

IMIDAZO[1,2-A]PYRAZIN DERIVATIVES AND THEIR USE IN THE TREATMENT OF A HELMINTH INFECTION

Field of Invention

5 This invention relates to compounds of formula (I), (II) and (III) and pharmaceutically acceptable salts or solvates thereof which impair viability of *Schistosoma* and *Fasciola* parasites. The invention also relates to pharmaceutical compositions comprising such compounds, salts or solvates thereof and to the use of such compounds as medicaments, in particular in the treatment or prevention of a helminth infection such as in particular schistosomiasis, also known as bilharzia, and/or
10 fascioliasis.

Background to the invention

Schistosomiasis is one of the major neglected diseases affecting over 200 million people across sub-Saharan Africa, the Middle East and South America. It is a parasitic
15 disease caused by flatworms of the genus *Schistosoma*, such as but not limited to *S. mansoni*, *S. haematobium* and *S. japonicum*. Infections are due to the larval stage of the worm, which then develop through a juvenile stage to adult worms (Colley, D. G., Bustinduy, A. L., Secor, W. E., and King, C. H. (2014) Human schistosomiasis. Lancet 383, 2253.).

20 Two drugs, praziquantel and oxamniquine, are approved for the treatment of schistosomiasis. Oxamniquine has a narrow spectrum of activity i.e. only *S. mansoni* (Spangenberg T., ACS Infect. Dis. 2021, 7, 5, 939–942).

25 Based on a recently described method for high throughput screening using larval stage *Schistosoma* worms and subsequently used this methodology to identify a set of hit molecules. Paveley, R. A., et al. (2012) "Whole organism high-content screening by label-free, image-based Bayesian classification for parasitic diseases." PLoS Negl Trop Dis 6(7): e1762 and Mansour, N. R., et al. (2016) "High Throughput Screening Identifies Novel Lead Compounds with Activity against Larval, Juvenile and Adult
30 *Schistosoma mansoni* PLoS Negl Trop Dis 10(4): e0004659 a series based on imidazopyrazine derivative with single digit μM EC_{50} against the larval, juvenile and adult stages of *S. mansoni* was disclosed.

WO2018130853 A1 describes the preparation of bicyclic compounds and their use in the treatment of schistosomiasis.

5 WO2020016235 A1 describes the preparation of bicyclic compounds and their use in the treatment of schistosomiasis.

There remains a need in the art for further compounds active as anti-schistosomes which combine good pharmacokinetic properties, sufficient activity (preferably against all three main infective species of worm and against both juvenile and adult worms) and adequate solubility.

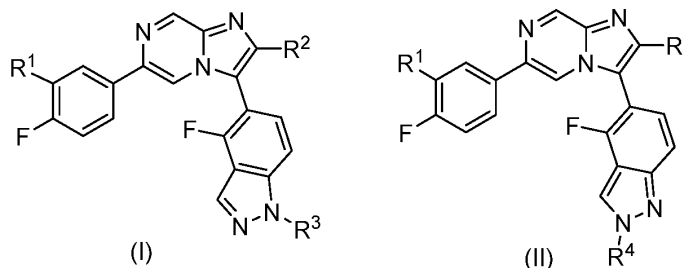
We surprisingly found that compounds with the formula (I), (II), (III), have sufficient potency in combination with other advantageous properties such as in particular solubility.

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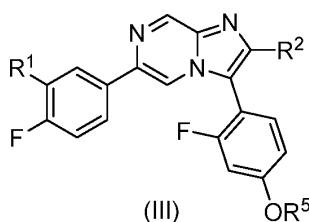
Summary of the Invention

In a first embodiment, the invention provides a compound of formula (I), (II) or (III) or a pharmaceutically acceptable salt or solvate thereof,

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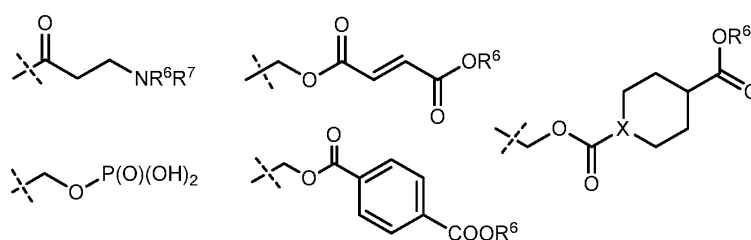
wherein:

R¹ is cyclopropyl, cyclobutyl, F or C1-C3 alkyl optionally substituted with up to five F atoms;

R^2 is cyclopropyl, cyclobutyl, F or C1-C3 alkyl optionally substituted with up to five F atoms;

R^3 and R^4 represent each, independently from one another, a residue selected from following group:

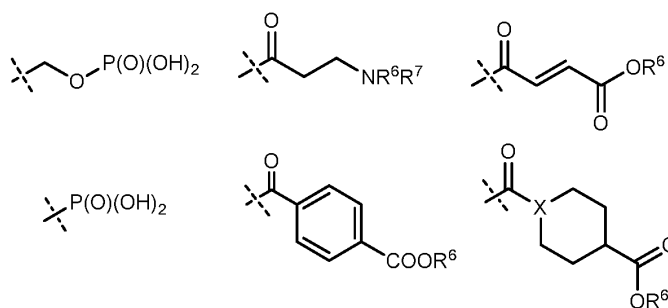
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R^5 is a residue selected from following group:

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X is CH or N; and

R^6 and R^7 represent each, independently from one another, H or CH_3 .

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In a second embodiment, the present invention provides a compound of formula (I), (II) or (III), as defined above, or a pharmaceutically acceptable salt or solvate thereof, for use in therapy.

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In a third embodiment, the present invention provides a compound of formula (I), (II) or (III), as defined above, or a pharmaceutically acceptable salt or solvate thereof, for use in the treatment of a helminth infection with blood and/or liver flukes. In particular, the present invention provides a compound of formula (I), (II) or (III), as defined above, or a pharmaceutically acceptable salt or solvate thereof, for use in the treatment of helminth infections, wherein the helminth infection is schistosomiasis and/or fascioliasis.

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In a fourth embodiment, the present invention provides the use of a compound of formula (I), (II) or (III), as defined above, or a pharmaceutically acceptable salt

or solvate thereof, for the manufacture of a medicament for the treatment of a helminth infection such as in particular schistosomiasis and/or fascioliasis.

5 In a fifth embodiment, the present invention provides a method for treating a helminth infection such as in particular schistosomiasis and/or fascioliasis comprising administering a therapeutically effective amount of a compound of formula (I), (II) or (III), as defined above, or a pharmaceutically acceptable salt or solvate thereof, to a patient in need thereof.

10 In a sixth embodiment, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I), (II) or (III), as defined above, or a pharmaceutically acceptable salt or solvate thereof. In a further embodiment, such a pharmaceutical composition further comprises an anthelmintic agent. And in further important embodiment such a pharmaceutical composition further comprises a pharmaceutically acceptable carrier, adjuvant or excipient thereof.

Detailed description of the Invention

Definitions

20 The following definitions apply to the terms as used throughout this specification, unless otherwise limited in specific instances.

As used herein, the term "C1-C3 alkyl" means both straight and branched chain saturated hydrocarbon groups having 1, 2 or 3 carbon atoms, such as: methyl, ethyl, n-propyl and iso-propyl.

25 "Pharmaceutically acceptable salt" means a salt such as those described in standard texts on salt formation, see for example: P. Stahl, *et al.*, Handbook of Pharmaceutical Salts: Properties, Selection and Use (VCHA/Wiley-VCH, 2002), or S.M. Berge, *et al.*, "Pharmaceutical Salts" (1977) *Journal of Pharmaceutical Sciences*, **66**, 1-19. Suitable salts according to the invention include those
30 formed with organic or inorganic acids or bases. In particular, suitable salts formed with acids according to the invention include those formed with mineral acids, strong organic carboxylic acids, such as alkanecarboxylic acids of 1 to 4 carbon atoms which are unsubstituted or substituted, for example, by halogen,

such as saturated or unsaturated dicarboxylic acids, such as hydroxycarboxylic acids, such as amino acids, or with organic sulfonic acids, such as C1-C4 alkyl- or aryl-sulfonic acids which are unsubstituted or substituted, for example by halogen. Pharmaceutically acceptable acid addition salts include those formed from hydrochloric, hydrobromic, sulphuric, nitric, citric, tartaric, acetic, phosphoric, lactic, pyruvic, acetic, trifluoroacetic, succinic, perchloric, fumaric, maleic, glycolic, lactic, salicylic, oxaloacetic, methanesulfonic, ethanesulfonic, p-toluenesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic, benzenesulfonic, isethionic, ascorbic, malic, phthalic, aspartic, and glutamic acids, lysine and arginine. Other acids, which may or may not in themselves be pharmaceutically acceptable, may be useful as intermediates in obtaining the compounds of the invention and their pharmaceutical acceptable acid addition salts.

Pharmaceutically acceptable base salts include ammonium salts, alkali metal salts, for example those of potassium and sodium, alkaline earth metal salts, for example those of calcium and magnesium, and salts with organic bases, for example dicyclohexylamine, N-methyl-D-glucamine, morpholine, thiomorpholine, piperidine, pyrrolidine, a mono-, di- or tri-lower alkylamine, for example ethyl-, tert-butyl-, diethyl-, diisopropyl-, triethyl-, tributyl- or dimethyl-propylamine, or a mono-, di- or trihydroxy lower alkylamine, for example mono-, di- or triethanolamine. Corresponding internal salts may furthermore be formed.

"Pharmaceutically acceptable solvate" means a molecular complex comprising the compound of the invention and one or more pharmaceutically acceptable solvent molecules, for example, water or ethanol. Those skilled in the art of organic chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as "solvates". For example, a complex with water is known as a "hydrate". Solvates, such as hydrates, exist when the drug substance incorporates solvent, such as water, in the crystal lattice in either any organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as "solvates". For example, a complex with water is known as a "hydrate". Solvates, such as hydrates, exist when the

5 drug substance incorporates solvent, such as water, in the crystal lattice in either stoichiometric or non-stoichiometric amounts. Drug substances are routinely screened for the existence of hydrates since these may be encountered at any stage of the drug manufacturing process or upon storage of the drug substance or dosage form. Solvates are described in S. Byrn *et al.*, *Pharmaceutical Research*, 1995, **12(7)**: p. 954-954, and Water-Insoluble Drug Formulation, 2nd ed. R. Liu, CRC Press, page 553, which are incorporated herein by reference.

10 "Therapy", "treatment" and "treating" include both preventative and curative treatment of a condition, disease or disorder in humans or animals. It also includes slowing, interrupting, controlling or stopping the progression of a condition, disease or disorder in humans or animals. It also includes preventing, curing, slowing, interrupting, controlling or stopping the symptoms of a condition, disease or disorder in a human or an animal.

15 Throughout the invention, "preventive" and "prevention" include in particular (without being limited to) chemopreventive and chemoprevention.

According to the present invention a "patient" may be a human or an animal.

20 Throughout the invention, all residues which occur more than once may be identical or different, i.e. are independent of one another. For example, in formula (I) or formula (II) each instance of R¹ and R² may have a different meaning (within the scope of the corresponding definition).

25 The compounds of formula (I) according to the present invention may – also depending on the nature of substituents they may bear – have one or more centers of chirality. They may accordingly occur in various enantiomeric and diastereomeric forms, as the case may be, and be in racemic or optically active form. The invention, therefore, also relates to the optically active forms, enantiomers, racemates, diastereomers, mixtures thereof in all ratios, collectively: "stereoisomers". It may be desirable to use a specific stereoisomer, e.g. one specific enantiomer or diastereomer of a certain compound. In these cases, a
30 compound according to the present invention obtained as a racemate or even intermediates thereof – may be separated into the stereoisomeric (enantiomeric, diastereoisomeric) compounds by chemical or physical measures known to the person skilled in the art. The compounds of the invention which have one or more

centers of chirality and which occur as racemates or as mixtures of enantiomers or diastereoisomers can for example be fractionated or resolved by methods known per se into their optically pure or enriched isomers, i.e. enantiomers or diastereomers. The separation of the compounds of the invention can take place by chromatographic methods, e.g. column separation on chiral or nonchiral phases, or by recrystallization from an optionally optically active solvent or by use of an optically active acid or base or by derivatization with an optically active reagent such as, for example, an optically active alcohol, and subsequent elimination of the radical. Another approach that may be applied to obtain one or more specific stereoisomers of a compound of the present invention in an enriched or pure form makes use of stereoselective synthetic procedures, e.g. applying starting material in a stereoisomerically enriched or pure form (for instance using the pure or enriched (*R*)- or (*S*)-enantiomer of a particular starting material bearing a chiral center) or utilizing chiral reagents or catalysts, in particular enzymes.

A dashed line that bisects a bond line (see for example shown in the above-described definitions of R^3 and R^4) shows the bond via which a certain residue is attached its adjacent atom.

The term "pharmaceutically acceptable carrier, adjuvant, or excipient" refers to a nontoxic carrier, adjuvant, or excipient that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable carriers, adjuvants or excipient that are used in the compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene- polyoxypropylene-block polymers, polyethylene glycol and wool fat.

An anthelmintic agent is an agent that acts against human and animal diseases caused by infection with parasitic worms (helminths) such as for example praziquantel or triclabendazole.

This invention is also directed a compound of formula (I), (II) or (III), as defined above, or a pharmaceutically acceptable salt or solvate thereof, for use in therapy, in particular for the treatment of schistosomiasis and/or fascioliasis.

5 This invention is also directed a medicament (or a pharmaceutical composition or formulation) including a compound of formula (I), (II) or (III), as defined above, or a pharmaceutically acceptable salt or solvate thereof, for use in therapy, in particular for the treatment of schistosomiasis and/or fascioliasis.

10 This invention is also directed to the use of a compound of formula (I), (II) or (III), as defined above, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treatment of schistosomiasis and/or fascioliasis.

15 This invention is also directed to a method for treating schistosomiasis and/or fascioliasis comprising administering a therapeutically effective amount of a compound of formula (I), (II) or (III), as defined above, as defined above, or a pharmaceutically acceptable salt or solvate thereof, to a patient in need thereof.

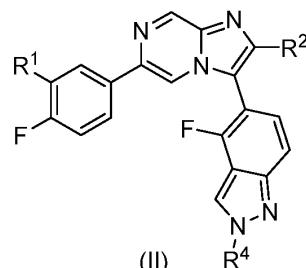
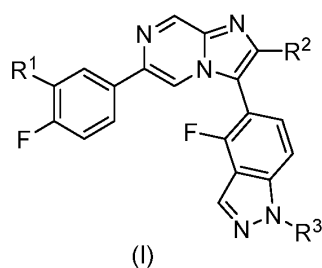
20 The amount of active ingredient, which is required to achieve a therapeutic effect will, of course, vary with the particular compound, the route of administration, the subject under treatment, including the type, species, age, weight, sex, and medical condition of the subject and the renal and hepatic function of the subject, and the particular disorder or disease being treated, as well as its severity. An ordinarily skilled physician, veterinarian or clinician can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

25 Compounds

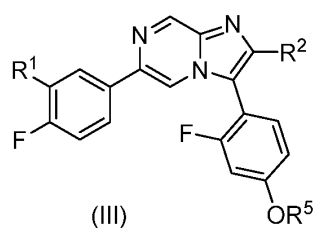
The invention provides a compound of formula (I), (II) or (III) or a pharmaceutically acceptable salt or solvate thereof,

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wherein:

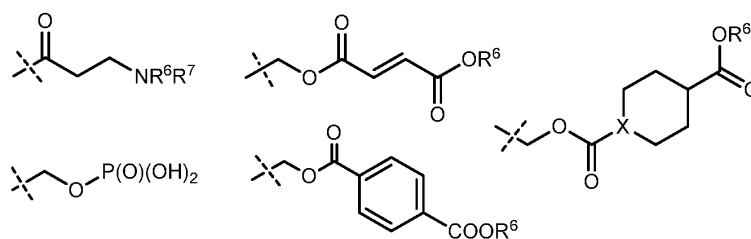
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R¹ is cyclopropyl, cyclobutyl, F or C1-C3 alkyl optionally substituted with up to five F atoms;

R² is cyclopropyl, cyclobutyl, F or C1-C3 alkyl optionally substituted with up to five F atoms;

R³ and **R⁴** represent each, independently from one another, a residue selected from following group:

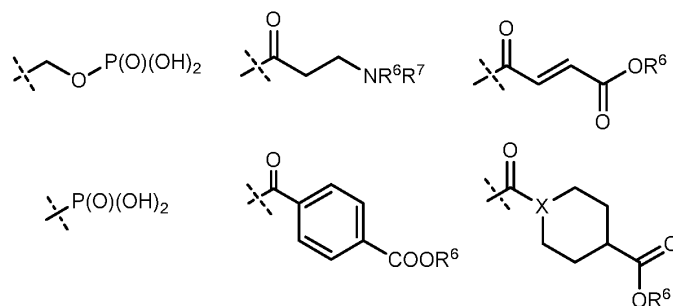
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R⁵ is a residue selected from following group:

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X is CH or N; and

R⁶ and **R⁷** represent each, independently from one another, H or CH₃.

In some embodiment the compound of the present invention is of formula (I) as defined above.

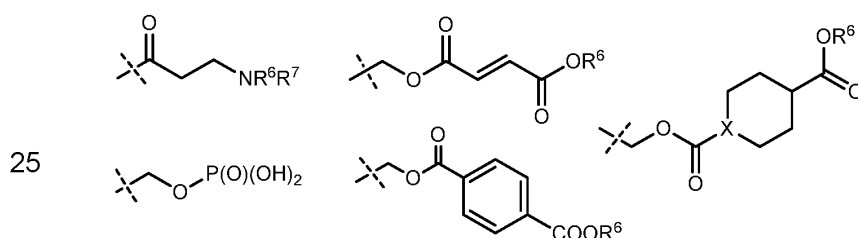
5 In some embodiment the compound of the present invention is of formula (II) as defined above.

In some embodiment the compound of the present invention is of formula (II) as defined above.

10 R^1 is selected from a group consisting of cyclopropyl, cyclobutyl, F or C1-C3 alkyl optionally substituted with up to five F atoms. Preferably R^1 is selected from a group consisting of cyclopropyl, F or C1-C3 alkyl optionally substituted with up to five F atoms. Even more preferably R^1 is selected from a group consisting of F, cyclopropyl, methyl, ethyl, n-propyl, iso-propyl, CHF_2 , CF_3 and CH_2CF_3 . R^1 is most preferably iso-propyl.

15 R^2 is selected from a group consisting of cyclopropyl, cyclobutyl, F or C1-C3 alkyl optionally substituted with up to five F atoms. Preferably R^2 is selected from a group consisting of cyclopropyl, F or C1-C3 alkyl optionally substituted with up to five F atoms. Even more preferably R^2 is selected from a group consisting of F, cyclopropyl, methyl, ethyl, n-propyl, iso-propyl, CHF_2 , CF_3 and CH_2CF_3 . R^2 is most preferably cyclopropyl.

20 R^3 is selected from a group consisting of:

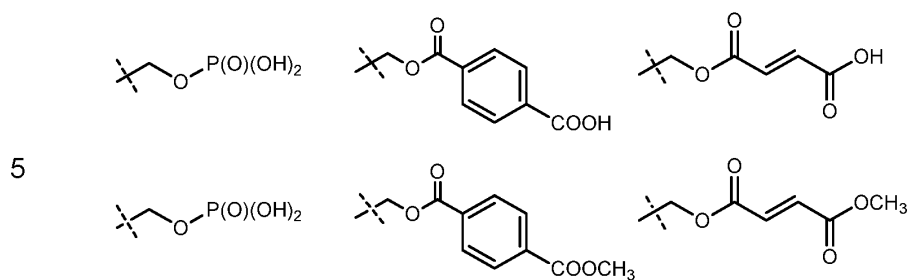


wherein

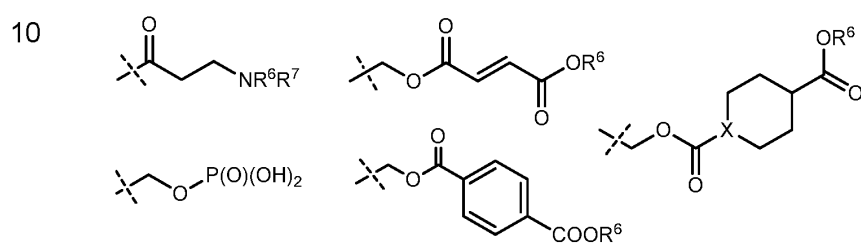
30 R^6 and R^7 represent each, independently from one another, H or CH_3 (preferably R^6 and R^7 represent each H), and

X is CH or N.

Preferably R^3 is selected from a group consisting of:



R^4 is selected from a group consisting of:

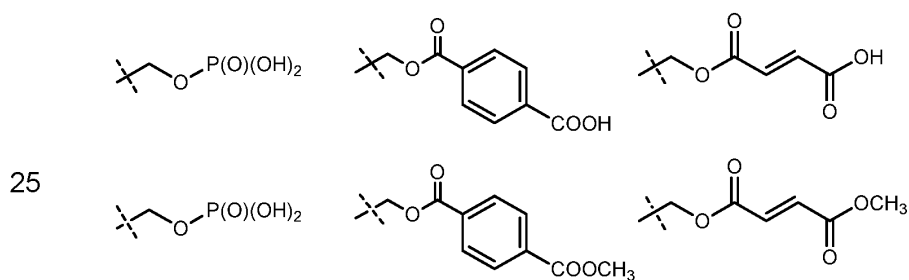


wherein

R^6 and R^7 represent each, independently from one another, H or CH_3 (preferably R^6 and R^7 represent each H), and

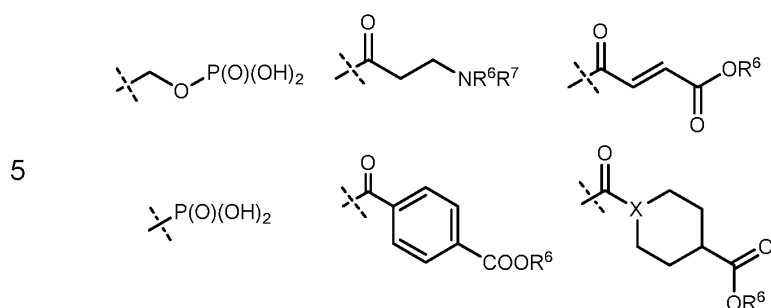
X is CH or N.

20 Preferably R^4 is selected from a group consisting of:



R^5 is selected from a group consisting of:

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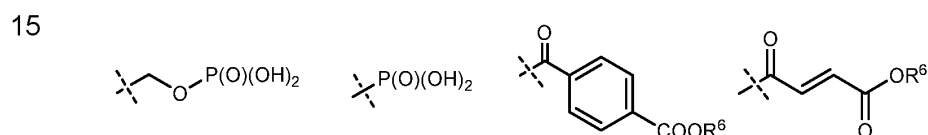


wherein

10 **R⁶** and **R⁷** represent each, independently from one another, H or CH₃ (preferably **R⁶** and **R⁷** represent each H), and

X is CH or N.

R⁵ is preferably selected from a group consisting of:



wherein

20 **R⁶** and **R⁷** represent each, independently from one another, H or CH₃ (preferably **R⁶** and **R⁷** represent each H).

Preferred embodiments of the present invention encompass a compound of formula (I) or (II).

