

NOVEL COMPOUNDS AND THEIR USE IN THE TREATMENT OF SCHISTOSOMIASIS

Field of Invention

This invention relates to compounds of formula (1a), (1b), (1c) and (1d) and pharmaceutically acceptable salts or solvates thereof which have activity as inhibitors of *Schistosoma* growth. The invention also relates to pharmaceutical compositions comprising such compounds, salts or solvates and to the use of such compounds as medicaments, in particular in the treatment or prevention of schistosomiasis, also known as bilharzia.

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 disease caused by flatworms of the genus *Schistosoma*, such as *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.

Two drugs, praziquantel and oxamniquine, are approved for the treatment of schistosomiasis. Oxamniquine has a narrow spectrum of activity (only *S. mansoni*). Praziquantel is used worldwide against all three worm species but is known to lack efficacy against juvenile worms. Artemether also shows activity against schistosomes in humans when tested in repeated doses but as it is used extensively in artemesin-based combination therapies for malaria treatment, it is not considered a viable compound for schistosomiasis treatment and control as its use against helminth infections might generate drug-resistant malaria parasites (Keiser J, Utzinger J. Curr Opin Infect Dis. 2007 Dec;20(6):605-12).

The current status of research into novel anti-schistosomes was the subject of an edition of Future Medicinal Chemistry (2015 Volume 7, Issue 6). There are many examples of repurposing of existing drug molecules and applications of known human drug mechanisms to discover new treatments for schistosomiasis. The former includes Abdulla, M. H., et al. (2009) "*Drug discovery for schistosomiasis: hit and lead compounds identified in a library of known drugs by medium-throughput phenotypic screening.*" PLoS Negl Trop Dis 3(7): e478; Dissous, C. and C. G. Grevelding (2011) "*Piggy-backing the concept of cancer drugs for schistosomiasis treatment: a tangible perspective?*" Trends Parasitol 27(2): 59-66; and Neves B.J. "*The antidepressant drug paroxetine as a new lead candidate in schistosome drug discovery*" Medicinal Chemistry Communications, 2016, 7, 1176.

Applications of known human drug targets in the field include Kuntz, A. N., et al. (2007). "*Thioredoxin glutathione reductase from *Schistosoma mansoni*: an essential parasite enzyme*

and a key drug target." PLoS Med **4**(6): e206; Long, T., et al. (2010). "Schistosoma mansoni Polo-like kinase 1: A mitotic kinase with key functions in parasite reproduction." Int J Parasitol **40**(9): 1075-1086; Rojo-Arreola, L., et al. (2014). "Chemical and genetic validation of the statin drug target to treat the helminth disease, schistosomiasis PLoS One **9**(1): e87594; Jacques, S. A., et al. (2015). "Discovery of Potent Inhibitors of Schistosoma mansoni NAD(+) Catabolizing Enzyme." Journal of Medicinal Chemistry **2015** **58**(8): 3582-3592; Mader, P., et al. (2016). "Biarylalkyl Carboxylic Acid Derivatives as Novel Antischistosomal Agents." ChemMedChem **2016**, **11**, 1 – 11; Heimbürg, T., et al. (2016). "Structure-Based Design and Synthesis of Novel Inhibitors Targeting HDAC8 from Schistosoma mansoni for the Treatment of Schistosomiasis." J Chem Inf Model **2014** **54**(10): 3005-3019 and Journal of Medicinal Chemistry **2016** **59**(6): 2423-2435.

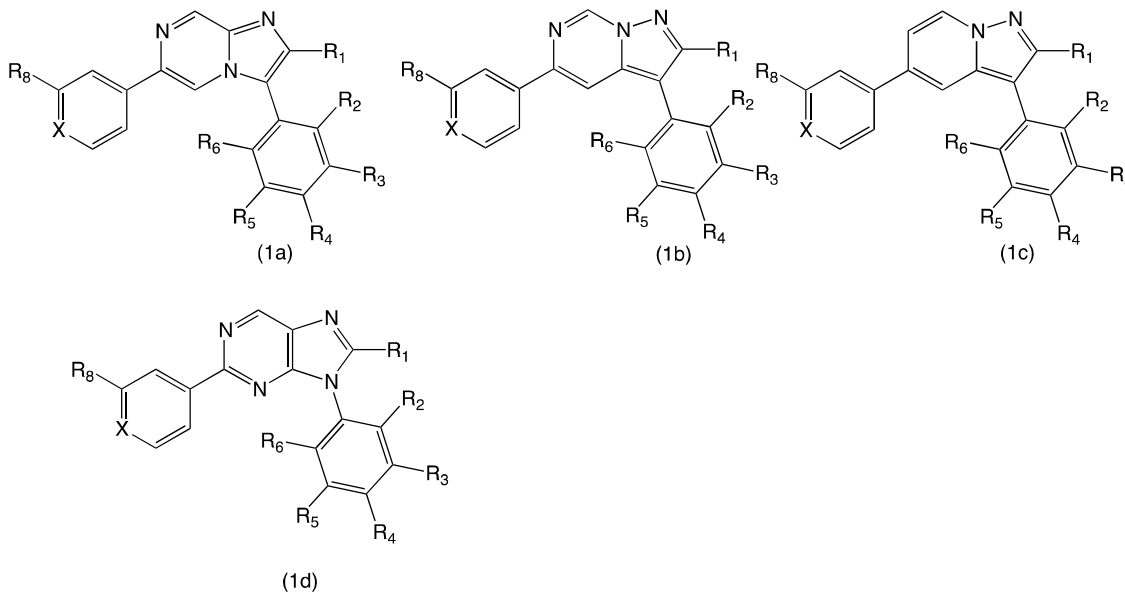
Large-scale testing on intact Schistosoma was limited by the available technology Ramirez B, B. Q et al (2007) "Schistosomes: challenges in compound screening." Expert Opinion on Drug Discovery **2**: S53-361; Sayed, A. A., et al. (2008) "Identification of oxadiazoles as new drug leads for the control of schistosomiasis." Nat Med **14**(4): 407-412. We have recently described a novel method for high throughput screening using larval stage Schistosoma 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 Schistosoma mansoni PLoS Negl Trop Dis **10**(4): e0004659. The latter paper disclosed an imidazopyrazine derivative (LSHTM-1945) with relatively weak activity of 4.9-6.7µM against the larval, juvenile and adult stages of S. mansoni.

WO2014078813A1 discloses the preparation of imidazopyrazines for treating parasitic diseases, predominantly malaria, leishmaniasis and trypanosomiasis. WO2012080232A1 discloses the preparation of substituted imidazopyrazines as Mps-1 and TKK inhibitors useful in the treatment of hyperproliferative disorders. WO2007096764A2 discloses the preparation of bicyclic heteroaryl derivatives as cannabinoid receptor modulators. In addition, Kayagil, I. and S. Demirayak (2011). "Synthesis of some 2,3,6,8-tetraarylimidazo[1,2-a]pyrazine derivatives by using either reflux or microwave irradiation method, and investigation their anticancer activities." Turk. J. Chem. **35**(1): 13-24. WO2016133935 discloses a series of pyrazolo[1,5-c]pyrimidines as kinase inhibitors for the treatment of a variety of cancers.

There remains a need in the art for further compounds active as anti-schistosomes with good pharmacokinetic properties, combined with sufficient activity against all three main infective species of worm and against both juvenile and adult worms.

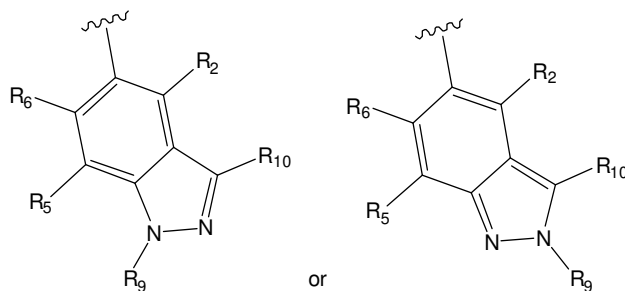
5 Summary of the Invention

In one embodiment, the invention provides a compound of formula (1a), (1b), (1c) or (1d) or a pharmaceutically acceptable salt or solvate thereof,



wherein:

- 10 **R₁** is C₁-C₄ alkyl optionally substituted with up to five F atoms, C₃-C₆ cycloalkyl optionally substituted with one methyl group, or C₄-C₇ cycloalkylmethyl;
- R₂** is H, F, Cl or OMe;
- R₃** is H, OH, OMe, OPO(OH)OH or OCH₂OPO(OH)OH;
- R₄** is H, OH, OMe, OPO(OH)OH or OCH₂OPO(OH)OH;
- 15 provided that **R₃** and **R₄** cannot both be H;
- or **R₃** and **R₄** combine, together with the phenyl ring to which they are attached, to form an indazole group as shown below



R₅ is H, F, Cl or OMe;

R₆ is H, F, Cl or OMe;

X is N or C-R₇

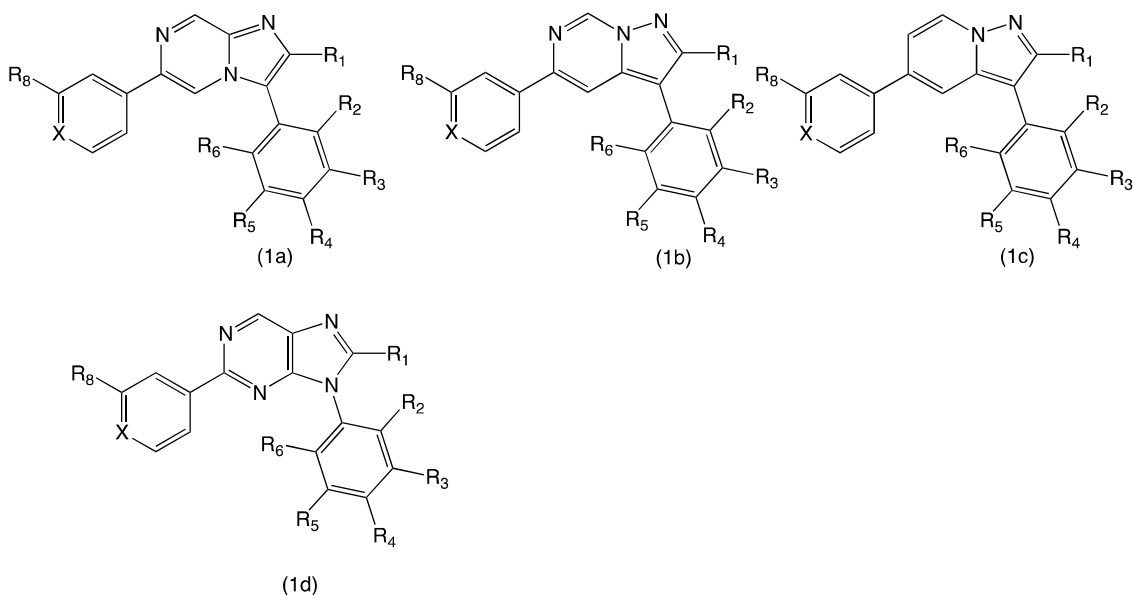
R₇ (where present) is H or F;

- 5 **R₈** is SF₅, Br, C₁-C₃ alkyl optionally substituted with up to seven F atoms, C₃-C₄ cycloalkyl, OCH₂C≡CH or OC₁-C₃ alkyl optionally substituted with up to seven F atoms;

R₉ is H; and

R₁₀ is H, F or Me.

- 10 Disclosed herein is a compound of formula (1a), (1b), (1c) or (1d) or a pharmaceutically acceptable salt or solvate thereof,



wherein:

R₁ is C₁-C₄ alkyl optionally substituted with up to five F atoms, C₃-C₆ cycloalkyl optionally substituted with one methyl group, or C₄-C₇ cycloalkylmethyl;

- 15 **R₂** is H, F, Cl or OMe;

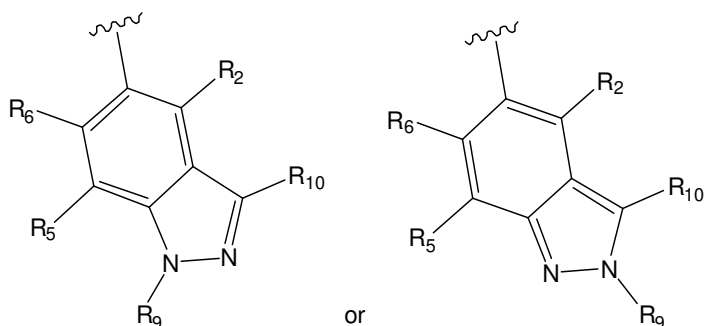
R₃ is H, OH, OMe, OPO(OH)OH or OCH₂OPO(OH)OH;

R₄ is H, OH, OMe, OPO(OH)OH or OCH₂OPO(OH)OH;

provided that **R₃** and **R₄** cannot both be H;

or **R₃** and **R₄** combine, together with the phenyl ring to which they are attached, to form an

- 20 indazole group as shown below



R₅ is H, F, Cl or OMe;

R₆ is H, F, Cl or OMe;

X is N or C-**R₇**, wherein **R₇** is H or F;

- 5 **R₈** is SF₅, Br, C₁-C₃ alkyl optionally substituted with up to seven F atoms, C₃-C₄ cycloalkyl, OCH₂C≡CH or OC₁-C₃ alkyl optionally substituted with up to seven F atoms;

R₉ is H; and

R₁₀ is H, F or Me.

- 10 In one embodiment, the present invention provides a compound of formula (1a), (1b), (1c) or (1d) as defined above, or a pharmaceutically acceptable salt or solvate thereof, for use in therapy.

Disclosed herein is a compound of formula (1a), (1b), (1c) or (1d), as defined above, or a pharmaceutically acceptable salt or solvate thereof, for use in the treatment of schistosomiasis.

- 15 Disclosed herein is the use of a compound of formula 1a), (1b), (1c) or (1d) as defined above, or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment of schistosomiasis.

- 20 In one embodiment, the present invention provides a method for treating schistosomiasis comprising administering a therapeutically effective amount of a compound of formula (1a), (1b), (1c) or (1d) as defined above, or a pharmaceutically acceptable salt or solvate thereof, to a patient in need thereof.

- 25 Disclosed herein is a pharmaceutical composition comprising (i) a therapeutically effective amount of a compound of formula (1a), (1b), (1c) or (1d) as defined above, or a pharmaceutically acceptable salt or solvate thereof; and (ii) a pharmaceutically acceptable excipient.

Detailed Description of the Invention

A. Definitions

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

As used herein, the term "alkyl" means both straight and branched chain saturated hydrocarbon groups. Examples of alkyl groups include methyl, ethyl, n-propyl, iso-propyl, n-butyl, t-butyl, i-butyl, and sec-butyl groups.

As used herein, the term "cycloalkyl" means a cyclic saturated hydrocarbon group. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

As used herein, the term "cycloalkylmethyl" means a cyclic saturated hydrocarbon group linked to the rest of the molecule via a methylene bridge. Examples of

cycloalkylmethyl groups include cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl and cyclohexylmethyl.

As used herein, the term "halogen" or "halo" means fluorine, chlorine, bromine or iodine. Fluorine, chlorine and bromine are particularly preferred.

"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 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-

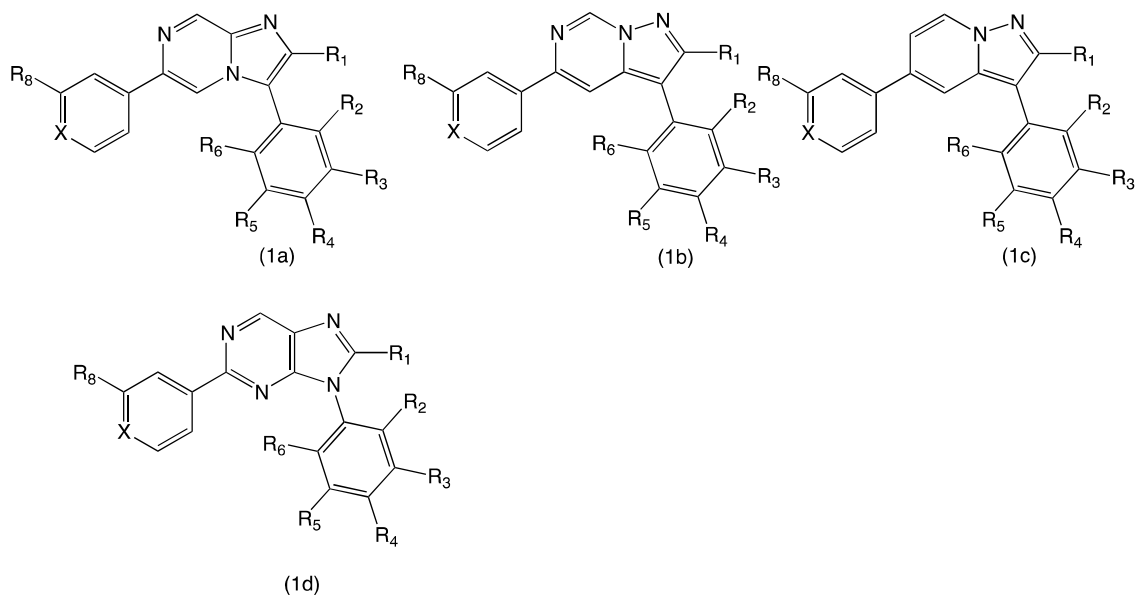
methyl-D-glucamine, morpholine, thiomorpholine, piperidine, pyrrolidine, a mono-, di- or tri-lower alkylamine, for example ethyl-, tert-butyl-, diethyl-, diisopropyl-, triethyl-, tributyl- or dimethyl-propylamine, or a mono-, di- or trihydroxy lower alkylamine, for example mono-, di- or triethanolamine. Corresponding internal salts may furthermore be formed.

5 “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
10 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 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
15 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.

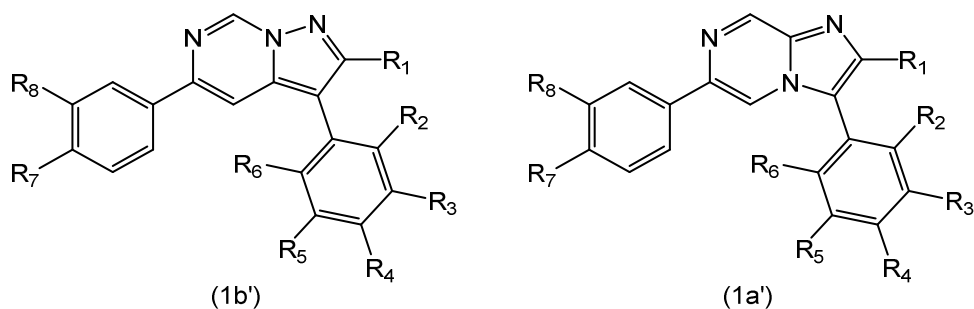
 “Therapy”, “treatment” and “treating” include both preventative and curative treatment of a condition, disease or disorder. It also includes slowing, interrupting, controlling or stopping
20 the progression of a condition, disease or disorder. It also includes preventing, curing, slowing, interrupting, controlling or stopping the symptoms of a condition, disease or disorder.

B. Compounds

 The invention provides a compound of formula (1a), (1b), (1c) or (1d) as defined above,
25 or a pharmaceutically acceptable salt or solvate thereof



The invention also provides a compound of formula (1a') or (1b') or a pharmaceutically acceptable salt or solvate thereof,



5

wherein:

R₁ is C₁-C₄ alkyl optionally substituted with up to five F atoms, C₃-C₆ cycloalkyl optionally substituted with one methyl group, or C₄-C₇ cycloalkylmethyl;

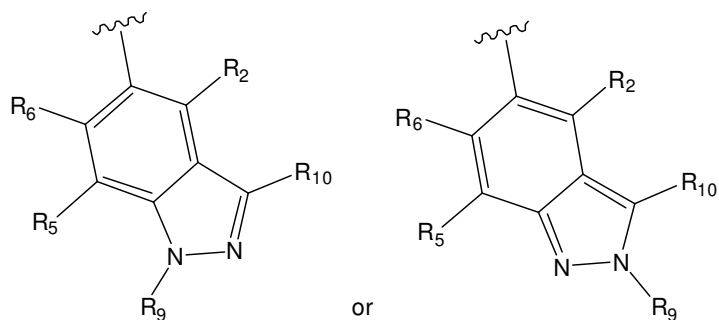
R₂ is H, F, Cl or OMe;

10 **R₃** is H, OH, OMe, OPO(OH)OH or OCH₂OPO(OH)OH;

R₄ is H, OH, OMe, OPO(OH)OH or OCH₂OPO(OH)OH;

provided that **R₃** and **R₄** cannot both be H;

or **R₃** and **R₄** combine, together with the phenyl ring to which they are attached, to form an indazole group as shown below



R₅ is H, F, Cl or OMe;

R₆ is H, F, Cl or OMe;

R₇ is H or F;

5 **R₈** is SF₅ or C₁-C₃ alkyl substituted with three to seven F atoms;

R₉ is H; and

R₁₀ is H, F or Me.

B0. Core Structures

10 In some embodiments the compound of the invention is of formula (1a), as defined above.

In other embodiments the compound of the invention is of formula (1b), as defined above.

15 In other embodiments the compound of the invention is of formula (1c), as defined above.

In other embodiments the compound of the invention is of formula (1d), as defined above.

In other embodiments the compound of the invention is of formula (1a'), as defined above.

20 In other embodiments the compound of the invention is of formula (1b'), as defined above.

B1. Substituent **R₁**

25 **R₁** is selected from the group consisting of C₁-C₄ alkyl optionally substituted with up to five F atoms, C₃-C₆ cycloalkyl optionally substituted with one methyl group, and C₄-C₇ cycloalkylmethyl.

R₁ is preferably selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, cyclopropyl optionally substituted with one methyl group, cyclobutyl, cyclopropylmethyl, CHF₂, CF₃ and CH₂CF₃.

R₁ is more preferably selected from the group consisting of ethyl, isopropyl, cyclopropyl, cyclobutyl, CF₃ and CH₂CF₃.

B2. Substituent **R**₂

5 **R**₂ is selected from the group consisting of H, F, Cl and OMe.

R₂ is preferably selected from the group consisting of H, F and Cl.

R₂ is more preferably F or Cl.

R₂ is most preferably F

10 B3. Substituent **R**₃

R₃ is selected from the group consisting of H, OH, OMe, OPO(OH)OH and OCH₂OPO(OH)OH.

R₃ is preferably selected from the group consisting of H, OH, OMe and OPO(OH)OH.

R₃ is more preferably H.

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B4. Substituent **R**₄

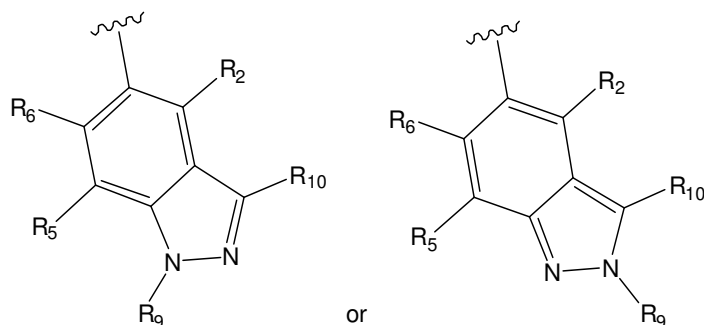
R₄ is selected from the group consisting of H, OH, OMe, OPO(OH)OH and OCH₂OPO(OH)OH.

R₄ is preferably selected from the group consisting of H, OH, OMe and OPO(OH)OH.

20

R₄ is more preferably OH.

Alternatively, and preferably, substituents **R**₃ and **R**₄ may combine, together with the phenyl ring to which they are attached, to form an indazole group as shown below



wherein:

25 **R**₉ is H; and

R₁₀ is selected from the group consisting of H, F and Me.

In a preferred embodiment of the indazole, **R**₁₀ is selected from the group consisting of H and Me

In a more preferred embodiment of the indazole, substituents **R**₉ and **R**₁₀ are both H.

B5. Substituent R_5

R_5 is selected from the group consisting of H, F, Cl and OMe.

R_5 is preferably selected from the group consisting of H and OMe.

5 R_5 is more preferably H.

B6. Substituent R_6

R_6 is selected from the group consisting of H, F, Cl and OMe.

R_6 is preferably selected from the group consisting of H and F.

