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Canadian Intellectual Property Office

CA 3095277 A1 2019/10/31

(21) 3 095 277

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2019/04/19
(87) Date publication PCT/PCT Publication Date: 2019/10/31
(85) Entrée phase nationale/National Entry: 2020/09/25
(86) N° demande PCT/PCT Application No.: EP 2019/060216
(87) N° publication PCT/PCT Publication No.: 2019/206828
(30) Priorité/Priority: 2018/04/23 (EP18168671.8)

(51) Cl.Int./Int.Cl. *C07D 471/04* (2006.01), *A61K 31/437* (2006.01), *A61P 31/16* (2006.01)

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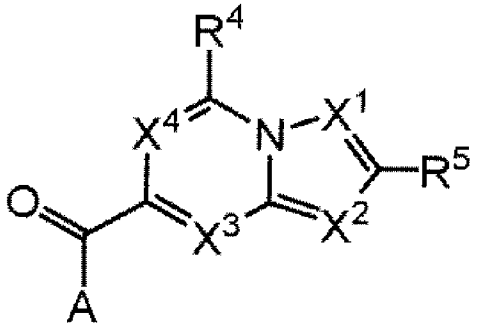
(54) Titre : COMPOSES HETEROAROMATIQUES AYANT UNE ACTIVITE CONTRE VRS
(54) Title: HETEROAROMATIC COMPOUNDS HAVING ACTIVITY AGAINST RSV



(I)

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

(21) 3 095 277

(13) A1

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
31 October 2019 (31.10.2019)

WIPO | PCT

(10) International Publication Number
WO 2019/206828 A1

(51) International Patent Classification:
C07D 471/04 (2006.01) *A61K 31/437* (2006.01)
A61P 31/16 (2006.01)

(21) International Application Number:
PCT/EP2019/060216

(22) International Filing Date:
19 April 2019 (19.04.2019)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
18168671.8 23 April 2018 (23.04.2018) EP

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

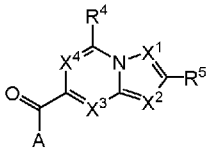
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:
— *with international search report (Art. 21(3))*

WO 2019/206828 A1

(54) Title: HETEROAROMATIC COMPOUNDS HAVING ACTIVITY AGAINST RSV



(I)

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

HETEROAROMATIC COMPOUNDS HAVING ACTIVITY AGAINST RSV

Field of the Invention

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

Background

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

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

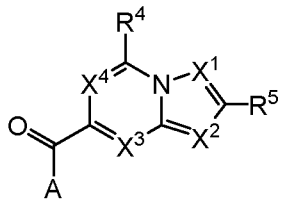
Today only two drugs have been approved for use against RSV infection. A first one is ribavirin, a nucleoside analogue that provides an aerosol treatment for serious RSV infection in hospitalized children. The aerosol route of administration, the toxicity (risk of teratogenicity), the cost and the highly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

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

Compounds that exhibit anti-RSV activity are disclosed in WO-2016/174079 and WO-2011/163518.

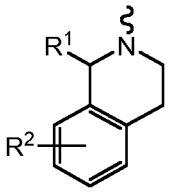
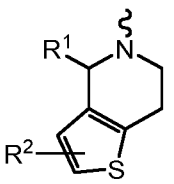
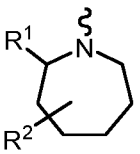
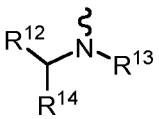
Detailed description of the Invention

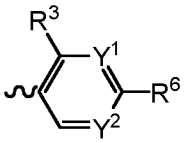
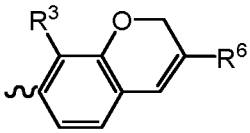
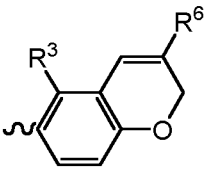
The present invention relates to compounds of formula (I)



(I)

including any stereochemically isomeric form thereof, wherein

A is  (a-1),  (a-2),  (a-3), or  (a-4);

R^5 is  (b-1),  (b-2), or  (b-3);

X^1, X^2, X^3 and X^4 are selected from X^1 is CH, X^2 is CH, X^3 is CH and X^4 is CH;
or X^1 is N, X^2 is CH, X^3 is CH and X^4 is CH,
or X^1 is CH, X^2 is N, X^3 is CH and X^4 is CH,
or X^1 is N, X^2 is CH, X^3 is CH and X^4 is N,
or X^1 is N, X^2 is N, X^3 is CH and X^4 is CH, and
or X^1 is CH, X^2 is N, X^3 is N and X^4 is CH,
wherein each CH is optionally substituted with halo, C_{1-4}alkyl or C_{1-4}alkyloxy;

Y^1 and Y^2 are each independently selected from CH, CF and N;

R^1 is CH_3 or CH_2CH_3;

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

R^{12} is C_{1-2}alkyl;

R^{13} and R^{14} are each independently selected from C_{1-6}alkyl;

R^3 is halo;

R^4 is C_{1-6}alkyl; C_{3-6}cycloalkyl; di(C_{1-4}alkyl)amino, pyrrolidinyl, Heteroaryl[1]; C_{1-4}alkyl substituted with Heteroaryl[1]; 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;

R^6 is C_{2-6}alkenyl substituted with one or two substituents selected from C_{1-6}alkyl, -(CO)-OR^7 or -(CO)-NR^8R^9; or

-NR^9-(CO)-Heterocycle wherein said Heterocycle is substituted with one or two substituents each independently selected from halo, hydroxy of C_{1-4}alkyloxy; or

C_{3-6}cycloalkyl or Heterocycle, wherein said C_{3-6}cycloalkyl and Heterocycle is substituted with one or two substituents each independently selected from

C_{1-6}alkyl;

C_{1-6}alkyl substituted with one, two or three substituents each independently selected from halo, hydroxy, hydroxycarbonyl, aminocarbonyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl substituted with one or two substituents each independently selected from C_{1-4}alkyl, halo, hydroxycarbonyl, and C_{1-4}alkyl substituted with hydroxycarbonyl;

C_{3-6}alkenyl;

C_{3-6}alkenyl substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, -(CO)-OR^7 or -(CO)-NR^8R^9;

hydroxy;

cyano;

-(CO)-O-R^7;

-(CO)-$NR^{10}R^{11}$;

-(CO)-NR^9-SO_2-R^8;

-(CO)-NR^9-(CO)-SO_2-R^8;

-O-(CO)-$NR^{10}R^{11}$;

-NR^8R^9;

-NR^9-(CO)-C_{1-4}alkyl;

-NR^9-(CO)-C_{3-6}cycloalkyl;

-NR^9-(CO)-O-R^8;

-NR^9-(CO)-NR^9-R^8;

-NR^9-SO_2-R^8;

-SO_2-R^8;

-SO_2-$NR^{10}R^{11}$; or

-SO_2-NR^9-(CO)-R^8;

Heteroaryl[2];

wherein

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

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

each R^9 is independently selected from hydrogen or C_{1-4}alkyl;

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

Heterocycle is azetidinyl, pyrrolodinyl, piperidinyl, or homopiperidinyl;

Heteroaryl^1 is thienyl, pyridinyl or pyrimidinyl, wherein each Heteroaryl^1 is optionally substituted with one or two substituents each independently selected from C_{1-4}alkyl, halo, amino, and aminocarbonyl;

Heteroaryl^2 is pyrrolyl, pyrazolyl or thiazolyl; wherein each Heteroaryl^2 is optionally substituted with one or two substituents each independently selected from C_{1-4}alkyl, halo, -(CO)-OR^7 or -(CO)-NR^8R^9;

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-methyl-propyl 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_{2-6}alkenyl defines bivalent straight or branched chain hydrocarbon radicals containing from 2 to 6 carbon atoms such as, for example, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,5-pentanediyl, 1,6-hexanediyl, and the branched isomers thereof;
- C_{3-6}alkenyl defines straight and branched chain hydrocarbon radicals containing one double bond and having from 3 to 6 carbon atoms such as, for example, 2-propenyl, 3-butenyl, 2-butenyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-butenyl, 3-hexenyl, 2-hexenyl 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.

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

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

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

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

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

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

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

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

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

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

when a compound of formula (I) is for instance specified as cis, this means that the compound is substantially free of the trans isomer.

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

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

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

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

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

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

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

one or more atoms of the compound) with one or more stable isotopes include, for example, compounds of formula (I) that are isotopically enriched or labelled with one or more atoms such as deuterium, ^{13}C, ^{14}C, ^{14}N, ^{15}O or the like.

A first group of compounds are compounds of formula (I) wherein X^1 is CH, X^2 is CH, X^3 is CH and X^4 is CH.

A second group of compounds are compounds of formula (I) wherein X^1 is N, X^2 is CH, X^3 is CH and X^4 is CH.

A third group of compounds are compounds of formula (I) wherein wherein X^1 is CH, X^2 is N, X^3 is CH and X^4 is CH.

A fourth group of compounds are compounds of formula (I) wherein X^1 is N, X^2 is CH, X^3 is CH and X^4 is N.

A fifth group of compounds are compounds of formula (I) wherein X^1 is N, X^2 is N, X^3 is CH and X^4 is CH.

A sixth group of compounds are compounds of formula (I) wherein X^1 is CH, X^2 is N, X^3 is N and X^4 is CH.

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

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

A ninth group of compound are compounds of formula (I) wherein R^4 is C_{3-6}cycloalkyl.

A tenth group of compound are compounds of formula (I) wherein R^5 is of formula (b-1) wherein Y^1 and Y^2 are CH.

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 C_{3-6}cycloalkyl , in particular cyclopropyl; or

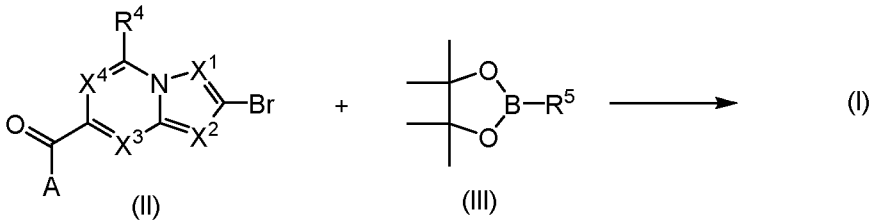
g) R^4 is C_{1-4}alkyl, in particular ethyl; or

h) R^4 is Heteroaryl^1 wherein Heteroaryl^1 is pyridinyl; or

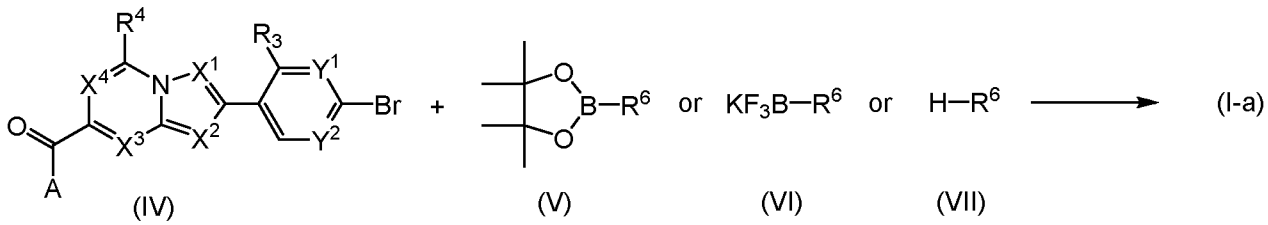
i) R^5 is of formula (b-1) wherein Y^1 and Y^2 are CH and R^3 is halo, in particular R^3 is fluoro; and

j) R^6 is C_{3-6}cycloalkyl or pyrrolidinyl, wherein said C_{3-6}cycloalkyl or pyrrolidinyl are substituted with one or two substituents each independently selected from -(CO)-O-R^7 or -(CO)-$NR^{10}R^{11}$.

In general compounds of formula (I) can be prepared by reacting an intermediate of formula (II) with an alkylboronate intermediate of formula (III) in at least one reaction-inert solvent and optionally in the presence of at least one transition metal coupling reagent and/or at least one suitable ligand, the said process further optionally comprising converting a compound of formula (I) into an addition salt thereof. Suitable metal coupling reagents and/or suitable ligands for this reaction are, e.g. palladium compounds such as palladium tetra(triphenylphosphine), tris(dibenzylidene-acetone dipalladium, 2,2'-bis(diphenylphosphino)-1,1'-binaphtyl and the like.



Compounds of formula (I-a), defined as compounds of formula (I) wherein R^5 is of formula (b-1), can also be prepared by reacting an intermediate of formula (IV) with either an intermediate of formula (V), (VI) or (VII) in a reaction-inert solvent and optionally in the presence of at least one transition metal coupling reagent and/or at least one suitable ligand, the said process further optionally comprising converting a compound of formula (I) into an addition salt thereof.



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

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

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

The compounds of formula (I) as prepared in the hereinabove described processes may be synthesized in the form of racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. Those compounds of formula (I) that are obtained in racemic form may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali. An alternative manner of separating the enantiomeric forms of the compounds of formula (I) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

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

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

Additionally the present invention provides pharmaceutical compositions comprising at least one pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of formula (I). Also provided are pharmaceutical compositions comprising a pharmaceutically

acceptable carrier, a therapeutically active amount of a compound of formula (I), and another antiviral agent, in particular a RSV inhibiting compound.

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

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.

Experimental part

A. Abbreviations

µw or MW	microwave
AcOH	acetic acid
aq.	aqueous
br	broad
cataCXium® A	di(1-adamantyl)-*n*-butylphosphine CAS [321921-71-5]
d	doublet
DCE	1,2-dichloroethane
DCM	dichloromethane
DIPA	diisopropylamine
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-(dimethylamino)pyridine CAS [1122-58-3]
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
Et_2O	diethyl ether
Et_3N	triethylamine
EtOAc	ethyl acetate
EtOH	ethanol
h	hour
HATU	1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate CAS [148893-10-1]
i-PrMgCl	isopropylmagnesium chloride
KOAc	potassium acetate
LDA	lithium diisopropylamide

LiHMDS	lithium bis(trimethylsilyl)amide
m	multiplet
m/z	mass-to-charge ratio
MeCN	acetonitrile
MeMgBr	methylmagnesium bromide
$MeNH_2$	methylamine
MeOH	methanol
Me-THF	2-methyltetrahydrofuran CAS [96-47-9]
min	minute(s)
MTBE	*tert*-butyl methyl ether
NMR	Nuclear Magnetic Resonance
o/n	overnight
$P(Cy)_3$	tricyclohexylphosphine CAS [2622-14-2]
$Pd(OAc)_2$	palladium (II) acetate CAS [3375-31-3]
$PdCl_2$	palladium(II) chloride CAS [7647-10-1]
$PdCl_2$(dppf)	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) CAS [72287-26-4]
$PdCl_2$(dppf).DCM	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane CAS [95464-05-4]
$PdCl_2$(dtbpf)	[1,1'-bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II) CAS [95408-45-0]
$(Ph)_2O$	diphenyl ether
PPACA	propylphosphonic anhydride CAS [68957-94-8]
PPh_3	triphenylphosphine
ppm	parts per million
q	quartet
quin	quintuplet
$Rh_2(OAc)_4$	rhodium(II) acetate dimer CAS [15956-28-2]
rt	room temperature
s	singulet
Selectfluor®	1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) CAS [140681-55-6]
sext	sextuplet
t	triplet
t-BuOK	potassium *tert*-butoxide
TFA	trifluoroacetic acid

	CAS [76-05-1]
TFAA	trifluoroacetic anhydride CAS [407-25-0]
THF	tetrahydrofuran
XantPhos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene CAS [161265-03-8]
Δ	heat

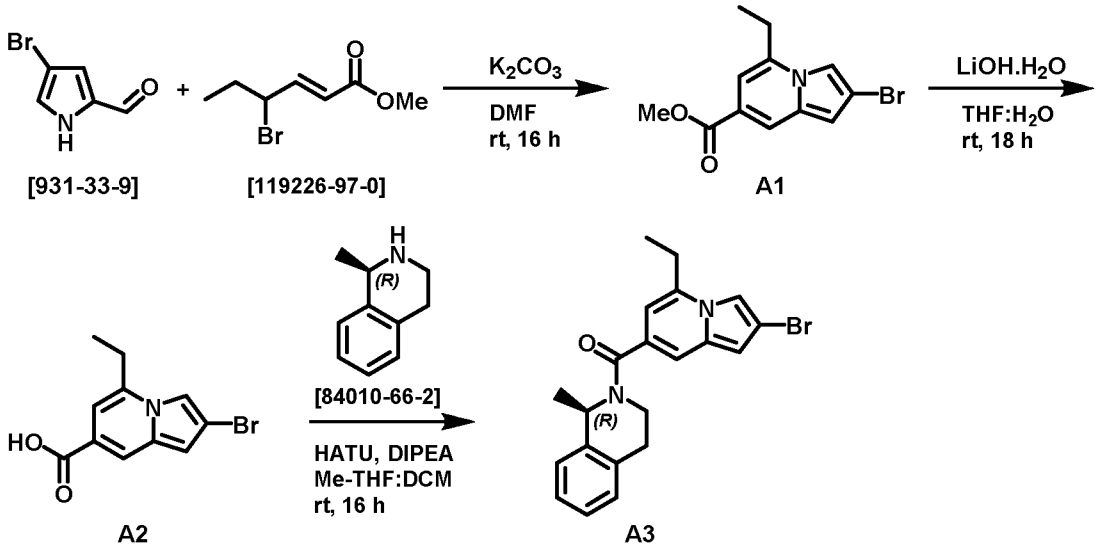
The stereochemical configuration for some compounds has been designated as R^* or S^* (or *R or *S) when the absolute stereochemistry is undetermined (even if the bonds are drawn stereospecifically) although the compound itself has been isolated as a single stereoisomer and is enantiomerically pure. This means that the absolute stereoconfiguration of the stereocentre indicated by * is undetermined (even if the bonds are drawn stereospecifically) although the compound is enantiomerically pure at the indicated centre.

B. Compound synthesis

Indolizines

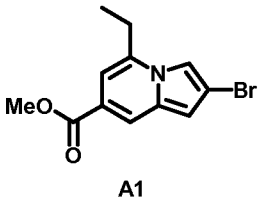
Synthesis of intermediates

Synthesis of Intermediate A3



*Intermediate **A1***

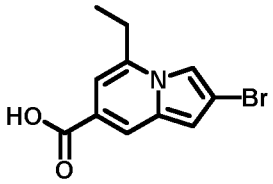
Methyl 2-bromo-5-ethylindolizine-7-carboxylate



A mixture of intermediate 4-bromo-1H-pyrrole-2-carbaldehyde [931-33-9] (1.41 g, 8.10 mmol), methyl-4-bromohex-2-enoate [119226-97-0] (2.26 g, 9.72 mmol, 89% purity) and potassium carbonate (2.46 g, 17.3 mmol) in DMF (38 mL) was stirred at rt for 16 h. The reaction mixture was poured out into water 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 in vacuo. The crude mixture was purified by preparative LC (regular SiOH, 30 µm, 200 g Interchim®, dry loading (Celite®), mobile phase gradient: heptane / EtOAc from 100:0 to 50:50) to afford intermediate **A1** (0.65 g, 28%).

Intermediate A2

2-Bromo-5-ethylindolizine-7-carboxylic acid

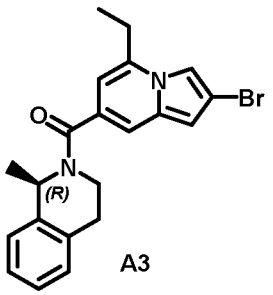


A2

A mixture of intermediate **A1** (0.65 g, 2.30 mmol) and lithium hydroxide monohydrate (193 mg, 4.61 mmol) in THF (15 mL) and H_2O (5 mL) was stirred at rt for 16 h. An additional amount of lithium hydroxide monohydrate (97.0 mg, 2.30 mmol) was added and the reaction mixture was stirred at rt for a further 2 h. The reaction mixture was diluted with a 1N aqueous solution of HCl. The layers were separated and the aqueous phase was extracted with EtOAc (twice). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was evaporated in vacuo to afford intermediate **A2** (617 mg, 95%).

Intermediate A3

(1*R*)-2-(2-Bromo-5-ethylindolizine-7-carbonyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline

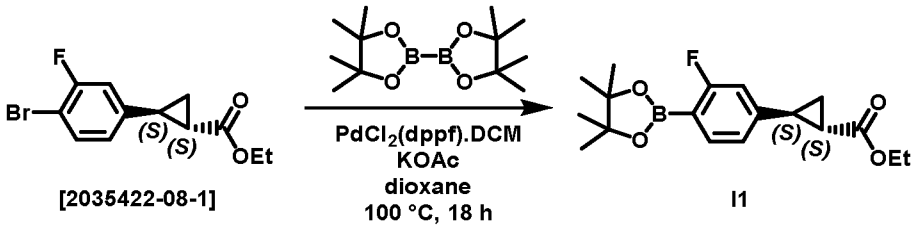


A3

To a mixture of intermediate **A2** (617 mg, 2.19 mmol) and (1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline [84010-66-2] (0.40 mL, 2.62 mmol) in 2-methyltetrahydrofuran (20 mL) were added HATU (1.66 g, 4.37 mmol) and DIPEA (1.51 mL, 8.76 mmol). The reaction mixture was stirred at rt for 16 h. DCM (5 mL) was added and the reaction mixture was stirred at rt for another 2 h. The precipitate was filtered off and the filtrate was evaporated to dryness. The crude mixture was purified by preparative LC (regular SiOH, 30 µm, 40 g Interchim®, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 80:20 to 40:60) to give intermediate **A3** (700 mg, 81%).

Synthesis of Intermediate I1

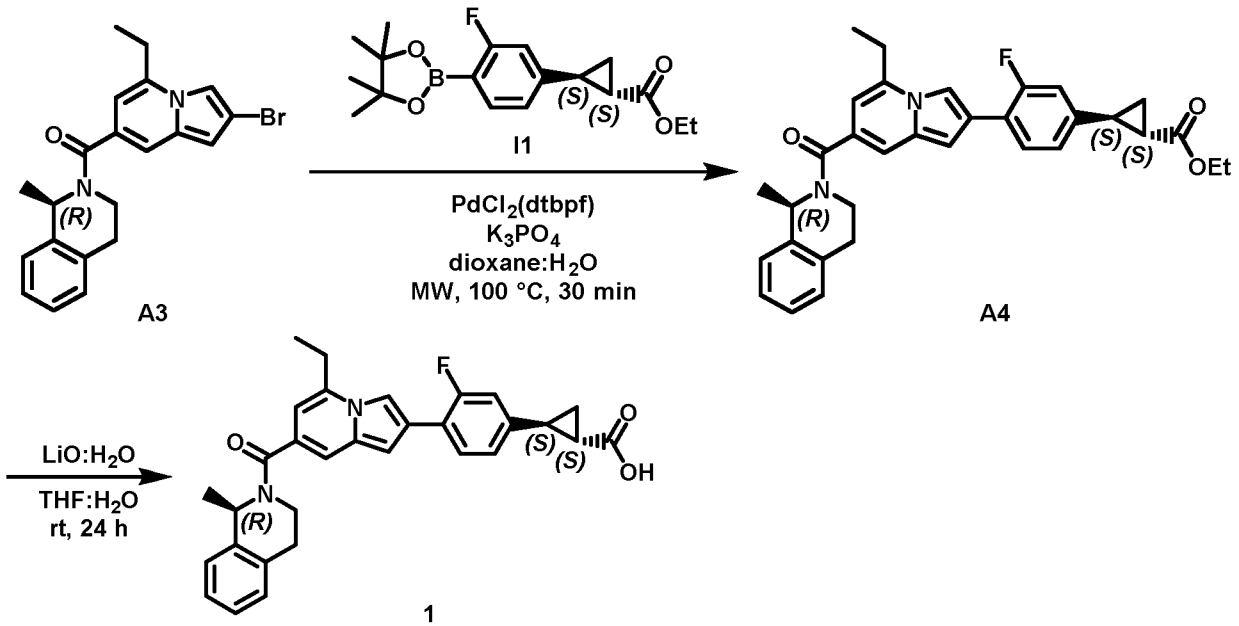
Ethyl (1*S*,2*S*)-2-[3-fluoro-4-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]cyclopropane-1-carboxylate



In a sealed tube bis(pinacolato)diboron (10.0 g, 39.4 mmol) and potassium acetate (6.80 g, 69.3 mmol) were added to a solution of ethyl (1*S*,2*S*)-2-(4-bromo-3-fluorophenyl)cyclopropane-1-carboxylate [2035422-08-1] (10.0 g, 34.8 mmol) in 1,4-dioxane (170 mL) under nitrogen atmosphere. The mixture was purged with nitrogen and [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II), complex with DCM (2.80 g, 3.42 mmol) was added. The reaction mixture was purged again with nitrogen and stirred at 100°C for 18 h. The reaction mixture was diluted with EtOAc. 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 preparative LC (irregular SiOH, 15-40 µm, Merck 400 g, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 100:0 to 0:25) to afford intermediate **I1** (9.26 g, 80%) as a colorless oil.

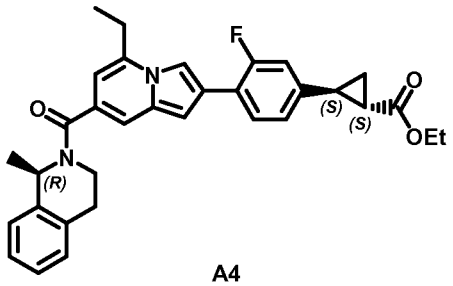
Synthesis of Final Compounds

Compound 1



Intermediate A4

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

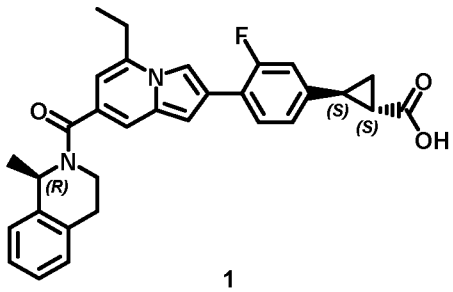


A4

To a degassed mixture of intermediate **A3** (250 mg, 0.63 mmol), intermediate **I1** (427 mg, 1.28 mmol) and potassium phosphate tribasic (401 mg, 1.89 mmol) in 1,4-dioxane (6.3 mL) and H_2O (1.6 mL) was added [1,1'-bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II) (41.0 mg, 62.9 µmol). The reaction 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 30 min. 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 the solvent was evaporated in vacuo. The crude mixture was purified by preparative LC (regular SiOH, 30 µm, 40 g Interchim®, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 80:20 to 30:70) to give intermediate **A4** (216 mg, 65%).

Compound 1

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

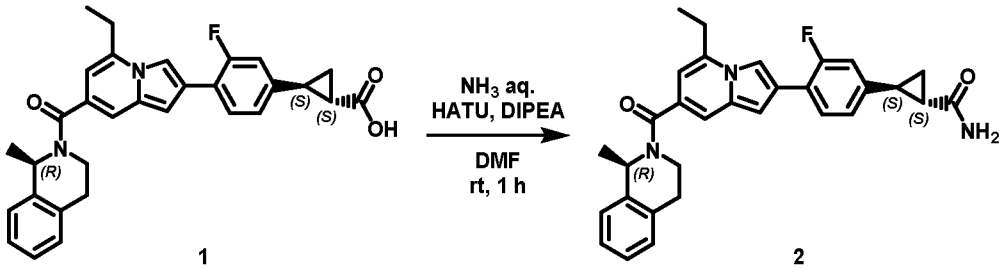


1

A mixture of intermediate **A4** (216 mg, 0.41 mmol) and lithium hydroxide monohydrate (51.7 mg, 1.23 mmol) in THF (5.8 mL) and H_2O (2.9 mL) was stirred at rt for 24 h. The reaction mixture was diluted with a 1N aqueous solution of HCl and H_2O. The precipitate was filtered off and dried to give compound **1** (124 mg, 61%).

Compound 2

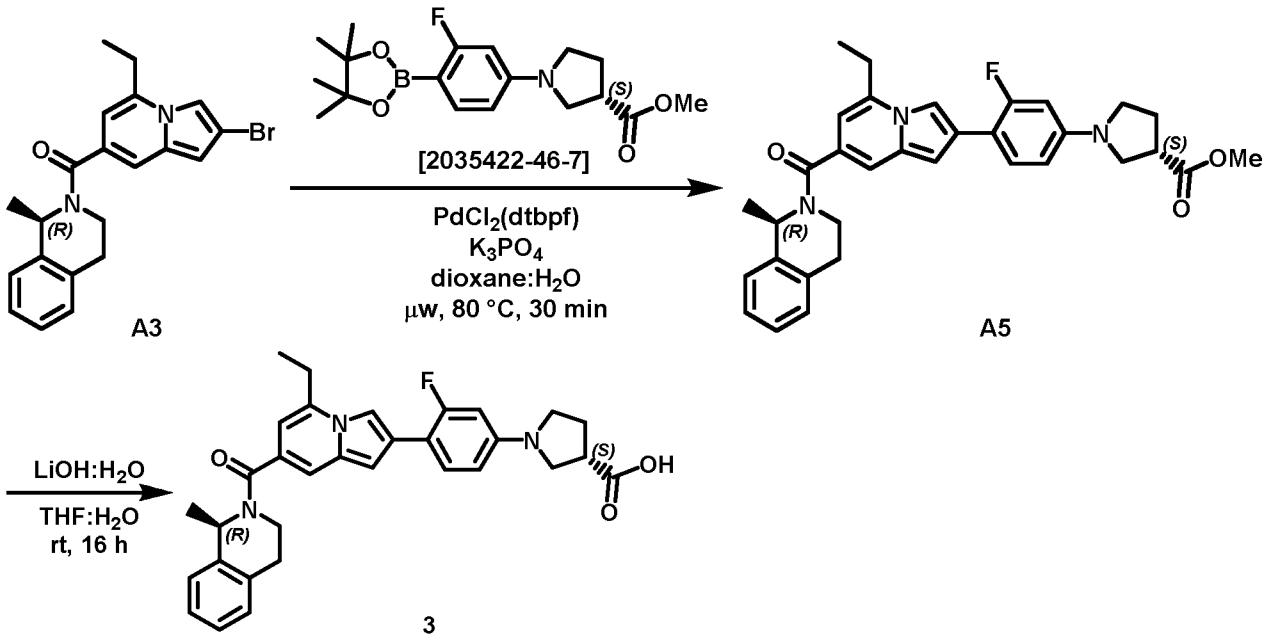
(1*S*,2*S*)-2-(4-{5-Ethyl-7-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-7,8-dihydroindolizin-2-yl}-3-fluorophenyl)cyclopropane-1-carboxamide



1 2

A mixture of compound **1** (112 mg, 0.23 mmol), HATU (111 mg, 0.29 mmol) and DIPEA (116 µL, 0.68 mmol) in DMF (1.3 mL) was stirred at rt for 1 h. Ammonia (28% in H_2O, 152 µL, 2.26 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 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 residue was taken up in MeOH. The solid was filtered off (100 mg) and dissolved in DCM. The organic phase was washed with a 1% aqueous solution of $NaHCO_3$ (twice), dried over $MgSO_4$, filtered and the solvent was evaporated in vacuo. The residue was taken up in MeOH. The solid was filtered off and dried under high vacuum at 60°C for 5 h to give compound **2** (34 mg, 30%).

