

PIPERIDINE SUBSTITUTED PYRAZOLO[1,5-A]PYRIMIDINE DERIVATIVES WITH INHIBITORY ACTIVITY ON THE REPLICATION OF THE RESPIRATORY SYNCYTIAL VIRUS (RSV)

Field of the Invention

5 The invention concerns novel substituted bicyclic pyrazolo pyrimidine compounds having antiviral activity, in particular, having an inhibitory activity on the replication of the respiratory syncytial virus (RSV). The invention further concerns the preparation of such novel compounds, compositions comprising these compounds, and the compounds for use in the treatment of respiratory syncytial virus infection.

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Background

Human RSV or Respiratory Syncytial Virus is a large RNA virus, member of the family of Paramyxoviridae, subfamily pneumoviridae together with bovine RSV virus. Human RSV is responsible for a spectrum of respiratory tract diseases in people of all
15 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)
20 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
25 infection with an RSV isolate from the same subgroup in the following winter season. Re-infection with RSV is thus common, despite the existence of only two subtypes, A and B.

Today only three drugs have been approved for use against RSV infection. A first one
30 is ribavirin, a nucleoside analogue that provides an aerosol treatment for serious RSV infection in hospitalized children. The aerosol route of administration, the toxicity (risk of teratogenicity), the cost and the highly variable efficacy limit its use. The other two drugs, RespiGam[®] (RSV-IG) and Synagis[®] (palivizumab), polyclonal and monoclonal antibody immunostimulants, are intended to be used in a preventive way. Both are
35 very expensive, and require parenteral administration.

Other attempts to develop a safe and effective RSV vaccine have all met with failure thus far. Inactivated vaccines failed to protect against disease, and in fact in some cases

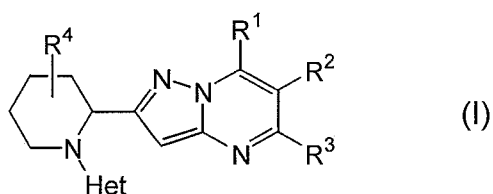
enhanced disease during subsequent infection. Live attenuated vaccines have been tried with limited success. Clearly there is a need for an efficacious non-toxic and easy to administer drug against RSV replication. It would be particularly preferred to provide drugs against RSV replication that could be administered perorally.

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Compounds that exhibit anti-RSV activity are disclosed in WO-2011/163518, WO-2013/096681 and WO-2013/158776.

Summary

- 10 The present disclosure, in one aspect, relates to a compound of formula (I), including any stereochemically isomeric form thereof, wherein



- 15 R^1 is hydrogen, hydroxy, C_{1-4} alkyl, mono- or di(C_{1-4} alkyl)amino, or Heterocyclyl¹;
 R^2 is hydrogen or C_{1-4} alkyl;
 R^3 is C_{1-4} alkyl, halo, C_{3-6} cycloalkyl, mono- or di(C_{1-4} alkyl)amino, or Heterocyclyl²;
 R^4 is hydrogen, C_{1-6} alkyl, hydroxy, or halo;

- 20 Heterocyclyl¹ is azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;
wherein each Heterocyclyl¹ is optionally substituted with one or two
substituents selected from C_{1-4} alkyl, hydroxy, halo,
polyhalo C_{1-4} alkyl, C_{1-4} alkyloxycarbonyl, amino,
 C_{1-4} alkylaminocarbonyl, or C_{1-4} alkylsulfonyl;

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- Heterocyclyl² is azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;
wherein each Heterocyclyl² is optionally substituted with one or two
substituents selected from C_{1-4} alkyl, hydroxy, halo,
polyhalo C_{1-4} alkyl, C_{1-4} alkyloxycarbonyl, amino,
30 C_{1-4} alkyloxycarbonylamino, or C_{1-4} alkylsulfonyl;

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- Het is selected from furanyl, thiophenyl, pyrazolyl, oxazolyl, thiazolyl, pyridyl,
pyridazinyl, pyrimidinyl, pyrazinyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl,
quinoxalinyl, 1,5-naphthyridinyl, 1,6-naphthyridinyl, 1,7-naphthyridinyl,
35 1,8-naphthyridinyl, pyrido[2,3-d]pyrimidinyl, pyrido[3,2-d]pyrimidinyl, 9H-purinyl,

thiazolo[5,4-d]pyrimidinyl, 7H-pyrrolo[2,3-d]pyrimidinyl, oxazolo[5,4-d]pyrimidinyl, thieno[2,3-d]pyrimidinyl, or thieno[3,2-d]pyrimidinyl; wherein each Het is optionally substituted with one, two or three substituents each independently selected from halo, C₁₋₄alkyl, C₁₋₄alkyloxy, C₁₋₄alkylthio, hydroxy, amino, mono- or di(C₁₋₄alkyl)amino, 5 hydroxycarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylsulfonylamino, aminocarbonyl, trifluoromethyl, C₁₋₄alkyloxycarbonylamino, di(C₁₋₄alkyloxycarbonyl)amino, C₁₋₄alkylsulfonylaminocarbonyl, C₁₋₄alkylaminocarbonyl, C₁₋₄alkyloxyC₁₋₆alkyl-oxycarbonylamino, di(C₁₋₄alkyl)aminosulfonylaminocarbonyl, C₃₋₆cycloalkyl-sulfonylaminocarbonyl, HO-NH-(C=NH)-; oxazolyl or triazolyl each optionally 10 substituted with one or two C₁₋₄alkyl; or a pharmaceutically acceptable acid addition salt thereof.

The present disclosure, in another aspect, relates to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically active amount 15 of a compound as defined herein.

The present disclosure, in another aspect, relates to a process for preparing a pharmaceutical composition as defined herein wherein a therapeutically active amount of a compound as defined herein is intimately mixed with a pharmaceutically 20 acceptable carrier.

The present disclosure, in another aspect, relates to a compound as defined herein for use as a medicine.

25 The present disclosure, in another aspect, relates to a compound as defined herein, or a pharmaceutical composition as defined herein for use in the treatment of a respiratory syncytial virus infection.

As used in the foregoing definitions:

- 30 - halo is generic to fluoro, chloro, bromo and iodo;
- C₁₋₄alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, 1-methyl-ethyl, 2-methylpropyl and the like;
- C₁₋₆alkyl is meant to include C₁₋₄alkyl and the higher homologues thereof having 35 5 or 6 carbon atoms, such as, for example, 2-methylbutyl, pentyl, hexyl and the like;
- C₃₋₆cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl;

- polyhaloC₁₋₄alkyl is defined as polyhalosubstituted C₁₋₄alkyl, in particular C₁₋₄alkyl (as hereinabove defined) substituted with 2 to 6 halogen atoms such as difluoromethyl, trifluoromethyl, trifluoroethyl, and the like.

- 5 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
10 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
15 tautomeric forms thereof.

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

5 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
10 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. Therefore, the invention includes enantiomers, diastereomers, racemates, E isomers, Z isomers, cis isomers, trans isomers and mixtures thereof, whenever chemically
15 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
20 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,
25 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%
30 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
35 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.

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

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

The 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.

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

- a) R¹ is hydrogen; or
- b) R¹ is C₁₋₄alkyl, mono- or di(C₁₋₄alkyl)amino, or Heterocyclyl¹; or
- 5 c) R¹ is Heterocyclyl¹; or
- d) R² is hydrogen; or
- e) R² is C₁₋₄alkyl; or
- f) R³ is C₃₋₆cycloalkyl; or
- g) R³ is C₁₋₄alkyl, mono- or di(C₁₋₄alkyl)amino; or
- 10 h) R³ is Heterocyclyl²; or
- i) R⁴ is hydrogen; or
- j) Heterocyclyl¹ is piperazinyl optionally substituted with one substituent selected from C₁₋₄alkyl, hydroxy, halo, polyhaloC₁₋₄alkyl, C₁₋₄alkyloxycarbonyl, amino, C₁₋₄alkylaminocarbonyl, or C₁₋₄alkylsulfonyl; or
- 15 k) Heterocyclyl¹ is morpholinyl optionally substituted with one substituent selected from C₁₋₄alkyl, hydroxy, halo, polyhaloC₁₋₄alkyl, C₁₋₄alkyloxycarbonyl, amino, C₁₋₄alkylaminocarbonyl, or C₁₋₄alkylsulfonyl; or
- l) Het is quinazolinyl optionally substituted with one, two or three substituents each independently selected from halo, C₁₋₄alkyl, C₁₋₄alkyloxy, C₁₋₄alkylthio, hydroxy,
- 20 amino, mono- or di(C₁₋₄alkyl)amino, hydroxycarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylsulfonylamino, aminocarbonyl, trifluoromethyl, C₁₋₄alkyloxycarbonyl-amino, di(C₁₋₄alkyloxycarbonyl)amino, C₁₋₄alkylsulfonylaminocarbonyl, C₁₋₄alkylaminocarbonyl, C₁₋₄alkyloxyC₁₋₆alkyloxycarbonylamino, di(C₁₋₄alkyl)aminosulfonylaminocarbonyl, C₃₋₆cycloalkylsulfonylaminocarbonyl,
- 25 HO-NH-(C=NH)-; oxazolyl or triazolyl each optionally substituted with one or two C₁₋₄alkyl.

In a first embodiment the present invention concerns compounds of formula (I), including any stereochemically isomeric form thereof, wherein

- 30 R¹ is hydrogen, C₁₋₄alkyl, mono- or di(C₁₋₄alkyl)amino, or Heterocyclyl¹;
- R² is hydrogen or C₁₋₄alkyl;
- R³ is C₃₋₆cycloalkyl or Heterocyclyl²;
- R⁴ is hydrogen;
- Heterocyclyl¹ is piperazinyl or morpholinyl; wherein each Heterocyclyl¹ is optionally
- 35 substituted with one substituent selected from C₁₋₄alkyloxycarbonyl, C₁₋₄alkylaminocarbonyl, or C₁₋₄alkylsulfonyl;

Heterocyclyl² is azetidiny, or pyrrolidiny; wherein each Heterocyclyl² is optionally substituted with one substituent selected from hydroxy or amino;

Het is selected from quinazolinyl, pyrido[2,3-d]pyrimidinyl, thiazolo[5,4-d]-pyrimidinyl, 7H-pyrrolo[2,3-d]pyrimidinyl, oxazolo[5,4-d]pyrimidinyl, or thieno[2,3-d]pyrimidinyl; wherein each Het is optionally substituted with one, two or three substituents each independently selected from halo, C₁₋₄alkyl, C₁₋₄alkyloxy, C₁₋₄alkylthio, hydroxy, hydroxycarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylsulfonylamino, aminocarbonyl, trifluoromethyl, C₁₋₄alkyloxy-carbonylamino, di(C₁₋₄alkyloxycarbonyl)amino, C₁₋₄alkylsulfonylamino-carbonyl, C₁₋₄alkylaminocarbonyl, C₁₋₄alkyloxyC₁₋₆alkyloxycarbonylamino, di(C₁₋₄alkyl)aminosulfonylamino-carbonyl, C₃₋₆cycloalkylsulfonylamino-carbonyl, HO-NH-(C=NH)-; oxazolyl or triazolyl each optionally substituted with one or two C₁₋₄alkyl;

or a pharmaceutically acceptable acid addition salt thereof.

A first group of compounds of formula (I) are those compounds of formula (I) wherein R¹ is Heterocyclyl¹, R² is hydrogen, and R³ is Heterocyclyl².

A second group of compounds of formula (I) are those compounds of formula (I) wherein R¹ is hydrogen, R² is C₁₋₄alkyl, and R³ is Heterocyclyl².

A third group of compounds of formula (I) are those compounds of formula (I) wherein R¹ is hydrogen, R² is hydrogen, and R³ is Heterocyclyl².

A fourth group of compounds of formula (I) are those compounds of formula (I) wherein R¹ is C₁₋₄alkyl, R² is hydrogen, and R³ is Heterocyclyl².

A 5th group of compounds of formula (I) are those compounds of formula (I) wherein R¹ is hydrogen, R² is hydrogen, and R³ is C₁₋₄alkyl.

A 6th group of compounds of formula (I) are those compounds of formula (I) wherein R¹ is hydrogen, R² is hydrogen, and R³ is C₃₋₆cycloalkyl.

A 7th group of compounds of formula (I) are those compounds of formula (I) wherein Het is quinazolinyl.

Compounds of formula (I), or their pharmaceutically acceptable salts, can be prepared according to the reaction schemes discussed herein below using synthetic methods known in the art of organic chemistry, or modifications and derivatisations that are familiar to those skilled in the art. The starting materials used herein are commercially available or may be prepared by routine methods known in the art such as those methods disclosed in standard reference books. Preferred methods include, but are not limited to, those described below.

During any of the following synthetic sequences it may be necessary and /or desirable to protect sensitive or reactive groups on any of the molecules concerned. This can be achieved by means of conventional protecting groups well known to the skilled person.

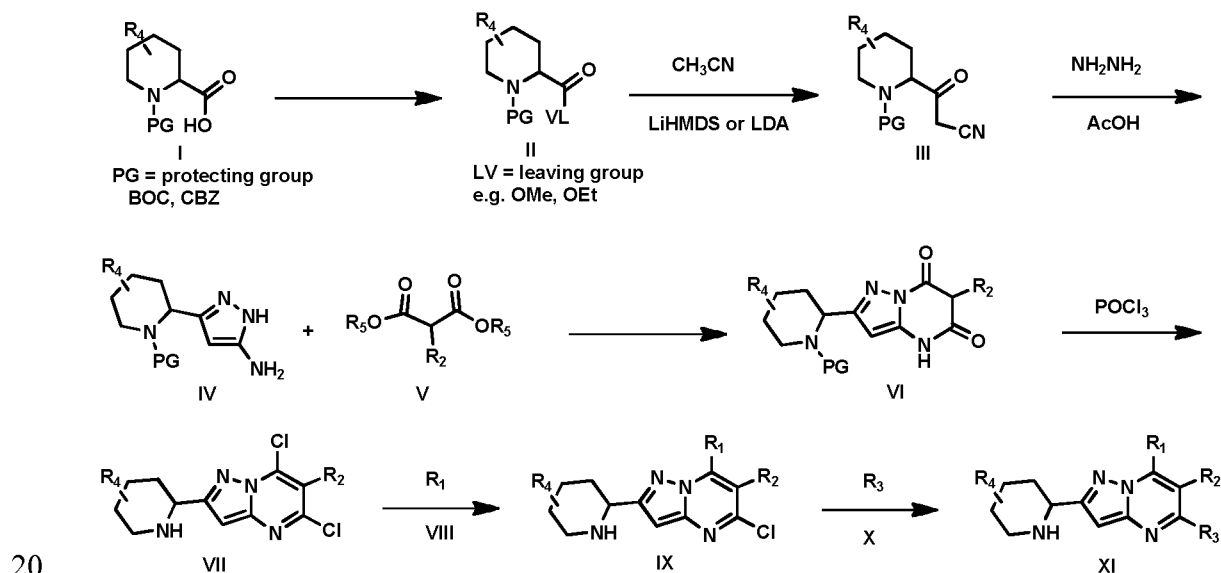
Unless otherwise indicated, the substituents in the schemes are defined as above. Isolation and purification of the products is accomplished by standard procedures, which are known to a chemist of ordinary skill.

General schemes 1-3 describe methods that were used to prepare compounds of the invention. The general methods described in these schemes can also be used to prepare additional compounds of the invention.

The starting material **I** is a protected (PG) piperidine bearing a carboxyl group on the carbon atom adjacent to the ring nitrogen that preferably has the (S) stereochemistry. This piperidine can also be substituted with different groups. Protecting groups on the piperidine ring nitrogen are preferably BOC or CBZ and can be introduced or removed during the synthesis using methods described in; Green and Wutts, protecting groups in Organic Synthesis 3rd Edition. In scheme 1 the carboxylic acid group on the N-protected cyclic aminoheterocycle **I** is first activated with a leaving group. Typical leaving groups are alkyl ester (e.g. methyl or ethyl ester) and these are generated by treatment of the carboxylic acid with the appropriate alcohol under non- or low-aqueous acidic conditions or by treatment with methyl iodide in the presence of a base like cesium carbonate or a like. Alternatively the acid can be activated as the Weinreb amide using standard peptide coupling procedures e.g. EDCI/HOBT, HATU, DCC, etc. Once the acid is activated as the ester or Weinreb amide **II**, the addition of an acetonitrile anion is performed. The anion generated from acetonitrile and a strong base e.g. lithium or sodium hexamethyldisilazide (LiHMDS) or alkyl lithium bases e.g. nBuLi, and when reacted with the ester or Weinreb amide generates the cyano ketone **III**. Reaction of the cyano ketone with hydrazine acetate salt then generates the

aminopyrrazole intermediate **IV**. This is a key intermediate in the formation of the bicyclic heterocycles **VI** with different side chains through different condensation reactions. Condensation of amino pyrrazole **IV** with the malonate **V** generates the bicyclic analog **VI**. Treatment of **VI** with neat POCl_3 under elevated temperature (in some cases organic bases like diisopropylethyl amine or triethylamine can improve the reaction) then affords the dichloride **VII**. Under the POCl_3 conditions acidic labile protecting groups e.g. BOC are typically removed but if this is partial further treatment with acid e.g. 4N HCl in dioxane can be used to remove the remaining BOC protected material. If other protecting groups are utilized then procedures described in Green and Wutts, Protecting groups in Organic Synthesis 3rd Edition can be used to remove the protecting group. Displacement of the chloride adjacent to the bridgehead nitrogen on **VII** can be effected with nucleophiles **VIII**, typically at room temperature to provide **IX**. A typical nucleophile **VIII** would be an amine that can be reacted in the absence or presence of a base such as triethylamine. The second and less reactive chloride is then displaced typically at elevated temperatures above 50°C . The result of these nucleophilic amine displacements are compounds of structure **XI** (scheme 1).

Scheme 1



Compounds **XIII** may be synthesized according to embodiments disclosed herein from a compound having an amino group **XI**, and a heterocyclic halide compound **XII**. The reaction may be performed in the presence of a base and a Group 8-10 transition metal catalyst. One example of a reaction between a heterocyclic halide compound and an

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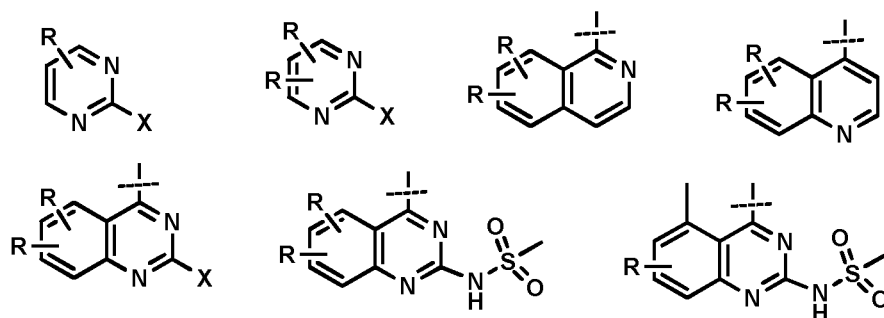
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amine to produce an N-heterocyclic amine compound may be represented in scheme 2. Briefly, a heterocyclic halide **XII** compound is reacted with an amine compound **XI** in the presence of a base and a Group 8-10 transition metal (M) complex including a chelating ligand (LL) to form an N-aryl amine compound. The transition metal catalyst according to embodiments disclosed herein is a Group 8-10 transition metal complex. In certain embodiments, the Group 8-10 transition metal comprises at least one of palladium, platinum, and nickel. In some embodiments, the Group 8-10 transition metal is palladium.

- 10 The heterocyclic compound used in the process of the present invention may be any heterocyclic compound of formula **XII** :



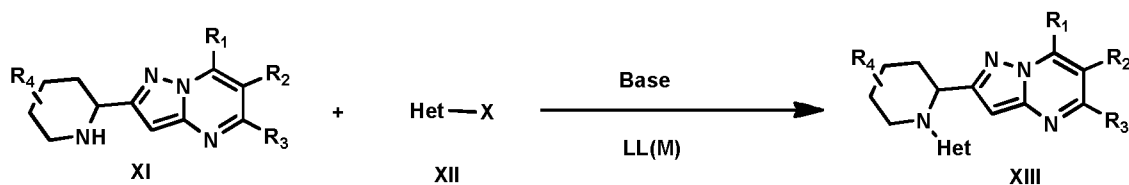
- 15 Preferred heterocyclic groups in compound of formula **XII** :



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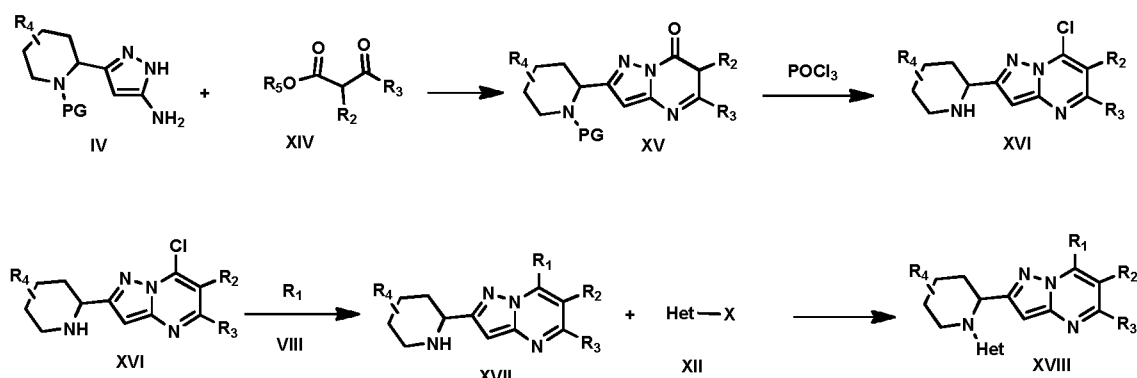
In formula **XII**, X may be any halide atom (F, Cl, Br, I), or any sulfur-containing leaving group (e.g., triflate, sulfonate, tosylate, and the like) known in the art. Chlorides are especially preferred in the process of the present invention.

- 25 Scheme 2



An alternative condensation of the aminopyrrazole **IV** using beta-keto esters **VIX** (e.g. 2-methylacetoacetate) in the presence of acid (acetic acid) at elevated temperature leads to the pyrrazo-pyrimidinone scaffold **XV**. Treatment of **XV** with neat POCl₃ under elevated temperature (in some cases hindered bases like diisopropylethyl amine can improve the reaction) then affords the dichloride **XVI**. Under the POCl₃ conditions acidic labile protecting groups e.g. BOC are typically removed but if this is partial further treatment with acid e.g. 4N HCl in dioxane can be used to remove the remaining BOC protected material. If other protecting groups are utilized then procedures described in Green and Wutts, Protecting groups in Organic Synthesis 3rd Edition can be used to remove the protecting group. Displacement of the chloride adjacent to the bridgehead nitrogen on **XVI** can be effected with nucleophiles **VIII**, typically at room temperature to provide compounds of type **XVII**. A typical nucleophile would be an amine that can be reacted in the absence or presence of a base such as triethylamine then allows the free amine **XVII** to be alkylated by a variety of heterocycles as described in scheme 2 to produces the final compounds **XVIII** scheme 3.

Scheme 3

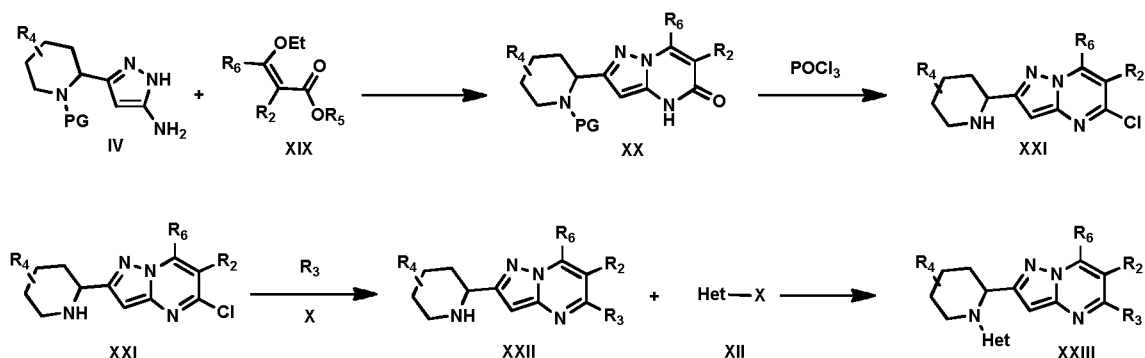


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A further alternative cyclisation of the amino pyrrole **IV** involves treatment with an acrylate e.g. **XIX** in the presence of base e.g. cesium carbonate, and heat to generate **XX**. Further treatment of **XX** to activate that OH as a leaving group can include conversion to a chloride **XXI** using POCl₃ and heat. Acidic protecting groups e.g. BOC can be removed under the POCl₃ conditions, or if not, following procedures outlined in Green and Wurtts, Protecting groups in Organic Synthesis 3rd Edition, any protecting groups can be removed. The chloride can be displaced by nucleophiles **X** to generate compounds **XXII**. Finally the free NH compound **XXII** is then alkylated as previously described in scheme 2 to give compounds of type **XXIII** (scheme 4).

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Scheme 4



- 5 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
10 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
15 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
20 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
25 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
30 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 bioavailability, including an acceptable half-life, AUC and peak values and lacking unfavourable phenomena such as insufficient quick onset and tissue retention.

- 5 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).

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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).

- 15 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, 25 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 30 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 35 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.

- 10 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, 15 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. 25 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. 35 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 isotoning, 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.

- 5 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
10 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
15 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
20 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
25 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.

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

Experimental partAbbreviations

(M+H) ⁺	protonated molecular ion
aq.	aqueous
Boc	<i>tert</i> -butyloxycarbonyl
br	broad
CH ₃ Cl	chloroform
CH ₃ CN	acetonitrile
CH ₃ OH	methanol
CH ₃ ONa	sodium methanolate
d	doublet
DCM	dichloromethane
DIEA	<i>N,N</i> -diisopropylethylamine
DIPE	diisopropylether
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
Et	ethyl
eq.	equivalent
EtOAc	ethyl acetate
HOAc	acetic acid
LiHMDS	lithium bis(trimethylsilyl)amide
m/z:	mass-to-charge ratio
Me	methyl
MeCN	acetonitrile
MeOH	methanol
EtOH	ethanol
MHz	megahertz
min	minute(s)
N ₂	nitrogen
Na ₂ SO ₄	sodium sulfate
NMR	nuclear magnetic resonance (spectroscopy)
Pd(OAc) ₂	palladium (II) acetate
Ph	phenyl
q	quartet
RT	room temperature
s	singlet

sat	saturated
t	triplet
TEA	triethyl amine
TFA	trifluoroacetic acid
THF	tetrahydrofuran

NMR

For a number of compounds, ^1H NMR spectra were recorded on a Bruker DPX-400 spectrometer operating at 400 MHz or on a Bruker DPX-360 operating at 360 MHz using chloroform-*d* (deuterated chloroform, CDCl_3) or DMSO-*d*₆ (deuterated DMSO, dimethyl-*d*₆ sulfoxide) as solvent. Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS), which was used as internal standard.

Optical rotation:

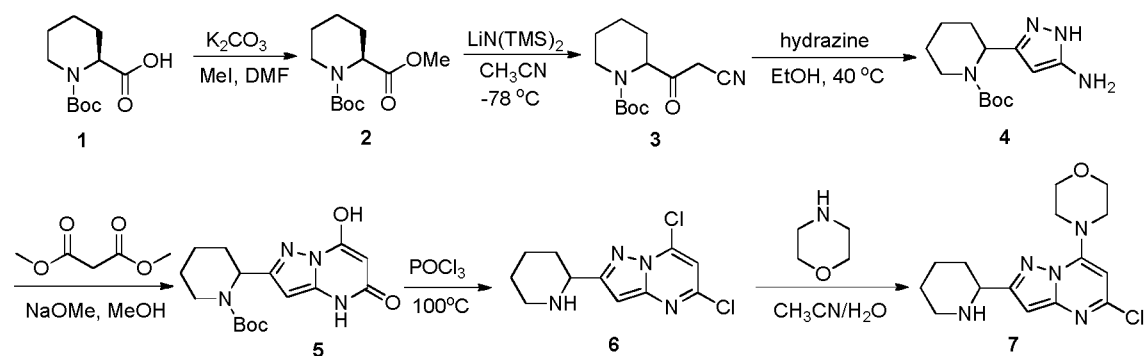
The optical rotation was measured using a Perkin Elmer 341 polarimeter. $[\alpha]_{\text{D}}^{20}$ indicates the optical rotation measured with light at the wavelength of the D-line of sodium (589 nm) at a temperature of 20°C. The cell pathlength is 1 dm. Behind the actual value the concentration and solvent of the solution which was used to measure the optical rotation are mentioned.

Experimental part

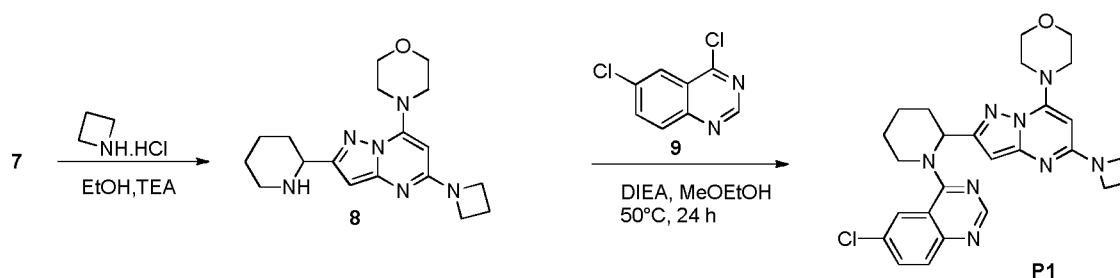
A. Chemical of intermediates and compounds of formula (I)

Synthesis of 4-(5-(azetidin-1-yl)-2-(1-(6-chloroquinazolin-4-yl)piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-7-yl)morpholine P1

Scheme 5



- 19 -



Step 1 : Synthesis of (S)-1-*tert*-butyl 2-methyl piperidine-1,2-dicarboxylate **2**

Potassium carbonate (108.50 g, 785.09 mmol) was added to a solution of (S)-1-(*tert*-butoxycarbonyl)piperidine-2-carboxylic acid **1** (90 g, 392.55 mmol) in DMF (900 ml).

- 5 Iodomethane (83.58 g, 588.82 mmol) was added to the mixture. The mixture was stirred at room temperature overnight. Ethyl acetate was added to the reaction mixture. The resulting mixture was washed with water and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated under vacuum to give intermediate **2** (90 g, yield: 85 %).

10 $m/z = 244$ (M+H)⁺.

Step 2 : synthesis of *tert*-butyl 2-(2-cyanoacetyl)piperidine-1-carboxylate **3**

To a solution of CH₃CN (1.30 ml, 24.66 mmol) in dry THF (40 ml) was added dropwise LiHMDS (22.61 ml, 22.61 mmol) at -78 °C. The solution was stirred for 15 20 minutes at -78 °C. A solution of **2** (5 g, 22.55 mmol) in dry THF (10 ml) was added dropwise to the mixture. The resulting mixture was stirred for 2 hours. Then the mixture was cooled to -78 °C and a solution of HOAc (5 ml, 76.67 mmol) in THF (50 ml) was added dropwise to the mixture. The solution was warmed to room temperature. The solvent was removed under vacuum. The residue was dissolved in 20 ethyl acetate and washed with brine, dried Na₂SO₄, filtered and concentrated under vacuum to give the crude intermediate **3** (4 g, yield: 69%).

$m/z = 253$ (M+H)⁺.

Step 3 : *tert*-butyl 2-(5-amino-1*H*-pyrazol-3-yl)piperidine-1-carboxylate **4**

- 25 Hydrazine hydrate (100 ml) and ethanol (500 ml) were added to intermediate **3** (80 g, 317.70 mmol). The mixture was stirred at room temperature overnight. The solvent was removed under vacuum. The residue was dissolved in ethyl acetate, washed with brine. The organic layer was dried over Na₂SO₄, filtered and concentrated under vacuum to give intermediate **4** (80 g, yield: 76%).

30 $m/z = 267$ (M+H)⁺.

Step 4 : synthesis of *tert*-butyl 2-(7-hydroxy-5-oxo-4,5-dihydropyrazolo[1,5-a]-pyrimidin-2-yl)piperidine-1-carboxylate **5**

Intermediate **4** (70 g, 262.82 mmol) was dissolved in methanol (700 ml), then Dimethyl malonate (85.19 g, 394.23 mmol) was added to the solution, followed by the addition
5 of a solution of CH₃ONa in CH₃OH (25%, 85.19 g, 394.23 mmol). The reaction mixture was heated to reflux overnight. The solvent was removed under vacuum. Water was added to the residue, the pH was adjusted to 6-7 by addition of acetic acid, the mixture was extracted with ethyl acetate, the organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated under vacuum to give intermediate **5**
10 (85 g, yield: 63%) which was used for the next reaction directly.
 $m/z = 335 (M+H)^+$.

Step 5 : synthesis of 5,7-dichloro-2-(piperidin-2-yl)pyrazolo[1,5-a]pyrimidine **6**

Intermediate **5** (25 g, 74.77 mmol) was added to neat POCl₃ (100 ml). The reaction
15 mixture was heated to 100°C for 3 hours. The solvent was evaporated to yield intermediate **6** (15 g, yield: 63%) which was used for the next reaction directly.
 $m/z = 272 (M+H)^+$.

Step 6 : synthesis of 4-(5-chloro-2-(piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-7-yl)-morpholine **7**

Intermediate **6** (35 g, 129.08 mmol) was added to CH₃CN (100 ml) and H₂O (100 ml). To the above mixture was added NaHCO₃ (21.69 g, 258.16 mmol) and morpholine (11.25 g, 129.08 mmol). The reaction mixture was stirred at room temperature for
20 1 hour, solvents were then evaporated, dichloromethane was added, the mixture was
25 filtered and the filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent: dichloromethane: ethyl acetate from 1:0 to 0:1) to yield intermediate **7** (25 g, yield: 51%).
 $m/z = 322 (M+H)^+$.

Step 7 : synthesis of 4-(5-(azetidin-1-yl)-2-(piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-7-yl)morpholine **8**

Azetidine hydrochloride (29.07 g, 310.75 mmol) and TEA (62.89 g, 621.49 mmol) were added to a solution of intermediate **7** (20 g, 62.15 mmol) in ethanol (1000 ml). The resulting mixture was heated to 80°C for 2 hours. The solvent was evaporated. The
35 resulting crude material was purified by column chromatography over silica gel (eluent: methanol/ ethyl acetate 1/10). The collected fractions were concentrated under vacuum. The residue was dissolved in CH₃CN (200 ml). K₂CO₃ (100 g, 723.54 mmol) was

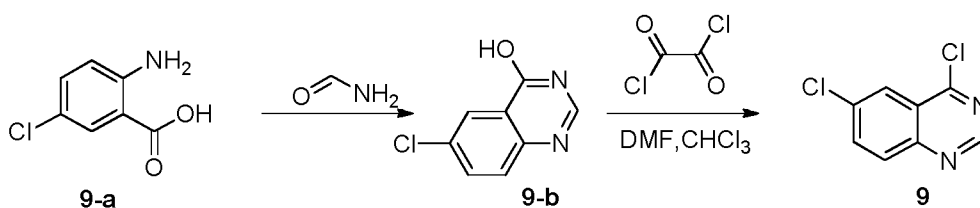
added to the solution. The mixture was stirred overnight at room temperature. The resulting mixture was filtered and evaporated to remove the solvent in vacuum. The residue was lyophilized. Intermediate **8** was isolated (6 g, yield: 27%).

$m/z = 343$ (M+H)⁺.

5

¹H NMR (400 MHz, CDCl₃) δ ppm 1.52-1.66 (m, 4 H) 1.90 (m, 1 H) 1.97 (m, 1 H) 2.37-2.40 (m, 2 H) 2.79 (m, 1 H) 3.31 (m, 1 H) 3.55-3.58 (m, 4 H) 3.81 (m, 1 H) 3.93-3.95 (m, 4 H) 4.09-4.13 (m, 4 H) 5.09 (s, 1 H) 6.04 (s, 1 H).

10 Step 8 : synthesis of 4,6-dichloroquinazoline **9**



Synthesis of 6-chloroquinazolin-4-ol **9-b**

2-Amino-5-chlorobenzoic acid **9-a** (5 g, 29 mmol) was added to formamide (30 ml).

15 The reaction mixture was heated to 100°C for 3 hours. The solid was collected by filtration. The solid was washed several times with ethanol to yield intermediate **9-b** (5 g, 86 %). $m/z = 181$ (M+H)⁺.

Synthesis of 4,6-dichloroquinazoline **9**

20 Intermediate **9-b** (3 g, 16.61 mmol) was dissolved in CHCl₃ (30 ml). Oxalyl chloride (2.8 g, 33.22 mmol) and DMF (0.1 ml) were added. The mixture was heated to 100°C for 3 hours. Solvent was evaporated to get intermediate **9** (2.5 g, yield: 68 %). $m/z = 200$ (M+H)⁺.