10

B7. Substituent X

X is N or C- R_7 , where R_7 is selected from the group consisting of H and F.

In one embodiment, X is C- R_7 .

15 B8. Substituent R_8

R_8 is selected from the group consisting of SF_5 , Br, C₁-C₃ alkyl optionally substituted with up to to seven F atoms; C₃-C₄ cycloalkyl; $OCH_2C\equiv CH$ and OC₁-C₃ alkyl optionally substituted with up to to seven F atoms.

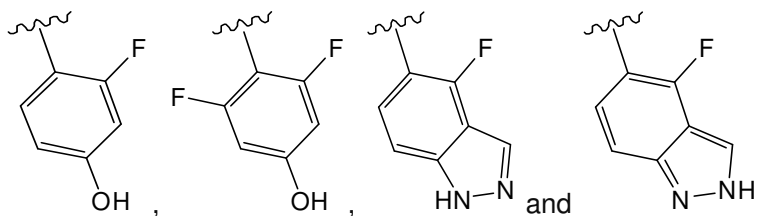
20 Alternatively, R_8 is selected from the group consisting of SF_5 and C₁-C₃ alkyl substituted with three to seven F atoms.

R_8 is preferably selected from the group consisting of cyclopropyl, cyclobutyl, isopropyl, CH_2CF_3 , OCF_3 , O^iPr , CF_3 , CF_2CF_3 and SF_5 .

25 Alternatively, R_8 is preferably selected from the group consisting of CF_3 , CF_2CF_3 and SF_5 .

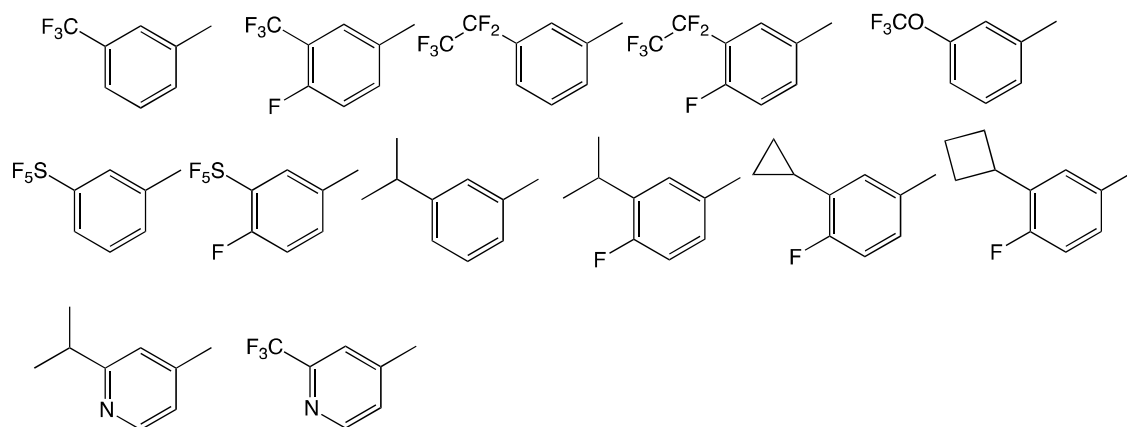
B9. Combinations of Substituents R_2 to R_6

Preferred combinations of substituents R_2 to R_6 include:

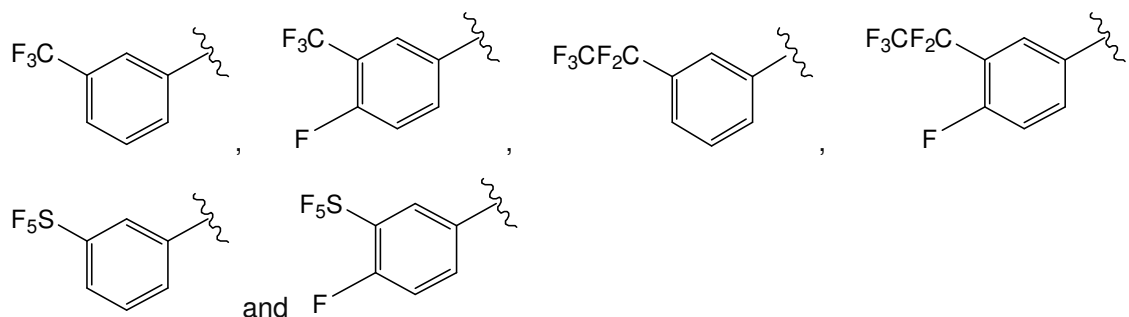


30 B10. Combinations of Substituents X and R_8

Preferred combinations of substituents X and R_8 include:



Alternative preferred combinations of substituents **X** and **R₈** include:



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B11. Specific Embodiments of Compounds of Formula (1a), (1b), (1c) and (1d)

Various embodiments of substituents **R₁**, **R₂**, **R₃**, **R₄**, **R₅**, **R₆**, **X**, **R₇**, **R₈**, **R₉** and **R₁₀** have been discussed in **B1** to **B10** above. These “substituent” embodiments can be combined with any of the “core structure” embodiments, discussed in **B0** above, to form further embodiments of compounds of formula (1a), (1a’), (1b), (1b’), (1c) and (1d). All embodiments of compounds of formula (1a), (1a’), (1b), (1b’), (1c) and (1d) formed by combining the “substituent” embodiments and “core structure” embodiments, discussed above, are within the scope of the present invention, and some further preferred embodiments of the compounds of formula (1a), (1a’), (1b), (1b’), (1c) and (1d) are provided below.

In a preferred aspect of the first embodiment, the invention provides a compound of formula (1a), (1a’), (1b), (1b’), (1c) or (1d) or a pharmaceutically acceptable salt or solvate thereof, wherein:

- R₁** is methyl, ethyl, n-propyl, isopropyl, cyclopropyl optionally substituted with one methyl group, cyclobutyl, cyclopropylmethyl, CHF₂, CF₃ or CH₂CF₃;
- R₂** is H, F or OMe; or **R₂** is H, F or Cl;

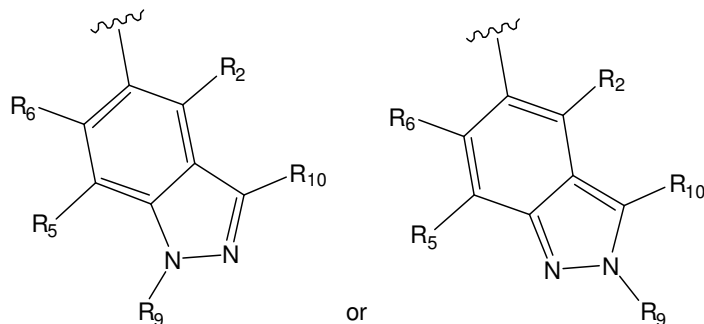
R₃ is H, OH, OMe or OPO(OH)OH;

R₄ is H, OH, OMe or OPO(OH)OH;

provided that **R₃** and **R₄** cannot both be H;

or **R₃** and **R₄** combine, together with the phenyl ring to which they are attached, to form an

5 indazole group as shown below;



R₅ is H or OMe;

R₆ is H or F;

X is **N** or **C-R₇** where **R₇** is H or F; or **X** is **C-R₇** where **R₇** is H or F;

10 **R₈** is CF₃, CF₂CF₃, CH₂CF₃, CH(CH₃)₂, OCF₃, OCH(CH₃)₂, cyclopropyl, cyclobutyl or SF₅; or

R₈ is CF₃, CF₂CF₃ or SF₅;

R₉ is H; and

R₁₀ is H.

In a more preferred aspect of the first embodiment, the invention provides a compound
15 of formula (1a), (1a'), (1b), (1b'), or (1c) or a pharmaceutically acceptable salt or solvate thereof,

wherein:

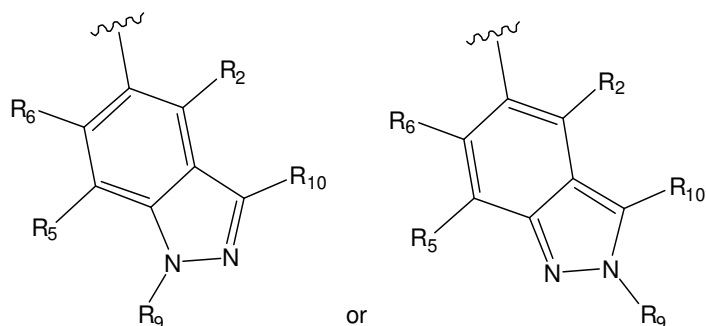
R₁ is ethyl, isopropyl, cyclopropyl, cyclobutyl, CF₃ or CH₂CF₃; or **R₁** is ethyl, isopropyl, cyclopropyl, CF₃ or CH₂CF₃;

20 **R₂** is F;

R₃ is H;

R₄ is OH;

or **R₃** and **R₄** combine, together with the phenyl ring to which they are attached, to form an indazole group as shown below;



R₅ is H;

R₆ is H or F;

X is C-**R₇** where **R₇** is H or F;

5 **R₈** is CF₃, CF₂CF₃, CH(CH₃)₂ or SF₅; or **R₈** is CF₃, CF₂CF₃ or SF₅;

R₉ is H; and

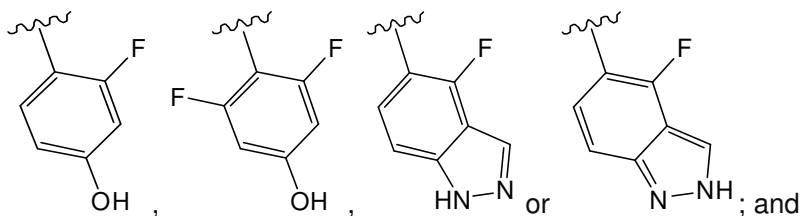
R₁₀ is H.

In an even more preferred aspect of the first embodiment, the invention provides a compound of formula (1a), (1a'), (1b), (1b'), (1c) or (1d) or a pharmaceutically acceptable salt or solvate thereof,

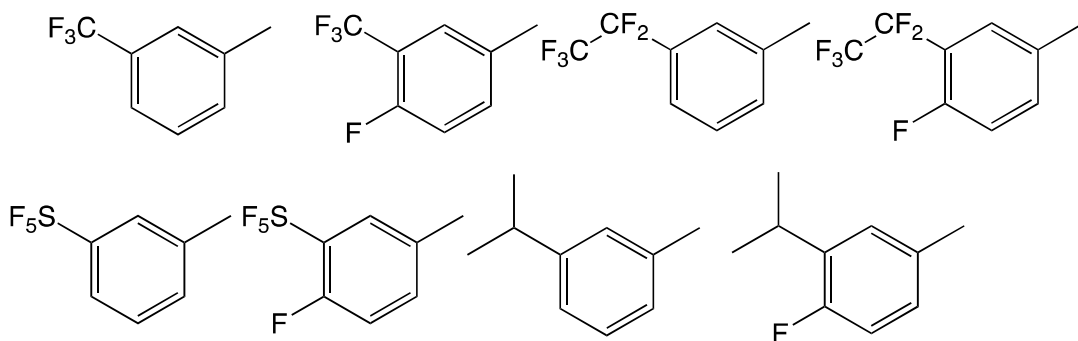
wherein:

R₁ is ethyl, isopropyl, cyclopropyl, CF₃ or CH₂CF₃;

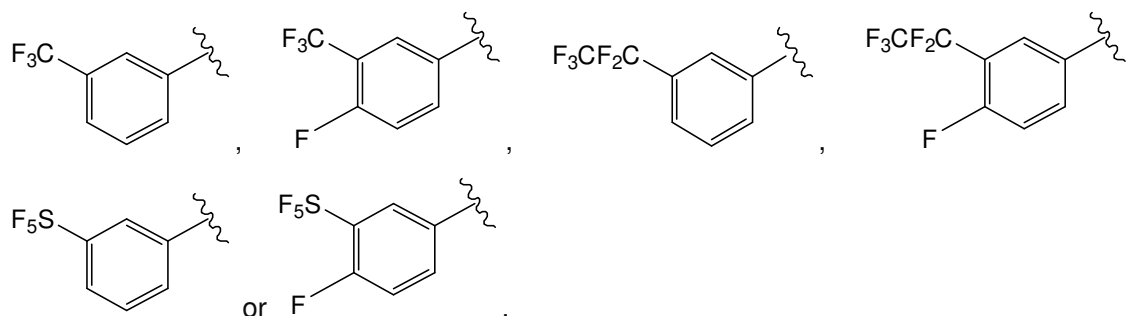
R₂ to **R₆** are selected to provide the structure:



15 **R₇** and **R₈** are selected to provide the structure



or **R₇** and **R₈** are selected to provide the structure:



The following compounds represent specific embodiments of the invention:

- Example 1: 2-methoxy-5-[2-(propan-2-yl)-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol
- Example 2: 4-fluoro-5-{6-[4-fluoro-3-(trifluoromethyl)phenyl]-2-(propan-2-yl)imidazo[1,2-a]pyrazin-3-yl}-1H-indazole
- Example 3: 3-fluoro-4-[2-(propan-2-yl)-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenoxyphosphonic acid
- Example 4: 4-[2-methyl-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol
- Example 5: 2-methoxy-4-(2-methyl-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl)phenol
- Example 6: 3-fluoro-4-[2-methyl-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol
- Example 7: 2-methoxy-5-[2-ethyl-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol
- Example 8: 3-fluoro-4-[2-ethyl-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol
- Example 9: 3-fluoro-4-[2-(propan-2-yl)-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol
- Example 10: 3-fluoro-4-[2-methyl-6-[4-fluoro-3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol
- Example 11: 3-fluoro-4-[2-difluoromethyl-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol
- Example 12: 3-fluoro-4-[2-trifluoromethyl-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol
- Example 13: 2-methoxy-5-[2-cyclopropyl-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol
- Example 14: 3-fluoro-4-[2-cyclopropyl-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol
- Example 15: 3, 5-difluoro-4-[2-methyl-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol

- Example 16: 3, 5-difluoro-4-[2-methyl-6-[4-fluoro-3-(trifluoromethyl)phenyl] imidazo[1,2-a]pyrazin-3-yl]phenol
- Example 17: 3, 5-difluoro-4-[2-(propan-2-yl)-6-[4-fluoro-3-(trifluoromethyl) phenyl] imidazo[1,2-a]pyrazin-3-yl]phenol
- 5 Example 18: 2-methoxy-5-[2-(propan-1-yl)-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol
- Example 19: 3,5-difluoro-4-[2-(propan-2-yl)-6-[3-(trifluoromethyl)phenyl] imidazo[1,2-a]pyrazin-3-yl]phenol
- Example 20: 4-(2-isopropyl-6-(3-(trifluoromethyl)phenyl)imidazo[1,2-a]pyrazin-3-yl)-3-methoxyphenol
- 10 Example 21: 4-fluoro -5-{2-propan-2-yl-6-[3-trifluoromethylphenyl]imidazo[1,2-a]pyrazin-3-yl}-1H-indazole
- Example 22: 7-methoxy-5-{2-(propan-2-yl)-6-[3-trifluoromethylphenyl]imidazo[1,2-a]pyrazin-3-yl}-1H-indazole
- 15 Example 23: 2-methoxy-5-(2-methyl-5-(3-(trifluoromethyl)phenyl)pyrazolo[1,5-c]pyrimidin-3-yl)phenol
- Example 24: 3,5-difluoro-4-(2-isopropyl-5-(3-(trifluoromethyl)phenyl)pyrazolo[1,5-c]pyrimidin-3-yl)phenol
- Example 25: 5-(2-isopropyl-5-(3-(trifluoromethyl)phenyl)pyrazolo[1,5-c]pyrimidin-3-yl)-2-methoxyphenol
- 20 Example 26: 2-methoxy-5-[2-(cyclopropylmethyl)-6-[3-(trifluoromethyl)phenyl]imidazo [1,2-a]pyrazin-3-yl]phenol
- Example 27: 2-methoxy-5-[2-(propan-2-yl)-6-[4-fluoro-3-(trifluoromethyl)phenyl] imidazo[1,2-a]pyrazin-3-yl]phenol
- 25 Example 28: 2-methoxy-5-[2-(propan-2-yl)-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenoxyphosphonic acid
- Example 29: 4-fluoro -5-{2-trifluoromethyl-6-[3-(pentafluoroethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl}- 1H-indazole
- Example 30: 2-methoxy-5-[2-(trifluoromethyl)-6-[3-(pentafluoroethyl)phenyl] imidazo[1,2-a]pyrazin-3-yl]phenol
- 30 Example 31: 3, 5-difluoro-4-[2-methyl-6-[3-(pentafluorosulfanyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol
- Example 32: 2-cyclopropyl-6-(4-fluoro-3-(trifluoromethyl)phenyl)-3-(1H-indazol-4-yl)imidazo[1,2-a]pyrazine
- 35 Example 33: 3, 5-difluoro-4-[2-(1-methyl-cycloprop-1-yl)-6-[4-fluoro-3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol

- Example 34: 4-(2-cyclopropyl-6-(4-fluoro-3-(trifluoromethyl)phenyl)imidazo[1,2-a]pyrazin-3-yl)-3,5-difluorophenol
- Example 35: 4-(2-cyclobutyl-6-(4-fluoro-3-(trifluoromethyl)phenyl)imidazo[1,2-a]pyrazin-3-yl)-3,5-difluorophenol
- 5 Example 36: 3, 5-difluoro-4-[2-ethyl-6-[4-fluoro-3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol
- Example 37: 4-fluoro -5-{2-ethyl-6-[3-(pentafluoroethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl}-1H-indazole
- Example 38: 3,5-difluoro-4-(6-(4-fluoro-3-(trifluoromethyl)phenyl)-2-(2,2,2-trifluoroethyl)imidazo[1,2-a]pyrazin-3-yl)phenol
- 10 Example 39: 3, 5-difluoro-4-[2-(propan-2-yl)-6-[3-(pentafluorosulfanyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol
- Example 40: 3,5-difluoro-4-{6-[4-fluoro-3-(trifluoromethyl)phenyl]-2-(propan-2-yl)imidazo[1,2-a]pyrazin-3-yl}phenoxyphosphonic acid
- 15 Example 41: 3,5-difluoro-4-{6-[4-fluoro-3-(trifluoromethyl)phenyl]-2-methyl-imidazo[1,2-a]pyrazin-3-yl}phenoxyphosphonic acid
- Example 42: 3,5-difluoro-4-(5-(4-fluoro-3-(trifluoromethyl)phenyl)-2-methylpyrazolo[1,5-c]pyrimidin-3-yl)phenol
- Example 43: 2-cyclopropyl-3-(4-fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-(trifluoromethyl)phenyl)imidazo[1,2-a]pyrazine
- 20 Example 44: 4-[2-Cyclopropyl-6-(4-fluoro-3-pentafluoroethyl-phenyl)-imidazo[1,2-a]pyrazin-3-yl]-3,5-difluoro-phenol
- Example 45: 4-{2-ethyl-6-[4-fluoro-3-(1,1,2,2,2-pentafluoroethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl}-3,5-difluorophenol
- 25 Example 46: 2-cyclopropyl-3-(4-fluoro-1H-indazol-5-yl)-6-(3-(pentafluoro-λ6-sulfaneyl)phenyl)imidazo[1,2-a]pyrazine
- Example 47: 3,5-difluoro-4-(5-(4-fluoro-3-(trifluoromethyl)phenyl)-2-isopropylpyrazolo[1,5-c]pyrimidin-3-yl)phenol
- Example 48: 4-(2-ethyl-5-(4-fluoro-3-(trifluoromethyl)phenyl)pyrazolo[1,5-c]pyrimidin-3-yl)-3,5-difluorophenol
- 30 Example 49: 3,5-difluoro-4-[2-methyl-6-[3-(pentafluoroethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol
- Example 50: 3-(4-Fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-trifluoromethyl phenyl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine

- Example 51: 2-Isopropyl-3-(3-methyl-1H-indazol-5-yl)-6-(3-trifluoromethyl-phenyl)-imidazo[1,2-a]pyrazine
- Example 52: 4-[2-Ethyl-6-(3-pentafluoroethyl-phenyl)-imidazo[1,2-a]pyrazin-3-yl]-3,5-difluorophenol
- 5 Example 53: 3,5-Difluoro-4-[6-(4-fluoro-3-pentafluoroethyl-phenyl)-2-methyl-imidazo[1,2-a]pyrazin-3-yl]-phenol
- Example 54: 5-{2-cyclopropyl-6-[4-fluoro-3-(1,1,2,2,2-pentafluoroethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl}-4-fluoro-1H-indazole
- Example 55: 4-Fluoro-5-[5-(4-fluoro-3-trifluoromethyl-phenyl)-2-isopropylpyrazolo[1,5-a]pyridin-3-yl]-1H-indazole
- 10 Example 56: 4-[2-Cyclopropyl-6-(4-fluoro-3-pentafluorosulfanyl-phenyl)-imidazo[1,2-a]pyrazin-3-yl]-3,5-difluorophenol
- Example 57: 2-Cyclopropyl-3-(4-fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-pentafluorosulfanyl-phenyl)-imidazo[1,2-a]pyrazine
- 15 Example 58: 3-(4-Fluoro-1H-indazol-5-yl)-5-(4-fluoro-3-pentafluoroethyl-phenyl)-2-isopropylpyrazolo[1,5-c]pyrimidine
- Example 59: 2-Cyclopropyl-3-(4-fluoro-1H-indazol-5-yl)-5-(4-fluoro-3-pentafluoroethyl-phenyl)-pyrazolo[1,5-c]pyrimidine
- Example 60: 4-[2-Cyclopropyl-5-(4-fluoro-3-trifluoromethyl-phenyl)-pyrazolo[1,5-c]pyrimidin-3-yl]-3,5-difluorophenol
- 20 Example 61: 3-(4-Fluoro-1H-indazol-5-yl)-5-(4-fluoro-3-trifluoromethyl-phenyl)-2-isopropylpyrazolo[1,5-c]pyrimidine
- Example 62: Phosphoric acid mono-{4-[2-cyclopropyl-6-(4-fluoro-3-trifluoromethyl-phenyl)-imidazo[1,2-a]pyrazin-3-yl]-3,5-difluorophenyl} ester
- 25 Example 63: 3-(4-Fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-pentafluoroethyl-phenyl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine
- Example 64: 3-(4-Fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-pentafluorosulfanyl-phenyl)-2-methyl-imidazo[1,2-a]pyrazine
- Example 65: 3-(4-Fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-pentafluorosulfanyl-phenyl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine
- 30 Example 66: 3-(4-Fluoro-1H-indazol-5-yl)-6-(3-isopropyl-phenyl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine
- Example 67: 3-(4-Fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-isopropyl-phenyl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine
- 35 Example 68: 3-(4-Fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-pentafluorosulfanyl-phenyl)-2-isopropyl-imidazo[1,2-a]pyrazine

- Example 69: 3-(4-Fluoro-1H-indazol-5-yl)-6-[4-fluoro-3-(2,2,2-trifluoro-ethyl)-phenyl]-2-trifluoromethyl-imidazo[1,2-a]pyrazine
- Example 70: 3-(4-Fluoro-1H-indazol-5-yl)-2-trifluoromethyl-6-(3-trifluoromethyl-phenyl)-imidazo[1,2-a]pyrazine
- 5 Example 71: 3-(4-Fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-trifluoromethoxy-phenyl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine
- Example 72: 3-(4-Fluoro-1H-indazol-5-yl)-6-(3-trifluoromethoxy-phenyl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine
- Example 73: 6-(3-Bromo-phenyl)-3-(4-fluoro-1H-indazol-5-yl)-2-isopropyl-imidazo[1,2-a]pyrazine
- 10 a]pyrazine
- Example 74: 3-(4-Fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-isopropyl-phenyl)-2-isopropyl-imidazo[1,2-a]pyrazine
- Example 75: 2-Ethyl-3-(4-fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-isopropyl-phenyl)-imidazo[1,2-a]pyrazine
- 15 Example 76: 2-Cyclobutyl-3-(4-fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-trifluoromethyl-phenyl)-imidazo[1,2-a]pyrazine
- Example 77: 2-Cyclobutyl-3-(4-fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-isopropyl-phenyl)-imidazo[1,2-a]pyrazine
- Example 78: 3-(4-Fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-prop-2-ynyloxy-phenyl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine
- 20 trifluoromethyl-imidazo[1,2-a]pyrazine
- Example 79: 2-Cyclopropyl-3-(4-fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-isopropyl-phenyl)-imidazo[1,2-a]pyrazine
- Example 80: 4-[2-Cyclopropyl-6-(4-fluoro-3-isopropyl-phenyl)-imidazo[1,2-a]pyrazin-3-yl]-3,5-difluoro-phenol
- 25 Example 81: 3-(4-Fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-isopropoxy-phenyl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine
- Example 82: 6-(3-Cyclobutyl-4-fluoro-phenyl)-3-(4-fluoro-1H-indazol-5-yl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine
- Example 83: 3-(4-Chloro-1H-indazol-5-yl)-6-(4-fluoro-3-isopropyl-phenyl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine
- 30 imidazo[1,2-a]pyrazine
- Example 84: 6-(3-Cyclopropyl-4-fluoro-phenyl)-3-(4-fluoro-1H-indazol-5-yl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine
- Example 85: 6-(3-Bromo-4-fluoro-phenyl)-3-(4-fluoro-1H-indazol-5-yl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine
- 35 Example 86: 3-(4-Fluoro-1H-indazol-5-yl)-6-(3-isopropoxy-phenyl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine

Example 87: 3-(4-Fluoro-1H-indazol-5-yl)-6-(2-isopropyl-pyridin-4-yl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine

Example 88: 3-(4-Fluoro-1H-indazol-5-yl)-2-trifluoromethyl-6-(2-trifluoromethyl-pyridin-4-yl)-imidazo[1,2-a]pyrazine

5 Example 89: 3,5-Difluoro-4-[2-(4-fluoro-3-trifluoromethyl-phenyl)-8-isopropyl-purin-9-yl]-phenol

Example 90: 3-fluoro-4-[8-(propan-2-yl)-2-[3-(trifluoromethyl)phenyl]-9H-purin-9-yl]phenol

C. Compositions

10 The compounds of the invention intended for pharmaceutical use may be administered alone or in combination with one or more other compounds of the invention or in combination with one or more other drugs (or as any combination thereof). Generally, they will be administered as a formulation in association with one or more pharmaceutically acceptable excipients. Accordingly, the present invention is also directed to a pharmaceutical composition
15 comprising (i) a therapeutically effective amount of a compound of formula (1a), (1b), (1c) or (1d) as defined above, or a pharmaceutically acceptable salt or solvate thereof; and (ii) a pharmaceutically acceptable excipient.

