COMPOUNDS FOR USE IN THE TREATMENT OF FASCIOLIASIS

Field of Invention

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

Background to the Invention

Fasciola hepatica, also known as the common liver fluke or sheep liver fluke, is a parasitic trematode of the class Trematoda, phylum Platyhelminthes. *Fasciola gigantica* is another trematode so closely related to *F. hepatica* in terms of genetics, behaviour, and morphological and anatomical structures that it is notoriously difficult to distinguish them, Rokni MB, Mirhendi H, Mizani A, Mohebali M, Sharbatkhori M, Kia EB, Abdoli H, Izadi S (2010). "*Identification and differentiation of Fasciola hepatica and Fasciola gigantica using a simple PCR-restriction enzyme method*". Experimental *Parasitology*.**124**(2) 209–213. These fluke species infect the livers of various mammals, including humans. The disease caused by the fluke is called fascioliasis or fasciolosis. Fascioliasis is one of the most important diseases of ruminant livestock animals and impacts millions of people, inducing chronic liver pathologies Mas-Coma S, Valero MA, Bargues MD (2014) Fascioliasis. Adv Ecp Med Bio 766: 77–114. Fascioliasis is often acquired through eating the parasite's metacercariae encysted on plants.

Triclabendazole (TCBZ) is the only medicine recommended by WHO against fascioliasis in humans. Cure rates are high, while adverse reactions following treatment are usually temporary and mild. The recommended regimen is 10 mg/kg body weight administered as a single dose in both clinical practice and preventive chemotherapy interventions. In clinical practice, where treatment failure occurs, the dosage may be increased to 20 mg/kg body weight in two divided doses 12-24 hours apart.

Triclabendazole is also used in control of fascioliasis of livestock in many countries. Nevertheless, long-term veterinary use of triclabendazole has caused appearance of resistance in *F. hepatica*. In animals, triclabendazole resistance has been described in Australia (Overend DJ, Bowen FL (1995). "*Resistance of Fasciola hepatica to triclabendazole*". Aust. Vet. J.**72**(7): 275–6), Ireland (O'Brien, D.J., (1998). "*Fasciolosis: a threat to livestock*". Irish Vet. J. **51**, 539–541), Scotland (Mitchell GB, Maris L, Bonniwell MA

(1998). "*Triclabendazole-resistant liver fluke in Scottish sheep*".Vet. Rec.**143** (14): 399) and the Netherlands (Moll L, Gaasenbeek CP, Vellema P, Borgsteede FH (2000). "*Resistance of Fasciola hepatica against triclabendazole in cattle and sheep in The Netherlands*". Vet. Parasitol. 91 (1–2): 153–8). A more recent paper has suggested that in addition to TCBZ resistance on at least 30 properties worldwide, it has been demonstrated in people in The Netherlands, Chile, Turkey and Peru, Jane M. Kelley, Timothy P. Elliott, Travis Beddoe, Glenn Anderson, Philip Skuce, Terry W. Spithill (2016) "*Current Threat of Triclabendazole Resistance in Fasciola hepatica*", Trends in Parasitology, **32 (6)**, 458-469. Another feature of the use of triclabendazole in the management of liver fluke in cattle is the extended withdrawal period of 56 days. Tribex (5% oral suspension of triclabendazole for sheep) "Summary of Product Characteristics", 2013. It has therefore been suggested that additional treatment options are required, Geary TG (2012) "*Are new anthelmintics needed to eliminate human helminthiases?"* Curr Opin Infect Dis **25**: 709–717.

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. haemotobium* 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. Arthemether 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-schistomes 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 and Pasche, V., et al. (2018). "*Screening a repurposing library, the Medicines for Malaria Venture Stasis Box, against Schistosoma mansoni*." Parasit Vectors 11(1): 298.

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; Heimburg, 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.