25 Step 9 : synthesis of 4-(5-(azetidin-1-yl)-2-(1-(6-chloroquinazolin-4-yl)piperidin-2-yl)-pyrazolo[1,5-a]pyrimidin-7-yl)morpholine **P1**

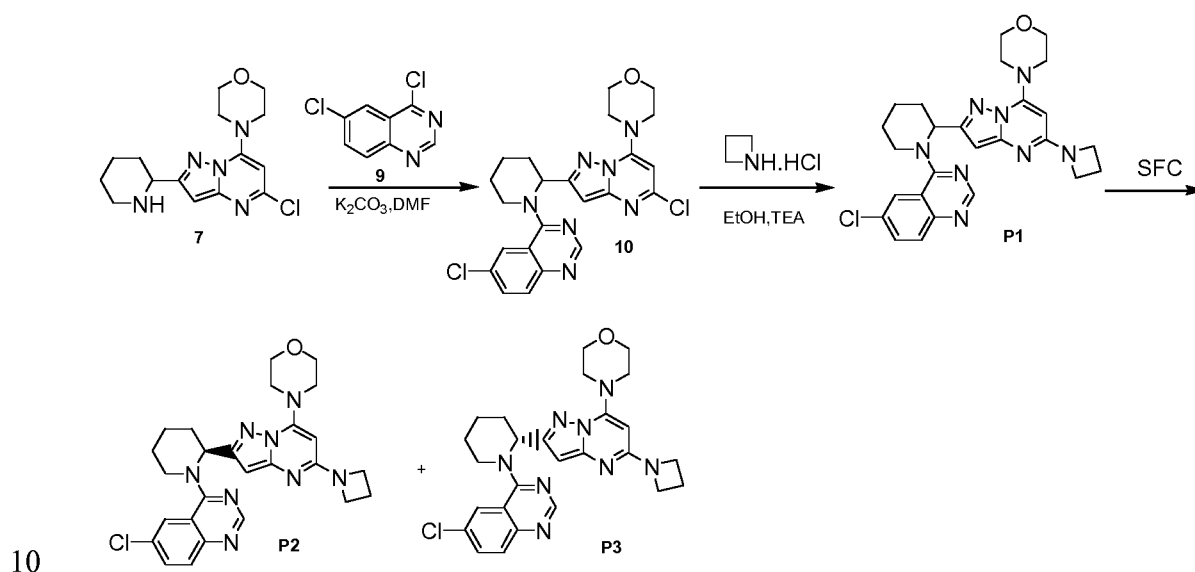
Intermediate **8** TFA salt (400 mg, 0.87 mmol) was dissolved in methoxyethanol (20 mL), intermediate **9** (235 mg, 1.18 mmol) and diisopropyl ethylamine (0.6 mL, 3.5 mmol) were added. The resulting mixture was stirred at 50°C for 24 hours. The mixture was poured in an iced watered solution and stirred for 15 minutes. The solid was successively filtered off, washed with water, dissolved in dichloromethane, dried over MgSO₄ and filtered. The resulting solution was concentrated and the solid was dried in the oven to yield a yellowish solid compound **P1** (380 mg, 85%).

30

$m/z = 506$ (M+H)⁺.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.66 - 1.86 (m, 5 H), 1.99 - 2.12 (m, 1 H), 2.25 - 2.37 (m, 3 H), 3.47 - 3.58 (m, 6 H), 3.63 - 3.75 (m, 5 H), 3.96 - 4.07 (m, 5 H), 4.21 (d, J=13.4 Hz, 1 H), 5.25 (s, 1 H), 5.81 - 5.86 (m, 1 H), 5.89 (s, 1 H), 7.72 (dd, J=9.0, 2.2 Hz, 1 H), 7.78 (d, J=9.0 Hz, 1 H), 8.07 (d, J=2.2 Hz, 1 H), 8.57 (s, 1 H)

Synthesis of (S)-4-(5-(azetidin-1-yl)-2-(1-(6-chloroquinazolin-4-yl)piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-7-yl)morpholine **P2 and (R)-4-(5-(azetidin-1-yl)-2-(1-(6-chloroquinazolin-4-yl)piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-7-yl)morpholine **P3****



Step 1 : synthesis of 4-(5-chloro-2-(1-(6-chloroquinazolin-4-yl)piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-7-yl)morpholine **10**

To a solution of intermediate **7** (1 g, 3.11 mmol) and intermediate **9** (0.62 g, 3.11 mmol) in DMF (20 ml) was added K₂CO₃ (2.15 g, 15.54 mmol). The resulting mixture was stirred overnight at room temperature. Water was added, the mixture was extracted with ethyl acetate, the organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by column chromatography over silica gel (eluent: petroleum ether: ethyl acetate from 10:1 to 0:1) to yield intermediate **10** (450 mg, yield: 27%).
 $m/z = 485 (M+H)^+$.

Step 2 : synthesis of (S)-4-(5-(azetidin-1-yl)-2-(1-(6-chloroquinazolin-4-yl)piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-7-yl)morpholine **P2 and (R)-4-(5-(azetidin-1-yl)-2-(1-(6-chloroquinazolin-4-yl)piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-7-yl)morpholine **P3****

- 23 -

Azetidine hydrochloride (0.39 g, 4.13 mmol) and TEA (0.84 g, 8.26 mmol) were added to a solution of intermediate **10** (0.4 g, 0.83 mmol) in ethanol (50 ml). The solution was heated to 80°C for 2 hours. The solvent was evaporated. The residue was purified by SFC. The desired fractions were collected and evaporated. The residue was lyophilized to yield compound **P2** (44.10 mg, yield: 10%) and compound **P3** (43.30 mg, yield: 10%).

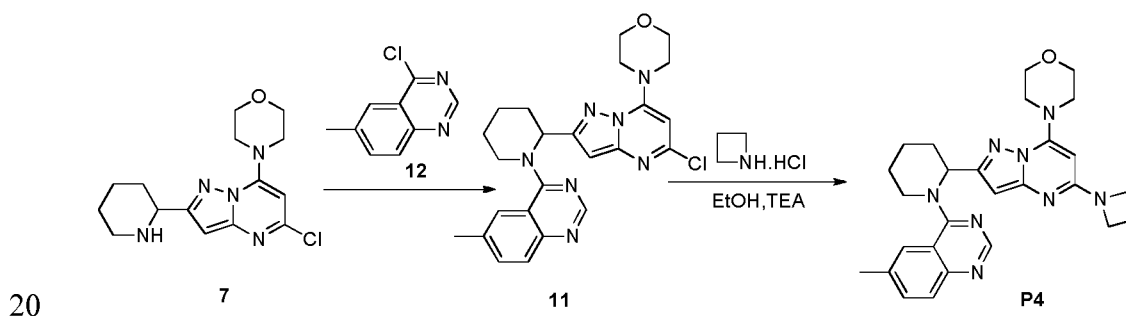
$m/z = 506 (M+H)^+$.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.79-1.83 (m, 4 H) 2.01-2.06 (m, 1 H) 2.37-2.49 (m, 3 H) 3.45-3.49 (m, 3 H) 3.55-3.63 (m, 2 H) 3.80-3.90 (m, 4 H) 4.15 (m, 4 H) 4.25 (m, 1 H) 5.10 (s, 1 H) 5.90 (s, 1 H) 6.10 (s, 1 H) 7.61(dd, J₁= 9.2 Hz, J₂= 2.4 Hz, 1 H) 7.80(d, J=9.2 Hz, 2 H) 8.03 (d, J=2.0 Hz, 1 H) 8.68 (s, 1 H).

P2 : $[\alpha]_D^{20} = -280.83^\circ$ (589 nm, c = 0.24 w/v %, DMF, 20°C)

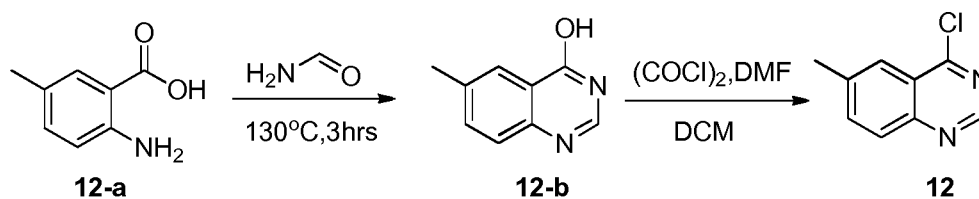
P3 : $[\alpha]_D^{20} = +270^\circ$ (589 nm, c = 0.24 w/v %, DMF, 20°C)

Synthesis of 4-(5-(azetidin-1-yl)-2-(1-(6-methylquinazolin-4-yl)piperidin-2-yl)-pyrazolo[1,5-a]pyrimidin-7-yl)morpholine **P4**



Step 1: synthesis of 4-(5-chloro-2-(1-(6-methylquinazolin-4-yl)piperidin-2-yl)-pyrazolo[1,5-a]pyrimidin-7-yl)morpholine **11**

25 Synthesis of 6-methylquinazolin-4-ol **12-b**



- 24 -

2-Amino-5-methylbenzoic acid **12-a** (5 g, 33.08 mmol) was added to formamide (30 ml). The reaction mixture was heated to 100°C for 6 hours. The solid was collected by filtration and washed several times with ethanol to give intermediate **12-b** (4.5 g, 76 %).

5 $m/z = 161 (M+H)^+$.

Synthesis of 4-chloro-6-methylquinazoline **12**

Intermediate **12-b** (2.1 g, 13.11 mmol) was dissolved in $CHCl_3$ (30 ml). Oxalyl chloride (1.97 g, 23.26 mmol) and DMF (0.1 ml) were added. The mixture was heated to 100°C
10 for 3 hours. The solvent was evaporated to get intermediate **12** (1.5 g, 58 %).
 $m/z = 179 (M+H)^+$.

To a solution of intermediate **7** (0.5 g, 1.55 mmol) and intermediate **12** (0.28 g, 1.55 mmol) in CH_3CN (10 ml) was added K_2CO_3 (1.07 g, 7.77 mmol). The resulting mixture
15 was stirred for 72 hours at 50°C. The solvent was evaporated and the residue was dissolved in CH_2Cl_2 . The resulting mixture was filtered and filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent: petroleum ether: ethyl acetate from 0:1 to 1:1) to yield intermediate **11** (350 mg, yield: 44%).
 $m/z = 464 (M+H)^+$.

20

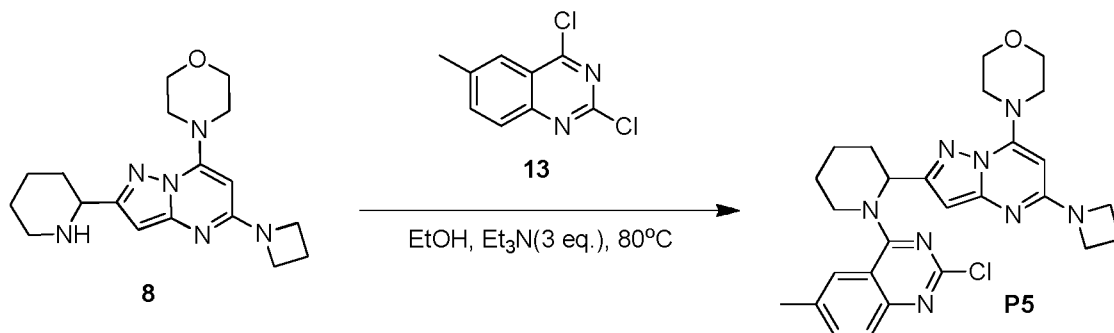
Step 2 : synthesis of 4-(5-chloro-2-(1-(6-methylquinazolin-4-yl)piperidin-2-yl)-pyrazolo[1,5-a]pyrimidin-7-yl)morpholine **P4**

Azetidine hydrochloride (0.30 g, 3.24 mmol) and TEA (0.66 g, 6.47 mmol) were added to a solution of intermediate **11** (0.3 g, 0.65 mmol) in ethanol (10 ml). The solution was
25 heated to 80°C for 2 hours. The solvent was evaporated. The residue was purified by HPLC. The desired fraction was collected and neutralized to pH=8-9 with $NaHCO_3$ solution and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated under vacuum. The residue was lyophilized to yield compound **P4** (111.00 mg, 35%).

30 $m/z = 485 (M+H)^+$.

^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.67-1.79 (m, 4 H) 2.17 (m, 1 H) 2.42 (m, 6 H) 3.43-3.45 (m, 3 H) 3.60-3.61 (m, 2 H) 3.81 (m, 4 H) 4.11 (m, 4 H) 4.23 (m, 1 H) 5.09 (s, 1 H) 5.89 (s, 1 H) 6.15 (s, 1 H) 7.52(d, J=9.2 Hz, 1 H) 7.76-7.78(m, 2 H) 8.66 (s,
35 1 H).

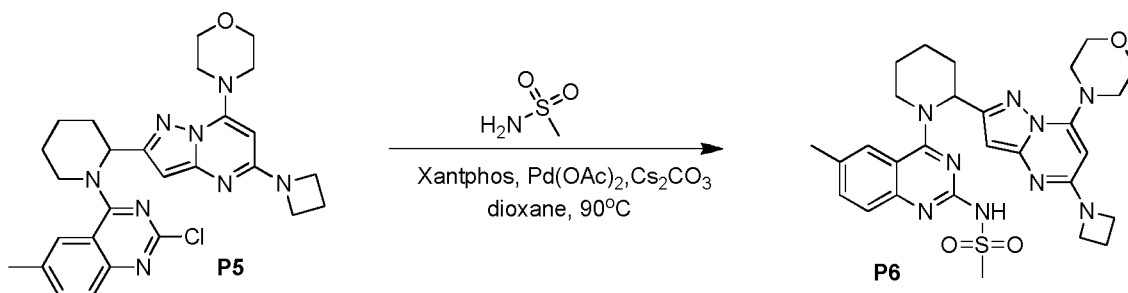
Synthesis of 4-(5-(azetidin-1-yl)-2-(1-(2-chloro-6-methylquinazolin-4-yl)piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-7-yl)morpholine P5



- 5 A mixture of intermediate **8** (500 mg, 1.460 mmol, 1 eq.), the commercially available 2,4-dichloro-6-methylquinazoline **13** (622 mg, 2.920 mmol, 2 eq.) and Et₃N (443 mg, 4.38 mmol, 3 eq.) in ethanol (20ml) was stirred at 80°C for 16 hours. The mixture was cooled to room temperature. The precipitate was filtered and collected. The solid was washed with cooled ethanol (2x3 ml) to yield compound **P5** (540 mg, 69%)
- 10 $m/z = 520 (M+H)^+$.

- ¹H NMR (400 MHz, CDCl₃) δ ppm 1.66 - 1.88 (m, 4 H) 1.97 - 2.13 (m, 1 H) 2.32 - 2.54 (m, 6 H) 3.38 - 3.52 (m, 3 H) 3.55 - 3.68 (m, 2 H) 3.86 (m, 4 H) 4.13 (t, J=7.53 Hz, 4 H) 4.34 (d, J=12.80 Hz, 1 H) 5.10 (s, 1 H) 5.96 (br. s., 1 H) 6.13 (s, 1 H) 7.51 (dd, J₁=8.53, J₂=1.51 Hz, 1 H) 7.69 (d, J=8.53 Hz, 1 H) 7.74 (s, 1 H).
- 15

Synthesis of N-(4-(2-(5-(azetidin-1-yl)-7-morpholinopyrazolo[1,5-a]pyrimidin-2-yl)piperidin-1-yl)-6-methylquinazolin-2-yl)methanesulfonamide P6



20

Palladium acetate (8.6 mg, 0.038 mmol, 0.1 eq.) was added to a mixture of compound **P5** (200 mg, 0.385 mmol, 1 eq.), methanesulfonamide (73 mg, 0.77 mmol, 2 eq.), Xantphos (22 mg, 0.038 mmol, 0.1 eq.) and Cs₂CO₃ (250 mg, 0.77 mmol, 2 eq.) in Dioxane (6 ml). The resulting mixture was stirred at 90°C for 1.5 hours under

- 26 -

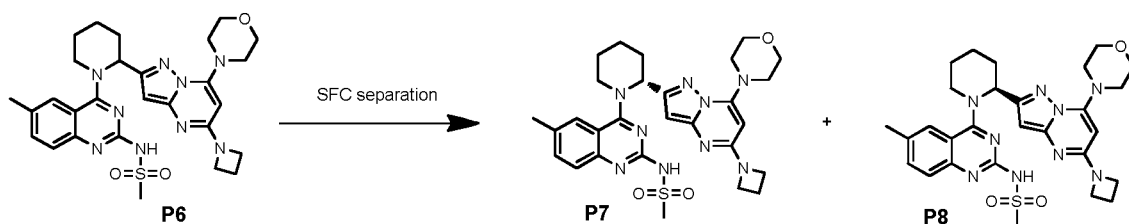
microwave. The precipitate was filtered and washed with ethyl acetate to yield the title compound **P6** (98 mg, 42.34%).

$m/z = 578 (M+H)^+$.

¹HNMR (400MHz, CDCl₃): δ ppm 1.89 (m, 4H) 1.90 (m, 1H) 2.31 (s, 3 H) 2.40 (m, 2 H) 2.51 (m, 1H) 3.20 (s, 3H) 3.50 (m, 3H) 3.68 (m, 1H) 3.89 (m, 4H) 4.13 (m, 4H) 4.62 (br, 1H) 5.13 (s, 1H) 6.12 (s, 1H) 7.41-7.43 (d, J= 8.4 Hz, 1H) 7.46-7.49 (d, J = 8.8 Hz, 1H) 7.66 (s, 1H).

(R)-N-(4-(2-(5-(azetidin-1-yl)-7-morpholinopyrazolo[1,5-a]pyrimidin-2-yl)-piperidin-1-yl)-6-methylquinazolin-2-yl)methanesulfonamide P7 and (S)-N-(4-(2-(5-(azetidin-1-yl)-7-morpholinopyrazolo[1,5-a]pyrimidin-2-yl)piperidin-1-yl)-6-methylquinazolin-2-yl)methanesulfonamide P8

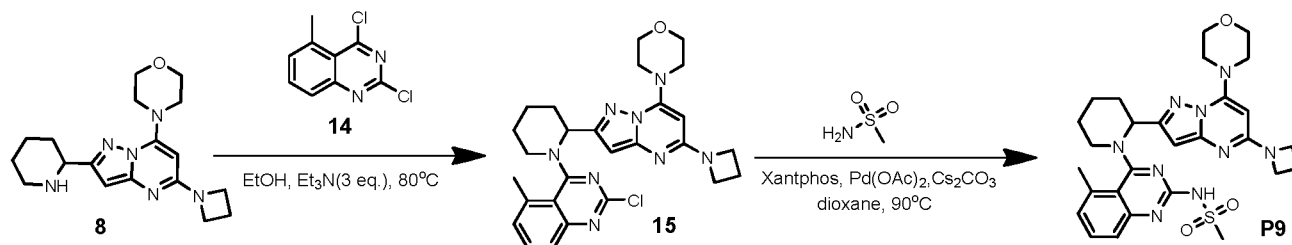
A purification was performed via Prep SFC (Stationary phase: Chiralpak Diacel AS 20 x 250 mm, Mobile phase: CO₂, EtOH with 0.2% iPrNH₂) giving both relative enantiomers :



$m/z = 578 (M+H)^+$.

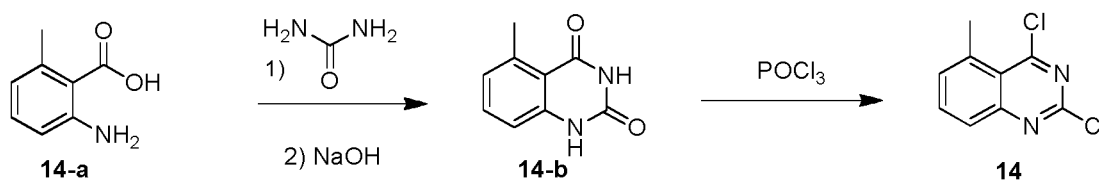
¹HNMR (400MHz, CDCl₃): δ ppm 1.89 (m, 4H) 1.90 (m, 1H) 2.31 (s, 3 H) 2.40 (m, 2 H) 2.51 (m, 1H) 3.20 (s, 3H) 3.50 (m, 3H) 3.68 (m, 1H) 3.89 (m, 4H) 4.13 (m, 4H) 4.62 (br, 1H) 5.13 (s, 1H) 6.12 (s, 1H) 7.41-7.43 (d, J= 8.4 Hz, 1H) 7.46-7.49 (d, J = 8.8 Hz, 1H) 7.66 (s, 1H).

Synthesis of N-(4-(2-(5-(azetidin-1-yl)-7-morpholinopyrazolo[1,5-a]pyrimidin-2-yl)piperidin-1-yl)-5-methylquinazolin-2-yl)methanesulfonamide P9



5

Synthesis of 2,4-dichloro-5-methylquinazoline 14



Step 1 : synthesis of 5-methylquinazoline-2,4(1H,3H)-dione 14-b

2-Amino-6-methylbenzoic acid **14-a** (10 g, 66.15 mmol) and urea (39.73 g, 661.54 mmol) were heated to 160°C and stirred for 6 hours, the reaction mixture was cooled to 100°C and 40 ml of H₂O was added. The obtained suspension was left to stir for 10 min and cooled to room temperature. The precipitate was filtered off and was dissolved in an aqueous 0.2 M sodium hydroxide solution (100 ml). The solution was heated to 100°C for 5 min, causing a white precipitate to form. The reaction mixture was stirred at room temperature overnight, the solution was neutralized to pH=7 with concentrated HCl and the white solid was filtered off. The obtained solid was washed with water, triturated with hot ethyl acetate (100 ml), and cooled to room temperature. The filtrate was collected and dried under vacuum to yield intermediate **14-b** (6.4 g, yield: 49%).

$m/z = 177 (M+H)^+$.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.64 (s, 3 H) 6.93 (d, *J*=7.48 Hz, 1 H) 7.01 (d, *J*=8.14 Hz, 1 H) 7.44 (t, *J*=7.81 Hz, 1 H) 10.99 (s, 1 H) 11.03 (br. s., 1 H)

25

Step 2 : synthesis of 2,4-dichloro-5-methylquinazoline 14

A mixture of intermediate **14-b** (1 g, 5.68 mmol), diethylaniline (2.267 ml, 14.19 mmol) in POCl₃ (5 ml) was refluxed for 2 hours. The mixture was cautiously poured over crushed ice. The mixture was neutralized to pH = 7 with saturated

NaHCO₃. The resulting mixture was extracted with CH₂Cl₂ (2x15 ml). The combined organic layers were washed with brine, dried over Na₂SO₄ and filtered. The filtrate was concentrated under vacuum to yield intermediate **14** (950 mg, yield: 68%).

$m/z = 214 (M+H)^+$.

5

Step 3 : synthesis of 4-(5-(azetidin-1-yl)-2-(1-(2-chloro-6-methylquinazolin-4-yl)-piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-7-yl)morpholine **15**

A mixture of intermediate **8** (500 mg, 1.46 mmol), intermediate **14** (933.13 mg, 4.38 mmol) and triethyl amine (443.21 mg, 4.38 mmol) in EtOH (20 ml) was stirred at 80°C for 16 hours. The mixture was cooled to room temperature. The precipitate was filtered and collected. The solid was washed with cooled ethanol (2x5 ml) to yield the desired compound **15** (400 mg, 48%).

10

$m/z = 520 (M+H)^+$.

Step 4 : synthesis of N-(4-(2-(5-(azetidin-1-yl)-7-morpholinopyrazolo[1,5-a]pyrimidin-2-yl)piperidin-1-yl)-5-methylquinazolin-2-yl)methanesulfonamide **P9**

15

To a mixture of compound **15** (200 mg, 0.385 mmol), methanesulfonamide (73.24 mg, 0.77 mmol), xantphos (23.15 mg, 0.04 mmol) and Cs₂CO₃ (250.88 mg, 0.77 mmol) in dioxane (6 ml) Pd(OAc)₂ (9 mg, 0.04 mmol) were added. The resulting mixture was stirred at 120°C for 1.5h under microwave. The mixture was filtered. The precipitate was treated with MeOH and filtered. The combined filtrates were concentrated under vacuum. The residue was purified and the pH of the fractions containing product was adjusted to 7~8 with saturated NaHCO₃. The organic solvent was evaporated under vacuum. The aqueous concentrate was extracted with CH₂Cl₂ (30 ml). The organic layer was concentrated under vacuum to yield compound **P9** (105 mg, yield: 45%).

20

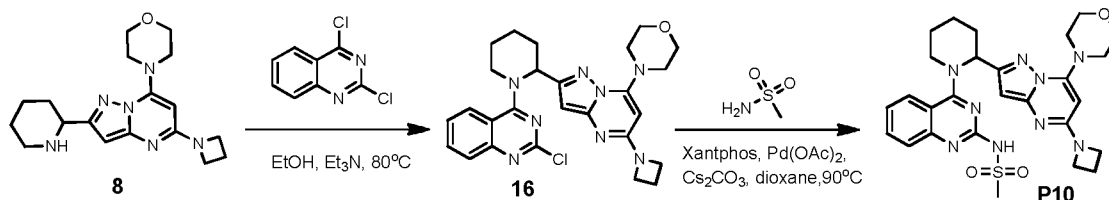
25

$m/z = 578 (M+H)^+$.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.55-1.85 (m, 4 H) 2.10-2.62 (m, 5 H) 2.69-2.85 (m, 5 H) 3.35 (s, 3 H) 3.59-3.86 (m, 8 H) 4.07-4.17 (m, 4 H) 5.21 (s, 1 H) 5.75 (s, 1 H) 7.17-7.23 (m, 2 H) 7.55-7.58 (m, 1 H).

30

Synthesis of N-(4-(2-(5-(azetidin-1-yl)-7-morpholinopyrazolo[1,5-a]pyrimidin-2-yl)piperidin-1-yl)quinazolin-2-yl)methanesulfonamide **P10**



5

Step 1 : synthesis of 4-(5-(azetidin-1-yl)-2-(1-(2-chloroquinazolin-4-yl)piperidin-2-yl)-pyrazolo[1,5-a]pyrimidin-7-yl)morpholine **16**

The mixture of **8** (250 mg, 0.73 mmol, 1 eq.), 2,4-dichloroquinazoline (290 mg, 1.46 mmol, 2 eq.) and triethylamine (221 mg, 2.19 mmol, 3 eq.) in ethanol was stirred at 90°C for 4 hours. The reaction was concentrated. The residue was purified by flash chromatography (50% EtOAc in petroleum ether) to obtain **16** in 75% purity. After crystallization from EtOAc and petroleum ether, the title intermediate **16** was obtained as a white solid (160 mg, 43.42%)

$m/z = 506 (M+H)^+$.

¹HNMR (CDCl₃ 400MHz) δ ppm 1.72-1.84 (m, 4H) 2.03 (m, 1H) 2.38-2.50 (m, 3H) 3.47-3.52 (m, 3H) 3.61-3.68 (m, 2H) 3.84-3.93 (m, 4H) 4.12-4.15 (t, $J = 7.4$ Hz, 4H) 4.41-4.45 (d, $J = 12.80$ Hz, 1H) 5.11(s, 1H) 5.96 (br.s, 1H) 6.15 (s, 1H) 7.29-7.33 (m, 1H) 7.66-7.70 (m, 1H) 7.78-7.80 (d, $J = 8.5$ Hz, 1H) 7.98-8.00 (d, $J = 8.3$ Hz, 1H).

Step 2 : synthesis of N-(4-(2-(5-(azetidin-1-yl)-7-morpholinopyrazolo[1,5-a]pyrimidin-2-yl)piperidin-1-yl)quinazolin-2-yl)methanesulfonamide **P10**

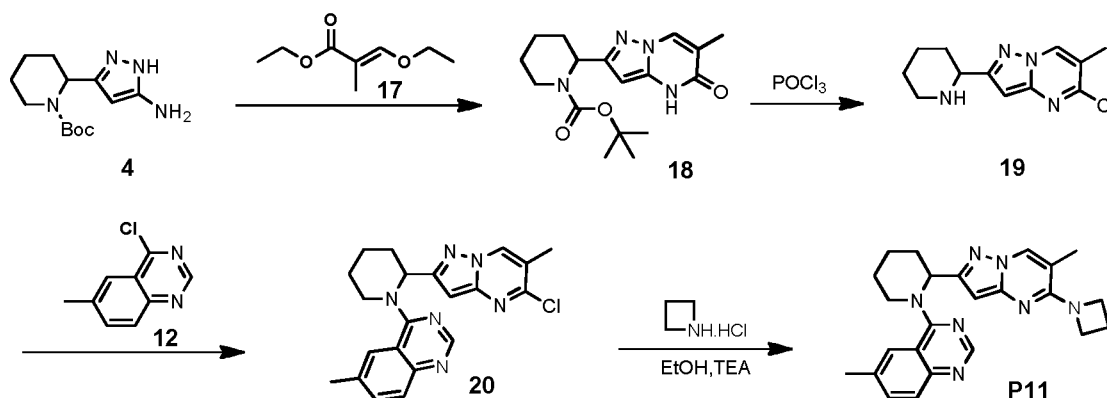
A mixture of intermediate **16** (60 mg, 119 μmol, 1 eq.), methanesulfonamide (34 mg, 357 μmol, 3 eq.), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (14 mg, 0.2 eq.), palladium(II) acetate (5.3 mg, 0.2 eq.) and Cesium carbonate (116 mg, 357 μmol, 3eq.) in 1,4-dioxane (5 mL) was stirred at 110°C for 18h under N₂. The reaction mixture was diluted with water and extracted with EtOAc (3 x 20mL). The combined organic layers were concentrated. The residue was purified by HPLC, and the fractions were lyophilized. The solid was treated with SAX-SPE to obtain compound **P10** as a yellow solid (24mg, 34%)

$m/z = 564 (M+H)^+$.

¹HNMR (400MHz, CD₃OD): δ ppm 1.89 (br, 4H) 2.22 (m, 1H) 2.58 (m, 3H) 3.08 (s, 3H) 3.59 (br, 1H) 3.89 (d, 4H) 3.91 (m, 4H) 4.38 (t, $J = 7.5$ Hz, 4H) 4.62 (br, 1H) 5.27

(s, 1H) 6.29 (s, 1H) 6.33 (br, 1H) 7.39 (t, $J = 7.3$ Hz, 1H) 7.49 (d, $J = 8.5$ Hz, 1H) 7.79 (t, $J = 7.3$ Hz, 1H) 8.01 (d, $J = 8$ Hz, 1H).

Synthesis of 4-(2-(5-(azetidin-1-yl)-6-methylpyrazolo[1,5-a]pyrimidin-2-yl)-piperidin-1-yl)-6-methylquinazoline P11



Step 1 : synthesis of *tert*-butyl 2-(6-methyl-5-oxo-4,5-dihydropyrazolo[1,5-a]-pyrimidin-2-yl)piperidine-1-carboxylate **18**

The intermediate **4** (5.00 g, 18.08 mmol) was dissolved in dry DMF (112 ml), then Cs_2CO_3 (9.00 g, 27.62 mmol) and (E)-ethyl 3-ethoxy-2-methylacrylate **17** (4.30 g, 27.18 mmol) were added and the mixture was heated at 130°C for 3 days. DMF was evaporated and the dark brown oil was poured into iced water. After warming to room temperature, the product was extracted with EtOAc (3 times). The organic layers were dried over Na_2SO_4 , filtered and evaporated and the resulting residue was purified by column chromatography eluting with a gradient starting from 0% to 10% MeOH and dichloromethane. After evaporation of the concerning fractions, we obtain intermediate **18** as a yellow solid (1100 mg, 18%).

^1H NMR (400 MHz, CDCl_3) δ ppm 1.35 - 1.71 (m, 13 H) 1.73 - 1.88 (m, 1 H) 2.09 (d, $J = 1.10$ Hz, 3 H) 2.32 (d, $J = 13.64$ Hz, 1 H) 2.70 - 2.92 (m, 1 H) 3.93 - 4.13 (m, 1 H) 5.35 - 5.54 (m, 1 H) 5.71 (s, 1 H) 7.99 (s, 1 H) 10.56 - 10.76 (m, 1 H)
 $m/z = 333.20$ ($\text{M} + \text{H}$)⁺

Step 2 : synthesis of 5-chloro-6-methyl-2-(piperidin-2-yl)pyrazolo[1,5-a]pyrimidine **19**
 POCl_3 (6.15 ml, 66.19 mmol) was added to intermediate **18** (1100 mg, 3.31 mmol) at room temperature, then the mixture was heated at 100°C for 1.5 hours. The reaction mixture was cooled to room temperature and POCl_3 was evaporated. The residue was

co-evaporated 3 times with toluene to get brown foam intermediate **19** which was used as such in the next step.

$$m/z = 250.96 (M+H)^+$$

5 Step 3 : synthesis of 4-(6-methyl-2-(1-(6-methylquinazolin-4-yl)piperidin-2-yl)-pyrazolo[1,5-a]pyrimidin-5-yl)morpholine **20**

The crude intermediate **19** (150 mg, 0.30 mmol) and 4-chloro-6-methylquinazoline **12** (107 mg, 0.60 mmol) were dissolved in 2-methoxyethanol (3.79 ml) and then di-isopropylethyl amine (619 μ l, 3.59 mmol) was added. The solution was heated at
10 100°C overnight. The heating was stopped and the mixture was cooled to room temperature. To the reaction mixture was added morpholine (1.035 ml, 11.97 mmol) and the mixture was heated at 70°C for 3 hours. Then it was evaporated to dryness. The resulting residue was purified by column chromatography eluting with 2.5% (MeOH/NH₃) and dichloromethane. The oil obtained was recrystallized in di-isopropyl
15 ether. The formed off-white crystals were filtered to get intermediate **20** (52 mg, 38%).
 $m/z = 444.25 (M+H)^+$
MP = 180.64°C

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.57 - 1.80 (m, 4 H) 1.92 - 2.08 (m, 1 H) 2.24
20 (s, 3 H) 2.34 - 2.46 (m, 4 H) 3.20 - 3.28 (m, 4 H) 3.45 (br. t, *J*=11.20, 11.20 Hz, 1 H) 3.67 - 3.83 (m, 4 H) 4.21 (br. d, *J*=13.90 Hz, 1 H) 5.85 (br. s., 1 H) 6.20 (s, 1 H) 7.64 (br. d, *J*=8.40 Hz, 1 H) 7.71 (d, *J*=8.58 Hz, 1 H) 7.83 (br. s, 1 H) 8.56 (s, 1 H) 8.71 (s, 1 H)

25 Step 4 : synthesis of 4-(2-(5-(azetidin-1-yl)-6-methylpyrazolo[1,5-a]pyrimidin-2-yl)-piperidin-1-yl)-6-methylquinazoline **P11**

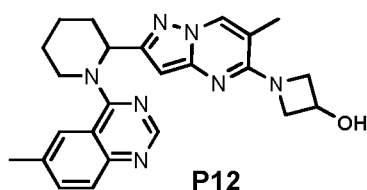
A solution of intermediate **20** (145 mg, 0.37 mmol), azetidine hydrochloride (69 mg, 0.74 mmol) and di-isopropylethyl ether (191 μ l, 1.11 mmol) in EtOH (10 ml) was heated at 65°C for 3.5 hours. All solvent was evaporated and the yellow wet solid was
30 refluxed in acetonitril. The remaining insoluble solid was filtered off hot and the filtrate was cooled to room temperature. The mixture was stirred overnight. The crystals were filtered off and washed with acetonitril. The product was again recrystallized in MeOH and acetonitril. The white crystals were filtered and washed with acetonitril to get the title product **P11** (72 mg, 47%).
35 $m/z = 414.12 (M+H)^+$
MP = 205.49°C

- 32 -

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.58 - 1.79 (m, 4 H) 1.88 - 2.03 (m, 1 H) 2.15 (d, $J=0.88$ Hz, 3 H) 2.27 (quin, $J=7.59$ Hz, 2 H) 2.32 - 2.40 (m, 1 H) 2.42 (s, 3 H) 3.37 - 3.49 (m, 1 H) 4.15 - 4.28 (m, 5 H) 5.77 - 5.84 (m, 1 H) 5.96 (s, 1 H) 7.63 (dd, $J=8.58$, 1.76 Hz, 1 H) 7.71 (d, $J=8.58$ Hz, 1 H) 7.82 (br. s, 1 H) 8.40 - 8.45 (m, 1 H) 8.56 (s, 1 H)

5

Synthesis of 1-(6-methyl-2-(1-(6-methylquinazolin-4-yl)piperidin-2-yl)pyrazolo-[1,5-a]pyrimidin-5-yl)azetidin-3-ol P12



10

Compound **P12** was prepared in the same manner as compound **P11** using intermediate **20** and azetidin-3-ol as starting materials.

$m/z = 430.12$ ($\text{M}+\text{H}$)⁺

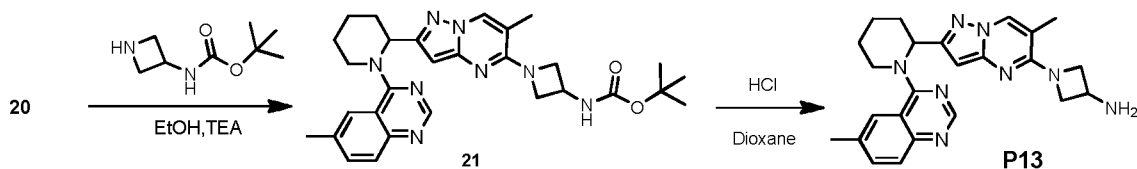
MP = 233.08°C

15

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.53 - 1.80 (m, 4 H) 1.87 - 2.03 (m, 1 H) 2.14 (s, 3 H) 2.31 - 2.40 (m, 1 H) 2.42 (s, 3 H) 3.38 - 3.50 (m, 1 H) 3.93 (dd, $J=9.13$, 4.73 Hz, 2 H) 4.16 - 4.28 (m, 1 H) 4.32 - 4.44 (m, 2 H) 4.46 - 4.59 (m, 1 H) 5.61 - 5.71 (m, 1 H) 5.76 - 5.84 (m, 1 H) 5.98 (s, 1 H) 7.58 - 7.67 (m, 1 H) 7.67 - 7.75 (m, 1 H) 7.83 (br. s, 1 H) 8.45 (br. s, 1 H) 8.56 (s, 1 H)

20

Synthesis of 1-(6-methyl-2-(1-(6-methylquinazolin-4-yl)piperidin-2-yl)pyrazolo-[1,5-a]pyrimidin-5-yl)azetidin-3-amine P13



25

Step 1 : synthesis of *tert*-butyl 1-(6-methyl-2-(1-(6-methylquinazolin-4-yl)piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-5-yl)azetidin-3-ylcarbamate **21**

Intermediate **21** was prepared in the same manner as compound **P11** using intermediate **20** and *tert*-butylazetidin-3-ylcarbamate as starting materials.