Pharmaceutical compositions suitable for the delivery of compounds of the present invention and methods for their preparation will be readily apparent to those skilled in the art.

20 Such compositions and methods for their preparation may be found, for example, in "Remington's Pharmaceutical Sciences", 19th Edition (Mack Publishing Company, 1995).

D. Methods of Use

This invention is also directed to compounds of formula (1a), (1b), (1c) and (1d) as
25 defined above, or a pharmaceutically acceptable salt or solvate thereof, for use in therapy, in particular for the treatment of schistosomiasis.

This invention is also directed to the use of compounds of formula (1a), (1b), (1c) and (1d), as defined above, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treatment of schistosomiasis.

30 This invention is also directed to a method for treating schistosomiasis comprising administering a therapeutically effective amount of a compound of formula (1a), (1b), (1c) or (1d) as defined above, or a pharmaceutically acceptable salt or solvate thereof, to a patient in need thereof.

The amount of active ingredient which is required to achieve a therapeutic effect will,
35 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.

5

E. General Synthetic Methodology

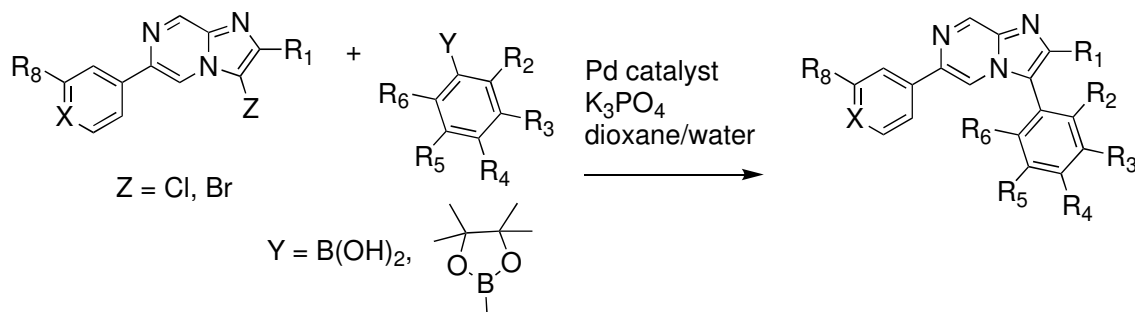
The methods used for the synthesis of the compounds of the invention are illustrated by the schemes below. The starting materials and reagents used in preparing these compounds are available from commercial suppliers or can be prepared by methods obvious to those skilled in the art.

10

General Method 1A

The invention also provides a process for the preparation of *Schistosoma* growth inhibitors where R_1 - R_6 and **X** are defined according to the invention and R_8 is CF_3 , CF_2CF_3 or $CH(CH_3)_2$. The process involves reacting an appropriate 3-chloro or 3-bromo-imidazo[1,2-a]pyrazine with an appropriate arylboronic acid or aryl pinacol borane under Suzuki conditions in the presence of a palladium catalyst.

15

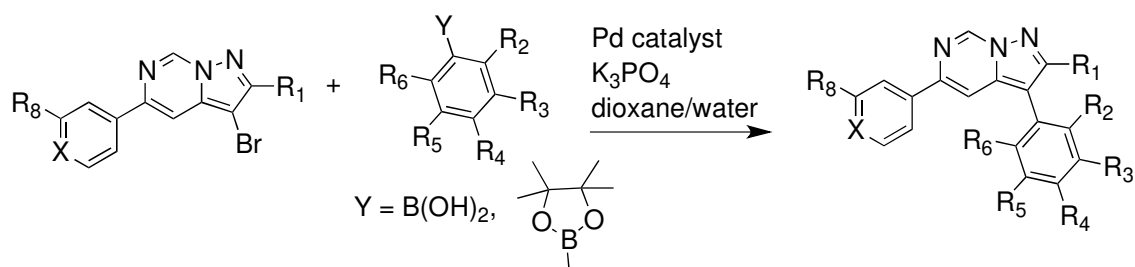


20

General Method 1B

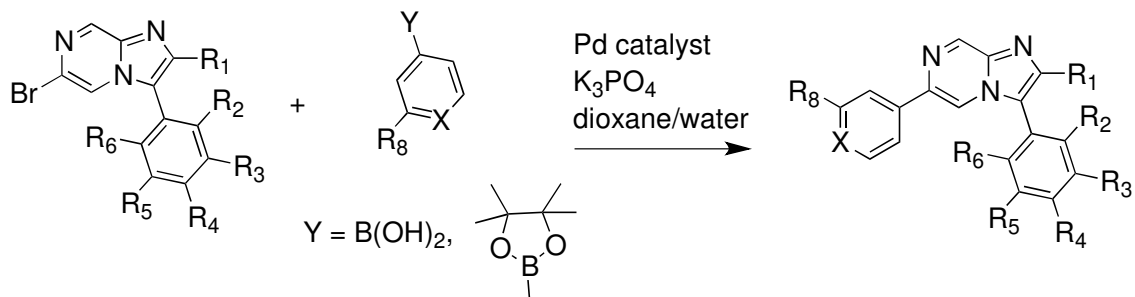
The invention also provides a process for the preparation of *Schistosoma* growth inhibitors where R_1 - R_6 and **X** are defined according to the invention and R_8 is CF_3 or CF_2CF_3 . The process involves reacting an appropriate 3-bromo-pyrazolo[1,5-c]pyrimidine with an appropriate arylboronic acid or aryl pinacol borane under Suzuki conditions in the presence of a palladium catalyst.

25



General Method 2

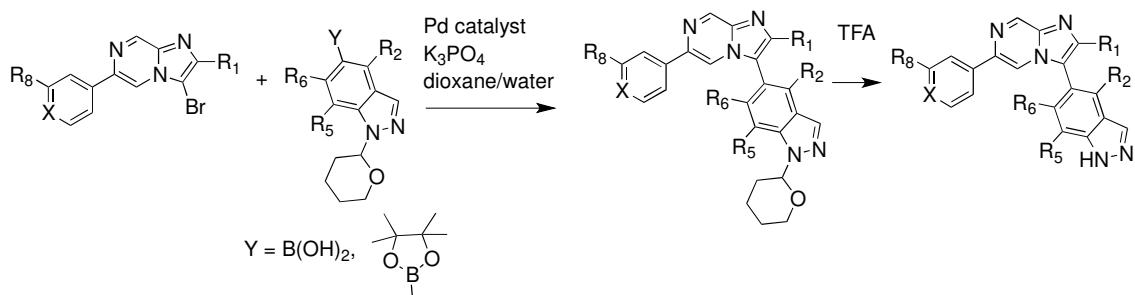
The invention also provides a process for the preparation of *Schistosoma* growth inhibitors where R₁-R₆ and X are defined according to the invention and R₈ is CF₂CF₃ or SF₅. The process involves reacting an appropriate 6-bromo-imidazo[1,2-a]pyrazine with an appropriate arylboronic acid or aryl pinacol borane under Suzuki conditions in the presence of a palladium catalyst.



10

General Method 3A

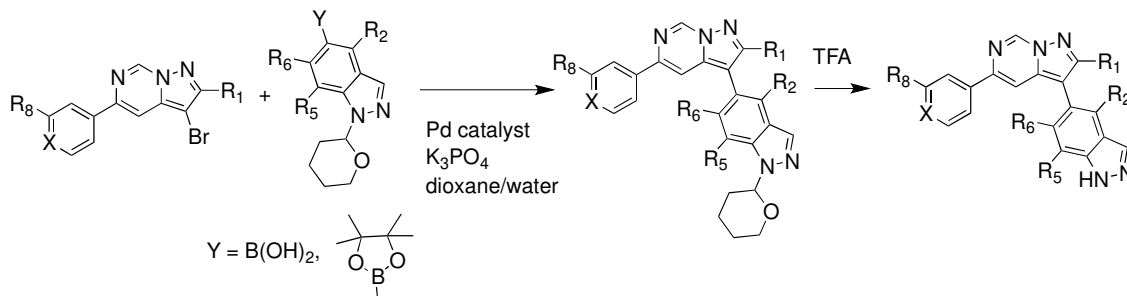
The invention also provides a process for the preparation of *Schistosoma* growth inhibitors where R₁-R₆ and X are defined according to the invention and R₈ is CF₃, CF₂CF₃, CH(CH₃)₂, CH₂CF₃, OCF₃, OCH(CH₃)₂, OCH₂C≡CH, cPr, cBu or SF₅. The process involves reacting an appropriate 3-bromo or 3-chloro-imidazo[1,2-a]pyrazine with an appropriate THP-protected indazole pinacol borane under Suzuki conditions in the presence of a palladium catalyst. The THP group can be removed under acidic conditions e.g. with TFA or HCl in an alcoholic solvent.



General Method 3B

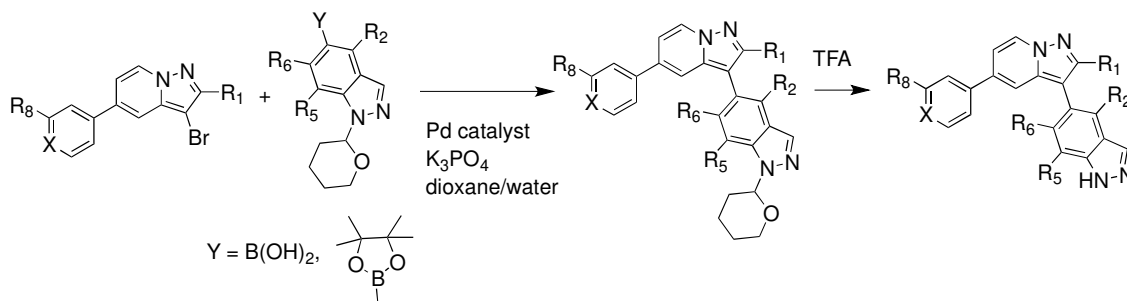
The invention also provides a process for the preparation of *Schistosoma* growth inhibitors where R_1 - R_6 and **X** are defined according to the invention and R_8 is CF_3 or CF_2CF_3 .

- 5 The process involves reacting an appropriate 3-bromo-pyrazolo[1,5-c]pyrimidine with an appropriate THP-protected indazole pinacol borane under Suzuki conditions in the presence of a palladium catalyst. The THP group can be removed under acidic conditions e.g. with TFA or HCl in an alcoholic solvent.



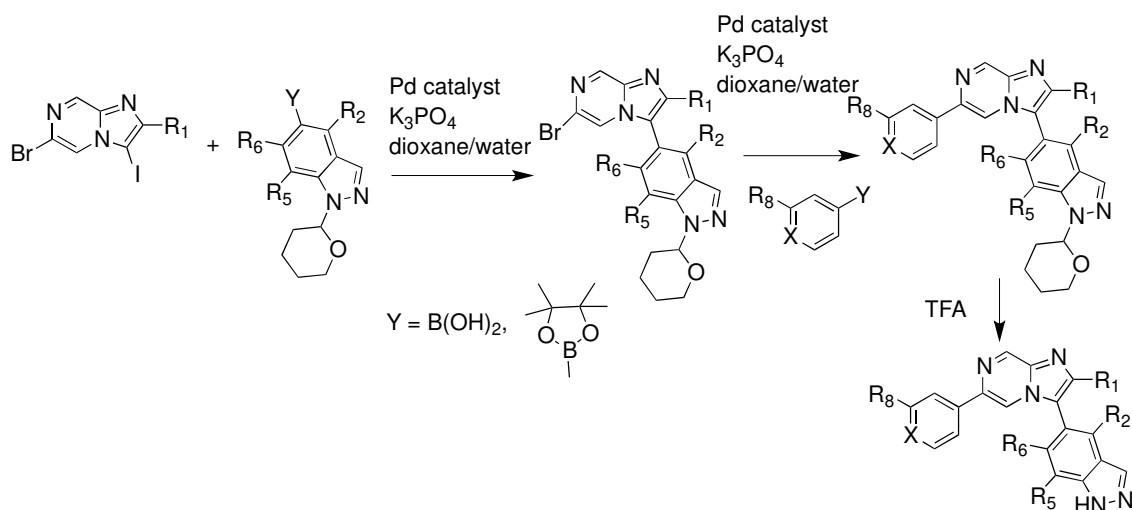
10 General Method 3C

The invention also provides a process for the preparation of *Schistosoma* growth inhibitors where R_1 - R_8 and **X** are defined according to the invention. The process involves reacting an appropriate 3-bromo-pyrazolo[1,5-c]pyridine with an appropriate THP-protected indazole pinacol borane under Suzuki conditions in the presence of a palladium catalyst. The THP group can be removed under acidic conditions e.g. with TFA or HCl in an alcoholic solvent.



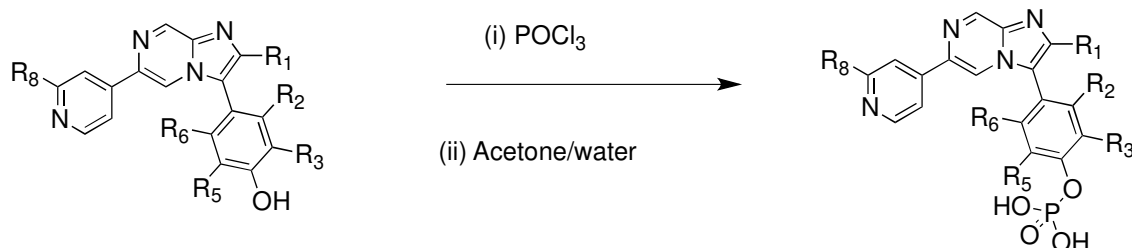
General Method 3D

The invention also provides a process for the preparation of *Schistosoma* growth inhibitors where R_1 - R_8 and **X** are defined according to the invention. The process involves reacting an appropriate 3-iodo-imidazo[1,2-a]pyrazine with an appropriate THP-protected indazole pinacol borane under Suzuki conditions in the presence of a palladium catalyst. The THP group can be removed under acidic conditions e.g. with TFA or HCl in an alcoholic solvent.



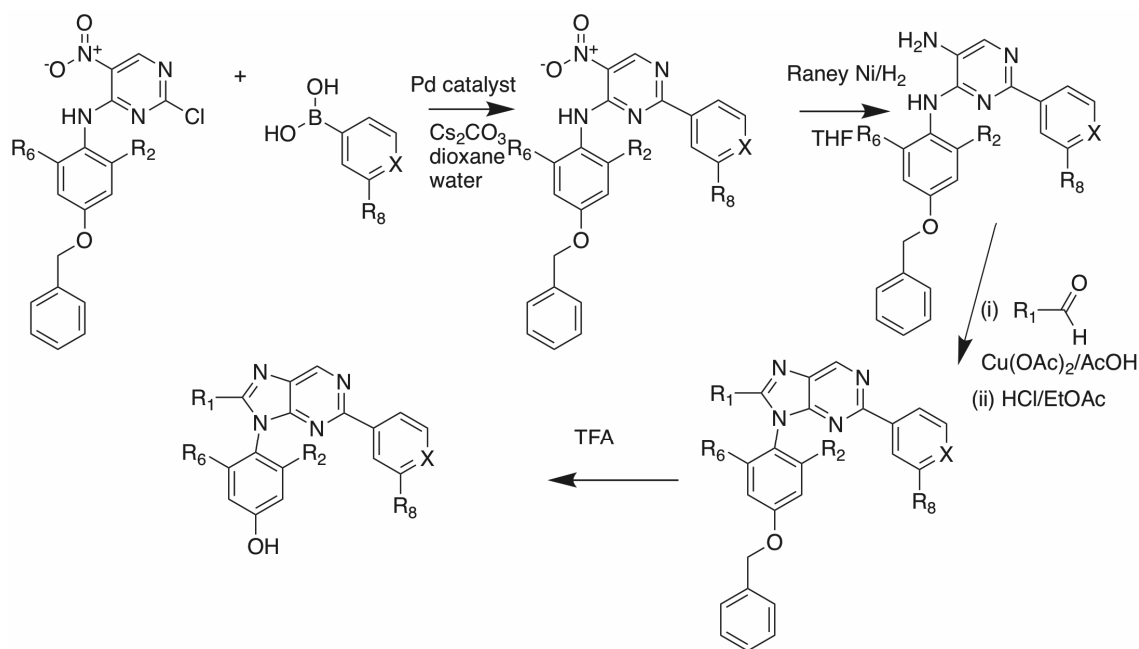
General Method 4

The invention also provides a process for the preparation of *Schistosoma* growth inhibitors where R₁, R₂ and R₅-R₈ and X are defined according to the invention, and R₃ or R₄ are OPO(OH)OH. The process involves reacting an appropriate hydroxyphenyl imidazo[1,2-a]pyrazine with phosphorus oxychloride in pyridine, followed by treatment of the crude product with acetone/water.



General Method 5

The invention also provides a process for the preparation of *Schistosoma* growth inhibitors where R₁, R₂, R₆, R₈ and X are defined according to the invention. The process involves coupling of an appropriate chloropyrimidine and arylboronic acid to give an intermediate, which is reduced with Raney Ni. The resulting diamine is reacted with an alkylaldehyde to provide an intermediate that is aromatised to a purine derivative and finally deprotected under acidic conditions.



F. Synthesis of Example Compounds

General Experimental Details

5

LC-MS

Compounds requiring purification under basic conditions were purified on an LC-MS system equipped with a YMC Actus Triart C18 5μm (20 x 250mm) column or Gemini NX 5μm C18 (100 x 30mm) columns, using a gradient elution of acetonitrile in water containing 20mM Ammonium bicarbonate (10–45% over 30min then 95% acetonitrile for 2 minutes).

10

UPLC

Method A: Formic Acid / Ammonium acetate (3 min runtime-UPLC) (3 min)

Column - Restek Ultra AQ C18 (30 x 2.1 mm, 3u), (mobile phase: 98% [0.05% modifier in water] and 2% [CH₃CN] held for 0.75 min, then to 90% [0.05% Modifier in water] and 10% [CH₃CN] in 1.0 min, further to 2% [0.05% Modifier in water] and 98% [CH₃CN] in 2.0 min, held this mobile phase composition up to 2.25 min and finally back to initial condition in 3.0 min). Flow = 1.5ml/min

15

Method E: (General-5 min)

Column - Zorbax C18 (50 x 4.6 mm, 5u, 130A), (mobile phase: from 90% [10 mM NH₄OAc in water] and 10% [CH₃CN] to 70% [10 mM NH₄OAc in water] and 30% [CH₃CN] in 1.5 min,

20

further to 10% [10 mM NH₄OAc in water] and 90% [CH₃CN] in 3.0 min, held this mobile phase composition up to 4.0 min and finally back to initial condition in 5.0 min). Flow = 1.2ml/min.

NMR

¹H NMR and ¹³C spectra were recorded on 400 MHz and 101 MHz respectively instruments at room temperature unless specified otherwise were referenced to residual solvent signals. Data are presented as follows: chemical shift in ppm, integration, multiplicity (br = broad, app = apparent, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet) and coupling constants in Hz.

Preparation of Starting Materials

All of the starting materials for making the intermediates and example compounds were obtained from commercial sources or using literature methods with the exception of the following compounds.

Starting Material 1

4-fluoro-1-(oxan-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole

To a stirred solution of 5-bromo-4-fluoro-1-(oxan-2-yl)-1H-indazole (800 mg, 2.7 mmol) in dioxane (20 mL) were added bis(pinacolato)diboron (1.36g, 5.3 mmol) and potassium acetate (787 mg, 8.0 mmol) in sealed tube and the resulting mixture was stirred and degased by using argon gas for 5min. After that Pd(dppf)Cl₂.DCM (218 mg, 0.27 mmol) was added and the resulting mixture was refluxed at 110 °C for 6 h. After completion, reaction mixture was evaporated under reduced pressure. The residue was suspended into water and extracted with ethyl acetate. Combined organic layer was dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The crude compound was purified by column chromatography using silica gel eluted with 0-10% EtOAc in hexane to give the title compound as a yellow color oil (900mg, 97%). UPLC rt 1.9 min MH⁺ 347. ¹H NMR (400 MHz, CDCl₃) δ 8.09 (s, 1H), 7.67 (dd, 1H), 7.31 (d, 1H), 5.69 (dd, 1H), 4.01 (d, 1H), 3.73 (t, 1H), 2.53 (m, 1H), 2.12 (m, 1H), 2.05 (m, 1H), 1.75 (m, 2H), 1.68 (m, 1H), 1.40 (s, 12H).

Starting Material 2

2-(4-Fluoro-3-pentafluoroethyl-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane

To a stirred solution of 4-Bromo-1-fluoro-2-pentafluoroethyl-benzene (1 g, 3.4 mmol) in 1,4-dioxane (25 ml) was added bispinacolatodiborane (1.7 g, 6.8 mmol) followed by potassium acetate (1 g, 10.2 mmol). The reaction mixture was deoxygenated with argon, then to the

reaction mixture was added [1,1'-Bis(diphenylphosphino)ferrocene]palladium(II) chloride, complex with dichloromethane (0.28 g, 0.34 mmol) and the reaction mixture was allowed to stir at 90°C for 16 hours under nitrogen. After complete consumption of the starting material (monitored by TLC) the reaction mixture was filtered throw a celite bed to remove the catalyst, the mother liquir was evaporated under reduced pressure, the residue was diluted with ethyl acetate, washed successively with water and brine, the organic layer dried over sodium sulphate and evaporated under reduced pressure to get the product, which was used without further purification.

10 *Starting Material 3*

4-Fluoro-1-(tetrahydro-pyran-2-yl)-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-indazole

Step 1

4-Bromo-3-fluoro-2-methyl-phenylamine

15 To a stirred solution of 3-fluoro-2-methylaniline (15.0 g, 120 mmol) in ACN (300.0 mL) was added N-Bromosuccinimide (23 g, 132 mmol) portion wise at 10°C. The reaction mixture was stirred at ambient temperature for 3 h, and was evaporated under reduced pressure. The reaction mixture was diluted with saturated Na₂S₂O₃ (100.0 mL) at 10°C and extracted with EtOAc (2 X 100 mL). Combined organic layer was washed with brine, dried over anhydrous
20 Na₂SO₄ and evaporated under reduced pressure to get desired crude, which was purified by column chromatography(100-200 mesh silica gel, eluent: 15% ethyl acetate in hexane) of the title compound (15 g, 61%) as a brown solid. LCMS rt 3.27 min MH+204. 1H NMR (400 MHz, DMSO-d₆) δ 7.09 (t, J=8.2, 1H), 6.40 (d, J=8.52, 1H), 1.98 (s, 3H).