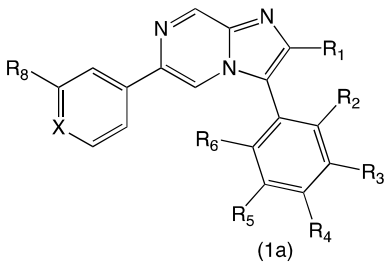
WO2014078813A1 discloses the preparation of imidazopyrazines for treating parasitic diseases, predominantly malaria, leishmaniasis and trypanosomiasis. WO2012080232A1 discloses the preparation of substituted imidazopyrazines as Mps-1 and TKK inhibitors useful in the treatment of hyperproliferative disorders. 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*

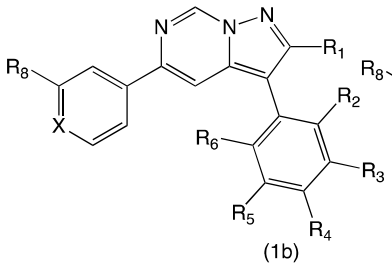
derivatives by using either reflux or microwave irradiation method, and investigation their anticancer activities." Turk. J. Chem. **35**(1): 13-24. WO2016133935 discloses a series of pyrazolo[1,5-c]pyrimidines as kinase inhibitors for the treatment of a variety of cancers. WO2018130853A1 discloses compounds of formula (1a), (1b), (1c) and (1d) and pharmaceutically acceptable salts or solvates thereof which have activity as inhibitors of *Schistosoma* growth.

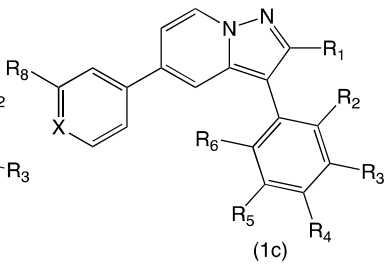
There remains a need in the art for further compounds active as anti-flukicides and as anti-schistosomes with good pharmacokinetic properties, combined (in the case of anti-schistosomes) with sufficient activity against all three main infective species of worm and against both juvenile and adult worms.

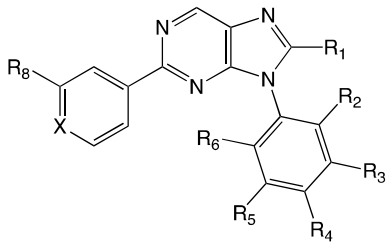
Summary of the Invention

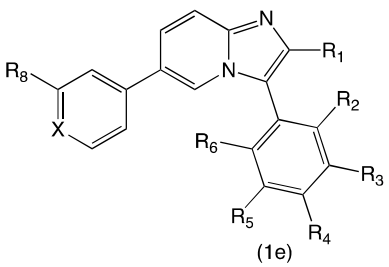
In one embodiment, the invention provides a compound of formula (1a), (1b), (1c), (1d) or (1e) or a pharmaceutically acceptable salt or solvate thereof,


(1a)


(1b)


(1c)


(1d)


(1e)

wherein:

R_1 is C_1-C_4 alkyl optionally substituted with up to five F atoms, C_3-C_6 cycloalkyl optionally substituted with one methyl group, or C_4-C_7 cycloalkylmethyl;

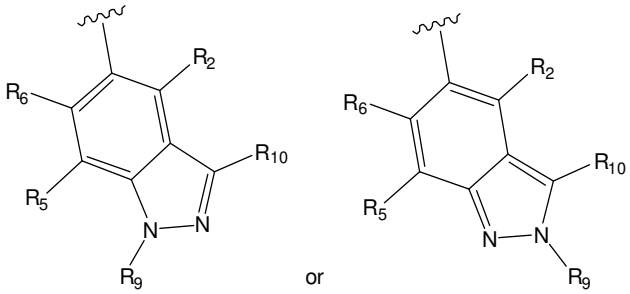
R_2 is H, F, Cl or OMe;

R_3 is H, OH, OMe, OPO(OH)OH or $OCH_2OPO(OH)OH$;

R_4 is H, OH, OMe, OPO(OH)OH or $OCH_2OPO(OH)OH$;

provided that **R_3** and **R_4** cannot both be H;

or **R_3** and **R_4** combine, together with the phenyl ring to which they are attached, to form an indazole group as shown below



R_5 is H, F, Cl or OMe;

R_6 is H, F, Cl or OMe;

X is N or C-R_7

R_7 (where present) is H or F;