25 Further preferred embodiments of the present invention include a compound of formula (I), (II) or (III), wherein

R¹ is *iso*-propyl; and

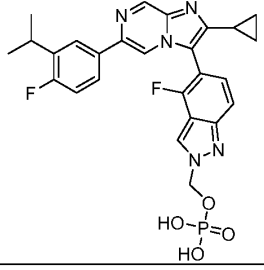
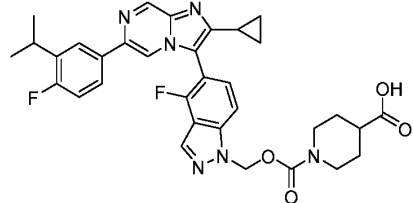
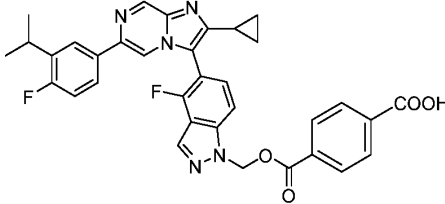
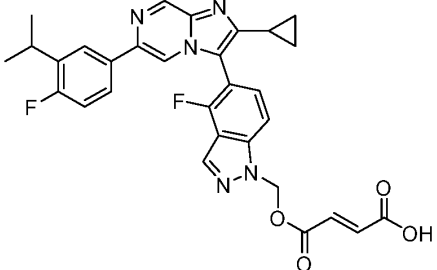
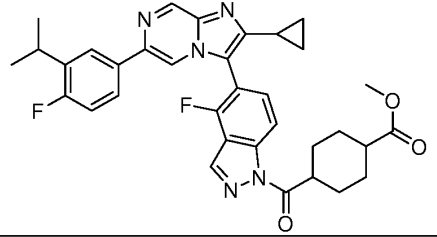
R² is cyclopropyl.

30 Among these preferred embodiments particular important embodiments include a compound of formula (I) or (II), wherein

R¹ is *iso*-propyl; and

R² is cyclopropyl.

A compound as defined above, wherein the compounds is selected from following group:

5	Compound ID		
10	A1	[(5-{2-cyclopropyl-6-[4-fluoro-3-(propan-2-yl)phenyl]imidazo[1,2-a]pyrazin-3-yl}-4-fluoro-2H-indazol-2-yl)methoxy]phosphonic acid	
15	A2	1-[[{(5-{2-cyclopropyl-6-[4-fluoro-3-(propan-2-yl)phenyl]imidazo[1,2-a]pyrazin-3-yl}-4-fluoro-1H-indazol-1-yl)methoxy]carbonyl]piperidine-4-carboxylic acid	
20	A3	4-[[{(5-{2-cyclopropyl-6-[4-fluoro-3-(propan-2-yl)phenyl]imidazo[1,2-a]pyrazin-3-yl}-4-fluoro-1H-indazol-1-yl)methoxy]carbonyl]benzoic acid	
25	A5	(2E)-4-[(5-{2-cyclopropyl-6-[4-fluoro-3-(propan-2-yl)phenyl]imidazo[1,2-a]pyrazin-3-yl}-4-fluoro-1H-indazol-1-yl)methoxy]-4-oxobut-2-enoic acid	
30	A6	methyl 4-(5-{2-cyclopropyl-6-[4-fluoro-3-(propan-2-yl)phenyl]imidazo[1,2-a]pyrazin-3-yl}-4-fluoro-1H-indazole-1-carbonyl)cyclohexane-1-carboxylate	

5	A7	3-amino-1-(5-{2-cyclopropyl-6-[4-fluoro-3-(propan-2-yl)phenyl]imidazo[1,2-a]pyrazin-3-yl}-4-fluoro-1H-indazol-1-yl)propan-1-one	
10	A8	[(5-{2-cyclopropyl-6-[4-fluoro-3-(propan-2-yl)phenyl]imidazo[1,2-a]pyrazin-3-yl}-4-fluoro-1H-indazol-1-yl)methoxy]phosphonic acid	
15	A9	(2E)-4-[(4-fluoro-5-{6-[4-fluoro-3-(propan-2-yl)phenyl]-2-(trifluoromethyl)imidazo[1,2-a]pyrazin-3-yl]-1H-indazol-1-yl)methoxy]-4-oxobut-2-enoic acid	
20	A10	[(4-fluoro-5-{6-[4-fluoro-3-(propan-2-yl)phenyl]-2-(trifluoromethyl)imidazo[1,2-a]pyrazin-3-yl]-1H-indazol-1-yl)methoxy]phosphonic acid	
25	A11	[(3-fluoro-4-{6-[4-fluoro-3-(propan-2-yl)phenyl]-2-(trifluoromethyl)imidazo[1,2-a]pyrazin-3-yl}phenoxy)methoxy]phosphonic acid	
30	A12	(3-fluoro-4-{6-[4-fluoro-3-(propan-2-yl)phenyl]-2-(trifluoromethyl)imidazo[1,2-a]pyrazin-3-yl}phenoxy)phosphonic acid	

5	A13	(2E)-4-(3-fluoro-4-{6-[4-fluoro-3-(propan-2-yl)phenyl]-2-(trifluoromethyl)imidazo[1,2-a]pyrazin-3-yl}phenoxy)-4-oxobut-2-enoic acid	
10	A14	[(4-{2-cyclopropyl-6-[4-fluoro-3-(propan-2-yl)phenyl]imidazo[1,2-a]pyrazin-3-yl}-3-fluorophenoxy)methoxy]phosphonic acid	
15	A15	(4-{2-cyclopropyl-6-[4-fluoro-3-(propan-2-yl)phenyl]imidazo[1,2-a]pyrazin-3-yl}-3-fluorophenoxy)phosphonic acid	
20	A16	(2E)-4-(4-{2-cyclopropyl-6-[4-fluoro-3-(propan-2-yl)phenyl]imidazo[1,2-a]pyrazin-3-yl}-3-fluorophenoxy)-4-oxobut-2-enoic acid	

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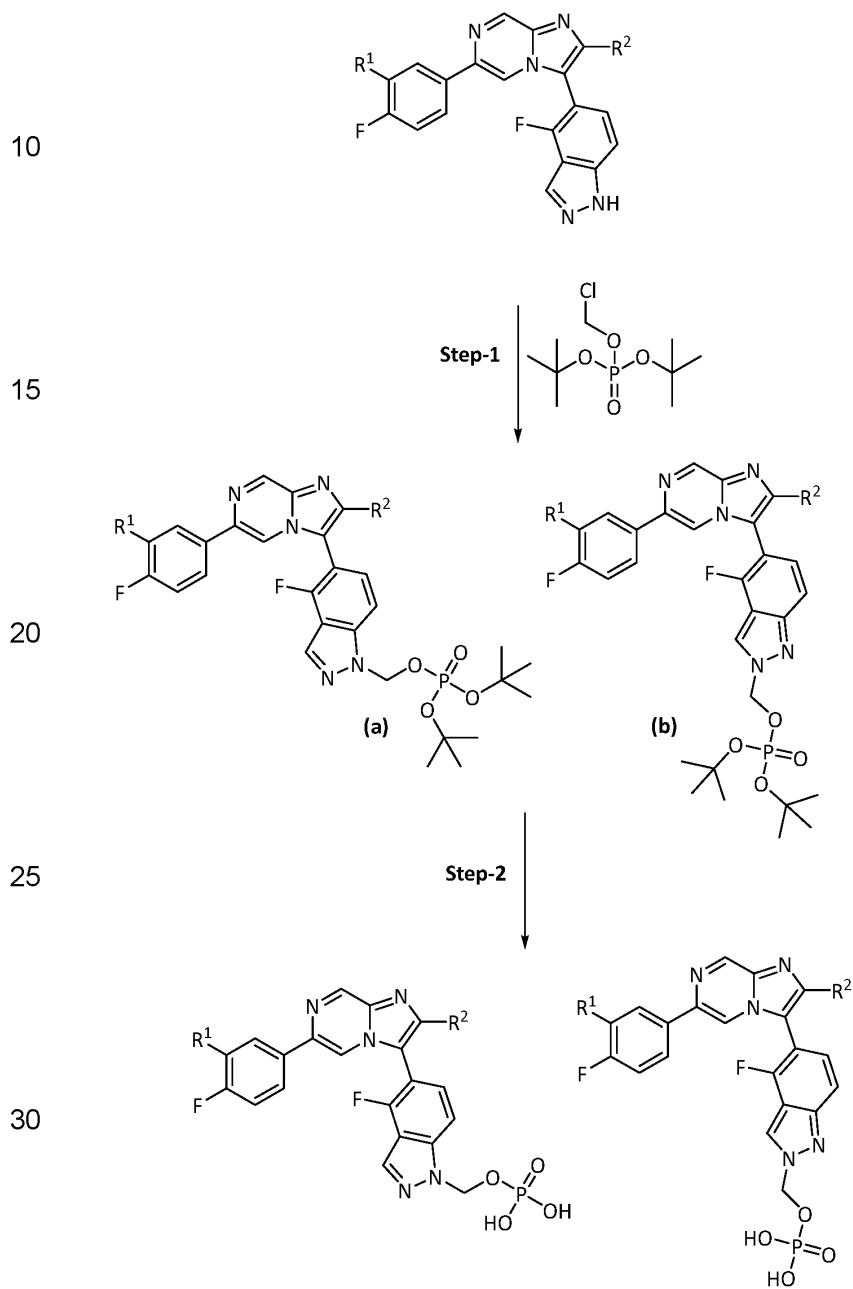
General Synthetic Methodology

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The methods used for the synthesis of the compounds of the invention are illustrated by the schemes below. The starting materials and reagents used in preparing these compounds are available from commercial suppliers or can be prepared by methods obvious to those skilled in the art. A general synthesis of starting materials SM1, SM2, SM3 and SM4 is for example described in detail in WO2018130853 A1. In addition, synthetic procedures for SM1, SM2, SM3 and SM4 are described in the following experimental section.

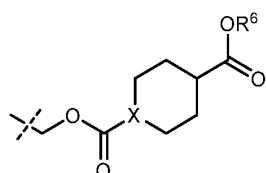
General Procedure 1:

The invention provides a process for the preparation of compounds of formula (I) and (II), wherein residues R^1 and R^2 are defined according to the invention and R^3 and R^4 represent $\text{CH}_2\text{OPO}(\text{OH})_2$. The process involves SM1 or SM2, that is *N*-alkylated to provide an intermediate that in the next step may then undergo hydrolysis to form the corresponding phosphate derivative.

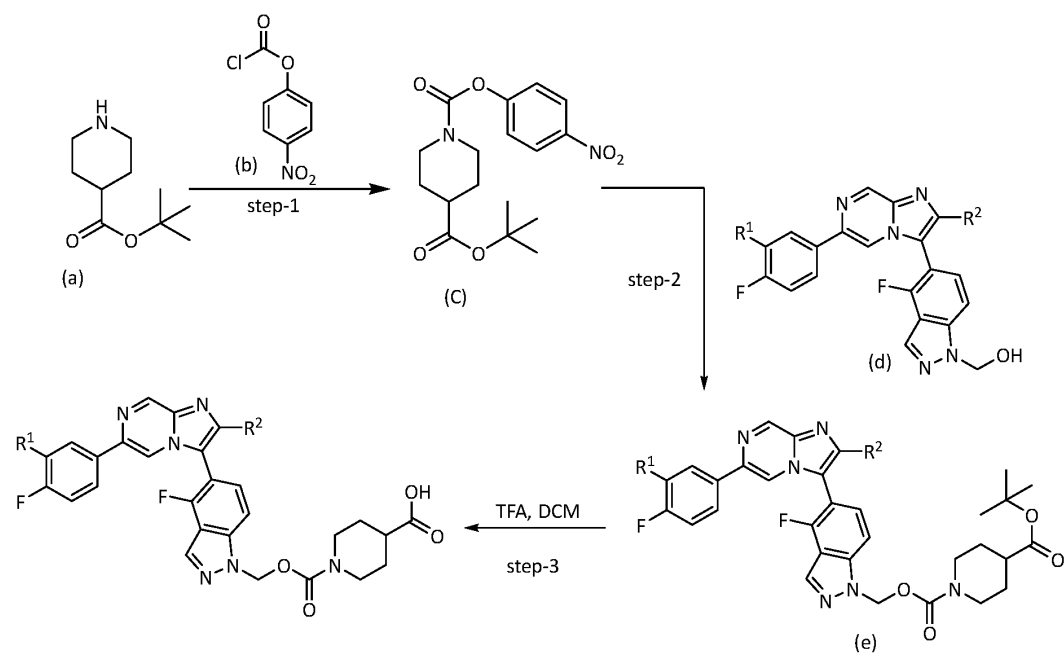


General Procedure 2:

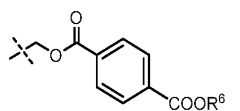
The invention provides a process for the preparation of compounds of formula (I) and (II), wherein residues R^1 and R^2 are defined according to the invention and R^3 is:



The process involves SM1 or SM2 that is condensed with formaldehyde before being treated with a reagent to form a carbamate. The ester function may then undergo hydrolysis to form the corresponding carboxylic acid.

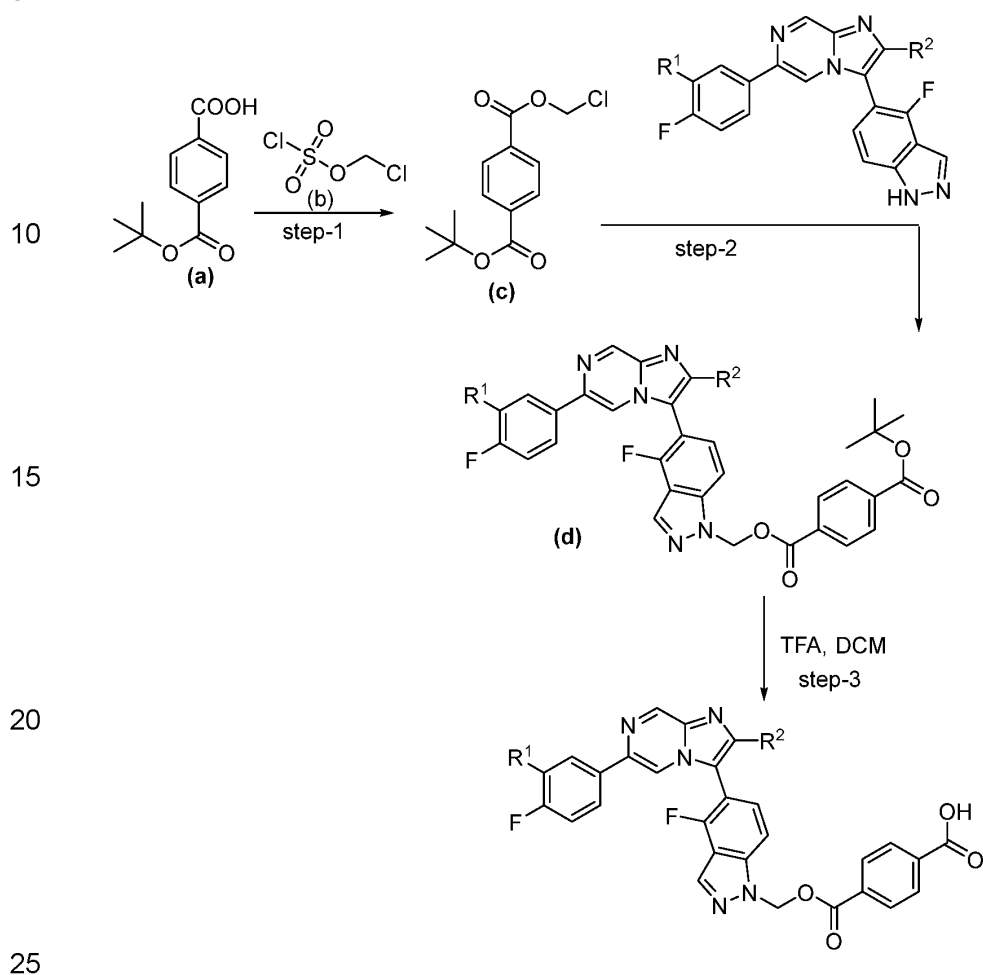
General Procedure 3:

The invention provides a process for the preparation of compounds of formula (I) and (II), wherein residues R^1 and R^2 are defined according to the invention and R^3 is:



The process involves SM or SM2 that is treated with an alkylating reagent to form the corresponding *N*-alkylated adduct. The ester function may then undergo hydrolysis to form the corresponding carboxylic acid.

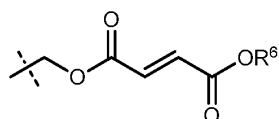
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General Procedure 4:

The invention provides a process for the preparation of compounds of formula (I) and (II), wherein residues R^1 and R^2 are defined according to the invention and R^3 is:

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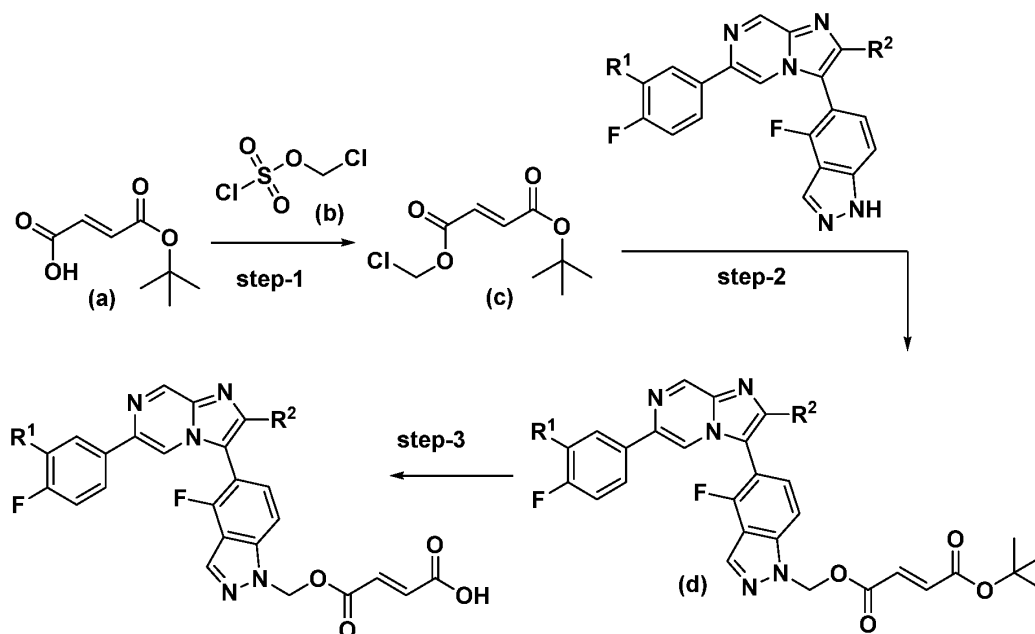


The process involves SM1, SM2, SM3 or SM4 that is treated with an alkylating reagent to form the corresponding *N*-alkylated adduct. The ester function may then undergo hydrolysis to form the corresponding carboxylic acid.

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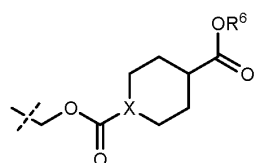


General Procedure 5:

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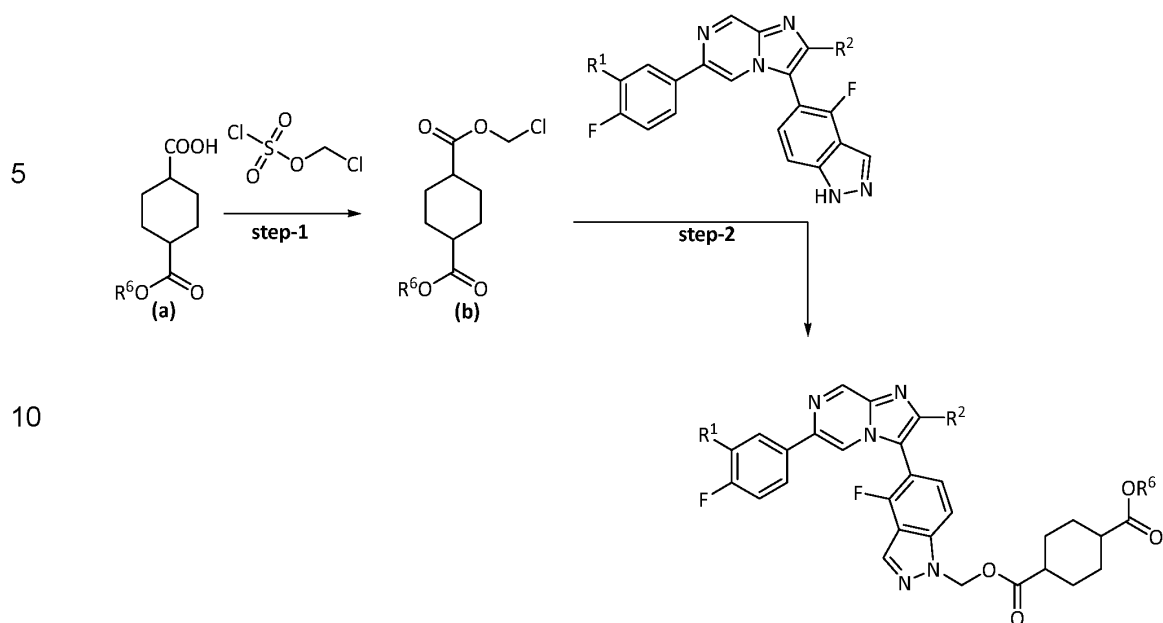
The invention provides a process for the preparation of compounds of formula (I) and (II), wherein residues R^1 and R^2 are defined according to the invention and R^3 is:

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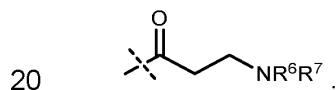


with $R^6 = CH_3$. The process involves SM1 or SM2 that is treated with an alkylating reagent to form the corresponding *N*-alkylated adduct.

30

**General Procedure 6:**

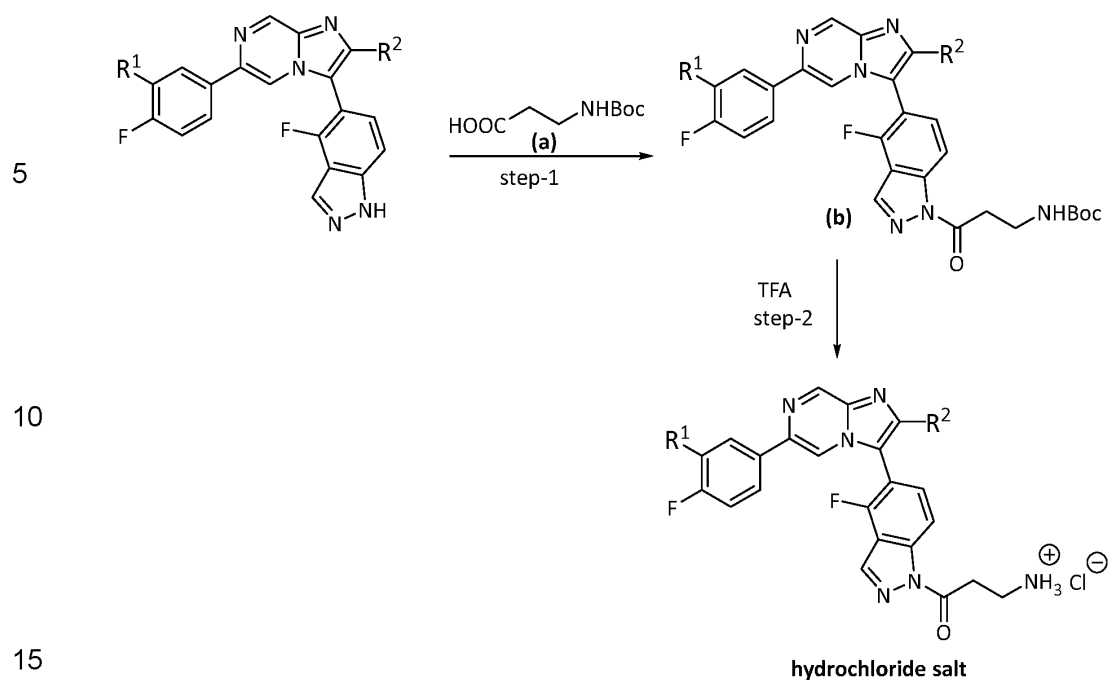
The invention provides a process for the preparation of compounds of formula (I) and (II), wherein residues R^1 and R^2 are defined according to the invention and R^3 is:



The process involves SM1 or SM2 that is esterified to form the corresponding adduct. In a second step the amine was deprotected.