Step 2

25 4-Bromo-3-fluoro-2-methyl-phenylamine

To a stirred solution of 4-Bromo-3-fluoro-2-methyl-phenylamine (15.0 g, 73.5 mmol) in acetic acid (200 mL) was added sodium nitrite (10 g, 147 mmol) portion wise at 10°C and reaction mixture was stirred at rt for 16 h . Upon completion, aqueous NaOH (50%) was added to the reaction mixture at -10°C dropwise with vigorous stirring until pH was ~7-8. The mixture was
30 then extracted with ethyl acetate. The organic layer was dried over sodium sulphate and concentrated under reduced pressure to get the crude compound which was purified by column chromatography on silica gel (0-40% EtOAc in Hexane) to afford the title compound (10 g, 63%) as a off white solid. LCMS rt 3.03 min MH+214. 1H NMR (400 MHz, CDCl₃) δ 10.44 (brs, 1H), 8.14 (s, 1H), 7.49-7.45 (m, 1H), 7.19 (d, J=8.76, 1H).

35 Step 3

5-Bromo-4-fluoro-1-(tetrahydro-pyran-2-yl)-1H-indazole

To a stirred solution of 5-Bromo-4-fluoro-1H-indazole (10.0 g, 46 mmol) in dichloromethane (300.0 mL) was 3,4-dihydropyran (11.7 g, 139 mmol) followed by PTSA (800 mg, 4.6 mmol) and the reaction mixture was stirred at ambient temperature for 12 h under nitrogen. After completion, the reaction mixture was diluted with DCM, washed successively with saturated NaHCO₃ solution and brine, combined organic layer was dried over anhydrous Na₂SO₄ and evaporated under reduced pressure to get the crude compound, which was purified by column chromatography (100-200 mesh silica gel, eluent: 5% ethyl acetate in hexane) to get the title compound (8 g, 57%) as a off white solid.

LCMS rt 3.83 min MH⁺299. ¹H NMR (400 MHz, CDCl₃) δ 8.05 (s, 1H), 7.46-7.43 (m, 1H), 7.28 (d, J=8.84, 1H), 5.69-5.67 (m, 1H), 3.99-3.86 (m, 1H), 3.74-3.70 (m, 1H), 2.53-2.45 (m, 1H), 2.13-2.09 (m, 2H), 1.86-1.71 (m, 4H).

Step 4

4-Fluoro-1-(tetrahydro-pyran-2-yl)-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-indazole

To a stirred solution of 5-Bromo-4-fluoro-1-(tetrahydro-pyran-2-yl)-1H-indazole (8 g, 26.7 mmol) in 1,4-dioxane (200 ml) was added bispinacolatodiborane (13.6 g, 53.5 mmol) followed by potassium acetate (7.8 g, 80.3 mmol). The reaction mixture was deoxygenated with argon, then to the reaction mixture was added [1,1'-Bis(diphenylphosphino)ferrocene]-palladium(II) chloride, complex with dichloromethane (2.2 g, 2.67 mmol) and the reaction mixture was allowed to stir at 90°C for 16 hours under nitrogen. The solvent was evaporated under reduced pressure, the residue was diluted with ethyl acetate, filtered over celite bed. Filtrate was then washed successively with water and brine. The organic layer was dried over sodium sulphate and evaporated under reduced pressure to give the crude product, which was purified by column chromatography(100-200 mesh silica gel, eluent: 5% ethyl acetate in hexane) to get the title compound (6 g, 64%) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.08 (s, 1H), 7.68-7.65 (m, 1H), 7.31 (d, J=8.56, 1H), 5.70-5.67 (m, 1H), 4.02-3.99 (m, 1H), 3.76-3.70 (m, 1H), 2.54-2.52 (m, 1H), 2.16-2.03 (m, 2H), 1.77-1.65 (m, 4H), 1.36 (s, 12H).

Preparation of Intermediates 1-61

Intermediate 1

3-bromo-2-(propan-2-yl)-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazine

Step 1

6-bromo-2-(propan-2-yl)imidazo[1,2-a]pyrazine

2-amino-5-bromopyrazine (10g, 57mmol) and 1-bromo-3-methyl-butan-2-one (20mL) were dissolved in acetonitrile (50 mL) and heated at 100 °C in a sealed tube for 3 days. The

reaction was quenched with sodium bicarbonate solution and filtered and extracted with ethyl acetate, organic layer was dried over sodium sulphate and concentrated to give a brown liquid that was purified by column chromatography (100-200 mesh silica gel, eluent; 50% ethyl acetate in DCM) to give the title compound as a brown semi solid (3.5g, 25%). UPLC rt 2.7 min MH⁺ 242. ¹H NMR (400 MHz, DMSO-d₆) δ 8.79 (s, 1H), 8.18 (s, 1H), 7.45 (s, 1H), 3.15 (h, 1H), 1.36 (d, 6H).

Step 2

2-(propan-2-yl)-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazine

A mixture of 6-bromo-2-(propan-2-yl)imidazo[1,2-a]pyrazine (2.0g, 8.3mmol) and 3-(trifluoromethyl)phenylboronic acid (1.9g, 10mmol) was dissolved in dioxane:H₂O (3:1, 20mL) and treated with K₃PO₄ (5.3g, 25mmol). The mixture was degassed for 20-30 min, treated with Pd-dppf-DCM complex (2.0g, 2.5mmol) and heated at 90 °C for 16h. After completion, the reaction was quenched with water and extracted with ethyl acetate. The organic layer was dried over sodium sulphate and concentrated to get crude compound, which was purified by column chromatography (100-200 mesh silica gel, eluent:10% ethyl acetate in DCM) to give the title compound (2.3g, 90%). UPLC rt 3.4 min MH⁺ 306. ¹H NMR (400 MHz, DMSO-d₆) δ 9.12 (s, 1H), 8.43 (s, 1H), 8.19 (s, 1H), 8.10 (d, 1H), 7.65 (d, 1H), 7.59 (t, 1H), 7.54 (s, 1H), 3.21 (h, 1H), 1.40 (d, 6H).

Step 3

3-bromo-2-(propan-2-yl)-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazine

2-(propan-2-yl)-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazine (2.3g, 7.5mmol) was dissolved in DCE (25 mL) and treated with N-Bromosuccinimide (1.6g, 9.1 mmol) and the mixture was heated at 85-90 °C for 8h. The reaction mixture was concentrated and the crude was purified by combiflash chromatography to get the title compound as a brown solid (1.5g, 52%) UPLC rt 4.0 min MH⁺ 386. ¹H NMR (400 MHz, DMSO-d₆) δ 9.07 (s, 1H), 8.38 (s, 1H), 8.25 (s, 1H), 8.15 (d, 1H), 7.68 (d, 1H), 7.62 (t, 1H), 3.30 (h, 1H), 1.40 (d, 6H).

Intermediate 37

3-Chloro-6-(4-fluoro-3-pentafluoroethyl-phenyl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine

Step-1:

6-Bromo-2-trifluoromethyl-imidazo[1,2-a]pyrazine

To a stirred solution of 2-amino-5-bromo-pyrazine (2 g, 11.5 mmol) in isopropanol (60 ml) was added 3-Bromo-1,1,1-trifluoroacetone (3 g, 3 mmol) and the mixture was allowed to stir at 90°C for 72 h. After complete consumption of the starting material (monitored by both TLC and LCMS) the solvent was evaporated under reduced pressure, the residue was diluted with ethyl acetate basified with saturated bicarbonate solution, filtered over celite bed.

Aqueous part was discarded and organic part was washed successively with saturated sodium bicarbonate solution and brine, the organic layer dried over sodium sulphate, evaporated under reduced pressure to get crude compound, which was purified by column chromatography (100-200 mesh silica gel, eluent:20% ethyl acetate in DCM) to give the title compound (1 g, 32.7%) as brown solid. LCMS rt 2.87 min MH⁺ 266. ¹H NMR (400 MHz, DMSO-d₆) δ 9.13 (s, 1H) 8.99 (s, 1H), 8.64 (s, 1H).

Step-2:

6-Bromo-3-chloro-2-trifluoromethyl-imidazo[1,2-a]pyrazine

To a stirred solution of 6-Bromo-2-trifluoromethyl-imidazo[1,2-a]pyrazine (1 g, 3.75 mmol) in dry DMF (25 ml) was added N-Chlorosuccinimide (753 mg, 5.63 mmol) and the reaction mixture was allowed stir at 90°C 24 h.. After complete consumption of the starting material (monitored by both TLC and LCMS) the reaction mixture was diluted with ethyl acetate, washed successively with water and brine. The organic part was dried over sodium sulphate and evaporated under reduced pressure to get crude compound which was purified by column chromatography (100-200 mesh silica gel, eluent:10% ethyl acetate in DCM) to give the title compound (900 mg, 79.7%) of as light brown solid.

LCMS rt 3.16 min MH⁺ 301. ¹H NMR (400 MHz, DMSO-d₆) δ 9.17 (s, 1H) 8.94 (s, 1H).

Step-3:

3-Chloro-6-(4-fluoro-3-pentafluoroethyl-phenyl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine

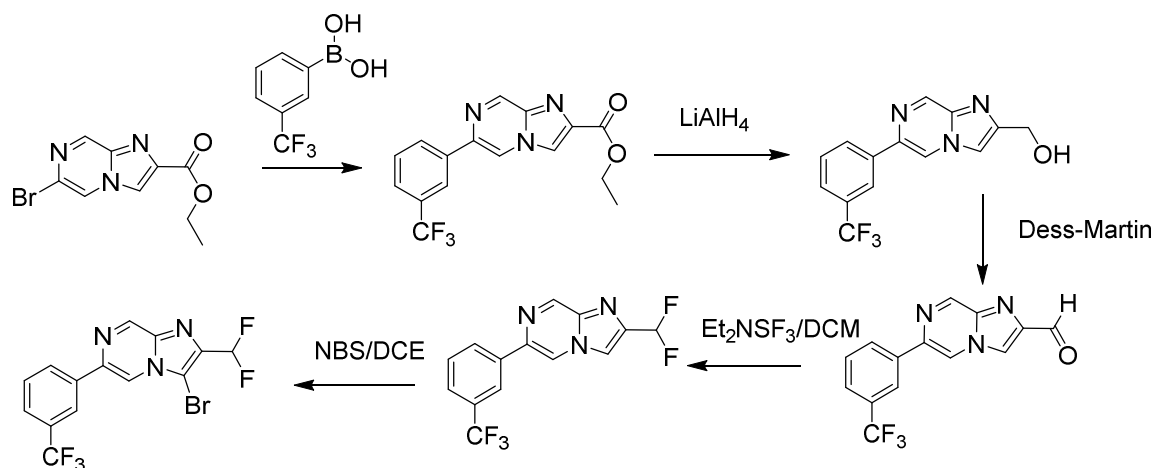
A mixture of 6-Bromo-3-chloro-2-trifluoromethyl-imidazo[1,2-a]pyrazine (800 mg, 2.67 mmol) and 2-(4-Fluoro-3-pentafluoroethyl-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (1 g, 2.93 mmol) was dissolved in 1,4-dioxane:H₂O (4:1, 15mL) and treated with K₃PO₄ (1.7 g, 8 mmol). The mixture was degassed for 20-30 min, treated with Bis(diphenylphosphino)ferrocene]palladium(II) chloride, complex with dichloromethane (217 mg, 0.27 mmol) and heated at 90 °C for 16h. After completion, the reaction was quenched with water and extracted with ethyl acetate. The organic layer was dried over sodium sulphate and concentrated to get crude compound, which was purified by column chromatography (100-200 mesh silica gel, eluent: 10% ethyl acetate in DCM) to give the title compound (700 mg, 60.5%). LCMS rt 4 min MH⁺ 434. ¹H NMR (400 MHz, DMSO-d₆) δ 9.40 (s,1H), 9.26 (s, 1H), 8.63 (br. s, 1H), 8.53(d, J=5.08 Hz, 1H), 7.75-7.70 (m, 1H).

Intermediates 2-4, 6-9, 12-14, 16-20, 23-24, 28-29,30-31, 33, 38-61

Prepared using a similar method to Intermediate 1 or 37 from the appropriate halo-ketone and boronic acid or boronate.

Intermediate 5

Prepared by a modification of the route to the above intermediates using the scheme below.



5 Intermediates 15, 21 and 25

Prepared from the appropriate 3-iodo imidazo[1,2-a]pyrazine using the method below

Intermediate 15

4-{6-bromo-2-methylimidazo[1,2-a]pyrazin-3-yl}-3,5-difluorophenol

10 Step 1

6-bromo-2-methyl imidazo[1,2-a]pyrazine

2-amino-5-bromopyrazine (10g, 57mmol) and 1-bromo-2,2-dimethoxy-propane (15 g) were dissolved in IPA (30 mL) and heated at 100 °C in a sealed tube for 3 days. The reaction was quenched with sodium bicarbonate solution and filtered and extracted with ethyl acetate; the organic layer was dried over sodium sulphate and concentrated to give a brown solid that was used for the next step without further purification.

Step 2

6-bromo-3-iodo-2-methyl-imidazo[1,2-a]pyrazine

To a well stirred solution of 6-bromo-2-methyl imidazo[1,2-a]pyrazine (3 g, 14.15 mmol) in DMF (15 ml) was added N-Iodoosuccinimide (3.82g, 16.98 mmol) and the reaction mixture was allowed to stir at 80°C for 12 h under nitrogen. After complete consumption of the SM (Monitored by LCMS) the reaction mixture was diluted with ethyl acetate, washed successively with water and brine, dried over sodium sulphate and evaporated under reduced pressure to get the crude compound, which was purified by column chromatography (100-200 mesh silica gel, eluent; 20% ethyl acetate in hexane) to give the title compound as a yellowish solid [1.5

g, 31% (After two steps)]. LCMS rt 2.89 min MH^+ 338. 1H NMR (400 MHz, DMSO- d_6) δ 8.74 (s, 1H), 8.49 (s, 1H), 2.44 (s, 3 H).

Step 3

4-{6-bromo-2-methylimidazo[1,2-a]pyrazin-3-yl}-3,5-difluorophenol

- 5 A mixture of 6-bromo-3-iodo-2-methyl-imidazo[1,2-a]pyrazine (120 mg, 0.355 mmol) and 2,6-difluoro-4-hydroxyphenylboronic acid (61.8 mg, 0.355 mmol) was dissolved in THF:H₂O (3:1, 4 mL) and treated with KF (62 mg, 1.065 mmol). The mixture was degassed for 20-30 min, treated with bis(tri-tert-butylphosphine)palladium(0) (18 mg, 0.036 mmol) and heated at 120°C for 1h under microwave irradiation (200 watt). After completion, the reaction
10 was quenched with water and extracted with ethyl acetate. The organic layer was dried over sodium sulphate and concentrated to get crude compound, which was used in the preparation of Example 31 without further purification.

Intermediate 11

- 15 3-bromo-2-(propan-2-yl)-5-[3-(trifluoromethyl)phenyl]pyrazolo[1,5-c]pyrimidine

Step 1

[4-bromo-3-(propan-2-yl)-1H-pyrazol-5-yl]methanol

- To the stirred solution of ethyl 4-bromo-3-(propan-2-yl)-1H-pyrazole-5-carboxylate (400 mg, 1.5 mmol) in THF (4 mL) was added 2.5 M LAH (Lithium Aluminium Hydride) solution
20 (2.5M in THF, 87 μ L, 2.3mmol) in THF at 0°C and stirred for 3h. The reaction was then quenched by saturated solution of Na₂SO₄ and filtered with celite and evaporated under reduced pressure to give the title compound (290 mg, 86%). UPLC rt 3.1 min MH^+ 261. 1H NMR (400 MHz, DMSO- d_6) δ 12.79 (s, 1H), 4.95 (br.s, 1H), 4.37 (s, 2H), 2.94 (m, 1H), 1.21 (d, 6H).

- 25 Step 2

4-bromo-5-(bromomethyl)-3-(propan-2-yl)-1H-pyrazole

- To ice cold [4-bromo-3-(propan-2-yl)-1H-pyrazol-5-yl]methanol (280 mg, 1.28 mmol) was added SOBr₂ (7 mL) and the mixture was heated at 40 °C for 2 h. Volatiles were removed under vacuum and the residue triturated with hexane to afford the title compound as a pale
30 yellow solid HBr salt (300 mg, 83%) UPLC rt 2.5 min MH^+ 283. 1H NMR (400 MHz, DMSO- d_6) δ 4.53 (s, 2H), 2.98 (m, 1H), 1.22 (d, 6H).

Step 3

3-bromo-2-(propan-2-yl)-5-[3-(trifluoromethyl)phenyl]pyrazolo[1,5-c]pyrimidine

- To a solution of 4-bromo-5-(bromomethyl)-3-(propan-2-yl)-1H-pyrazole (100mg, 0.36
35 mmol) in DCM (2 mL) at -10 °C was added 1-(3-trifluoromethylphenyl)-1-tosyl methyl

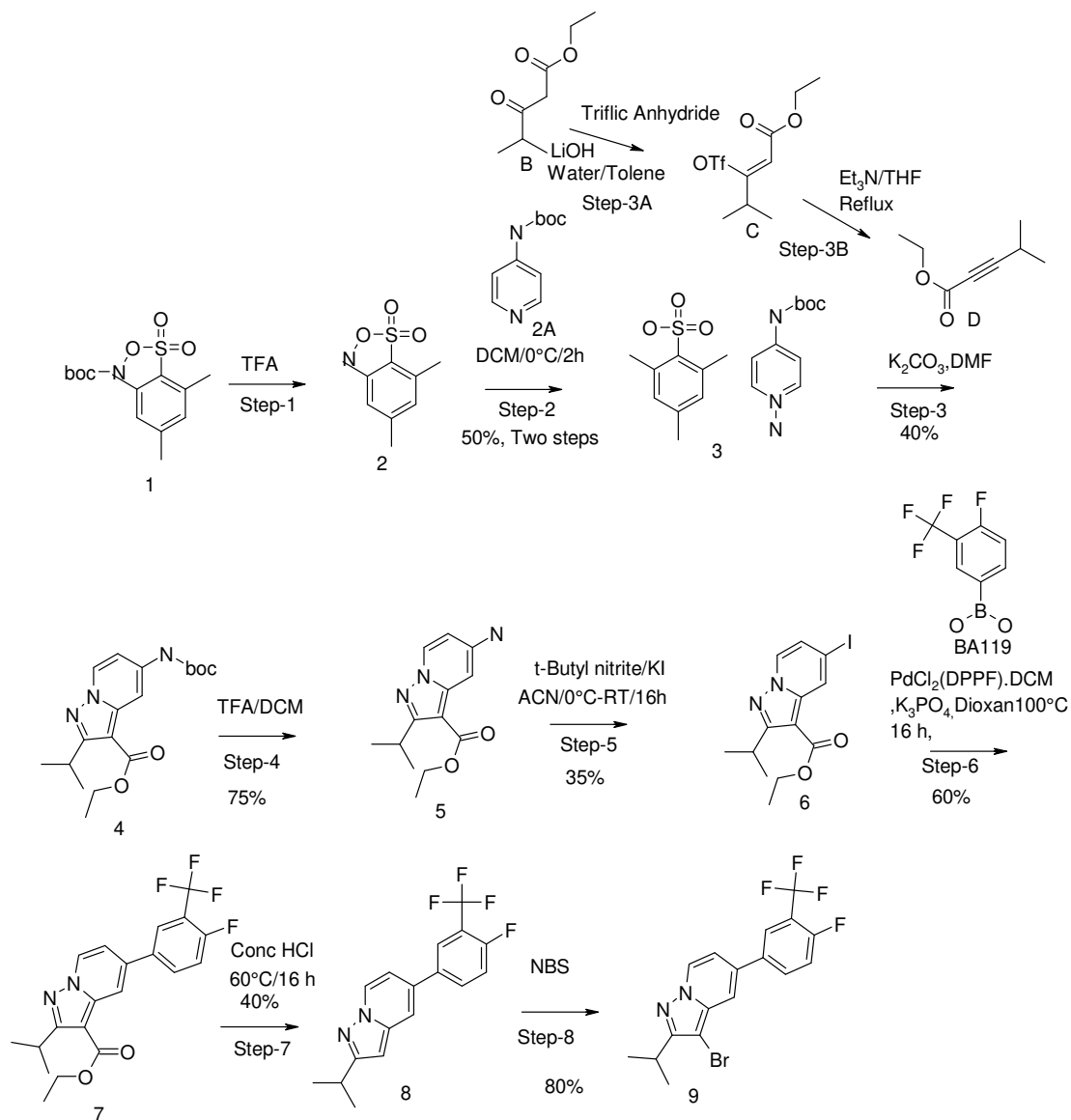
isocyanide (120mg, 0.36 mmol) and benzyl triethylammonium chloride (16mg, 0.07 mmol) and then added drop wise a solution of 30%-NaOH in water (2 mL). The resultant reaction mixture was maintained at -10 °C for 3 h. The mixture was extracted into DCM, the organic layer was dried and concentrated under vacuum to afford crude product. The crude was chromatographed on silica gel column using 3%-EtOAc in hexane to afford title compound as a colourless solid (30mg, 22%). UPLC rt 2.7 min MH⁺ 384. ¹H NMR (400 MHz, DMSO-d₆) δ 9.59 (s, 1H), 8.57 (s, 1H), 8.54 (d, 1H), 8.27 (s, 1H), 7.82 (d, 1H), 7.75 (t, 1H), 3.25 (h, 1H), 1.36 (d, 6H).

10 *Intermediates 10, 22, 26, 27, and 34-36*

Prepared from the appropriate pyrazole derivative and tosyl isocyanide. 1-(4-fluoro-3-trifluoromethylphenyl)-1-tosyl methyl isocyanide was prepared from (4-fluoro-3-trifluoromethylphenyl) methyl isocyanide and tosyl fluoride. 1-(4-fluoro-3-pentafluoroethylphenyl)-1-tosyl methyl isocyanide was prepared from (4-fluoro-3-pentafluoroethylphenyl) methyl isocyanide and tosyl fluoride.

Intermediate 32

3-bromo-2-(propan-2-yl)-5-[3-(trifluoromethyl)phenyl]pyrazolo[1,5-a]pyridine



Step-1

2-[(aminooxy)sulfonyl]-1,3,5-trimethylbenzene

TFA (160 ml) was added drop wise to *tert*-butyl [(mesitylsulfonyl)oxy]carbamate **1** (40 g, 126.98 mmol) at 0°C and the reaction mixture was allowed to stir at this temperature for 1h. The reaction mixture was poured slowly into ice water. The precipitate formed was filtered and washed thoroughly with water to remove trace amount of TFA to afford 2-[(aminooxy)sulfonyl]-1,3,5-trimethylbenzene. The solid was dissolved in DCM (200 mL) and the solution was used in the next step immediately without further analysis.

Step-2

tert-butyl N-(1-amino{4}-pyridin-4-yl)carbamate. 2,4,6-trimethylbenzene-1-sulfonic acid

To a solution of Pyridin-4-yl-carbamic acid tert-butyl ester (2.30 g, 11.06 mmol) in DCM (30 mL) was added drop wise a solution of compound 2-[(aminooxy)sulfonyl]-1,3,5-trimethylbenzene in DCM (30 mL) at 0-5 °C and continued stirring at this temperature for 2 h. The reaction mixture was concentrated under reduced pressure to afford the target compound (2 g, 50% in two step) as brown gum. It was used in the next step without further purification. ¹H NMR (400 MHz, DMSO-d₆) δ 10.93 (1H, br. s), 8.54 (2H, d, J=6.9 Hz), 7.85 (2H, d, J=6.8 Hz), 6.73 (2H, s), 2.16 (3H, s), 1.51 (9H, s) [possibly SO₃H proton was not seen in the NMR].

