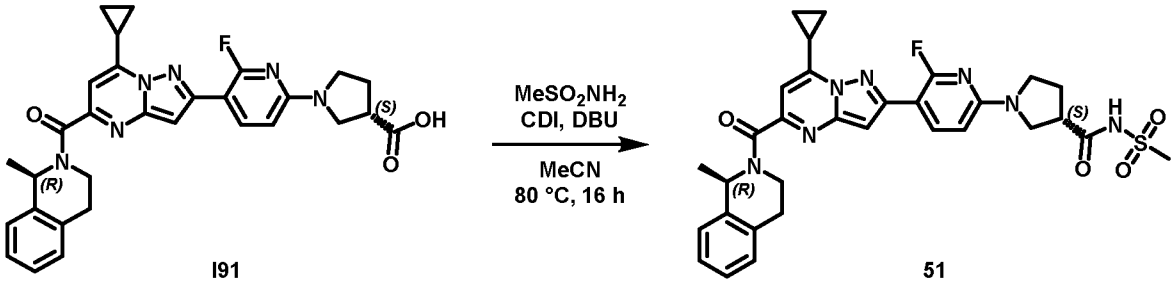


50

A sealed tube was charged with intermediate **I89** (220 mg, 0.73 mmol), (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] (538 mg, 0.73 mmol, 62% purity), potassium phosphate tribasic (0.46 g, 2.18 mmol), 1,4-dioxane (5.0 mL) and H_2O (1.3 mL) and purged with nitrogen. [1,1'-Bis(di-*tert*-butylphosphino)ferrocene] palladium dichloride (47.5 mg, 72.8 µmol) was added and the mixture was purged 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 brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude mixture was purified by preparative LC (irregular SiOH, 30 µm, 24 g GraceResolv™, liquid injection (DCM), mobile phase gradient: DCM / *i*-PrOH from 99:1 to 80:20). A second purification was carried out by reverse phase (spherical C18 25 µm, 40 g YMC-ODS-25, liquid injection (MeCN / H_2O), mobile phase gradient: (0.2% aq.NH_4HCO_3) / MeCN from 65:35 to 25:75). The residue was taken up in MeCN. The solid was filtered off and dried under high vacuum at 50°C for 16 h to give compound **50** (190 mg, 47%).

Compound 51

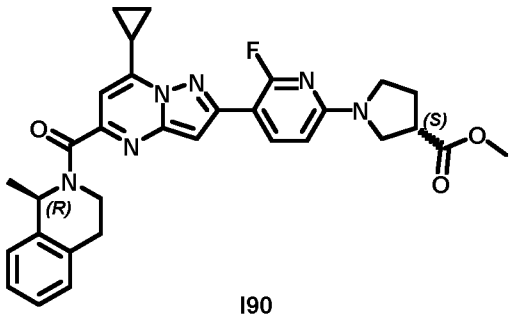




I91 51

Intermediate **I90**

Methyl (3*S*)-1-(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)pyrrolidine-3-carboxylate

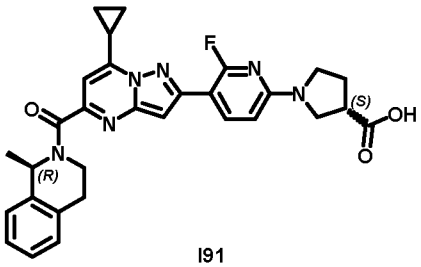


I90

A sealed tube was charged with intermediate **I87** (180 mg, 0.50 mmol, 84% purity), (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] (289 mg, 0.50 mmol, 69% purity), potassium phosphate tribasic (323 mg, 1.52 mmol), 1,4-dioxane (5.5 mL) and H_2O (1.4 mL) and purged with nitrogen. [1,1'-Bis(di-*tert*-butylphosphino)ferrocene] palladium dichloride (33.2 mg, 50.9 µmol) was added and the mixture was purged 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 brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude mixture was purified by preparative LC (regular SiOH, 30 µm, 24 g GraceResolv™, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 80:20 to 60:40) to afford intermediate **I90** (200 mg, 72%) as a yellow foam.

Intermediate **I91**

(3*S*)-1-(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)pyrrolidine-3-carboxylic acid

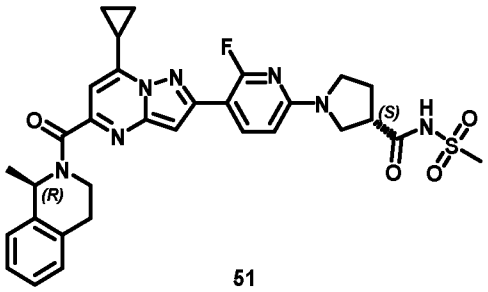


I91

Lithium hydroxide monohydrate (45.4 mg, 1.08 mmol) was added to a solution of intermediate **I90** (200 mg, 361 μmol) in THF (3.1 mL) and H_2O (980 μL). 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 organic phase was washed with H_2O, 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 / AcOH from 30:46.5:1.5 to 0:97.5:2.5 to afford intermediate **I91** (160 mg, 82%).

Compound 51

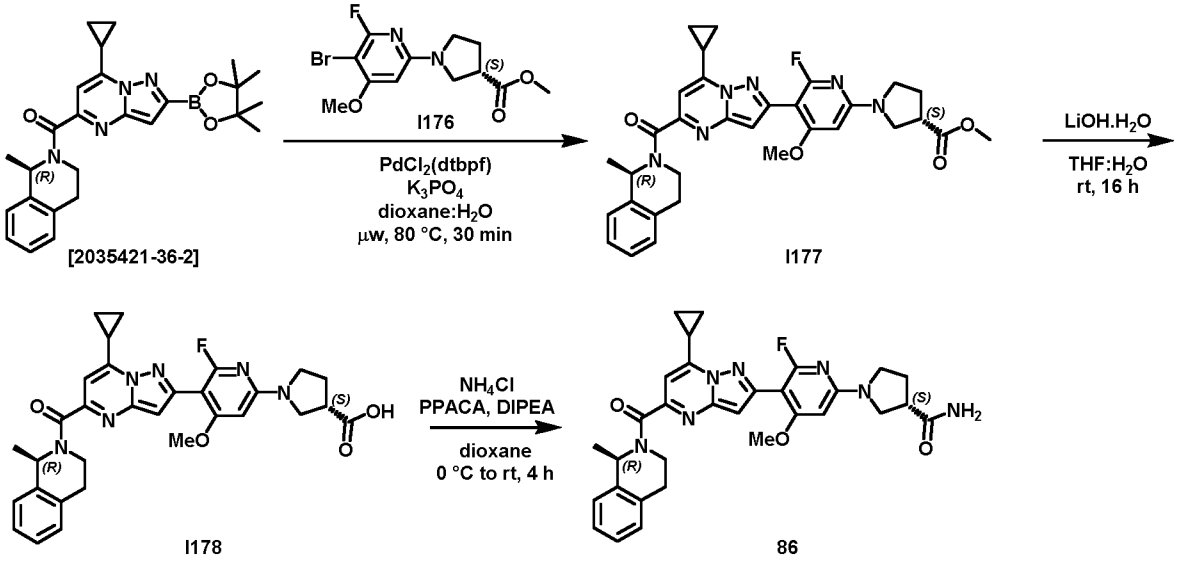
(3*S*)-1-(5-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-pyrazolo[1,5-a]pyrimidin-2-yl}-6-fluoropyridin-2-yl)-N-methanesulfonylpyrrolidine-3-carboxamide



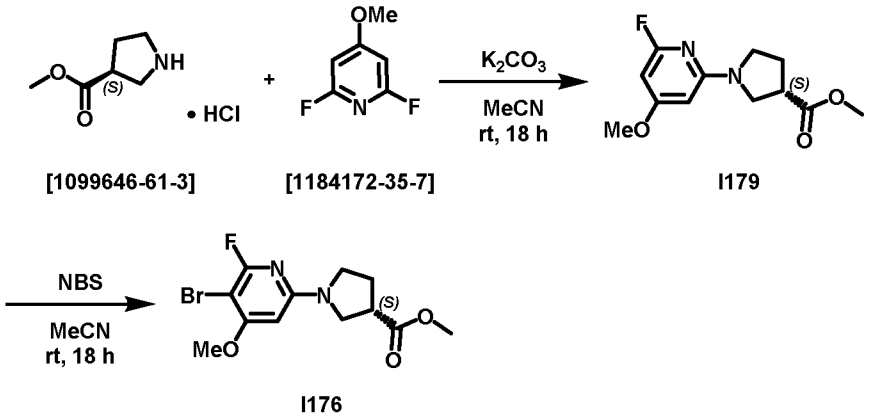
51

A mixture of intermediate **I91** (160 mg, 260 μmol) 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 methanesulfonamide [3144-09-0] (41.9 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 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 under reduced pressure. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 μm, 40 g GraceResolv™, liquid injection (DCM), mobile phase gradient: DCM / MeOH from 100:0 to 92:8) to give compound **51** (60 mg, 33%) as a yellow foam.

Compound 86

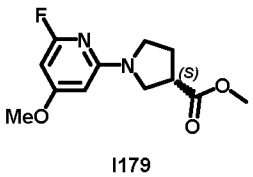


Synthesis of intermediate **I176**



Intermediate **I179**

Methyl (3*S*)-1-(6-fluoro-4-methoxypyridin-2-yl)pyrrolidine-3-carboxylate



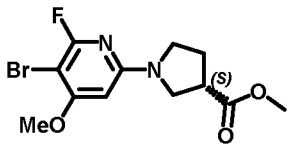
I179

A mixture of 2,6-difluoro-4-methoxypyridine [1184172-35-7] (100 mg, 689 µmol), (*S*)-methyl pyrrolidine-3-carboxylate hydrochloride [1099646-61-3] (114 mg, 689 µmol) and potassium carbonate (286 mg, 2.07 mmol) in MeCN (6.9 mL) was stirred at rt for 18 h.

The reaction mixture was filtered over a pad of Celite® and the filtrate was concentrated 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 90:10 to 60:40) to afford intermediate **I179** (68 mg, 38%) as a yellow oil.

Intermediate **I176**

Methyl (3*S*)-1-(5-bromo-6-fluoro-4-methoxypyridin-2-yl)pyrrolidine-3-carboxylate



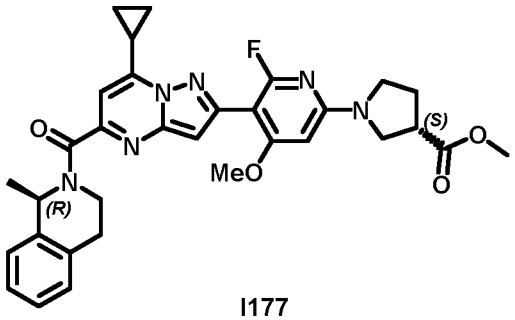
I176

A mixture of intermediate **I179** (425 mg, 1.67 mmol) and NBS (298 mg, 1.67 mmol) in MeCN (8.4 mL) was stirred at rt for 18 h. 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 99:1 to 40:60) to give intermediate **I176** (556 mg, 87%).

Synthesis of compound 86

Intermediate **I177**

Methyl (3*S*)-1-(5-{7-cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-6-fluoro-4-methoxypyridin-2-yl)pyrrolidine-3-carboxylate



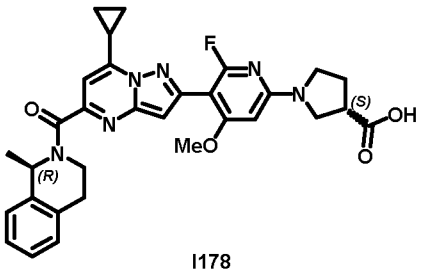
I177

A sealed tube was charged with intermediate **I176** (120 mg, 0.36 mmol), (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] (236 mg, 0.36 mmol, 70% purity), potassium phosphate tribasic (229 mg, 1.08 mmol), 1,4-dioxane (3.1 mL) and H_2O (0.8 mL) and purged with nitrogen. [1,1'-Bis(di-*tert*-butylphosphino)ferrocene] palladium dichloride (23.5 mg, 36.0 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. The layers were separated and 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, 15-40 µm, 24 g Grace®, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 80:20 to 20:80) to afford intermediate **I177** (195 mg, 93%).

Intermediate **I178**

(3*S*)-1-(5-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-pyrazolo[1,5-a]pyrimidin-2-yl}-6-fluoro-4-methoxypyridin-2-yl)pyrrolidine-3-carboxylic acid

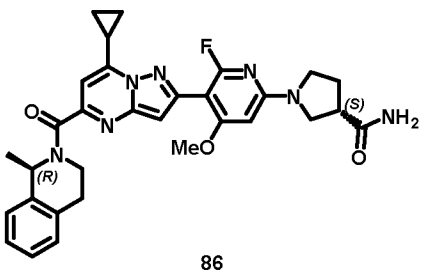


I178

Lithium hydroxide monohydrate (41.9 mg, 1.00 mmol) was added to a solution of intermediate **I177** (195 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 H_2O, dried over $MgSO_4$, filtered and concentrated in vacuo to afford intermediate **I178** (185 mg, 97%).

Compound 86

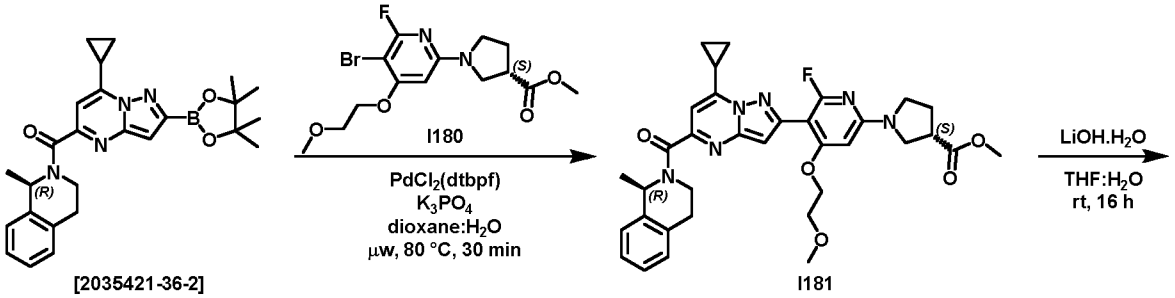
(3*S*)-1-(5-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-pyrazolo[1,5-a]pyrimidin-2-yl}-6-fluoro-4-methoxypyridin-2-yl)pyrrolidine-3-carboxamide

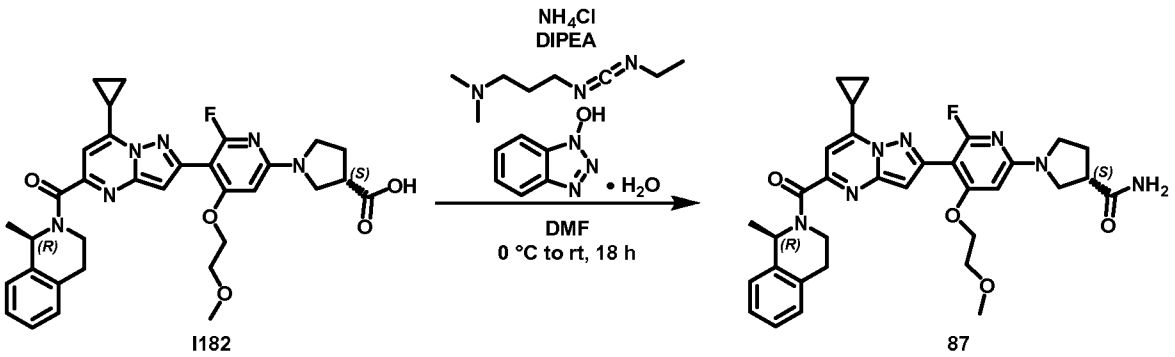


86

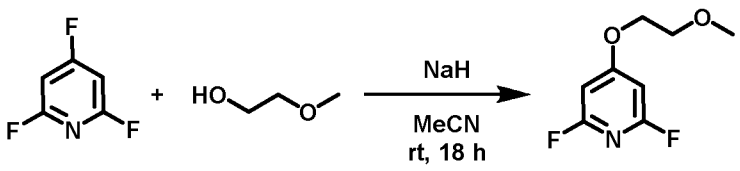
A mixture of intermediate **I178** (185 mg, 324 µmol), ammonium chloride (69.4 mg, 1.30 mmol) and DIPEA (467 µL, 2.71 mmol) in 1,4-dioxane (2.5 mL) was stirred at 0°C. PPACA (50% wt in EtOAc, 463 µL, 778 µmol) was added slowly. The reaction mixture was stirred at 0°C for 10 min and at rt for 4 h. The reaction mixture was diluted with H_2O and EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with a 10% aqueous solution of $KHSO_4$ and brine, dried over $MgSO_4$, filtered and evaporated in vacuo. The crude mixture was purified 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 75:25 to 35:65). The residue was solubilized in Et_2O and evaporated in vacuo. The product was dried under vacuum at 50°C for 72 h and at 65°C for 8 h to give compound **86** (100 mg, 54%).

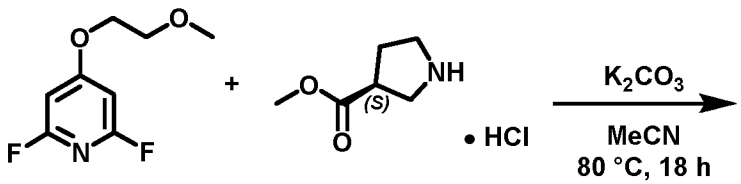
Compound 87



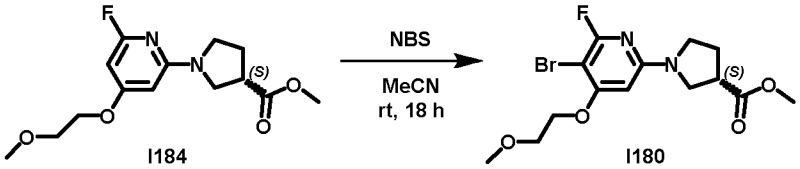


Synthesis of intermediate **I180**





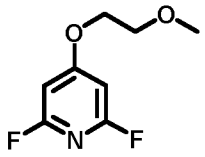
I183 [1099646-61-3]



I184 I180

Intermediate **I183**

2,6-Difluoro-4-(2-methoxyethoxy)pyridine

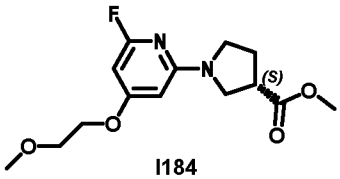


I183

To a mixture of 2,4,6-trifluoropyridine [3512-17-2] (300 mg, 2.25 mmol) and 2-methoxy-ethanol [109-86-4] (179 µL, 2.25 mmol) in MeCN (9.4 mL) was added sodium hydride (60% in mineral oil, 90.2 mg, 2.25 mmol). The reaction mixture was stirred at rt for 18 h. The reaction mixture was diluted with EtOAc. The organic phase was washed with H_2O, dried over $MgSO_4$, filtered and 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 90:10 to 40:60) to afford intermediate **I183** (230 mg, 54%).

Intermediate **I184**

Methyl (3*S*)-1-[6-fluoro-4-(2-methoxyethoxy)pyridin-2-yl]pyrrolidine-3-carboxylate



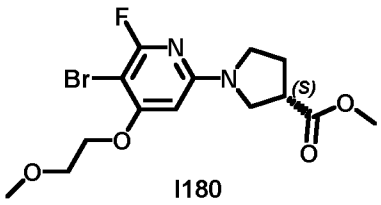
I184

A mixture of intermediate **I183** (230 mg, 1.22 mmol), (*S*)-methyl pyrrolidine-3-carboxylate hydrochloride [1099646-61-3] (201 mg, 1.22 mmol) and potassium carbonate (504 mg, 3.65 mmol) in MeCN (12 mL) was stirred at 80°C for 18 h. The reaction mixture

was filtered over a pad of Celite® and the filtrate was 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 from 90:10 to 60:40) to afford intermediate **I184** (150 mg, 41%) as a yellow oil.

Intermediate **I180**

Methyl (3*S*)-1-[5-bromo-6-fluoro-4-(2-methoxyethoxy)pyridin-2-yl]pyrrolidine-3-carboxylate



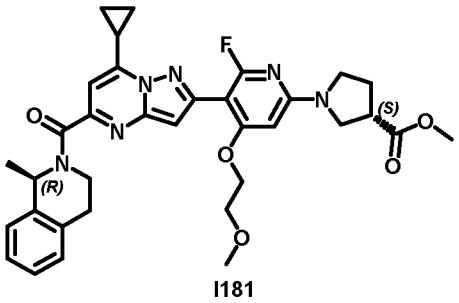
I180

A mixture of intermediate **I184** (150 mg, 503 µmol) and NBS (89.5 mg, 503 mmol) in MeCN (2.5 mL) was stirred at rt for 18 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: heptane / EtOAc from 90:10 to 40:60) to afford intermediate **I180** (218 mg, 93%) as a yellow oil.

Synthesis of compound 87

Intermediate **I181**

Methyl (3*S*)-1-(5-{7-cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-6-fluoro-4-(2-methoxyethoxy)pyridin-2-yl)pyrrolidine-3-carboxylate



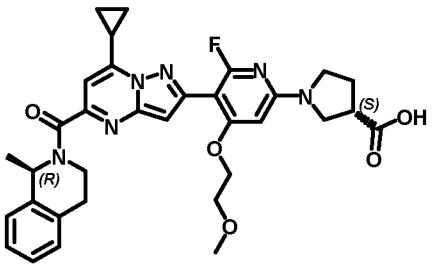
I181

A sealed tube was charged with intermediate **I180** (124 mg, 329 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] (215 mg, 329 µmol, 70% purity), potassium phosphate tribasic (209 mg, 986 µmol), 1,4-dioxane (2.8 mL) and H_2O (0.7 mL) and purged with nitrogen. [1,1'-Bis(di-*tert*-butylphosphino)ferrocene]

palladium dichloride (21.4 mg, 32.9 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 phase was 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 Grace®, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 80:20 to 20:80) to afford intermediate **I181** (185 mg, 90%).

Intermediate **I182**

(3*S*)-1-(5-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-6-fluoro-4-(2-methoxyethoxy)pyridin-2-yl)pyrrolidine-3-carboxylic acid

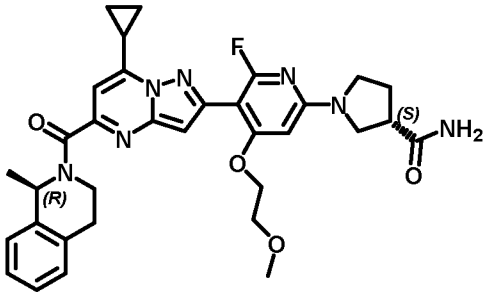


I182

Lithium hydroxide monohydrate (37.0 mg, 883 µmol) was added to a solution of intermediate **I181** (185 mg, 294 µmol) in THF (2.6 mL) and H_2O (0.8 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 H_2O, dried over $MgSO_4$, filtered and concentrated to afford intermediate **I182** (170 mg, 94%).

Compound 87

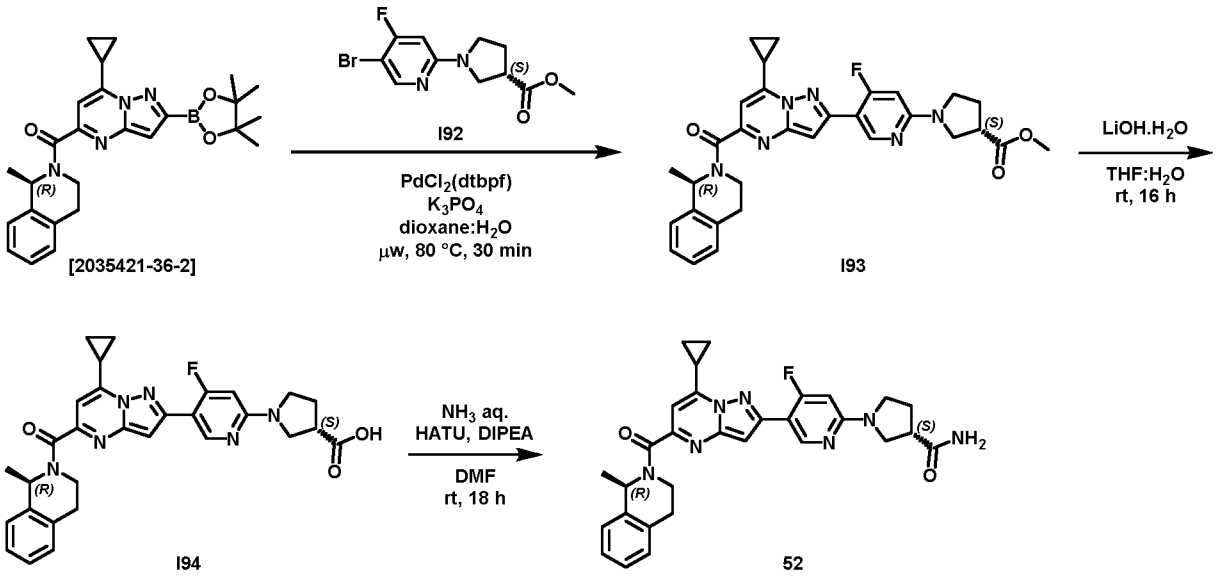
(3*S*)-1-(5-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-pyrazolo[1,5-a]pyrimidin-2-yl}-6-fluoro-4-(2-methoxyethoxy)pyridin-2-yl)pyrrolidine-3-carboxamide



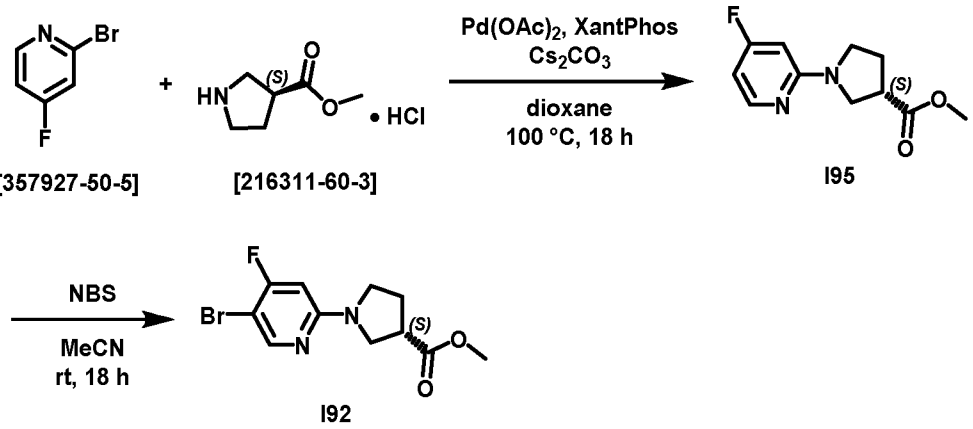
87

A mixture of intermediate **I182** (170 mg, 277 µmol), ammonium chloride (17.8 mg, 332 µmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (51.5 mg, 332 µmol) and 1-hydroxybenzotriazole hydrate (63.5 mg, 415 µmol) in DMF (14 mL) was stirred at 0°C. DIPEA (238 µL, 1.38 mmol) was added slowly and the reaction mixture was stirred at rt for 18 h. The reaction mixture was evaporated in vacuo. The residue was dissolved in brine 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 (Stationary phase: YMC-actus Triart C18 10µm 30*150mm, Mobile phase gradient: (0.2% aq.NH_4HCO_3) / MeCN from 70:30 to 30:70). The residue was suspended in MeCN (~2 mL) and stirred under reflux until complete solubilization. The heating source was stopped and the flask was left in the oil bath with a gentle stirring while crystallization occurred (4 h). The solid was filtered off, washed with MeCN and dried under vacuum at 50°C for 18 h to give compound **87** (115 mg, 68%) as a white solid.

Compound 52



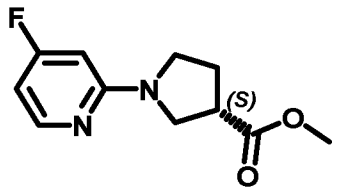
Synthesis of intermediate **I92**



[357927-50-5] [216311-60-3] I95 I92

Intermediate **I95**

Methyl (3*S*)-1-(4-fluoropyridin-2-yl)pyrrolidine-3-carboxylate

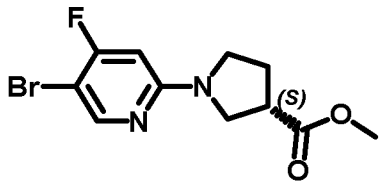


I95

A sealed tube was charged with 2-bromo-4-fluoropyridine [357927-50-5] (200 mg, 1.14 mmol), (*S*)-methyl pyrrolidine-3-carboxylate hydrochloride [216311-60-3] (188 mg, 1.14 mmol) and cesium carbonate (1.11 g, 3.41 mmol) and purged with nitrogen. 1,4-Dioxane (9.2 mL) was added and the mixture was degassed with nitrogen. Palladium acetate (25.5 mg, 0.11 mmol) and XantPhos (65.8 mg, 0.11 mmol) were added. The reaction mixture was stirred at 100°C for 18 h. The reaction mixture was poured out into water and the aqueous phase was extracted with EtOAc and filtered over Celite®. The filtrate was washed with brine, 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: heptane / EtOAc from 90:10 to 40:60) to afford intermediate **I95** (32 mg, 13%) as a colorless oil.

Intermediate **I92**

Methyl (3*S*)-1-(5-bromo-4-fluoropyridin-2-yl)pyrrolidine-3-carboxylate



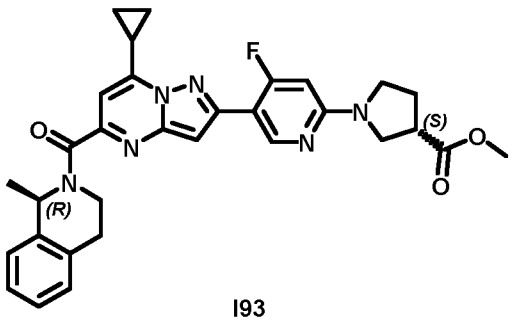
I92

A mixture of intermediate **I95** (60.0 mg, 268 µmol) and NBS (47.6 mg, 268 µmol) in MeCN (2.7 mL) was stirred at rt for 18 h. The mixture was evaporated under reduced pressure. The crude product was purified by preparative LC (irregular SiOH, 15-40 µm, 12 g GraceResolv™, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 100:0 to 50:50) to afford intermediate **I92** (68 mg, 84%) as a colorless oil.

Synthesis of compound 52

Intermediate **I93**

Methyl (3*S*)-1-(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)pyrrolidine-3-carboxylate



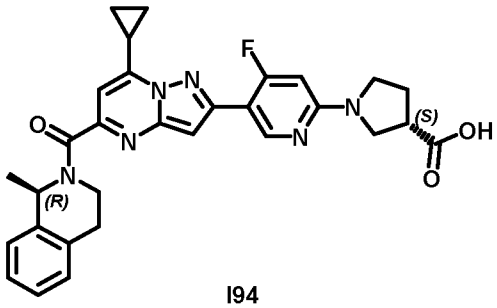
I93

A sealed tube was charged with intermediate **I92** (234 mg, 0.77 mmol), (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] (472 mg, 0.77 mmol, 75% purity), potassium phosphate tribasic (492 mg, 2.32 mmol), 1,4-dioxane (7.8 mL) and H_2O (2.0 mL) and purged with nitrogen. [1,1'-Bis(di-*tert*-butylphosphino)ferrocene] palladium acetate (50.3 mg, 77.2 µmol) was added and the mixture was purged 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 brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude mixture was

purified by preparative LC (regular SiOH, 30 µm, 80 g Interchim®, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 40:60 to 0:100) to afford intermediate **I93** (400 mg, 93%) as a yellow oil.

Intermediate **I94**

(3*S*)-1-(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)pyrrolidine-3-carboxylic acid

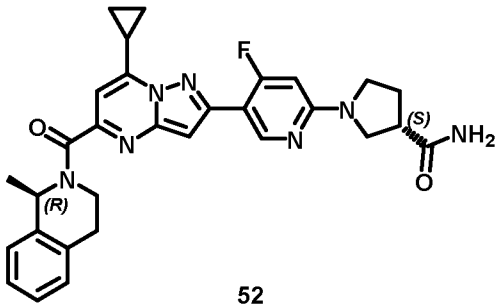


I94

Lithium hydroxide monohydrate (90.8 mg, 2.16 mmol) was added to a solution of intermediate **I93** (400 mg, 0.72 mmol) in THF (6.3 mL) and H_2O (2.0 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 organic layer was washed with H_2O, 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 / AcOH from 80:19.5:0.5 to 0:97.5:2.5) to afford intermediate **I94** (380 mg, 97%).

Compound 52

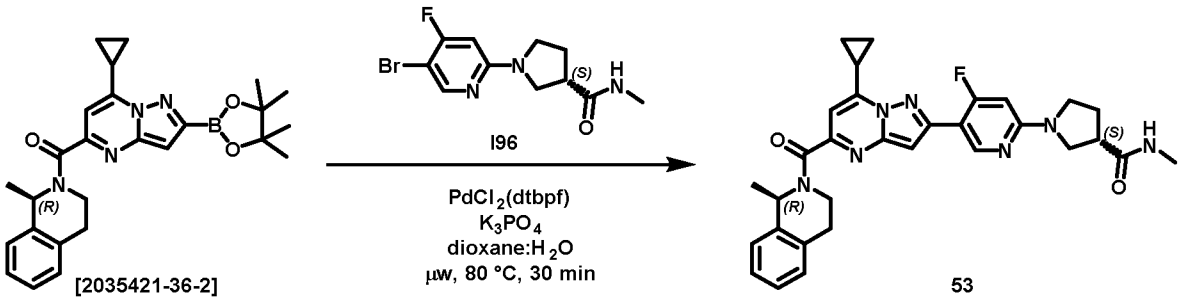
(3*S*)-1-(5-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-pyrazolo[1,5-a]pyrimidin-2-yl}-4-fluoropyridin-2-yl)pyrrolidine-3-carboxamide



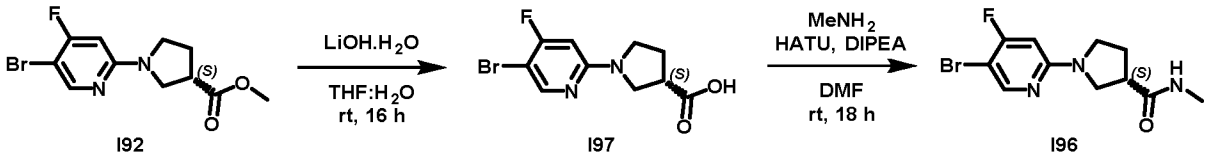
52

A mixture of intermediate **I94** (180 mg, 333 µmol), HATU (190 mg, 499 µmol) and DIPEA (172 µL, 1.0 mmol) in DMF (9 mL) was stirred at rt for 1 h. Ammonia (28% in H_2O, 113 µL, 1.67 mmol) was added and the reaction mixture was stirred at rt for 18 h. The reaction mixture was diluted with H_2O 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 under reduced pressure. The crude mixture was purified by preparative LC (regular SiOH, 30 µm, 24 g GraceResolv™, liquid injection (DCM), mobile phase gradient: DCM / *i*-PrOH from 100:0 to 70:30). The residue (120 mg) was dissolved in DCM and washed with a 1% aqueous solution of $NaHCO_3$ (3 times), brine, dried over MgSO4, filtered and concentrated in vacuo to give compound **52** (90 mg, 50%).

Compound 53

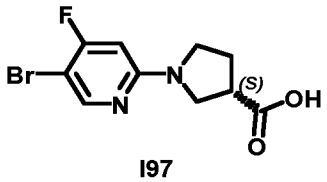


Synthesis of intermediate **I96**



Intermediate **I97**

(3*S*)-1-(5-Bromo-4-fluoropyridin-2-yl)pyrrolidine-3-carboxylic acid

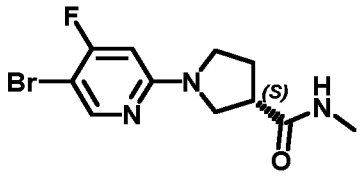


Lithium hydroxide monohydrate (66.4 mg, 1.58 mmol) was added to a solution of intermediate **I92** (160 mg, 0.53 mmol) in THF (12 mL) and H_2O (3.0 mL). The reaction

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 H_2O, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford intermediate **I97** (150 mg, 98%) as a yellow foam.

Intermediate **I96**

(3*S*)-1-(5-Bromo-4-fluoropyridin-2-yl)-N-methylpyrrolidine-3-carboxamide

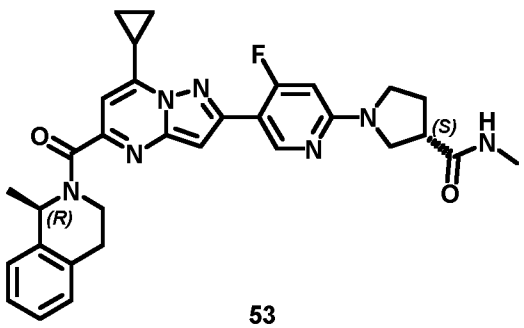


I96

A mixture of intermediate **I97** (150 mg, 519 µmol), HATU (296 mg, 0.78 mmol) and DIPEA (268 µL, 1.56 mmol) in DMF (8 mL) was stirred at rt for 1 h. Methylamine (2.0 M in THF, 1.30 mL, 2.59 mmol) was added and the reaction mixture was stirred at rt for 18 h. The reaction mixture was diluted with H_2O and EtOAc. The layers were separated. The organic phase was washed with a 1% aqueous solution of $NaHCO_3$ (twice), dried over $MgSO_4$ 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 / *i*-PrOH from 100:0 to 80:20) to afford intermediate **I96** (140 mg, 89%) as a yellow oil.

Synthesis of compound 53

(3*S*)-1-(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-methylpyrrolidine-3-carboxamide



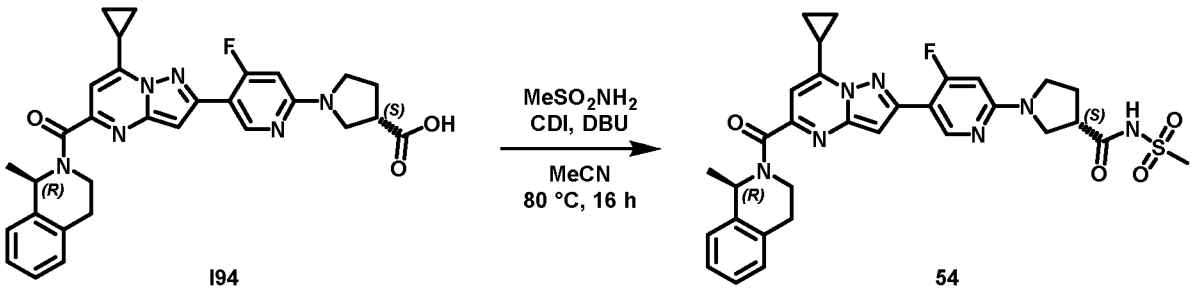
53

A sealed tube was charged with intermediate **I96** (140 mg, 0.46 mmol), (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] (212 mg, 0.46 mmol, 63% purity), potassium phosphate tribasic (0.29 g, 1.39 mmol), 1,4-dioxane (3.2 mL) and H_2O (0.8 mL) and purged with nitrogen. [1,1'-Bis(di-*tert*-butylphosphino)ferrocene] palladium dichloride (30.2 mg, 46.3 µmol) was added and the mixture was purged 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 brine, dried over $MgSO_4$, filtered and evaporated 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 / *i*-PrOH from 99:1 to 80:20). A second purification was carried out by reverse phase (spherical C18 25 µm, 40 g YMC-ODS-25, liquid injection (MeCN, H_2O), mobile phase gradient (0.2% aq.NH_4HCO_3) / MeCN from 65:35 to 25:75). The residue was crystallized from EtOH, filtered off and dried under high vacuum at 50°C for 16 h to give compound **53** (90 mg, 35%).

Compound 54

(3*S*)-1-(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-methanesulfonylpyrrolidine-3-carboxamide

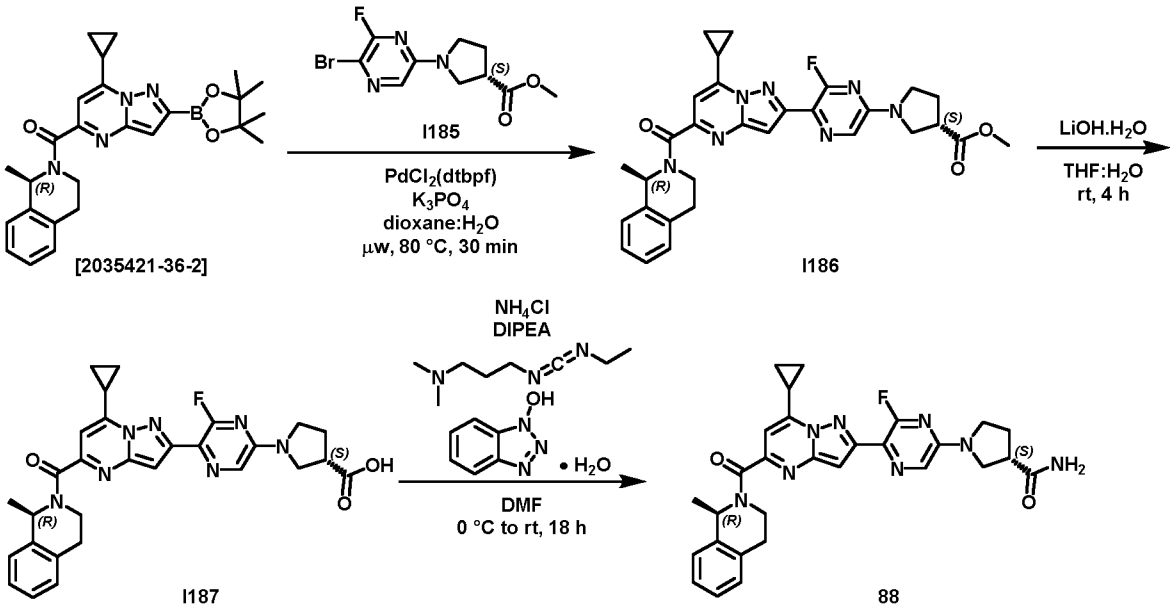


I94 54

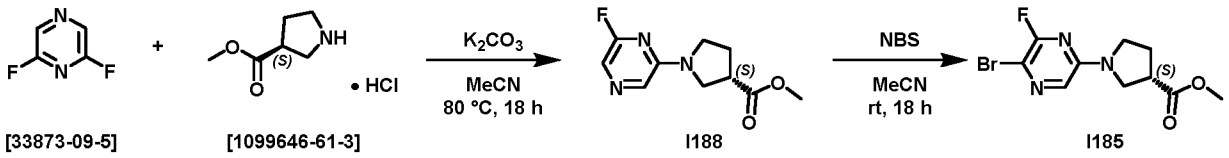
A mixture of intermediate **I94** (185 mg, 342 µmol) and CDI (83.2 mg, 0.51 mmol) in MeCN (3.5 mL) was stirred at rt for 2 h. DBU (102 µL, 0.68 mmol) and methanesulfonamide [3144-09-0] (65.1 mg, 0.68 mmol) were added. The reaction mixture was stirred at 80°C for 16 h. A 1N aqueous solution of HCl and 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 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 92:8). A second purification was carried out: 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 85:15 to 45:55). The product was freeze-dried to give compound **54** (140 mg, 66%) as a white solid.

Compound 88

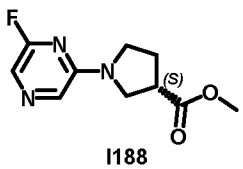


Synthesis of intermediate **I185**



Intermediate **I188**

Methyl (3*S*)-1-(6-fluoropyrazin-2-yl)pyrrolidine-3-carboxylate

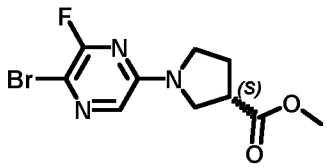


A mixture of 2,6-difluoropyrazine [33873-09-5] (726 mg, 6.26 mmol), (*S*)-methyl pyrrolidine-3-carboxylate hydrochloride [1099646-61-3] (1.14 g, 6.88 mmol) and potassium carbonate (2.59 g, 18.8 mmol) in MeCN (48 mL) was stirred at 80°C for 18 h. The reaction mixture was diluted with H_2O and EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc (twice). The combined organic extracts were

dried over $MgSO_4$, filtered and concentrated in vacuo to afford intermediate **I188** (1.1 g, 77%).

Intermediate **I185**

Methyl (3*S*)-1-(5-bromo-6-fluoropyrazin-2-yl)pyrrolidine-3-carboxylate



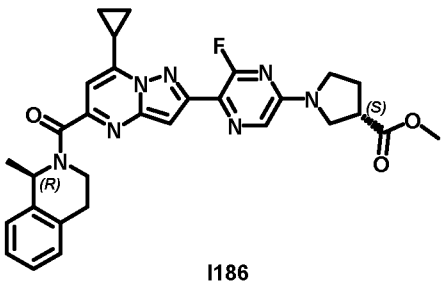
I185

A mixture of intermediate **I188** (1.00 g, 4.59 mmol) and NBS (817 mg, 4.59 mmol) in MeCN (51 mL) was stirred at rt for 18 h. The reaction mixture was diluted with H_2O and EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc (twice). The combined organic extracts were washed with an aqueous solution of $NaHCO_3$ (twice), dried over $MgSO_4$, filtered and concentrated in vacuo to afford intermediate **I185** (1.42 g).

Synthesis of compound 88

Intermediate **I186**

Methyl (3*S*)-1-(5-{7-cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-6-fluoropyrazin-2-yl)pyrrolidine-3-carboxylate



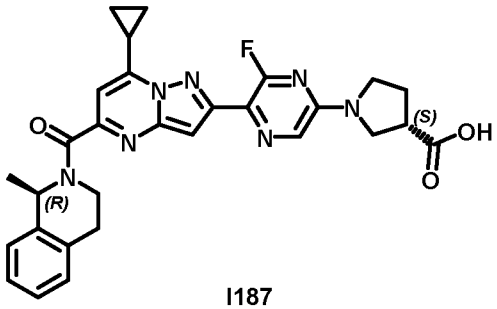
I186

A sealed tube was charged with intermediate **I185** (207 mg, 682 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] (527 mg, 1.02 mmol, 89% purity), potassium phosphate tribasic (434 mg, 2.05 mmol), 1,4-dioxane (13 mL) and H_2O (2 mL) and purged with nitrogen. [1,1'-Bis(di-*tert*-butylphosphino)ferrocene] palladium dichloride (44.4 mg, 68.2 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 EtOAc and brine. The layers were separated and the

aqueous phase was extracted with EtOAc. The combined organic extracts were washed with H_2O (twice), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 40 g GraceResolv™, liquid injection (DCM), mobile phase gradient: DCM / EtOAc from 100:0 to 70:30). A second purification was performed by preparative LC (irregular SiOH, 15-40 µm, 24 g GraceResolv™, liquid injection (DCM), mobile phase gradient: heptane / (EtOAc/MeOH (9:1)) from 90:10 to 60:40) to afford intermediate **I186** (100 mg, 26%) as a pale yellow solid.

Intermediate **I187**

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

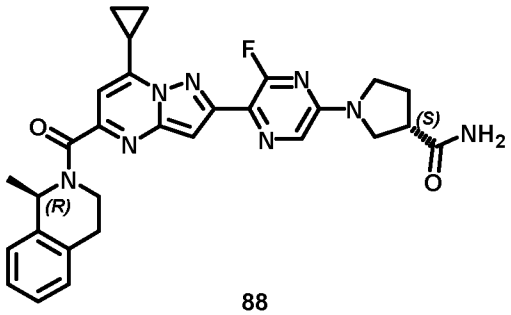


I187

Lithium hydroxide monohydrate (41.6 mg, 0.99 mmol) was added to a solution of intermediate **I186** (100 mg, 0.18 mmol) in THF (5.2 mL) and H_2O (1.3 mL). The reaction mixture was stirred at rt for 4 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 H_2O, dried over $MgSO_4$, filtered and evaporated in vacuo to afford intermediate **I187** (90 mg, 81%, 88% purity) as a yellow oil.

Compound 88

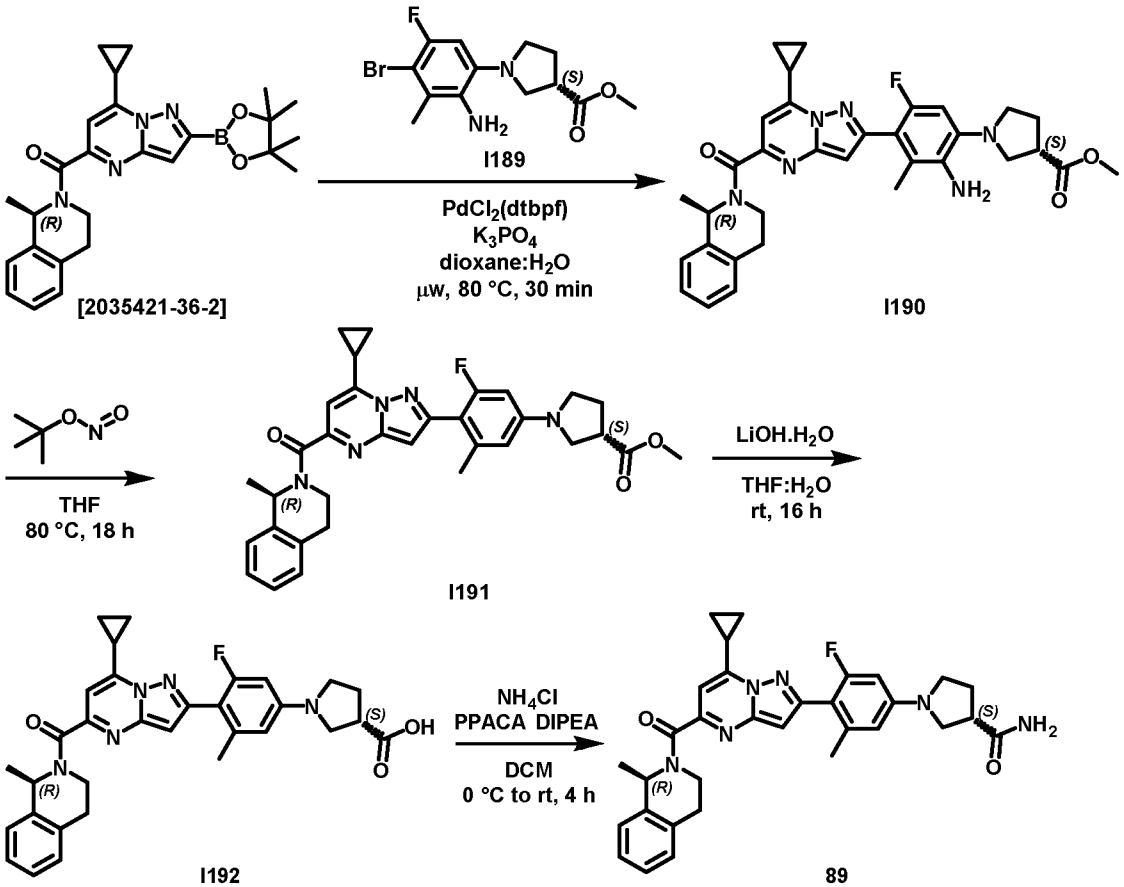
(3*S*)-1-(5-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-pyrazolo[1,5-a]pyrimidin-2-yl}-6-fluoropyrazin-2-yl)pyrrolidine-3-carboxamide



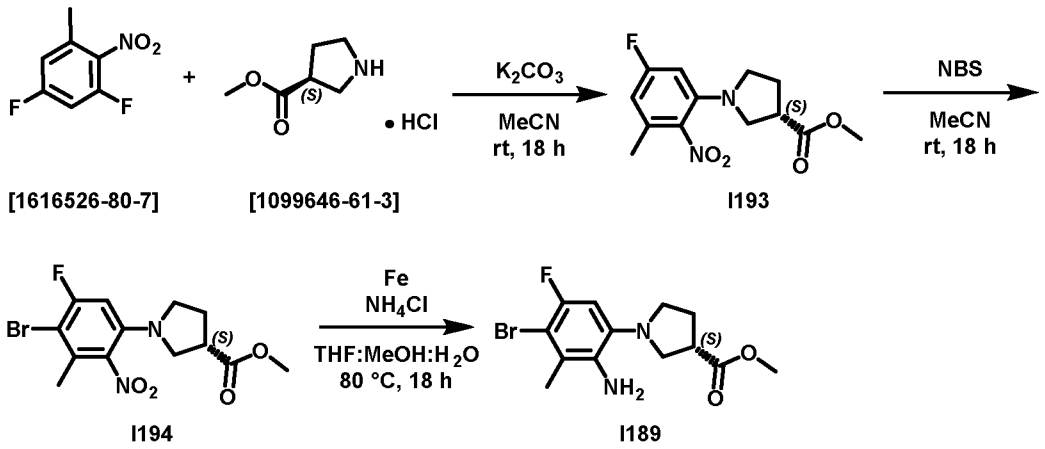
88

A mixture of intermediate **I187** (80.0 mg, 0.13 mmol, 88% purity), ammonium chloride (8.34 mg, 156 µmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (27.6 µL, 156 µmol) and 1-hydroxybenzotriazole hydrate (29.9 mg, 195 µmol) in DMF (6.4 mL) was stirred at 0°C. DIPEA (112 µL, 0.65 mmol) was added slowly. The reaction mixture was stirred at rt for 18 h. The reaction mixture was evaporated in vacuo. The residue was dissolved in brine 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 residue was triturated with MeCN. The solid was filtered off and dried. The residue (45 mg) 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 65:35 to 25:75). The residue (24 mg) was solubilized in MeCN (2 mL), extended with water (10 mL) and freeze-dried to give compound **88** (19 mg, 27%) as a yellow fluffy solid.

Compound 89

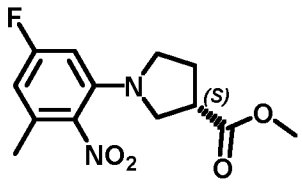


Synthesis of intermediate **I189**



Intermediate **I193**

Methyl (3*S*)-1-(5-fluoro-3-methyl-2-nitrophenyl)pyrrolidine-3-carboxylate

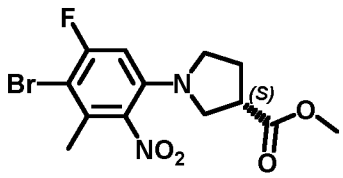


I193

A mixture of 1,5-difluoro-3-methyl-2-nitrobenzene [1616526-80-7] (125 mg, 722 µmol), (*S*)-methyl pyrrolidine-3-carboxylate hydrochloride [1099646-61-3] (132 mg, 795 µmol) and potassium carbonate (299 mg, 2.17 mmol) in MeCN (7.2 mL) was stirred at rt for 18 h. The reaction mixture was filtered over a pad of Celite® and the filtrate 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 60:40) to afford intermediate **I193** (118 mg, 58%) as a yellow oil.

Intermediate **I194**

Methyl (3*S*)-1-(4-bromo-5-fluoro-3-methyl-2-nitrophenyl)pyrrolidine-3-carboxylate

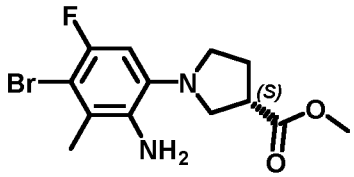


I194

A mixture of intermediate **I193** (725 mg, 2.57 mmol) and NBS (457 mg, 2.57 mmol) in MeCN (12.8 mL) was stirred at rt for 18 h. The solvent was evaporated in vacuo to afford intermediate **I194** (1.10 g, 95%, 80% purity).

Intermediate **I189**

Methyl (3*S*)-1-(2-amino-4-bromo-5-fluoro-3-methylphenyl)pyrrolidine-3-carboxylate



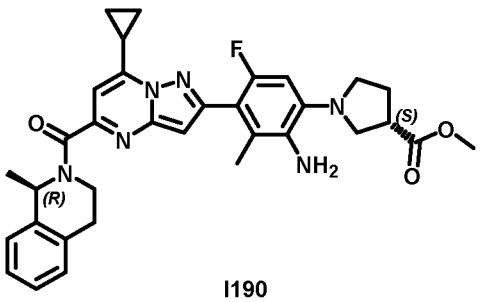
I189

In a sealed tube a mixture of intermediate **I194** (1.10 g, 2.44 mmol, 80% purity), iron (680 mg, 12.2 mmol) and ammonium chloride (1.31 g, 24.4 mmol) in THF (7.7 mL), MeOH (7.7 mL) and H_2O (3.9 mL) was stirred at 80°C for 18 h. The reaction mixture was diluted with EtOAc and H_2O. The layers were separated and 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, 15-40 µm, 12 g Grace®, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 99:1 to 60:40) to afford intermediate **I189** (666 mg, 83%) as a colorless oil.

Synthesis of compound 89

Intermediate **I190**

Methyl (3*S*)-1-(2-amino-4-{7-cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydro-isoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-5-fluoro-3-methylphenyl)-pyrrolidine-3-carboxylate



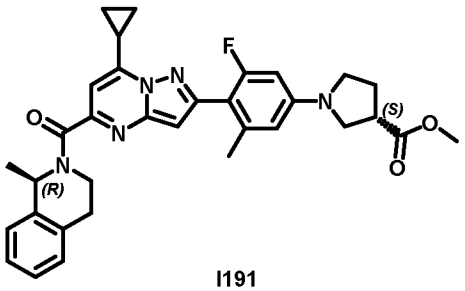
I190

A sealed tube was charged with intermediate **I189** (615 mg, 1.86 mmol), (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] (1.22 g, 1.86 mmol, 70% purity), potassium phosphate tribasic (1.18 g, 5.57 mmol), 1,4-dioxane (15.8 mL) and

H_2O (4.0 mL) and purged with nitrogen. [1,1'-Bis(di-*tert*-butylphosphino)ferrocene] palladium dichloride (121 mg, 186 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 phase was washed with brine, dried over $MgSO_4$, filtered and evaporated in vacuo. The crude mixture was combined with other samples (105 mg, 317 µmol and 50 mg, 151 µmol) and purified by preparative LC (irregular SiOH, 15-40 µm, 40 g Grace®, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 80:20 to 20:80) to afford intermediate **I190** (1.4 g, 78%, 75% purity).

Intermediate **I191**

Methyl (3*S*)-1-(4-{7-cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluoro-5-methylphenyl)pyrrolidine-3-carboxylate

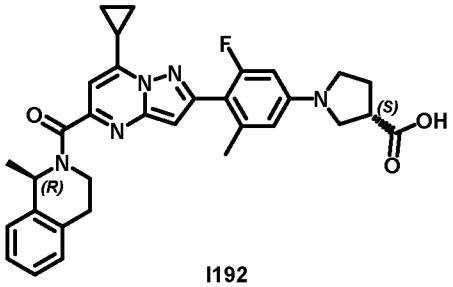


I191

In a sealed tube a mixture of intermediate **I190** (700 mg, 901 µmol, 75% purity) and *tert*-butyl nitrite (118 µL, 991 µmol) in THF (14.7 mL) was stirred at 80°C for 18 h. 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 80:20 to 0:100) to afford intermediate **I191** (186 mg, 36%).

Intermediate **I192**

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

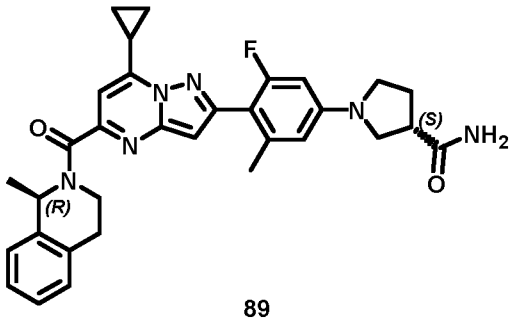


I192

Lithium hydroxide monohydrate (62.1 mg, 1.48 mmol) was added to a solution of intermediate **I191** (280 mg, 493 µmol) in THF (4.3 mL) and H_2O (1.3 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 H_2O, dried over $MgSO_4$, filtered and concentrated in vacuo to afford intermediate **I192** (250 mg, 92%) as a yellow foam.

Compound 89

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

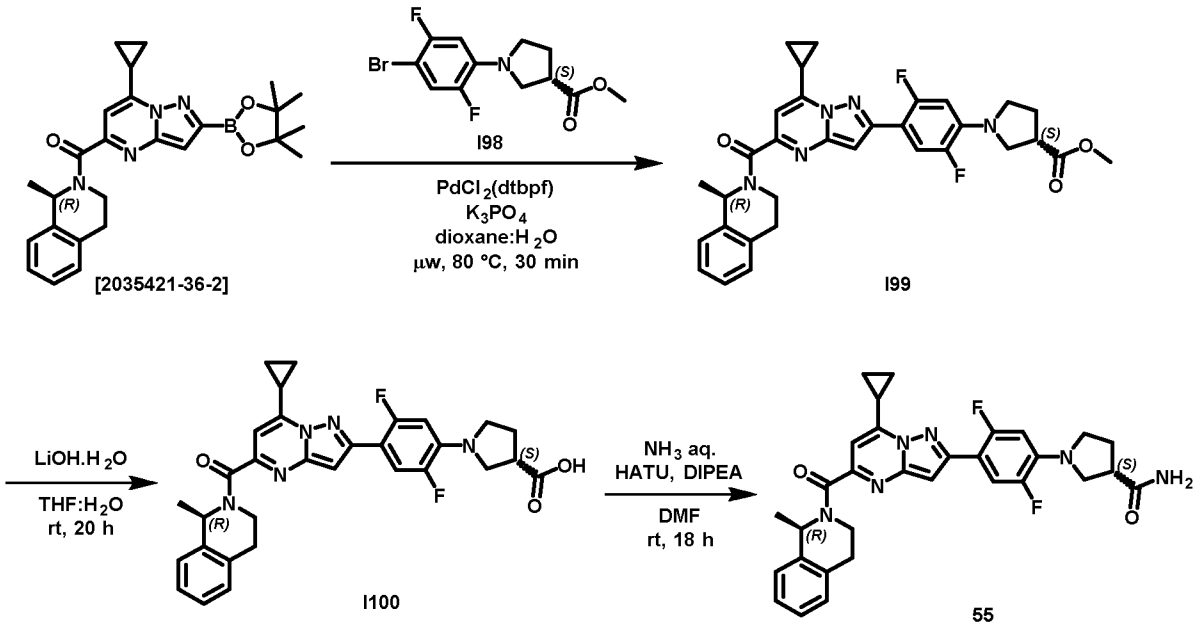


89

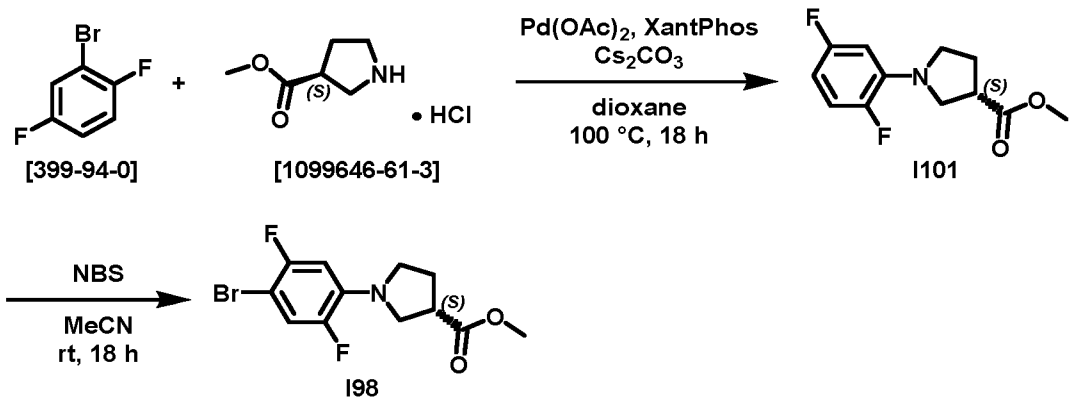
A mixture of intermediate **I192** (220 mg, 397 µmol), ammonium chloride (85.0 mg, 1.59 mmol) and DIPEA (572 µL, 3.32 mmol) in DCM (2.2 mL) was stirred at 0°C. PPACA (50 wt. % in EtOAc, 572 µL, 0.96 mmol) was added slowly. The reaction mixture was stirred at 0°C for 10 min and at rt for 4 h. The reaction mixture was cooled to 0°C and ammonium chloride (85.0 mg, 1.59 mmol), DIPEA (572 µL, 3.32 mmol) and PPACA (50 wt. % in EtOAc, 572 µL, 0.96 mmol) were added slowly. The reaction mixture was stirred at 0°C for 10 min and at rt for 4 h. The reaction mixture was diluted with H_2O and EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with a 10% aqueous solution of $KHSO_4$ and 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 Grace®, liquid injection (DCM), mobile phase

gradient: DCM / *i*-PrOH from 99:1 to 85:15). 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 65:35 to 25:75). The residue was solubilized in EtOAc, concentrated to dryness and dried under vacuum at 50°C for 72 h and at 65°C for 8 h to give compound **89** (100 mg, 46%).

Compound 55

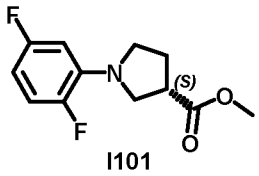


Synthesis of intermediate **I98**



Intermediate **I101**

Methyl (3*S*)-1-(2,5-difluorophenyl)pyrrolidine-3-carboxylate

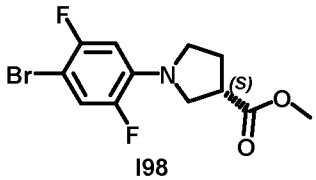


I101

A mixture of (*S*)-methyl pyrrolidine-3-carboxylate hydrochloride [1099646-61-3] (1.00 g, 6.04 mmol), 1-bromo-2,5-difluorobenzene [399-94-0] (1.02 mL, 9.06 mmol) and cesium carbonate (5.90 g, 18.1 mmol) in 1,4-dioxane (50 mL) was purged with nitrogen for 15 min. XantPhos (349 mg, 0.60 mmol) and palladium acetate (136 mg, 0.60 mmol) were added and the resulting mixture was purged with nitrogen. The reaction mixture was stirred at 100°C for 18 h. The reaction mixture was filtered through a pad of Celite®. EtOAc and brine were 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 evaporated under reduced pressure. The crude mixture was purified by preparative LC (regular SiOH, 30 µm, 80 g Grace®, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 100:0 to 80:20) to afford intermediate **I101** (780 mg, 54%) as a colorless oil.