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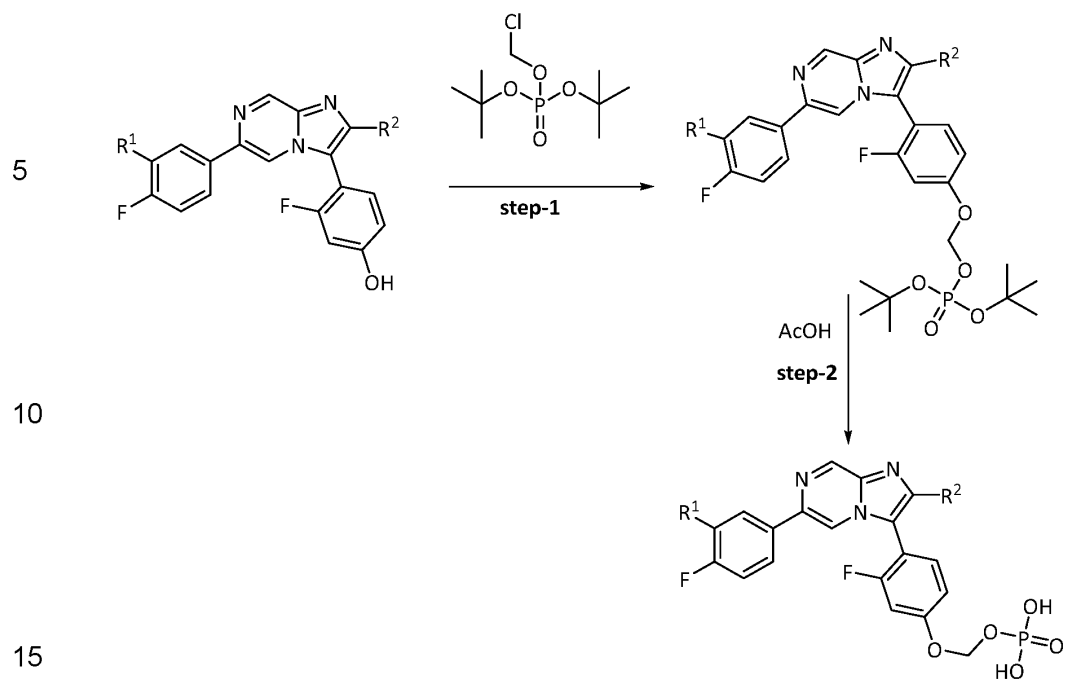


General Procedure 7:

The invention provides a process for the preparation of compounds of formula (III), wherein residues R^1 and R^2 are defined according to the invention and R^5 is $\text{CH}_2\text{OPO}(\text{OH})_2$. The process involves SM3 or SM4 that is O-alkylated to provide an intermediate that in the next step may then undergo hydrolysis to form the corresponding phosphate derivative.

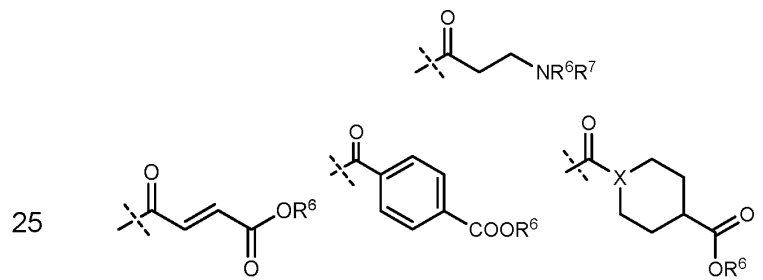
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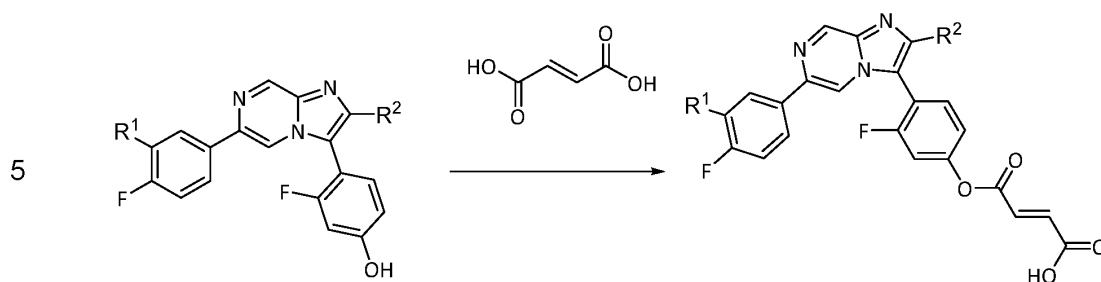


General Procedure 8:

The invention provides a process for the preparation of compounds of formula (III), wherein residues R^1 and R^2 are defined according to the invention and R^5 is one of the following residues:



The process involves SM3 or SM4 that is esterified as shown exemplarily below:



Examples

Abbreviations

ACN: acetonitrile

AcOH: acetic acid

Bispin: Bis-(pinacolato)-diboran

DMAP: 4-Dimethylaminopyridine

DCM: dichloromethane

DMF: dimethylformamid

DMSO: dimethylsulfoxide

EA : Ethyl Acetate

EDC: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide

HPLC: High Pressure Liquid Chromatography

prep-HPLC: preparative High Pressure Liquid Chromatography

LCMS (or LS-MS): Liquid Chromatography-Mass spectrometry

NMR: Nuclear Magnetic Resonance

pet ether: petroleum ethers

PyBop: benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate

RT: Room Temperature

TEA: triethyl amine

TFA: Trifluoroacetic acid

THF: Tetrathydrofuran

TLC: Thin Layer Chromatography

TMS-Br: trimethylsilyl bromide

HPLC Methods:

"TFA method"

Column: X Bridge C8 (50X4.6)mm,3.5 μ m, mobile phase: A:0.1% TFA in water
Mobile phase: B:ACN, Flow:2.0 mL/minTIME(min)

5 "HCOOH method"

Column:X Bridge C8(50X4.6)mm,3.5 μ m, mobile phase A:0.1% FA in water. Mobile
phase D: ACN Flow rate:2.0 ml/min"

10 "Ammoniumbicarbonate method"

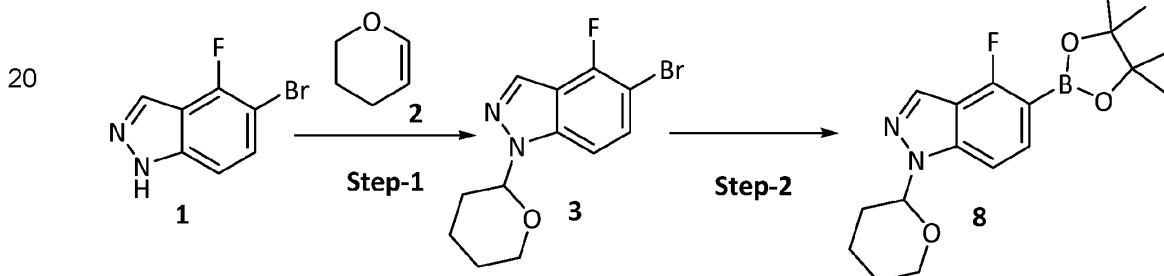
Column:X-Bridge C8(50X4.6)mm,3.5 μ m, mobile phase:A:10mM Ammonium
bicarbonate in water, Mobile phase B: ACN Flow:1.0mL/min

15 "Ammonium acetate method"

Column:X-Bridge C8(50X4.6)mm,3.5 μ m, mobile phase:A:10mM Ammonium acetate
in water Mobile phase B: ACN Flow:1.0mL/min"

Synthesis of SM1

Synthesis of Boronate ester Compound 8:



25 **Step-1:** To a stirred solution of 5-bromo-4-fluoro-1H-indazole (150 g, 698 mmol) in DCM (2.0 L) was added *p*-toluenesulfonic acid (60.1 g, 349 mmol) followed by 3,4-dihydro-2H-pyran (70.4 g, 837 mmol) at 25°C, and the reaction mixture was stirred at 25°C for 16 hours. After completion of reaction, the reaction mixture was diluted with water (2.0 L) and extracted with DCM (2.0 mL). The organic layer was washed with water (500.0 mL) and brine (500.0 mL). The collected organic layer was dried with sodium sulphate, filtered and the filtrate was evaporated under reduced pressure to obtain crude product.

30 The crude product was purified by flash column chromatography using 230-

400 mesh silica gel and 15-32% ethyl acetate in pet ether as eluent to afford **compound 3** (160 g, 76.7 % yield) as an off white solid.

LCMS: Calculated for C₁₂H₁₂BrFN₂O, Exact Mass: 298.01, Observed 301.0 (M+2), RT. 2.88 min, 84.17 % (Max).

¹H NMR (400 MHz, DMSO-d₆): δ 8.09 (d, J = 0.80 Hz, 1H), 7.50-7.48 (m, 1H), 7.32-7.28 (m, 1H), 5.73-5.70 (m, 1H), 4.03-3.99 (m, 1H), 3.79-3.73-(m, 1H), 2.54 (t, J = 9.20 Hz, 1H), 2.18-2.08 (m, 2H), 1.81-1.68 (m, 3H).

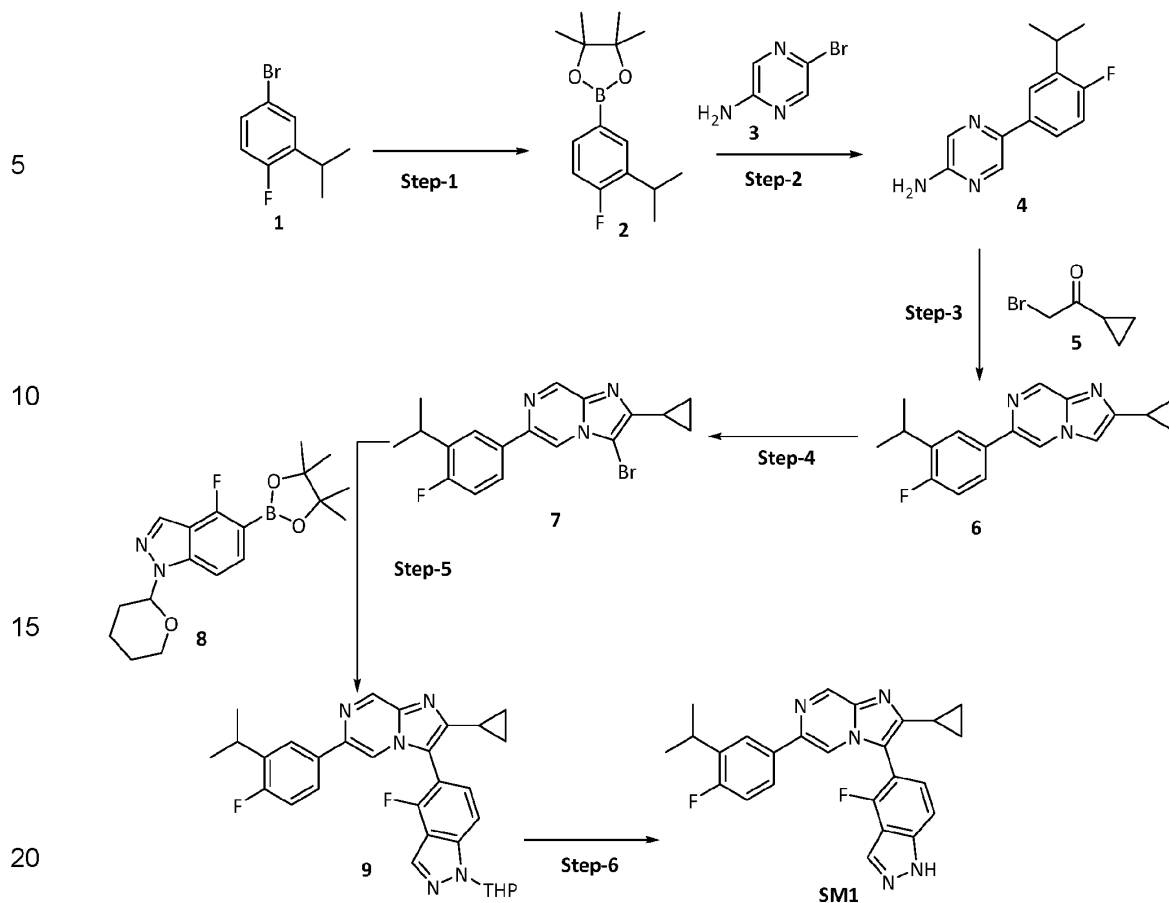
Step-2: To a stirred solution of **compound 3** (160 g, 531.11 mmol) and bispin (163.06 g, 642.14 mmol) in Dioxane (1100 mL) was added potassium acetate (130.12 g, 1327.7 mmol). The reaction mixture was degassed by continuous bubbling of nitrogen for 30 minutes. After that PdCl₂(dppf)-CH₂Cl₂ adduct (43.3 g, 53.11 mmol) was added at 25°C, and the reaction mixture was stirred at 100°C for 16 hours. After completion of reaction, the reaction mixture was diluted with water (2.0 L) and extracted with ethyl acetate (2.0 L). The organic layer was washed with water (1.0L) and brine (1.0 L). The collected organic layer was dried with sodium sulphate, filtered and the filtrate was evaporated under reduced pressure to obtain crude product. The crude product was purified by flash column chromatography using 230-400 mesh silica gel and 5-10% ethyl acetate in pet ether as eluent to afford **compound 8** (174 g, 93.9 % yield) as a gummy solid.

LCMS: Calculated for C₁₈H₂₄BFN₂O₃, Exact Mass: 347.1, Observed 301.0 (M+2), RT. 2.97 min, 94.07 % (Max),

HPLC: 3.95 min, 99.91 % (Max).

¹H NMR (400 MHz, CDCl₃): δ 8.12 (t, J = 2.00 Hz, 1H), 7.72-7.69(m, 1H), 7.40-7.26 (m, 1H), 5.74-5.71(m, 1H), 4.05-4.01 (m, 1H), 3.78-3.72 (m, 1H), 2.54 (s, 1H), 2.55-2.06 (m, 2H), 1.80-1.75 (3H), 1.37 (s, 12H).

Synthesis of SM1



Step-1: To a stirred solution of 4-bromo-1-fluoro-2-isopropylbenzene (300 g, 1.382 mol) in dioxane (3.0 L), was added bispin (421.13 g, 1.658 mol) and potassium acetate (203.44 g, 2.073 mol). The reaction mixture was degassed by continuous bubbling of nitrogen for 30 minutes. After that $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ adduct (56.42 g, 69.1 mmol) was added at 25°C, and the reaction mixture was stirred at 100°C for 16 hours. After completion of reaction, reaction mixture was filtered through celite, filtrate was evaporated under reduced pressure to obtain crude **Compound 2** (366.0 g) as a black liquid. Crude was directly used for next step

GCMS: Calculated for $\text{C}_{15}\text{H}_{22}\text{BF}_2\text{O}_2$, Exact Mass: 264.17, Observed 264.1, RT. 3.909 min, 73.84 % (Max),

Step-2: To a stirred solution of 5-bromopyrazin-2-amine (200 g, 1.149 mol) in Dioxane (2.5 L) and Water (630.0 mL), was added **Compound 2** (364.13 g, 1.379 mol) and potassium carbonate (237.8 g, 1.723 mol). The reaction mixture was degassed by continuous bubbling of nitrogen for 30 minutes. After that tetrakis(triphenylphosphine)palladium(0) (66.35 g, 57.45 mmol) was added at 25°C, and the reaction mixture was stirred at 110°C for 16 hours. After completion of reaction, the reaction mixture was diluted with water (3000.0 mL) and extracted with ethyl acetate (2000.0 mL). The organic layer was washed with water (500.0 mL) and brine (500.0 mL). The collected organic layer was dried with sodium sulphate, filtered and the filtrate was evaporated under reduced pressure to obtain crude product. The crude product was purified by column chromatography using 60-120 mesh silica gel and 35-40% ethyl acetate in pet ether as eluent to afford **Compound 4** (230.0 g, 87.7%), as an off white solid.

LCMS: Calculated for C₁₃H₁₄FN₃, Exact Mass: 231.12, Observed 232.2(M+H), RT. 2.032 min, 98.20 % (Max),

¹H NMR (400 MHz, DMSO-d₆): δ 8.51 (d, J = 1.20 Hz, 1H), 7.95 (d, J = 1.60 Hz, 1H), 7.87 (dd, J = 2.40, 7.60 Hz, 1H), 7.77-7.73 (m, 1H), 7.19-7.14 (m, 1H), 6.54 (s, 2H), 3.21 (t, J = 6.80 Hz, 1H), 1.27 (d, J = 6.80 Hz, 1H).

Step-3: To a stirred solution of **Compound 4** (230 g, 994 mmol) in Acetonitrile (2.5 L) was added 2-bromo-1-cyclopropylethan-1-one (195 g, 1193 mmol) at 25°C, and the reaction mixture was stirred at 100°C for 16 hours. After completion of reaction, reaction mixture was filtered and washed with acetonitrile (500.0 mL) and dried to afford **Compound 6** (220 g, 74.9 % yield) as an off white solid.

LCMS: Calculated for C₁₈H₁₈FN₃, Exact Mass: 295.15, Observed 296.2 (M+H), RT. 2.096 min, 91.08 % (Max).

¹H NMR (400 MHz, DMSO-d₆): δ 9.26 (s, 1H), 9.16 (s, 1H), 8.077 (s, 1H), 8.02 (dd, J = 2.80, 9.60 Hz, 1H), 7.92-7.87 (m, 1H), 7.30 (t, J = 11.60 Hz, 1H), 3.25 (t, J = 9.20 Hz, 1H), 2.26-2.22 (m, 1H), 1.30 (d, J = 9.20 Hz, 6H), 1.12-1.08 (m, 2H), 0.98-0.96 (m, 2H).

Step-4: To a stirred solution of **Compound 6** (220 g 745.6 mmol) in DCM (10.0 mL), was added NBS (146.02 g, 820.33 mmol) at 25°C, and the reaction mixture was stirred at 25°C for 30 minutes. After completion of reaction, the reaction mixture was diluted with water (2.0 L) and extracted with DCM (2.0 L). The organic layer was washed with water (1.0 L). The collected organic layer was dried with sodium sulphate, filtered and the filtrate was evaporated under reduced pressure to obtain crude product. The crude was washing with acetonitrile (1.0 L) to afford **compound 7** (91 g, 32.6 % yield), as an off white solid.

LCMS: Calculated for C₁₈H₁₇BrFN₃, Exact Mass: 374.06, Observed 376.0 (M+2), RT. 3.306 min, 99.79 % (Max).

¹H NMR (400 MHz, DMSO-d₆): δ 9.02 (d, J = 2.00 Hz, 1H), 8.70 (d, J = 1.60 Hz, 1H), 8.09 (dd, J = 2.80, 9.80 Hz, 1H), 5.01-7.96 (m, 1H), 3.25 (t, J = 9.20 Hz, 1H), 3.27 (t, J = 9.60 Hz, 1H), 2.19-2.09 (m, 1H), 1.30 (d, J = 9.20 Hz, 6H), 1.10-1.06 (m, 2H), 1.03-1.00 (m, 2H).

Step-5: In a 50.0 mL sealed tube **compound 7** (90 g, 240.64 mmol) was dissolved in Dioxane (1.0 L) and Water (400.0 mL), followed by addition of **compound 8** (91.58 g, 264.70 mmol) and tripotassium phosphate (76.52 g, 360.96 mmol). The reaction mixture was degassed by continuous bubbling of nitrogen for 30 minutes. After that tetrakis(triphenylphosphine)palladium(0) (13.89 g, 12.032 mmol) was added at 25°C, and the reaction mixture was stirred at 110°C for 16 hours. After completion of reaction, the reaction mixture was diluted with water (2.0 L) and extracted with ethyl acetate (2.0L). The organic layer was washed with water (1.0 L) and brine (1.0 L). The collected organic layer was dried with sodium sulphate, filtered and the filtrate was evaporated under reduced pressure to obtain crude product. The crude product was purified by flash column chromatography using 230-400 mesh silica gel and 25-30% ethyl acetate in pet ether as eluent to afford **compound 9** (107 g, 86.6 % yield) as a gummy solid.

LCMS: Calculated for C₃₀H₂₉F₂N₅O, Exact Mass: 513.23, Observed 514.3 (M+H), RT. 2.57 min, 94.8 % (Max),

¹H NMR (400 MHz, DMSO-d₆): δ 9.10 (d, J = 1.60 Hz, 1H), 8.55 (s, 1H), 8.40 (s, 1H), 8.02 (d, J = 7.60 Hz, 1H), 7.85 (d, J = 11.60 Hz, 2H), 7.70 (t, J = 11.60 Hz, 1H), 7.16-7.13 (m, 1H), 6.00 (d, J = 10.40 Hz, 1H), 3.95 (d, J = 10.40 Hz, 1H), 3.82 (t, J = 8.00 Hz, 1H), 2.11-1.95 (m, 4H), 1.80 (d, J = 6.80 Hz, 2H), 1.62 (s, 2H), 1.26 (d, J = 9.20 Hz, 6H), 1.07-0.97 (m, 4H).

Step-6: To a stirred solution of **compound 9** (107 g, 208.57 mmol) in DCM (1.0 L), was added TFA (398.94 mL, 5214.25 mmol) at 0°C, and the reaction mixture was stirred at 25°C for 16 hours. After completion of reaction, reaction was evaporated under reduced pressure to obtain crude. The crude was neutralized sodium bi carbonate solution (2.0 L) and extracted with 20 % methanol in DCM (8.0 L). The collected organic layer was dried with sodium sulphate, filtered and the filtrate was evaporated under reduced pressure to obtain crude product. The crude was washed with methanol (2.0 L) to afford **SM1** (57 g, 63.70 % yield) as an off white solid.

Pd content Removal: To a stirred solution **SM1** (57 g) in THF (3.0 L), was added SiliaMetS® Thiol (1.0g), SiliaMetS® Diamine (1.0g), SiliaMetS® (Cystine (1.0g), SiliaMetS® DMT (1.0g), SiliaMetS® Thio urea (1.0g) at 25°C, and the reaction mixture was stirred at 25°C for 16 hours. Then filtered through celite washed with THF, concentrated, and repeated the same process twice. After three treatments, filtrate was evaporated under reduced pressure to afford solid. The solid was washed with methanol and filtered to afford **SM1** as an off white solid. Although LC-MS and HPLC >95%, NMR showed traces THF and DCM.