Compound 3

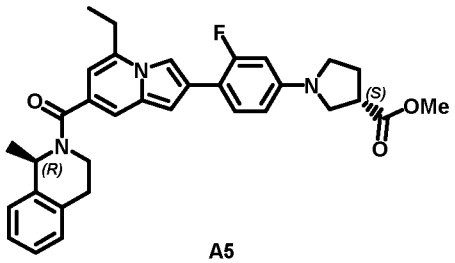


A3 A5

3

*Intermediate **A5***

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

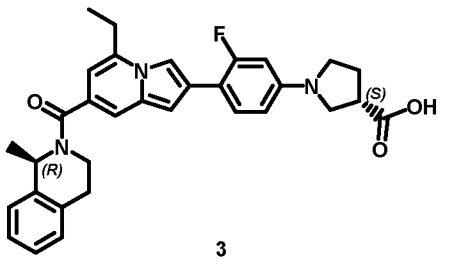


A5

To a degassed mixture of intermediate **A3** (170 mg, 0.43 mmol), methyl (3*S*)-1-[3-fluoro-4-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrrolidine-3-carboxylate [2035422-46-7] (164 mg, 0.47 mmol) and potassium phosphate tribasic (272 mg, 1.28 mmol) in 1,4-dioxane (4 mL) and H_2O (1 mL) was added [1,1'-bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II) (27.9 mg, 42.8 µmol). 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 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 the solvent was evaporated in vacuo. The crude mixture was purified by preparative LC (regular SiOH, 30 µm, 40 g Interchim®, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 80:20 to 30:70) to afford intermediate **A5** (100 mg, 43%).

*Compound **3***

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



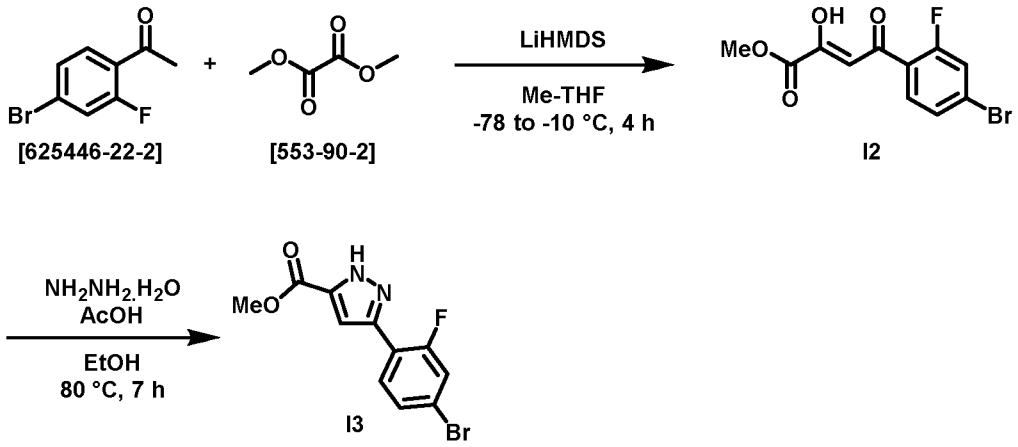
3

A mixture of intermediate **A5** (100 mg, 185 µmol) and lithium hydroxide monohydrate (23.3 mg, 0.55 mmol) in THF (2.6 mL) and H_2O (1.3 mL) was stirred at rt for 16 h. The reaction mixture was diluted with a 1N aqueous solution of HCl and H_2O. The mixture was extracted with EtOAc (twice). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was evaporated in vacuo. The residue was diluted with MeCN and EtOAc, and evaporated to dryness to give compound **3** (100 mg, quant.) as an orange solid.

Pyrazolo[1,5-a]pyridines

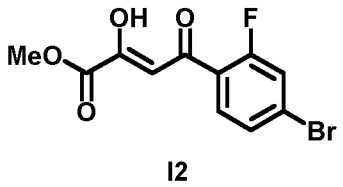
Synthesis of Intermediates

Synthesis of Intermediate I3



*Intermediate **I2***

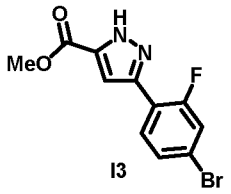
Methyl-4-(4-bromo-2-fluorophenyl)-2-hydroxy-4-oxobut-2-enoate



Lithium bis(trimethylsilyl)amide (1.5 M in THF, 50 mL, 75.0 mmol) was added to a mixture of 4-bromo-2-fluoroacetophenone [625446-22-2] (15.0 g, 69.1 mmol) in 2-methyltetrahydrofuran (150 mL) at -78°C. The reaction mixture was stirred at this temperature for 15 min and a solution of dimethyl oxalate [553-90-2] (8.33 g, 70.6 mmol) in 2-methyltetrahydrofuran (100 mL) was added. The reaction mixture was stirred at -10°C for 4 h. A 3N aqueous solution of HCl was added and the aqueous phase was extracted with EtOAc (twice). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was evaporated in vacuo to afford intermediate **I2** (21.9 g, quant.) as a yellow solid.

*Intermediate **I3***

Methyl 3-(4-bromo-2-fluorophenyl)-1H-pyrazole-5-carboxylate



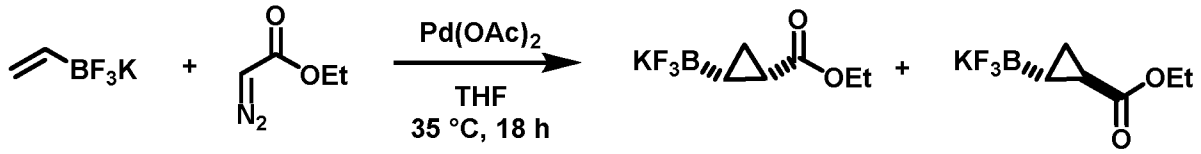
I3

A mixture of intermediate **I2** (21.9 g, 68.6 mmol), hydrazine monohydrate (80% in H_2O, 4.2 mL, 70.0 mmol) and acetic acid (0.9 mL, 15.6 mmol) in ethanol (200 mL) was stirred at 80°C for 7 h. The reaction mixture was cooled down and a precipitate was formed. The precipitate was filtered off, washed with EtOH and dried under vacuum at 50°C for 4 h to afford intermediate **I3** (13.2 g, 64%) as a white solid.

Synthesis of Intermediates I4 and I5

I4: Ethyl *cis*-2-(trifluoro-λ^4-boranyl)cyclopropane-1-carboxylate potassium

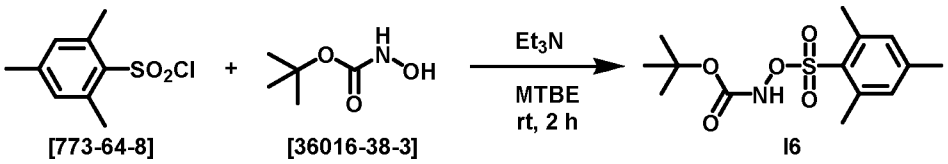
I5: Ethyl *trans*-2-(trifluoro-λ^4-boranyl)cyclopropane-1-carboxylate potassium

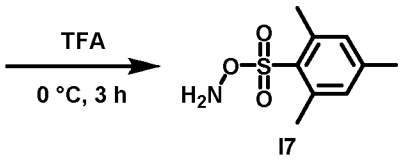


[13682-77-4] **[623-73-4]** **I4** ***(cis:trans* 80:20)** **I5** ***(cis:trans* 14:86)**

Potassium vinyltrifluoroborate [13682-77-4] (2.00 g, 15.0 mmol) was solubilized in THF (20.5 mL). Palladium acetate (33.5 mg, 0.15 mmol) was added and the reaction mixture was stirred at 35°C. Ethyl diazoacetate (85 wt.% in DCM, 2.00 mL, 16.4 mmol) in THF (2 mL) was added with a syringe pump over 4 h and the reaction mixture was stirred at 35°C for 18 h. The reaction mixture was diluted with heptane at rt and the mixture was stirred for 30 min. The suspension was filtered off and crystallized from acetone (20 mL) at -18°C. The solid was filtered off to afford intermediate **I4** (*cis*:*trans* 80:20, 520 mg, 16%) as a grey solid. The filtrate was washed with activated charcoal, filtered and concentrated to dryness. The residue was diluted with EtOH (20 mL) and heated at 50°C. Filtration of the gummy suspension delivered intermediate **I5** (*cis*:*trans* 14:86, 1.83 g, 56%) as a white solid.

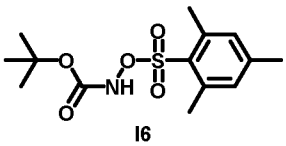
Synthesis of Intermediate I7





*Intermediate **I6***

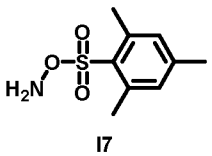
tert-Butyl N-[(2,4,6-trimethylbenzenesulfonyl)oxy]carbamate



To a mixture of 2-mesitylenesulfonyl chloride [773-64-8] (5.47 g, 25.0 mmol) and *tert*-butyl N-hydroxycarbamate [36016-38-3] (3.67 g, 27.5 mmol) in MTBE (51 mL) at 0°C was added Et_3N (3.82 mL, 27.5 mmol) dropwise. The reaction mixture was stirred at rt for 2 h. The suspension was filtered and the solid was washed with MTBE. The filtrate was dried over $MgSO_4$, filtered and concentrated in vacuo to afford intermediate **I6** (8.75 g, quant., 90% purity) as a yellow oil.

*Intermediate **I7***

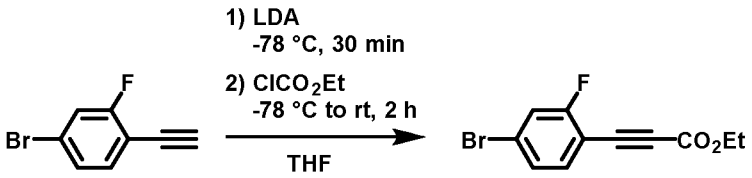
Amino 2,4,6-trimethylbenzene-1-sulfonate



A solution of intermediate **I6** (8.75 g, 25.0 mmol, 90% purity) in TFA (10 mL) was stirred at 0°C for 3 h. The reaction mixture was poured out into iced water. The precipitate was filtered off, washed with H_2O and dried under vacuum to give intermediate **I7** (1 g, 19%) as a white solid.

Synthesis of Intermediate I8

Ethyl 3-(4-bromo-3-fluorophenyl)prop-2-ynoate

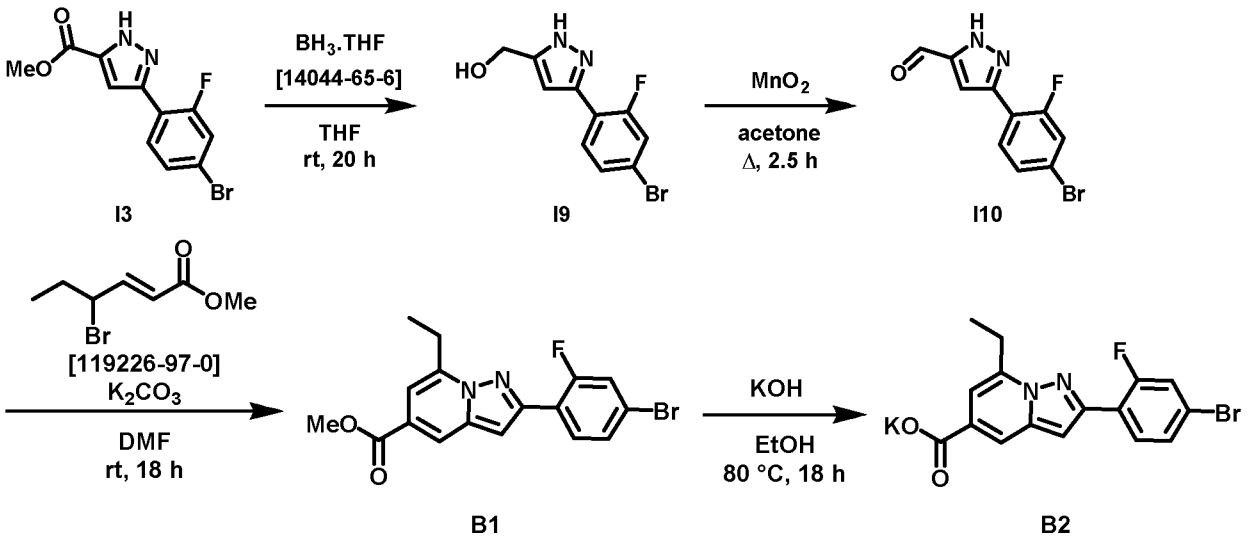


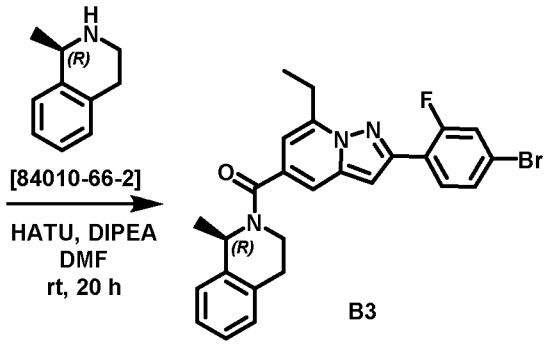
[302912-33-0] I8

n-Butyllithium (1.6 M in hexane, 1.5 mL, 2.40 mmol) was added to a solution of DIPA (0.4 mL, 2.85 mmol) in THF (15 mL) at -78°C. The reaction mixture was stirred at for 30 min and a solution of 4-bromo-2-fluoroacetylene [302912-33-0] (0.47 g, 2.35 mmol) in THF (5 mL) was added. The reaction mixture was stirred at -78°C for 30 min. Ethyl chloroformate (0.5 mL, 5.23 mmol) was added and the reaction mixture was stirred at -78°C for 30 min and at rt for 2 h. The reaction mixture was quenched by the addition of a 10% aqueous solution of NH_4Cl and diluted with EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated in vacuo. 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 100:0 to 85:15) to give intermediate **I8** (505 mg, 79%).

Synthesis of Pyrazolo[1,5-a]pyridine Intermediates

Synthesis of Intermediate B3

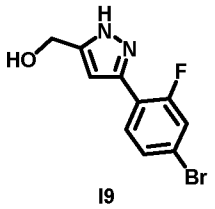




B3

*Intermediate **I9***

[3-(4-Bromo-2-fluorophenyl)-1H-pyrazol-5-yl]methanol

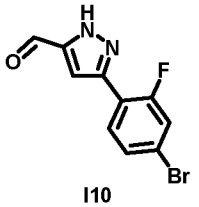


I9

Boran tetrahydrofuran complex (1.0 M in THF, 70 mL, 70.0 mmol) was added slowly to a solution of intermediate **I3** (7.07 g, 23.6 mmol) in THF (200 mL). The reaction mixture was stirred at rt for 20 h. The reaction mixture was quenched by the careful addition of MeOH. The solution was diluted with EtOAc and brine. 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 diluted with DCM. The precipitate was filtered off, washed with DCM and dried to afford intermediate **I9** (3.24 g, 50%) as a white solid.

*Intermediate **I10***

3-(4-Bromo-2-fluorophenyl)-1H-pyrazole-5-carbaldehyde

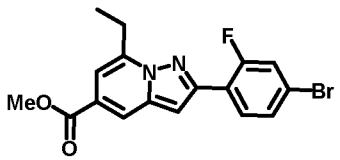


I10

A mixture of intermediate **I9** (6.41 g, 23.6 mmol) and manganese dioxide (20.0 g; 230 mmol) in acetone (300 mL) was stirred under reflux for 2.5 h. The reaction mixture was filtered over a pad of Celite® and the filtrate was evaporated in vacuo to afford intermediate **I10** (1.77 g, 28%) as a white solid.

*Intermediate **B1***

Methyl 2-(4-bromo-2-fluorophenyl)-7-ethylpyrazolo[1,5-a]pyridine-5-carboxylate

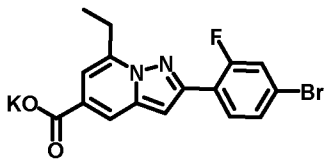


B1

A mixture of intermediate **I10** (1.77 g, 6.58 mmol), methyl-4-bromohex-2-enoate [119226-97-0] (1.60 g, 7.34 mmol) and potassium carbonate (1.90 g, 13.8 mmol) in DMF (50 mL) 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 in vacuo. The residue was diluted with MeOH and triturated in MeOH. The solid was filtered off and washed with MeOH to afford intermediate **B1** (1.4 g, 56%) as a white solid.

*Intermediate **B2***

Potassium 2-(4-bromo-2-fluorophenyl)-7-ethylpyrazolo[1,5-a]pyridine-5-carboxylate

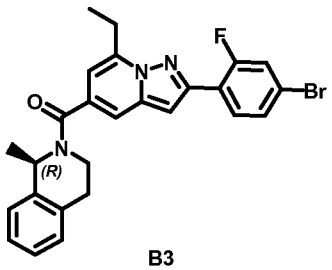


B2

Potassium hydroxide (730 mg, 11.1 mmol, 85% purity) was added to a solution of intermediate **B1** (1.40 g, 3.71 mmol) in EtOH (35 mL). The reaction mixture was stirred at 80°C for 18 h. The reaction mixture was cooled down and a precipitate was observed. The precipitate was filtered off to afford intermediate **B2** (975 mg, 65%) as a white solid.

*Intermediate **B3***

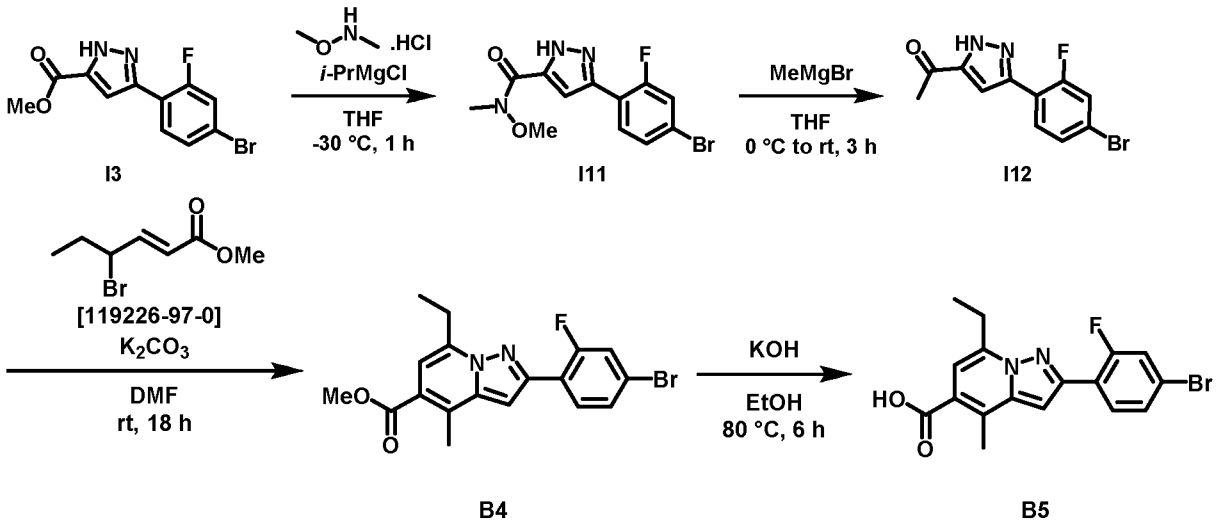
(1*R*)-2-[2-(4-Bromo-2-fluorophenyl)-7-ethylpyrazolo[1,5-a]pyridine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline



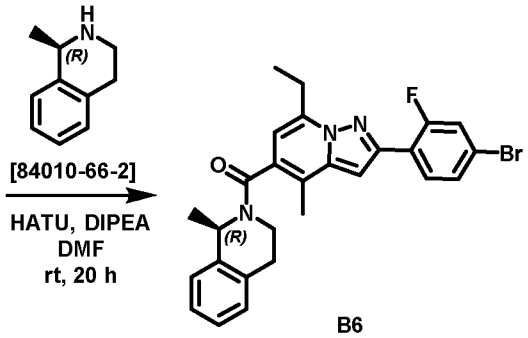
B3

A mixture of intermediate **B2** (500 mg, 1.25 mmol), (1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline [84010-66-2] (220 mg, 1.5 mmol), HATU (640 mg, 1.68 mmol) and DIPEA (640 µL, 3.71 mmol) in DMF (25 mL) was stirred at rt for 20 h. 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 brine, dried over $MgSO_4$, filtered and evaporated in vacuo. 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 0:100) to give intermediate **B3** (622 mg, quant.) as a white foam.

Synthesis of Intermediate B6



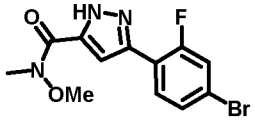
I3 I11 I12 B4 B5



B6

*Intermediate **I11***

3-(4-Bromo-2-fluorophenyl)-N-methoxy-N-methyl-1H-pyrazole-5-carboxamide

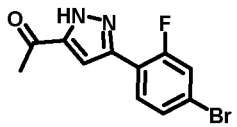


I11

Under nitrogen atmosphere a mixture of intermediate **I3** (500 mg, 1.67 mmol) and N,O-dimethylhydroxylamine hydrochloride (489 mg, 5.02 mmol) in THF (2 mL) was stirred at -30°C. Isopropylmagnesium chloride (2.0 M in THF, 5.0 mL, 10.0 mmol) was added and the reaction mixture was stirred at -30°C for 1 h. The reaction was quenched by the addition of a 1N aqueous solution of HCl and diluted with EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated in vacuo to afford intermediate **I11** (538 mg, 98%) as a white solid.

*Intermediate **I12***

1-[3-(4-Bromo-2-fluorophenyl)-1H-pyrazol-5-yl]ethan-1-one

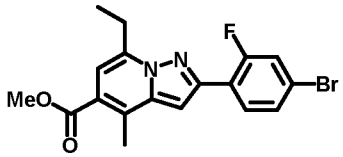


I12

Under nitrogen atmosphere methylmagnesium bromide (3.0 M in Et_2O, 1.1 mL, 3.30 mmol) was added to a solution of intermediate **I11** (538 mg, 1.64 mmol) in THF (2 mL) at 0°C. The reaction mixture was stirred at rt for 3 h. The reaction was quenched by the addition of an aqueous solution of NH_4Cl and diluted with EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated in vacuo to afford intermediate **I12** (447 mg, 96%) as a white solid.

*Intermediate **B4***

Methyl 2-(4-bromo-2-fluorophenyl)-7-ethyl-4-methylpyrazolo[1,5-a]pyridine-5-carboxylate

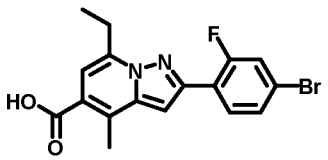


B4

A mixture of intermediate **I12** (380 mg, 1.34 mmol), methyl-4-bromohex-2-enoate [119226-97-0] (365 mg, 1.50 mmol, 85% purity) and potassium carbonate (388 mg, 2.81 mmol) in DMF (10 mL) 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 in vacuo. 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 60:40) to afford intermediate **B4** (182 mg, 35%) as a white solid.

*Intermediate **B5***

2-(4-Bromo-2-fluorophenyl)-7-ethyl-4-methylpyrazolo[1,5-a]pyridine-5-carboxylic acid

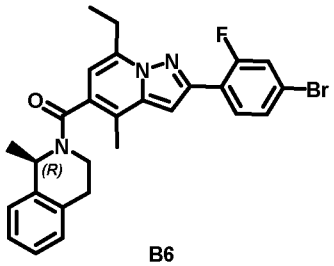


B5

Potassium hydroxide (100 mg, 1.52 mmol, 85% purity) was added to a solution of intermediate **B4** (200 mg, 0.51 mmol) in EtOH (5 mL). The reaction mixture was stirred at 80°C for 6 h. The reaction mixture was diluted with EtOAc 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 brine, dried over $MgSO_4$, filtered and evaporated in vacuo to afford intermediate **B5** (180 mg, 93%).

*Intermediate **B6***

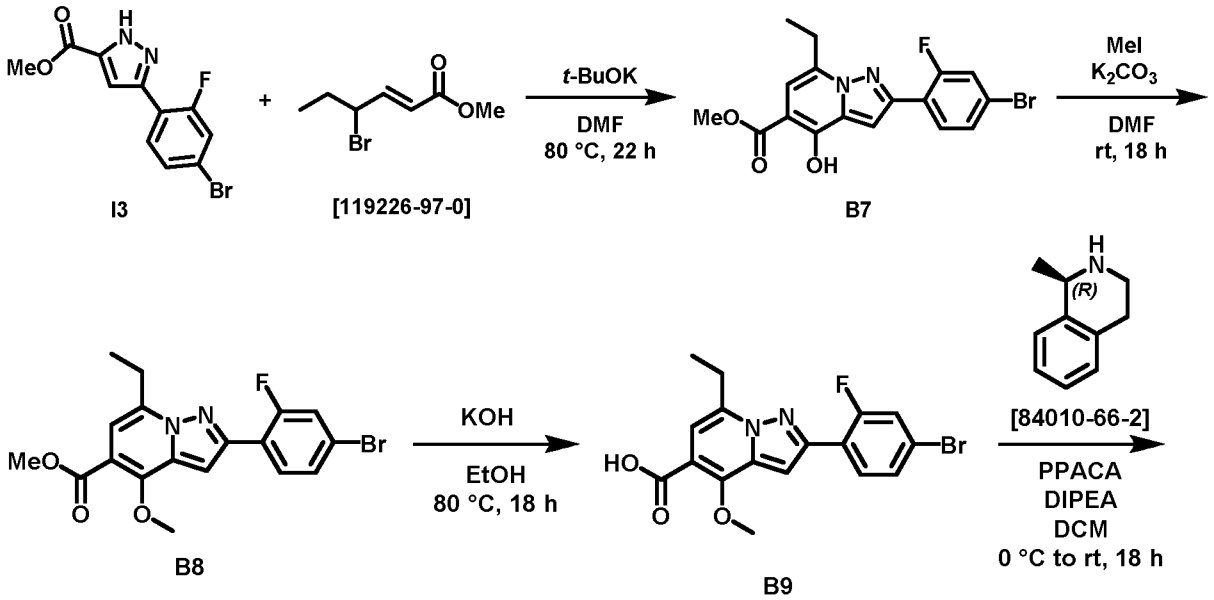
(1*R*)-2-[2-(4-Bromo-2-fluorophenyl)-7-ethyl-4-methylpyrazolo[1,5-a]pyridine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline

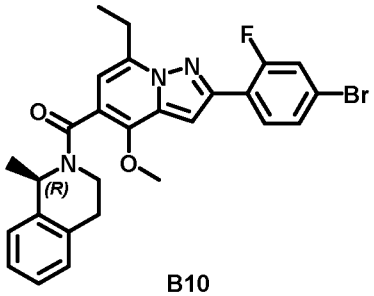


B6

A mixture of intermediate **B5** (180 mg, 0.48 mmol), (1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline [84010-66-2] (83.4 mg, 0.57 mmol), HATU (246 mg, 0.65 mmol) and DIPEA (246 µL, 1.43 mmol) in DMF (8 mL) was stirred at rt for 20 h. 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 dried over $MgSO_4$, filtered and evaporated in vacuo. 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 90:10 to 0:100) to afford intermediate **B6** (232 mg, 96%) as a white foam.

Synthesis of Intermediate B10

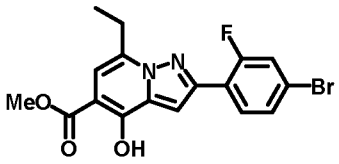




B10

*Intermediate **B7***

Methyl 2-(4-bromo-2-fluorophenyl)-7-ethyl-4-hydroxypyrazolo[1,5-a]pyridine-5-carboxylate

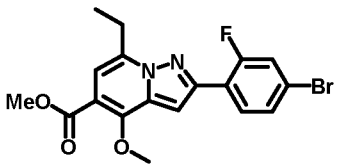


B7

A mixture of intermediate **I3** (5.78 g, 19.3 mmol), methyl-4-bromohex-2-enoate [119226-97-0] (11.0 g; 42.9 mmol) and potassium *tert*-butoxide (8.00 g, 71.3 mmol) in DMF (120 mL) was stirred at 80°C for 18 h. An additional amount of intermediate **I2** (1.60 g, 6.30 mmol) and potassium *tert*-butoxide (2.00 g, 17.8 mmol) were added and the reaction mixture was stirred at 80°C for another 4 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 in vacuo. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 220 g Grace®, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 100:0 to 65:35) to afford intermediate **B7** (1.85 g, 24%) as a white solid.