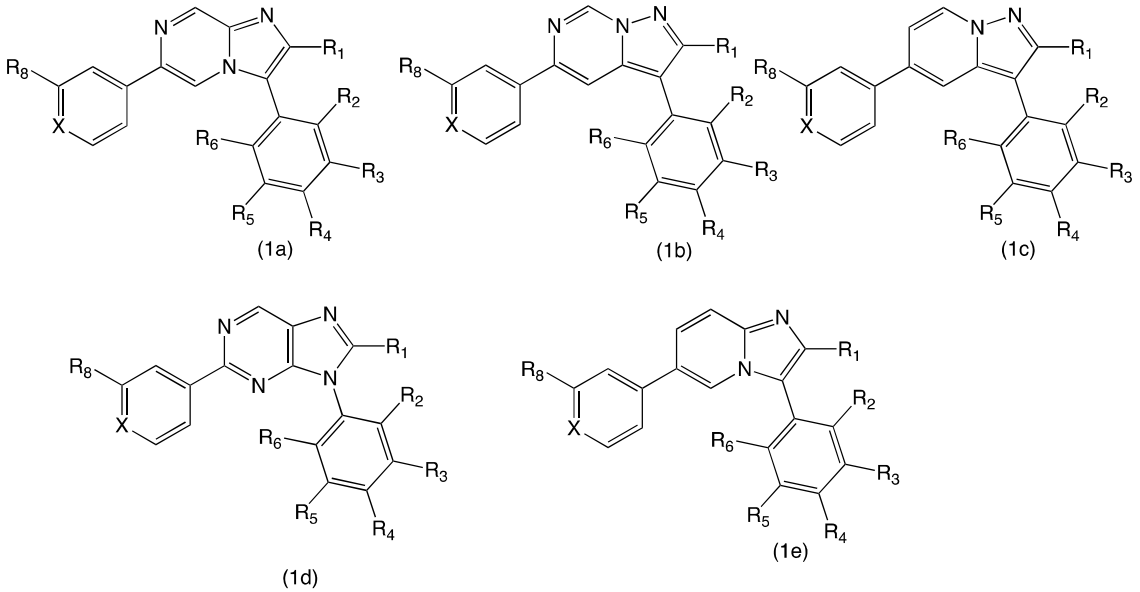
R_8 is SF_5, Br, C_1-C_3 alkyl optionally substituted with up to seven F atoms, C_3-C_4 cycloalkyl, $OCH_2C{\equiv}CH$ or OC_1-C_3 alkyl optionally substituted with up to seven F atoms;

R_9 is H; and

R_{10} is H, F or Me

for use in the treatment or prevention of fascioliasis.

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



wherein:

R_1 is C_1-C_4 alkyl optionally substituted with up to five F atoms, C_3-C_6 cycloalkyl optionally substituted with one methyl group, or C_4-C_7 cycloalkylmethyl;

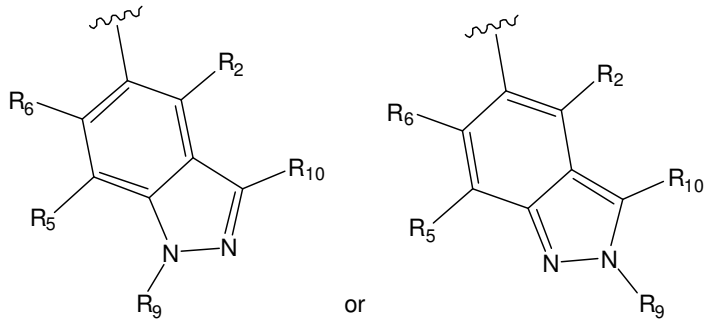
R_2 is H, F, Cl or OMe;

R_3 is H, OH, OMe, OPO(OH)OH or $OCH_2OPO(OH)OH$;

R_4 is H, OH, OMe, OPO(OH)OH or $OCH_2OPO(OH)OH$;

provided that **R_3** and **R_4** cannot both be H;

or **R_3** and **R_4** combine, together with the phenyl ring to which they are attached, to form an indazole group as shown below



R_5 is H, F, Cl or OMe;

R_6 is H, F, Cl or OMe;

X is N or C-**R_7**, wherein **R_7** is H or F;

R_8 is SF_5, Br, C_1-C_3 alkyl optionally substituted with up to seven F atoms, C_3-C_4 cycloalkyl, $OCH_2C{\equiv}CH$ or OC_1-C_3 alkyl optionally substituted with up to seven F atoms;

R_9 is H; and

R_{10} is H, F or Me

for the manufacture of a medicament for the treatment or prevention of fascioliasis.