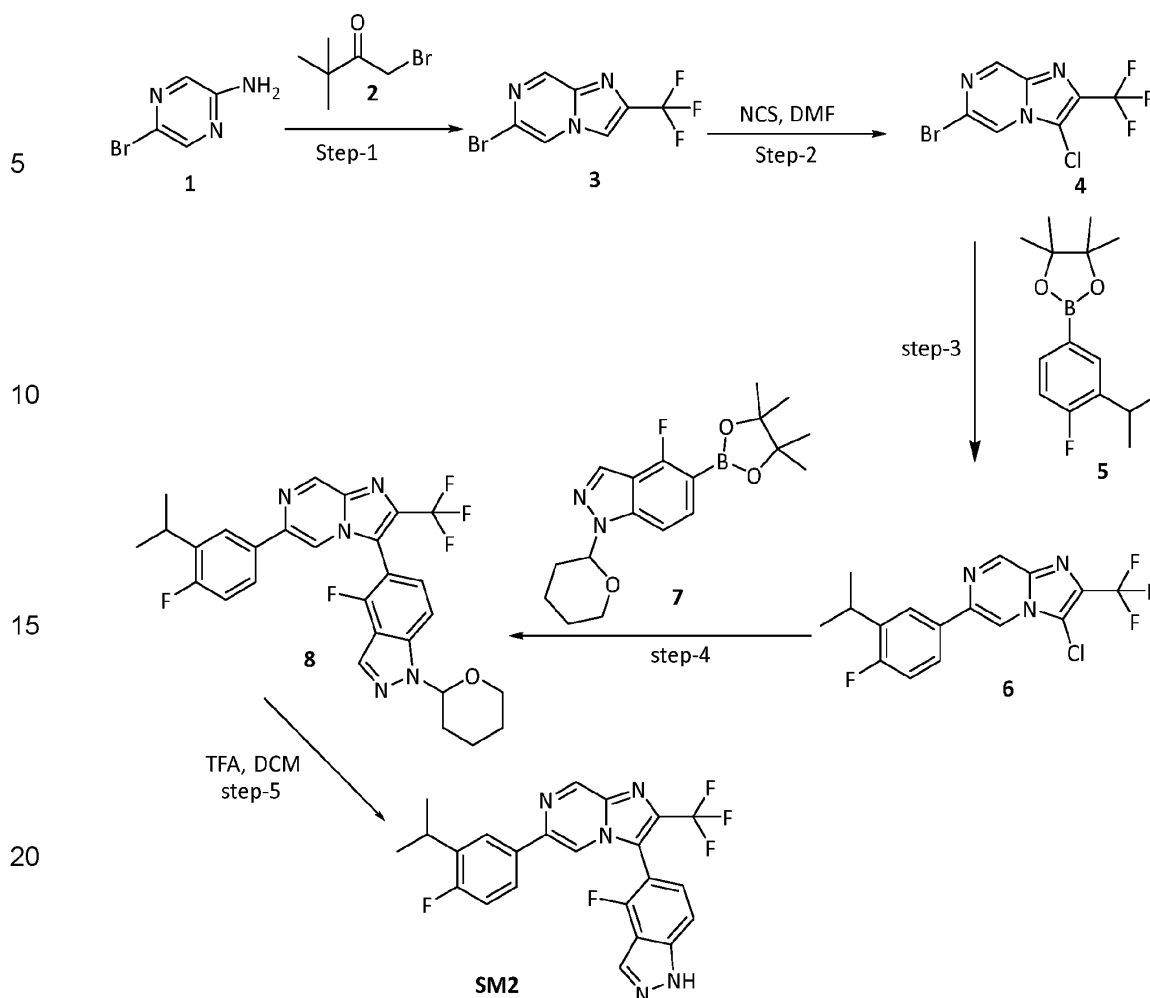
Removal of THF (or) DCM: To remove the trapped solvent THF and DCM, **SM1** was slowly dissolved in hot DMSO (2.0 L) and stirred for 30 minutes at 25 °C. After that Water (2.0 L) was added at 25 °C and stirred for 3h. The resulting solid was filtered and washed with water (1.0 L). The solid was dried under reduced pressure to afford **SM1** as an off white solid.

Removal of DMSO: To remove trapped DMSO, the compound was stirred with methanol (1.5 mL) and water (1.5 mL) at 90°C for 16 hours. Then the mixture was cooled to 35°C and filtered. The solid was washed with methanol (500.0 mL) and water (500.0 mL) to afford **SM1** (50 g as an off white solid).

LCMS: Calculated for C₂₅H₂₁F₂N₅, Exact Mass: 429.18, Observed 430.2 (M+H), RT. 2.28 min, 99.37 % (Max), **HPLC:** 5.16 min, 97.72 % (Max).

¹H NMR (400 MHz, DMSO-d₆): δ 13.65 (s, 1H), 9.10 (d, J = 1.20 Hz, 1H), 8.53 (t, J = 1.60 Hz, 1H), 8.36 (d, J = 0.80 Hz, 1H), 8.01 (dd, J = 2.40, 7.40 Hz, 1H), 7.86-7.82 (m, 1H), 7.65-7.59 (m, 2H), 7.18 (t, J = 1.60 Hz, 1H), 3.23-3.16 (m, 1H), 1.98-1.92 (m, 1H), 1.26 (d, J = 6.80 Hz, 6H), 1.04-0.98 (m, 4H).

Synthesis of SM2



Step-1: A mixture of 5-bromopyrazin-2-amine (140 g, 805 mmol) and 3-bromo-1,1,1-trifluoro-2-propanone (292 g, 1529 mmol) in 2-propanol (4200 mL) was stirred at 80°C for 4 h and then at 90°C for 80 h. After completion of reaction, the reaction mixture was evaporated in vacuum to obtain crude. The crude was purified by flash column and the product was eluted at 8-10% ethyl acetate in pet ether. The fractions were combined and evaporated in vacuum to obtain **Compound 3** (120 g, 54.7 %).

LCMS: Calculated for C₇H₃BrF₃N₃, 266.021, Observed 268.0 (M+H), RT. 1.813 min, 97.63 % (Max),

GCMS: 3.933 min, 96.32 % (Max).

¹H NMR (400 MHz, DMSO): δ 9.14 (s, 1H), 9.00 (s, 1H), 8.64 (s, 1H).

Step-2: To a stirred solution of 6-bromo-2-(trifluoromethyl)imidazo[1,2-a]pyrazine (75 g, 282 mmol) in DMF (2000 ml) was added *N*-chlorosuccinimide (56.5 g, 423 mmol) and stirred at 90°C for 16 h. The reaction was monitored by TLC. The reaction was diluted with cold water (500 mL) and extracted in ethyl acetate (2 x 250 mL). The organic phase was washed with cold water (2 x 200 mL), brine solution (250 mL) and dried in vacuum to obtain crude. The crude was purified by flash column and the product was eluted at 2-5% ethyl acetate in pet ether. The fractions were evaporated in vacuum to obtain **Compound 4** (82 g, 92%) as a pale yellow solid.

LCMS: Calculated for C₂₁H₁₅FN₂O₄S, 300.46, Observed 300.0 (M-H), RT. 2.227 min, 95.22 % (Max),

¹H NMR (400 MHz, DMSO): δ 9.18 (s, 1H), 8.96 (s, 1H).

Step-3: To a stirred solution of 6-bromo-3-chloro-2-(trifluoromethyl)imidazo[1,2-a]pyrazine (6.5 g, 21.63 mmol) in Dioxane (60 ml) and Water (20 ml), were added 2-(4-fluoro-3-isopropylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6.00 g, 22.71 mmol) and K₂CO₃ (4.48 g, 32.4 mmol). The reaction mixture was degassed by continuous bubbling of nitrogen for 10 minutes. After that tetrakis(triphenylphosphine)palladium(0) (2.500 g, 2.163 mmol) was added at 25 °C, and the reaction mixture was stirred at 100 °C for 16 h. TLC monitoring confirms the completion of reaction. Reaction mixture was filtered through celite, extracted over EA and washed with water and brine solution. Organic layer was dried over sodium sulphate, concentrated and purified by column chromatography to get **Compound 6** (4.25 g, 54.9%).

LCMS: Calculated for C₁₆H₁₂ClF₄N₃ 357.7, Observed 358.1 (M+H), RT. 3.37 min, 99.3 % (Max),

¹H NMR (400 MHz, DMSO-d₆): δ 9.38 (d, J = 1.20 Hz, 1H), 9.01 (d, J = 1.20 Hz, 1H), 8.15-8.13 (m, 1H), 8.08-8.04 (m, 1H), 7.32-7.28 (m, 1H), 3.34-3.22 (m, 1H), 1.31 (d, J = 7.20 Hz, 6H).

Step-4: To a stirred solution of 3-bromo-6-(4-fluoro-3-isopropylphenyl)-2-(trifluoromethyl)imidazo[1,2-a]pyrazine (4.25 g, 10.57 mmol) in Dioxane (50

ml) and Water (15 ml), added tripotassium phosphate (3.36 g, 15.85 mmol) and 4-fluoro-1-(tetrahydro-2H-pyran-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (4.39 g, 12.68 mmol). The reaction mixture was degassed by continuous bubbling of nitrogen for 10 minutes. After that tetrakis(triphenylphosphine)palladium(0) (1.221 g, 1.057 mmol) was added at 25°C, and The reaction mixture was stirred at 110°C for 16 h. TLC monitoring confirms the completion of reaction. Reaction mixture was extracted over ethyl acetate, washed with water. Organic layer was dried over sodium sulphate, concentrated and purified by column to get compound **8** (5.2 g, 89%).

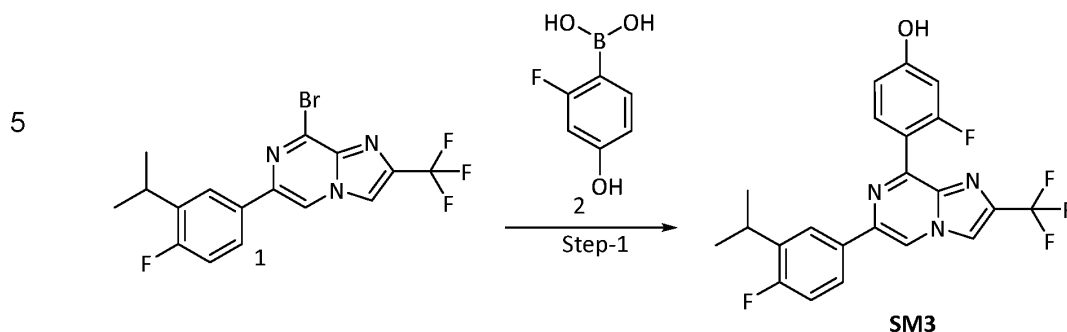
LCMS: Calculated for C₂₈H₁₄F₅N₅O 541.53, Observed 542.1 (M+H), RT. 3.16 min, 98.4% (Max),

¹H NMR (400 MHz, DMSO-d₆): δ 9.45 (d, J = 1.20 Hz, 1H), 8.66 (d, J = 23.60 Hz, 1H), 8.44 (d, J = 3.20 Hz, 1H), 8.07-8.03 (m, 1H), 7.91-7.84 (m, 2H), 7.68-7.64 (m, 1H), 7.22-7.17 (m, 1H), 6.01 (d, J = 9.20 Hz, 1H), 3.97-3.94 (m, 1H), 3.85-3.78 (m, 1H), 3.24-3.17 (m, 1H), 2.47-2.34 (m, 1H), 2.08-2.00 (m, 2H), 1.82-1.80 (m, 1H), 1.64-1.62 (m, 2H), 1.17 (d, J = 7.20 Hz, 6H).

Step-5: To a stirred solution of 3-(4-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)-6-(4-fluoro-3-isopropylphenyl)-2-(trifluoromethyl)imidazo[1,2-a]pyrazine (5.2 g, 9.60 mmol) in DCM (35 mL), were added TFA (35 mL, 9.60 mmol) at 0°C, and the reaction mixture was stirred at 25°C for 16 hours. TLC monitoring confirms the completion of reaction. Reaction mixture was concentrated, neutralized with 10% NaHCO₃ solution and extracted over DCM. Organic layer was dried over sodium sulphate, concentrated and washed with ACN to get **SM2** (2.2 g, 49.6%) as an off white solid.

LCMS: Calculated for C₂₃H₁₆F₅N₅ 457.41, Observed 458.0 (M+H), RT. 2.27 min, 99.0 % (Max),

¹H NMR (400 MHz, DMSO-d₆): δ 9.44 (d, J = 1.60 Hz, 1H), 8.62 (s, 1H), 8.38 (s, 1H), 8.03 (dd, J = 2.40, 7.60 Hz, 1H), 7.89-7.85 (m, 1H), 7.65-7.58 (m, 1H), 7.58-7.55 (m, 1H), 7.21-7.17 (m, 1H), 3.23-3.16 (m, 1H), 1.25 (d, J = 6.80 Hz, 6H).

Synthesis of SM3

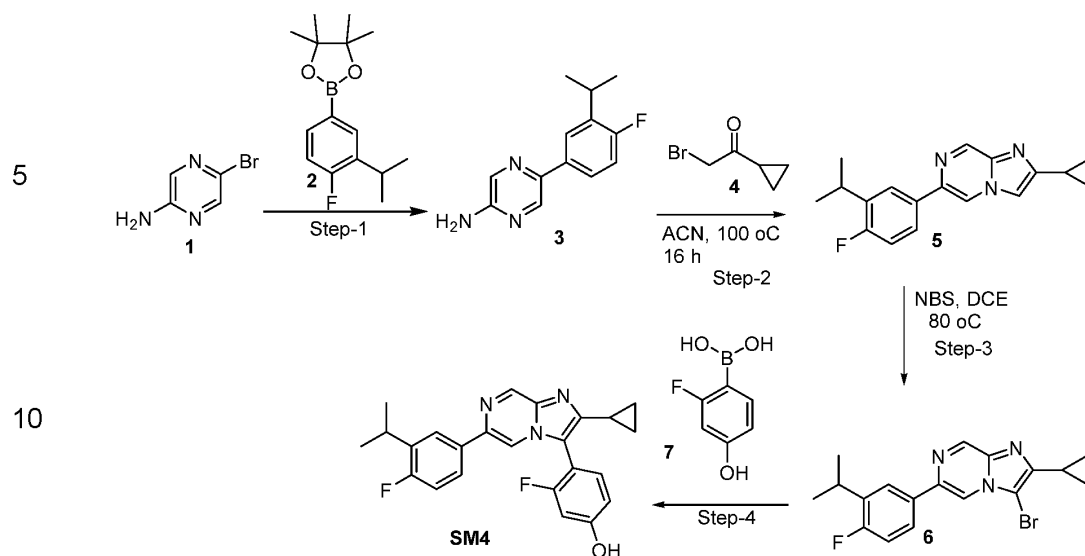
Step-1: To a stirred solution of **compound 1** (400 mg, 0.995 mmol) and Compound 2 (2-fluoro-4-hydroxyphenyl)boronic acid (217 mg, 1.392 mmol) added potassium carbonate (137 mg, 0.995 mmol) in 1,4-Dioxane (14 mL), amyl alcohol (14.00 mL) and water (3 mL). Then degasified 5 min and added Pd(bis(di-tert-butyl)-4-dimethylaminophenylphosphine)Cl₂ (35.2 mg, 0.050 mmol)). The reaction mixture was stirred about 1 h at 130°C in microwave. Then removed the solvents and purified by preparative HPLC to get SM3 (45 mg, 10%),

LCMS: Calculated for C₂₂H₁₆F₅N₃O 433.38, Observed 434.2 (M+H), RT. 3.0 min, 99.1 % (Max),

HPLC: 6.2 min, 99.8% (Max).

¹H NMR (400 MHz, DMSO-d₆): δ 9.00 (s, 1H), 8.71 (s, 1H), 7.74 (d, J = 2.00 Hz, 1H), 7.65-7.61 (m, 2H), 7.58 (d, J = 6.80 Hz, 1H), 7.47-7.44 (m, 1H), 7.44-7.27 (m, 2H), 3.20-3.13 (m, 1H), 1.17 (d, J = 6.80 Hz, 6H).

Synthesis of SM4



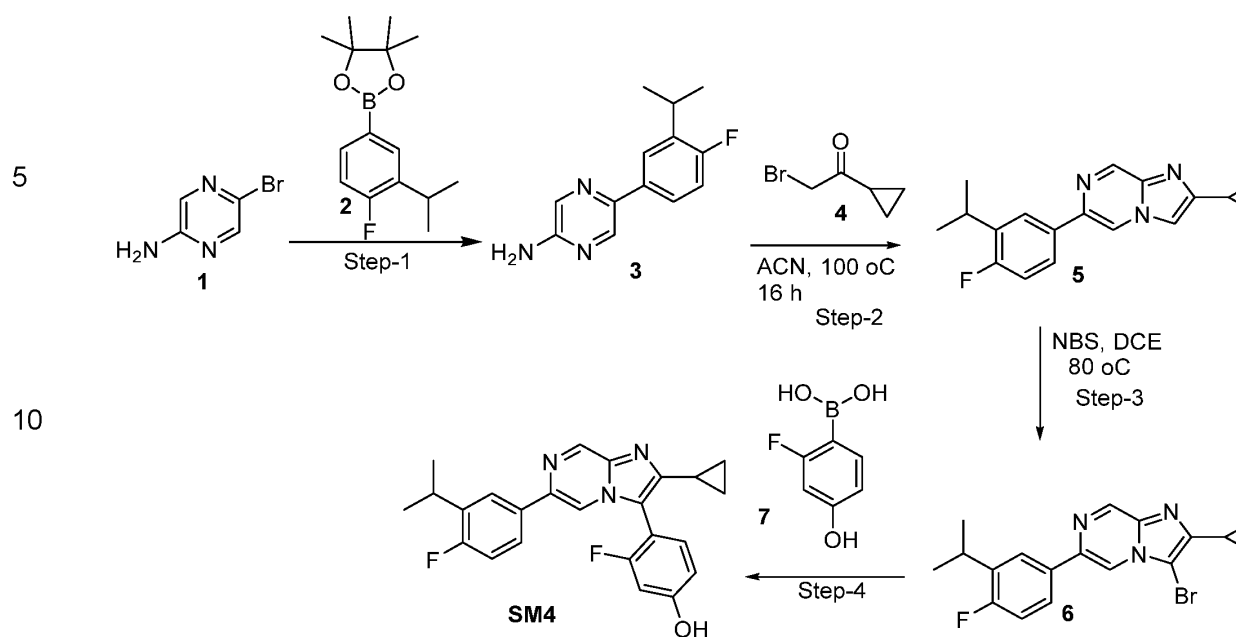
Step-1: To a stirred solution of Compound 1 (1.2 g, 6.90 mmol), 2-(4-fluoro-3-isopropylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.004 g, 7.59 mmol), K₂CO₃ (1.906 g, 13.79 mmol) in 1,4-Dioxane (12 ml) and Water (4 ml). Then degasified 5 min and added tetrakis(triphenylphosphine)palladium(0) (0.797 g, 0.690 mmol). The reaction mixture refluxed at 110 °C for 16 h. The reaction mixture was extracted with ethylacetate to get Compound 3 (900 mg, 60.9%)

LCMS: Calculated for C₁₃H₁₄FN₃ 231.12, Observed 232.2(M+H), RT. 2.12min, 98.1 % (Max).

Step-2: To a stirred solution of compound 3 (500 mg, 2.162 mmol) in Acetonitrile (6 ml) and added 2-bromo-1-cyclopropylethan-1-one (352 mg, 2.162 mmol). The reaction mixture refluxed at 100 °C for 16 h, solid filtered to get **Compound 5** (425 mg, 80%)

LCMS: Calculated for C₁₈H₁₈FN₃ 295.15, Observed 296.1 (M+H), RT. 2.5 min, 96.9 % (Max), **¹H NMR** (400 MHz, DMSO-d₆): δ 9.28 (s, 2H), 8.02-7.90 (m, 3H), 7.33-7.27 (m, 1H), 3.25 (t, J = 9.20 Hz, 1H), 2.28-2.21 (m, 1H), 1.29 (d, J = 8.80 Hz, 6H), 1.12-1.08 (m, 2H), 1.09-0.99 (m, 2H),

Step-3: To a stirred solution of **Compound 5** (422 mg, 1.429 mmol) in DCE (6 ml) and added NBS (280 mg, 1.572 mmol). The reaction mixture refluxed at



Step-1: To a stirred solution of Compound 1 (1.2 g, 6.90 mmol), 2-(4-fluoro-3-isopropylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.004 g, 7.59 mmol), K₂CO₃ (1.906 g, 13.79 mmol) in 1,4-Dioxane (12 ml) and Water (4 ml). Then degasified 5 min and added tetrakis(triphenylphosphine)palladium(0) (0.797 g, 0.690 mmol). The reaction mixture refluxed at 110 °C for 16 h. The reaction mixture was extracted with ethylacetate to get Compound 3 (900 mg, 60.9%)

LCMS: Calculated for C₁₃H₁₄FN₃ 231.12, Observed 232.2(M+H), RT. 2.12min, 98.1 % (Max).

Step-2: To a stirred solution of compound 3 (500 mg, 2.162 mmol) in Acetonitrile (6 ml) and added 2-bromo-1-cyclopropylethan-1-one (352 mg, 2.162 mmol). The reaction mixture refluxed at 100 °C for 16 h, solid filtered to get **Compound 5** (425 mg, 80%)

LCMS: Calculated for C₁₈H₁₈FN₃ 295.15, Observed 296.1 (M+H), RT. 2.5 min, 96.9 % (Max), **¹H NMR** (400 MHz, DMSO-*d*₆): δ 9.28 (s, 2H), 8.02-7.90 (m, 3H), 7.33-7.27 (m, 1H), 3.25 (t, J = 9.20 Hz, 1H), 2.28-2.21 (m, 1H), 1.29 (d, J = 8.80 Hz, 6H), 1.12-1.08 (m, 2H), 1.09-0.99 (m, 2H),

Step-3: To a stirred solution of **Compound 5** (422 mg, 1.429 mmol) in DCE (6 ml) and added NBS (280 mg, 1.572 mmol). The reaction mixture refluxed at

80 °C for 3 h. The reaction mixture was extracted with dichloromethane. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated to get **Compound 6** (305 mg, 72.2 %)

5 **LCMS:** Calculated for C₁₈H₁₇BrFN₃ 373.06, Observed 373.9 (M+H), RT. 3.1 min, 95.7 % (Max).