30

$m/z = 529.25$ ($\text{M}+\text{H}$)⁺

- 33 -

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.40 (s, 9 H) 1.67 - 1.89 (m, 4 H) 1.98 - 2.11 (m, 1 H) 2.15 (d, *J*=0.88 Hz, 3 H) 2.41 - 2.46 (m, 4 H) 3.60 - 3.74 (m, 1 H) 4.02 - 4.11 (m, 2 H) 4.27 - 4.37 (m, 1 H) 4.37 - 4.46 (m, 2 H) 4.61 - 4.75 (m, 1 H) 6.12 (s, 1 H)
 5 6.22 - 6.35 (m, 1 H) 7.10 - 7.30 (m, 1 H) 7.80 - 7.88 (m, 2 H) 7.97 (br. s, 1 H) 8.37 (s, 1 H) 8.74 (s, 1 H)

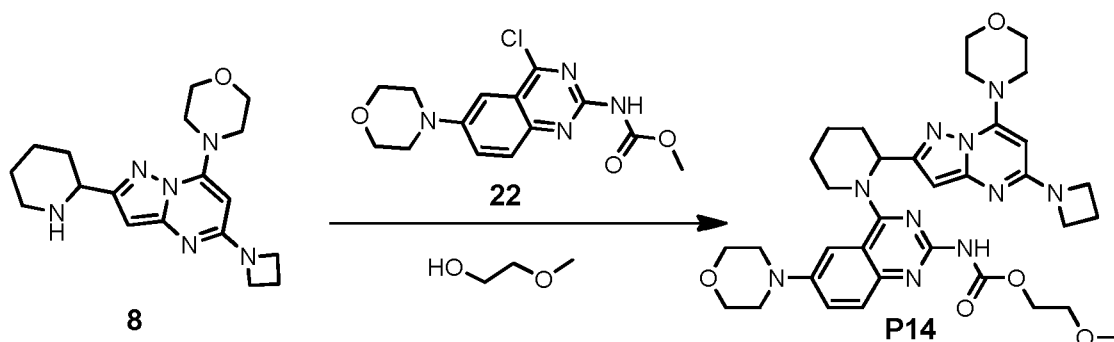
Step 2 : synthesis of 1-(6-methyl-2-(1-(6-methylquinazolin-4-yl)piperidin-2-yl)-pyrazolo[1,5-a]pyrimidin-5-yl)azetidin-3-amine **P13**

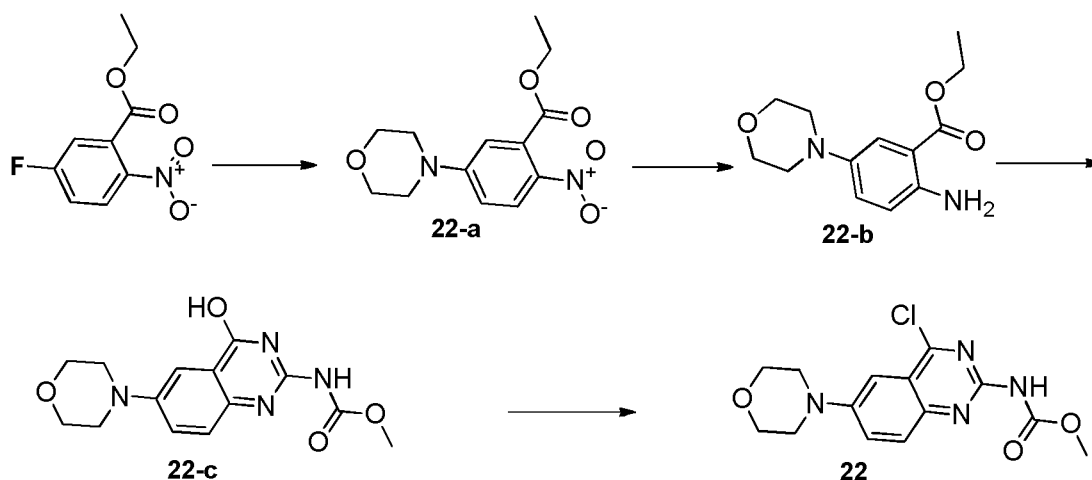
10 A solution of intermediate **21** (215 mg, 0.39 mmol) and a 4M solution of HCl in dioxane (6 ml, 24 mmol) were stirred at room temperature for 2 hours. Dioxane was evaporated and the crude was purified by column chromatography eluting with a gradient starting from 0.5% to 10% (MeOH/NH₃) and dichloromethane. After evaporation of the solvent we obtain the title compound **P13** as a white solid (18 mg,
 15 10%).

m/z = 429.20 (M+H)⁺

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.57 - 1.75 (m, 4 H) 1.88 - 2.03 (m, 1 H) 2.11 - 2.20 (m, 3 H) 2.31 - 2.40 (m, 1 H) 2.42 (s, 3 H) 3.37 - 3.49 (m, 1 H) 3.70 - 3.89 (m, 3 H) 4.16 - 4.27 (m, 1 H) 4.29 - 4.39 (m, 2 H) 5.76 - 5.84 (m, 1 H) 5.96 (s, 1 H) 7.63 (dd, *J*=8.58, 1.76 Hz, 1 H) 7.71 (d, *J*=8.36 Hz, 1 H) 7.82 (br. s, 1 H) 8.42 - 8.46 (m, 1 H) 8.55 (s, 1 H).

25 Synthesis of 2-methoxyethyl 4-(2-(5-(azetidin-1-yl)-7-morpholinopyrazolo[1,5-a]pyrimidin-2-yl)piperidin-1-yl)-6-morpholinoquinazolin-2-ylcarbamate **P14**



Synthesis of methyl (4-chloro-6-morpholinoquinazolin-2-yl)carbamate **22**5 Step 1 : synthesis of ethyl 5-morpholino-2-nitrobenzoate **22-a**

Ethyl 5-fluoro-2-nitrobenzoate (5 g, 23.46 mmol) was dissolved in DMF (150 ml) and then morpholine (6.13 g, 70.37 mmol) was added. The reaction mixture was stirred 4 hours at room temperature. The solvent was removed under reduced pressure and the crude was re-dissolved in dichloromethane, washed with 1M HCl-solution, dried over
10 MgSO_4 , filtered and evaporated to dryness to yield intermediate **22-a**.

Step 2: synthesis of ethyl 2-amino-5-morpholinobenzoate **22-b**

Ethyl 5-morpholino-2-nitrobenzoate **22-a** (6.574 g, 23.46 mmol) was dissolved in a mixture of EtOH (150 ml) and THF (250 ml), then Pd/C (10%) (2.496 g, 2.35 mmol)
15 was added and the reaction mixture was set under a hydrogen atmosphere for 2 hours. The reaction mixture was filtered over dicalite and the filtrate was evaporated to dryness yielding the wanted intermediate **22-b** as a brown solid (6.24 g, quantitative).

Step 3 : synthesis of methyl 4-hydroxy-6-morpholinoquinazolin-2-ylcarbamate **22-c**

Ethyl 2-amino-5-morpholinobenzoate **22-b** (6.24 g, 24.93 mmol), 1,3-bis(methoxycarbonyl)-2-methyl-2-thiopseudourea (5.91 g, 28.67 mmol) and acetic acid (7.14 ml, 124.65 mmol) were dissolved in 100 ml MeOH and stirred overnight at 75°C. Extra acetic acid (1 ml, 17.47 mmol) was added and the reaction mixture was stirred at 75°C
20 for 7 days. The pH was set to 5 with acetic acid. The volatiles were evaporated to dryness. Then the residue was re-dissolved in 15 ml MeOH and 100 ml water was added. The precipitate was filtered off, washed with diethylether to yield the title
25 intermediate **22-c** as a brown solid (5.28 g, 70%).

Step 4 : synthesis of methyl 4-chloro-6-morpholinoquinazolin-2-ylcarbamate **22**

Methyl (4-hydroxy-6-morpholinoquinazolin-2-yl)carbamate **22-c** (1.00 g, 3.29 mmol) was suspended in dry acetonitril (12.38 ml), then POCl₃ (1.15 ml, 12.4 mmol) was added at room temperature and the mixture was refluxed for 4.5 hours. After cooling to room temperature, the reaction mixture was evaporated to dryness. The residue was co-evaporated with toluene. The crude was dissolved in DCM and it was washed with saturated sodium hydrogencarbonate solution in water. The organic layer was dried over Na₂SO₄, filtered and evaporated. The residue was triturated in di-isopropylether. The solid was filtered off to get the title intermediate **22** as a dark brown solid.

10 $m/z = 323.15$ (M+H)⁺

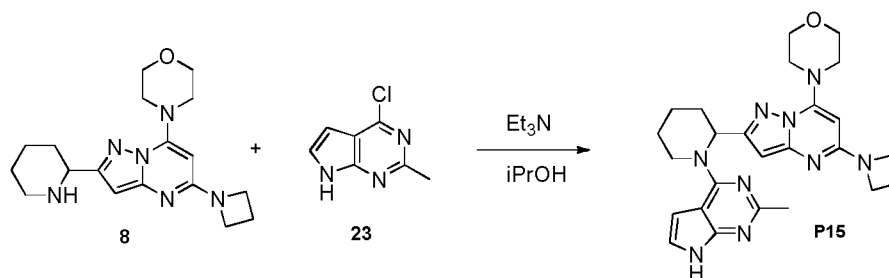
Step 5 : synthesis of 2-methoxyethyl 4-(2-(5-(azetidin-1-yl)-7-morpholinopyrazolo-[1,5-a]pyrimidin-2-yl)piperidin-1-yl)-6-morpholinoquinazolin-2-ylcarbamate **P14**

15 A solution of intermediate **8** (80 mg, 0.23 mmol), methyl (4-chloro-6-morpholinoquinazolin-2-yl)carbamate **22** (152 mg, 0.23 mmol) and diisopropyl ethyl amine (117 μ l, 0.68 mmol) in 2-methoxyethanol (1.79 ml) was heated at 100°C overnight. The solvents were evaporated and the residue was purified by column chromatography eluting with a gradient starting from 0.5% to 10% MeOH in DCM. After evaporation
20 of the solvent we obtain an oil that was triturated in di-isopropyl ether and the suspension was sonicated for 5 minutes. The solid was filtered and washed with some di-isopropyl ether to get the title compound **P14** as a brown powder (38 mg, 24%).

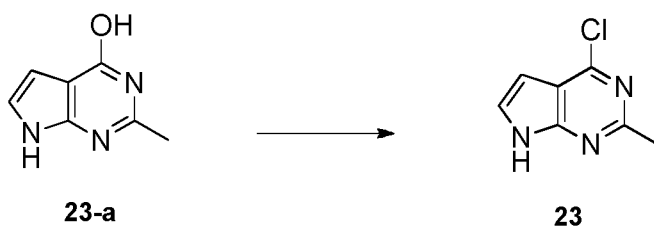
$m/z = 673.34$ (M+H)⁺

25 ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.58 - 1.80 (m, 4 H) 1.93 - 2.06 (m, 1 H) 2.24 - 2.40 (m, 3 H) 2.95 - 3.11 (m, 4 H) 3.28 (s, 3 H) 3.30 - 3.34 (m, 1 H) 3.42 - 3.59 (m, 6 H) 3.64 - 3.75 (m, 8 H) 4.01 (t, *J*=7.37 Hz, 4 H) 4.14 - 4.22 (m, 2 H) 4.22 - 4.32 (m, 1 H) 5.33 (s, 1 H) 5.70 - 5.81 (m, 1 H) 6.00 (s, 1 H) 7.17 (d, *J*=2.20 Hz, 1 H) 7.51 (d, *J*=9.24 Hz, 1 H) 7.56 (dd, *J*=9.68, 2.64 Hz, 1 H) 9.83 (br. s., 1 H)

30

Synthesis of 4-(5-(azetidin-1-yl)-2-(1-(2-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-7-yl)morpholine **P15**

Synthesis of 4-chloro-2-methyl-7H-pyrrolo[2,3-d]pyrimidine **23**



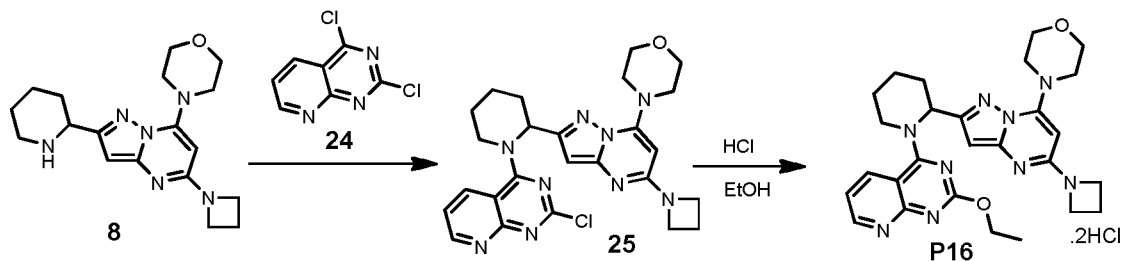
- 5 2-Methyl-3H-pyrrolo[2,3-d]pyrimidin-4(7H)-one **23-a** (10.54 g, 70.6 mmol) was dissolved in Toluene (20 mL) under inert atmosphere. DIPEA (24 mL, 141 mmol, 2 eq.) and POCl₃ (19.5 mL, 212 mmol, 3 eq.) were added dropwise at 70°C and the mixture was then heated to 106°C. After 16 hours, the solution was concentrated in vacuo, extracted with ethyl acetate and washed with saturated NaHCO₃ solution. The combined organic layers were dried over Na₂SO₄, and concentrated in vacuo to yield a grey oil which was suspended in water/heptanes to afford a white solid intermediate **23** (5.9 g, 50%).

15 **Synthesis of 4-(5-(azetidin-1-yl)-2-(1-(2-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-7-yl)morpholine P15**

- To a solution of intermediate **8** (100 mg, 0.28 mmol) in isopropanol (3 mL) was added intermediate **23** (47 mg, 0.28 mmol, 1 eq.) and Et₃N (0.118 mL, 0.84 mmol, 3 eq.) in a sealed pressure tube. The solution was heated to 140°C and stirred during 16 hours. After cooling to room temperature, the solution was concentrated in vacuum and purified by Prep HPLC to yield the title compound **P15** (36 mg, 27 %).
- 20 $m/z = 474 (M+H)^+$

- ¹H NMR (600 MHz, DMSO-*d*₆) δ ppm 1.52 - 1.58 (m, 1 H) 1.58 - 1.69 (m, 2 H) 1.73 (d, *J*=11.74 Hz, 1 H) 1.91 (br. s., 1 H) 2.24 - 2.32 (m, 2 H) 2.32 - 2.38 (m, 1 H) 2.36 (s, 3 H) 3.27 (t, *J*=12.03 Hz, 1 H) 3.47 (br. s., 4 H) 3.58 - 3.68 (m, 4 H) 3.97 (t, *J*=7.34 Hz, 4 H) 4.61 (d, *J*=11.74 Hz, 1 H) 5.23 (s, 1 H) 5.71 (s, 1 H) 6.21 (br. s., 1 H) 6.42 (br. s., 1 H) 6.98 (br. s., 1 H) 11.17 (br. s., 1 H)

Synthesis of 4-(5-(azetidin-1-yl)-2-(1-(2-ethoxypyrido[2,3-d]pyrimidin-4-yl)-piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-7-yl)morpholine **P16**



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Step 1 : synthesis of 4-(5-(azetidin-1-yl)-2-(1-(2-chloropyrido[2,3-d]pyrimidin-4-yl)-piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-7-yl)morpholine **25**

Intermediate **8** (200 mg, 0.584 mmol) was dissolved in ethanol (10 mL), then 2,4-dichloropyrido[2,3-d]pyrimidine **24** (117 mg, 0.58 mmol) and triethylamine (177 mg, 1.75 mmol) were added. The resulting mixture was stirred at 90°C for 12 hours. The solvent was evaporated. This crude product was purified by column chromatography over silica gel (eluent: methanol/ ethyl acetate 1/10). The resulting residue was lyophilized to yield a white solid (78.3 mg, 27%).

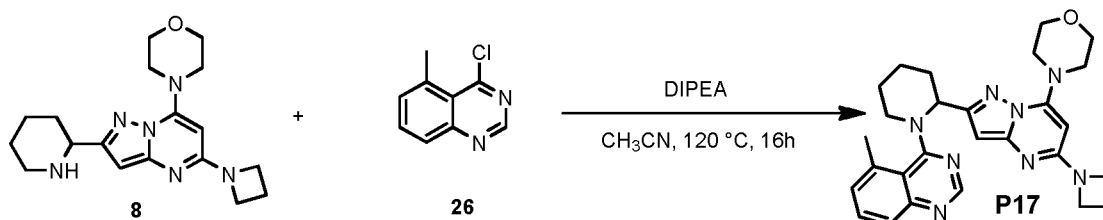
Step 2 : synthesis of 4-(5-(azetidin-1-yl)-2-(1-(2-ethoxypyrido[2,3-d]pyrimidin-4-yl)-piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-7-yl)morpholine **P16**

To a solution of intermediate **25** (67 mg, 0.13 mmol) in EtOH (10 mL) was added 100 μ L HCl.iPrOH (6N) and the solution was heated to 40°C during 16 hours. The resulting solution was concentrated in vacuum and purified by column chromatography eluting with a gradient starting from 0% to 10% MeOH in DCM. After evaporation the title compound **P16** (20 mg, 25%) was obtained.

$m/z = 516 (M+H)^+$

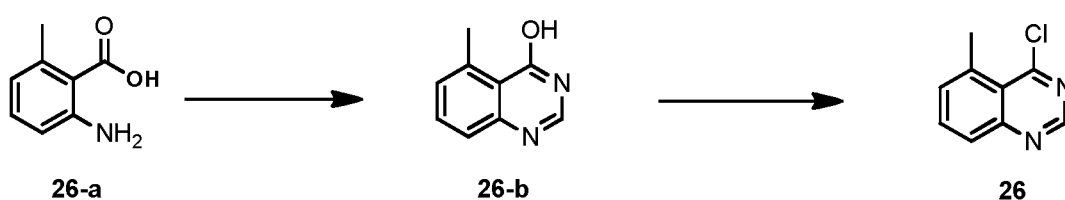
^1H NMR (400 MHz, DMSO- d_6) δ ppm 1.33 (t, $J=7.04$ Hz, 3 H) 1.71 (br. s., 4 H) 1.92 - 2.11 (m, 1 H) 2.23 - 2.39 (m, 3 H) 3.40 - 3.58 (m, 5 H) 3.61 - 3.74 (m, 4 H) 4.01 (t, $J=7.37$ Hz, 4 H) 4.20 (br. d, $J=13.90$ Hz, 1 H) 4.40 (q, $J=7.00$ Hz, 2 H) 5.28 (s, 1 H) 5.79 - 5.88 (m, 1 H) 5.91 (s, 1 H) 7.19 (dd, $J=8.58, 4.40$ Hz, 1 H) 8.38 (dd, $J=8.14, 1.54$ Hz, 1 H) 8.76 - 8.82 (m, 1 H)

Synthesis of 4-(5-(azetidin-1-yl)-2-(1-(5-methylquinazolin-4-yl)piperidin-2-yl)-pyrazolo[1,5-a]pyrimidin-7-yl)morpholine P17



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Synthesis of 4-chloro-5-methylquinazoline 26



Step 1: synthesis of 5-methylquinazolin-4-ol 26-b

2-Amino-6-methylbenzoic acid **26-a** (4g, 26 mmol) was dissolved in 10 mL formamide and the solution was heated to 120°C. After 4 hours water was added and the solid filtered off. The solid was further washed with water and dried into the oven yielding intermediate **26-b** (3.25 g, 77%).

15 $m/z = 160 (M+H)^+$

^1H NMR (400 MHz, DMSO- d_6) δ ppm 2.77 (s, 3 H) 7.25 (d, $J=7.48$ Hz, 1 H) 7.46 (d, $J=7.70$ Hz, 1 H) 7.62 (t, $J=7.90$ Hz, 1 H) 7.98 (s, 1 H) 11.89 (br. s, 1 H)

Step 2: synthesis of 4-chloro-5-methylquinazoline 26

Into a solution of intermediate **26-b** (100 mg, 0.62 mmol) in acetonitrile (2 mL) was added DIPEA (0.23 mL, 1.88 mmol, 3 eq.). The resulting solution was heated to 70°C and stirred for 10 minutes. POCl₃ was then added to the solution dropwise. After 16 hours, the solution was concentrated in vacuo to yield intermediate **26**.

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Synthesis of 4-(5-(azetidin-1-yl)-2-(1-(5-methylquinazolin-4-yl)piperidin-2-yl)-pyrazolo[1,5-a]pyrimidin-7-yl)morpholine P17

To a solution of intermediate **8** (230 mg, 0.67 mmol) in CH₃CN (10 mL) in a sealed tube was added DIPEA (2.3 mL, 13.4 mmol, 20 eq.) and 4-chloro-5-methylquinazoline **26** (120 mg, 0.67 mmol, 1 eq.). The solution was heated at 120°C and stirred during

30

16 hours. After cooling to room temperature, the solution was concentrated in vacuum and the crude purified by Prep HPLC to yield compound **P17** (28 mg, 9%).

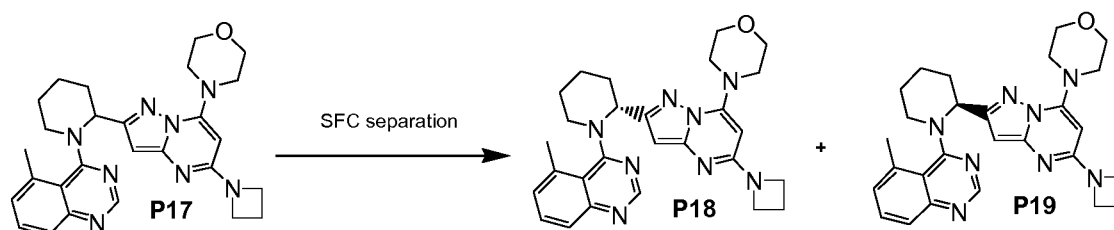
$m/z = 485 (M+H)^+$

- ¹H NMR (600 MHz, DMSO-*d*₆) δ ppm 1.54 - 1.86 (m, 4 H) 2.08 - 2.13 (m, 2 H) 2.28 - 2.33 (m, 2 H) 2.86 (s, 3 H) 3.28 - 3.31 (m, 2 H) 3.39 - 3.44 (m, 2 H) 3.49 - 3.54 (m, 2 H) 3.62 - 3.69 (m, 4 H) 4.00 (t, $J=7.41$ Hz, 4 H) 5.31 (s, 1 H) 5.75 (t, $J=4.40$ Hz, 1 H) 5.97 (s, 1 H) 7.37 (d, $J=6.90$ Hz, 1 H) 7.60 - 7.63 (m, 1 H) 7.67 - 7.71 (m, 1 H) 8.53 (s, 1 H)

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Synthesis of (R)-4-(5-(azetidin-1-yl)-2-(1-(5-methylquinazolin-4-yl)piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-7-yl)morpholine P18 and (S)-4-(5-(azetidin-1-yl)-2-(1-(5-methylquinazolin-4-yl)piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-7-yl)morpholine P19

- 15 A purification was performed via Prep SFC (Stationary phase: Chiralpak Diacel AS 20 x 250 mm, Mobile phase: CO₂, EtOH with 0.2% iPrNH₂) giving both relative enantiomers :

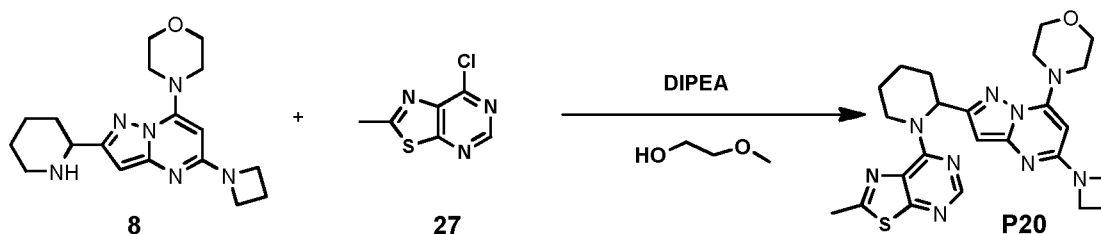


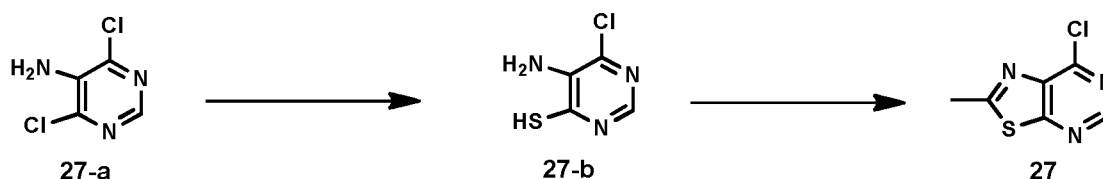
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P18 : $[\alpha]_D^{20} = +210.64^\circ$ (589 nm, $c = 0.3855$ w/v %, DMF, 20°C)

Synthesis of 4-(5-(azetidin-1-yl)-2-(1-(2-methylthiazolo[5,4-d]pyrimidin-7-yl)piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-7-yl)morpholine P20

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Synthesis of 7-chloro-2-methylthiazolo[5,4-d]pyrimidine 27**5 Step 1: synthesis of 5-amino-6-chloropyrimidine-4-thiol 27-b**

To a solution of sulfanylsodium hydrate (2.48 g, 33.54 mmol) in water (6 mL) was added MeOH (50 mL) and 4,6-dichloropyrimidin-5-amine **27-a** (5 g, 30.49 mmol). The resulting mixture was stirred at reflux for one hour and at ambient temperature overnight. The mixture was evaporated and the residue was dried in vacuo, to yield intermediate **27-b** (3.63 g, 74%).

$m/z = 161 (M+H)^+$

Step 2: synthesis of 7-chloro-2-methylthiazolo[5,4-d]pyrimidine 27

A solution of 5-amino-6-chloro-pyrimidine-4-thiol **27-b** (4.7 g, 29.1 mmol) in triethylorthoacetate (150 mL) was stirred at 150°C for one hour. The reaction mixture was allowed to cool to room temperature and was then evaporated to dryness. The residue was triturated in diisopropylether with some acetonitrile. The precipitate was collected by filtration and dried in vacuo to yield intermediate **27** (0.9 g, 4.85 mmol)

20 Synthesis of 4-(5-(azetidin-1-yl)-2-(1-(2-methylthiazolo[5,4-d]pyrimidin-7-yl)-piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-7-yl)morpholine P20

A solution of intermediate **8** (378.9 mg, 1 mmol), 7-chloro-2-methyl-thiazolo[5,4-d]-pyrimidine **27** (185.6 mg, 1 mmol), Hunig's base (0.7 mL, 4.22 mmol) and 2-methoxyethanol (10 mL) was stirred at 100°C overnight. The mixture was evaporated and the residue was dissolved in dichloromethane and washed twice with water. The organic layer was dried over MgSO₄, filtered and evaporated. The residue was purified over silica with dichloromethane/methanol 100/0 to 95/5 as gradient. The corresponding fractions were evaporated. The residue was crystallised in diisopropylether and 10% acetonitrile. The white crystals were collected by filtration and dried in vacuo to yield compound **P20** (163 mg, 33%).

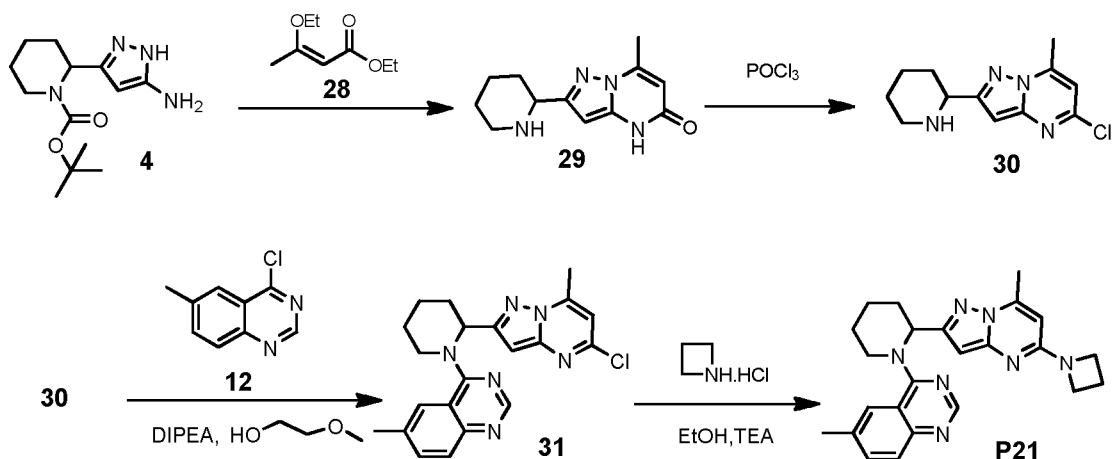
$m/z = 491.62 (M+H)^+$

mp: 229.8°C

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.48 - 1.83 (m, 2 H), 1.91 - 2.06 (m, 1 H), 2.29

(quin, $J=7.5$ Hz, 1 H), 2.39 (d, $J=13.7$ Hz, 1 H), 2.72 (s, 3 H), 3.21 (m, $J=2.4$ Hz, 1 H), 3.42 - 3.54 (m, 4 H), 3.56 - 3.70 (m, 4 H), 3.98 (t, $J=7.5$ Hz, 4 H), 5.16 - 5.30 (m, 2 H), 5.73 (s, 1 H), 6.98 (br. s., 1 H), 8.32 (s, 1 H)

5 Synthesis of 4-(2-(5-(azetidin-1-yl)-7-methylpyrazolo[1,5-a]pyrimidin-2-yl)-piperidin-1-yl)-6-methylquinazoline P21



10 Step 1: synthesis of 7-methyl-2-(piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-5(4H)-one 29

The commercially available (Z)-ethyl 3-ethoxybut-2-enoate **28** (33 g, 208.60 mmol) and Cs_2CO_3 (54 g, 165.74 mmol) were added to a solution of intermediate **4** (30 g, 112.64 mmol) in DMF (180 ml). The mixture was stirred at 110°C for 12 hours. The precipitate was filtered off and washed with ethyl acetate (100 ml). The filtrate was concentrated under vacuum. The residue was dissolved in ethyl acetate (300 ml) and washed with brine (2 x 100 ml). The organic layer was dried (MgSO_4), filtered and the filtrate was concentrated under vacuum. The residue was washed with isopropyl ether (200 ml) and then dried (vacuum, 45 °C, 1 hour) to yield intermediate **29** (25 g, 65.37%).

20 $m/z = 233 (\text{M}+\text{H})^+$

Step 2 : synthesis of 5-chloro-7-methyl-2-(piperidin-2-yl)pyrazolo[1,5-a]pyrimidine 30

A mixture of intermediate **29** (22.5 g, 67.69 mmol) in POCl_3 (377.5 g) was stirred at 100°C for 2 hours. The solvent was evaporated under vacuum. Acetonitrile (200 ml) was added. The mixture was neutralized with NH_3 (7 M in methanol) to pH = 8. The solvent was evaporated under vacuum. The residue was purified by column chromatography over silica gel (eluent: dichloromethane/methanol 10/1) to yield intermediate **30** (13.97 g, 80.47%).

$m/z = 251 (M+H)^+$

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.52 - 1.73 (m, 4 H) 1.76 - 1.86 (m, 1 H) 1.99 - 2.02 (m, 1 H) 2.70 (s, 3 H) 2.83-2.88 (m, 1 H) 3.15-3.18 (d, *J*=12.0 Hz, 1 H) 4.14-4.17 (dd, *J*₁=10.8, *J*₂=2.8 Hz, 1 H) 6.81 (s, 1 H) 7.14 (s, 1 H)

Step 3 : synthesis of 4-(2-(5-chloro-7-methylpyrazolo[1,5-a]pyrimidin-2-yl)piperidin-1-yl)-6-methylquinazoline **31**

A solution of intermediate **30** (501.5 mg, 2 mmol) and 4-chloro-6-methyl-quinazoline **12** (535.9 mg, 3 mmol) in methoxyethanol (5 mL) was stirred at 120°C overnight. The mixture was evaporated and the residue was dissolved in dichloromethane, washed twice with water, dried over MgSO₄, filtered and evaporated. The residue was purified over silica with dichloromethane/methanol-NH₃ 98/2. The corresponding fractions were evaporated and the residue was crystallized in di-isopropylether with 10% acetonitrile. The greenish precipitate was filtered off and dried in vacuum to yield intermediate **31** (645 mg, 82%)

$m/z = 392.9 (M+H)^+$

mp: 154.2°C

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.62 - 1.81 (m, 2 H), 2.45 (s, 3 H), 2.69 (s, 2 H), 4.16 (br. s., 1 H), 5.95 (br. s., 1 H), 6.60 (s, 1 H), 7.00 (s, 1 H), 7.63 (d, *J*=1.6 Hz, 1 H), 7.66 - 7.79 (m, 1 H), 7.86 (s, 1 H), 8.55 (s, 1 H)

Synthesis of 4-(2-(5-(azetidin-1-yl)-7-methylpyrazolo[1,5-a]pyrimidin-2-yl)-piperidin-1-yl)-6-methylquinazoline **P21**

A solution of intermediate **31** (196.45 mg, 0.5 mmol), azetidine hydrochloride (93.56 mg, 1 mmol), Hunig's base (0.26 mL, 1.5 mmol) and ethanol (5 mL) was stirred at 60°C, over weekend. The mixture was evaporated and the residue was triturated in water and stirred for one hour. The precipitate was filtered off and recrystallized in acetonitrile. The white crystals were collected by filtration and dried in vacuo to yield compound **P21** (175 mg, 84%)

$m/z = 413.5 (M+H)^+$

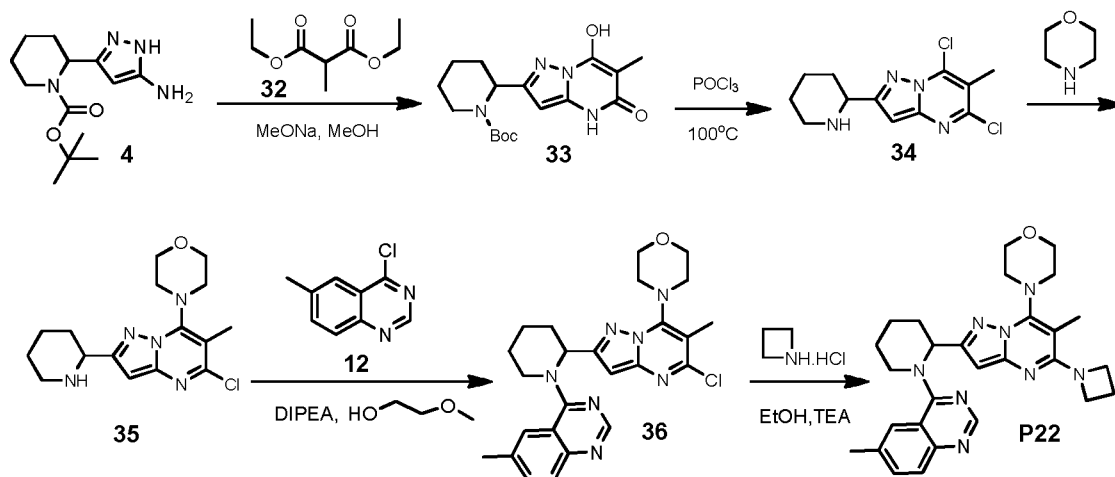
mp: 192.43°C

¹H NMR (360 MHz, DMSO-*d*₆) δ ppm 1.58 - 1.78 (m, 4 H), 1.90 - 2.05 (m, 1 H), 2.25 - 2.39 (m, 3 H), 2.43 (s, 3 H), 2.54 (s, 3 H), 4.03 (t, *J*=7.5 Hz, 4 H), 5.80 (br. s., 1 H), 6.00 (s, 1 H), 6.12 (d, *J*=1.1 Hz, 1 H), 7.65 (d, *J*=1.8 Hz, 1 H), 7.68 - 7.74 (m, 1 H),

7.89 (s, 1 H), 8.57 (s, 1 H)

Synthesis of 4-(2-(5-(azetidin-1-yl)-6-methyl-7-(piperidin-1-yl)pyrazolo[1,5-a]-pyrimidin-2-yl)piperidin-1-yl)-6-methylquinazoline P22

5



Step 1: synthesis of *tert*-butyl 2-(7-hydroxy-6-methyl-5-oxo-4,5-dihydropyrazolo-[1,5-a]pyrimidin-2-yl)piperidine-1-carboxylate **33**

- 10 Freshly prepared sodium methanolate (50 ml, 93.87 mmol) was added to a solution of intermediate **4** (5 g, 18.77 mmol) and diethyl 2-methylmalonate **32** (3.93 g, 22.53 mmol) in methanol (50 ml). The solution was refluxed for 15 hours. The solvent was evaporated under vacuum. Water was added to the residue, the solution was adjusted to pH = 4-5 by addition of acetic acid. The mixture was extracted with ethyl acetate
- 15 (3x300 ml), the combined organic layers were washed with brine (2x100 ml), dried (Na₂SO₄), filtered and concentrated under vacuum to give the crude intermediate **33** (8.5 g, yield: 91%).
- $m/z = 349 (M+H)^+$

20 Step 2 : 5,7-dichloro-6-methyl-2-(piperidin-2-yl)pyrazolo[1,5-a]pyrimidine **34**

- Phosphorus trichlorid (30 ml) was added to intermediate **33** (6.5 g, 18.66 mmol) at 0°C. The mixture was stirred at 100°C for 15 hours. The solvent was evaporated under vacuum. The residue was dissolved in CH₃CN (30 ml). The solution was adjusted to pH=7 by addition of ammonia methanol solution. The solvent was evaporated under
- 25 vacuum. The residue was purified by column chromatography over silica gel (eluent: dichloromethane/methanol 20/1 (0.5% ammonia methanol solution)). The desired fractions were collected and the solvent was evaporated under vacuum. The residue

was washed with ethyl acetate. The solid was dried under vacuum to yield intermediate **34** (1.12 g, 21%).