In one embodiment, the invention provides the use of a compound of formula (1a), (1b), (1c), (1d) or (1e) as defined above, or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment or prevention of fascioliasis.

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

The compounds of formula (1e) and pharmaceutically acceptable salts or solvates thereof are novel. Accordingly, disclosed herein is a compound of formula (1e)**,** or a pharmaceutically acceptable salt or solvate thereof, wherein **R_1**, **R_2**, **R_3**, **R_4**, **R_5**, **R_6**, **X**, **R_7**, **R_8**, **R_9** and **R_{10}** are as defined above.

Disclosed herein is a compound of formula (1e) as defined above, or a pharmaceutically acceptable salt or solvate thereof, for use in therapy.

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

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

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

Disclosed herein is a pharmaceutical composition comprising (i) a therapeutically effective amount of a compound of formula (1e) 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 C_1-C_4 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-glucomine, morpholine, thiomorpholine, piperidine, pyrrolidine, a mono-, di- or tri-lower alkylamine, for example ethyl-, tert-butyl-, diethyl-, diisopropyl-, triethyl-, tributyl- or dimethyl-propylamine, or a mono-, di- or trihydroxy lower alkylamine, for example mono-, di- or triethanolamine. Corresponding internal salts may furthermore be formed.

“Pharmaceutically acceptable solvate” means a molecular complex comprising the compound of the invention and one or more pharmaceutically acceptable solvent molecules, for example, water or ethanol. Those skilled in the art of organic chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as "solvates". For example, a complex with water is known as a "hydrate". Solvates, such as hydrates, exist when the drug substance incorporates solvent, such as water, in the crystal lattice in either stoichiometric or non-stoichiometric amounts. Drug substances are routinely screened for the existence of hydrates since these may be encountered at any stage of the drug manufacturing process or upon storage of the drug substance or dosage form. Solvates are described in S. Byrn *et al.*, *Pharmaceutical Research*, 1995. **12**(7): p. 954-954, and Water-Insoluble Drug Formulation, 2nd ed. R. Liu, CRC Press, page 553, which are incorporated herein by reference.

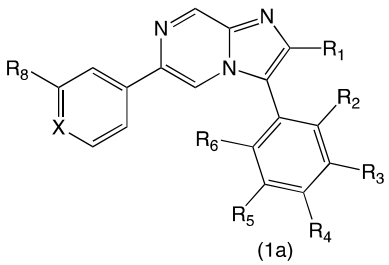
“Therapy”, “treatment” and “treating” include both preventative and curative treatment of a condition, disease or disorder. It also includes slowing, interrupting, controlling or stopping

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.

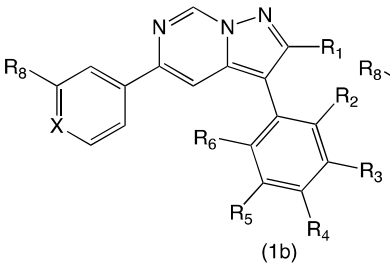
The term “patient” includes both humans and animals.

B. Compounds

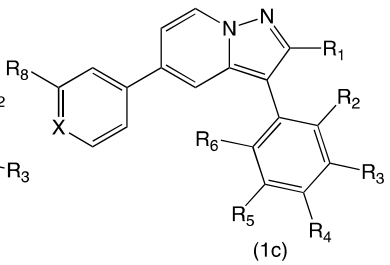
The invention provides a compound of formula (1a), (1b), (1c), (1d) or (1e) as defined above, or a pharmaceutically acceptable salt or solvate thereof for use in the treatment or prevention of fascioliasis.



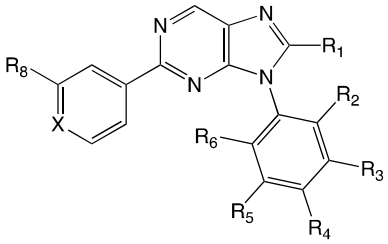
(1a)



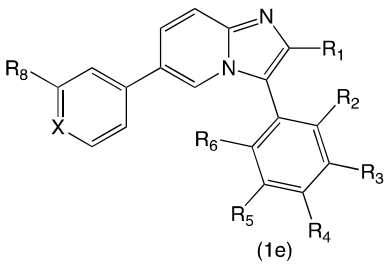
(1b)