*Intermediate **B8***

Methyl 2-(4-bromo-2-fluorophenyl)-7-ethyl-4-methoxypyrazolo[1,5-a]pyridine-5-carboxylate



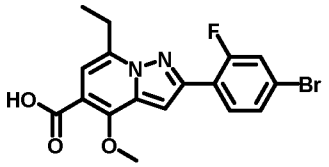
B8

A mixture of intermediate **B7** (100 mg, 0.25 mmol), methyl iodide (19.0 µL, 305 µmol) and potassium carbonate (70.3 mg, 0.51 mmol) in DMF (2 mL) 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 in vacuo. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 12 g Grace®, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 100:0 to 60:40) to afford intermediate **B8** (85 mg, 82%) as a white solid.

*Intermediate **B9***

2-(4-Bromo-2-fluorophenyl)-7-ethyl-4-methoxypyrazolo[1,5-a]pyridine-5-carboxylic acid

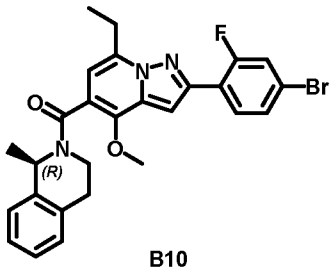


B9

Potassium hydroxide (41.1 mg, 0.62 mmol, 85% purity) was added to a solution of intermediate **B8** (85.0 mg, 0.21 mmol) in EtOH (2 mL). The reaction mixture was stirred at 80°C for 18 h. The mixture was diluted with EtOAc 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 brine, dried over $MgSO_4$, filtered and evaporated in vacuo to afford intermediate **B9** (80 mg, 97%) as a white solid.

*Intermediate **B10***

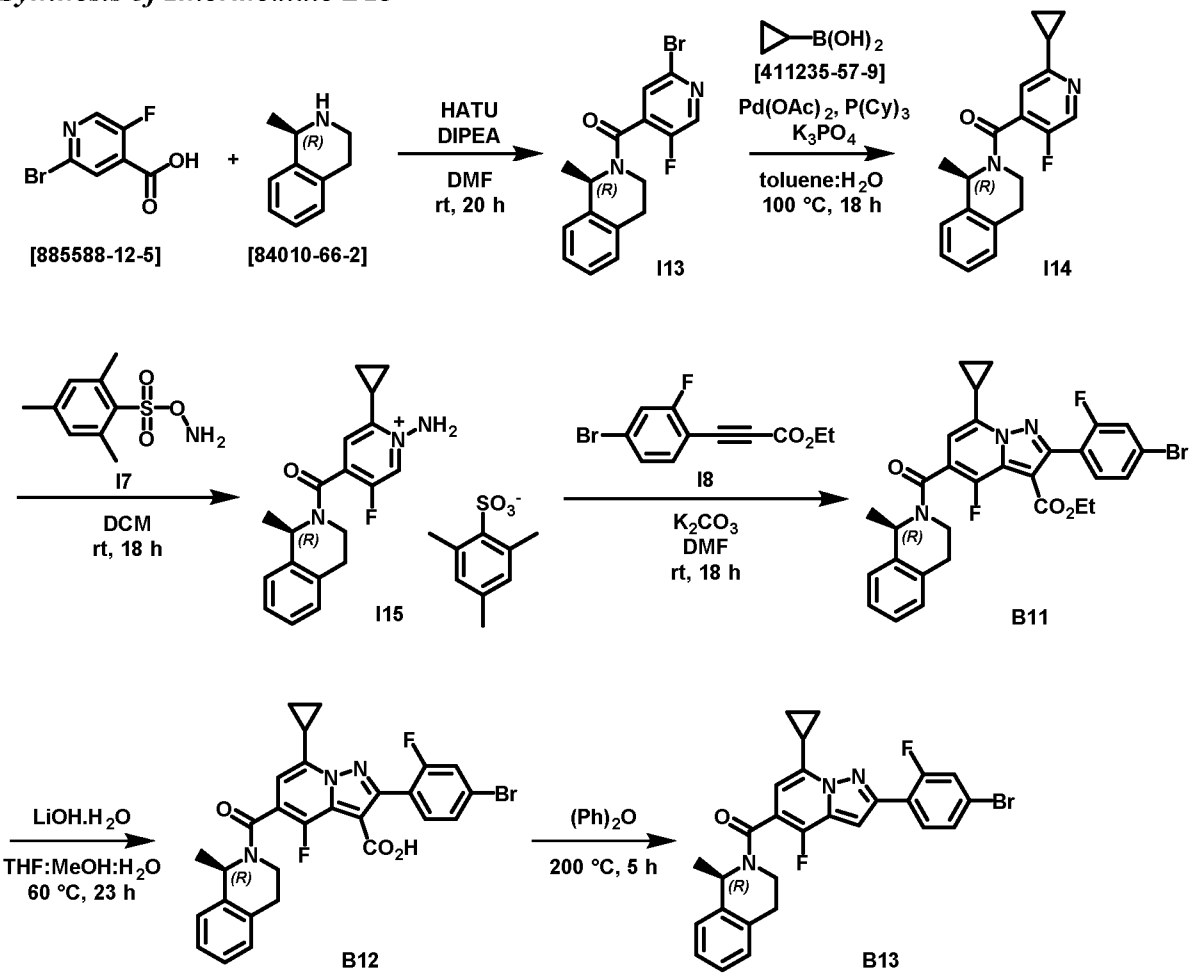
(1*R*)-2-[2-(4-Bromo-2-fluorophenyl)-7-ethyl-4-methoxypyrazolo[1,5-a]pyridine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline



B10

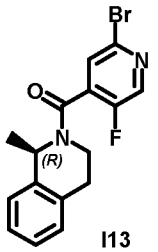
A mixture of intermediate **B9** (80.0 mg, 0.20 mmol), (1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline [84010-66-2] (34.8 mg, 0.24 mmol) and DIPEA (174 µL, 1.01 mmol) in DCM (1 mL) was stirred at 0°C. PPACA (50 wt. % in EtOAc, 0.30 mL, 0.51 mmol) was added slowly. The reaction mixture was stirred at 0°C for 10 min and at rt for 18 h. The reaction mixture was diluted with EtOAc 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 brine, dried over $MgSO_4$, filtered and evaporated in vacuo to afford intermediate **B10** (83 mg, 78%) as a white foam.

Synthesis of Intermediate B13



*Intermediate **I13***

(1*R*)-2-(2-Bromo-5-fluoropyridine-4-carbonyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline



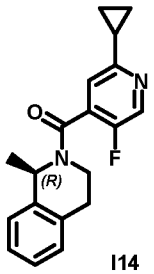
I13

A mixture of 2-bromo-5-fluoroisonicotinic acid [885588-12-5] (1.00 g, 4.55 mmol), (1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline [84010-66-2] (803 mg, 5.45 mmol), HATU (2.34 g, 6.14 mmol) and DIPEA (2.34 mL, 13.5 mmol) in DMF (50 mL) was stirred at rt for 20 h. 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 dried over $MgSO_4$, filtered and evaporated in vacuo. 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 0:100) to afford intermediate **I13** (1.62 g, quant.).

*Intermediate **I14***

(1*R*)-2-(2-Cyclopropyl-5-fluoropyridine-4-carbonyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline

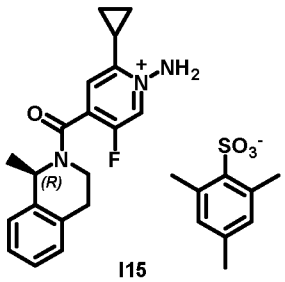


I14

To a solution of intermediate **I13** (1.50 g, 4.30 mmol) in toluene (30 mL) were added cyclopropylboronic acid [411235-57-9] (738 mg, 8.59 mmol), potassium phosphate tribasic (2.28 g, 10.7 mmol), tricyclohexylphosphine (361 mg, 1.29 mmol) and H_2O (4.5 mL). The mixture was purged with nitrogen (3 times) and palladium acetate (145 mg, 644 µmol) was added. 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. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 80 g GraceResolv™, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 100:0 to 90:10 and from 50:50 to 85:15) to afford intermediate **I14** (1.15 g, 86%) as a colorless gum.

*Intermediate **I15***

1-Amino-2-cyclopropyl-5-fluoro-4-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyridin-1-ium 2,4,6-trimethylbenzene-1-sulfonate

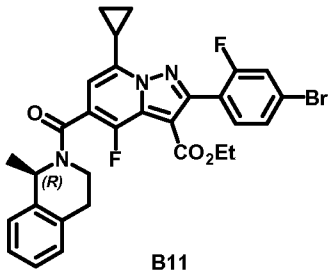


I15

A mixture of intermediate **I14** (1.24 g, 4.00 mmol) and intermediate **I7** (1.00 g, 4.65 mmol) in DCM (10 mL) was stirred at rt for 18 h. The reaction mixture was evaporated in vacuo to afford intermediate **I15** (1.88 g, 90%) as a white foam.

*Intermediate **B11***

Ethyl 2-(4-bromo-2-fluorophenyl)-7-cyclopropyl-4-fluoro-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyridine-3-carboxylate

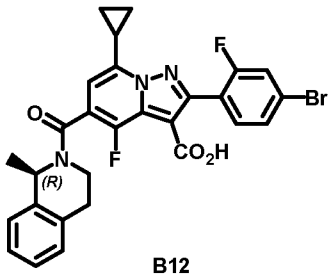


B11

A mixture of intermediate **I15** (1.00 g, 1.90 mmol), intermediate **I8** (550 mg, 2.03 mmol) and potassium carbonate (526 mg, 3.81 mmol) in DMF (15 mL) 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 in vacuo. 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 100:0 to 50:50) to afford intermediate **B11** (515 mg, 45%) as a yellow foam.

*Intermediate **B12***

2-(4-Bromo-2-fluorophenyl)-7-cyclopropyl-4-fluoro-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydro-isoquinoline-2-carbonyl]pyrazolo[1,5-a]pyridine-3-carboxylic acid

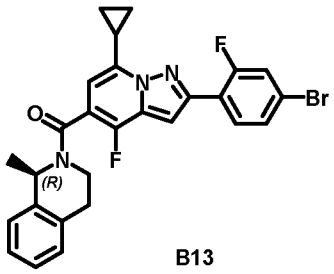


B12

Lithium hydroxide monohydrate (545 mg, 13.0 mmol) was added to a solution of intermediate **B11** (515 mg, 0.87 mmol) in THF (6 mL) and H_2O (4 mL). The reaction mixture was stirred at 60°C for 18 h. An additional amount of lithium hydroxide monohydrate (545 mg, 13.0 mmol) and MeOH (2 mL) were added and the reaction mixture was stirred at 60°C for 5 h. A 10% aqueous solution of $KHSO_4$ was added until pH was 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 **B12** (520 mg, quant.) as a pale yellow gum.

*Intermediate **B13***

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

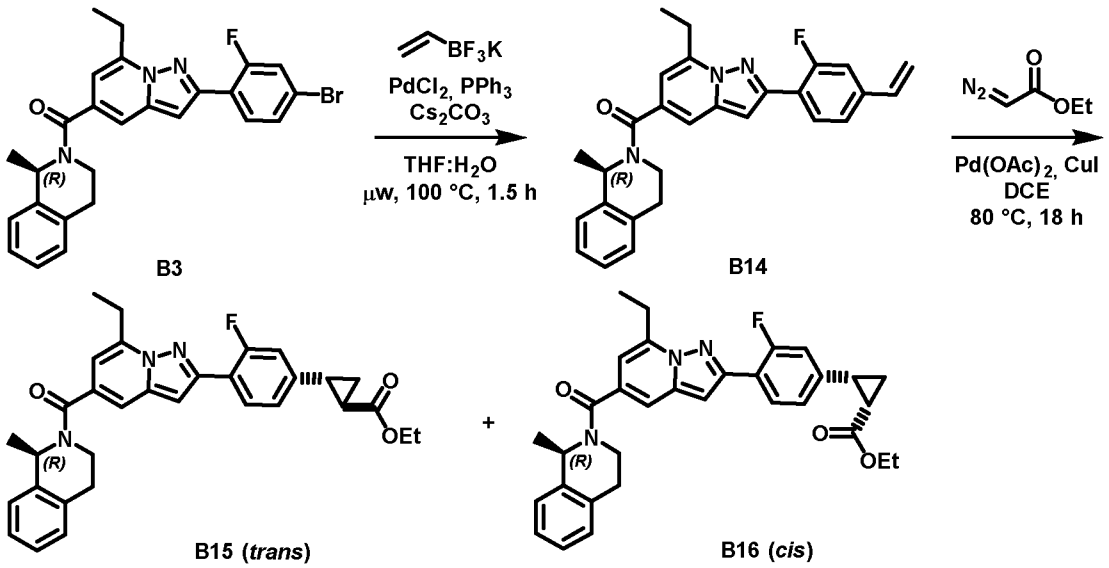


B13

A solution of intermediate **B12** (520 mg, 0.87 mmol) in diphenyl ether (5 mL) was stirred at 200°C for 5 h. The reaction mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 80 g Grace®, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 100:0 to 80:20) to give intermediate **B13** (129 mg, 28%) as an off-white foam.

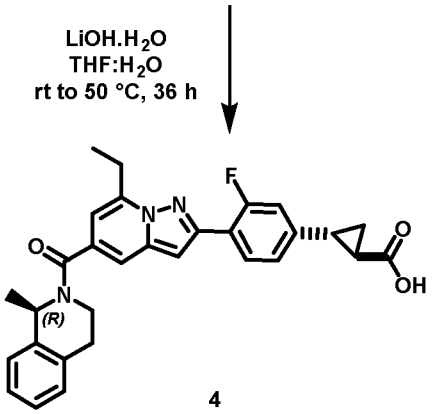
Synthesis of the final compounds

Compound 4



B3 B14

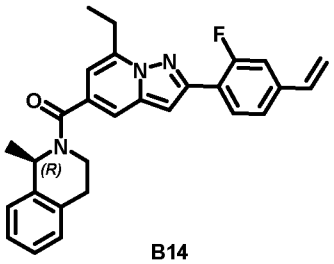
B15 (*trans*) B16 (*cis*)



4

*Intermediate **B14***

(1*R*)-2-[2-(4-Ethenyl-2-fluorophenyl)-7-ethylpyrazolo[1,5-a]pyridine-5-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline



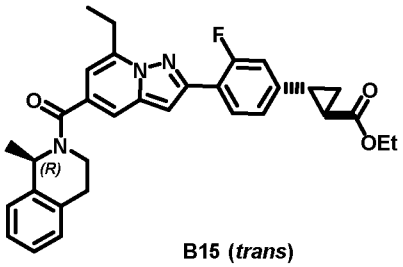
B14

Palladium chloride (7.00 mg, 39.5 µmol) was added to a degassed mixture of intermediate **B3** (400 mg, 0.81 mmol), potassium vinyltrifluoroborate [13682-77-4] (325 mg, 2.43 mmol), cesium carbonate (1.20 g, 3.68 mmol) and triphenylphosphine (30.0 mg, 114 µmol) in THF and H_2O (9:1, 15 mL). The reaction 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 1.5 h. The reaction mixture was diluted with EtOAc and H_2O. The layers were separated and the organic phase was washed with H_2O, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude mixture was purified by preparative LC (regular SiOH, 30 µm, 40 g Grace®, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 100:0 to 60:40) to afford intermediate **B14** (249 mg, 70%) as a white foam.

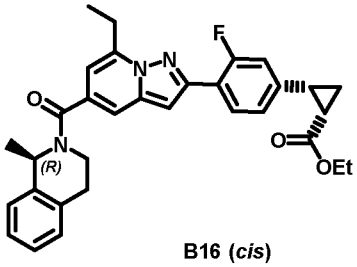
*Intermediates **B15** and **B16***

B15: Ethyl *trans*-2-(4-{7-ethyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyridin-2-yl}-3-fluorophenyl)cyclopropane-1-carboxylate

B16: Ethyl *cis*-2-(4-{7-ethyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyridin-2-yl}-3-fluorophenyl)cyclopropane-1-carboxylate



B15 (*trans*)

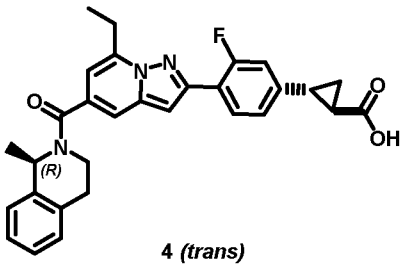


B16 (*cis*)

A mixture of intermediate **B14** (249 mg, 567 µmol), copper iodide (43.2 mg, 227 µmol) and palladium acetate (25.4 mg, 113 µmol) in DCE (3 mL) was stirred at 80°C. Ethyl diazoacetate [623-73-4] (85% purity, 0.42 mL, 3.40 mmol) was added with a syringe pump over 2 h and the reaction mixture was stirred at 80°C for 18 h. The reaction mixture was filtered over a pad of Celite®. The filtrate was 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: heptane / EtOAc from 100:0 to 50:50) to afford intermediate **B15** (33 mg, 11%) as a white foam and intermediate **B16** (30 mg, 10%) as a colorless gum.

Compound 4

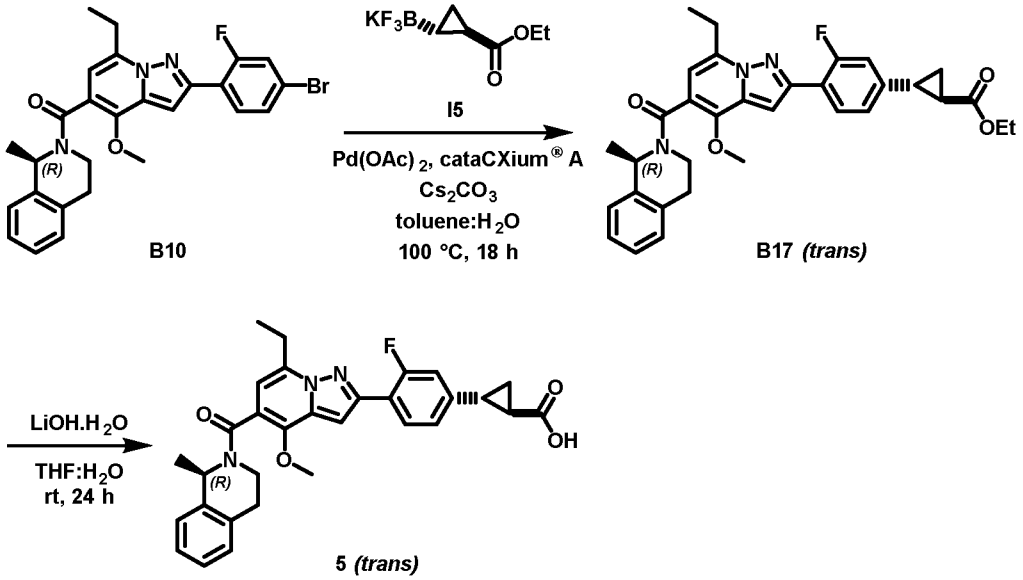
Trans-2-(4-{7-ethyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyridin-2-yl}-3-fluorophenyl)cyclopropane-1-carboxylic acid



4 (*trans*)

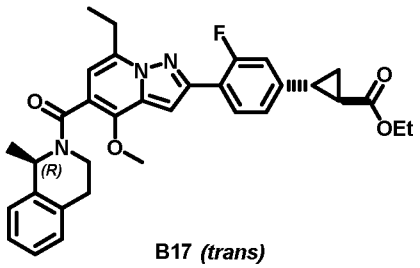
Lithium hydroxide monohydrate (13.3 mg, 318 µmol) was added to a solution of intermediate **B15** (33.0 mg, 62.8 µmol) in THF (1.8 mL) and H_2O (0.75 mL). The reaction mixture was stirred at rt for 18 h and at 50°C for another 18 h. A 10% aqueous solution of $KHSO_4$ was added until pH 6 and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with H_2O, dried over $MgSO_4$, filtered and evaporated in vacuo. The residue was diluted in H_2O and MeCN (1:1) and freeze-dried to give compound **4** (23 mg, 74%) as a white solid.

Compound 5



*Intermediate **B17***

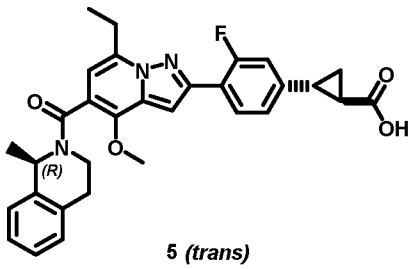
Ethyl *trans*-2-(4-{7-ethyl-4-methoxy-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyridin-2-yl}-3-fluorophenyl)cyclopropane-1-carboxylate



To a mixture of intermediate **B10** (68.0 mg, 0.13 mmol), intermediate **I5** (*cis*:*trans* 14:86, 29.5 mg, 0.13 mmol) and cesium carbonate (118 mg, 0.36 mmol) in toluene (1.5 mL) and H_2O (0.15 mL) was added cataCXium® A (10.8 mg, 30.2 µmol) and palladium acetate (4.92 mg, 2.19 µmol). The reaction mixture was purged with nitrogen and stirred at 100°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 evaporated in vacuo. 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 60:40) to afford intermediate **B17** (43 mg, 60%) as a white foam.

*Compound **5***

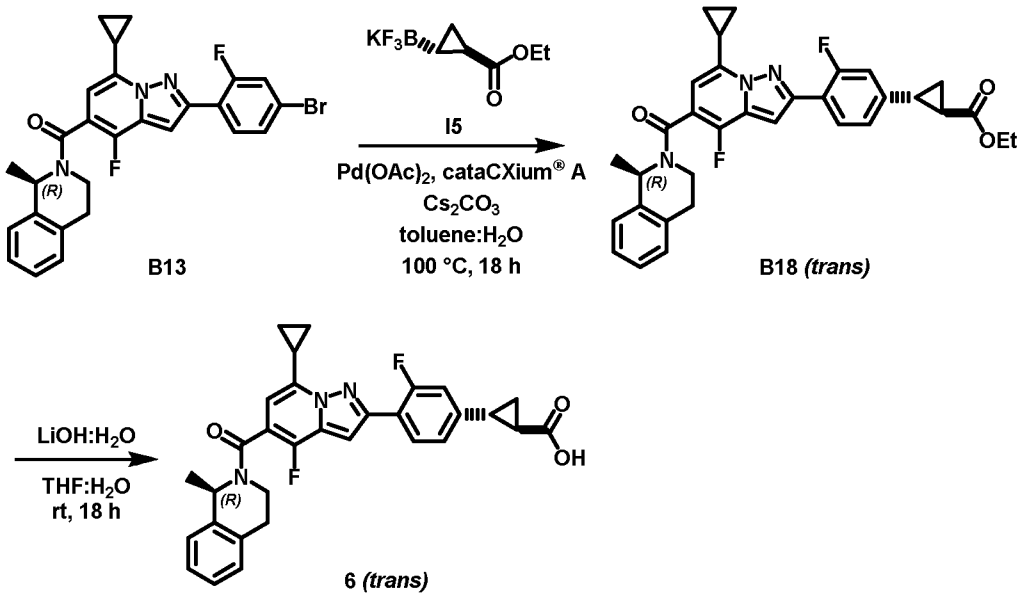
trans-2-(4-{7-Ethyl-4-methoxy-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyridin-2-yl}-3-fluorophenyl)cyclopropane-1-carboxylic acid



5 (*trans*)

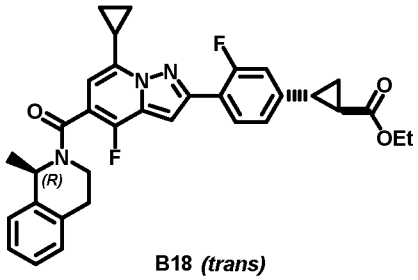
Lithium hydroxide monohydrate (17.9 mg, 0.43 mmol) was added to a solution of intermediate **B17** (43.0 mg, 77.4 µmol) in THF (2.4 mL) and H_2O (1 mL). The reaction mixture was stirred at rt for 24 h. A 10% aqueous solution of $KHSO_4$ was added until pH 6 and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with H_2O, dried over $MgSO_4$, filtered and evaporated in vacuo. The crude mixture was purified by reverse phase (spherical C18, 25 µm, 40 g YMC-ODS-25, liquid injection (MeCN), mobile phase gradient: 0.2% aq.NH_4HCO_3 / MeCN from 75:25 to 35:65). The fractions containing the product were combined, concentrated and freeze-dried to give compound **5** (27 mg, 66%) as a white solid.

Compound 6



*Intermediate **I33***

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

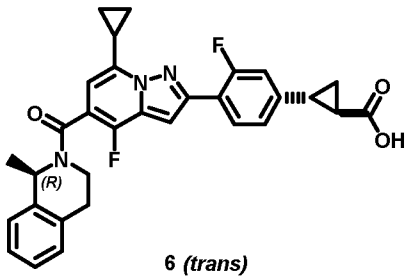


B18 *(trans)*

To a mixture of intermediate **B13** (50.0 mg, 95.7 µmol), intermediate **I5** (*cis*:*trans* 14:86, 42.1 mg, 0.19 mmol) and cesium carbonate (93.6 mg, 0.29 mmol) in toluene (1 mL) and H_2O (0.1 mL) were added cataCXium® A (8.24 mg, 23.0 µmol) and palladium acetate (3.44 mg, 15.3 µmol). The reaction mixture was purged with nitrogen and stirred at 100°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 evaporated in vacuo. 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 60:40) to afford intermediate **B18** (36 mg, 68%) as an off-white solid.

*Compound **6***

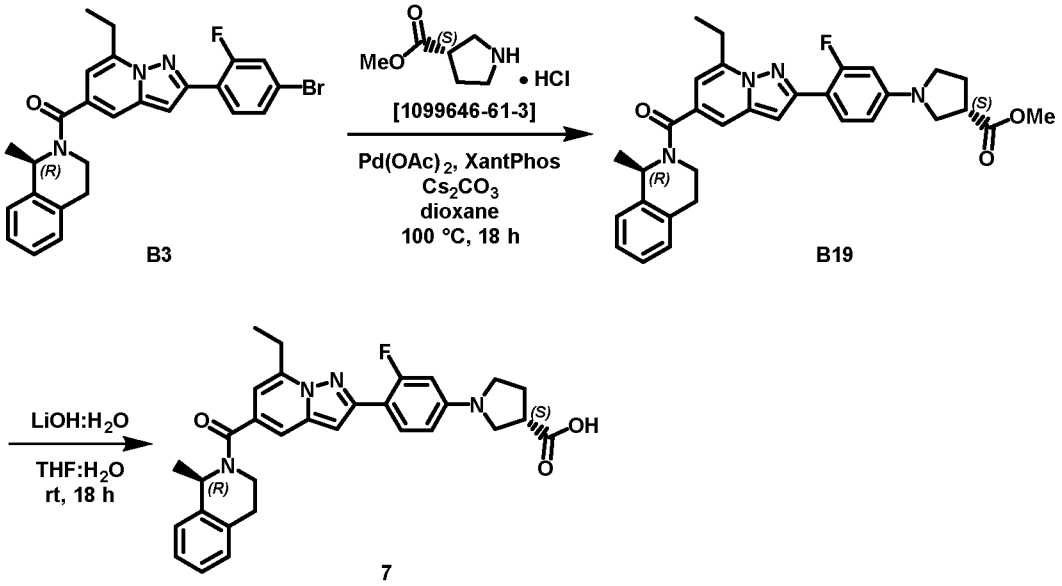
trans-2-(4-{7-Cyclopropyl-4-fluoro-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyridin-2-yl}-3-fluorophenyl)cyclopropane-1-carboxylic acid



6 *(trans)*

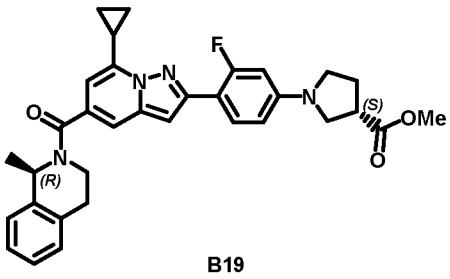
Lithium hydroxide monohydrate (15.0 mg, 0.36 mmol) was added to a solution of intermediate **B18** (36.0 mg, 64.8 µmol) in THF (2 mL) and H_2O (0.9 mL). The reaction mixture was stirred at rt for 18 h. A 10% aqueous solution of $KHSO_4$ was added until pH 6 and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with H_2O, dried over $MgSO_4$, filtered and evaporated in vacuo. The residue was dissolved in MeCN and H_2O (1:1) and freeze-dried to give compound **6** (30 mg, 88%) as a white solid.

Compound 7



*Intermediate **I34***

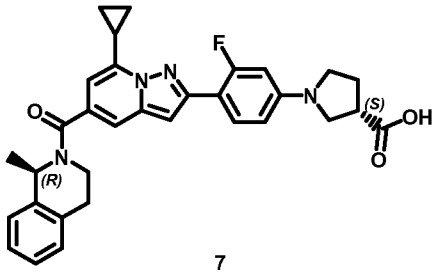
Methyl (3*S*)-1-(4-{7-cyclopropyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyridin-2-yl}-3-fluorophenyl)pyrrolidine-3-carboxylate



A sealed tube was charged with intermediate **B3** (36.0 mg, 73.1 µmol), (*S*)-methyl pyrrolidine-3-carboxylate hydrochloride [1099646-61-3] (15.0 mg, 90.6 µmol), cesium carbonate (70.0 mg, 215 µmol) and XantPhos (5.00 mg, 8.64 µmol) and purged with nitrogen. 1,4-Dioxane (1.5 mL) was added and the mixture was purged again with nitrogen. Palladium acetate (2.00 mg, 8.91 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 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 50:50) to afford intermediate **B19** (36 mg, 91%) as a white solid.