Intermediate **I98**

Methyl (3*S*)-1-(4-bromo-2,5-difluorophenyl)pyrrolidine-3-carboxylate



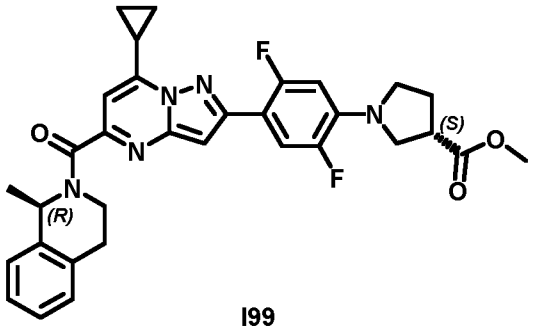
I98

To a solution of intermediate **I101** (780 mg, 3.23 mmol) in MeCN (28 mL) was slowly added NBS (633 mg, 3.56 mmol). The reaction mixture was stirred at rt for 18 h. The reaction mixture was diluted with EtOAc and H_2O. 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 under reduced pressure. The crude mixture was purified by preparative LC (regular SiOH, 30 µm, 80 g Grace®, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 100:0 to 90:10) to afford intermediate **I98** (817 mg, 79%) as a white powder.

Synthesis of compound **55**

Intermediate **I99**

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

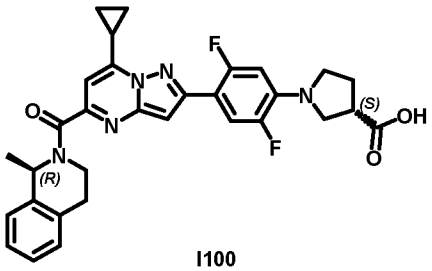


I99

A sealed tube was charged intermediate **I98** (200 mg, 625 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] (551 mg, 625 µmol, 52% purity), potassium phosphate tribasic (451 mg, 2.12 mmol), 1,4-dioxane (10 mL) and H_2O (3 mL) and purged with nitrogen. [1,1'-Bis-(di-*tert*-butylphosphino)ferrocene] palladium dichloride (44.8 mg 68.8 µmol) was added and the mixture was purged 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 brine, 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 Grace®, dry loading (SiOH), mobile phase gradient: heptane / EtOAc from 100:0 to 60:40). The residue (397 mg) was purified by preparative LC (spherical C18 25 µm, 40 g YMC-ODS-25, dry loading (C18), mobile phase gradient: (0.2% aq.NH_4HCO_3) / MeCN from 60:40 to 0:100) to afford intermediate **I99** (320 mg, 88%) as a yellow solid.

Intermediate **I100**

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

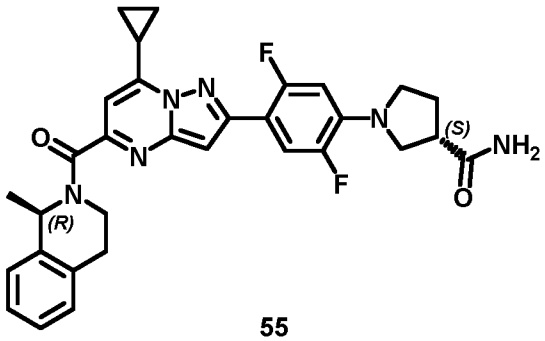


I100

Lithium hydroxide monohydrate (117 mg, 2.80 mmol) was added to a solution of intermediate **I99** (320 mg, 0.56 mmol) in THF (9 mL) and H_2O (1.8 mL). The reaction mixture was stirred at rt for 20 h. A 10% aqueous solution of $KHSO_4$ and EtOAc were 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 concentrated under reduced pressure. The crude mixture was purified by preparative LC (spherical C18 25 µm, 40 g YMC-ODS-25, dry loading (C18), mobile phase gradient: (0.2% aq.NH_4HCO_3) / MeCN from 75:25 to 35:65), to give intermediate **I100** (280 mg, 90%) as a yellow solid.

Compound 55

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

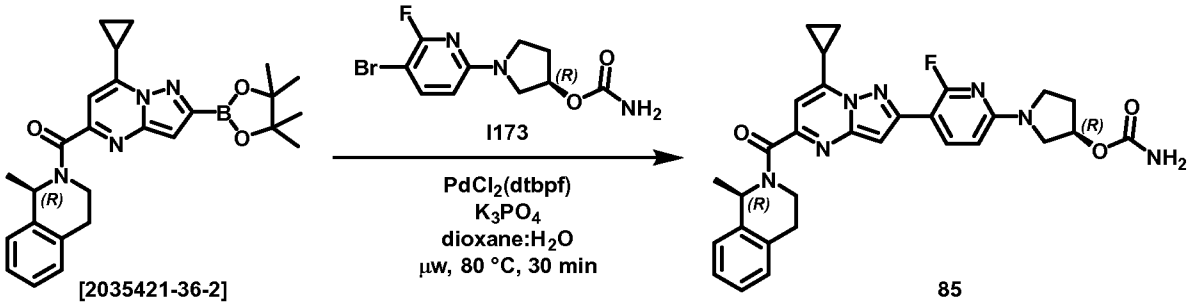


55

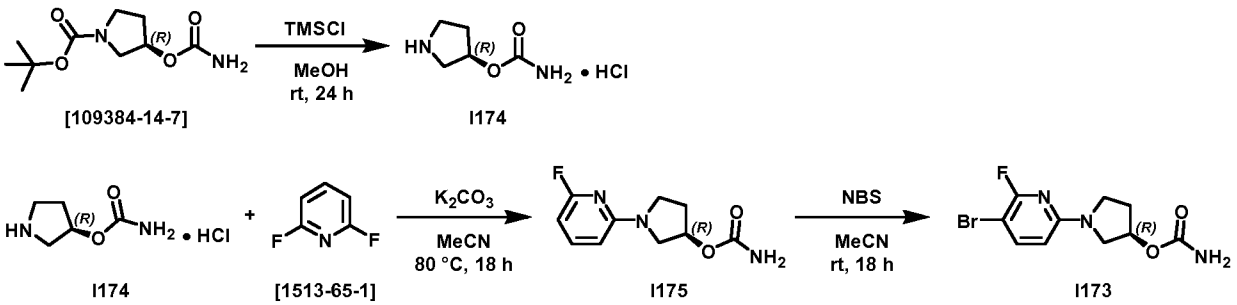
A mixture of intermediate **I100** (142 mg, 255 µmol), HATU (145 mg, 382 µmol) and DIPEA (132 µL, 0.76 mmol) in DMF (7 mL) was stirred at rt for 1 h. Ammonia (28% in H_2O, 86.1 µL, 1.27 mmol) was added and the reaction mixture was stirred at rt for 18 h. The reaction mixture was diluted with H_2O and 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 under reduced pressure. The crude mixture was purified by preparative LC (spherical C18 25 µm, 40 g YMC-ODS-25, dry loading (C18), mobile phase gradient (0.2% aq.NH_4HCO_3) / MeCN from 60:40 to 0:100). A second purification was carried out: preparative LC (spherical C18 25 µm, 40 g YMC-ODS-25,

dry loading (C18), mobile phase gradient: (0.2% aq.NH_4HCO_3) / MeCN from 60:40 to 0:100). The residue (80 mg) was purified by reverse phase (Stationary phase: YMC-actus Triart C18 10 µm 30*150mm, Mobile phase gradient: (0.2% aq. NH_4HCO_3) / MeCN from 50:50 to 0:100) to give compound **55** (60 mg, 47%) as a white solid.

Compound 85

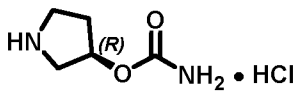


Synthesis of intermediate **I173**



Intermediate **I174**

(3*R*)-Pyrrolidin-3-yl carbamate hydrochloride

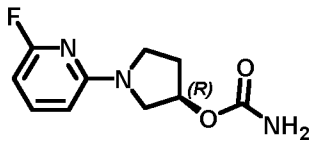


I174

A solution of *tert*-butyl (3*R*)-3-(carbamoyloxy)pyrrolidine-1-carboxylate [109384-14-7] (4.28 g, 18.6 mmol) and chlorotrimethylsilane (9.5 mL, 74.8 mmol) in MeOH (90 mL) was stirred at rt for 24 h. The mixture was evaporated in vacuo to afford intermediate **I174** (3.02 g, 98%).

Intermediate **I175**

(3*R*)-1-(6-Fluoropyridin-2-yl)pyrrolidin-3-yl carbamate

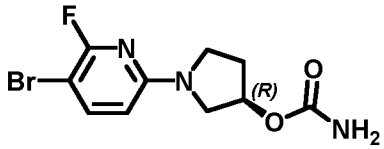


I175

A mixture of 2,6-difluoropyridine [1513-65-1] (628 mg, 5.46 mmol), intermediate **I174** (1.00 g, 6.00 mmol) and potassium carbonate (2.26 g, 16.4 mmol) in MeCN (42 mL) was stirred at 80°C for 18 h. The reaction mixture was diluted with H_2O 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 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 90:10 to 50:50) to afford intermediate **I175** (187.9 mg, 15%) as a white solid.

Intermediate **I173**

(3*R*)-1-(5-Bromo-6-fluoropyridin-2-yl)pyrrolidin-3-yl carbamate

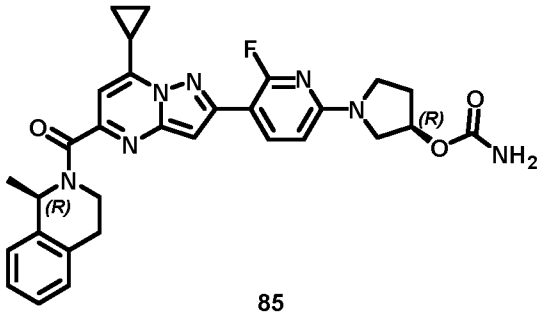


I173

A mixture of intermediate **I175** (188 mg, 834 µmol) and NBS (149 mg, 834 µmol) in MeCN (9.2 mL) was stirred at rt for 18 h. The reaction mixture was diluted with H_2O and EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc (twice). The combined organic extracts were washed with $NaHCO_3$ (twice), 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™, dry loading (Celite®), mobile phase gradient: heptane / EtOAc from 80:20 to 50:50) to afford intermediate **I173** (180 mg, 71%) as a white solid.

Synthesis of compound 85

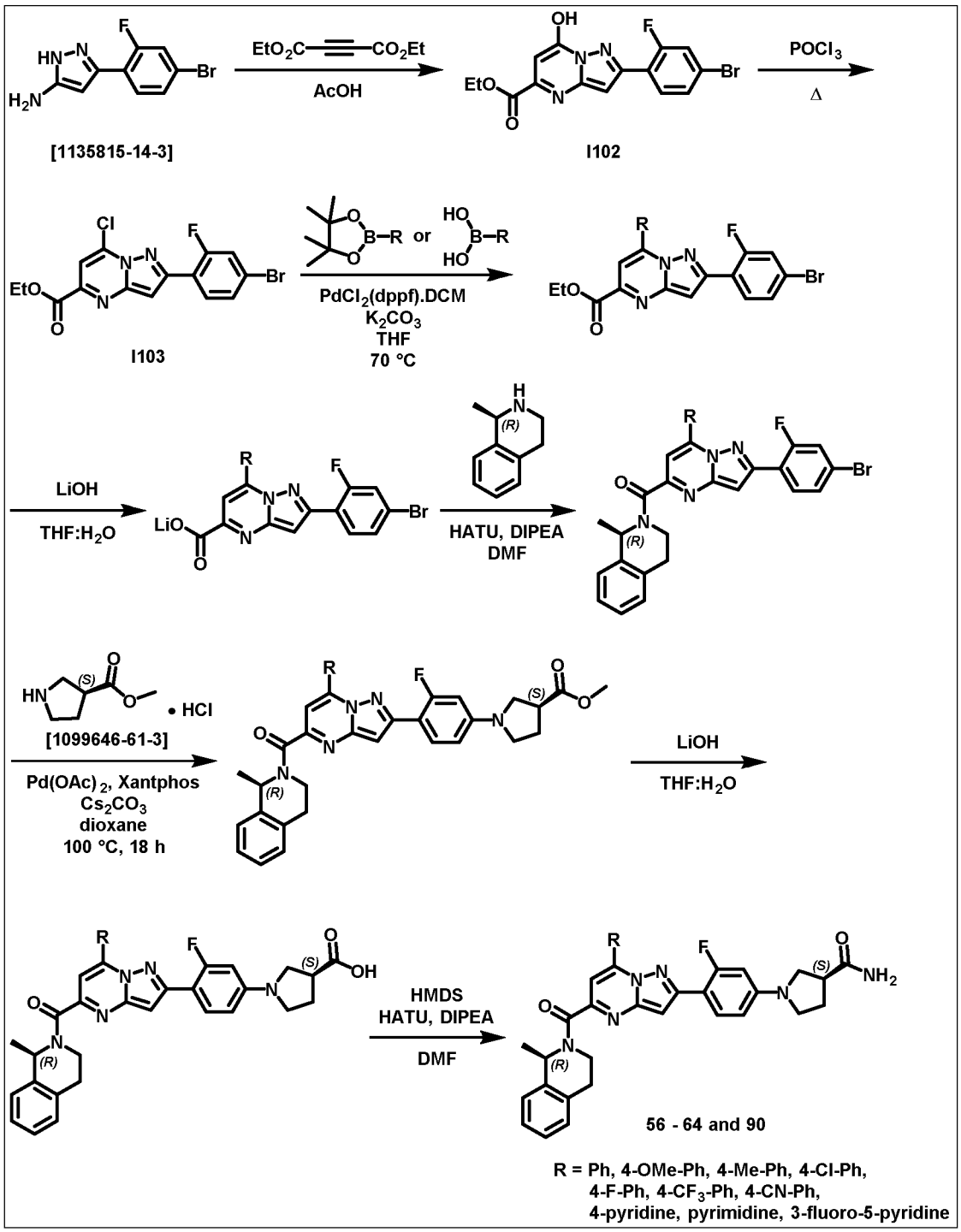
(3*R*)-1-(5-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-pyrazolo[1,5-a]pyrimidin-2-yl}-6-fluoropyridin-2-yl)pyrrolidin-3-yl carbamate



85

A sealed tube was charged with intermediate **I173** (120 mg, 395 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] (305 mg, 592 µmol, 89% purity), potassium phosphate tribasic (251 mg, 1.18 mmol), 1,4-dioxane (7.3 mL) and H_2O (1.1 mL) and purged with nitrogen. [1,1'-Bis(di-*tert*-butylphosphino)ferrocene] palladium dichloride (25.7 mg, 39.5 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 brine. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with H_2O (twice), 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: DCM / EtOAc from 100:0 to 80:20). The residue (100 mg) was triturated with MeCN. The solid was filtered off and dried under high vacuum at 50°C for 2 h to give compound **85** (28 mg, 13%) as a pale yellow solid.

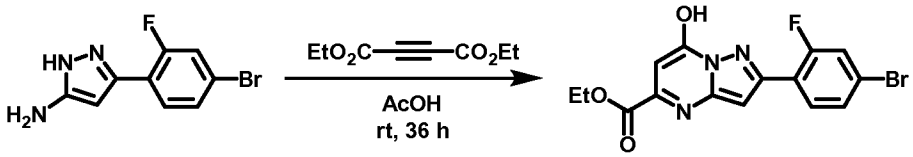
General Scheme



Synthesis of intermediates **I102** and **I103**

Intermediate **I102**

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

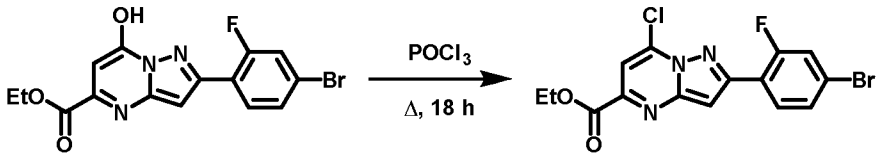


[1135815-14-3] I102

A mixture of 3-(4-bromo-2-fluorophenyl)-1H-pyrazol-5-amine (15.0 g, 58.6 mmol) and diethyl acetylenedicarboxylate (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 for 30 min. The precipitate was filtered off and dried under vacuum to afford intermediate **I102** (18.6 g, 84%).

Intermediate **I103**

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



I102 I103

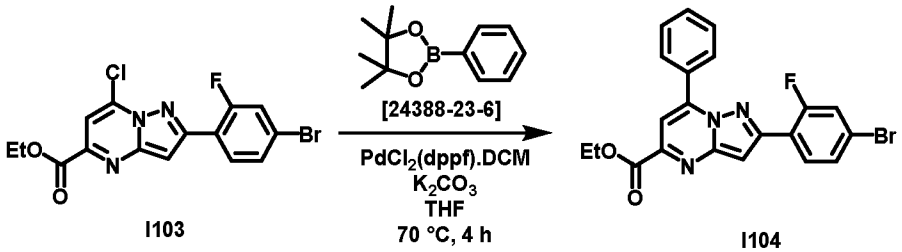
A mixture of intermediate **I102** (15.0 g, 39.5 mmol) in phosphorous (V) oxychloride (147 mL) was stirred under reflux for 18 h. The solvent was evaporated to dryness. H_2O was added slowly to the residue and the mixture was stirred at 0°C for 30 min. The precipitate was filtered off and dried under vacuum to afford intermediate **I103** (15.3 g, 97%).

Synthesis of compounds 56 to 64 and 90

Compound 56

Intermediate **I104**

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



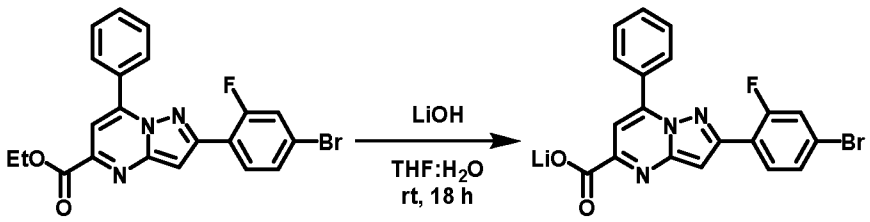
I103 I104

A mixture of intermediate **I103** (1.50 g, 3.76 mmol) and 2-phenyl-4,4,5,5-tetramethyl-1,2,3-dioxaborolane [24388-23-6] (691 mg, 3.39 mmol) in THF (30 mL) was degassed

with nitrogen for 10 min. [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium, complex with dichloromethane (308 mg, 376 µmol) and potassium carbonate (2.0 M in H_2O, 5.64 mL, 11.3 mmol) were added and the reaction mixture was stirred at 70°C for 4 h. The reaction mixture was poured out into water and EtOAc. The layers were separated and the organic phase was washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude mixture was purified by flash chromatography over silica gel (15-40 µm, cartridge 80 g, mobile phase gradient: heptane / EtOAc from 100:0 to 70:30) to afford intermediate **I104** (1.15 g, 69%). The product was used in the next step without further purification.

Intermediate **I105**

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

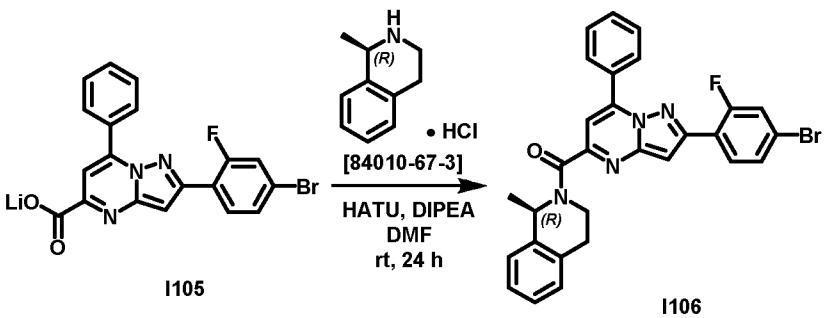


I104 I105

A mixture of intermediate **I104** (1.15 g, 2.61 mmol) and lithium hydroxide (125 mg, 5.22 mmol) in THF (13 mL) and H_2O (3 mL) was stirred at rt for 18 h. The solvent was evaporated under reduced pressure. Few drops of H_2O were added to the residue. The precipitate was filtered off and dried under vacuum to afford intermediate **I105** (1.2 g). The product was used in the next step without further purification.

Intermediate **I106**

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

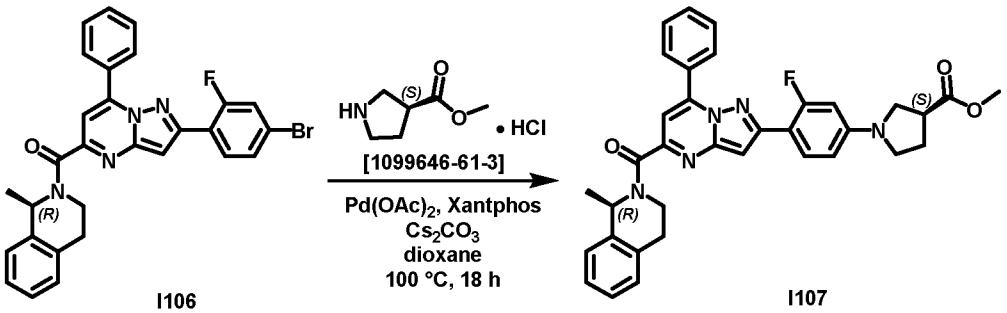


I105 I106

DIPEA (1.38 mL, 7.89 mmol) and HATU (1.30 g, 3.42 mmol) were added to a mixture of (1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride [84010-67-3] (0.58 g, 3.16 mmol) and intermediate **I105** (1.10 g, 2.63 mmol) in DMF (30 mL). The reaction mixture was stirred at rt for 24 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 (15-40 µm, 80 g GraceResolv™, mobile phase gradient: heptane / EtOAc from 100:0 to 75:25) to afford intermediate **I106** (1.3 g, 66%, 72% purity).

Intermediate **I107**

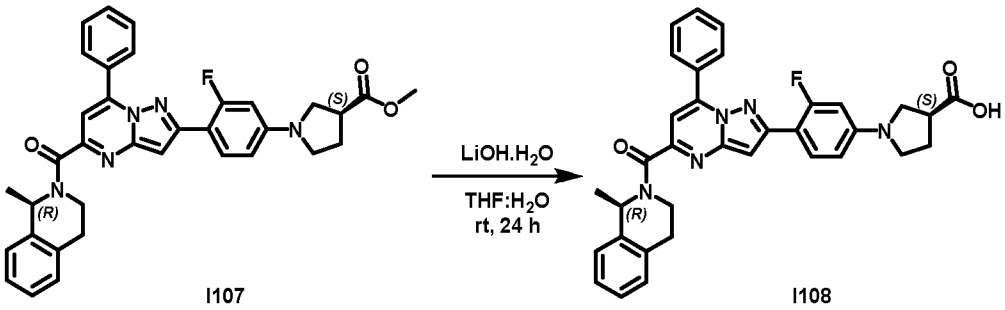
Methyl (3*S*)-1-(3-fluoro-4-{5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-7-phenylpyrazolo[1,5-a]pyrimidin-2-yl}phenyl)pyrrolidine-3-carboxylate



A mixture of intermediate **I106** (1.3 g, 1.73 mmol, 72% purity), (*S*)-methyl pyrrolidine-3-carboxylate hydrochloride [1099646-61-3] (419 mg, 2.08 mmol), cesium carbonate (1.69 g, 5.19 mmol) and XantPhos (100 mg, 0.17 mmol) was purged with nitrogen. 1,4-Dioxane (20 mL) was added and the mixture was purged again with nitrogen. Palladium acetate (38.8 mg, 0.17 mmol) was added. The reaction mixture was purged with nitrogen and stirred at 100°C for 18 h. The reaction mixture was diluted with EtOAc and H_2O. 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 the solvent was removed under reduced pressure. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 40 g Grace®, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 100:0 to 70:30) to afford intermediate **I107** (550 mg, 54%).

Intermediate **I108**

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

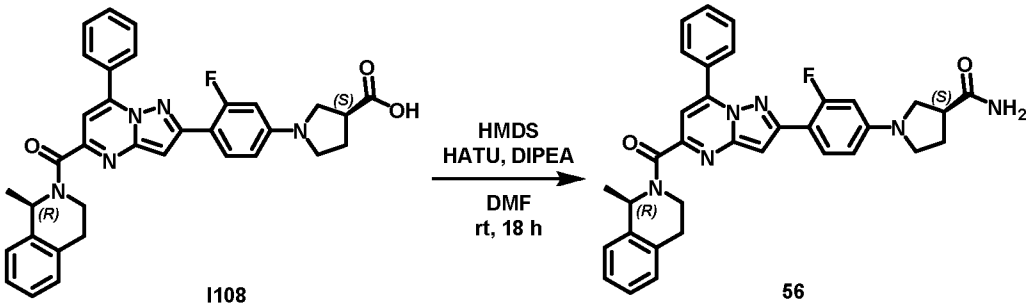


I107 I108

Lithium hydroxide monohydrate (195 mg, 4.66 mmol) was added to a solution of intermediate **I107** (550 mg, 0.93 mmol) in THF (7.6 mL) and H_2O (2.5 mL). The reaction mixture was stirred at rt for 24 h. Few drops of H_2O 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 under reduced pressure to afford intermediate **I108** (470 mg, 88%). The product was used as such in the next step.

Compound 56

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



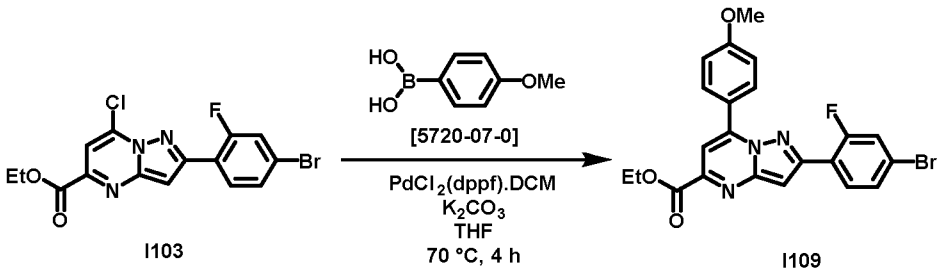
I108 56

A mixture of intermediate **I108** (230 mg, 0.40 mmol), HMDS (102 µL, 0.48 mmol), HATU (228 mg, 0.60 mmol) and DIPEA (138 µL, 0.80 mmol) in DMF (5 mL) was stirred at rt for 18 h. The reaction mixture was diluted with H_2O and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with H_2O, brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude mixture was purified by flash chromatography over silica gel (15-40 µm, 12 g Grace®, mobile phase gradient: DCM / MeOH from 100:0 to 96:4). The pure fractions were collected and concentrated to dryness. The residue (155 mg) was taken up in Et_2O, filtered and dried under vacuum to give compound **56** (101 mg, 44%).

Compound 57

Intermediate **I109**

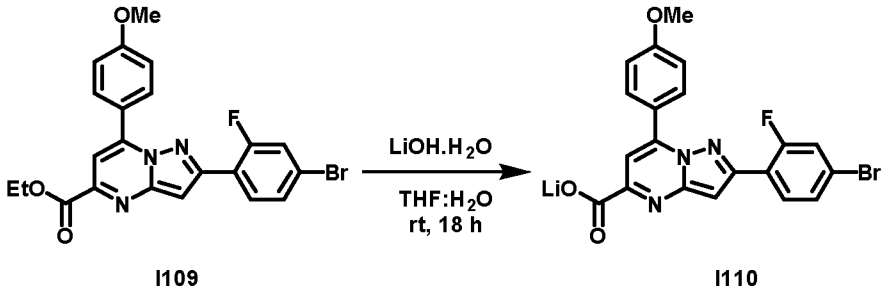
Ethyl 2-(4-bromo-2-fluorophenyl)-7-(4-methoxyphenyl)pyrazolo[1,5-a]pyrimidine-5-carboxylate



Intermediate **I109** (880 mg, 54%, 87% purity) was synthesized from intermediate **I103** and 4-methoxyphenylboronic acid [5720-07-0] according to the procedure reported for the synthesis of intermediate **I104**.

Intermediate **I110**

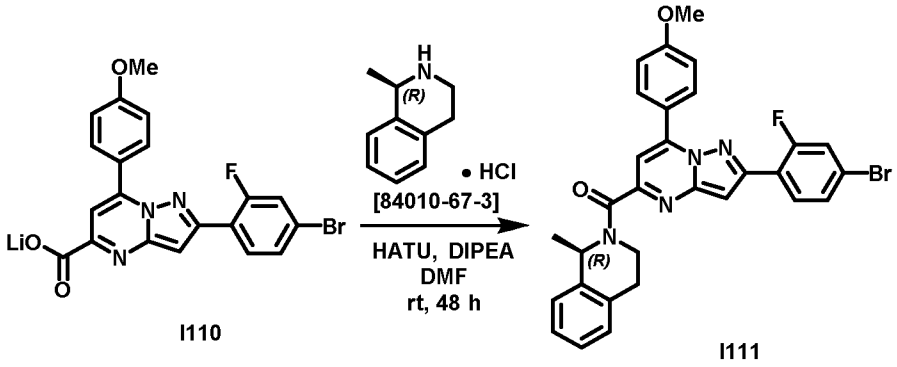
Lithio 2-(4-bromo-2-fluorophenyl)-7-(4-methoxyphenyl)pyrazolo[1,5-a]pyrimidine-5-carboxylate



Intermediate **I110** (150 mg, 90%) was synthesized from intermediate **I109** and lithium hydroxide monohydrate according to the procedure reported for the synthesis of intermediate **I105**.

Intermediate **I111**

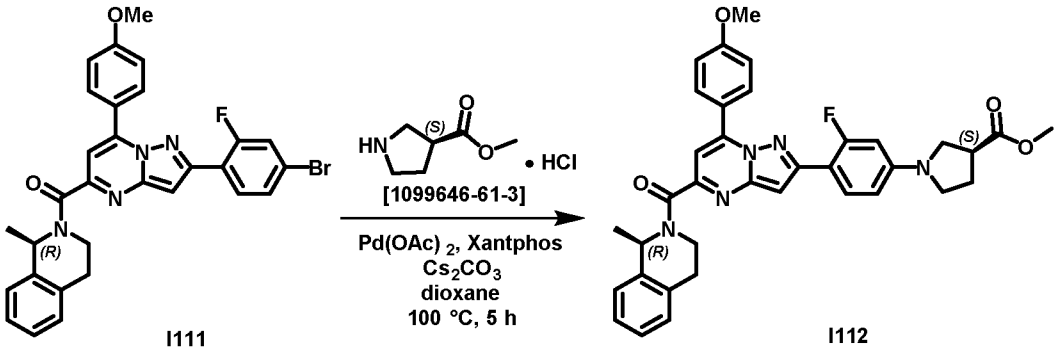
(1*R*)-2-[2-(4-Bromo-2-fluorophenyl)-7-(4-methoxyphenyl)pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline



Intermediate **I111** (740 mg, 48%) was synthesized from intermediate **I110** and (1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinolone hydrochloride [84010-67-3] according to the procedure reported for the synthesis of intermediate **I106** with a reaction time of 48 h.

Intermediate **I112**

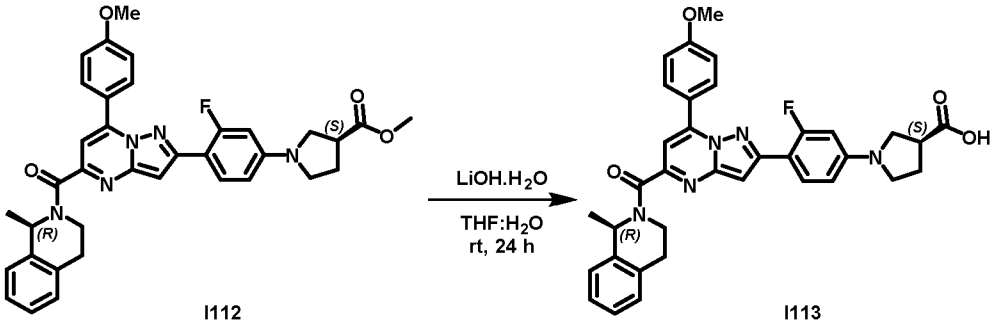
Methyl (3*S*)-1-{3-fluoro-4-[7-(4-methoxyphenyl)-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl]phenyl}pyrrolidine-3-carboxylate



Intermediate **I112** (290 mg, 67%) was synthesized from intermediate **I111** and (*S*)-methyl pyrrolidine-3-carboxylate hydrochloride [1099646-61-3] according to the procedure reported for the synthesis of intermediate **I107** with a shorter reaction time of 5 h.

Intermediate **I113**

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

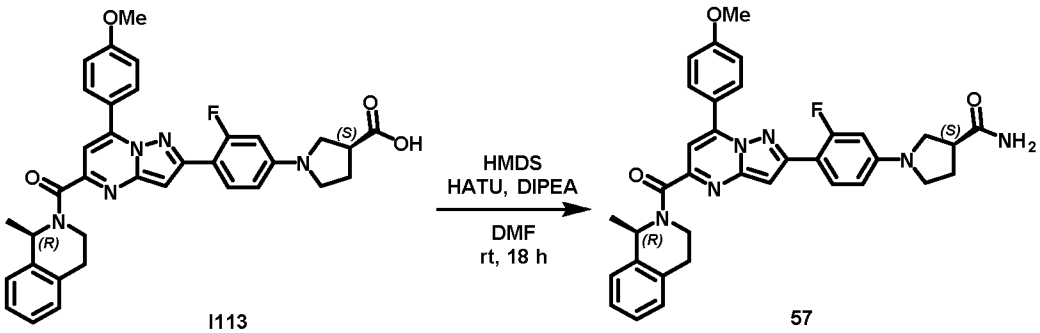


I112 I113

Intermediate **I113** was synthesized from intermediate **I112** according to the procedure reported for the synthesis of intermediate **I108**. The crude mixture was purified by flash chromatography over silica gel (15-40 µm, cartridge 24 g, mobile phase gradient: DCM / MeOH from 100:0 to 97:3) to afford intermediate **I113** (245 mg, 93%).

Compound 57

(3*S*)-1-{3-Fluoro-4-[7-(4-methoxyphenyl)-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydro-isoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl]phenyl}pyrrolidine-3-carboxamide



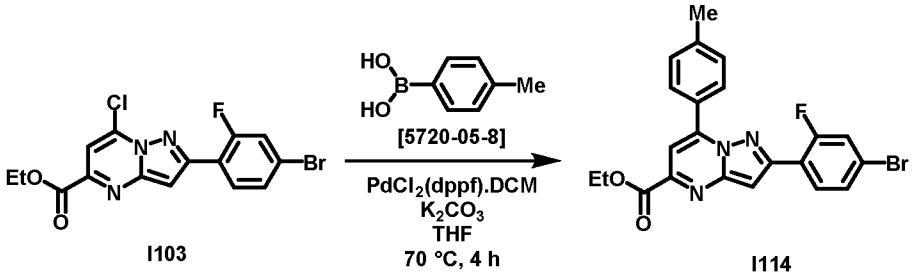
I113 57

Compound **57** (117 mg, 56%) was synthesized from intermediate **I113** according to the procedure reported for the synthesis of compound **56**.

Compound 58

Intermediate **I114**

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

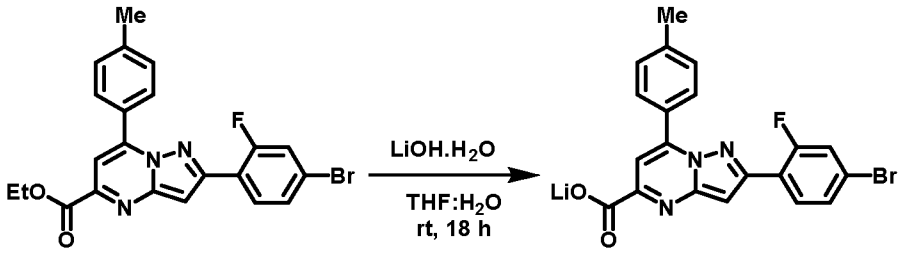


I103 I114

Intermediate **I114** (1.35 g, 70%, 88% purity) was synthesized from intermediate **I103** and 4-tolylboronic acid [5720-05-8] according to the procedure reported for the synthesis of intermediate **I104**.

Intermediate **I115**

Lithio 2-(4-bromo-2-fluorophenyl)-7-(4-methylphenyl)pyrazolo[1,5-a]pyrimidine-5-carboxylate

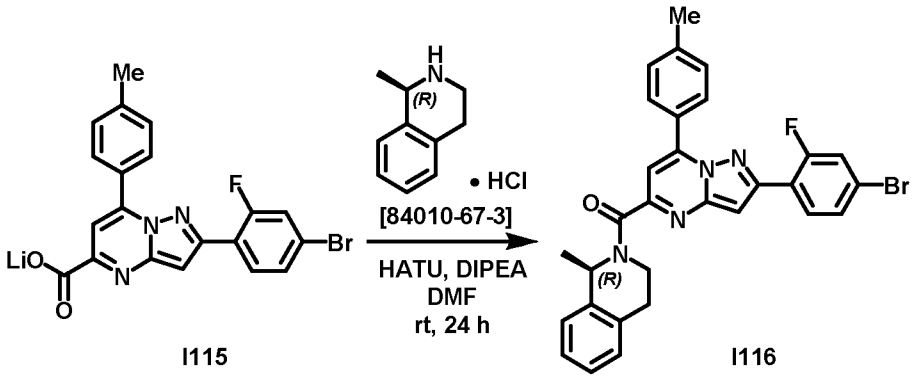


I114 I115

Intermediate **I115** (1.5 g) was synthesized from intermediate **I114** and lithium hydroxide monohydrate according to the procedure reported for the synthesis of intermediate **I105**.

Intermediate **I116**

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

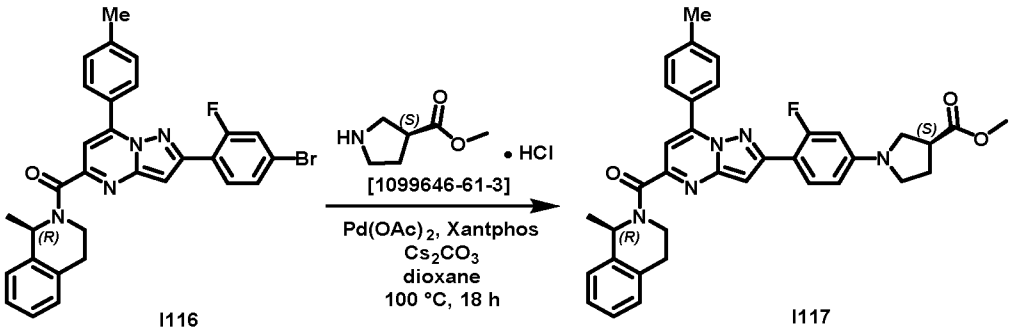


I115 I116

Intermediate **I116** (1.25 g, 65%) was synthesized from intermediate **I115** and (1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride [84010-67-3] according to the procedure reported for the synthesis of intermediate **I106**.

Intermediate **I117**

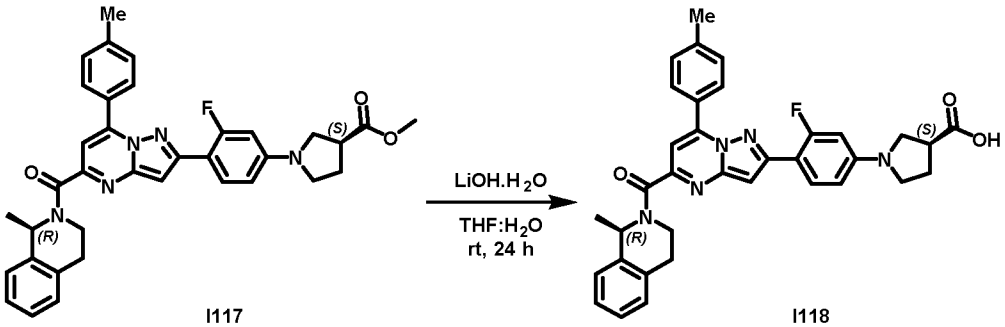
Methyl (3*S*)-1-(3-fluoro-4-{5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-7-(4-methylphenyl)pyrazolo[1,5-a]pyrimidin-2-yl}phenyl)pyrrolidine-3-carboxylate



Intermediate **I117** (300 mg, 61%) was synthesized from intermediate **I116** and (*S*)-methyl pyrrolidine-3-carboxylate hydrochloride [1099646-61-3] according to the procedure reported for the synthesis of intermediate **I107**.

Intermediate **I118**

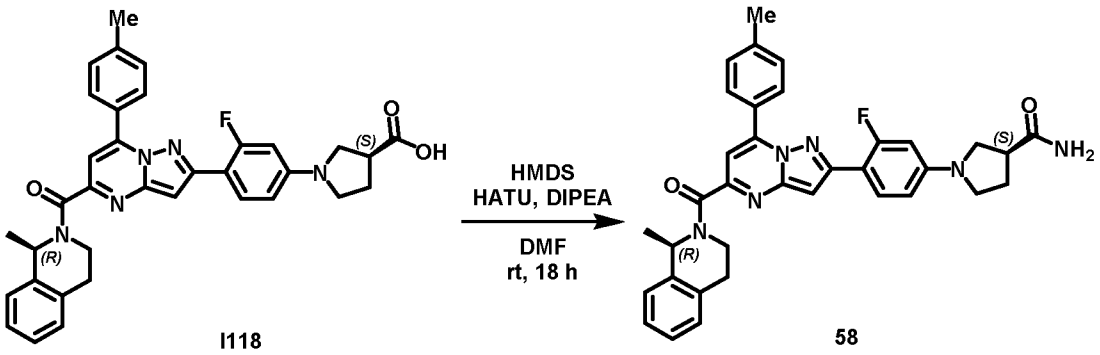
(3*S*)-1-(3-Fluoro-4-{5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-7-(4-methylphenyl)pyrazolo[1,5-a]pyrimidin-2-yl}phenyl)pyrrolidine-3-carboxylic acid



Intermediate **I118** was synthesized from intermediate **I117** according to the procedure reported for the synthesis of intermediate **I107**. The crude mixture was purified by flash chromatography on silica gel (15-40 µm, cartridge 12 g, mobile phase gradient: DCM / MeOH from 100:0 to 96:4). The pure fractions were collected and evaporated to dryness to afford intermediate **I118** (255 mg, 87%).

Compound 58

(3*S*)-1-(3-Fluoro-4-{5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-7-(4-methylphenyl)pyrazolo[1,5-a]pyrimidin-2-yl}phenyl)pyrrolidine-3-carboxamide

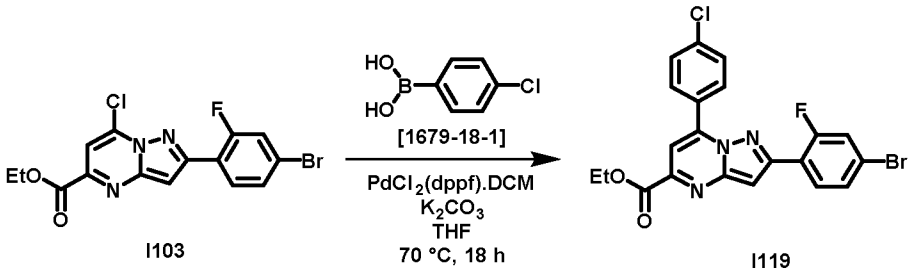


Compound **58** (102 mg, 51%) was synthesized from intermediate **I118** according to the procedure reported for the synthesis of compound **56**.

Compound 59

Intermediate **I119**

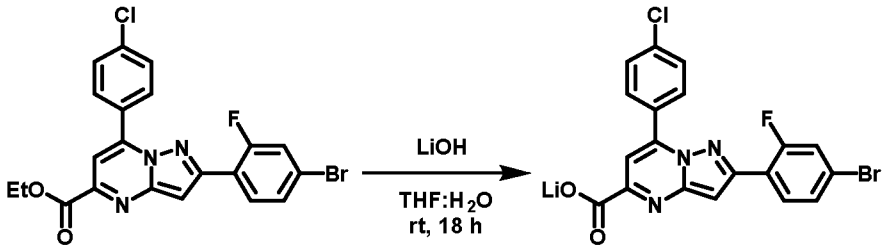
Ethyl 2-(4-bromo-2-fluorophenyl)-7-(4-chlorophenyl)pyrazolo[1,5-a]pyrimidine-5-carboxylate



A mixture of intermediate **I103** (2.00 g, 5.02 mmol) and 4-chlorophenylboronic acid [1679-18-1] (706 mg, 4.52 mmol) in THF (40 mL) was degassed with nitrogen for 10 min. [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium, complex with dichloromethane (410 mg, 0.50 mmol) and potassium carbonate (2.0 M in H_2O, 7.53 mL, 15.1 mmol) were added and the reaction mixture was stirred at 70°C for 18 h. The reaction mixture was poured out into water and the precipitated was filtered off. The solid was dried under vacuum at 60°C to afford intermediate **I119** (2.2 g, 92%). The product was sued in the next step without further purification.

Intermediate **I120**

Lithio 2-(4-bromo-2-fluorophenyl)-7-(4-chlorophenyl)pyrazolo[1,5-a]pyrimidine-5-carboxylate

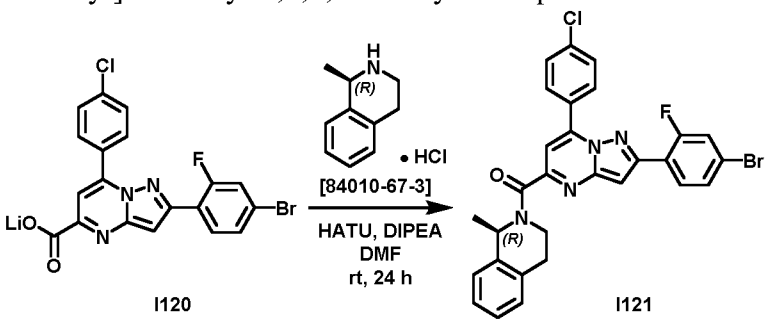


I119 I120

Intermediate **I120** (2.0 g, 95%) was synthesized from intermediate **I119** and lithium hydroxide according to the procedure reported for the synthesis of intermediate **I105**.

Intermediate **I121**

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

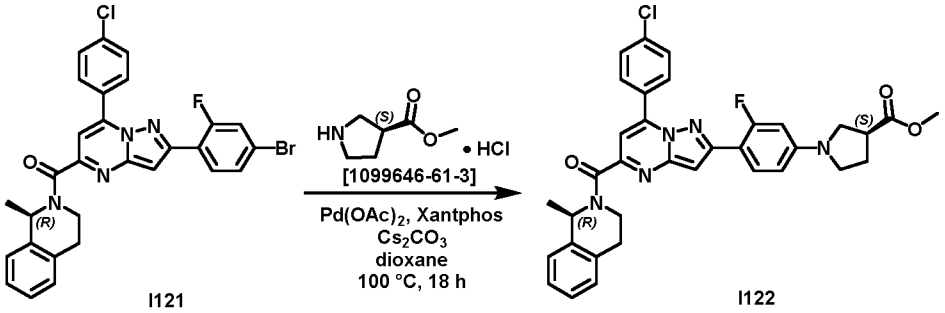


I120 I121

Intermediate **I121** (1.4 g, 55%) was synthesized from intermediate **I120** and (1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride [84010-67-3] according to the procedure reported for the synthesis of intermediate **I106**.

Intermediate **I122**

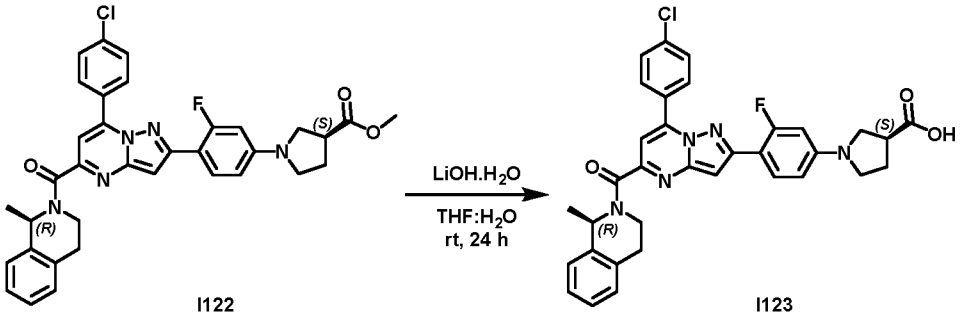
Methyl (3*S*)-1-{4-[7-(4-chlorophenyl)-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl]-3-fluorophenyl}pyrrolidine-3-carboxylate



Intermediate **I122** (290 mg, 48%) was synthesized from intermediate **I121** and (*S*)-methyl pyrrolidine-3-carboxylate hydrochloride [1099646-61-3] according to the procedure reported for the synthesis of intermediate **I107**.

Intermediate **I123**

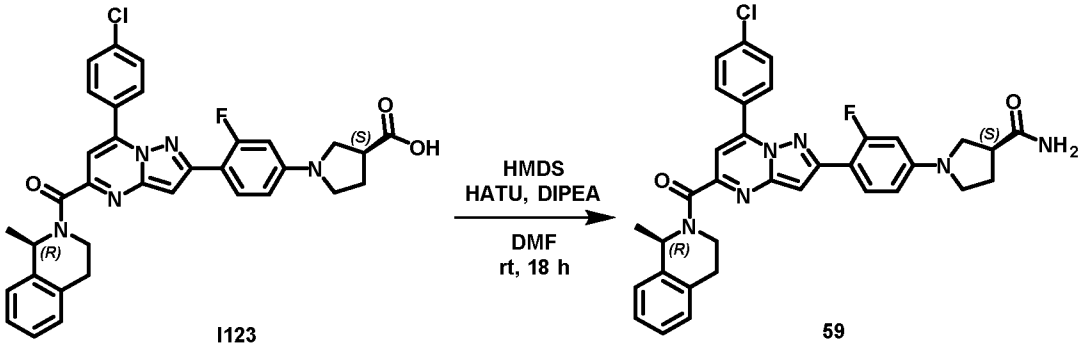
(3*S*)-1-{4-[7-(4-Chlorophenyl)-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl]-3-fluorophenyl}pyrrolidine-3-carboxylic acid



Intermediate **I123** (245 mg, 86%) was synthesized from intermediate **I122** according to the procedure reported for the synthesis of intermediate **I107**.

Compound **59**

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

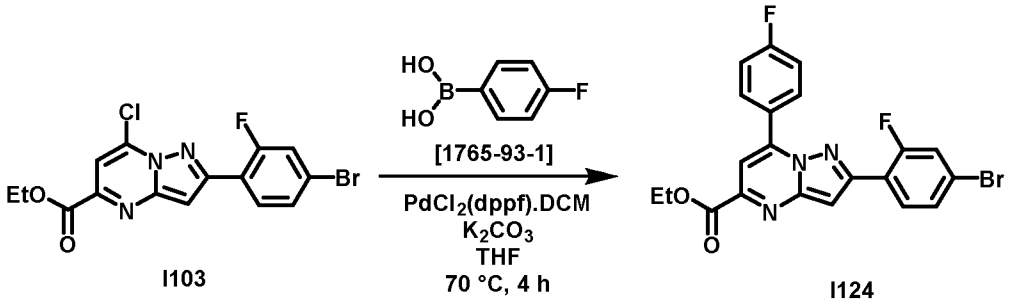


Compound **59** was synthesized from intermediate **I123** according to the procedure reported for the synthesis of compound **56**. The residue (125 mg) was taken up in DIPE. The solid was filtered off and dried under vacuum to give compound **59** (85 mg, 45%).

Compound 60

Intermediate **I124**

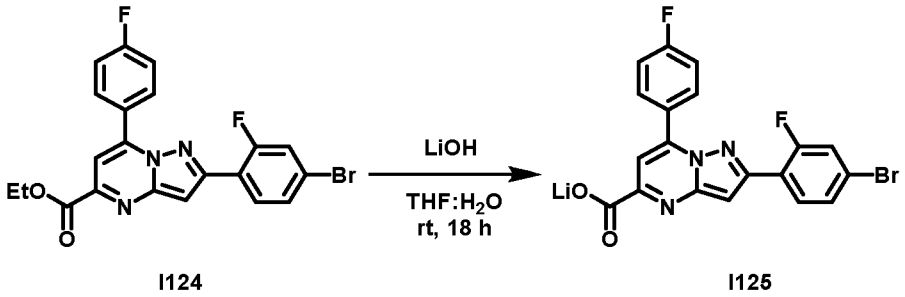
Ethyl 2-(4-bromo-2-fluorophenyl)-7-(4-fluorophenyl)pyrazolo[1,5-a]pyrimidine-5-carboxylate



Intermediate **I124** (940 mg, 48%) was synthesized from intermediate **I103** and 4-fluorobenzeneboronic acid [1765-93-1] according to the procedure reported for the synthesis of intermediate **I119** with a shorter reaction time of 4 h.

Intermediate **I125**

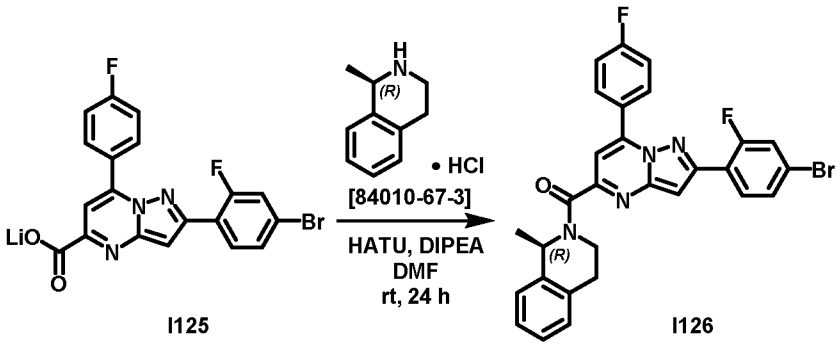
Lithio 2-(4-bromo-2-fluorophenyl)-7-(4-fluorophenyl)pyrazolo[1,5-a]pyrimidine-5-carboxylate



Intermediate **I125** (940 mg) was synthesized from intermediate **I124** and lithium hydroxide according to the procedure reported for the synthesis of intermediate **I105**.

Intermediate **I126**

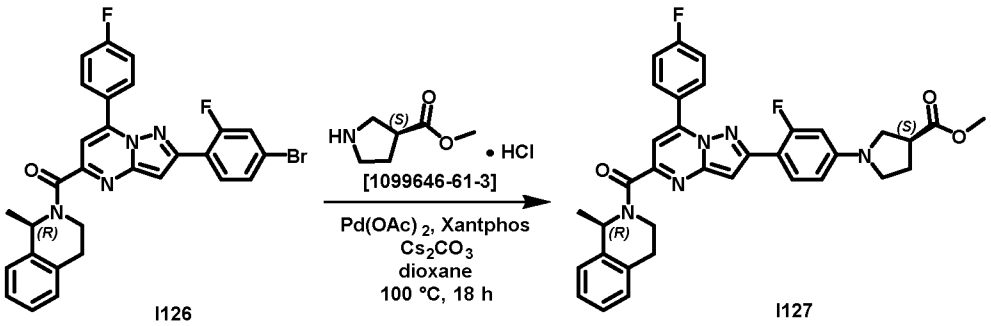
(1*R*)-2-[2-(4-Bromo-2-fluorophenyl)-7-(4-fluorophenyl)pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline



Intermediate **I126** (970 mg, 79%) was synthesized from intermediate **I125** and (1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride [84010-67-3] according to the procedure reported for the synthesis of intermediate **I106**.

Intermediate **I127**

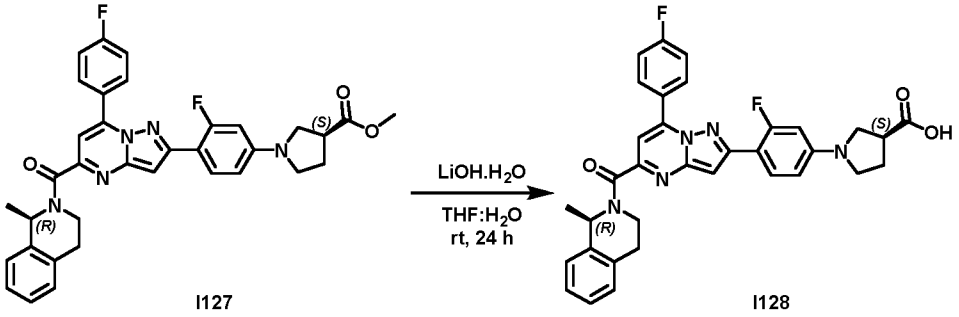
Methyl (3*S*)-1-{3-fluoro-4-[7-(4-fluorophenyl)-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl]phenyl}pyrrolidine-3-carboxylate



Intermediate **I127** (340 mg, 65%) was synthesized from intermediate **I126** and (*S*)-methyl pyrrolidine-3-carboxylate hydrochloride [1099646-61-3] according to the procedure reported for the synthesis of intermediate **I107**.

Intermediate **I128**

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

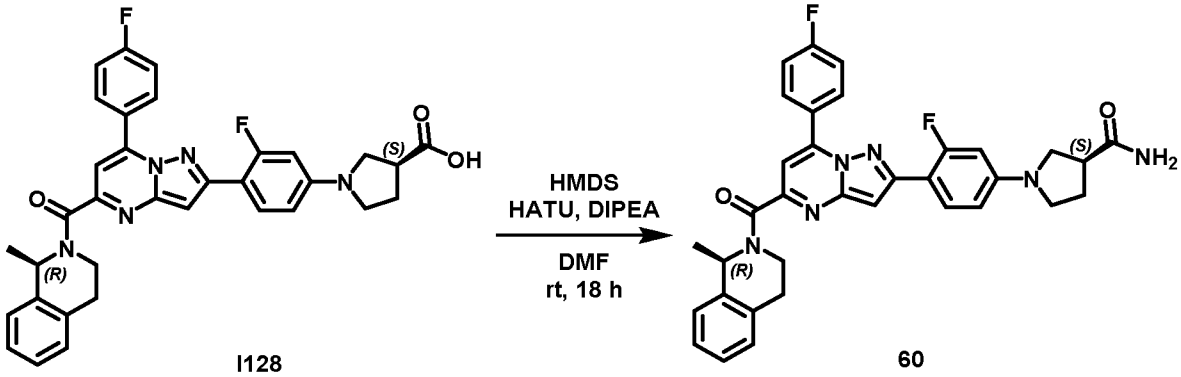


I127 I128

Intermediate **I128** (300 mg, 90%) was synthesized from intermediate **I127** according to the procedure reported for the synthesis of intermediate **I107**.

Compound 60

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



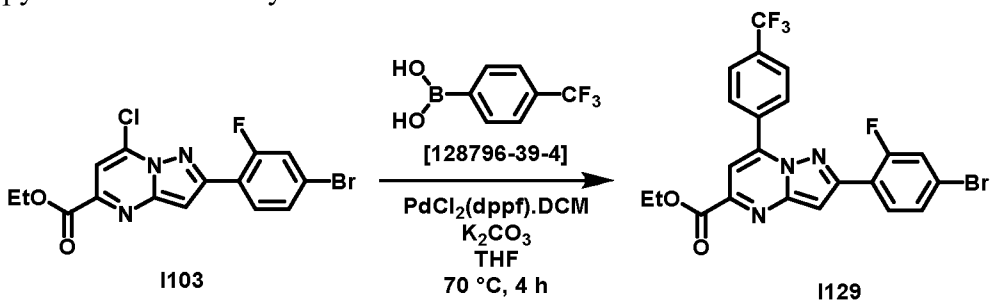
I128 60

Compound **60** was synthesized from intermediate **I128** according to the procedure reported for the synthesis of compound **56**. The residue (190 mg) was taken up in DIPE. The solid was filtered off and dried under vacuum to give compound **60** (125 mg, 42%).

Compound 61

Intermediate **I129**

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

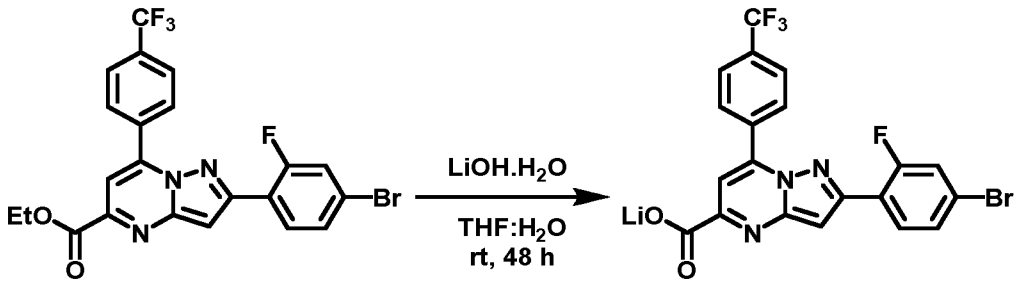


I103 I129

Intermediate **I129** (1.1 g, 51%) was synthesized from intermediate **I103** and 4-(trifluoromethyl)phenylboronic acid [128796-39-4] according to the procedure reported for the synthesis of intermediate **I104**.

Intermediate **I130**

Lithio 2-(4-bromo-2-fluorophenyl)-7-[4-(trifluoromethyl)phenyl]pyrazolo[1,5-a]pyrimidine-5-carboxylate

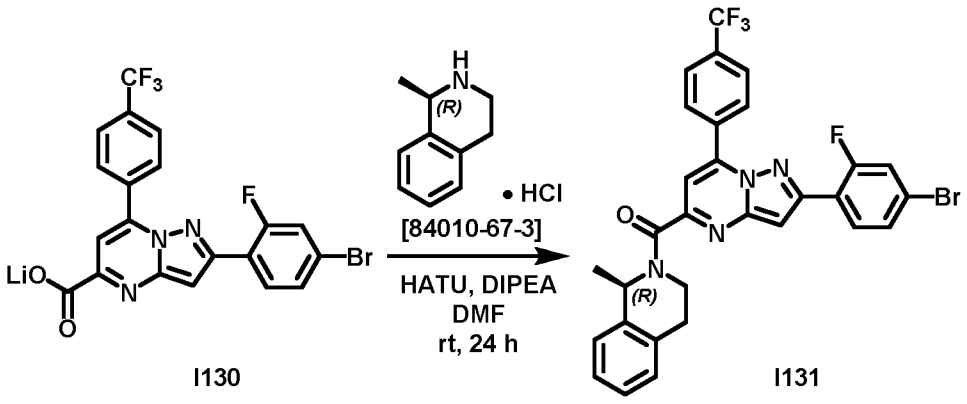


I129 I130

Intermediate **I130** (1.1 g) was synthesized from intermediate **I129** and lithium hydroxide monohydrate according to the procedure reported for the synthesis of intermediate **I105** with a reaction time of 48 h.

Intermediate **I131**

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

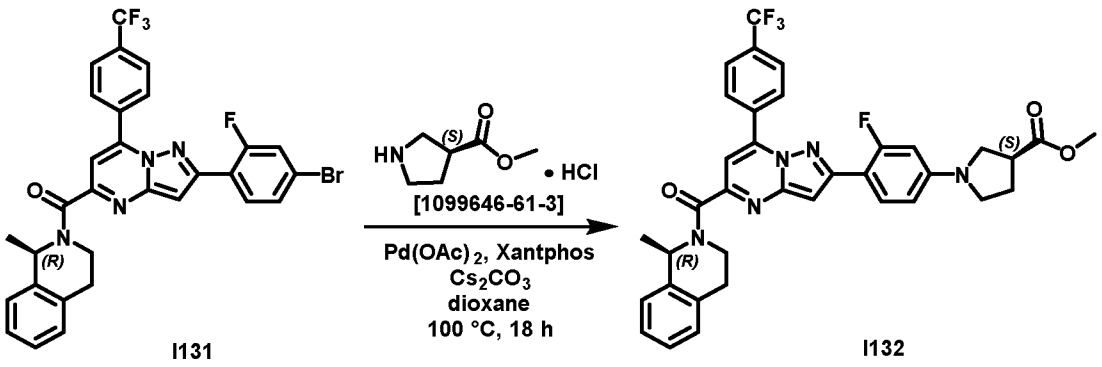


I130 I131

Intermediate **I131** (1.17 g, 74%, 87% purity) was synthesized from intermediate **I130** and (1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride [84010-67-3] according to the procedure reported for the synthesis of intermediate **I106**.

Intermediate **I132**

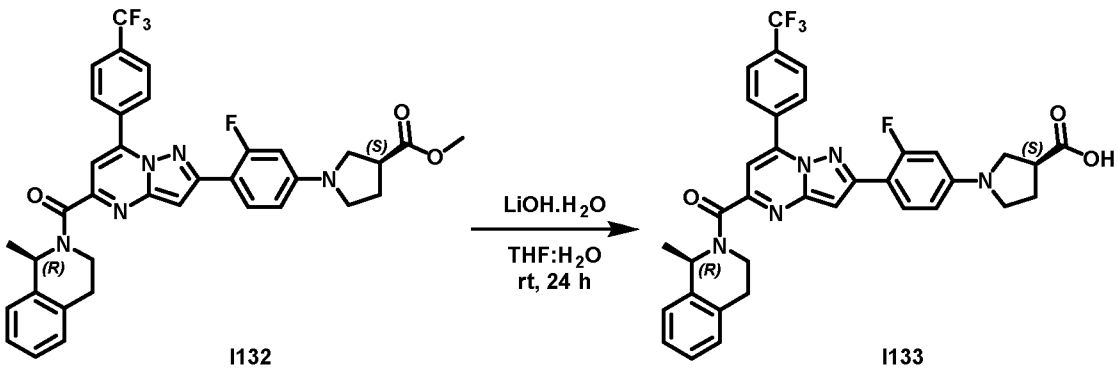
Methyl (3*S*)-1-(3-fluoro-4-{5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-7-[4-(trifluoromethyl)phenyl]pyrazolo[1,5-a]pyrimidin-2-yl}phenyl)pyrrolidine-3-carboxylate



Intermediate **I132** (240 mg, 57%) was synthesized from intermediate **I131** and (*S*)-methyl pyrrolidine-3-carboxylate hydrochloride [1099646-61-3] according to the procedure reported for the synthesis of intermediate **I107**.

Intermediate **I133**

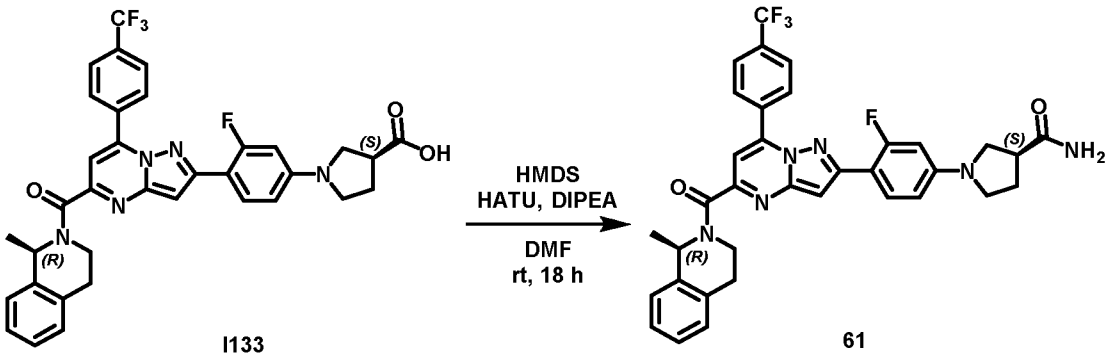
(3*S*)-1-(3-Fluoro-4-{5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-7-[4-(trifluoromethyl)phenyl]pyrazolo[1,5-a]pyrimidin-2-yl}phenyl)pyrrolidine-3-carboxylic acid



Intermediate **I133** (210 mg, 66%) was synthesized from intermediate **I132** according to the procedure reported for the synthesis of intermediate **I107**.