(1c)

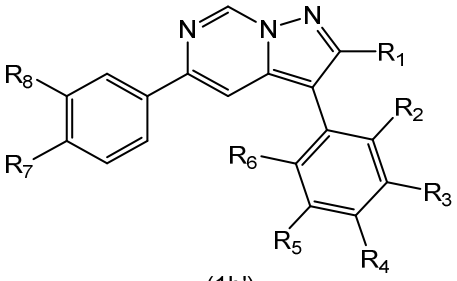


(1d)

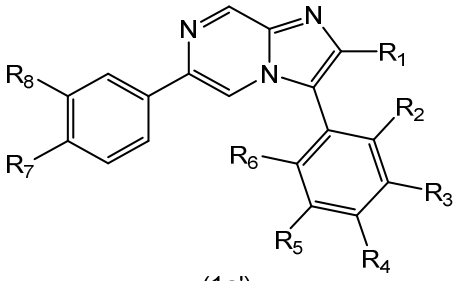


(1e)

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



(1b')



(1a')

wherein:

R_1 is C_1-C_4 alkyl optionally substituted with up to five F atoms, C_3-C_6 cycloalkyl optionally substituted with one methyl group, or C_4-C_7 cycloalkylmethyl;

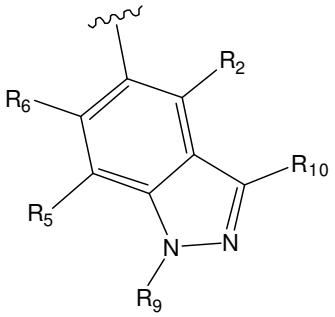
R_2 is H, F, Cl or OMe;

R_3 is H, OH, OMe, OPO(OH)OH or $OCH_2OPO(OH)OH$;

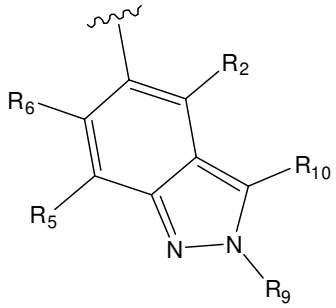
R_4 is H, OH, OMe, OPO(OH)OH or $OCH_2OPO(OH)OH$;

provided that **R_3** and **R_4** cannot both be H;

or **R_3** and **R_4** combine, together with the phenyl ring to which they are attached, to form an indazole group as shown below



or



R_5 is H, F, Cl or OMe;

R_6 is H, F, Cl or OMe;

R_7 is H or F;

R_8 is SF_5 or C_1-C_3 alkyl substituted with three to seven F atoms;

R_9 is H; and

R_{10} is H, F or Me

for use in the treatment or prevention of fascioliasis.

The invention also provides a compound of formula (1e) as defined above, or a pharmaceutically acceptable salt or solvate thereof.

B0. Core Structures

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

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

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

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

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

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

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

B1. Substituent **R_1**

R_1 is selected from the group consisting of C_1-C_4 alkyl optionally substituted with up to five F atoms, C_3-C_6 cycloalkyl optionally substituted with one methyl group, and C_4-C_7 cycloalkylmethyl.

R_1 is preferably selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, cyclopropyl optionally substituted with one methyl group, cyclobutyl, cyclopropylmethyl, CHF_2, CF_3 and CH_2CF_3.

R_1 is more preferably selected from the group consisting of ethyl, isopropyl, cyclopropyl, cyclobutyl, CF_3 and CH_2CF_3.

B2. Substituent **R_2**

R_2 is selected from the group consisting of H, F, Cl and OMe.

R_2 is preferably selected from the group consisting of H, F and Cl.

R_2 is more preferably F or Cl.

R_2 is most preferably F

B3. Substituent **R_3**

R_3 is selected from the group consisting of H, OH, OMe, OPO(OH)OH and $OCH_2OPO(OH)OH$.

R_3 is preferably selected from the group consisting of H, OH, OMe and OPO(OH)OH.

R_3 is more preferably H.