Compound 7

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

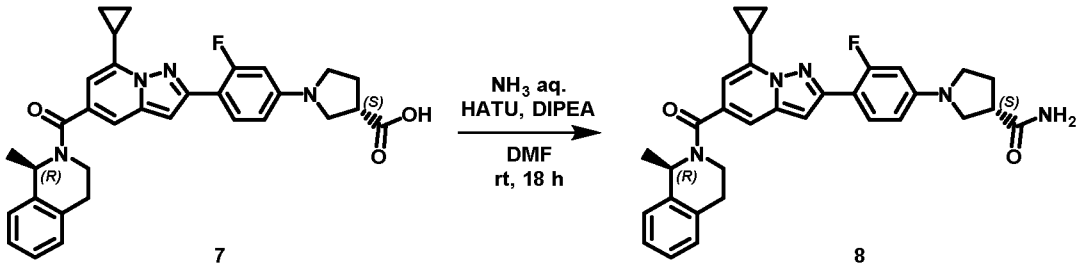


7

Lithium hydroxide monohydrate (15.0 mg, 0.36 mmol) was added to a solution of intermediate **B19** (36.0 mg, 66.7 µmol) in THF (2 mL) and H_2O (1 mL). The reaction mixture was stirred at rt for 18 h. A 10% aqueous solution of $KHSO_4$ was added until pH was 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. The crude mixture was purified by preparative LC (spherical C18 25 µm, 40 g YMC-ODS-25, liquid injection (MeOH, H_2O), mobile phase gradient: 0.2% aq.NH_4HCO_3 / MeCN from 90:10 to 50:50). The fractions containing the product were combined, concentrated and freeze-dried to give compound **7** (8 mg, 23%) as a pale pink solid.

Compound 8

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

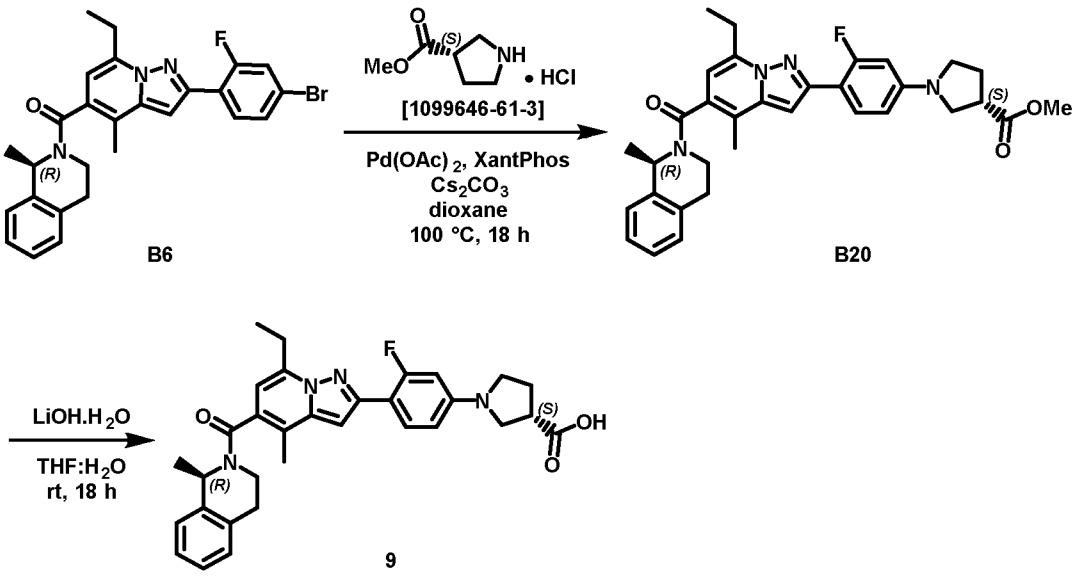


7 8

A mixture of compound **7** (100 mg, 0.19 mmol), HATU (108 mg, 0.29 mmol) and DIPEA (98 µL, 0.57 mmol) in DMF (3 mL) was stirred at rt for 1 h. Ammonia (28% in H_2O, 64 µL, 0.95 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 1% aqueous solution of $NaHCO_3$, 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, solid loading (Celite®), mobile phase gradient: 0.2% aq.NH_4HCO_3 / MeCN from 65:35 to 25:75). The

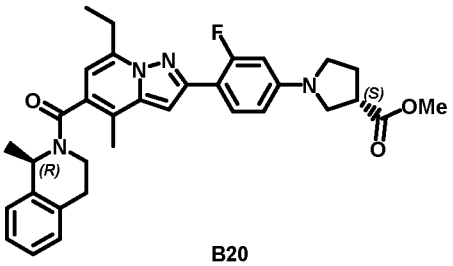
fractions containing the product were combined, evaporated in vacuo and freeze-dried to give compound **8** (50 mg, 50%) as a yellow solid.

Compound 9



*Intermediate **I35***

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

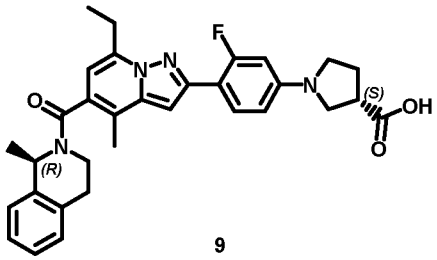


A sealed tube was charged with intermediate **B6** (75.0 mg, 148 µmol), (*S*)-methyl pyrrolidine-3-carboxylate hydrochloride [1099646-61-3] (30.4 mg, 183 µmol), cesium carbonate (142 mg, 435 µmol) and XantPhos (10.1 mg, 17.5 µmol) and purged with nitrogen. 1,4-Dioxane (3 mL) was added and the mixture was purged again with nitrogen. Palladium acetate (4.05 mg, 18.0 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 evaporated in vacuo. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 50 g Merck, liquid injection (DCM), mobile phase

gradient: heptane / EtOAc from 100:0 to 50:50) to afford intermediate **B20** (59 mg, 72%) as a white solid.

*Compound **9***

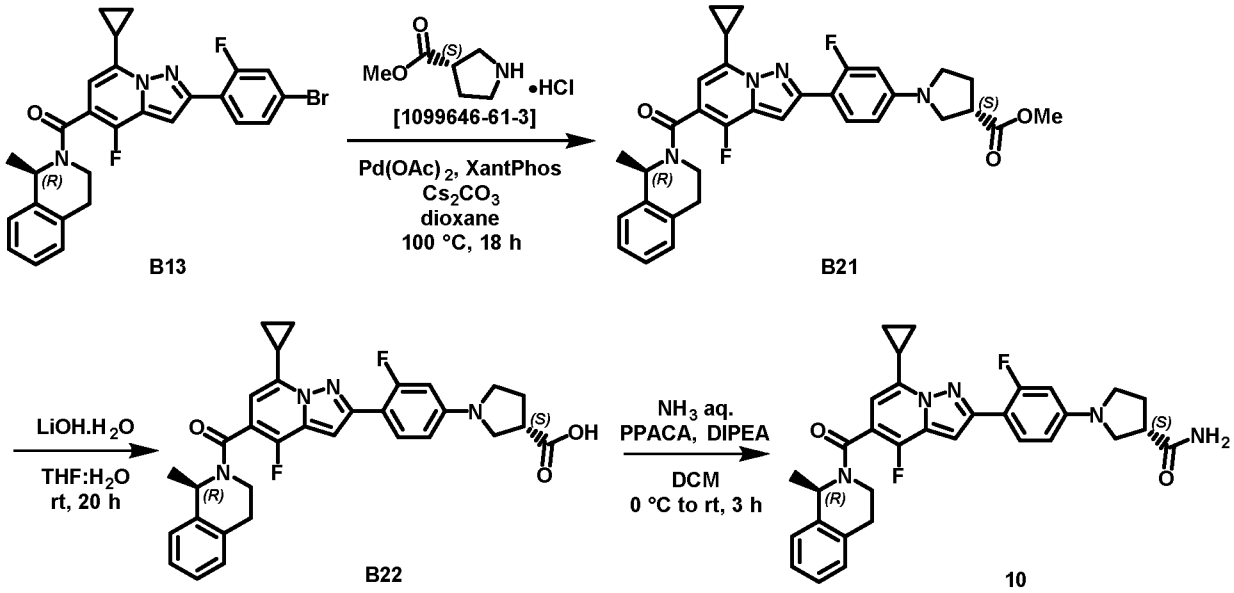
(3*S*)-1-(4-{7-Ethyl-4-methyl-5-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrazolo[1,5-a]pyridin-2-yl}-3-fluorophenyl)pyrrolidine-3-carboxylic acid



9

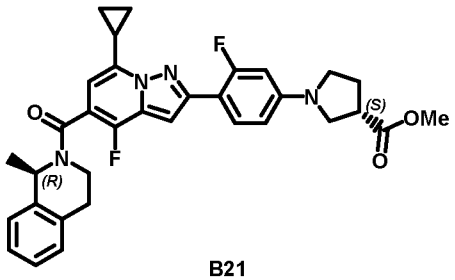
Lithium hydroxide monohydrate (24.6 mg, 0.59 mmol) was added to a solution of intermediate **B20** (59.0 mg, 106 µmol) in THF (3.3 mL) and H_2O (1.4 mL). The reaction mixture was stirred at rt for 18 h. A 10% aqueous solution of $KHSO_4$ was added until pH 6 and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with H_2O, dried over $MgSO_4$, filtered and evaporated in vacuo. The crude mixture was purified by reverse phase (spherical C18, 25 µm, 40 g YMC-ODS-25, liquid injection (MeCN, MeOH, H_2O), mobile phase gradient: 0.2% aq.NH_4HCO_3 / MeCN from 75:25 to 35:65). The fractions containing the product were combined, concentrated in vacuo and freeze-dried to give compound **9** (46 mg, 80%) as a white solid.

Compound 10



*Intermediate **B21***

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

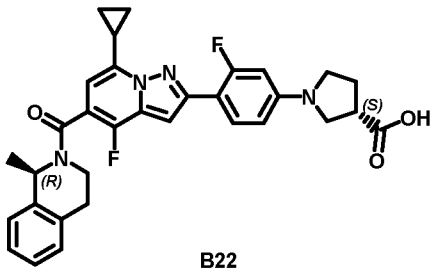


B21

A mixture of intermediate **B13** (74.0 mg, 142 µmol), (*S*)-methyl pyrrolidine-3-carboxylate hydrochloride [1099646-61-3] (28.3 mg, 171 µmol) and cesium carbonate (142 mg, 435 µmol) in 1,4-dioxane (2.1 mL) was purged with nitrogen. Palladium acetate (3.54 mg, 15.8 µmol) and XantPhos (8.50 mg, 14.7 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 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 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 **B21** (47 mg, 58%) as an off-white solid.

*Intermediate **B22***

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



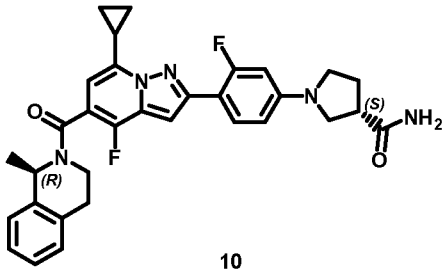
B22

Lithium hydroxide monohydrate (18.3 mg, 437 µmol) was added to a solution of intermediate **B21** (45.0 mg, 78.9 µmol) in THF (0.6 mL) and H_2O (0.2 mL). The reaction mixture was stirred at rt for 20 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 **B22** (43 mg, 98%) as a white solid.

*Compound **10***

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

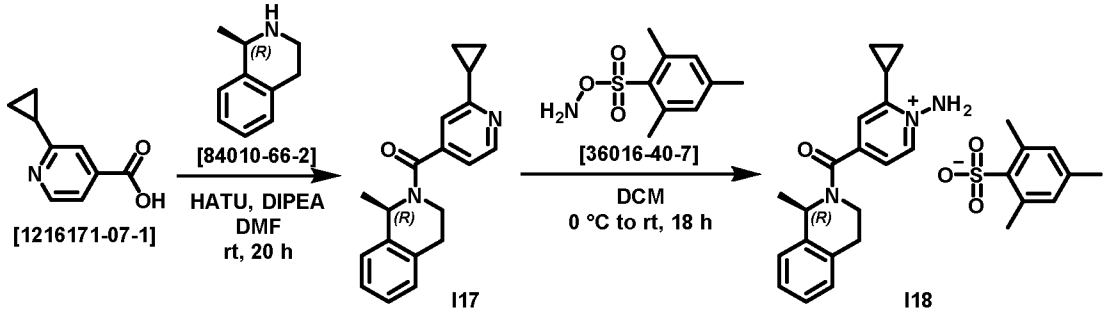


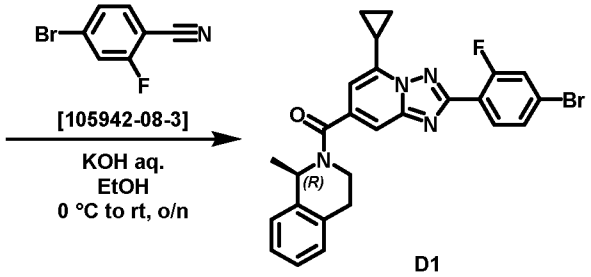
10

A mixture of intermediate **B22** (43.0 mg, 77.3 µmol) and DIPEA (70 µL, 406 µmol) in DCM (1 mL) was stirred at 0°C. PPACA (50 wt. % in EtOAc, 0.12 mL, 202 µmol) was added slowly at 0°C. The reaction mixture was stirred at rt for 30 min. Ammonia (28% in H_2O, 25 µL, 371 µmol) was added and the mixture was stirred at rt for 3 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 reverse phase (spherical C18, 25 µm, 40 g YMC-ODS-25, liquid injection (MeCN, MeOH, H_2O), mobile phase gradient: 0.2% aq.NH_4HCO_3 / MeCN from 90:10 to 25:75). The fractions containing the product were combined and diluted with EtOAc. 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 brine, dried over $MgSO_4$, filtered and evaporated in vacuo. The residue was diluted with MeCN and H_2O (1:1) and freeze-dried to give compound **10** (17 mg, 40%) as a white solid.

Triazolopyridines

Synthesis of the triazolopyridine intermediates

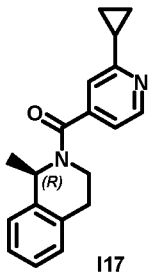




D1

*Intermediate **I17***

(1*R*)-2-(2-Cyclopropylpyridine-4-carbonyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline

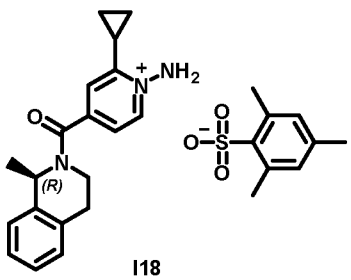


I17

A mixture of 2-cyclopropylpyridine-4-carboxylic acid [1216171-07-1] (730 mg, 4.47 mmol), (1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline [84010-66-2] (790 mg, 5.37 mmol), HATU (2.21 g, 5.82 mmol) and DIPEA (2.3 mL, 13.4 mmol) in DMF (26 mL) was stirred at rt for 20 h. The reaction mixture was diluted with H_2O and EtOAc. The layers were separated and the aqueous phase was extracted twice with EtOAc. The combined organic extracts were washed with brine (4 times), dried over $MgSO_4$, filtered and evaporated in vacuo. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 40 g GraceResolv™, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 70:30 to 20:80) to afford intermediate **I17** (1.25 g, 96%) as a colorless oil.

*Intermediate **I18***

1-Amino-2-cyclopropyl-4-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyridin-1-ium 2,4,6-trimethylbenzene-1-sulfonate

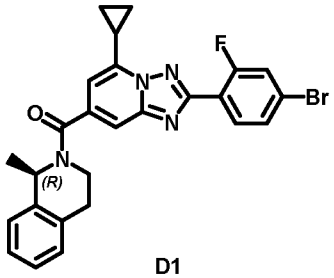


I18

To a suspension of *o*-(2,4,6-trimethylbenzenesulfonyl)hydroxylamine [36016-40-7] (1.46 g, 6.77 mmol) in DCM (12 mL) cooled with an ice bath was added dropwise a solution of intermediate **I17** (1.80 g, 6.16 mmol) in DCM (3.6 mL). The reaction mixture was stirred at rt for 18 h. The reaction mixture was diluted with Et_2O until the formation of a precipitate was observed. The precipitate was filtered off and washed with Et_2O to give a first crop of intermediate **I18** (2.5 g, 80%). The filtrate was concentrated in vacuo to afford a second crop of intermediate **I18** (600 mg, 20%).

*Intermediate **D1***

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

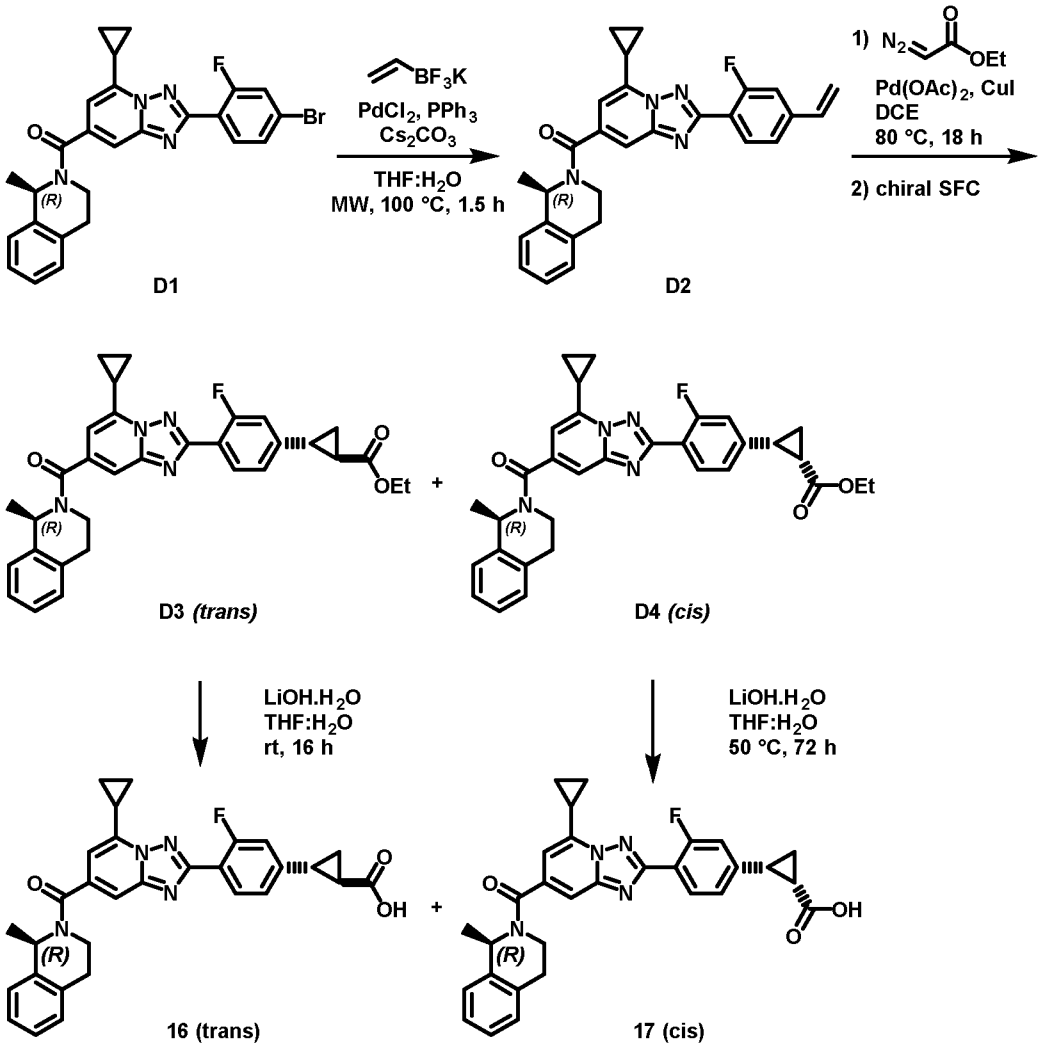


D1

A mixture of intermediate **I18** (500 mg, 985 µmol) and 4-bromo-2-fluorobenzonitrile [105942-08-3] (217 mg, 1.08 mmol) in EtOH (10 mL) was cooled to 0°C. Potassium hydroxide (2.0 M in H_2O, 542 µL, 1.08 mmol) was added dropwise and the reaction mixture was stirred at rt overnight. Solvent was evaporated in vacuo. The residue was diluted with H_2O and DCM. The layers were separated and the aqueous phase was extracted with DCM (3 times). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude mixture was purified by preparative LC (regular SiOH, 30 µm, 40 g GraceResolv™, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 80:20 to 50:50) to give intermediate **D1** (87 mg, 17%) as a white foam.

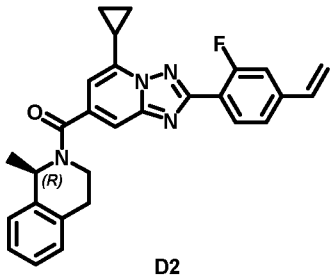
Synthesis of Final Compounds

Compounds 16 and 17



*Intermediate **D2***

(1*R*)-2-[5-Cyclopropyl-2-(4-ethenyl-2-fluorophenyl)-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline



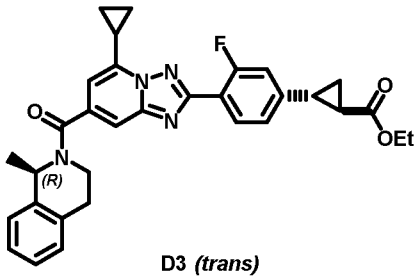
D2

Palladium chloride (1.82 mg, 10.3 µmol) was added to a degassed mixture of intermediate **D1** (116 mg, 0.23 mmol), potassium vinyltrifluoroborate [13682-77-4] (92.2 mg, 0.69 mmol), cesium carbonate (325 mg, 1.00 mmol) and triphenylphosphine (8.05 mg, 30.7 µmol) in THF and H_2O (9:1, 3.5 mL). The reaction 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 1.5 h. The reaction mixture was diluted with EtOAc and H_2O. The layers were separated and the organic phase was washed with H_2O, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude mixture was purified by preparative LC (regular SiOH, 30 µm, 12 g GraceResolv™, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 90:10 to 40:60) to afford intermediate **D2** (83 mg, 80%) as a yellow solid.

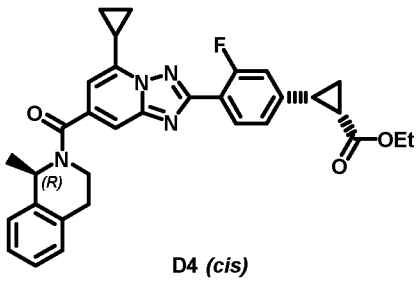
*Intermediate **D3** and **D4***

D3: Ethyl *trans*-2-(4-{5-cyclopropyl-7-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-[1,2,4]triazolo[1,5-a]pyridin-2-yl}-3-fluorophenyl)cyclopropane-1-carboxylate

D4: Ethyl *cis*-2-(4-{5-cyclopropyl-7-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]-[1,2,4]triazolo[1,5-a]pyridin-2-yl}-3-fluorophenyl)cyclopropane-1-carboxylate



D3 *(trans)*

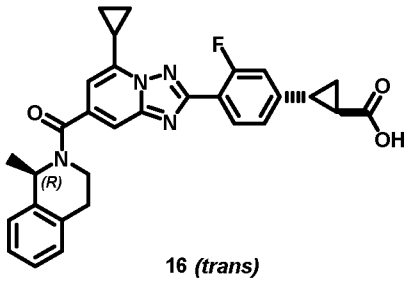


D4 *(cis)*

A mixture of intermediate **D2** (225 mg, 497 µmol), copper (I) iodide (9.47 mg, 49.7 µmol), palladium acetate (11.2 mg, 49.7 µmol) in DCE (4.0 mL) was stirred at 80°C and ethyl diazoacetate (0.37 mL, 2.98 mmol, 85% purity) in DCE (1.6 mL) was added with a syringe pump over 4 h. 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 in vacuo. The crude mixture (140 mg) was combined with another fraction (81 mg) and purified by preparative LC (irregular SiOH, 15-40 µm, 220 g GraceResolv™, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 70:30 to 40:60) to afford intermediate **D3** (65 mg, 18%) and intermediate **D4** (45 mg, 12%) as colorless oils.

*Compound **16***

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

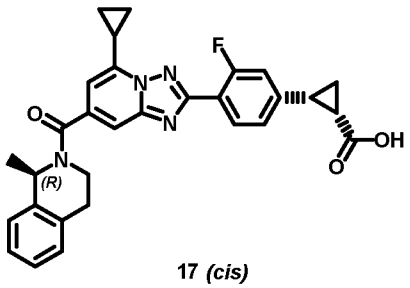


16 *(trans)*

Lithium hydroxide monohydrate (15.2 mg, 0.36 mmol) was added to a solution of intermediate **D3** (65.0 mg, 0.12 mmol) in THF (1.1 mL) and H_2O (0.3 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. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 12 g GraceResolv™, liquid injection (DCM), mobile phase gradient: heptane / EtOAc / AcOH from 80:19.5:0.5 to 40:58.5:1.5) to give compound **16** (42 mg, 68%).

Compound 17

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

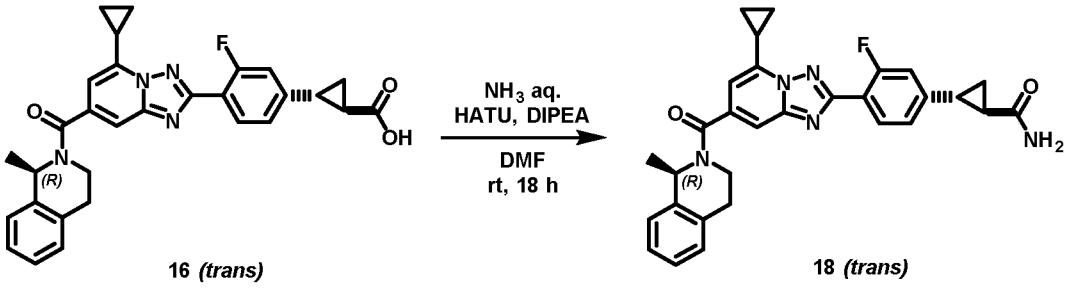


17 *(cis)*

Lithium hydroxide monohydrate (11.0 mg, 0.25 mmol) was added to a solution of intermediate **D4** (45.0 mg, 83.5 µmol) in THF (1 mL) and H_2O (0.3 mL). The reaction mixture was stirred at rt for 16 h. An additional amount of lithium hydroxide monohydrate (11.0 mg, 0.25 mmol) was added and the reaction mixture was stirred at 50°C for 72 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, 12 g GraceResolv™, liquid injection (DCM), mobile phase gradient: heptane / EtOAc / AcOH from 80:19.5:0.5 to 40:58.5:1.5) to give compound **17** (33 mg, 77%).

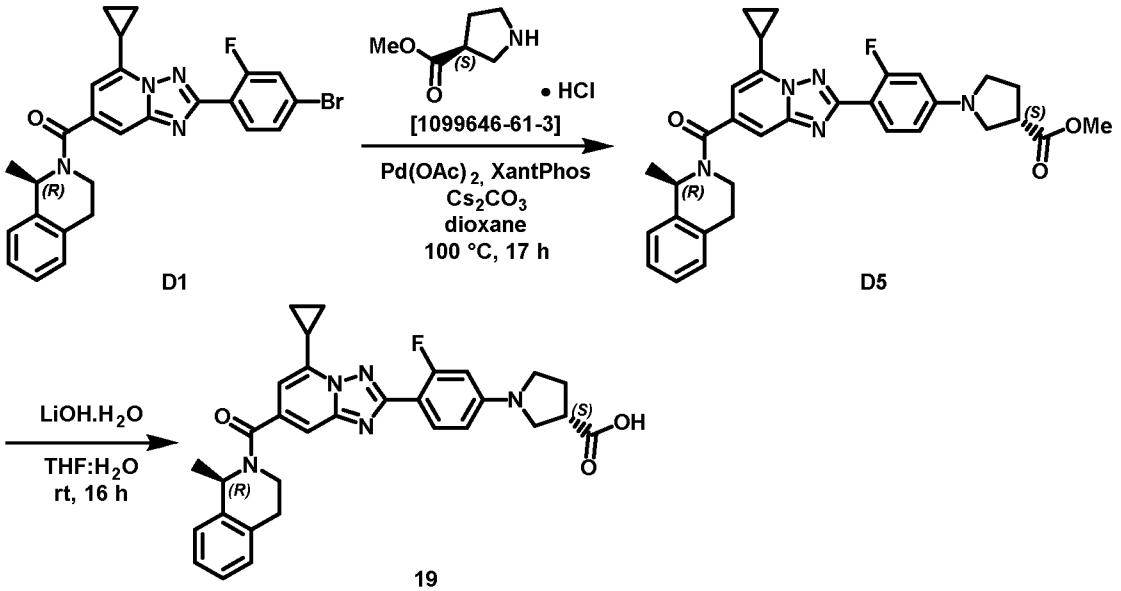
Compound 18

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



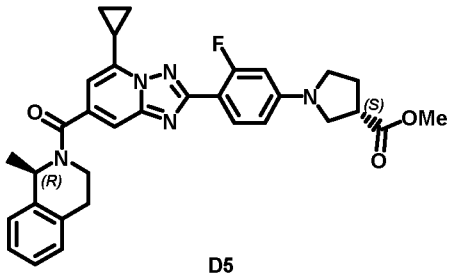
A mixture of compound **16** (18.0 mg, 35.3 µmol), HATU (20.1 mg, 52.9 µmol) and DIPEA (18 µL, 106 µmol) in DMF (1 mL) was stirred at rt for 1 h. Ammonia (28% in H_2O, 12 µL, 176 µmol) was added and the reaction mixture was stirred at rt for 18 h. The reaction mixture was diluted with H_2O and EtOAc. 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 (regular SiOH, 30 µm, 12 g GraceResolv™, liquid injection (DCM), mobile phase gradient: DCM / *i*-PrOH from 100:0 to 80:20). The residue was freeze-dried (MeCN / H_2O) to give compound **18** (11 mg, 61%) as a white solid.