Step-3A

ethyl 4-methyl-2-[(trifluoromethane)sulfonyloxy]pent-2-enoate

Ethyl isobutyrylacetate (5 g, 31 mmol) was added to a round-bottom flask and dissolved in toluene (150 ml). The solution was cooled with an ice bath to 5-10°C (internal temperature) followed by addition of a saturated aqueous solution of LiOH (50 mL, 240 mmol) in one portion. The resulting biphasic mixture was vigorously stirred at 5-10°C for ~5 minutes followed by the addition of triflic anhydride (13 ml, 79 mmol) dropwise at a rate to maintain the internal temperature between 5-15°C. Upon completion of the reaction (as judged by TLC, typically <10 min), the biphasic solution was diluted with water and the layers were separated. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with water, brine and dried over sodium sulphate. The organic layer was filtered and concentrated under reduced pressure to get the title compound (6.2 g, 67%) as colourless liquid. ¹H NMR (400 MHz, DMSO-d₆) 6.09 (1H, s), 4.19-4.13 (2H, m), 2.57-2.53 (1H, m), 1.24-1.14 (9H, m)

Step-3B

Ethyl-4-methylpent-2-ynoate

To a stirred solution of Ethyl ethyl 4-methyl-2-[(trifluoromethane)sulfonyloxy]pent-2-enoate (6.1 g, 21 mmol) in dry THF (40 ml) was added triethyl amine (4 ml, 29 mmol) and the reaction mixture was allowed to stir at 80°C for 16 h under nitrogen. The reaction mixture was then cooled to RT and evaporated under reduced pressure to afford the title compound (2.5 g, 84.2%) as yellow oil.

¹H NMR (400 MHz, DMSO-d₆) 4.16-4.10 (1H, m), 3.09-3.06 (2H, m), d 1.24-1.14 (9H, m).

Step-3

ethyl-[[[(tert-butoxy)carbonyl]amino]-2-(propan-2-yl)pyrazolo[1,5-a]pyridine-3-carboxylate

To a stirred solution of tert-butyl N-(1-amino{4}-pyridin-4-yl)carbamate. 2,4,6-trimethylbenzene-1-sulfonic acid (4.5 g, 11 mmol) in dry DMF (12 ml) was added ethyl-4-methylpent-2-ynoate (1.5 g, 11 mmol) followed by potassium carbonate (3 g, 22 mmol) and the reaction mixture was allowed to stir at room temperature for 16 h under nitrogen. After

complete consumption of the SM (Monitored by LCMS) the reaction mixture was diluted with ethyl acetate, washed successively with water and brine, dried over sodium sulphate and evaporated under reduced pressure to get the crude compound, which was purified by column chromatography (100-200 mesh silica gel, eluent; 20% ethyl acetate in hexane) to give the title compound as a brown solid (1.6 g, 44%). LCMS rt 4.20 min MH⁺ 348. ¹H NMR (400 MHz, DMSO-d₆) δ 9.93 (s, 1H), 8.61 (d, 1H, J=7.44 Hz), 8.29 (s, 1H), 7.08 (d, 1H, J=7.44 Hz), 4.28-4.24 (m, 2H), 3.68-3.65 (m, 1H), 1.38-1.15 (m, 18 H).

Step-4

Ethyl-5-amino-2-(propan-2-yl)pyrazolo[1,5-a]pyridine-3-carboxylate

To a stirred solution of ethyl-5-[[tert-butoxy]carbonyl]amino-2-(propan-2-yl)pyrazolo[1,5-a]pyridine-3-carboxylate (1.7 g, 4.8 mmol) in dry DCM (12 ml) was added trifluoroacetic acid (3.6 ml) at 0°C and the reaction mixture was allowed to stir at room temperature for 1 h under nitrogen. After complete consumption of the SM (Monitored by LCMS) the volatiles were evaporated under reduced pressure to get the crude compound, which was purified by column chromatography (100-200 mesh silica gel, eluent; 30% ethyl acetate in hexane) to give the title compound as a off white solid (0.9 g, 75%). LCMS rt 3.34 min MH⁺ 248. ¹H NMR (400 MHz, DMSO-d₆) δ 8.30 (d, 1H, J=7.32 Hz), 6.90 (s, 1H), 6.41 (d, 1H, J=7.44 Hz), 6.18 (brs, 2H), 4.23-4.18 (m, 2H), 3.63-3.56 (m, 1H), 1.32-1.18 (m, 9 H).

Step-5

Ethyl-5-iodo-2-(propan-2-yl)pyrazolo[1,5-a]pyridine-3-carboxylate

To a stirred solution of ethyl-5-amino-2-(propan-2-yl)pyrazolo[1,5-a]pyridine-3-carboxylate (800 mg, 3.23 mmol) in dry acetonitrile (20 ml) at 0°C were added tert-Butyl nitrite (0.8 ml, 6.47 mmol) followed by potassium iodide (1.1 g, 6.47 mmol) and the reaction mixture was allowed to stir at 70°C for 16 h under nitrogen. After complete consumption of the SM (Monitored by LCMS) the reaction mixture was diluted with ethyl acetate, washed successively with water and brine, dried over sodium sulphate and evaporated under reduced pressure to get the crude compound, which was purified by column chromatography over silica gel (100-200 mesh silica gel, eluent; 10% ethyl acetate in hexane) to give the title compound as a white solid (550 mg, 47.41%). LCMS rt 2.78 min MH⁺ 359 (non-polar method). ¹H NMR (400 MHz, DMSO-d₆) δ 8.59 (d, 1H, J=7.28 Hz), 8.39 (s, 1H), 7.33 (d, 1H, J=5.08 Hz), 4.31-4.30 (m, 2H), 3.72-3.69 (m, 1H), 1.35-1.29 (m, 9 H).

Step-6

Ethyl-5-[4-fluoro-3-(trifluoromethyl)phenyl]-2-(propan-2-yl)pyrazolo[1,5-a]pyridine-3-carboxylate

Ethyl-5-iodo-2-(propan-2-yl)pyrazolo[1,5-a]pyridine-3-carboxylate (0.25 g, 0.69 mmol) and 4-fluoro-3-(trifluoromethyl)phenylboronic acid (0.21 g, 1.03 mmol) were dissolved in dioxane/water (4:1, 5 mL) and treated with K_3PO_4 (0.44 g, 2.07 mmol). The solution was degassed 20-30 min before addition of $PdCl_2(dppf)$. DCM catalyst (57 mg, 0.07 mmol). The reaction mixture was heated to 90 °C for 16h, cooled to room temperature, and partitioned between ethyl acetate and water. The organic layer was dried over sodium sulphate and concentrated under reduced pressure. The crude product was purified by column chromatography (100-200 mesh silica gel, by elution with 10% ethyl acetate in hexane). Fractions containing the desired product were combined and evaporated under reduced pressure to give the title compound (240 mg, 85%) UPLC rt 1.94 min MH^+ 395(3 min run)

1H NMR (400 MHz, $DMSO-d_6$) δ 8.91(d, $J=7.36$ Hz, 1H), 8.26 (s, 1H) 8.20-8.19 (m, 1H), 8.13 (d, $J=6.64$ Hz, 1H), 7.70 (t, $J=10.16$ Hz, 1H), 7.52 (dd, $J=7.2$ Hz, 1.02 Hz, 1H), 4.36-4.30 (m, 2H), 3.77-3.74 (m, 1H), 1.38-1.32 (m, 9 H).

Step-7

5-[4-fluoro-3-(trifluoromethyl)phenyl]-2-(propan-2-yl)pyrazolo[1,5-a]pyridine

Ethyl-5-[4-fluoro-3-(trifluoromethyl)phenyl]-2-(propan-2-yl)pyrazolo[1,5-a]pyridine-3-carboxylate (0.25 g, 0.63 mmol) was taken in conc HCl (60 ml) and the reaction mass was heated to reflux for 16 h. After complete consumption of the SM (Monitored by LCMS) the reaction mixture was cooled to 0°C, to it was added 2N NaOH dropwise until pH8. It was then extracted with ethyl acetate, washed successively with water and brine, dried over sodium sulphate and evaporated under reduced pressure to get the crude compound, which was purified by column chromatography over silica gel (100-200 mesh silica gel, eluent; 10% ethyl acetate in hexane) to give the title compound as a white solid (90 mg, 44%). UPLC rt 1.87 min (3 min run) MH^+ 323.

1H NMR (400 MHz, $DMSO-d_6$) δ .8.66 (d, $J=7.04$ Hz, 1H), 8.16-8.10 (m, 2H) 8.01 (s, 1H), 7.65 (t, $J=9.64$ Hz, 1H), 7.21 (d, $J=7.08$ Hz, 1H) 6.49 (s, 1H), 3.12-3.09 (m, 1H), 1.34-1.30 (m, 6 H).

Step-8

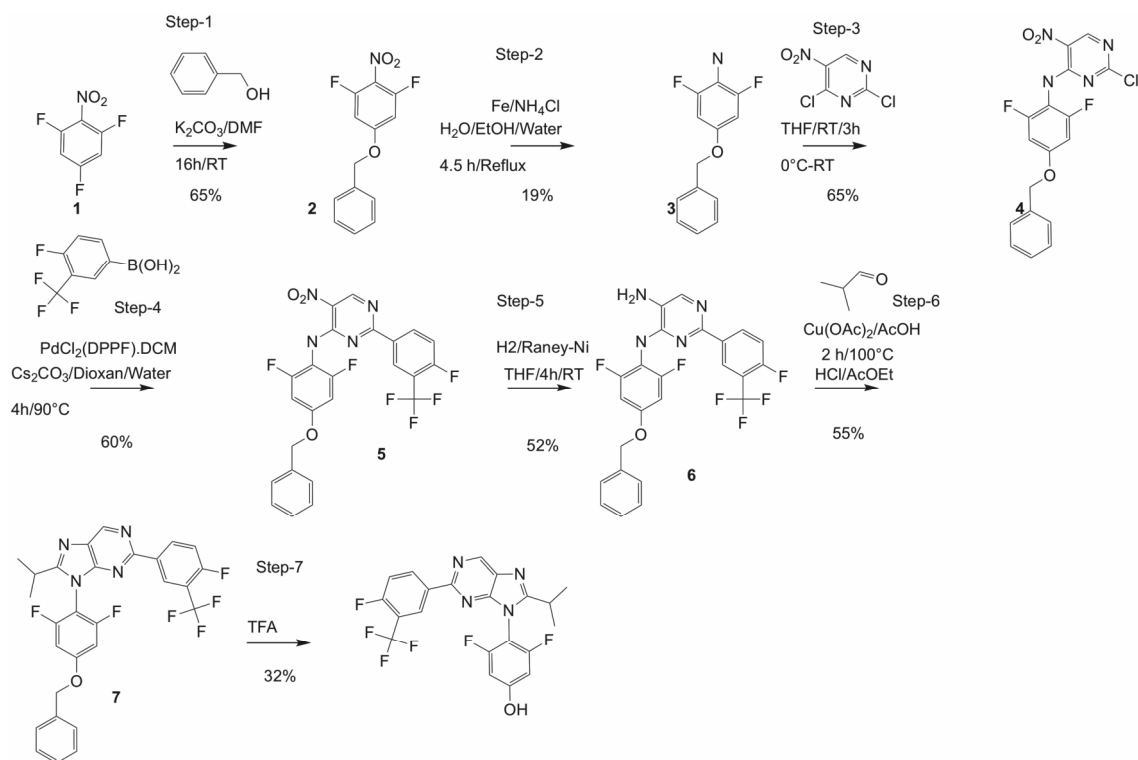
3-bromo-5-[4-fluoro-3-(trifluoromethyl)phenyl]-2-(propan-2-yl)pyrazolo[1,5-a]pyridine

To a stirred solution of 5-[4-fluoro-3-(trifluoromethyl)phenyl]-2-(propan-2-yl)pyrazolo[1,5-a]pyridine (86 mg, 0.26 mmol) in dry acetonitrile (5 ml) at 0°C were added N-Bromosuccinimide (57 mg, 0.32 mmol) and the reaction mixture was allowed to stir at 70°C for 1 h under nitrogen. After complete consumption of the SM (Monitored by LCMS) the reaction mixture was diluted with ethyl acetate, washed successively with water and brine,

dried over sodium sulphate and evaporated under reduced pressure to get the 89 mg of the title compound as brown solid which was used for the next step without further purification.

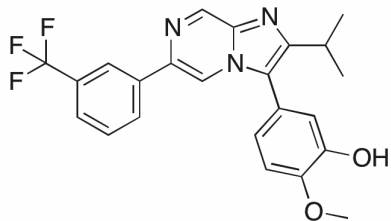
Intermediate 62

- 5 9-[4-(benzyloxy)-2,6-difluorophenyl]-8-(propan-2-yl)-2-[3-(trifluoromethyl)phenyl]-9H-purine was prepared by an analogous route to Example 89 step 6 product starting from 2,4,6-trifluoronitrobenzene according the following scheme



10 Preparation of Examples 1-90

Example 1



2-methoxy-5-[2-(propan-2-yl)-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol

- 3-bromo-2-(propan-2-yl)-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazine (1.5g, 3.9mmol) and 2-methoxy-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenol (1.46g, 5.9mmol) were dissolved in dioxane/water (4:1, 30mL) and treated with K_3PO_4 (2.48g,

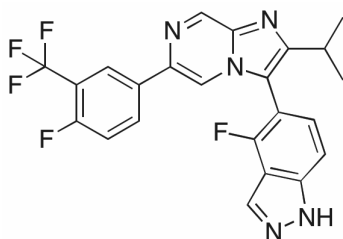
11.7mmol. The solution was degassed 20-30 min before addition of Pd-118 catalyst (0.25g, 0.39mmol), The reaction mixture was heated to 90 °C for 16h, cooled to room temperature, and partitioned between ethyl acetate and water. The organic layer was dried over sodium sulphate and concentrated under reduced pressure. The crude product was purified by
5 column chromatography (100-200 mesh silica gel, by elution with 20% ethyl acetate in DCM). Fractions containing the desired product were combined and evaporated under reduced pressure. The product was crystallised from methanol to give the title compound (600mg, 36%) UPLC rt 1.9 min MH⁺ 428.

¹H NMR (400 MHz, DMSO-d₆) δ 9.37 (s, 1H), 9.15 (s, 1H), 8.66 (s, 1H), 8.36 (s, 1H), 8.27 (d, 1H), 7.75 (d, 1H), 7.70 (d, 1H), 7.16 (d, 1H), 7.03 (d, 1H), 6.96 (s, 1H), 3.87 (s, 3H), 3.17 (h, 1H), 1.28 (d, 6H).

Examples 4-9

Prepared using similar conditions from the corresponding 3-chloroimidazo[1,2-a]pyrazines

Example 2



4-fluoro-5-{6-[4-fluoro-3-(trifluoromethyl)phenyl]-2-(propan-2-yl)imidazo[1,2-a]pyrazin-3-yl}-
1H-indazole

Step 1

3-bromo-2-(propan-2-yl)-6-[4-fluoro-3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazine (500 mg, 1.24 mmol) and 4-fluoro-1-(oxan-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (861 mg, 2.49 mmol) were dissolved in dioxane/water (4:1, 15 mL) and treated with K₃PO₄ (791 mg, 3.73 mmol). The solution was degassed with argon for 5 min before
25 addition of tetrakis(triphenylphosphine) palladium (0) catalyst (143 mg, 0.12 mmol). The reaction vessel was sealed and the mixture was heated to 100 °C for 3 h, cooled to room temperature, filtered over a celite bed to remove the solids, then partitioned between ethyl acetate and water. The organic layer was dried over sodium sulphate and concentrated under reduced pressure. The crude product was purified by column chromatography (100-200 mesh
30 silica gel, by elution with 20% ethyl acetate in DCM). Fractions containing the desired product were combined and evaporated under reduced pressure then triturated with ether and pentane

to give the title compound 4-fluoro-5-{6-[4-fluoro-3-(trifluoromethyl)phenyl]-2-(propan-2-yl)imidazo[1,2-a]pyrazin-3-yl}-1-(oxan-2-yl)-1H-indazole (600mg, 89%) UPLC rt 4.27min MH⁺ 542.

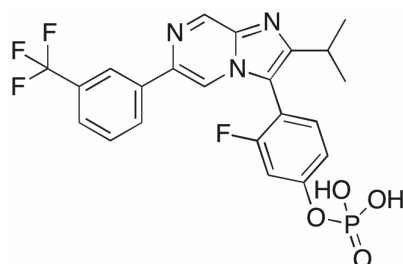
Step 2

5 4-fluoro-5-{6-[4-fluoro-3-(trifluoromethyl)phenyl]-2-(propan-2-yl)imidazo[1,2-a]pyrazin-3-yl}-1-(oxan-2-yl)-1H-indazole (600 mg, 1.1 mmol) was dissolved in a 30% solution of TFA in DCM (4 mL) and was stirred at room temperature for 2 h. The solvents were removed under reduced pressure then the crude reaction mixture was diluted with dichloromethane, washed successively with sodium bicarbonate solution, water and brine, the organic layer was dried
10 over sodium sulphate and concentrated under reduced pressure to get the crude product which was purified by reverse-phase prep-HPLC to give the title compound (125 mg, 25%). UPLC rt 3.5 min MH⁺ 458.

¹H NMR (400 MHz, DMSO-d₆) δ 13.85 (s, 1H), 9.20 (s, 1H), 8.76 (s, 1H), 8.41 (d, 2H), 8.35 (s, 1H), 7.61 (t, 1H), 7.54 (t, 1H), 7.50 (t, 1H), 3.05 (h, 1H), 1.27 (dd 6H).

15

Example 3



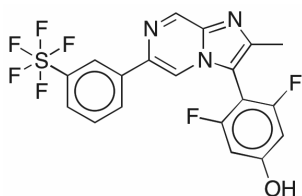
3-fluoro-4-[2-(propan-2-yl)-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenoxyphosphonic acid

20 A solution of 3-fluoro-4-[2-(propan-2-yl)-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol (Example 9 600 mg, 1.45 mmol) in DCM (10 mL) was cooled to 0°C and treated with pyridine (4 mL) followed by dropwise addition of phosphorous oxychloride (4 mL) solution in DCM (10mL). The reaction mixture was stirred for 5 h at RT. Two further charges of pyridine and POCl₃ were added at 0°C to drive the reaction to completion over 3 days. The
25 reaction was quenched by dropwise addition of (1:1) acetone:water) (100 ml). Volatile solvents were then removed under reduced pressure. The resulting oil was dissolved in DMF and purified by revers-phase prep-HPLC to give the title compound (104mg, 15%). UPLC rt 2.6 min MH⁺ 496.

¹H NMR (400 MHz, DMSO-d₆) δ 9.17 (s, 1H), 8.61 (s, 1H), 8.39 (s, 1H), 8.30 (d, 1H), 7.72 (d, 1H), 7.67 (t, 1H), 7.44 (t, 1H), 7.32 (d, 1H), 7.16 (d, 1H), 3.17 (h, 1H), 1.25 (d, 6H).

30

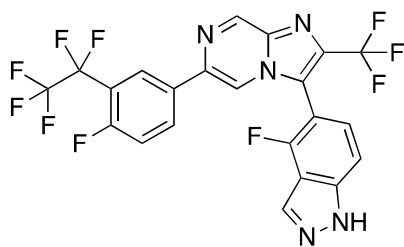
Example 31



3, 5-difluoro-4-[2-methyl-6-[3-(pentafluorosulfanyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol

- 5 A mixture 4-{6-bromo-2-methylimidazo[1,2-a]pyrazin-3-yl}-3,5-difluorophenol (40 mg, 0.118 mmol) and 3-(pentafluorosulfanyl)benzeneboronic acid, pinacol ester (58 mg, 0.176 mmol) was dissolved in dioxane/water (4:1, 5 mL) and treated with K_3PO_4 (49.8 mg, 0.235 mmol). The solution was degassed 20-30 min before addition of [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) chloride, complex with dichloromethane (19
- 10 mg, 0.024 mmol). The reaction mixture was heated to 90 °C for 16 h. The solvents were removed under reduced pressure then the crude reaction mixture was diluted with dichloromethane, washed successively with water and brine, the organic layer was dried over sodium sulphate and concentrated under reduced pressure to get the crude product which was purified by reverse-phase prep-HPLC to give the title compound (4 mg, 7%).
- 15 UPLC rt 3.02 min MH^+ 464. 1H NMR (400 MHz, $DMSO-d_6$) δ 9.12 (s, 1H), 9.20 (s, 1H), 8.33 (s, 1H), 7.98 (m, 2H), 7.77 (d, 1H), 7.56 (t, 1H), 6.68 (d, 1H), 6.41 (m, 1H), 2.47. (s, 3H)

Example 63



- 20 Step 1
- 6-(4-Fluoro-3-pentafluoroethyl-phenyl)-3-[4-fluoro-1-(tetrahydro-pyran-2-yl)-1H-indazol-5-yl]-2-trifluoromethyl-imidazo[1,2-a]pyrazine
- A mixture of 3-Chloro-6-(4-fluoro-3-pentafluoroethyl-phenyl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine (620 mg, 1.43 mmol) and 4-Fluoro-1-(tetrahydro-pyran-2-yl)-5-(4,4,5,5-
- 25 tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-indazole (1 g, 2.9 mmol) was dissolved in 1,4-dioxane:H₂O (4:1, 15mL) and treated with K_3PO_4 (0.91 g, 4.3 mmol). The mixture was degassed for 20-30 min, treated with palladium-tetrakis(triphenylphosphine) (331 mg, 0.28 mmol) and heated at 90 °C for 16h. After completion, the reaction was quenched with water

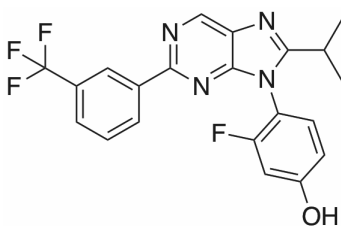
and extracted with ethyl acetate. The organic layer was dried over sodium sulphate and concentrated to get crude compound, which was purified by column chromatography (100-200 mesh silica gel, eluent:10% ethyl acetate in DCM) to give the title compound (480 mg, 54.3%). LCMS rt 4.33 min MH+ 618. ¹H NMR (400 MHz, DMSO-d₆) δ 9.47 (s, 1H), 8.92-8.86 (m, 1H), 8.44-8.41 (m, 3H), 7.87-7.84(m, 1H), 7.66-7.59 (m, 2H), 6.02 (d, J=8.84 Hz, 1H), 3.96-3.80 (m, 1H), 2.08-1.62 (m, 5H).