Compound 61

(3*S*)-1-(3-Fluoro-4-{5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-7-[4-(trifluoromethyl)phenyl]pyrazolo[1,5-a]pyrimidin-2-yl}phenyl)pyrrolidine-3-carboxamide



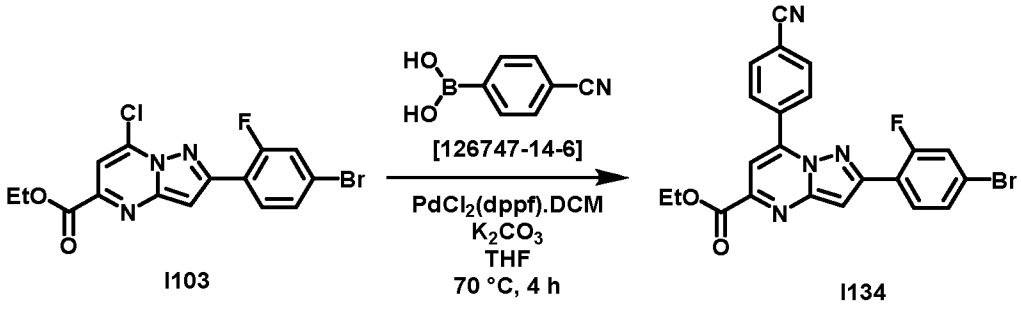
I133 61

Compound **61** (82 mg, 44%) was synthesized from intermediate **I133** according to the procedure reported for the synthesis of compound **56**.

Compound 62

Intermediate **I134**

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

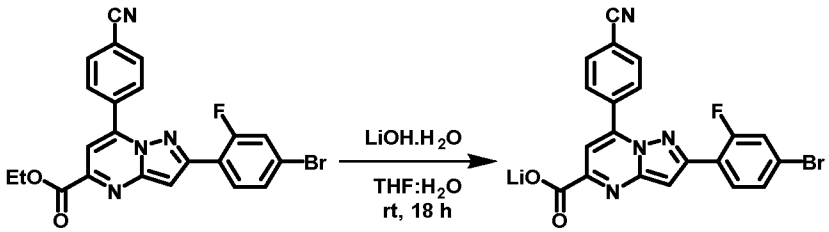


I103 I134

Intermediate **I134** (730 mg, 42%) was synthesized from intermediate **I103** and 4-cyanophenylboronic acid [126747-14-6] according to the procedure reported for the synthesis of intermediate **I104**.

Intermediate **I135**

Lithio 2-(4-bromo-2-fluorophenyl)-7-(4-cyanophenyl)pyrazolo[1,5-a]pyrimidine-5-carboxylate

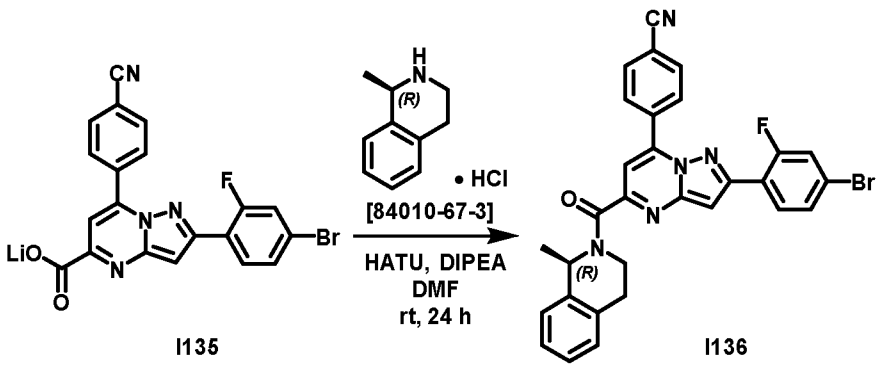


I134 I135

Intermediate **I135** (0.8 g) was synthesized from intermediate **I134** and lithium hydroxide monohydrate according to the procedure reported for the synthesis of intermediate **I105**.

Intermediate **I136**

4-[2-(4-Bromo-2-fluorophenyl)-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-7-yl]benzonitrile

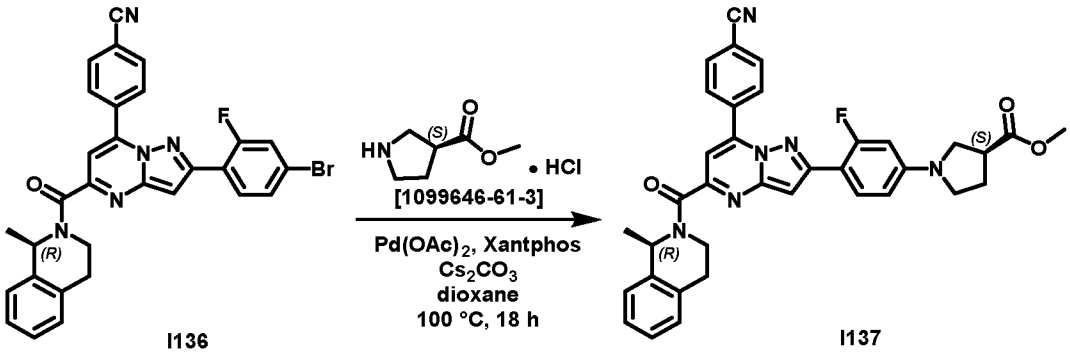


I135 I136

Intermediate **I136** (620 mg, 61%) was synthesized from intermediate **I135** and (1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride [84010-67-3] according to the procedure reported for the synthesis of intermediate **I106**.

Intermediate **I137**

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

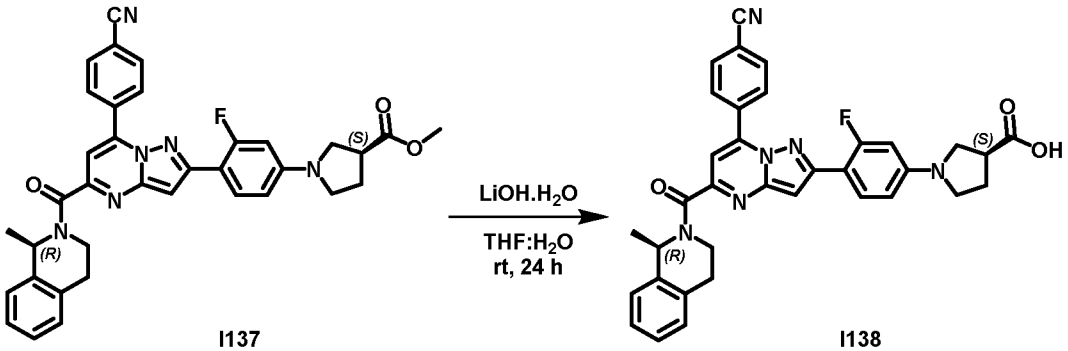


I136 I137

Intermediate **I137** (380 mg, 56%) was synthesized from intermediate **I136** and (*S*)-methyl pyrrolidine-3-carboxylate hydrochloride [1099646-61-3] according to the procedure reported for the synthesis of intermediate **I107**.

Intermediate **I138**

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

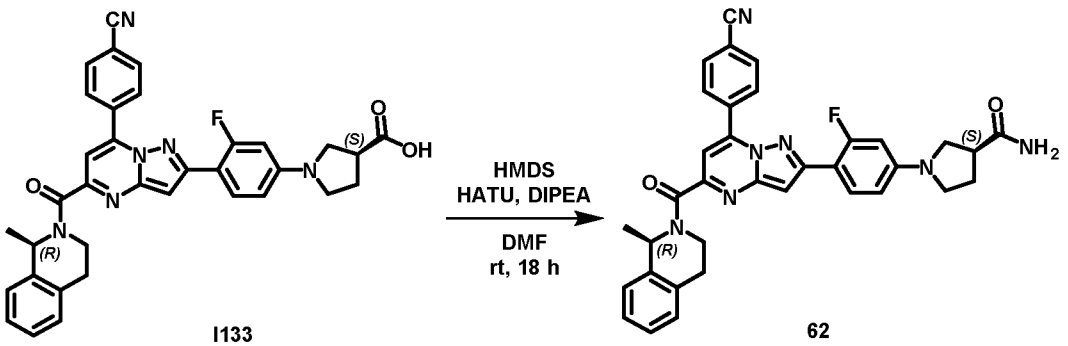


I137 I138

Intermediate **I138** was synthesized from intermediate **I137** according to the procedure reported for the synthesis of intermediate **I107**. The crude mixture was purified by flash chromatography on silica gel (15-40 µm, Grace® 12 g, mobile phase gradient: DCM / MeOH from 100:0 to 96:4). The pure fractions were collected and evaporated to dryness to afford intermediate **I138** (265 mg, 71%).

Compound 62

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



I133 62

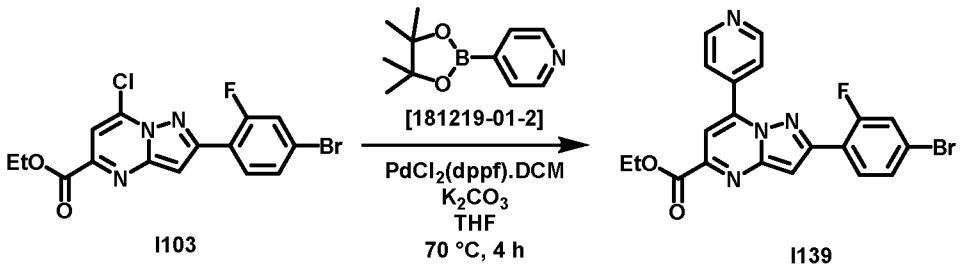
Compound **62** was synthesized from intermediate **I133** according to the procedure reported for the synthesis of compound **56**. The residue (125 mg) was taken up in DIPE and DCM

(3 drops). The solid was filtered off and dried under vacuum to give compound **62** (45 mg, 20%).

Compound 63

Intermediate **I139**

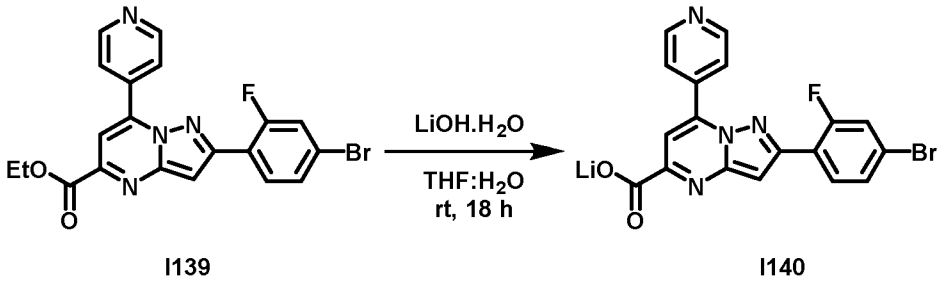
Ethyl 2-(4-bromo-2-fluorophenyl)-7-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine-5-carboxylate



Intermediate **I139** was synthesized from intermediate **I103** and 4-pyridineboronic acid pinacol ester [181219-01-2] according to the procedure reported for the synthesis of intermediate **I104**. The crude mixture was purified by flash chromatography over silica gel (15-40 µm, 40 g GraceResolv™, mobile phase gradient: heptane / EtOAc from 90:10 to 50:50) to afford intermediate **I139** (350 mg, 21%).

Intermediate **I140**

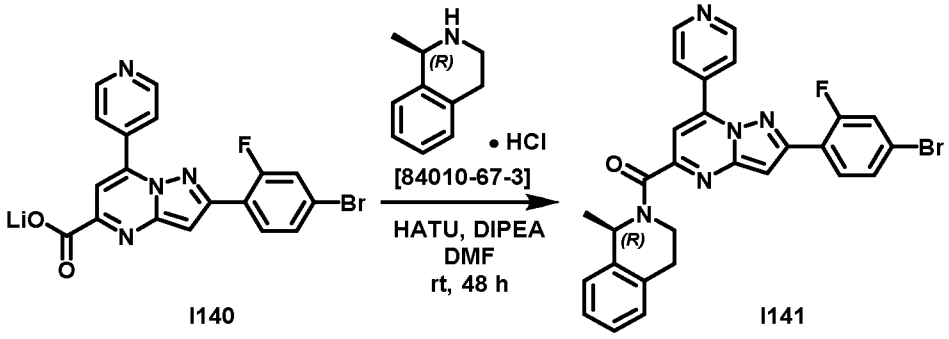
Lithio 2-(4-bromo-2-fluorophenyl)-7-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine-5-carboxylate



Intermediate **I140** (410 mg) was synthesized from intermediate **I139** and lithium hydroxide monohydrate according to the procedure reported for the synthesis of intermediate **I105**.

Intermediate **I141**

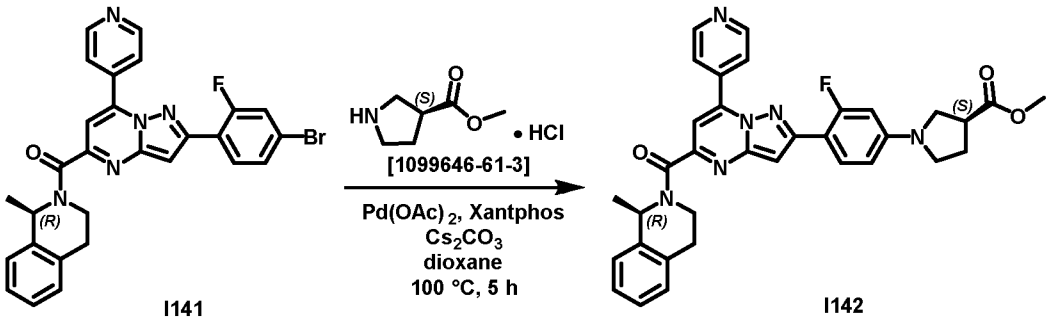
(1*R*)-2-[2-(4-Bromo-2-fluorophenyl)-7-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline



Intermediate **I141** (345 mg, 67%) was synthesized from intermediate **I140** and (1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride [84010-67-3] according to the procedure reported for the synthesis of intermediate **I106** with a reaction time of 48 h.

Intermediate **I142**

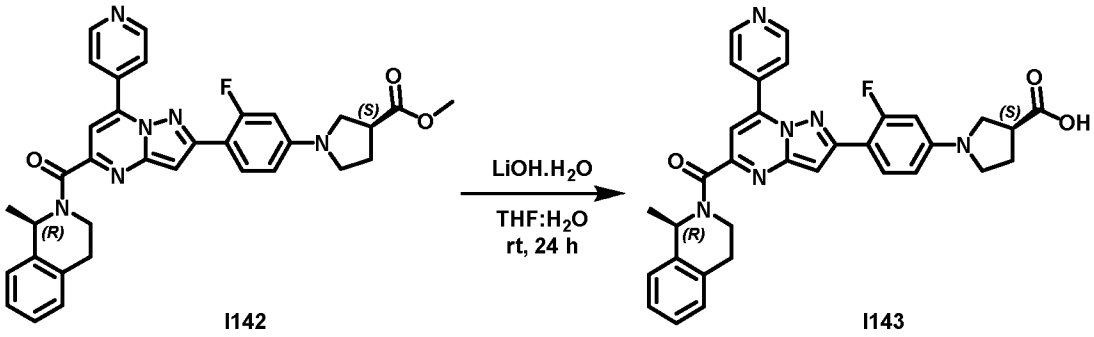
Methyl (3*S*)-1-(3-fluoro-4-{5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-7-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-2-yl}phenyl)pyrrolidine-3-carboxylate



Intermediate **I142** was synthesized from intermediate **I141** and (*S*)-methyl pyrrolidine-3-carboxylate hydrochloride [1099646-61-3] according to the procedure reported for the synthesis of intermediate **I107** with a reaction time of 5 h. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 40 g Grace®, liquid injection (DCM), mobile phase gradient: DCM / MeOH from 100:0 to 95:5) to afford intermediate **I142** (220 mg, 59%).

Intermediate **I143**

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

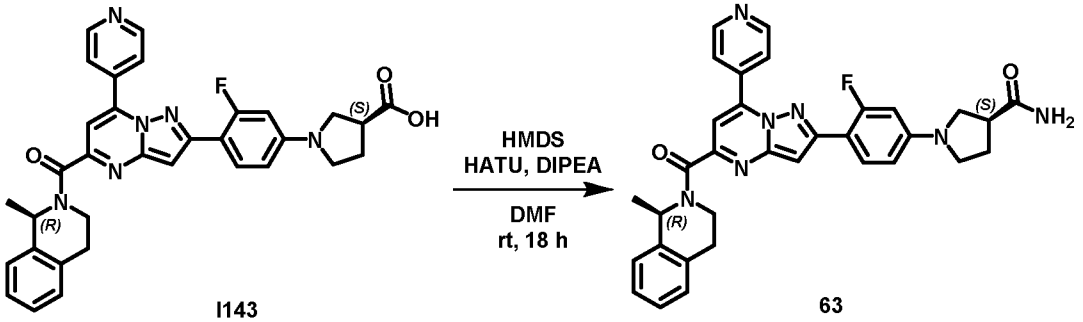


I142 I143

Intermediate **I143** was synthesized from intermediate **I142** according to the procedure reported for the synthesis of intermediate **I107**. The crude mixture was purified by flash chromatography on silica gel (15-40 µm, 12 g Grace®, mobile phase gradient: DCM / MeOH from 100:0 to 96:4). The pure fractions were collected and evaporated to dryness. The residue (125 mg) was taken up in DIPE. The solid was filtered off and dried under vacuum to afford intermediate **I143** (39 mg, 18%).

Compound 63

(3*S*)-1-(3-Fluoro-4-{5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-7-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-2-yl}phenyl)pyrrolidine-3-carboxamide



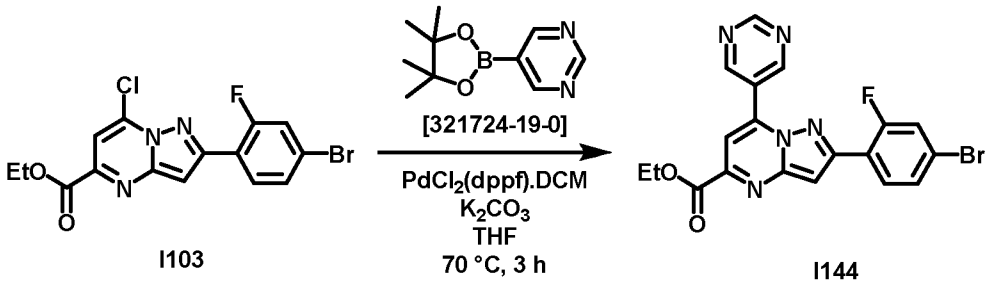
I143 63

Compound **63** was synthesized from intermediate **I143** according to the procedure reported for the synthesis of compound **56**. The residue (53 mg) was taken up in DIPE. The solid was filtered off and dried under vacuum to give compound **63** (23 mg, 27%).

Compound 64

Intermediate **I144**

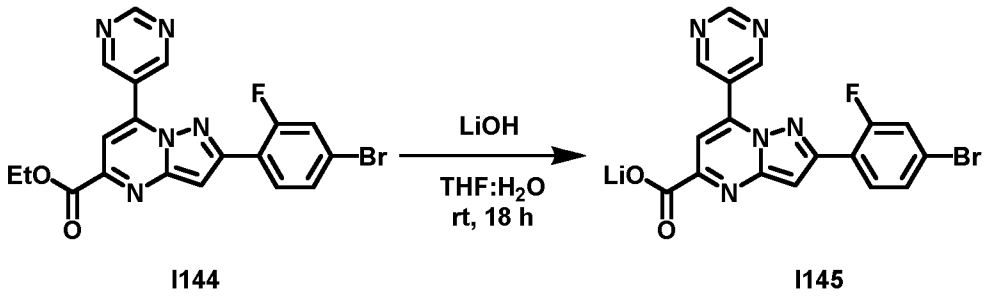
Ethyl 2-(4-bromo-2-fluorophenyl)-7-(pyrimidin-5-yl)pyrazolo[1,5-a]pyrimidine-5-carboxylate



Intermediate **I144** (3.4g) was synthesized from intermediate **I103** and 5-pyrimidineboronic acid pinacol ester [321724-19-0] according to the procedure reported for the synthesis of intermediate **I119** with a shorter reaction time of 3 h.

Intermediate **I145**

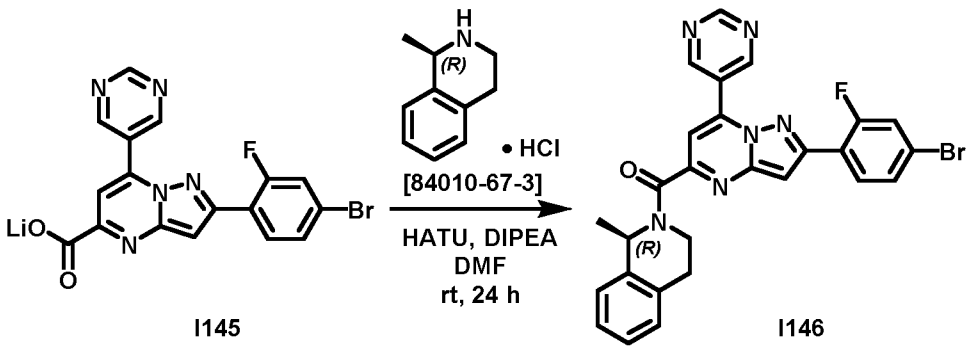
Lithio 2-(4-bromo-2-fluorophenyl)-7-(pyrimidin-5-yl)pyrazolo[1,5-a]pyrimidine-5-carboxylate



Intermediate **I145** (3.0 g, 99%) was synthesized from intermediate **I144** and lithium hydroxide according to the procedure reported for the synthesis of intermediate **I105**.

Intermediate **I146**

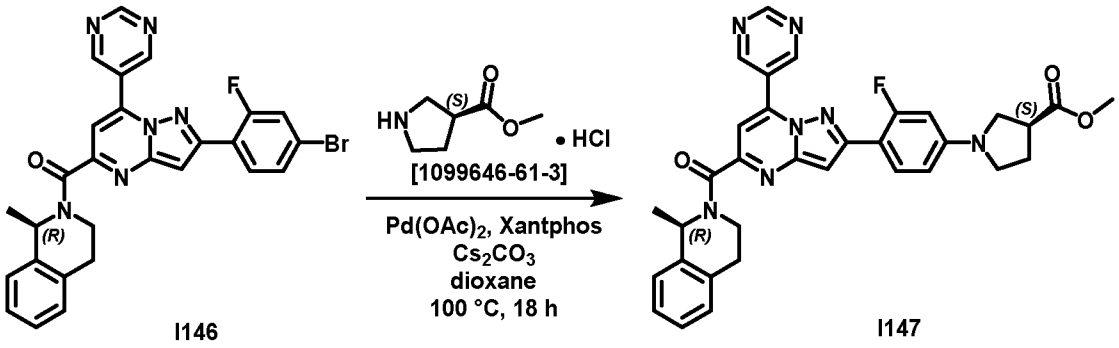
(1*R*)-2-[2-(4-Bromo-2-fluorophenyl)-7-(pyrimidin-5-yl)pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline



Intermediate **I146** (1.32 g, 34%) was synthesized from intermediate **I145** and (1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride [84010-67-3] according to the procedure reported for the synthesis of intermediate **I106**.

Intermediate **I147**

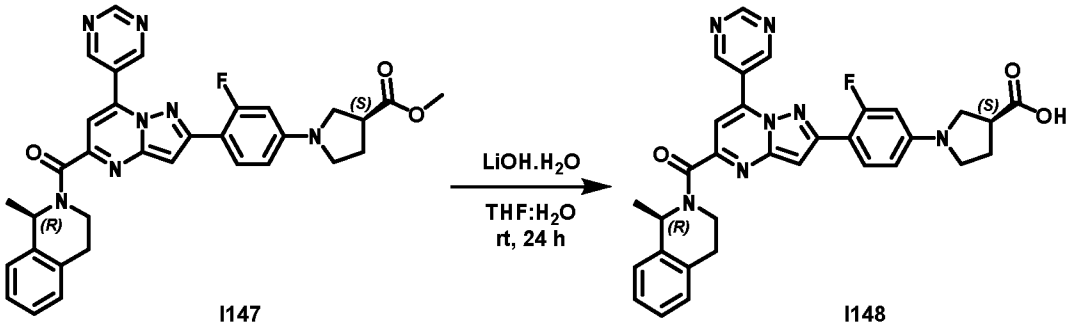
Methyl (3*S*)-1-(3-fluoro-4-{5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-7-(pyrimidin-5-yl)pyrazolo[1,5-a]pyrimidin-2-yl}phenyl)pyrrolidine-3-carboxylate



Intermediate **I147** was synthesized from intermediate **I146** and (*S*)-methyl pyrrolidine-3-carboxylate hydrochloride [1099646-61-3] according to the procedure reported for the synthesis of intermediate **I107**. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 40 g Grace®, liquid injection (DCM), mobile phase gradient: DCM / MeOH from 100:0 to 96:4) to afford intermediate **I147** (180 mg, 25%).

Intermediate **I148**

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

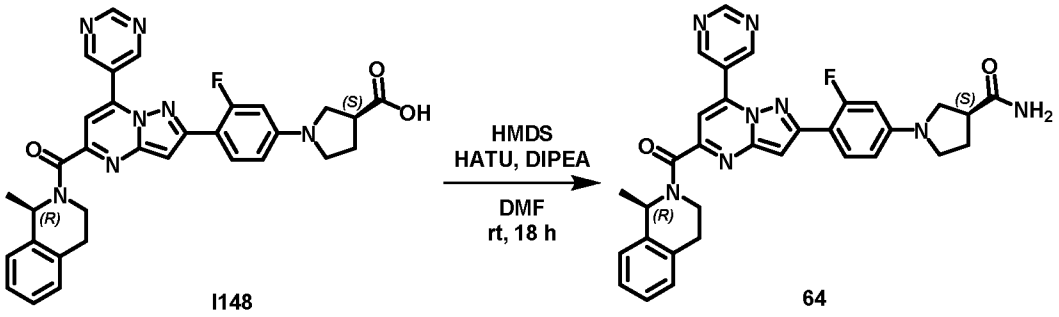


Intermediate **I148** was synthesized from intermediate **I147** according to the procedure reported for the synthesis of intermediate **I107**. The crude mixture was purified by flash chromatography on silica gel (15-40 µm, 24 g Grace®, mobile phase gradient: DCM /

MeOH from 100:0 to 96:4). The pure fractions were collected and evaporated to dryness to afford intermediate **I148** (130 mg, 74%).

Compound 64

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



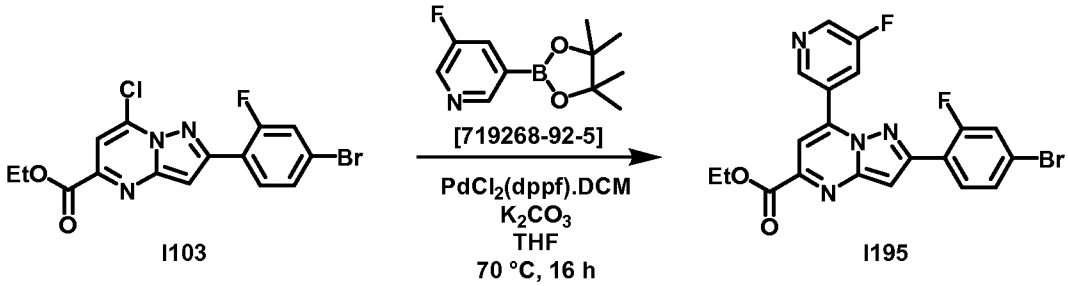
I148 64

Compound **64** was synthesized from intermediate **I148** according to the procedure reported for the synthesis of compound **56**. The residue (75 mg) was taken up in DIPE. The solid was filtered off and dried under vacuum to give compound **64** (40 mg, 42%).

Compound 90

Intermediate **I195**

Ethyl 2-(4-bromo-2-fluorophenyl)-7-(5-fluoropyridin-3-yl)pyrazolo[1,5-a]pyrimidine-5-carboxylate



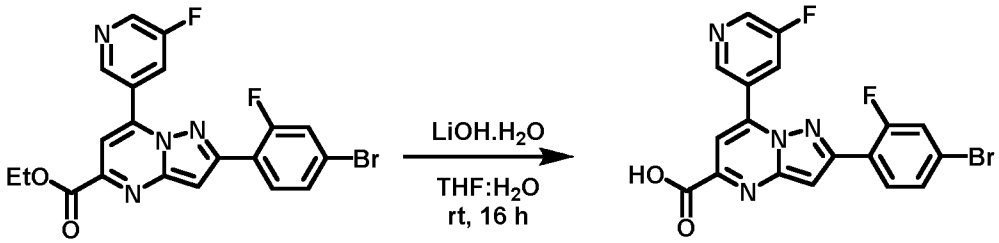
I103 I195

Intermediate **I195** was synthesized from intermediate **I103** and 3-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine [719268-92-5] according to the procedure reported for the synthesis of intermediate **I104** with a reaction time of 16 h. The reaction mixture was filtered over a pad of Celite® and washed with H_2O and EtOAc. The filtrate was decanted and the organic layer was washed with H_2O (twice), dried over $MgSO_4$, filtered and evaporated to dryness. The crude mixture was purified by flash chromatography (irregular SiOH, 15-40 µm, 25 g GraceResolv™, liquid injection (DCM),

mobile phase gradient: heptane / EtOAc from 90:10 to 0:100) to afford intermediate **I195** (246 mg, 43%) as a yellow solid.

Intermediate **I196**

2-(4-Bromo-2-fluorophenyl)-7-(5-fluoropyridin-3-yl)pyrazolo[1,5-a]pyrimidine-5-carboxylic acid

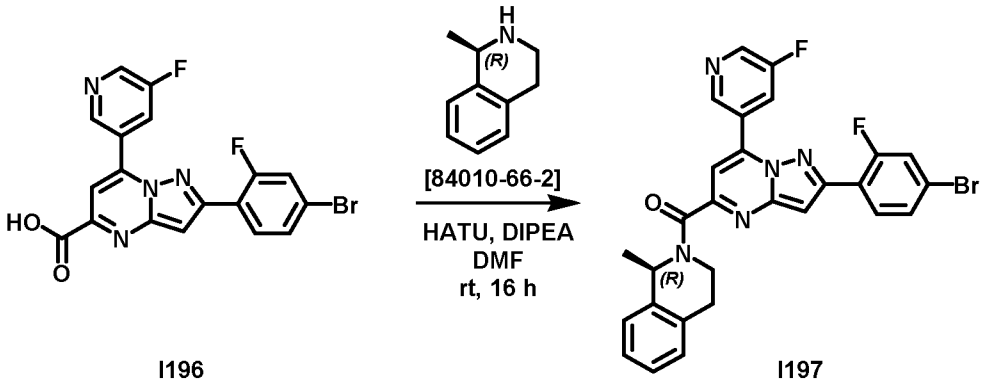


I195 I196

Lithium hydroxide monohydrate (86.5 mg, 2.06 mmol) was added to a solution of intermediate **I195** (246 mg, 412 µmol) in THF (10 mL) and H_2O (4 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 suspension was filtered off to afford intermediate **I196** (122 mg, 60%, 87% purity).

Intermediate **I197**

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

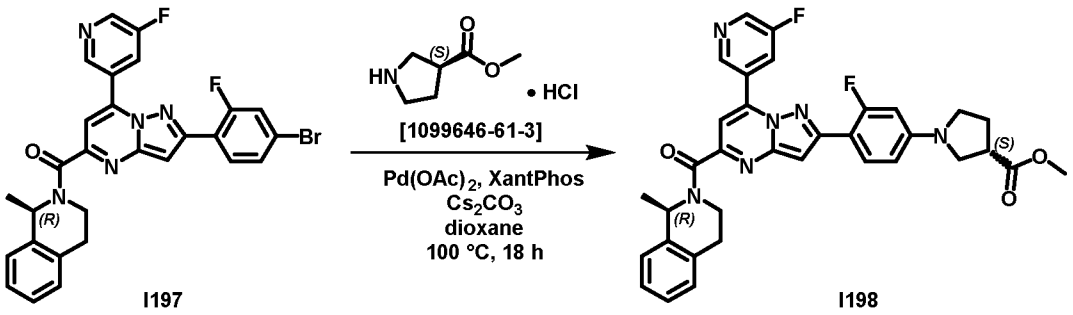


I196 I197

Intermediate **I197** (100 mg, 72%) was synthesized from intermediate **I196** and (1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline [84010-66-2] according to the procedure reported for the synthesis of intermediate **I106** with a reaction time of 16 h.

Intermediate **I198**

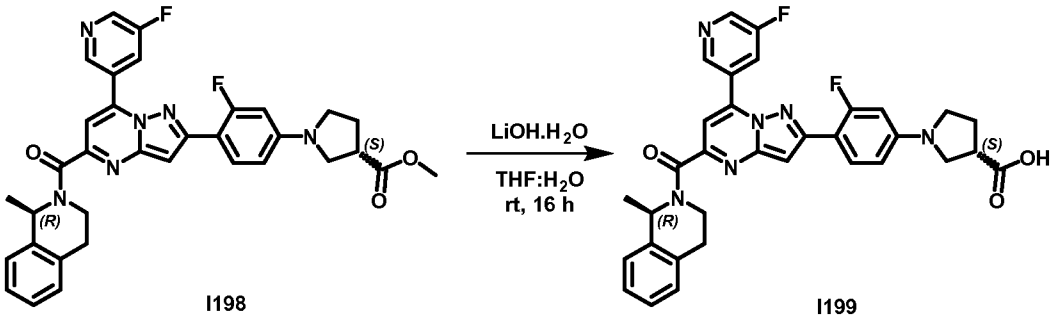
Methyl (3*S*)-1-{3-fluoro-4-[7-(5-fluoropyridin-3-yl)-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl]phenyl}pyrrolidine-3-carboxylate



Intermediate **I198** was synthesized from intermediate **I197** and (*S*)-methyl pyrrolidine-3-carboxylate hydrochloride [1099646-61-3] according to the procedure reported for the synthesis of intermediate **I107**. The reaction mixture was filtered over a pad of Celite® and washed with EtOAc and H_2O. The filtrate was decanted and the organic phase was washed with H_2O (twice), dried over $MgSO_4$, filtered and evaporated to dryness. 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 90:10 to 60:40) to afford intermediate **I198** (81 mg, 75%) as a yellow solid.

Intermediate **I199**

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

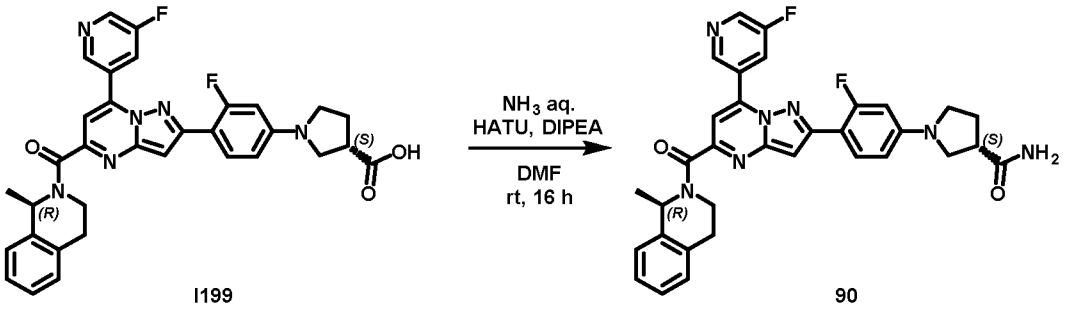


Lithium hydroxide monohydrate (17.2 mg, 0.41 mmol) was added to a solution of intermediate **I198** (81.0 mg, 133 µmol) in THF (1.2 mL) and H_2O (0.4 mL). The reaction mixture was stirred at rt for 16 h. A 10% aqueous solution of $KHSO_4$ was added until pH 3 and the aqueous phase was extracted with EtOAc (twice). The combined organic extracts

were washed with brine, dried over $MgSO_4$, filtered and concentrated to dryness to afford intermediate **I199** (68 mg, 86%) as an orange solid.

Compound 90

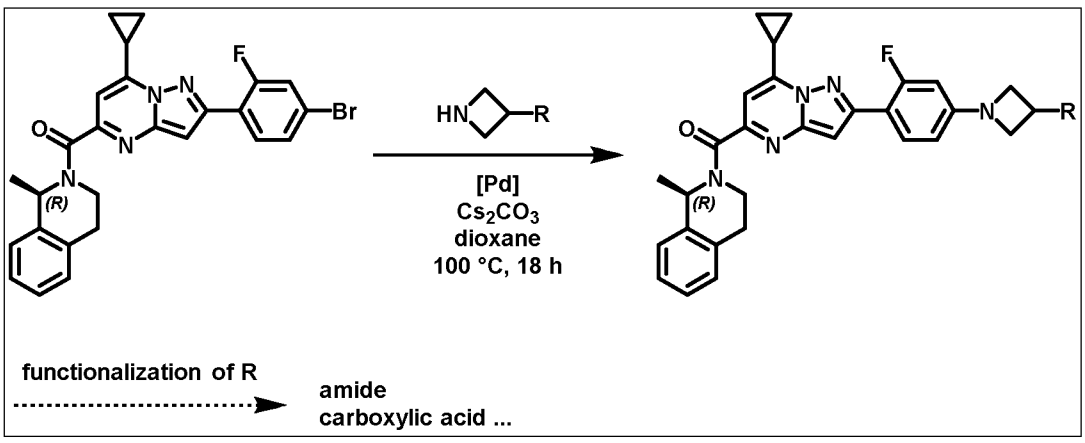
(3*S*)-1-{3-Fluoro-4-[7-(5-fluoropyridin-3-yl)-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl]phenyl}pyrrolidine-3-carboxamide



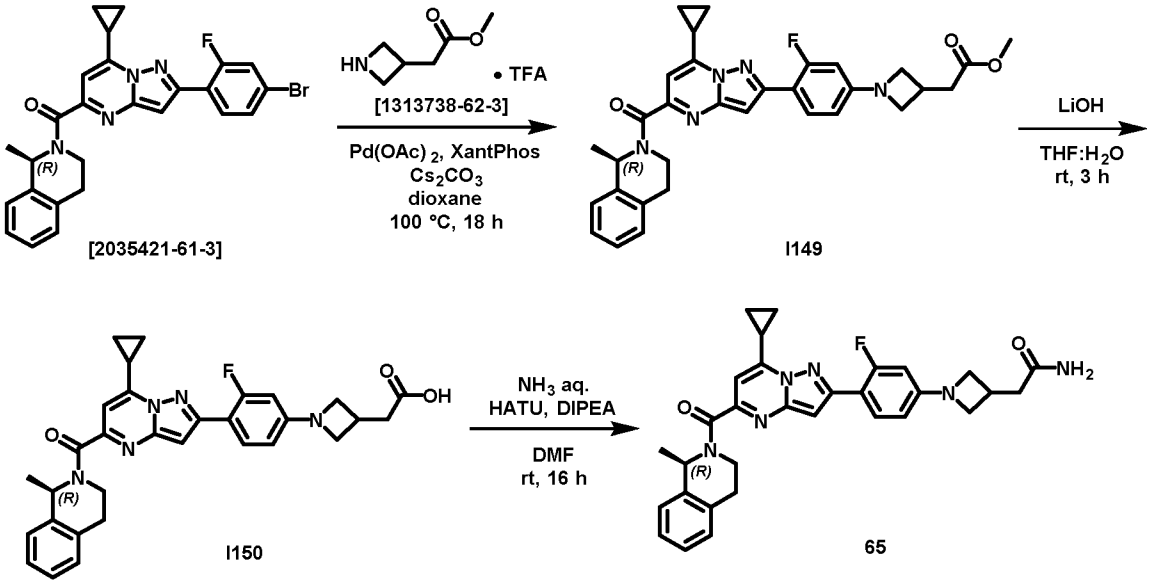
I199 90

In a screw cap vial a mixture of intermediate **I199** (68.0 mg, 114 µmol), HATU (65.0 mg, 171 µmol) and DIPEA (59 µL, 343 µmol) in DMF (1.1 mL) was stirred at rt for 30 min. Ammonia (30% in H_2O, 216 µL, 3.43 mmol) was added and the reaction mixture was stirred at rt for 16 h. The reaction mixture was diluted with EtOAc and H_2O. Additional amount of HATU (21 mg, 55 µmol), DIPEA (20 µL, 114 µmol) and ammonia (30% in H_2O, 100 µL, 1.58 mmol) were added. The reaction mixture was stirred at rt for 20 h. The layers were separated and the organic phase was washed with H_2O and brine (3 times), dried over $MgSO_4$, filtered and concentrated in vacuo. 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 (25 mg) was dried under high vacuum at 60°C for 16 h to give compound **90** (18 mg, 27%) as an orange solid.

General scheme

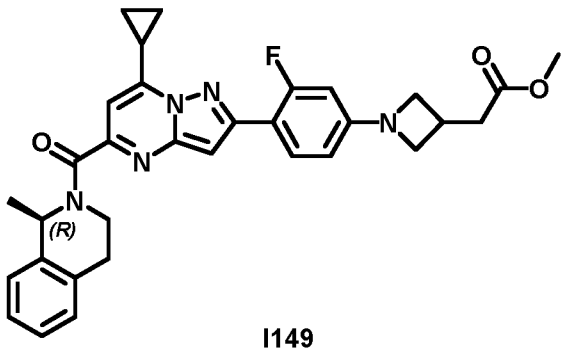


Compound 65



Intermediate **I149**

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



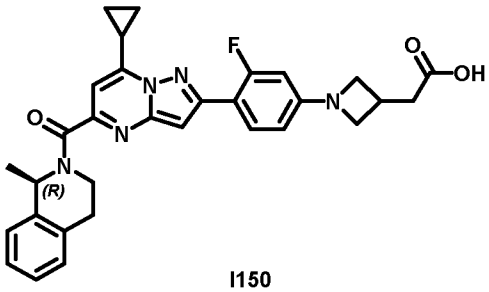
I149

A mixture of (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropylpyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] (250 mg, 495 µmol), methyl-3-azetidineacetate trifluoroacetate salt [1313738-62-3] (144 mg, 594 µmol) and cesium carbonate (645 mg, 1.98 mmol) in 1,4-dioxane (5.9 mL) was degassed with nitrogen. Palladium acetate (11.1 mg, 49.5 µmol) and XantPhos (28.6 mg, 49.5 µmol) were added and the mixture was purged again with nitrogen. The reaction mixture was stirred at 100°C for 18 h. The reaction mixture was combined with another fraction (50 mg, 98.9 µmol) and diluted with EtOAc and H_2O. The mixture was filtered over a pad of Celite® and the filtrate was decanted. The organic phase was washed with

brine, dried over $MgSO_4$, filtered and concentrated to dryness. 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 90:10 to 20:80) to afford intermediate **I149** (178 mg, 54%) as a yellow foam.

Intermediate **I150**

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

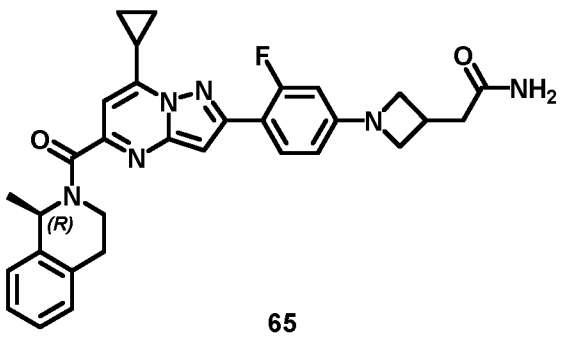


I150

Lithium hydroxide (23.1 mg, 965 µmol) was added to a solution of intermediate **I149** (178 mg, 322 µmol) in THF (3.6 mL) and H_2O (1.5 mL). The reaction mixture was stirred at rt for 3 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 H_2O (twice), dried over $MgSO_4$, filtered and concentrated to dryness to afford intermediate **I150** (183 mg, 95%, 90% purity) as a yellow solid.

Compound 65

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



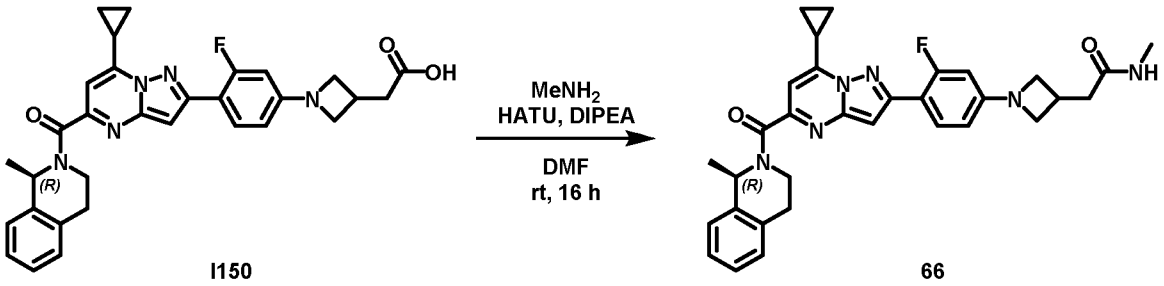
65

HATU (174 mg, 458 µmol) was added to a mixture of intermediate **I150** (183 mg, 305 µmol, 90% purity) and DIPEA (158 µL, 916 µmol) in DMF (3 mL). The mixture was

stirred at rt for 10 min and ammonia (30% in H_2O, 578 µL, 9.16 mmol) was added. The reaction mixture was stirred at rt for 16 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 (twice), dried over $MgSO_4$, filtered and concentrated to dryness. 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 70:30 to 0:100). EtOAc was added and a precipitate was formed. The suspension was concentrated under reduced pressure to dryness and the product was dried under high vacuum to give compound **65** (104 mg, 63%) as a yellow solid.

Compound 66

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

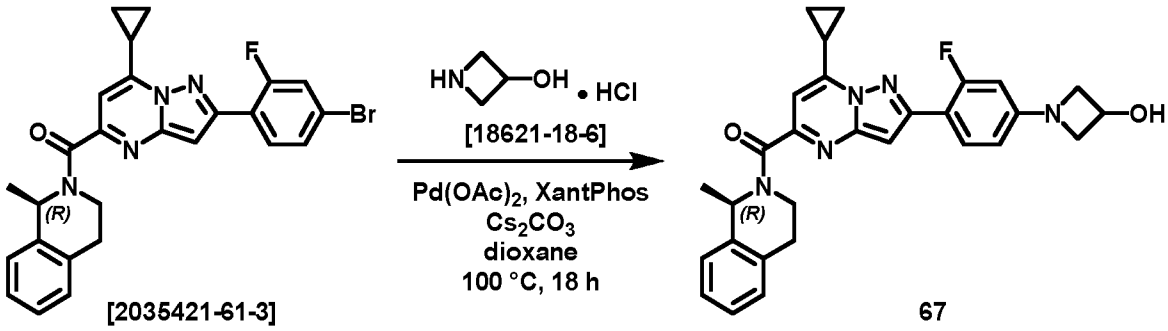


I150 66

HATU (154 mg, 406 µmol) was added to a mixture of intermediate **I150** (146 mg, 271 µmol) and DIPEA (140 µL, 812 µmol) in DMF (2.6 mL). The reaction mixture was stirred at rt for 10 min and methylamine (2.0 M in THF, 162 µL, 324 µmol) was added. The reaction mixture was stirred at rt for 2 h. Methylamine (2.0 M in THF, 298 µL, 595 µmol) was added again and the reaction mixture was stirred at rt for 16 h. H_2O, brine and EtOAc were added. 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 70:30 to 0:100). EtOAc was added and the mixture was concentrated under reduced pressure to dryness. The product was dried under high vacuum at 60°C for 16 h to give compound **66** (72 mg, 48%) as a yellow solid.

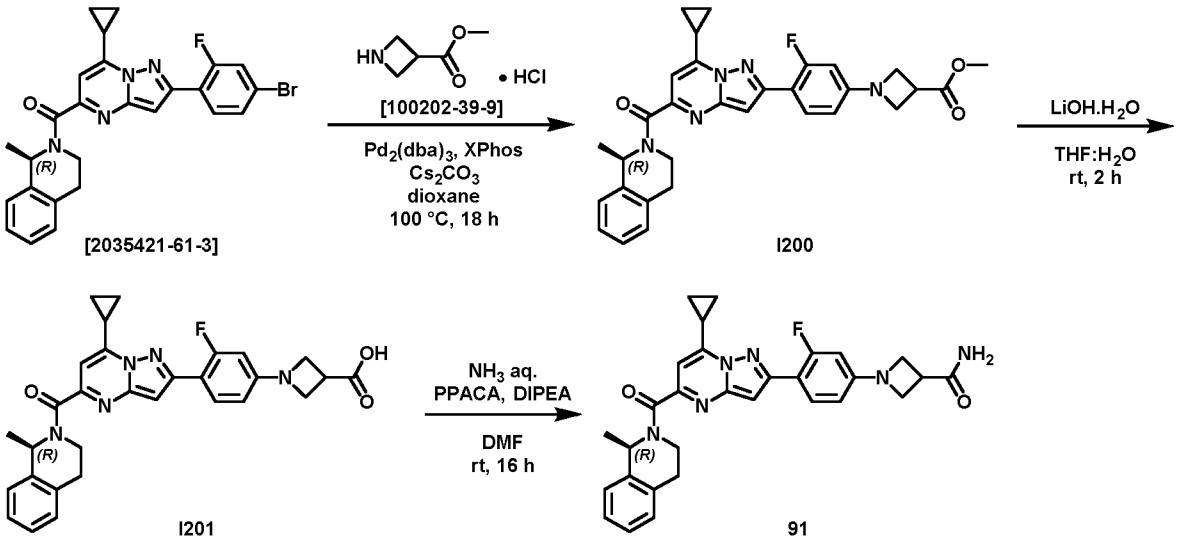
Compound 67

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



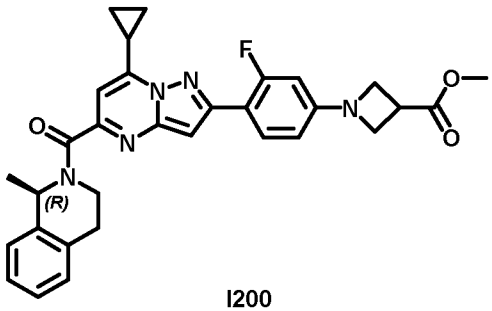
In a screw cap vial were added (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] (250 mg, 495 µmol) 3-hydroxyazetidine hydrochloride [18621-18-6] (65.0 mg, 594 µmol), cesium carbonate (644 mg, 1.98 mmol) and 1,4-dioxane (5.9 mL). The mixture was purged with nitrogen. XantPhos (28.6 mg, 49.5 µmol) and palladium acetate (11.1 mg, 49.5 µmol) were added and the reaction mixture was purged again with nitrogen and stirred at 100°C for 18 h. The reaction mixture was filtered over a pad of Celite® and washed with EtOAc and H_2O. The filtrate was decanted and the organic phase was washed with H_2O (twice), dried over $MgSO_4$, filtered and evaporated to dryness. The crude mixture was purified by flash chromatography (irregular SiOH, 15-40 µm, 12 g GraceResolv™, dry loading (SiOH), mobile phase gradient: heptane / EtOAc from 90:10 to 60:40). A second purification by flash chromatography was performed (irregular SiOH, 15-40 µm, 12 g GraceResolv™, dry loading (SiOH), mobile phase gradient: heptane / EtOAc from 90:10 to 60:40). The solid (103 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) / MeOH from 50:50 to 0:100). The fractions containing the product were collected, concentrated to dryness and co-evaporated with MeOH (twice). The product was dried under high vacuum at 60°C for 20 h to give compound **67** (80 mg, 33%) as a yellow solid.

Compound 91



Intermediate **I200**

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

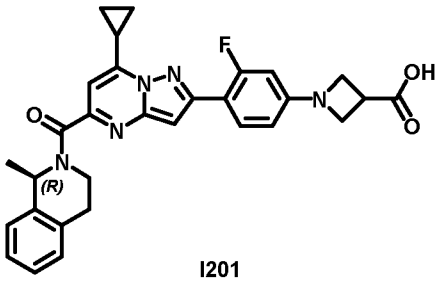


I200

A mixture of (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropylpyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] (250 mg, 495 µmol), methyl azetidine-3-carboxylate hydrochloride [100202-39-9] (112 mg, 742 µmol) and cesium carbonate (645 mg, 1.98 mmol) in 1,4-dioxane (9 mL) was degassed with nitrogen. Tris(dibenzylideneacetone)dipalladium (18.1 mg, 19.8 µmol) and XPhos (21.2 mg, 44.5 µmol) were added and the mixture was purged with nitrogen. The reaction mixture was stirred at 100°C for 18 h. The reaction mixture was filtered over a pad of Celite® and washed with H_2O and EtOAc. The filtrate was decanted and the organic phase was washed with brine (twice), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude mixture was purified by flash chromatography (irregular SiOH, 15-40 µm, 12 g GraceResolv™, dry loading (SiOH), mobile phase gradient: heptane / EtOAc from 80:20 to 20:80) to afford intermediate **I200** (249 mg, 93%) as a yellow foam.

Intermediate **I201**

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

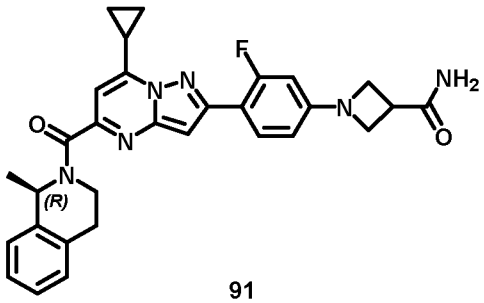


I201

Lithium hydroxide monohydrate (38.7 mg, 923 µmol) was added to a solution of intermediate **I200** (249 mg, 461 µmol) in THF (3.5 mL) and H_2O (1.5 mL). The reaction mixture was stirred at rt for 2 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 **I201** (245 mg, 89%) as a yellow solid.

Compound 91

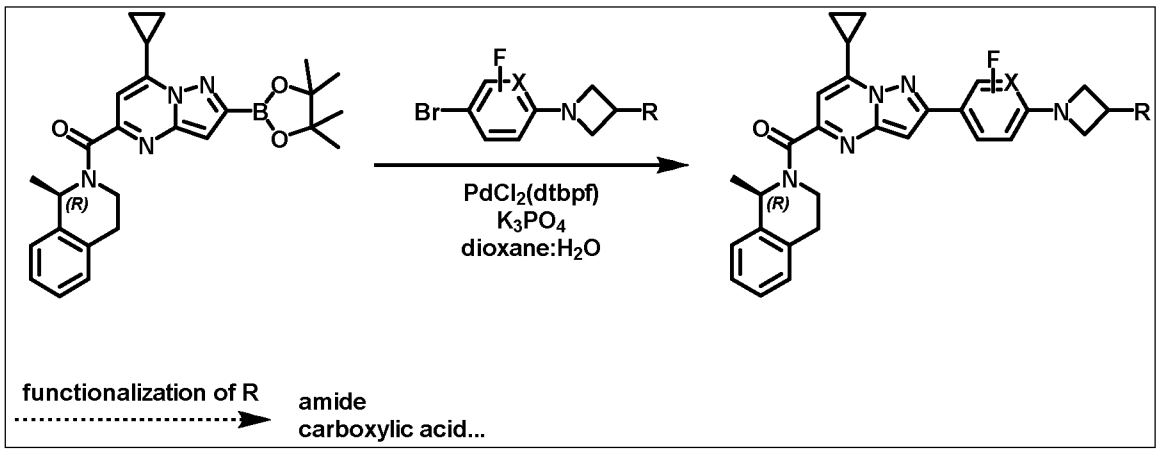
1-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)azetidine-3-carboxamide



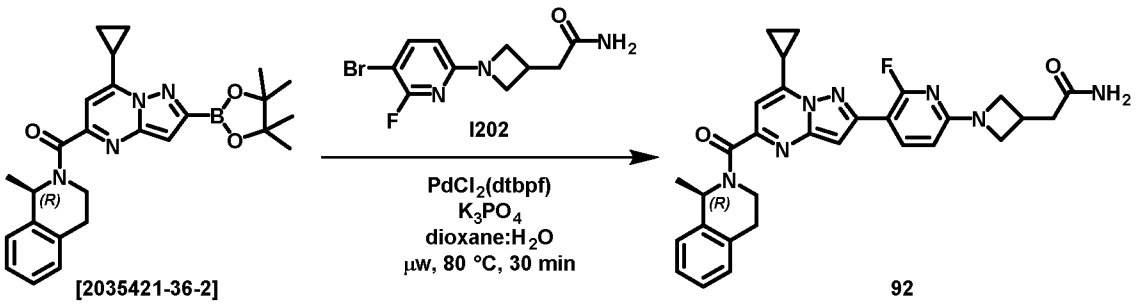
91

At 0°C PPACA (50 wt. % in EtOAc, 617 µL, 1.04 mmol) was added dropwise to a mixture of intermediate **I201** (218 mg, 415 µmol), DIPEA (357 µL, 2.07 mmol) and ammonia (28% in H_2O, 841 µL, 12.4 mmol) in DMF (4 mL). The reaction mixture was stirred at rt for 16 h. The layers were separated and the organic phase was washed with 1M aqueous solution of NaOH and brine (3 times), dried over $MgSO_4$, filtered and concentrated 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 50:50 to 0:100). The residue (63 mg) was dried under high vacuum at 60°C for 16 h to give compound **91** (58 mg, 27%) as a yellow solid.

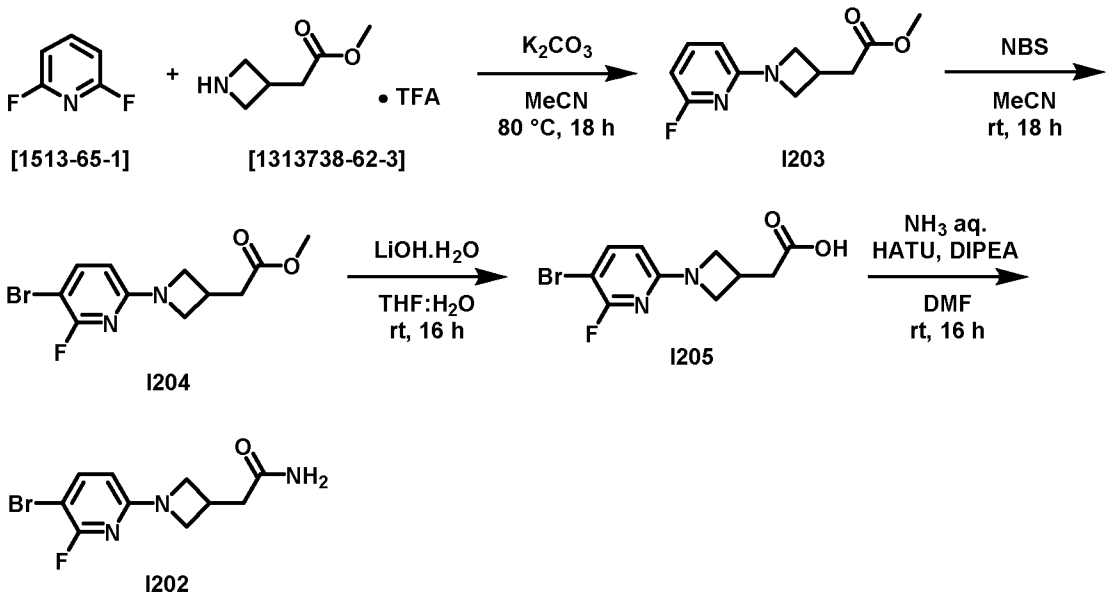
General scheme



Compound 92

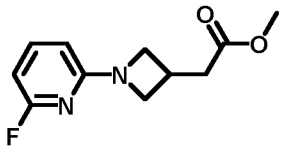


Synthesis of intermediate **I202**



Intermediate **I203**

Methyl 2-[1-(6-fluoropyridin-2-yl)azetidin-3-yl]acetate

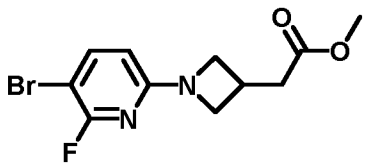


I203

Methyl 3-azetidine acetate trifluoroacetate salt [1313738-62-3] (275 mg, 1.13 mmol) and potassium carbonate (426 mg, 3.08 mmol) were added to a solution of 2,6-difluoropyridine [1513-65-1] (93.2 µL, 1.03 mmol) in MeCN (7 mL). The reaction mixture was stirred at 80°C for 18 h. The reaction mixture was filtered over a pad of Celite® and the filtrate was concentrated to dryness. 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 100:0 to 50:50) to afford intermediate **I203** (195 mg, 85%) as a colorless oil.

Intermediate **I204**

Methyl 2-[1-(5-bromo-6-fluoropyridin-2-yl)azetidin-3-yl]acetate

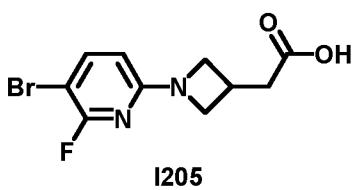


I204

A mixture of intermediate **I203** (195 mg, 0.87 mmol) and NBS (186 mg, 1.05 mmol) in MeCN (9 mL) was stirred at rt for 18 h. The reaction mixture was concentrated to dryness. The crude mixture was purified by flash chromatography (irregular SiOH, 15-40 µm, 12 g GraceResolv™, dry loading (SiOH), mobile phase gradient: heptane / EtOAc from 90:10 to 60:40) to afford intermediate **I204** (147 mg, 56%) as a white solid.

Intermediate **I205**

2-[1-(5-Bromo-6-fluoropyridin-2-yl)azetidin-3-yl]acetic acid

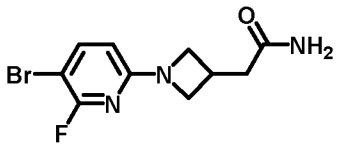


I205

Lithium hydroxide monohydrate (61 mg, 1.45 mmol) was added to a solution of intermediate **I204** (147 mg, 485 µmol) in THF (4 mL) and H_2O (1.3 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 H_2O, dried over $MgSO_4$, filtered and concentrated in vacuo to afford intermediate **I205** (135 mg, 96%) as a white solid.

Intermediate **I202**

2-[1-(5-Bromo-6-fluoropyridin-2-yl)azetidin-3-yl]acetamide

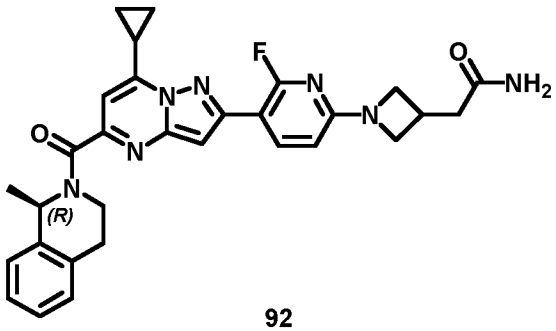


I202

A mixture of intermediate **I205** (135 mg, 467 µmol), HATU (266 mg, 700 µmol) and DIPEA (241 µL, 1.40 mmol) in DMF (2.3 mL) was stirred at rt for 30 min. Ammonia (30% in H_2O, 884 µL, 14.0 mmol) was added and the reaction mixture was stirred at rt for 16 h. The reaction mixture was diluted with EtOAc and H_2O. The layers were separated and the organic phase was washed with water and brine (3 times), dried over $MgSO_4$, filtered and concentrated. The crude mixture was purified by flash chromatography (irregular SiOH, 15-40 µm, 12 g GraceResolv™, dry loading (SiOH), mobile phase gradient: heptane / EtOAc from 50:50 to 0:100) to afford intermediate **I202** (94 mg, 70%) as a white solid.

Synthesis of compound 92

2-[1-(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)azetidin-3-yl]acetamide

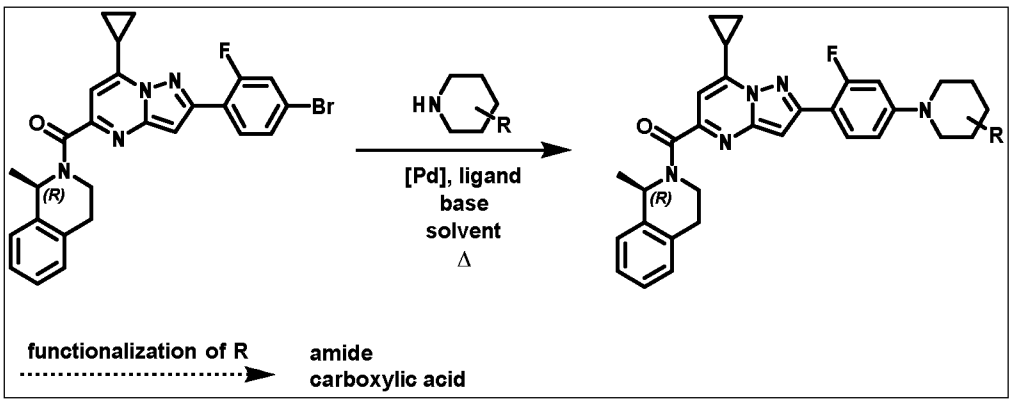


92

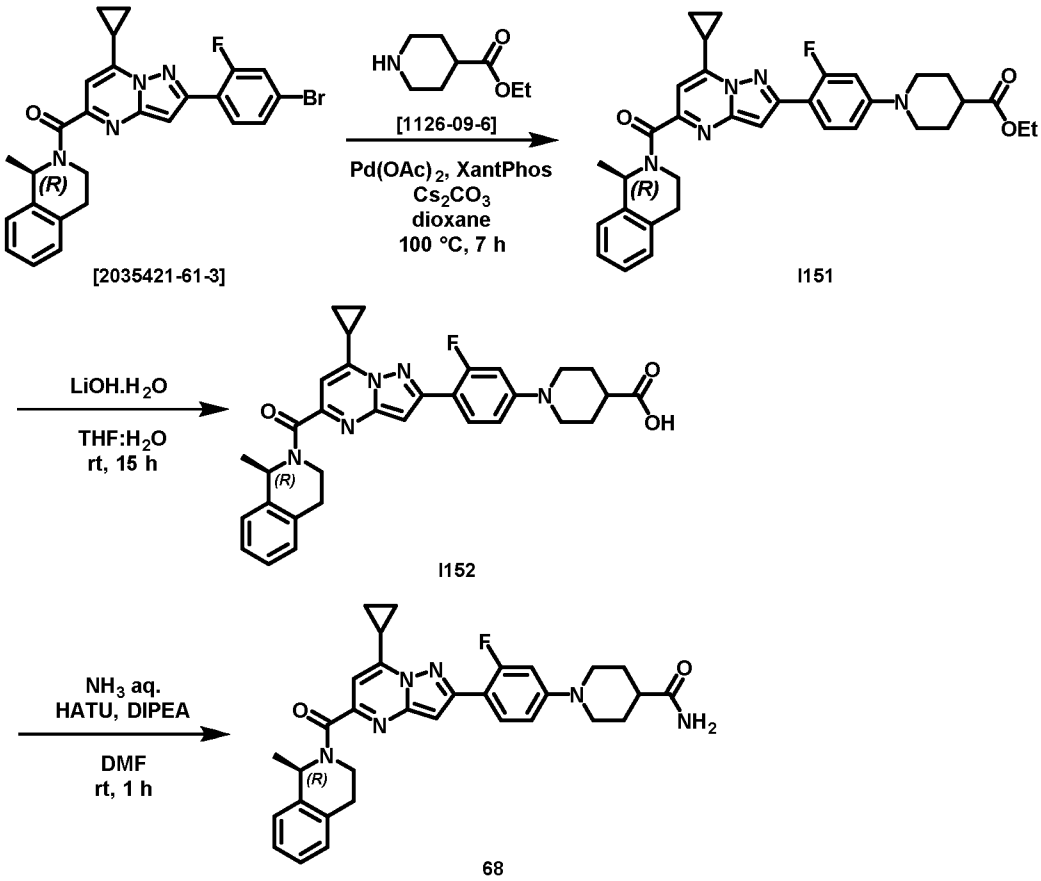
A sealed tube was charged with (1*R*)-2-[7-cyclopropyl-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline

[2035421-36-2] (150 mg, 203 µmol, 62 % purity), intermediate **I202** (64 mg, 223 µmol), potassium phosphate tribasic (129 mg, 609 µmol), 1,4-dioxane (2.5 mL) and H_2O (0.6 mL) and purged with nitrogen. [1,1'-Bis(di-*tert*-butylphosphino)ferrocene] dichloropalladium (13.2 mg, 20.3 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 H_2O. The layers were separated 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™, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 50:50 to 0:100). The residue was taken up in EtOAc, sonicated and concentrated to dryness. The solid was dried under high vacuum at 60°C for 16 h to give compound **92** (47 mg, 43%) as a yellow solid.