Compound 19



*Intermediate **D5***

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

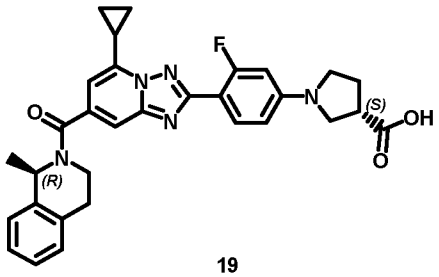


D5

A sealed tube was charged with intermediate **D1** (85 mg; 168 µmol), (*S*)-methyl pyrrolidine-3-carboxylate hydrochloride [1099646-61-3] (33.4 mg, 0.20 mmol), cesium carbonate (164 mg, 505 µmol) and XantPhos (9.73 mg, 16.8 µmol) and purged with nitrogen. 1,4-Dioxane (2.5 mL) was added and the mixture was purged again with nitrogen. Palladium acetate (3.78 mg, 16.8 µmol) was added and the mixture was purged with nitrogen. The reaction mixture was 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 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 90:10 to 20:80) to afford intermediate **D5** (82 mg, 88%) as a yellow oil.

*Compound **19***

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



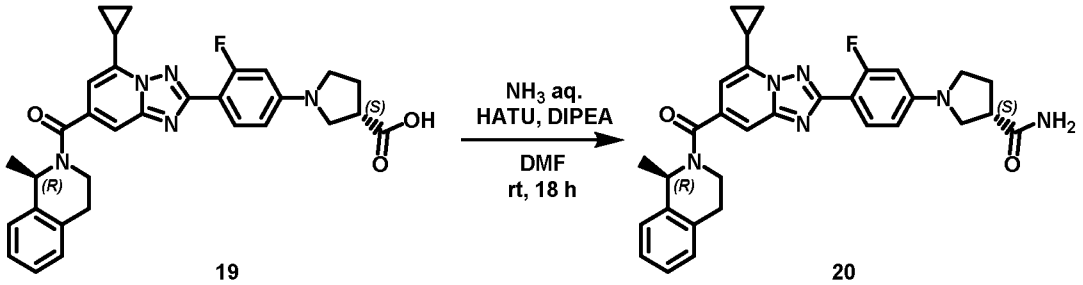
19

Lithium hydroxide monohydrate (18.6 mg, 0.44 mmol) was added to a solution of intermediate **D5** (82.0 mg, 14.8 µmol) in THF (1.86 mL) and H_2O (580 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 combined organic extracts were washed with H_2O, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude mixture was purified twice by preparative LC (irregular SiOH, 15-40 µm, 12 g GraceResolv™, liquid injection (DCM), mobile phase gradient: heptane / EtOAc / AcOH from 80:20:0.5 to 0:97.5:2.5). The residue was co-evaporated with MeCN and dried under vacuum at 50°C for 16 h to give an oil (60 mg, 96% purity). A third 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 90:10 to 50:50). The product was taken up in MeCN to give compound **19** (48 mg, 60%) as a white solid.

Compound 20

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

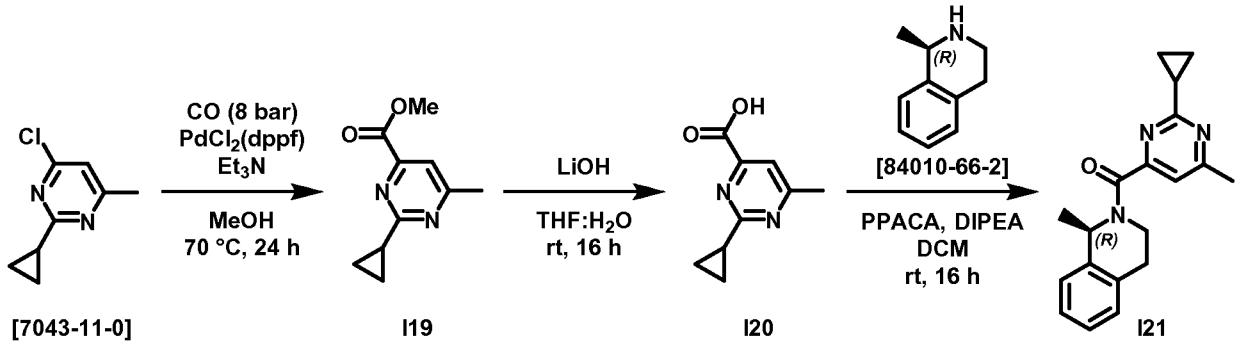


19 20

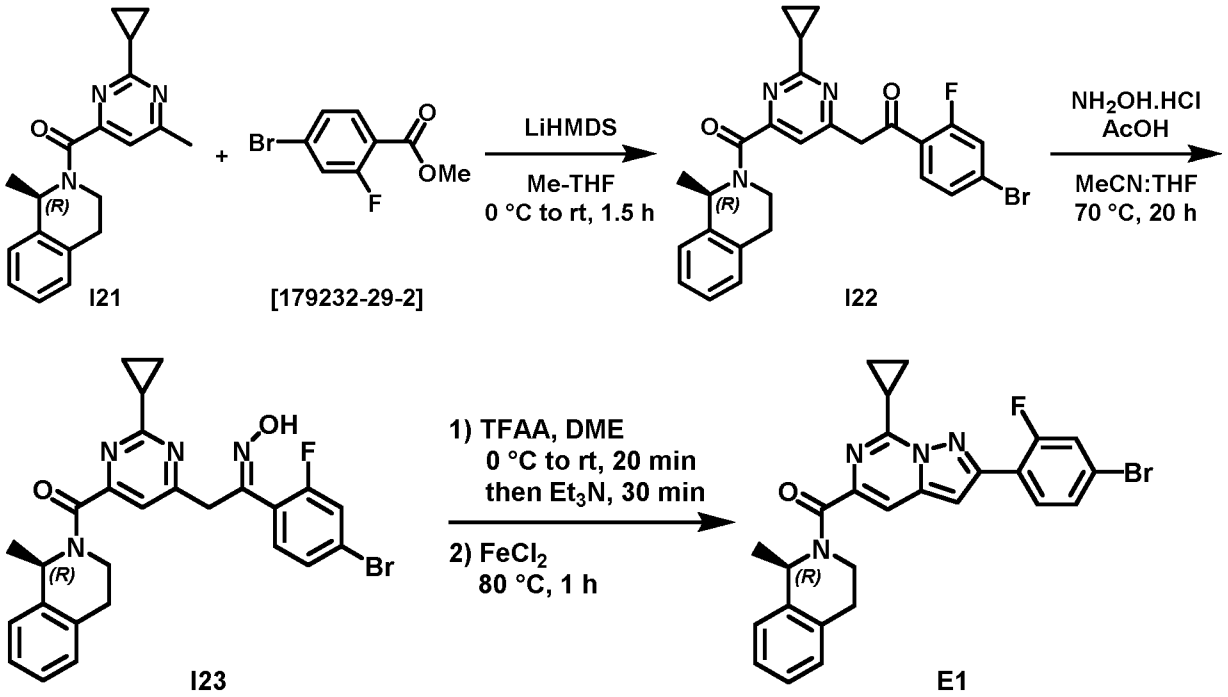
A mixture of compound **19** (180 mg, 334 µmol), HATU (190 mg, 500 µmol) and DIPEA (172 µL, 1.00 mmol) in DMF (9.2 mL) was stirred at rt for 1 h. Ammonia (28% in H_2O, 113 µL, 1.67 mmol) was added and the reaction mixture was stirred at rt for 18 h. The reaction mixture was diluted with H_2O and EtOAc. The layers were separated and the 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, 30 µm, 12 g GraceResolv™, liquid injection (DCM), mobile phase gradient: DCM / *i*-PrOH from 100:0 to 80:20). The residue was taken up in EtOH and dried under vacuum at 50°C for 16 h to give compound **20** (70 mg, 39%) as a white solid.

Pyrazolo[1,5-c]pyrimidines

Synthesis of the pyrazolo[1,5-c]pyrimidine core



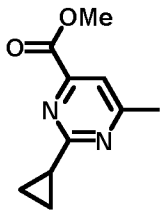
[7043-11-0] I19 I20 I21



I21 [179232-29-2] I22 I23 E1

*Intermediate **I19***

Methyl 2-cyclopropyl-6-methylpyrimidine-4-carboxylate

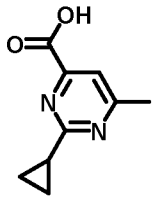


I19

In an autoclave, a mixture of 4-chloro-2-cyclopropyl-6-methylpyrimidine [7043-11-0] (1.00 g, 5.93 mmol) and Et_3N (1.6 mL, 11.8 mmol) in methanol (20 mL) was purged with nitrogen (3 times). [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium (II) (217 mg, 297 µmol) was added. The mixture was purged with CO (3 times). The autoclave was pressurized with CO at 8 bars and the reaction mixture was stirred at 70°C for 24 h. The reaction mixture was concentrated to dryness. The residue 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 concentrated to dryness. The crude mixture was purified by flash chromatography (irregular SiOH, 15-40 µm, 40 g GraceResolv™, dry loading (SiOH), mobile phase gradient: heptane / EtOAc from 90:10 to 40:60) to afford intermediate **I19** (1.07 g, 94%) as a colorless oil.

*Intermediate **I20***

2-Cyclopropyl-6-methylpyrimidine-4-carboxylic acid

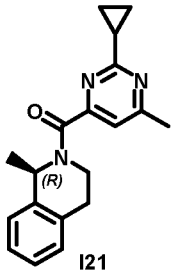


I20

Lithium hydroxide (266 mg, 11.1 mmol) was added to a solution of intermediate **I19** (1.07 g, 5.57 mmol) in THF (36 mL) and H_2O (18 mL). The reaction mixture was stirred at rt for 16 h. A 10% aqueous solution of $KHSO_4$ was added until pH 3 and the mixture was diluted with EtOAc. The layers were separated and the organic phase was washed with brine and H_2O (twice), dried over $MgSO_4$, filtered and concentrated to dryness to afford intermediate **I20** (678 mg, 68%) as a white solid.

*Intermediate **I21***

(1*R*)-2-(2-Cyclopropyl-6-methylpyrimidine-4-carbonyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline

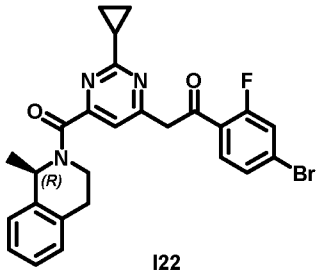


I21

PPACA [68957-94-8] (50 wt.% in DMF, 4.8 mL, 8.11 mmol) was added dropwise to a mixture of intermediate **I20** (578 mg, 3.24 mmol) and (1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline [84010-66-2] (554 mg, 3.76 mmol) at 0°C. A solution of DIPEA (2.8 mL, 16.2 mmol) in DCM (16 mL) was added and the reaction mixture was stirred at rt for 16 h. The reaction mixture was combined with another fraction (50 mg, 281 µmol) and diluted with EtOAc. The mixture was washed with a 1M aqueous solution of NaOH and brine (3 times), 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: heptane / EtOAc from 80:20 to 30:70) to afford intermediate **I21** (1.1 g) as a colorless oil.

*Intermediate **I22***

1-(4-Bromo-2-fluorophenyl)-2-{2-cyclopropyl-6-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrimidin-4-yl}ethan-1-one

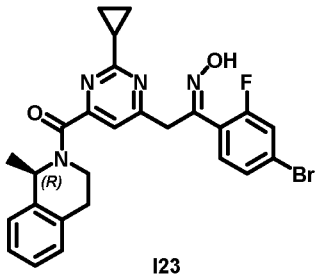


I22

Lithium bis(trimethylsilyl)amide (1.0 M in THF, 6.1 mL, 6.10 mmol) was added dropwise to a mixture of intermediate **I21** (895 mg, 2.91 mmol) and methyl 4-bromo-2-fluorobenzoate [179232-29-2] (714 mg, 3.06 mmol) in 2-methyltetrahydrofuran (7.4 mL) at 0°C. The reaction mixture was left to warm up to rt and stirred at this temperature for 1.5 h. The reaction mixture was quenched by the addition of H_2O at 0°C. 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 to dryness. The crude mixture was purified by flash chromatography (irregular SiOH, 15-40 µm, 40 g GraceResolv™, dry loading (SiOH), mobile phase gradient: heptane / EtOAc from 90:10 to 30:70) to afford intermediate **I22** (1.38 g, 93%) as a yellow solid.

*Intermediate **I23***

N-[1-(4-Bromo-2-fluorophenyl)-2-{2-cyclopropyl-6-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]pyrimidin-4-yl}ethylidene]hydroxylamine

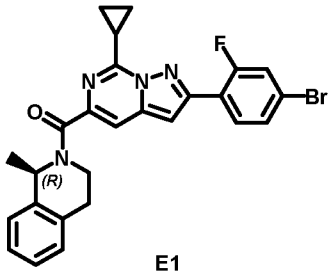


I23

Hydroxylamine hydrochloride (957 mg, 13.8 mmol) and acetic acid sodium salt (1.13 g, 13.8 mmol) were added to a suspension of intermediate **I22** (1.40 g, 2.75 mmol) in MeCN (13 mL) and THF (13 mL). The reaction mixture was stirred at 70°C for 20 h. The reaction mixture was 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 to dryness. The crude mixture was purified by flash chromatography (irregular SiOH, 15-40 µm, 40 g GraceResolv™, dry loading (SiOH), mobile phase gradient: heptane / EtOAc from 90:10 to 20:80) to afford intermediate **I23** (920 mg, 64%) as a yellow solid.

*Intermediate **E1***

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

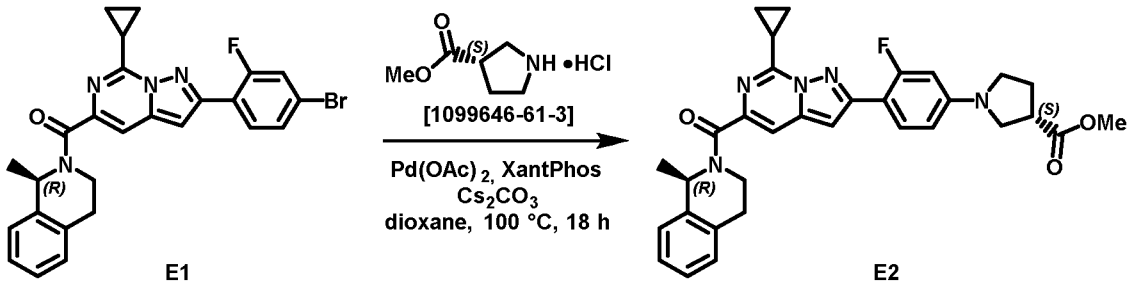


E1

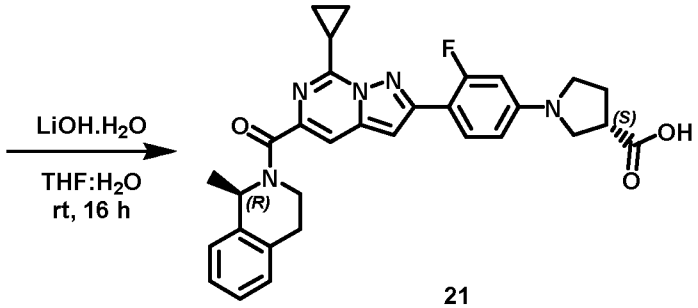
Trifluoroacetic anhydride (244 µL, 1.76 mmol) was added dropwise to a solution of intermediate **I23** (920 mg, 1.76 mmol) in DME (3.8 mL) at 0°C. The reaction mixture was warmed up to rt and stirred for 20 min. The mixture was cooled to 0°C and Et_3N (489 µL, 3.52 mmol) was added dropwise. The reaction mixture was warmed up to rt and stirred for 30 min. The mixture was cooled again to 0°C and iron (II) chloride (223 mg, 1.76 mmol) was added. The reaction mixture was stirred at 80°C for 1 h. The black mixture was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ and diluted with EtOAc. The mixture was filtered over a pad of Celite®. The filtrate was decanted and 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, 40 g GraceResolv™, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 90:10 to 60:40) to afford intermediate **E1** (659 mg, 74%) as a yellow solid.

Synthesis of final compounds

Compound 21



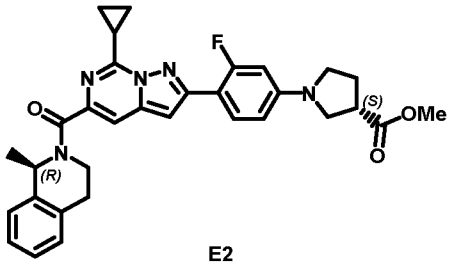
E1 E2



21

*Intermediate **E2***

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

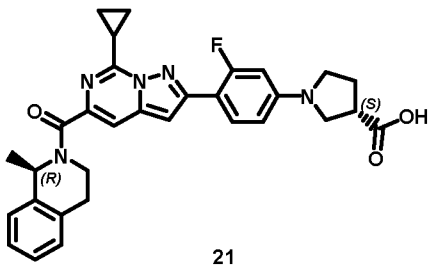


E2

In a screw cap vial a mixture of intermediate **E1** (659 mg, 1.30 mmol), (*S*)-methyl pyrrolidine-3-carboxylate hydrochloride [1099646-61-3] (316 mg, 1.56 mmol) and cesium carbonate (1.27 g, 3.91 mmol) in 1,4-dioxane (13.5 mL) was purged with nitrogen. XantPhos (75 mg; 130 µmol) and palladium acetate (29.3 mg, 130 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 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 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 90:10 to 60:40) to afford intermediate **E2** (622 mg, 86%) as a yellow solid.

*Compound **21***

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

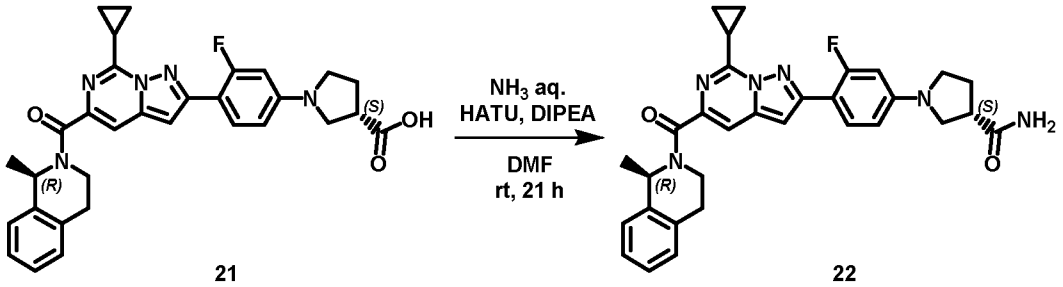


21

Lithium hydroxide monohydrate (10.9 mg, 0.26 mmol) was added to a solution of intermediate **E2** (72.0 mg, 0.13 mmol) in THF (1 mL) and H_2O (0.5 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. The residue was dried under high vacuum at 60°C for 2 h to give compound **20** (53 mg, 76%) as a beige solid.

Compound 22

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

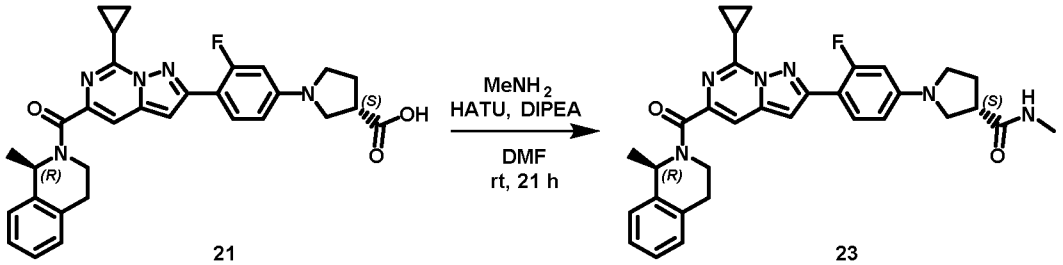


21 22

HATU (146 mg, 384 µmol) was added to a mixture of compound **21** (150 mg, 256 µmol, 92% purity) and DIPEA (132 µL, 767 µmol) in DMF (1.4 mL). The reaction mixture was stirred at rt for 10 min and ammonia (0.5 M in 1,4-dioxane, 7.6 mL, 3.84 mmol) was added. The reaction mixture was stirred at rt for 16 h. An additional amount of ammonia (0.5 M in 1,4-dioxane, 2.6 mL, 1.28 mmol) was added and the reaction mixture was stirred at rt for another 5 h. The reaction mixture was diluted with H_2O, brine and EtOAc. The layers were separated and the organic phase was washed with 1 M aqueous solution of NaOH (twice) and brine (3 times), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was diluted with a solution of DCM and MeOH (8:2) and the solid was filtered off to give a first fraction (16 mg). The filtrate was concentrated in vacuo and purified by flash chromatography (irregular SiOH, 15-40 µm, 12 g GraceResolv™, dry loading (SiOH), mobile phase gradient: DCM / MeOH from 98:2 to 80:20) to give a second fraction (20 mg). The aqueous layer was acidified with a 3M aqueous solution of HCl until pH 1 and then extracted with DCM (twice), dried over $MgSO_4$, filtered and concentrated in vacuo to give a third fraction (40 mg). All the fractions were combined and purified by flash chromatography (irregular SiOH, 15-40 µm, 12 g GraceResolv™, dry loading (SiOH), mobile phase gradient: DCM / MeOH from 98:2 to 80:20). The residue (34 mg) was dried under high vacuum at 60°C for 16 h to give compound **22** (30 mg, 22%) as a beige solid.

Compound 23

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



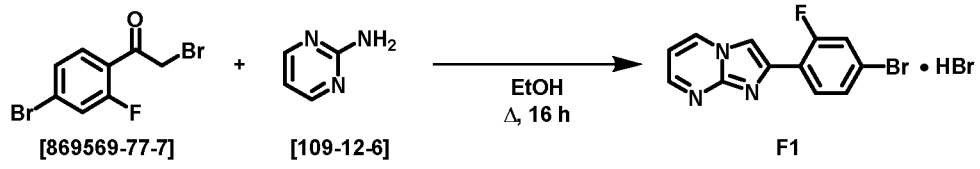
21 23

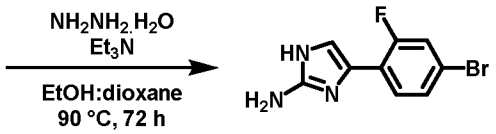
HATU (146 mg, 384 µmol) was added to a mixture of compound **21** (150 mg, 256 µmol, 92% purity) and DIPEA (154 µL, 895 µmol) in DMF (1.4 mL). The reaction mixture was stirred at rt for 10 min and methylamine (2.0 M in THF, 448 µL, 895 µmol) was added. The reaction mixture was stirred at rt for 16 h. Additional amount of methylamine (2.0 M in THF, 448 µL, 895 µmol) was added and the reaction mixture was stirred at rt for another 5 h. The reaction mixture was diluted with H_2O, brine and EtOAc. The layers were separated and the organic phase was washed with 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™, dry loading (SiOH), mobile phase gradient: heptane / EtOAc from 70:30 to 0:100). The residue was co-evaporated with MeCN then with EtOAc and dried under high vacuum at 60°C for 16 h to give compound **23** (72 mg, 51%) as a yellow solid.

Imidazo[1,2-a]pyrimidines

Synthesis of Intermediates

Synthesis of Intermediate I2

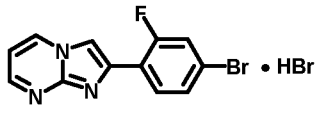




F2

*Intermediate **F1***

2-(4-Bromo-2-fluorophenyl)imidazo[1,2-a]pyrimidine hydrobromide

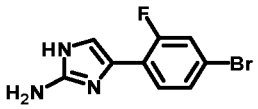


F1

A mixture of 1-(4-bromo-2-fluorophenyl)-2-bromo-1-ethanone [869569-77-7] (5.00 g, 16.9 mmol) and 2-aminopyridine [109-12-6] (1.61 g, 16.9 mmol) in EtOH (300 mL) was stirred under reflux for 16 h. The reaction mixture was cooled to rt and the resulting precipitate was filtered off to afford a first crop of intermediate **F1** (1.2 g, 19%). The filtrate was partially evaporated in vacuo and the precipitate was filtered off to afford a second crop of intermediate **F1** (1.4 g, 22%).

*Intermediate **F2***

4-(4-Bromo-2-fluorophenyl)-1H-imidazol-2-amine

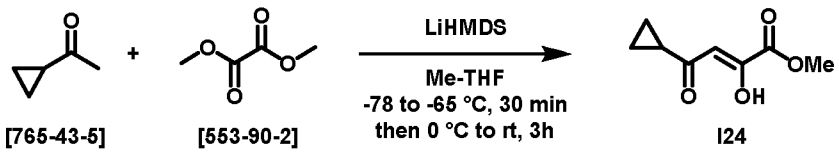


F2

A mixture of intermediate **F1** (2.25 g, 6.03 mmol), Et_3N (1.26 mL, 9.05 mmol) and hydrazine monohydrate (2.34 mL, 48.3 mmol) in EtOH (70 mL) and 1,4-dioxane (45 mL) was stirred at 90°C for 72 h. The reaction mixture was concentrated to dryness. The residue was diluted with H_2O and EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc (once). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and the solvent was concentrated in vacuo. The residue (1.54 g) was taken up in DCM. The precipitate was filtered off and dried to afford intermediate **F2** (1.01 g, 65%).

Synthesis of Intermediate I24

Methyl 4-cyclopropyl-2-hydroxy-4-oxobut-2-enoate



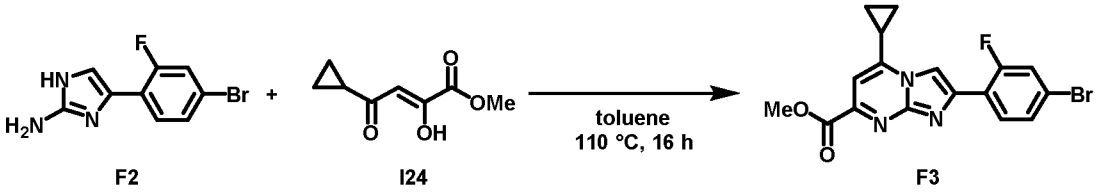
[765-43-5] [553-90-2] I24

In a 6 L non-jacketed reactor equipped with mechanical stirring and under a nitrogen atmosphere, cyclopropyl methyl ketone [765-43-5] (255 mL, 2.73 mol) was added over 30 min

to a mixture of lithium bis(trimethylsilyl)amide (500 g, 2.99 mol) in 2-methyltetrahydrofuran (3.5 L) at -78°C. [The temperature was maintained below -65°C during the addition.] The reaction mixture was stirred at -70°C for 30 min and added to a solution of dimethyl oxalate [553-90-2] (321 g, 2.72 mol) in 2-methyltetrahydrofuran (2.5 L) at 0°C in a 10 L non-jacketed reactor equipped with mechanical stirring and under a nitrogen atmosphere. The resulting reaction mixture was stirred for 3 h and warmed to rt slowly. The reaction mixture was quenched by the addition of a 3N aqueous solution of HCl (2 L). The layers were separated and the aqueous phase was extracted with EtOAc (twice). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was evaporated in vacuo. The crude mixture (620 g) was purified by preparative LC (irregular SiOH, 15-40 µm, 750 g Grace®, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 90:10 to 70:30) to afford intermediate **I24** (468 g, 96%) as a colorless oil. The product crystallized on standing.

Synthesis of Intermediate F3

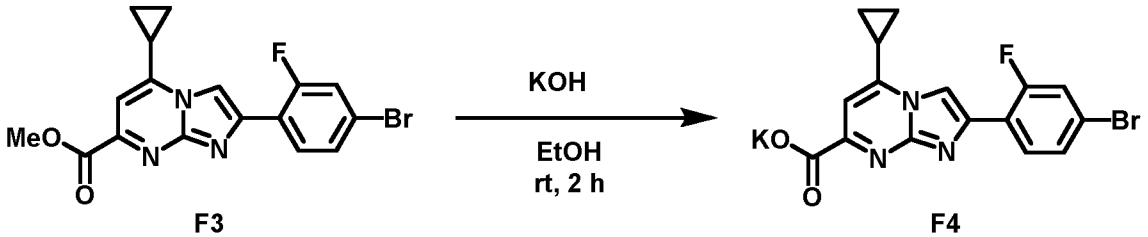
Methyl 2-(4-bromo-2-fluorophenyl)-5-cyclopropylimidazo[1,2-a]pyrimidine-7-carboxylate



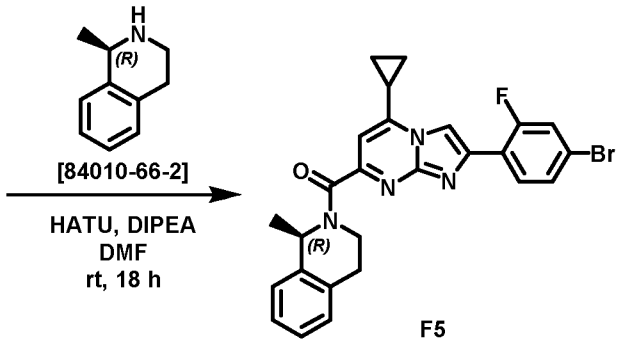
F2 I24 F3

A mixture of intermediate **F2** (653 mg, 2.55 mmol) and intermediate **I24** (639 mg, 3.57 mmol) in toluene (29 mL) was stirred at 110°C for 16 h. The solvent was evaporated to dryness. The residue was triturated in MeOH and the solid was filtered off to afford intermediate **F3** (578 mg, 58%).