¹H NMR (400 MHz, MeOD): δ 8.89 (s, 1H), 8.56 (s, 1H), 8.02-8.00 (m, 1H), 7.87-7.83 (m, 1H), 7.18 (t, J = 8.80 Hz, 1H), 2.23-2.20 (m, 1H), 2.04 (s, 7H), 1.37 (d, J = 6.80 Hz, 6H), 1.15-1.12 (m, 4H),

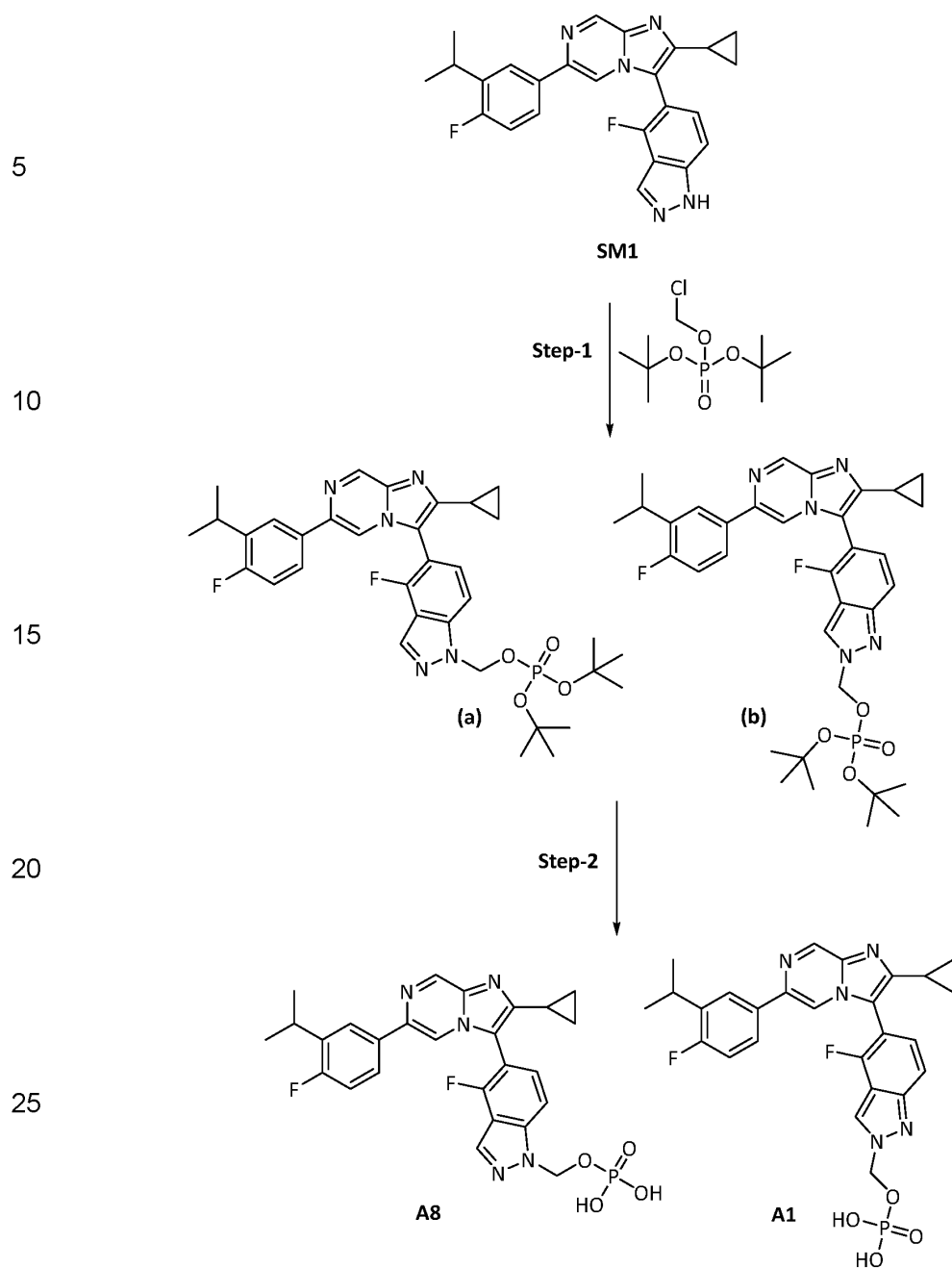
10 **Step-4:** To a stirred solution of **Compound 6** (300 mg, 0.802 mmol), 3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (191 mg, 0.802 mmol), potassium carbonate (222 mg, 1.603 mmol) in 1,4-Dioxane (8 ml) and Water (2 ml). Then degasified 5 min and added tetrakis(triphenylphosphine)palladium(0) (93 mg, 0.080 mmol). The reaction mixture refluxed at 130 °C for 1 h in microwave. The reaction mixture was extracted with ethylacetate. The combined organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The resulting residue was purified through preparative HPLC to get **SM4** (110 mg, 50%)

15 **LCMS:** Calculated for C₂₄H₂₁F₂N₃O 405.45, Observed 406.3 (M+H), RT. 2.3 min, 99.9 % (Max).

HPLC: 4.8 min, 98.2 % (Max).

20 **¹H NMR (400 MHz, DMSO-d₆):** δ 10.41 (s, 1H), 9.06 (s, 1H), 8.40 (t, J = 1.60 Hz, 1H), 8.01-7.98 (m, 1H), 7.86-7.82 (m, 1H), 7.22-7.17 (m, 1H), 6.89-6.84 (m, 2H), 3.24-3.20 (m, 1H), 1.95-1.92 (m, 1H), 1.27 (d, J = 6.80 Hz, 6H), 1.00 (t, J = 8.40 Hz, 4H),

25 **Synthesis of Compound A1 and A8 (Approach 1):**



Step-1: To a stirred solution of **SM1** (2.5 g, 5.82 mmol) in DMF (10 ml), were added cesium carbonate (5.68 mg, 17.46 mmol) and di-*tert*-butyl (chloromethyl) phosphate (2.26 g, 8.74 mmol) at 25°C. The reaction mixture was stirred at 60°C for 16 h. After the completion of the reaction, reaction mixture was quenched with water and

5 extracted with ethyl acetate. The organic layer was washed with water and brine. The organic layer was dried over sodium sulphate and concentrated to obtain crude product. The crude was purified by column chromatography using silica gel 230-400 mesh using 27-30% ethyl acetate in pet ether as eluent to afford compound (a) and compound (b) (2.6 g, 68.6%) as a gummy solid. LCMS showed two peaks corresponds to product mass.

LCMS: Calculated for C₃₄H₄₀F₂N₅O₄P, Exact mass 651.28, Observed 652.2 (M+H), RT. 3.100, and 3.188 min, 28.9 and 66.9% (Max) respectively.

10 **Step-2:** The mixture comprising compound (a) and compound (b) (2.6 g, 0.460 mmol) was taken in acetic Acid (20.0 mL) and water (20.0 mL) and stirred at 60 °C for 3 hours. After completion of reaction, reaction mixture was evaporated under reduced pressure to get crude mixture and purified by prep HPLC. Fractions collected were lyophilized to afford **Compound A1** (270 mg, 28.2 % yield) and **Compound A8** (290 mg, 30.2%) as an off white solid. **Peak 1** complies with **Compound A1** and **peak 2** complies with **Compound A8**

15

Compound A1:

LCMS: Calculated for C₂₆H₂₄F₂N₅O₄P, Exact mass 539.15, Observed 540.03 (M+H), RT. 1.54 min, 97.69% (Max).

HPLC: 3.711 min, 97.40% (Max).

20 **¹H NMR (400 MHz, DMSO-d₆):** δ 9.10 (s, 1H), 8.88 (s, 1H), 8.54 (s, 1H), 8.02 (d, J = 7.20 Hz, 1H), 7.83-7.86 (m, 1H), 7.75 (d, J = 8.80 Hz, 1H), 7.55 (t, J = 8.40 Hz, 1H), 7.18 (t, J = 9.60 Hz, 1H), 6.17 (d, J = 10.80 Hz, 2H), 3.20 (t, J = 7.20 Hz, 1H), 1.93-2.05 (m, 1H), 1.26 (d, J = 7.20 Hz, 6H), 0.96-1.05 (m, 4H).

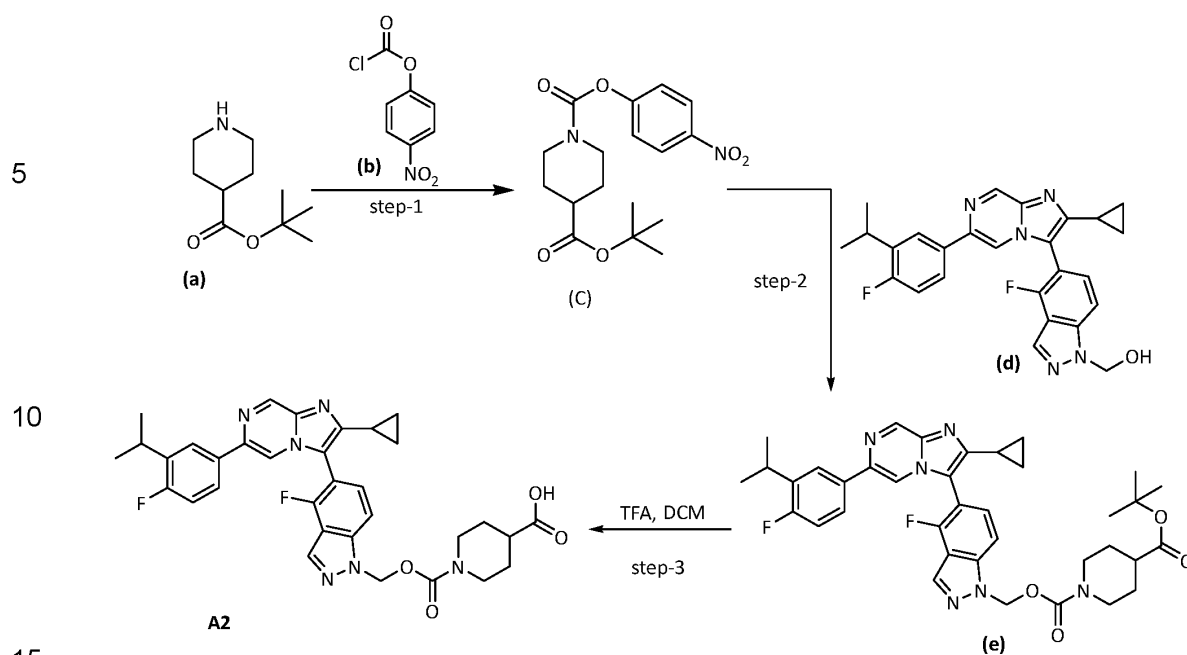
Compound A8:

25 **LCMS:** Calculated for C₂₆H₂₄F₂N₅O₄P, Exact mass 539.15, Observed 540.1 (M+H), RT. 1.61 min, 96.27% (Max).

HPLC: 3.87 min, 94.37% (Max).

30 **¹H NMR (400 MHz, DMSO-d₆):** δ 9.11 (s, 1H), 8.54-8.49 (m, 2H), 8.02 (d, J = 6.00 Hz, 1H), 7.76-7.87 (m, 3H), 7.18 (t, J = 9.60 Hz, 1H), 6.24 (d, J = 8.40 Hz, 2H), 3.42-3.49 (m, 2H), 3.20 (t, J = 6.40 Hz, 1H), 1.91-1.99 (m, 1H), 1.26 (d, J = 6.80 Hz, 1H), 0.96-1.05 (m, 4H).

Synthesis of Compound A2:



Step-1: To a stirred solution of tert-butyl piperidine-4-carboxylate (350 mg, 1.889 mmol) and 4-nitrophenyl carbonochloridate (457 mg, 2.267 mmol) in DCM (10 mL), was added TEA (0.790 ml, 5.67 mmol) at 0°C. The reaction mixture was stirred at 25 °C for 16 h. After the completion of reaction, the reaction mixture was quenched with water and extracted with DCM. The organic phase was dried over sodium sulphate, concentrated. The crude obtained was purified by column in 35% ethyl acetate to get compound (c) (660 mg, 100 %).

¹H-NMR (400 MHz, DMSO-d₆): δ 8.28 (d, J = 4.80 Hz, 2H), 8.19 (d, J = 9.20 Hz, 2H), 4.05 (s, 1H), 3.62 (s, 1H), 2.49-2.50 (m, 1H), 1.54-1.54 (m, 2H), 1.42-1.52 (m, 2H), 1.18 (s, 9H),

Step-2: To a stirred solution of **Compound (c)** (153 mg, 0.435 mmol) and **Compound (d)** (200 mg, 0.435 mmol) in DMF (10 mL), was added potassium tert-butoxide (73.3 mg, 0.653 mmol). The reaction mixture was stirred at 25 °C for 16 h. After the completion of the reaction, the reaction mixture was quenched with water and extracted with ethylacetate. The combined organic layer was washed with water and brine solution. The organic phase was dried over sodium sulphate, concentrated. The resulting residue was purified by prep-HPLC to get **Compound (e)** (106 mg, 36.2%).
LCMS: Calculated for: C₃₇H₄₀F₂N₆O₄ 670.76, Observed 671.5 (M+H), RT.2.6 min, 99.4% (Max),

¹H-NMR (400 MHz, DMSO-d₆): δ 9.11 (s, 2H), 8.51-8.54 (m, 1H), 8.03 (d, J = 2.40 Hz, 1H), 8.01 (d, J = 2.00 Hz, 1H), 7.91-7.93 (m, 1H), 7.19 (t, J = 1.60 Hz, 1H), 6.48 (d, J = 18.40 Hz, 2H), 4.01-4.06 (m, 2H), 3.17-3.20 (m, 1H), 2.00 (s, 1H), 1.94-1.97 (m, 2H), 1.38 (s, 10H), 1.21 (s, 6H), 1.01-1.18 (m, 4H).

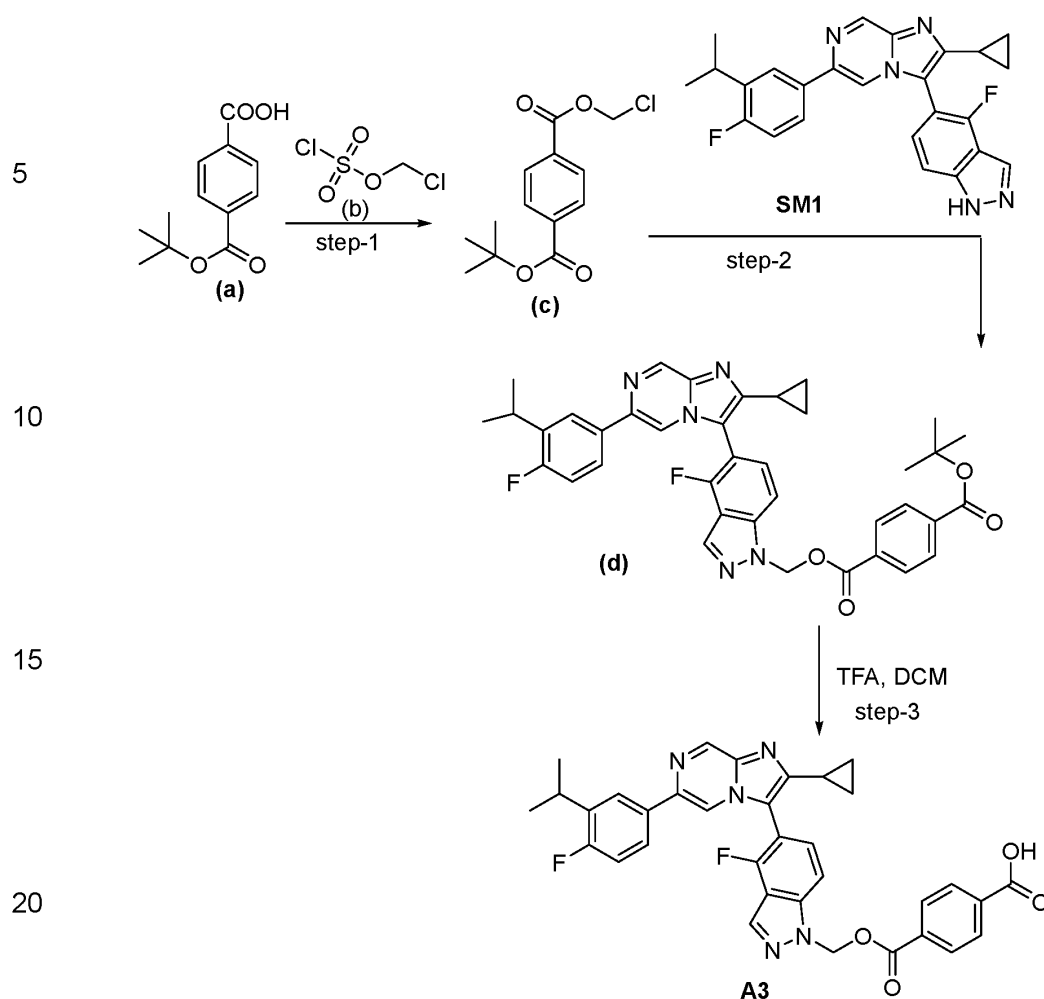
Step-3: To a stirred solution of compound (e) (106 mg, 0.158 mmol) in DCM (4 mL) at 0 °C, was added TFA (0.037 mL, 0.474 mmol) at 0°C. The reaction mixture was stirred at 25 °C for 2 h. After the completion of reaction, the reaction mixture was concentrated and the crude product obtained was purified by prep-HPLC to get **Compound A2** (25 mg, 25.6 %),

LCMS: Calculated for: C₃₃H₃₂F₂N₆O₄ 614.65, Observed 615.3 (M+H), RT.2.1 min, 99.5% (Max),

HPLC: 4.9 min, 99.9% (Max),

¹H-NMR (400 MHz, DMSO-d₆): δ 9.11 (s, 1H), 8.54 (s, 1H), 8.26 (s, 1H), 8.00-8.01 (m, 1H), 7.92 (m, 1H), 7.78-7.85 (m, 1H), 7.17-7.22 (m, 1H), 6.48 (d, J = 17.20 Hz, 2H), 3.20-3.88 (m, 4H), 2.93-3.18 (m, 1H), 2.67-2.68 (m, 2H), 2.45-2.50 (m, 3H), 2.40-2.41 (m, 2H), 1.80 (s, 6H), 1.01-1.38 (m, 4H).

Synthesis of Compound A3:



Step 1: To a stirred solution of **Compound (a)** (300 mg, 1.350 mmol) and sodium bicarbonate (454 mg, 5.40 mmol) in DCM (6 mL) and Water (6.00 mL), was added tetrabutylammonium hydrogen sulfate (45.8 mg, 0.135 mmol) at 0 °C and the reaction kept for stirring for 10 min. Then added **Compound (b)** (312 mg, 1.890 mmol) and the reaction mixture was stirred at 25 °C for 16 h. The reaction progress was monitored by TLC and LCMS. After the completion of reaction, the reaction mixture was quenched with water and extracted with DCM. The combined organic layer was then dried over anhydrous sodium sulphate and concentrated under reduced pressure to get the crude. The crude product was purified by flash column chromatography using 230-400 mesh silica gel using 5-6% ethyl acetate in pet ether as eluent to afford **Compound (c)** (242mg, 66.2%).

¹H NMR (400 MHz, DMSO-d₆): δ 8.06-8.12 (m, 4H), 6.14 (s, 2H), 1.57 (s, 9H).

5 **Step 2:** To a stirred solution of **SM1** (300 mg, 0.698 mmol) in THF (10 mL), was added potassium tert-butoxide (117 mg, 0.419 mmol) and **Compound (c)** (232 mg, 1.047 mmol) at 25°C. The reaction mixture was stirred at 25°C for 4 h. The reaction progress was monitored by TLC and LCMS. After the completion of reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was then dried over anhydrous sodium sulphate and concentrated under reduced pressure to get the crude. The crude product was purified by flash column chromatography using silica gel 230-400 mesh using 15% ethyl acetate in pet ether as eluent to afford **Compound (d)** (304mg, 65.6%).

10 **LCMS:** Calculated for C₃₈H₃₅F₂N₅O₄, Exact mass 663.726, Observed 664.4 (M+H), RT. 2.744min, 98.876 (Max).

¹H NMR (400 MHz, DMSO-d₆): δ 9.11 (d, J = 1.60 Hz, 1H), 8.58 (d, J = 5.60 Hz, 2H), 8.01-8.09 (m, 7H), 7.83 (d, J = 8.40 Hz, 2H), 7.17 (t, J = 13.60 Hz, 1H), 6.82 (s, 2H), 1.56 (s, 9H), 1.16-1.26 (m, 6H), 1.02-1.26 (m, 5H).

15 **Step 3:** To a stirred solution of **Compound (d)** (304 mg, 0.458 mmol) in DCM (2 mL), was added TFA (0.118 mL, 0.458 mmol) at 0°C. The reaction mixture was stirred at 25 °C for 16 h. The reaction progress was monitored by TLC and LCMS. After the completion of the reaction, the reaction mixture was concentrated and crude product obtained was purified by Prep-HPLC to afford **Compound A3** (81.89 mg, 29. %) as an off white solid.

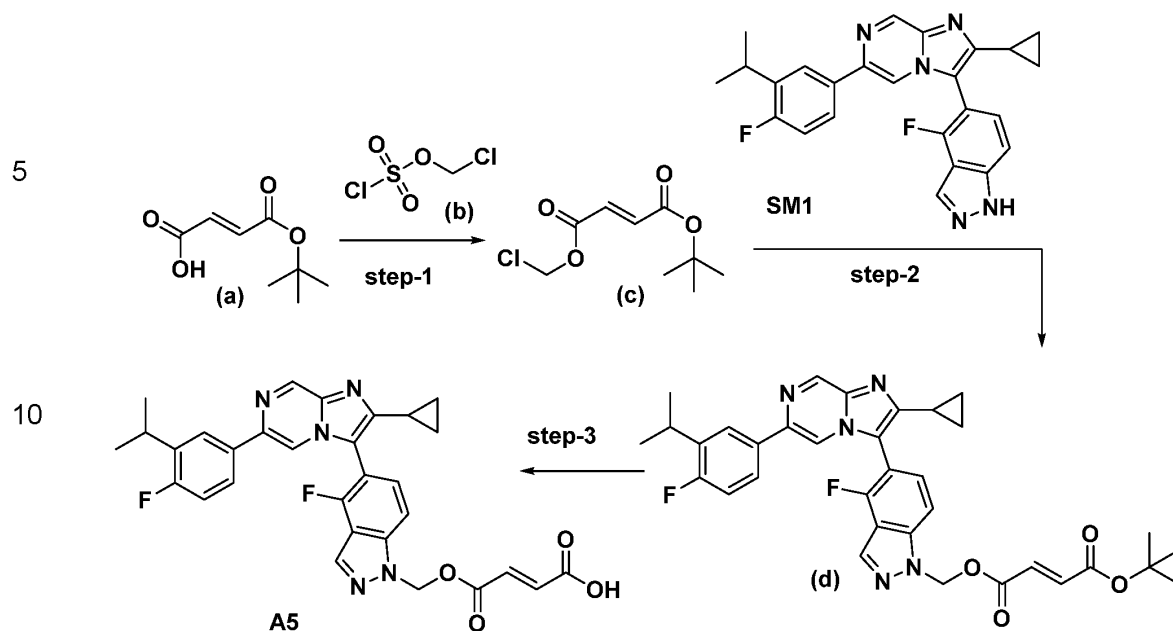
20 **LCMS:** Calculated for C₃₄H₂₇F₂N₅O₄, Exact mass 607.618, Observed 608.3 (M+H), RT. 2.285min, 99.93% (Max).

HPLC: 5.409 min, 99.94% (Max).

25 **¹H NMR (400 MHz, DMSO-d₆):** δ 13.43 (s, 1H), 9.11 (d, J = 1.20 Hz, 1H), 8.57-8.60 (m, 2H), 8.07 (s, 6H), 7.80-7.85 (m, 2H), 7.15-7.19 (m, 1H), 6.83 (s, 2H), 3.18-3.23 (m, 1H), 1.93-1.98 (m, 1H), 1.25 (d, J = 6.80 Hz, 6H), 0.99-1.05 (m, 4H).

Synthesis of Compound A5:

30



Step 1: To a stirred solution of **Compound (a)** (250 mg, 1.452 mmol) and sodium bicarbonate (488 mg, 5.81 mmol) in DCM (6 ml) and water (6.00 mL), was added tetrabutylammonium hydrogen sulfate (49.3 mg, 0.145 mmol) at 0 °C. The reaction mixture was kept for stirring for 10 min. Then added **Compound (b)** (0.206 mL, 2.033 mmol) at 0 °C. The reaction mixture was stirred at 25 °C for 16 h. The reaction progress was monitored by TLC and LCMS. After the completion of reaction, the reaction mixture was diluted with water and extracted with DCM. The combined organic layer was then dried over anhydrous sodium sulphate and concentrated under reduced pressure to get the crude. The crude product was purified by flash column chromatography using 230-400 mesh silica gel and 7% ethyl acetate in pet ether as eluent to afford **Compound (c)** (234 mg, 73%).

¹H NMR (400 MHz, DMSO-d₆): δ 6.72-6.82 (m, 2H), 5.97 (s, 2H), 1.48 (s, 9H).

Step 2: To a stirred solution of **SM1** (150 mg, 0.349 mmol) in THF (6 mL), was added potassium tert-butoxide (47.0 mg, 0.419 mmol). After stirring at 25°C for 15 minutes, solution of **Compound (c)** (117 mg, 0.524 mmol) in THF (3 mL) was added dropwise. The reaction mixture was stirred at 25°C for 16 h. The reaction progress was monitored by TLC and LCMS. After the completion of reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was then dried over anhydrous sodium sulphate and concentrated under reduced pressure to get the crude. The crude product was purified by flash column

chromatography using 230-400 mesh silica gel using 19% ethyl acetate in pet ether as eluent to afford **Compound (d)** (94mg, 51.3%).

LCMS: Calculated for C₃₄H₃₃F₂N₅O₄, Exact mass 615.682, Observed 614.5 (M+H), RT. 2.635min, 93.63% Max).