$m/z = 286 (M+H)^+$

- 5 $^1\text{H NMR}$ (400 MHz, CDCl_3) δ ppm 1.22-1.25 (m, 1 H) 1.65-1.68 (m, 2 H) 2.04 - 2.08 (m, 1 H) 2.24 - 2.28 (m, 2 H) 2.53 (s, 3 H) 3.08 (br. s., 1 H) 3.57 (br. s., 1 H) 3.69 - 3.80 (m, 1 H) 4.48 (br. s., 1 H) 7.21 (s, 1 H).

Step 3 : synthesis of 5-chloro-6-methyl-7-(piperidin-1-yl)-2-(piperidin-2-yl)pyrazolo-
10 [1,5-a]pyrimidine **35**

A solution of intermediate **34** (1120 mg, 3.93 mmol), morpholine (377 mg, 4.32 mmol), Hunig's base (1.35 mL, 7.85 mmol) in ethanol (25 mL) was stirred at room temperature overnight. The mixture was evaporated and the residue was crystallised in diisopropyl-
15 ether with about 50% acetonitrile. The crystals were collected by filtration and dried in vacuo to yield intermediate **35** (1060 mg, 80%)

$m/z = 335.8 (M+H)^+$

Step 4 : 4-(2-(5-chloro-6-methyl-7-(piperidin-1-yl)pyrazolo[1,5-a]pyrimidin-2-yl)-
20 piperidin-1-yl)-6-methylquinazoline **36**

A solution of intermediate **35** (1060 mg, 3.16 mmol), 4-chloro-6-methyl-quinazoline **12** (845.7 mg, 4.73 mmol), Hunig's base (1.1 mL, 6.32 mmol) and 2-methoxyethanol (20 mL) was stirred at 100°C overnight. The mixture was evaporated and the residue was taken up in water and extracted with dichloromethane 3 times. The combined organic layer was successively dried over MgSO_4 , filtered and evaporated. The residue was
25 purified over a silicagel chromatography with dichloromethane/methanol 98/2 as eluent. The corresponding fractions were evaporated to yield intermediate **36** (1400 mg, 92%)

Step 5: synthesis of 4-(2-(5-(azetidin-1-yl)-6-methyl-7-(piperidin-1-yl)pyrazolo-
30 [1,5-a]pyrimidin-2-yl)piperidin-1-yl)-6-methylquinazoline **P22**

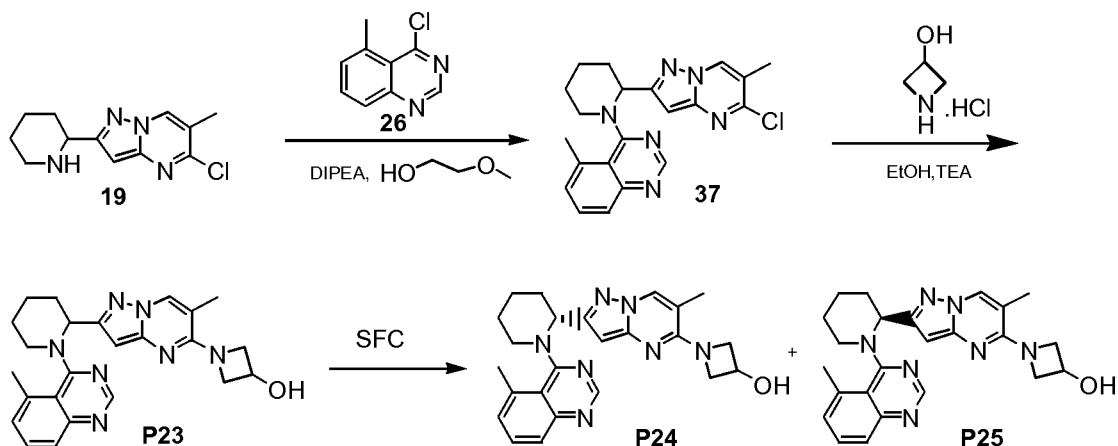
Compound **P22** was prepared in the same manner as compound **P21** using intermediate **36** as starting material.

$m/z = 498.6 (M+H)^+$

- 35 $^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.58 - 1.87 (m, 4 H) 1.98 - 2.06 (m, 1 H) 2.07 (s, 3 H) 2.24 (quin, $J=7.57$ Hz, 2 H) 2.34 - 2.40 (m, 1 H) 2.42 - 2.46 (m, 3 H) 3.34 -

3.40 (m, 4 H) 3.49 (br ddd, $J=13.62, 10.60, 3.63$ Hz, 1 H) 3.64 - 3.71 (m, 4 H) 4.10 (t, $J=7.67$ Hz, 4 H) 4.19 (br d, $J=14.13$ Hz, 1 H) 5.81 - 5.88 (m, 1 H) 5.92 (s, 1 H) 7.59 (dd, $J=8.48, 1.61$ Hz, 1 H) 7.65 - 7.73 (m, 1 H) 7.86 (s, 1 H) 8.53 (s, 1 H)

5 **Synthesis of 1-(6-methyl-2-(1-(5-methylquinazolin-4-yl)piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-5-yl)azetidin-3-ol P23**



- 10 P24 : $[\alpha]_D^{20} = +251.32^\circ$ (589 nm, $c = 0.3975$ w/v %, DMF, 20°C)
 P25 : $[\alpha]_D^{20} = -264.8^\circ$ (589 nm, $c = 0.375$ w/v %, DMF, 20°C)

Step 1: synthesis of 4-(2-(5-chloro-6-methylpyrazolo[1,5-a]pyrimidin-2-yl)piperidin-1-yl)-5-methylquinazoline 37

- 15 Intermediate **19** (500 mg, 1.72 mmol) was dissolved in 2-methoxyethanol (30 mL). DIPEA (0.89 mL, 5.17 mmol, 3 eq.) and 4-chloro-5-methylquinazoline **26** (324.26 mg, 1.72 mmol, 1 eq.) were added to the solution and heated to 80°C . After 16 hours stirring, the solution was concentrated in vacuo and purified via column chromatography (DCM/(NH_3/MeOH) 7N): 9/1) to yield the desired intermediate **37**
 20 (735 mg, 86%).
 LCMS $m/z = 393$ ($\text{M}+\text{H}$)⁺

Step 2: synthesis of 1-(6-methyl-2-(1-(5-methylquinazolin-4-yl)piperidin-2-yl)-pyrazolo[1,5-a]pyrimidin-5-yl)azetidin-3-ol P23

- 25 Intermediate **37** (735 mg, 1.5 mmol) was dissolved in EtOH (50 mL). Azetidin-3-ol hydrochloride (327 mg, 3 mmol, 2 eq.) and DIPEA (0.77 mL, 4.5 mmol, 3 eq.) were added and the solution was heated to reflux during 16 hours. The solution was then cooled to room temperature, ice was added and the solution was stirred for 1 hour. The

- 46 -

solid was filtered off and dried into the oven to yield compound **P23** (440 mg, 68%)

LCMS $m/z = 430$ (M+H)⁺

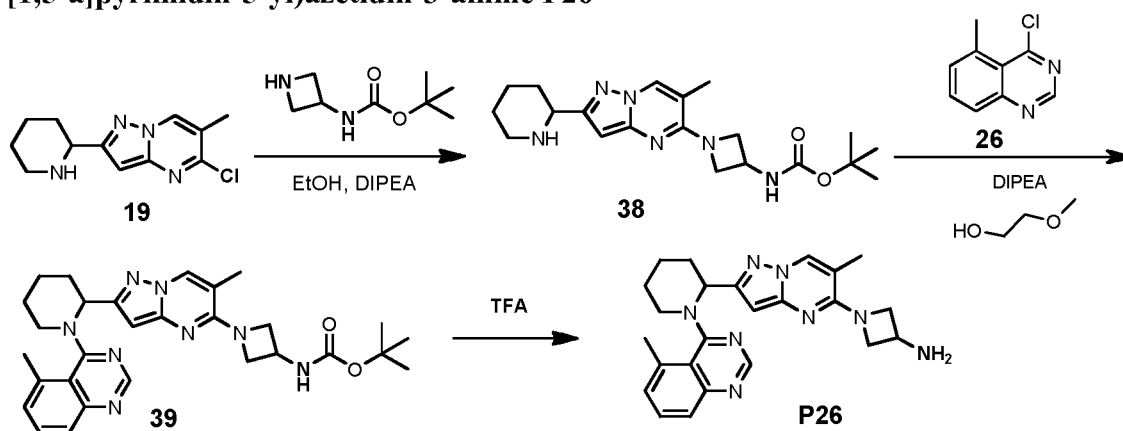
¹H NMR (400 MHz, 420 K, DMSO-*d*₆) δ ppm 1.41 - 1.70 (m, 3 H) 1.76 - 1.89 (m, 1 H)
 2.11 (d, $J=1.21$ Hz, 3 H) 2.13 - 2.31 (m, 2 H) 2.81 (s, 3 H) 3.42 - 3.60 (m, 2 H) 3.90
 5 (dd, $J=9.28, 4.84$ Hz, 2 H) 4.34 (t, $J=8.10$ Hz, 2 H) 4.46 - 4.55 (m, 1 H) 4.73 - 5.12 (m,
 1 H) 5.47 - 5.58 (m, 1 H) 5.64 (br. s., 1 H) 7.21 - 7.33 (m, 1 H) 7.46 - 7.63 (m, 2 H)
 8.10 (s, 1 H) 8.45 (s, 1 H)

(R)-1-(6-methyl-2-(1-(5-methylquinazolin-4-yl)piperidin-2-yl)pyrazolo[1,5-a]-
 10 pyrimidin-5-yl)azetidin-3-ol **P24** and (S)-1-(6-methyl-2-(1-(5-methylquinazolin-4-yl)-
 piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-5-yl)azetidin-3-ol **P25**

These two enantiomers were isolated by SFC separation using compound **P23**

A purification was performed via Prep SFC (Stationary phase: Chiralpak Diacel AS 20
 x 250 mm, Mobile phase: CO₂, EtOH with 0.2% iPrNH₂) giving both relative
 15 enantiomers :

Synthesis of 1-(6-methyl-2-(1-(5-methylquinazolin-4-yl)piperidin-2-yl)pyrazolo- [1,5-a]pyrimidin-5-yl)azetidin-3-amine **P26**



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Step 1: synthesis of *tert*-butyl(1-(6-methyl-2-(piperidin-2-yl)pyrazolo[1,5-a]- pyrimidin-5-yl)azetidin-3-yl)carbamate **38**

A solution of intermediate **19** (1300 mg, 5.185 mmol), *tert*-butylazetidin-3-ylcarbamate
 (1786 mg, 10.37 mmol) and Hunig's base (2 ml, 11.606 mmol) in EtOH (30 ml) was
 25 heated at 70°C for 3 hours. After cooling to room temperature, dicalite was added and
 the mixture was evaporated to dryness. The crude was purified by column
 chromatography. The column was eluted with a gradient starting with 100% DCM to
 10% MeOH and 90% DCM. The fractions containing product were evaporated and the

residue was recrystallized in ACN. After filtration we get a white crystalline solid, this is a mixture of the desired title intermediate **38** and starting reagent *tert*-butylazetidin-3-ylcarbamate (2204 mg), which was used as such in the next step.

$m/z = 387.26 (M+H)^+$

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Step 2: synthesis of *tert*-butyl(1-(6-methyl-2-(1-(5-methylquinazolin-4-yl)piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-5-yl)azetidin-3-yl)carbamate **39**

The crude made in step 1, intermediate **38** (250 mg, 0.647 mmol), 4-chloro-5-methylquinazoline **26** (182 mg, 0.97 mmol) and Hunig's base (368 μ l, 2.135 mmol) were
10 mixed in 2-methoxyethanol (4.36 ml) and heated at 100°C for 3 hours. The reaction mixture was evaporated and the residue was purified by column chromatography by eluting with a gradient starting with 100% DCM to 5% MeOH and 95% DCM. All fractions containing product were evaporated to get yellow foam which was only 52% pure (315 mg). The crude was used as such in step 3.

15 $m/z = 529.28 (M+H)^+$

Step 3 : 1-(6-methyl-2-(1-(5-methylquinazolin-4-yl)piperidin-2-yl)pyrazolo[1,5-a]-pyrimidin-5-yl)azetidin-3-amine **P26**

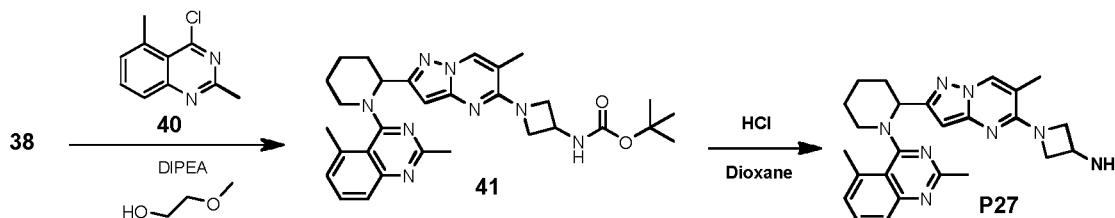
The crude made in step 2, intermediate **39** (157 mg, 0.297 mmol) was dissolved in
20 DCM (1.9 ml). Then TFA (227 μ l, 2.97 mmol) was added and the reaction mixture was stirred at room temperature for 16 hours. The mixture was basified by 7 M NH₃ in MeOH and all solvents were evaporated. The residue was triturated in water and the formed solid was filtered off and purified by column chromatography. The column was eluted with a gradient starting from 100% DCM to 10% (MeOH/NH₃) and 90% DCM.
25 All pure fractions were evaporated to get the title product **P26** as a white solid (76 mg, 59%).

$m/z = 429.30 (M+H)^+$

MP = 221.07°C

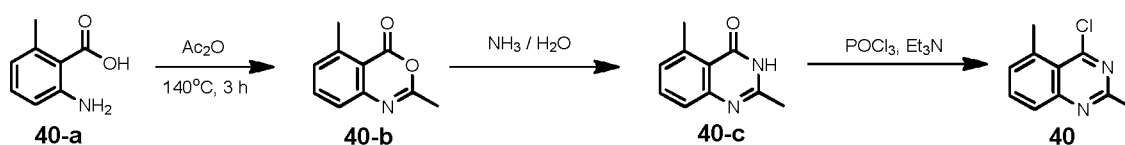
30 ¹H NMR at 150°C (400MHz, DMSO-*d*₆) δ ppm 8.46 (s, 1H), 8.10 (s, 1H), 7.64 - 7.53 (m, 2H), 7.28 (d, *J*=5.9 Hz, 1H), 5.75 - 5.37 (m, 2H), 4.41 - 4.22 (m, 2H), 3.87 - 3.71 (m, 3H), 3.60 - 3.37 (m, 2H), 2.81 (s, 3H), 2.31 - 2.12 (m, 2H), 2.10 (s, 3H), 1.94 - 1.32 (m, 6H)

Synthesis of 1-(2-(1-(2,5-dimethylquinazolin-4-yl)piperidin-2-yl)-6-methyl-pyrazolo[1,5-a]pyrimidin-5-yl)azetidin-3-amine P27



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Synthesis of 4-chloro-2,5-dimethylquinazoline 40



10 Step 1: synthesis of 2,5-dimethyl-4H-benzo[d][1,3]oxazin-4-one 40-b

A solution of 2-amino-6-methylbenzoic acid **40-a** (20.0 g, 132 mmol) in acetic anhydride (100 ml) was stirred at 140°C for 3 hours. The mixture was concentrated under vacuum to give the title intermediate **40-b** (20.0 g, 77.7%).

15 Step 2: synthesis of 2,5-dimethylquinazolin-4(3H)-one 40-c

A mixture of intermediate **40-b** (20.0 g, 114 mmol) and ammonium hydroxide (50 ml) was refluxed overnight. The mixture was cooled to 25°C. The solid was collected by filtration and washed with water. The filter cake was dried under vacuum at 40°C for 1 hour to yield the title intermediate **40-c** (20 g, 90.5%).

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Step 3: synthesis of 4-chloro-2, 5-dimethylquinazoline 40

Triethyl amine (5.05 g, 49.9 mmol) was added to a mixture of intermediate **40-c** (2.90 g, 16.7 mmol) in phosphorus oxychloride (108 g, 709 mmol) at 0°C. The mixture was refluxed for 3 hours. The solvent was evaporated under vacuum. The residue was dissolved in toluene (50 ml) and the solution was added to ice water (50 g). The organic layer was separated and washed successively with water (2 x 50 ml), 10% aqueous NaHCO₃ solution (2 x 50 ml), water (2 x 50 ml), brine (50 ml). The organic layer was dried (MgSO₄), filtered and the filtrate was concentrated under vacuum to yield intermediate **40** (1.91 g, 58.61%).

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¹H NMR (400 MHz, CDCl₃) δ ppm 2.80 (s, 3 H) 3.00 (s, 3H) 7.41 (d, J=7.28 Hz, 1 H) 7.68 - 7.76 (m, 1 H) 7.78 - 7.85 (m, 1 H).

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Step 4: synthesis of *tert*-butyl(1-(2-(1-(2,5-dimethylquinazolin-4-yl)piperidin-2-yl)-6-methylpyrazolo[1,5-a]pyrimidin-5-yl)azetidin-3-yl)carbamate **41**

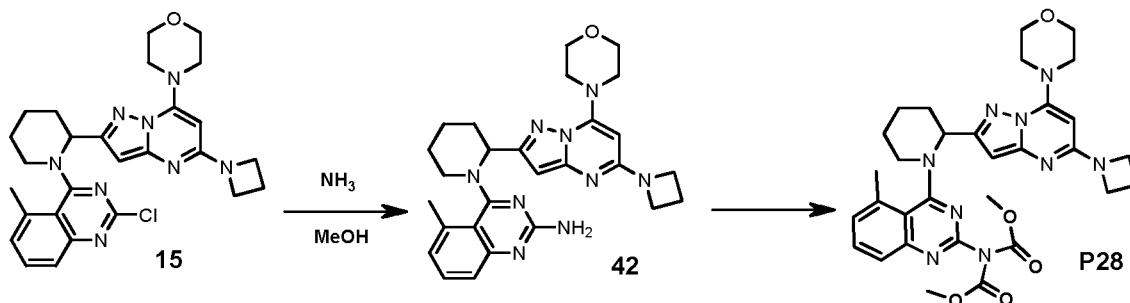
The crude intermediate **38**, (250 mg, 0.647 mmol), intermediate **40** (190 mg, 0.97 mmol) and Hunig's base (368 μ l, 2.135 mmol) were mixed in 2-methoxyethanol (4.36 ml) and heated at 100°C for 3 hours. The reaction mixture was evaporated and the residue was purified by column chromatography by eluting with a gradient starting with 100% DCM to 5% MeOH and 95% DCM. All fractions containing product were evaporated to get a yellow foam of intermediate **41** which was only 55% pure (427 mg). The crude was used as such in step 5.
 $m/z = 543.36$ (M+H)⁺

Step 5: synthesis of 1-(2-(1-(2,5-dimethylquinazolin-4-yl)piperidin-2-yl)-6-methylpyrazolo[1,5-a]pyrimidin-5-yl)azetidin-3-amine **P27**

The crude intermediate **41** (427 mg (only 55% pure), 0.433 mmol) was dissolved in a 4 M solution of HCl in dioxane (21.64 ml, 86.551 mmol) and the reaction mixture was stirred at room temperature for 2 hours. The mixture was diluted with dichloromethane and then basified with saturated Na₂CO₃ solution. The product was extracted with dichloromethane (3x15 mL). The organic layers were dried over Na₂SO₄, filtered and evaporated. The crude was purified by column chromatography. The silica column was eluted with a gradient starting from 100% DCM to 4% (MeOH/NH₃) and 96% DCM. All pure fractions were evaporated. The residue was triturated in DIPE to get the title product **P27** as a white solid (11 mg, 6%).
 $m/z = 443.6$ (M+H)⁺
MP = 176.85°C

¹H NMR at 150°C (400MHz, DMSO-*d*₆) δ ppm 8.10 (s, 1H), 7.56 - 7.43 (m, 2H), 7.19 (d, *J*=6.8 Hz, 1H), 5.74 - 5.44 (m, 2H), 4.39 - 4.25 (m, 2H), 3.83 - 3.71 (m, 3H), 3.53 - 3.38 (m, 2H), 2.79 (s, 3H), 2.45 (s, 3H), 2.26 - 2.13 (m, 2H), 2.11 (s, 3H), 1.94 - 1.38 (m, 6H)

Synthesis of dimethyl (4-{2-[5-(azetidin-1-yl)-7-(morpholin-4-yl)pyrazolo[1,5-*a*]-pyrimidin-2-yl]piperidin-1-yl}-5-methylquinazolin-2-yl)imidodicarbonate **P28**



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Step 1: synthesis of 4-(2-(5-(azetidin-1-yl)-7-(morpholin-4-yl)pyrazolo[1,5-*a*]-pyrimidin-2-yl)piperidin-1-yl)-5-methylquinazolin-2-amine **42**

A suspension of intermediate **15** (1031 mg, 1.902 mmol) in a 7 M solution of NH₃ in MeOH (25 ml, 175 mmol) was heated in a sealed metal reactor at 120°C for 4 days.

10 After evaporation, the residue was purified by HPLC purification. The purified product was dissolved in a mixture of DCM and DIPE, and the solution was evaporated again to get the title intermediate **42** as a white solid (473 mg, 47%).

$m/z = 500.3 (M+H)^+$

MP = 252.24°C

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¹H NMR at 150°C (400MHz, DMSO-*d*₆) δ ppm 7.36 - 7.27 (m, 1H), 7.16 - 7.10 (m, 1H), 6.90 - 6.83 (m, 1H), 5.71 - 5.60 (m, 1H), 5.54 - 5.41 (m, 2H), 5.31 - 5.22 (m, 1H), 5.17 (s, 1H), 3.98 (t, *J*=7.5 Hz, 4H), 3.78 - 3.28 (m, 10H), 2.76 (s, 3H), 2.28 (quin, *J*=7.4 Hz, 2H), 2.21 - 2.07 (m, 2H), 1.90 - 1.44 (m, 4H)

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Step 2: synthesis of dimethyl (4-{2-[5-(azetidin-1-yl)-7-(morpholin-4-yl)pyrazolo[1,5-*a*]-pyrimidin-2-yl]piperidin-1-yl}-5-methylquinazolin-2-yl)imidodicarbonate **P28**

Intermediate **42** (100 mg, 0.188 mmol) was dissolved in DCM (2.21 ml). Then DIPEA (117 μl, 0.678 mmol) and methyl chloroformate (cas = 79-22-1, 29 μl, 0.376 mmol) were added. The reaction mixture was stirred at room temperature for 2 hours. DCM was evaporated and the residue was triturated in water. The suspension was sonicated for 30 minutes and stirred at room temperature overnight. The solid was filtered and washed with water and DIPE to obtain the title compound **P28** as a white powder

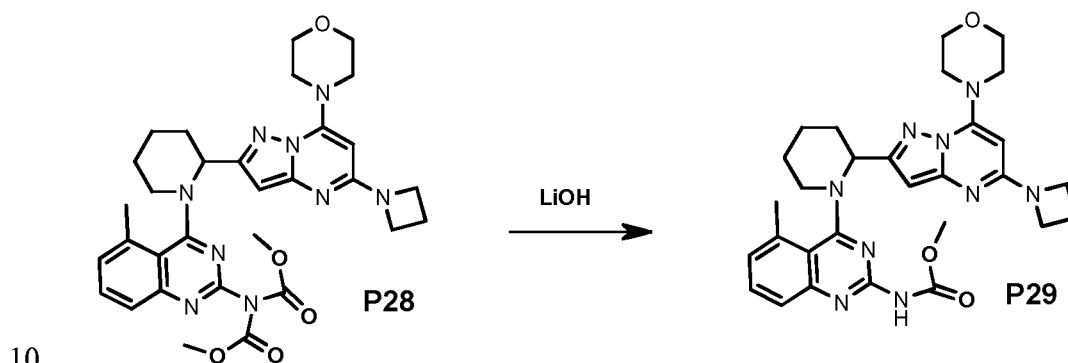
30 (40 mg, 31%).

$m/z = 616.6 (M+H)^+$

MP = 136.62°C

¹H NMR (400MHz, DMSO-*d*₆) δ ppm 7.79 - 7.66 (m, 1H), 7.65 - 7.55 (m, 1H), 7.48 - 7.39 (m, 1H), 6.05 - 4.99 (m, 3H), 4.09 - 3.02 (m, 20H), 2.89 - 2.73 (m, 3H), 2.38 - 1.94 (m, 4H), 1.87 - 1.40 (m, 4H)

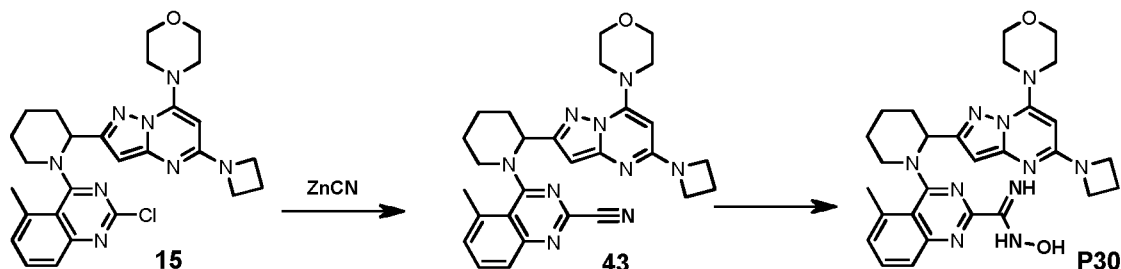
Synthesis of methyl (4-(2-(5-(azetidin-1-yl)-7-morpholinopyrazolo[1,5-a]-pyrimidin-2-yl)piperidin-1-yl)-5-methylquinazolin-2-yl)carbamate **P29**



Compound **P28** (200 mg, 0.279 mmol) was dissolved in MeOH (6.0 ml) and THF (6.0 ml). Then a solution of LiOH (17 mg, 0.722 mmol) in water (4.3 ml) was added. The resulting mixture was stirred at room temperature for 3 hours. Then it was neutralized with 1 M HCl solution and diluted with some water. The suspension was stirred at room temperature overnight. The white solid was collected by filtration and the desired product was dried in vacuum oven overnight to yield a white solid **P29** (71 mg, 43%).

20 ¹H NMR at 80°C (400MHz, DMSO-*d*₆) δ ppm 9.70 - 9.32 (m, 1H), 7.53 (dd, *J*=7.3, 8.1 Hz, 1H), 7.38 (d, *J*=8.1 Hz, 1H), 7.14 (d, *J*=7.0 Hz, 1H), 6.25 - 4.79 (m, 3H), 3.99 (t, *J*=7.4 Hz, 4H), 3.80 - 3.67 (m, 5H), 3.65 (s, 3H), 3.60 - 3.32 (m, 5H), 2.77 (s, 3H), 2.35 - 2.13 (m, 4H), 1.91 - 1.33 (m, 4H)
 25 *m/z* = 558.3 (M+H)⁺

Synthesis of 4-(2-(5-(azetidin-1-yl)-7-morpholinopyrazolo[1,5-a]pyrimidin-2-yl)-piperidin-1-yl)-N-hydroxy-5-methylquinazoline-2-carboximidamide P30



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Step 1: synthesis of 4-(2-(5-(azetidin-1-yl)-7-morpholinopyrazolo[1,5-a]pyrimidin-2-yl)piperidin-1-yl)-5-methylquinazoline-2-carbonitrile **43**

A yellow solution of **15** (2000 mg, 3.689 mmol), zinc cyanide (cas = 557-21-1, 521 mg, 4.433 mmol) and 1,1'-bis(diphenylphosphino)ferrocene (cas = 12150-46-8, 372 mg, 0.671 mmol) in NMP (44.6 ml) was degassed with N₂ during 30 minutes. Then tris(dibenzylideneacetone)dipalladium(0) (cas = 51364-51-3, 327 mg, 0.357 mmol) was added and the reaction vessel was sealed and heated at 90°C for 20 hours. The reaction mixture was quenched with water (176 ml) and a precipitation was formed immediately. This suspension was stirred at room temperature overnight. The solid was filtered and washed with water to get a dark brown solid. The wet brown solid was dissolved in DCM and the remaining water was removed by separation and drying over Na₂SO₄. The residue was recrystallized in ACN and the mixture was stirred overnight. The black crystals were filtered, washed with ACN and MeOH to get purple/grey crystals. The solid was recrystallized again in ACN and stirred for 6 hours. Then the formed purple crystals intermediate **43** was filtered, washed with a little ACN and dried in the vacuum oven (1685 mg, 81%).

$m/z = 510.3 (M+H)^+$

Step 2: synthesis of 4-(2-(5-(azetidin-1-yl)-7-morpholinopyrazolo[1,5-a]pyrimidin-2-yl)piperidin-1-yl)-N-hydroxy-5-methylquinazoline-2-carboximidamide **P30**

To a solution of hydroxylamine hydrochloride (3753 mg, 54 mmol) in water (12.5 ml) was added Na₂CO₃ (625 mg, 5.9 mmol) and the mixture was stirred for 30 minutes. Then a suspension of intermediate **43** (1132 mg, 2 mmol) in EtOH (50 ml) was added at room temperature. The resulting mixture was stirred for 16 hours. Iced water was added. After stirring for 2 hours, the beige solid was filtered and washed with DIPE. The crude was suspended in a mixture of 95% DCM and 5% MeOH and the remaining precipitate was filtered off. The filtrate was purified by column chromatography. The

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- 53 -

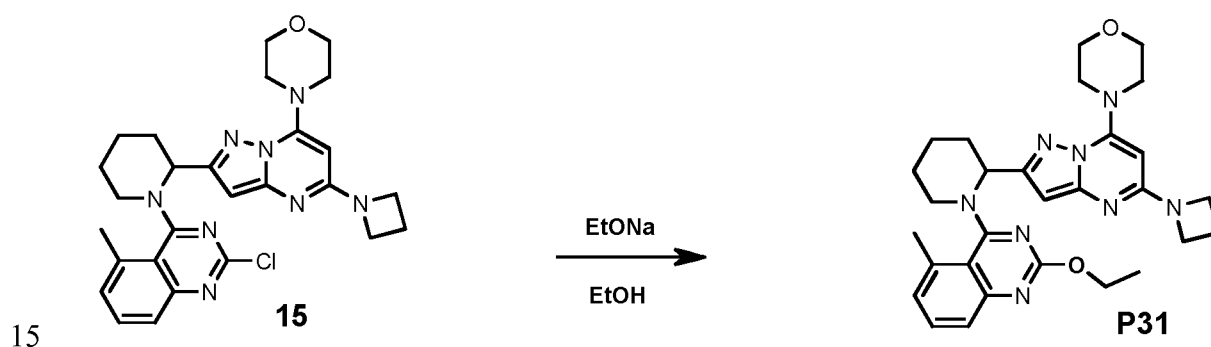
silica column was eluted by a gradient starting with 100% DCM to 10% (MeOH/NH₃) and 90% DCM. After evaporation of the pure fractions we get the desired product **P30** as a beige solid (38 mg, 3%).

$m/z = 543.6$ (M+H)⁺

5 MP = 205.46°C

¹H NMR (400MHz, DMSO-*d*₆) δ ppm 9.82 - 9.46 (m, 1H), 7.71 - 7.56 (m, 2H), 7.32 (dd, *J*=1.4, 6.3 Hz, 1H), 5.97 - 5.40 (m, 4H), 5.20 (s, 1H), 3.98 (t, *J*=7.4 Hz, 4H), 3.81 - 3.29 (m, 10H), 2.84 (s, 3H), 2.28 (quin, *J*=7.4 Hz, 2H), 2.23 - 2.11 (m, 2H), 1.90 - 1.38 (m, 4H)

Synthesis of 4-(5-(azetidin-1-yl)-2-(1-(2-ethoxy-5-methylquinazolin-4-yl)piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-7-yl)morpholine P31



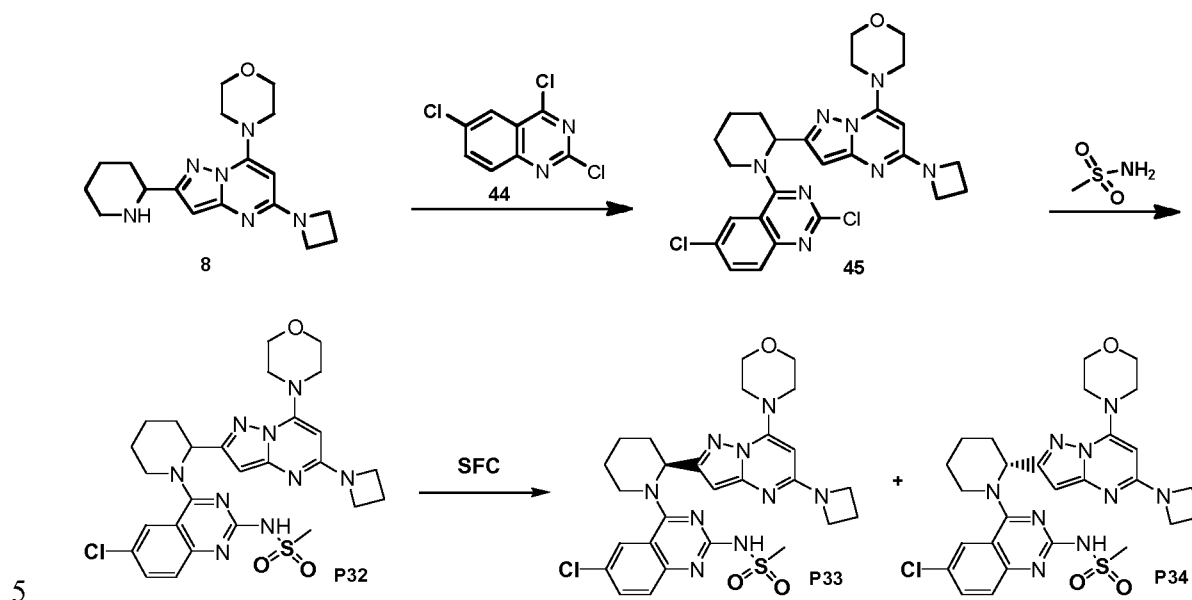
A suspension of intermediate **15** (150 mg, 0.277 mmol) in EtOH (2.39 ml) was treated with NaOEt (21% in EtOH) (525 μl, 1.407 mmol). The sample was flushed with N₂, sealed and heated at 80°C for 48 hours. The reaction mixture was evaporated to dryness and the residue was purified by column chromatography by eluting with a gradient starting from 100% DCM to 10% MeOH and 90% DCM. All fractions containing product were evaporated to get white foam. The foam was recrystallized with DIPE and 5% ACN and the mixture was stirred for 3 days. The white crystalline title compound **P31** was obtained by filtration (46 mg, 29%).

25 $m/z = 529.3$ (M+H)⁺

MP = 186.90°C

¹H NMR (400MHz, DMSO-*d*₆) δ ppm 7.52 - 7.42 (m, 1H), 7.35 (d, *J*=8.1 Hz, 1H), 7.09 (d, *J*=7.0 Hz, 1H), 5.70 - 5.58 (m, 1H), 5.41 - 5.28 (m, 1H), 5.18 (s, 1H), 4.39 - 4.27 (m, 2H), 4.05 - 3.90 (m, 4H), 3.74 - 3.57 (m, 4H), 3.56 - 3.37 (m, 6H), 2.80 (s, 3H), 2.35 - 2.23 (m, 2H), 2.22 - 2.11 (m, 2H), 1.94 - 1.40 (m, 4H), 1.27 (t, *J*=6.9 Hz, 3H)

Synthesis of (S)-N-(4-(2-(5-(azetidin-1-yl)-7-morpholinopyrazolo[1,5-a]pyrimidin-2-yl)piperidin-1-yl)-6-chloroquinazolin-2-yl)methanesulfonamide P32



P33 : $[\alpha]_D^{20} = -209.83^\circ$ (589 nm, c = 0.3765 w/v %, DMF, 20°C)

P34 : $[\alpha]_D^{20} = +192.15^\circ$ (589 nm, c = 0.242 w/v %, DMF, 20°C)

10 Step 1: synthesis of 4-(5-(azetidin-1-yl)-2-(1-(2,6-dichloroquinazolin-4-yl)piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-7-yl)morpholine 45

Intermediate **8** (1341 mg, 2.92 mmol), 2,4,6-trichloroquinazoline **44** (cas = 20028-68-6, 768 mg, 2.83 mmol) and DIPEA (cas = 7087-68-5, 1.24 ml, 7.183 mmol) were mixed in 2-methoxyethanol (14.7 ml) and heated at 60°C for 2 hours. The cooled reaction mixture was added slowly to iced water and the mixture was warmed to room temperature. The formed bright yellow precipitate was successively filtered, washed with water and DIPE and dried in the vacuum oven. The product was purified by column chromatography by eluting with a gradient starting with 100% DCM to 5% MeOH and 95% DCM. After evaporation of the fractions a yellow foam was isolated as intermediate **45** (781 mg, 49%).