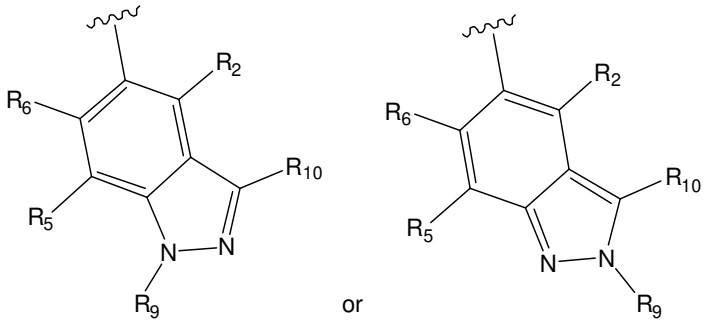
B4. Substituent **R_4**

R_4 is selected from the group consisting of H, OH, OMe, OPO(OH)OH and $OCH_2OPO(OH)OH$.

R_4 is preferably selected from the group consisting of H, OH, OMe and OPO(OH)OH.

R_4 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:

R_9 is H; and

R_{10} 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.

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.

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**.

B8. Substituent **R_8**

R_8 is selected from the group consisting of SF_5, Br, C_1-C_3 alkyl optionally substituted with up to to seven F atoms; C_3-C_4 cycloalkyl; $OCH_2C{\equiv}CH$ and OC_1-C_3 alkyl optionally substituted with up to to seven F atoms.

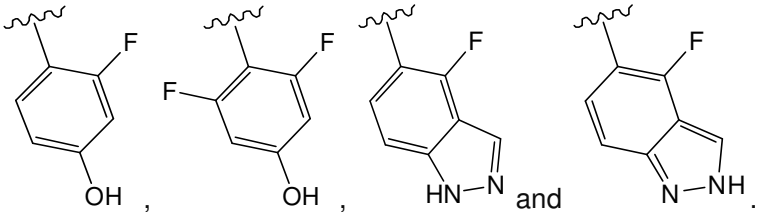
Alternatively, **R_8** is selected from the group consisting of SF_5 and C_1-C_3 alkyl substituted with three to seven F atoms.

R_8 is preferably selected from the group consisting of cyclopropyl, cyclobutyl, isopropyl, CH_2CF_3, OCF3, O^iPr, CF_3, CF_2CF_3 and SF_5.

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

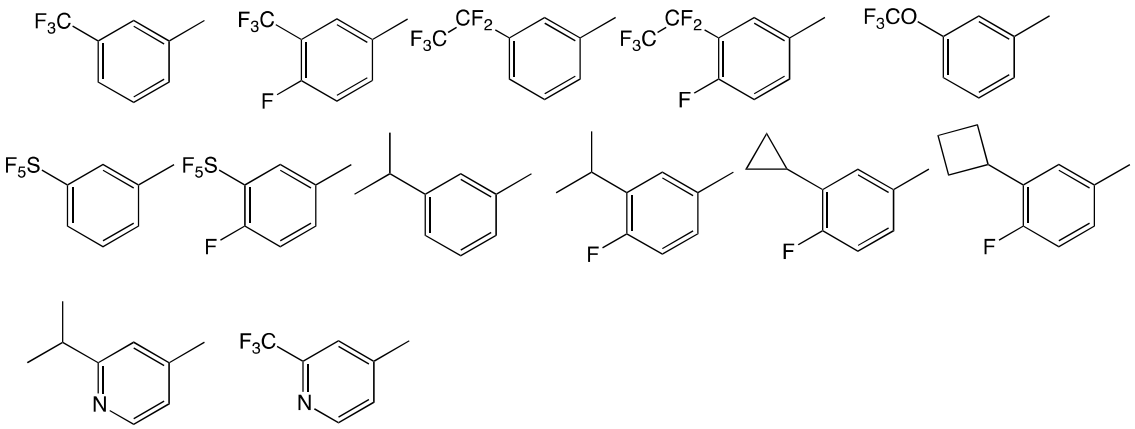
B9. Combinations of Substituents **R_2** to **R_6**

Preferred combinations of substituents **R_2** to **R_6** include:

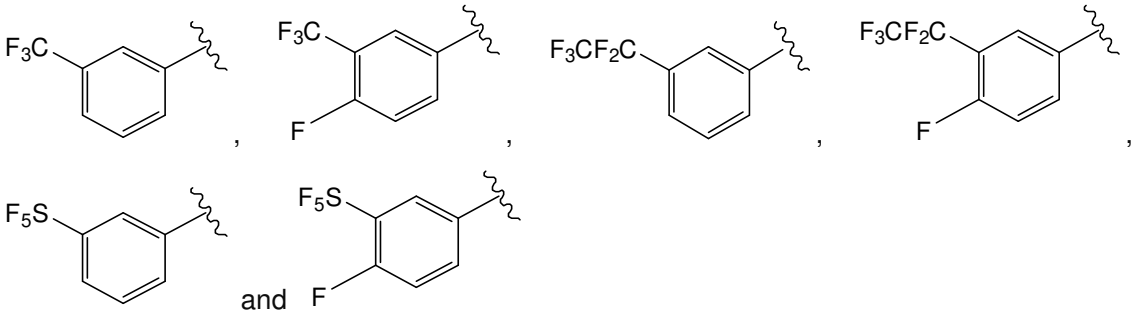


B10. Combinations of Substituents **X** and **R_8**

Preferred combinations of substituents **X** and **R_8** include:



Alternative preferred combinations of substituents **X** and **R_8** include:



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

Various embodiments of substituents **R_1**, **R_2**, **R_3**, **R_4**, **R_5**, **R_6**, **X**, **R_7**, **R_8**, **R_9** and **R_{10}** 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), (1d) and (1e). All embodiments of compounds of formula (1a), (1a’), (1b), (1b’), (1c), (1d) and (1e) 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), (1d) and (1e) are provided below.

In a preferred aspect of the first to ninth embodiments, the invention provides (i) a compound of formula (1a), (1a’), (1b), (1b’), (1c), (1d) or (1e) or a pharmaceutically acceptable salt or solvate thereof, for use in the treatment or prevention of fascioliasis; (ii) use of a compound of formula (1a), (1a’), (1b), (1b’), (1c), (1d) or (1e) or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for use in the treatment of fascioliasis; (iii) a method for treating or preventing fascioliasis comprising administering a therapeutically effective amount of a compound of formula (1a), (1a’), (1b), (1b’), (1c), (1d) or (1e), or a pharmaceutically acceptable salt or solvate thereof, to a patient in need thereof; (iv) a compound of formula (1e), or a pharmaceutically acceptable salt or solvate thereof; (v) a compound of formula (1e), or a pharmaceutically acceptable salt or solvate thereof, for use in therapy; (vi) a compound of formula (1e), or a pharmaceutically acceptable salt or solvate thereof, for use in the treatment of schistosomiasis; (vii) the use of a compound of formula (1e), or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment of schistosomiasis (viii) a method for treating schistosomiasis comprising administering a therapeutically effective amount of a compound of formula (1e), or a pharmaceutically acceptable salt or solvate thereof, to a patient in need thereof; and (ix) a pharmaceutical composition comprising (i) a therapeutically effective amount of a compound of formula (1e), or a pharmaceutically acceptable salt or solvate thereof; and (ii) a pharmaceutically acceptable excipient

wherein:

$\mathbf{R_1}$ is methyl, ethyl, n-propyl, isopropyl, cyclopropyl optionally substituted with one methyl group, cyclobutyl, cyclopropylmethyl, CHF_2, CF_3 or CH_2CF_3;

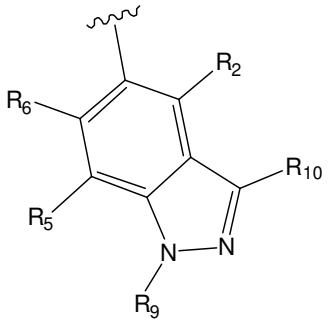
$\mathbf{R_2}$ is H, F or OMe; or $\mathbf{R_2}$ is H, F or Cl;

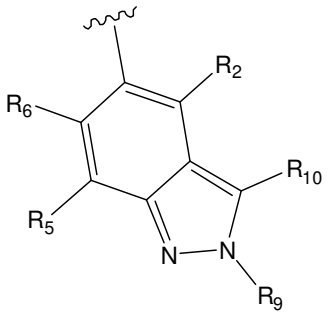
$\mathbf{R_3}$ is H, OH, OMe or OPO(OH)OH;

$\mathbf{R_4}$ is H, OH, OMe or OPO(OH)OH;

provided that $\mathbf{R_3}$ and $\mathbf{R_4}$ cannot both be H;

or $\mathbf{R_3}$ and $\mathbf{R_4}$ combine, together with the phenyl ring to which they are attached, to form an indazole group as shown below;



or


R_5 is H or OMe;

R_6 is H or F;

X is **N** or C-**R_7** where **R_7** is H or F; or **X** is C-**R_7** where **R_7** is H or F;

R_8 is CF_3, CF_2CF_3, CH_2CF_3, $CH(CH_3)_2$, OCF_3, $OCH(CH_3)_2$, cyclopropyl, cycolbutyl or SF_5; or **R_8** is CF_3, CF_2CF_3 or SF_5;

R_9 is H; and

R_{10} is H.