General scheme

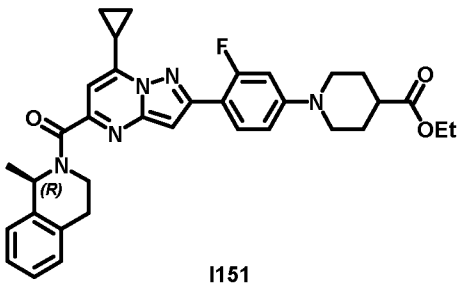


Compound 68



Intermediate **I151**

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

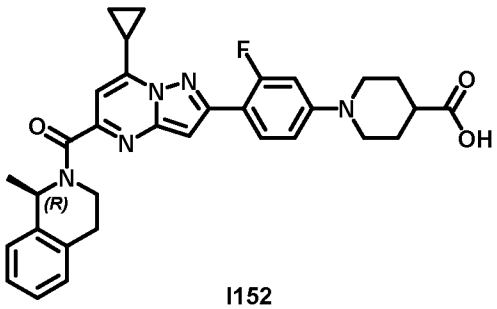


A mixture of (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropylpyrazolo[1,5-a]-pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] (200 mg, 0.40 mmol), ethyl piperidine-4-carboxylate [1126-09-6] (87.1 mg, 0.55 mmol), cesium carbonate (516 mg, 1.58 mmol) and XantPhos (27.5 mg, 47.5 µmol) was purged with nitrogen. 1,4-Dioxane (5 mL) was added and the mixture was purged again with nitrogen.

Palladium acetate (10.6 mg, 47.5 µmol) was added. The reaction mixture was purged with nitrogen and stirred at 100°C for 7 h. The reaction mixture was diluted with EtOAc and H_2O. 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 the solvent was removed under reduced pressure. The crude mixture was purified by flash chromatography over silica gel (Interchim® 40 g, 30 µM, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 90:10 to 60:40) to afford intermediate **I151** (180 mg, 78%) as a yellow solid.

Intermediate **I152**

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

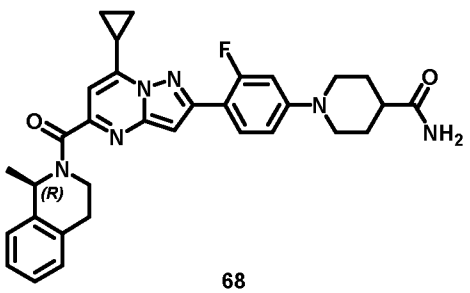


I152

A mixture of intermediate **I151** (171mg, 0.29 mmol) and lithium hydroxide monohydrate (86.4 mg, 2.06 mmol) in THF (5 mL) and H_2O (1.5 mL) was stirred at rt for 15 h. An aqueous solution of citric acid (7 equiv. in 10 ml) was added 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 **I152** (160 mg, 98%) as a beige solid.

Compound 68

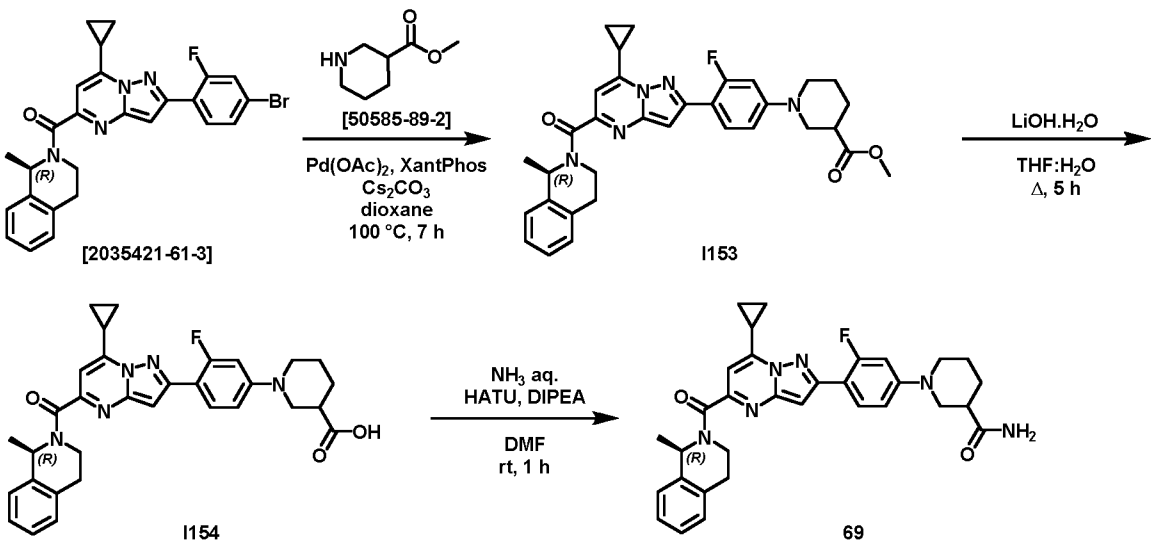
1-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)piperidine-4-carboxamide



68

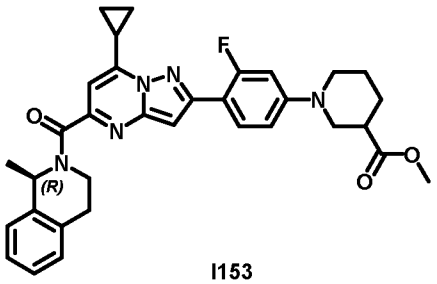
To a solution of intermediate **I152** (0.16 g, 0.29 mmol) in DMF (4 mL) were added DIPEA (0.15 mL, 0.87 mmol) and HATU (0.17 g, 0.43 mmol). The mixture was stirred at rt for 15 min. Ammonia (30% in H_2O, 33 µL, 1.73 mmol) was added and the reaction mixture was stirred at rt for 1 h. The reaction mixture was diluted with H_2O and EtOAc. The layers were separated and the organic phase was washed with H_2O (3 times) and brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude mixture was purified by flash chromatography over silica gel (Interchim® 12 g, 30 µM, liquid injection (DCM), mobile phase gradient: DCM / MeOH, from 100:0 to 97:3) to give compound **68** (75 mg, 47%) as a yellow solid.

Compound 69



Intermediate **I153**

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

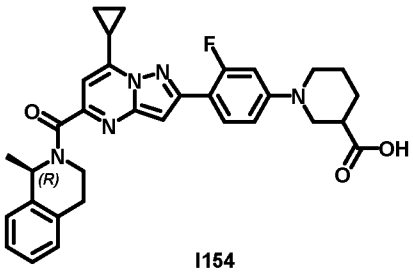


I153

Intermediate **I153** was synthesized from (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropylpyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydro-isoquinoline [2035421-61-3] and methyl piperidine-3-carboxylate [50585-89-2] according to the procedure reported for the synthesis of intermediate **I151**. Intermediate **I153** (0.18 g, 65%) was obtained as a yellow solid.

Intermediate **I154**

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

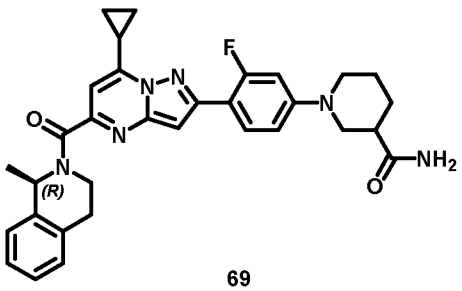


I154

Intermediate **I154** was synthesized from intermediate **I153** according to the procedure reported for the synthesis of intermediate **I152**. The reaction mixture was stirred under reflux for 5 h. Intermediate **I154** (0.17 g, 98%) was obtained as a yellow solid.

Compound 69

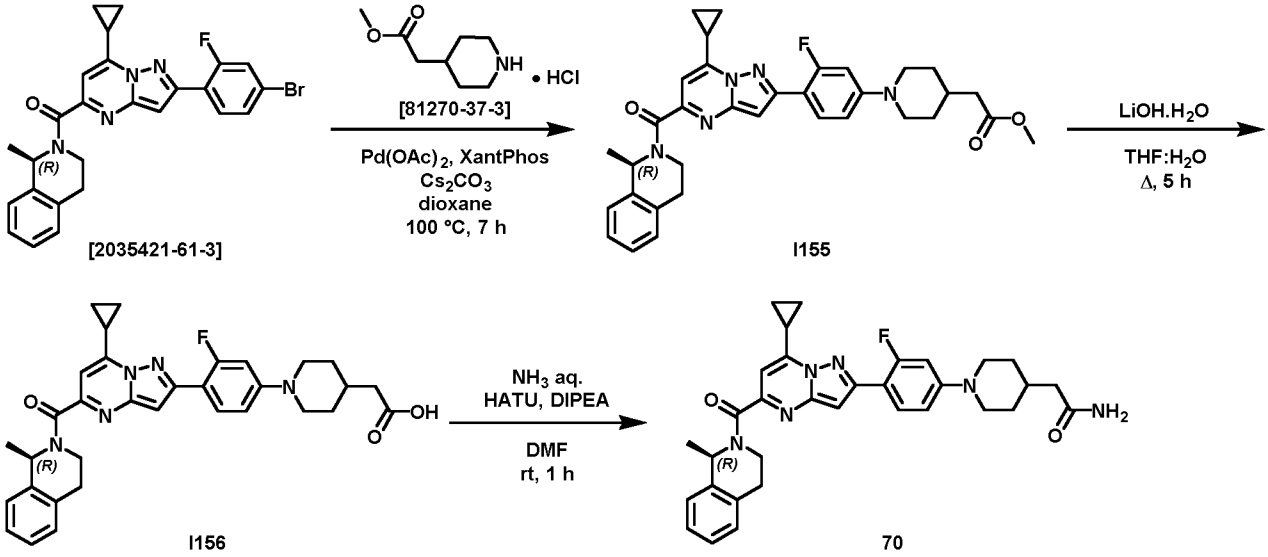
1-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)piperidine-3-carboxamide



69

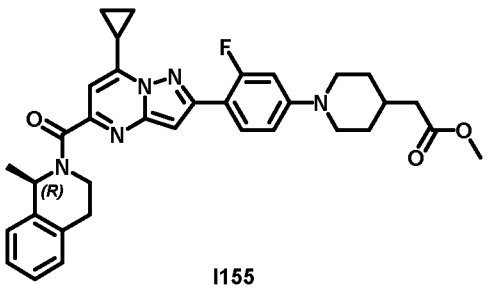
Compound **69** was synthesized from intermediate **I154** according to the procedure reported for the synthesis of compound **68**. Compound **69** (80 mg, 49%) was obtained as a yellow solid.

Compound 70



Intermediate **I155**

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

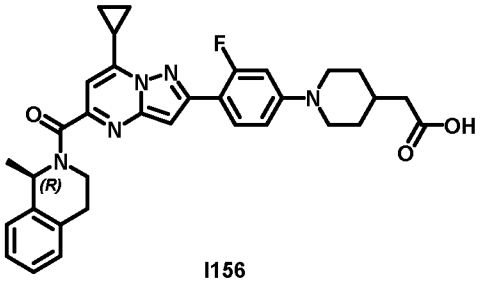


Intermediate **I155** was synthesized from (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropylpyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydro-isoquinoline [2035421-61-3] and methyl 2-(piperidine-4-yl)acetate hydrochloride [81270-37-3] according to the procedure reported for the synthesis of intermediate **I151**.

Intermediate **I155** (023 g, 65%) was obtained as a yellow solid.

Intermediate **I156**

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

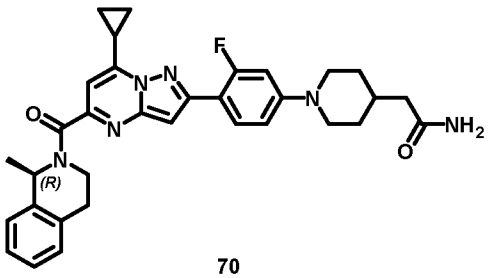


I156

Intermediate **I156** was synthesized from intermediate **I155** according to the procedure reported for the synthesis of intermediate **I152**. The reaction mixture was stirred under reflux for 5 h. Intermediate **I156** (0.21 g, quant.) was obtained as a yellow solid.

Compound **70**

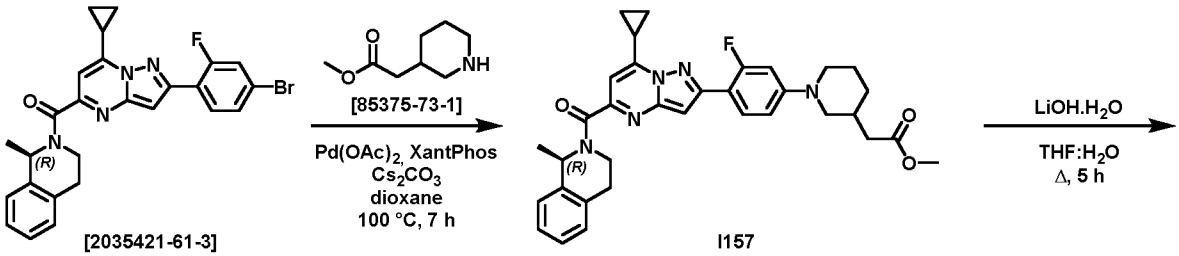
2-[1-(4-{7-Cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-pyrazolo[1,5-a]pyrimidin-2-yl}-3-fluorophenyl)piperidin-4-yl]acetamide



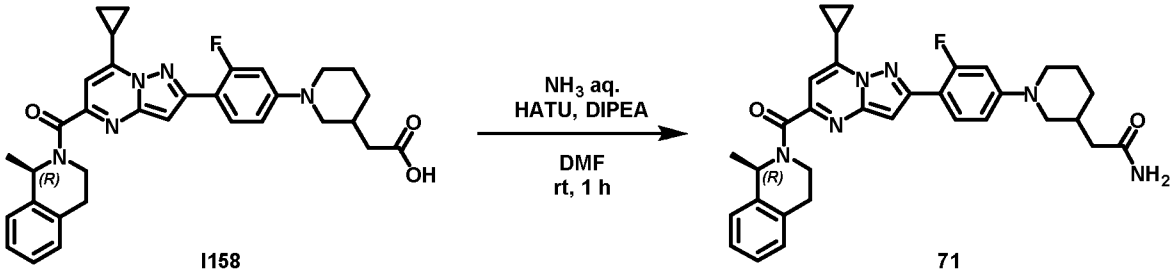
70

Compound **70** was synthesized from intermediate **I156** according to the procedure reported for the synthesis of compound **68**. Compound **70** (85 mg, 40%) was obtained as a beige solid.

Compound 71



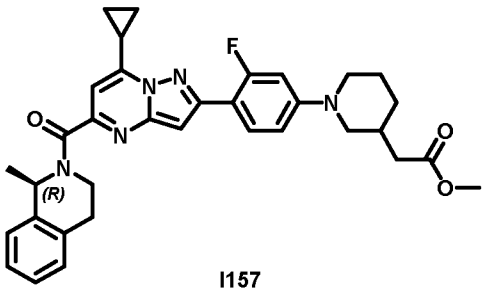
[2035421-61-3] I157



I158 71

Intermediate **I157**

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

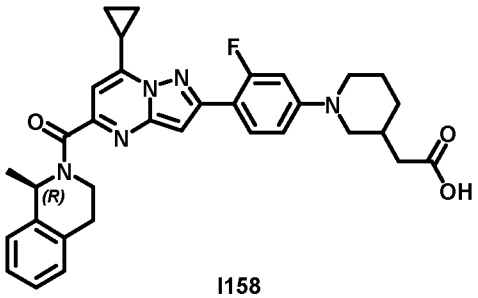


I157

Intermediate **I157** was synthesized from (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropylpyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] and methyl 3-piperidinyl acetate [85375-73-1] according to the procedure reported for the synthesis of intermediate **I151**. Intermediate **I157** (0.23 g, 67%) was obtained as a yellow solid.

Intermediate **I158**

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

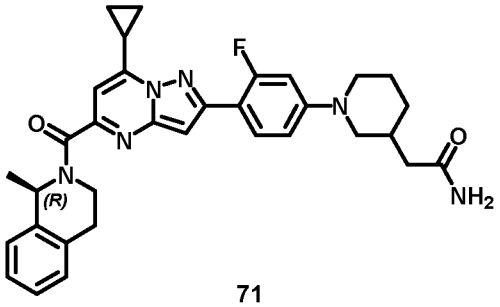


I158

Intermediate **I158** was synthesized from intermediate **I157** according to the procedure reported for the synthesis of intermediate **I152**. The reaction mixture was stirred under reflux for 5 h. Intermediate **I158** (214 mg, quant.) was obtained as a yellow solid.

Compound 71

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

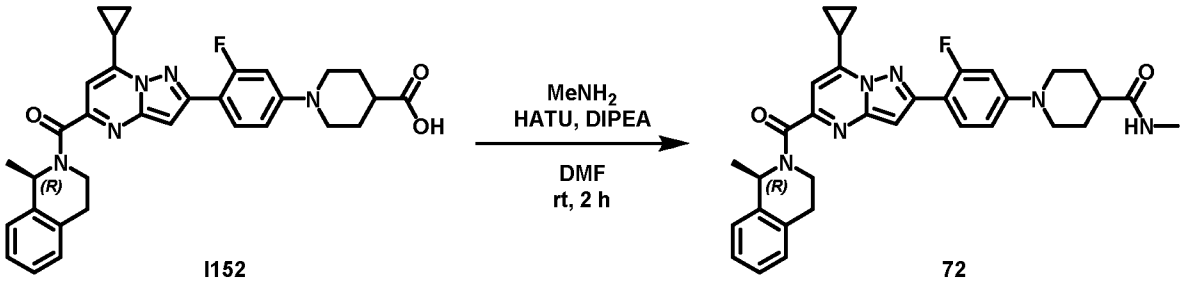


71

Compound **71** was synthesized from intermediate **I158** according to the procedure reported for the synthesis of compound **68**. Compound **71** (90 mg, 42%) was obtained as a yellow solid.

Compound 72

1-(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*-methylpiperidine-4-carboxamide

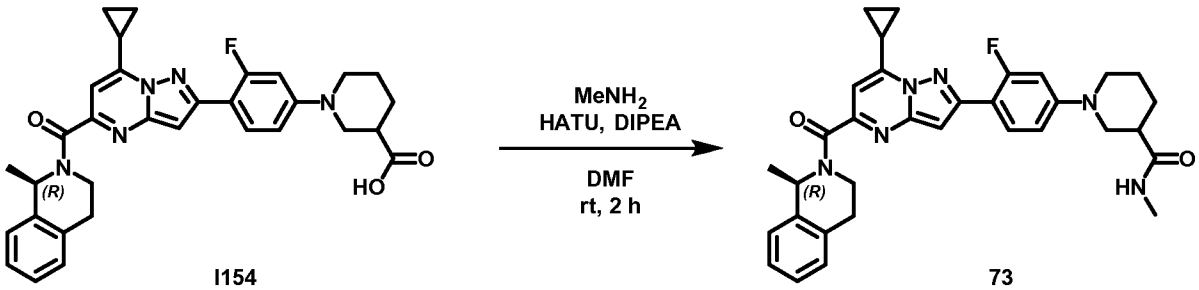


I152 72

To a solution of intermediate **I152** (207 mg, 0.37 mmol) in DMF (2.5 mL) was added DIPEA (0.19 mL, 1.12 mmol) and HATU (0.21 g, 0.56 mmol). The mixture was stirred at rt for 15 min and methylamine (2.0 M in THF, 0.11 mL, 2.22 mmol) was added dropwise. The reaction mixture was stirred at rt for 2 h. The reaction mixture was diluted with H_2O and EtOAc. The layers were separated and the organic phase was washed with H_2O (3 times), brine, dried over $MgSO_4$, filtered and evaporated to dryness to give compound **72** (110 mg, 52%) as a beige solid.

Compound 73

1-(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-methylpiperidine-3-carboxamide

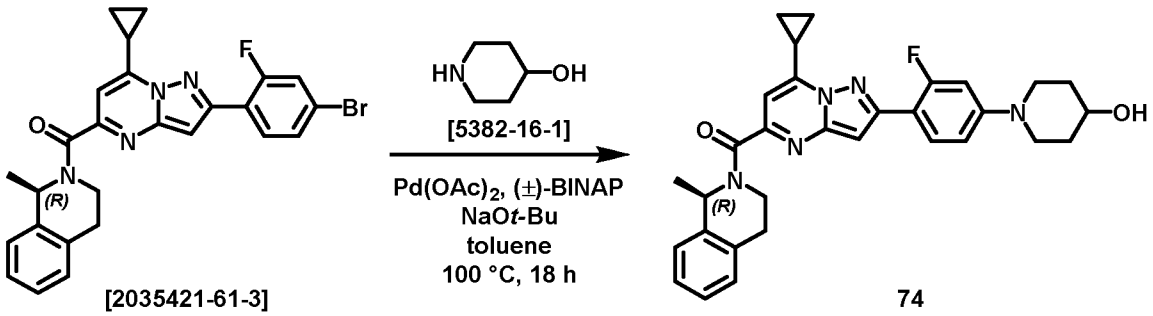


I154 73

Compound **73** was synthesized from intermediate **I154** according to the procedure reported for the synthesis of compound **72**. The product was purified by flash chromatography over silica gel (30 µm, 12 g Interchim®, liquid injection (DCM), mobile phase gradient: DCM / MeOH from 100:0 to 98:2) to give compound **73** (160 mg, 64%) as a yellow solid.

Compound 74

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



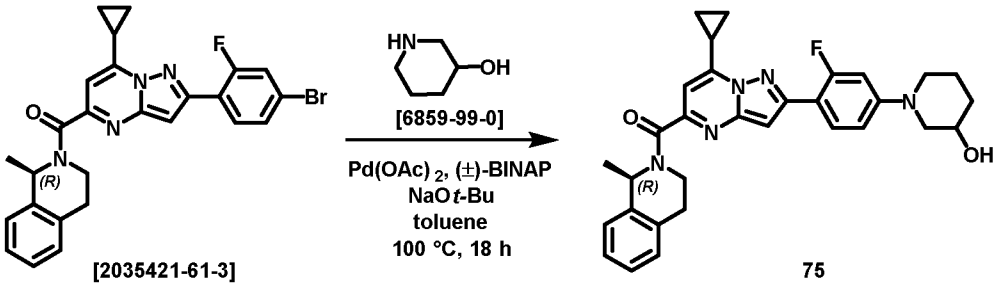
[2035421-61-3] 74

In a screw cap vial were added (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] (200 mg, 396 µmol), 4-hydroxypiperidine [5382-16-1] (40.0 mg, 396 µmol), sodium *tert*-butoxide (76.1 mg, 0.79 mmol) and toluene (3.3 mL). The mixture was purged with nitrogen. Palladium acetate (4.44 mg, 19.8 µmol) and (±)-BINAP (12.3 mg, 19.8 µmol) were added and the reaction mixture was purged again with nitrogen. The reaction mixture was stirred at 100°C for 18 h. The reaction mixture was diluted with EtOAc and H_2O and filtered over a pad of Celite®. The filtrate was decanted and the organic phase was washed with H_2O (twice), dried over $MgSO_4$, filtered and concentrated to dryness. The crude

mixture was purified by flash chromatography (irregular SiOH, 15-40 µm, 12 g GraceResolv™, dry loading (SiOH), mobile phase gradient: heptane / EtOAc from 50:50 to 0:100). The solid was dried under high vacuum at 60°C for 16 h to give compound **74** (99 mg, 46%) as a yellow solid.

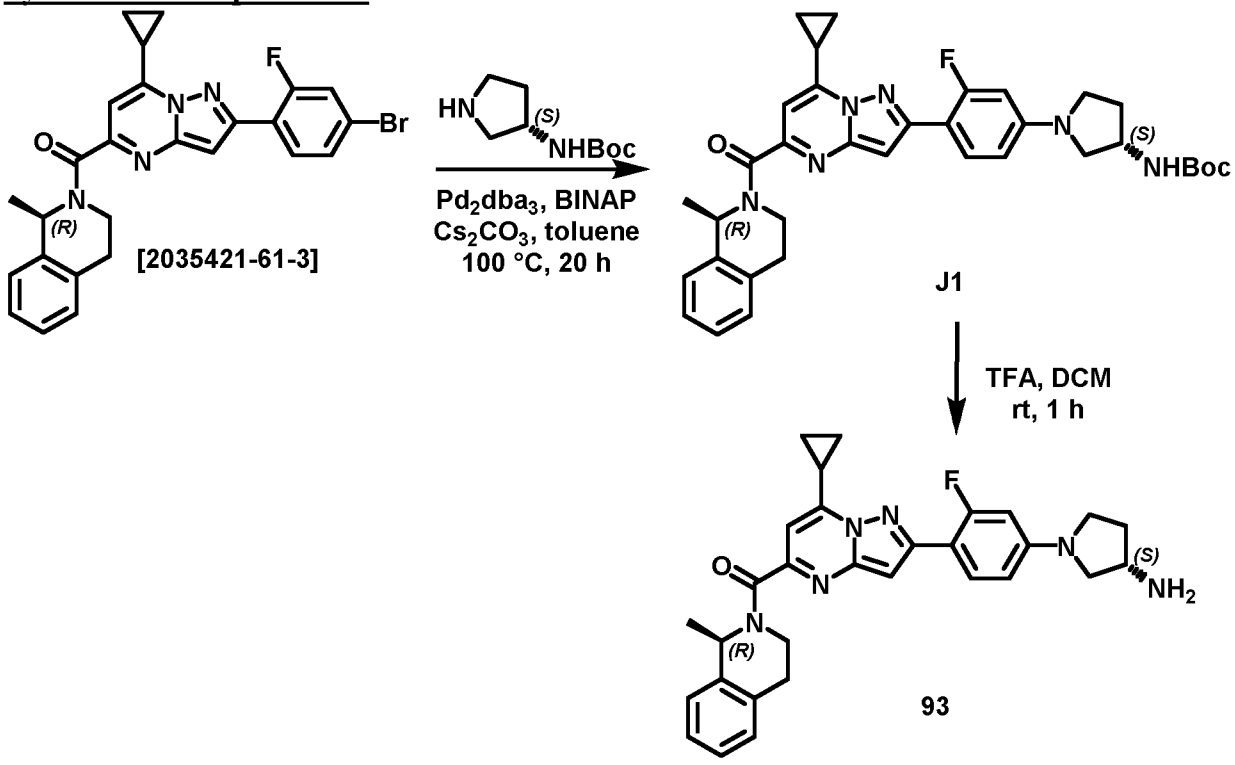
Compound 75

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



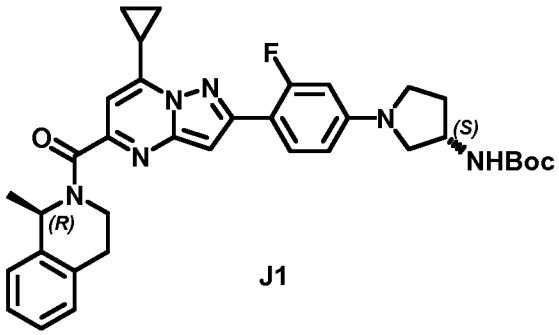
Compound **75** was synthesized from (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] and 3-hydroxypiperidine [6859-99-0] according to the procedure reported for the synthesis of compound **74**. Compound **75** (140 mg, 54%) was obtained as a yellow solid.

Synthesis of compound 93:



Intermediate **J1**:

tert-butyl ((S)-1-(4-(7-cyclopropyl-5-((R)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)pyrazolo[1,5-a]pyrimidin-2-yl)-3-fluorophenyl)pyrrolidin-3-yl)carbamate

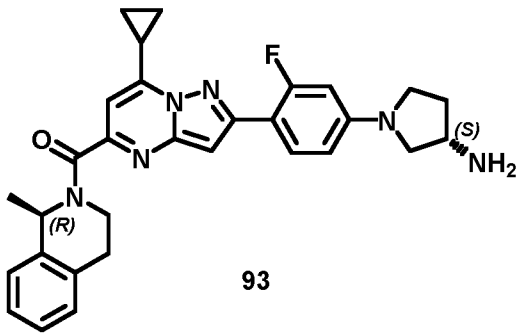


J1

In a Schlenk tube, a mixture of (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] (300 mg; 0.572 mmol), *(S)*-3-(BOC-amino)pyrrolidine (214 mg; 1.15 mmol) and Cs_2CO_3 (657 mg; 2.015 mmol) in toluene (12 mL) was degassed with N_2. BINAP (36 mg; 0.058 mmol) and Pd_2dba_3 (53 mg; 0.058 mmol) were added and the reaction mixture was purged with N_2. The mixture was heated at 100 °C for 20 h. Brine and EtOAc were added to the reaction mixture, the aqueous layer was extracted with EtOAc (twice). The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by preparative LC (irregular SiOH 15-40 µm, 40 g GraceResolv®, mobile phase gradient: from DCM/EtOAc: 100/0 to 70/30) to give Intermediate **J1** as a yellow solid (0.315 g, 90%).

Compound 93:

(2-(4-((S)-3-aminopyrrolidin-1-yl)-2-fluorophenyl)-7-cyclopropylpyrazolo[1,5-a]pyrimidin-5-yl)((R)-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone

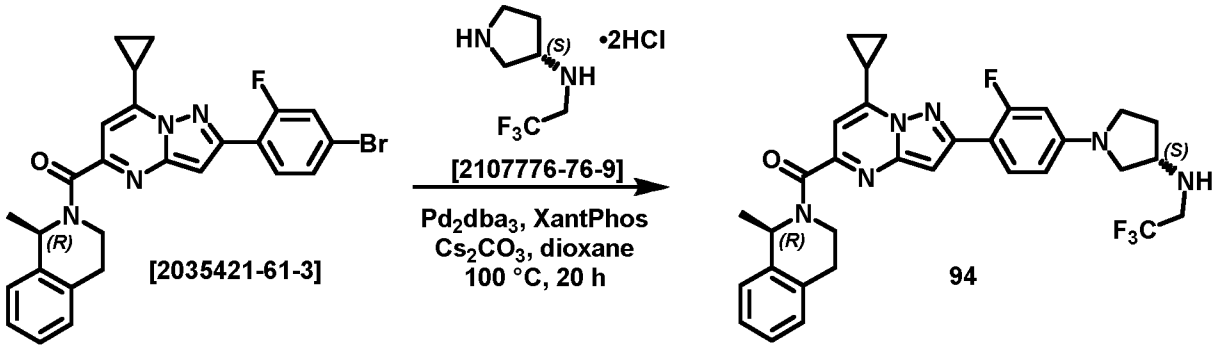


93

TFA (1.2 mL; 15 mmol) was added to a solution of intermediate **J1** (315 mg; 0.516 mmol) in DCM (6.2 mL). The reaction mixture was stirred at rt for 1 h. DCM and an aqueous solution of $NaHCO_3$ (sat) were added. The layers were separated, and the organic layer was dried over $MgSO_4$, filtered and the solvent was removed in vacuo to give 226 mg of a yellow foam which was triturated in MTBE then filtered over frit and dried under high vacuum at 50 °C overnight to give compound **93** as a yellow solid (120 mg, 46%).

Compound 94:

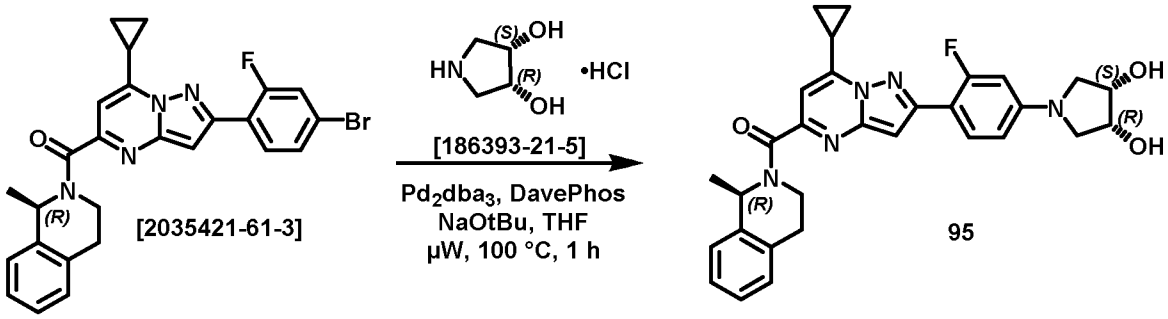
(7-cyclopropyl-2-(2-fluoro-4-((S)-3-((2,2,2-trifluoroethyl)amino)pyrrolidin-1-yl)phenyl)pyrazolo[1,5-a]pyrimidin-5-yl)((R)-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone



In a Schenlk tube, a mixture of (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] (127 mg; 0.243 mmol), (3S)-N-(2,2,2-trifluoroethyl)pyrrolidin-3-amine hydrochloride [2107776-76-9] (100 mg; 0.365 mmol)) and Cs_2CO_3 (396 mg; 1.22 mmol) in dioxane (5 mL) was degassed with N_2. $Pd(OAc)_2$ (5 mg; 24 µmol) and XantPhos (14 mg; 0.024 mmol) were added and the reaction mixture was purged with N_2. The mixture was heated at 100 °C for 20 h. Brine and EtOAc were added to the reaction mixture, the aqueous layer was extracted with EtOAc (twice). The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by preparative LC (irregular SiOH, 15-40 µm, 12 g GraceResolv®, mobile phase gradient: from heptane/EtOAc 90/10 to 60/40) the pure fraction was collected and evaporated to dryness. The residue was purified by Reverse phase (Stationary phase: YMC-actus Triart® C18 10µm 30*150mm, Mobile phase: Gradient from 35% aq. NH_4HCO_3 0.2%, 65% MeCN to 0% aq. NH_4HCO_3 0.2%, 100% MeCN) to give a yellow oil which was taken up in MTBE (~2 mL). Heptane was added until solid appeared and the mixture was evaporated in vacuo then dried under high vacuum to give compound **94** as a yellow solid (56 mg, 39%).

Compound 95:

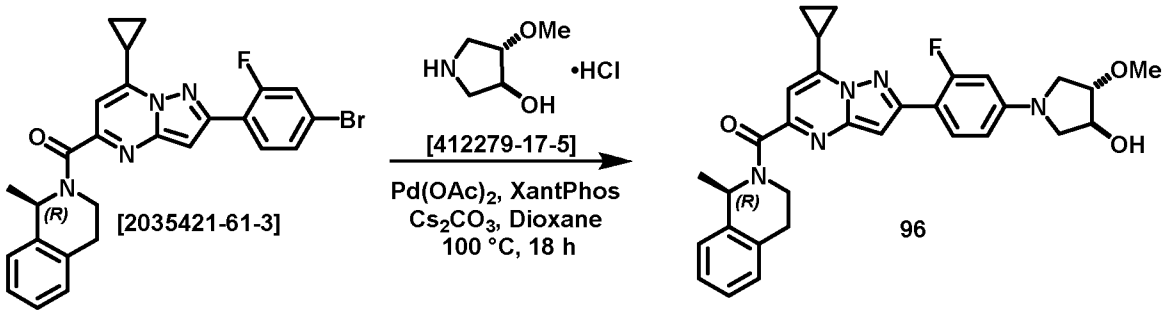
(7-cyclopropyl-2-(4-((3R,4S)-3,4-dihydroxypyrrolidin-1-yl)-2-fluorophenyl)pyrazolo[1,5-a]pyrimidin-5-yl)((R)-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone



In a sealed tube, a mixture of (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] (250 mg, 0.475 mmol), NaO^{t}Bu (160 mg, 1.66 mmol) and cis-Pyrrolidine-3,4-diol hydrochloride [186393-21-5] (99 mg, 0.712 mmol) in THF (5.6 mL) was degassed with N_2 for 10 min. DavePhos (19 mg, 0.048 mmol) and Pd_2dba_3 (43 mg, 0.048 mmol) were added and the reaction mixture was purged with N_2. The mixture was heated at 100 °C using a single mode microwave (Biotage Initiator® EXP 60) with a power output ranging from 0 to 400 W for 1 h. Water and EtOAc were added. The aqueous layer was extracted with EtOAc (twice), the combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by preparative LC (irregular SiOH 15-40 µm, 24 g GraceResolv®, mobile phase gradient: from DCM/Isopropanol 99/1 to 88/12) The fractions containing product were collected and evaporated to dryness. The residue was purified 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 65:35 to 25:75). The fractions containing product were evaporated, then taken-up in EtOAc and evaporated again three times to give 90 mg of a solid which was taken-up with MTBE and stirred at 50 °C for 24 h. The suspension was cooled down to rt, filtered over glass frit and washed with MTBE (2 x 2 mL). The solid was dried under vacuum to give compound **95** as a yellow solid (60 mg, 24%).

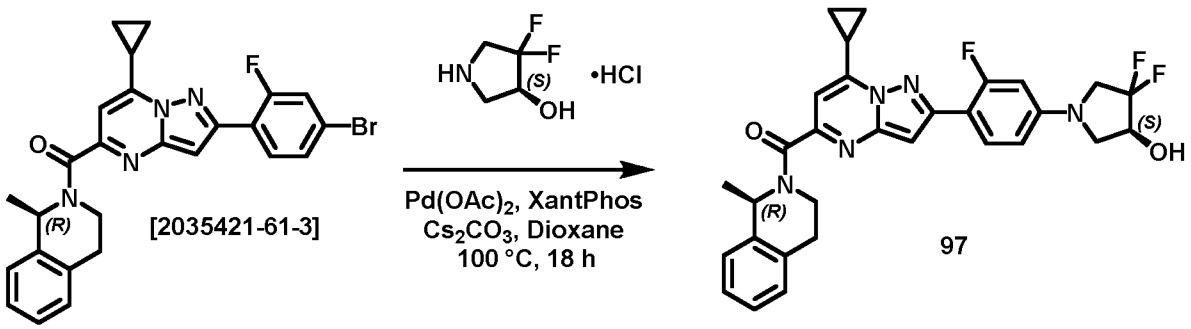
Compound 96:

(7-cyclopropyl-2-(2-fluoro-4-((trans)-3-hydroxy-4-methoxypyrrolidin-1-yl)phenyl)pyrazolo[1,5-a]pyrimidin-5-yl)((R)-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone



A mixture of (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] (200 mg, 0.38 mmol), *trans*-4-methoxy-3-pyrrolidinol hydrochloride (70 mg, 0.46 mmol) and Cs_2CO_3 (371 mg, 1.14 mmol) was charged in a sealed tube and purged with N_2. Dioxane (7.9 mL, 93 mmol) was added and the mixture was degassed with N_2, then $Pd(OAc)_2$ (8.5 mg, 0.038 mmol) and XantPhos (22 mg, 0.038 mmol) were added. The reaction mixture was stirred and heated at 100 °C for 18 h. Water and EtOAc were added to the reaction mixture. The layers were separated. The aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by preparative LC (irregular SiOH 15-40 µm, 24 g GraceResolv®, mobile phase gradient: from heptane 75%, EtOAc 25% to Heptane 0%, EtOAc 100%) to give 250 mg of a white gum. The product was purified by preparative LC (spherical C18 25 µm, 40 g YMC-ODS-25, mobile phase gradient 0.2% aq. NH_4HCO_3 / MeCN from 60:40 to 10:90). The fractions containing product were evaporated under vacuum and the residue was taken-up in Et_2O and evaporated under vacuum three times and the sample was dried under vacuum to give compound **96** as a yellow solid (110 mg, 53%).

Synthesis of Compound 97:

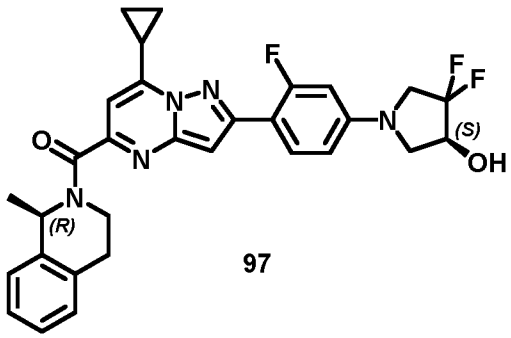


4,4-difluoro-3S-hydroxypyrrolidine hydrochloride

4,4-difluoro-3S-hydroxypyrrolidine hydrochloride was synthetized with the same procedure as the 3R enantiomer described in *J. Org. Chem.* **2016**, *81*, 4359−4363.

Compound 97:

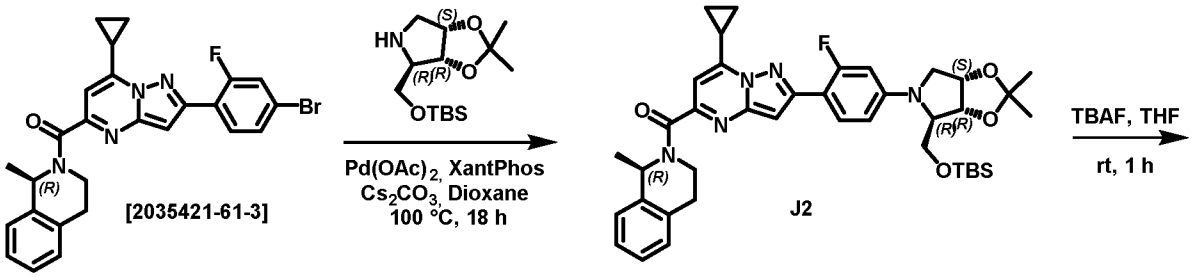
(7-cyclopropyl-2-(4-((S)-3,3-difluoro-4-hydroxypyrrolidin-1-yl)-2-fluorophenyl)pyrazolo[1,5-a]pyrimidin-5-yl)((R)-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone

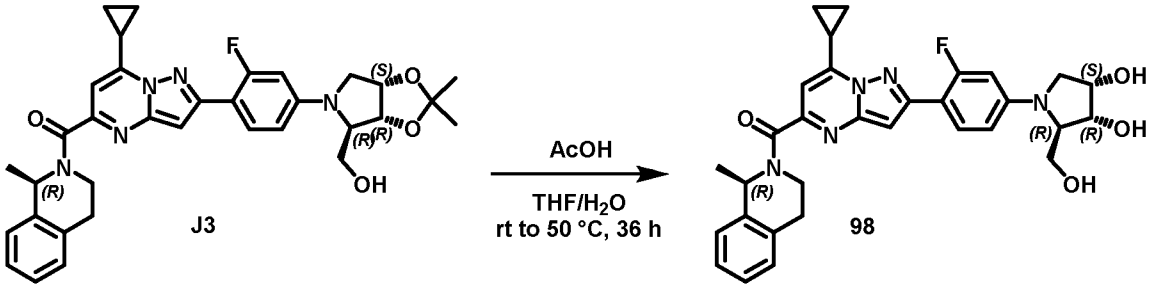


97

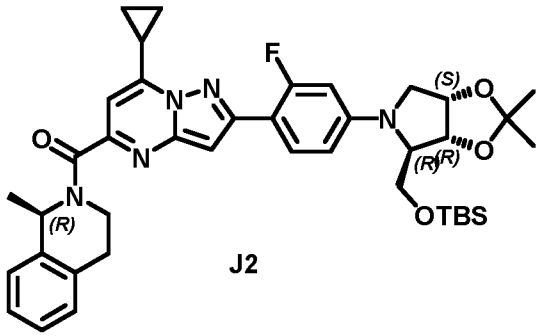
A mixture of (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] (149 mg, 0.295 mmol) 4,4-difluoro-3S-hydroxypyrrolidine hydrochloride (47 mg, 0.295 mmol) and Cs_2CO_3 (480 mg, 1.47 mmol) was charged in a sealed tube and purged with N_2. Dioxane (6.0 mL) was added and the mixture was degassed with N_2, then $Pd(OAc)_2$ (6.6 mg, 0.030 mmol) and XantPhos (17 mg, 0.030 mmol) were added. The reaction mixture was stirred and heated at 100 °C for 18 h. The reaction mixture was poured out into water and extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated till dryness. The residue was purified by preparative LC (irregular SiOH, 15-40 µm, GraceResolv® 24 g, mobile phase gradient: from heptane/EtOAc 80/20 to 0/100). The fractions containing product were evaporated under vacuum. The residue was taken up with Et_2O and evaporated to dryness (3 times) to give a yellow solid which was taken-up with Et_2O and the suspension was filtered and dried under high vacuum to give compound **97** as yellow solid (65 mg, 40%).

Synthesis of compound 98:



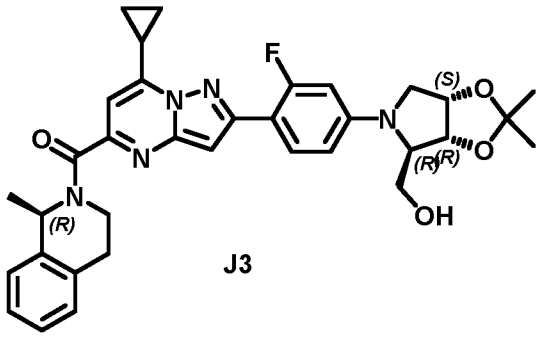


Intermediate **J2**:
(2-(4-((3aR,4R,6aS)-4-(((tert-butyldimethylsilyl)oxy)methyl)-2,2-dimethyltetrahydro-5H-[1,3]dioxolo[4,5-c]pyrrol-5-yl)-2-fluorophenyl)-7-cyclopropylpyrazolo[1,5-a]pyrimidin-5-yl)((R)-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone



A mixture of (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] (200 mg, 0.396 mmol), [153172-31-7] (0.171 g, 0.594 mmol) and Cs_2CO_3 (387 mg, 1.19 mmol) was charged in a sealed tube and purged with N_2. Dioxane (8.2 mL) was added and the mixture was degassed with N_2, then $Pd(OAc)_2$ (8.8 mg, 0.040 mmol) and XantPhos (23 mg, 0.040 mmol) were added. The reaction mixture was purged with N_2 then was stirred and heated at 100 °C for 18 h. The reaction mixture was poured out into water and extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), filtered and evaporated till dryness. The residue was purified by preparative LC (irregular SiOH, 15-40 µm, GraceResolv® 24 g, mobile phase gradient: from heptane/EtOAc 99/1 to 30/70). The fractions containing product were evaporated under vacuum to give intermediate **J2** (230 mg, 70% purity, 57%)

Intermediate **J3**:
(7-cyclopropyl-2-(2-fluoro-4-((3aR,4R,6aS)-4-(hydroxymethyl)-2,2-dimethyltetrahydro-5H-[1,3]dioxolo[4,5-c]pyrrol-5-yl)phenyl)pyrazolo[1,5-a]pyrimidin-5-yl)((R)-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone

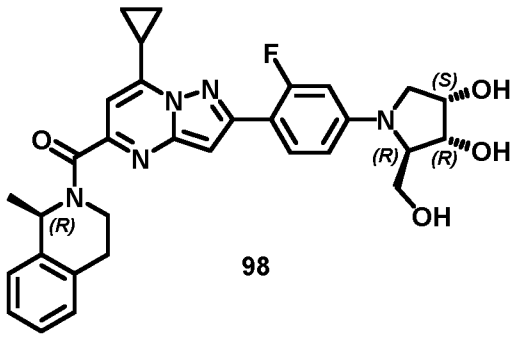


J3

TBAF 1M in THF (238 µL, 0.238 mmol) was added dropwise to a stirred solution of intermediate **J2** (230 mg, 0.226 mmol, 70% purity) in THF (4.2 mL) at rt. The mixture was stirred at rt for 1 h. Then, the mixture was diluted with sat $_{aq}$NaCl and water and extracted with EtOAc. The organic layer was separated, washed with sat $_{aq}$NaCl, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by preparative LC (irregular SiOH 15-40 µm, 12 g GraceResolv®, dry loading (celite®), mobile phase gradient: from Heptane/EtOAc 80/20 to 20/80) to give intermediate **J3** as a white solid. (135 mg, quant).

Compound 98:

(7-cyclopropyl-2-(4-((2R,3R,4S)-3,4-dihydroxy-2-(hydroxymethyl)pyrrolidin-1-yl)-2-fluorophenyl)pyrazolo[1,5-a]pyrimidin-5-yl)((R)-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone

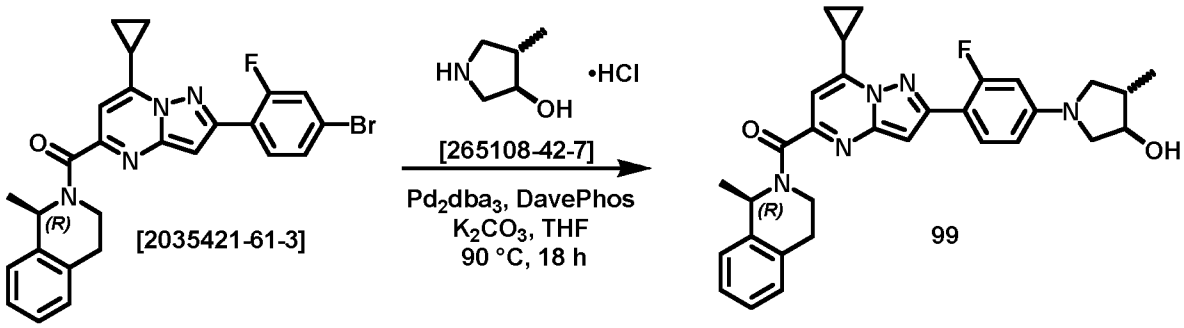


98

A mixture of intermediate **J3** (135 mg, 0.226 mmol), AcOH (2.1 mL, 36 mmol), in THF (0.8 mL) and H_2O (0.8 mL) was stirred at rt for 18 h, then at 50 °C for 18 h. Water and EtOAc were added. The aqueous layer was extracted with EtOAc (twice), the combined organic layers were dried over $MgSO_4$, filtered, concentrated in vacuo and coevaporated (3 times) with EtOAc. The residue was purified by preparative LC (irregular SiOH 15-40 µm, 24 g GraceResolv®, mobile phase gradient: from DCM/^{i}PrOH 99/1 to 84/16). The fraction containing product was evaporated and the residue was taken-up in MeCN and evaporated under vacuum three times. Then it was taken-up in MeCN, the suspension was filtered and dried under high vacuum to give compound **98** as yellow solid (54 mg, 43%).

Compound 99:

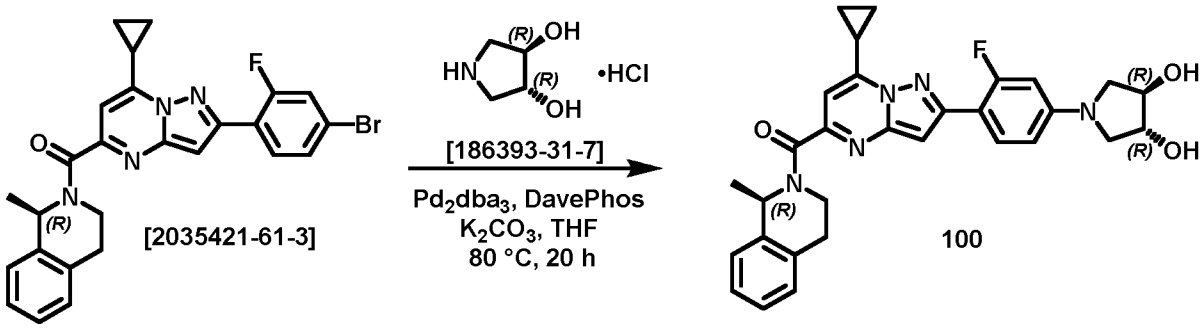
(7-cyclopropyl-2-(2-fluoro-4-((trans)-3-hydroxy-4-methylpyrrolidin-1-yl)phenyl)pyrazolo[1,5-a]pyrimidin-5-yl)((R)-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone



A mixture of (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] (300 mg; 0.594 mmol), *Trans*-4-Methylpyrrolidin-3-ol hydrochloride (82 mg; 0.594 mmol) and K_2CO_3 (287 mg; 2.08 mmol) was charged in a sealed tube and purged with N_2. THF (4 mL) was added and the mixture was degassed with N_2, then DavePhos (23 mg; 59.4 µmol) and $Pd_2(dba)_3$ (54 mg; 59.4 µmol) were added. The reaction mixture was purged with N_2 then was stirred and heated at 90 °C for 18 h. Water and EtOAc were added. The aqueous layer was extracted with EtOAc (twice), the combined organic layers were dried over $MgSO_4$, filtered, concentrated in vacuo and purified by preparative LC (irregular SiOH 15-40 µm, 24 g GraceResolv®, mobile phase gradient: from DCM / MeOH 100:0 to 90:10) The fraction containing product was collected and evaporated to dryness. The residue was purified by preparative LC (spherical C18 25 µm, 40 g YMC-ODS-25, mobile phase gradient 0.2% aq. NH_4HCO_3 / MeCN from 50:50 to 0:100) The fractions containing product were extracted with EtOAc. The organic layer was dried ($MgSO_4$), evaporated to give 163 mg of a yellow foam which was precipitated with EtOAc and heptane, filtered and dried to give compound **99** as yellow solid (105 mg, 34%).

Compound 100:

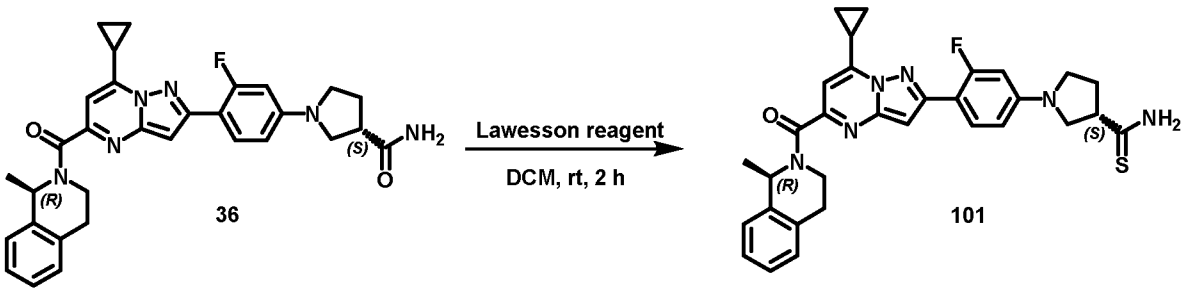
(7-cyclopropyl-2-(4-((3R,4R)-3,4-dihydroxypyrrolidin-1-yl)-2-fluorophenyl)pyrazolo[1,5-a]pyrimidin-5-yl)((R)-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone



In a sealed tube, a mixture of (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] (300 mg; 0.59 mmol), 3*R*,4*R*-Pyrrolidinediol (85.7 mg; 0.83 mmol) and K_2CO_3 (287 mg; 2.08 mmol) in THF (7 mL) was degassed with N_2 for 10 min. DavePhos (23.4 mg; 59.4 µmol) and $Pd_2(dba)_3$ (54.4 mg; 59.4 µmol) were added and the reaction mixture was purged with N_2. The mixture was heated at 80 °C for 20 h. Water and EtOAc were added to the mixture and an extraction was performed. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, evaporated and purified by preparative LC (irregular SiOH, 15-40 µm, 50 g Merck, mobile phase gradient: from DCM/^{i}PrOH 100/0 to 90/10) to give 145 mg of a yellow oil. This fraction was taken up in MeOH (3 times) and evaporated then the residue was coevaporated in ^{i}PrOAc (3 times) to give compound **100** as a yellow solid (135 mg, 43%).

Compound 101:

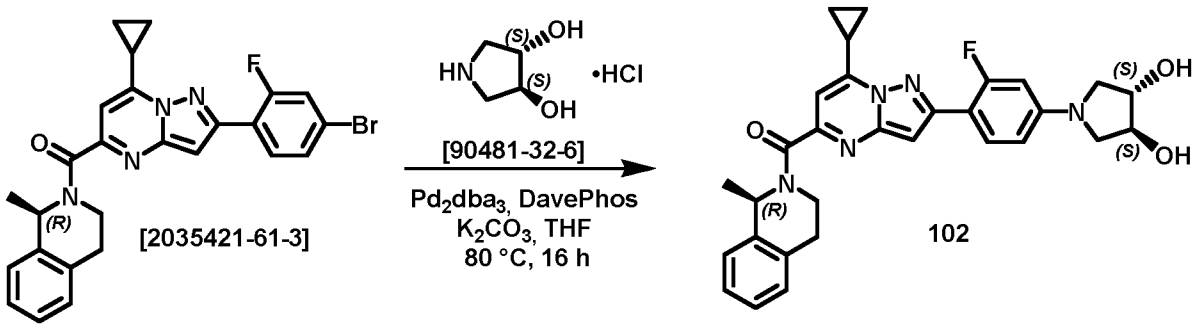
(S)-1-(4-(7-cyclopropyl-5-((R)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)pyrazolo[1,5-a]pyrimidin-2-yl)-3-fluorophenyl)pyrrolidine-3-carbothioamide



A mixture of compound **36** (118 mg; 0.22 mmol), Lawesson reagent (53 mg; 0.13 mmol) and DCM (1 mL) was stirred at rt for 2 h. The mixture was directly purified by flash chromatography (irregular SiOH 15-40 µm, 40 g GraceResolv®, mobile phase gradient, Heptane/EtOAc from 90/10 to 30/70). The fractions containing product were evaporated and coevaporated with EtOH. The solid was dried under vacuum to give compound **101** as a yellow solid (73 mg, 60%).

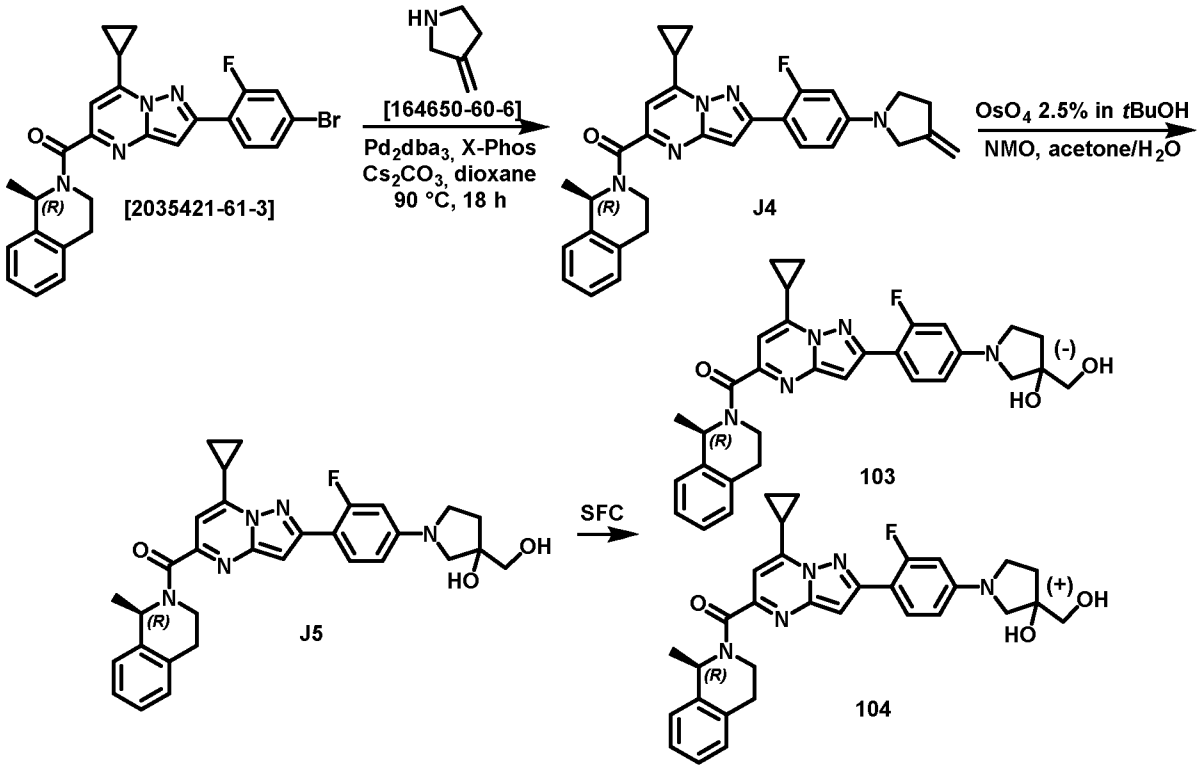
Compound 102:

(7-cyclopropyl-2-(4-((3S,4S)-3,4-dihydroxypyrrolidin-1-yl)-2-fluorophenyl)pyrazolo[1,5-a]pyrimidin-5-yl)((R)-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone



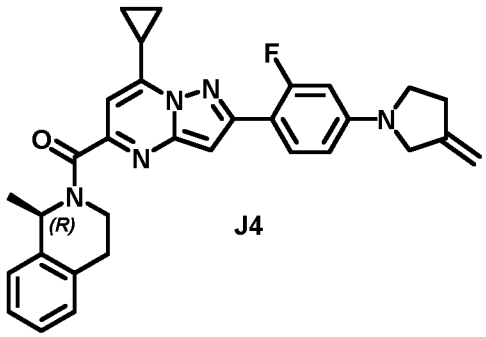
Under N_2, a mixture of (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] (6.8 g, 13.5 mmol) 3*S*, 4*S*-Pyrrolidinediol (1.9 g, 18.8 mmol) and K_2CO_3 (6.5 g, 47.1 mmol) in THF (125 mL) was degassed with N_2 for 10 min. DavePhos (530 mg, 1.35 mmol) and Pd_2dba_3 (1.2 g, 1.35 mmol) were added and the reaction mixture was purged with N_2. The mixture was heated at reflux (80 °C) for 16 h. Water and EtOAc were added. The aqueous layer was extracted with EtOAc (twice), the combined organic layers were dried over $MgSO_4$, filtered, concentrated in vacuo and purified by preparative LC (irregular SiOH 15-40 µm, 330 g GraceResolv®, mobile phase gradient: from DCM/MeOH 100/0 to 90/10) The fractions containing product were collected and evaporated to dryness. The residue and SiliaMetS® Thiol (1.2 g; 1.61 mmol) in THF (100 mL) was stirred at rt for 3 h, then filtered over celite® and the filtrate was evaporated to dryness to give 4.8 g of a yellow foam. The solid was suspended in EtOAc (~210 mL in total) and heated at reflux until complete solubilization. Then the heating source was stopped (the flask was kept in the oil bath during the crystallization with a gentle stirring allowing slow cooling) for 42 h. The suspension was cooled down to rt, filtered over glass frit, washed with cold EtOAc. The solid was dried under vacuum to give 2.75 g of a first batch of compound **102** as a yellow solid. The filtrate was evaporated, the residue was suspended in EtOAc (~60 mL in total) and heated at reflux until complete solubilization (oil bath 90 °C). Then the heating source was stopped (the flask was kept in the oil bath during the crystallization with a gentle stirring allowing slow cooling) for 42 h. The suspension was cooled down to rt, filtered over glass frit, washed with cooled EtOAc. The solid was dried under vacuum at 50 °C for 2 h to give 0.944 g of a second batch of compound **102** as a yellow solid. Both batches and 22 mL of EtOAc were stirred at rt for 24 h. The suspension was filtered over glass frit, washed with cold EtOAc. The solid was dried under vacuum to give compound **102** as a yellow solid (3.27 g, 46%).

Synthesis of compound 103 and 104:



Intermediate **J4:**

(R)-(7-cyclopropyl-2-(2-fluoro-4-(3-methylenepyrrolidin-1-yl)phenyl)pyrazolo[1,5-a]pyrimidin-5-yl)(1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone

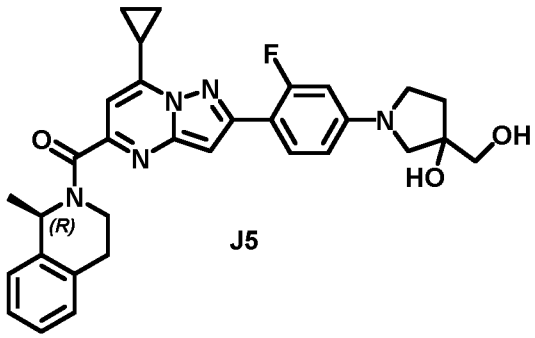


J4

A mixture of (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] (325 mg; 0.644 mmol), Cs_2CO_3 (1.05 g; 3.22 mmol) and 3-methylidenepyrrolidine•TFA (294 mg; 0.644 mmol) was charged in a sealed tube and purged with N_2. Dioxane (6 ml) was added and the mixture was degassed with N_2, then Pd_2dba_3 (29.5 mg; 0.0322 mmol) and X-Phos (46 mg; 0.096 mmol) were added. The reaction mixture was purged with N_2 then was stirred and heated at 90 °C for 18 h. Water and EtOAc were added, the layers were

separated. The aqueous layer was extracted with EtOAc (twice), the combined organic layers were dried over $MgSO_4$, filtered, concentrated in vacuo and purified by preparative LC (irregular SiOH 15-40 µm, 40 g GraceResolv®, mobile phase gradient: Heptane/EtOAc: from 90/10 to 60/40) to give intermediate **J4** as a yellow solid (259 mg, 70%).