Step 2

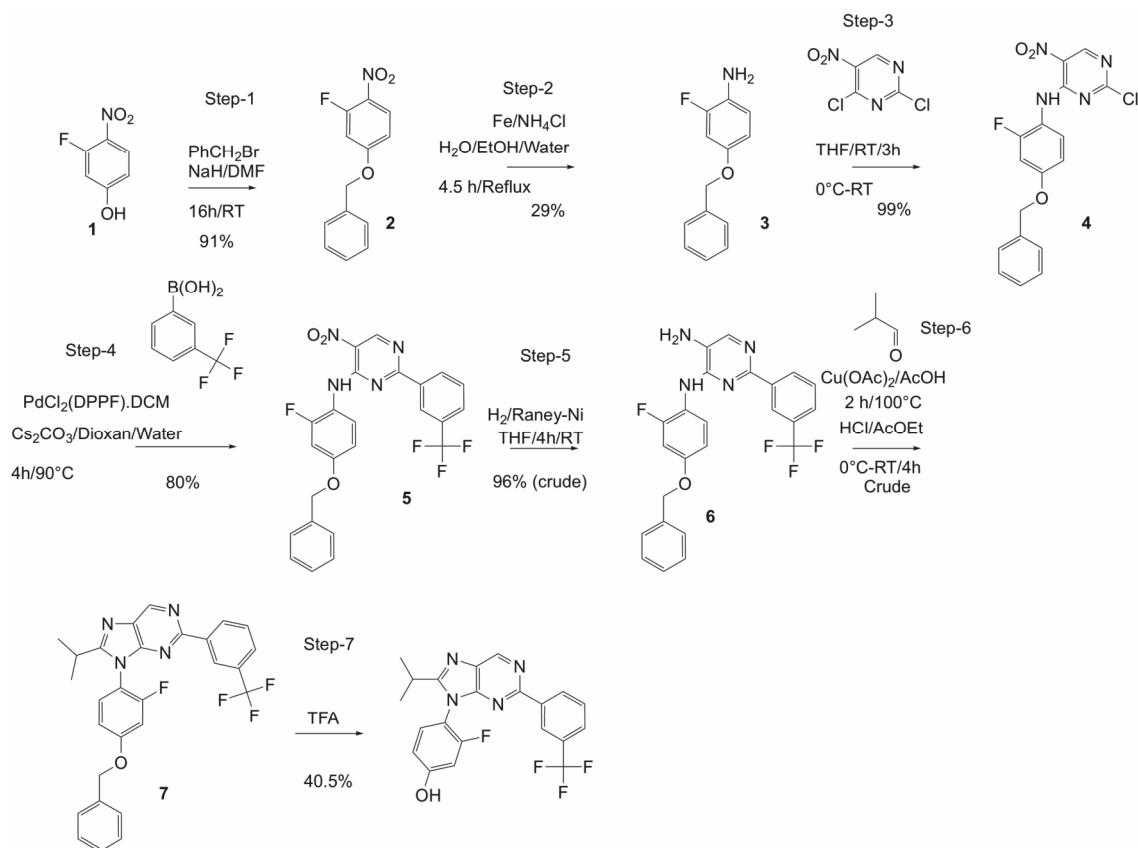
3-(4-Fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-pentafluoroethyl-phenyl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine

- 10 To a stirred solution of 6-(4-Fluoro-3-pentafluoroethyl-phenyl)-3-[4-fluoro-1-(tetrahydro-pyran-2-yl)-1H-indazol-5-yl]-2-trifluoromethyl-imidazo[1,2-a]pyrazine (480 mg, 0.78 mmol) was added 20 ml of 30% TFA in DCM at 0°C and the reaction mixture was allowed to stir at room temperature for 1 h under nitrogen. After complete consumption of the starting material (monitored by both TLC and LCMS) the volatiles were evaporated under reduced pressure,
- 15 the crude compound was diluted with dichloromethane, washed successively with sodium bicarbonate solution and brine, the organic layer dried over sodium sulphate, evaporated under reduced pressure to get crude, which was purified by reverse phase prep-HPLC to get 150 mg of the title compound (150 mg, 36.2%). UPLC rt 1.96 min (3 min run) MH+ 534. ¹H NMR (400 MHz, DMSO-d₆) δ 13.73 (s, 1H), 9.47 (s, 1H) 8.44-8.38 (m, 3H), 7.64-7.53 (m,
- 20 3H).

Example 90



Synthetic Scheme:



Step 1

4-Benzyloxy-2-fluoro-1-nitro-benzene (2)

To a stirred solution of 3-Fluoro-4-nitro-phenol (3.8 g, 24.2 mmol) in DMF (30 mL) was added sodium hydride (1.74 g, 72.6 mmol) portion wise at 0°C under argon, the reaction mass was stirred at the same temperature for 30 min, after that was added benzyl bromide (3.18 ml, 26.6 mmol) to the reaction mass dropwise at 0°C and the reaction mixture was allowed to stir for another 4 h at room temperature. After complete conversion of the starting material, the reaction mixture was pored into crushed ice to precipitate a solid which was collected by filtration to get 5.5 g (91%) of the title compound as a yellow solid. LCMS rt 3.52 min MH- 245. ¹H NMR (400 MHz, CDCl₃) δ 8.10-7.97 (m, 1H), 7.46-7.32 (m, 5H), 6.82-6.78 (m, 1H), 6.64-6.56 (m, 1H), 5.19-5.08 (m, 2H).

Step 2

4-Benzyloxy-2-fluoro-phenylamine (3)

To a stirred solution of 4-Benzyloxy-2-fluoro-1-nitro-benzene (2) (5.5 g, 22.26 mmol) in ethanol (150 mL) and water (30 mL) was added iron powder (4.98 g, 89.07 mmol) followed by ammonium chloride (9.44 g, 178.2 mmol) and the reaction mixture was allowed to stir at 70°C for 4 h. After complete consumption of the SM the reaction mass was filtered through

celite bed, the mother liquours were evaporated, the crude reaction mass was then diluted with ethyl acetate, washed successively with water and brine, dried over sodium sulphate, evaporated under reduced pressure to give crude product, which was purified by column chromatography (100-200 mesh silica gel, eluent:30% ethyl acetate in hexane) to get 1.4 g (28.9%) of the title compound as a brown liquid. LCMS rt 3.32 min MH⁺ 218. ¹H NMR (400 MHz, CDCl₃) δ 7.38-7.29 (m, 5H), 6.72-6.659 (m, 3H), 5.03 (s, 2H), 3.43 (br.s, 2H).

Step 3

N-[4-(benzyloxy)-2-fluorophenyl]-2-chloro-5-nitropyrimidin-4-amine (4)

To a stirred solution of 4-Benzyloxy-2-fluoro-phenylamine (3) (1.4 g, 6.45 mmol) in THF(25 mL) was added 2,4-Dichloro-5-nitro-pyrimidine (1.5 g, 7.74 mmol) at 0°C under argon and the reaction mixture was allowed to stir at room temperature for 4 h. After complete consumption of the SM, the reaction mass was poured into crushed ice to give precipitate, which was collected by filtration to get 2.4 g (99.2%) the title compound as a red solid. LCMS rt 3.65 min MH⁺ 375. ¹H NMR (400 MHz, CDCl₃) δ 10.10 (brs, 1H), 9.16 (s, 1H), 7.93-7.89 (m, 1H), 7.43-7.34 (m, 6H), 6.85-6.682 (m, 2H), 5.07 (s, 2H).

Step-4

N-[4-(benzyloxy)-2-fluorophenyl]-5-nitro-2-[3-(trifluoromethyl)phenyl]pyrimidin-4-amine (5)

N-[4-(benzyloxy)-2-fluorophenyl]-2-chloro-5-nitropyrimidin-4-amine (4) (2.4 g, 6.41 mmol) and 3-trifluoromethylphenylboronic acid (1.81 g, 9.62 mmol) were dissolved in dioxane/water (4:1, 40 mL) and treated with Cs₂CO₃ (4.17 g, 12.83 mmol). The solution was degassed 20-30 min before addition of PdCl₂(dppf). DCM catalyst (524 mg, 0.64 mmol), The reaction mixture was heated to 90 °C for 16h, cooled to room temperature, and partitioned between ethyl acetate and water. The organic layer was dried over sodium sulphate and concentrated under reduced pressure. The crude product was purified by column chromatography (100-200 mesh silica gel, by elution with 20% ethyl acetate in hexane). Fractions containing the desired product were combined and evaporated under reduced pressure to give the title compound as orange solid (2.5 g, 80.4 %) LCMS rt 4.3 min MH⁺ 483 ¹H NMR (400 MHz, DMSO-d₆) δ 9.98 (s, 1H), 9.4 (s, 1H), 8.64 (s, 1H), 8.52-8.51 (m, 1H) 7.89-7.57 (m, 3H), 7.47-7.37 (m, 5H), 6.9-6.71 (m, 3H), 5.11 (s, 2H).

Step 5

4-N-[4-(benzyloxy)-2-fluorophenyl]-2-[3-(trifluoromethyl)phenyl]pyrimidine-4,5-diamine (6)

To a stirred solution of 4 N-[4-(benzyloxy)-2-fluorophenyl]-5-nitro-2-[3-(trifluoromethyl)phenyl]pyrimidin-4-amine (5) (220 mg, 0.455 mmol) in THF(10 mL) was added Raney nickel (100 mg). The reaction vessel was filled with hydrogen and the reaction mixture was allowed to stir at 1 atm hydrogen pressure for 1 h. After complete consumption of the SM (monitored by TLC) the reaction mass was filtered through a Celite

bed, the mother liquor was evaporated to get 200 mg (96.8%) of the title compound as crude which was used for the next step without further purification. LCMS rt 3.75 min MH⁺ 353.

Step 6

9-[4-(benzyloxy)-2-fluorophenyl]-8-(propan-2-yl)-2-[3-(trifluoromethyl)phenyl]-9H-purine

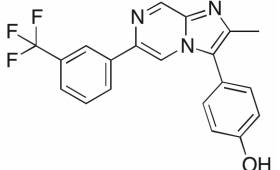
- 5 To a stirred solution of 4-N-[4-(benzyloxy)-2-fluorophenyl]-2-[3-(trifluoromethyl)phenyl]pyrimidine-4,5-diamine (6) (200 mg, 0.441 mmol) in acetic acid (20 mL) was added isobutyraldehyde (44 μ L, 0.485 mmol) followed by copper acetate (80 mg, 0.441 mmol) and the reaction mixture was allowed to stir at 100°C for 2 h under nitrogen. . After complete consumption of the SM (monitored by TLC) the reaction mixture was diluted
10 with DCM, washed successively with sodium bicarbonate and brine, dried over sodium sulphate, evaporated under reduced pressure to get the crude title compound, which was used for the next step without further purification. LCMS rt 4.50 min MH⁺ 507.

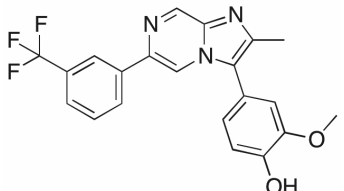
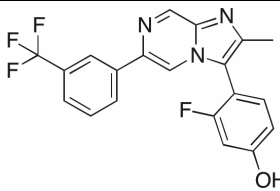
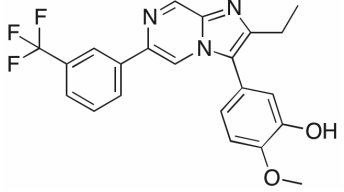
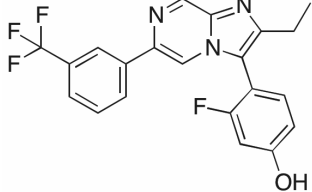
Step-7

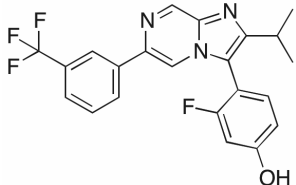
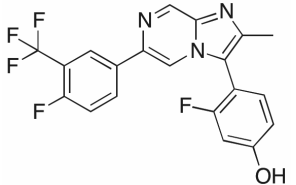
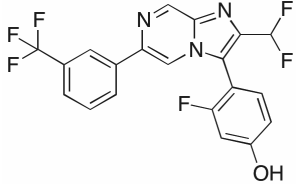
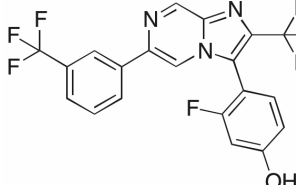
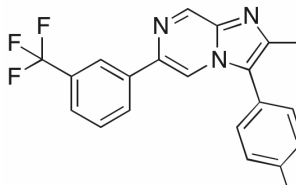
3-fluoro-4-[8-(propan-2-yl)-2-[3-(trifluoromethyl)phenyl]-9H-purin-9-yl]phenol

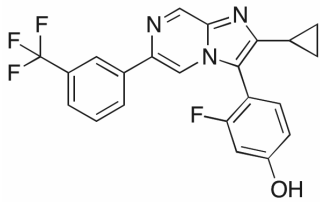
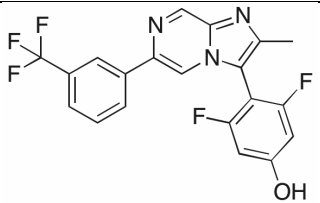
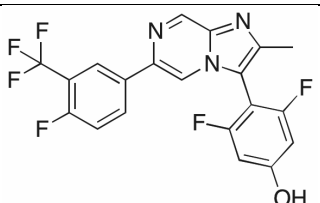
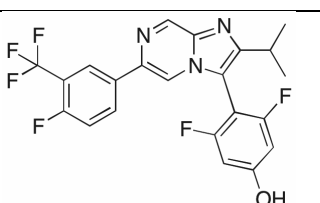
- 15 To a stirred solution of 9-[4-(benzyloxy)-2-fluorophenyl]-8-(propan-2-yl)-2-[3-(trifluoromethyl)phenyl]-9H-purine (7) (150 mg, 0.29 mmol) in 1,2-Dichloroethane (7 mL) was added trifluoroacetic acid (4.5 mL) and the reaction mixture was allowed to stir at 90°C for 16 h. After complete consumption of the starting material (monitored by both TLC and LCMS) the volatiles were evaporated under reduced pressure, the crude compound was diluted with
20 dichloromethane, washed successively with sodium bicarbonate solution and brine, the organic layer dried over sodium sulphate, evaporated under reduced pressure to get crude, which was purified by reverse phase prep-HPLC to get 50 mg of the title compound (40.5%) as off white solid. UPLC rt 3.23 min MH⁺ 417. ¹H NMR (400 MHz, DMSO-d₆) δ 10.61 (s, 1H), 9.21 (s, 1H) 8.58-8.54 (m, 2H), 7.85-7.57 (m, 3H), 6.96-6.87 (m, 2H), 3.04-3.01 (m, 1H),
25 1.31-1.22 (m, 6H).

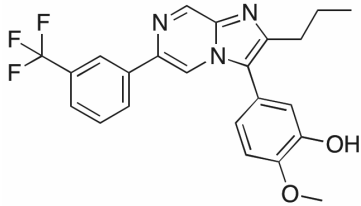
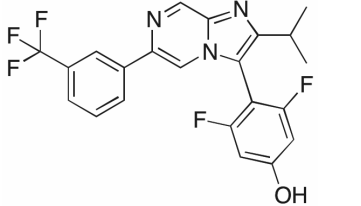
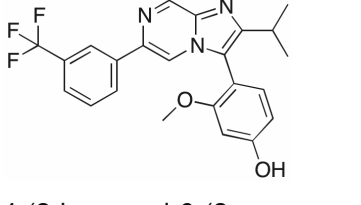
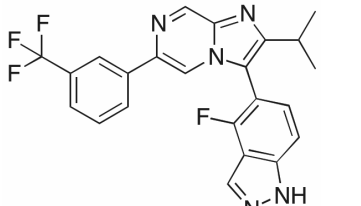
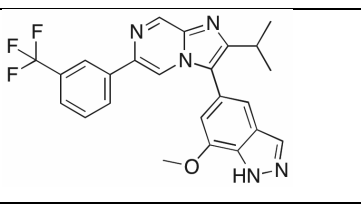
The following compounds were made by analogous methods:

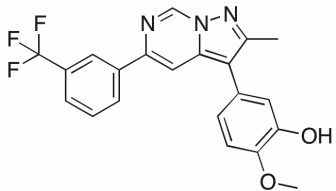
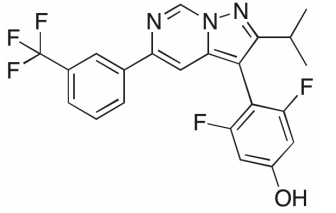
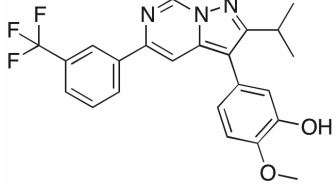
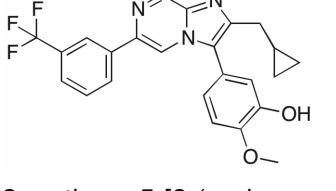
Ex No	Structure	General method	Intermediate N ^o	Yield	Characterisation
4		1A	2	24 mg, 29 %	UPLC rt 2.92 min, MH ⁺ 370

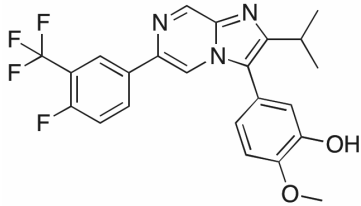
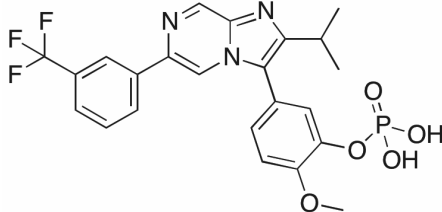
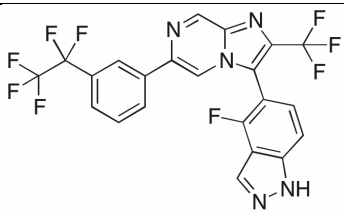
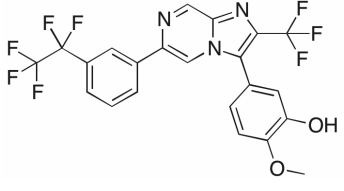
	4-[2-methyl-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol				
5	 2-methoxy-4-(2-methyl-6-(3-(trifluoromethyl)phenyl)imidazo[1,2-a]pyrazin-3-yl)phenol	1A	2	22 mg, 25%	UPLC rt 3.08 min, MH ⁺ 400
6	 3-fluoro-4-[2-methyl-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol	1A	2	10 mg, 11%	UPLC 2.98 rt min, MH ⁺ 388
7	 2-methoxy-5-[2-ethyl-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol	1A	3	37 mg, 34%	UPLC rt 3.04 min, MH ⁺ 414
8	 3-fluoro-4-[2-ethyl-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol	1A	3	8 mg, 11 %	UPLC rt 1.84 min (3 min Run) MH ⁺ 402

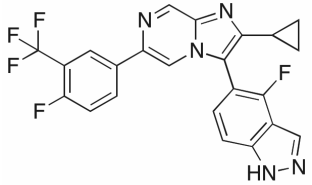
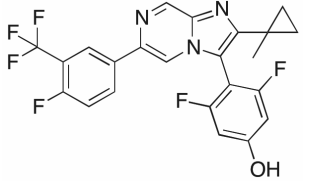
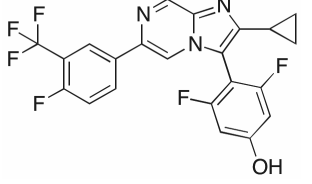
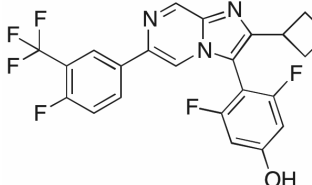
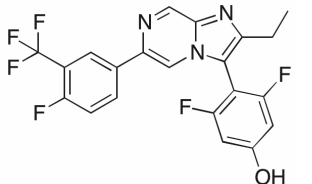
9	 3-fluoro-4-[2-(propan-2-yl)-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol	1A	1	5 mg, 7 %	UPLC rt 3.11 min, MH ⁺ 416
10	 3-fluoro-4-[2-methyl-6-[4-fluoro-3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol	1B	4	5 mg, 15 %	UPLC rt 2.92 min, MH ⁺ 406
11	 3-fluoro-4-[2-difluoromethyl-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol	1B	5	5 mg, 11 %	UPLC rt 1.62 min(3 min Run) MH ⁺ 424
12	 3-fluoro-4-[2-trifluoromethyl-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol	1B	6	25 mg, 20 %	UPLC rt 1.65 min (3 min Run) MH ⁺ 442
13	 3-fluoro-4-[2-(cyclopropyl)-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol	1B	7	25 mg, 37 %	UPLC rt 1.69 min (3 min Run) MH ⁺ 426

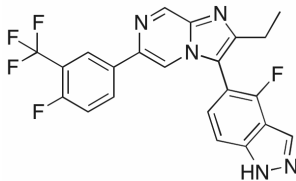
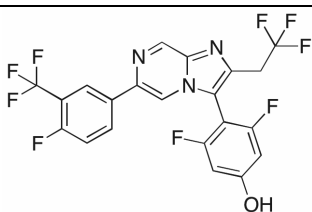
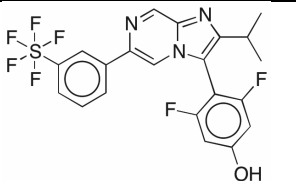
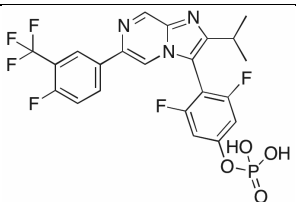
	2-methoxy-5-[2-cyclopropyl-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol				
14	 3-fluoro-4-[2-cyclopropyl-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol	1B	7	30 mg, 23 %	UPLC rt 1.67 min (3 min Run) MH ⁺ 414
15	 3, 5-difluoro-4-[2-methyl-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol	1B	1	25 mg, 22%	UPLC rt 1.60 min (3 min Run) MH ⁺ 406
16	 3, 5-difluoro-4-[2-methyl-6-[4-fluoro-3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol	1B	4	12 mg, 11 %	UPLC rt 1.85 min (3 min Run) MH ⁺ 424
17	 3, 5-difluoro-4-[2-(propan-2-yl)-6-[4-fluoro-3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol	1B	8	14 mg, 12.5 %	UPLC rt 2.60 min, MH ⁺ 452

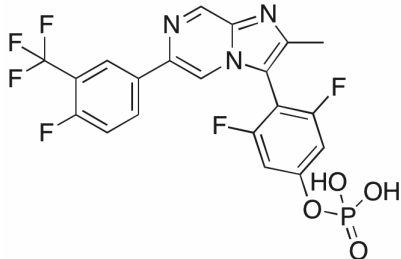
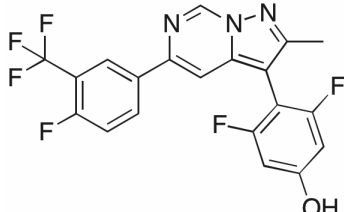
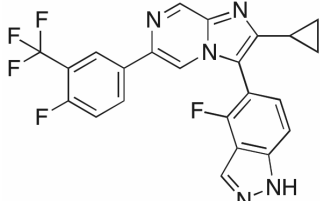
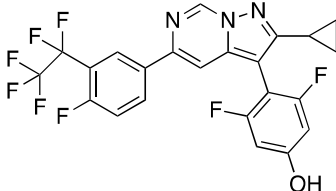
18	 2-methoxy-5-[2-(propan-1-yl)-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol	1B	9	10 mg, 14 %	UPLC rt 1.89 min(3 min Run) MH ⁺ 428
19	 3,5-difluoro-4-[2-(propan-2-yl)-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol	1B	1	7 mg, 5 %	UPLC rt 2.62 min, MH ⁺ 432
20	 4-(2-isopropyl-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl)-3-methoxyphenol	1B	1	12 mg, 15 %	UPLC rt 3.13 min, MH ⁺ 428
21	 4-fluoro -5-[2-propan-2-yl-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]- 1H-indazole	2	1	5 mg, 62 %	UPLC rt 3.20 min, MH ⁺ 440
22		2	1	12 mg, 51 %	UPLC rt1.89 min (3 min Run) MH ⁺ 452

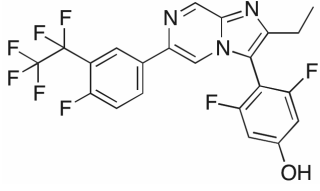
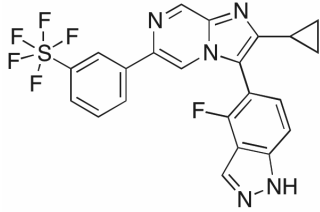
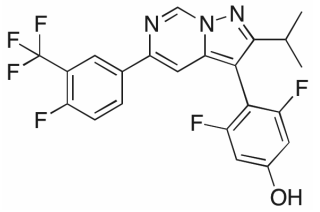
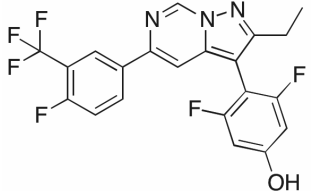
	7-methoxy-5-{2-(propan-2-yl)-6-[3-trifluoromethylphenyl]imidazo[1,2-a]pyrazin-3-yl}-1H-indazole				
23	 2-methoxy-5-(2-methyl-5-(3-(trifluoromethyl)phenyl)pyrazolo[1,5-c]pyrimidin-3-yl)phenol	1B	10	60 mg, 54 %	UPLC rt 1.92 min (3 min Run) MH ⁺ 400
24	 3,5-difluoro-4-(2-isopropyl-5-(3-(trifluoromethyl)phenyl)pyrazolo[1,5-c]pyrimidin-3-yl)phenol	1B	11	36 mg, 40 %	UPLC rt 2.19 min (3 min Run) MH ⁺ 434
25	 5-(2-isopropyl-5-(3-(trifluoromethyl)phenyl)pyrazolo[1,5-c]pyrimidin-3-yl)-2-methoxyphenol	1B	11	37 mg, 42 %	UPLC rt 3.46 min, MH ⁺ 428
26	 2-methoxy-5-[2-(cyclopropylmethyl)-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol	1B	12	20 mg, 25 %	UPLC rt 3.17 min, MH ⁺ 440