Synthesis of Intermediate F5



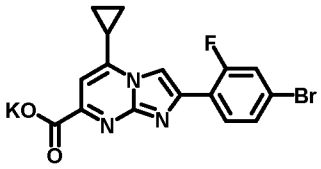
F3 F4



F5

*Intermediate **F4***

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

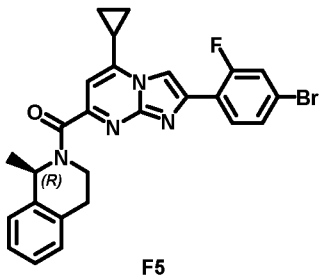


F4

A mixture of intermediate **F3** (528 mg, 1.35 mmol) and potassium hydroxide (152 mg, 2.71 mmol) in EtOH (20 mL) was stirred at rt for 2 h. The reaction mixture was combined with another fraction (50 mg, 128 µmol). The suspension was filtered off. The solid was dried and co-evaporated with toluene (twice) to afford intermediate **F4** (484 mg, 79%).

*Intermediate **F5***

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

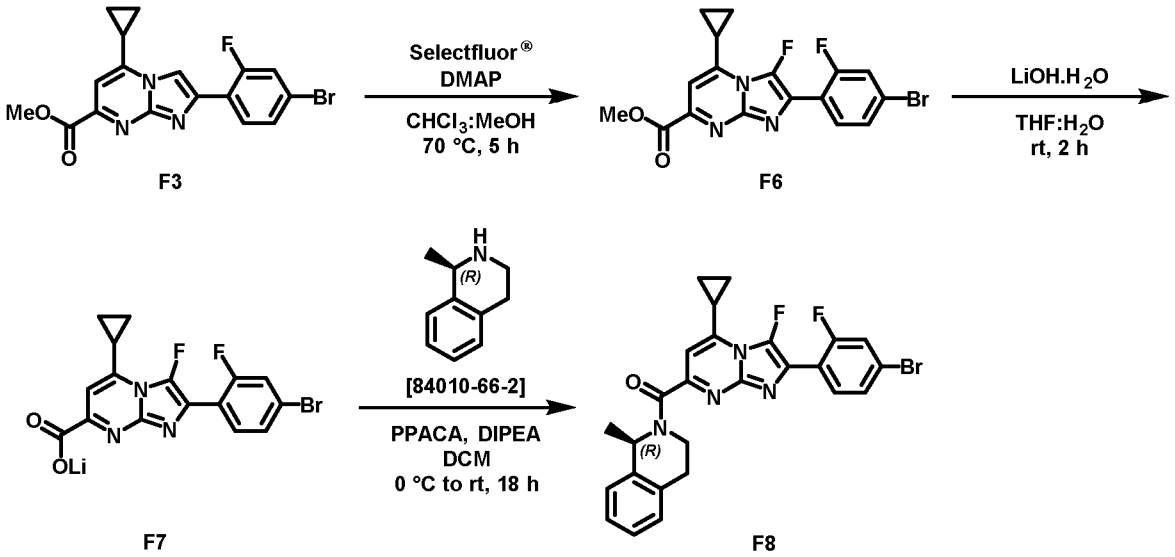


F5

HATU (477 mg, 1.26 mmol) was added to a mixture of intermediate **F4** (260 mg, 0.63 mmol), (*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline [84010-66-2] (111 mg, 0.75 mmol) and DIPEA (0.43 mL, 2.52 mmol) in DMF (4 mL). The reaction mixture was stirred at rt for 18 h. The reaction mixture was diluted with H_2O, brine and EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine (3 times), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 24 g GraceResolv™, liquid injection

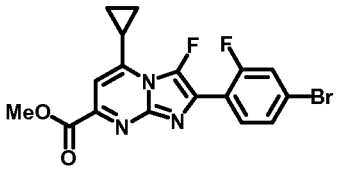
(DCM), mobile phase gradient: heptane / EtOAc from 90:10 to 60:40) to give intermediate **F5** (306 mg, 96%) as an off-white foam.

Synthesis of Intermediate F8



*Intermediate **F6***

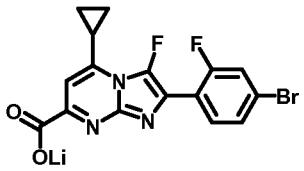
Methyl 2-(4-bromo-2-fluorophenyl)-5-cyclopropyl-3-fluoroimidazo[1,2-a]pyrimidine-7-carboxylate



In a Schlenk tube, a mixture of intermediate **F3** (242 mg, 0.62 mmol), selectfluor® (264 mg, 744 µmol) and DMAP (83.0 mg, 0.68 mmol) in $CHCl_3$ (7.5 mL) and MeOH (7.5 mL) was stirred at 70°C for 5 h. Additional amount of selectfluor® (132 mg, 372 µmol) and DMAP (45.0 mg, 0.37 mmol) were added and the reaction mixture was stirred at 70°C for 18 h. Extra amount of selectfluor® (132 mg, 372 µmol) and DMAP (45.0 mg, 0.37 mmol) were added and the reaction mixture was stirred at 70°C for another 22 h. The reaction mixture was concentrated in vacuo. The crude mixture was combined with another batch (269 mg, 0.69 mmol) and purified by preparative LC (irregular SiOH, 15-40 µm, 40 g GraceResolv™, liquid injection (DCM), mobile phase gradient: DCM / EtOAc from 90:10 to 70:30). A second purification was performed by preparative LC (irregular SiOH, 15-40 µm, 40 g GraceResolv™, liquid injection (DCM), mobile phase gradient: heptane / (EtOAc/MeOH 9:1) from 90:10 to 70:30) to afford intermediate **F6** (153 mg, 29%).

*Intermediate **F7***

Lithio 2-(4-bromo-2-fluorophenyl)-5-cyclopropyl-3-fluoroimidazo[1,2-a]pyrimidine-7-carboxylate

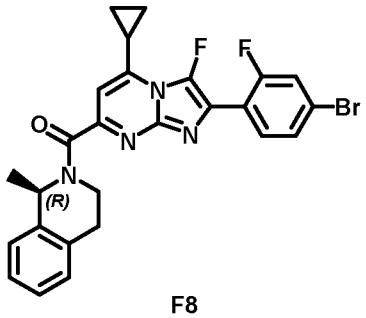


F7

Lithium hydroxide monohydrate (47.2 mg, 1.12 mmol) was added to a solution of intermediate **F6** (153 mg, 375 µmol) in THF (11 mL) and H_2O (2.5 mL). The reaction mixture was stirred at rt for 2 h. The reaction mixture was concentrated to dryness and co-evaporated with toluene (twice) to afford intermediate **F7** (153 mg, quant.) as a yellowish solid.

*Intermediate **F8***

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

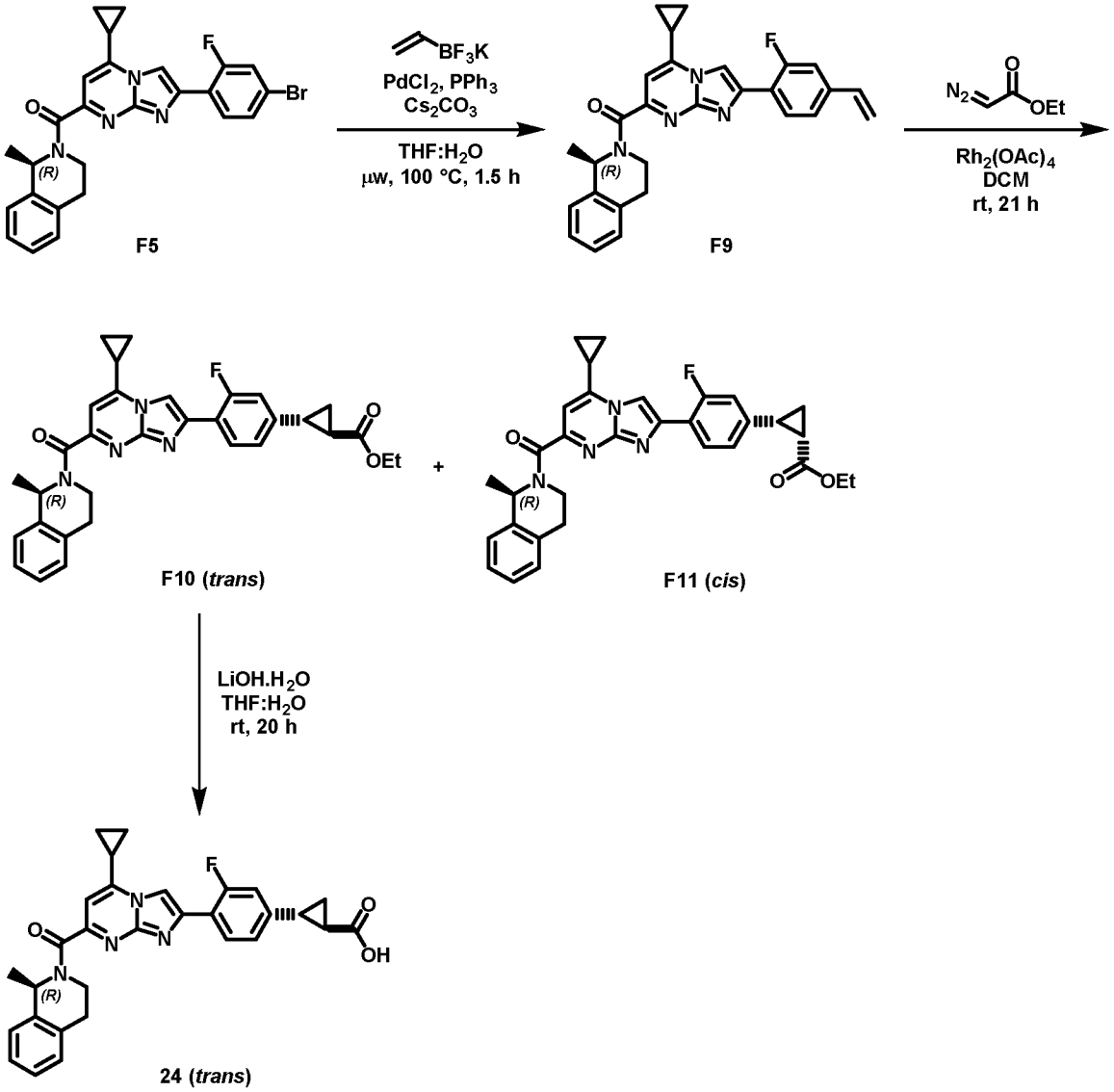


F8

A mixture of intermediate **F7** (138 mg, 0.35 mmol), (*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline [84010-66-2] (62.0 mg, 0.42 mmol) and DIPEA (304 µL, 1.76 mmol) in DCM (1 mL) was stirred at 0°C. PPACA (50 wt.% in EtOAc, 521 µL, 875 µmol) was added slowly. The reaction mixture was stirred at 0°C for 10 min and at rt for 18 h. Additional amount of (*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline (26.0 mg, 0.18 mmol) and PPACA (50 wt.% in EtOAc, 208 µL, 350 µmol) were added at 0°C and the reaction mixture was stirred at rt for another 22 h. The reaction mixture was diluted with H_2O. The layers were separated and the organic phase was extracted. 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, 12 g GraceResolv™, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 90:10 to 60:40) to afford intermediate **F8** (80 mg, 44%) as a yellowish gum.

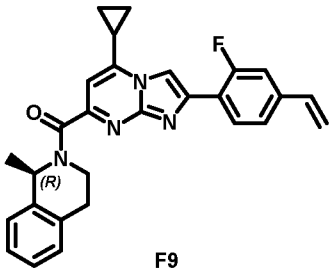
Synthesis of Final Compounds

Compound 24



*Intermediate **F9***

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



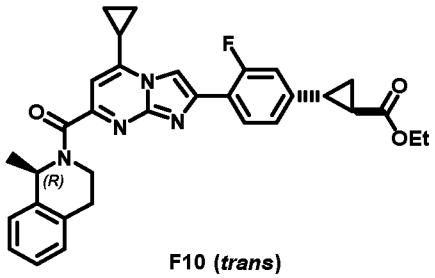
F9

Palladium(II) chloride (5.00 mg, 28.8 µmol) was added to a degassed mixture of intermediate **F5** (324 mg, 641 µmol), potassium vinyltrifluoroborate (258 mg, 1.92 mmol), cesium carbonate (909 mg, 2.79 mmol) and triphenylphosphine (22.0 mg, 83.8 µmol) in THF and H_2O (9:1, 10 mL). The reaction 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 1.5 h. Additional amount of palladium(II) chloride (5.00 mg, 28.8 µmol) and triphenylphosphine (22.0 mg, 83.8 µmol) were added and the reaction 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 1.5 h. The reaction mixture was diluted with EtOAc and H_2O. The layers were separated and the organic phase was washed with H_2O, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude mixture was purified by preparative LC (regular SiOH, 30 µm, 12 g Interchim®, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 90:10 to 60:40) to afford intermediate **F9** (207 mg, 71%) as an off-white solid.

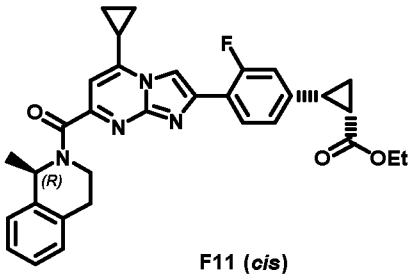
*Intermediate **F10** and **F11***

F10: Ethyl *trans*-2-(4-{5-cyclopropyl-7-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]imidazo[1,2-a]pyrimidin-2-yl}-3-fluorophenyl)cyclopropane-1-carboxylate

F11: Ethyl *cis*-2-(4-{5-cyclopropyl-7-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]imidazo[1,2-a]pyrimidin-2-yl}-3-fluorophenyl)cyclopropane-1-carboxylate



F10 (*trans*)

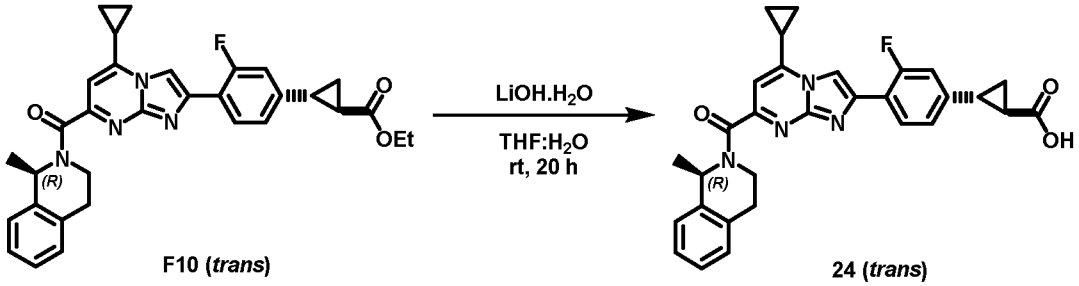


F11 (*cis*)

Under a nitrogen atmosphere a solution of ethyl diazoacetate [623-73-4] (150 µL, 1.21 mmol) in DCM (4 mL) was added with a syringe pump over 40 min to a mixture of intermediate **F9** (182 mg, 402 µmol) and rhodium acetate dimer (9.00 mg, 40.7 µmol) in DCM (9 mL). The reaction mixture was stirred at rt for 3 h. An additional amount of ethyl diazoacetate (150 µL, 1.21 mmol) in DCM (4 mL) was added with a syringe pump over 40 min and the reaction mixture was stirred at rt for 18 h. The reaction mixture 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 70:30) to give 3 fractions as a mixture of diastereoisomers (76 mg). The fractions were purified again by preparative LC (irregular SiOH, 15-40 µm, 40 g GraceResolv™, liquid injection (DCM), mobile phase gradient: heptane / EtOAc from 100:0 to 70:30) to afford intermediate **F10** (25 mg, 12%), intermediate **F11** (11 mg, 5%) and a mixture of intermediates **F10** and **F11** (7 mg, 3%).

*Compound **24***

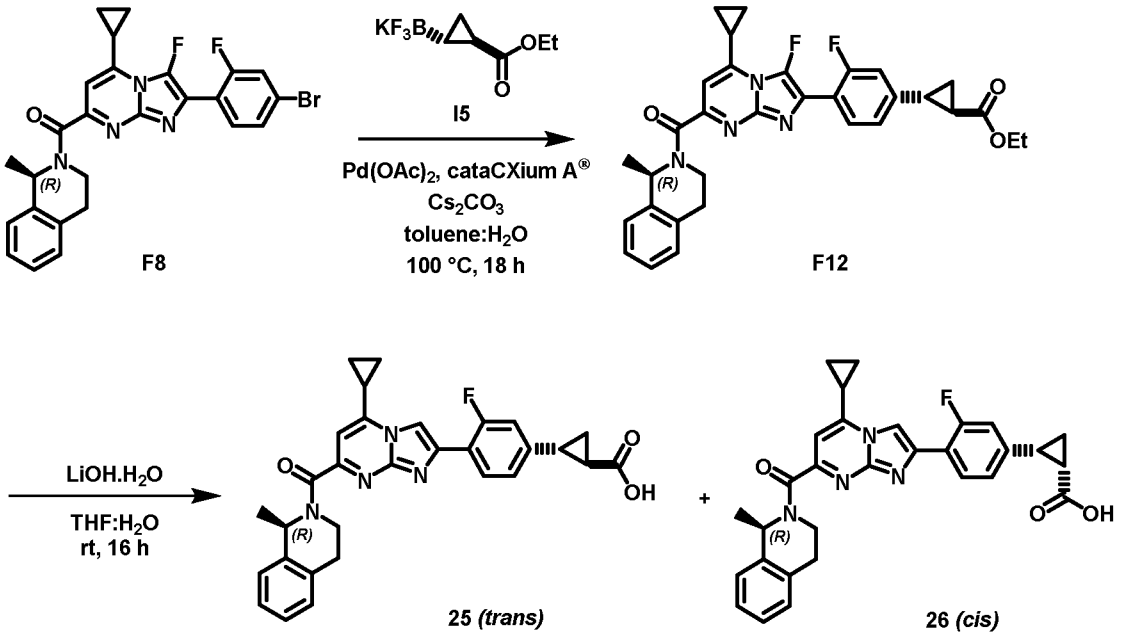
trans-2-(4-{5-Cyclopropyl-7-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]imidazo[1,2-a]pyrimidin-2-yl}-3-fluorophenyl)cyclopropane-1-carboxylic acid



F10 (*trans*) 24 (*trans*)

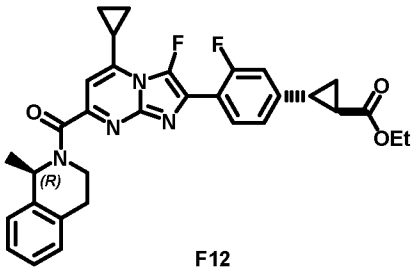
Lithium hydroxide monohydrate (5.87 mg, 0.14 mmol) was added to a solution of intermediate **F10** (25.0 mg, 46.4 µmol) in THF (0.8 mL) and H_2O (0.4 mL). The reaction mixture was stirred at rt for 20 h. The reaction mixture was diluted with brine and a 10% aqueous solution of $KHSO_4$ and DCM were added. The layers were separated and the aqueous phase was extracted with DCM (twice). The combined organic extracts were washed with a solution of water and brine (1:1), dried over $MgSO_4$, filtered and evaporated in vacuo. The crude mixture was purified by preparative LC (irregular SiOH, 15-40 µm, 4 g GraceResolv™, liquid injection (DCM), mobile phase gradient: DCM / MeOH from 100:0 to 96:4). The residue (19 mg) was purified by reverse phase (spherical C18, 25 µm, 40 g YMC-ODS-25, dry loading (Celite®), mobile phase gradient: 0.2% aq.NH_4HCO_3 / MeCN from 85:15 to 45:55). The fractions containing the product were combined and a 1N aqueous solution of HCl was added until pH 1. The aqueous layer was extracted with DCM (3 times). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo. The solid (14 mg) was purified by achiral SFC (Stationary phase: CHIRALPAK AS-H 5µm 250*20mm, mobile phase: 70% CO_2, 30% MeOH). The residue was solubilized in MeOH (2 mL), extended with water (10 mL) and freeze-dried to give compound **24** (7 mg, 30%) as a white fluffy solid.

Compounds 25 and 26



*Intermediate **F12***

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

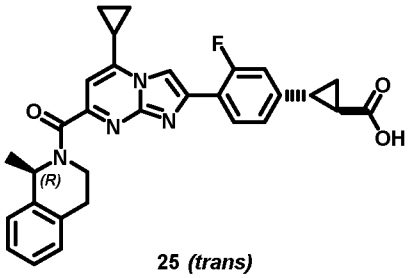


To a mixture of intermediate **F8** (70.0 mg, 134 µmol), intermediate **I5** (*cis*:*trans* 12:88, 32.4 mg, 147 µmol) and cesium carbonate (121 mg, 372 µmol) in toluene (1.5 mL) and H_2O (150 µL) under a nitrogen atmosphere were added cataCxium A® (11.1 mg, 31.0 µmol) and palladium acetate (5.06 mg, 22.5 µmol). 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. The combined organic extracts were washed with brine, 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 100:0 to 70:30) to afford intermediate **F12** (*cis*:*trans* 85:15, 56 mg, 75%) as a colorless gum.

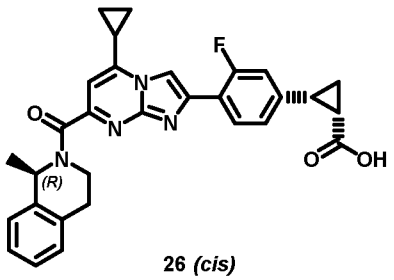
*Compounds **25** and **26***

25: *trans*-2-(4-{5-cyclopropyl-3-fluoro-7-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]imidazo[1,2-a]pyrimidin-2-yl}-3-fluorophenyl)cyclopropane-1-carboxylic acid

26: *cis*-2-(4-{5-cyclopropyl-3-fluoro-7-[(1*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl]imidazo[1,2-a]pyrimidin-2-yl}-3-fluorophenyl)cyclopropane-1-carboxylic acid



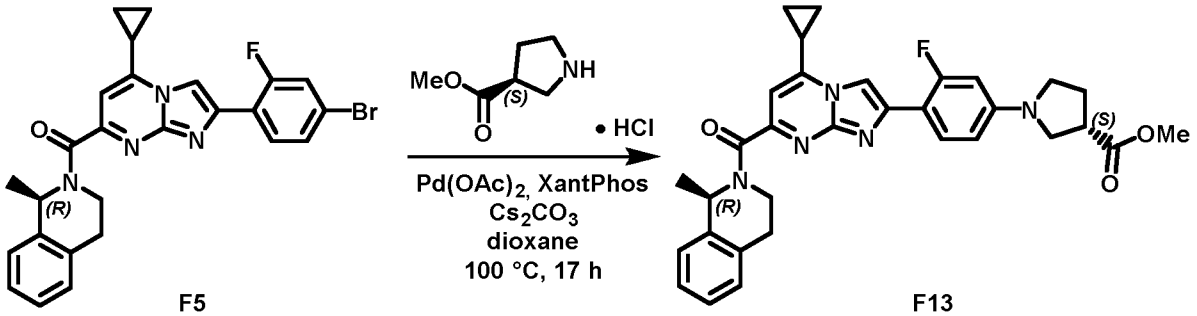
25 (trans)



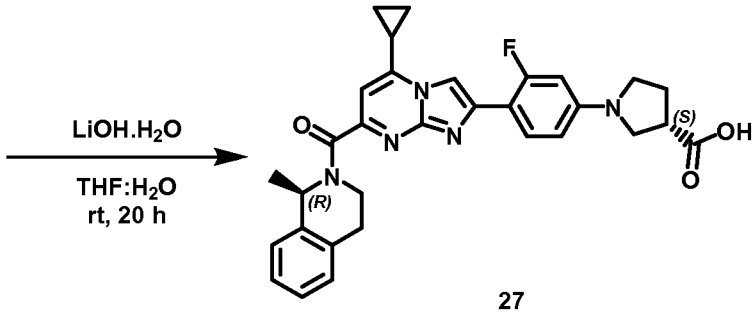
26 (cis)

Lithium hydroxide monohydrate (12.7 mg, 302 µmol) was added to a solution of intermediate **F12** (*cis*:*trans* 85:15, 56.0 mg, 101 µmol) in THF (1.8 mL) and H_2O (0.3 mL). The reaction mixture was stirred at rt for 16 h. The reaction mixture was diluted with brine and a 10% aqueous solution of $KHSO_4$ was added. The aqueous phase was extracted with EtOAc (twice). The combined organic extracts were washed with H_2O, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude mixture was purified by achiral SFC (Stationary phase: DIETHYLAMINOPROPYL 5µm 150x30mm, Mobile phase: 50% CO_2, 50% MeOH) to give 2 fractions: A and B. Fraction A (15 mg) was solubilized in MeCN (2 mL), extended with water (10 mL) and freeze-dried to give compound **25** (15 mg, 28%) as a yellowish fluffy solid. Fraction B (18 mg) was solubilized in MeCN (2 mL), extended with water (10 mL) and freeze-dried to give compound **26** (18 mg, 34%) as a yellowish fluffy solid.

Compound 27



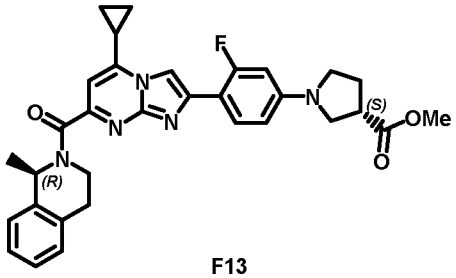
F5 F13



27

*Intermediate **F13***

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

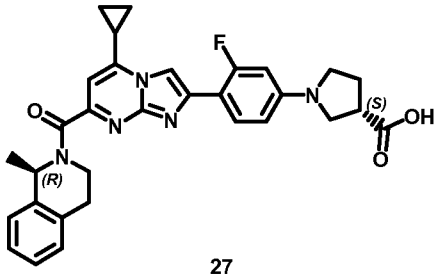


F13

A sealed tube was charged with intermediate **F5** (251 mg, 497 µmol), (*S*)-methyl pyrrolidine-3-carboxylate hydrochloride [1099646-61-3] (98.7 mg, 596 µmol), cesium carbonate (485 mg, 1.49 mmol) and XantPhos (28.7 mg, 49.7 µmol) and purged with nitrogen. 1,4-Dioxane (7.5 mL) was added and the mixture was purged again with nitrogen. Palladium acetate (11.2 mg, 49.7 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 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 90:10 to 50:50) to afford intermediate **F13** (187 mg, 68%) as a yellow foam.

Compound 27

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

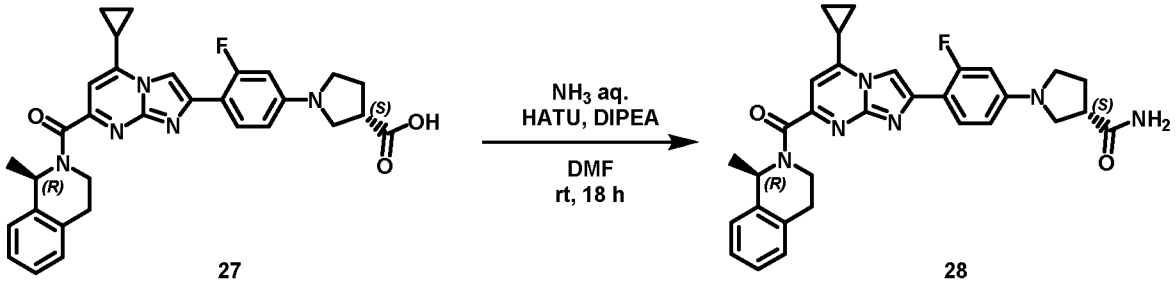


27

Lithium hydroxide monohydrate (40.0 mg, 953 µmol) was added to a solution of intermediate **F13** (175 mg, 316 µmol) in THF (4.2 mL) and H_2O (1.8 mL). The reaction mixture was stirred at rt for 20 h. The reaction mixture was diluted with brine and a 10% aqueous solution of $KHSO_4$ 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 H_2O and brine (1:1), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude mixture was triturated in MeOH. The solid was filtered off and dried under high vacuum at 50°C for 3 h to give compound **27** (146 mg, 86%) as a yellow solid.

Compound 28

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



27 28

A mixture of compound **27** (107 mg, 198 µmol), HATU (113 mg, 297 µmol) and DIPEA (107 µL, 0.62 mmol) in DMF (5.4 mL) was stirred at rt for 1 h. Ammonia (28% in H_2O, 68 µL, 1.00 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 washed with 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: DCM / MeOH from 100:0 to 96:4). The residue was triturated in MeOH. The solid was filtered off and dried under high vacuum at 50°C for 20 h to give compound **28** (71 mg, 66%) as a yellow solid.

C. Compound identification

^{1}H-NMR

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

NMR spectra were recorded at ambient temperature unless otherwise stated.