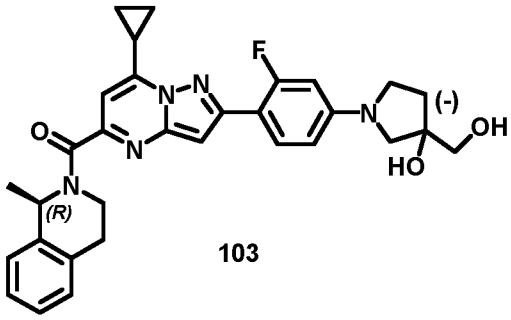
Intermediate **J5**:
(7-cyclopropyl-2-(2-fluoro-4-(3-hydroxy-3-(hydroxymethyl)pyrrolidin-1-yl)phenyl)pyrazolo[1,5-a]pyrimidin-5-yl)((R)-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone



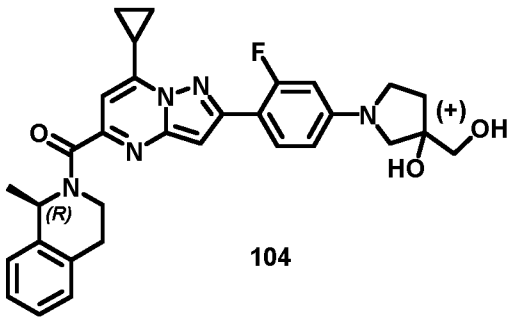
J5

NMO (141 mg; 1.20 mmol) and OsO4 2.5% in ^{t}BuOH (0.263 ml; 0.0201 mmol) were added to a solution of **J4** (234 mg; 0.401 mmol) in a mixture of acetone (2 ml) and H_2O (0.2 ml). The reaction mixture was stirred at rt for 3.5 h. The reaction mixture was quenched with a 10% aqueous solution of $Na_2S_2O_3$ and the resulting mixture was stirred at rt for 30 min. DCM was added and the layers were separated. The aqueous layer was extracted with DCM/MeOH (90/10) mixture (3 times). The organic layers were combined, washed with water, dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative LC (irregular SiOH, 15-40 µm, 12 g GraceResov®, mobile phase gradient: DCM/MeOH: from 99/1 to 95/5). The fraction containing product was combined and evaporated to dryness. The residue was purified by preparative LC (spherical C18, 25 µm, 40 g YMC-ODS-25, mobile phase gradient 0.2% aq. NH_4HCO_3 / MeCN from 65:35 to 25:75) to give 128 mg of a yellow solid. This solid was purified again by preparative LC (spherical C18, 25 µm, 40 g YMC-ODS-25, mobile phase gradient 0.2% aq. NH_4HCO_3 / MeCN from 65:35 to 25:75) the fractions containing product were extended with water and freeze-dried to give a yellow solid. The solid and SiliaMetS® Thiol (30 mg; 0.0401 mmol) in THF (3 mL) was stirred at rt for 18 h, then filtered over PTFE and the filtrate was evaporated to dryness to give Intermediate **J5** as yellow solid (80 mg, 37%).

Compound 103 & 104:



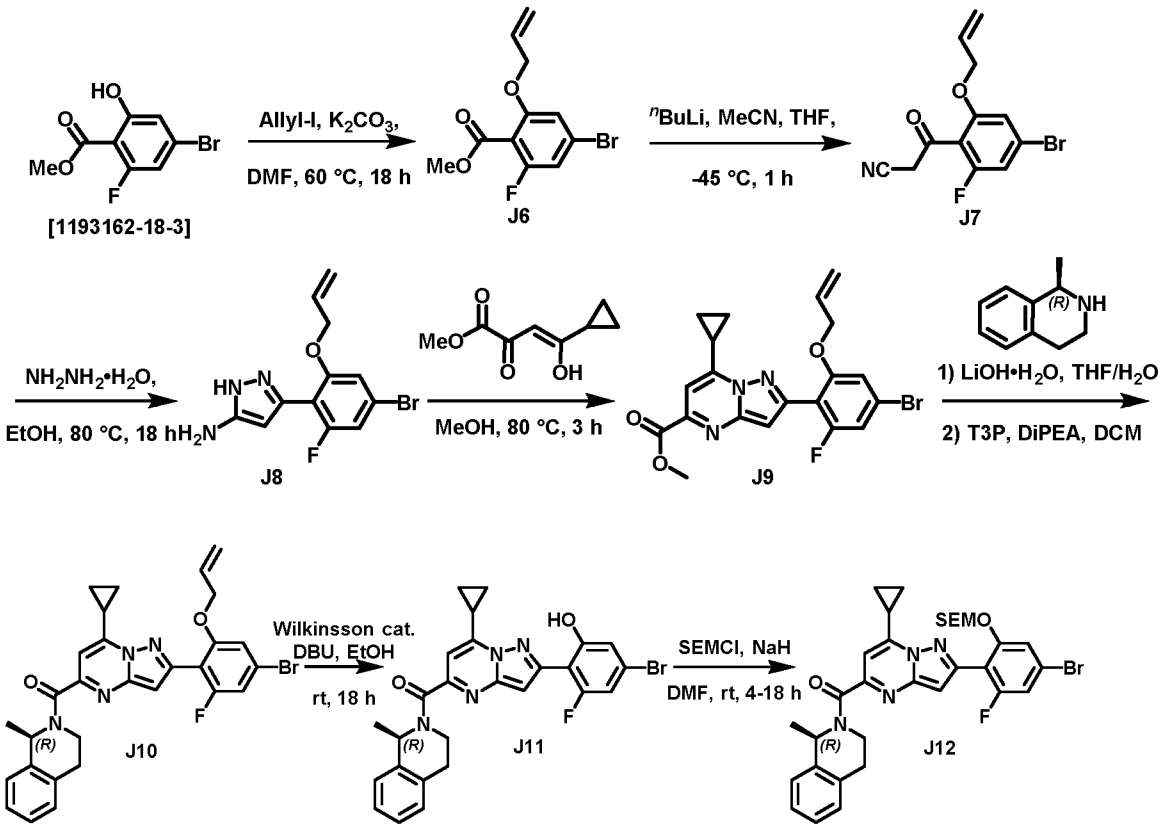
103

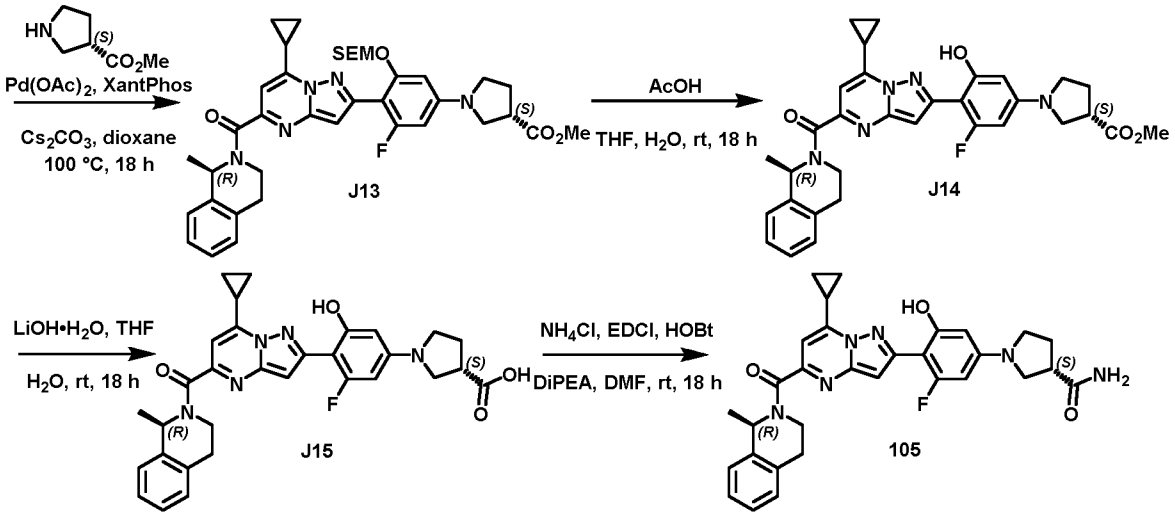


104

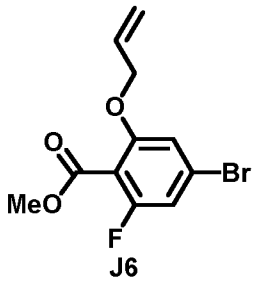
J5 was separated via chiral SFC (Stationary phase: CHIRALPAK AS-H 5µm 250*20mm, Mobile phase: 75% CO_2, 25% EtOH (0.3% $^{i}PrNH_2$)) the fractions contained product were evaporated to dryness then diluted with MeCN, extented with water and freeze-dried to give 28 mg of compound **103** having a (-) specific optical rotation as a yellow solid and 28 mg of compound **104** having a (+) specific optical rotation as a yellow solid.

Synthesis of compound 105 :



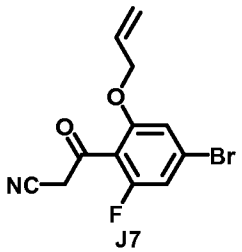


Intermediate **J6** : methyl 2-(allyloxy)-4-bromo-6-fluorobenzoate



A mixture of Methyl 4-bromo-2-fluoro-6-hydroxybenzoate [1193162-18-3] (5 g; 20.1 mmol), allyl iodide (5.5 mL; 60.2 mmol) and K_2CO_3 (8.76 g; 63.3 mmol) in DMF (80 mL) was stirred at 60°C for 18 h. EtOAc and water were added, and an extraction was performed. The organic layer was washed with brine, dried ($MgSO_4$), filtered, evaporated and purified by preparative LC (irregular SiOH, 15-40 µm, 220 g GraceResolv®, mobile phase gradient: from heptane/EtOAc 100/0 to 85/15) to give intermediate **J6** as a white solid (5.55 g, 96%).

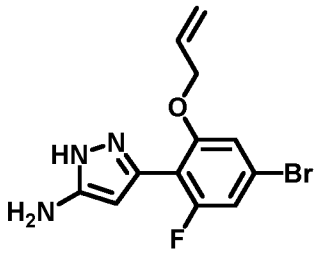
Intermediate **J7** : 3-(2-(allyloxy)-4-bromo-6-fluorophenyl)-3-oxopropanenitrile



Under N_2, ^{n}BuLi 1.6M in hexanes (57 mL; 91.9 mmol) was added to THF (100 mL) at -78°C then a solution of MeCN (4.78 mL; 91.6 mmol) was added dropwise. The resulting slurry was stirred for 1 h at -78°C then a solution of intermediate **J6** (13.4 g; 46.4 mmol) in

THF (150 mL) was added. After 30 min at -78°C the reaction mixture was warmed to -45°C and allowed to stir for 1 h. The reaction was quenched with HCl 1N and then extracted with EtOAc. The organic layer was separated, washed with water then brine, dried ($MgSO_4$), filtered and evaporated to give intermediate **J7** as orange oil (14.4 g, Quant.).

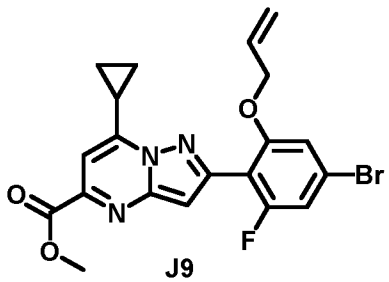
Intermediate **J8** : 3-(2-(allyloxy)-4-bromo-6-fluorophenyl)-1H-pyrazol-5-amine



J8

A mixture of intermediate **J7** (14.4 g; 48.3 mmol) and Hydrazine hydrate (80% purity) (2.95 mL; 48.3 mmol) in EtOH (192 mL) was stirred at 80 °C for 18 h. The mixture was evaporated to give intermediate **J8** as yellow solid (14.4 g, 96%).

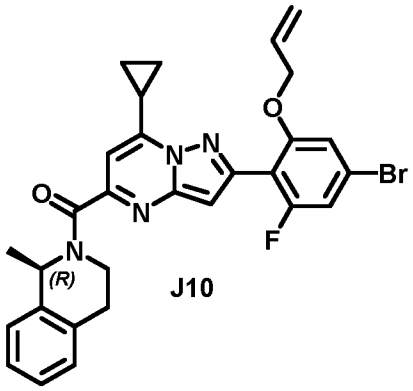
Intermediate **J9 :** methyl 2-(2-(allyloxy)-4-bromo-6-fluorophenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-5-carboxylate



J9

A mixture of **J8** (14.4 g; 46.1 mmol) and Methyl 4-cyclopropyl-2,4-dioxobutanoate [167408-67-5] (8.26 g; 46.1 mmol) in EtOH (200 mL) was stirred at 80 °C for 3 h. The mixture was cooled to rt and a precipitate was formed. The precipitate was filtered and dried on the frit to give intermediate **J9** as yellow solid (7.96 g, 38%).

Intermediate **J10**:
(R)-(2-(2-(allyloxy)-4-bromo-6-fluorophenyl)-7-cyclopropylpyrazolo[1,5-a]pyrimidin-5-yl)(1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone

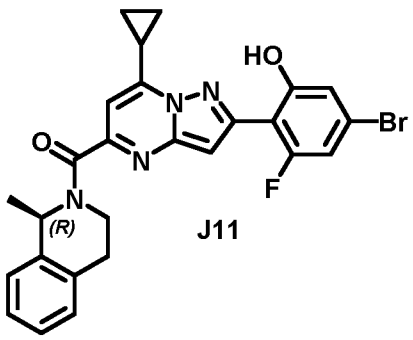


J10

A mixture of **J9** (7.96 g; 17.8 mmol), $LiOH•H_2O$ (4.12 g; 98.1 mmol), THF (80 mL) and H_2O (23 mL) was stirred at rt for 2 days. EtOAc and 10% aq. $KHSO_4$ were added to the mixture and an extraction was performed. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to give 6.57 g of acid intermediate as yellow solid. The acid (6.57 g; 15.2 mmol), 1R-methyl-1,2,3,4-tetrahydroisoquinoline (2.59 g; 17.6 mmol) and DiPEA (13 mL; 76 mmol) in DCM (77 mL) were stirred at 0 °C. T3P (22.6 mL; 37.9 mmol) was added slowly (5 min.) at 0 °C. The mixture was stirred at 0 °C for 10 min then at rt for 3 h. Water and EtOAc were added. An extraction was performed. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to give intermediate **J10** as a brown foam (9.0 g, Quant.).

Intermediate **J11:**

(R)-(2-(4-bromo-2-fluoro-6-hydroxyphenyl)-7-cyclopropylpyrazolo[1,5-a]pyrimidin-5-yl)(1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone



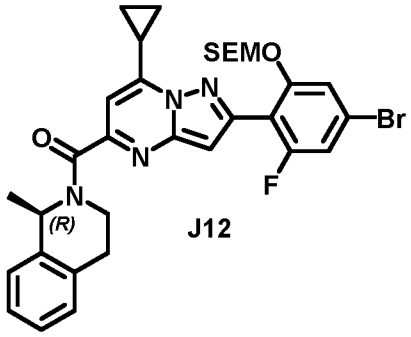
J11

A mixture of **J10** (5 g; 8.91 mmol), Wilkinson catalyst (824 mg; 0.89 mmol), DBU (1.33 mL; 8.91 mmol) and EtOH (60 mL) was stirred at rt for 18 h. The mixture was evaporated and purified by preparative LC (irregular SiOH 15-40 µm, GraceResolv® 220 g, dry loading (celite®) mobile phase Heptane/EtOAc from 100:0 to 70:30) to give 2 g of intermediate **J11** as brown solid, and 2 impure fractions (3 g and 2.4 g). The first impure fraction (3 g) was purified by Reverse phase LC (Stationary phase: spherical C18 25 µm,

300 g YMC-ODS-25, dry loading (C18), Mobile phase: Gradient: 0.2% aq. NH_4HCO_3 / MeCN, from 50:50 to 0:100). The fractions containing the product were combined, MeCN was evaporated in vacuo, water and EtOAc were added and an extraction was performed. The organic layer was washed with water, dried over $MgSO_4$, filtered and evaporated to give 700 mg of intermediate **J11** as a brown oil. The second impure fraction (2.4 g) was purified by Reverse phase LC (Stationary phase: spherical C18 25 µm, 300 g YMC-ODS-25, dry loading (C18), Mobile phase: Gradient: 0.2% aq. NH_4HCO_3 / MeCN, from 50:50 to 0:100). The fractions containing the product were combined, MeCN was evaporated in vacuo, water and EtOAc were added and an extraction was performed. The organic layer was washed with water, dried over $MgSO_4$, filtered and evaporated to give 1 g of intermediate **J11** as a brown foam (Global yield 80%, 3.7 g).

Intermediate **J12:**

(R)-(2-(4-bromo-2-fluoro-6-((2-(trimethylsilyl)ethoxy)methoxy)phenyl)-7-cyclopropylpyrazolo[1,5-a]pyrimidin-5-yl)(1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone

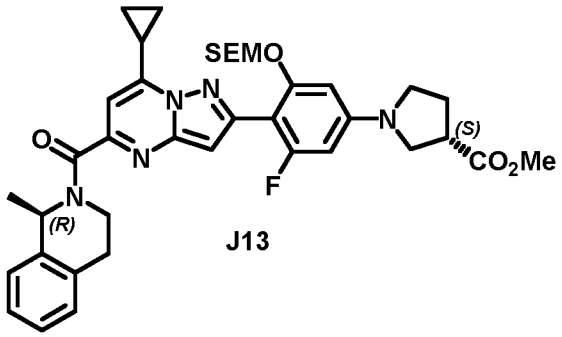


J12

A mixture of **J11** (2,7 g; 5.18 mmol) and NaH 60% in mineral oil (311 mg; 7.77 mmol) in DMF (20 mL) was stirred at 0 °C for 15 min. SEMCl (1.83 mL; 10.4 mmol) was added slowly at 0 °C under N_2. The mixture was stirred at rt for 4 h. An extraction was performed with EtOAc and water. The organic layer was washed with brine, dried ($MgSO_4$), evaporated and purified by preparative LC (irregular SiOH, 15-40 µm, 120 g GraceResolv®, mobile phase gradient: from heptane/EtOAc 100/0 to 70/30) to give intermediate **J12** as a colorless oil (2.3 g, 68%).

Intermediate **J13**:

methyl (S)-1-(4-(7-cyclopropyl-5-((R)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)pyrazolo[1,5-a]pyrimidin-2-yl)-3-fluoro-5-((2-(trimethylsilyl)ethoxy)-methoxy)phenyl)pyrrolidine-3-carboxylate

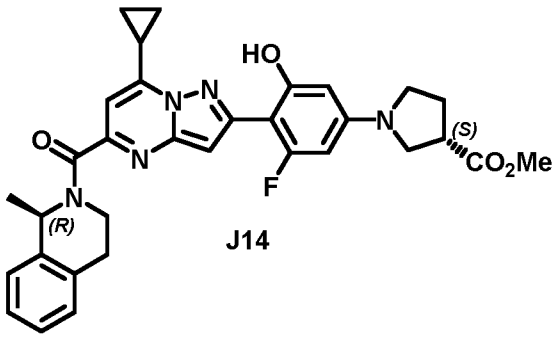


J13

A sealed tube was charged with **J12** (800 mg; 1.23 mmol), *(S)*-methyl Pyrrolidine-3-carboxylate hydrochloride (238 mg; 1.44 mmol), Cs_2CO_3 (1.17 g; 3.59 mmol) and dioxane (13 mL) and purged with N_2. XantPhos (69 mg; 0.12 mmol) was added and the mixture was purged again with N_2, then $Pd(OAc)_2$ (27 mg; 0.12 mmol) was added. The reaction mixture was purged with N_2 and heated at 100 °C for 17 h. The mixture was filtered through a pad of celite ®, water and EtOAc were added and an extraction was performed. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, evaporated and purified by preparative LC (irregular SiOH 15-40 µm, 24 g GraceResolv®, mobile phase gradient: from heptane/EtOAc 100/0 to 50/50) to give intermediate **J13** as a yellow foam (578 mg, 67%).

Intermediate **J14**:

methyl (S)-1-(4-(7-cyclopropyl-5-((R)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)pyrazolo[1,5-a]pyrimidin-2-yl)-3-fluoro-5-hydroxyphenyl)pyrrolidine-3-carboxylate

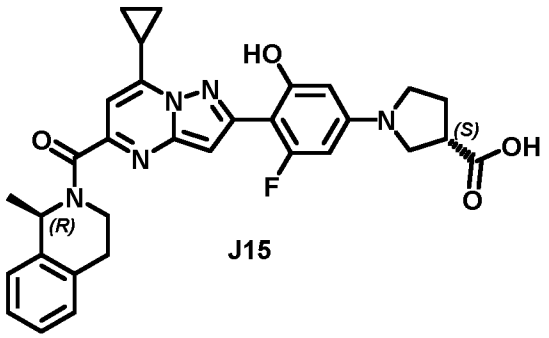


J14

A mixture of **J13** (2.5 g; 3.57 mmol), AcOH (30 mL), THF (10 mL) and H_2O (10 mL) was stirred at rt for 18 h. $AqNaHCO_3$ and EtOAc were added and an extraction was performed. The organic layer was washed with brine, dried ($MgSO_4$), filtered, evaporated and purified by preparative LC (irregular SiOH 15-40 µm, 220 g GraceResolv®, mobile phase gradient: from heptane/EtOAc 100/0 to 50/50) to give intermediate **J14** as a yellow solid (1.56 g, 77%).

Intermediate **J15**

(S)-1-(4-(7-cyclopropyl-5-((R)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)pyrazolo[1,5-a]pyrimidin-2-yl)-3-fluoro-5-hydroxyphenyl)pyrrolidine-3-carboxylic acid

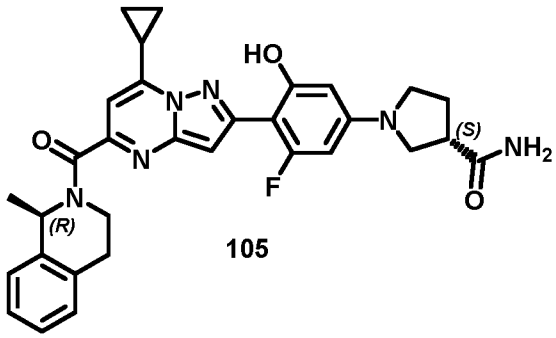


J15

A mixture of **J14** (600 mg; 1.05 mmol), $LiOH \cdot H_2O$ (243 mg; 5.80 mmol), THF (5 mL) and H_2O (1 mL) was stirred at rt for 18 h. EtOAc and 10% aq. $KHSO_4$ were added to the mixture and an extraction was performed. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to give intermediate **J15** as yellow solid (550 mg, 94%).

Compound 105:

(S)-1-(4-(7-cyclopropyl-5-((R)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)pyrazolo[1,5-a]pyrimidin-2-yl)-3-fluoro-5-hydroxyphenyl)pyrrolidine-3-carboxamide

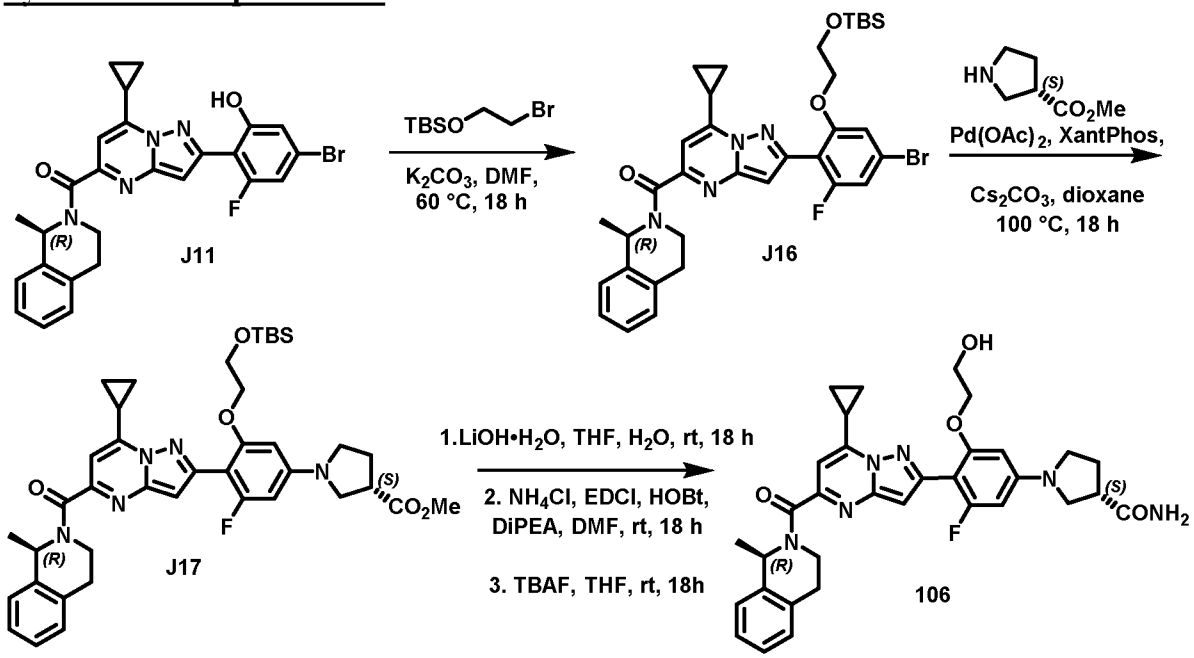


105

A mixture of **J15** (250 mg; 0.45 mmol), ammonium chloride (48 mg; 0.90 mmol), EDCI (140 mg; 0.90 mmol) and $HOBt \cdot H_2O$ (138 mg; 0.90 mmol) in DMF (8 mL) was stirred at 0 °C. DiPEA (0.39 mL; 2.25 mmol) was added slowly at 0 °C. The mixture was stirred at rt for 18 h. EtOAc and brine were added to the mixture and an extraction was performed. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, evaporated and purified by Reverse phase LC (Stationary phase: spherical C18 25 µm, 40 g YMC-ODS-25, dry loading (C18), Mobile phase: Gradient: 0.2% aq. NH_4HCO_3 / MeCN,

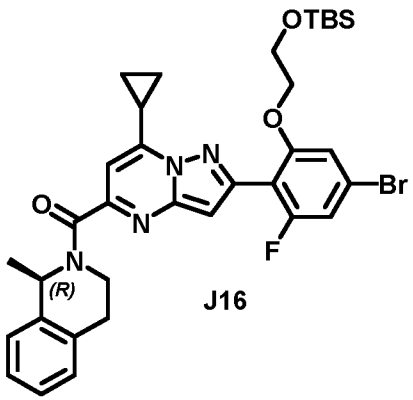
from 65:35 to 25:75). MeCN was evaporated, EtOAc was added and an extraction was performed. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, evaporated and coevaporated 3 times with EtOAc, to give compound **105** as a yellow solid (140 mg, 56%).

Synthesis of compound 106:



Intermediate **J16**:

(R)-(2-(4-bromo-2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)-6-fluorophenyl)-7-cyclopropylpyrazolo[1,5-a]pyrimidin-5-yl)(1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone

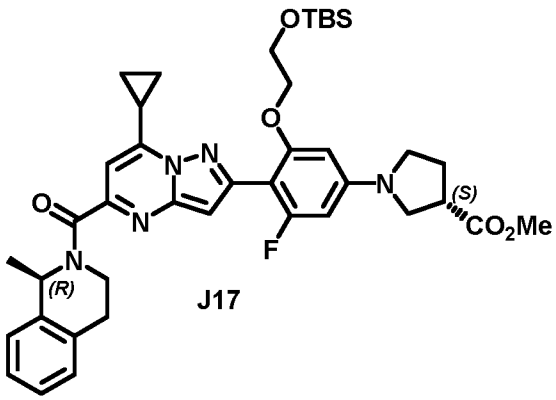


A mixture of **J11** (226 mg; 0.43 mmol), (2-bromotethoxy)-tert-butyldimethylsilane (93 µL; 0.43 mmol) and K_2CO_3 (189 mg; 1.37 mmol) in DMF (5 mL) was stirred at 60 °C for 18 h. EtOAc and water were added and an extraction was performed. The organic layer was

washed with brine, dried ($MgSO_4$), evaporated and purified by preparative LC (irregular SiOH, 15-40 µm, 120 g GraceResolv®, mobile phase gradient: from heptane/EtOAc 100/0 to 70/30) to give intermediate **J16** as a colorless oil (243 mg, 82%).

Intermediate **J17**:

methyl (S)-1-(3-(2-((tert-butyldimethylsilyl)oxy)ethoxy)-4-(7-cyclopropyl-5-((R)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)pyrazolo[1,5-a]pyrimidin-2-yl)-5-fluorophenyl)pyrrolidine-3-carboxylate

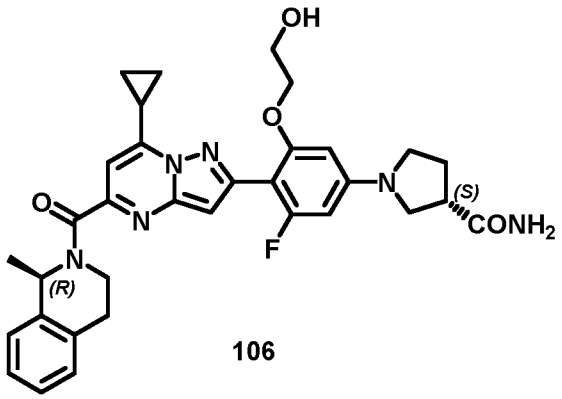


J17

A sealed tube was charged with **J16** (243 mg; 0.36 mmol), *(S)*-methyl Pyrrolidine-3-carboxylate hydrochloride (59 mg; 0.36 mmol), Cs_2CO_3 (349 mg; 1.1 mmol) in dioxane (4 mL) and purged with N_2. XantPhos (21 mg; 0.036 mmol) and $Pd(OAc)_2$ (8 mg; 0.036 mmol) were added and the mixture was purged again with N_2. The mixture was stirred at 100°C for 18 h. EtOAc and water were added to the mixture. An extraction was performed. the organic layer was washed with brine, dried ($MgSO_4$) evaporated and purified by preparative LC (irregular SiOH, 15-40 µm, 40 g GraceResolv®, mobile phase gradient: from heptane/EtOAc 100/0 to 40/60) to give intermediate **J17** as yellow foam (188 mg, 72%).

Compound 106:

(S)-1-(4-(7-cyclopropyl-5-((R)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)pyrazolo[1,5-a]pyrimidin-2-yl)-3-fluoro-5-(2-hydroxyethoxy)phenyl)pyrrolidine-3-carboxamide

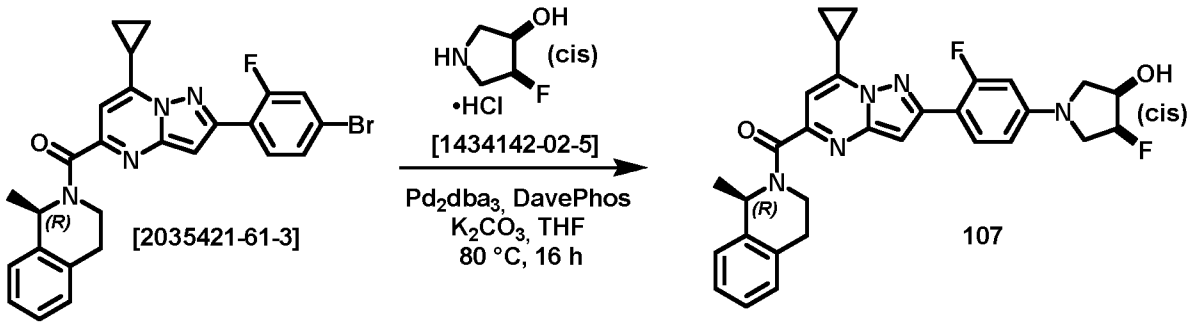


106

$LiOH•H_2O$ (58 mg; 1.4 mmol) was added to a solution of **J16** (188 mg; 0.26 mmol) in THF (7 mL) and H_2O (3 mL) and the reaction mixture was stirred at rt for 18 h. An aqueous solution of $KHSO_4$ 10% was added until pH=6 and the aqueous layer was extracted with EtOAc. The organic layer was washed with water, dried over $MgSO_4$, filtered and evaporated to give 190 mg of a yellow solid. To this solid, NH_4Cl (28 mg; 0.52 mmol), EDCI•HCl (80 mg; 0.418 mmol) and $HOBt•H_2O$ (79 mg; 0.52 mmol) in DMF (4 mL) were added. Then DIPEA (222 µL; 1.3 mmol) was added slowly at 0 °C and the mixture was stirred at rt for 18 h. Brine and EtOAc were added and an extraction was performed. The organic layer was washed with brine (3x), dried ($MgSO_4$), filtered and evaporated to give 182 mg of a yellow solid. TBAF 1M in THF (0.255 mL; 0.255 mmol) and THF (2 mL) were added and the mixture was stirred at rt for 18 h. Brine and EtOAc were added and an extraction was performed. The organic layer was dried ($MgSO_4$), evaporated and purified by preparative LC (spherical C18 25 µm, 40 g YMC-ODS-25, mobile phase gradient 0.2% aq. NH_4HCO_3 / MeCN from 95:05 to 30:70) the fraction containing product was concentrated, EtOAc was added and an extraction was performed. The organic layer was dried ($MgSO_4$), filtered and evaporated to give compound **106** as yellow solid (82 mg, 54%).

Compound 107:

(7-cyclopropyl-2-(2-fluoro-4-(cis-3-fluoro-4-hydroxypyrrolidin-1-yl)phenyl)pyrazolo[1,5-a]pyrimidin-5-yl)((R)-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone



In a sealed tube, a mixture of (1*R*)-2-[2-(4-bromo-2-fluorophenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline [2035421-61-3] (200 mg; 0.396 mmol), *cis*-4-fluoropyrrolidin-3-ol hydrochloride [1434142-02-5] (79 mg; 0.56 mmol) and K_2CO_3 (219 mg; 1.58 mmol) in THF (4.7 mL) was degassed with N_2 for 10 min. DavePhos (16 mg; 0.040 mmol) and Pd_2dba_3 (36 mg; 0.040 mmol) were added and the reaction mixture was purged with N_2. The mixture was heated at 80 °C for 20 h. Water and EtOAc were added and an extraction was performed. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by preparative LC (irregular SiOH 15-40 µm, 12 g GraceResolv®, mobile phase gradient: from DCM/MeOH 100/00 to 97/3). The fraction containing product was combined and evaporated to dryness. The residue was purified by Reverse phase (Stationary phase: YMC-actus Triart® C18 10µm 30*150mm, Mobile phase: Gradient from 40% aq. NH_4HCO_3 0.2%, 60% MeCN to 10% aq. NH_4HCO_3 0.2%, 90% MeCN) to give 102 mg of a yellow gum which was taken up in a mixture of EtOAc and Heptane, evaporated in vacuo to give 100 mg of yellow foam. The solid was purified again by Reverse phase (Stationary phase: YMC-actus Triart® C18 10µm 30*150mm, Mobile phase: Gradient from 40% aq. NH_4HCO_3 0.2%, 60% MeCN to 10% aq. NH_4HCO_3 0.2%, 90% MeCN). The fractions containing product were collected and evaporated. The residue was taken up in MeCN (2 mL) extended with water (10 mL) and freeze-dried to give compound **107** as a fluffy yellow solid (39 mg, 19%).

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-d_6) δ ppm 8.03 (t, *J*=8.7 Hz, 1H), 7.32 (d, *J*=7.3 Hz, 1H), 7.10 - 7.25 (m, 3H), 6.94 - 6.98 (m, 1H), 6.82 (br s, 1H), 6.53 - 6.61 (m, 2H), 5.59 (q, *J*=6.6 Hz,

1H), 3.81 (dd, *J*=13.9, 4.1 Hz, 1H), 3.55 - 3.70 (m, 3H), 3.34 - 3.53 (m, 3H), 2.83 - 3.07 (m, 2H), 2.72 (br d, *J*=16.4 Hz, 1H), 2.34 - 2.46 (m, 1H), 2.22 - 2.34 (m, 1H), 1.52 (d, *J*=6.9 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.21 - 1.30 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.03 (t, *J*=8.7 Hz, 1H), 7.10 - 7.25 (m, 3H), 7.07 (br d, *J*=7.6 Hz, 1H), 6.94 - 6.98 (m, 1H), 6.78 (s, 1H), 6.53 - 6.61 (m, 2H), 4.96 (q, *J*=6.8 Hz, 1H), 4.51 - 4.59 (m, 1H), 3.55 - 3.70 (m, 3H), 3.34 - 3.53 (m, 2H), 3.22 - 3.30 (m, 1H), 2.83 - 3.07 (m, 3H), 2.34 - 2.46 (m, 1H), 2.22 - 2.34 (m, 1H), 1.55 (d, *J*=6.6 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.21 - 1.30 (m, 2H).

Compound 2

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 16.31 (br s, 1H), 8.02 (t, *J*=8.8 Hz, 1H), 7.32 (br d, *J*=7.1 Hz, 1H), 7.06 - 7.26 (m, 3H), 6.92 - 6.97 (m, 1H), 6.81 (s, 1H), 6.58 (br d, *J*=9.1 Hz, 1H), 6.51 (dd, *J*=14.7, 1.5 Hz, 1H), 5.58 (q, *J*=6.7 Hz, 1H), 3.97 (quin, *J*=7.2 Hz, 1H), 3.77 - 3.87 (m, 2H), 3.60 (dd, *J*=9.9, 6.8 Hz, 1H), 3.42 - 3.54 (m, 3H), 2.85 - 3.06 (m, 2H), 2.71 (br d, *J*=16.2 Hz, 1H), 2.44 - 2.57 (m, 1H partially obscured by DMSO peak), 2.25 - 2.35 (m, 1H), 1.52 (d, *J*=6.6 Hz, 3H), 1.30 - 1.38 (m, 2H), 1.22 - 1.29 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 16.31 (br s, 1H), 8.02 (t, *J*=8.8 Hz, 1H), 7.06 - 7.26 (m, 4H), 6.92 - 6.97 (m, 1H), 6.77 (s, 1H), 6.58 (br d, *J*=9.1 Hz, 1H), 6.51 (dd, *J*=14.7, 1.5 Hz, 1H), 4.96 (q, *J*=6.6 Hz, 1H), 4.55 (br d, *J*=12.1 Hz, 1H), 3.97 (quin, *J*=7.2 Hz, 1H), 3.77 - 3.87 (m, 1H), 3.60 (dd, *J*=9.9, 6.8 Hz, 1H), 3.42 - 3.54 (m, 3H), 2.85 - 3.06 (m, 3H), 2.44 - 2.57 (m, 1H partially obscured by DMSO peak), 2.25 - 2.35 (m, 1H), 1.55 (d, *J*=7.1 Hz, 3H), 1.30 - 1.38 (m, 2H), 1.22 - 1.29 (m, 2H).

Compound 3

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 16.34 (br s, 1H), 8.03 (t, *J*=8.6 Hz, 1H), 7.32 (d, *J*=7.1 Hz, 1H), 7.05 - 7.26 (m, 3H), 6.91 - 6.97 (m, 1H), 6.81 (s, 1H), 6.58 (br d, *J*=8.6 Hz, 1H), 6.51 (dd, *J*=14.7, 2.0 Hz, 1H), 5.58 (q, *J*=6.9 Hz, 1H), 3.98 (quin, *J*=7.2 Hz, 1H), 3.77 - 3.88 (m, 2H), 3.60 (dd, *J*=9.6, 6.6 Hz, 1H), 3.41 - 3.55 (m, 3H), 2.85 - 3.07 (m, 2H), 2.71 (br d, *J*=15.7 Hz, 1H), 2.39 - 2.50 (m, 1H obscured by solvent peak), 2.23 - 2.36 (m, 1H), 1.52 (d, *J*=6.6 Hz, 3H), 1.30 - 1.38 (m, 2H), 1.20 - 1.29 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 16.34 (br s, 1H), 8.03 (t, *J*=8.6 Hz, 1H), 7.05 - 7.26 (m, 4H), 6.91 - 6.97 (m, 1H), 6.77 (s, 1H), 6.58 (br d, *J*=8.6 Hz, 1H), 6.51 (dd, *J*=14.7, 2.0 Hz, 1H), 4.96 (q, *J*=6.9 Hz, 1H), 4.50 - 4.59 (m, 1H), 3.98 (quin, *J*=7.2 Hz, 1H), 3.77 - 3.88 (m, 1H), 3.60 (dd, *J*=9.6, 6.6 Hz, 1H), 3.41 - 3.55 (m, 2H), 3.21 - 3.28 (m, 1H), 2.85 - 3.07 (m, 3H), 2.39 - 2.50 (m, 1H obscured by solvent peak), 2.23 - 2.36 (m, 1H), 1.55 (d, *J*=7.1 Hz, 3H), 1.30 - 1.38 (m, 2H), 1.20 - 1.29 (m, 2H).

Compound 4

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.43 (br s, 1H), 8.03 (t, *J*=8.8 Hz, 1H), 7.32 (d, *J*=7.6 Hz, 1H), 7.06 - 7.25 (m, 3H), 6.92 - 6.98 (m, 1H), 6.81 (s, 1H), 6.56 (br d, *J*=8.8 Hz, 1H), 6.48 (br dd, *J*=14.5, 1.6 Hz, 1H), 5.59 (q, *J*=6.6 Hz, 1H), 3.81 (br dd, *J*=13.7, 3.6 Hz, 1H), 3.64 - 3.71 (m, 1H), 3.60 (quin, *J*=7.1 Hz, 1H), 3.38 - 3.56 (m, 4H), 2.83 - 3.06 (m, 2H), 2.62 - 2.74 (m, 1H), 2.34 - 2.44 (m, 1H), 2.19 - 2.27 (m, 1H), 1.52 (d, *J*=6.6 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.21 - 1.30 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.43 (br s, 1H), 8.03 (t, *J*=8.8 Hz, 1H), 7.06 - 7.25 (m, 3H), 6.92 - 6.98 (m, 1H), 6.78 (s, 1H), 6.75 (d, *J*=8.5 Hz, 1H), 6.56 (br d, *J*=8.8 Hz, 1H), 6.48 (br dd, *J*=14.5, 1.6 Hz, 1H), 4.96 (q, *J*=6.6 Hz, 1H), 4.52 - 4.58 (m, 1H), 3.64 - 3.71 (m, 1H), 3.60 (quin, *J*=7.1 Hz, 1H), 3.38 - 3.56 (m, 3H), 3.23 - 3.29 (m, 1H), 2.83 - 3.06 (m, 3H), 2.34 - 2.44 (m, 1H), 2.19 - 2.27 (m, 1H), 1.56 (d, *J*=6.6 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.21 - 1.30 (m, 2H).

Compound 5

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.00 (t, *J*=8.8 Hz, 1H), 7.31 (d, *J*=7.1 Hz, 1H), 7.05 - 7.26 (m, 3H), 6.90 - 6.96 (m, 1H), 6.81 (s, 1H), 6.53 (dd, *J*=8.6, 1.5 Hz, 1H), 6.45 (dd, *J*=13.9, 1.5 Hz, 1H), 5.58 (q, *J*=6.7 Hz, 1H), 4.61 (d, *J*=6.1 Hz, 2H), 4.54 (d, *J*=6.1 Hz, 2H), 3.81 (br dd, *J*=14.2, 4.04 Hz, 1H), 3.59 (s, 2H), 3.41 - 3.50 (m, 1H), 3.29 - 3.37 (m, 2H partially obscured by H_2O peak), 2.85 - 3.06 (m, 2H), 2.71 (br d, *J*=16.7 Hz, 1H), 2.29 (t, *J*=6.8 Hz, 2H), 1.51 (d, *J*=7.1 Hz, 3H), 1.29 - 1.38 (m, 2H), 1.21 - 1.29 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.00 (t, *J*=8.8 Hz, 1H), 7.05 - 7.26 (m, 4H), 6.90 - 6.96 (m, 1H), 6.77 (s, 1H), 6.53 (dd, *J*=8.6, 1.5 Hz, 1H), 6.45 (dd, *J*=13.9, 1.5 Hz, 1H), 4.93 (q, *J*=6.1 Hz, 1H), 4.61 (d, *J*=6.1 Hz, 2H), 4.54 (d, *J*=6.1 Hz, 2H), 4.50 - 4.58 (m,

1H), 3.59 (s, 2H), 3.29 - 3.37 (m, 2H partially obscured by H_2O peak), 3.21 - 3.29 (m, 1H), 2.85 - 3.06 (m, 3H), 2.29 (t, *J*=6.8 Hz, 2H), 1.54 (d, *J*=7.1 Hz, 3H), 1.29 - 1.38 (m, 2H), 1.21 - 1.29 (m, 2H).

Compound 6

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.02 (t, *J*=8.8 Hz, 1H) 7.32 (d, *J*=7.1 Hz, 1H), 7.06 - 7.25 (m, 3H), 6.92 - 6.96 (m, 1H), 6.81 (s, 1H), 6.52 (dd, *J*=8.6, 2.0 Hz, 1H), 6.46 (dd, *J*=14.7, 1.5 Hz, 1H), 5.58 (q, *J*=6.4 Hz, 1H), 4.26 (q, *J*=13.1 Hz, 4H), 3.77 - 3.84 (m, 1H), 3.60 (s, 2H), 3.38 - 3.50 (m, 3H), 2.84 - 3.05 (m, 2H), 2.71 (br d, *J*=16.2 Hz, 1H), 2.28 - 2.33 (m, 2H), 1.52 (d, *J*=6.6 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.29 - 1.21 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.02 (t, *J*=8.8 Hz, 1H), 7.06 - 7.25 (m, 4H) 6.92 - 6.96 (m, 1H), 6.77 (s, 1H), 6.52 (dd, *J*=8.6, 2.0 Hz, 1H), 6.45 (dd, *J*=14.7, 1.5 Hz, 1H), 4.95 (q, *J*=7.1 Hz, 1H), 4.52 - 4.58 (m, 1H), 4.26 (q, *J*=13.1 Hz, 4H), 3.60 (s, 2H), 3.38 - 3.50 (m, 2H), 3.22 - 3.30 (m, 1H), 2.84 - 3.05 (m, 3H), 2.28 - 2.33 (m, 2H), 1.54 (d, *J*=7.1 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.29 - 1.21 (m, 2H).

Compound 7

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.19 (br d, *J*=6.6 Hz, 1H), 8.01 (t, *J*=8.8 Hz, 1H), 7.32 (br d, *J*=7.6 Hz, 1H), 7.05 - 7.25 (m, 3H), 6.91 - 6.96 (m, 1H), 6.80 (s, 1H), 6.52 (br d, *J*=9.1 Hz, 1H), 6.46 (br d, *J*=14.7 Hz, 1H), 5.58 (q, *J*=7.1 Hz, 1H), 4.34 - 4.42 (m, 1H), 3.77 - 3.85 (m, 1H), 3.55 (br dd, *J*=10.1, 6.1 Hz, 1H), 3.34 - 3.50 (m, 3H), 3.14 (br dd, *J*=10.1, 3.5 Hz, 1H), 2.85 - 3.06 (m, 2H), 2.71 (br d, *J*=16.7 Hz, 1H), 2.13 - 2.24 (m, 1H), 1.86 - 1.96 (m, 1H), 1.82 (s, 3H), 1.52 (d, *J*=6.6 Hz, 3H), 1.30 - 1.38 (m, 2H), 1.19 - 1.30 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.19 (br d, *J*=6.6 Hz, 1H), 8.01 (t, *J*=8.8 Hz, 1H), 7.05 - 7.25 (m, 4H), 6.91 - 6.96 (m, 1H), 6.77 (s, 1H), 6.52 (br d, *J*=9.1 Hz, 1H), 6.46 (br d, *J*=14.7 Hz, 1H), 4.96 (q, *J*=6.6 Hz, 1H), 4.51 - 4.59 (m, 1H), 4.34 - 4.42 (m, 1H), 3.55 (br dd, *J*=10.1, 6.1 Hz, 1H), 3.34 - 3.50 (m, 2H), 3.21 - 3.30 (m, 1H), 3.14 (br dd, *J*=10.1, 3.5 Hz, 1H), 2.85 - 3.06 (m, 3H), 2.13 - 2.24 (m, 1H), 1.86 - 1.96 (m, 1H), 1.83 (s, 3H), 1.55 (d, *J*=6.6 Hz, 3H), 1.30 - 1.38 (m, 2H), 1.19 - 1.30 (m, 2H).

Compound 8

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.19 (d, *J*=6.9 Hz, 1H), 8.01 (t, *J*=8.8 Hz, 1H), 7.32 (d, *J*=7.6 Hz, 1H), 7.21 - 7.25 (m, 1H), 7.10 - 7.21 (m, 2H), 6.94 (d, *J*=3.5 Hz, 1H), 6.81 (s, 1H), 6.53 (br d, *J*=8.8 Hz, 1H), 6.46 (dd, *J*=14.5, 1.9 Hz, 1H), 5.59 (q, *J*=6.8 Hz, 1H), 4.35 - 4.42 (m, 1H), 3.81 (br dd, *J*=13.7, 3.6 Hz, 1H), 3.56 (dd, *J*=9.9, 6.5 Hz, 1H), 3.33 - 3.50 (m, 3H), 3.14 (dd, *J*=10.1, 4.1 Hz, 1H), 2.85 - 3.05 (m, 2H), 2.72 (br d, *J*=16.1 Hz, 1H), 2.15 - 2.23 (m, 1H), 1.88 - 1.95 (m, 1H), 1.82 (s, 3H), 1.52 (d, *J*=6.9 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.22 - 1.30 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.19 (d, *J*=6.9 Hz, 1H), 8.01 (t, *J*=8.8 Hz, 1H), 7.10 - 7.21 (m, 3H), 7.06 - 7.09 (m, 1H), 6.93 (d, *J*=3.5 Hz, 1H), 6.77 (s, 1H), 6.53 (br d, *J*=8.8 Hz, 1H), 6.46 (dd, *J*=14.5, 1.9 Hz, 1H), 4.96 (q, *J*=6.5 Hz, 1H), 4.52 - 4.58 (m, 1H), 4.35 - 4.42 (m, 1H), 3.56 (dd, *J*=9.9, 6.5 Hz, 1H), 3.33 - 3.50 (m, 2H), 3.23 - 3.30 (m, 1H), 3.14 (dd, *J*=10.1, 4.1 Hz, 1H), 2.85 - 3.05 (m, 3H), 2.15 - 2.23 (m, 1H), 1.88 - 1.95 (m, 1H), 1.82 (s, 3H), 1.55 (d, *J*=6.6 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.22 - 1.30 (m, 2H).

Compound 9

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.00 (t, *J*=9.1 Hz, 1H), 7.55 (br d, *J*=6.1 Hz, 1H), 7.32 (br d, *J*=7.6 Hz, 1H), 7.05 - 7.25 (m, 3H), 6.90 - 6.96 (m, 1H), 6.80 (s, 1H), 6.51 (br d, *J*=8.6 Hz, 1H), 6.44 (br d, *J*=14.7 Hz, 1H), 5.58 (q, *J*=6.9 Hz, 1H), 4.16 - 4.25 (m, 1H), 3.81 (br dd, *J*=12.9, 2.8 Hz, 1H), 3.51 - 3.60 (m, 1H), 3.55 (s, 3H), 3.34 - 3.51 (m, 3H), 3.16 (br dd, *J*=9.6, 4.6 Hz, 1H), 2.85 - 3.06 (m, 2H), 2.71 (br d, *J*=16.2 Hz, 1H), 2.14 - 2.25 (m, 1H), 1.87 - 2.02 (m, 1H), 1.50 (d, *J*=7.1 Hz, 3H), 1.30 - 1.38 (m, 2H), 1.20 - 1.29 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.00 (t, *J*=9.1 Hz, 1H), 7.55 (br d, *J*=6.1 Hz, 1H), 7.05 - 7.25 (m, 4H), 6.90 - 6.96 (m, 1H), 6.77 (s, 1H), 6.51 (br d, *J*=8.6 Hz, 1H), 6.44 (br d, *J*=14.7 Hz, 1H), 4.96 (q, *J*=6.6 Hz, 1H), 4.55 (br d, *J*=12.6 Hz, 1H), 4.16 - 4.25 (m, 1H), 3.55 (s, 3H), 3.34 - 3.51 (m, 3H), 3.21 - 3.29 (m, 1H), 3.16 (br dd, *J*=9.6, 4.6 Hz, 1H), 2.85 - 3.06 (m, 3H), 2.14 - 2.25 (m, 1H), 1.87 - 2.02 (m, 1H), 1.55 (d, *J*=7.1 Hz, 3H), 1.30 - 1.38 (m, 2H) 1.20 - 1.29 (m, 2H).

Compound 10

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.00 (t, *J*=8.8 Hz, 1H), 7.55 (br d, *J*=6.1 Hz, 1H), 7.32 (br d, *J*=7.6 Hz, 1H), 7.05 - 7.26 (m, 3H), 6.91 - 6.95 (m, 1H), 6.80 (s, 1H), 6.51 (br d, *J*=9.1 Hz, 1H), 6.45 (dd, *J*=14.7, 1.5 Hz, 1H), 5.58 (q, *J*=6.6 Hz, 1H), 4.16 - 4.25 (m, 1H), 3.81 (br dd, *J*=12.9, 3.8 Hz, 1H), 3.52 - 3.59 (m, 4H), 3.39 - 3.51 (m, 3H), 3.13 - 3.20 (m, 1H), 2.82 - 3.06 (m, 2H), 2.71 (br d, *J*=17.2 Hz, 1H), 2.13 - 2.24 (m, 1H), 1.88 - 1.99 (m, 1H), 1.52 (d, *J*=7.1 Hz, 3H), 1.29 - 1.37 (m, 2H), 1.20 - 1.29 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.00 (t, *J*=8.8 Hz, 1H), 7.55 (br d, *J*=6.1 Hz, 1H), 7.05 - 7.26 (m, 4H), 6.91 - 6.95 (m, 1H), 6.77 (s, 1H), 6.51 (br d, *J*=9.1 Hz, 1H), 6.45 (dd, *J*=14.7, 1.5 Hz, 1H), 4.96 (q, *J*=7.1 Hz, 1H), 4.51 - 4.58 (m, 1H), 4.16 - 4.25 (m, 1H), 3.52 - 3.59 (m, 3H), 3.39 - 3.51 (m, 2H), 3.21 - 3.29 (m, 1H), 3.13 - 3.20 (m, 1H), 2.82 - 3.06 (m, 3H), 2.67 - 2.76 (m, 1H), 2.13 - 2.24 (m, 1H), 1.88 - 1.99 (m, 1H), 1.53 (d, *J*=7.1 Hz, 3H), 1.29 - 1.37 (m, 2H), 1.20 - 1.29 (m, 2H).

Compound 11

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.00 (t, *J*=8.6 Hz, 1H), 7.48 (br d, *J*=7.1 Hz, 1H), 7.29 - 7.35 (m, 1H), 7.05 - 7.25 (m, 3H), 6.94 (br s, 1H), 6.80 (br s, 1H), 6.53 (br d, *J*=9.1 Hz, 1H), 6.47 (br d, *J*=14.2 Hz, 1H), 5.54 - 5.62 (m, 1H), 4.03 - 4.13 (m, 1H), 3.76 - 3.85 (m, 1H), 3.59 - 3.67 (m, 1H), 3.39 - 3.52 (m, 2H), 3.32 - 3.37 (m, 1H partially obscured by H_2O), 3.17 - 3.24 (m, 1H), 3.00 (s, 3H), 2.82 - 2.98 (m, 2H), 2.65 - 2.76 (m, 1H), 2.23 - 2.32 (m, 1H), 1.93 - 2.04 (m, 1H), 1.47 - 1.54 (m, 3H), 1.30 - 1.40 (m, 2H), 1.20 - 1.30 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.00 (t, *J*=8.6 Hz, 1H), 7.48 (br d, *J*=7.1 Hz, 1H), 7.05 - 7.25 (m, 4H), 6.94 (br s, 1H), 6.77 (br s, 1H), 6.53 (br d, *J*=9.1 Hz, 1H), 6.47 (br d, *J*=14.2 Hz, 1H), 4.91 - 5.00 (m, 1H), 4.51 - 4.58 (m, 1H), 4.03 - 4.13 (m, 1H), 3.59 - 3.67 (m, 1H), 3.39 - 3.52 (m, 2H), 3.24 - 3.28 (m, 1H), 3.17 - 3.24 (m, 1H), 3.00 (s, 3H), 2.82 - 2.98 (m, 3H), 2.23 - 2.32 (m, 1H), 1.93 - 2.04 (m, 1H), 1.58 - 1.53 (m, 3H), 1.30 - 1.40 (m, 2H), 1.20 - 1.30 (m, 2H).

Compound 12

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.01 (t, *J*=8.7 Hz, 1H), 7.49 (d, *J*=6.6 Hz, 1H), 7.32 (d, *J*=7.3 Hz, 1H), 7.06 - 7.25 (m, 3H), 6.91 - 6.96 (m, 1H), 6.81 (s, 1H), 6.53 (br d, *J*=8.8 Hz, 1H), 6.47 (br d, *J*=14.8 Hz, 1H), 5.59 (q, *J*=6.6 Hz, 1H), 4.05 - 4.13 (m, 1H), 3.81 (br dd, *J*=12.5, 3.3 Hz, 1H), 3.63 (br dd, *J*=9.8, 6.6 Hz, 1H), 3.41 - 3.50 (m, 2H), 3.33 - 3.36 (m, 1H), 3.21 (dd, *J*=9.9, 5.5 Hz, 1H), 3.01 (s, 3H), 2.83 - 2.98 (m, 2H), 2.72 (br d, *J*=16.4 Hz, 1H), 2.23 - 2.33 (m, 1H), 1.93 - 2.03 (m, 1H), 1.52 (d, *J*=6.9 Hz, 3H), 1.30 - 1.38 (m, 2H), 1.21 - 1.30 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.01 (t, *J*=8.7 Hz, 1H), 7.49 (d, *J*=6.6 Hz, 1H), 7.06 - 7.25 (m, 4H), 6.91 - 6.96 (m, 1H), 6.77 (s, 1H), 6.53 (br d, *J*=8.8 Hz, 1H), 6.47 (br d, *J*=14.8 Hz, 1H), 4.96 (q, *J*=6.7 Hz, 1H), 4.52 - 4.59 (m, 1H), 4.05 - 4.13 (m, 1H), 3.63 (br dd, *J*=9.8, 6.6 Hz, 1H), 3.41 - 3.50 (m, 2H), 3.24 - 3.30 (m, 1H), 3.21 (dd, *J*=9.9, 5.5 Hz, 1H), 3.02 - 3.06 (m, 1H), 3.01 (s, 3H), 2.83 - 2.98 (m, 2H), 2.23 - 2.33 (m, 1H), 1.93 - 2.03 (m, 1H), 1.55 (d, *J*=6.6 Hz, 3H), 1.30 - 1.38 (m, 2H), 1.21 - 1.30 (m, 2H).

Compound 13

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.99 (t, *J*=8.8 Hz, 1H), 7.32 (d, *J*=7.6 Hz, 1H), 7.06 - 7.25 (m, 3H), 6.91 - 6.95 (m, 1H), 6.80 (s, 1H), 6.51 (dd, *J*=8.7, 1.7 Hz, 1H), 6.43 (dd, *J*=14.8, 1.6 Hz, 1H), 5.59 (q, *J*=6.4 Hz, 1H), 5.01 (d, *J*=3.8 Hz, 1H), 4.43 (br s, 1H), 3.82 (br dd, *J*=13.7, 4.3 Hz, 1H), 3.33 - 3.50 (m, 4H), 3.16 (br d, *J*=10.4 Hz, 1H), 2.82 - 3.05 (m, 2H), 2.72 (br d, *J*=16.1 Hz, 1H), 2.02 - 2.11 (m, 1H), 1.89 - 1.96 (m, 1H), 1.52 (d, *J*=6.6 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.22 - 1.29 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.99 (t, *J*=8.8 Hz, 1H), 7.06 - 7.25 (m, 4H), 6.91 - 6.95 (m, 1H), 6.76 (s, 1H), 6.51 (dd, *J*=8.7, 1.7 Hz, 1H), 6.43 (dd, *J*=14.8, 1.6 Hz, 1H), 5.01 (d, *J*=3.8 Hz, 1H), 4.97 (q, *J*=6.6 Hz, 1H), 4.52 - 4.58 (m, 1H), 4.43 (br s, 1H), 3.60 (dt, *J*=12.1, 6.1 Hz, 1H), 3.33 - 3.50 (m, 2H), 3.23 - 3.28 (m, 1H), 3.16 (br d, *J*=10.4 Hz, 1H), 2.82 - 3.05 (m, 3H), 2.02 - 2.11 (m, 1H), 1.89 - 1.96 (m, 1H), 1.55 (d, *J*=6.6 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.22 - 1.29 (m, 2H).

Compound 14

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.99 (t, *J*=8.8 Hz, 1H), 7.32 (br d, *J*=7.1 Hz, 1H), 7.05 - 7.25 (m, 3H), 6.90 - 6.94 (m, 1H), 6.80 (s, 1H), 6.51 (dd, *J*=8.8, 1.8 Hz, 1H), 6.43

(dd, *J*=14.4, 1.3 Hz, 1H), 5.58 (q, *J*=6.6 Hz, 1H), 5.02 (d, *J*=3.5 Hz, 1H), 4.42 (br s, 1H), 3.77 - 3.85 (m, 1H), 3.34 - 3.51 (m, 4H), 3.16 (br d, *J*=10.1 Hz, 1H), 2.85 - 3.07 (m, 2H), 2.71 (br d, *J*=16.2 Hz, 1H), 2.00 - 2.12 (m, 1H), 1.88 - 1.97 (m, 1H), 1.52 (d, *J*=7.1 Hz, 3H), 1.21 - 1.37 (m, 4H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.99 (t, *J*=8.8 Hz, 1H), 7.05 - 7.25 (m, 4H), 6.90 - 6.94 (m, 1H), 6.76 (s, 1H), 6.51 (dd, *J*=8.8, 1.8 Hz, 1H), 6.43 (dd, *J*=14.4, 1.3 Hz, 1H), 5.02 (d, *J*=3.5 Hz, 1H), 4.96 (q, *J*=6.6 Hz, 1H), 4.51 - 4.59 (m, 1H), 4.42 (br s, 1H), 3.34 - 3.51 (m, 3H), 3.22 - 3.29 (m, 1H), 3.16 (br d, *J*=10.1 Hz, 1H), 2.85 - 3.07 (m, 3H), 2.00 - 2.12 (m, 1H), 1.88 - 1.97 (m, 1H), 1.55 (br d, *J*=7.1 Hz, 3H), 1.21 - 1.37 (m, 4H).

Compound 15

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.01 (br t, *J*=8.8 Hz, 1H), 7.32 (br d, *J*=8.1 Hz, 1H), 7.05 - 7.25 (m, 3H), 6.91 - 6.96 (m, 1H), 6.81 (s, 1H), 6.54 (br d, *J*=8.6 Hz, 1H), 6.49 (br d, *J*=15.2 Hz, 1H), 5.54 - 5.62 (m, 1H), 5.27 (br s, 1H), 3.81 (br d, *J*=14.2 Hz, 1H), 3.60 (br dd, *J*=10.9, 4.3 Hz, 1H), 3.30 - 3.51 (m, 5H, partially obscured by H_2O peak), 2.85 - 3.07 (m, 2H), 2.64 - 2.75 (m, 1H), 2.55 - 2.62 (m, 3H), 2.19 - 2.29 (m, 1H), 2.04 - 2.14 (m, 1H), 1.52 (br d, *J*=7.1 Hz, 3H), 1.30 - 1.38 (m, 2H), 1.21 - 1.29 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.01 (br t, *J*=8.8 Hz, 1H), 7.05 - 7.25 (m, 4H), 6.91 - 6.96 (m, 1H), 6.77 (s, 1H), 6.54 (br d, *J*=8.6 Hz, 1H), 6.49 (br d, *J*=15.2 Hz, 1H), 5.27 (br s, 1H), 4.92 - 5.00 (m, 1H), 4.51 - 4.59 (m, 1H), 3.60 (br dd, *J*=10.9, 4.3 Hz, 1H), 3.30 - 3.51 (m, 3H partially obscured by H_2O peak), 3.21 - 3.28 (m, 1H), 2.85 - 3.07 (m, 3H), 2.64 - 2.75 (m, 1H), 2.55 - 2.62 (m, 3H), 2.19 - 2.29 (m, 1H), 2.04 - 2.14 (m, 1H), 1.54 (br d, *J*=7.6 Hz, 3H), 1.30 - 1.38 (m, 2H), 1.21 - 1.29 (m, 2H).

Compound 16

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.01 (t, *J*=8.8 Hz, 1H), 7.32 (br d, *J*=7.6 Hz, 1H), 7.05 - 7.25 (m, 4H), 6.91 - 6.95 (m, 1H), 6.81 (s, 1H), 6.55 (br d, *J*=9.6 Hz, 1H), 6.48 (br d, *J*=14.7 Hz, 1H), 5.58 (q, *J*=6.7 Hz, 1H), 5.27 (br s, 1H), 3.81 (br dd, *J*=14.2, 3.5 Hz, 1H), 3.61 (br dd, *J*=11.1, 4.6 Hz, 1H), 3.34 - 3.51 (m, 4H), 2.85 - 3.07 (m, 2H), 2.71 (br d, *J*=16.7 Hz, 1H), 2.54 - 2.59 (m, 3H), 2.19 - 2.30 (m, 1H), 2.08 - 2.13 (m, 1H), 1.52 (d, *J*=6.6 Hz, 3H), 1.29 - 1.38 (m, 2H), 1.20 - 1.29 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.01 (t, *J*=8.8 Hz, 1H), 7.05 - 7.25 (m, 5H), 6.91 - 6.95 (m, 1H), 6.77 (s, 1H), 6.55 (br d, *J*=9.6 Hz, 1H), 6.48 (br d, *J*=14.7 Hz, 1H), 5.27 (br s, 1H), 4.91 - 5.00 (m, 1H), 4.51 - 4.59 (m, 1H), 3.61 (br dd, *J*=11.1, 4.6 Hz, 1H), 3.34 - 3.51 (m, 2H), 3.21 - 3.29 (m, 1H), 2.85 - 3.07 (m, 3H), 2.64 - 2.76 (m, 1H), 2.54 - 2.59 (m, 3H), 2.19 - 2.30 (m, 1H), 2.08 - 2.13 (m, 1H), 1.54 (d, *J*=7.1 Hz, 3H), 1.29 - 1.38 (m, 2H), 1.20 - 1.29 (m, 2H).