¹H NMR (400MHz, DMSO-*d*₆) δ ppm 8.12 (d, *J*=2.2 Hz, 1H), 7.85 (dd, *J*=2.2, 9.0 Hz, 1H), 7.74 (d, *J*=8.8 Hz, 1H), 6.07 (s, 1H), 5.97 - 5.88 (m, 1H), 5.35 (s, 1H), 4.34 - 4.20 (m, 1H), 4.02 (t, *J*=7.5 Hz, 4H), 3.77 - 3.60 (m, 4H), 3.59 - 3.34 (m, 5H), 2.42 - 2.22 (m, 3H), 2.09 - 1.93 (m, 1H), 1.79 - 1.59 (m, 4H)

m/z = 539.3 (M+H)⁺

Step 2: synthesis of N-(4-(2-(5-(azetidin-1-yl)-7-morpholinopyrazolo[1,5-a]pyrimidin-2-yl)piperidin-1-yl)-6-chloroquinazolin-2-yl)methanesulfonamide **P32**

The intermediate **45** (750 mg, 1.39 mmol), methane sulfonamide (264 mg, 2.781 mmol), cesium carbonate (cas = 534-17-8, 1132 mg, 3.476 mmol), 4,5-bis-(diphenylphosphino)-9,9-dimethylxanthene (cas = 161265-03-8, 241 mg, 0.417 mmol) and palladium(II)acetate (cas = 3375-31-3, 94 mg, 0.417 mmol) were mixed in dioxane (10 ml). The suspension was degassed with N₂ for 10 minutes. The reaction vessel was sealed and then heated at 110°C for 30 minutes in a μ -wave oven. The reaction mixture was filtered and the filtrate was evaporated to dryness to be purified by column chromatography by eluting with a gradient starting with 100% DCM to 10% (MeOH/NH₃) and 90% DCM. After evaporation of the concerning fractions we get the title product **P32** as a brown solid (507 mg, 59%).

$m/z = 598.2$ (M+H)⁺

¹H NMR (400MHz, DMSO-*d*₆) δ ppm 12.06 (br. s., 1H), 8.13 - 7.91 (m, 1H), 7.76 (dd, $J=2.2, 9.0$ Hz, 1H), 7.41 (d, $J=8.8$ Hz, 1H), 6.38 - 5.80 (m, 2H), 5.37 (s, 1H), 4.56 - 4.30 (m, 1H), 4.03 (t, $J=7.5$ Hz, 4H), 3.79 - 3.64 (m, 4H), 3.60 - 3.35 (m, 5H), 3.11 - 2.87 (m, 3H), 2.44 - 2.25 (m, 3H), 2.09 - 1.89 (m, 1H), 1.82 - 1.60 (m, 4H)

Step 3: synthesis of (S)-N-(4-(2-(5-(azetidin-1-yl)-7-morpholinopyrazolo[1,5-a]-pyrimidin-2-yl)piperidin-1-yl)-6-chloroquinazolin-2-yl)methanesulfonamide **P33** and (R)-N-(4-(2-(5-(azetidin-1-yl)-7-morpholinopyrazolo[1,5-a]-pyrimidin-2-yl)piperidin-1-yl)-6-chloroquinazolin-2-yl)methanesulfonamide **P34**

Compound **P32** (400 mg, 0.669 mmol) was purified by SFC to obtain the title compound, pure enantiomer **P33**, as a yellowish solid (173 mg, 43%) and pure enantiomer **P34**, as a yellowish solid (187 mg, 46%).

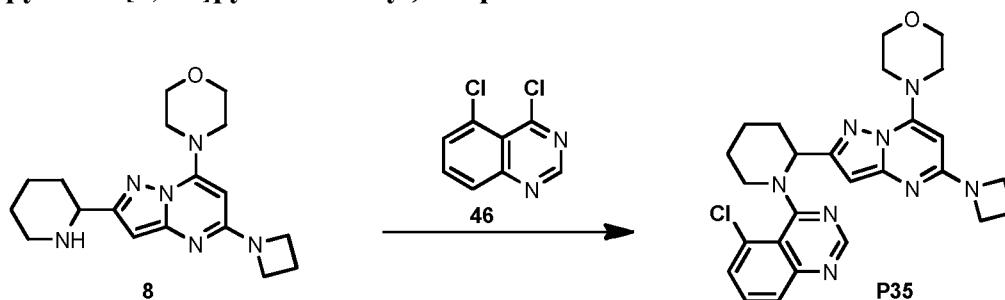
P33, SFC: 100% pure, $R_t = 1.94$ min

$m/z = 598.2$ (M+H)⁺

P34, SFC: 98.65% Pure, 1.35% $R_t = 1.89$ min and 98.65% $R_t = 2.74$ min.

$m/z = 598.2$ (M+H)⁺

Synthesis of 4-(5-(azetidin-1-yl)-2-(1-(5-chloroquinazolin-4-yl)piperidin-2-yl)-pyrazolo[1,5-a]pyrimidin-7-yl)morpholine P35

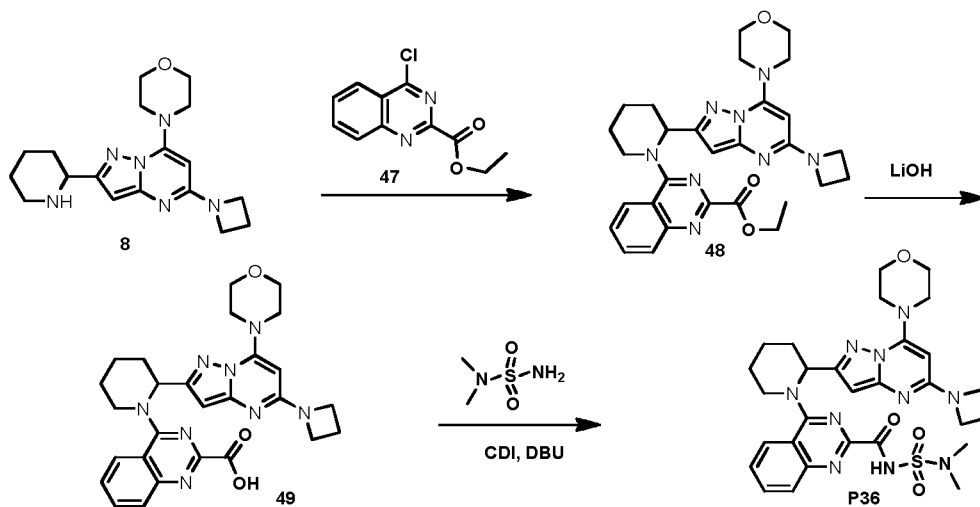


- 5 To a solution of intermediate **8** (300 mg, 0.63 mmol) in 2-methoxyethanol (20 mL) was added 4,5-dichloroquinazoline **46** (CAS: 2148-55-2, 1.1 eq., 139 mg, 0.7 mmol) and DIPEA (3 eq., 0.33 mL, 1.9 mmol). The solution was heated to 80°C for 16 hours. The solution was concentrated in vacuum, extracted with DCM and washed with water. The combined organics were collected and dried with MgSO₄, filtered off and concentrated
- 10 in vacuum. The crude was purified by column chromatography eluting with a gradient starting from 0 % to 10 % MeOH in DCM. After evaporation compound **P35** (190 mg, 57 %) was obtained.

LCMS $m/z = 505 (M+H)^+$

- 15 ¹H NMR (400 MHz, 420 K, DMSO-*d*₆) δ ppm 1.48 - 1.90 (m, 4 H) 2.22 - 2.35 (m, 4 H) 3.43 - 3.56 (m, 5 H) 3.64 - 3.76 (m, 4 H) 3.84 (d, $J=13.89$ Hz, 1 H) 3.93 - 4.04 (m, 4 H) 5.18 (s, 1 H) 5.62 (s, 1 H) 5.66 (br. s., 1 H) 7.51 (dd, $J=7.16$, 1.61 Hz, 1 H) 7.61 - 7.66 (m, 1 H) 7.67 - 7.70 (m, 1 H) 8.45 (s, 1 H)

- 20 **Synthesis of 4-(2-(5-(azetidin-1-yl)-7-morpholinopyrazolo[1,5-a]pyrimidin-2-yl)-piperidin-1-yl)-N-(N,N-dimethylsulfamoyl)quinazoline-2-carboxamide P36**



Step 1: synthesis of ethyl 4-(2-(5-(azetidin-1-yl)-7-morpholinopyrazolo[1,5-a]-pyrimidin-2-yl)piperidin-1-yl)quinazoline-2-carboxylate **48**

To a solution of intermediate **8** (1.2 g, 3.4 mmol) in 2-methoxyethanol (40 mL) was added ethyl 4-chloroquinazoline-2-carboxylate **47** (0.97 g, 4.06 mmol) and DIPEA (3 eq., 1.75 mL, 10 mmol). The solution was stirred at 80°C for 48 hours. After cooling to room temperature the solution was concentrated in vacuum and purified by column chromatography eluting with a gradient starting from 0 % to 10 % MeOH in DCM to give intermediate **48** (998 mg, 75 % pure, 40 % yield) which was used as such into the next step.

LCMS $m/z = 543 (M+H)^+$

Step 2: synthesis of 4-(2-(5-(azetidin-1-yl)-7-morpholinopyrazolo[1,5-a]pyrimidin-2-yl)piperidin-1-yl)quinazoline-2-carboxylic acid **49**

To a solution of intermediate **48** (998 mg, 75% pure, 1.3 mmol) in 25 ml THF/water (3/1), was added LiOH (3 eq., 93 mg, 3.9 mmol). The solution was stirred at room temperature during 16 hours. The solution was then adjusted to pH = 6 and the mixture was concentrated *in vacuum* giving intermediate **49** (828 mg, 76% pure, 94 % yield), which was used as such in the next step.

LCMS $m/z = 515 (M+H)^+$

Step 3: synthesis of 4-(2-(5-(azetidin-1-yl)-7-morpholinopyrazolo[1,5-a]pyrimidin-2-yl)piperidin-1-yl)-N-(N,N-dimethylsulfamoyl)quinazoline-2-carboxamide **P36**

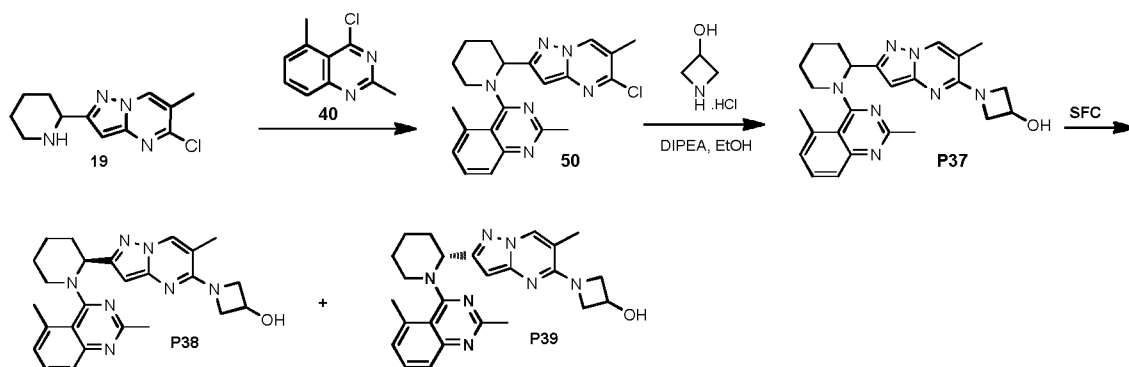
To a solution intermediate **49** (300 mg, 0.37 mmol) was added CDI (120 mg, 0.73 mmol) in 3 mL THF/DMF (1/1) solution. The solution was heated to 50°C and stirred for one hour. *N,N*-Dimethylsulfamide (136 mg, 1.1 mmol) and DBU (0.165 mL, 1.1 mmol) was added to the solution and stirred for an additional hour at 50°C. The solution was extracted with DCM and washed with water. The combined organics were dried with MgSO₄ and concentrated in vacuum. The crude was further purified by column chromatography eluting with a gradient starting from 0 % to 10 % MeOH in DCM. After evaporation the crude was taken up in water and the solid filtered off and dried into the oven to yield compound **P36** (53 mg, 22%) as a white solid.

LCMS $m/z = 621 (M+H)^+$

¹H NMR (400 MHz, 360 K, DMSO-*d*₆) δ ppm 1.69 - 1.81 (m, 4 H) 2.02 - 2.13 (m, 1 H) 2.26 - 2.35 (m, 3 H) 2.35 - 2.42 (m, 1 H) 2.90 (s, 6 H) 3.49 - 3.57 (m, 5 H) 3.62 - 3.72 (m, 4 H) 4.01 (t, *J*=7.48 Hz, 4 H) 4.37 (d, *J*=13.42 Hz, 1 H) 5.27 (s, 1 H) 5.94 (s, 1 H)

6.05 (br. s, 1 H) 7.57 - 7.61 (m, 1 H) 7.83 - 7.88 (m, 1 H) 7.93 (dd, $J=8.36, 1.10$ Hz, 1 H) 8.15 (d, $J=8.58$ Hz, 1 H)

Synthesis of 1-(2-(1-(2, 5-dimethylquinazolin-4-yl)piperidin-2-yl)-6-methyl-pyrazolo[1,5-a]pyrimidin-5-yl)azetidin-3-ol P37



Step 1: synthesis of 4-(2-(5-chloro-6-methylpyrazolo[1,5-a]pyrimidin-2-yl)piperidin-1-yl)-2,5-dimethylquinazoline **50**

To a solution of intermediate **19** (200 mg, 0.58 mmol) in 2-methoxyethanol (40 mL) was added 4-chloro-2, 5-dimethyl-quinazoline **40** (1 eq., 114 mg, 0.58 mmol, CAS nr. 147006-57-3) and DIPEA (3 eq., 0.3 mL, 1.7 mmol). The solution was heated to 80°C for 16 hours. After cooling to room temperature the solution was concentrated in vacuum and purified by column chromatography eluting with a gradient starting from 0 % to 10 % MeOH in DCM. After evaporation the crude was triturated with diethyl ether to afford intermediate **50** (140 mg, 90 % pure, 53% yield). The solid was used as such in the next step.

LCMS $m/z = 407$ ($M+H$)⁺

20

Step 2: synthesis of 1-(2-(1-(2,5-dimethylquinazolin-4-yl)piperidin-2-yl)-6-methyl-pyrazolo[1,5-a]pyrimidin-5-yl)azetidin-3-ol **P37**

Intermediate **50** (140 mg, 0.31 mmol) was dissolved in 5 mL EtOH at room temperature. Then azetidin-3-ol hydrochloride (68 mg, 0.62 mmol) and DIPEA (0.16 mL, 0.92 mmol) were added. The resulting solution was refluxed for 16 hours. The mixture was then concentrated in vacuum and taken up in water/EtOH (3/1) the resulting solid was filtered off and dried into the oven to give compound **P37** (65 mg, 48 %).

LCMS $m/z = 444$ ($M+H$)⁺

30

- 59 -

¹H NMR (400 MHz, 420 K, DMSO-*d*₆) δ ppm 1.41 - 1.70 (m, 3 H) 1.76 - 1.89 (m, 1 H) 2.12 (d, *J*=0.81 Hz, 3 H) 2.23 - 2.33 (m, 2 H) 2.49 (s, 3 H) 2.75 (s, 3 H) 3.53 - 3.64 (m, 2 H) 3.94 (dd, *J*=9.69, 4.04 Hz, 2 H) 4.36 (t, *J*=8.10 Hz, 2 H) 4.48 - 4.56 (m, 1 H) 5.74 (br. s., 1 H) 5.79 (br. s., 1 H) 7.27 (d, *J*=7.27 Hz, 1 H) 7.43 - 7.54 (m, 1 H) 7.55 - 7.63 (m, 1 H) 8.12 (s, 1 H)

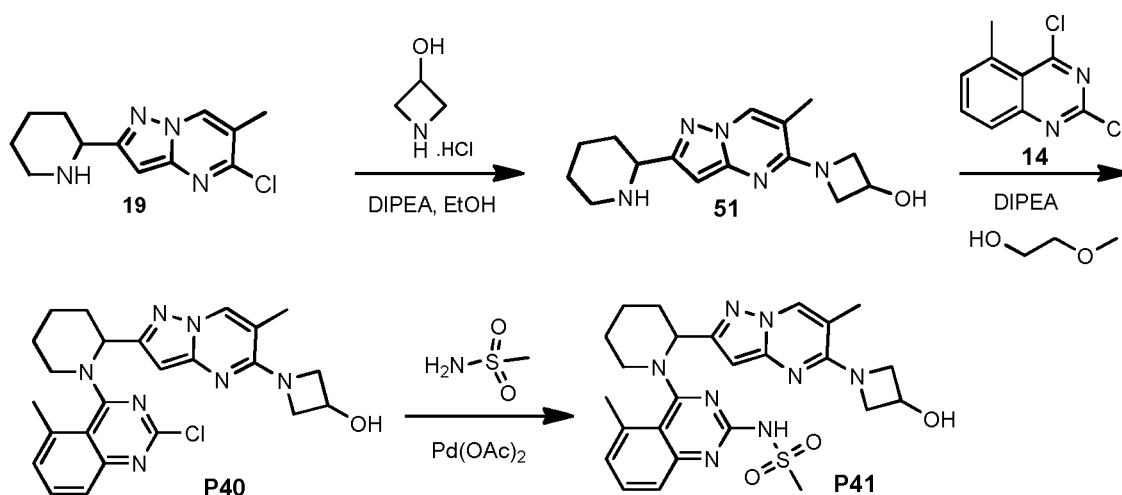
Compound **P37** (400 mg, 0.669 mmol) was purified by SFC to obtain the title compound, pure enantiomer **P38** (44 mg) :

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.47 - 1.77 (m, 4 H) 1.86 - 2.00 (m, 1 H) 2.13 (d, *J*=0.66 Hz, 3 H) 2.25 - 2.43 (m, 4 H) 2.50 (s, 3 H) 3.32 - 3.46 (m, 1 H) 3.92 (dd, *J*=9.79, 4.73 Hz, 2 H) 4.20 (d, *J*=12.76 Hz, 1 H) 4.28 - 4.42 (m, 2 H) 4.43 - 4.57 (m, 1 H) 5.65 (d, *J*=6.16 Hz, 1 H) 5.78 (br. s., 1 H) 5.96 (s, 1 H) 7.56 (dd, *J*=8.80, 1.76 Hz, 1 H) 7.60 (d, *J*=8.36 Hz, 1 H) 7.76 (s, 1 H) 8.45 (s, 1 H)

and pure enantiomer **P39** (55 mg) :

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.45 - 1.77 (m, 4 H) 1.89 - 2.03 (m, 1 H) 2.15 (s, 3 H) 2.28 - 2.43 (m, 4 H) 2.51 (br. s., 3 H) 3.35 - 3.47 (m, 1 H) 3.94 (dd, *J*=9.79, 4.73 Hz, 2 H) 4.23 (d, *J*=12.76 Hz, 1 H) 4.38 (t, *J*=8.80 Hz, 2 H) 4.45 - 4.62 (m, 1 H) 5.62 (br. s., 1 H) 5.83 (br. s., 1 H) 5.98 (s, 1 H) 7.57 (dd, *J*=8.58, 1.32 Hz, 1 H) 7.62 (d, *J*=8.58 Hz, 1 H) 7.78 (s, 1 H) 8.46 (s, 1 H).

Synthesis of N-(4-(2-(5-(3-hydroxyazetidin-1-yl)-6-methylpyrazolo[1,5-a]-pyrimidin-2-yl)piperidin-1-yl)-5-methylquinazolin-2-yl)methanesulfonamide **P41**



Step 1: synthesis of 1-(6-methyl-2-(piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-azetidin-3-ol **51**

To a solution of the intermediate **19** (4.1 g, 11.9 mmol) in EtOH (50 mL) was added azetidin-3-ol hydrochloride (1.04 g, 14.3 mmol, 1.2 eq.) and DIPEA (10.2 mL, 60 mmol, 5 eq.) and the solution was refluxed overnight. After cooling to ambient temperature, the solution was concentrated in vacuum. The crude was dissolved in DCM/MeOH (9/1) and the salts filtered off. The filtrate was concentrated in vacuum and purified via column chromatography (DCM/NH₃(MeOH 7N): 9/1) to obtain intermediate **51** (1.9 g, 56%).

LCMS $m/z = 288$ (M+H)⁺

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.56 - 1.84 (m, 5 H) 1.96 - 2.07 (m, 1 H) 2.16 (d, $J=0.88$ Hz, 3 H) 2.82 - 2.96 (m, 1 H) 3.16 - 3.23 (m, 1 H) 3.95 (dd, $J=9.57, 4.95$ Hz, 2 H) 4.12 (dd, $J=11.11, 2.97$ Hz, 1 H) 4.34 - 4.44 (m, 2 H) 4.48 - 4.58 (m, 1 H) 6.16 (s, 1 H) 8.40 (s, 1 H).

Step 2: synthesis of 1-(2-(1-(2-chloro-5-methylquinazolin-4-yl)piperidin-2-yl)-6-methylpyrazolo[1,5-a]pyrimidin-5-yl)azetidin-3-ol **P40**

To a solution of intermediate **51** (500 mg, 1.74 mmol) in 2-methoxyethanol (30 mL) was added 2, 4-dichloro-5-methylquinazoline **14** (1.2 eq., 808 mg, 2.08 mmol) and DIPEA (3 eq., 0.9 mL, 5.2 mmol). The solution was stirred at 50°C during 2 hours and the mixture was concentrated in vacuum and extracted with DCM and washed with water. The combined organics were dried with MgSO₄ and concentrated in vacuum. The crude was further purified on HPLC to give the title product **P40** (130 mg, 16%).

LCMS $m/z = 464$ (M+H)⁺

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.39 - 1.55 (m, 1 H) 1.55 - 1.70 (m, 2 H) 1.73 - 1.89 (m, 1 H) 2.05 - 2.20 (m, 4 H) 2.23 - 2.32 (m, 1 H) 3.43 - 3.70 (m, 2 H) 3.89 - 3.98 (m, 2 H) 4.32 - 4.41 (m, 2 H) 4.47 - 4.56 (m, 1 H) 5.06 - 5.18 (m, 1 H) 5.59 - 5.68 (m, 1 H) 5.68 - 5.79 (m, 1 H) 7.25 - 7.33 (m, 1 H) 7.44 - 7.52 (m, 1 H) 7.58 - 7.66 (m, 1 H) 8.11 - 8.19 (m, 1 H)

Step 3: synthesis of N-(4-(2-(5-(3-hydroxyazetidin-1-yl)-6-methylpyrazolo[1,5-a]pyrimidin-2-yl)piperidin-1-yl)-5-methylquinazolin-2-yl)methanesulfonamide **P41**

To a solution of compound **P40** (130 mg, 0.28 mmol) in 1,4-dioxane (5 mL) was added

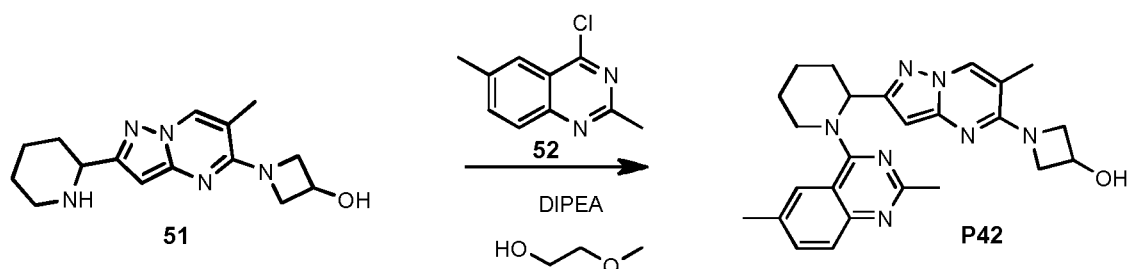
- 61 -

methanesulfonamide (2 eq., 53 mg, 0.56 mmol), cesium carbonate (2.5 eq., 0.7 mmol, 228 mg), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.3 eq., 48.6 mg, 0.084 mmol) and Pd(OAc)₂ (0.3 eq., 18.87 mg, 0.084 mmol) in a sealed tube. The mixture was heated to 120°C during 5 minutes in a microwave. The solution was filtered over dicalite, washed with dichloromethane and concentrated *in vacuo*. The crude was further purified by HPLC to give compound **P41** (42 mg, 30 %) as a white powder.

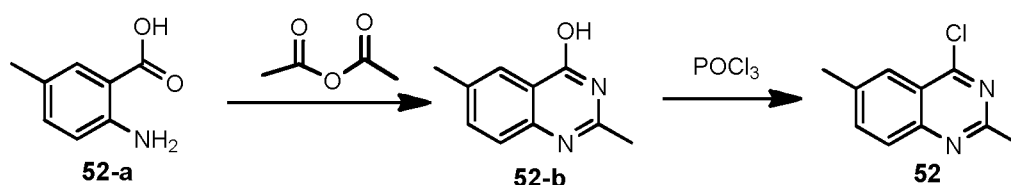
LCMS $m/z = 523 (M+H)^+$

¹H NMR (400 MHz, 420 K, DMSO-d₆) δ ppm 1.46 (m, J=9.46 Hz, 1 H) 1.62 (m, 2 H) 1.80 (m, 1 H) 2.07 - 2.18 (m, 4 H) 2.24 - 2.36 (m, 1 H) 2.63 (s, 3 H) 2.97 (s, 3 H) 3.57 (m, 1 H) 3.68 - 3.80 (m, 1 H) 3.90 - 3.98 (m, 2 H) 4.33 - 4.41 (m, 2 H) 4.45 - 4.59 (m, 1 H) 5.05 (br. s., 1 H) 5.82 (br. s., 1 H) 5.94 (br. s., 1 H) 7.05 (d, J=7.04 Hz, 1 H) 7.22 (d, J=8.14 Hz, 1 H) 7.47 (t, J=7.05 Hz, 1 H) 8.16 (s, 1 H) 9.88 - 11.04 (m, 1 H).

Synthesis of 1-(2-(1-(2,6-dimethylquinazolin-4-yl)piperidin-2-yl)-6-methylpyrazolo[1,5-a]pyrimidin-5-yl)azetidin-3-ol **P42**



Synthesis of 4-chloro-2,6-dimethylquinazoline **52**



Step 1: synthesis of 2,6-dimethylquinazolin-4-ol **52-b**

2-amino-5-methylbenzoic acid **52-a** (8 g, 53 mmol) was dissolved in acetic anhydride (80 mL) and heated at 130°C for 2 hours. The solution was then concentrated in vacuum to give the solid intermediate which was further dissolved in a solution of EtOH (100 mL) and NH₃.H₂O (80 mL) and heated to 80°C. After 48 hours, the

solution was cooled and the solid filtered off and dried in the oven to give 2,6-dimethylquinazolin-4-ol **52-b** (6.3 g, 70%).

LCMS $m/z = 175$ (M+H)⁺

- 5 ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.32 (s, 3 H) 2.41 (s, 3 H) 7.46 (d, $J=8.36$ Hz, 1 H) 7.56 (dd, $J=8.14, 1.98$ Hz, 1 H) 7.76 - 7.92 (m, 1 H) 11.91 (br. s, 1 H)

Step 2: synthesis of 4-chloro-2,6-dimethylquinazoline **52**

- To a solution of 2,6-dimethylquinazolin-4-ol **52-b** (500 mg, 2.87 mmol) in Toluene
10 (10 mL) was added DIPEA (0.989 mL, 5.74 mmol, 2 eq.) and POCl₃ (0.4 mL, 4.3 mmol, 1.5 eq.). The solution was heated to 80°C and stirred for 2 hours. The mixture was concentrated in vacuum and diluted with dichloromethane then washed with a saturated water solution of NaHCO₃. The combined organics were dried with MgSO₄, concentrated in vacuum and purified on column chromatography
15 (Heptane/EtOAc: 1/1) to give intermediate **52** (300 mg, 90% purity, 48%).
LCMS $m/z = 193$ (M+H)⁺

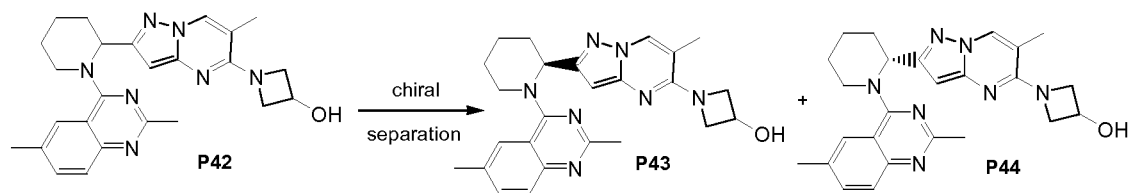
Step 3: synthesis of 1-(2-(1-(2,6-dimethylquinazolin-4-yl)piperidin-2-yl)-6-methylpyrazolo[1,5-a]pyrimidin-5-yl)azetidin-3-ol **P42**

- 20 Intermediate **51** (240 mg, 0.83 mmol) was added to a solution of 4-chloro-2,6-dimethylquinazoline **52** (1.7 eq., 300 mg, 1.4 mmol) and DIPEA (3 eq. 0.43 mL, 2.5 mmol) in 2-methoxyethanol (5 mL). The solution was heated at 140°C and stirred for 16 hours. After cooling to ambient temperature the mixture was extracted with DCM and washed with water. The combined organics were collected and dried with
25 MgSO₄, filtered off and concentrated in vacuum. The crude was further purified by HPLC to give compound **P42** (167 mg, 45 %).
LCMS $m/z = 444$ (M+H)⁺

- 30 ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.56 - 1.75 (m, 4 H) 1.88 - 2.02 (m, 2 H) 2.14 (s, 3 H) 2.34 (s, 1 H) 2.39 (s, 3 H) 3.94 (dd, $J=9.46, 5.28$ Hz, 2 H) 4.20 (d, $J=12.76$ Hz, 1 H) 4.37 (t, $J=8.10$ Hz, 2 H) 4.51 (br. s, 1 H) 5.54 - 5.72 (m, 1 H) 5.81 (br. s, 1 H) 5.96 (s, 1 H) 7.53 - 7.63 (m, 2 H) 7.77 (s, 1 H) 8.45 (s, 1 H)

- 35 **Synthesis of (S)-1-(2-(1-(2,6-dimethylquinazolin-4-yl)piperidin-2-yl)-6-methylpyrazolo[1,5-a]pyrimidin-5-yl)azetidin-3-ol **P43** and (R)-1-(2-(1-(2,6-dimethylquinazolin-4-yl)piperidin-2-yl)-6-methylpyrazolo[1,5-a]pyrimidin-5-yl)azetidin-3-ol **P44****

- 63 -



A further purification was performed via Prep SFC (stationary phase: chiralpak Diacel
 5 AS 20 x 250 mm, Mobile phase: CO₂, EtOH with 0.2% iPrNH₂) giving both relative
 enantiomers :

P43 :

LCMS $m/z = 444$ (M+H)⁺

10

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.68 (s, 4 H) 1.89 - 2.03 (m, 1 H) 2.15 (s, 3 H)
 2.28 - 2.43 (m, 4 H) 2.51 (br. s., 3 H) 3.35 - 3.47 (m, 1 H) 3.94 (dd, $J=9.79$, 4.73 Hz,
 2 H) 4.23 (d, $J=12.76$ Hz, 1 H) 4.38 (t, $J=8.80$ Hz, 2 H) 4.45 - 4.62 (m, 1 H) 5.62 (br. s.,
 1 H) 5.83 (br. s., 1 H) 5.98 (s, 1 H) 7.57 (dd, $J=8.58$, 1.32 Hz, 1 H) 7.62 (d, $J=8.58$ Hz,
 15 1 H) 7.78 (s, 1 H) 8.46 (s, 1 H)

P44 :

LCMS $m/z = 444$ (M+H)⁺

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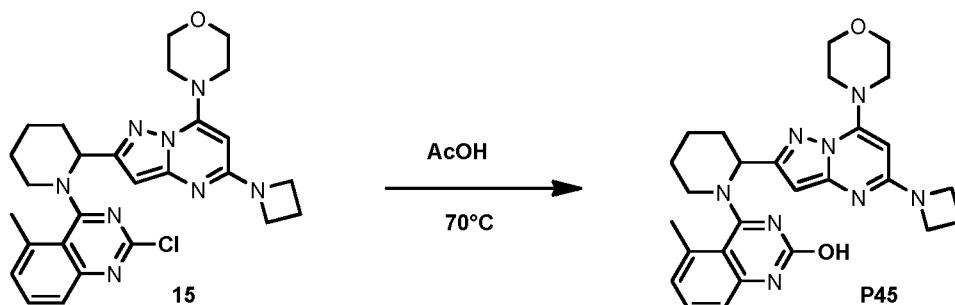
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.47 - 1.77 (m, 4 H) 1.86 - 2.00 (m, 1 H) 2.13
 (d, $J=0.66$ Hz, 3 H) 2.25 - 2.43 (m, 4 H) 2.50 (s, 3 H) 3.32 - 3.46 (m, 1 H) 3.92 (dd,
 $J=9.79$, 4.73 Hz, 2 H) 4.20 (d, $J=12.76$ Hz, 1 H) 4.28 - 4.42 (m, 2 H) 4.43 - 4.57 (m,
 1 H) 5.65 (d, $J=6.16$ Hz, 1 H) 5.78 (br. s., 1 H) 5.96 (s, 1 H) 7.56 (dd, $J=8.80$, 1.76 Hz,
 1 H) 7.60 (d, $J=8.36$ Hz, 1 H) 7.76 (s, 1 H) 8.45 (s, 1 H)

25

P43 : $[\alpha]_D^{20} = +295.23^\circ$ (589 nm, $c = 0.377$ w/v %, DMF, 20°C)

P44 : $[\alpha]_D^{20} = -269.05^\circ$ (589 nm, $c = 0.378$ w/v %, DMF, 20°C)

Synthesis of 4-(2-(5-(azetidin-1-yl)-7-morpholinopyrazolo[1,5-a]pyrimidin-2-yl)-piperidin-1-yl)-5-methylquinazolin-2-ol P45



5

A solution of intermediate **15** (100 mg, 0.193 mmol) in acetic acid (2 mL) was warmed to 70°C for 3 hours. The reaction mixture was allowed to cool down to room temperature and water was added. The resulting mixture was diluted with dichloromethane and washed with aqueous solution of sodium bicarbonate. The organic layers were dried over MgSO₄ and the solvent was evaporated to yield product **P45** (80 mg, 80%).

10

$m/z = 501.6$ (M+H)⁺

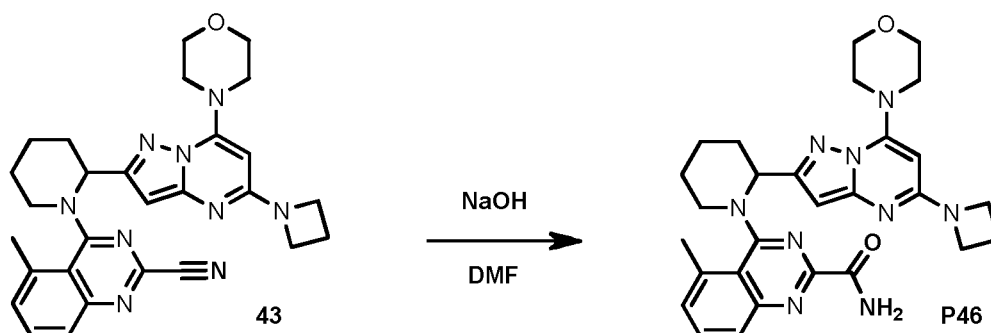
MP = 223.59°C

15

¹H NMR at 100°C (400MHz, DMSO-*d*₆) δ ppm 10.31 (br. s., 1H), 7.35 (t, *J*=7.7 Hz, 1H), 7.02 (d, *J*=8.1 Hz, 1H), 6.90 (d, *J*=7.5 Hz, 1H), 6.24 - 5.34 (m, 2H), 5.24 (s, 1H), 4.10 - 3.43 (m, 14H), 2.65 (s, 3H), 2.37 - 2.06 (m, 4H), 1.89 - 1.39 (m, 4H)

Synthesis of 4-(2-(5-(azetidin-1-yl)-7-morpholinopyrazolo[1,5-a]pyrimidin-2-yl)-piperidin-1-yl)-5-methylquinazoline-2-carboxamide P46

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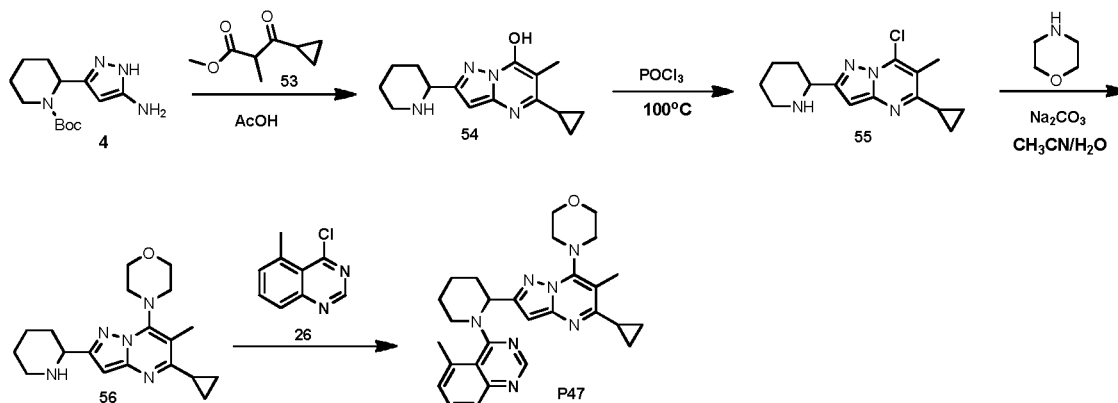
To a solution of intermediate **43** (100 mg, 0.17 mmol) in DMF (5 mL) was added 10 mL NaOH (1M in H₂O) in a sealed tube. The solution was heated to 130°C for

10 minutes in a microwave. The solution was then adjusted to pH = 6-7 with 1 molar aqueous solution of hydrochloric acid. The solution was further extracted with DCM, and the combined organics were washed with a saturated NaHCO₃ solution and brine. The organic layer was further dried with MgSO₄ and concentrated *in vacuo*. The resulting material was purified on HPLC to compound **P46** (68 mg, 73 %)

LCMS $m/z = 528 (M+H)^+$

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.14 - 1.87 (m, 4 H) 1.98 - 2.41 (m, 4 H) 2.84 (s, 3 H) 3.19 - 3.27 (m, 2 H) 3.40 - 3.83 (m, 7 H) 3.85 - 4.28 (m, 5 H) 5.12 - 5.44 (m, 2 H) 5.87 (s, 1 H) 7.38 - 7.50 (m, 1 H) 7.55 - 7.81 (m, 3 H) 7.89 - 8.03 (m, 1 H).