¹H NMR (400 MHz, DMSO-d₆): δ 9.11 (d, J = 1.60 Hz, 1H), 8.55-8.57 (m, 2H), 8.01-8.03 (m, 1H), 7.95-7.93 (m, 1H), 7.79-7.86 (m, 2H), 7.15-7.20 (m, 1H), 6.71 (d, J = 1.20 Hz, 2H), 6.67 (s, 2H), 3.17-3.24 (m, 1H), 1.92-2.00 (m, 1H), 1.45 (d, J = 5.20 Hz, 9H), 1.25-1.27 (m, 6H), 0.99-1.05 (m, 4H).

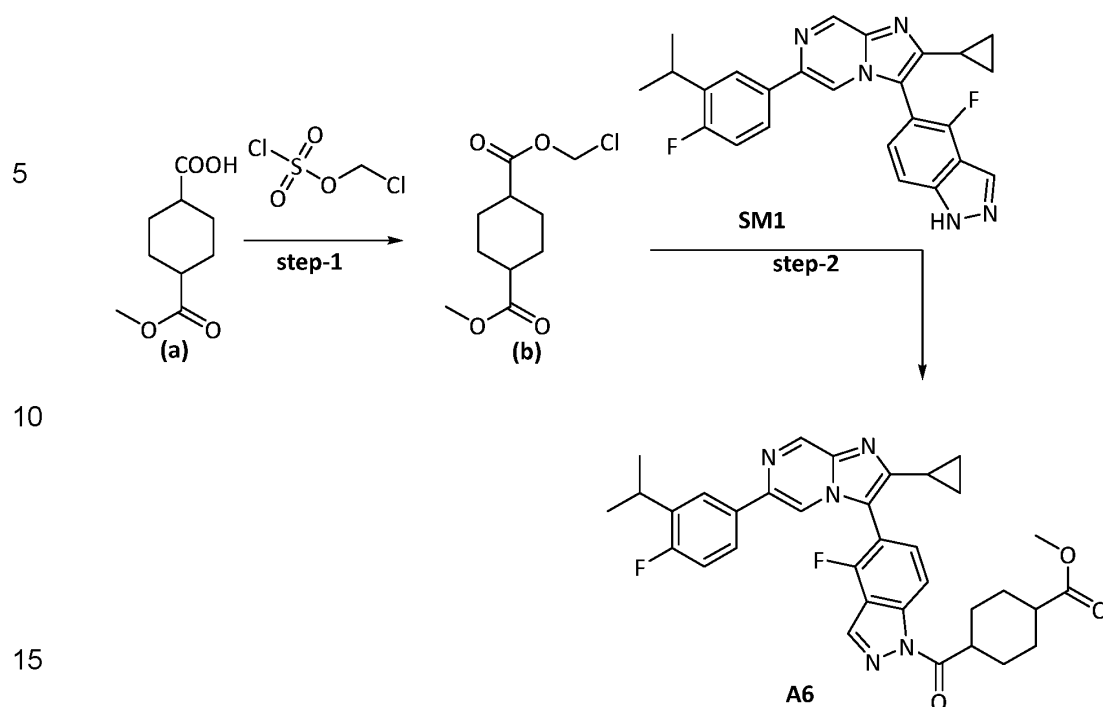
Step 3: To a stirred solution of **Compound (d)** (114 mg, 0.186 mmol) in DCM (4 mL), was added TFA (0.048 mL, 0.186 mmol) at 0°C. The reaction mixture was stirred at 25 °C for 16 h. The reaction progress was monitored by TLC and LCMS. After the completion of the reaction, the reaction mixture was concentrated and purified by Preparative HPLC. The fraction obtained was then lyophilized to afford **Compound A5** (45.82 mg, 44.2%).

LCMS: Calculated for C₃₀H₂₅F₂N₅O₄, Exact mass 557.558, Observed 558.3 (M+H), RT. 2.219min, 99.4% (Max).

HPLC: 5.080min, 99.9% (Max).

¹H NMR (400 MHz, DMSO-d₆): δ 13.35 (s, 1H), 9.11 (d, J = 1.20 Hz, 1H), 8.55-8.58 (m, 2H), 8.02 (dd, J = 2.40, 7.40 Hz, 1H), 7.94-7.96 (m, 1H), 7.78-7.87 (m, 2H), 7.18 (t, J = 1.6 Hz, 1H), 6.72-6.80 (m, 2H), 6.67-6.68 (m, 2H), 3.18-3.22 (m, 2H), 1.26 (d, J = 7.20 Hz, 6H), 0.99-1.05 (m, 4H).

Synthesis of Compound A6:



Step-1: To a stirred solution of **Compound (a)** and sodium bicarbonate (451 mg, 5.37 mmol) in DCM (6 mL) and Water (6 mL), was added tetrabutylammonium hydrogen sulfate (45.6 mg, 0.134 mmol) at 0°C. The reaction mixture was stirred for 10 min and added chloromethyl sulfurochloridate (310 mg, 1.880 mmol). The reaction mixture was stirred at 25°C for 16 h. TLC monitoring confirms the completion of reaction. Reaction mixture was quenched with water and extracted over DCM. Organic layer was dried over sodium sulphate, concentrated to get crude mixture. The resulting residue was purified through silica gel (230-400 mesh) column chromatography using 10% ethyl acetate in petroleum ether as eluent to get **Compound (b)** (260 mg, 83%).

¹H NMR (400 MHz, DMSO-*d*₆): δ 5.73 (s, 2H), 3.70 (m, 1H), 2.11-2.14 (m, 2H), 2.07-2.10 (m, 4H), 1.56-1.58 (m, 4H).

Step-2: To a stirred solution of **SM1** (200 mg, 0.466 mmol) in THF (10 mL), were added 1-chloromethyl 4-methyl cyclohexane-1,4-dicarboxylate (193 mg, 0.699 mmol) and potassium *tert*-butoxide (78 mg, 0.699 mmol). The reaction mixture was stirred at room temperature for 16 h. TLC monitoring confirms the completion of the reaction. Reaction mixture was quenched with water, extracted over ethyl acetate. The combined organic layer was washed with brine solution, dried over sodium sulphate and concentrated to get crude residue. After

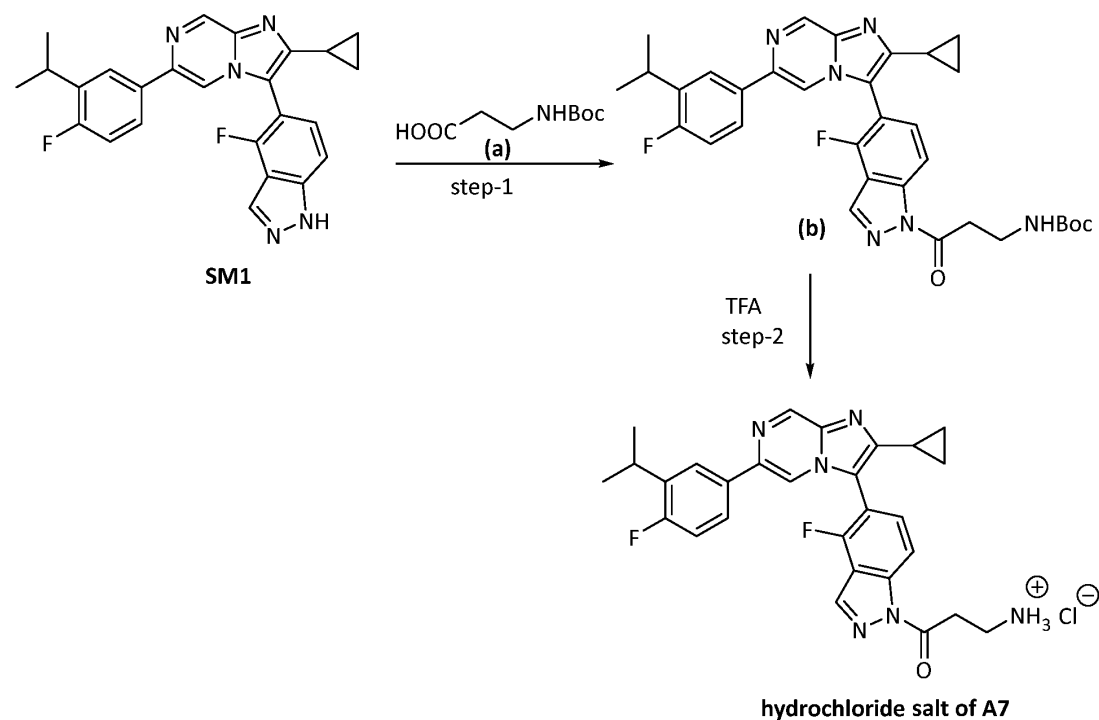
column purification **Compound A6** was isolated and purified by preparative **Compound A6** (50 mg, 17.25%).

LCMS: Calculated for $C_{34}H_{33}F_2N_5O_3$ 597.67, Observed 598.4 (M+H), RT. 2.62 min, 95.47 % (Max).

HPLC: 6.30 min, 96.09 % (Max).

1H NMR (400 MHz, DMSO- d_6): δ 9.13 (s, 1H), 8.84 (s, 1H), 8.61 (s, 1H), 8.38 (d, J = 8.40 Hz, 1H), 8.02 (d, J = 7.60 Hz, 1H), 7.96 (t, J = 7.20 Hz, 1H), 7.85-7.87 (m, 1H), 7.18 (t, J = 9.20 Hz, 1H), 3.63 (s, 3H), 3.17-3.22 (m, 1H), 2.06-2.13 (m, 4H), 1.95-2.00 (m, 1H), 1.48-1.69 (m, 4H), 1.26 (d, J = 6.80 Hz, 6H), 1.00-1.05 (m, 4H).

Synthesis of Compound A7 (Hydrochloride Salt):



Step 1: To a stirred solution of **SM1** (190 mg, 0.442 mmol) and DIPEA (86 mg, 0.664 mmol) in DMF (6 mL), was added PyBOP (460 mg, 0.885 mmol) and **Compound (a)** (126 mg, 0.664 mmol). The reaction mixture was stirred at 25°C for 16 h. The reaction mixture was extracted with ethyl acetate and washed with water. The organic layer was dried over sodium sulphate, concentrated and purified by column purification through silica gel (230-400 mesh) using 30% ethyl acetate in petroleum ether to get **Compound (b)** (160 mg, 58.9 %).

LCMS: Calculated for C₃₃H₃₄F₂N₆O₃ 600.671, Observed 601.3 (M+H), RT. 3.28 min, 97.95% (Max).

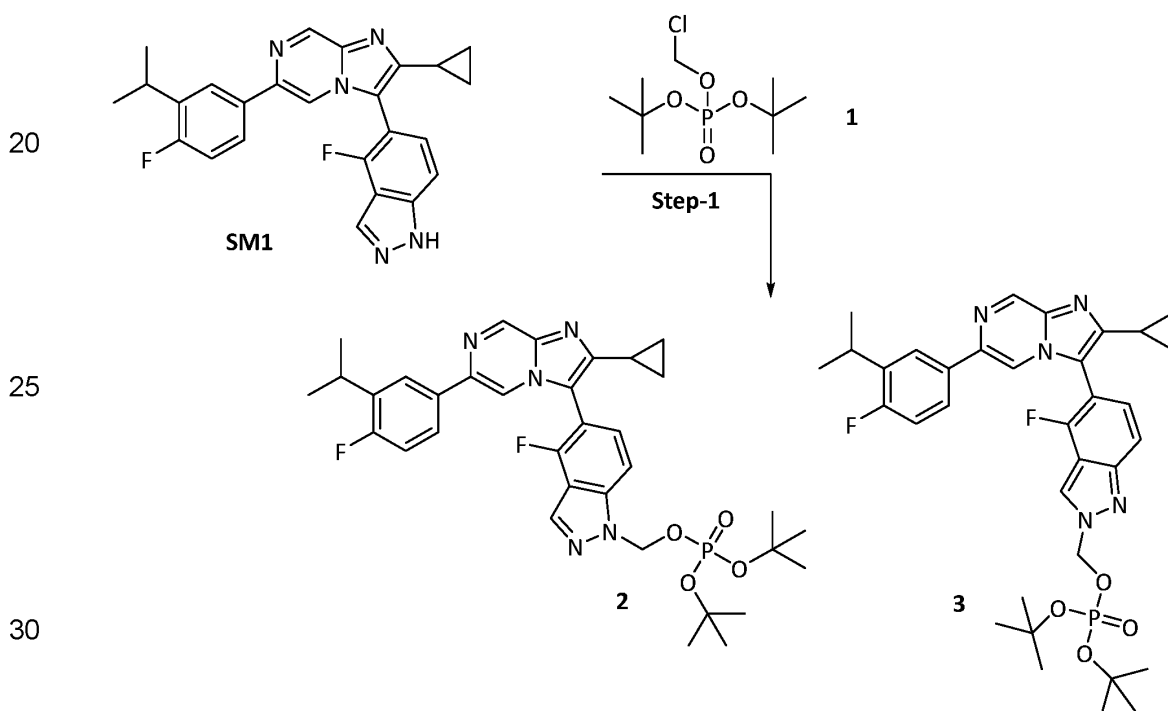
5 **Step 2:** To a stirred solution of **Compound (b)** (100 mg, 0.166 mmol) in DCM (5 ml), was added trifluoroacetic acid (0.552 mL, 7.16 mmol) and the reaction mixture was stirred at 25°C for 16 hours. The reaction mixture was concentrated at 25°C and purified by preparative HPLC in HCl method. Then the sample was lyophilized to get the hydrochloride salt of **Compound A7** (72 mg, 78%).

10 **LCMS:** Calculated for C₂₈H₂₇ClF₂N₆O 500.55, Observed 501.1 (M+H), RT. 2.03 min, 97.12% (Max).

HPLC: 4.141 min, 97.87% (Max).

¹H NMR (400 MHz, DMSO-*d*⁶): δ 9.14 (s, 1H), 8.86 (s, 1H), 8.58 (s, 1H), 8.36 (s, 1H), 8.02-7.99 (m, 2H), 8.04 (d, J = 15.20 Hz, 2H), 7.86 (d, J = 2.40 Hz, 1H), 7.19 (d, J = 1.60 Hz, 1H), 3.66 (t, J = 6.80 Hz, 2H), 3.30 (t, J = 6.40 Hz, 2H), 3.22-3.19 (m, 1H), 1.98-1.94 (m, 1H), 1.26 (d, J = 6.80 Hz, 6H), 1.06-0.99 (m, 4H).

Synthesis of Compound A8 (Approach 2):



Step-1: To a stirred solution of **SM1** (27 g, 62.9 mmol) in DMF (75 mL), was added Cs₂CO₃ (30.7 g, 94 mmol) and di-*tert*-butyl (chloromethyl) phosphate (**Compound 1**)

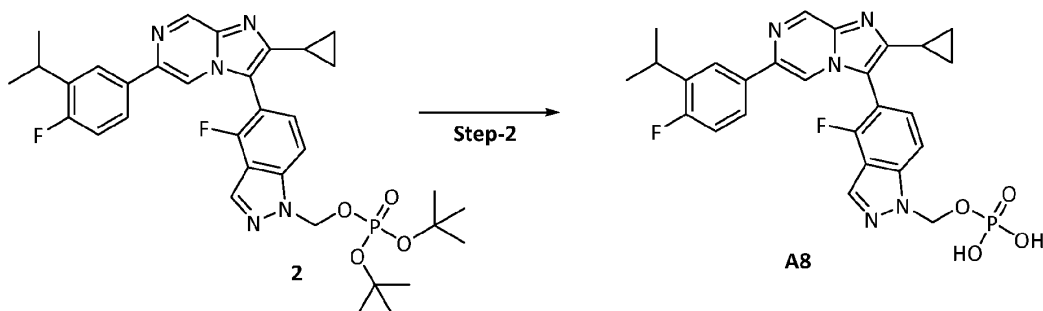
(17.8 g, 69.2 mmol) at 25 °C. The reaction mixture was stirred at 60°C for 4 h. The reaction progress was monitored by TLC. After the completion of reaction, the reaction mixture was quenched with water and extracted over ethyl acetate. The organic fractions were washed with brine (150 mL), dried over sodium sulphate and evaporated in vacuum to obtain crude mixture of **Compound 2** and **Compound 3**. The crude was purified by SFC and the fractions were concentrated and did work up using DCM (400 mL) and water (2 x 250 mL).

LCMS (Crude): Calculated for C₃₄H₄₀F₂N₅O₄P, Exact mass 651.28, Observed 652.2 (M+H), RT. 2.469, and 2.533 min, 43.32% and 49.46% (Max) respectively.

The crude residue obtained from step-1 was purified by SFC to get **Compound 2** (18.8 g, 41.4%) and **Compound 3** (6.6 g, 15.0%).

Compound 2:

LCMS: Calculated for C₃₄H₄₀F₂N₅O₄P, Exact mass 651.28, Observed 652.2 (M+H), RT. 2.566 min, 93.05% (Max).

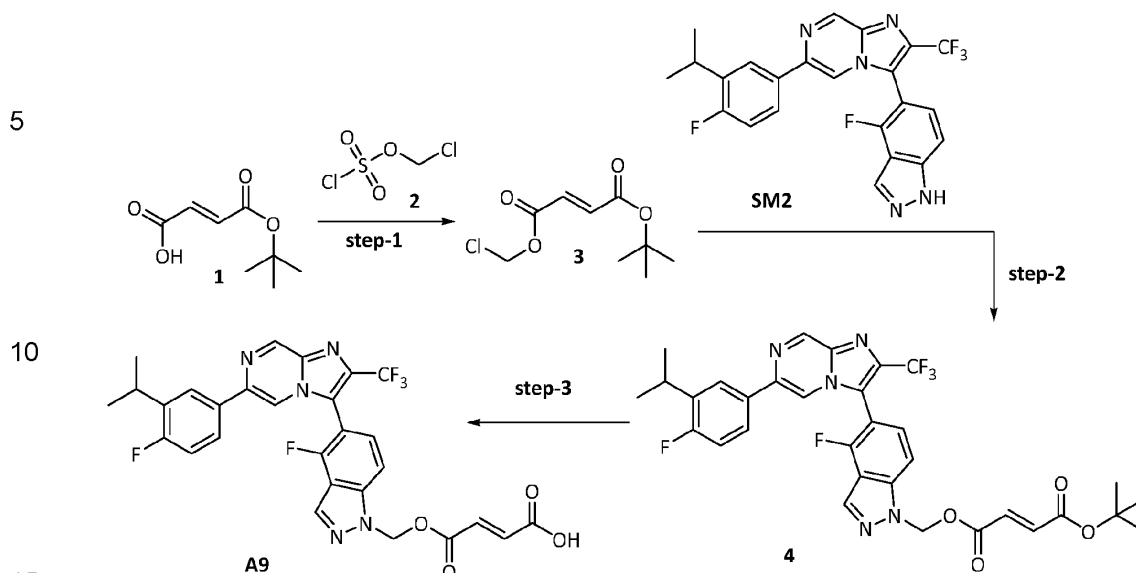


Step-2: Compound 2 (18.8 g, 6.75 mmol) was taken in IPA (188 mL) and Water (188 mL). Stirred at 50 °C for 20 h. The reaction was monitored by LCMS and HPLC. After the completion of reaction, the reaction mixture was cooled to RT, solid precipitated was filtered, washed with IPA (100 mL) and dried in vacuum to get **Compound A8** (11.2 g, 71.97%).

LCMS: Calculated for C₂₆H₂₄F₂N₅O₄P, Exact mass 539.15, Observed 540.0 (M+H), RT. 1.798 min, 98.82% (Max).

HPLC: 3.896 min, 99.80% (Max).

¹H NMR (400 MHz, DMSO-d₆): δ 9.11 (s, 1H), 8.55 (s, 1H), 8.49 (s, 1H), 8.02-8.00 (m, 1H), 7.88-7.76 (m, 3H), 7.19-7.15 (m, 1H), 6.24 (d, J = 8.40 Hz, 2H), 3.23-3.18 (m, 1H), 1.97-1.93 (m, 1H), 1.26 (d, J = 6.80 Hz, 6H), 1.04-0.99 (m, 4H).

Synthesis of Compound A9:

Step-1: To a stirred solution of (*E*)-4-(*tert*-butoxy)-4-oxobut-2-enoic acid (500 mg, 2.90 mmol) and sodium bicarbonate (976 mg, 11.62 mmol) in DCM (12 mL) and water (12 mL), was added tetrabutylammonium hydrogen sulfate (99 mg, 0.290 mmol) at 0 °C and the reaction kept for stirring for 10 min. Then added chloromethyl sulfurochloridate (671 mg, 4.07 mmol) and reaction mixture was stirred at room temperature for 16 h. The reaction progress was monitored by TLC. After the completion of reaction, reaction mixture was quenched with water and extracted over DCM. Organic layer was dried over sodium sulphate, concentrated and purified by column. The product was eluted at 6% ethyl acetate in petroleum ether. The fractions were evaporated in vacuum to obtain **Compound 3** (0.50 g, 78%).

¹H NMR (400 MHz, DMSO-*d*⁶): δ 6.81-6.71 (m, 2H), 5.97 (s, 2H), 1.47 (s, 9H).

Step-2: To a stirred solution of **SM2** (300 mg, 0.656 mmol) in THF (3 mL), was added potassium *tert*-butoxide (110 mg, 0.984 mmol). After cooling to 0°C, *tert*-butyl(chloromethyl) fumarate (174 mg, 0.787 mmol) in THF (1 mL) was added dropwise. The reaction mixture was stirred at RT for 2 h. TLC monitoring confirms the completion of reaction. Reaction mixture was quenched with water and extracted over ethyl acetate. Organic layer was dried over sodium sulphate, concentrated and purified by column. The product was eluted at 14% ethyl acetate in petroleum ether. The fractions were evaporated in vacuum to obtain **Compound 4** (250 mg, 29.38%).

LCMS: Calculated for C₃₂H₂₈F₅N₅O₄ 641.60, Observed 642.1 (M+H), RT. 2.87 min, 98.7% (Max).

Step-3: To a stirred solution of **Compound 4** (250 mg, 0.390 mmol) in DCM (2 mL), was added TFA (1481 mg, 3.90 mmol) at 0°C. The reaction mixture was stirred at RT for 16 h. After the completion of reaction, the reaction mixture was concentrated to get crude mixture and purified by preparative HPLC. The fractions were lyophilized to get **Compound A9** (0.1 g, 43.6%) as an off white solid.

LCMS: Calculated for C₂₈H₂₀F₅N₅O₄ 585.49, Observed 586.2 (M+H), RT. 2.5 min, 98.87 % (Max).