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

Compound 1

Major rotamer (80%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.37 (br s, 1H), 7.93 (s, 1H), 7.80 (t, J=8.4 Hz, 1H), 7.54 (s, 1H), 7.16 - 7.34 (m, 4H), 7.14 (dd, J=12.8, 1.4 Hz, 1H), 7.11 (dd, J=8.2, 1.6 Hz, 1H), 7.05 (s, 1H), 6.51 (br s, 1H), 5.47 - 5.61 (m, 1H), 3.83 - 3.98 (m, 1H), 3.38 - 3.59 (m, 1H), 2.98 - 3.10 (m, 1H), 2.95 (q, J=7.3 Hz, 2H), 2.78 (br d, J=15.8 Hz, 1H), 2.43 - 2.48 (m, 1H), 1.87 - 1.93 (m, 1H), 1.52 (br d, J=6.6 Hz, 3H), 1.40 - 1.49 (m, 2H), 1.37 (br t, J=6.9 Hz, 3H).

Minor rotamer (20%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.37 (br s, 1H), 7.93 (s, 1H), 7.80 (t, J=8.4 Hz, 1H), 7.54 (s, 1H), 7.16 - 7.34 (m, 4H), 7.14 (dd, J=12.8, 1.4 Hz, 1H), 7.11 (dd, J=8.2, 1.6 Hz, 1H), 7.05 (s, 1H), 6.51 (br s, 1H), 4.94 - 5.11 (m, 1H), 4.39 - 4.60 (m, 1H), 3.38 - 3.59 (m, 1H), 2.98 - 3.10 (m, 1H), 2.95 (q, J=7.3 Hz, 2H), 2.78 (br d, J=15.8 Hz, 1H), 2.43 - 2.48 (m, 1H), 1.87 - 1.93 (m, 1H), 1.52 (br d, J=6.6 Hz, 3H), 1.40 - 1.49 (m, 2H), 1.37 (br t, J=6.9 Hz, 3H).

Compound 2

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.86 (s, 1H), 7.75 (t, J=8.4 Hz, 1H), 7.48 (s, 1H), 7.27 - 7.40 (br s, 1H), 7.13 - 7.23 (m, 4H), 6.98 - 7.07 (m, 3H), 6.54 - 6.85 (br s, 1H), 6.48 (s, 1H), 5.37 (br s, 1H), 4.10 (br s, 1H), 3.41 (br t, J=11.2 Hz, 1H), 2.91 - 3.03 (m, 4H), 2.78 (br d, J=16.1 Hz, 1H), 2.27 - 2.33 (m, 1H), 1.89 - 1.95 (m, 1H), 1.52 (d, J=6.6 Hz, 3H), 1.37 (t, J=7.4 Hz, 3H), 1.19 - 1.25 (m, 1H).

Compound 3

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.51 (br s, 1H), 7.79 (s, 1H), 7.67 (t, J=8.8 Hz, 1H), 7.49 (s, 1H), 7.21 - 7.34 (m, 1H), 7.17 (br s, 3H), 6.94 (s, 1H), 6.39 - 6.51 (m, 3H), 5.48 (s, 1H), 3.94 (s, 1H), 3.41 - 3.54 (m, 3H), 3.33 - 3.40 (m, 2H), 3.17 - 3.26 (m, 1H), 2.97 - 3.08 (m, 1H),

2.89 - 2.97 (m, 2H), 2.77 (br d, J=15.2 Hz, 1H), 2.12 - 2.28 (m, 2H), 1.52 (br d, J=6.6 Hz, 3H), 1.36 (br t, J=7.3 Hz, 3H).

Compound 4

Major rotamer (70%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.39 (br s, 1H), 8.07 (t, J=8.0 Hz, 1H), 7.76 (br s, 1H), 7.32 (br s, 1H), 7.06 - 7.26 (m, 6H), 6.86 (br s, 1H), 5.58 (br s, 1H), 3.71 - 3.84 (m, 1H), 3.43 - 3.54 (m, 1H), 3.16 - 3.26 (m, 2H), 2.93 - 3.09 (m, 1H), 2.70 - 2.87 (m, 1H), 1.90 - 1.97 (m, 1H), 1.36 - 1.55 (m, 8H), 1.23 (br s, 1H).

Minor rotamer (30%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.39 (br s, 1H), 8.07 (t, J=8.0 Hz, 1H), 7.76 (br s, 1H), 7.06 - 7.26 (m, 7H), 6.79 (br s, 1H), 4.90 (br s, 1H), 4.55 (br s, 1H), 3.43 - 3.54 (m, 1H), 3.16 - 3.26 (m, 2H), 2.93 - 3.09 (m, 1H), 2.70 - 2.87 (m, 1H), 1.90 - 1.97 (m, 1H), 1.36 - 1.55 (m, 8H), 1.23 (br s, 1H).

Compound 5

Major rotamer (70%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.06 (br s, 1H), 7.97 (t, J=7.9 Hz, 1H), 7.26 (br d, J=7.6 Hz, 1H), 6.96 - 7.20 (m, 6 H), 6.55 - 6.70 (m, 1H), 5.58 (q, J=6.5 Hz, 1H), 3.51 - 4.08 (m, 4H), 3.34 - 3.47 (m, 1H), 2.74 - 3.13 (m, 4H), 2.60 - 2.70 (m, 1H), 1.80 - 1.88 (m, 1H), 1.45 (d, J=6.9 Hz, 3H), 1.27 - 1.42 (m, 5H).

Minor rotamer (30%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.06 (br s, 1H), 7.96 (t, J=7.6Hz, 1H), 6.96 - 7.20 (m, 7H), 6.55 - 6.70 (m, 1H), 4.65 - 4.79 (m, 1H), 4.52 - 4.60 (m, 1H), 3.51 - 4.08 (m, 3H), 3.34 - 3.47 (m, 1H), 2.74 - 3.13 (m, 4H), 2.60 - 2.70 (m, 1H), 1.80 - 1.88 (m, 1H), 1.27 - 1.42 (m, 8H).

Compound 6

Major rotamer (70%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.39 (br s, 1H), 8.07 (t, J=7.8 Hz, 1H), 7.32 (d, J=7.6 Hz, 1H), 7.09 - 7.27 (m, 6H), 6.65 (d, J=6.1 Hz, 1H), 5.62 (q, J=6.6 Hz, 1H), 3.65 (br dd, J=13.9, 3.8 Hz, 1H), 3.44 - 3.56 (m, 1H), 2.82 - 2.98 (m, 1H), 2.68 - 2.78 (m, 2H), 1.89 - 2.00 (m, 1H), 1.52 (d, J=7.1 Hz, 3H), 1.39 - 1.48 (m, 2H), 1.11 - 1.19 (m, 2H), 0.97 - 1.08 (m, 2H).

Minor rotamer (30%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.39 (br s, 1H), 8.06 (t, J=7.8 Hz, 1H), 7.09 - 7.27 (m, 7H), 6.65 (d, J=6.1 Hz, 1H), 4.82 (q, J=6.6 Hz, 1H), 4.59 (br d, J=13.6 Hz, 1H), 3.24 - 3.29 (m,

1H), 2.82 - 2.98 (m, 2H), 2.68 - 2.78 (m, 1H), 1.89 - 2.00 (m, 1H), 1.39 - 1.49 (m, 5H), 1.11 - 1.19 (m, 2H), 0.97 - 1.08 (m, 2H).

Compound 7

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.96 (t, J=8.8 Hz, 1H), 7.67 (br s, 1H), 7.31 (br s, 1H), 7.14 - 7.28 (m, 3H), 6.94 (d, J=4.1 Hz, 1H), 6.77 (br s, 1H), 6.51 (dd, J=8.8, 2.2 Hz, 1H), 6.43 (dd, J=14.7, 2.0 Hz, 1H), 5.58 (br s, 1H), 3.78 (br d, J=10.4 Hz, 1H), 3.47 (br d, J=6.9 Hz, 3H), 3.14 - 3.24 (m, 3H), 3.08 - 3.15 (m, 1H), 2.90 - 3.07 (m, 1H), 2.75 (br d, J=17.3 Hz, 1H), 2.11 - 2.24 (m, 2H), 1.52 (d, J=6.6 Hz, 3H), 1.34 - 1.46 (br s, 3H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.96 (t, J=8.8 Hz, 1H), 7.67 (br s, 1H), 7.14 - 7.28 (m, 3H), 7.10 (br s, 1H), 6.94 (d, J=4.1 Hz, 1H), 6.70 (br s, 1H), 6.51 (dd, J=8.8, 2.2 Hz, 1H), 6.43 (dd, J=14.7, 2.0 Hz, 1H), 4.90 (br s, 1H), 4.55 (br s, 1H), 3.47 (br d, J=6.9 Hz, 3H), 3.14 - 3.24 (m, 2H), 3.08 - 3.15 (m, 1H), 2.90 - 3.07 (m, 2H), 2.79 - 2.87 (m, 1H), 2.11 - 2.24 (m, 2H), 1.52 (d, J=6.6 Hz, 3H), 1.34 - 1.46 (br s, 3H).

Compound 8

Major rotamer (60%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.97 (t, J=8.8 Hz, 1H), 7.68 (br s, 1H), 7.51 (br s, 1H), 7.08 - 7.35 (m, 4H), 7.00 (br s, 1H), 6.95 (d, J=3.8 Hz, 1H), 6.78 (br s, 1H), 6.51 (dd, J=8.8, 1.9 Hz, 1H), 6.43 (dd, J=14.8, 1.6 Hz, 1H), 5.58 (br s, 1H), 3.78 (br d, J=8.5 Hz, 1H), 3.44 - 3.53 (m, 2H), 3.35 - 3.44 (m, 2H), 3.14 - 3.24 (m, 2H), 3.08 (br quin, J=7.6 Hz, 1H), 2.92 - 3.12 (m, 1H), 2.75 (br d, J=14.8 Hz, 1H), 2.15 - 2.25 (m, 1H), 2.05 - 2.14 (m, 1H), 1.52 (d, J=6.6 Hz, 3H), 1.41 (br s, 3H).

Minor rotamer (30%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.97 (t, J=8.8 Hz, 1H), 7.68 (br s, 1H), 7.51 (br s, 1H), 7.08 - 7.35 (m, 4H), 7.00 (br s, 1H), 6.95 (d, J=3.8 Hz, 1H), 6.71 (br s, 1H), 6.51 (dd, J=8.8, 1.9 Hz, 1H), 6.43 (dd, J=14.8, 1.6 Hz, 1H), 4.90 (br s, 1H), 4.55 (br s, 1H), 3.44 - 3.53 (m, 1H), 3.35 - 3.44 (m, 2H), 3.27 - 3.31 (m, 1H), 3.14 - 3.24 (m, 2H), 3.08 (br quin, J=7.6 Hz, 1H), 2.92 - 3.12 (m, 1H), 2.79 - 2.88 (br s, 1H), 2.15 - 2.25 (m, 1H), 2.05 - 2.14 (m, 1H), 1.52 (d, J=6.6 Hz, 3H), 1.41 (br s, 3H).

Compound 9

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.91 - 8.01 (m, 1H), 7.33 (br d, J=7.6 Hz, 1H), 7.23 (br t, J=7.6 Hz, 1H), 7.07 - 7.21 (m, 2H), 6.84 - 7.00 (m, 1H), 6.32 - 6.74 (m, 3H), 5.63 - 5.72 (m, 1H),

4.63 - 4.72 (m, 1H), 3.44 - 3.55 (m, 3H), 3.32 - 3.38 (m, 2H), 3.13 - 3.22 (m, 3H), 2.85 - 3.01 (m, 1H), 2.66 - 2.78 (m, 1H), 2.37 (br s, 3H), 2.13 - 2.27 (m, 2H), 1.54 (br d, J=6.0 Hz, 3H), 1.32 - 1.45 (m, 3H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.91 - 8.01 (m, 1H), 7.07 - 7.21 (m, 4H), 6.84 - 7.00 (m, 1H), 6.32 - 6.74 (m, 3H), 4.74 - 4.79 (m, 1H), 3.44 - 3.55 (m, 3H), 3.32 - 3.38 (m, 3H), 3.13 - 3.22 (m, 3H), 2.85 - 3.01 (m, 2H), 2.31 (br s, 3H), 2.13 - 2.27 (m, 2H), 1.32 - 1.45 (m, 6H).

Compound 10

Major rotamer (70%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.98 (t, J=8.8 Hz, 1H), 7.51 (br s, 1H), 7.32 (br d, J=7.6 Hz, 1H), 7.23 (br t, J=7.1 Hz, 1H), 7.09 - 7.21 (m, 2H), 6.96 - 7.06 (m, 3H), 6.50 - 6.58 (m, 1H), 6.45 (br dd, J=14.8, 1.9 Hz, 1H), 5.62 (q, J=6.2 Hz, 1H), 3.65 (br d, J=14.8 Hz, 1H), 3.50 (br t, J=8.8 Hz, 2H), 3.34 - 3.44 (m, 3H), 3.09 (quin, J=7.5 Hz, 1H), 2.82 - 2.95 (m, 1H), 2.68 - 2.77 (m, 2H), 2.16 - 2.24 (m, 1H), 2.05 - 2.15 (m, 1H), 1.52 (d, J=6.6 Hz, 3H), 1.15 (br d, J=8.5 Hz, 2H), 0.96 - 1.08 (m, 2H).

Minor rotamer (30%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.97 (t, J=8.8 Hz, 1H), 7.51 (br s, 1H), 7.09 - 7.21 (m, 4H), 6.96 - 7.06 (m, 3H), 6.50 - 6.58 (m, 1H), 6.45 (br dd, J=14.8, 1.9 Hz, 1H), 4.81 (q, J=6.6 Hz, 1H), 4.55 - 4.63 (m, 1H), 3.50 (br t, J=8.8 Hz, 2H), 3.34 - 3.44 (m, 2H), 3.24 - 3.30 (m, 1H), 3.09 (quin, J=7.5 Hz, 1H), 2.82 - 2.95 (m, 2H), 2.68 - 2.77 (m, 1H), 2.16 - 2.24 (m, 1H), 2.05 - 2.15 (m, 1H), 1.42 (br d, J=6.6 Hz, 3H), 1.15 (br d, J=8.5 Hz, 2H), 0.96 - 1.08 (m, 2H).

Compound 11

^{1}H NMR (500 MHz, DMSO-d_6, 77°C) δ ppm 12.03 (br s, 1H), 8.32 (d, J=3.5 Hz, 1H), 8.17 (t, J=8.2 Hz, 1H), 7.50 (s, 1H), 7.12 - 7.23 (m, 6H), 6.66 (s, 1H), 5.37 (br s, 1H), 4.00 (br s, 1H), 3.42 (br s, 1H), 2.97 (ddd, J=16.7, 11.4, 6.0 Hz, 1H), 2.77 (br d, J=16.1 Hz, 1H), 2.29 - 2.37 (m, 1H), 1.88 - 1.94 (m, 1H), 1.52 (d, J=6.6 Hz, 3H), 1.48 (br dt, J=9.3, 4.8 Hz, 1H), 1.38 - 1.44 (m, 1H), 1.13 - 1.17 (m, 2H), 0.86 - 0.92 (m, 2H).

Compound 12

Major rotamer (75%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.62 (s, 1H), 8.33 (d, J=4.1 Hz, 1H), 8.19 (t, J=8.0 Hz, 1H), 7.62 (br s, 1H), 7.30 (br s, 1H), 7.09 - 7.25 (m, 5H), 6.95 (br s, 1H), 6.84 (br s, 1H), 5.54 (br s, 1H), 3.82 (br s, 1H), 3.46 (br s, 1H), 3.03 (br s, 1H), 2.77 (br d, J=15.8 Hz, 1H), 2.53 - 2.62 (m, 1H), 2.25 - 2.33 (m, 1H), 1.87 - 1.98 (m, 1H), 1.51 (br d, J=6.6 Hz, 3H), 1.36 - 1.42 (m, 1H), 1.27 - 1.33 (m, 1H), 1.04 - 1.17 (m, 4H).

Minor rotamer (25%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.62 (s, 1H), 8.33 (d, J=4.1 Hz, 1H), 8.19 (t, J=8.0 Hz, 1H), 7.62 (br s, 1H), 7.09 - 7.25 (m, 6H), 6.95 (br s, 1H), 6.84 (br s, 1H), 4.95 (br s, 1H), 4.51 (br s, 1H), 3.46 (br s, 1H), 3.03 (br s, 1H), 2.77 (br d, J=15.8 Hz, 1H), 2.53 - 2.62 (m, 1H), 2.25 - 2.33 (m, 1H), 1.87 - 1.98 (m, 1H), 1.51 (br d, J=6.6 Hz, 3H), 1.36 - 1.42 (m, 1H), 1.27 - 1.33 (m, 1H), 1.04 - 1.17 (m, 4H).

Compound 13

Major rotamer (70%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.17 (br d, J=2.8 Hz, 1H), 8.07 (br t, J=8.8 Hz, 1H), 7.50 (br s, 2H), 7.31 (br s, 1H), 7.04 - 7.25 (m, 3H), 6.99 (br s, 1H), 6.69 (br s, 1H), 6.50 (br d, J=8.5 Hz, 1H), 6.44 (d, J=14.5 Hz, 1H), 5.57 (br s, 1H), 3.74 (br s, 1H), 3.35 - 3.56 (m, 4H), 3.20 - 3.31 (m, 1H), 3.08 (quin, J=7.5 Hz, 1H), 3.00 (br s, 1H), 2.68 - 2.86 (m, 1H), 2.33 (br s, 1H), 2.15 - 2.24 (m, 1H), 2.04 - 2.15 (m, 1H), 1.52 (br d, J=6.6 Hz, 3H), 1.12 (br s, 2H), 0.89 (br s, 2H).

Minor rotamer (30%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.17 (br d, J=2.8 Hz, 1H), 8.07 (br t, J=8.8 Hz, 1H), 7.50 (br s, 2H), 7.04 - 7.25 (m, 4H), 6.99 (br s, 1H), 6.62 (br s, 1H), 6.50 (br d, J=8.5 Hz, 1H), 6.44 (d, J=14.5 Hz, 1H), 4.89 (br s, 1H), 4.54 (br s, 1H), 3.35 - 3.56 (m, 4H), 3.20 - 3.31 (m, 1H), 3.08 (quin, J=7.5 Hz, 1H), 3.00 (br s, 1H), 2.68 - 2.86 (m, 1H), 2.33 (br s, 1H), 2.15 - 2.24 (m, 1H), 2.04 - 2.15 (m, 1H), 1.52 (br d, J=6.6 Hz, 3H), 1.12 (br s, 2H), 0.89 (br s, 2H).

Compound 14

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.52 (br s, 1H), 8.98 (br s, 1H), 8.80 (br d, J=3.5 Hz, 1H), 8.29 (br s, 1H), 8.06 (t, J=8.8 Hz, 1H), 7.84 (d, J=3.2 Hz, 1H), 7.71 (br s, 1H), 7.62 - 7.70 (m, 1H), 7.28 - 7.36 (m, 1H), 7.09 - 7.27 (m, 3H), 7.04 (br s, 1H), 6.52 (dd, J=8.8, 2.2 Hz, 1H), 6.42 (dd, J=14.7, 2.0 Hz, 1H), 5.61 (br d, J=5.0 Hz, 1H), 3.89 (br d, J=10.4 Hz, 1H), 3.43 - 3.58 (m, 2H), 3.28 - 3.40 (m, 3H), 3.21 (br quin, J=7.1 Hz, 1H), 2.93 - 3.11 (m, 1H), 2.70 - 2.87 (m, 1H), 2.12 - 2.27 (m, 2H), 1.54 (br s, 3H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.52 (br s, 1H), 8.98 (br s, 1H), 8.80 (br d, J=3.5 Hz, 1H), 8.29 (br s, 1H), 8.06 (t, J=8.8 Hz, 1H), 7.84 (d, J=3.2 Hz, 1H), 7.71 (br s, 1H), 7.62 - 7.70 (m, 1H), 7.09 - 7.27 (m, 4H), 6.97 (br s, 1H), 6.52 (dd, J=8.8, 2.2 Hz, 1H), 6.42 (dd, J=14.7, 2.0 Hz, 1H), 5.04 (br s, 1H), 4.57 (br s, 1H), 3.43 - 3.58 (m, 2H), 3.28 - 3.40 (m, 3H), 3.21 (br quin, J=7.1 Hz, 1H), 2.93 - 3.11 (m, 1H), 2.70 - 2.87 (m, 1H), 2.12 - 2.27 (m, 2H), 1.54 (br s, 3H).

Compound 15

Major rotamer (70%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.91 - 9.03 (m, 1H), 8.80 (br d, J=3.2 Hz, 1H), 8.30 (br s, 1H), 8.06 (t, J=8.8 Hz, 1H), 7.83 (d, J=3.2 Hz, 1H), 7.71 (br s, 1H), 7.62 - 7.69 (m, 1H), 7.44 - 7.56 (m, 1H), 7.31 (br s, 1H), 7.09 - 7.26 (m, 3H), 7.03 (br s, 1H), 6.94 - 7.01 (m, 1H), 6.50 (dd, J=8.8, 2.2 Hz, 1H), 6.38 (dd, J=15.1, 1.9 Hz, 1H), 5.61 (br d, J=4.7 Hz, 1H), 3.89 (br d, J=11.0 Hz, 1H), 3.50 - 3.59 (m, 1H), 3.47 (br t, J=8.8 Hz, 1H), 3.35 - 3.41 (m, 2H), 3.25 - 3.32 (m, 1H), 2.96 - 3.12 (m, 2H), 2.70 - 2.88 (m, 1H), 2.14 - 2.24 (m, 1H), 2.02 - 2.14 (m, 1H), 1.54 (br s, 3H).

Minor rotamer (30%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.91 - 9.03 (m, 1H), 8.80 (br d, J=3.2 Hz, 1H), 8.30 (br s, 1H), 8.06 (t, J=8.8 Hz, 1H), 7.83 (d, J=3.2 Hz, 1H), 7.71 (br s, 1H), 7.62 - 7.69 (m, 1H), 7.44 - 7.56 (m, 1H), 7.09 - 7.26 (m, 4H), 6.94 - 7.01 (m, 2H), 6.50 (dd, J=8.8, 2.2 Hz, 1H), 6.38 (dd, J=15.1, 1.9 Hz, 1H), 5.04 (br s, 1H), 4.57 (br s, 1H), 3.47 (br t, J=8.8 Hz, 2H), 3.35 - 3.41 (m, 2H), 3.25 - 3.32 (m, 1H), 2.96 - 3.12 (m, 2H), 2.70 - 2.88 (m, 1H), 2.14 - 2.24 (m, 1H), 2.02 - 2.14 (m, 1H), 1.54 (br s, 3H).

Compound 16

Major rotamer (70%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.42 (br s, 1H), 8.10 (br t, J=7.9 Hz, 1H), 7.76 (s, 1H), 7.32 (br d, J=7.6 Hz, 1H), 7.14 - 7.28 (m, 5H), 6.90 (s, 1H), 5.59 (q, J=6.6 Hz, 1H), 3.65 (br dd, J=13.2, 3.2, 1H), 3.40 - 3.48 (m, 1H), 2.93 - 3.04 (m, 1H), 2.73 - 2.87 (m, 1H), 2.69 (br d, J=16.4 Hz, 1H), 2.53 - 2.55 (m, 1H), 1.94 - 2.00 (m, 1H), 1.50 - 1.55 (m, 3H), 1.44 - 1.50 (m, 2H), 1.15 - 1.27 (m, 4H).

Minor rotamer (30%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.42 (br s, 1H), 8.10 (br t, J=7.9 Hz, 1H), 7.73 (s, 1H), 7.14 - 7.28 (m, 4H), 7.08 - 7.13 (m, 1H), 7.03 - 7.07 (m, 1H), 6.84 (s, 1H), 4.79 (q, J=6.9 Hz, 1H), 4.53 - 4.59 (m, 1H), 3.23 - 3.29 (m, 1H), 2.93 - 3.04 (m, 1H), 2.73 - 2.87 (m, 2H), 2.53 - 2.55 (m, 1H), 1.94 - 2.00 (m, 1H), 1.50 - 1.55 (m, 3H), 1.44 - 1.50 (m, 2H), 1.15 - 1.27 (m, 4H).

Compound 17

Major rotamer (70%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.03 (br s, 1H), 8.03 - 8.10 (m, 1H), 7.76 (s, 1H), 7.32 (br d, J=7.6 Hz, 1H), 7.28 (d, J=8.5 Hz, 1H), 7.13 - 7.26 (m, 4H), 6.91 (s, 1H), 5.59 (q, J=6.5 Hz, 1H), 3.65 (br dd, J=13.6, 4.1 Hz, 1H), 3.41 - 3.49 (m, 1H), 2.93 - 3.05 (m, 1H), 2.73 - 2.81 (m,

1H), 2.65 - 2.73 (m, 2H), 2.08 - 2.15 (m,1H), 1.58 - 1.64 (m, 1H), 1.53 (br d, J=6.9 Hz, 3H), 1.38 (td, J=8.1, 4.9 Hz, 1H), 1.16 - 1.27 (m, 4H).

Minor rotamer (30%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.03 (br s, 1H), 8.03 - 8.10 (m, 1H), 7.74 (s, 1H), 7.28 (d, J=8.5 Hz, 1H), 7.13 - 7.26 (m, 3H), 7.04 - 7.13 (m, 1H), 6.85 (s, 1H), 4.79 (q, J=6.6 Hz, 1H), 4.56 (br dd, J=12.5, 4.9 Hz, 1H), 3.22 - 3.29 (m, 1H), 2.93 - 3.05 (m, 1H), 2.81 - 2.87 (m, 1H), 2.73 - 2.81 (m, 1H), 2.65 - 2.73 (m, 2H), 2.08 - 2.15 (m, 1H), 1.58 - 1.64 (m, 1H), 1.49 (br d, J=6.6 Hz, 3H), 1.38 (td, J=8.1, 4.9 Hz, 1H), 1.16 - 1.27 (m, 4H).

Compound 18

Major rotamer (70%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.11 (t, J=7.9 Hz, 1H), 7.75 (s, 1H), 7.64 (br s, 1H), 7.32 (br d, J=7.3 Hz, 1H), 7.14 - 7.25 (m, 5H), 6.98 (br s, 1H), 6.90 (s, 1H), 5.59 (q, J=6.7 Hz, 1H), 3.64 (br dd, J=13.9, 3.5 Hz, 1H), 3.40 - 3.48 (m, 1H), 2.93 - 3.04 (m, 1H), 2.74 - 2.80 (m, 1H), 2.69 (br d, J=16.4 Hz, 1H), 2.31 - 2.35 (m, 1H), 1.94 - 1.99 (m, 1H), 1.53 (br d, J=6.9 Hz, 3H), 1.41 (br dt, J=9.5, 4.5 Hz, 1H), 1.32 - 1.37 (m, 1H), 1.15 - 1.27 (m, 4H).

Minor rotamer (30%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.11 (t, J=7.9 Hz, 1H), 7.73 (s, 1H), 7.64 (br s, 1H), 7.14 - 7.25 (m, 4H), 7.08 - 7.13 (m, 1H), 7.03 - 7.07 (m, 1H), 6.98 (br s, 1H), 6.84 (s, 1H), 4.78 (q, J=6.9 Hz, 1H), 4.53 - 4.60 (m, 1H), 3.23 - 3.30 (m, 1H), 2.93 - 3.04 (m, 1H), 2.80 - 2.87 (m, 1H), 2.74 - 2.80 (m, 1H), 2.31 - 2.35 (m, 1H), 1.94 - 1.99 (m, 1H), 1.48 (br d, J=6.3 Hz, 3H), 1.41 (br dt, J=9.5, 4.5 Hz, 1H), 1.32 - 1.37 (m, 1H), 1.15 - 1.27 (m, 4H).

Compound 19

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.63 (br s, 1H), 8.02 (br t, J=8.7 Hz, 1H), 7.66 (s, 1H), 7.32 (br d, J=7.6 Hz, 1H), 7.21 - 7.25 (m, 1H), 7.14 - 7.21 (m, 2H), 6.81 (s, 1H), 6.54 (dd, J=8.8, 1.9 Hz, 1H), 6.46 (dd, J=14.2, 1.6 Hz, 1H), 5.58 (q, J=6.3 Hz, 1H), 3.65 (br dd, J=13.4, 3.6 Hz, 1H), 3.48 - 3.57 (m, 2H), 3.36 - 3.47 (m, 3H), 3.16 - 3.24 (m, 1H), 2.93 - 3.05 (m, 1H), 2.73 - 2.81 (m, 1H), 2.69 (br d, J=15.8 Hz, 1H), 2.14 - 2.29 (m, 2H), 1.52 (br d, J=6.6 Hz, 3H), 1.13 - 1.27 (m, 4H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.63 (br s, 1H), 8.02 (br t, J=8.7 Hz, 1H), 7.64 (br s, 1H), 7.14 - 7.21 (m, 2H), 7.03 - 7.13 (m, 2H), 6.75 (s, 1H), 6.54 (dd, J=8.8, 1.9 Hz, 1H), 6.46 (dd, J=14.2, 1.6 Hz, 1H), 4.78 (q, J=7.3 Hz, 1H), 4.52 - 4.60 (m, 1H), 3.48 - 3.57 (m, 2H), 3.36 -

3.47 (m, 3H), 3.16 - 3.24 (m, 1H), 2.93 - 3.05 (m, 1H), 2.81 - 2.86 (m, 1H), 2.73 - 2.81 (m, 1H), 2.14 - 2.29 (m, 2H), 1.49 (br d, J=6.3 Hz, 3H), 1.13 - 1.27 (m, 4H).