Compound 17

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.02 (t, *J*=8.3 Hz, 1H), 7.32 (d, *J*=6.1 Hz, 1H), 7.05 - 7.25 (m, 3H), 6.93 - 6.97 (m, 1H), 6.81 (s, 1H), 6.54 - 6.64 (m, 2H), 5.58 (q, *J*=7.1 Hz, 1H), 4.10 - 4.18 (m, 1H), 3.78 - 3.85 (m, 1H), 3.70 (d, *J*=7.1 Hz, 2H), 3.36 - 3.56 (m, 3H), 3.09 (s, 3H), 2.82 - 3.06 (m, 2H), 2.68 - 2.76 (m, 1H), 2.39 - 2.46 (m, 2H), 1.52 (br d, *J*=6.6 Hz, 3H), 1.20 - 1.38 (m, 4H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.02 (t, *J*=8.3 Hz, 1H), 7.05 - 7.25 (m, 4H), 6.93 - 6.97 (m, 1H), 6.78 (s, 1H), 6.54 - 6.64 (m, 2H), 4.96 (q, *J*=6.9 Hz, 1H), 4.51 - 4.59 (m, 1H), 4.10 - 4.18 (m, 1H), 3.70 (d, *J*=7.1 Hz, 2H), 3.36 - 3.56 (m, 2H), 3.21 - 3.28 (m, 1H), 3.09 (s, 3H), 2.82 - 3.06 (m, 3H), 2.39 - 2.46 (m, 2H), 1.55 (br d, *J*=7.1 Hz, 3H), 1.20 - 1.38 (m, 4H).

Compound 18

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.02 (t, *J*=8.6 Hz, 1H), 7.32 (br d, *J*=7.1 Hz, 1H), 7.05 - 7.25 (m, 3H), 6.93 - 6.98 (m, 1H), 6.82 (s, 1H), 6.54 - 6.64 (m, 2H), 5.58 (q, *J*=7.1 Hz, 1H), 4.14 (quin, *J*=6.7 Hz, 1H), 3.81 (br dd, *J*=13.6, 4.6 Hz, 1H), 3.70 (d, *J*=7.1 Hz, 2H), 3.32 - 3.65 (m, 3H), 3.09 (s, 3H), 2.85 - 3.06 (m, 2H), 2.71 (br d, *J*=16.2 Hz, 1H), 2.38 - 2.46 (m, 2H), 1.52 (d, *J*=7.1 Hz, 3H), 1.30 - 1.39 (m, 2H), 1.21 - 1.30 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.02 (t, *J*=8.6 Hz, 1H), 7.05 - 7.25 (m, 4H), 6.93 - 6.98 (m, 1H), 6.78 (s, 1H), 6.54 - 6.64 (m, 2H), 4.96 (q, *J*=6.1 Hz, 1H), 4.51 - 4.59 (m, 1H), 4.14 (quin, *J*=6.7 Hz, 1H), 3.70 (d, *J*=7.1 Hz, 2H), 3.32 - 3.65 (m, 2H), 3.22 - 3.31 (m, 1H), 3.09 (s, 3H), 2.85 - 3.06 (m, 3H), 2.38 - 2.46 (m, 2H), 1.55 (d, *J*=6.6 Hz, 3H), 1.30 - 1.39 (m, 2H), 1.21 - 1.30 (m, 2H).

Compound 19

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.03 (t, *J*=8.8 Hz, 1H), 7.32 (d, *J*=7.1 Hz, 1H), 7.04 - 7.26 (m, 5H), 6.93 - 6.97 (m, 1H), 6.81 (s, 1H), 6.57 (dd, *J*=9.1, 2.0 Hz, 1H), 6.51 (dd, *J*=14.2, 2.0 Hz, 1H), 5.58 (q, *J*=7.1 Hz, 1H), 3.89 - 3.97 (m, 1H), 3.77 - 3.85 (m, 1H), 3.61 - 3.73 (m, 2H), 3.37 - 3.54 (m, 3H), 2.85 - 3.06 (m, 2H), 2.71 (br d, *J*=16.7 Hz, 1H), 2.35 - 2.43 (m, 2H), 1.52 (d, *J*=6.6 Hz, 3H), 1.30 - 1.38 (m, 2H), 1.22 - 1.29 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.03 (t, *J*=8.8 Hz, 1H), 7.04 - 7.26 (m, 6H), 6.93 - 6.97 (m, 1H), 6.78 (s, 1H), 6.57 (dd, *J*=9.1, 2.0 Hz, 1H), 6.51 (dd, *J*=14.2, 2.0 Hz, 1H), 4.97 (q, *J*=7.1 Hz, 1H), 4.51 - 4.58 (m, 1H), 3.89 - 3.97 (m, 1H), 3.61 - 3.73 (m, 2H), 3.37 - 3.54 (m, 2H), 3.22 - 3.29 (m, 1H), 2.85 - 3.06 (m, 3H), 2.35 - 2.43 (m, 2H), 1.55 (d, *J*=6.6 Hz, 3H), 1.30 - 1.38 (m, 2H), 1.22 - 1.29 (m, 2H).

Compound 20

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.78 (br s, 1H), 7.96 (t, *J*=8.8 Hz, 1H), 7.25 (d, *J*=7.6 Hz, 1H), 6.99 - 7.20 (m, 3H), 6.86 - 6.91 (m, 1H), 6.75 (s, 1H), 6.45 - 6.55 (m, 2H), 5.52 (q, *J*=6.9 Hz, 1H), 4.30 - 4.38 (m, 1H), 3.72 - 3.78 (m, 1H), 3.58 - 3.71 (m, 2H), 3.33 - 3.46 (m, 3H), 2.78 - 3.01 (m, 2H), 2.65 (br d, *J*=16.2 Hz, 1H), 2.29 - 2.39 (m, 2H partially obscured by H_2O peak), 1.97 (s, 3H), 1.45 (d, *J*=6.6 Hz, 3H), 1.23 - 1.32 (m, 2H), 1.16 - 1.23 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.78 (br s, 1H), 7.96 (t, *J*=8.8 Hz, 1H), 6.99 - 7.20 (m, 4H), 6.86 - 6.91 (m, 1H), 6.71 (s, 1H), 6.45 - 6.55 (m, 2H), 4.89 (q, *J*=7.1 Hz, 1H), 4.45 - 4.52 (m, 1H), 4.30 - 4.38 (m, 1H), 3.58 - 3.71 (m, 2H), 3.33 - 3.46 (m, 2H), 3.15 - 3.22 (m, 1H), 2.78 - 3.01 (m, 3H), 2.29 - 2.39 (m, 2H partially obscured by H_2O peak), 1.97 (s, 3H), 1.48 (d, *J*=7.1 Hz, 3H), 1.23 - 1.32 (m, 2H), 1.16 - 1.23 (m, 2H).

Compound 21

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.02 (t, *J*=8.8 Hz, 1H), 7.32 (br d, *J*=7.6 Hz, 1H), 7.06 - 7.26 (m, 4H), 6.93 - 6.97 (m, 1H), 6.81 (s, 1H), 6.58 (br d, *J*=8.65Hz, 1H), 6.53 (br d, *J*=14.7 Hz, 1H), 5.58 (q, *J*=7.1 Hz, 1H), 4.08 - 4.16 (m, 1H), 3.81 (br dd, *J*=13.9, 3.8 Hz, 1H), 3.34 - 3.73 (m, 5H), 2.85 - 3.07 (m, 2H), 2.71 (br d, *J*=16.7 Hz, 1H), 2.64 (d, *J*=5.1 Hz, 3H), 2.32 - 2.41 (m, 2H), 1.52 (d, *J*=6.6 Hz, 3H), 1.21 - 1.38 (m, 4H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.02 (t, *J*=8.8 Hz, 1H), 7.06 - 7.26 (m, 5H), 6.93 - 6.97 (m, 1H), 6.78 (s, 1H), 6.58 (br d, *J*=8.6 Hz, 1H) 6.53 (br d, *J*=14.7 Hz, 1H), 4.96 (q, *J*=6.1 Hz, 1H), 4.51 - 4.59 (m, 1H), 4.08 - 4.16 (m, 1H), 3.34 - 3.73 (m, 4H), 3.21 - 3.31 (m, 1H), 2.85 - 3.07 (m, 3H), 2.64 (d, *J*=5.1 Hz, 3H), 2.32 - 2.41 (m, 2H), 1.55 (br d, *J*=7.1 Hz, 3H), 1.21 - 1.38 (m, 4H).

Compound 22

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.02 (br t, *J*=8.6 Hz, 1H), 7.32 (br d, *J*=7.1 Hz, 1H), 7.05 - 7.26 (m, 3H), 6.92 - 6.98 (m, 1H), 6.81 (s, 1H), 6.52 - 6.64 (m, 2H), 5.58 (q, *J*=6.2 Hz, 1H), 4.23 (quin, *J*=7.3 Hz, 1H), 3.77 - 3.86 (m, 1H), 3.71 (br t, *J*=9.4 Hz, 1H), 3.32 - 3.60 (m, 5H), 2.90 - 3.07 (m, 1H), 2.87 (s, 6H), 2.68 - 2.76 (m, 1H), 2.24 - 2.45 (m, 2H partially obscured by DMSO peak), 1.52 (br d, *J*=6.6 Hz, 3H), 1.21 - 1.38 (m, 4H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.02 (br t, *J*=8.6 Hz, 1H), 7.05 - 7.26 (m, 4H), 6.92 - 6.98 (m, 1H), 6.78 (s, 1H), 6.52 - 6.64 (m, 2H), 4.96 (q, *J*=6.6 Hz, 1H), 4.55 (br d, *J*=10.1 Hz, 1H), 4.23 (quin, *J*=7.3 Hz, 1H), 3.71 (br t, *J*=9.4 Hz, 1H), 3.32 - 3.60 (m, 4H), 3.20 - 3.29 (m, 1H), 2.90 - 3.07 (m, 2H), 2.87 (s, 6H), 2.24 - 2.45 (m, 2H partially obscured by DMSO peak), 1.55 (br d, *J*=6.6 Hz, 3H), 1.21 - 1.38 (m, 4H).

Compound 23

Major rotamer (70%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.99 (br t, *J*=8.5 Hz, 1H), 7.37 (br s, 1H), 7.32 (br d, *J*=7.3 Hz, 1H), 7.06 - 7.25 (m, 3H), 6.75 - 6.95 (m, 3H), 6.48 (d, *J*=8.5 Hz, 1H), 6.39 (d, *J*=14.5 Hz, 1H), 5.59 (q, *J*=6.0 Hz, 1H), 3.81 (br dd, *J*=12.8, 3.0 Hz, 1H), 3.22 - 3.50 (m, 3H), 3.12 (br d, *J*=9.8 Hz, 1H), 2.83 - 3.06 (m, 2H), 2.67 - 2.75 (m, 2H), 2.18 - 2.27 (m, 2H), 1.95 - 2.03 (m, 1H), 1.77 - 1.85 (m, 1H), 1.52 (br d, *J*=6.6 Hz, 3H), 1.21 - 1.37 (m, 4H), 1.14 (s, 3H).

Minor rotamer (30%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.99 (br t, *J*=8.5 Hz, 1H), 7.37 (br s, 1H), 7.06 - 7.25 (m, 4H), 6.75 - 6.95 (m, 3H), 6.48 (br d, *J*=8.5 Hz, 1H), 6.39 (br d, *J*=14.5 Hz, 1H), 4.96 (q, *J*=6.6 Hz, 1H), 4.55 (br d, *J*=10.7 Hz, 1H), 3.22 - 3.50 (m, 3H), 3.12 (br d, *J*=9.8 Hz, 1H), 2.83 - 3.06 (m, 2H), 2.67 - 2.75 (m, 2H), 2.18 - 2.27 (m, 2H), 1.95 - 2.03 (m, 1H), 1.77 - 1.85 (m, 1H), 1.55 (br d, *J*=6.6 Hz, 3H), 1.21 - 1.37 (m, 4H), 1.14 (s, 3H).

Compound 24

Major rotamer (70%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.99 (br t, *J*=8.7 Hz, 1H), 7.29 - 7.40 (m, 2H), 7.06 - 7.25 (m, 3H), 6.90 - 6.95 (m, 1H), 6.74 - 6.87 (m, 2H), 6.48 (d, *J*=8.5 Hz, 1H), 6.39 (d, *J*=14.5 Hz, 1H), 5.59 (q, *J*=6.6 Hz, 1H), 3.81 (br dd, *J*=13.1, 3.9 Hz, 1H), 3.21 - 3.52 (m, 4H), 3.12 (br d, *J*=9.5 Hz, 1H), 2.82 - 3.06 (m, 2H), 2.67 - 2.76 (m, 1H), 2.17 - 2.29 (m, 2H), 1.95 - 2.05 (m, 1H), 1.77 - 1.85 (m, 1H), 1.52 (br d, *J*=6.6 Hz, 3H), 1.20 - 1.40 (m, 4H), 1.14 (s, 3H).

Minor rotamer (30%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.99 (br t, *J*=8.7 Hz, 1H), 7.29 - 7.40 (m, 1H), 7.06 - 7.25 (m, 4H), 6.90 - 6.95 (m, 1H), 6.74 - 6.87 (m, 2H), 6.48 (br d, *J*=8.5 Hz, 1H), 6.39 (br d, *J*=14.5 Hz, 1H), 4.96 (q, *J*=6.6 Hz, 1H), 4.55 (br d, *J*=14.2 Hz, 1H), 3.21 - 3.52 (m, 4H), 3.12 (br d, *J*= 9.5 Hz, 1H), 2.82 - 3.06 (m, 3H), 2.17 - 2.29 (m, 2H), 1.95 - 2.05 (m, 1H), 1.77 - 1.85 (m, 1H), 1.55 (br d, *J*=6.6 Hz, 3H), 1.20 - 1.40 (m, 4H), 1.14 (s, 3H).

Compound 25

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.96 - 8.03 (m, 1H), 7.34 - 7.40 (m, 2H), 7.02 (d, *J*=5.0 Hz, 1H), 6.91 - 6.95 (m, 1H), 6.76 - 6.86 (m, 2H), 6.48 (d, *J*=8.5 Hz, 1H), 6.39 (d, *J*=14.8 Hz, 1H), 5.53 (q, *J*=6.2 Hz, 1H), 3.92 (br dd, *J*=13.6, 4.7 Hz, 1H), 3.34 - 3.45 (m, 4H), 3.12 (br d, *J*=9.8 Hz, 1H), 2.80 - 3.01 (m, 2H), 2.75 (br d, *J*=16.4 Hz, 1H), 2.18 - 2.27 (m, 2H), 1.96 - 2.03 (m, 1H), 1.77 - 1.85 (m, 1H), 1.46 (br d, *J*=6.6 Hz, 3H), 1.31 - 1.38 (m, 2H), 1.22 - 1.29 (m, 2H), 1.14 (s, 3H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.96 - 8.03 (m, 1H), 7.34 - 7.40 (m, 1H), 7.29 (d, *J*=5.4 Hz, 1H), 6.91 - 6.95 (m, 1H), 6.76 - 6.86 (m, 3H), 6.48 (d, *J*=8.5 Hz, 1H), 6.39 (d, *J*=14.8 Hz, 1H), 4.90 (q, *J*=6.9 Hz, 1H), 4.70 (br dd, *J*=12.3, 4.1 Hz, 1H), 3.34 - 3.45 (m, 3H), 3.16 - 3.25 (m, 1H), 3.12 (br d, *J*=9.8 Hz, 1H), 2.80 - 3.01 (m, 3H), 2.18 - 2.27 (m, 2H), 1.96 - 2.03 (m, 1H), 1.77 - 1.85 (m, 1H), 1.50 (br d, *J*=6.6 Hz, 3H), 1.31 - 1.38 (m, 2H), 1.22 - 1.29 (m, 2H), 1.14 (s, 3H).

Compound 26

Major rotamer (70%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.95 - 8.03 (m, 1H), 7.34 - 7.41 (m, 2H), 7.02 (d, *J*=5.0 Hz, 1H), 6.91 - 6.95 (m, 1H), 6.76 - 6.86 (m, 2H), 6.48 (d, *J*=8.8 Hz, 1H), 6.39 (d, *J*=14.2 Hz, 1H), 5.53 (q, *J*=6.3 Hz, 1H), 3.93 (dd, *J*=13.2, 4.4 Hz, 1H), 3.29 - 3.46 (m, 3H), 3.16 - 3.26 (m, 1H), 3.12 (br d, *J*=9.8 Hz, 1H), 2.81 - 3.00 (m, 2H), 2.75 (br d, *J*=15.1 Hz,

1H), 2.18 - 2.27 (m, 2H), 1.95 - 2.03 (m, 1H), 1.76 - 1.85 (m, 1H), 1.46 (d, *J*=6.6 Hz, 3H), 1.21 - 1.39 (m, 4H), 1.14 (s, 3H).

Minor rotamer (30%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.95 - 8.03 (m, 1H), 7.34 - 7.41 (m, 1H), 7.29 (d, *J*=5.0 Hz, 1H), 6.91 - 6.95 (m, 1H), 6.76 - 6.86 (m, 3H), 6.48 (d, *J*=8.8 Hz, 1H), 6.39 (d, *J*=14.2 Hz, 1H), 4.90 (q, *J*=6.6 Hz, 1H), 4.70 (dd, *J*=12.6, 4.7 Hz, 1H), 3.29 - 3.46 (m, 4H), 3.12 (br d, *J*=9.8 Hz, 1H), 2.81 - 3.00 (m, 3H), 2.18 - 2.27 (m, 2H), 1.95 - 2.03 (m, 1H), 1.76 - 1.85 (m, 1H), 1.50 (d, *J*=6.6 Hz, 3H), 1.21 - 1.39 (m, 4H), 1.14 (s, 3H).

Compound 27

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.99 (br t, *J*=8.8 Hz, 1H), 7.32 (br d, *J*=7.3 Hz, 1H), 7.06 - 7.25 (m, 4H), 6.89 - 6.95 (m, 2H), 6.80 (s, 1H), 6.50 (br d, *J*=8.5 Hz, 1H), 6.42 (br d, *J*=15.1 Hz, 1H), 5.59 (q, *J*=6.6 Hz, 1H), 3.81 (br dd, *J*=13.6, 3.5 Hz, 1H), 3.39 - 3.50 (m, 2H), 3.21 - 3.31 (m, 2H), 3.13 (br t, *J*=9.6 Hz, 1H), 2.83 - 3.07 (m, 2H), 2.70 (br d, *J*=21.1 Hz, 1H), 2.54 - 2.62 (m, 1H), 1.92 - 2.00 (m, 1H), 1.75 - 1.86 (m, 1H), 1.52 (d, *J*=6.6 Hz, 3H), 1.30 - 1.38 (m, 2H), 1.22 - 1.29 (m, 2H), 1.13 (s, 6H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.99 (br t, *J*=8.8 Hz, 1H), 7.06 - 7.25 (m, 5H), 6.89 - 6.95 (m, 2H), 6.76 (s, 1H), 6.50 (br d, *J*=8.5 Hz, 1H), 6.42 (br d, *J*=15.1 Hz, 1H), 4.96 (q, *J*=6.5 Hz, 1H), 4.55 (br dd, *J*=12.9, 3.2 Hz, 1H), 3.39 - 3.50 (m, 2H), 3.21 - 3.31 (m, 2H), 3.13 (br t, *J*=9.6 Hz, 1H), 2.83 - 3.07 (m, 3H), 2.54 - 2.62 (m, 1H), 1.92 - 2.00 (m, 1H), 1.75 - 1.86 (m, 1H), 1.55 (d, *J*=6.9 Hz, 3H), 1.30 - 1.38 (m, 2H), 1.22 - 1.29 (m, 2H), 1.13 (s, 6H).

Compound 28

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.99 (t, *J*=8.8 Hz, 1H), 7.32 (d, *J*=7.6 Hz, 1H), 7.05 - 7.25 (m, 4H), 6.89 - 6.95 (m, 2H), 6.80 (s, 1H), 6.50 (d, *J*=8.8 Hz, 1H), 6.42 (dd, *J*=14.8, 1.6 Hz, 1H), 5.58 (q, *J*=6.5 Hz, 1H), 3.81 (br dd, *J*=13.6, 4.1 Hz, 1H), 3.40 - 3.51 (m, 2H), 3.22 - 3.31 (m, 2H), 3.13 (t, *J*=9.6 Hz, 1H), 2.86 - 3.05 (m, 2H), 2.70 (br d, *J*=20.8 Hz, 1H), 2.55 - 2.63 (m, 1H), 1.92 - 2.00 (m, 1H), 1.75 - 1.85 (m, 1H), 1.52 (d, *J*=6.6 Hz, 3H), 1.31 - 1.38 (m, 2H), 1.21 - 1.29 (m, 2H), 1.13 (s, 6H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.99 (t, *J*=8.8 Hz, 1H), 7.05 - 7.25 (m, 5H), 6.89 - 6.95 (m, 2H), 6.76 (s, 1H), 6.50 (d, *J*=8.8 Hz, 1H), 6.42 (dd, *J*=14.8, 1.6 Hz, 1H), 4.96 (q,

J=6.5 Hz, 1H), 4.55 (br dd, *J*=12.9, 2.8 Hz, 1H), 3.40 - 3.51 (m, 2H), 3.22 - 3.31 (m, 2H), 3.13 (t, *J*=9.6 Hz, 1H), 2.86 - 3.05 (m, 3H), 2.55 - 2.63 (m, 1H), 1.92 - 2.00 (m, 1H), 1.75 - 1.85 (m, 1H), 1.55 (d, *J*=6.9 Hz, 3H), 1.31 - 1.38 (m, 2H), 1.21 - 1.29 (m, 2H), 1.13 (s, 6H).

Compound 29

Major rotamer (70%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.99 (t, *J*=8.8 Hz, 1H), 7.38 (d, *J*=5.0 Hz, 1H), 7.13 (br s, 1H), 7.02 (d, *J*=5.0 Hz, 1H), 6.89 - 6.95 (m, 2H), 6.79 - 6.81 (m, 1H), 6.50 (br d, *J*=8.8 Hz, 1H), 6.42 (br d, *J*=14.8 Hz, 1H), 5.53 (q, *J*=6.8 Hz, 1H), 3.92 (br dd, *J*=13.7, 4.6 Hz, 1H), 3.38 - 3.45 (m, 2H), 3.09 - 3.29 (m, 3H), 2.90 - 3.01 (m, 2H), 2.70 (br d, *J*=17.0 Hz, 1H), 2.55 - 2.62 (m, 1H), 1.92 - 2.00 (m, 1H), 1.75 - 1.85 (m, 1H), 1.46 (d, *J*=6.6 Hz, 3H), 1.31 - 1.37 (m, 2H), 1.21 - 1.29 (m, 2H), 1.13 (s, 6H).

Minor rotamer (30%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.98 (t, *J*=8.8 Hz, 1H), 7.29 (d, *J*=5.0 Hz, 1H), 7.13 (br s, 1H), 6.89 - 6.95 (m, 2H), 6.79 - 6.81 (m, 1H), 6.77 (s, 1H), 6.50 (br d, *J*=8.8 Hz, 1H), 6.42 (br d, *J*=14.8 Hz, 1H), 4.90 (q, *J*=6.7 Hz, 1H), 4.70 (br dd, *J*=12.8, 4.6 Hz, 1H), 3.38 - 3.45 (m, 2H), 3.09 - 3.29 (m, 3H), 2.90 - 3.01 (m, 3H), 2.55 - 2.62 (m, 1H), 1.92 - 2.00 (m, 1H), 1.75 - 1.85 (m, 1H), 1.50 (d, *J*=6.6 Hz, 3H), 1.31 - 1.37 (m, 2H), 1.21 - 1.29 (m, 2H), 1.13 (s, 6H).

Compound 30

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.00 (br t, *J*=8.8 Hz, 1H), 7.31 (br d, *J*=7.1 Hz, 1H), 7.05 - 7.26 (m, 3H), 6.93 (br s, 1H), 6.80 (s, 1H), 6.51 (br d, *J*=8.6 Hz, 1H), 6.44 (br d, *J*=15.2 Hz, 1H), 5.55 - 5.62 (m, 1H), 4.66 (br t, *J*=9.1 Hz, 1H), 3.86 - 3.95 (m, 1H), 3.77 - 3.85 (m, 1H), 3.52 - 3.59 (m, 1H), 3.41 - 3.51 (m, 2H), 2.85 - 3.12 (m, 3H), 2.68 - 2.76 (m, 1H), 2.15 - 2.25 (m, 1H), 1.83 - 1.95 (m, 1H), 1.49 - 1.57 (m, 3H), 1.38 (s, 3H), 1.34 (s, 3H), 1.21 - 1.34 (m, 4H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.00 (br t, *J*=8.8 Hz, 1H), 7.05 - 7.26 (m, 4H), 6.93 (br s, 1H), 6.76 (s, 1H), 6.51 (br d, *J*=8.6 Hz, 1H), 6.44 (br d, *J*=15.2 Hz, 1H), 4.92 - 4.99 (m, 1H), 4.66 (br t, *J*=9.1 Hz, 1H), 4.51 - 4.58 (m, 1H), 3.86 - 3.95 (m, 1H), 3.52 - 3.59 (m, 1H), 3.41 - 3.51 (m, 1H), 3.22 - 3.29 (m, 1H), 2.85 - 3.12 (m, 4H), 2.15 - 2.25 (m, 1H), 1.83 - 1.95 (m, 1H), 1.49 - 1.57 (m, 3H), 1.38 (s, 3H), 1.34 (s, 3H), 1.21 - 1.34 (m, 4H).

Compound 31

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.00 (t, *J*=8.7 Hz, 1H), 7.32 (d, *J*=7.3 Hz, 1H), 7.06 - 7.25 (m, 3H), 6.91 - 6.96 (m, 1H), 6.80 (s, 1H), 6.51 (br d, *J*=8.5 Hz, 1H), 6.44 (dd, *J*=14.8, 1.3 Hz, 1H), 5.59 (q, *J*=6.6 Hz, 1H), 4.66 (t, *J*=9.0 Hz, 1H), 3.86 - 3.95 (m, 1H), 3.78 - 3.84 (m, 1H), 3.56 (dd, *J*=9.8, 6.6 Hz, 1H), 3.42 - 3.50 (m, 2H), 3.08 (dd, *J*=9.8, 6.0 Hz, 1H), 2.83 - 3.05 (m, 2H), 2.72 (br d, *J*=16.4 Hz, 1H), 2.16 - 2.24 (m, 1H), 1.84 - 1.94 (m, 1H), 1.52 (d, *J*=6.6 Hz, 3H), 1.38 (s, 3H), 1.35 (s, 3H), 1.30 - 1.34 (m, 2H), 1.22 - 1.28 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.00 (t, *J*=8.7 Hz, 1H), 7.06 - 7.25 (m, 4H), 6.91 - 6.96 (m, 1H), 6.77 (s, 1H), 6.51 (br d, *J*=8.5 Hz, 1H), 6.44 (dd, *J*=14.8, 1.3 Hz, 1H), 4.96 (q, *J*=6.7 Hz, 1H), 4.66 (t, *J*=9.0 Hz, 1H), 4.52 - 4.58 (m, 1H), 3.86 - 3.95 (m, 1H), 3.56 (dd, *J*=9.8, 6.6 Hz, 1H), 3.42 - 3.50 (m, 1H), 3.23 - 3.30 (m, 1H), 3.08 (dd, *J*=9.8, 6.0 Hz, 1H), 2.83 - 3.05 (m, 3H), 2.16 - 2.24 (m, 1H), 1.84 - 1.94 (m, 1H), 1.55 (d, *J*=6.6 Hz, 3H), 1.38 (s, 3H), 1.35 (s, 3H), 1.30 - 1.34 (m, 2H), 1.22 - 1.28 (m, 2H).

Compound 32

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.99 (br t, *J*=8.7 Hz, 1H), 7.51 (br s, 1H), 7.32 (br d, *J*=7.6 Hz, 1H), 7.06 - 7.26 (m, 3H), 7.02 (br s, 1H), 6.90 - 6.95 (m, 1H), 6.80 (s, 1H), 6.53 (br d, *J*=8.5 Hz, 1H), 6.45 (br d, *J*=14.5 Hz, 1H), 5.59 (q, *J*=6.6 Hz, 1H), 4.02 - 4.11 (m, 1H), 3.82 (br dd, *J*=13.2, 4.1 Hz, 1H), 3.55 (t, *J*=8.5 Hz, 1H), 3.40 - 3.52 (m, 1H), 3.22 - 3.36 (m, 2H partially obscured by H_2O peak), 2.84 - 3.06 (m, 2H), 2.72 (br d, *J*=16.1 Hz, 1H), 2.11 - 2.21 (m, 1H), 1.91 (br dd, *J*=11.8, 6.5 Hz, 1H), 1.52 (br d, *J*=6.6 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.21 - 1.29 (m, 2H), 1.16 (d, *J*=6.0 Hz, 3H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.99 (br t, *J*=8.7 Hz, 1H), 7.51 (br s, 1H), 7.06 - 7.26 (m, 4H), 7.02 (br s, 1H), 6.90 - 6.95 (m, 1H), 6.77 (s, 1H), 6.53 (br d, *J*=8.5 Hz, 1H), 6.45 (br d, *J*=14.5 Hz, 1H), 4.97 (q, *J*=6.5 Hz, 1H), 4.55 (br d, *J*=12.6 Hz, 1H), 4.02 - 4.11 (m, 1H), 3.55 (t, *J*=8.5 Hz, 1H), 3.40 - 3.52 (m, 1H), 3.22 - 3.36 (m, 2H partially obscured by H_2O peak), 2.84 - 3.06 (m, 3H), 2.11 - 2.21 (m, 1H), 1.91 (br dd, *J*=11.8, 6.5 Hz, 1H), 1.55 (br d, *J*=6.6 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.21 - 1.29 (m, 2H), 1.16 (d, *J*=6.0 Hz, 3H).

Compound 33

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.99 (t, *J*=8.8 Hz, 1H), 7.49 (br s, 1H), 7.32 (d, *J*=7.3 Hz, 1H), 7.05 - 7.26 (m, 3H), 7.01 (br s, 1H), 6.91 - 6.96 (m, 1H), 6.81 (s, 1H), 6.56 (br d, *J*=8.8 Hz, 1H), 6.48 (br d, *J*=14.8 Hz, 1H), 5.59 (q, *J*=6.6 Hz, 1H), 3.93 - 4.02 (m, 1H), 3.82 (br dd, *J*=13.7, 4.3 Hz, 1H), 3.55 - 3.62 (m, 1H), 3.42 - 3.53 (m, 2H), 2.86 - 3.06 (m, 3H), 2.72 (br d, *J*=16.1 Hz, 1H), 2.39 - 2.47 (m, 1H), 1.87 - 1.95 (m, 1H), 1.52 (d, *J*=6.6 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.23 - 1.30 (m, 2H), 1.18 (d, *J*=6.0 Hz, 3H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.99 (t, *J*=8.8 Hz, 1H), 7.49 (br s, 1H), 7.05 - 7.26 (m, 4H), 7.01 (br s, 1H), 6.91 - 6.96 (m, 1H), 6.77 (s, 1H), 6.56 (br d, *J*=8.8 Hz, 1H), 6.48 (br d, *J*=14.8 Hz, 1H), 4.97 (q, *J*=6.6 Hz, 1H), 4.51 - 4.58 (m, 1H), 3.93 - 4.02 (m, 1H), 3.55 - 3.62 (m, 1H), 3.42 - 3.53 (m, 1H), 3.22 - 3.30 (m, 1H), 2.86 - 3.06 (m, 4H), 2.39 - 2.47 (m, 1H), 1.87 - 1.95 (m, 1H), 1.55 (d, *J*=6.6 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.23 - 1.30 (m, 2H), 1.18 (d, *J*=6.3 Hz, 3H).

Compound 34

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.99 (br t, *J*=8.7 Hz, 1H), 7.51 (br s, 1H), 7.32 (br d, *J*=7.3 Hz, 1H), 7.06 - 7.25 (m, 3H), 7.02 (br s, 1H), 6.90 - 6.96 (m, 1H), 6.80 (s, 1H), 6.53 (br d, *J*=8.5 Hz, 1H), 6.45 (br d, *J*=14.8 Hz, 1H), 5.59 (q, *J*=6.4 Hz, 1H), 4.04 - 4.11 (m, 1H), 3.82 (br dd, *J*=13.6, 3.8 Hz, 1H), 3.55 (br t, *J*=8.5 Hz, 1H), 3.42 - 3.50 (m, 1H), 3.22 - 3.36 (m, 2H partially obscured by H_2O peak), 2.85 - 3.06 (m, 2H), 2.72 (br d, *J*=16.4 Hz, 1H), 2.12 - 2.21 (m, 1H), 1.91 (br dd, *J*=11.5, 6.8 Hz, 1H), 1.52 (d, *J*=6.9 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.22 - 1.30 (m, 2H), 1.16 (d, *J*=6.0 Hz, 3H).

Minor rotamer

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.99 (br t, *J*=8.7 Hz, 1H), 7.51 (br s, 1H), 7.06 - 7.25 (m, 4H), 7.02 (br s, 1H), 6.90 - 6.96 (m, 1H), 6.76 (s, 1H), 6.53 (br d, *J*=8.5 Hz, 1H), 6.45 (br d, *J*=14.8 Hz, 1H), 4.97 (q, *J*=6.2 Hz, 1H), 4.55 (br dd, *J*=12.9, 3.2 Hz, 1H), 4.04 - 4.11 (m, 1H), 3.55 (br t, *J*=8.5 Hz, 1H), 3.42 - 3.50 (m, 1H), 3.22 - 3.36 (m, 2H partially obscured by H_2O peak), 2.85 - 3.06 (m, 3H), 2.12 - 2.21 (m, 1H), 1.91 (br dd, *J*=11.5, 6.8 Hz, 1H), 1.55 (d, *J*=6.9 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.22 - 1.30 (m, 2H), 1.16 (d, *J*=6.0 Hz, 3H).

Compound 35

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.99 (br t, *J*=8.8 Hz, 1H), 7.49 (br s, 1H), 7.32 (br d, *J*=7.6 Hz, 1H), 7.06 - 7.26 (m, 3H), 7.01 (br s, 1H), 6.91 - 6.96 (m, 1H), 6.81 (s, 1H), 6.57 (br d, *J*=8.8 Hz, 1H), 6.48 (br d, *J*=15.1 Hz, 1H), 5.59 (q, *J*=6.6 Hz, 1H), 3.94 - 4.02 (m, 1H), 3.82 (br dd, *J*=13.7, 3.6 Hz, 1H), 3.55 - 3.61 (m, 1H), 3.42 - 3.53 (m, 2H), 2.83 - 3.06 (m, 3H), 2.72 (br d, *J*=16.1 Hz, 1H), 2.39 - 2.48 (m, 1H), 1.87 - 1.95 (m, 1H), 1.52 (br d, *J*=6.9 Hz, 3H), 1.30 - 1.38 (m, 2H), 1.22 - 1.30 (m, 2H), 1.18 (d, *J*=6.0 Hz, 3H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.99 (br t, *J*=8.8 Hz, 1H), 7.49 (br s, 1H), 7.06 - 7.26 (m, 4H), 7.01 (br s, 1H), 6.91 - 6.96 (m, 1H), 6.77 (s, 1H), 6.57 (br d, *J*=8.8 Hz, 1H), 6.48 (br d, *J*=15.1 Hz, 1H), 4.97 (q, *J*=6.4 Hz, 1H), 4.55 (br d, *J*=10.4 Hz, 1H), 3.94 - 4.02 (m, 1H), 3.55 - 3.61 (m, 1H), 3.42 - 3.53 (m, 1H), 3.23 - 3.30 (m, 1H), 2.83 - 3.06 (m, 4H), 2.39 - 2.48 (m, 1H), 1.87 - 1.95 (m, 1H), 1.55 (br d, *J*=6.9 Hz, 3H), 1.30 - 1.38 (m, 2H), 1.22 - 1.30 (m, 2H), 1.18 (d, *J*=6.0 Hz, 3H).

Compound 36

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.00 (t, *J*=8.8 Hz, 1H), 7.51 (br s, 1H), 7.32 (d, *J*=7.6 Hz, 1H), 7.06 - 7.25 (m, 3H), 7.01 (br s, 1H), 6.91 - 6.95 (m, 1H), 6.81 (s, 1H), 6.52 (br d, *J*=8.8 Hz, 1H), 6.45 (br d, *J*=14.5 Hz, 1H), 5.59 (q, *J*=6.8 Hz, 1H), 3.81 (br dd, *J*=13.6, 3.8 Hz, 1H), 3.46 - 3.54 (m, 1H), 3.34 - 3.46 (m, 3H), 3.29 - 3.32 (m, 1H partially obscured by H_2O peak), 3.10 (quin, *J*=7.6 Hz 1H), 2.85 - 3.05 (m, 2H), 2.72 (br d, *J*=16.1 Hz, 1H), 2.16 - 2.24 (m, 1H), 2.06 - 2.15 (m, 1H), 1.52 (d, *J*=6.6 Hz, 3H), 1.30 - 1.38 (m, 2H), 1.22 - 1.30 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.00 (t, *J*=8.8 Hz, 1H), 7.51 (br s, 1H), 7.06 - 7.25 (m, 4H), 7.01 (br s, 1H), 6.91 - 6.95 (m, 1H), 6.77 (s, 1H), 6.52 (br d, *J*=8.8 Hz, 1H), 6.45 (br d, *J*=14.5 Hz, 1H), 4.96 (q, *J*=6.6 Hz, 1H), 4.55 (br dd, *J*=12.6, 3.2 Hz, 1H), 3.46 - 3.54 (m, 1H), 3.34 - 3.46 (m, 2H), 3.29 - 3.32 (m, 1H partially obscured by H_2O peak), 3.22 - 3.26 (m, 1H), 3.10 (quin, *J*=7.6 Hz, 1H), 2.85 - 3.05 (m, 3H), 2.16 - 2.24 (m, 1H), 2.06 - 2.15 (m, 1H), 1.55 (d, *J*=6.9 Hz, 3H), 1.30 - 1.38 (m, 2H), 1.22 - 1.30 (m, 2H).

Compound 37

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.97 - 8.03 (m, 2H), 7.32 (d, *J*=7.3 Hz, 1H), 7.06 - 7.25 (m, 3H), 6.94 (d, *J*=3.5 Hz, 1H), 6.80 (s, 1H), 6.52 (dd, *J*=8.8, 1.9 Hz, 1H), 6.45 (dd,

J=14.8, 1.9 Hz, 1H), 5.59 (q, *J*=6.6 Hz, 1H), 3.81 (br dd, *J*=13.7, 3.6 Hz, 1H), 3.32 - 3.54 (m, 5H), 3.04 - 3.12 (m, 1H), 2.83 - 3.04 (m, 2H), 2.72 (br d, *J*=16.1 Hz, 1H), 2.62 (d, *J*=4.4 Hz, 3H), 2.14 - 2.22 (m, 1H), 2.06 - 2.14 (m, 1H), 1.52 (d, *J*=6.6 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.22 - 1.30 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.97 - 8.03 (m, 2H), 7.06 - 7.25 (m, 4H), 6.93 (d, *J*=3.5 Hz, 1H), 6.77 (s, 1H), 6.52 (dd, *J*=8.8, 1.9 Hz, 1H), 6.45 (dd, *J*=14.8, 1.9 Hz, 1H), 4.96 (q, *J*=6.6 Hz, 1H), 4.52 - 4.58 (m, 1H), 3.32 - 3.54 (m, 4H), 3.23 - 3.30 (m, 1H), 3.04 - 3.12 (m, 1H), 2.83 - 3.04 (m, 3H), 2.62 (d, *J*=4.4 Hz, 3H), 2.14 - 2.22 (m, 1H), 2.06 - 2.14 (m, 1H), 1.55 (d, *J*=6.6 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.22 - 1.30 (m, 2H).

Compound 38

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.00 (t, *J*=8.8 Hz, 1H), 7.32 (d, *J*=7.3 Hz, 1H), 7.06 - 7.25 (m, 3H), 6.94 (d, *J*=3.8 Hz, 1H), 6.80 (s, 1H), 6.53 (dd, *J*=8.8, 1.9 Hz, 1H), 6.46 (dd, *J*=14.7, 2.1 Hz, 1H), 5.59 (q, *J*=6.6 Hz, 1H), 3.81 (br dd, *J*=13.9, 3.5 Hz, 1H), 3.53 - 3.60 (m, 2H), 3.33 - 3.51 (m, 4H), 3.09 (s, 3H), 2.89 - 3.05 (m, 2H), 2.86 (s, 3H), 2.72 (br d, *J*=16.1 Hz, 1H), 2.18 - 2.26 (m, 1H), 2.06 - 2.14 (m, 1H), 1.52 (d, *J*=6.9 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.22 - 1.30 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.00 (br d, *J*=8.8 Hz, 1H), 7.06 - 7.25 (m, 4H), 6.93 (d, *J*=3.5 Hz, 1H), 6.77 (s, 1H), 6.53 (dd, *J*=8.8, 1.9 Hz, 1H), 6.46 (dd, *J*=14.7, 2.1 Hz, 1H), 4.96 (q, *J*=6.7 Hz, 1H), 4.52 - 4.58 (m, 1H), 3.53 - 3.60 (m, 2H), 3.33 - 3.51 (m, 3H), 3.21 - 3.30 (m, 1H), 3.09 (s, 3H), 2.89 - 3.05 (m, 3H), 2.86 (s, 3H), 2.18 - 2.26 (m, 1H), 2.06 - 2.14 (m, 1H), 1.55 (d, *J*=6.9 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.22 - 1.30 (m, 2H).

Compound 39

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.00 (t, *J*=8.8 Hz, 1H), 7.32 (d, *J*=7.6 Hz, 1H), 7.05 - 7.26 (m, 4H), 6.91 - 6.96 (m, 1H), 6.80 (s, 1H), 6.52 (br d, *J*=9.1 Hz, 1H), 6.45 (br d, *J*=14.7 Hz, 1H), 5.58 (q, *J*=7.1 Hz, 1H), 3.77 - 3.85 (m, 1H), 3.35 - 3.55 (m, 5H), 3.09 - 3.19 (m, 1H), 2.84 - 3.07 (m, 2H), 2.71 (br d, *J*=16.2 Hz, 1H), 2.10 - 2.26 (m, 2H), 1.52 (d, *J*=6.6 Hz, 3H), 1.30- 1.39 (m, 2H), 1.20 -1.30 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.00 (t, *J*=8.8 Hz, 1H), 7.05 - 7.26 (m, 4H), 6.91 - 6.96 (m, 2H), 6.76 (s, 1H), 6.52 (br d, *J*=9.1 Hz, 1H), 6.45 (br d, *J*=14.7 Hz, 1H), 4.96 (q,

J=6.4 Hz, 1H), 4.51 - 4.58 (m, 1H), 3.35 - 3.55 (m, 5H), 3.09 - 3.19 (m, 1H), 2.84 - 3.07 (m, 3H), 2.10 - 2.26 (m, 2H), 1.54 (d, *J*=7.1 Hz, 3H), 1.30 - 1.39 (m, 2H), 1.20 - 1.30 (m, 2H).

Compound 40

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.94 (br s, 1H), 8.01 (t, *J*=8.8 Hz, 1H), 7.32 (d, *J*=7.6 Hz, 1H), 7.05 - 7.25 (m, 3H), 6.91 - 6.97 (m, 1H), 6.80 (s, 1H), 6.54 (br d, *J*=9.1 Hz, 1H), 6.47 (dd, *J*=14.9, 1.8 Hz, 1H), 5.58 (q, *J*=6.6 Hz, 1H), 3.81 (br dd, *J*=13.1, 4.0 Hz, 1H), 3.35 - 3.57 (m, 5H), 3.21 - 3.29 (m, 1H), 3.19 (s, 3H), 2.85 - 3.06 (m, 2H), 2.71 (br d, *J*=16.2 Hz, 1H), 2.21 - 2.30 (m, 1H), 2.11 - 2.21 (m, 1H), 1.52 (d, *J*=7.1 Hz, 3H), 1.30 - 1.38 (m, 2H), 1.22 - 1.29 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.94 (br s, 1H), 8.01 (t, *J*=8.8 Hz, 1H), 7.05 - 7.25 (m, 4H), 6.91 - 6.97 (m, 1H), 6.77 (s, 1H), 6.54 (br d, *J*=9.1 Hz, 1H), 6.47 (dd, *J*=14.9, 1.8 Hz, 1H), 4.96 (q, *J*=6.2 Hz, 1H), 4.51 - 4.58 (m, 1H), 3.35 - 3.57 (m, 5H), 3.21 - 3.29 (m, 1H), 3.19 (s, 3H), 2.85 - 3.06 (m, 3H), 2.21 - 2.30 (m, 1H), 2.11 - 2.21 (m, 1H), 1.55 (d, *J*=6.6 Hz, 3H), 1.30 - 1.38 (m, 2H), 1.22 - 1.29 (m, 2H).

Compound 41

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.97 (s, 1H), 8.01 (t, *J*=8.8 Hz, 1H), 7.38 (d, *J*=5.6 Hz, 1H), 7.02 (d, *J*=5.1 Hz, 1H), 6.92 - 6.96 (m, 1H), 6.77 - 6.82 (m, 1H), 6.54 (br d, *J*=8.6 Hz, 1H), 6.48 (br d, *J*=14.7 Hz, 1H), 5.53 (q, *J*=7.1 Hz, 1H), 3.92 (br dd, *J*=13.6, 4.6 Hz, 1H), 3.52 - 3.59 (m, 1H), 3.33 - 3.48 (m, 4H), 3.27 (s, 3H), 3.15 - 3.26 (m, 1H), 2.81 - 3.00 (m, 2H), 2.74 (br d, *J*=14.7 Hz, 1H), 2.23 - 2.31 (m, 1H), 2.12 - 2.21 (m, 1H), 1.46 (d, *J*=6.6 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.22 - 1.29 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.97 (s, 1H), 7.98 (t, *J*=8.6 Hz, 1H), 7.29 (d, *J*=5.1 Hz, 1H), 6.92 - 6.96 (m, 1H), 6.77 - 6.82 (m, 2H), 6.54 (br d, *J*=8.6 Hz, 1H), 6.48 (br d, *J*=14.7 Hz, 1H), 4.90 (q, *J*=6.1 Hz, m, 1H), 4.67 - 4.74 (m, 1H), 3.52 - 3.59 (m, 1H), 3.33 - 3.48 (m, 4H), 3.27 (s, 3H), 3.15 - 3.26 (m, 1H), 2.81 - 3.00 (m, 3H), 2.23 - 2.31 (m, 1H), 2.12 - 2.21 (m, 1H), 1.50 (d, *J*=6.6 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.22 - 1.29 (m, 2H).

Compound 42

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.99 (t, *J*=8.8 Hz, 1H), 7.34 - 7.40 (m, 2H), 7.02 (d, *J*=5.0 Hz, 1H), 6.92 - 6.95 (m, 1H), 6.77 - 6.86 (m, 2H), 6.50 (br d, *J*=8.8 Hz, 1H), 6.41 (br d, *J*=14.8 Hz, 1H), 5.53 (q, *J*=6.5 Hz, 1H), 3.92 (br dd, *J*=13.9, 4.7 Hz, 1H), 3.49 (dd, *J*=9.0, 7.7 Hz, 1H), 3.36 - 3.45 (m, 2H), 3.27 - 3.31 (m, 1H), 2.82 - 3.01 (m, 3H), 2.75 (br dd, *J*=15.9, 2.1 Hz, 1H), 2.58 - 2.68 (m, 1H), 2.24 (d, *J*= 7.6Hz, 2H), 2.10 - 2.18 (m, 1H), 1.64 - 1.74 (m, 1H), 1.46 (d, *J*=6.6 Hz, 3H), 1.30 - 1.38 (m, 2H), 1.21 - 1.29 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.99 (t, *J*=8.8 Hz, 1H), 7.34 - 7.40 (m, 1H), 7.29 (d, *J*=5.0 Hz, 1H), 6.92 - 6.95 (m, 1H), 6.77 - 6.86 (m, 3H), 6.50 (br d, *J*=8.8 Hz, 1H), 6.41 (br d, *J*=14.8 Hz, 1H), 4.90 (q, *J*=6.3 Hz, 1H), 4.70 (br dd, *J*=12.6, 4.4 Hz, 1H), 3.49 (dd, *J*=9.0, 7.7 Hz, 1H), 3.36 - 3.45 (m, 1H), 3.27 - 3.31 (m, 1H), 3.21 (td, *J*=12.3 Hz, 1H), 2.82 - 3.01 (m, 4H), 2.58 - 2.68 (m, 1H), 2.24 (d, *J*=7.6 Hz, 2H), 2.10 - 2.18 (m, 1H), 1.64 - 1.74 (m, 1H), 1.50 (d, *J*=6.6 Hz, 3H), 1.30 - 1.38 (m, 2H), 1.21 - 1.29 (m, 2H).

Compound 43

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.99 (br t, *J*=8.8 Hz, 1H), 7.34 - 7.40 (m, 2H), 7.02 (d, *J*=5.4 Hz, 1H), 6.91 - 6.95 (m, 1H), 6.77 - 6.86 (m, 2H), 6.50 (br d, *J*=8.8 Hz, 1H), 6.41 (br d, *J*=14.8 Hz, 1H), 5.53 (q, *J*=6.4 Hz, 1H), 3.92 (br dd, *J*=13.7, 4.6 Hz, 1H), 3.49 (br t, *J*=8.4 Hz, 1H), 3.35 - 3.44 (m, 2H), 3.27 - 3.32 (m, 1H), 2.83 - 3.01 (m, 3H), 2.75 (br dd, *J*=16.1, 2.2 Hz, 1H), 2.58 - 2.68 (m, 1H), 2.24 (d, *J*=7.6 Hz, 2H), 2.10 - 2.18 (m, 1H), 1.64 - 1.74 (m, 1H), 1.46 (d, *J*=6.6 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.22 - 1.30 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.99 (br t, *J*=8.8 Hz, 1H), 7.34 - 7.40 (m, 1H), 7.29 (d, *J*=5.0 Hz, 1H), 6.91 - 6.95 (m, 1H), 6.77 - 6.86 (m, 3H), 6.50 (br d, *J*=8.8 Hz, 1H), 6.41 (br d, *J*=14.8 Hz, 1H), 4.90 (q, *J*=6.5 Hz, 1H), 4.70 (br dd, *J*=12.9, 4.4 Hz, 1H), 3.49 (br t, *J*=8.4 Hz, 1H), 3.35 - 3.44 (m, 1H), 3.27 - 3.32 (m, 1H), 3.21 (br td, *J*=12.2, 4.3 Hz, 1H), 2.83 - 3.01 (m, 4H), 2.58 - 2.68 (m, 1H), 2.24 (d, *J*=7.6 Hz, 2H), 2.10 - 2.18 (m, 1H), 1.64 - 1.74 (m, 1H), 1.50 (d, *J*=6.6 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.22 - 1.30 (m, 2H).

Compound 44

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.00 (t, *J*=8.8 Hz, 1H), 7.35 - 7.40 (m, 2H), 7.00 - 7.05 (m, 2H), 6.92 - 6.95 (m, 1H), 6.77 - 6.82 (m, 1H), 6.49 (br d, *J*=8.8 Hz, 1H), 6.41 (dd, *J*=14.7, 1.7 Hz, 1H), 5.53 (q, *J*=6.6 Hz, 1H), 3.92 (dd, *J*=13.7, 4.9 Hz, 1H), 3.72 (d, *J*=9.8

Hz, 1H), 3.33 - 3.45 (m, 3H), 3.12 (d, *J*=9.8 Hz, 1H), 2.80 - 3.00 (m, 2H), 2.75 (dd, *J*=16.2, 2.7 Hz, 1H), 2.33 - 2.40 (m, 1H), 1.85 - 1.92 (m, 1H), 1.46 (d, *J*=6.9 Hz, 3H), 1.31 (s, 3H), 1.21 - 1.29 (m, 4H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.99 (br t, *J*=8.8 Hz, 1H), 7.35 - 7.40 (m, 1H), 7.29 (d, *J*=5.0 Hz, 1H), 7.00 - 7.05 (m, 1H), 6.92 - 6.95 (m, 1H), 6.77 - 6.82 (m, 2H), 6.49 (br d, *J*=8.8 Hz, 1H), 6.41 (dd, *J*=14.7, 1.7 Hz, 1H), 4.90 (q, *J*=6.5 Hz, 1H), 4.70 (br dd, *J*=12.8, 4.3 Hz, 1H), 3.72 (d, *J*=9.8 Hz, 1H), 3.33 - 3.45 (m, 2H), 3.21 (td, *J*=12.3, 4.4 Hz, 1H), 3.12 (d, *J*=9.8 Hz, 1H), 2.80 - 3.00 (m, 3H), 2.33 - 2.40 (m, 1H), 1.85 - 1.92 (m, 1H), 1.50 (d, *J*=6.6 Hz, 3H), 1.31 (s, 3H), 1.21 - 1.29 (m, 4H).

Compound 45

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.00 (t, *J*=8.8 Hz, 1H), 7.34 - 7.40 (m, 2H), 7.00 - 7.04 (m, 2H), 6.91 - 6.95 (m, 1H), 6.76 - 6.81 (m, 1H), 6.49 (br d, *J*=9.1 Hz, 1H), 6.40 (dd, *J*=14.7, 2.0 Hz, 1H), 5.53 (q, *J*=6.7 Hz, 1H), 3.92 (dd, *J*=13.9, 5.3 Hz, 1H), 3.72 (d, *J*=10.1 Hz, 1H), 3.33 - 3.45 (m, 3H), 3.12 (d, *J*=10.1 Hz, 1H), 2.81 - 3.01 (m, 2H), 2.75 (dd, *J*=16.4, 2.7 Hz, 1H), 2.34 - 2.41 (m, 1H), 1.84 - 1.93 (m, 1H), 1.46 (d, *J*=7.1 Hz, 3H), 1.31 (s, 3H), 1.22 - 1.29 (m, 4H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.99 (br t, *J*=8.8 Hz, 1H), 7.34 - 7.40 (m, 1H), 7.29 (d, *J*=5.1 Hz, 1H), 7.00 - 7.04 (m, 1H), 6.91 - 6.95 (m, 1H), 6.76 - 6.81 (m, 2H), 6.49 (br d, *J*=9.1 Hz, 1H), 6.40 (dd, *J*=14.7, 2.0 Hz, 1H), 4.90 (q, *J*=6.1 Hz, 1H), 4.70 (dd, *J*=12.6, 4.0 Hz, 1H), 3.72 (d, *J*=10.1 Hz, 1H), 3.33 - 3.45 (m, 2H), 3.16 - 3.25 (m, 1H), 3.12 (d, *J*=10.1 Hz, 1H), 2.81 - 3.01 (m, 3H), 2.34 - 2.41 (m, 1H), 1.84 - 1.93 (m, 1H), 1.49 (d, *J*=6.6 Hz, 3H), 1.31 (s, 3H), 1.22 - 1.29 (m, 4H).

Compound 46

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.00 (t, *J*=8.8 Hz, 1H), 7.49 (br s, 1H), 7.38 (d, *J*=5.0 Hz, 1H), 7.01 (d, *J*=5.4 Hz, 1H), 6.98 (br s, 1H), 6.92 - 6.95 (m, 1H), 6.77 - 6.81 (m, 1H), 6.52 (br d, *J*=8.8 Hz, 1H), 6.44 (dd, *J*=14.8, 1.6 Hz, 1H), 5.53 (q, *J*=6.8 Hz, 1H), 3.93 (dd, *J*=13.7, 4.9 Hz, 1H), 3.48 - 3.53 (m, 1H), 3.36 - 3.45 (m, 3H), 3.31 - 3.35 (m, 1H), 3.09 (quin, *J*=7.6 Hz, 1H), 2.80 - 3.00 (m, 2H), 2.75 (dd, *J*=15.9, 2.7 Hz, 1H), 2.16 - 2.24 (m, 1H), 2.06 - 2.15 (m, 1H), 1.46 (d, *J*=6.6 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.23 - 1.30 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.99 (br t, *J*=8.8 Hz, 1H), 7.49 (br s, 1H), 7.29 (d, *J*=5.0 Hz, 1H), 6.98 (br s, 1H), 6.92 - 6.95 (m, 1H), 6.77 - 6.81 (m, 2H), 6.52 (br d, *J*=8.8 Hz, 1H), 6.44 (dd, *J*=14.8, 1.6 Hz, 1H), 4.91 (q, *J*=6.3 Hz, 1H), 4.71 (br dd, *J*=12.5, 4.6 Hz, 1H), 3.48 - 3.53 (m, 1H), 3.36 - 3.45 (m, 2H), 3.31 - 3.35 (m, 1H), 3.17 - 3.24 (m, 1H), 3.09 (quin, *J*=7.6 Hz, 1H), 2.80 - 3.00 (m, 3H), 2.16 - 2.24 (m, 1H), 2.06 - 2.15 (m, 1H), 1.50 (d, *J*=6.6 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.23 - 1.30 (m, 2H).

Compound 47

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.00 (t, *J*=8.8 Hz, 1H), 7.49 (br s, 1H), 7.18 - 7.26 (m, 2H), 6.91 - 7.07 (m, 3H), 6.80 (s, 1H), 6.52 (dd, *J*=8.8, 1.9 Hz, 1H), 6.44 (dd, *J*=14.8, 1.6 Hz, 1H), 5.60 (q, *J*=6.8 Hz, 1H), 3.83 (br dd, *J*=13.6, 4.1 Hz, 1H), 3.47 - 3.54 (m, 1H), 3.32 - 3.47 (m, 4H), 3.09 (quin, *J*=7.6 Hz, 1H), 2.83 - 3.01 (m, 2H), 2.71 (br d, *J*=16.1 Hz, 1H), 2.16 - 2.25 (m, 1H), 2.06 - 2.15 (m, 1H), 1.52 (d, *J*=6.9 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.22 - 1.30 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.00 (t, *J*=8.8 Hz, 1H), 7.49 (br s, 1H), 7.18 - 7.26 (m, 1H), 6.91 - 7.07 (m, 4H), 6.76 (s, 1H), 6.52 (dd, *J*=8.8, 1.9 Hz, 1H), 6.44 (dd, *J*=14.8, 1.6 Hz, 1H), 4.98 (q, *J*=6.4 Hz, 1H), 4.55 (dt, *J*=12.8, 3.7 Hz, 1H), 3.47 - 3.54 (m, 1H), 3.32 - 3.47 (m, 3H), 3.20 - 3.28 (m, 1H), 3.09 (quin, *J*=7.6 Hz, 1H), 2.83 - 3.01 (m, 3H), 2.16 - 2.25 (m, 1H), 2.06 - 2.15 (m, 1H), 1.55 (d, *J*=6.6 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.22 - 1.30 (m, 2H).

Compound 48

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.09 (t, *J*=8.8 Hz, 1H), 7.38 (dd, *J*=8.1, 5.7 Hz, 1H), 6.99 - 7.09 (m, 3H), 6.84 (s, 1H), 6.81 - 6.85 (m, 1H), 6.77 (dd, *J*=14.2, 2.2 Hz, 1H), 6.16 (d, *J*=6.0 Hz, 1H), 5.59 (q, *J*=6.4 Hz, 1H), 3.82 (br dd, *J*=13.7, 4.3 Hz, 1H), 3.59 (td, *J*=8.6, 3.9 Hz, 1H), 3.49 - 3.55 (m, 1H), 3.41 - 3.48 (m, 1H), 3.16 - 3.23 (m, 1H), 2.94 - 3.05 (m, 2H), 2.87 - 2.94 (m, 2H), 2.74 (br d, *J*=16.7 Hz, 1H), 2.28 - 2.35 (m, 1H), 1.78 - 1.86 (m, 1H), 1.51 (d, *J*=6.9 Hz, 3H), 1.31 - 1.39 (m, 2H), 1.22 - 1.30 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.09 (t, *J*=8.8 Hz, 1H), 7.14 (dd, *J*=8.5, 6.0 Hz, 1H), 6.99 - 7.09 (m, 2H), 6.96 (td, *J*=8.7, 2.5 Hz, 1H), 6.81 - 6.85 (m, 1H), 6.80 (s, 1H), 6.77 (dd, *J*=14.2, 2.2 Hz, 1H), 6.16 (d, *J*=6.0 Hz, 1H), 4.97 (q, *J*=6.7 Hz, 1H), 4.54 (dt, *J*=12.6, 3.8 Hz, 1H), 3.59 (td, *J*=8.6, 3.9 Hz, 1H), 3.49 - 3.55 (m, 1H), 3.24 - 3.28 (m, 1H),

3.16 - 3.23 (m, 1H), 2.94 - 3.05 (m, 3H), 2.87 - 2.94 (m, 2H), 2.28 - 2.35 (m, 1H), 1.78 - 1.86 (m, 1H), 1.53 (d, *J*=6.6 Hz, 3H), 1.31 - 1.39 (m, 2H), 1.22 - 1.30 (m, 2H).

Compound 49

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.36 (t, *J*=9.4 Hz, 1H), 7.51 (br s, 1H), 7.32 (d, *J*=7.1 Hz, 1H), 7.05 - 7.25 (m, 3H), 7.00 (br s, 1H), 6.91 - 6.95 (m, 1H), 6.82 (s, 1H), 6.53 (dd, *J*=8.6, 1.5 Hz, 1H), 5.58 (q, *J*=6.9 Hz, 1H), 3.81 (br dd, *J*=13.4, 3.8 Hz, 1H), 3.39 - 3.69 (m, 5H), 2.83 - 3.13 (m, 3H), 2.71 (br d, *J*=16.2 Hz, 1H), 2.15 - 2.25 (m, 1H), 2.04 - 2.15 (m, 1H), 1.52 (d, *J*=7.1 Hz, 3H), 1.30 - 1.38 (m, 2H), 1.20 - 1.30 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.36 (t, *J*=9.4 Hz, 1H), 7.51 (br s, 1H), 7.05 - 7.25 (m, 4H), 7.00 (br s, 1H), 6.91 - 6.95 (m, 1H), 6.79 (s, 1H), 6.53 (dd, *J*=8.6, 1.5 Hz, 1H), 4.96 (q, *J*=6.6 Hz, 1H), 4.50 - 4.59 (m, 1H), 3.39 - 3.69 (m, 4H), 3.21 - 3.29 (m, 1H), 2.83 - 3.13 (m, 4H), 2.15 - 2.25 (m, 1H), 2.04 -2.15 (m, 1H), 1.55 (br d, *J*=6.6 Hz, 3H), 1.30 - 1.38 (m, 2H), 1.20 - 1.30 (m, 2H).

Compound 50

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.36 (t, *J*=9.3 Hz, 1H), 8.00 (q, *J*=4.4 Hz, 1H), 7.32 (d, *J*=7.6 Hz, 1H), 7.06 - 7.26 (m, 3H), 6.91 - 6.97 (m, 1H), 6.83 (s, 1H), 6.53 (br d, *J*=8.2 Hz, 1H), 5.58 (q, *J*=6.5 Hz, 1H), 3.81 (br dd, *J*=13.9, 3.8 Hz, 1H), 3.63 - 3.70 (m, 1H), 3.55 - 3.62 (m, 1H), 3.40 - 3.53 (m, 3H), 2.82 - 3.11 (m, 3H), 2.72 (br d, *J*=16.1 Hz, 1H), 2.62 (d, *J*=4.4 Hz, 3H), 2.14 - 2.23 (m, 1H), 2.04 - 2.14 (m, 1H), 1.52 (d, *J*=6.9 Hz, 3H), 1.30 - 1.38 (m, 2H), 1.21 - 1.30 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.36 (t, *J*=9.3 Hz, 1H), 8.00 (q, *J*=4.4 Hz, 1H), 7.06 - 7.26 (m, 4H), 6.91 - 6.97 (m, 1H), 6.79 (s, 1H), 6.53 (br d, *J*=8.2 Hz, 1H), 4.96 (q, *J*=6.7 Hz, 1H), 4.52 - 4.59 (m, 1H), 3.63 - 3.70 (m, 1H), 3.55 - 3.62 (m, 1H), 3.40 - 3.53 (m, 2H), 3.23 - 3.30 (m, 1H), 2.82 - 3.11 (m, 4H), 2.62 (d, *J*=4.4 Hz, 3H), 2.14 - 2.23 (m, 1H), 2.04 - 2.14 (m, 1H), 1.55 (d, *J*=6.6 Hz, 3H), 1.30 - 1.38 (m, 2H), 1.21 - 1.30 (m, 2H).

Compound 51

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.99 (br s, 1H), 8.38 (t, *J*=9.3 Hz, 1H), 7.32 (d, *J*=7.3 Hz, 1H), 7.05 - 7.26 (m, 3H), 6.92 - 6.98 (m, 1H), 6.83 (s, 1H), 6.56 (br dd, *J*=7.3, 1.0 Hz, 1H), 5.58 (q, *J*=6.5 Hz, 1H), 3.81 (dd, *J*=14.0, 3.9 Hz, 1H), 3.66 - 3.73 (m, 1H),

3.58 - 3.64 (m, 1H), 3.42 - 3.57 (m, 3H), 3.25 (s, 3H), 3.21 - 3.29 (m, 1H), 2.83 - 3.06 (m, 2H), 2.72 (br d, *J*=16.4 Hz, 1H), 2.23 - 2.32 (m, 1H), 2.13 - 2.22 (m, 1H), 1.52 (d, *J*=6.9 Hz, 3H), 1.24 - 1.37 (m, 4H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.99 (br s, 1H), 8.38 (t, *J*=9.3 Hz, 1H), 7.05 - 7.26 (m, 4H), 6.92 - 6.98 (m, 1H), 6.79 (s, 1H), 6.56 (br dd, *J*=7.3, 1.0 Hz, 1H), 4.96 (q, *J*=6.6 Hz, 1H), 4.52 - 4.58 (m, 1H), 3.66 - 3.73 (m, 1H), 3.58 - 3.64 (m, 1H), 3.42 - 3.57 (m, 2H), 3.25 (s, 3H), 3.21 - 3.29 (m, 2H), 2.83 - 3.06 (m, 3H), 2.23 - 2.32 (m, 1H), 2.13 - 2.22 (m, 1H), 1.55 (d, *J*=6.6 Hz, 3H), 1.24 - 1.37 (m, 4H).

Compound 52

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.84 (d, *J*=11.1 Hz, 1H), 7.52 (br s, 1H), 7.32 (br d, *J*=7.6 Hz, 1H), 6.95 - 7.27 (m, 5H), 6.84 (s, 1H), 6.45 (br d, *J*=14.2 Hz, 1H), 5.59 (q, *J*=6.6 Hz, 1H), 3.80 (br dd, *J*=13.4, 4.0 Hz, 1H), 3.40 - 3.73 (m, 5H), 2.85 - 3.13 (m, 3H), 2.71 (br d, *J*=16.2 Hz, 1H), 2.03 - 2.25 (m, 2H), 1.48 - 1.54 (m, 3H), 1.22 - 1.40 (m, 4H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.84 (d, *J*=11.1 Hz, 1H), 7.52 (br s, 1H), 6.95 - 7.27 (m, 6H), 6.81 (s, 1H), 6.45 (br d, *J*=14.2 Hz, 1H), 4.95 (q, *J*=6.6 Hz, 1H), 4.50 - 4.61 (m, 1H), 3.40 - 3.73 (m, 4H), 3.21 - 3.30 (m, 1H), 2.85 - 3.13 (m, 4H), 2.03 - 2.25 (m, 2H), 1.52 - 1.59 (m, 3H), 1.22 - 1.40 (m, 4H).