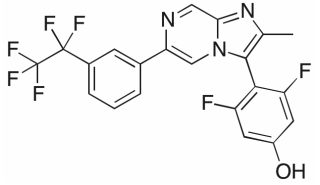
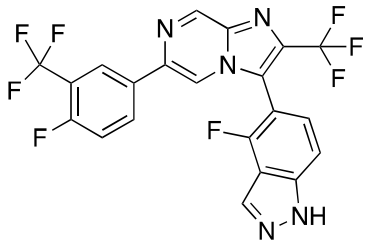
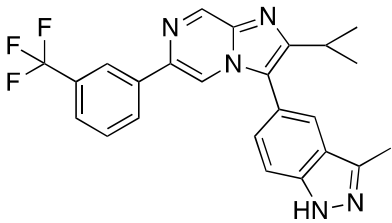
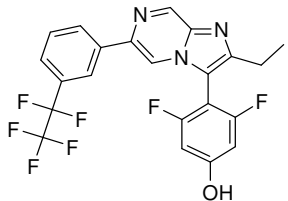
27	 2-methoxy-5-[2-(propan-2-yl)-6-[4-fluoro-3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol	1B	8	40 mg, 30 %	UPLC rt 1.93 min (3 min Run) MH ⁺ 446
28	 2-methoxy-5-[2-(propan-2-yl)-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenoxyphosphonic acid	3	Ex.1	50 mg, 20 %	UPLC rt 2.10 min, MH ⁺ 508
29	 4-fluoro-5-{2-trifluoromethyl-6-[3-(pentafluoroethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl}-1H-indazole	2	13	20 mg, 55 %	UPLC rt 2.62 min, MH ⁺ 516
30	 2-methoxy-5-[2-(trifluoromethyl)-6-[3-(pentafluoroethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol	1B	14	30 mg, 47 %	UPLC rt 3.38 min, MH ⁺ 502

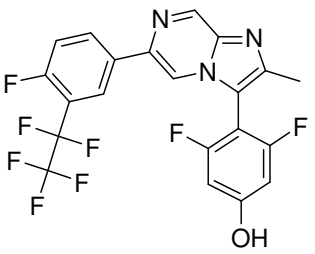
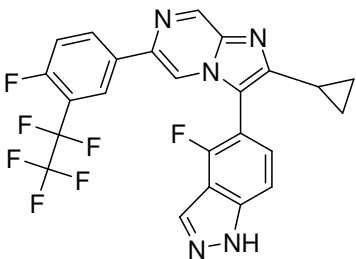
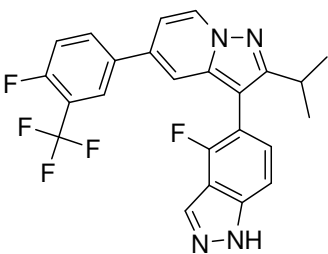
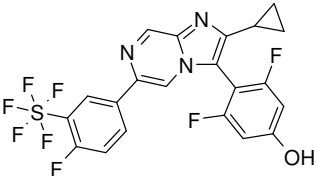
32	 4-fluoro-5-{2-cyclopropyl-6-[3-trifluoromethylphenyl]imidazo[1,2-a]pyrazin-3-yl}-1H-indazole	2	17	125 mg, 21%	UPLC rt 3.09 min, MH ⁺ 456
33	 3,5-difluoro-4-[2-(1-methylcycloprop-1-yl)-6-[4-fluoro-3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol	1B	16	3 mg, 10 %	UPLC rt 3.36 min, MH ⁺ 464
34	 4-(2-cyclopropyl-6-(4-fluoro-3-(trifluoromethyl)phenyl)imidazo[1,2-a]pyrazin-3-yl)-3,5-difluorophenol	1A	17	165 mg, 30 %	UPLC rt3.14 min, MH ⁺ 450
35	 4-(2-cyclobutyl-6-(4-fluoro-3-(trifluoromethyl)phenyl)imidazo[1,2-a]pyrazin-3-yl)-3,5-difluorophenol	1B	18	72 mg, 64 %	UPLC rt 3.37 min, MH ⁺ 464
36	 4-(2-cyclopropyl-6-(4-fluoro-3-(trifluoromethyl)phenyl)imidazo[1,2-a]pyrazin-3-yl)-3,5-difluorophenol	1B	19	20 mg, 17 %	UPLC rt 3.09 min, MH ⁺ 438

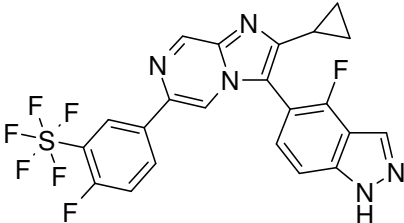
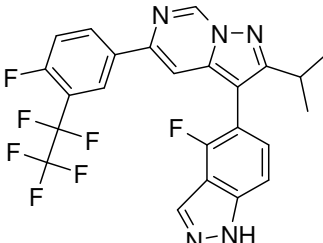
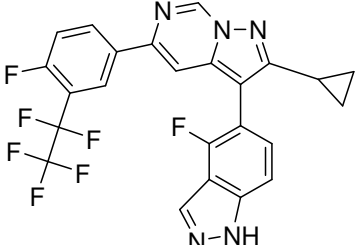
	3, 5-difluoro-4-[2-ethyl-6-[4-fluoro-3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol				
37	 4-fluoro-5-{2-ethyl-6-[3-(pentafluoroethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]-1H-indazole	2	19	12 mg, 65 %	UPLC rt 3.02 min, MH ⁺ 444
38	 3,5-difluoro-4-(6-(4-fluoro-3-(trifluoromethyl)phenyl)-2-(2,2,2-trifluoroethyl)imidazo[1,2-a]pyrazin-3-yl)phenol	1B	20	5 mg, 12 %	UPLC rt 2.54 min, MH ⁺ 492
39	 3, 5-difluoro-4-[2-(propan-2-yl)-6-[3-(pentafluorosulfanyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol	4	21	14 mg, 15 %	UPLC rt 3.36 min, MH ⁺ 492
40	 3,5-difluoro-4-{6-[4-fluoro-3-(trifluoromethyl)phenyl]-2-(propan-2-yl)imidazo[1,2-a]pyrazin-3-yl}phenoxyphosphonic acid	3	Ex 17	13 mg, 28 %	UPLC rt 2.27 min, MH ⁺ 532

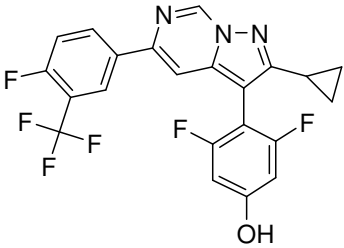
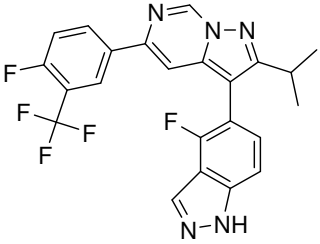
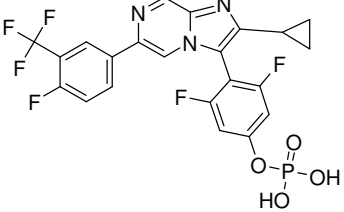
41	 3,5-difluoro-4-{6-[4-fluoro-3-(trifluoromethyl)phenyl]-2-methylimidazo[1,2-a]pyrazin-3-yl}phenoxyphosphonic acid	3	Ex 16	26 mg, 58 %	UPLC rt 2.19 min, MH ⁺ 504
42	 3,5-difluoro-4-(5-(4-fluoro-3-(trifluoromethyl)phenyl)-2-methylpyrazolo[1,5-c]pyrimidin-3-yl)phenol	1B	22	40 mg, 56%	UPLC rt 3.37 min, MH ⁺ 424
43	 2-cyclopropyl-3-(4-fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-(trifluoromethyl)phenyl)imidazo[1,2-a]pyrazine	2	17	5 mg,55 %	UPLC rt 2.73 min, MH ⁺ 456
44	 4-[2-Cyclopropyl-6-(4-fluoro-3-pentafluoroethyl-phenyl)-2-methylpyrazolo[1,5-c]pyrimidin-3-yl]phenol	2	23	7 mg, 14 %	UPLC rt 2.66 min, MH ⁺ 500

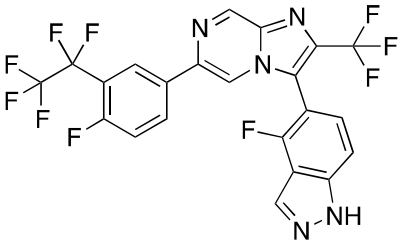
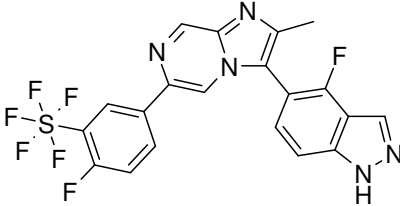
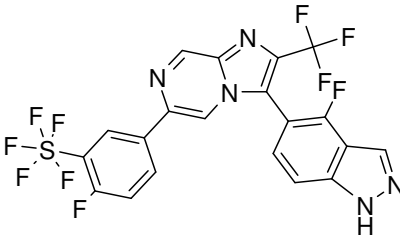
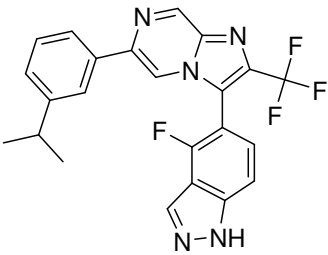
	imidazo[1,2-a]pyrazin-3-yl]-3,5-difluoro-phenol				
45	 4-{2-ethyl-6-[4-fluoro-3-(1,1,2,2,2-pentafluoroethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl}-3,5-difluorophenol	1B	24	6 mg, 9 %	UPLC rt 3.37 min, MH ⁺ 488
46	 2-cyclopropyl-3-(4-fluoro-1H-indazol-5-yl)-6-(3-(pentafluoro-λ6-sulfaneyl)phenyl)imidazo[1,2-a]pyrazine	4B	25	9 mg, 55%	UPLC rt 3.16 min, MH ⁺ 494
47	 3,5-difluoro-4-(5-(4-fluoro-3-(trifluoromethyl)phenyl)-2-(propan-2-yl)-pyrazolo[1,5-c]pyrimidin-3-yl)phenol	1B	26	10 mg, 17%	UPLC rt 3.57 min, [M-H] ⁻ 450
48	 4-(2-ethyl-5-(4-fluoro-3-(trifluoromethyl)phenyl)pyrazolo[1,5-c]pyrimidin-3-yl)-3,5-difluorophenol	1B	27	7 mg, 12%	UPLC rt 3.43 min, MH ⁺ 438

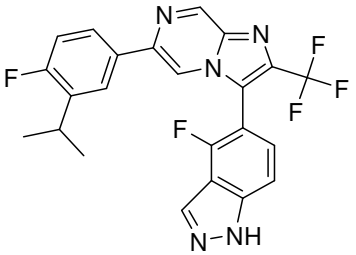
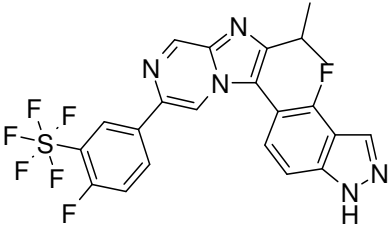
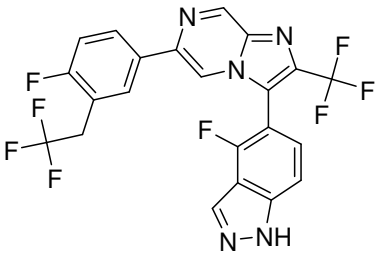
49	 3,5-difluoro-4-[2-methyl-6-[3-(pentafluoroethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol	1B	28	20 mg, 24%	UPLC rt 3.17 min, MH ⁺ 456
50	 3-(4-Fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-trifluoromethyl phenyl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine	2	29	81 mg, 27 %	UPLC rt 3.22 min, [M-H] ⁻ 482
51	 2-Isopropyl-3-(3-methyl-1H-indazol-5-yl)-6-(3-trifluoromethyl-phenyl)-imidazo[1,2-a]pyrazine	3A	1	33 mg, 39%	UPLC rt 2.02 min (3 min Run) MH ⁺ 436
52	 4-[2-Ethyl-6-(3-pentafluoroethyl-phenyl)-imidazo[1,2-a]pyrazin-3-yl]-3,5-difluoro-phenol	1A	30	75 mg, 67%	HPLC rt 11.49 min, MH ⁻ 468

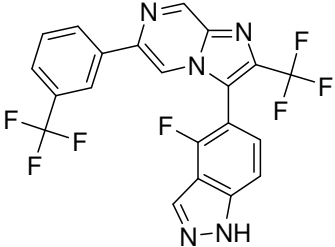
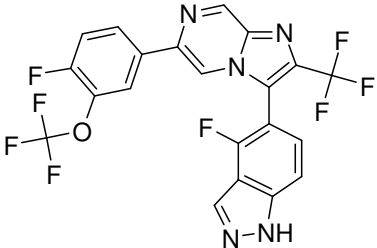
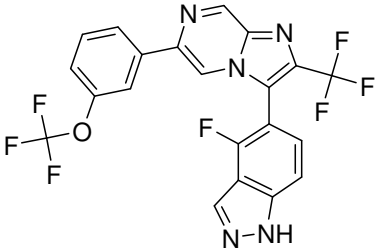
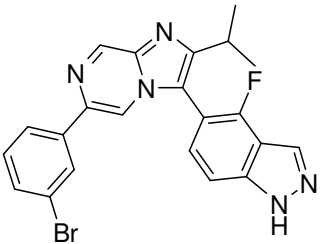
53	 3,5-Difluoro-4-[6-(4-fluoro-3-pentafluoroethyl-phenyl)-2-methyl-imidazo[1,2-a]pyrazin-3-yl]-phenol	2	31	7 mg, 10.6%	UPLC 3.16 rt min, MH ⁺ 474
54	 2-Cyclopropyl-3-(4-fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-pentafluoroethyl-phenyl)-imidazo[1,2-a]pyrazine	3A	23	5 mg,6%	UPLC rt 3.23 min, MH ⁺ 506
55	 4-Fluoro-5-[5-(4-fluoro-3-trifluoromethyl-phenyl)-2-isopropylpyrazolo[1,5-a]pyridin-3-yl]-1H-indazole	3C	32	15 mg, 17.75%	UPLC rt 3.32 min, MH ⁺ 455
56		2	33	3 mg, 2.81%	UPLC rt 1.82 min (3 min Run), MH ⁺ 508

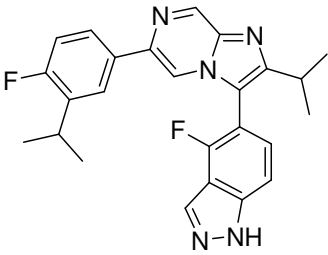
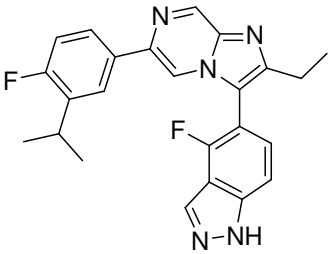
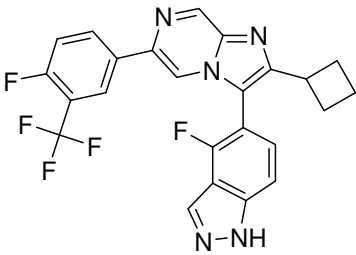
	4-[2-Cyclopropyl-6-(4-fluoro-3-pentafluorosulfanyl-phenyl)-imidazo[1,2-a]pyrazin-3-yl]-3,5-difluoro-phenol				
57	 2-Cyclopropyl-3-(4-fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-pentafluorosulfanyl-phenyl)-imidazo[1,2-a]pyrazine	3A	33	11 mg, 16.54%	UPLC rt 3.27 min, MH ⁺ 514
58	 3-(4-Fluoro-1H-indazol-5-yl)-5-(4-fluoro-3-pentafluoroethyl-phenyl)-2-isopropyl-pyrazolo[1,5-c]pyrimidine	3B	34	22 mg, 65.05%	UPLC rt 1.92 min (3 min Run), MH ⁺ 508
59	 2-Cyclopropyl-3-(4-fluoro-1H-indazol-5-yl)-5-(4-fluoro-3-pentafluoroethyl-phenyl)-pyrazolo[1,5-c]pyrimidine	3B	35	17 mg, 23.07%	UPLC rt 1.92 min (3 min Run), MH ⁺ 504

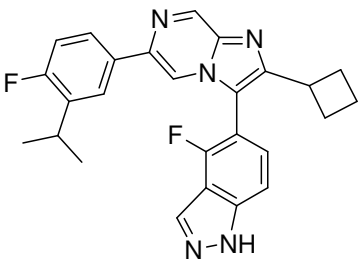
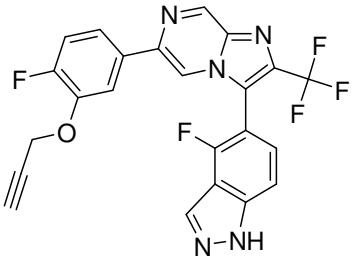
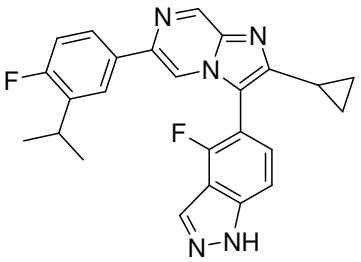
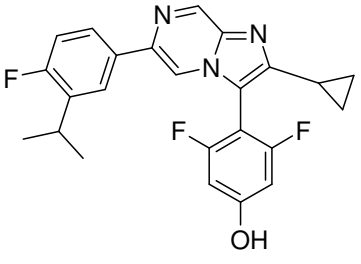
60	 4-[2-Cyclopropyl-5-(4-fluoro-3-trifluoromethyl-phenyl)-pyrazolo[1,5-c]pyrimidin-3-yl]-3,5-difluorophenol	1B	35	34 mg, 43.24%	UPLC rt 3.57 min, MH ⁺ 448
61	 3-(4-Fluoro-1H-indazol-5-yl)-5-(4-fluoro-3-trifluoromethyl-phenyl)-2-isopropyl-pyrazolo[1,5-c]pyrimidine	3B	36	33 mg, 39.03%	UPLC rt 3.58 min, MH ⁺ 456
62	 Phosphoric acid mono-{4-[2-cyclopropyl-6-(4-fluoro-3-trifluoromethyl-phenyl)-imidazo[1,2-a]pyrazin-3-yl]-3,5-difluorophenyl} ester	4	Example 34	32 mg, 18-22%	UPLC rt 2.08 min, MH ⁺ 530

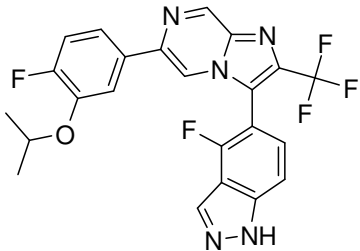
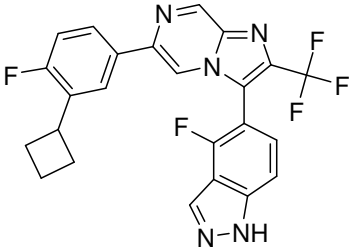
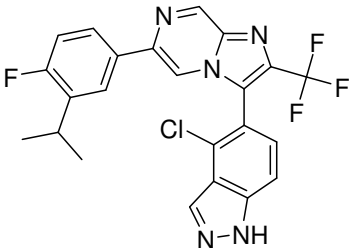
63	 3-(4-Fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-pentafluoroethyl-phenyl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine	3A	37	150 mg, 35-40%	UPLC rt 1.97 min (3 min Run), MH ⁺ 534
64	 3-(4-Fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-pentafluorosulfanyl-phenyl)-2-methyl-imidazo[1,2-a]pyrazine	3D	38	12 mg, 10.81%	UPLC rt 3.03 min, MH ⁺ 486
65	 3-(4-Fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-pentafluorosulfanyl-phenyl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine	3A	39	10 mg, 6.79%	UPLC rt 3.26 min, MH ⁺ 540
66		3A	40	46 mg, 45.63%	UPLC rt 2.59 min, MH ⁺ 440

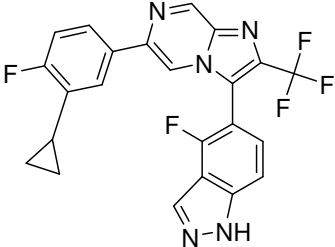
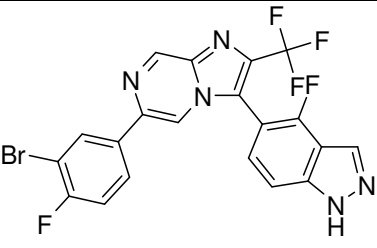
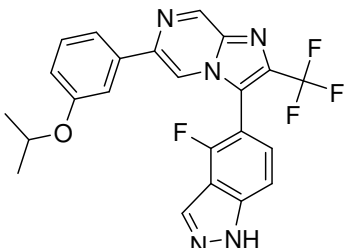
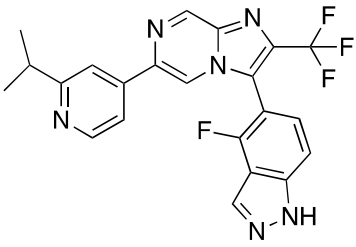
	3-(4-Fluoro-1H-indazol-5-yl)-6-(3-isopropyl-phenyl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine				
67	 3-(4-Fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-isopropyl-phenyl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine	3A	41	50 mg, 25-30%	UPLC rt 2.10 min (3 min Run), MH ⁺ 458
68	 3-(4-Fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-pentafluorothio-phenyl)-2-isopropyl-imidazo[1,2-a]pyrazine	3D	42	35 mg, 21.54%	UPLC rt 2.66 min, MH ⁺ 516
69	 3-(4-Fluoro-1H-indazol-5-yl)-6-[4-fluoro-3-(2,2,2-trifluoro-ethyl)-phenyl]-2-trifluoromethyl-imidazo[1,2-a]pyrazine	3A	43	3 mg, 2.34%	UPLC rt 1.75 min (3 min Run), MH ⁺ 498

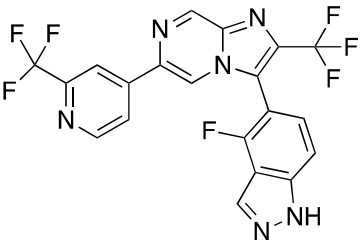
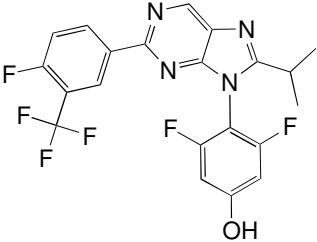
70	 3-(4-Fluoro-1H-indazol-5-yl)-2-trifluoromethyl-6-(3-trifluoromethyl-phenyl)-imidazo[1,2-a]pyrazine	3A	44	35 mg, 47.48%	UPLC rt 1.76 min (3 min Run), MH ⁺ 466
71	 3-(4-Fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-trifluoromethoxy-phenyl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine	3A	45	35 mg, 25.54%	UPLC rt 1.79 min (3 min Run), MH ⁺ 500
72	 3-(4-Fluoro-1H-indazol-5-yl)-6-(3-trifluoromethoxy-phenyl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine	3A	46	80 mg, 37.56%	UPLC rt 1.78 min (3 min Run), MH ⁺ 482
73		3D	47	10 mg, 14.82%	UPLC rt 1.82 min (3 min Run), MH ⁺ 450

	6-(3-Bromo-phenyl)-3-(4-fluoro-1H-indazol-5-yl)-2-isopropyl-imidazo[1,2-a]pyrazine				
74	 3-(4-Fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-isopropyl-phenyl)-2-isopropyl-imidazo[1,2-a]pyrazine	3A	48	25 mg, 14.92%	UPLC rt 2.73 min, MH ⁺ 432
75	 2-Ethyl-3-(4-fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-isopropyl-phenyl)-imidazo[1,2-a]pyrazine	3A	49	50 mg, 13.79%	HPLC rt 13.19 min, MH ⁺ 418
76	 2-Cyclobutyl-3-(4-fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-trifluoromethyl-phenyl)-imidazo[1,2-a]pyrazine	3A	50	50 mg, 34.65%	UPLC rt 1.93 min (3 min Run), MH ⁺ 470