Compound 20

Major rotamer (70%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.01 (br t, J=8.6 Hz, 1H), 7.66 (s, 1H), 7.51 (br s, 1H), 7.32 (d, J=7.6 Hz, 1H), 7.14 - 7.26 (m, 3H), 7.00 (br s, 1H), 6.81 (s, 1H), 6.52 (dd, J=8.8, 1.3 Hz, 1H), 6.43 (br d, J=14.1 Hz, 1H), 5.58 (q, J=7.1 Hz, 1H), 3.65 (br d, J=13.6 Hz, 1H), 3.48 - 3.54 (m, 1H), 3.37 - 3.48 (m, 3H), 3.34 - 3.37 (m, 1H), 3.09 (quin, J=7.6 Hz, 1H), 2.92 - 3.04 (m, 1H), 2.73 - 2.87 (m, 1H), 2.69 (br d, J=17.7 Hz, 1H), 2.16 - 2.26 (m, 1H), 2.05 - 2.15 (m, 1H), 1.52 (br d, J=6.6 Hz, 3H), 1.19 - 1.27 (m, 2H), 1.08 - 1.18 (m, 2H).

Minor rotamer (30%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.01 (br t, J=8.6 Hz, 1H), 7.63 (br s, 1H), 7.51 (br s, 1H), 7.14 - 7.26 (m, 2H), 7.04 - 7.14 (m, 2H), 7.00 (br s, 1H), 6.75 (br s, 1H), 6.52 (dd, J=8.8, 1.3 Hz, 1H), 6.43 (br d, J=14.1 Hz, 1H), 4.78 (q, J=5.6 Hz, 1H), 4.51 - 4.60 (m, 1H), 3.48 - 3.54 (m, 1H), 3.37 - 3.48 (m, 3H), 3.21 - 3.28 (m, 1H), 3.09 (quin, J=7.6 Hz, 1H), 2.92 - 3.04 (m, 1H), 2.73 - 2.87 (m, 2H), 2.16 - 2.26 (m, 1H), 2.05 - 2.15 (m, 1H), 1.49 (br d, J=6.6 Hz, 3H), 1.19 - 1.27 (m, 2H), 1.08 - 1.18 (m, 2H).

Compound 21

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.56 (br s, 1H), 8.02 (t, J=8.8 Hz, 1H), 7.75 (s, 1H), 7.30 (d, J=7.6 Hz, 1H), 7.17 - 7.24 (m, 2H), 7.06 - 7.17 (m, 1H), 7.02 (d, J=3.8 Hz, 1H), 6.55 (br d, J=8.8 Hz, 1H), 6.49 (br dd, J=14.7, 2.0 Hz, 1H), 5.50 (q, J=6.7 Hz, 1H), 3.94 (br dd, J=13.4, 4.3 Hz, 1H), 3.52 - 3.58 (m, 1H), 3.46 - 3.52 (m, 1H), 3.34 - 3.43 (m, 3H), 3.19 - 3.30 (m, 2H), 3.01 - 3.10 (m, 1H), 2.77 (br d, J=16.4 Hz, 1H), 2.22 - 2.29 (m, 1H), 2.14 - 2.22 (m, 1H), 1.50 (d, J=6.9 Hz, 3H), 1.20 - 1.38 (m, 4H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.56 (br s, 1H), 8.02 (t, J=9.0 Hz, 1H), 7.67 (s, 1H), 7.17 - 7.24 (m, 2H), 7.06 - 7.17 (m, 2H), 6.98 (d, J=3.5 Hz, 1H), 6.55 (br d, J=8.8 Hz, 1H), 6.49 (br dd, J=14.7, 2.0 Hz, 1H), 5.06 (q, J=6.6 Hz, 1H), 4.50 (br dd, J=12.6, 5.0 Hz, 1H), 3.52 - 3.58 (m, 1H), 3.46 - 3.52 (m, 1H), 3.34 - 3.43 (m, 3H), 3.19 - 3.30 (m, 2H), 2.86 - 2.96 (m, 1H), 2.80 - 2.86 (m, 1H), 2.22 - 2.29 (m, 1H), 2.14 - 2.22 (m, 1H), 1.56 (d, J=6.6 Hz, 3H), 1.20 - 1.38 (m, 4H).

Compound 22

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.02 (t, J=8.8 Hz, 1H), 7.74 (s, 1H), 7.52 (br s, 1H), 7.30 (br d, J=6.8 Hz, 1H), 7.17 - 7.25 (m, 2H), 7.05 - 7.16 (m, 1H), 6.96 - 7.05 (m, 2H), 6.53 (br d, J=8.8 Hz, 1H), 6.46 (br dd, J=15.2, 1.6 Hz, 1H), 5.50 (q, J=6.4 Hz, 1H), 3.95 (br dd, J=13.9, 4.2 Hz, 1H), 3.50 (br t, J=8.7 Hz, 1H), 3.35 - 3.46 (m, 3H), 3.20 - 3.31 (m, 2H), 3.00 - 3.14 (m, 2H), 2.73 - 2.87 (m, 1H), 2.15 - 2.25 (m, 1H), 2.05 - 2.15 (m, 1H), 1.50 (d, J=6.7 Hz, 3H), 1.25 - 1.39 (m, 4H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.02 (t, J=8.8 Hz, 1H), 7.67 (s, 1H), 7.52 (br s, 1H), 7.17 - 7.25 (m, 2H), 7.05 - 7.16 (m, 2H), 6.96 - 7.05 (m, 2H), 6.53 (br d, J=8.8 Hz, 1H), 6.46 (br dd, J=15.2, 1.6 Hz, 1H), 5.05 (q, J=6.9 Hz, 1H), 4.46 - 4.54 (m, 1H), 3.50 (br t, J=8.7 Hz, 1H), 3.35 - 3.46 (m, 3H), 3.20 - 3.31 (m, 2H), 3.00 - 3.14 (m, 1H), 2.73 - 2.87 (m, 2H), 2.15 - 2.25 (m, 1H), 2.05 - 2.15 (m, 1H), 1.56 (br d, J=6.5 Hz, 3H), 1.25 - 1.39 (m, 4H).

Compound 23

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.96 - 8.06 (m, 2H), 7.74 (s, 1H), 7.30 (br d, J=7.3 Hz, 1H), 7.17 - 7.26 (m, 2H), 7.06 - 7.16 (m, 1H), 7.01 (br d, J=2.8 Hz, 1H), 6.53 (br d, J=8.2 Hz, 1H), 6.45 (br d, J=15.1 Hz, 1H), 5.50 (q, J=6.3 Hz, 1H), 3.94 (br d, J=9.5 Hz, 1H), 3.51 (t, J=8.2 Hz, 1H), 3.34 - 3.47 (m, 3H), 3.19 - 3.29 (m, 2H), 3.01 - 3.13 (m, 2H), 2.73 - 2.85 (m, 1H), 2.62 (br d, J=4.4 Hz, 3H), 2.05 - 2.24 (m, 2H), 1.50 (br d, J=6.6 Hz, 3H), 1.21 - 1.39 (m, 4H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.96 - 8.06 (m, 2H), 7.67 (s, 1H), 7.17 - 7.26 (m, 2H), 7.06 - 7.16 (m, 2H), 6.98 (br d, J=2.8 Hz, 1H), 6.53 (br d, J=8.2 Hz, 1H), 6.45 (br d, J=15.1 Hz, 1H), 5.06 (q, J=6.7 Hz, 1H), 4.46 - 4.54 (m, 1H), 3.51 (t, J=8.2 Hz, 1H), 3.34 - 3.47 (m, 3H), 3.19 - 3.29 (m, 2H), 3.01 - 3.13 (m, 1H), 2.73 - 2.85 (m, 2H), 2.62 (br d, J=4.4 Hz, 3H), 2.05 - 2.24 (m, 2H), 1.56 (br d, J=6.3 Hz, 3H), 1.21 - 1.39 (m, 4H).

Compound 24

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.42 (br s, 1H), 8.38 - 8.43 (m, 1H), 8.19 (br t, J=8.0 Hz, 1H), 7.33 (d, J=7.6 Hz, 1H), 7.15 - 7.26 (m, 5H), 6.98 (s, 1H), 5.60 (q, J=6.6 Hz, 1H), 3.91 (br dd, J=13.7, 3.9 Hz, 1H), 3.44 - 3.52 (m, 1H), 2.99 - 3.08 (m, 1H), 2.73 (br d, J=15.8 Hz, 1H), 2.52 - 2.59 (m, 2H), 1.87 - 2.03 (m, 2H), 1.53 (d, J=6.6 Hz, 3H), 1.38 - 1.50 (m, 2H), 1.02 - 1.17 (m, 3H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.42 (br s, 1H), 8.38 - 8.43 (m, 1H), 8.19 (br t, J=8.0 Hz, 1H), 7.15 - 7.26 (m, 4H), 7.10 - 7.15 (m, 1H), 7.07 (d, J=7.3 Hz, 1H), 6.93 (s, 1H), 5.04 (q, J=6.6 Hz, 1H), 4.57 (br dd, J=12.5, 3.9 Hz, 1H), 3.23 - 3.30 (m, 1H), 2.83 - 2.97 (m, 1H), 2.52 - 2.59 (m, 3H), 1.87 - 2.03 (m, 2H), 1.59 (d, J=6.9 Hz, 3H), 1.38 - 1.50 (m, 2H), 1.02 - 1.17 (m, 3H).

Compound 25

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.82 (t, J=8.0 Hz, 1H), 7.32 (d, J=7.6 Hz, 1H), 7.11 - 7.26 (m, 5H), 6.98 (s, 1H), 5.59 (q, J=6.8 Hz, 1H), 3.91 (br dd, J=13.6, 3.8 Hz, 1H), 3.44 - 3.52 (m, 1H), 2.98 - 3.07 (m, 1H), 2.83 - 2.96 (m, 1H), 2.73 (br d, J=16.1 Hz, 1H), 2.57 - 2.63 (m, 1H), 2.39 - 2.47 (m, 2H), 1.88 - 1.94 (m, 1H), 1.53 (d, J=6.6 Hz, 3H), 1.43 - 1.49 (m, 1H), 1.39 (br s, 1H), 1.11 - 1.18 (m, 3H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.82 (t, J=8.0 Hz, 1H), 7.11 - 7.26 (m, 5H), 7.04 (d, J=7.3 Hz, 1H), 6.93 (s, 1H), 5.03 (q, J=6.6 Hz, 1H), 4.55 (br dd, J=12.8, 3.9 Hz, 1H), 3.44 - 3.52 (m, 1H), 2.98 - 3.07 (m, 1H), 2.83 - 2.96 (m, 1H), 2.57 - 2.63 (m, 1H), 2.39 - 2.47 (m, 3H), 1.88 - 1.94 (m, 1H), 1.58 (d, J=6.6 Hz, 3H), 1.43 - 1.49 (m, 1H), 1.39 (br s, 1H), 1.11 - 1.18 (m, 3H).

Compound 26

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.53 - 7.61 (m, 1H), 7.32 (d, J=7.3 Hz, 1H), 7.05 - 7.26 (m, 6H), 5.54 - 5.63 (m, 1H), 3.84 - 3.93 (m, 1H), 3.44 - 3.54 (m, 1H), 2.97 - 3.08 (m, 1H), 2.82 - 2.97 (m, 1H), 2.73 (br dd, J=16.2, 2.4 Hz, 1H), 2.39 - 2.46 (m, 2H partially obscured by DMSO peak), 1.92 (br s, 1H), 1.67 - 1.76 (m, 1H), 1.53 (d, J=6.9 Hz, 3H), 1.43 - 1.49 (m, 1H), 1.34 - 1.41 (m, 1H), 0.83 - 1.06 (m, 3H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.53 - 7.61 (m, 1H), 7.05 - 7.26 (m, 7H), 5.04 (quin, J=7.0 Hz, 1H), 4.52 - 4.58 (m, 1H), 3.44 - 3.54 (m, 1H), 2.97 - 3.08 (m, 1H), 2.82 - 2.97 (m, 1H),2.39 - 2.46 (m, 3H partially obscured by DMSO peak), 1.92 (br s, 1H), 1.67 - 1.76 (m, 1H), 1.59 (dd, J=10.9, 6.8 Hz, 3H), 1.43 - 1.49 (m, 1H), 1.34 - 1.41 (m, 1H), 0.83 - 1.06 (m, 3H).

Compound 27

Major rotamer (65%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.55 (br s, 1H), 8.19 - 8.24 (m, 1H), 8.09 (t, J=9.0 Hz, 1H), 7.32 (d, J=7.6 Hz, 1H), 7.15 - 7.26 (m, 3H), 6.93 (s, 1H), 6.55 (dt, J=8.8, 2.7 Hz, 1H), 6.49

(dd, J=14.8, 1.6 Hz, 1H), 5.60 (q, J=6.6 Hz, 1H), 3.93 (br dd, J=13.7, 3.9 Hz, 1H), 3.43 - 3.57 (m, 3H), 3.34 - 3.43 (m, 2H), 3.20 - 3.26 (m, 1H), 3.01 - 3.10 (m, 1H), 2.74 (br d, J=15.8 Hz, 1H), 2.14 - 2.29 (m, 2H), 1.53 (d, J=6.9 Hz, 3H), 1.19 - 1.26 (m, 2H), 1.02 - 1.13 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.55 (br s, 1H), 8.19 - 8.24 (m, 1H), 8.09 (t, J=9.0 Hz, 1H), 7.15 - 7.26 (m, 2H), 7.10 - 7.15 (m, 1H), 7.08 (d, J=7.6 Hz, 1H), 6.89 (s, 1H), 6.55 (dt, J=8.8, 2.7 Hz, 1H), 6.49 (dd, J=14.8, 1.6 Hz, 1H), 5.07 (q, J=6.6 Hz, 1H), 4.57 (br dd, J=12.3, 4.4 Hz, 1H), 3.43 - 3.57 (m, 2H), 3.34 - 3.43 (m, 2H), 3.26 - 3.31 (m, 1H), 3.20 - 3.26 (m, 1H), 2.83 - 2.97 (m, 2H), 2.14 - 2.29 (m, 2H), 1.59 (d, J=6.6 Hz, 3H), 1.19 - 1.26 (m, 2H), 1.02 - 1.13 (m, 2H).

Compound 28

Major rotamer (65%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.20 (br s, 1H), 8.08 (br t, J=8.8 Hz, 1H), 7.50 (br s, 1H), 7.32 (d, J=7.1 Hz, 1H), 7.05 - 7.27 (m, 3H), 7.00 (br s, 1H), 6.93 (s, 1H), 6.53 (br d, J=9.1 Hz, 1H), 6.46 (br d, J=14.7 Hz, 1H), 5.60 (q, J=6.4 Hz, 1H), 3.93 (br dd, J=13.9, 4.3 Hz, 1H), 3.34 - 3.55 (m, 4H), 3.22 - 3.30 (m, 1H partially obscured by H2O peak), 3.02 - 3.13 (m, 2H), 2.73 (br d, J=16.7 Hz, 1H), 2.15 - 2.25 (m, 1H), 2.04 - 2.15 (m, 1H), 1.53 (d, J=7.1 Hz, 3H), 1.17 - 1.29 (m, 2H), 0.98 - 1.14 (m, 2H).

Minor rotamer (35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.20 (br s, 1H), 8.08 (br t, J=8.8 Hz, 1H), 7.50 (br s, 1H), 7.05 - 7.27 (m, 4H), 7.00 (br s, 1H), 6.88 (s, 1H), 6.53 (br d, J=9.1 Hz, 1H), 6.46 (br d, J=14.7 Hz, 1H), 5.06 (q, J=6.6 Hz, 1H), 4.53 - 4.62 (m, 1H), 3.34 - 3.55 (m, 4H), 3.22 - 3.30 (m, 1H partially obscured by H_2O peak), 3.02 - 3.13 (m, 1H), 2.82 - 2.97 (m, 2H), 2.15 - 2.25 (m, 1H), 2.04 - 2.15 (m, 1H), 1.59 (d, J=6.6 Hz, 3H), 1.17 - 1.29 (m, 2H), 0.98 - 1.14 (m, 2H).

LC-MS data

General procedure

The High Performance Liquid Chromatography (HPLC) measurement was performed using a LC pump, a diode-array (DAD) or a UV detector and a column as specified in the respective methods. If necessary, additional detectors were included (see table of methods below).
Flow from the column was brought to the Mass Spectrometer (MS) which was configured with an atmospheric pressure ion source. It is within the knowledge of the skilled person to set the tune parameters (e.g. scanning range, dwell time…) in order to obtain ions allowing the identification of the compound's nominal monoisotopic molecular weight (MW). Data acquisition was performed with appropriate software.

Compounds are described by their experimental retention times (R_t) and ions. If not specified differently in the table of data, the reported molecular ion corresponds to the $[M+H]^+$ (protonated molecule) and/or $[M-H]^-$ (deprotonated molecule). In case the compound was not directly ionizable the type of adduct is specified (i.e. $[M+NH_4]^+$, $[M+HCOO]^-$, etc…). For molecules with multiple isotopic patterns (Br, Cl..), the reported value is the one obtained for the lowest isotope mass. All results were obtained with experimental uncertainties that are commonly associated with the method used.

Hereinafter, "SQD" means Single Quadrupole Detector, "RT" room temperature, "BEH" bridged ethylsiloxane/silica hybrid, "HSS" High Strength Silica, "DAD" Diode Array Detector.

Table: LCMS Method codes (Flow expressed in mL/min; column temperature (T) in °C; Run time in minutes).

Method code	Instrument	Column	Mobile phase	gradient	Flow Column T	Run time
A	Waters: Acquity UPLC® - DAD and Quattro Micro™	Waters: BEH C18 (1.7µm, 2.1x100mm)	A: 95% CH_3COONH_4 7mM / 5% CH_3CN, B: CH_3CN	84.2% A for 0.49min, to 10.5% A in 2.18min, held for 1.94min, back to 84.2% A in 0.73min, held for 0.73min.	0.343 40	6.2
B	Waters: Acquity® H-Class - DAD and SQD2™	Waters: BEH C18 (1.7µm, 2.1x100mm)	A: 95% CH_3COONH_4 7mM / 5% CH_3CN, B: CH_3CN	84.2% A to 10.5% A in 2.18 min, held for 1.96 min, back to 84.2% A in 0.73 min, held for 0.73 min.	0.343 40	6.1
C	Waters: Acquity UPLC® H-Class - DAD and SQD2™	Waters BEH®C18 (1.7µm, 2.1x50mm)	A: 95% CH_3COONH_4 7mM / 5% CH_3CN, B: CH_3CN	From 95% A to 5% A in 1min, held for 1.6min, back to 95% A in 0.2min, held for 0.5min.	0.5 40	3.3

Co. No.	Rt	MW (theor)	BPM1 [M+H]+	LC/GC/MS Method
1	2.68	496.2	497.2	A
2	3.19	495.2	496.3	A
3	2.71	525.2	526.3	A
4	2.61	497.2	498.3	A
5	2.52	527.2	528.6	B
6	2.69	527.2	528.3	A
7	2.66	526.2	527.3	A
8	3.2	525.3	526.3	A
9	2.7	540.3	541.4	A
10	3.27	555	556.3	A
11	1.19	509.2	510.4	C
12	2.98	508.2	509.3	A
13	2.94	537.2	538.4	A
14	2.21	575.2	576.4	A
15	2.56	574.2	575.5	A
16	2.37	510.2	511.3	A
17	2.37	510.2	511.3	A
18	2.83	509.2	510.3	A
19	2.4	539.2	540.3	A
20	2.73	538.2	539.5	B
21	2.69	539.2	540.4	A
22	3.21	538.2	539.4	A
23	3.33	552.2	553.5	A
24	2.34	510.2	511.2	A
25	2.37	528.2	529.3	A
26	2.31	528.2	529.4	A
27	2.39	539.2	540.3	A
28	2.81	538.2	539.3	A

Optical rotation

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

Co. No.	$[\alpha]_D^{20}$	c (w/v %)	Co. No.	$[\alpha]_D^{20}$	c (w/v %)
1	+109.29°	0.28	19	+4.44°	0.27
2	+129.07°	0.258	20	-29.74°	0.252
3	+7.69°	0.234	21	+37.88°	0.264
8	-30.77°	0.26	22	+4.96°	0.262
9	-24.07°	0.27	23	-6.08°	0.296
10	-56.43°	0.28	27	+42.19°	0.32

Co. No.	$[\alpha]_D^{20}$	c (w/v %)	Co. No.	$[\alpha]_D^{20}$	c (w/v %)
14	+14.16°	0.219	28	-10°	0.25
15	-29.28°	0.222			

E. Pharmacological examples

E.1 Antiviral activity

Black 384-well clear-bottom microtiter plates (Corning, Amsterdam, The Netherlands) were filled via acoustic drop ejection using the echo liquid handler (Labcyte, Sunnyvale, California). 200 nL of compound stock solutions (100% DMSO) were transferred to the assay plates. 9 serial 4-fold dilutions of compound were made, creating per quadrant the same compound concentration. The assay was initiated by adding 10 µL of culture medium to each well (RPMI medium without phenol red, 10% FBS-heat inactivated, 0.04% gentamycin (50 mg/mL). All addition steps are done by using a multidrop dispenser (Thermo Scientific, Erembodegem, Belgium). Next, rgRSV224 virus (MOI = 1) diluted in culture medium was added to the plates. rgRSV224 virus is an engineered virus that includes an additional GFP gene (Hallak LK, Spillmann D, Collins PL, Peeples ME. Glycosaminoglycan sulfation requirements for respiratory syncytial virus infection; Journal of virology (2000), 74(22), 10508-13) and was in-licensed from the NIH (Bethesda, MD, USA). Finally, 20 µL of a HeLa cell suspension (3,000 cells/well) were plated. Medium, virus- and mock-infected controls were included in each test. The wells contain 0.05% DMSO per volume. Cells were incubated at 37°C in a 5% CO2 atmosphere. Three days post-virus exposure, viral replication was quantified by measuring GFP expression in the cells by an in house developed MSM laser microscope (Tibotec, Beerse, Belgium). The EC_{50} was defined as the 50% inhibitory concentration for GFP expression. In parallel, compounds were incubated for three days in a set of white 384-well microtiter plates (Corning) and the cytotoxicity of compounds in HeLa cells was determined by measuring the ATP content of the cells using the ATPlite kit (Perkin Elmer, Zaventem, Belgium) according to the manufacturer's instructions. The CC_{50} was defined as the 50% concentration for cytotoxicity.

Table : antiviral data (averaged data of several repeat experiments)

Co. No.	RSV HELA EC_{50} (µM)	TOX HELA CC_{50} (µM)	Co. No.	RSV HELA EC_{50} (µM)	TOX HELA CC_{50} (µM)
1	0.195	45.10	15	0.480	20.60
2	0.344	52.70	16	0.182	79.40
3	0.218	44.00	17	2.010	>100
4	0.219	57.60	18	0.178	47.90
5	1.700	47.20	19	0.100	60.90
6	0.090	50.20	20	0.102	45.60

Co. No.	RSV HELA EC_{50} (µM)	TOX HELA CC_{50} (µM)	Co. No.	RSV HELA EC_{50} (µM)	TOX HELA CC_{50} (µM)
7	0.064	48.00	21	0.564	29.80
8	0.054	53.40	22	0.870	>100
9	0.596	50.60	23	0.882	>100
10	0.062	40.40	24	0.105	69.70
11	0.197	39.90	25	0.112	22.30
12	0.203	59.00	26	3.420	77.20
13	0.294	23.40	27	0.159	40.40
14	1.150	52.80	28	0.112	22.30

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

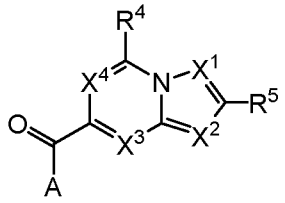
Active ingredient	5 to 1000 mg

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.

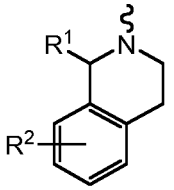
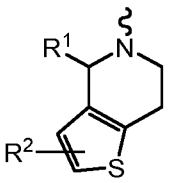
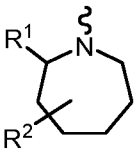
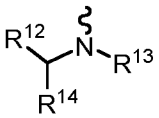
Claims

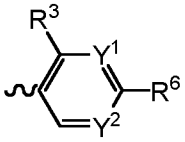
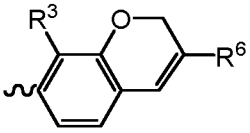
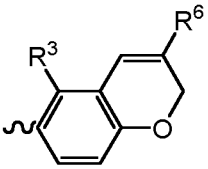
1. A compound of formula (I) wherein



(I)

including any stereochemically isomeric form thereof, wherein

A is  (a-1),  (a-2),  (a-3), or  (a-4);

R^5 is  (b-1),  (b-2), or  (b-3);

X^1, X^2, X^3 and X^4 are selected from X^1 is CH, X^2 is CH, X^3 is CH and X^4 is CH;
or X^1 is N, X^2 is CH, X^3 is CH and X^4 is CH,
or X^1 is CH, X^2 is N, X^3 is CH and X^4 is CH,
or X^1 is N, X^2 is CH, X^3 is CH and X^4 is N,
or X^1 is N, X^2 is N, X^3 is CH and X^4 is CH, and
or X^1 is CH, X^2 is N, X^3 is N and X^4 is CH,
wherein each CH is optionally substituted with halo, C_{1-4}alkyl or C_{1-4}alkyloxy;

Y^1 and Y^2 are each independently selected from CH, CF and N;

R^1 is CH_3 or CH_2CH_3;

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

R^{12} is C_{1-2}alkyl;

R^{13} and R^{14} are each independently selected from C_{1-6}alkyl;

R^3 is halo;

R^4 is C_{1-6}alkyl; C_{3-6}cycloalkyl; di(C_{1-4}alkyl)amino, pyrrolidinyl, Heteroaryl[1]; C_{1-4}alkyl substituted with Heteroaryl[1]; 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[1]; C_{1-4}alkyl substituted with Heteroaryl[1];

R^6 is C_{2-6}alkenyl substituted with one or two substituents selected from C_{1-6}alkyl, -(CO)-OR^7 or -(CO)-NR^8R^9; or

-NR^9-(CO)-Heterocycle wherein said Heterocycle is substituted with one or two substituents each independently selected from halo, hydroxy of C_{1-4}alkyloxy; or C_{3-6}cycloalkyl or Heterocycle, wherein said C_{3-6}cycloalkyl and Heterocycle is substituted with one or two substituents each independently selected from

C_{1-6}alkyl;

C_{1-6}alkyl substituted with one, two or three substituents each independently selected from halo, hydroxy, hydroxycarbonyl, aminocarbonyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl substituted with one or two substituents each independently selected from C_{1-4}alkyl, halo, hydroxycarbonyl, and C_{1-4}alkyl substituted with hydroxycarbonyl;

C_{3-6}alkenyl;

C_{3-6}alkenyl substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, -(CO)-OR^7 or -(CO)-NR^8R^9;

hydroxy;

cyano;

-(CO)-O-R^7;

-(CO)-$NR^{10}R^{11}$;

-(CO)-NR^9-SO_2-R^8;

-(CO)-NR^9-(CO)-SO_2-R^8;

-O-(CO)-$NR^{10}R^{11}$;

-NR^8R^9;

-NR^9-(CO)-C_{1-4}alkyl;

-NR^9-(CO)-C_{3-6}cycloalkyl;

-NR^9-(CO)-O-R^8;

-NR^9-(CO)-NR^9-R^8;

-NR^9-SO_2-R^8;

-SO_2-R^8;

-SO_2-$NR^{10}R^{11}$; or

-SO_2-NR^9-(CO)-R^8;

Heteroaryl[2];

wherein

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

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

each R^9 is independently selected from hydrogen or C_{1-4}alkyl;

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

Heterocycle is azetidinyl, pyrrolodinyl, piperidinyl, or homopiperidinyl;

Heteroaryl^1 is thienyl, pyridinyl or pyrimidinyl, wherein each Heteroaryl^1 is optionally substituted with one or two substituents each independently selected from C_{1-4}alkyl, halo, amino, and aminocarbonyl;

Heteroaryl^2 is pyrrolyl, pyrazolyl or thiazolyl; wherein each Heteroaryl^2 is optionally substituted with one or two substituents each independently selected from C_{1-4}alkyl, halo, -(CO)-OR^7 or -(CO)-NR^8R^9;

or a pharmaceutically acceptable acid addition salt thereof.

2. The compound as claimed in claim 1 wherein radical A is of formula (a-1).

3. The compound as claimed in claim 1 wherein radical A is of formula (a-2).

4. The compound as claimed in claim 1 wherein X^1 is CH, X^2 is N, X^3 is N and X^4 is CH.

5. The compound as claimed in claim 1 wherein X^1 is N, X^2 is N, X^3 is CH and X^4 is CH.

6. The compound as claimed in any one of claims 1 to 5 wherein R^5 is of formula (b-1) wherein Y^1 and Y^2 are CH.

7. The compound as claimed in any one of claims 1 to 6 wherein R^3 is fluoro.

8. The compound as claimed in any one of claims 1 to 7 wherein R^4 is C_{3-6}cycloalkyl.

9. The compound as claimed in any one of claims 1 to 8 wherein R^6 is C_{3-6}cycloalkyl or pyrrolidinyl, wherein said C_{3-6}cycloalkyl or pyrrolidinyl are substituted with one or two substituents each independently selected from -(CO)-O-R^7 or -(CO)-$NR^{10}R^{11}$.

10. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically active amount of a compound as claimed in any of claims 1 to 9.

11. The pharmaceutical composition according to claim 10, which further comprises another antiviral agent.

12. The pharmaceutical composition according to claim 11, wherein the other antiviral agent is a RSV inhibiting compound.

13. A process for preparing a pharmaceutical composition as claimed in any one of claims 10 to 12 wherein a therapeutically active amount of a compound as claimed in any one of claims 1 to 9 is intimately mixed with a pharmaceutically acceptable carrier.

14. A compound as claimed in any one of claims 1 to 9 for use as a medicine.

15. A compound as claimed in any one of claims 1 to 9, or a pharmaceutical composition as claimed in any one of claims 10 to 12, for use in the treatment of a respiratory syncytial virus infection.