Compound 53

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.84 (d, *J*=11.1 Hz, 1H), 8.00 (q, *J*=4.6 Hz, 1H), 7.32 (br d, *J*=7.1 Hz, 1H), 7.05 - 7.25 (m, 3H), 6.95 - 7.00 (m, 1H), 6.84 (s, 1H), 6.45 (d, *J*=14.2 Hz, 1H), 5.58 (q, *J*=6.6 Hz, 1H), 3.80 (br dd, *J*=13.6, 4.0 Hz, 1H), 3.56 - 3.73 (m, 2H), 3.39 - 3.53 (m, 3H), 2.85 - 3.11 (m, 3H), 2.68 - 2.76 (m, 1H), 2.62 (d, *J*=4.6 Hz, 3H), 2.03 - 2.23 (m, 2H), 1.48 - 1.58 (m, 3H), 1.22 - 1.38 (m, 4H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.84 (d, *J*=11.1 Hz, 1H), 8.00 (q, *J*=4.6 Hz, 1H), 7.05 - 7.25 (m, 4H), 6.95 - 7.00 (m, 1H), 6.81 (s, 1H), 6.45 (d, *J*=14.2 Hz, 1H), 4.91 - 4.99 (m, 1H), 4.51 - 4.59 (m, 1H), 3.56 - 3.73 (m, 2H), 3.39 - 3.53 (m, 2H), 3.21 - 3.29 (m, 1H), 2.85 - 3.11 (m, 4H), 2.62 (d, *J*=4.6 Hz, 3H), 2.03 - 2.23 (m, 2H), 1.48 - 1.58 (m, 3H), 1.22 - 1.38 (m, 4H).

Compound 54

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.97 (br s, 1H), 8.85 (d, *J*=11.4 Hz, 1H), 7.32 (d, *J*=7.3 Hz, 1H), 7.06 - 7.25 (m, 3H), 6.99 (br d, *J*=2.8 Hz, 1H), 6.85 (s, 1H), 6.48 (br d, *J*=13.9 Hz, 1H), 5.59 (q, *J*=6.7 Hz, 1H), 3.77 - 3.84 (m, 1H), 3.67 - 3.74 (m, 1H), 3.59 - 3.65 (m, 1H), 3.51 - 3.58 (m, 1H), 3.42 - 3.51 (m, 2H), 3.18 - 3.28 (m, 1H), 3.22 (s, 3H), 2.86 - 3.05 (m, 2H), 2.71 (br d, *J*=16.3 Hz, 1H), 2.21 - 2.30 (m, 1H), 2.12 - 2.21 (m, 1H), 1.52 (d, *J*=6.6 Hz, 3H), 1.31 - 1.37 (m, 2H), 1.24 - 1.31 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.97 (br s, 1H), 8.84 (d, *J*=11.4 Hz, 1H), 7.06 - 7.25 (m, 4 H), 6.98 (br d, *J*=2.8 Hz, 1H), 6.81 (s, 1H), 6.48 (br d, *J*=13.9 Hz, 1H), 4.95 (q, *J*=6.6 Hz, 1H), 4.52 - 4.58 (m, 1H), 3.67 - 3.74 (m, 1H), 3.59 - 3.65 (m, 1H), 3.51 - 3.58 (m, 1H), 3.42 - 3.51 (m, 1H), 3.18 - 3.28 (m, 2H), 3.22 (s, 3H), 2.86 - 3.05 (m, 3H), 2.21 - 2.30 (m, 1H), 2.12 - 2.21 (m, 1H), 1.54 (d, *J*=6.6 Hz, 3H), 1.31 - 1.37 (m, 2H), 1.24 - 1.31 (m, 2H).

Compound 55

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.81 (dd, *J*=14.5, 6.9 Hz, 1H), 7.50 (br s, 1H), 7.32 (d, *J*=7.3 Hz, 1H), 7.21 - 7.25 (m, 1H), 7.15 - 7.21 (m, 2H), 6.97 - 7.03 (m, 2H), 6.84 (s, 1H), 6.64 (dd, *J*=13.6, 7.6 Hz, 1H), 5.58 (q, *J*=6.6 Hz, 1H), 3.80 (br dd, *J*=13.7, 3.9 Hz, 1H), 3.59 - 3.66 (m, 1H), 3.53 - 3.59 (m, 1H), 3.42 - 3.52 (m, 3H), 2.83 - 3.07 (m, 3H), 2.71 (br d, *J*=16.1 Hz, 1H), 2.11 - 2.19 (m, 1H), 2.00 - 2.09 (m, 1H), 1.52 (d, *J*=6.9 Hz, 3H), 1.31 - 1.38 (m, 2H), 1.22 - 1.30 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.81 (dd, *J*=14.5, 6.9 Hz, 1H), 7.50 (br s, 1H), 7.15 - 7.21 (m, 2H), 7.10 - 7.15 (m, 1H), 7.08 (d, *J*=7.6 Hz, 1H), 6.97 - 7.03 (m, 2H), 6.81 (s, 1H), 6.64 (dd, *J*=13.6, 7.6 Hz, 1H), 4.95 (q, *J*=6.7 Hz, 1H), 4.54 (br dd, *J*= 12.6, 3.8 Hz, 1H), 3.59 - 3.66 (m, 1H), 3.53 - 3.59 (m, 1H), 3.42 - 3.52 (m, 2H), 3.22 - 3.30 (m, 1H), 2.83 - 3.07 (m, 4H), 2.11 - 2.19 (m, 1H), 2.00 - 2.09 (m, 1H), 1.54 (d, *J*=6.6 Hz, 3H), 1.31 - 1.38 (m, 2H), 1.22 - 1.30 (m, 2H).

Compound 56

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.28 - 8.31 (m, 2H), 7.91 (t, *J*=8.7 Hz, 1H), 7.61 - 7.68 (m, 3H), 7.51 (br s, 1H), 7.32 - 7.40 (m, 2H), 7.09 - 7.27 (m, 3H), 7.03 - 7.08 (m, 1H), 7.00 (br s, 1H), 6.51 (br d, *J*=8.8 Hz, 1H), 6.45 (br d, *J*=14.8 Hz, 1H), 5.63 (q, *J*=6.8 Hz,

1H), 3.99 (br dd, *J*=14.0, 4.3 Hz, 1H), 3.46 - 3.58 (m, 2H), 3.27 - 3.44 (m, 3H partially obscured by H_2O peak), 3.03 - 3.12 (m, 2H), 2.76 (br d, *J*=16.7 Hz, 1H), 2.16 - 2.23 (m, 1H), 2.05 - 2.14 (m, 1H), 1.55 (d, *J*=6.9 Hz, 3H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.24 - 8.28 (m, 2H), 7.91 (t, *J*=8.7 Hz, 1H), 7.61 - 7.68 (m, 3H), 7.51 (br s, 1H), 7.32 - 7.40 (m, 1H), 7.09 - 7.27 (m, 4H), 7.03 - 7.08 (m, 1H), 7.00 (br s, 1H), 6.51 (br d, *J*=8.8 Hz, 1H), 6.45 (br d, *J*=14.8 Hz, 1H), 5.14 (q, *J*=6.9 Hz, 1H), 4.59 (br dd, *J*=12.6, 3.8 Hz, 1H), 3.46 - 3.58 (m, 1H), 3.27 - 3.44 (m, 3H partially obscured by H_2O peak), 3.03 - 3.12 (m, 2H), 2.85 - 3.00 (m, 2H), 2.16 - 2.23 (m, 1H), 2.05 - 2.14 (m, 1H), 1.61 (d, *J*=6.6 Hz, 3H).

Compound 57

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.39 (d, *J*=8.8 Hz, 2H), 7.94 (t, *J*=8.7 Hz, 1H), 7.51 (br s, 1H), 7.37 (s, 1H), 7.32 - 7.36 (m, 1H), 7.09 - 7.42 (m, 8H), 6.98 - 7.05 (m, 1H), 6.51 (br d, *J*=8.8 Hz, 1H), 6.45 (br d, *J*=14.5 Hz, 1H), 5.63 (q, *J*=6.3 Hz, 1H), 3.97 (br dd, *J*=13.9, 3.8 Hz, 1H), 3.90 (s, 3H), 3.47 - 3.56 (m, 2H), 3.36 - 3.44 (m, 2H), 3.26 - 3.32 (m, 1H partially obscured by H_2O peak), 3.02 - 3.12 (m, 2H), 2.75 (br d, *J*=17.0 Hz, 1H), 2.16 - 2.24 (m, 1H), 2.06 - 2.15 (m, 1H), 1.55 (d, *J*=6.6 Hz, 3H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.35 (d, *J*=8.8 Hz, 2H), 7.94 (t, *J*=8.7 Hz, 1H), 7.51 (br s, 1H), 7.32 - 7.36 (m, 1H), 7.09 - 7.27 (m, 6H), 6.98 - 7.05 (m, 2H), 6.51 (br d, *J*=8.8 Hz, 1H), 6.45 (br d, *J*=14.5 Hz, 1H), 5.12 (q, *J*=6.0 Hz, 1H), 4.59 (br dd, *J*=13.2, 3.8 Hz, 1H), 3.89 (s, 3H), 3.47 - 3.56 (m, 1H), 3.36 - 3.44 (m, 2H), 3.26 - 3.32 (m, 1H partially obscured by H_2O peak), 3.02 - 3.12 (m, 2H), 2.85 - 2.99 (m, 2H), 2.16 - 2.24 (m, 1H), 2.06 - 2.15 (m, 1H), 1.60 (d, *J*=6.6 Hz, 3H).

Compound 58

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.23 (br d, *J*=7.9 Hz, 2H), 7.91 (br t, *J*=8.7 Hz, 1H), 7.42 - 7.48 (m, 3H), 7.31 - 7.40 (m, 2H), 7.08 - 7.27 (m, 3H), 6.97 - 7.08 (m, 2H), 6.51 (br d, *J*=8.5 Hz, 1H), 6.45 (br d, *J*=14.8 Hz, 1H), 5.63 (q, *J*=6.5 Hz, 1H), 3.98 (br dd, *J*=13.1, 3.6 Hz, 1H), 3.45 - 3.57 (m, 2H), 3.35 - 3.44 (m, 2H), 3.02 - 3.18 (m, 2H), 2.75 (br d, *J*=16.1 Hz, 1H), 2.41 - 2.47 (m, 4H), 2.15 - 2.25 (m, 1H), 2.05 - 2.15 (m, 1H), 1.55 (br d, *J*=6.6 Hz, 3H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.20 (br d, *J*=7.9 Hz, 2H), 7.91 (br t, *J*=8.7 Hz, 1H), 7.42 - 7.48 (m, 3H), 7.31 - 7.40 (m, 1H), 7.08 - 7.27 (m, 4H), 6.97 - 7.08 (m, 2H), 6.51 (br d, *J*=8.5 Hz, 1H), 6.45 (br d, *J*=14.8 Hz, 1H), 5.13 (q, *J*=6.4 Hz, 1H), 4.59 (br dd, *J*=13.2, 4.4 Hz, 1H), 3.45 - 3.57 (m, 2H), 3.35 - 3.44 (m, 2H), 3.02 - 3.18 (m, 1H), 2.85 - 3.00 (m, 2H), 2.41 - 2.47 (m, 4H), 2.15 - 2.25 (m, 1H), 2.05 - 2.15 (m, 1H), 1.60 (br d, *J*=6.6 Hz, 3H).

Compound 59

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.34 (d, *J*=8.5 Hz, 2H), 7.92 (t, *J*=8.7 Hz, 1H), 7.69 - 7.74 (m, 2H), 7.51 (br s, 1H), 7.43 (s, 1H), 7.34 (d, *J*=7.6 Hz, 1H), 7.08 - 7.26 (m, 3H), 7.04 - 7.08 (m, 1H), 7.00 (br s, 1H), 6.50 (br d, *J*=8.8 Hz, 1H), 6.45 (br d, *J*=14.8 Hz, 1H), 5.63 (q, *J*=6.5 Hz, 1H), 3.95 - 4.01 (m, 1H), 3.46 - 3.59 (m, 2H), 3.27 - 3.44 (m, 3H partially obscured by H_2O peak), 3.02 - 3.12 (m, 2H), 2.75 (br d, *J*=17.0 Hz, 1H), 2.16 - 2.24 (m, 1H), 2.05 - 2.14 (m, 1H), 1.55 (d, *J*=6.6 Hz, 3H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.31 (d, *J*=8.5 Hz, 2H), 7.92 (t, *J*=8.7 Hz, 1H), 7.69 - 7.74 (m, 2H), 7.51 (br s, 1H), 7.38 (s, 1H), 7.08 - 7.26 (m, 4H), 7.04 - 7.08 (m, 1H), 7.00 (br s, 1H), 6.50 (br d, *J*=8.8 Hz, 1H), 6.45 (br d, *J*=14.8 Hz, 1H), 5.13 (q, *J*=6.6 Hz, 1H), 4.56 - 4.62 (m, 1H), 3.46 - 3.59 (m, 1H), 3.27 - 3.44 (m, 3H partially obscured by H_2O peak), 3.02 - 3.12 (m, 2H), 2.85 - 2.99 (m, 2H), 2.16 - 2.24 (m, 1H), 2.05 - 2.14 (m, 1H), 1.60 (d, *J*=6.6 Hz, 3H).

Compound 60

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.34 - 8.44 (m, 2H), 7.92 (t, *J*=8.8 Hz, 1H), 7.45 - 7.54 (m, 3H), 7.41 (s, 1H), 7.34 (d, *J*=7.6 Hz, 1H), 7.08 - 7.27 (m, 3H), 7.03 - 7.07 (m, 1H), 6.94 - 7.02 (m, 1H), 6.50 (br d, *J*=8.8 Hz, 1H), 6.45 (dd, *J*=14.5, 1.6 Hz, 1H), 5.63 (q, *J*=6.7 Hz, 1H), 3.98 (br dd, *J*=13.4, 3.9 Hz, 1H), 3.47 - 3.57 (m, 2H), 3.27 - 3.45 (m, 3H partially obscured by H_2O peak), 3.03 - 3.12 (m, 2H), 2.75 (br d, *J*=16.1 Hz, 1H), 2.16 - 2.24 (m, 1H), 2.05 - 2.15 (m, 1H), 1.55 (d, *J*=6.6 Hz, 3H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.34 - 8.44 (m, 2H), 7.92 (t, *J*=8.8 Hz, 1H), 7.45 - 7.54 (m, 3H), 7.36 (s, 1H), 7.08 - 7.27 (m, 4H), 7.03 - 7.07 (m, 1H), 6.94 - 7.02 (m, 1H), 6.50 (br d, *J*=8.8 Hz, 1H), 6.45 (dd, *J*=14.5, 1.6 Hz, 1H), 5.13 (q, *J*=6.7 Hz, 1H), 4.59 (br dd, *J*=12.8, 4.9 Hz, 1H), 3.47 - 3.57 (m, 1H), 3.27 - 3.45 (m, 3H partially obscured by H_2O

peak), 3.03 - 3.12 (m, 2H), 2.85 - 3.00 (m, 2H), 2.16 - 2.24 (m, 1H), 2.05 - 2.15 (m, 1H), 1.61 (d, *J*=6.6 Hz, 3H).

Compound 61

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.49 (d, *J*=8.2 Hz, 2H), 7.98 - 8.05 (m, 2H), 7.91 (t, *J*=8.8 Hz, 1H), 7.42 - 7.51 (m, 2H), 7.34 (d, *J*=7.3 Hz, 1H), 7.07 - 7.27 (m, 4H), 6.98 (br s, 1H), 6.49 (br d, *J*=8.8 Hz, 1H), 6.45 (dd, *J*=14.7, 1.7 Hz, 1H), 5.64 (q, *J*=6.5 Hz, 1H), 4.00 (br dd, *J*=13.9, 3.8 Hz, 1H), 3.46 - 3.58 (m, 2H), 3.27 - 3.44 (m, 3H), 3.03 - 3.12 (m, 2H), 2.76 (br d, *J*=16.7 Hz, 1H), 2.16 - 2.24 (m, 1H), 2.06 - 2.14 (m, 1H), 1.56 (d, *J*=6.6 Hz, 3H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.46 (d, *J*=8.2 Hz, 2H), 7.98 - 8.05 (m, 2H), 7.91 (t, *J*=8.8 Hz, 1H), 7.42 - 7.51 (m, 2H), 7.07 - 7.27 (m, 5H), 6.98 (br s, 1H), 6.49 (br d, *J*=8.8 Hz, 1H), 6.45 (dd, *J*=14.7, 1.7 Hz, 1H), 5.15 (q, *J*=6.8 Hz, 1H), 4.59 (br dd, *J*=13.1, 4.6 Hz, 1H), 3.46 - 3.58 (m, 1H), 3.27 - 3.44 (m, 3H), 3.03 - 3.12 (m, 2H), 2.85 - 3.00 (m, 2H), 2.16 - 2.24 (m, 1H), 2.06 - 2.14 (m, 1H), 1.61 (d, *J*=6.6 Hz, 3H).

Compound 62

Major rotamer

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.47 (d, *J*=8.2 Hz, 2H), 8.09 - 8.14 (m, 2H), 7.90 (t, *J*=8.8 Hz, 1H), 7.43 - 7.53 (m, 2H), 7.34 (br d, *J*=7.6 Hz, 1H), 7.07 - 7.27 (m, 4H), 7.00 (br s, 1H), 6.49 (br d, *J*=8.8 Hz, 1H), 6.45 (br d, *J*=15.1 Hz, 1H), 5.63 (q, *J*=6.8 Hz, 1H), 3.99 (br dd, *J*=13.1, 3.9 Hz, 1H), 3.46 - 3.57 (m, 2H), 3.28 - 3.44 (m, 3H partially obscured by H_2O peak), 3.02 - 3.12 (m, 2H), 2.75 (br d, *J*=16.4 Hz, 1H), 2.16 - 2.23 (m, 1H), 2.05 - 2.14 (m, 1H), 1.55 (d, *J*=6.9 Hz, 3H).

Minor rotamer

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.44 (br d, *J*=8.5 Hz, 2H), 8.09 - 8.14 (m, 2H), 7.90 (t, *J*=8.8 Hz, 1H), 7.43 - 7.53 (m, 2H), 7.07 - 7.27 (m, 5H), 7.00 (br s, 1H), 6.49 (br d, *J*=8.8 Hz, 1H), 6.45 (br d, *J*=15.1 Hz, 1H), 5.11 - 5.17 (m, 1H), 4.56 - 4.62 (m, 1H), 3.46 - 3.57 (m, 1H), 3.28 - 3.44 (m, 3H partially obscured by H_2O peak), 3.02 - 3.12 (m, 2H), 2.85 - 2.99 (m, 2H), 2.16 - 2.23 (m, 1H), 2.05 - 2.14 (m, 1H), 1.61 (br d, *J*=6.6 Hz, 3H).

Compound 63

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.84 - 8.91 (m, 2H), 8.28 (br d, *J*=5.4 Hz, 2H), 7.93 (br t, *J*=8.7 Hz, 1H), 7.49 - 7.58 (m, 2H), 7.34 (br d, *J*=7.6 Hz, 1H), 7.06 - 7.27 (m, 4H),

7.00 (br s, 1H), 6.51 (br d, *J*=8.8 Hz, 1H), 6.46 (br d, *J*=14.5 Hz, 1H), 5.64 (q, *J*=6.1 Hz, 1H), 3.95 - 4.02 (m, 1H), 3.47 - 3.58 (m, 2H), 3.36 - 3.44 (m, 2H), 3.03 - 3.12 (m, 3H), 2.75 (br d, *J*=16.1 Hz, 1H), 2.16 - 2.24 (m, 1H), 2.06 - 2.15 (m, 1H), 1.56 (br d, *J*=6.6 Hz, 3H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.84 - 8.91 (m, 2H), 8.25 (br d, *J*=5.7 Hz, 2H), 7.93 (br t, *J*=8.7 Hz, 1H), 7.49 - 7.58 (m, 2H), 7.06 - 7.27 (m, 5H), 7.00 (br s, 1H), 6.51 (br d, *J*=8.8 Hz, 1H), 6.46 (br d, *J*=14.5 Hz, 1H), 5.10 - 5.17 (m, 1H), 4.56 - 4.63 (m, 1H), 3.47 - 3.58 (m, 2H), 3.36 - 3.44 (m, 2H), 3.03 - 3.12 (m, 2H), 2.85 - 3.00 (m, 2H), 2.16 - 2.24 (m, 1H), 2.06 - 2.15 (m, 1H), 1.61 (br d, *J*=6.6 Hz, 3H).

Compound 64

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.68 (s, 2H), 9.34 - 9.46 (m, 1H), 7.90 (br t, *J*=8.6 Hz, 1H), 7.67 (s, 1H), 7.50 (br s, 1H), 6.95 - 7.37 (m, 6H), 6.52 (br d, *J*=8.6 Hz, 1H), 6.45 (br d, *J*=14.7 Hz, 1H), 5.59 - 5.68 (m, 1H), 3.96 (br d, *J*=9.6 Hz, 1H), 3.45 - 3.66 (m, 2H), 3.33 - 3.44 (m, 3H), 3.01 - 3.20 (m, 2H), 2.75 (br d, *J*=17.7 Hz, 1H), 2.04 - 2.26 (m, 2H), 1.56 (br d, *J*=6.1 Hz, 3H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.65 (s, 2H), 9.34 - 9.46 (m, 1H), 7.90 (br t, *J*=8.6 Hz, 1H), 7.63 (s, 1H), 7.50 (br s, 1H), 6.95 - 7.37 (m, 6H), 6.52 (br d, *J*=8.6 Hz, 1H), 6.45 (br d, *J*=14.7 Hz, 1H), 5.08 - 5.16 (m, 1H), 4.60 (br d, *J*=11.1 Hz, 1H), 3.45 - 3.66 (m, 1H), 3.33 - 3.44 (m, 3H), 3.01 - 3.20 (m, 2H), 2.84 - 3.01 (m, 2H), 2.04 - 2.26 (m, 2H), 1.61 (br d, *J*=6.1 Hz, 3H).

Compound 65

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.98 (t, *J*=8.5 Hz, 1H), 7.29 - 7.41 (m, 2H), 7.05 - 7.25 (m, 3H), 6.91 - 6.96 (m, 1H), 6.85 (br s, 1H), 6.81 (s, 1H), 6.31 - 6.41 (m, 2H), 5.58 (q, *J*=6.8 Hz, 1H), 4.04 (t, *J*=7.8 Hz, 2H), 3.81 (br dd, *J*=13.1, 3.5 Hz, 1H), 3.59 (dd, *J*=7.3, 5.9 Hz, 2H), 3.42 - 3.51 (m, 1H), 2.85 - 3.06 (m, 3H), 2.71 (br d, *J*=16.1 Hz, 1H), 2.44 - 2.48 (m, 2H partially obscured by DMSO peak), 1.52 (d, *J*=6.7 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.21 - 1.29 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.98 (t, *J*=8.5 Hz, 1H), 7.29 - 7.41 (m, 1H), 7.05 - 7.25 (m, 4H), 6.91 - 6.96 (m, 1H), 6.85 (br s, 1H), 6.78 (s, 1H), 6.31 - 6.41 (m, 2H), 4.96

(q, *J*=6.7 Hz, 1H), 4.51 - 4.59 (m, 1H), 4.04 (t, *J*=7.8 Hz, 2H), 3.59 (dd, *J*=7.3, 5.9 Hz, 2H), 3.22 - 3.30 (m, 1H), 2.85 - 3.06 (m, 4H), 2.44 - 2.48 (m, 2H partially obscured by DMSO peak), 1.55 (d, *J*=6.6 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.21 - 1.29 (m, 2H).

Compound 66

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.98 (t, *J*=8.5 Hz, 1H), 7.81 - 7.85 (m, 1H), 7.32 (d, *J*=7.6 Hz, 1H), 7.06 - 7.25 (m, 3H), 6.94 (d, *J*=3.5 Hz, 1H), 6.81 (s, 1H), 6.37 (dd, *J*=8.7, 2.0 Hz, 1H), 6.34 (br d, *J*=13.6 Hz, 1H), 5.58 (q, *J*=6.5 Hz, 1H), 4.03 (t, *J*=7.7 Hz, 2H), 3.81 (br dd, *J*=13.6, 3.8 Hz, 1H), 3.59 (dd, *J*=7.4, 5.8 Hz, 2H), 3.42 - 3.50 (m, 1H), 2.81 - 3.05 (m, 3H), 2.71 (br d, *J*=16.7 Hz, 1H), 2.58 (d, *J*=4.4 Hz, 3H), 2.47 - 2.49 (m, 2H), 1.52 (d, *J*=6.9 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.22 - 1.30 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.98 (br t, *J*=8.7 Hz, 1H), 7.81 - 7.85 (m, 1H), 7.06 - 7.25 (m, 4H), 6.93 (d, *J*=3.5 Hz, 1H), 6.78 (s, 1H), 6.37 (dd, *J*=8.7, 2.0 Hz, 1H), 6.34 (br d, *J*=13.6 Hz, 1H), 4.96 (q, *J*=6.7 Hz, 1H), 4.52 - 4.58 (m, 1H), 4.03 (t, *J*=7.7 Hz, 2H), 3.59 (dd, *J*=7.4, 5.8 Hz, 2H), 3.23 - 3.30 (m, 1H), 2.81 - 3.05 (m, 4H), 2.58 (d, *J*=4.4 Hz, 3H), 2.47 - 2.49 (m, 2H), 1.55 (d, *J*=6.6 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.22 - 1.30 (m, 2H).

Compound 67

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.98 (br t, *J*=8.4 Hz, 1H), 7.32 (br d, *J*=7.3 Hz, 1H), 7.06 - 7.26 (m, 3H), 6.92 - 6.96 (m, 1H), 6.81 (s, 1H), 6.33 - 6.43 (m, 2H), 5.70 (d, *J*=6.3 Hz, 1H), 5.58 (q, *J*=7.0 Hz, 1H), 4.58 - 4.65 (m, 1H), 4.16 (t, *J*=7.3 Hz, 2H), 3.81 (br dd, *J*=13.2, 4.1 Hz, 1H), 3.63 (dd, *J*=7.9, 4.7 Hz, 2H), 3.43 - 3.50 (m, 1H), 2.83 - 3.06 (m, 2H), 2.72 (br d, *J*=16.4 Hz, 1H), 1.52 (d, *J*=6.6 Hz, 3H), 1.30 - 1.36 (m, 2H), 1.21 - 1.29 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.98 (br t, *J*=8.4 Hz, 1H), 7.06 - 7.26 (m, 4H), 6.92 - 6.96 (m, 1H), 6.78 (s, 1H), 6.33 - 6.43 (m, 2H), 5.70 (d, *J*=6.3 Hz, 1H), 4.96 (q, *J*=6.4 Hz, 1H), 4.58 - 4.65 (m, 1H), 4.51 - 4.57 (m, 1H), 4.16 (t, *J*=7.3 Hz, 2H), 3.63 (dd, *J*=7.9, 4.7 Hz, 2H), 3.22 - 3.29 (m, 1H), 2.83 - 3.06 (m, 3H), 1.55 (d, *J*=6.6 Hz, 3H), 1.30 - 1.36 (m, 2H), 1.21 - 1.29 (m, 2H).

Compound 68

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.00 (t, *J*=9.0 Hz, 1H), 7.28 - 7.36 (m, 2H), 7.06 - 7.25 (m, 3H), 6.95 - 6.99 (m, 1H), 6.92 (br d, *J*=8.8 Hz, 1H), 6.88 (br d, *J*=15.1 Hz, 1H), 6.83 (s, 1H), 6.80 (br s, 1H), 5.59 (q, *J*=6.8 Hz, 1H), 3.89 (br d, *J*=12.9 Hz, 2H), 3.82 (br dd, *J*=13.9, 3.8 Hz, 1H), 3.43 - 3.50 (m, 1H), 2.97 - 3.05 (m, 1H), 2.91 - 2.97 (m, 1H), 2.79 - 2.91 (m, 2H), 2.72 (br d, *J*=16.4 Hz, 1H), 2.29 - 2.38 (m, 1H), 1.76 - 1.83 (m, 2H), 1.62 (br qd, *J*=12.2, 3.6 Hz, 2H), 1.52 (d, *J*=6.9 Hz, 3H), 1.31 - 1.38 (m, 2H), 1.24 - 1.30 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.00 (t, *J*=9.0 Hz, 1H), 7.28 - 7.36 (m, 1H), 7.06 - 7.25 (m, 4H), 6.95 - 6.99 (m, 1H), 6.92 (br d, *J*=8.8 Hz, 1H), 6.88 (br d, *J*=15.1 Hz, 1H), 6.80 (br s, 1H), 6.79 (s, 1H), 4.97 (q, *J*=6.6 Hz, 1H), 4.55 (br dd, *J*=12.9, 3.2 Hz, 1H), 3.89 (br d, *J*=12.9 Hz, 2H), 3.23 - 3.30 (m, 1H), 2.91 - 2.97 (m, 2H), 2.79 - 2.91 (m, 3H), 2.29 - 2.38 (m, 1H), 1.76 - 1.83 (m, 2H), 1.62 (br qd, *J*=12.2, 3.6 Hz, 2H), 1.55 (d, *J*=6.6 Hz, 3H), 1.31 - 1.38 (m, 2H), 1.24 - 1.30 (m, 2H).

Compound 69

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.00 (t, *J*=8.9 Hz, 1H), 7.41 (br s, 1H), 7.32 (d, *J*=7.2 Hz, 1H), 7.05 - 7.25 (m, 3H), 6.86 - 7.00 (m, 4H), 6.83 (s, 1H), 5.59 (q, *J*=6.6 Hz, 1H), 3.89 (br d, *J*=13.0 Hz, 1H), 3.78 - 3.86 (m, 2H), 3.41 - 3.52 (m, 1H), 2.86 - 3.07 (m, 3H), 2.78 - 2.85 (m, 1H), 2.72 (br d, *J*=16.3 Hz, 1H), 2.36 - 2.46 (m, 1H), 1.85 - 1.93 (m, 1H), 1.68 - 1.76 (m, 1H), 1.50 - 1.65 (m, 2H), 1.52 (d, *J*=6.8 Hz, 3H), 1.30 - 1.39 (m, 2H), 1.22 - 1.30 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.00 (t, *J*=8.9 Hz, 1H), 7.41 (br s, 1H), 7.05 - 7.25 (m, 4H), 6.86 - 7.00 (m, 4H), 6.80 (s, 1H), 4.97 (q, *J*=6.6 Hz, 1H), 4.55 (br dd, *J*=11.6, 3.9 Hz, 1H), 3.89 (br d, *J*=13.0 Hz, 1H), 3.78 - 3.86 (m, 1H), 3.22 - 3.31 (m, 1H), 2.86 - 3.07 (m, 4H), 2.78 - 2.85 (m, 1H), 2.36 - 2.46 (m, 1H), 1.85 - 1.93 (m, 1H), 1.68 - 1.76 (m, 1H), 1.50 - 1.65 (m, 2H), 1.55 (br d, *J*=6.7 Hz, 3H), 1.30 - 1.39 (m, 2H), 1.22 - 1.30 (m, 2H).

Compound 70

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.99 (t, *J*=9.0 Hz, 1H), 7.32 (d, *J*=7.6 Hz, 1H), 7.27 (br s, 1H), 7.05 - 7.25 (m, 3H), 6.95 - 6.98 (m, 1H), 6.90 (br d, *J*=8.8 Hz, 1H), 6.85 (dd, *J*=15.4, 1.9 Hz, 1H), 6.82 (s, 1H), 6.76 (br s, 1H), 5.59 (q, *J*=6.6 Hz, 1H), 3.79 - 3.89 (m,

3H), 3.43 - 3.50 (m, 1H), 2.98 - 3.05 (m, 1H), 2.86 - 2.98 (m, 1H), 2.81 (t, *J*=11.7 Hz, 2H), 2.72 (br d, *J*=16.4 Hz, 1H), 2.01 (s, 2H), 1.85 - 1.95 (m, 1H), 1.74 (br d, *J*=11.7 Hz, 2H), 1.52 (d, *J*=6.6 Hz, 3H), 1.31 - 1.37 (m, 2H), 1.22 - 1.30 (m, 4H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.99 (t, *J*=9.0 Hz, 1H), 7.27 (br s, 1H), 7.05 - 7.25 (m, 4H), 6.95 - 6.98 (m, 1H), 6.90 (br d, *J*=8.8 Hz, 1H), 6.85 (dd, *J*=15.4, 1.9 Hz, 1H), 6.79 (s, 1H), 6.76 (br s, 1H), 4.97 (q, *J*=6.5 Hz, 1H), 4.55 (br dd, *J*=13.1, 3.3 Hz, 1H), 3.79 - 3.89 (m, 2H), 3.23 - 3.30 (m, 1H), 2.86 - 2.98 (m, 3H), 2.81 (t, *J*=11.7 Hz, 2H), 2.03 (s, 2H), 1.85 - 1.95 (m, 1H), 1.74 (br d, *J*=11.7 Hz, 2H), 1.55 (d, *J*=6.6 Hz, 3H), 1.31 - 1.37 (m, 2H), 1.22 - 1.30 (m, 4H).

Compound 71

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.99 (br t, *J*=8.9 Hz, 1H), 7.34 (br s, 1H), 7.32 (br d, *J*=7.9 Hz, 1H), 7.06 - 7.26 (m, 3H), 6.94 - 6.98 (m, 1H), 6.88 (br d, *J*=8.9 Hz, 1H), 6.83 (s, 1H), 6.80 - 6.86 (m, 2H), 5.59 (q, *J*=6.6 Hz, 1H), 3.72 - 3.86 (m, 3H), 3.42 - 3.51 (m, 1H), 2.82 - 3.07 (m, 3H), 2.72 (br d, *J*=16.3 Hz, 1H), 2.63 (dd, *J*=12.1, 10.5 Hz, 1H), 1.92 - 2.14 (m, 3H), 1.74 - 1.83 (m, 1H), 1.65 - 1.73 (m, 1H), 1.52 (br d, *J*=6.8 Hz, 3H), 1.30 - 1.38 (m, 2H), 1.24 - 1.30 (m, 2H), 1.12 - 1.23 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.99 (br t, *J*=8.9 Hz, 1H), 7.34 (br s, 1H), 7.06 - 7.26 (m, 4H), 6.94 - 6.98 (m, 1H), 6.88 (br d, *J*=8.9 Hz, 1H), 6.80 - 6.86 (m, 2H), 6.79 (s, 1H), 4.97 (q, *J*=6.5 Hz, 1H), 4.55 (br dd, *J*=12.0, 3.3 Hz, 1H), 3.72 - 3.86 (m, 2H), 3.22 - 3.31 (m, 1H), 2.82 - 3.07 (m, 4H), 2.63 (dd, *J*=12.1, 10.5 Hz, 1H), 1.92 - 2.14 (m, 3H), 1.74 - 1.83 (m, 1H), 1.65 - 1.73 (m, 1H), 1.55 (br d, *J*=6.7 Hz, 3H), 1.30 - 1.38 (m, 2H), 1.24 - 1.30 (m, 2H), 1.12 - 1.23 (m, 2H).

Compound 72

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.00 (br t, *J*=8.5 Hz, 1H), 7.76 (br d, *J*=3.8 Hz, 1H), 7.32 (br d, *J*=7.3 Hz, 1H), 7.06 - 7.27 (m, 3H), 6.85 - 7.00 (m, 3H), 6.83 (s, 1H), 5.59 (q, *J*=6.3 Hz, 1H), 3.89 (d, *J*=12.3 Hz, 2H), 3.82 (br d, *J*=9.8 Hz, 1H), 3.46 (br t, *J*=11.2 Hz, 1H), 2.79 - 3.06 (m, 4H), 2.72 (br d, *J*=15.8 Hz, 1H), 2.58 (d, *J*=4.1 Hz, 3H), 2.29 - 2.38 (m, 1H), 1.72 - 1.80 (m, 2H), 1.59 - 1.69 (m, 2H), 1.52 (br d, *J*=6.3 Hz, 3H), 1.30 - 1.38 (m, 2H), 1.23 - 1.30 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.00 (br t, *J*=8.5 Hz, 1H), 7.76 (br d, *J*=3.8 Hz, 1H), 7.06 - 7.27 (m, 4H), 6.85 - 7.00 (m, 3H), 6.79 (s, 1H), 4.97 (q, *J*=6.3 Hz, 1H), 4.55 (br d, *J*=9.8 Hz, 1H), 3.89 (d, *J*=12.3 Hz, 2H), 3.22 - 3.30 (m, 1H), 2.79 - 3.06 (m, 5H), 2.58 (d, *J*=4.1 Hz, 3H), 2.29 - 2.38 (m, 1H), 1.72 - 1.80 (m, 2H), 1.59 - 1.69 (m, 2H), 1.55 (br d, *J*=6.6 Hz, 3H), 1.30 - 1.38 (m, 2H), 1.23 - 1.30 (m, 2H).

Compound 73

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.00 (br t, *J*=8.8 Hz, 1H), 7.86 (br d, *J*=4.4 Hz, 1H), 7.32 (br d, *J*=7.6 Hz, 1H), 7.06 - 7.26 (m, 3H), 6.85 - 7.00 (m, 3H), 6.83 (s, 1H), 5.59 (q, *J*=6.3 Hz, 1H), 3.78 - 3.92 (m, 3H), 3.43 - 3.52 (m, 1H), 2.79 - 3.06 (m, 3H), 2.67 - 2.75 (m, 2H), 2.60 (br d, *J*=4.1 Hz, 3H), 2.35 - 2.45 (m, 1H), 1.85 (br d, *J*=10.7 Hz, 1H), 1.68 - 1.76 (m, 1H), 1.56 - 1.67 (m, 2H), 1.52 (br d, *J*=6.6 Hz, 3H), 1.31 - 1.38 (m, 2H), 1.23 - 1.30 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.00 (br t, *J*=8.8 Hz, 1H), 7.86 (br d, *J*=4.4 Hz, 1H), 7.06 - 7.26 (m, 3H), 6.85 - 7.00 (m, 4H), 6.79 (s, 1H), 4.97 (q, *J*=6.0 Hz, 1H), 4.55 (br d, *J*=11.0 Hz, 1H), 3.78 - 3.92 (m, 2H), 3.22 - 3.30 (m, 1H), 2.79 - 3.06 (m, 4H), 2.67 - 2.75 (m, 1H), 2.60 (br d, *J*=4.1 Hz, 3H), 2.35 - 2.45 (m, 1H), 1.85 (br d, *J*=10.7 Hz, 1H), 1.68 - 1.76 (m, 1H), 1.56 - 1.67 (m, 2H), 1.55 (br d, *J*=6.6 Hz, 3H), 1.31 - 1.38 (m, 2H), 1.23 - 1.30 (m, 2H).

Compound 74

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.99 (br t, *J*=9.0 Hz, 1H), 7.32 (br d, *J*=7.3 Hz, 1H), 7.06 - 7.26 (m, 3H), 6.94 - 6.98 (m, 1H), 6.91 (br d, *J*=9.1 Hz, 1H), 6.86 (br d, *J*=15.4 Hz, 1H), 6.83 (s, 1H), 5.59 (q, *J*=6.8 Hz, 1H), 4.72 (d, *J*=4.1 Hz, 1H), 3.81 (br dd, *J*=12.9, 4.1 Hz, 1H), 3.65 - 3.73 (m, 3H), 3.43 - 3.50 (m, 1H), 2.83 - 3.06 (m, 4H), 2.72 (br d, *J*=16.1 Hz, 1H), 1.79 - 1.86 (m, 2H), 1.52 (d, *J*=6.6 Hz, 3H), 1.41 - 1.50 (m, 2H), 1.31 - 1.38 (m, 2H), 1.22 - 1.30 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.99 (br t, *J*=9.0 Hz, 1H), 7.06 - 7.26 (m, 4H), 6.94 - 6.98 (m, 1H), 6.91 (br d, *J*=9.1 Hz, 1H), 6.86 (br d, *J*=15.4 Hz, 1H), 6.79 (s, 1H), 4.96 (q, *J*=6.6 Hz, 1H), 4.72 (d, *J*=4.1 Hz, 1H), 4.55 (br dd, *J*=12.3, 3.2 Hz, 1H), 3.65 - 3.73 (m, 3H), 3.23 - 3.30 (m, 1H), 2.83 - 3.06 (m, 5H), 1.79 - 1.86 (m, 2H), 1.55 (d, *J*=6.9 Hz, 3H), 1.41 - 1.50 (m, 2H), 1.31 - 1.38 (m, 2H), 1.22 - 1.30 (m, 2H).

Compound 75

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.99 (br t, *J*=9.0 Hz, 1H), 7.32 (d, *J*=7.3 Hz, 1H), 7.06 - 7.25 (m, 3H), 6.94 - 6.98 (m, 1H), 6.88 (br d, *J*=8.8 Hz, 1H), 6.82 (s, 1H), 6.82 (br dd, *J*=15.3, 1.4 Hz, 1H), 5.59 (q, *J*=6.6 Hz, 1H), 4.87 (d, *J*=4.4 Hz, 1H), 3.81 (br dd, *J*=13.7, 3.9 Hz, 1H), 3.71 (br d, *J*=12.6 Hz, 1H), 3.55 - 3.66 (m, 2H), 3.42 - 3.51 (m, 1H), 2.83 - 3.05 (m, 3H), 2.69 - 2.76 (m, 2H), 1.87 - 1.94 (m, 1H), 1.73 - 1.80 (m, 1H), 1.52 (d, *J*=6.6 Hz, 3H), 1.28 - 1.41 (m, 4H), 1.22 - 1.30 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.99 (br t, *J*=9.0 Hz, 1H), 7.06 - 7.25 (m, 4H), 6.94 - 6.98 (m, 1H), 6.88 (br d, *J*=8.8 Hz, 1H), 6.82 (br dd, *J*=15.3, 1.4 Hz, 1H), 6.79 (s, 1H), 4.96 (q, *J*=6.6 Hz, 1H), 4.87 (d, *J*=4.4 Hz, 1H), 4.55 (br dd, *J*=12.1, 4.3 Hz, 1H), 3.71 (br d, *J*=12.6 Hz, 1H), 3.55 - 3.66 (m, 2H), 3.23 - 3.30 (m, 1H), 2.83 - 3.05 (m, 4H), 2.69 - 2.76 (m, 1H), 1.87 - 1.94 (m, 1H), 1.73 - 1.80 (m, 1H), 1.55 (d, *J*=6.6 Hz, 3H), 1.28 - 1.41 (m, 4H), 1.22 - 1.30 (m, 2H).

Compound 76

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.76 (br s, 1H), 8.02 (t, *J*=8.9 Hz, 1H), 7.32 (d, *J*=7.2 Hz, 1H), 7.09 - 7.26 (m, 3H), 6.92 - 6.97 (m, 1H), 6.81 (s, 1H), 6.55 (br d, *J*=8.7 Hz, 1H), 6.49 (br d, *J*=14.7 Hz, 1H), 5.59 (q, *J*=6.6 Hz, 1H), 4.49 - 4.59 (m, 1H), 3.81 (br dd, *J*=13.6, 4.5 Hz, 1H), 3.64 (dd, *J*=10.2, 6.8 Hz, 1H), 3.44 - 3.52 (m, 2H), 3.35 - 3.44 (m, 1H), 3.28 - 3.31 (m, 1H), 2.85 - 3.06 (m, 2H), 2.72 (br d, *J*=16.1 Hz, 1H), 2.23 - 2.32 (m, 1H), 2.02 - 2.12 (m, 1H), 1.52 (d, *J*=6.7 Hz, 3H), 1.30 - 1.38 (m, 2H), 1.21 - 1.30 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.76 (br s, 1H), 8.02 (t, *J*=8.9 Hz, 1H), 7.09 - 7.26 (m, 3H), 7.05 - 7.09 (m, 1H), 6.92 - 6.97 (m, 1H), 6.78 (s, 1H), 6.55 (br d, *J*=8.7 Hz, 1H), 6.49 (br d, *J*=14.7 Hz, 1H), 4.96 (q, *J*=6.9 Hz, 1H), 4.49 - 4.59 (m, 2H), 3.64 (dd, *J*=10.2, 6.8 Hz, 1H), 3.44 - 3.52 (m, 1H), 3.35 - 3.44 (m, 2H), 3.21 - 3.28 (m, 1H), 2.85 - 3.06 (m, 3H), 2.23 - 2.32 (m, 1H), 2.02 - 2.12 (m, 1H), 1.55 (d, *J*=6.7 Hz, 3H), 1.30 - 1.38 (m, 2H), 1.21 - 1.30 (m, 2H).

Compound 77

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.01 (t, *J*=8.8 Hz, 1H), 7.32 (d, *J*=7.6 Hz, 1H), 7.20 - 7.25 (m, 1H), 7.15 - 7.20 (m, 2H), 6.94 (d, *J*=3.8 Hz, 1H), 6.81 (s, 1H), 6.66 (br s, 1H),

6.55 (br d, *J*=8.8 Hz, 1H), 6.52 (br s, 1H), 6.49 (br dd, *J*=14.5, 1.6 Hz, 1H), 5.59 (q, *J*=6.6 Hz, 1H), 5.23 (br s, 1H), 3.81 (br dd, *J*=13.9, 3.5 Hz, 1H), 3.60 (dd, *J*=11.5, 4.6 Hz, 1H), 3.41 - 3.51 (m, 2H), 3.33 - 3.41 (m, 2H), 2.83 - 3.06 (m, 2H), 2.72 (br d, *J*=16.4 Hz, 1H), 2.19 - 2.29 (m, 1H), 2.06 - 2.13 (m, 1H), 1.52 (d, *J*=6.6 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.21 - 1.30 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.01 (t, *J*=8.8 Hz, 1H), 7.15 - 7.20 (m, 2H), 7.10 - 7.14 (m, 1H), 7.08 (d, *J*=7.3 Hz, 1H), 6.93 (d, *J*=3.8 Hz, 1H), 6.77 (s, 1H), 6.66 (br s, 1H), 6.55 (br d, *J*=8.8 Hz, 1H), 6.52 (br s, 1H), 6.49 (br dd, *J*=14.5, 1.6 Hz, 1H), 5.23 (br s, 1H), 4.96 (q, *J*=6.7 Hz, 1H), 4.55 (br dd, *J*=12.3, 3.8 Hz, 1H), 3.60 (dd, *J*=11.5, 4.6 Hz, 1H), 3.41 - 3.51 (m, 2H), 3.33 - 3.41 (m, 1H), 3.22 - 3.30 (m, 1H), 2.83 - 3.06 (m, 3H), 2.19 - 2.29 (m, 1H), 2.06 - 2.13 (m, 1H), 1.55 (d, *J*=6.6 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.21 - 1.30 (m, 2H).

Compound 78

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.01 (t, *J*=8.8 Hz, 1H), 7.32 (d, *J*=7.3 Hz, 1H), 7.21 - 7.25 (m, 1H), 7.15 - 7.21 (m, 2H), 6.94 (d, *J*=3.5 Hz, 1H), 6.81 (s, 1H), 6.66 (br s, 1H), 6.54 (br d, *J*=8.8 Hz, 1H), 6.52 (br s, 1H), 6.49 (br d, *J*=14.8 Hz, 1H), 5.59 (q, *J*=6.5 Hz, 1H), 5.23 (br s, 1H), 3.81 (br dd, *J*=14.3, 4.3 Hz, 1H), 3.60 (dd, *J*=11.5, 4.6 Hz, 1H), 3.33 - 3.50 (m, 4H), 2.82 - 3.06 (m, 2H), 2.72 (br d, *J*=16.4 Hz, 1H), 2.19 - 2.29 (m, 1H), 2.05 - 2.14 (m, 1H), 1.52 (d, *J*=6.6 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.21 - 1.29 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.01 (t, *J*=8.8 Hz, 1H), 7.15 - 7.21 (m, 2H), 7.10 - 7.15 (m, 1H), 7.08 (d, *J*=7.3 Hz, 1H), 6.93 (d, *J*=3.8 Hz, 1H), 6.77 (s, 1H), 6.66 (br s, 1H), 6.54 (br d, *J*=8.8 Hz, 1H), 6.52 (br s, 1H), 6.49 (br d, *J*=14.8 Hz, 1H), 5.23 (br s, 1H), 4.96 (q, *J*=6.8 Hz, 1H), 4.51 - 4.58 (m, 1H), 3.60 (dd, *J*=11.5, 4.6 Hz, 1H), 3.33 - 3.50 (m, 3H), 3.23 - 3.30 (m, 1H), 2.82 - 3.06 (m, 3H), 2.19 - 2.29 (m, 1H), 2.05 - 2.14 (m, 1H), 1.55 (d, *J*=6.6 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.21 - 1.29 (m, 2H).

Compound 79

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.00 (br t, *J*=8.7 Hz, 1H), 7.38 (br s, 1H), 7.32 (br d, *J*=7.3 Hz, 1H), 7.10 - 7.26 (m, 3H), 6.98 - 7.03 (m, 1H), 6.93 (br d, *J*=8.6 Hz, 1H), 6.84 - 6.90 (m, 2H), 5.59 (q, *J*=6.8 Hz, 1H), 3.91 - 4.01 (m, 1H), 3.77 - 3.86 (m, 1H), 3.42 - 3.52 (m, 1H), 3.17 - 3.32 (m, 4H), 2.68 - 3.15 (m, 6H), 2.02 - 2.21 (m, 2H), 1.52 (d, *J*=6.7 Hz, 3H), 1.31 - 1.39 (m, 2H), 1.21 - 1.30 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.00 (br t, *J*=8.7 Hz, 1H), 7.38 (br s, 1H), 7.10 - 7.26 (m, 3H), 7.08 (br d, *J*=7.2 Hz, 1H), 6.98 - 7.03 (m, 1H), 6.93 (br d, *J*=8.6 Hz, 1H), 6.84 - 6.90 (m, 1H), 6.84 - 6.91 (m, 1H), 6.82 (s, 1H), 4.96 (q, *J*=6.4 Hz, 1H), 4.52 - 4.59 (m, 1H), 3.91 - 4.01 (m, 1H), 3.17 - 3.32 (m, 4H), 2.68 - 3.15 (m, 7H), 2.02 - 2.21 (m, 2H), 1.55 (br d, *J*=6.6 Hz, 3H), 1.31 - 1.39 (m, 2H), 1.21 - 1.30 (m, 2H).

Compound 80

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.00 (t, *J*=8.8 Hz, 1H), 7.41 (s, 1H), 7.32 (d, *J*=7.3 Hz, 1H), 7.14 - 7.25 (m, 3H), 7.04 (s, 1H), 6.93 (d, *J*=3.8 Hz, 1H), 6.80 (s, 1H), 6.54 (dd, *J*=8.8, 2.2 Hz, 1H), 6.43 (dd, *J*=14.8, 1.9 Hz, 1H), 5.59 (q, *J*=6.8 Hz, 1H), 4.20 (quin, *J*=6.5 Hz, 1H), 3.82 (ddd, *J*=9.8, 5.4, 1.3 Hz, 1H), 3.41 - 3.50 (m, 2H), 3.17 - 3.25 (m, 1H), 2.86 - 3.08 (m, 3H), 2.72 (br d, *J*=16.1 Hz, 1H), 2.27 - 2.35 (m, 1H), 1.96 - 2.04 (m, 1H), 1.52 (d, *J*=6.6 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.21 - 1.30 (m, 2H), 1.02 (d, *J*=6.3 Hz, 3H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.00 (t, *J*=8.8 Hz, 1H), 7.41 (s, 1H), 7.14 - 7.25 (m, 2H), 7.10 - 7.15 (m, 1H), 7.06 - 7.09 (m, 1H), 7.04 (s, 1H), 6.92 (d, *J*=3.8 Hz, 1H), 6.77 (s, 1H), 6.54 (dd, *J*=8.8, 2.2 Hz, 1H), 6.43 (dd, *J*=14.8, 1.9 Hz, 1H), 4.96 (q, *J*=6.5 Hz, 1H), 4.55 (ddd, *J*=12.9, 5.7, 1.9 Hz, 1H), 4.20 (quin, *J*=6.5 Hz, 1H), 3.41 - 3.50 (m, 1H), 3.25 - 3.29 (m, 1H), 3.17 - 3.25 (m, 1H), 2.86 - 3.08 (m, 4H), 2.27 - 2.35 (m, 1H), 1.96 - 2.04 (m, 1H), 1.55 (d, *J*=6.6 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.21 - 1.30 (m, 2H), 1.02 (d, *J*=6.3 Hz, 3H).

Compound 81

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.98 (t, *J*=8.8 Hz, 1H), 7.47 (br s, 1H), 7.32 (d, *J*=7.6 Hz, 1H), 7.06 - 7.25 (m, 3H), 6.87 - 6.98 (m, 2H), 6.80 (s, 1H), 6.53 (dd, *J*=9.0, 1.7 Hz, 1H), 6.44 (br d, *J*=14.8 Hz, 1H), 5.59 (q, *J*=6.9 Hz, 1H), 4.01 - 4.08 (m, 1H), 3.82 (br dd, *J*=13.2, 4.1 Hz, 1H), 3.35 - 3.50 (m, 2H), 3.21 - 3.30 (m, 1H), 2.82 - 3.05 (m, 2H), 2.68 - 2.75 (m, 2H), 2.20 - 2.29 (m, 1H), 2.06 - 2.15 (m, 1H), 1.52 (d, *J*=6.9 Hz, 3H), 1.29 - 1.37 (m, 2H), 1.25 - 1.29 (m, 2H), 1.22 (br d, *J*=6.3 Hz, 3H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.98 (t, *J*=8.8 Hz, 1H), 7.47 (br s, 1H), 7.06 - 7.25 (m, 4H), 6.87 - 6.98 (m, 2H), 6.76 (s, 1H), 6.53 (dd, *J*=9.0, 1.7 Hz, 1H), 6.44 (br d, *J*=14.8 Hz, 1H), 4.97 (q, *J*=7.1 Hz, 1H), 4.55 (br dd, *J*=12.6, 3.8 Hz, 1H), 4.01 - 4.08 (m, 1H),

3.35 - 3.50 (m, 2H), 3.22 - 3.30 (m, 1H), 2.82 - 3.05 (m, 3H), 2.68 - 2.75 (m, 1H), 2.20 - 2.29 (m, 1H), 2.06 - 2.15 (m, 1H), 1.55 (d, *J*=6.6 Hz, 3H), 1.29 - 1.37 (m, 2H), 1.25 - 1.29 (m, 2H), 1.22 (br d, *J*=6.3 Hz, 3H).

Compound 82

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.98 (t, *J*=8.8 Hz, 1H), 7.47 (br s, 1H), 7.32 (d, *J*=7.3 Hz, 1H), 7.21 - 7.25 (m, 1H), 7.15 - 7.21 (m, 2H), 6.87 - 6.96 (m, 2H), 6.80 (s, 1H), 6.53 (br d, *J*=8.8 Hz, 1H), 6.44 (dd, *J*=15.0, 1.7 Hz, 1H), 5.58 (q, *J*=6.5 Hz, 1H), 4.00 - 4.08 (m, 1H), 3.82 (br dd, *J*=13.9, 3.8 Hz, 1H), 3.40 - 3.50 (m, 2H), 3.28 - 3.35 (m, 1H obscured by H_2O peak), 2.82 - 3.06 (m, 2H), 2.68 - 2.76 (m, 2H), 2.19 - 2.29 (m, 1H), 2.06 - 2.14 (m, 1H), 1.52 (d, *J*=6.6 Hz, 3H), 1.30 - 1.38 (m, 2H), 1.25 - 1.30 (m, 2H), 1.22 (d, *J*=6.3 Hz, 3H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.98 (t, *J*=8.8 Hz, 1H), 7.47 (br s, 1H), 7.15 - 7.21 (m, 2H), 7.10 - 7.14 (m, 1H), 7.06 - 7.10 (m, 1H), 6.87 - 6.96 (m, 2H), 6.76 (s, 1H), 6.53 (br d, *J*=8.8 Hz, 1H), 6.44 (dd, *J*=15.0, 1.7 Hz, 1H), 4.97 (q, *J*=6.5 Hz, 1H), 4.55 (br dd, *J*=12.8, 3.6 Hz, 1H), 4.00 - 4.08 (m, 1H), 3.40 - 3.50 (m, 1H), 3.28 - 3.35 (m, 1H obscured by H_2O peak), 3.21 - 3.27 (m, 1H), 2.82 - 3.06 (m, 3H), 2.68 - 2.76 (m, 1H), 2.19 - 2.29 (m, 1H), 2.06 - 2.14 (m, 1H), 1.55 (d, *J*=6.6 Hz, 3H), 1.30 - 1.38 (m, 2H), 1.25 - 1.30 (m, 2H), 1.22 (d, *J*=6.3 Hz, 3H).

Compound 83

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.00 (t, *J*=8.8 Hz, 1H), 7.41 (s, 1H), 7.32 (d, *J*=7.3 Hz, 1H), 7.15 - 7.26 (m, 3H), 7.04 (s, 1H), 6.93 (d, *J*=3.5 Hz, 1H), 6.80 (s, 1H), 6.54 (br d, *J*=8.8 Hz, 1H), 6.43 (dd, *J*=14.8, 1.6 Hz, 1H), 5.59 (q, *J*=6.6 Hz, 1H), 4.20 (quin, *J*=6.5 Hz, 1H), 3.82 (br dd, *J*=13.6, 3.8 Hz, 1H), 3.41 - 3.50 (m, 2H), 3.17 - 3.25 (m, 1H), 2.86 - 3.07 (m, 3H), 2.72 (br d, *J*=16.1 Hz, 1H), 2.27 - 2.35 (m, 1H), 2.00 (dt, *J*=12.6, 6.6 Hz, 1H), 1.52 (d, *J*=6.6 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.21 - 1.29 (m, 2H), 1.02 (d, *J*=6.3 Hz, 3H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.00 (t, *J*=8.8 Hz, 1H), 7.41 (s, 1H), 7.15 - 7.26 (m, 2H), 7.10 - 7.15 (m, 1H), 7.06 - 7.09 (m, 1H), 7.04 (s, 1H), 6.92 (d, *J*=3.8 Hz, 1H), 6.77 (s, 1H), 6.54 (br d, *J*=8.8 Hz, 1H), 6.43 (dd, *J*=14.8, 1.6 Hz, 1H), 4.97 (q, *J*=6.6 Hz, 1H), 4.55 (br dd, *J*=12.9, 3.2 Hz, 1H), 4.20 (quin, *J*=6.5 Hz, 1H), 3.41 - 3.50 (m, 1H), 3.25 - 3.29 (m, 1H), 3.17 - 3.25 (m, 1H), 2.86 - 3.07 (m, 4H), 2.27 - 2.35 (m, 1H), 2.00 (dt, *J*=12.6, 6.6 Hz,

1H), 1.55 (d, *J*=6.9 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.21 - 1.29 (m, 2H), 1.02 (d, *J*=6.3 Hz, 3H).

Compound 84

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.31 (d, *J*=7.8 Hz, 1H), 8.89 (d, *J*=4.0 Hz, 1H), 8.15 - 8.23 (m, 1H), 8.05 (t, *J*=8.8 Hz, 1H), 7.91 (s, 1H), 7.65 - 7.72 (m, 1H), 7.52 (br s, 1H), 7.34 (d, *J*=7.2 Hz, 1H), 7.06 - 7.27 (m, 4H), 7.02 (br s, 1H), 6.55 (dd, *J*=8.9, 1.8 Hz, 1H), 6.48 (dd, *J*=14.6, 1.7 Hz, 1H), 5.64 (q, *J*=6.5 Hz, 1H), 4.07 (br dd, *J*=13.0, 4.2 Hz, 1H), 3.48 - 3.54 (m, 2H), 3.34 - 3.47 (m, 3H), 3.00 - 3.14 (m, 2H), 2.77 (br d, *J*=16.6 Hz, 1H), 2.16 - 2.26 (m, 1H), 2.07 - 2.16 (m, 1H), 1.56 (d, *J*=6.7 Hz, 3H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.30 (d, *J*=8.3 Hz, 1H), 8.86 (br d, *J*=4.3 Hz, 1H), 8.15 - 8.23 (m, 1H), 8.05 (t, *J*=8.8 Hz, 1H), 7.86 (s, 1H), 7.65 - 7.72 (m, 1H), 7.52 (br s, 1H), 7.06 - 7.27 (m, 5H), 7.02 (br s, 1H), 6.55 (dd, *J*=8.9, 1.8 Hz, 1H), 6.48 (dd, *J*=14.6, 1.7 Hz, 1H), 5.17 (q, *J*=7.0 Hz, 1H), 4.57 - 4.64 (m, 1H), 3.55 - 3.59 (m, 1H), 3.34 - 3.47 (m, 3H), 3.27 - 3.31 (m, 1H), 3.00 - 3.14 (m, 1H), 2.93 - 3.00 (m, 1H), 2.84 - 2.91 (m, 1H), 2.16 - 2.26 (m, 1H), 2.07 - 2.16 (m, 1H), 1.61 (d, *J*=6.8 Hz, 3H).

Compound 85

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.38 (br t, *J*=9.3 Hz, 1H), 7.32 (br d, *J*=7.5 Hz, 1H), 7.15 - 7.26 (m, 3H), 6.93 - 6.97 (m, 1H), 6.83 (s, 1H), 6.58 (br d, *J*=8.3 Hz, 1H), 6.46 - 6.72 (m, 2H), 5.58 (q, *J*=7.0 Hz, 1H), 5.21 (br s, 1H), 3.76 - 3.85 (m, 1H), 3.60 - 3.71 (m, 2H), 3.52 - 3.59 (m, 1H), 3.41 - 3.52 (m, 2H), 2.81 - 3.07 (m, 2H), 2.72 (br d, *J*=16.5 Hz, 1H), 2.18 - 2.29 (m, 1H), 2.06 - 2.15 (m, 1H), 1.52 (br d, *J*=6.7 Hz, 3H), 1.30 - 1.39 (m, 2H), 1.21 - 1.30 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.38 (br t, *J*=9.3 Hz, 1H), 7.15 - 7.26 (m, 2H), 7.09 - 7.15 (m, 1H), 7.08 (br d, *J*=7.6 Hz, 1H), 6.93 - 6.97 (m, 1H), 6.80 (s, 1H), 6.58 (br d, *J*=8.3 Hz, 1H), 6.46 - 6.72 (m, 2H), 5.21 (br s, 1H), 4.96 (q, *J*=7.0 Hz, 1H), 4.51 - 4.58 (m, 1H), 3.60 - 3.71 (m, 2H), 3.52 - 3.59 (m, 1H), 3.41 - 3.52 (m, 2H), 2.81 - 3.07 (m, 3H), 2.18 - 2.29 (m, 1H), 2.06 - 2.15 (m, 1H), 1.55 (br d, *J*=6.8 Hz, 3H), 1.30 - 1.39 (m, 2H), 1.21 - 1.30 (m, 2H).

Compound 86

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.52 (br s, 1H), 7.32 (d, *J*=7.6 Hz, 1H), 7.09 - 7.25 (m, 3H), 7.01 (br s, 1H), 6.82 (d, *J*=12.0 Hz, 2H), 6.00 (s, 1H), 5.59 (q, *J*=6.6 Hz, 1H), 3.89 (s, 3H), 3.82 (br dd, *J*=13.7, 3.6 Hz, 1H), 3.62 - 3.70 (m, 1H), 3.54 - 3.62 (m, 1H), 3.48 - 3.54 (m, 1H), 3.44 - 3.48 (m, 1H), 3.39 - 3.44 (m, 1H), 3.07 (quin, *J*=7.6 Hz, 1H), 2.81 - 2.95 (m, 2H), 2.71 (br d, *J*=16.4 Hz, 1H), 2.14 - 2.23 (m, 1H), 2.04 - 2.14 (m, 1H), 1.52 (d, *J*=6.9 Hz, 3H), 1.22 - 1.35 (m, 4H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.52 (br s, 1H), 7.09 - 7.21 (m, 4H), 7.01 (br s, 1H), 6.80 (d, *J*=22.1 Hz, 2H), 6.00 (s, 1H), 4.96 (q, *J*=6.7 Hz, 1H), 4.55 (br dd, *J*=13.1, 3.0 Hz, 1H), 3.89 (s, 3H), 3.62 - 3.70 (m, 1H), 3.54 - 3.62 (m, 1H), 3.48 - 3.54 (m, 1H), 3.39 - 3.44 (m, 1H), 3.21 - 3.30 (m, 1H), 3.07 (quin, *J*=7.6 Hz, 1H), 2.96 - 3.04 (m, 2H), 2.81 - 2.95 (m, 1H), 2.14 - 2.23 (m, 1H), 2.04 - 2.14 (m, 1H), 1.54 (d, *J*=6.6 Hz, 3H), 1.22 - 1.35 (m, 4H).

Compound 87

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.50 (br s, 1H), 7.32 (d, *J*=7.6 Hz, 1H), 7.07 - 7.25 (m, 3H), 7.00 (br s, 1H), 6.92 (s, 1H), 6.80 (s, 1H), 6.02 (s, 1H), 5.58 (q, *J*=6.8 Hz, 1H), 4.26 - 4.33 (m, 2H), 3.80 (br dd, *J*=13.9, 3.8 Hz, 1H), 3.67 - 3.72 (m, 2H), 3.64 (br t, *J*=9.1 Hz, 1H), 3.53 - 3.61 (m, 1H), 3.50 (dd, *J*=10.4, 6.9 Hz, 1H), 3.37 - 3.48 (m, 2H), 3.29 (s, 3H), 3.03 - 3.10 (m, 1H), 2.82 - 2.96 (m, 2H), 2.71 (br d, *J*=16.1 Hz, 1H), 2.14 - 2.22 (m, 1H), 2.04 - 2.13 (m, 1H), 1.52 (d, *J*=6.9 Hz, 3H), 1.23 - 1.34 (m, 4H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.50 (br s, 1H), 7.07 - 7.25 (m, 4H), 7.00 (br s, 1H), 6.92 (s, 1H), 6.77 (s, 1H), 6.02 (s, 1H), 4.96 (q, *J*=6.1 Hz, 1H), 4.55 (br dd, *J*=11.7, 4.4 Hz, 1H), 4.26 - 4.33 (m, 2H), 3.67 - 3.72 (m, 2H), 3.64 (br t, *J*=9.1 Hz, 1H), 3.53 - 3.61 (m, 1H), 3.50 (dd, *J*=10.4, 6.9 Hz, 1H), 3.37 - 3.48 (m, 1H), 3.28 (s, 3H), 3.23 - 3.28 (m, 1H), 3.03 - 3.10 (m, 1H), 2.96 - 3.03 (m, 2H), 2.82 - 2.96 (m, 1H), 2.14 - 2.22 (m, 1H), 2.04 - 2.13 (m, 1H), 1.54 (d, *J*=6.6 Hz, 3H), 1.23 - 1.34 (m, 4H).