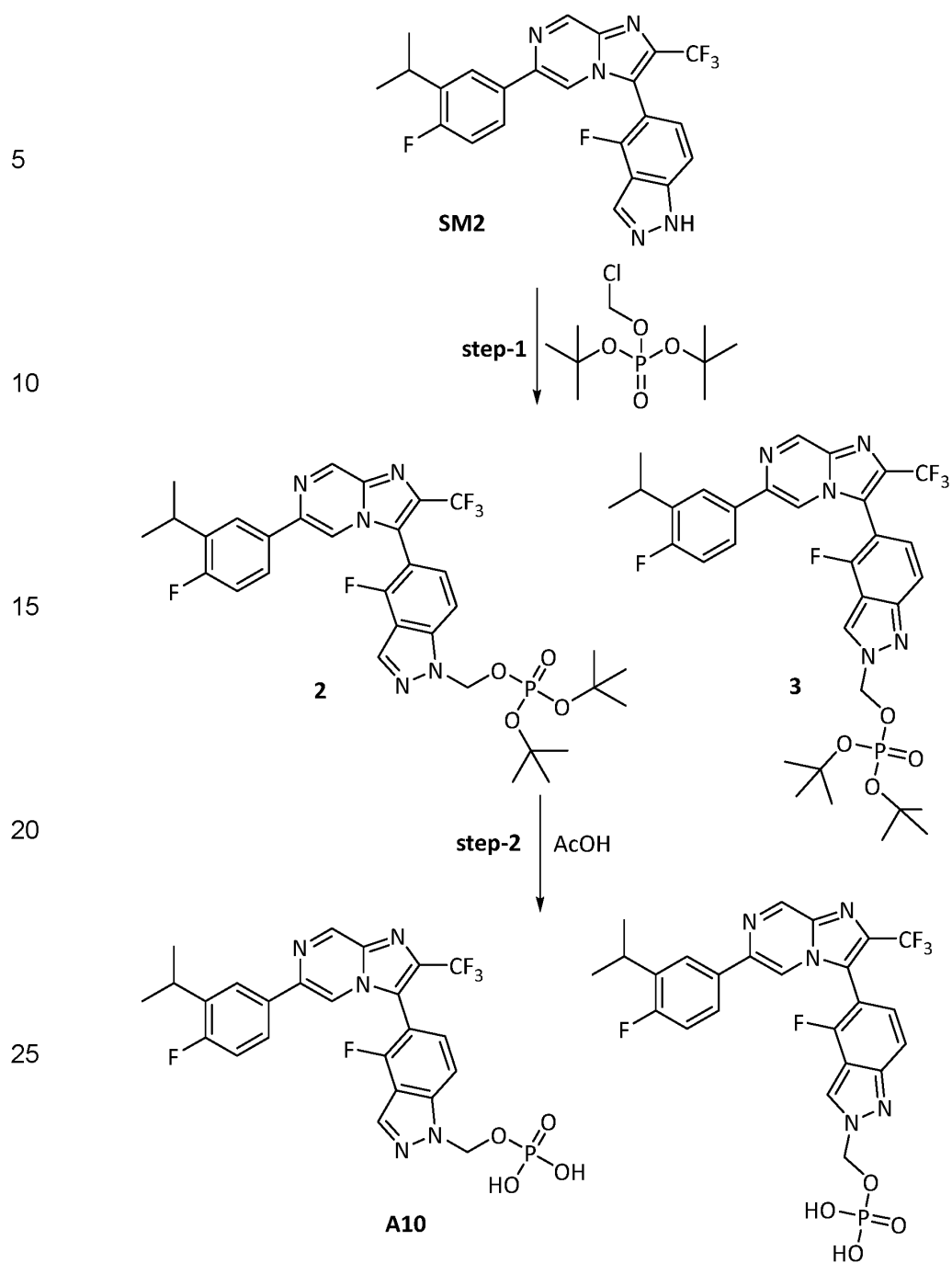
HPLC: 5.65 min, 99.54 % (Max).

¹H NMR (400 MHz, DMSO-d₆): δ 9.45 (d, J = 1.20 Hz, 1H), 8.70 (s, 1H), 8.56 (d, J = 0.40 Hz, 1H), 8.06-8.03 (m, 1H), 7.96-7.90 (m, 1H), 7.90-7.88 (m, 1H), 7.76-7.72 (m, 1H), 7.23-7.18 (m, 1H), 6.81-6.77 (m, 1H), 6.70-6.67 (m, 1H), 6.59-6.56 (m, 1H), 6.46-6.42 (m, 1H), 3.24-3.15 (m, 1H), 1.26 (d, J = 7.20 Hz, 1H).

¹³C NMR (400 MHz, DMSO-d₆): δ 166.62, 165.10, 162.28, 159.84, 154.89, 152.35, 144.42, 144.07, 139.68, 139.20, 135.44, 133.34, 132.35, 130.99, 128.26, 126.43, 120.66, 120.15, 116.24, 114.89, 108.25, 104.39, 71.17, 27.70, 22.85.

¹⁹F NMR (400 MHz, DMSO-d₆): δ -119.0, -115.8, -73.46.

Synthesis of Compound A10:



Step-1: To a stirred solution **SM2** (1 g, 2.186 mmol) in DMF (10 mL), was added cesium carbonate (2.137 g, 6.56 mmol) and di-*tert*-butyl (chloromethyl) phosphate (0.848 g, 3.28 mmol) at 25°C, and the reaction mixture was stirred at 60°C for 4 h. Reaction monitoring by LC-MS showed 26% and 2% of both regioisomers along with

32% and 27% of mono *tert*-butyl cleaved product mass. Then the reaction mixture was extracted with ethyl acetate and washed with water. Organic layer was dried over sodium sulphate, concentrated and taken the crude mixture of **Compound 2** and **Compound 3** (1.5 g) as such for next step.

Step-2: Mixture of **Compound 2** and **Compound 3** (1.5 g, 2.006 mmol) was taken in acetic acid (3 mL) and water (3 mL) and stirred at 60°C for 2 h. TLC monitoring confirms the completion of reaction. Reaction mixture was concentrated to get crude mixture with 31% and 29% of both regioisomers by LC-MS. After preparative HPLC purification, two fractions were isolated and lyophilized. Peak 1 complies with **Compound A10** (0.28 g, 22.4%)

LCMS: Calculated for C₂₄H₁₉F₅N₅O₄P 567.41, Observed 568.2 (M+H), RT. 2.2 min, 96.2 % (Max),

HPLC: 4.41 min, 97.31% (Max).

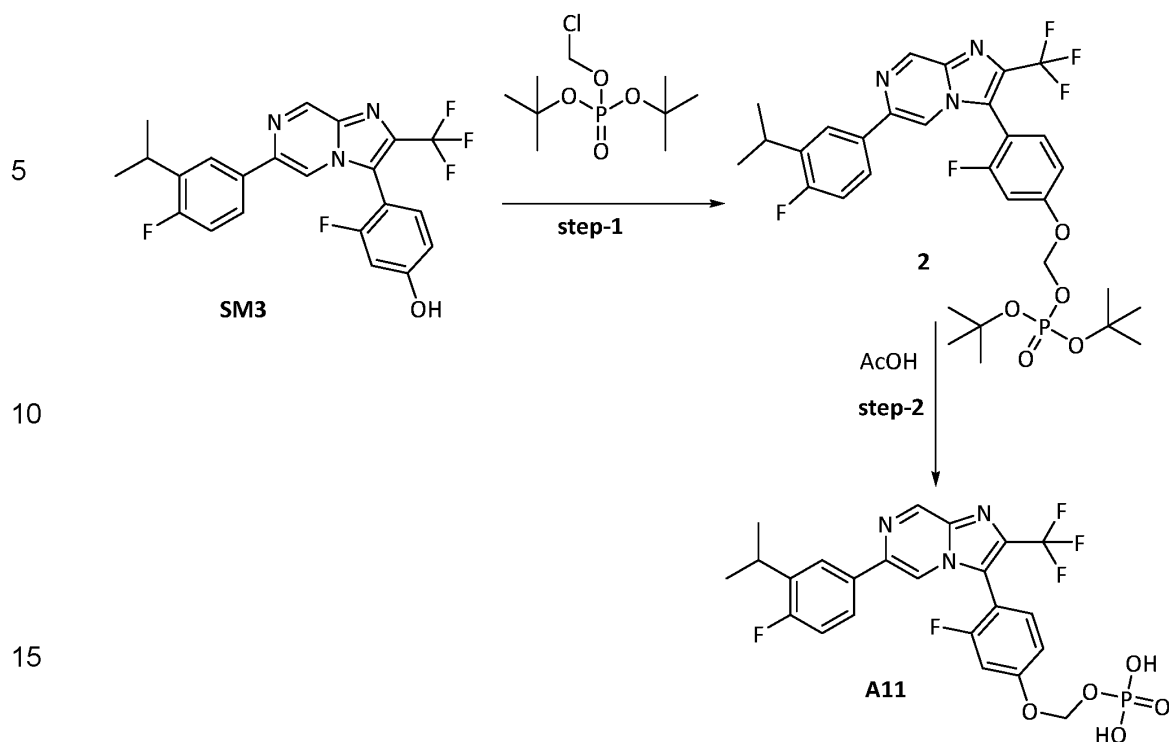
¹H NMR (400 MHz, DMSO-d₆): δ 9.45 (d, J = 1.60 Hz, 1H), 8.93 (d, J = 0.80 Hz, 1H), 8.65 (s, 1H), 8.05-8.03 (m, 1H), 7.91-7.87 (m, 1H), 7.75 (d, J = 8.80 Hz, 1H), 7.50-7.46 (m, 1H), 7.23-7.18 (m, 1H), 6.18 (d, J = 10.80 Hz, 2H), 3.26-3.17 (m, 1H), 1.26 (d, J = 7.20 Hz, 6H).

¹³C NMR (400 MHz, DMSO-d₆): δ 162.28, 159.83, 155.68, 153.1, 151.72, 144.46, 139.42, 135.40, 134.44, 132.37, 128.82, 126.41, 124.80, 123.37, 120.60, 116.15, 115.49, 114.77, 102.74, 76.47, 27.69, 22.86.

¹⁹F NMR (400 MHz, DMSO-d₆): δ -119.0, -115.8, -73.46.

³¹P NMR (400 MHz, DMSO-d₆): δ -2.63.

Synthesis of Compound A11:



Step-1: To a solution of **SM3** (250 mg, 0.577 mmol) in DMF (5 mL), were added cesium carbonate (564 mg, 1.731 mmol) and di-*tert*-butyl(chloromethyl) phosphate (179 mg, 0.692 mmol). The reaction mixture was stirred at 60°C for 16 h. Reaction monitoring by LC-MS confirms the completion of reaction. Then the reaction mixture was quenched with water and extracted over ethyl acetate. Organic layer was dried over sodium sulphate, concentrated to get crude mixture of **Compound 2** and taken for next step as such.

LCMS: Calculated for C₃₁H₃₅F₅N₃O₅P 655.6, Observed 656.3 (M+H), RT. 2.9 min, 73.5 % (Max),

Step-2: **Compound 2** (370 mg, 0.564 mmol) was taken in water (3 mL) and acetic acid (3 mL) and stirred at 60 °C for 6 h. Crude mixture showed 52% product mass by LC-MS. After preparative HPLC purification, fraction was lyophilized to get **Compound A11** (0.1 g, 32.6%) as an off white solid.

LCMS: Calculated for C₂₃H₁₉F₅N₃O₅P 543.39, Observed 544.0 (M+H), RT. 2.12 min, 99.79 % (Max),

HPLC: 4.6 min, 99.8 % (Max).

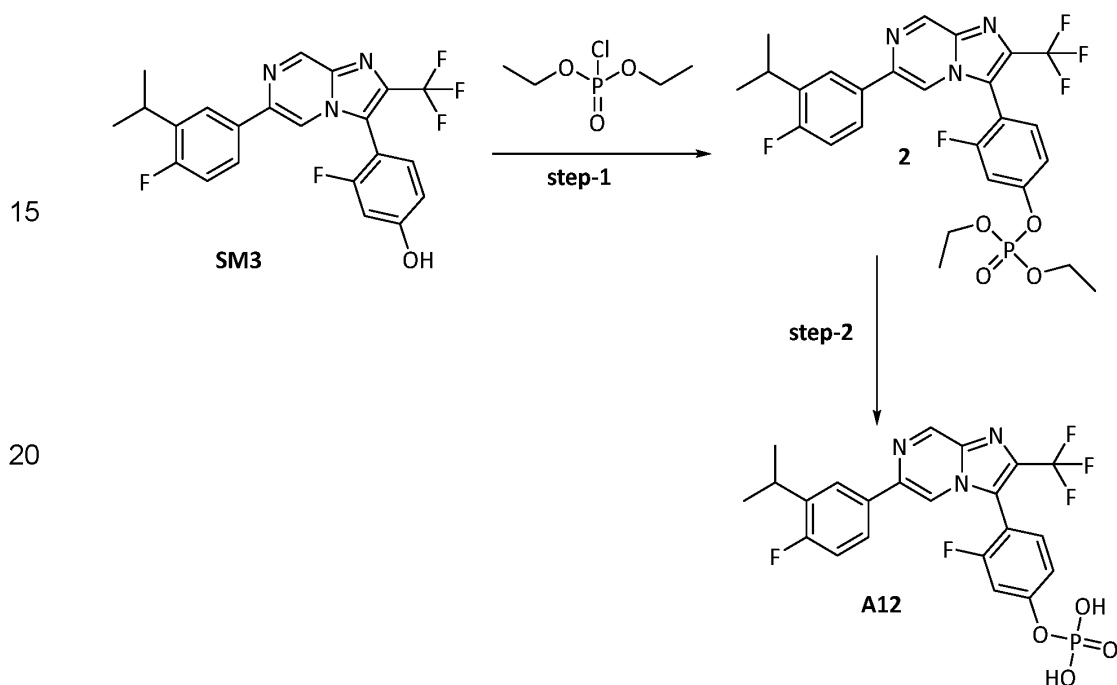
¹H NMR (400 MHz, DMSO-d⁶): δ 9.43 (d, J = 1.60 Hz, 1H), 7.91-7.87 (m, 1H), 7.70 (t, J = 8.40 Hz, 1H), 7.29 (d, J = 2.40 Hz, 1H), 7.27-7.16 (m, 2H), 5.70 (d, J = 11.60 Hz, 2H), 3.26-3.19 (m, 1H), 1.28 (d, J = 6.80 Hz, 6H).

¹³C NMR (400 MHz, DMSO-d⁶): δ 162.77, 160.13, 159.50, 144.45, 139.65, 139.12, 135.41, 134.39, 133.77, 135.37, 126.49, 123.76, 120.187, 116.19, 114.61, 113.31, 106.67, 104.66, 87.85, 27.71, 22.88.

¹⁹F NMR (400 MHz, DMSO-d⁶): δ -119.0, -110.1, -74.7.

³¹P NMR (400 MHz, DMSO-d⁶): δ -2.97.

Synthesis of Compound A12:



Step-1: To a stirred solution of **SM3** (300 mg, 0.692 mmol) in Chloroform (15 mL), were added TEA (210 mg, 2.077 mmol) and diethyl phosphorochloridate (358 mg, 2.077 mmol). Stirred at 62°C for 16 h. TLC monitoring confirms the completion of reaction. Reaction mixture was quenched with water and extracted over DCM. Organic layer was dried over sodium sulphate, concentrated and purified by column to get **Compound 2** (0.260 g, 51.2%).

LCMS: Calculated for C₂₆H₂₅F₅N₃O₄P 569.47, Observed 570.0 (M+H), RT. 2.68 min, 77.7 % (Max),

Step-2: To a stirred solution of **Compound 2** (260 mg, 0.457 mmol) in DCM (8 mL), was added TMS-Br (1398 mg, 9.13 mmol). The reaction mixture was stirred at reflux for 16 h. TLC monitoring confirms the completion of reaction. Reaction mixture was concentrated to get crude mixture with 71% product mass and purified by preparative HPLC. After purification, fraction was lyophilized to get **Compound A12** (80 mg, 33.4%).

LCMS: Calculated for C₂₂H₁₇F₅N₃O₄P 513.36, Observed 514.1 (M+H), RT. 1.85 min, 97.9 % (Max),

HPLC: 4.34 min, 99.9 % (Max).

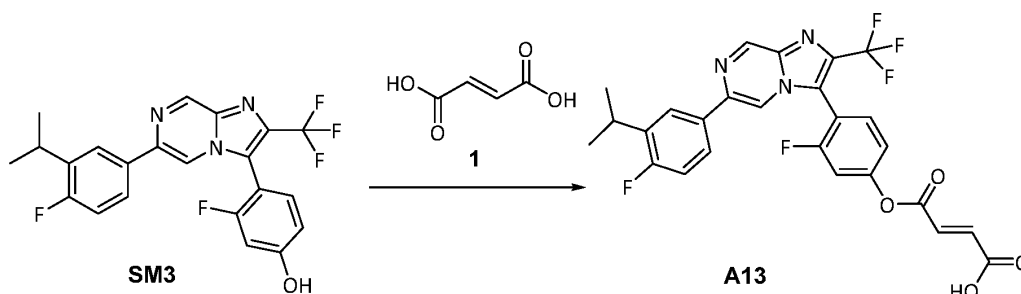
¹H NMR (400 MHz, DMSO-d₆): δ 9.40 (d, J = 1.20 Hz, 1H), 8.51 (s, 1H), 8.03-8.00 (m, 1H), 7.88-7.84 (m, 1H), 7.55 (t, J = 8.80 Hz, 1H), 7.36 (d, J = 2.00 Hz, 1H), 7.33 (d, J = 2.40 Hz, 1H), 7.19-7.09 (m, 1H), 3.24-3.18 (m, 1H), 1.26 (d, J = 6.80 Hz, 6H).

¹³C NMR (400 MHz, DMSO-d₆): δ 162.26, 161.92, 159.81, 159.47, 144.42, 139.56, 139.04, 135.36, 134.47, 132.67, 126.33, 123.30, 120.54, 116.64, 116.05, 114.48, 108.18, 107.69, 27.68, 22.85.

¹⁹F NMR (400 MHz, DMSO-d₆): δ -119.1, -111.1, -73.5.

³¹P NMR (400 MHz, DMSO-d₆): δ -5.68.

Synthesis of Compound A13:



To a stirred solution of **SM3** (300mg, 0.692 mmol) in DMF (8 mL), was added *N*-methylmorpholine (0.228 mL, 2.077 mmol), EDC (199 mg, 1.038 mmol) and **Compound 1** (88 mg, 0.761 mmol). Stirred at RT for 16 h. After the completion of reaction, the reaction mixture was evaporated under reduced pressure. The resulted residue was purified by preparative HPLC in TFA method and fraction was lyophilized to get **Compound A13** (59 mg, 16%).

LCMS: Calculated for C₂₆H₁₈F₅N₃O₄ 531.439, Observed 531.9(M+H), RT. 2.825 min, 99.338 % (Max).

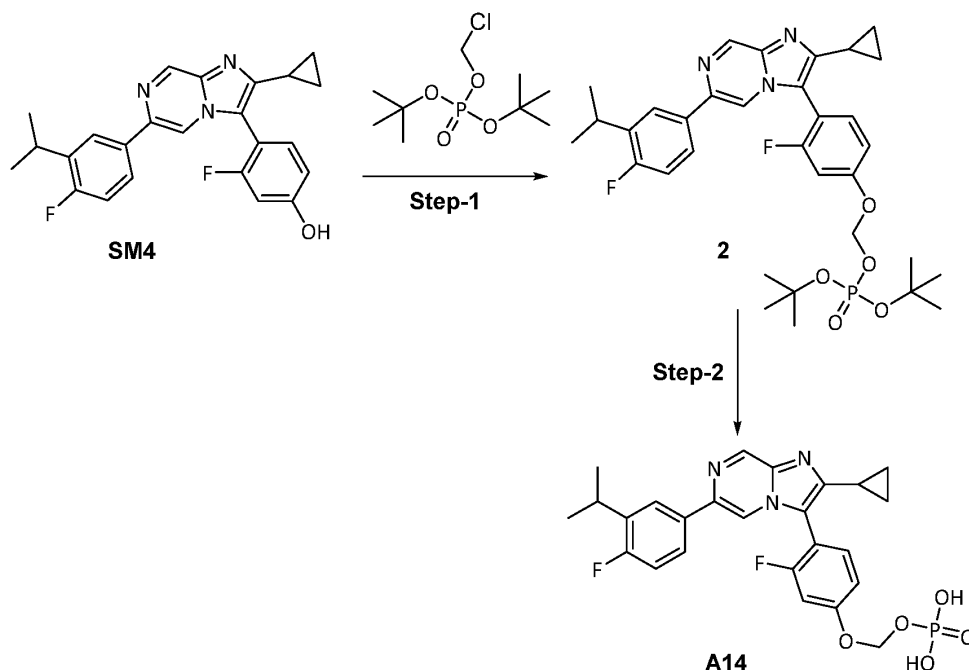
HPLC: 5.674 min, 99.149 % (Max.)

¹H NMR (400 MHz, DMSO-d₆): δ 13.46 (s, 1H), 9.45 (d, J = 1.20 Hz, 1H), 8.63 (s, 1H), 8.05-8.02 (m, 1H), 7.92-7.88 (m, 2H), 7.84 (t, J = 8.40 Hz, 1H), 7.62-7.59 (m, 1H), 7.43-7.41 (m, 1H), 7.25 (t, J = 1.60 Hz, 2H), 3.24-3.19 (m, 1H), 1.27 (d, J = 7.20 Hz, 6H).

¹³C NMR (400 MHz, DMSO-d₆): δ 165.99, 163.15, 162.32, 161.78, 159.87, 159.30, 153.32, 144.47, 139.50, 137.10, 135.43, 134.37, 133.68, 132.36, 131.93, 126.42, 120.57, 119.42, 116.20, 114.79, 111.23, 72.75, 60.72, 27.69, 22.88.

¹⁹F NMR (400 MHz, DMSO-d₆): δ -118.98, -109.77, -74.24.

Synthesis of Compound A14:



Step-1: To a stirred solution of **SM4** in DMF (5 mL), were added cesium carbonate (0.422 g, 1.295 mmol) and di-*tert*-butyl(chloromethyl)phosphate (0.134 g, 0.518 mmol). The reaction mixture was stirred at 60 °C for 4 h. The reaction progress was monitored by LCMS. After the completion of reaction, the reaction mixture was quenched with water and extracted in ethyl acetate. The organic layer was washed with brine solution, dried over sodium sulphate and evaporated in vacuum to obtain **Compound 2** (190 g, 0.291 mmol, 67.3 %). Crude product was taken for next step as such.

LCMS: Calculated for $C_{33}H_{40}F_2N_3O_5P$, 627.670, Observed 628.3 (M+H), RT. 3.318 min, 96.01 % (Max),

Step-2: Compound 2 (0.19 g, 0.303 mmol) was taken in acetic acid (3 mL) and water (3.00 mL) and stirred at 60°C for 16 h. The reaction progress was monitored by LCMS. After the completion of reaction, the reaction mixture was evaporated in vacuum to obtain crude mixture. The crude was purified by prep-HPLC, and the fractions were lyophilized to obtain **A14** 32 mg, 20.39%) as a white solid.

LCMS: Calculated for $C_{25}H_{24}F_2N_3O_5P$, 515.454, Observed 516.1 (M-H), RT. 2.458 min, 99.41% (Max),

HPLC: 4.621 min, 98.91 % (Max).