Synthesis of 4-(5-cyclopropyl-6-methyl-2-(1-(5-methylquinazolin-4-yl)piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-7-yl)morpholine **P47**



Step 1: synthesis of 5-cyclopropyl-6-methyl-2-(piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-7-ol **54**

To a solution of intermediate **4** (16 g, 60 mmol) in acetic acid (100 mL) was added methyl 3-cyclopropyl-2-methyl-3-oxopropanoate **53** (30 g, 180 mmol). The resulting mixture was stirred at 100°C overnight.

The resulting mixture was concentrated under vacuum and the residue (46 g, 98%) was used as such in the next step.

Step 2: synthesis of 7-chloro-5-cyclopropyl-6-methyl-2-(piperidin-2-yl)pyrazolo[1,5-a]pyrimidine **55**

The mixture of intermediate **54** (45 g, 79 mmol) and phosphoryl trichloride (220 g) was stirred at 110°C for one hour. The solvent was removed and the residue was dissolved in ice watered solution and basified by addition of sodium carbonate (19.8 g, 238 mmol). This solution was used as such in the next step.

Step 3: synthesis of 4-(5-cyclopropyl-6-methyl-2-(piperidin-2-yl)pyrazolo[1,5-a]-pyrimidin-7-yl)morpholine **56**

To the solution of intermediate **55** acetonitrile (250 mL) and morpholine (20.7 g, 238 mmol) were added. The resulting mixture was refluxed overnight. The reaction mixture was allowed to cool down to room temperature and the solvent was removed under vacuum. The resulting water solution was extracted with dichloromethane and the organic layers were dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography using dichloromethane and methanol as eluent.

Intermediate **56** (2 g, 7%) was isolated.

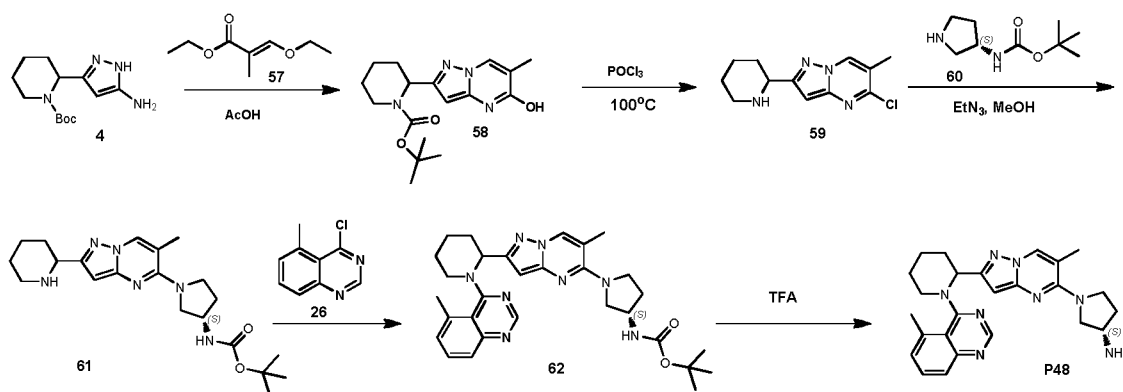
Step 4: synthesis of 4-(5-cyclopropyl-6-methyl-2-(1-(5-methylquinazolin-4-yl)-piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-7-yl)morpholine **P47**

To a solution intermediate **56** (200 mg, 0.56 mmol) in 5 mL 2-methoxyethanol was added 4-chloro-5-methyl-quinazoline **26** (1.2 eq., 126 mg, 0.67 mmol) and DIPEA (3 eq., 0.289 mL, 1.68 mmol). The solution was stirred at 80°C for 48 hours. After cooling to room temperature the solution was concentrated in vacuo and purified on HPLC to give the title product **P47** (110 mg, 41 %).

LCMS $m/z = 484$ (M+H)⁺

¹H NMR (400 MHz, 420 K, DMSO-*d*₆) δ ppm 0.90 - 1.11 (m, 4 H) 1.50 - 1.61 (m, 1 H) 1.61 - 1.76 (m, 2 H) 1.80 - 1.92 (m, 1 H) 2.07 - 2.18 (m, 1 H) 2.20 - 2.32 (m, 2 H) 2.35 (s, 3 H) 2.84 (s, 3 H) 3.28 - 3.40 (m, 4 H) 3.47 - 3.65 (m, 2 H) 3.66 - 3.78 (m, 4 H) 5.56 - 5.67 (m, 1 H) 6.00 (br. s., 1 H) 7.30 (d, $J=6.46$ Hz, 1 H) 7.55 - 7.66 (m, 2 H) 8.46 (s, 1 H)

Synthesis of (3S)-1-(6-methyl-2-(1-(5-methylquinazolin-4-yl)piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-5-yl)pyrrolidin-3-amine **P48**



Step 1: synthesis of *tert*-butyl 2-(5-hydroxy-6-methylpyrazolo[1,5-a]pyrimidin-2-yl)-piperidine-1-carboxylate **58**

To a solution of intermediate **4** (14.43 g, 54.18 mmol) in DMF (270 ml), (E)-ethyl 3-ethoxy-2-methylacrylate **57** (9.00 g, 56.9 mmol) and Cs₂CO₃ (26.48 g, 81.27 mmol) were added. The resulting mixture was stirred at 130°C for 12 hours. The solvent was evaporated under vacuum. The residue was successively dissolved in ethyl acetate (300 ml), washed with saturated aqueous NH₄Cl solution, with brine and dried over Na₂SO₄. After filtration, the filtrate was concentrated under vacuum to 100 ml. After 16 hours, the precipitate was filtered off. The filter cake was washed with ethyl acetate (2 x 30 ml) and dried (vacuum, 45°C, 1 hour) to give intermediate **58** (11.80 g, 65.52%).

Step 2: synthesis of 5-chloro-6-methyl-2-(piperidin-2-yl)pyrazolo[1,5-a]pyrimidine **59**

A mixture of intermediate **58** (11.80 g, 35.50 mmol) in phosphoryl trichloride (178 ml) was stirred at 80°C for 1 hour. The solvent was evaporated under vacuum. The residue was dissolved in acetonitrile (200 ml). The mixture was neutralized with ammonia (7 M in methanol) to pH = 7-8. The precipitate was filtered off and the filtrate was concentrated. The residue was purified by flash column chromatography over silica gel (eluent: dichloromethane/1% NH₃ in methanol 10/1). The collected fractions were concentrated to give intermediate **59** (3.715 g, 40.44%).

Step 3: synthesis of *tert*-butyl((3*S*)-1-(6-methyl-2-(piperidin-2-yl)pyrazolo[1,5-a]-pyrimidin-5-yl)pyrrolidin-3-yl)carbamate **61**

The solution of intermediate **59** (3.58 g, 10.0 mmol, 70% purity), (S)-*tert*-butylpyrrolidin-3-ylcarbamate **60** (2.33 g, 12.5 mmol) and Et₃N (3.04 g, 30.0 mmol) in MeOH (50 ml) was stirred overnight at 70°C. The mixture was filtered and the filtrate was concentrated under vacuum. The residue was dissolved in CH₂Cl₂ and washed with brine. The separated organic layer was dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by silica column chromatography (eluent: CH₂Cl₂/MeOH 10:1). After concentration, the crude product was triturated with CH₃CN. The solid was filtered and washed with CH₃CN to give the title intermediate **62** (768 mg, 12% yield)

¹H NMR (400 MHz, CDCl₃) δ ppm 1.45 (s, 9 H) 1.62 (m, 1 H) 1.90 (m, 3 H) 2.16 (m, 3 H) 2.26 (s, 3 H) 3.12 (m, 1 H) 3.47 (m, 1 H) 3.49 (s, 3 H) 3.65 (m, 1 H) 3.72 (m, 1 H) 3.84 (m, 1 H) 4.26 (m, 1 H) 4.37 (m, 1 H) 4.90 (d, 1 H, J=6.8 Hz) 6.39 (s, 1 H) 7.99 (d, 1 H, J=4.8 Hz).

Step 4: synthesis of *tert*-butyl((3*S*)-1-(6-methyl-2-(1-(5-methylquinazolin-4-yl)-piperidin-2-yl)pyrazolo[1,5-*a*]pyrimidin-5-yl)pyrrolidin-3-yl)carbamate **62**

The intermediate **61** (300 mg, 0.694 mmol), 4-chloro-5-methyl-quinazoline **26** (170 mg, 0.902 mmol) and Hunig's base (395 μ l, 2.291 mmol) were mixed in 2-methoxyethanol (4.7 ml) and heated at 80°C for 2 hours. After cooling to room temperature, the reaction mixture was added slowly to iced water solution. The suspension was stirred at room temperature for 2 hours. The formed precipitate was filtered off, washed with water and then dried in the vacuum oven for 16 hours. The crude was purified by column chromatography by eluting with a gradient starting with 100% DCM to 10% MeOH and 90% DCM. After evaporation of the pure fractions we get crude of the title intermediate **62** (238 mg)

$$m/z = 543.4 \text{ (M+H)}^+$$

Step 5: synthesis of (3*S*)-1-(6-methyl-2-(1-(5-methylquinazolin-4-yl)piperidin-2-yl)pyrazolo[1,5-*a*]pyrimidin-5-yl)pyrrolidin-3-amine **P48**

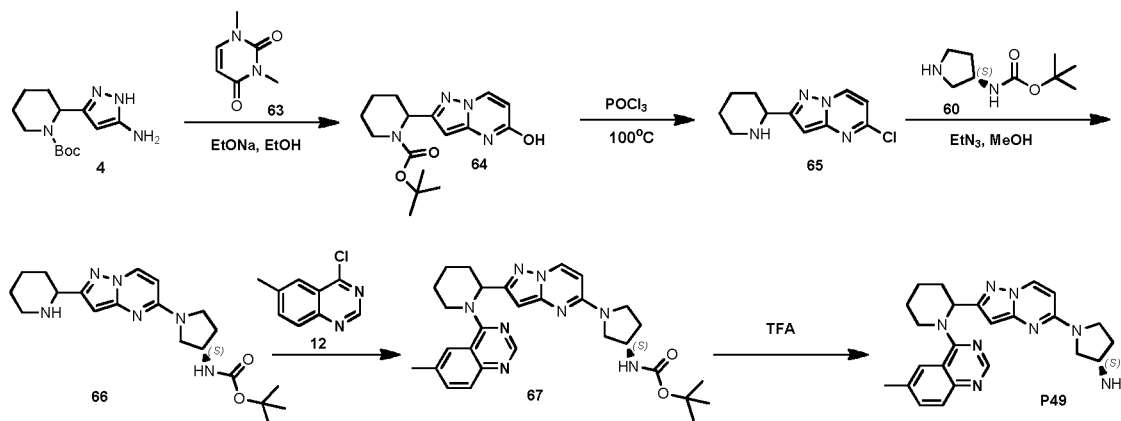
Intermediate **62** (238 mg, 0.386 mmol), was dissolved in DCM (2.5 ml) and trifluoroacetic acid (295 μ l, 3.859 mmol) was added. The mixture was stirred at room temperature for 16 hours. The reaction mixture was added drop wise to a cooled saturated solution of NaHCO₃. The product was extracted with DCM (3 times). The organic layers were dried over Na₂SO₄, filtered and evaporated to dryness. The crude was purified by column chromatography by eluting with a gradient starting with 100% DCM to 10% (MeOH/NH₃) and 90% DCM. After evaporation of the pure fractions a yellow foam was isolated. The foam was triturated in diethyl ether to get the title product **P48** as a white solid (152 mg, 85%).

¹H NMR (400MHz, DMSO-*d*₆) δ ppm 8.46 (s, 1H), 8.15 (s, 1H), 7.68 - 7.51 (m, 2H), 7.29 (d, *J*=6.4 Hz, 1H), 5.79 - 5.42 (m, 2H), 3.85 - 3.19 (m, 7H), 2.80 - 2.75 (m, 3H), 2.28 (s, 3H), 2.25 - 1.28 (m, 8H)

$$m/z = 443.3 \text{ (M+H)}^+$$

MP = 124.92°C

Synthesis of (3S)-1-(2-(1-(6-methylquinazolin-4-yl)piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-5-yl)pyrrolidin-3-amine P49



5

Step 1 : synthesis of *tert*-butyl 2-(5-hydroxypyrazolo[1,5-a]pyrimidin-2-yl)piperidine-1-carboxylate **64**

To a solution of intermediate **4** (5.00 g, 18.8 mmol) and 1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione **63** (2.90 g, 20.7 mmol) in ethanol (50 mL) sodium ethoxide (22 mL, 66 mmol) was added. The resulting solution was refluxed overnight. The solvent was evaporated under vacuum. Water was added to the residue and the pH was adjusted to 4-5 with HCl (1 N). The mixture was extracted with ethyl acetate, the organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated under vacuum to give the crude intermediate **64** (5 g, 75%).

15

Step 2 : synthesis of 5-chloro-2-(piperidin-2-yl)pyrazolo[1,5-a]pyrimidine **65**

A mixture of intermediate **64** (5 g, 15.7 mmol) in POCl₃ (50 mL) was stirred at 100°C for 2 hours. The solvent was evaporated under vacuum. The residue was washed with *tert*-butylmethyl ether to yield intermediate **65** (4.5 g, 19 mmol).

20

Step 3: synthesis of *tert*-butyl((3*S*)-1-(2-(piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-5-yl)pyrrolidin-3-yl)carbamate **66**

A mixture of intermediate **65** (4.5 g, 19 mmol), (*S*)-*tert*-butylpyrrolidin-3-ylcarbamate **60** (7.0 g, 38 mmol) and triethylamine (7.7 g, 76 mmol) in methanol (50 mL) was refluxed overnight. The mixture was filtered and the filtrate was concentrated under vacuum. The residue was dissolved in CH₃CN and stirred with K₂CO₃ (5.0 g, 38 mmol). The mixture was filtered and the filtrate was concentrated under vacuum. The residue was treated with H₂O and CH₂Cl₂. The separated organic layer was dried over

25

- 70 -

Na₂SO₄, filtered and concentrated under vacuum to give intermediate **66** (1.65 g, 22 %).

¹H NMR (400 MHz, CDCl₃) δ ppm 1.45 (s, 9 H) 1.51-1.72 (m, 1 H) 1.83-1.93 (m, 2 H) 1.94-2.07 (m, 3 H) 2.20-2.39 (m, 1 H) 2.73-2.93 (m, 1 H) 3.11-3.28 (m, 1 H) 3.35-3.49 (m, 1 H) 3.53-3.74 (m, 1 H) 3.75-3.95 (m, 1 H) 4.24-4.45 (m, 1 H) 4.59-4.90 (m, 1 H) 5.96-6.19 (m, 1 H) 8.12-8.30 (m, 1 H).

Step 4 : synthesis of tert-butyl((3S)-1-(2-(1-(6-methylquinazolin-4-yl)piperidin-2-yl)-pyrazolo[1,5-a]pyrimidin-5-yl)pyrrolidin-3-yl)carbamate **67**

Intermediate **66** (250 mg, 0.624 mmol), 4-chloro-6-methylquinazoline **12** (145 mg, 0.811 mmol) and DIPEA (355 µl, 2.058 mmol) were mixed in 2-methoxyethanol (4.2 ml) and heated at 80°C for 16 hours and at 90°C for 1 hour. After cooling to room temperature, the reaction mixture was added slowly to iced water. The suspension was stirred at room temperature overnight. The brown precipitate was filtered off, washed with water and then dried in the vacuum oven for 16 hours. The crude of the title intermediate **67** (250 mg) was used as such in the next step.

m/z = 529.4 (M+H)⁺

Step 5 : synthesis of (3S)-1-(2-(1-(6-methylquinazolin-4-yl)piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-5-yl)pyrrolidin-3-amine **P49**

Intermediate **67** (250 mg, 0.473 mmol) was dissolved in DCM (3.0 ml) and TFA (362 µl, 4.729 mmol) was added. The reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was quenched with saturated Na₂CO₃ solution and the product was extracted 3 times with DCM. The organic layers were evaporated and the product was purified by column chromatography by eluting with a gradient starting with 100% DCM to 10% (MeOH/NH₃) and 90% DCM. After evaporation of the pure fractions we get the desired product **P49** as a yellow foam (122 mg, 56%).

m/z = 429.3 (M+H)⁺

30

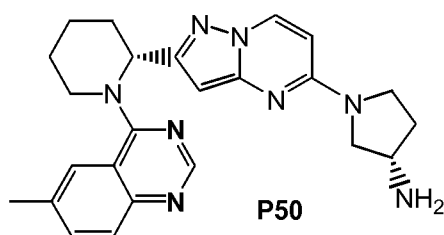
¹H NMR (400MHz, DMSO-*d*₆) δ ppm 8.63 - 8.53 (m, 2H), 7.82 (br. s, 1H), 7.71 (d, *J*=8.6 Hz, 1H), 7.63 (dd, *J*=1.5, 8.6 Hz, 1H), 6.30 (d, *J*=7.7 Hz, 1H), 5.91 (s, 1H), 5.84 - 5.77 (m, 1H), 4.29 - 4.17 (m, 1H), 3.72 - 2.99 (m, 6H), 2.47 - 1.58 (m, 13H)

¹H NMR at 100°C (400MHz, DMSO-*d*₆) δ ppm 8.52 (s, 1H), 8.42 (dd, *J*=0.7, 7.7 Hz, 1H), 7.86 - 7.81 (m, 1H), 7.68 (d, *J*=8.8 Hz, 1H), 7.58 (dd, *J*=1.8, 8.6 Hz, 1H), 6.24 (d, *J*=7.7 Hz, 1H), 5.86 (s, 1H), 5.84 - 5.79 (m, 1H), 4.26 - 4.18 (m, 1H), 3.66 - 3.43 (m,

- 71 -

5H), 3.19 - 3.12 (m, 1H), 2.42 (s, 3H), 2.40 - 2.30 (m, 1H), 2.14 - 1.92 (m, 3H), 1.86 - 1.59 (m, 6H)

Synthesis of (S)-1-(2-((R)-1-(6-methylquinazolin-4-yl)piperidin-2-yl)pyrazolo-
[1,5-a]pyrimidin-5-yl)pyrrolidin-3-amine P50



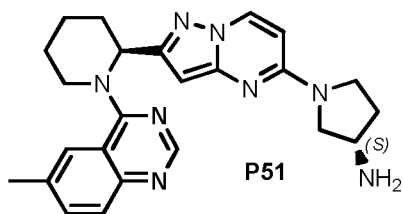
Product **P49** (100 mg, 0.233 mmol) was purified by SFC to obtain the title compound, pure enantiomer, as an off white solid **P50** (51 mg, 51%).

SFC: 100% pure at $R_t = 2.64$ min

$m/z = 429.2$ (M+H)⁺

P50 : $[\alpha]_D^{20} = -268.64^\circ$ (589 nm, c = 0.354 w/v %, DMF, 20°C)

Synthesis of (S)-1-(2-((S)-1-(6-methylquinazolin-4-yl)piperidin-2-yl)pyrazolo-
[1,5-a]pyrimidin-5-yl)pyrrolidin-3-amine P51

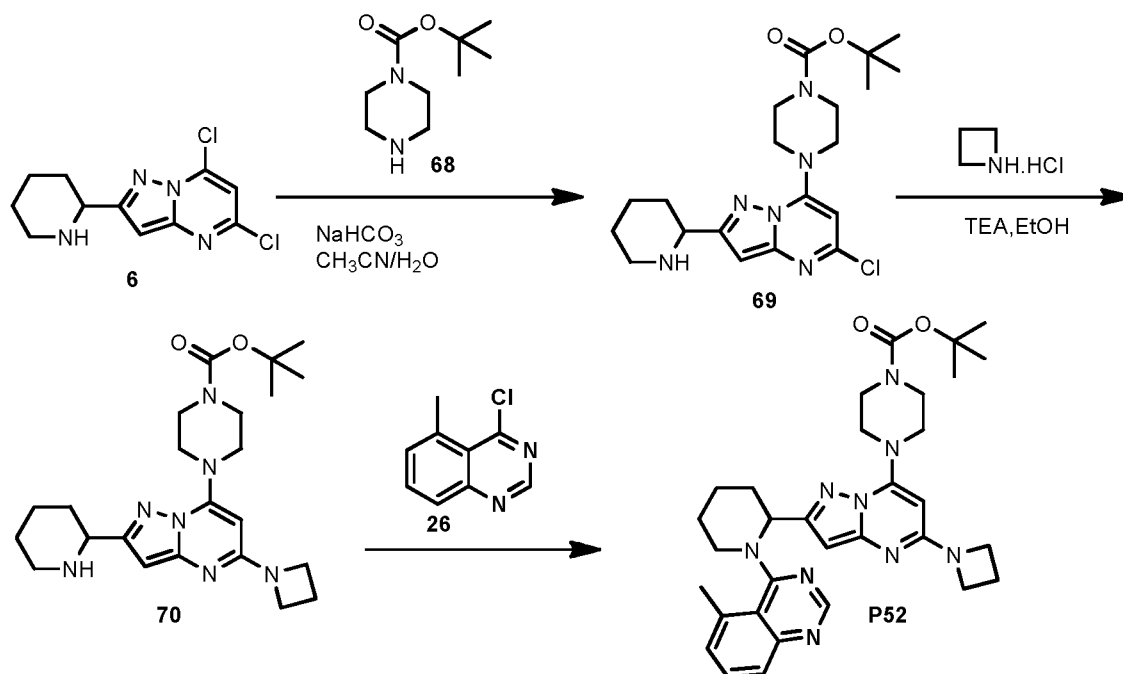


Product **P49** (100 mg, 0.233 mmol) was purified by SFC to obtain the title compound, pure enantiomer, as an off white solid **P51** (17 mg, 17%).

SFC: 100% pure at $R_t = 3.68$ min

$m/z = 429.3$ (M+H)⁺

Synthesis of *tert*-butyl4-(5-(azetidin-1-yl)-2-(1-(5-methylquinazolin-4-yl)piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-7-yl)piperazine-1-carboxylate P52



5

Step 1 : synthesis of *tert*-butyl4-(5-chloro-2-(piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-7-yl)piperazine-1-carboxylate **69**

A mixture of intermediate **6** (40.0 g, 125 mmol), *tert*-butylpiperazine-1-carboxylate **68** (25.7 g, 138 mmol) and NaHCO₃ (26.30 g, 313.5 mmol) in CH₃CN (300 ml) and H₂O (300 ml) was stirred at room temperature for 1 hours. The solvent was concentrated under vacuum. The concentrate was treated with CH₂Cl₂ (500 ml). The separated organic layer was washed with brine (200 ml), filtered and concentrated under vacuum to afford the title intermediate **69** (40 g, yield: 68%).

Step 2 : synthesis of *tert*-butyl4-(5-(azetidin-1-yl)-2-(piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-7-yl)piperazine-1-carboxylate **70**

A mixture of intermediate **69** (40 g, 95 mmol), azetidine hydrochloride (47.7 g, 510 mmol) and TEA (155.0 g, 1530 mmol) in ethanol (500 ml) was refluxed overnight. The mixture was filtered and the filtrate was concentrated under vacuum. The residue was treated with CH₂Cl₂ and H₂O. The separated organic layer was concentrated under vacuum. The residue was purified by column chromatography over silica gel (eluent: dichloromethane/methanol (1% of TEA contained) = 15/1). The product fractions were collected and the solvent was evaporated to afford the title intermediate **70** (17.96 g,

- 73 -

yield 42.71%).

$m/z = 515 (M+H)^+$

^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.49 (s, 9 H) 1.52 - 1.68 (m, 4 H) 1.91 - 2.05 (m, 4 H) 2.37 - 2.41 (m, 2 H) 2.78 - 2.83 (m, 1 H) 3.16 - 3.18 (m, 1 H) 3.51-3.53 (m, 4 H) 3.67 - 3.68 (m, 4 H) 3.79 - 3.82 (m, 1 H) 4.09 - 4.4.13 (m, 4 H) 5.10 (s, 1 H) 6.04 (s, 1 H).

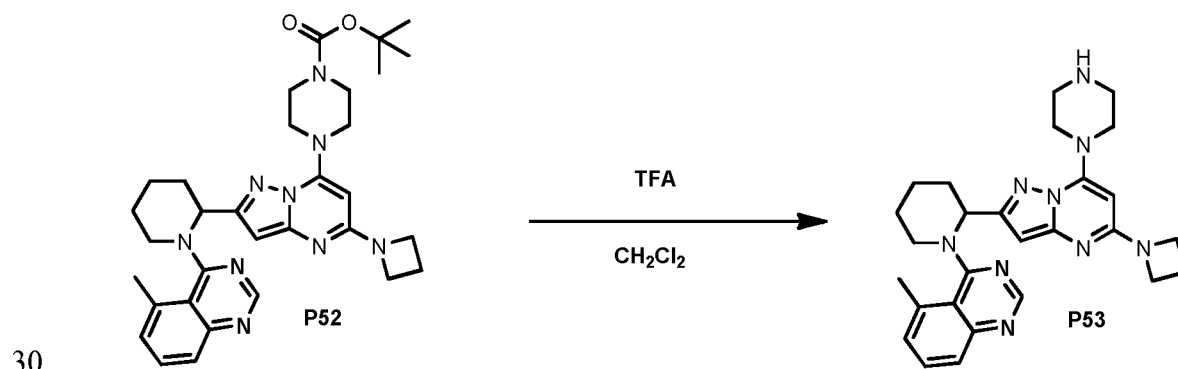
Step 3 : synthesis of *tert*-butyl 4-(5-(azetidin-1-yl)-2-(1-(5-methylquinazolin-4-yl)-piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-7-yl)piperazine-1-carboxylate **P52**

The mixture of intermediate **70** (3 g, 5.83 mmol), intermediate **26** (1.56 g, 8.75 mmol) was dissolved in 2-methoxyethanol (100 mL) then diisopropylethyl amine (2 mL, 11.66 mmol) was added. The resulting mixture was stirred at 50°C for three days. The mixture was allowed to cool down to room temperature and poured in iced watered solution. The resulting mixture was stirred until all the ice is melt then the resulting solid was filtered off. The solid was successively washed with water, dissolved in dichloromethane, dried over $MgSO_4$ and concentrated. The resulting residue was purified by column chromatography using dichloromethane and methanol to yield **P52** (3.3 g, 87%) as a white light yellow solid.

$m/z = 584 (M+H)^+$

^1H NMR (400 MHz, $DMSO-d_6$) δ ppm 1.39 - 1.49 (m, 9 H), 1.53 - 1.91 (m, 4 H), 2.03 - 2.36 (m, 4 H), 2.87 (s, 3 H), 3.29 - 3.51 (m, 8 H), 3.53 - 3.67 (m, 4 H), 3.90 - 4.04 (m, 2 H), 5.40 - 5.51 (m, 1 H), 5.64 (s, 1 H), 6.25 (br. s., 1 H), 7.27 - 7.42 (m, 1 H), 7.52 - 7.70 (m, 2 H), 8.47 (s, 1 H).

Synthesis of 4-(2-(5-(azetidin-1-yl)-7-(piperazin-1-yl)pyrazolo[1,5-a]pyrimidin-2-yl)piperidin-1-yl)-5-methylquinazoline **P53**



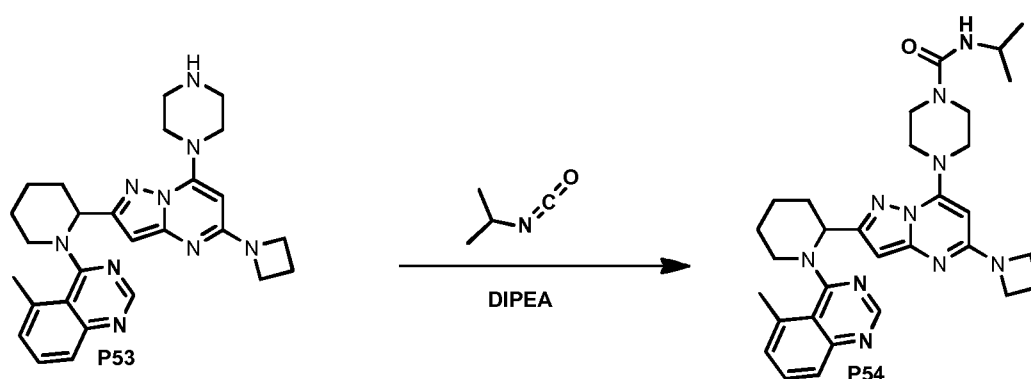
- 74 -

Compound **P52** (3 g, 5.139 mmol) was dissolved in DCM (150 ml) and TFA (4 ml, 51 mmol) was added. The reaction mixture was stirred at room temperature for 5 days. The reaction mixture was quenched with saturated Na₂CO₃ solution and the product was extracted 3 times with DCM. The organic layers were evaporated and the product was purified by column chromatography by eluting with a gradient starting with 100% DCM to 10% (MeOH/NH₃) and 90% DCM. After evaporation of the concerning fractions we get the desired product **P53** as a yellow foam (2.3 g, 92%).

$m/z = 484 (M+H)^+$

¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.57 (br. s., 1 H), 1.63 - 1.76 (m, 2 H), 1.80 - 1.95 (m, 1 H), 2.15 - 2.27 (m, 2 H), 2.32 (quin, J=7.4 Hz, 2 H), 2.90 - 3.08 (m, 5 H), 3.42 - 3.67 (m, 7 H), 3.77 - 3.96 (m, 1 H), 4.02 (t, J=7.4 Hz, 4 H), 5.20 (s, 1 H), 5.52 (br. s., 1 H), 5.63 (s, 1 H), 7.28 - 7.39 (m, 1 H), 7.57 - 7.68 (m, 2 H), 8.49 (s, 1 H)

Synthesis of 4-(5-(azetidin-1-yl)-2-(1-(5-methylquinazolin-4-yl)piperidin-2-yl)-pyrazolo[1,5-a]pyrimidin-7-yl)-N-isopropylpiperazine-1-carboxamide P54



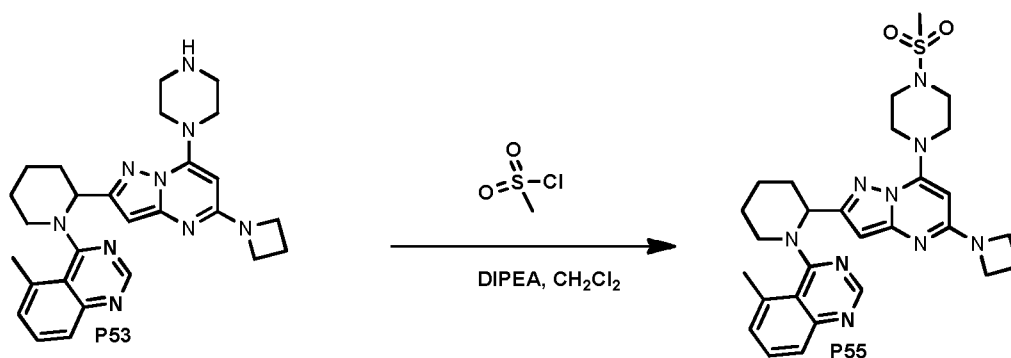
Compound **P53** (550 mg, 1.058 mmol) was suspended in dioxane and hunig's base was added. The resulting mixture was stirred for 10 minutes. The 2-isocyanatopropane (125 μL, 1.269 mmol) was then added at room temperature. The mixture was stirred overnight at room temperature. To the solution was added an excess of MeOH and the mixture was stirred overnight. The solvent was evaporated. The residue was dissolved in dichloromethane (50 ml) and the resulting solution was washed with water three times (20 ml). The water layers were extracted with dichloromethane. The combined organic layers were dried over MgSO₄ and filtered. The solvent was removed and the residue was triturated in diethyl ether and stirred overnight in this solvent. The white light powder was filtered and dried in the oven at 50°C to yield (85 mg, 14%) of

- 75 -

product **P54**. $m/z = 569 (M+H)^+$

¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.11 (d, J=6.4 Hz, 6 H), 1.52 (br. s., 1 H), 1.66 (d, J=9.9 Hz, 2 H), 1.84 (br. s., 1 H), 2.21 (br. s., 2 H), 2.28 (dt, J=14.5, 7.2 Hz, 2 H), 2.85 (br. s., 3 H), 3.30 - 3.62 (m, 10 H), 3.73 - 3.86 (m, 1 H), 3.98 (t, J=7.3 Hz, 4 H), 5.19 (s, 1 H), 5.42 - 5.81 (m, 3 H), 7.30 (d, J=5.7 Hz, 1 H), 7.50 - 7.70 (m, 2 H), 8.46 (s, 1 H)

Synthesis of 4-(2-(5-(azetidin-1-yl)-7-(4-(methylsulfonyl)piperazin-1-yl)pyrazolo-[1,5-a]pyrimidin-2-yl)piperidin-1-yl)-5-methylquinazoline P55

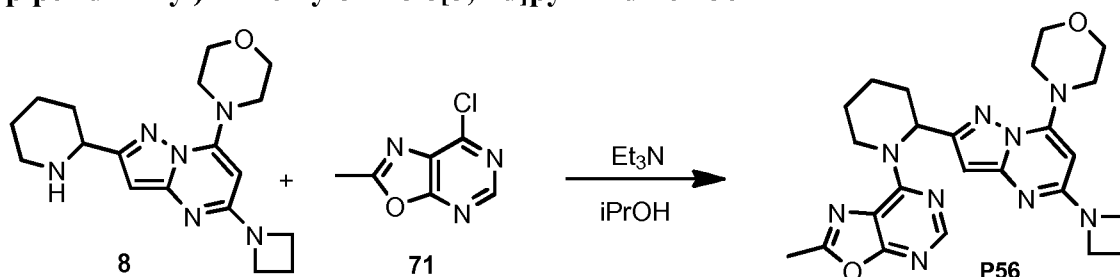


Compound **P53** (500 mg, 1.03 mmol) was dissolved in dichloromethane (25 mL) and diisopropylethyl amine (0.445 mL, 2.58 mmol) was added. The resulting mixture was stirred at room temperature for 10 minutes then methanesulfonyl chloride (0.2 mL, 1.55 mmol) was added. The resulting mixture was stirred at room temperature overnight. The resulting mixture was poured in water, extracted with dichloromethane, dried over MgSO₄ and concentrated. The resulting residue was purified by column chromatography using dichloromethane and methanol as eluent to yield compound **P55** 71% pure. This was further purified by HPLC to yield (28 mg, 5%) of compound **P55** as a white solid.

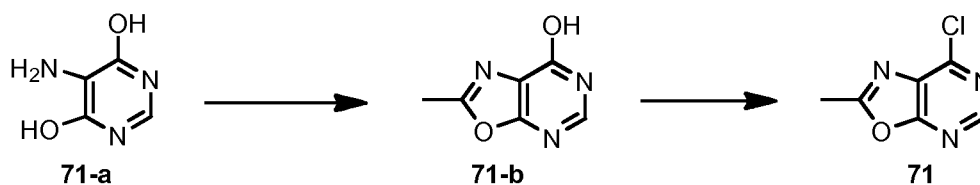
 $m/z = 562 (M+H)^+$

¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.58 (br. s., 1 H), 1.65 - 1.77 (m, 2 H), 1.78 - 1.94 (m, 1 H), 2.20 - 2.27 (m, 2 H), 2.27 - 2.38 (m, 2 H), 2.87 (s, 3 H), 2.91 (s, 3 H), 3.22 - 3.35 (m, 4 H), 3.44 - 3.68 (m, 6 H), 4.02 (t, J=7.4 Hz, 4 H), 5.26 (s, 1 H), 5.49 (br. s., 1 H), 5.67 (br. s., 1 H), 7.30 - 7.36 (m, 1 H), 7.58 - 7.67 (m, 2 H), 8.49 (s, 1 H)

Synthesis of 7-(2-(5-(azetidin-1-yl)-7-morpholinopyrazolo[1,5-a]pyrimidin-2-yl)-piperidin-1-yl)-2-methyloxazolo[5,4-d]pyrimidine P56



5 Synthesis of 7-chloro-2-methyloxazolo[5,4-d]pyrimidine 71



Step 1: synthesis of 2-methyloxazolo[5,4-d]pyrimidin-7-ol 71-b

- 10 A solution of 5-aminopyrimidine-4,6-diol **71-a** (5 g, 39 mmol) in acetic anhydride (80 mL) was heated at 120°C for 16 hours. The solution was then cooled and the solid filtered off and triturated with Et₂O. After filtration the solid was dried in the oven to yield the intermediate **71-b** (4g, 68 %).

$$m/z = 152 (M+H)^+$$

15

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.54 (s, 3 H) 8.18 (s, 1 H) 12.84 (br. s., 1 H)

Step 2: synthesis of 7-chloro-2-methyloxazolo[5,4-d]pyrimidine 71

- The intermediate **71-b** (100 mg, 0.66 mmol) was dissolved in acetonitrile (20 mL) under inert atmosphere. DIPEA (0.28 mL, 2.5 eq.) and POCl₃ (0.15 mL, 2.5 eq.) were added dropwise and the mixture was heated to 70°C. After 3 hours, the solution was concentrated in vacuo, extracted with ethyl acetate and washed with saturated NaHCO₃ solution. The combined organic layers were dried over MgSO₄, filtered and used as such into the next step.