Compound 88

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.08 (d, *J*=5.7 Hz, 1H), 7.53 (br s, 1H), 7.32 (d, *J*=7.6 Hz, 1H), 7.04 - 7.26 (m, 4H), 7.01 (br s, 1H), 6.84 (s, 1H), 5.59 (q, *J*=6.9 Hz, 1H),

3.80 (br dd, *J*=13.9, 3.5 Hz, 1H), 3.74 (dd, *J*=10.7, 7.9 Hz, 1H), 3.58 - 3.69 (m, 2H), 3.43 - 3.57 (m, 2H), 3.08 - 3.15 (m, 1H), 2.83 - 3.05 (m, 2H), 2.72 (br d, *J*=16.1 Hz, 1H), 2.19 - 2.28 (m, 1H), 2.09 - 2.17 (m, 1H), 1.52 (d, *J*=6.9 Hz, 3H), 1.31 - 1.38 (m, 2H), 1.22 - 1.30 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.08 (d, *J*=5.7 Hz, 1H), 7.53 (br s, 1H), 7.04 - 7.26 (m, 5H), 7.01 (br s, 1H), 6.80 (s, 1H), 4.96 (q, *J*=7.0 Hz, 1H), 4.55 (br dd, *J*=12.9, 3.2 Hz, 1H), 3.74 (dd, *J*=10.7, 7.9 Hz, 1H), 3.58 - 3.69 (m, 2H), 3.43 - 3.57 (m, 2H), 3.08 - 3.15 (m, 1H), 2.83 - 3.05 (m, 3H), 2.19 - 2.28 (m, 1H), 2.09 - 2.17 (m, 1H), 1.54 (d, *J*=6.6 Hz, 3H), 1.31 - 1.38 (m, 2H), 1.22 - 1.30 (m, 2H).

Compound 89

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.50 (br s, 1H), 7.32 (d, *J*=7.6 Hz, 1H), 7.10 - 7.25 (m, 3H), 6.99 (s, 1H), 6.84 (s, 1H), 6.81 (d, *J*=2.2 Hz, 1H), 6.36 (br s, 1H), 6.30 (dd, *J*=13.6, 1.9 Hz, 1H), 5.59 (q, *J*=6.6 Hz, 1H), 3.84 (br dd, *J*=13.9, 3.8 Hz, 1H), 3.44 - 3.51 (m, 2H), 3.34 - 3.42 (m, 2H), 3.23 - 3.31 (m, 1H), 3.07 (quin, *J*=7.8 Hz, 1H), 2.82 - 2.96 (m, 2H), 2.72 (br d, *J*=16.4 Hz, 1H), 2.37 (s, 3H), 2.15 - 2.23 (m, 1H), 2.05 - 2.14 (m, 1H), 1.52 (d, *J*=6.9 Hz, 3H), 1.22 - 1.34 (m, 4H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.50 (br s, 1H), 7.10 - 7.25 (m, 4H), 6.99 (s, 1H), 6.81 (s, 1H), 6.81 (d, *J*=2.2 Hz, 1H), 6.36 (br s, 1H), 6.30 (dd, *J*=13.6, 1.9 Hz, 1H), 4.99 (q, *J*=6.6 Hz, 1H), 4.56 (br dd, *J*=12.8, 3.3 Hz, 1H), 3.44 - 3.51 (m, 1H), 3.34 - 3.42 (m, 2H), 3.23 - 3.31 (m, 2H), 3.07 (quin, *J*=7.8 Hz, 1H), 2.96 - 3.04 (m, 2H), 2.82 - 2.96 (m, 1H), 2.37 (s, 3H), 2.15 - 2.23 (m, 1H), 2.05 - 2.14 (m, 1H), 1.55 (d, *J*=6.6 Hz, 3H), 1.22 - 1.34 (m, 4H).

Compound 90

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.35 (s, 1H), 8.85 (d, *J*=2.5 Hz, 1H), 8.68 - 8.73 (m, 1H), 7.90 (t, *J*=8.8 Hz, 1H), 7.62 (s, 1H), 7.51 (br s, 1H), 7.34 (d, *J*=7.3 Hz, 1H), 7.06 - 7.27 (m, 4H), 7.00 (br s, 1H), 6.53 (br d, *J*=8.8 Hz, 1H), 6.46 (dd, *J*=14.8, 1.9 Hz, 1H), 5.64 (q, *J*=6.8 Hz, 1H), 3.96 (br dd, *J*=13.9, 4.7 Hz, 1H), 3.51 - 3.58 (m, 1H), 3.46 - 3.51 (m, 1H), 3.29 - 3.45 (m, 3H partially obscured by H_2O peak), 3.03 - 3.12 (m, 2H), 2.76 (br d, *J*=16.4 Hz, 1H), 2.16 - 2.24 (m, 1H), 2.05 - 2.14 (m, 1H), 1.56 (d, *J*=6.6 Hz, 3H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.31 (s, 1H), 8.84 (d, *J*=2.8 Hz, 1H), 8.65 - 8.70 (m, 1H), 7.90 (t, *J*=8.8 Hz, 1H), 7.58 (s, 1H), 7.51 (br s, 1H), 7.06 - 7.27 (m, 5H), 7.00 (br s, 1H), 6.53 (br d, *J*=8.8 Hz, 1H), 6.46 (dd, *J*=14.8, 1.9 Hz, 1H), 5.12 (q, *J*=6.8 Hz, 1H), 4.56 - 4.63 (m, 1H), 3.46 - 3.51 (m, 1H), 3.29 - 3.45 (m, 4H partially obscured by H_2O peak), 3.03 - 3.12 (m, 1H), 2.84 - 2.99 (m, 2H), 2.16 - 2.24 (m, 1H), 2.05 - 2.14 (m, 1H), 1.62 (d, *J*=6.6 Hz, 3H).

Compound 91

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.00 (t, *J*=8.5 Hz, 1H), 7.51 (br s, 1H), 7.32 (d, *J*=7.6 Hz, 1H), 7.14 - 7.25 (m, 3H), 7.03 - 7.09 (m, 1H), 6.95 (d, *J*=3.5 Hz, 1H), 6.82 (s, 1H), 6.36 - 6.43 (m, 2H), 5.58 (q, *J*=6.6 Hz, 1H), 4.05 (t, *J*=8.0 Hz, 2H), 3.91 (t, *J*=6.8 Hz, 2H), 3.81 (br dd, *J*=13.7, 3.9 Hz, 1H), 3.43 - 3.51 (m, 2H), 2.83 - 3.05 (m, 2H), 2.72 (br d, *J*=16.1 Hz, 1H), 1.52 (d, *J*=6.9 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.22 - 1.30 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.00 (t, *J*=8.5 Hz, 1H), 7.51 (br s, 1H), 7.14 - 7.25 (m, 2H), 7.10 - 7.14 (m, 1H), 7.03 - 7.09 (m, 2H), 6.94 (d, *J*=3.8 Hz, 1H), 6.78 (s, 1H), 6.36 - 6.43 (m, 2H), 4.96 (m, 1H), 4.52 - 4.58 (m, 1H), 4.05 (t, *J*=8.0 Hz, 2H), 3.91 (t, *J*=6.8 Hz, 2H), 3.43 - 3.51 (m, 1H), 3.23 - 3.30 (m, 1H), 2.83 - 3.05 (m, 3H), 1.55 (d, *J*=6.6 Hz, 3H), 1.30 - 1.37 (m, 2H), 1.22 - 1.30 (m, 2H).

Compound 92

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.35 (t, *J*=9.1 Hz, 1H), 7.38 (br s, 1H), 7.32 (br d, *J*=7.1 Hz, 1H), 7.05 - 7.26 (m, 3H), 6.92 - 6.96 (m, 1H), 6.87 (br s, 1H), 6.84 (s, 1H), 6.41 (br d, *J*=7.8 Hz, 1H), 5.58 (q, *J*=6.7 Hz, 1H), 4.16 (t, *J*=8.3 Hz, 2H), 3.80 (br dd, *J*=13.8, 3.8 Hz, 1H), 3.73 (dd, *J*=8.4, 5.8 Hz, 2H), 3.41 - 3.51 (m, 1H), 2.85 - 3.07 (m, 3H), 2.71 (br d, *J*=16.6 Hz, 1H), 2.43 - 2.47 (m, 2H partially obscured by DMSO peak), 1.52 (d, *J*=6.8 Hz, 3H), 1.30 - 1.38 (m, 2H), 1.20 - 1.29 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.35 (t, *J*=9.1 Hz, 1H), 7.38 (br s, 1H), 7.05 - 7.26 (m, 4H), 6.92 - 6.96 (m, 1H), 6.87 (br s, 1H), 6.80 (s, 1H), 6.41 (br d, *J*=7.8 Hz, 1H), 4.95 (q, *J*=6.8 Hz, 1H), 4.51 - 4.59 (m, 1H), 4.16 (t, *J*=8.3 Hz, 2H), 3.73 (dd, *J*=8.4, 5.8 Hz, 2H), 3.22 - 3.31 (m, 1H), 2.85 - 3.07 (m, 4H), 2.43 - 2.47 (m, 2H partially obscured by DMSO peak), 1.55 (br d, *J*=6.7 Hz, 3H), 1.30 - 1.38 (m, 2H), 1.20 - 1.29 (m, 2H).

Compound 93:

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.99 (t, *J*=8.6 Hz, 1 H), 7.32 (br d, *J*=7.3 Hz, 1 H), 7.10 - 7.28 (m, 3 H), 6.89 - 6.98 (m, 1 H), 6.80 (s, 1 H), 6.49 (br d, *J*=9.4 Hz, 1 H), 6.40 (br d, *J*=14.7 Hz, 1 H), 5.54 – 5.63 (m, 1 H), 3.75 – 3.86 (m, 1 H), 3.19 - 3.66 (m, 6 H), 2.68 - 3.06 (m, 4 H), 2.01 - 2.16 (m, 2 H), 1.72 - 1.80 (m, 1 H), 1.46 - 1.59 (m, 3 H), 1.19 - 1.39 (m, 4 H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.99 (t, *J*=8.6 Hz, 1 H), 7.10 - 7.28 (m, 3 H), 7.07 (br d, *J*=7.5 Hz, 1 H), 6.89 - 6.98 (m, 1 H), 6.77 (s, 1 H), 6.49 (br d, *J*=9.4 Hz, 1 H), 6.40 (br d, *J*=14.7 Hz, 1 H), 4.91 - 5.00 (m, 1 H), 4.50 – 4.60 (m, 1 H), 3.19 - 3.66 (m, 6 H), 2.68 - 3.06 (m, 4 H), 2.01 - 2.16 (m, 2 H), 1.72 - 1.80 (m, 1 H), 1.46 - 1.59 (m, 3 H), 1.19 - 1.39 (m, 4 H).

Compound 94:

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.00 (t, *J*=8.8 Hz, 1 H), 7.32 (d, *J*=7.6 Hz, 1 H), 7.10 - 7.26 (m, 3 H), 6.87 - 7.00 (m, 1 H), 6.80 (s, 1 H), 6.50 (br d, *J*=8.7 Hz, 1 H), 6.43 (br d, *J*=14.9 Hz, 1 H), 5.59 (q, *J*=6.8 Hz, 1 H), 3.81 (br dd, *J*=14.0, 4.2 Hz, 1 H), 3.31 - 3.60 (m, 7 H), 3.06 – 3.15 (m, 1 H), 2.68 - 3.14 (m, 4 H), 2.03 - 2.21 (m, 1 H), 1.78 - 1.95 (m, 1 H), 1.45 - 1.60 (m, 3 H), 1.17 - 1.43 (m, 4 H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.00 (t, *J*=8.8 Hz, 1 H), 7.10 - 7.26 (m, 3 H), 7.08 (d, *J*=7.5 Hz, 1 H), 6.87 - 7.00 (m, 1 H), 6.77 (s, 1 H), 6.50 (br d, *J*=8.7 Hz, 1 H), 6.43 (br d, *J*=14.9 Hz, 1 H), 4.96 (d, *J*=6.6 Hz, 1 H), 4.50 - 4.60 (m, 1 H), 3.31 - 3.60 (m, 7 H), 3.06 – 3.15 (m, 1 H), 2.68 - 3.14 (m, 4 H), 2.03 - 2.21 (m, 1 H), 1.78 - 1.95 (m, 1 H), 1.45 - 1.60 (m, 3 H), 1.17 - 1.43 (m, 4 H).

Compound 95:

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.99 (t, *J*=8.8 Hz, 1 H) 7.31 (br d, *J*=7.6 Hz, 1 H) 7.04 - 7.27 (m, 3 H) 6.90 - 6.97 (m, 1 H) 6.70 - 6.88 (m, 1 H) 6.48 (br d, *J*=8.8 Hz, 1 H) 6.40 (dd, *J*=14.7, 1.4 Hz, 1 H) 5.59 (q, *J*=6.5 Hz, 1 H) 4.89 - 5.01 (m, 2 H) 4.18 (br d, *J*=3.5 Hz, 2 H) 3.82 (br dd, *J*=13.4, 3.9 Hz, 1 H) 3.40 - 3.55 (m, 3 H) 3.18 (br dd, *J*=9.8, 3.8 Hz, 2 H) 2.81 - 3.05 (m, 2 H) 2.65 - 2.78 (m, 1 H) 1.48 - 1.58 (m, 3 H) 1.19 - 1.39 (m, 4 H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.99 (t, *J*=8.8 Hz, 1 H) 7.04 - 7.27 (m, 4 H) 6.90 - 6.97 (m, 1 H) 6.70 - 6.88 (m, 1 H) 6.48 (br d, *J*=8.8 Hz, 1 H) 6.40 (dd, *J*=14.7, 1.4 Hz, 1 H) 4.89 - 5.01 (m, 3 H) 4.55 (br dd, *J*=12.9, 3.2 Hz, 1 H) 4.18 (br d, *J*=3.5 Hz, 2 H) 3.40 - 3.55 (m, 2 H) 3.23 - 3.28 (m, 1 H) 3.18 (br dd, *J*=9.8, 3.8 Hz, 2 H) 2.81 - 3.05 (m, 3 H) 1.48 - 1.58 (m, 3 H) 1.19 - 1.39 (m, 4 H).

Compound 96:

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.99 (t, *J*=8.5 Hz, 1 H) 7.32 (d, *J*=7.3 Hz, 1 H) 7.07 - 7.25 (m, 3 H) 6.91 - 6.95 (m, 1 H) 6.76 - 6.82 (m, 1 H) 6.52 (dd, *J*=8.8, 1.9 Hz, 1 H) 6.45 (dd, *J*=14.7, 2.0 Hz, 1 H) 5.59 (q, *J*=6.8 Hz, 1 H) 5.31 (d, *J*=3.8 Hz, 1 H) 4.26 (br s, 1 H) 3.78 - 3.85 (m, 2 H) 3.43 - 3.55 (m, 3 H) 3.26 - 3.41 (m, 4 H) 3.20 (d, *J*=10.7 Hz, 1 H) 2.84 - 3.05 (m, 2 H) 2.72 (br d, *J*=16.4 Hz, 1 H) 1.48 - 1.58 (m, 3 H) 1.21 - 1.37 (m, 4 H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.99 (t, *J*=8.5 Hz, 1 H) 7.07 - 7.25 (m, 4 H) 6.91 - 6.95 (m, 1 H) 6.76 - 6.82 (m, 1 H) 6.52 (dd, *J*=8.8, 1.9 Hz, 1 H) 6.45 (dd, *J*=14.7, 2.0 Hz, 1 H) 5.31 (d, *J*=3.8 Hz, 1 H) 4.96 (d, *J*=6.9 Hz, 1 H) 4.52 - 4.58 (m, 1 H) 4.26 (br s, 1 H) 3.78 - 3.85 (m, 1 H) 3.43 - 3.55 (m, 2 H) 3.26 - 3.41 (m, 5 H) 3.20 (d, *J*=10.7 Hz, 1 H) 2.84 - 3.05 (m, 3 H) 1.48 - 1.58 (m, 3 H) 1.21 - 1.37 (m, 4 H).

Compound 97:

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.03 (t, *J*=8.4 Hz, 1 H) 7.32 (d, *J*=7.6 Hz, 1 H) 7.06 - 7.24 (m, 3 H) 6.95 - 6.98 (m, 1 H) 6.78 - 6.83 (m, 1 H) 6.55 - 6.60 (m, 2 H) 6.15 (d, *J*=5.4 Hz, 1 H) 5.59 (q, *J*=6.6 Hz, 1 H) 4.36 - 4.43 (m, 1 H) 3.71 - 3.84 (m, 4 H) 3.43 - 3.50 (m, 1 H) 3.31 - 3.38 (m, 1 H) 2.84 - 3.05 (m, 2 H) 2.72 (br d, *J*=16.1 Hz, 1 H) 1.49 - 1.57 (m, 3 H) 1.22 - 1.38 (m, 4 H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.03 (t, *J*=8.4 Hz, 1 H) 7.06 - 7.24 (m, 4 H) 6.95 - 6.98 (m, 1 H) 6.78 - 6.83 (m, 1 H) 6.55 - 6.60 (m, 2 H) 6.15 (d, *J*=5.4 Hz, 1 H) 4.97 (q, *J*=6.6 Hz, 1 H) 4.52 - 4.58 (m, 1 H) 4.36 - 4.43 (m, 1 H) 3.71 - 3.84 (m, 3 H) 3.31 - 3.38 (m, 1 H) 3.23 - 3.28 (m, 1 H) 2.84 - 3.05 (m, 3 H) 1.49 - 1.57 (m, 3 H) 1.22 - 1.38 (m, 4 H).

Compound 98:

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.98 (t, *J*=8.8 Hz, 1 H) 7.31 (d, *J*=7.3 Hz, 1 H) 7.07 - 7.24 (m, 3 H) 6.91 - 6.95 (m, 1 H) 6.75 - 6.81 (m, 1 H) 6.55 (dd, *J*=8.8, 1.9 Hz, 1 H) 6.49 (dd, *J*=14.8, 1.9 Hz, 1 H) 5.59 (q, *J*=6.8 Hz, 1 H) 4.87 - 4.93 (m, 2 H) 4.83 (d, *J*=3.8 Hz, 1 H) 4.35 - 4.41 (m, 1 H) 4.06 (t, *J*=3.9 Hz, 1 H) 3.82 (br dd, *J*=13.6, 3.8 Hz, 1 H) 3.43 - 3.61 (m, 4 H) 3.38 (dt, *J*=11.7, 6.7 Hz, 1 H) 2.84 - 3.07 (m, 3 H) 2.72 (br d, *J*=16.4 Hz, 1 H) 1.49 - 1.57 (m, 3 H) 1.22 - 1.38 (m, 4 H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.98 (t, *J*=8.8 Hz, 1 H) 7.31 (d, *J*=7.3 Hz, 1 H) 7.07 - 7.24 (m, 3 H) 6.91 - 6.95 (m, 1 H) 6.75 - 6.81 (m, 1 H) 6.55 (dd, *J*=8.8, 1.9 Hz, 1 H) 6.49 (dd, *J*=14.8, 1.9 Hz, 1 H) 4.98 (br d, *J*=6.6 Hz, 1 H) 4.87 - 4.93 (m, 2 H) 4.83 (d, *J*=3.8 Hz, 1 H) 4.52 - 4.57 (m, 1 H) 4.35 - 4.41 (m, 1 H) 4.06 (t, *J*=3.9 Hz, 1 H) 3.43 - 3.61 (m, 3 H) 3.38 (dt, *J*=11.7, 6.7 Hz, 1 H) 3.23 - 3.26 (m, 1 H) 2.84 - 3.07 (m, 4 H) 1.49 - 1.57 (m, 3 H) 1.22 - 1.38 (m, 4 H).

Compound 99:

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.99 (t, *J*=8.8 Hz, 1 H) 7.03 - 7.36 (m, 4 H) 6.87 - 6.99 (m, 1 H) 6.80 (s, 1 H) 6.49 (br d, *J*=8.8 Hz, 1 H) 6.41 (br d, *J*=14.6 Hz, 1 H) 5.59 (q, *J*=6.6 Hz, 1 H) 5.16 (d, *J*=4.5 Hz, 1 H) 3.94 (quin, *J*=4.9 Hz, 1 H) 3.81 (br dd, *J*=13.8, 3.7 Hz, 1 H) 3.50 - 3.63 (m, 2 H) 3.40 - 3.50 (m, 1 H) 2.65 - 3.16 (m, 5 H) 2.13 - 2.23 (m, 1 H) 1.45 - 1.61 (m, 3 H) 1.19 - 1.41 (m, 4 H) 1.02 (d, *J*=6.8 Hz, 3 H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.99 (t, *J*=8.8 Hz, 1 H) 7.03 - 7.36 (m, 4 H) 6.87 - 6.99 (m, 1 H) 6.76 (s, 1 H) 6.49 (br d, *J*=8.8 Hz, 1 H) 6.41 (br d, *J*=14.6 Hz, 1 H) 5.16 (d, *J*=4.5 Hz, 1 H) 4.96 (q, *J*=6.4 Hz, 1 H) 4.49 - 4.61 (m, 1 H) 3.94 (quin, *J*=4.9 Hz, 1 H) 3.50 - 3.63 (m, 2 H) 3.20 - 3.29 (m, 1 H) 2.65 - 3.16 (m, 5 H) 2.13 - 2.23 (m, 1 H) 1.45 - 1.61 (m, 3 H) 1.19 - 1.41 (m, 4 H) 1.02 (d, *J*=6.8 Hz, 3 H).

Compound 100:

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d$_6$) δ ppm 7.99 (t, *J*=8.8, 1 H), 7.32 (d, *J*=7.6 Hz, 1 H), 7.09 – 7.26 (m, 3 H), 6.90 - 6.96 (m, 1 H), 6.80 (s, 1 H), 6.50 (dd, *J*=8.7, 1.7 Hz, 1 H), 6.42 (dd, *J*=14.7, 1.7 Hz, 1 H), 5.55 - 5.62 (m, 1 H), 5.17 (d, *J*=3.2 Hz, 2 H), 4.07 (br s, 2 H), 3.82 (br dd, *J*=13.7, 3.6 Hz, 1H), 3.53 (br dd, *J*=10.2, 3.6 Hz, 2 H), 3.43 - 3.50 (m, 1 H), 3.17 (d, *J*=10.4 Hz, 2 H), 2.68 - 3.06 (m, 3 H), 1.48 - 1.58 (m, 3 H) 1.21 - 1.38 (m, 4 H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.99 (t, *J*=8.8, 1 H), 7.09 – 7.26 (m, 3 H), 7.07 (d, *J*=7.6, 1 H), 6.90 - 6.96 (m, 1 H), 6.76 (s, 1 H), 6.50 (dd, *J*=8.7, 1.7 Hz, 1 H), 6.42 (dd, *J*=14.7, 1.7 Hz, 1 H), 5.17 (d, *J*=3.2 Hz, 2 H), 4.93 - 5.00 (m, 1 H), 4.55 (br dd, *J*=12.9, 3.2 Hz, 1 H), 4.07 (br s, 2 H), 3.53 (br dd, *J*=10.2, 3.6 Hz, 2 H), 3.22 - 3.29 (m, 1 H), 3.17 (d, *J*=10.4 Hz, 2 H), 2.68 - 3.06 (m, 3 H), 1.48 - 1.58 (m, 3 H) 1.21 - 1.38 (m, 4 H).

Compound 101:

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.64 (br s, 1 H) 9.40 (br s, 1 H) 8.00 (t, *J*=8.7 Hz, 1 H) 7.03 - 7.40 (m, 4 H) 6.88 - 7.01 (m, 1 H) 6.81 (s, 1 H) 6.37 - 6.59 (m, 2 H) 5.59 (q, *J*=6.7 Hz, 1 H) 3.81 (br dd, *J*=13.9, 4.1 Hz, 1 H) 3.21 - 3.67 (m, 6 H) 2.71 - 3.12 (m, 3 H) 2.25 (br d, *J*=6.1 Hz, 2 H) 1.48 - 1.60 (m, 3 H) 1.20 - 1.40 (m, 4 H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.64 (br s, 1 H) 9.40 (br s, 1 H) 8.00 (t, *J*=8.7 Hz, 1 H) 7.03 - 7.40 (m, 4 H) 6.88 - 7.01 (m, 1 H) 6.77 (s, 1 H) 6.37 - 6.59 (m, 2 H) 4.96 (q, *J*=6.8 Hz, 1 H) 4.55 (br d, *J*=11.2 Hz, 1 H) 3.21 - 3.67 (m, 6 H) 2.71 - 3.12 (m, 3 H) 2.25 (br d, *J*=6.1 Hz, 2 H) 1.48 - 1.60 (m, 3 H) 1.20 - 1.40 (m, 4 H).

Compound 102:

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.99 (br t, *J*=8.7 Hz, 1 H) 7.03 - 7.34 (m, 4 H) 6.93 (m, 1 H) 6.79 (s, 1 H) 6.50 (d, *J*=8.2 Hz, 1 H) 6.42 (d, *J*=14.8 Hz, 1 H) 5.59 (q, *J*=6.2 Hz, 1 H) 5.16 (br s, 2 H) 4.08 (br s, 2 H) 3.82 (br dd, *J*=13.6, 4.1 Hz, 1 H) 3.51 - 3.57 (m, 2 H) 3.42 - 3.51 (m, 1 H) 3.17 (d, *J*=10.4 Hz, 2 H) 2.69 - 3.08 (m, 3 H) 1.47 - 1.59 (m, 3 H) 1.22 - 1.40 (m, 4 H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.99 (br t, *J*=8.7 Hz, 1 H) 7.03 - 7.34 (m, 4 H) 6.93 (m, 1 H) 6.75 (s, 1 H) 6.50 (d, *J*=8.2 Hz, 1 H) 6.42 (d, *J*=14.8 Hz, 1 H) 5.16 (br s, 2 H) 4.92 - 5.02 (m, 1 H) 4.48 - 4.61 (m, 1 H) 4.08 (br s, 2 H) 3.51 - 3.57 (m, 2 H) 3.22 - 3.27 (m, 1 H) 3.17 (d, *J*=10.4 Hz, 2 H) 2.69 - 3.08 (m, 3 H) 1.47 - 1.59 (m, 3 H) 1.22 - 1.40 (m, 4 H).

Compound 103:

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.00 (t, *J*=8.8 Hz, 1 H), 7.32 (d, *J*=7.7 Hz, 1 H), 7.09 - 7.27 (m, 3 H), 6.89 - 6.96 (m, 1 H), 6.80 (s, 1 H), 6.44 - 6.55 (m, 1 H), 6.31 – 6.44 (m, 1 H), 5.52 – 5.64 (m, 1H), 4.91 (t, *J*=5.6 Hz, 1 H), 4. 85 (s, 1 H), 3.77 - 3.87 (m, 1 H), 3.36 - 3.56 (m, 6 H), 3.12 (br d, *J*=10.3 Hz, 1 H), 2.68 - 3.08 (m, 3 H), 2.02 - 2.17 (m, 1 H), 1.75 - 1.87 (m, 1 H), 1.40 - 1.60 (m, 3 H), 1.19 - 1.39 (m, 4 H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.00 (t, *J*=8.8 Hz, 1 H), 7.09 - 7.27 (m, 3 H), 7.08 (d, *J*=7.1 Hz, 1 H), 6.89 - 6.96 (m, 1 H), 6.76 (s, 1 H), 6.44 - 6.55 (m, 1 H), 6.31 – 6.44 (m, 1 H), 4.88 - 5.00 (m, 2 H), 4.85 (s, 1 H), 4.50 - 4.60 (m, 1 H), 3.36 - 3.56 (m, 5 H) 3.19 - 3.29 (m, 1 H), 3.12 (br d, *J*=10.3 Hz, 1 H) 2.68 - 3.08 (m, 3 H), 2.02 - 2.17 (m, 1 H), 1.75 - 1.87 (m, 1 H), 1.40 - 1.60 (m, 3 H), 1.19 - 1.39 (m, 4 H).

Compound 104:

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.00 (t, *J*=8.9 Hz, 1 H), 7.32 (d, *J*=7.4 Hz, 1 H), 7.09 - 7.27 (m, 3 H), 6.89 - 6.96 (m, 1 H), 6.80 (s, 1 H), 6.44 - 6.55 (m, 1 H), 6.34 – 6.44 (m, 1 H), 5.54 – 5.64 (m, 1 H), 4.91 (t, J=5.6 Hz, 1 H), 4. 85 (s, 1 H), 3.76 - 3.87 (m, 1 H), 3.36 - 3.53 (m, 6 H), 3.12 (br d, *J*=10.3 Hz, 1 H), 2.68 - 3.08 (m, 3 H), 2.02 - 2.17 (m, 1 H), 1.75 - 1.87 (m, 1 H), 1.46 - 1.60 (m, 3 H), 1.18 - 1.40 (m, 4 H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.00 (t, *J*=8.9 Hz, 1 H), 7.09 - 7.27 (m, 3 H), 7.08 (d, *J*=7.1 Hz, 1 H), 6.89 - 6.96 (m, 1 H), 6.76 (s, 1 H), 6.44 - 6.55 (m, 1 H), 6.34 – 6.44 (m, 1 H), 4.88 - 5.00 (m, 2 H), 4.85 (s, 1 H), 4.50 - 4.60 (m, 1 H), 3.36 - 3.53 (m, 5 H), 3.21 - 3.29 (m, 1 H), 3.12 (br d, *J*=10.3 Hz, 1 H), 2.68 - 3.08 (m, 3 H), 2.02 - 2.17 (m, 1 H), 1.75 - 1.87 (m, 1 H), 1.46 - 1.60 (m, 3 H) 1.18 - 1.40 (m, 4 H).

Compound 105:

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.22 (s, 1 H) 7.52 (br s, 1 H) 7.05 - 7.35 (m, 4 H) 7.02 (br s, 1 H) 6.93 - 6.98 (m, 1 H) 6.92 (s, 1 H) 6.09 (br d, *J*=14.7 Hz, 1 H) 5.96 (s, 1 H) 5.59 (q, *J*=6.5 Hz, 1 H) 3.80 (br dd, *J*=13.9, 3.9 Hz, 1 H) 3.23 - 3.51 (m, 5 H) 2.71 - 3.11 (m, 4 H) 2.05 - 2.23 (m, 2 H) 1.49 - 1.61 (m, 3 H) 1.22 - 1.37 (m, 4 H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.21 (s, 1 H) 7.52 (br s, 1 H) 7.05 - 7.35 (m, 4 H) 7.02 (br s, 1 H) 6.93 - 6.98 (m, 1 H) 6.88 (s, 1 H) 6.09 (br d, *J*=14.7 Hz, 1 H) 5.96 (s, 1 H) 4.94 (q, *J*=6.6 Hz, 1 H) 4.51 - 4.60 (m, 1 H) 3.23 - 3.51 (m, 5 H) 2.71 - 3.11 (m, 4 H) 2.05 - 2.23 (m, 2 H) 1.49 - 1.61 (m, 3 H) 1.22 - 1.37 (m, 4 H).

Compound 106:

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.51 (br s, 1 H) 7.09 - 7.36 (m, 4 H) 6.95 - 7.05 (m, 2 H) 6.79 (s, 1 H) 6.00 - 6.14 (m, 2 H) 5.59 (q, *J*=6.8 Hz, 1 H) 4.82 - 4.91 (m, 1 H) 4.08 - 4.20 (m, 2 H) 3.77 - 3.90 (m, 1 H) 3.66 - 3.75 (m, 2 H) 3.19 - 3.58 (m, 5 H) 2.69 - 3.14 (m, 4 H) 2.03 - 2.27 (m, 2 H) 1.46 - 1.61 (m, 3 H) 1.21 - 1.34 (m, 4 H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.51 (br s, 1 H) 7.09 - 7.36 (m, 4 H) 6.95 - 7.05 (m, 2 H) 6.76 (s, 1 H) 6.00 - 6.14 (m, 2 H) 4.95 (q, *J*=6.7 Hz, 1 H) 4.82 - 4.91 (m, 1 H) 4.55 (br d, *J*=15.5 Hz, 1 H) 4.08 - 4.20 (m, 2 H) 3.66 - 3.75 (m, 2 H) 3.19 - 3.58 (m, 5 H) 2.69 - 3.14 (m, 4 H) 2.03 - 2.27 (m, 2 H) 1.46 - 1.61 (m, 3 H) 1.21 - 1.34 (m, 4 H).

Compound 107:

Major diastereomer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.01 (t, *J*=8.9 Hz, 1 H) 7.29-7.35 (m, 1 H) 7.03 - 7.28 (m, 3 H) 6.89 - 7.02 (m, 1 H) 6.81 (s, 1 H) 6.54 (dd, *J*=9.0, 2.0 Hz, 1 H) 6.49 (dd, *J*=14.8, 2.0 Hz, 1 H) 5.47 - 5.65 (m, 2 H) 5.13 (dt, J=55.9, 2.0 Hz, 1 H) 4.26 - 4.49 (m, 1 H) 3.81 (br dd, *J*=13.7, 3.7 Hz, 1 H) 3.40 - 3.70 (m, 4 H) 3.16 (t, *J*=8.7 Hz, 1 H) 2.83 - 3.08 (m, 2 H) 2.72 (br d, *J*=16.1 Hz, 1 H) 1.52 (d, *J*=6.9 Hz, 3 H) 1.17 - 1.43 (m, 4 H).

Minor diastereomer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.01 (t, *J*=8.9 Hz, 1 H) 7.03 - 7.28 (m, 4 H) 6.89 - 7.02 (m, 1 H) 6.77 (s, 1 H) 6.54 (dd, *J*=9.0, 2.0 Hz, 1 H) 6.49 (dd, *J*=14.8, 2.0 Hz, 1 H) 5.47 - 5.65 (m, 1 H) 5.13 (dt, J=55.9, 2.0 Hz, 1 H) 4.96 (q, *J*=7.0 Hz, 1 H) 4.49 - 4.63 (m, 1 H) 4.26 - 4.49 (m, 1 H) 3.40 - 3.70 (m, 3 H) 3.22 - 3.28 (m, 1 H) 3.16 (t, *J*=8.7 Hz, 1 H) 2.83 - 3.08 (m, 3 H) 1.55 (d, *J*=6.9 Hz 3 H) 1.17 - 1.43 (m, 4 H).

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.
5	220.25°C	57	216.34°C
7	189.00°C	62	173.36°C
11	159.35°C	65	211.64°C
17	258.48°C	66	143.13°C
19	308.63°C	67	205.81°C
32	297.57°C	72	252.4°C
33	292.70°C	74	144.01°C
34	289.10°C	75	197.51°C
35	174.2°C	76	221.20°C
36	237.70°C	78	283.43°C
37	123.18°C	79	285.54°C
42	206.84°C	80	182.93°C
43	214.36°C	81	271.19°C
46	270.00°C	82	294.89°C
47	245.69°C	83	235.56°C
49	239.19°C	84	252.18°C
52	246.17°C	85	277.22°C
53	228.33°C	87	152.28°C
54	254.46°C	90	269.08°C
55	253.3°C	91	236.01°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. Compound (45) and compound (84) were measured at 546 nm.

Co. No.	$[\alpha]_D^{20}$	c (w/v %)	Co. No.	$[\alpha]_D^{20}$	c (w/v %)
2	-71.71°	0.2301	57	-14.84°	0.256
3	+16.14°	0.2478	58	-14.56°	0.261
4	+20.58°	0.2478	59	-17.81°	0.219
5	-33.57°	0.28	60	-16.33°	0.245
6	-26°	0.25	62	-15.91°	0.2389
7	-43.31°	0.254	63	-7.22°	0.263
8	-17.93°	0.29	64	-14.6°	0.274

Co. No.	$[\alpha]_D^{20}$	c (w/v %)	Co. No.	$[\alpha]_D^{20}$	c (w/v %)
9	-33.9°	0.2566	65	-33.21°	0.271
10	-22.37°	0.2637	66	-29.77°	0.262
11	-38.13°	0.278	67	-34.97	0.306
12	-17.67°	0.3	68	-32.74°	0.281
13	-19.36°	0.2583	70	-30.09°	0.216
14	-14.7°	0.2177	72	-30.0°	0.25
15	-59.7°	0.2345	74	-33.22°	0.292
16	+9.48°	0.2531	76	-16°	0.25
17	-5.25°	0.2478	77	-55.36°	0.28
18	-9.69°	0.3097	78	-6.88°	0.32
26	-26.64°	0.289	80	-12.58°	0.302
30	-52.69°	0.26	81	-46.29°	0.283
31	-3.7°	0.27	82	-9.12°	0.296
32	-53.33°	0.3	83	-47.3°	0.315
33	-59.38°	0.32	84	+5.37°	0.298
36	-17.69°	0.26	85	-79.09°	0.33
37	-24.1°	0.278	86	-39.12°	0.294
38	-13.23°	0.257	87	-30.74°	0.27
39	+16.45°	0.304	88	-33.33°	0.21
40	-23.33°	0.27	89	-36.49°	0.285
41	-28.71°	0.31	90	-14°	0.25
42	-18.8°	0.266	91	-32.08°	0.265
43	-48.52°	0.27	92	-29.01°	0.262
44	-79.23°	0.26	93	-30.94	0.32
45	+4.69°	0.32	94	-8.93	0.28
46	-25.65°	0.269	95	-31	0.3
47	-19.49°	0.272	96	-29.23	0.26
48	-265.35°	0.254	97	-18.13	0.32
49	-40.77°	0.26	98	-70.35	0.317
50	-35.58°	0.2867	100	-49.64	0.28
51	-27.51°	0.269	101	+33.93	0.28
52	-35.03°	0.294	102	-9.29	0.28
53	-40.42°	0.2301	103	-31.2	0.25
54	-20.06°	0.324	104	+28.57	0.28
55	-9.33°	0.3	105	-17.59	0.29
56	-14.65°	0.2389	106	-38.21	0.28

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 EC50 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 CC50 was defined as the 50% concentration for cytotoxicity.

Table : antiviral data

Co. No.	RSV HELA EC50 (µM)	TOX HELA CC50 (µM)	Co. No.	RSV HELA EC50 (µM)	TOX HELA CC50 (µM)
1	0.085	>100	55	0.016	>100
2	0.056	38.7	56	0.032	58.9
3	0.063	43.0	57	0.023	>100
4	0.049	23.0	58	0.036	>100
5	0.118	>25	59	0.047	N.A.
6	0.098	>100	60	0.029	41.3
7	0.037	71.5	61	0.193	>100
8	0.041	51.5	62	0.043	>100
9	0.108	>100	63	0.011	27.2

Co. No.	RSV HELA EC50 (μM)	TOX HELA CC50 (μM)	Co. No.	RSV HELA EC50 (μM)	TOX HELA CC50 (μM)
10	0.070	>100	64	0.029	8.9
11	0.044	>100	65	0.048	39.1
12	0.041	>100	66	0.040	36.4
13	0.058	80.5	67	0.030	36.5
14	0.039	81.2	68	0.058	26.6
15	0.100	>100	69	0.059	33.2
16	0.110	>100	70	0.104	28.2
17	0.050	>100	71	0.105	29.8
18	0.044	>100	72	0.087	>100
19	0.041	72.3	73	0.101	>100
20	0.052	55.9	74	0.076	48.1
21	0.045	>100	75	0.076	>100
22	0.145	>100	76	0.246	>100
23	0.032	30.3	77	0.082	>100
24	0.030	26.4	78	0.055	47,3
25	0.023	29.6	79	0.476	13,3
26	0.020	29.6	80	0.091	35,9
27	0.089	34.4	81	0.099	38,4
28	0.072	32.2	82	0,033	33,1
29	0.045	43.7	83	0.044	42,4
30	0.036	33.9	84	0.006	19,0
31	0.036	39.1	85	0.152	>100
32	0.060	32.1	86	0.161	49.5
33	0.043	34.5	87	0.215	47.4
34	0.037	23.1	88	0.017	47.6
35	0.033	25.5	89	0.165	33.4
36	0.012	29.3	90	0.046	N.A.
37	0.019	62.0	91	0.036	28,3
38	0.043	>100	92	0.071	41.5
39	0.291	53.1	93	0.039	13.4
40	0.061	52.3	94	0.19	>100
41	0.036	51.1	95	0.018	31.1
42	0.025	28.9	96	0.05	22.5
43	0.017	29.8	97	0.053	26.1
44	0.019	45.2	98	0.039	47.6
45	0.020	31.4	99	0.092	>100
46	0.007	31.3	100	0.011	23.8
47	0.009	41.5	101	0.058	45.4

Co. No.	RSV HELA EC50 (μM)	TOX HELA CC50 (μM)	Co. No.	RSV HELA EC50 (μM)	TOX HELA CC50 (μM)
49	0.024	32.3	102	0.026	44.4
50	0.031	35.1	103	0.019	35.8
51	0.131	67.9	104	0.025	28.2
52	0.014	41.3	105	0.025	83.6
53	0.035	>100	106	0.089	21
54	0.192	77.4	107	0.017	21.2

N.A. : not available

E.2 Pharmacokinetics after single intravenous administration in the fasted male Beagle dog

The test compound was dissolved in a 20 % (w/v) hydroxypropyl-β- cyclodextrin (HP-beta-CD) solution at a final concentration of 2 mg/mL for the intravenous formulation. NaOH was added to the formulations to facilitate dissolution and after total dissolution the pH was adjusted with HCl to 8.4. The intravenous (IV) formulation was made isotonic with mannitol. Prior to dosing, all formulations were stored at room temperature and protected from light. The IV formulation was dosed in a cephalic vein at 0.5 mL/kg to obtain a final dose of 1 mg/kg.

Three male Beagle dogs, with a mean weight of 10.9 ± 1.1 kg, were used. A complete concentration time profile was obtained from each individual animal. Prior to dosing, animals were fasted overnight. Their standard dry diet was returned to them at 2 hours post dose. Tap water was available *ad libitum*.

From each individual animal, blood samples were taken at 7 and 20 minutes, 1, 2, 4, 7, 24 and 48 hours after intravenous dose administration. Blood was collected from a jugular vein into 2 mL BD vacutainers™ K3E (Becton Dickinson). Samples were placed immediately on melting ice and plasma was obtained following centrifugation at 4°C for 10 minutes at approximately 1900 *x g*. All samples were shielded from daylight and stored at ≤ -18°C prior to analysis. Plasma samples were analysed using a qualified research LC-MS/MS method. The key analytical performance (linearity, upper and lower limit of quantification, accuracy and precision) of the method was reported together with the plasma concentrations. The lower limit of quantification (LLOQ) was 10.0 ng/mL.

Pharmacokinetic analysis was performed using Phoenix™ Professional (Version 6.3). A non-compartmental analysis using the linear/log trapezoidal rule with linear/log interpolation was used for all data.

The plasma concentration profile of Compound (37) and Compound (102) of the present invention has been reproduced in Figures 1 and 2.

The plasma concentration profile of Compound (W37) and Compound (W38) of WO-2016/174079 has been reproduced in Figures 3 and 4.

After intravenous administration at 1 mg/kg in dogs the compounds (W37) and (W38) of WO-2016/174079 show a rapid decline in plasma concentration in the first 8 hours after administration. The plasma concentration profile of Compound (37) and Compound (102) of the present invention does not show this rapid decline thereby indicating these compounds have improved metabolic stability properties and improved bio-availability.

Description of the drawings :
Figure 1 : plasma concentration profile of Compound (102)
Figure 2 : plasma concentration profile of Compound (37)
Figure 3 : plasma concentration profile of compound (W37) of WO-2016/174079
Figure 4 : plasma concentration profile of compound (W38) of WO-2016/174079

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

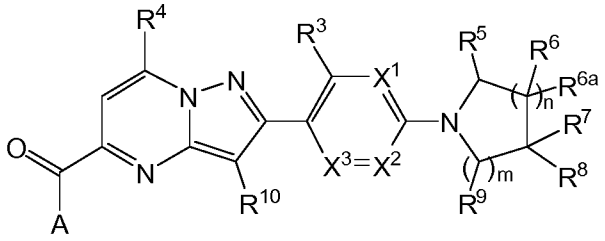
Active ingredient	5 to 1000 mg
Stearyl alcohol	3 g
Lanoline	5 g
White petroleum	15 g
Water	ad 100 g

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.

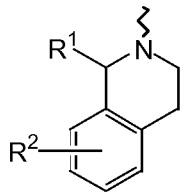
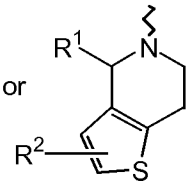
Claims

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 0, 1, or 2;

m is 1 or 2;

X^1, X^2 and X^3 are selected from X^1 is $CR^{11}$and X^2 is CR^{11} and X^3 is CR^{11},
or X^1 is N and X^2 is CR^{11} and X^3 is CR^{11},
or X^1 is CR^{11} and X^2 is N and X^3 is CR^{11},
or X^1 is CR^{11} and X^2 is CR^{11} and X^3 is N,
or X^1 is N and X^2 is CR^{11} and X^3 is N,
wherein each R^{11} is independently selected from the group consisting of hydrogen, halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkyloxyC_{1-4}alkyloxy, hydroxyC_{1-4}alkyl, and hydroxyC_{1-4}alkyloxy;

R^1 is CH_3 or CH_2CH_3;

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

R^3 is halo or CH_3O;

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

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

each R^6 is independently selected from the group consisting of hydrogen, C_{1-4}alkyl, hydroxy, halo and C_{1-4}alkyloxy;

each R^{6a} is independently selected from the group consisting of hydrogen and halo;
R^7 is hydrogen, C_{1-4}alkyl, or hydroxyC_{1-4}alkyl;
R^8 is -OH,
-CN,
-O-(CO)-$NR^{12}R^{13}$,
-C_{1-4}alkyl-(CO)-$NR^{12}R^{13}$,
-(CO)-$NR^{12}R^{13}$,
-(CS)-$NR^{12}R^{13}$,
-(CO)-NR^{12}-CN,
-(CO)-NR^{12}-SO_2-R^{14},
-NR^{12}-(CO)-R^{14},
-NR^{12}-(CO)-O-R^{14},
-NR^{12}-SO_2-R^{14},
-NH_2,
-NR^{12}-R^{15};
-SO_2-R^{14},
-SO_2-$NR^{12}R^{13}$,
-SO_2-NR^{12}-(CO)-R^{14}, or
-SO(=NH)(-R^{14}), or
Heteroaryl[1];
wherein
R^{12} and R^{13} are each independently selected from hydrogen and C_{1-4}alkyl, and;
R^{14} is C_{1-4}alkyl, or polyhaloC_{1-4}alkyl;
R^{15} is di(C_{1-4}alkyl)-(P=O)- or polyhaloC_{1-4}alkyl;
or R^7 and R^8 may be taken together to form -CH_2-(SO_2)-CH_2- or -CH_2-O-CH_2- ;
each R^9 is independently selected from the group consisting of hydrogen and C_{1-4}alkyl;
R^{10} is hydrogen, halo or C_{1-6}alkyl;
when n = 1 and m=1, R^8 and R^9 may be taken together to form -CH_2- ;
when n = 1 and m=1, R^5 and R^9 may be taken together to form -CH_2CH_2- ;
when n=1 and m=1, R^8 and R^9 may be taken together to form -CH_2-(CO)-O- ;
Heteroaryl is pyridinyl or pyrimidinyl, wherein each Heteroaryl is optionally substituted with one or two substituents each independently selected from C_{1-4}alkyl, halo, amino, and aminocarbonyl;
Heteroaryl[1] is tetrazolyl or oxadiazolyl;
or a pharmaceutically acceptable acid addition salt thereof.

2. The compound as claimed in claim 1 wherein
wherein
n is 0, 1, or 2;
m is 1 or 2;
X^1, X^2 and X^3 are selected from X^1 is $CR^{11}$and X^2 is CR^{11} and X^3 is CR^{11},
or X^1 is N and X^2 is CR^{11} and X^3 is CR^{11},
or X^1 is CR^{11} and X^2 is N and X^3 is CR^{11},
or X^1 is N and X^2 is CR^{11} and X^3 is N,
wherein each R^{11} is independently selected from the group consisting of hydrogen, halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkyloxyC_{1-4}alkyloxy, and hydroxyC_{1-4}alkyloxy;
R^1 is CH_3;
R^2 is hydrogen, or halo;
R^3 is halo;
R^4 is C_{3-6}cycloalkyl; phenyl; phenyl substituted with 1 substituent selected from halo, cyano, C_{1-4}alkyl, polyhaloC_{1-4}alkyl, and C_{1-4}alkyloxy; or Heteroaryl;
R^5 is hydrogen, C_{1-4}alkyl or hydroxyC_{1-4}alkyl;
each R^6 is independently selected from the group consisting of hydrogen, C_{1-4}alkyl, hydroxy, halo and C_{1-4}alkyloxy;
each R^{6a} is independently selected from the group consisting of hydrogen and halo;
R^7 is hydrogen, C_{1-4}alkyl, or hydroxyC_{1-4}alkyl;
R^8 is -OH,
-CN,
-O-(CO)-$NR^{12}R^{13}$,
-C_{1-4}alkyl-(CO)-$NR^{12}R^{13}$,
-(CO)-$NR^{12}R^{13}$,
-(CS)-$NR^{12}R^{13}$,
-(CO)-NR^{12}-CN,
-(CO)-NR^{12}-SO_2-R^{14},
-NR^{12}-(CO)-R^{14},
-NR^{12}-(CO)-O-R^{14},
-NR^{12}-SO_2-R^{14},
-NH_2,
-NR^{12}-R^{15};
-SO_2-R^{14},
-SO_2-$NR^{12}R^{13}$,
-SO_2-NR^{12}-(CO)-R^{14}, or

-SO(=NH)(-R^{14}), or
Heteroaryl^1;
wherein
R^{12} and R^{13} are each independently selected from hydrogen and C_{1-4}alkyl, and;
R^{14} is C_{1-4}alkyl or polyhaloC_{1-4}alkyl;
R^{15} is di(C_{1-4}alkyl)-(P=O)- or polyhaloC_{1-4}alkyl;
or R^7 and R^8 may be taken together to form -CH_2-(SO_2)-CH_2- or -CH_2-O-CH_2- ;
each R^9 is independently selected from the group consisting of hydrogen and C_{1-4}alkyl;
R^{10} is hydrogen;
when n=1 and m=1, R^8 and R^9 may be taken together to form -CH_2-(CO)-O- ;
Heteroaryl is pyridinyl or pyrimidinyl, wherein each Heteroaryl is optionally substituted with one substituent selected from halo;
Heteroaryl^1 is tetrazolyl or 5-oxo-4,5-dihydro-1,2,4-oxadiazolyl;

3. The compound as claimed in claim 1 wherein X^1 is $CR^{11}$and X^2 is CR^{11} and X^3 is CR^{11}.

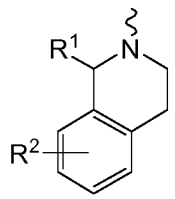
4. The compound as claimed in claim 1 wherein wherein X^1 is N and X^2 is CR^{11} and X^3 is CR^{11}; or X^1 is CR^{11} and X^2 is N and X^3 is CR^{11}; or X^1 is CR^{11} and X^2 is CR^{11} and X^3 is N; or X^1 is N and X^2 is CR^{11} and X^3 is N.

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

6. The compound as claimed in any one of claims 1 to 5 wherein n is 0 and m is 1.

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

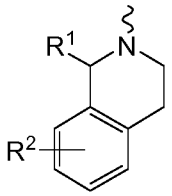
8. The compound as claimed in claim 1 wherein

A is 

n is 0 or 1;
m is 1;
X^1, X^2 and X^3 are selected from X^1 is $CR^{11}$and X^2 is CR^{11} and X^3 is CR^{11}, wherein each R^{11} is hydrogen;

R^1 is CH_3;
R^2 is hydrogen;
R^3 is halo;
R^4 is C_{3-6}cycloalkyl or Heteroaryl;
R^5 is hydrogen;
each R^6 is independently selected from the group consisting of hydrogen, hydroxy, and halo;
each R^{6a} is hydrogen;
R^7 is hydrogen or hydroxyC_{1-4}alkyl;
R^8 is -OH,
-C_{1-4}alkyl-(CO)-$NR^{12}R^{13}$, or
-(CO)-$NR^{12}R^{13}$,
wherein
R^{12} and R^{13} are each independently selected from hydrogen and C_{1-4}alkyl,
R^{10} is hydrogen;
Heteroaryl is pyridinyl;
or a pharmaceutically acceptable acid addition salt thereof.

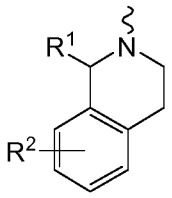
9. The compound as claimed in claim 1 wherein

A is 

n is 1;
m is 1;
X^1, X^2 and X^3 are selected from X^1 is $CR^{11}$and X^2 is CR^{11} and X^3 is CR^{11}, wherein each R^{11} is hydrogen;
R^1 is CH_3;
R^2 is hydrogen;
R^3 is halo;
R^4 is C_{3-6}cycloalkyl;
R^5 is hydrogen;
each R^6 is independently selected from the group consisting of hydrogen, hydroxy, and halo;
each R^{6a} is hydrogen;
R^7 is hydrogen or hydroxyC_{1-4}alkyl;
R^8 is -OH, or

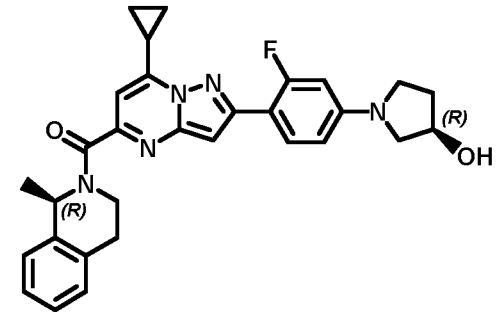
-(CO)-$NR^{12}R^{13}$,
wherein
R^{12} and R^{13} are each independently selected from hydrogen and C_{1-4}alkyl,
R^{10} is hydrogen;
or a pharmaceutically acceptable acid addition salt thereof.

10. The compound as claimed in claim 1 wherein

A is 

n is 1;
m is 1;
X^1, X^2 and X^3 are selected from X^1 is $CR^{11}$and X^2 is CR^{11} and X^3 is CR^{11}, wherein each R^{11} is hydrogen;
R^1 is CH_3;
R^2 is hydrogen;
R^3 is halo;
R^4 is C_{3-6}cycloalkyl;
R^5 is hydrogen;
each R^6 is independently selected from the group consisting of hydrogen and hydroxy;
each R^{6a} is hydrogen;
R^7 is hydrogen;
R^8 is -OH, or
-(CO)-$NR^{12}R^{13}$,
wherein
R^{12} and R^{13} are each independently selected from hydrogen and C_{1-4}alkyl,
R^{10} is hydrogen;
or a pharmaceutically acceptable acid addition salt thereof.

11. The compound according to claim 1, wherein the compound is selected from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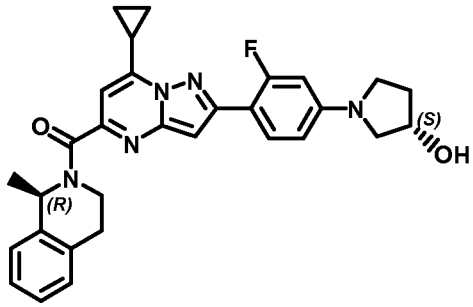
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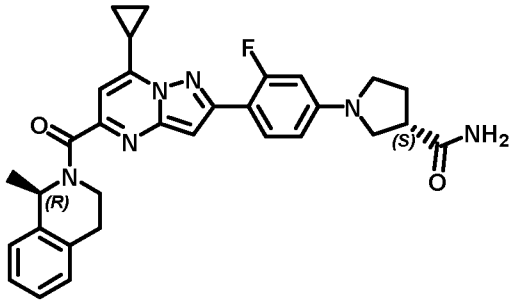
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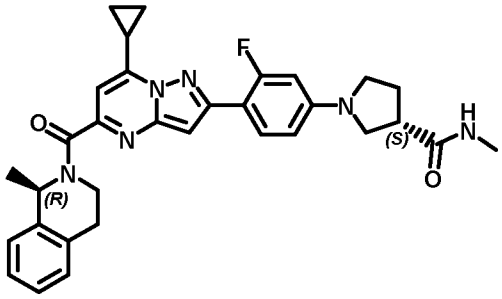
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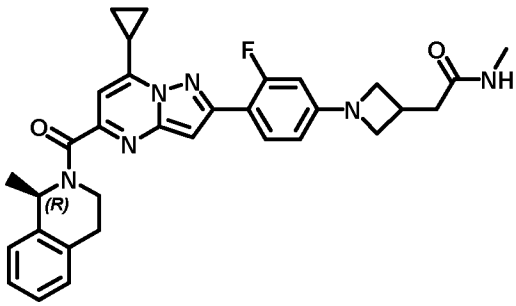
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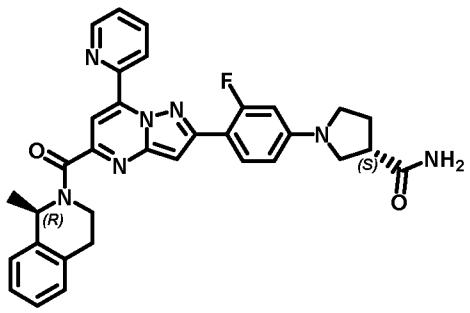
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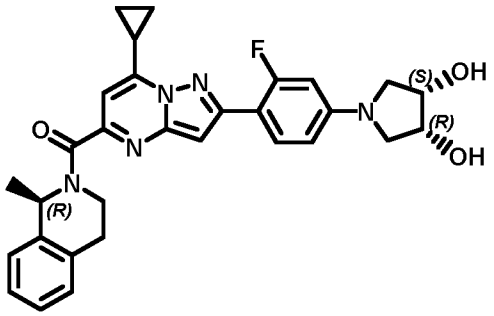
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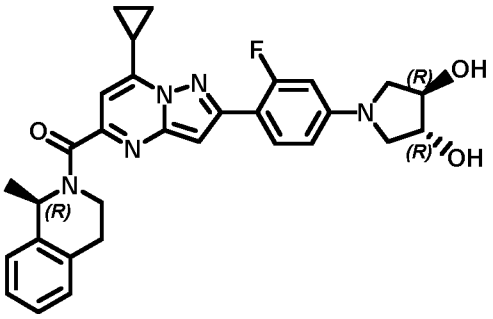
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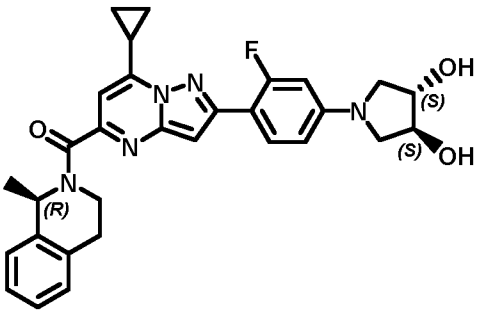
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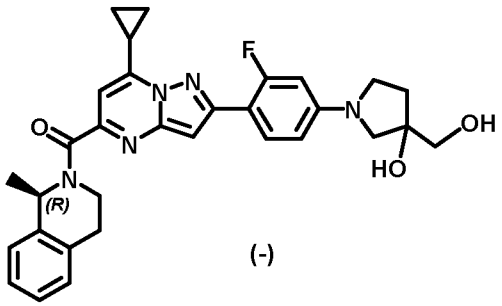
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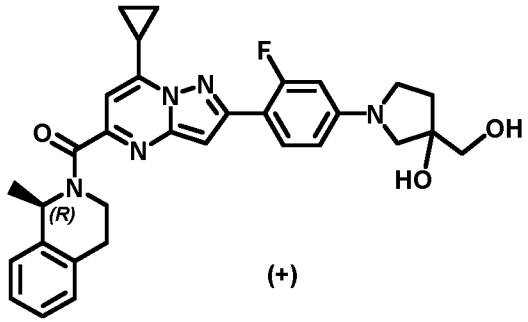

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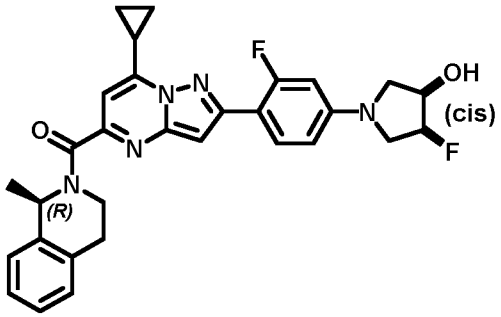

or a pharmaceutically acceptable acid addition salt thereof.

12. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically active amount of a compound as claimed in any one of claims 1 to 11.

13. The pharmaceutical composition according to claim 12, which further comprises another antiviral agent.

14. The pharmaceutical composition according to claim 13, wherein the other antiviral agent is a respiratory syncytial virus (RSV) inhibiting compound.

15. A process for preparing a pharmaceutical composition as claimed in any one of claims 12 to 14 wherein a therapeutically active amount of a compound as claimed in any one of claims 1 to 11 is intimately mixed with a pharmaceutically acceptable carrier.

16. A compound as claimed in any one of claims 1 to 11 for use as a medicine.

17. A compound as claimed in any one of claims 1 to 11, or a pharmaceutical composition as claimed in any one of claims 12 to 14, for use in the treatment of a respiratory syncytial virus infection.

18. 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 11.

Figure 1 : plasma concentration profile of Compound (102) - dog (1 mg/kg iv)

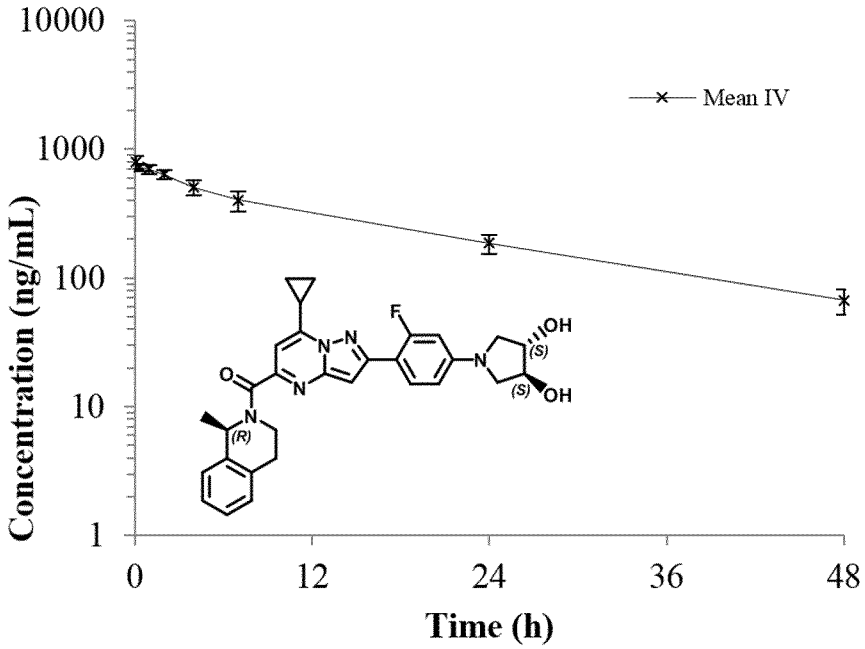

Figure 2 : plasma concentration profile of Compound (37) - dog (1 mg/kg iv)

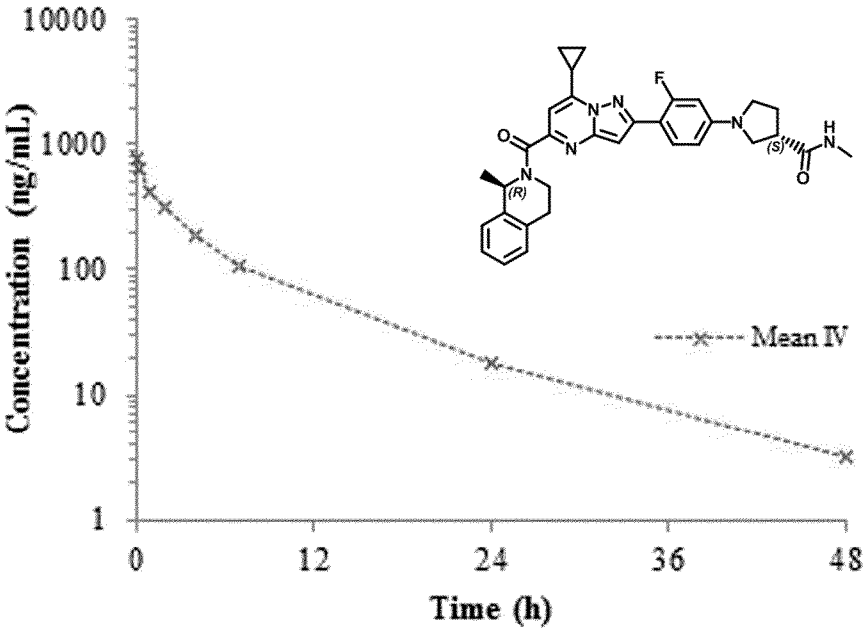

Figure 3 : plasma concentration profile of compound (W37) of WO-2016/174079 dog (1 mg/kg iv)

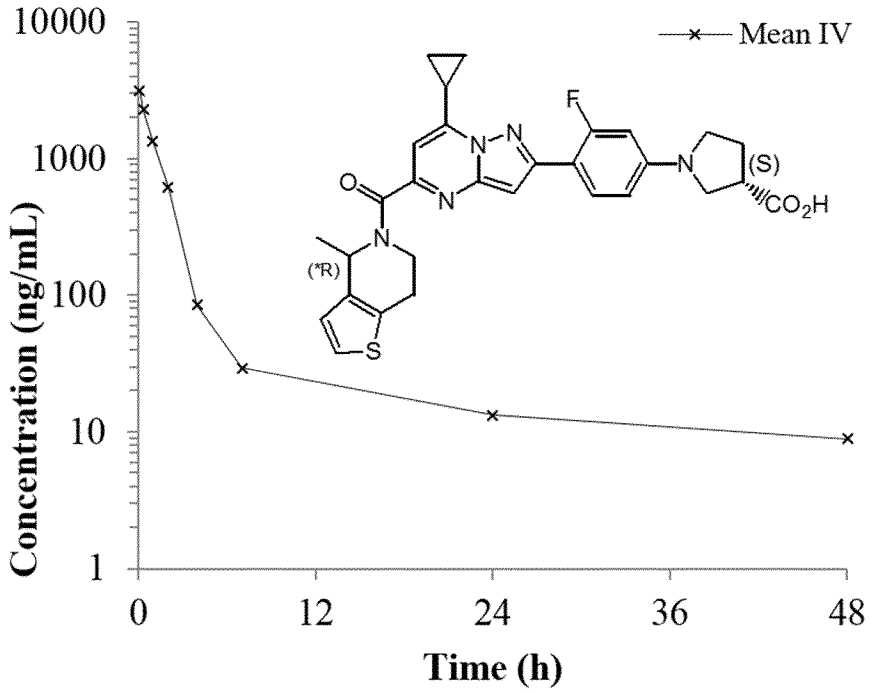

Figure 4 : plasma concentration profile of compound (W38) of WO-2016/174079 dog (1 mg/kg iv)