77	 2-Cyclobutyl-3-(4-fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-isopropyl-phenyl)-imidazo[1,2-a]pyrazine	3A	51	23 mg, 27.33%	HPLC rt 8.68 min, MH ⁺ 444
78	 3-(4-Fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-prop-2-ynyloxy-phenyl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine	3A	52	10 mg, 5.89%	UPLC rt 1.81 min (3 min Run), MH ⁺ 470
79	 2-Cyclopropyl-3-(4-fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-isopropyl-phenyl)-imidazo[1,2-a]pyrazine	3A	53	25 mg, 19.91%	UPLC rt 1.94 min (3 min Run), MH ⁺ 430
80	 2-Cyclopropyl-3-(4-fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-isopropyl-phenyl)-imidazo[1,2-a]pyrazine	1A	53	3 mg, 4.32%	UPLC rt 2.78 min, MH ⁺ 424

	4-[2-Cyclopropyl-6-(4-fluoro-3-isopropyl-phenyl)-imidazo[1,2-a]pyrazin-3-yl]-3,5-difluoro-phenol				
81	 3-(4-Fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-isopropoxy-phenyl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine	3A	54	80 mg, 40.96%	UPLC rt 2.75 min, MH ⁺ 474
82	 6-(3-Cyclobutyl-4-fluoro-phenyl)-3-(4-fluoro-1H-indazol-5-yl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine	3A	55	25 mg, 18.42%	UPLC rt 1.99 min (3 min Run), MH ⁺ 470
83	 3-(4-Chloro-1H-indazol-5-yl)-6-(4-fluoro-3-isopropyl-phenyl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine	3A	56	13 mg, 35.17%	UPLC rt 1.97 min (3 min Run), MH ⁺ 474

84	 6-(3-Cyclopropyl-4-fluoro-phenyl)-3-(4-fluoro-1H-indazol-5-yl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine	3A	57	25 mg, 24.68%	UPLC rt 1.90 min (3 min Run), MH ⁺ 456
85	 6-(3-Bromo-4-fluoro-phenyl)-3-(4-fluoro-1H-indazol-5-yl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine	3D	58	10 mg, 9.75%	UPLC rt 1.91 min (3 min Run), MH ⁺ 494
86	 3-(4-Fluoro-1H-indazol-5-yl)-6-(3-isopropoxy-phenyl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine	3A	59	50 mg, 35.9%	UPLC rt 2.73 min, MH ⁺ 456
87	 3-(4-Fluoro-1H-indazol-5-yl)-6-(3-isopropylpyridin-2-yl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine	3A	60	10 mg, 12%	UPLC rt 2.86 min, MH ⁺ 441

	3-(4-Fluoro-1H-indazol-5-yl)-6-(2-isopropyl-pyridin-4-yl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine				
88	 3-(4-Fluoro-1H-indazol-5-yl)-2-trifluoromethyl-6-(2-trifluoromethyl-pyridin-4-yl)-imidazo[1,2-a]pyrazine	3A	61	60 mg, 34.52%	UPLC rt 1.70 min (3 min Run), MH ⁺ 465
89	 3,5-Difluoro-4-[2-(4-fluoro-3-trifluoromethyl-phenyl)-8-isopropyl-purin-9-yl]-phenol	5	62	30 mg, 52.82%	UPLC rt 2.63 min, MH ⁺ 453

In vitro testing

The routine biological assays using adult or juvenile worms and cytotoxicity assays using MRC-5 cells have been disclosed previously in Mansour, N. R., et al. (2016). "High

- 5 *Throughput Screening Identifies Novel Lead Compounds with Activity against Larval, Juvenile and Schistosoma mansoni* PLoS Negl Trop Dis 10(4): e0004659. Cytotoxicity assays using the HepG2 cell line were carried out as described in Molecular Diversity (2015) 19, 251-261.
- (a) *S. mansoni* adult worms
- (b) *S. mansoni* juvenile worms
- 10 (c) *S. haematobium* adult worms
- (d) Cytotoxicity against human MRC-5 cell line
- (e) Cytotoxicity against human HepG2 cell lines

The compounds of Examples 1-90 exhibit one or more of the following compared to the compound disclosed in PLoS Negl Trop Dis **10**(4): e0004659

Example Number	(a) Adult (μM)	(b) Juvenile (μM)	(c) <i>S.haemotobium</i> (μM)	(d) Cytotox MRC-5 (μM)	(e) Cytotox HepG2 (μM)
LSHTM-1945	4.9	5.7		40.1	
1	0.058	0.013	< 0.195	21.8	>11.1
2	0.047	0.019			10.4
3	< 0.049	0.13			9.2
4	0.49	1.42			
5	0.52	1.27			
6	0.29	0.48		15.8	
7	0.09	0.082		>50	>30
8	0.100	0.086	<1.56	17.3	18.7
9	0.076	0.079		13.7	9
10	< 0.78	0.53		14.4	>11.1
11		0.49			
12	< 0.049	0.25			
13	0.072	0.063			
14		0.23			
15		0.17			8.4
16	0.12	0.22	0.04		7.6
17	0.044	0.026	0.023		7.1
18		0.29			
19	0.042	0.090			7.5
20	0.92	1.04			
21	0.037	0.051			15.1
22	0.43	0.53	0.15		
23		0.79			
24	0.022	< 0.012			8.4
25		0.11			
26		0.22			
27	< 0.049	0.149			
28		0.183			19.2
29	0.030	0.028			8.9

30	0.021	< 0.012			11.1
31		0.10			
32	0.063				16.1
33	0.056	0.080			7.9
34	0.069	0.088			8.9
35	0.059	0.073			5.7
36	0.053	0.051			8.3
37		0.11			13.1
38		0.14			
39	0.024	< 0.012			6.6
40	0.027	0.025			6.5
41		0.10			6.8
42		0.11			
43		0.11			
44	0.010	0.024			9.4
45		0.021			
46		0.036			20.7
47	0.022	0.027			8.9
48	0.011	0.032			9.8
49	0.034	0.035			9.3
50		0.060			
51		0.83			10.3
52	<0.012	0.010			8.0
53	0.019	0.020			8.8
54	0.023	0.037			
55	0.028	0.022			11.1
56	0.019	0.020			10.1
57	0.017	0.030			14.8
58	0.031	0.02			10.8
59	0.066	0.036			
60	0.017	0.021			
61	0.037	0.060			
62		0.0037			14.8
63	0.011	0.010	<0.006		11.7

64	0.026	0.077			
65	0.044	0.011			11.1
66	0.0052	0.0052			12.9
67	0.002	0.002			17.0
68	0.011	0.010			
69	0.012	0.010			5.3
70	0.025	0.041			
71	0.014	0.021			12.2
72	0.021	0.023			9.7
73	0.036	0.027			
74	0.004	0.005			11.0
75	0.004	0.005			11.3
76	0.037	0.036			
77	0.007	0.004			10.8
78	0.010	0.021			
79	0.005	0.005			15.7
80	0.004	0.005			
81	0.011	0.012			9.2
82	0.045	0.059			6.1
83	<0.012	0.015			6.6
84	0.012	0.019			10.5
85	0.048	0.007			
86	0.017	0.026			13.2
87	0.037	0.091			9.5
88	0.116	0.140			7.0
89	0.071	0.128			4.8
90	0.077	0.468			9.3

Preferred compounds of the invention are those which by inspection, appear to kill or significantly damage the worms at lower concentrations within the IC₅₀ range shown above. For example, preferred are compounds with IC₅₀ values against both adult and juvenile worms below 0.5µM; More preferred compounds are those with IC₅₀ values against both adult and juvenile worms below 0.1µM;

In vivo testing

Infection of mice and worm recovery

Methods for the subcutaneous infection of mice and subsequent worm recovery were as described in Mansour et al (2016) except that infection was with 150 cercariae and the perfusion medium was citrate saline (0.9% sodium chloride, 1.5% tri-sodium citrate). Perfusion was carried out 8 days (adult infections) or 15 days (juvenile infections) after treatment. Perfuseate was collected into 30mL universal tubes. RBC (Red Blood Cells) were removed by allowing the perfuseate to settle for 10 min, removal of most of the supernatant and washing once as above with 10mL perfusion medium. A drop of dilute aqueous saponin solution was added to lyse any remaining RBC and the worm suspension poured into a grid-marked small petri dish. The tube was rinsed out into the petri dish and examined for any remaining worms. Worms were counted using a dissecting microscope. The mouse livers removed after perfusion were squashed between two thick glass plates and examined visually and any remaining worms added to those counted as above.

Drug treatment

For testing efficacy against the juvenile worms, treatment was on day 25 post infection and for testing against the adult worms on day 42 post infection. Drugs were suspended in 7% Tween-80 / 3% Ethanol / double distilled water and drug dispersal was facilitated by vortexing and using a sonicating water bath (Formulation F1). Alternatively, drugs were suspended in 10% DMSO, 90% double distilled water containing 50mM Na₂HPO₄ with 0.5% Tween-80 by first dissolving or suspending the drug in DMSO then adding the DMSO solution/suspension to the aqueous solution (Formulation F2). In a further set of conditions, drugs were first dissolved in DMSO, then diluted with corn oil to give a 5% DMSO+drug solution/suspension (Formulation F3)

25

The drug solution/suspensions were given by oral gavage at the rate of 10ml/kg. Positive controls (artemether for juvenile worms and praziquantel for adult worms) were used in each experiment. Oral artemether at 400mg/kg single dose is equally or more effective in mice against juvenile compared with adult *S. mansoni* (Am J Trop Med Hyg. 2010 Jan;82(1):112-4. *Activity of artemether and mefloquine against juvenile and adult Schistosoma mansoni in athymic and immunocompetent NMRI mice*. Keiser J1, Vargas M, Doenhoff MJ) and so is a useful positive control for drug testing against juvenile stages in the murine screen.

30

Results for in vivo mouse model infected with adult and juvenile worms

Age of infection (worms)	Compound Example No (Formulation)	Oral Dose	Mean worm recovery	Percent worm reduction	P value
Adult	Negative control	N/A	38.8±5.4	N/A	N/A
	Positive control Praziquantel (F1)	400mg/kg	2.3±1.7	94	<0.0001
	17 (F1)	200mg/kg	0.3±0.8	99	<0.0001
Adult	Negative control	N/A	33.8±4.1	N/A	
	Positive control Praziquantel (F1)	50mg/kg	29.8±8.4	13	0.3
	Positive control Praziquantel (F1)	100mg/kg	12.2±6.3	64	0.0002
	Positive control Praziquantel (F1)	400mg/kg	2.6±1.5	92	<0.0001
	50 (F1)	12.5mg/kg	0.2	99	<0.0001
	50 (F1)	6.25mg/kg	7.4±8.1	78	0.0002
Juvenile	Negative control		33.0±7.2	-	
	Positive control, Artemether (F1)	400mg/kg	8.2±4.1	75	0.0002
	17 (F1)	200mg/kg	5.2±3.1	84	<0.0001
	17 (F1)	50mg/kg	20.6±8.5	38	0.038
	34 (F1)	50mg/kg	24.8±7.4	25	0.11
	2 (F1)	50mg/kg	4.0±4.1	88	<0.0001
	32 (F1)	50mg/kg	29.0±7.9	12	0.43
Juvenile	Negative control	N/A	33.2±9.09	N/A	N/A
	Positive control, Artemether (F1)	400mg/kg	8.6±4.16	74	0.0006
	PZQ (F1)	50mg/kg	26.2±9.44	21	0.2667
	29 (F2)	25mg/kg	4±1.41	88	0.0001
	29 (F2)	5mg/kg	14.8±6.61	55	0.0064
	2 (F1)	25mg/kg	7.2±3.9	78	0.0004
	2 (F2)	25mg/kg	4.4±3.91	87	0.0002
	45 (F1)	25mg/kg	31.8±5.76	4	0.7786
	50 (F1)	25mg/kg	0.8±0.84	98	<0.0001
Juvenile	Negative control		32.6±10.6	N/A	
	50 (F3)	6.25mg/kg	17.6±12.0	46	0.689
	29 (F3)	6.25mg/kg	2.0±2.6	94	0.0002
	63 (F3)	6.25mg/kg	0.6±1.0	98	0.0001
Juvenile	Negative control		32.8±14		
	67 (F3)	50mg/kg	0	100	0.0008

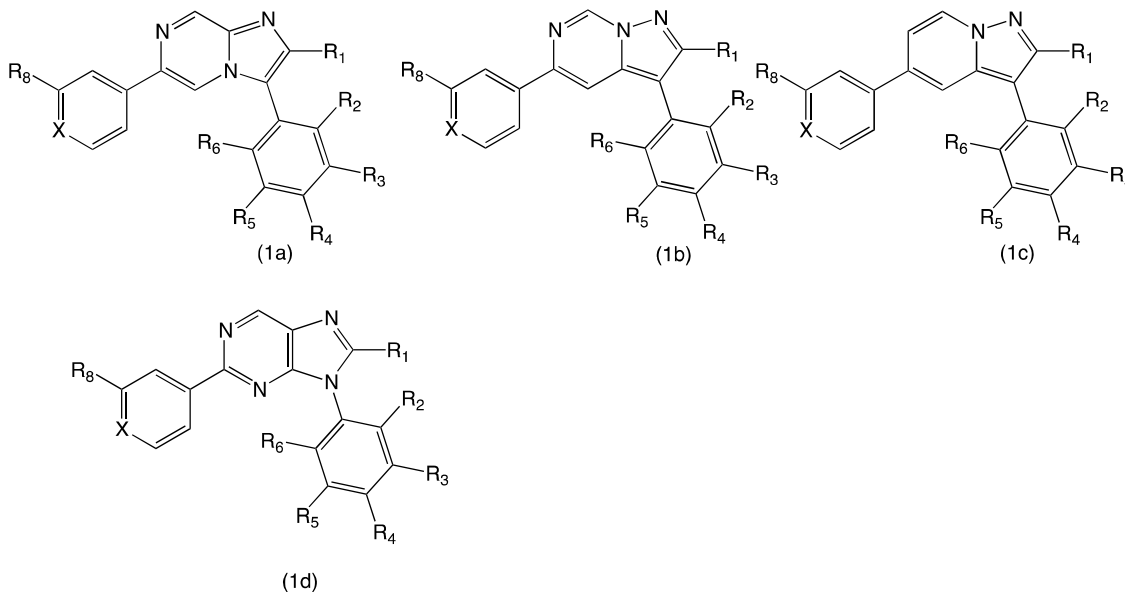
Preferred compounds are those which by inspection show a statistically significant (P value < 0.05) reduction in worm numbers of at least 50% when administered orally in the

mouse model of infection as described above. For example, compounds 2, 17, 29, 50, 63 and 67.

5 More preferred compounds are those which show a statistically significant (P value < 0.05) reduction in worm numbers of at least 50% when administered orally in the mouse model of infection as described above in a single dose of 25mg/kg or less. For example, compounds 2, 29, 50 and 63.

Claims

1. A compound of formula (1a), (1b), (1c) or (1d) or a pharmaceutically acceptable salt or solvate thereof,



5

wherein:

R₁ is C₁-C₄ alkyl optionally substituted with up to five F atoms, C₃-C₆ cycloalkyl optionally substituted with one methyl group, or C₄-C₇ cycloalkylmethyl;

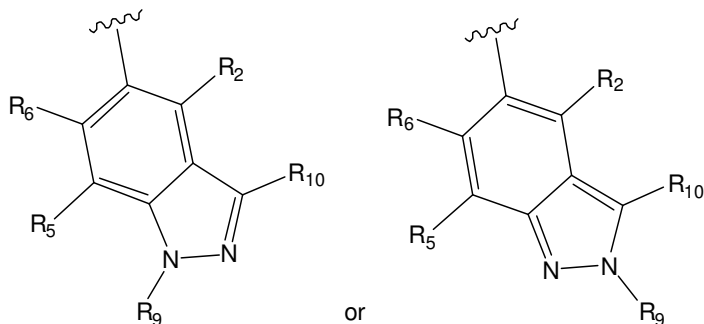
R₂ is H, F, Cl or OMe;

10 **R₃** is H, OH, OMe, OPO(OH)OH or OCH₂OPO(OH)OH;

R₄ is H, OH, OMe, OPO(OH)OH or OCH₂OPO(OH)OH;

provided that **R₃** and **R₄** cannot both be H;

or **R₃** and **R₄** combine, together with the phenyl ring to which they are attached, to form an indazole group as shown below



15

R₅ is H, F, Cl or OMe;

R₆ is H, F, Cl or OMe;

X is N or C-**R₇**, wherein **R₇** is H or F;

R₈ is SF₅, Br, C₁-C₃ alkyl optionally substituted with up to seven F atoms, C₃-C₄ cycloalkyl, OCH₂C≡CH or OC₁-C₃ alkyl optionally substituted with up to seven F atoms;

R₉ is H; and

R₁₀ is H, F or Me.

5

2. A compound according to claim 1, wherein **R₁** is methyl, ethyl, n-propyl, isopropyl, cyclopropyl optionally substituted with one methyl group, cyclobutyl, cyclopropylmethyl, CHF₂, CF₃ or CH₂CF₃, preferably **R₁** is ethyl, isopropyl, cyclopropyl, cyclobutyl, CF₃ or CH₂CF₃.

10

3. A compound according to any preceding claim, wherein **R₂** is H, F or Cl, preferably **R₂** is F or Cl.

4. A compound according to any preceding claim, wherein **R₃** is H, OH, OMe or

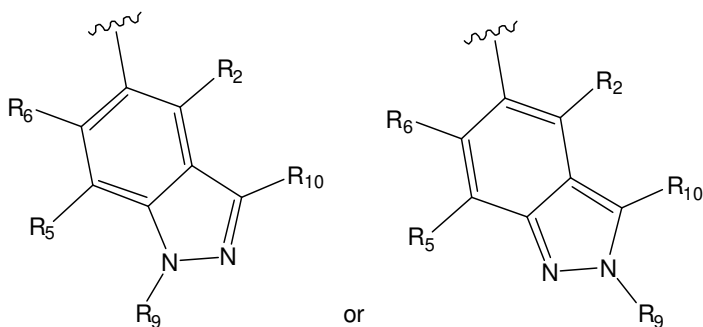
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OPO(OH)OH, preferably **R₃** is H.

5. A compound according to any preceding claim, wherein **R₄** is H, OH, OMe or OPO(OH)OH, preferably **R₄** is OH.

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6. A compound according to any one of claims 1 to 3, wherein substituents **R₃** and **R₄** combine, together with the phenyl ring to which they are attached, to form an indazole group as shown below



wherein **R₉** and **R₁₀** are both H.

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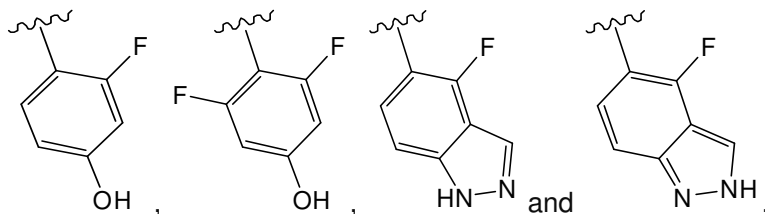
7. A compound according to any preceding claim, wherein **R₅** is H or OMe, preferably **R₅** is H.

8. A compound according to any preceding claim, wherein **R₆** is H or F.

9. A compound according to any preceding claim, wherein **X** is C-**R**₇ wherein **R**₇ is H or F.

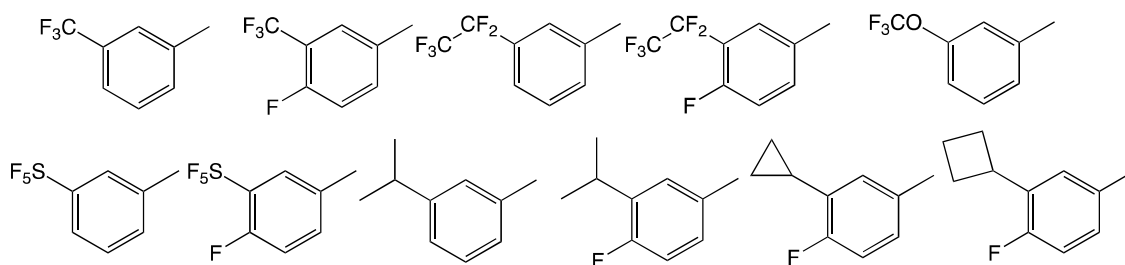
10. A compound according to any preceding claim, wherein **R**₈ is CF₃, CF₂CF₃, CH₂CF₃,
5 CH(CH₃)₂, OCF₃, OCH(CH₃)₂, cyclopropyl, cyclobutyl or SF₅.

11. A compound according to any preceding claim, wherein substituents **R**₂ to **R**₆ are chosen so as to provide the sub-structures:

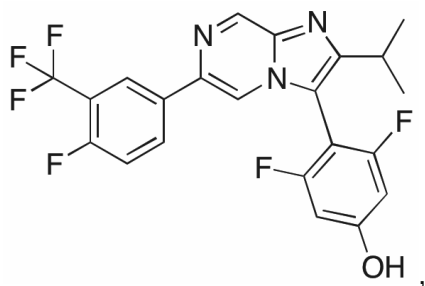


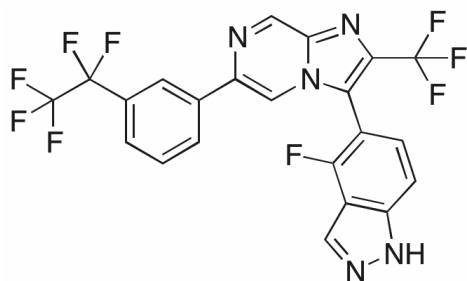
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12. A compound according to any preceding claim, wherein substituents **R**₇ and **R**₈ are chosen so as to provide the sub-structures:

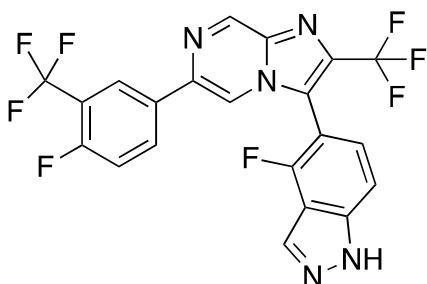


15 13. A compound according to claim 1, wherein the compound is:

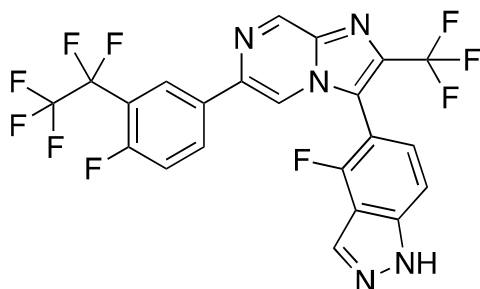




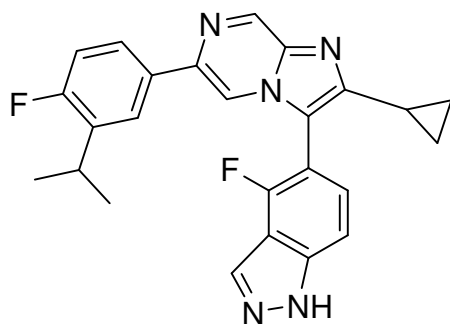
,



,



, or



.

- 5 **14.** A compound of formula (1a), (1b), (1c) or (1d) as defined in any one of claims 1 to 13, or a pharmaceutically acceptable salt or solvate thereof, for use in therapy, preferably for use in the treatment of schistosomiasis.

- 10 **15.** A pharmaceutical composition comprising (i) a therapeutically effective amount of a compound of formula (1a), (1b), (1c) or (1d) as defined in any one of claims 1 to 13, or a pharmaceutically acceptable salt or solvate thereof; and (ii) a pharmaceutically acceptable excipient.

16. Use of a compound of formula 1a), (1b), (1c) or (1d) as defined in any one of claims 1 to 13, or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment of schistosomiasis.

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