- 25 LCMS $m/z = 170 (M+H)^+$

- 77 -

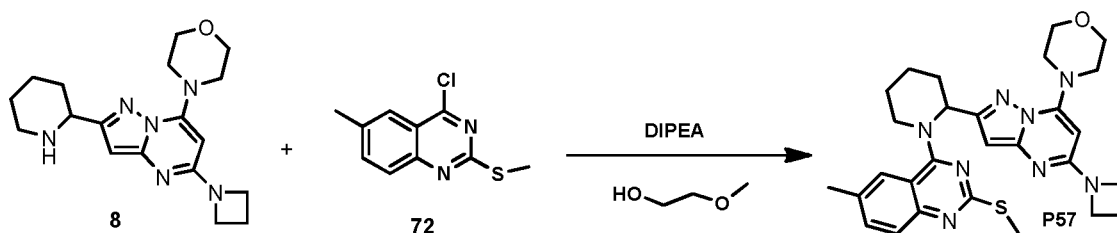
Synthesis of 7-(2-(5-(azetidin-1-yl)-7-morpholinopyrazolo[1,5-a]pyrimidin-2-yl)-piperidin-1-yl)-2-methyloxazolo[5,4-d]pyrimidine **P56**

To a solution of intermediate **71** (20 mg, 0.12 mmol) in iPrOH (2 mL) was added triethyl amine (0.05 mL, 0.35 mmol, 3 eq.) and intermediate **8** (40 mg, 0.12 mmol, 1 eq.). The solution underwent microwave irradiation during 3 hours at 120°C. The resulting solution was concentrated in vacuo and purified by Prep HPLC to yield the title compound **P56** (21 mg, 37 %) as a white solid.

$m/z = 476 (M+H)^+$

^1H NMR (400 MHz, DMSO- d_6) δ ppm 1.49 - 1.79 (m, 4 H) 1.84 - 2.02 (m, 1 H) 2.20 - 2.34 (m, 2 H) 2.40 (br. s., 1 H) 2.53 (s, 3 H) 3.15 - 3.27 (m, 1 H) 3.36 - 3.54 (m, 4 H) 3.55 - 3.69 (m, 4 H) 3.99 (t, $J=7.70$ Hz, 4 H) 4.99 (d, $J=13.32$ Hz, 1 H) 5.22 (s, 1 H) 5.73 (s, 1 H) 6.53 (d, $J=5.65$ Hz, 1 H) 8.24 (s, 1 H)

Synthesis of 4-(5-(azetidin-1-yl)-2-(1-(6-methyl-2-(methylthio)quinazolin-4-yl)-piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-7-yl)morpholine **P57**



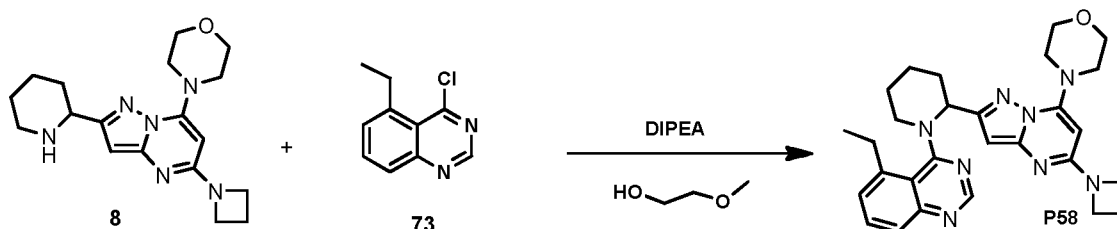
Intermediate **8** (1000 mg, 2.41 mmol), 4-chloro-6-methyl-2-(methylthio)quinazoline **72** (649.2 mg, 2.89 mmol) and DIPEA (0.83 ml, 4.8 mmol) were mixed in 2-methoxyethanol (30 ml) and heated at 50°C for 16 hours. The reaction mixture was allowed to cool down to room temperature and poured in iced watered solution. A solid was formed this was filter off. The solid was dissolved in dichloromethane and the solution obtained was successively dried over MgSO_4 and concentrated. The residue was purified by column chromatography to yield **P57** (1.2 g, 78% pure).

$m/z = 531 (M+H)^+$

^1H NMR (400 MHz, DMSO- d_6) δ ppm 1.69 (br. s., 4 H), 2.04 (dd, $J=13.1, 5.2$ Hz, 1 H), 2.24 - 2.38 (m, 3 H), 2.40 (s, 3 H), 2.48 (s, 3 H), 3.37 - 3.41 (m, 1 H), 3.49 (t, $J=4.5$ Hz, 4 H), 3.62 - 3.76 (m, 4 H), 4.00 (t, $J=7.5$ Hz, 4 H), 4.13 (d, $J=13.2$ Hz, 1 H), 5.30 (s, 1 H), 5.82 (d, $J=2.2$ Hz, 1 H), 5.93 (s, 1 H), 7.76 (s, 1 H)

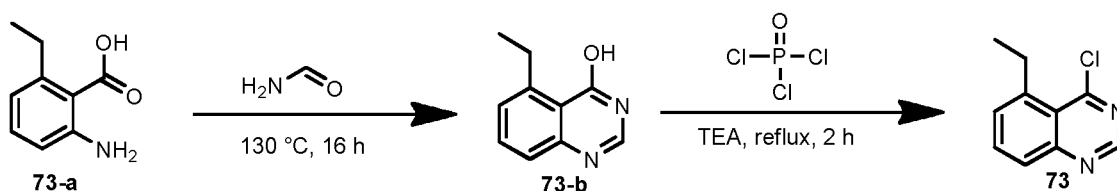
- 78 -

Synthesis of 4-(5-(azetidin-1-yl)-2-(1-(5-ethylquinazolin-4-yl)piperidin-2-yl)-pyrazolo[1,5-a]pyrimidin-7-yl)morpholine P58



5

Synthesis of 4-chloro-5-ethylquinazoline 73



Step 1 : synthesis of 5-ethylquinazolin-4-ol 73-b

A mixture of 2-amino-6-ethylbenzoic acid **73-a** (18.0 g, 109 mmol) in formamide (200 ml) was stirred at 130°C for 16 hours. The mixture was cooled to room temperature. The precipitate was filtered off and washed with water. The filter cake was dried in vacuum at 45°C for 1 hour. The resulting solid intermediate **73-b** was recovered (8.5 g, purity: 90%, yield: 40.3%).

Step 2 : synthesis of 4-chloro-5-ethylquinazoline 73

Triethylamine (19.51 ml, 140.0 mmol) was added to a mixture of 5-ethylquinazolin-4-ol **73-b** (7.0 g, 40 mmol) in phosphorus oxychloride (100 ml) at 0°C. The resulting mixture was refluxed for 3 hours. The solvent was evaporated under vacuum. The residue was dissolved in toluene (100 ml) and the mixture was added dropwise into ice (100 g). The organic layer was washed successively with water (2 x 100 ml), 10% sodium bicarbonate solution (2 x 100 ml), water (2 x 100 ml) and brine (1 x 100 ml). The organic layer was dried (Na₂SO₄), filtered and the filtrate was concentrated under vacuum. The residue was purified by flash column chromatography over silica gel (eluent: petroleum ether/ethyl acetate 10/1 to give intermediate **73** (3.313 g, purity: 96%, yield: 41.37%).

¹H NMR (400 MHz, CDCl₃) δ ppm 1.39 (t, *J*=7.46 Hz, 3 H) 3.48 (q, *J*=7.34 Hz, 2 H) 7.56 (d, *J*=7.34 Hz, 1 H) 7.84 (t, *J*=7.83 Hz, 1 H) 7.95 (d, *J*=8.31 Hz, 1 H) 8.96 (s, 1 H)

30

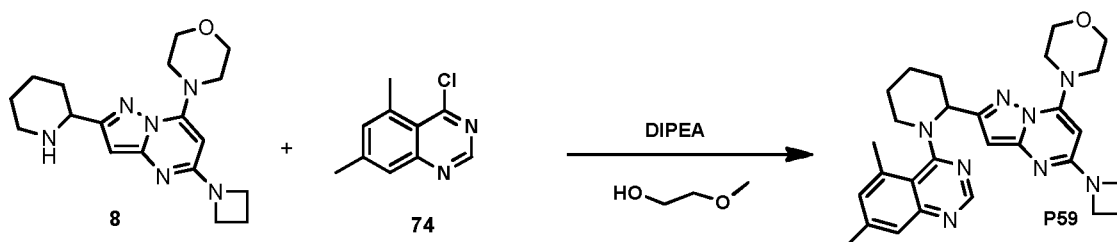
Step 3 : synthesis of 4-(5-(azetidin-1-yl)-2-(1-(5-ethylquinazolin-4-yl)piperidin-2-yl)-pyrazolo[1,5-a]pyrimidin-7-yl)morpholine **P58**

The mixture of intermediate **8** HCl salt (500 mg, 1.2 mmol) and intermediate **73** (348 mg, 1.5 mmol) was dissolved in 2-methoxyethanol (15 ml) and triethyl amine (0.415 ml, 2.4 mmol) was added. The resulting mixture was stirred at 50°C for 16 hours. The reaction mixture was allowed to cool down to room temperature and poured in iced watered solution. The resulting mixture was stirred until the ice melt then filtered off and the solid was washed with water. The solid was dissolved in dichloromethane, dried over MgSO₄ and concentrated. The solid was purified by column chromatography using dichloromethane and methanol to yield **P58** as a white powder (400 mg, 63%).

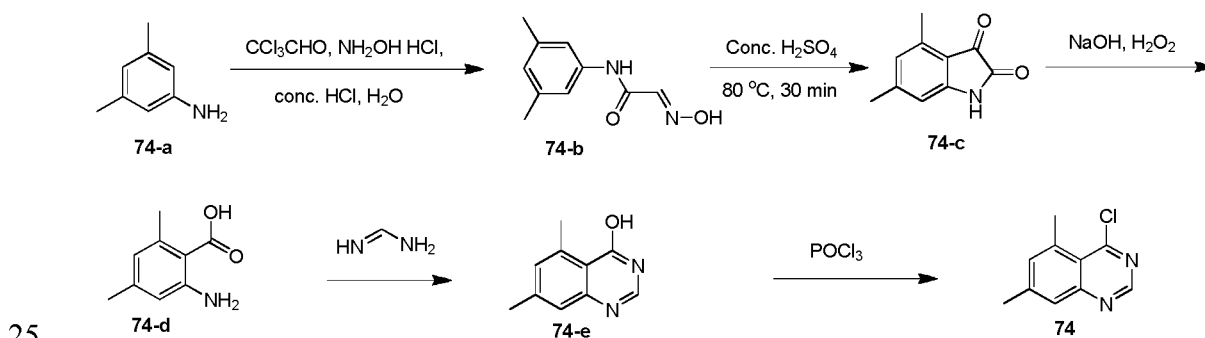
$$m/z = 499 (M+H)^+$$

¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.05 - 1.23 (m, 3 H), 1.42 - 1.57 (m, 1 H), 1.66 (d, J=8.1 Hz, 2 H), 1.73 - 1.91 (m, 1 H), 2.06 - 2.35 (m, 4 H), 3.10 - 3.41 (m, 3 H), 3.40 - 3.55 (m, 5 H), 3.58 - 3.78 (m, 5 H), 3.89 - 4.06 (m, 4 H), 5.18 (s, 1 H), 5.35 - 5.66 (m, 2 H), 7.37 (d, J=7.0 Hz, 1 H), 7.50 - 7.68 (m, 2 H), 8.43 (s, 1 H)

Synthesis of 4-(5-(azetidin-1-yl)-2-(1-(5,7-dimethylquinazolin-4-yl)piperidin-2-yl)-pyrazolo[1,5-a]pyrimidin-7-yl)morpholine **P59**



Synthesis of 4-chloro-5,7-dimethylquinazoline **74**



Step 1 : synthesis of (E)-N-(3,5-dimethylphenyl)-2-(hydroxyimino)acetamide **74-b**

Sodium sulfate (390.7 g, 2.750 mol) was added into a solution of chloral hydrate (76.5 g, 0.520 mol) in water (1500 mL) at room temperature. Then, a suspension of hydroxylamine hydrochloride (91.8 g, 1.32 mol), 3,5-dimethylaniline **74-a** (50 g, 0.41 mol) and concentrated hydrochloric acid (36.5%, 50 mL) was added. The mixture was heated at 45°C for 1.5 hours, then 75°C for 1 hour. The reaction mixture was cooled to room temperature. The precipitated brown solid was filtered and washed with cold water and hexane. The crude compound was dried under vacuum to give intermediate **74-b** (70 g, yield: 83.78%).

Step 2 : synthesis of 4,6-dimethylindoline-2,3-dione **74-c**

Intermediate **74-b** (15.00 g, 78.04 mmol) was dissolved in concentrated sulfuric acid (75 ml). The mixture was stirred at 80°C for 30 minutes. Then the mixture was cooled to room temperature and poured into ice water. Intermediate **75-c** was precipitated, filtered and washed with water (8.50 g, 49.74%).

Step 3 : synthesis of 2-amino-4,6-dimethylbenzoic acid **74-d**

H₂O₂ (123.7 g, 1200 mmol) was added to a mixture of intermediate **74-C** (35.00 g, 199.8 mmol) in NaOH solution (1225 mL, 0.33g/mL) at 70°C, over 5 minutes. The mixture was heated for another 15 minutes, then cooled to 15°C. Ice was added to the mixture. The resulting mixture was extracted with ethyl acetate (300 mL x 2). The pH of the solution was adjusted to 8 with addition of concentrated HCl at 0°C and acidified to pH ~6 with acetic acid. The mixture was extracted with ethyl acetate (300 mL x 2). The organic layers were combined, washed with brine, dried over MgSO₄ and filtered. The filtrate was concentrated to give intermediate **74-d** (17 g, yield: 41.20%).

Step 4: synthesis of 5,7-dimethylquinazolin-4-ol **74-e**

A mixture of intermediate **74-d** (15.0 g, 90.8 mmol) and formamidine acetate (94.5 g, 908 mmol) was stirred for 5 hours at 150°C. H₂O was added to the mixture and the mixture was stirred 10 minutes at room temperature. The precipitate was filtered off and washed with water. The filter cake was dried under vacuum to give intermediate **74-e** (17.5 g, yield: 39.83%).

Step 5 : synthesis of 4-chloro-5,7-dimethylquinazoline **74**

Triethylamine (30.50 ml, 301.4 mmol) was added to a mixture of intermediate **74-e** (17.50 g, 100.5 mmol) in POCl₃ (300 g, 1.96 mol) at 0°C. The resulting mixture was refluxed for 3 hours then was poured into ice water. The resulting mixture was

extracted with ethyl acetate. The organic layer was washed with NaHCO₃ solution (1%) and brine, dried over MgSO₄ and filtered. The filtrate was concentrated. The crude product was purified by chromatography over silica gel (eluent: hexanes/ethyl acetate from 0/1 to 1:1). The desired fractions were collected and concentrated to give
 5 intermediate **74** (4.806 g, 23.69%).

¹H NMR (400 MHz, CDCl₃) δ ppm 2.53 (s, 3 H) 3.00(s, 3 H) 7.34 (s, 1 H) 7.71 (s, 1 H) 8.90 (s, 1 H)

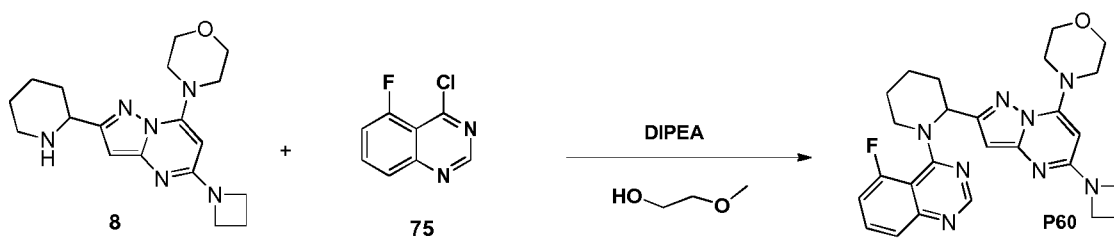
10 **Synthesis of 4-(5-(azetidin-1-yl)-2-(1-(5,7-dimethylquinazolin-4-yl)piperidin-2-yl)-pyrazolo[1,5-a]pyrimidin-7-yl)morpholine P59**

The mixture of intermediate **8** TFA salt (300 mg, 0.66 mmol) and intermediate **74** (177 mg, 0.92 mmol) was dissolved in 2-methoxyethanol (15 ml) and triethyl amine (0.34 ml, 1.97 mmol) was added. The resulting mixture was stirred at 50°C for 16
 15 hours. The reaction mixture was allowed to cool down to room temperature and poured in iced watered solution. The resulting mixture was stirred until the ice melt then filtered off and the solid was washed with water. The solid was dissolved in dichloromethane dried over MgSO₄ and concentrated. The solid was purified by column chromatography using dichloromethane and methanol to yield **P59** as a white powder
 20 (212 mg, 64%).

$m/z = 499 (M+H)^+$

¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.52 (br. s., 1 H), 1.65 (d, J=5.1 Hz, 2 H), 1.74 - 1.90 (m, 1 H), 2.17 (br. s., 2 H), 2.28 (quin, J=7.3 Hz, 2 H), 2.41 (s, 3 H), 2.80 (s, 3
 25 H), 3.35 - 3.58 (m, 6 H), 3.60 - 3.77 (m, 4 H), 3.98 (t, J=7.3 Hz, 4 H), 5.17 (s, 1 H), 5.41 (br. s., 1 H), 5.53 - 5.73 (m, 1 H), 7.14 (s, 1 H), 7.38 (s, 1 H), 8.42 (s, 1 H)

30 **Synthesis of 4-(5-(azetidin-1-yl)-2-(1-(5-fluoroquinazolin-4-yl)piperidin-2-yl)-pyrazolo[1,5-a]pyrimidin-7-yl)morpholine P60**



The mixture of intermediate **8** TFA salt (400 mg, 0.87 mmol) and 4-chloro-5-fluoro-

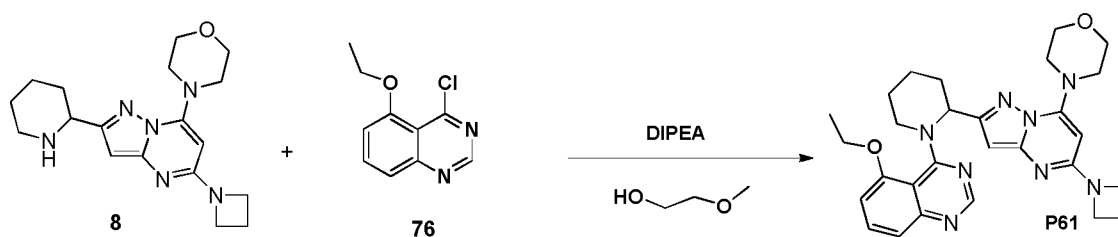
quinazoline **75** (208 mg, 1.14 mmol) was dissolved in 2-methoxyethanol (20 ml) and triethyl amine (0.604 ml, 3.5 mmol) was added. The resulting mixture was stirred at 50°C for 2 hours. The reaction mixture was allowed to cool down to room temperature and poured in iced watered solution. The resulting mixture was stirred until the ice melt
 5 then filtered off and the solid was washed with water. The solid was dissolved in dichloromethane, dried over MgSO₄ and concentrated to yield a white solid **P60** (145 mg, 34%).

$m/z = 489 (M+H)^+$

10 ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.57 - 1.90 (m, 4 H), 2.06 - 2.20 (m, 1 H), 2.26 - 2.43 (m, 3 H), 3.38 - 3.51 (m, 1 H), 3.54 (br. s., 4 H), 3.65 - 3.79 (m, 4 H), 3.92 (d, J=12.8 Hz, 1 H), 4.02 (t, J=7.4 Hz, 4 H), 5.23 (s, 1 H), 5.75 (s, 1 H), 5.80 (br. s., 1 H), 7.23 (dd, J=11.7, 7.9 Hz, 1 H), 7.61 (d, J=8.4 Hz, 1 H), 7.68 - 7.79 (m, 1 H), 8.51 (s, 1 H)

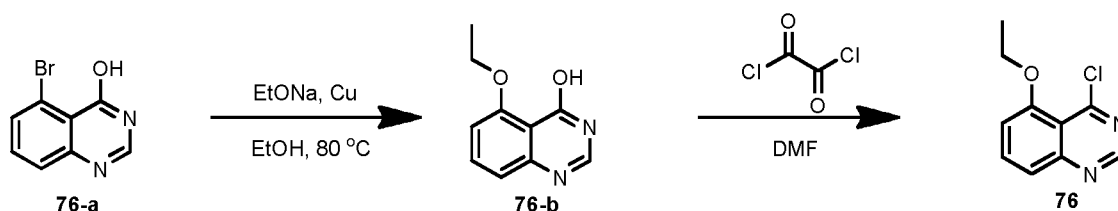
15

Synthesis of 4-(5-(azetidin-1-yl)-2-(1-(5-ethoxyquinazolin-4-yl)piperidin-2-yl)-pyrazolo[1,5-a]pyrimidin-7-yl)morpholine P61



20

Synthesis of 4-chloro-5-ethoxyquinazoline 76



25 Step 1 : synthesis of 5-ethoxyquinazolin-4-ol 76-b

Sodium hydride (8.00 g, 200 mmol, 60% in mineral oil) was added to ethanol (300 ml) at 0°C. After stirred for 30 min at 0°C 5-bromoquinazolin-4-ol **76-a** (15.00 g, 66.65 mmol) and copper (1.70 g, 26.7 mmol) were added. The reaction mixture was stirred at 80°C for 18 h and then cooled to room temperature. The mixture was filtered
 30 through a pad of Celite. The filtrate was concentrated in vacuum. The residue was

taken up in water and the pH was adjusted to 8 by addition of a solution of hydrochloric acid 37%. The solution was extracted with CH₂Cl₂. The organic phase was dried over Na₂SO₄, filtered and evaporated in vacuum. The residue was purified by column chromatography over silica gel (eluent: petroleum ether/ethyl acetate 2/1) to afford
5 intermediate **76-b** (5 g, yield: 35%).

Step 2: synthesis of 4-chloro-5-ethoxyquinazoline **76**

Oxalyl chloride (12.5 mmol) was added dropwise to a solution of intermediate **76-b** (5.00 g, 26.3 mmol) and DMF (2.5 ml) in CH₃Cl (100 ml). The solution was refluxed
10 overnight. The reaction solution was concentrated under vacuum. The residue was purified over silica gel on a glass filter (eluent: CH₂Cl₂/ethyl acetate 1/1). The desired fractions were collected and the solvent was evaporated to afford intermediate **77** (2.81 g, yield: 49%).

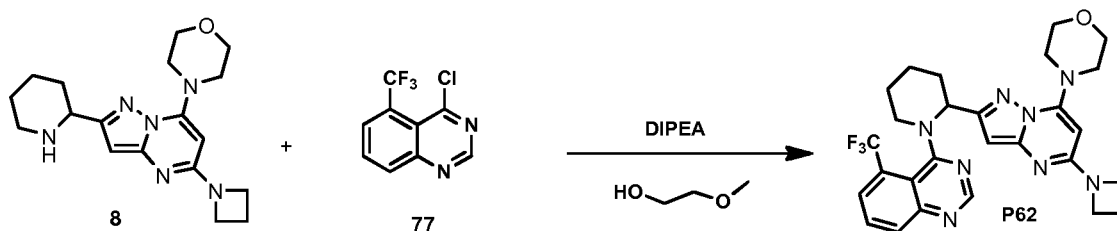
15 ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.34 - 1.48 (m, 3 H) 4.14 - 4.23 (m, 2 H) 7.15 - 7.23 (m, 1 H) 7.27 - 7.36 (m, 1 H) 7.77 - 7.87 (m, 1 H) 8.90 (s, 1 H)

The mixture of intermediate **8** TFA salt (500 mg, 1.1 mmol) and 4-chloro-5-ethoxyquinazoline **76** (320 mg, 1.5 mmol) was dissolved in 2-methoxyethanol (20 ml) and
20 triethyl amine (0.566 ml, 3.3 mmol) was added. The resulting mixture was stirred at 50°C for 4 days. The reaction mixture was allowed to cool down to room temperature and poured in iced watered solution. The resulting mixture was stirred until the ice melt then filtered off and the solid was washed with water. The solid was dissolved in dichloromethane dried over MgSO₄ and concentrated to yield a residue that was
25 purified by preparative HPLC to yield **P61** as a white solid (76 mg, 13%).

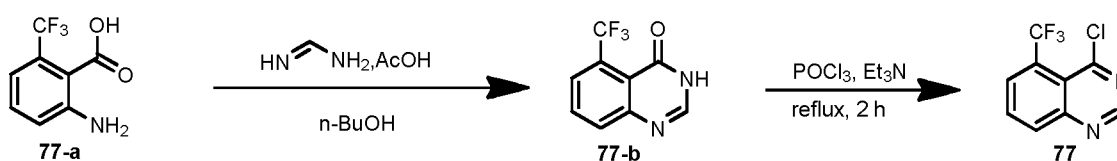
$m/z = 515 (M+H)^+$

30 ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.33 - 1.49 (m, 3 H), 1.51 - 1.92 (m, 4 H), 2.08 - 2.24 (m, 1 H), 2.25 - 2.43 (m, 3 H), 3.27 - 3.47 (m, 1 H), 3.48 - 3.63 (m, 4 H), 3.65 - 3.82 (m, 4 H), 3.87 - 4.10 (m, 5 H), 4.15 - 4.35 (m, 2 H), 5.22 (s, 1 H), 5.67 (br. s., 1 H), 5.83 (br. s., 1 H), 6.98 (d, J=7.7 Hz, 1 H), 7.31 (d, J=8.1 Hz, 1 H), 7.55 - 7.69 (m, 1 H), 8.38 (br. s., 1 H)

Synthesis of 4-(5-(azetidin-1-yl)-2-(1-(5-(trifluoromethyl)quinazolin-4-yl)piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-7-yl)morpholine P62



5 Synthesis of 4-chloro-5-(trifluoromethyl)quinazoline 77



Step 1 : synthesis of 5-(trifluoromethyl)quinazolin-4(3H)-one 77-b

10 A mixture of 2-amino-6-(trifluoromethyl)benzoic acid **77-a** (9.00 g, 43.9 mmol) and formamidine acetate (22.84 g, 219.4 mmol) in n-butanol (180 ml) was stirred at 100°C for 5 hours. The solvent was evaporated under vacuum. The residue was washed with ethanol (2 x 50 ml) and then dried in vacuum at 45°C for 1 hour to give intermediate **77-b** (9 g, yield: 91%).

15

Step 2 : synthesis of 4-chloro-5-(trifluoromethyl)quinazoline 77

Triethyl amine (29.3 ml, 210 mmol) was added to a mixture of intermediate **77-b** (8.00 g, 37.4 mmol) in phosphorus oxychloride (331 g, 2.16 mol) at 0°C. The mixture was refluxed for 2 hours. The solvent was evaporated under vacuum. The residue was dissolved in ethyl acetate (200 ml) and the mixture was added to ice (200 g). The separated organic layer was washed successively with water (1 x 100 ml), 10% sodium bicarbonate aqueous solution (2 x 100 ml), water (1 x 100 ml) and brine (1 x 100 ml). The separated organic layer was dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by column chromatography over silica gel (eluent: petroleum ether/ethyl acetate 1/0 to 1/1) to give intermediate **77** (7.97 g, 91.38%).

25

¹H NMR (400 MHz, CDCl₃) δ ppm 7.89 - 8.06 (m, 1 H) 8.22 (d, *J*=7.50 Hz, 1 H) 8.31 (d, *J*=8.38 Hz, 1 H) 9.11 (s, 1 H)

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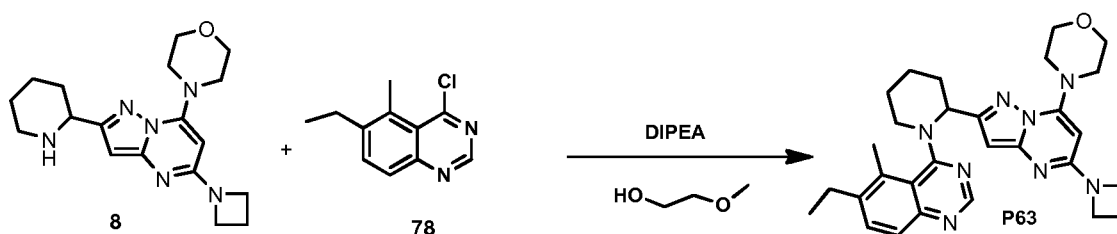
Synthesis of 4-(5-(azetidin-1-yl)-2-(1-(5-(trifluoromethyl)quinazolin-4-yl)piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-7-yl)morpholine P62

The mixture of intermediate **8** TFA salt (300 mg, 0.65 mmol), intermediate **77** (183 mg, 0.78 mmol) was dissolved in 2-methoxyethanol (20 mL) then diisopropylethyl amine (0.45 mL, 2.6 mmol) was added. The resulting mixture was stirred at 50°C overnight. The mixture was allowed to cool down to room temperature and poured in iced watered solution. The resulting mixture was stirred until all the ice is melt then the resulting solid was filtered off. The solid was successively washed with water, dissolved in dichloromethane, dried over MgSO₄ and concentrated to yield **P62** (250 mg, 70%) as a white light solid.

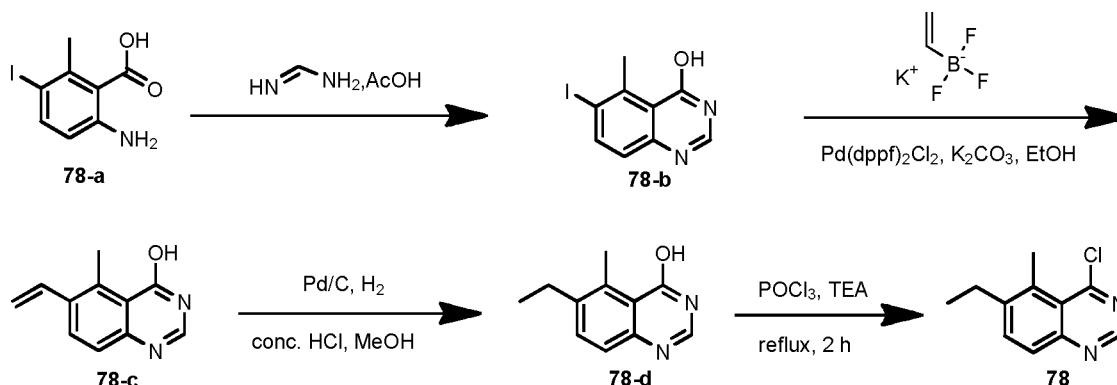
$m/z = 539 (M+H)^+$

¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.37 - 1.60 (m, 1 H), 1.69 (br. s., 2 H), 1.82 (d, J=11.9 Hz, 1 H), 2.07 - 2.40 (m, 4 H), 3.32 - 3.59 (m, 5 H), 3.62 - 3.80 (m, 5 H), 4.02 (t, J=7.4 Hz, 4 H), 5.20 (s, 1 H), 5.46 - 5.70 (m, 2 H), 7.81 - 7.91 (m, 2 H), 7.94 - 8.01 (m, 1 H), 8.49 (s, 1 H)

Synthesis of 4-(5-(azetidin-1-yl)-2-(1-(6-ethyl-5-methylquinazolin-4-yl)piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-7-yl)morpholine P63



Synthesis of 4-chloro-6-ethyl-5-methylquinazoline 78



Step 1 : synthesis of 6-iodo-5-methylquinazolin-4-ol **78-b**

A solution of 6-amino-3-iodo-2-methylbenzoic acid **78-a** (35.0 g, 126 mmol) and formamidine acetate (59.0 g, 567 mmol) in EtOH (500 ml) was refluxed overnight. The precipitate was filtered off and washed with ethanol to afford intermediate **78-b** (21 g, yield 52%).

Step 2 : synthesis of 5-methyl-6-vinylquinazolin-4-ol **78-c**

A solution of intermediate **78-b** (15.0 g, 52.4 mmol), potassium trifluoro(vinyl)borate (10.6 g, 79.0 mmol), Pd(dppf)₂Cl₂ (1.7 g, 2.6 mmol) and K₂CO₃ (21.74 g, 157.3 mmol) in EtOH (150 ml) was refluxed overnight. The solvent was evaporated under vacuum. The residue was treated with H₂O and CH₂Cl₂. The separated organic layer was dried over MgSO₄, filtrated and evaporated under vacuum. The residue was purified by high-performance liquid chromatography over SYNERGI (eluent: TFA water /acetonitrile 30/70 v/v). The product fractions were collected and the organic solvent was evaporated. The pH was adjusted to 7 with saturated NaHCO₃. The aqueous concentrate was extracted with CH₂Cl₂. The separated organic layer was concentrated under vacuum to afford intermediate **78-c** (3 g, yield 29%).

Step 3 : synthesis of 6-ethyl-5-methylquinazolin-4-ol **78-d**

A solution of intermediate **78-c** (3.0 g, 16 mmol) and HCl (11.5 ml) in MeOH (30 ml) was hydrogenated at room temperature (50 psi) with Pd/C (0.6 g) as a catalyst for 15 hours. After uptake of H₂ (32.50 mg, 16.11 mmol), the catalyst was filtered off and washed with methanol. The solvent was evaporated under vacuum to afford intermediate **78-d** (2.1 g, yield 66%).

Step 4 : synthesis of 4-chloro-6-ethyl-5-methylquinazoline **78**

A mixture of intermediate **78-d** (1.80 g, 9.56 mmol), triethylamine (2.220 ml, 15.95 mmol) and phosphorus oxychloride (60 ml) was refluxed for 2 hours. The solvent was evaporated under vacuum. The residue was dissolved in ethyl acetate (200 ml) and the mixture was added drop wise into ice (200 g). The separated organic layer was washed successively with water (1 x 100 ml), 10% sodium bicarbonate aqueous solution (2 x 100 ml), water (1 x 100 ml) and brine (1 x 100 ml). The organic layer was dried (MgSO₄), filtered and the filtrate was concentrated under vacuum. The residue was purified by column chromatography over silica gel (eluent: petroleum ether/ethyl acetate 1/0 to 5/1) to give intermediate **78** (1.434 g, 68.94%).

- 87 -

^1H NMR (400 MHz, CDCl_3) δ ppm 1.27 (t, $J=7.65$ Hz, 3 H) 2.88 (q, $J=7.53$ Hz, 2 H) 2.94 (s, 3 H) 7.75 (d, $J=8.53$ Hz, 1 H) 7.87 (d, $J=8.53$ Hz, 1 H) 8.89 (s, 1 H)

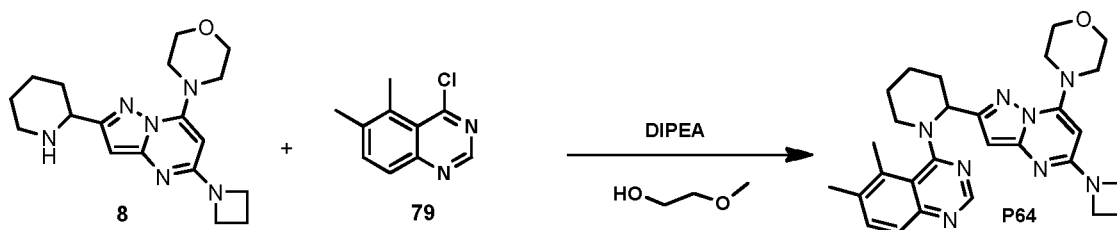
Step 5 : synthesis of 4-(5-(azetidin-1-yl)-2-(1-(6-ethyl-5-methylquinazolin-4-yl)-piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-7-yl)morpholine **P63**

The mixture of intermediate **8** TFA salt (400 mg, 0.87 mmol), intermediate **78** (235 mg, 1.14 mmol) was dissolved in 2-methoxyethanol (20 mL) then diisopropylethyl amine (0.604 mL, 3.5 mmol) was added. The resulting mixture was stirred at 50°C for 4 days. The mixture was allowed to cool down to room temperature and poured in iced watered solution. The resulting mixture was stirred until all the ice is melt then the resulting solid was filtered off. The solid was successively washed with water, dissolved in dichloromethane, dried over MgSO_4 and concentrated the residue was purified by preparative HPLC to yield **P63** (198 mg, 44%) as a white light solid.

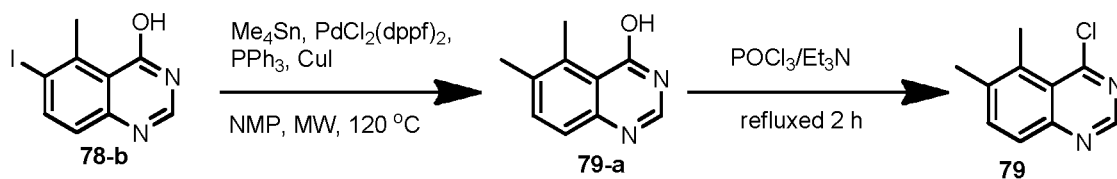
$m/z = 513 (\text{M}+\text{H})^+$

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.26 (t, $J=7.5$ Hz, 3 H), 1.37 - 1.58 (m, 1 H), 1.67 (br. s., 2 H), 1.77 - 1.94 (m, 1 H), 2.12 - 2.39 (m, 6 H), 2.75 - 2.89 (m, 6 H), 3.52 (br. s., 5 H), 3.65 - 3.80 (m, 4 H), 4.02 (t, $J=7.4$ Hz, 4 H), 5.21 (s, 1 H), 5.61 (s, 2 H), 7.49 - 7.63 (m, 2 H), 8.40 (s, 1 H)

Synthesis of 4-(5-(azetidin-1-yl)-2-(1-(5,6-dimethylquinazolin-4-yl)piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-7-yl)morpholine **P64**



Synthesis of 4-chloro-5,6-dimethylquinazoline **79**



Step 1 : synthesis of 5,6-dimethylquinazolin-4-ol **79-a**

PdCl₂(dppf)₂ (114 mg, 0.180 mmol) and PPh₃ (183 mg, 0.700 mmol) were added to a mixture of intermediate **78-b** (1.0 g, 3.5 mmol), Me₄Sn (940 mg, 5.20 mmol) and CuI (67 mg, 0.35 mmol) in NMP (15 ml) under N₂. The mixture was stirred under
5 microwave at 150°C for 0.5 hours. The resulting mixture was poured into water. The precipitate was filtered off and concentrated under vacuum. The residue was purified by column chromatography over silica gel (eluent: methanol/ethyl acetate 1/10) to afford intermediate **79-a** (0.7 g, yield: 27%).