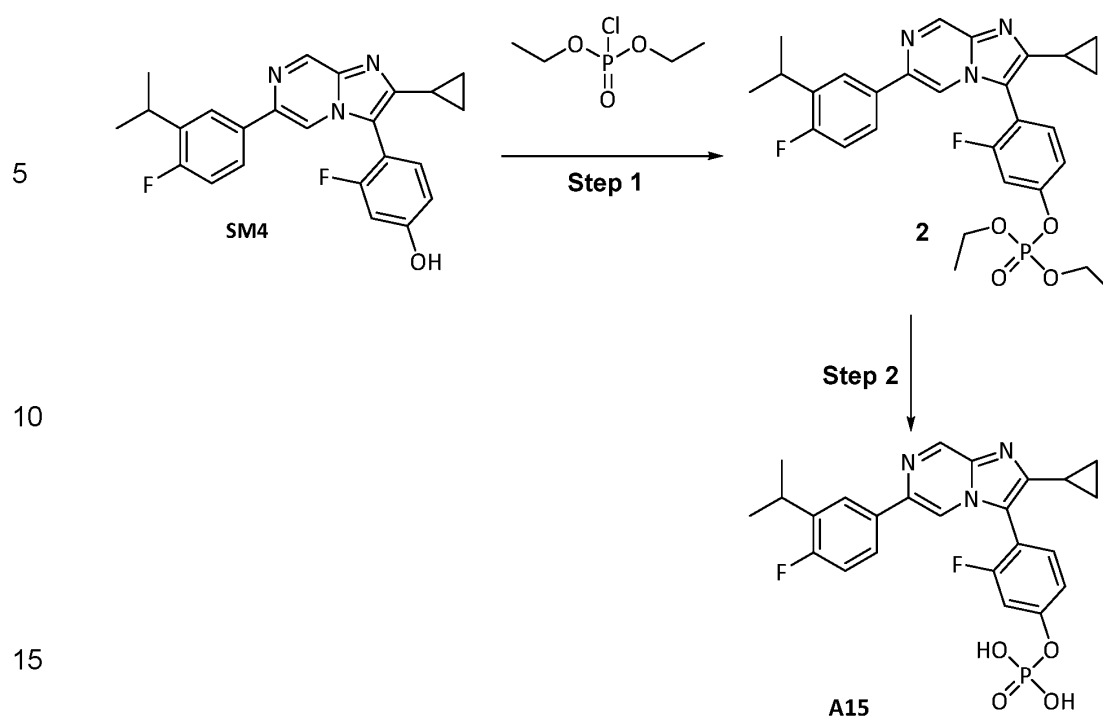
1H NMR (400 MHz, DMSO- d_6): δ 9.08 (s, 1H), 8.46 (s, 1H), 8.02-7.99 (m, 1H), 7.86-7.82 (m, 1H), 7.73-7.69 (m, 1H), 7.28-7.25 (m, 1H), 7.20-7.16 (m, 2H), 5.69 (d, J = 11.60 Hz, 2H), 3.24-3.17 (m, 1H), 1.95-1.90 (m, 1H), 1.27 (d, J = 6.80 Hz, 6H), 1.01 (d, J = 9.60 Hz, 4H),

^{13}C NMR (400 MHz, DMSO- d_6): δ 162.20, 161.95, 159.64, 159.13, 150.43, 141.42, 139.30, 138.13, 135.27, 133.27, 125.97, 117.56, 116.16, 115.93, 113.59, 113.49, 109.02, 105.06, 87.92, 27.65, 22.92, 9.48, 9.03.

^{19}F NMR (400 MHz, DMSO- d_6): δ -120.02, -109.15, -73.74.

^{31}P NMR (400 MHz, DMSO- d_6): δ -3.05.

Synthesis of Compound A15:



Step-1: To a stirred solution of **SM4** (200 mg, 0.493 mmol) in Chloroform (3 mL), was added TEA (0.208 mL, 1.480 mmol) and diethyl phosphorochloridate (255 mg, 1.480 mmol). Reaction mixture was stirred at 60 °C for 16 h. The reaction progress was monitored by LCMS. After the completion of reaction, the reaction mixture was concentrated, and crude mixture was purified by flash column using 45% ethyl acetate in pet-ether as eluent. The fractions collected were concentrated and dried under reduced pressure to obtain **Compound 2** (190 mg, 70.4 %) as colorless liquid.

LCMS: Calculated for $C_{28}H_{30}F_2N_3O_4P$, 541.536, Observed 542.00 (M+H), RT. 3.06min, 99.94% (Max).

1H NMR (400 MHz, DMSO- d_6): δ 9.10 (s, 1H), 8.52 (s, 1H), 8.01 (dd, J = 2.00, 7.40 Hz, 1H), 7.85-7.87 (m, 2H), 7.44 (dd, J = 1.60, 11.00 Hz, 1H), 7.36 (d, J = 8.40 Hz, 1H), 7.21 (t, J = 10.00 Hz, 1H), 4.28-4.21 (m, 4H), 3.21 (s, 1H), 1.95-1.92 (m, 1H), 1.37-1.31 (m, 6H), 1.28-1.23 (m, 6H), 1.07-1.00 (m, 4H).

Step-2: To a stirred solution of **Compound 2** (140 mg, 0.259 mmol) in DCM (3 mL), was added TMS-Br (0.671 mL, 5.17 mmol). Reaction mixture was stirred at 40°C for 13 h. The reaction progress was monitored by LCMS. After the completion of the reaction, the reaction mixture was evaporated in vacuum to obtain crude mixture and

purified by prep-HPLC. The fractions were lyophilized to obtain **Compound A15** (30 mg, 0.028 mmol, 10.82%) as a white solid.

LCMS: Calculated for $C_{24}H_{22}F_2N_3O_4P$, 485.428, Observed 486.0.(M+H), RT. 1.698 min, 97.77% (Max).

HPLC: 3.551 min, 97.76 % (Max).

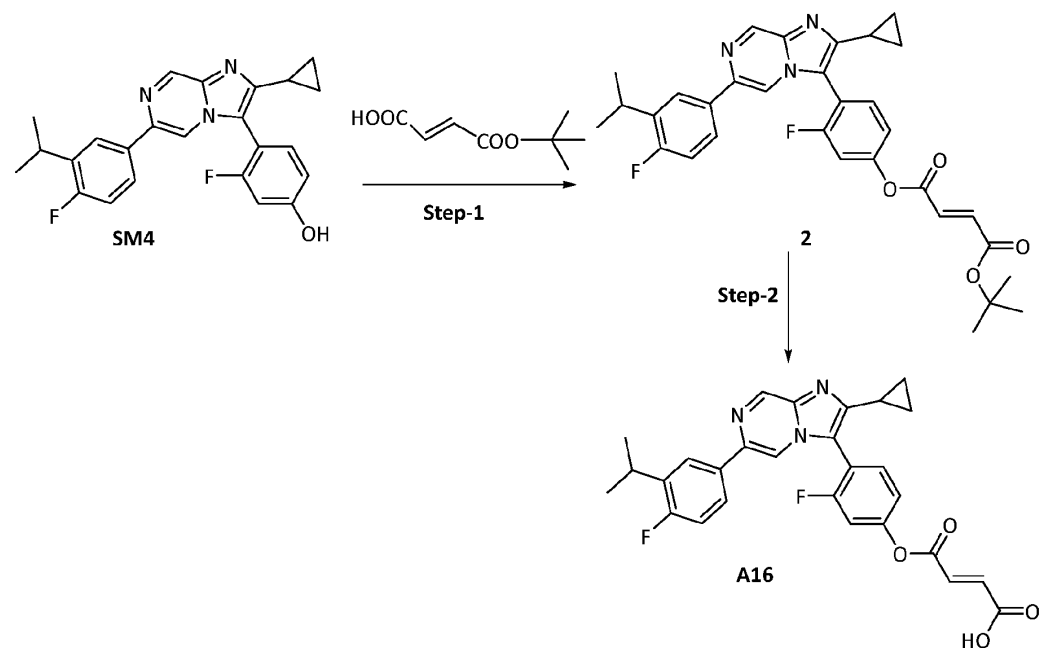
1H NMR (400 MHz, DMSO- d_6): δ 9.08 (s, 1H), 8.48 (s, 1H), 8.01 (dd, J = 2.40, 7.40 Hz, 1H), 7.86-7.82 (m, 1H), 7.74 (t, J = 8.40 Hz, 1H), 7.35-7.29 (m, 2H), 7.21-7.16 (m, 1H), 3.24-3.17 (m, 1H), 1.96-1.90 (m, 1H), 1.26 (d, J = 7.20 Hz, 6H), 1.02-0.99 (m, 4H).

^{13}C NMR (400 MHz, DMSO- d_6): δ 161.96, 161.71, 159.53, 159.25, 154.30, 150.51, 139.35, 138.17, 135.26, 133.19, 125.99, 117.37, 116.16, 115.93, 113.68, 110.79, 109.15, 108.90, 27.65, 22.91, 9.52, 9.02.

^{19}F NMR (400 MHz, DMSO- d_6): δ -120.0, -109.09, -74.13.

^{31}P NMR (400 MHz, DMSO- d_6): δ -6.43.

Synthesis of Compound A16:



Step-1: To a stirred solution **SM4** (200 mg, 0.493 mmol) and (E) -4-(*tert*-butoxy)-4-oxobut-2-enoic acid (102 mg, 0.592 mmol) in DCM (0.5 mL), were added DMAP (60.3 mg, 0.493 mmol and EDC HCl (115 mg, 0.740 mmol). Reaction mixture was stirred

at 25°C for 16 h. The reaction progress was monitored by LCMS. After the completion of reaction, the reaction mixture was evaporated in vacuum. The crude mixture was purified by flash column 20% ethyl acetate in petroleum ether as eluent. The collected fractions were concentrated and dried under reduced pressure to obtain **Compound 2** (100 mg, 33.0 %) as a yellow gummy solid.

LCMS: Calculated for $C_{32}H_{31}F_2N_3O_4$, 559.614, Observed 560.00 (M+H), RT. 3.474 min, 91.36% (Max).

1H -NMR (400 MHz, DMSO- d_6): δ 9.10 (s, 1H), 8.53 (s, 1H), 8.02 (d, J = 7.20 Hz, 1H), 8.00-7.83 (m, 2H), 7.58-7.54 (m, 1H), 7.41-7.38 (m, 1H), 7.20 (t, J = 11.60 Hz, 1H), 6.94 (s, 2H), 3.26-3.19 (m, 1H), 1.99-1.94 (m, 1H), 1.46 (s, 9H), 1.28-1.15 (m, 6H), 1.04-1.00 (m, 4H).

Step-2: To a stirred solution of **Compound 2** (100 mg, 0.179 mmol) in DCM (2 mL), was added TFA (0.6 mL, 7.79 mmol). Reaction mixture was stirred at 25°C for 2 h. The reaction was monitored by LCMS. After the completion of reaction, the reaction mixture was concentrated in vacuum to obtain crude. The crude product was purified by prep-HPLC purification, and the fractions were lyophilized for to obtain **Compound A16** (50 mg, 0.071 mmol) as white solid.

LCMS: Calculated for $C_{28}H_{23}F_2N_3O_4$, 503.506, Observed 504.1.(M+H), RT. 2.227min, 99.29% (Max).

HPLC: 5.101 min, 99.06 % (Max).

1H NMR (400 MHz, DMSO- d_6): δ 9.11 (s, 1H), 8.54 (s, 1H), 8.54 (dd, J = , Hz, 1H), 7.89-7.84 (m, 2H), 7.58 (dd, J = 2.00, 10.80 Hz, 1H), 7.40 (dd, J = 2.00, 8.40 Hz, 1H), 7.23-7.18 (m, 1H), 6.96 (s, 2H), 3.25-3.18 (m, 1H), 1.99-1.93 (m, 1H), 1.27 (d, J = 6.80 Hz, 6H), 1.05-1.01 (m, 4H).

^{13}C NMR (400 MHz, DMSO- d_6): δ 163.34, 161.99, 161.52, 159.55, 159.05, 152.22, 150.63, 141.43, 139.39, 138.27, 137.03, 135.29, 133.17, 132.87, 126.10, 125.96, 119.40, 117.14, 116.17, 115.94, 113.66, 111.52, 27.63, 22.91, 9.58, 9.02.

^{19}F NMR (400 MHz, DMSO- d_6): δ -119.93, -108.66, -74.87.

Activity and Solubility

Kinetic solubility

Solubility test was performed using a miniaturized shake flask method. 10 mM stock solutions of each of the compounds were used to prepare calibration standards

(10220 µM) in DMSO. The same 10 mM stock solutions were accurately dispensed in duplicate into 96-well plates and the DMSO dried down (MiVac Genevac, 90 minutes, 37°C). Thereafter, the samples were reconstituted (200 µM) in aqueous solution and shaken (20 hours, 25°C). The solutions were analyzed by means of HPLCDAD (Agilent 1200 Rapid Resolution HPLC with a diode array detector). Best fit calibration curves were constructed using the calibration standards, which were used to determine the aqueous samples' solubility.

Activity

Female NMRI mice (age 3 weeks, weight ca. 14-20 g) were purchased from Charles River (Sulzfeld). The animals were allowed to adapt for 1 week under controlled conditions (22°C, 50% humidity, 12 hours light, and free access to water and rodent diet) before experimental handling. To obtain adult schistosomes, NMRI mice were infected subcutaneously with 80 to 100 cercariae. After 49 days, the mice were euthanized with CO₂ and the worms collected from the hepatic portal and mesenteric veins. Three pairs of adult worms were placed in each well of a 24-well plate with 2-2.5 ml culture medium and the compound at various concentrations (e.g. 1 µM, 0.1 µM, 0.01 µM, 0.001 µM). Culture medium was composed of RPMI 1640 (Invitrogen, Carlsbad, CA) supplemented with 5 % fetal calf serum (iFCS, 100 U/ml) and 1% penicillin/streptomycin mixture (Invitrogen, 100 U/mL. Each compound was initially tested once in 2 wells. Schistosome incubated with no more than 1% DMSO served as control. Worms were kept in an incubator at 37°C and 5% CO₂ for up to 72 hours. After 24 hours, the condition of the worms was microscopically evaluated.

FaSSiF Solubility

2.0 mg of compound was accurately weighed into a Uniprep® syringeless filter (5ml 0.45 µm), and 2 mL of solvent was added and shaken for 24 hours at 37°C. The pH was checked after 6 to 8 hours and if the pH deviated by more than 0.05 units, it was adjusted with 0.1 N HCl or 0.1 N NaOH solutions. The suspension was filtered after 24 hours and the concentration of dissolved substance was determined by HPLC after suitable dilutions with corresponding buffer if required. The result was expressed in mg/ml.

Table 1:

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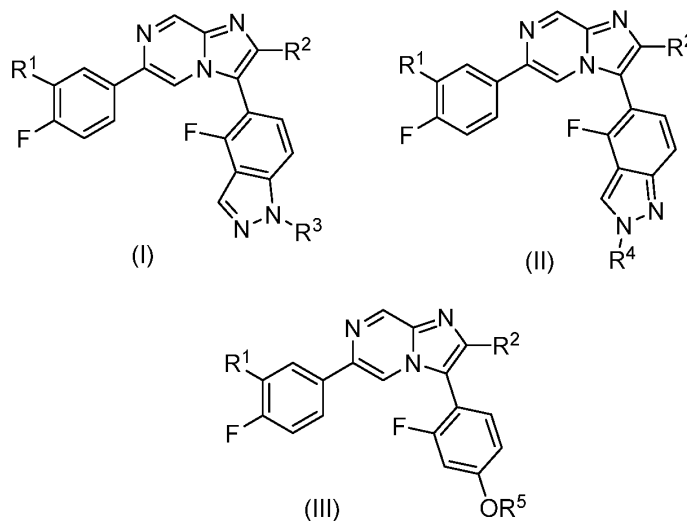
Compound	%dead at 0.1 μM (24h)	EC ₅₀ μM (24h)	Kinetic solubility (μM)	FaSSIF Solubility pH= 6.5 (mg/mL)
A1	100		A	B
A2	91		C	-
A3	100		A	C
A5	100		B	B
A6	78		C	-
A7	100		A	C
A8	100		A	B
A9	100	<0.001	C	B
A10	100	0.00018	A	B
A11	100	0.00016	A	B
A12	100	0.00015	A	B
A13	100	0.00014	B	B
A14	96	0.0001	A	A
A15	98	0.00014	A	A
A16	100	0.00014	A	B

“A”: Kinetic solubility ≥150 μM; “B”: Kinetic solubility 80-149μM; “C”: Kinetic solubility 20-80μM.

“A”: FaSSIF solubility >1 mg/mL; “B”: Kinetic solubility >0.1-1 mg/mL; “C”: Kinetic solubility 0.01-0.1 mg/mL.

Claims

1. A compound of formula (I), (II) or (III) or a pharmaceutically acceptable salt or solvate thereof,

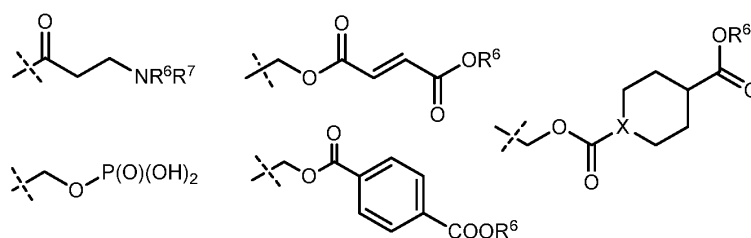


wherein:

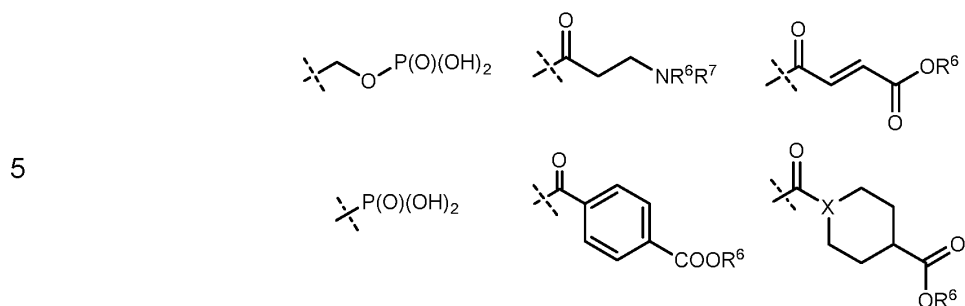
R¹ is cyclopropyl, cyclobutyl, F or C1-C3 alkyl optionally substituted with up to five F atoms;

R² is cyclopropyl, cyclobutyl, F or C1-C3 alkyl optionally substituted with up to five F atoms

R³ and R⁴ represent each, independently from one another, a residue selected from following group:



R⁵ is a residue selected from following group:



X is CH or N; and

R⁶ and **R⁷** represent each, independently from one another, H or CH₃.

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2. A compound according to claim 1, wherein **R⁶** and **R⁷** represent each H.

3. A compound according to claim 1 or 2, wherein

R¹ is methyl, ethyl, *n*-propyl, *iso*-propyl, CF₃ or F; and

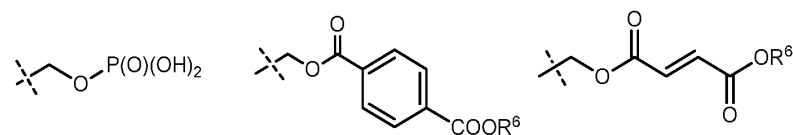
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R² is methyl, ethyl, *n*-propyl, *iso*-propyl, cyclopropyl, CF₃ or F.

4. A compound according to claim 1, 2 or 3, wherein

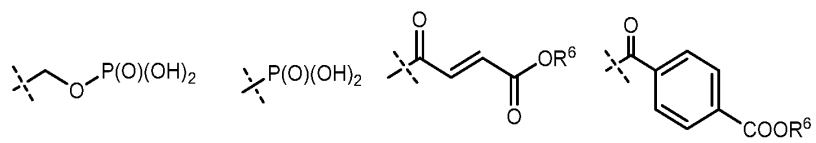
R³ and **R⁴** represent each, independently from one another, a residue selected from following group:

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and **R⁵** is a residue selected from following group:

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5. A compound of formula (I), (II) according to claim 1.

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6. A compound according to claim 1, 2, 3, 4 or 5, wherein

R¹ is *iso*-propyl; and

R² is cyclopropyl.

7. A compound selected from following group:

- 5 [(5-{2-cyclopropyl-6-[4-fluoro-3-(propan-2-yl)phenyl]imidazo[1,2-a]pyrazin-3-yl}-4-fluoro-2H-indazol-2-yl)methoxy]phosphonic acid;
- 1-[[5-{2-cyclopropyl-6-[4-fluoro-3-(propan-2-yl)phenyl]imidazo[1,2-a]pyrazin-3-yl}-4-fluoro-1H-indazol-1-yl)methoxy]carbonyl]piperidine-4-carboxylic acid;
- 4-[[5-{2-cyclopropyl-6-[4-fluoro-3-(propan-2-yl)phenyl]imidazo[1,2-a]pyrazin-3-yl}-4-fluoro-1H-indazol-1-yl)methoxy]carbonyl]benzoic acid;
- (2E)-4-[(5-{2-cyclopropyl-6-[4-fluoro-3-(propan-2-yl)phenyl]imidazo[1,2-a]pyrazin-3-yl}-4-fluoro-1H-indazol-1-yl)methoxy]-4-oxobut-2-enoic acid;
- 10 methyl 4-(5-{2-cyclopropyl-6-[4-fluoro-3-(propan-2-yl)phenyl]imidazo[1,2-a]pyrazin-3-yl}-4-fluoro-1H-indazole-1-carbonyl)cyclohexane-1-carboxylate;
- 3-amino-1-(5-{2-cyclopropyl-6-[4-fluoro-3-(propan-2-yl)phenyl]imidazo[1,2-a]pyrazin-3-yl}-4-fluoro-1H-indazol-1-yl)propan-1-one;
- 15 [(5-{2-cyclopropyl-6-[4-fluoro-3-(propan-2-yl)phenyl]imidazo[1,2-a]pyrazin-3-yl}-4-fluoro-1H-indazol-1-yl)methoxy]phosphonic acid;
- (2E)-4-[(4-fluoro-5-{6-[4-fluoro-3-(propan-2-yl)phenyl]-2-(trifluoromethyl)imidazo[1,2-a]pyrazin-3-yl}-1H-indazol-1-yl)methoxy]-4-oxobut-2-enoic acid;
- 20 [(4-fluoro-5-{6-[4-fluoro-3-(propan-2-yl)phenyl]-2-(trifluoromethyl)imidazo[1,2-a]pyrazin-3-yl}-1H-indazol-1-yl)methoxy]phosphonic acid;
- [(3-fluoro-4-{6-[4-fluoro-3-(propan-2-yl)phenyl]-2-(trifluoromethyl)imidazo[1,2-a]pyrazin-3-yl}phenoxy)methoxy]phosphonic acid;
- (3-fluoro-4-{6-[4-fluoro-3-(propan-2-yl)phenyl]-2-(trifluoromethyl)imidazo[1,2-a]pyrazin-3-yl}phenoxy)phosphonic acid;
- 25 (2E)-4-(3-fluoro-4-{6-[4-fluoro-3-(propan-2-yl)phenyl]-2-(trifluoromethyl)imidazo[1,2-a]pyrazin-3-yl}phenoxy)-4-oxobut-2-enoic acid;;
- [(4-{2-cyclopropyl-6-[4-fluoro-3-(propan-2-yl)phenyl]imidazo[1,2-a]pyrazin-3-yl}-3-fluorophenoxy)methoxy]phosphonic acid;
- (4-{2-cyclopropyl-6-[4-fluoro-3-(propan-2-yl)phenyl]imidazo[1,2-a]pyrazin-3-yl}-3-fluorophenoxy)phosphonic acid;
- 30 (2E)-4-(4-{2-cyclopropyl-6-[4-fluoro-3-(propan-2-yl)phenyl]imidazo[1,2-a]pyrazin-3-yl}-3-fluorophenoxy)-4-oxobut-2-enoic acid.

8. A compound as defined in any of claims 1 to 7, or a pharmaceutically acceptable salt or solvate thereof for use in therapy.
- 5 9. A compound as defined in any of claims 1 to 7, or a pharmaceutically acceptable salt or solvate thereof for use in the treatment of a helminth infection with blood and/or liver flukes.
- 10 10. A compound for use as defined in claim 9, wherein the helminth infection is schistosomiasis and/or fascioliasis.
- 11 11. Use of a compound as defined in any of claims 1 to 7, or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment of a helminth infection such as in particular schistosomiasis and/or fascioliasis.
- 15 12. A method for treating a helminth infection such as in particular schistosomiasis and/or fascioliasis comprising administering a therapeutically effective amount or a compound as defined in any of claims 1 to 7, or a pharmaceutically acceptable salt or solvate thereof, to a patient in need thereof.
- 20 13. A pharmaceutical composition comprising a therapeutically effective amount of a compound as defined in any one of claims 1 to 7, or a pharmaceutically acceptable salt or solvate thereof.
- 25 14. A pharmaceutical composition according to claim 13, further comprising an anthelmintic agent.
- 30 15. A pharmaceutical composition according to claim 13 or 14, further comprising a pharmaceutically acceptable carrier, adjuvant or excipient thereof.