10 Step 2 : synthesis of 4-chloro-5,6-dimethylquinazoline **79**

A mixture of intermediate **79-a** (700 mg, 4.02 mmol), phosphorus oxychloride (20 ml) and triethylamine (2.80 ml, 20.1 mmol) was refluxed for 2 hours. The solvent was evaporated under vacuum. The residue was dissolved in ethyl acetate (50 ml) and the mixture was added to ice (20g). The separated organic layer was successively washed
15 with water (1 x 20 ml), 10% sodium bicarbonate aqueous solution (2 x 20 ml), water (1 x 20 ml) and brine (1 x 20 ml). The organic layer was dried over magnesium sulfate, filtered, concentrated under vacuum. The residue was purified by column chromatography over silica gel (eluent: petroleum ether/ethyl acetate 1/0 to 10/1) to give intermediate **79** (598.30 mg, 73%).

20 ¹H NMR (400 MHz, CDCl₃) δ ppm 2.53 (s, 3 H) 2.92 (s, 3 H) 7.68 - 7.78 (m, 1 H) 7.80 - 7.89 (m, 1 H) 8.89 (s, 1 H).

Step 3 : synthesis of 4-(5-(azetidin-1-yl)-2-(1-(5,6-dimethylquinazolin-4-yl)piperidin-
25 2-yl)pyrazolo[1,5-a]pyrimidin-7-yl)morpholine **P64**

The mixture of intermediate **8** TFA salt (300 mg, 0.65 mmol), intermediate **79** (183 mg, 0.95 mmol) was dissolved in 2-methoxyethanol (15 mL) then diisopropylethyl amine (0.45 mL, 2.6 mmol) was added. The resulting mixture was stirred at 50°C for three days. The mixture was allowed to cool down to room temperature and poured in iced
30 watered solution. The resulting mixture was stirred until all the ice is melt then the resulting solid was filtered off. The solid was successively washed with water, dissolved in dichloromethane, dried over MgSO₄ and concentrated to yield compound **P64** (150 mg, 45%) as a white light solid.

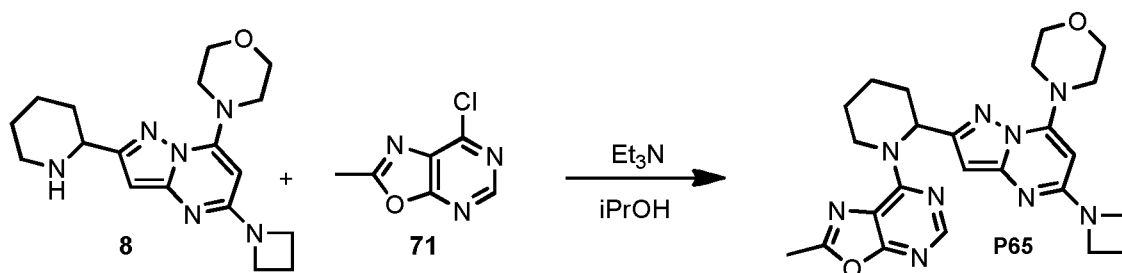
m/z = 499 (M+H)⁺

35 ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.67 (br. s., 3 H), 1.82 (d, J=11.7 Hz, 1 H), 2.09 - 2.37 (m, 4 H), 2.41 (s, 3 H), 2.67 - 2.86 (m, 4 H), 3.52 (br. s., 5 H), 3.65 - 3.83 (m, 4

- 89 -

H), 4.02 (t, $J=7.4$ Hz, 4 H), 5.21 (s, 1 H), 5.40 - 5.90 (m, 2 H), 7.48 - 7.59 (m, 2 H), 8.40 (s, 1 H)

Synthesis of 7-(2-(5-(azetidin-1-yl)-7-morpholinopyrazolo[1,5-a]pyrimidin-2-yl)-piperidin-1-yl)-2-methyloxazolo[5,4-d]pyrimidine P65

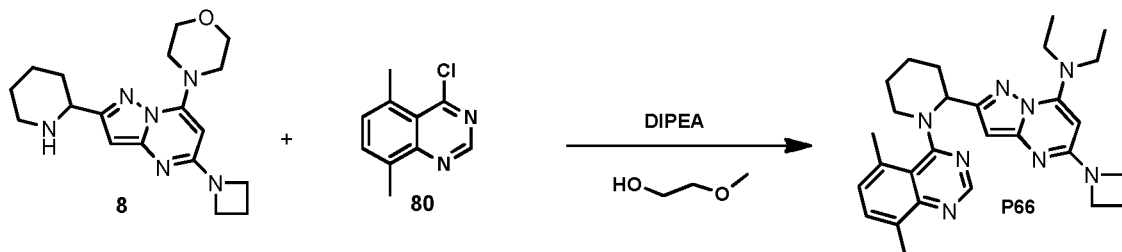


To a solution of intermediate **71** (20 mg, 0.12 mmol) in iPrOH (2 mL) was added triethyl amine (0.05 mL, 0.35 mmol, 3 eq.) and intermediate **8** (40 mg, 0.12 mmol, 1 eq.). The solution underwent microwave irradiation during 3 hours at 120°C. The resulting solution was concentrated in vacuum and purified by Prep HPLC to yield the title compound **P65** (21 mg, 37 %) as a white solid.

$m/z = 476$ (M+H)⁺

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.49 - 1.79 (m, 4 H) 1.84 - 2.02 (m, 1 H) 2.20 - 2.34 (m, 2 H) 2.40 (br. s., 1 H) 2.53 (s, 3 H) 3.15 - 3.27 (m, 1 H) 3.36 - 3.54 (m, 4 H) 3.55 - 3.69 (m, 4 H) 3.99 (t, $J=7.70$ Hz, 4 H) 4.99 (d, $J=13.32$ Hz, 1 H) 5.22 (s, 1 H) 5.73 (s, 1 H) 6.53 (d, $J=5.65$ Hz, 1 H) 8.24 (s, 1 H)

Synthesis of 4-(5-(azetidin-1-yl)-2-(1-(5,8-dimethylquinazolin-4-yl)piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-7-yl)morpholine P66



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The mixture of intermediate **8** TFA salt (300 mg, 0.65 mmol), 4-chloro-5,8-dimethylquinazoline **80** (175 mg, 0.9 mmol) was dissolved in 2-methoxyethanol (15 mL) then diisopropylethyl amine (0.45 mL, 2.6 mmol) was added. The resulting mixture was

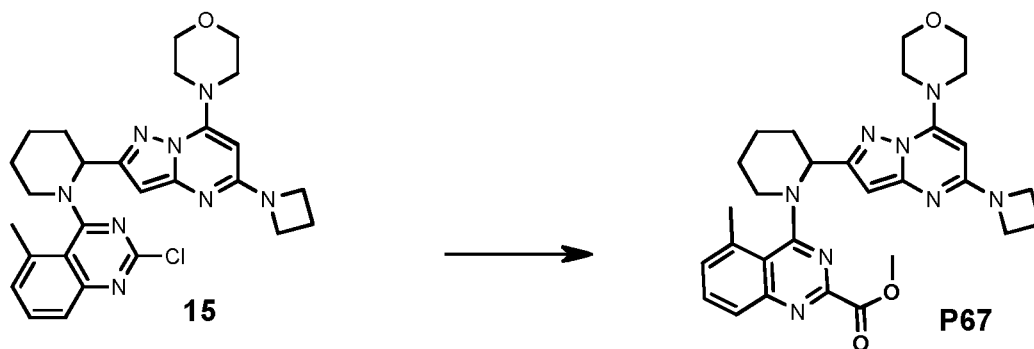
stirred at 50°C for three days. The mixture was allowed to cool down to room temperature and poured in iced watered solution. The resulting mixture was stirred until all the ice is melt then the resulting solid was filtered off. The solid wasn't pure it was dissolved in dichloromethane the water layer was extracted with dichloromethane all the organics were combined and dried over MgSO₄.

The solvent was removed and the residue was purified by column chromatography using dichloromethane and methanol. The compound **P66** was isolated as a white solid (150 mg, 46%).

$m/z = 499 (M+H)^+$

¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.51 (br. s., 1 H), 1.64 (d, J=7.7 Hz, 2 H), 1.82 (d, J=7.9 Hz, 1 H), 2.18 (br. s., 2 H), 2.28 (quin, J=7.4 Hz, 2 H), 2.56 (s, 3 H), 2.78 (s, 3 H), 3.35 - 3.56 (m, 6 H), 3.61 - 3.74 (m, 4 H), 3.98 (t, J=7.4 Hz, 4 H), 5.17 (s, 1 H), 5.46 (br. s., 1 H), 5.62 (br. s., 1 H), 7.18 (d, J=7.3 Hz, 1 H), 7.46 (d, J=7.3 Hz, 1 H), 8.50 (s, 1 H)

Synthesis of methyl 4-(2-(5-(azetidin-1-yl)-7-morpholinopyrazolo[1,5-a]pyrimidin-2-yl)piperidin-1-yl)-5-methylquinazoline-2-carboxylate **P67**



Intermediate **15** (100 mg, 0.13 mmol) was dissolved in 30 mL THF/MeOH (3/1) in an autoclave. Potassium acetate (20 mg, 0.20 mmol, 1.5 eq.), Pd(OAc)₂ (3 mg, 0.013 mmol, 0.1 eq.) and 1,3-bis(diphenylphosphino)propane (11 mg, 0.027 mmol, 0.2 eq.) were added. The autoclave was heated to 120°C under 50 bar carbon monoxide pressure during 8 hours. After cooling to room temperature the solution was concentrated *in vacuum* and diluted with DCM then washed with saturated solution of NaHCO₃. The combined organics were dried with MgSO₄, filtered off and concentrated *in vacuum*. The crude was further purified on HPLC giving methyl compound **P67**

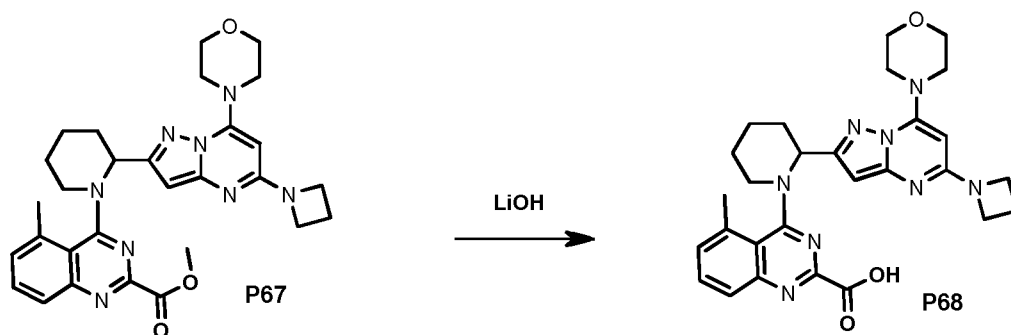
- 91 -

(43 mg, 60%).

 $m/z = 543 \text{ (M+H)}^+$

^1H NMR (400 MHz, 420 K, DMSO- d_6) δ ppm 1.42 - 1.59 (m, 1 H) 1.62 - 1.70 (m, 2 H)
 1.77 - 1.88 (m, 1 H) 2.14 - 2.33 (m, 4 H) 2.80 (s, 3 H) 3.43 - 3.55 (m, 5 H) 3.64 - 3.74
 (m, 5 H) 3.85 (s, 3 H) 3.99 (t, $J=7.41$ Hz, 4 H) 5.18 (s, 1 H) 5.61 (m, $J=3.98$ Hz, 1 H)
 5.66 (s, 1 H) 7.39 (t, $J=4.22$ Hz, 1 H) 7.66 (d, $J=4.30$ Hz, 2 H)

Synthesis of 4-(2-(5-(azetidin-1-yl)-7-morpholinopyrazolo[1,5-a]pyrimidin-2-yl)-piperidin-1-yl)-5-methylquinazoline-2-carboxylic acid P68

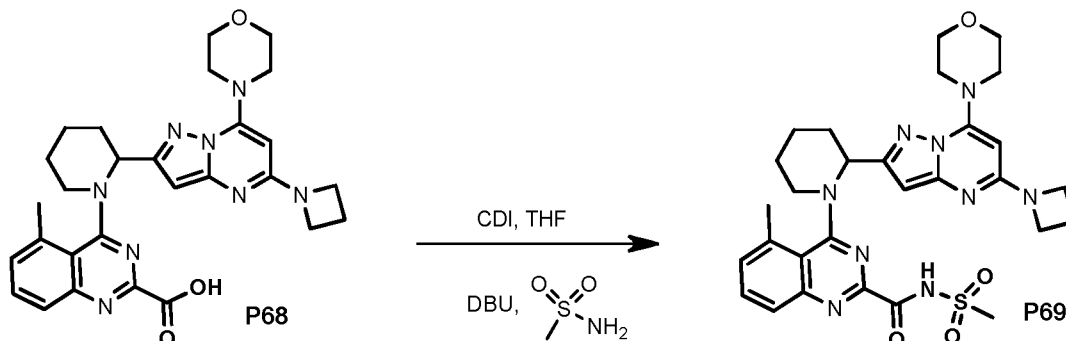


To a solution of compound **P67** (300 mg, 0.38 mmol) in 30 mL THF/water (3/1) was added LiOH (28 mg, 1.16 mmol, 3 eq.). The reaction mixture was stirred for 2 days at room temperature. The reaction mixture was then adjusted to pH = 6 with HCl (1M in water) and concentrated *in vacuum*. The crude was purified on HPLC to give compound **P68** (110 mg, 53%).

 $m/z = 529 \text{ (M+H)}^+$

^1H NMR (400 MHz, DMSO- d_6) δ ppm 1.44 - 1.62 (m, 1 H) 1.64 - 1.76 (m, 2 H) 1.78 - 1.91 (m, 1 H) 2.16 - 2.37 (m, 4 H) 3.24 (s, 3 H) 3.46 - 3.59 (m, 5 H) 3.68 - 3.77 (m, 5 H) 4.02 (t, $J=7.37$ Hz, 4 H) 5.22 (s, 1 H) 5.54 - 5.88 (m, 2 H) 7.39 - 7.44 (m, 1 H) 7.68 - 7.73 (m, 2 H)

Synthesis of 4-(2-(5-(azetidin-1-yl)-7-morpholinopyrazolo[1,5-a]pyrimidin-2-yl)-piperidin-1-yl)-5-methyl-N-(methylsulfonyl)quinazoline-2-carboxamide P69



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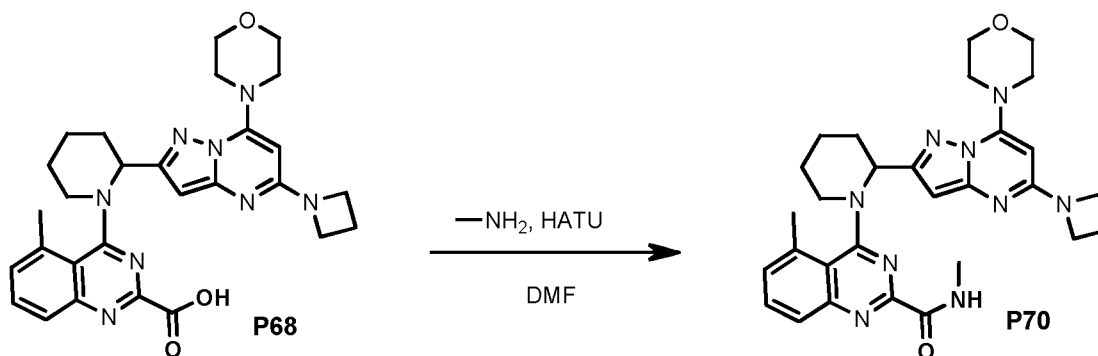
Compound **P68** (150 mg, 0.28 mmol) was dissolved in 10 mL THF and CDI (92 mg, 0.56 mmol, 2 eq.) was added. The mixture was heated to 50°C and after one hour stirring, DBU (0.08 mL, 0.56 mmol, 2 eq.) and methyl sulfonamide (70 mg, 0.74 mmol, 2.6 eq.) were added to the solution. After 1 hour stirring at 50°C the solution was concentrated *in vacuum* and purified by column chromatography eluting with a gradient starting from 0 % to 10 % MeOH in DCM giving compound **P69** (65 mg, 38 %).

$m/z = 606 \text{ (M+H)}^+$

$^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.46 - 1.60 (m, 1 H) 1.62 - 1.73 (m, 2 H) 1.77 - 1.89 (m, 1 H) 2.15 - 2.38 (m, 4 H) 2.80 (s, 3 H) 3.27 (s, 3 H) 3.42 - 3.60 (m, 5 H) 3.64 - 3.77 (m, 5 H) 4.00 (t, $J=7.42$ Hz, 4 H) 5.20 (s, 1 H) 5.68 - 5.77 (m, 2 H) 7.38 - 7.47 (m, 1 H) 7.65 - 7.76 (m, 2 H)

Synthesis of 4-(2-(5-(azetidin-1-yl)-7-morpholinopyrazolo[1,5-a]pyrimidin-2-yl)-piperidin-1-yl)-N,5-dimethylquinazoline-2-carboxamide P70

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To a solution of compound **P68** (240 mg, 0.45 mmol) in DMF (5 mL) was added

- 93 -

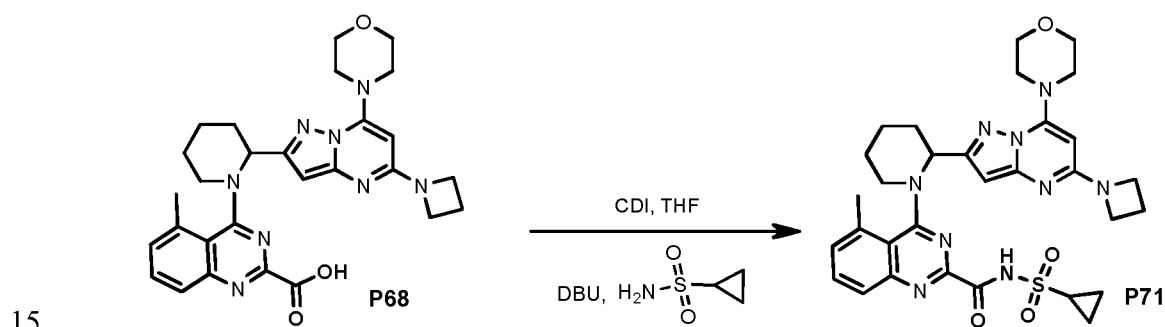
DIPEA (0.23 mL, 1.36 mmol, 3 eq.), methyl amine (0.08 mL, 0.90 mmol, 2 eq.) and HATU (431.5 mg, 1.135 mmol, 2.5 eq.). The resulting solution was stirred for 1 hour at room temperature. Water (5 mL) was added and the solution was concentrated *in vacuum* and purified on HPLC to give compound **P70** (87 mg, 36%).

5 $m/z = 542 \text{ (M+H)}^+$

$^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ ppm 1.45 - 1.60 (m, 1 H) 1.67 (br. s., 2 H) 1.76 - 1.90 (m, 1 H) 2.10 - 2.24 (m, 2 H) 2.28 (quin, $J=7.37$ Hz, 2 H) 2.79 - 2.87 (m, 6 H) 3.35 - 3.62 (m, 6 H) 3.61 - 3.75 (m, 4 H) 3.98 (t, $J=7.37$ Hz, 4 H) 5.19 (s, 1 H) 5.54 (br. s., 1 H) 5.68 (br. s., 1 H) 7.29 - 7.42 (m, 1 H) 7.58 - 7.72 (m, 2 H) 8.04 (br. s., 1 H)

10

Synthesis of 4-(2-(5-(azetidin-1-yl)-7-morpholinopyrazolo[1,5-a]pyrimidin-2-yl)-piperidin-1-yl)-N-(cyclopropylsulfonyl)-5-methylquinazoline-2-carboxamide **P71**



Compound **P68** (150 mg, 0.28 mmol) was dissolved in 10 mL THF and CDI (92 mg, 0.56 mmol, 2 eq.) was added. The mixture was heated to 50°C and after one hour stirring, DBU (0.12 mL, 0.85 mmol, 3 eq.) and cyclopropyl sulfonamide (85 mg, 0.709 mmol, 2.5 eq.) were added to the solution. After 1 hour stirring at 50°C the solution was concentrated *in vacuum* and purified by column chromatography eluting with a gradient starting from 0 % to 10 % MeOH in DCM and further purified on HPLC giving compound **P71** (65 mg, 44 %).

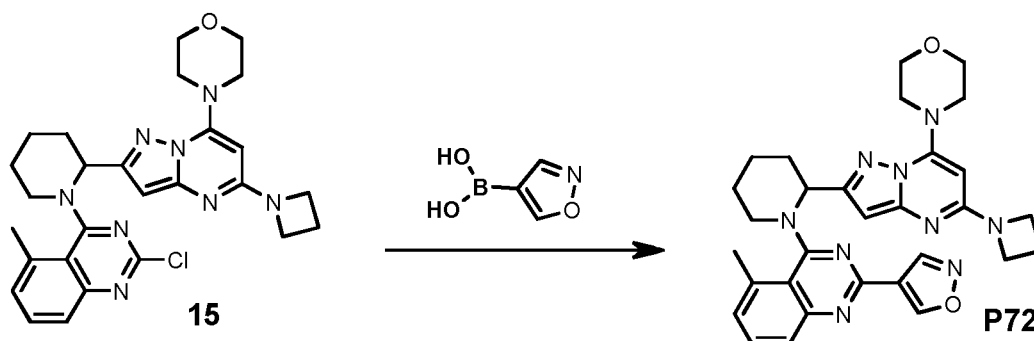
20

25 $m/z = 632 \text{ (M+H)}^+$

$^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ ppm 0.99 - 1.10 (m, 2 H) 1.13 - 1.26 (m, 2 H) 1.44 - 1.93 (m, 4 H) 2.12 - 2.35 (m, 4 H) 2.81 (s, 3 H) 2.95 - 3.02 (m, 1 H) 3.41 - 3.60 (m, 5 H) 3.63 - 3.75 (m, 5 H) 3.99 (t, $J=7.42$ Hz, 4 H) 5.19 (s, 1 H) 5.65 - 5.77 (m, 2 H) 7.42 (d, $J=6.67$ Hz, 1 H) 7.67 - 7.75 (m, 2 H)

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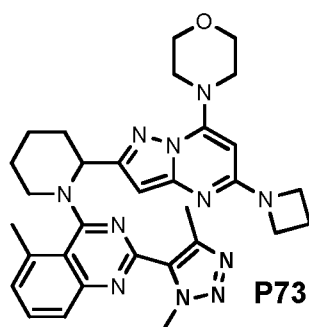
Synthesis of 4-(5-(azetidin-1-yl)-2-(1-(2-(isoxazol-4-yl)-5-methylquinazolin-4-yl)-piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-7-yl)morpholine P72



Intermediate **15** (200 mg, 0.369 mmol), isoxazol-4-ylboronic acid (cas = 1008139-25-0, 83 mg, 0.738 mmol) and K_2CO_3 (cas = 584-08-7, 102 mg, 0.738 mmol) were dissolved in 1,4-dioxane (3 ml) and water (0.3 ml). The solution was degazed by N_2 for 5 minutes. The reaction tube was sealed and the mixture was heated at 120°C for 30 minutes in a microwave oven. Then the solution was diluted with DCM and water. The product was extracted 2 times with DMC. The organic layers were dried over Na_2SO_4 , filtered and evaporated to dryness and the crude was purified by column chromatography eluting with a gradient of MeOH in DCM, starting with 0% to 5% MeOH. After evaporation of the concerning fractions we get a brown solid. The solid was triturated in hot DIPE. After cooling to room temperature, the precipitate was filtered. Because the product was still not pure, the brown solid was triturated once again with hot DIPE. After cooling the title compound **P72** was obtained by filtration (21 mg, 10%). $m/z = 552.3$ (M+H).

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.25 - 2.46 (m, 8 H) 2.66 (s, 3 H) 3.24 - 4.72 (m, 14 H) 5.09 - 9.25 (m, 8 H)

Synthesis of 4-(5-(azetidin-1-yl)-2-(1-(2-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-5-methylquinazolin-4-yl)piperidin-2-yl)pyrazolo[1,5-a]pyrimidin-7-yl)morpholine P73



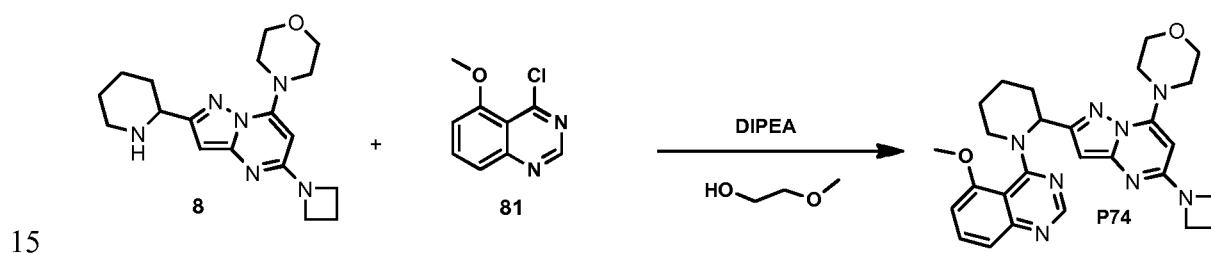
Compound **P73** was prepared in the same manner as compound **P72** using intermediate 15 and 1,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-1,2,3-triazole as starting material.

5 $m/z = 580$ (M+H).

MP : 238,91°C.

^1H NMR (400 MHz, CDCl_3) δ ppm 1.29 - 2.05 (m, 4 H) 2.12 - 2.49 (m, 4 H) 2.55 - 2.76 (m, 3 H) 2.82 - 3.00 (m, 3 H) 3.13 - 4.16 (m, 14 H) 4.30 - 4.49 (m, 3 H) 4.93 - 6.11 (m, 3 H) 7.27 - 7.34 (m, 1 H) 7.53 - 7.79 (m, 2 H)

Synthesis of 4-(5-(azetidin-1-yl)-2-(1-(5-methoxyquinazolin-4-yl)piperidin-2-yl)-pyrazolo[1,5-a]pyrimidin-7-yl)morpholine **P74**



The mixture of intermediate **8** TFA salt (300 mg, 0.65 mmol), 4-chloro-5-methoxyquinazoline **81** (153 mg, 0.78 mmol) was dissolved in 2-methoxyethanol (15 mL) then diisopropylethyl amine (0.45 mL, 2.6 mmol) was added. The resulting mixture was stirred at 50°C overnight. The mixture was allowed to cool down to room temperature and poured in iced water solution. The resulting mixture was stirred until all the ice is melt then the resulting solid was filtered off. The solid was successively washed with water, dissolved in dichloromethane, dried over MgSO_4 and concentrated to yield compound **P74** (267 mg, 81%) as a white light solid.

25 $m/z = 501$ (M+H).

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.58 - 1.82 (m, 4 H), 2.02 - 2.14 (m, 1 H), 2.22 - 2.39 (m, 3 H), 3.28 - 3.41 (m, 1 H), 3.45 - 3.56 (m, 4 H), 3.66 - 3.75 (m, 4 H), 3.92 (s, 3 H), 3.99 (t, $J=7.5$ Hz, 5 H), 5.18 (s, 1 H), 5.63 (s, 1 H), 5.68 (br. s., 1 H), 6.95 (d, $J=7.5$ Hz, 1 H), 7.28 (d, $J=8.4$ Hz, 1 H), 7.59 (t, $J=8.1$ Hz, 1 H), 8.35 (s, 1 H).

B. Pharmacological examples**B.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 μ L 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 μ L of a HeLa cell suspension (3,000 cells/well) were plated. Medium, virus- and mock-infected controls were included in each test. The wells contain 0.05% DMSO per volume. Cells were incubated at 37°C in a 5% CO₂ atmosphere. Three days post-virus exposure, viral replication was quantified by measuring GFP expression in the cells by an in house developed MSM laser microscope (Tibotec, Beerse, Belgium). The EC₅₀ was defined as the 50% inhibitory concentration for GFP expression. In parallel, compounds were incubated for three days in a set of white 384-well microtiter plates (Corning) and the cytotoxicity of compounds in HeLa cells was determined by measuring the ATP content of the cells using the ATPlite kit (Perkin Elmer, Zaventem, Belgium) according to the manufacturer's instructions. The CC₅₀ was defined as the 50% concentration for cytotoxicity.

Table B-1 : antiviral data and selectivity index

Co. No.	RSV HELA pEC ₅₀	SI TOX HELA	Co. No.	RSV HELA pEC ₅₀	SI TOX HELA
P1	6.1	4.4	P37	6.5	4.3
P2	6.5	4.4	P40	6.8	4.7
P3	5.4	4.6	P41	7.1	<4
P4	6.8	<4	P42	5.6	<4.6
P5	6.6	<5	P43	4.8	4.2

Co. No.	RSV HELA pEC ₅₀	SI TOX HELA	Co. No.	RSV HELA pEC ₅₀	SI TOX HELA
P6	8.3	<4.0	P44	6.1	4.2
P7	5.7	<4	P45	6.7	4.2
P8	8.1	<4	P46	6.5	4.3
P9	8.3	<4.6	P47	6.3	4.6
P10	6.2	<4.3	P48	7.9	4.5
P11	6.9	<4.6	P49	6.1	4.3
P12	6.7	<4	P50	6.2	4.3
P13	6.4	4.3	P51	6.5	4.3
P14	6.1	<4	P52	7.1	4.7
P15	6.6	4.0	P53	7.3	4.6
P16	7.1	4.3	P54	7.6	4.5
P17	8.4	4.4	P55	7.8	4.3
P18	<6	<4.3	P57	6.2	4.5
P19	8.0	<4.3	P58	6.3	<4
P20	6.2	5.4	P59	6.4	4.3
P21	6.4	<4.6	P60	6.9	4.3
P22	7.1	4.5	P61	7.5	<4
P23	7.8	<4.6	P62	7.0	4.3
P24	<4.6	<4.6	P63	6.4	4.4
P25	7.5	<4.6	P64	7.8	<4.6
P26	7.6	4.3	P65	7.8	<4.6
P27	6.2	4.5	P66	7.0	-
P28	6.1	<4	P67	6.9	<4.3
P29	6.4	4.5	P68	6.5	<4.6
P30	6.2	4.6	P69	6.5	<4
P31	6.8	4.8	P70	6.2	4.3
P32	7.3	<4	P71	6.4	<4
P33	7.88	4.2	P72	7.6	4.5
P34	6.2	4.3	P73	6.9	4.8
P35	7.2	4.4	P74	7.8	<4.6
P36	6.3	<4			

C. 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.

5

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

C.1. Tablets

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

- 15 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.

C.2. Suspension

- 20 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.

C.3. Injectable

- 25 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.

C.4. Ointment

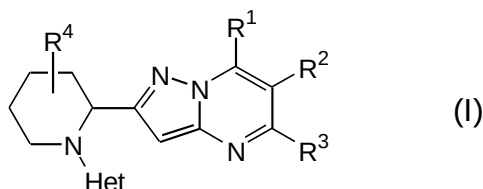
	Active ingredient	5 to 1000 mg
30	Stearyl alcohol	3 g
	Lanoline	5 g
	White petroleum	15 g
	Water	ad 100 g

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

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

Claims

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



5

R¹ is hydrogen, hydroxy, C₁₋₄alkyl, mono- or di(C₁₋₄alkyl)amino, or Heterocyclyl¹;

R² is hydrogen or C₁₋₄alkyl;

10 R³ is C₃₋₆cycloalkyl or Heterocyclyl²;

R⁴ is hydrogen, C₁₋₆alkyl, hydroxy, or halo;

Heterocyclyl¹ is azetidiny, pyrrolidiny, piperidiny, piperaziny, or morpholiny;

wherein each Heterocyclyl¹ is optionally substituted with one or two substituents selected from C₁₋₄alkyl, hydroxy, halo,

15 polyhaloC₁₋₄alkyl, C₁₋₄alkyloxycarbonyl, amino, C₁₋₄alkylaminocarbonyl, or C₁₋₄alkylsulfonyl;

Heterocyclyl² is azetidiny, pyrrolidiny, piperidiny, piperaziny, or morpholiny;

wherein each Heterocyclyl² is optionally substituted with one or two substituents selected from C₁₋₄alkyl, hydroxy, halo,

20 polyhaloC₁₋₄alkyl, C₁₋₄alkyloxycarbonyl, amino, C₁₋₄alkyloxycarbonylamino, or C₁₋₄alkylsulfonyl;

Het is selected from furanyl, thiophenyl, pyrazolyl, oxazolyl, thiazolyl, pyridyl,

pyridaziny, pyrimidinyl, pyraziny, quinolyl, isoquinolyl, cinnoliny,

quinazoliny, quinoxaliny, 1,5-naphthyridiny, 1,6-naphthyridiny,

25 1,7-naphthyridiny, 1,8-naphthyridiny, pyrido[2,3-d]pyrimidinyl,

pyrido[3,2-d]pyrimidinyl, 9H-puriny, thiazolo[5,4-d]pyrimidinyl,

7H-pyrrolo[2,3-d]pyrimidinyl, oxazolo[5,4-d]pyrimidinyl, thieno[2,3-d]-

pyrimidinyl, or thieno[3,2-d]pyrimidinyl; wherein each Het is optionally

substituted with one, two or three substituents each independently selected

30 from halo, C₁₋₄alkyl, C₁₋₄alkyloxy, C₁₋₄alkylthio, hydroxy, amino, mono- or di(C₁₋₄alkyl)amino, hydroxycarbonyl, C₁₋₄alkyloxycarbonyl,

C₁₋₄alkylsulfonylamino, aminocarbonyl, trifluoromethyl,

C₁₋₄alkyloxycarbonylamino, di(C₁₋₄alkyloxycarbonyl)amino,

C₁₋₄alkylsulfonylaminocarbonyl, C₁₋₄alkylaminocarbonyl,

C₁₋₄alkyloxyC₁₋₆alkyloxycarbonylamino, di(C₁₋₄alkyl)aminosulfonyl-aminocarbonyl, C₃₋₆cycloalkylsulfonylamino, HO-NH-(C=NH)-; oxazolyl or triazolyl each optionally substituted with one or two C₁₋₄alkyl; or a pharmaceutically acceptable acid addition salt thereof.

5

2. The compound as claimed in claim 1 wherein

R¹ is hydrogen, C₁₋₄alkyl, mono- or di(C₁₋₄alkyl)amino, or Heterocyclyl¹;

R² is hydrogen or C₁₋₄alkyl;

R³ is C₃₋₆cycloalkyl or Heterocyclyl²;

10

R⁴ is hydrogen;

Heterocyclyl¹ is piperazinyl or morpholinyl; wherein each Heterocyclyl¹ is optionally substituted with one substituent selected from C₁₋₄alkyloxycarbonyl, C₁₋₄alkylaminocarbonyl, or C₁₋₄alkylsulfonyl;

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Heterocyclyl² is azetidyl, or pyrrolidinyl; wherein each Heterocyclyl² is optionally substituted with one substituent selected from hydroxy or amino;

Het is selected from quinazolinyl, pyrido[2,3-d]pyrimidinyl, thiazolo[5,4-d]-pyrimidinyl, 7H-pyrrolo[2,3-d]pyrimidinyl, oxazolo[5,4-d]pyrimidinyl, or thieno[2,3-d]pyrimidinyl; wherein each Het is optionally substituted with one, two or three substituents each independently selected from halo, C₁₋₄alkyl, C₁₋₄alkyloxy, C₁₋₄alkylthio, hydroxy, hydroxycarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylsulfonylamino, aminocarbonyl, trifluoromethyl, C₁₋₄alkyloxy-carbonylamino, di(C₁₋₄alkyloxycarbonyl)amino, C₁₋₄alkylsulfonylamino-carbonyl, C₁₋₄alkylaminocarbonyl, C₁₋₄alkyloxyC₁₋₆alkyloxycarbonylamino, di(C₁₋₄alkyl)aminosulfonylamino, C₃₋₆cycloalkylsulfonylamino-carbonyl, HO-NH-(C=NH)-; oxazolyl or triazolyl each optionally substituted with one or two C₁₋₄alkyl.

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3. The compound as claimed in claim 1 wherein R¹ is Heterocyclyl¹, R² is hydrogen, and R³ is Heterocyclyl².

4. The compound as claimed in claim 1 wherein R¹ is hydrogen, R² is C₁₋₄alkyl, and R³ is Heterocyclyl².

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5. The compound as claimed in claim 1 wherein R¹ is hydrogen, R² is hydrogen, and R³ is Heterocyclyl².
- 5 6. The compound as claimed in claim 1 wherein R¹ is C₁₋₄alkyl, R² is hydrogen, and R³ is Heterocyclyl².
7. The compound as claimed in claim 1 wherein R¹ is hydrogen, R² is hydrogen, and R³ is C₃₋₆cycloalkyl.
- 10 8. The compound as claimed in any one of claims 1 to 7 wherein Het is quinazoliny.
9. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically active amount of a compound as claimed in any of claims 1 to 15 8.
10. A process for preparing a pharmaceutical composition as claimed in claim 9 wherein a therapeutically active amount of a compound as claimed in any of claims 1 to 8 is intimately mixed with a pharmaceutically acceptable carrier.
- 20 11. A compound as claimed in any of claims 1 to 8 for use as a medicine.
12. A compound as claimed in any of claims 1 to 8, or a pharmaceutical composition as claimed in claim 9 for use in the treatment of a respiratory syncytial virus 25 infection.