In a more preferred aspect of the first to ninth embodiments, the invention provides a compound of formula (1a), (1a'), (1b), (1b'), (1c), (1d) or (1e) or a pharmaceutically acceptable salt or solvate thereof,

wherein:

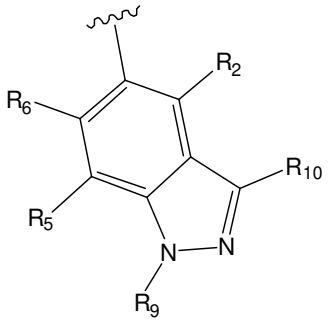
R_1 is ethyl, isopropyl, cyclopropyl, cyclobutyl, CF_3 or CH_2CF_3; or **R_1** is ethyl, isopropyl, cyclopropyl, CF_3 or CH_2CF_3;

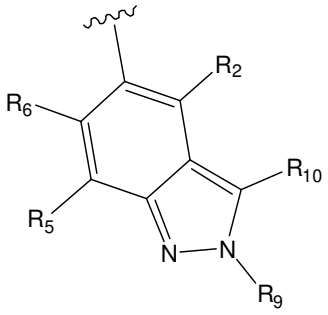
R_2 is F;

R_3 is H;

R_4 is OH;

or **R_3** and **R_4** combine, together with the phenyl ring to which they are attached, to form an indazole group as shown below;



or


R_5 is H;

R_6 is H or F;

X is C-**R_7** where **R_7** is H or F;

R_8 is CF_3, CF_2CF_3 $CH(CH_3)_2$ or SF_5; or **R_8** is CF_3, CF_2CF_3 or SF_5;

R_9 is H; and

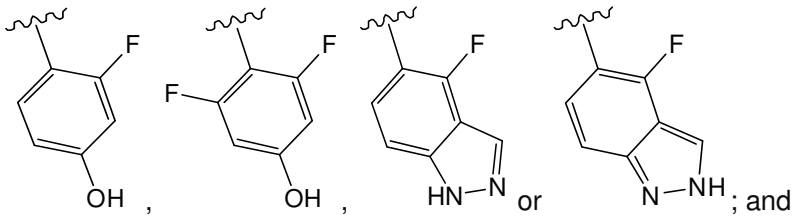
R_{10} is H.

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

wherein:

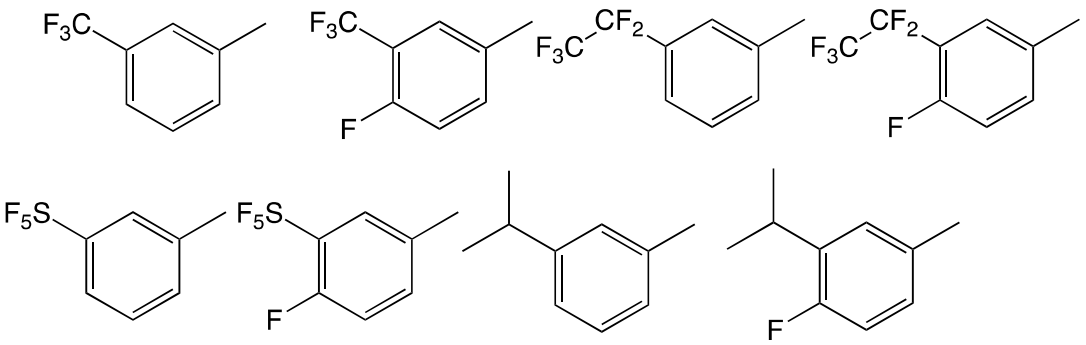
R_1 is ethyl, isopropyl, cyclopropyl, CF_3 or CH_2CF_3;

R_2 to **R_6** are selected to provide the structure:

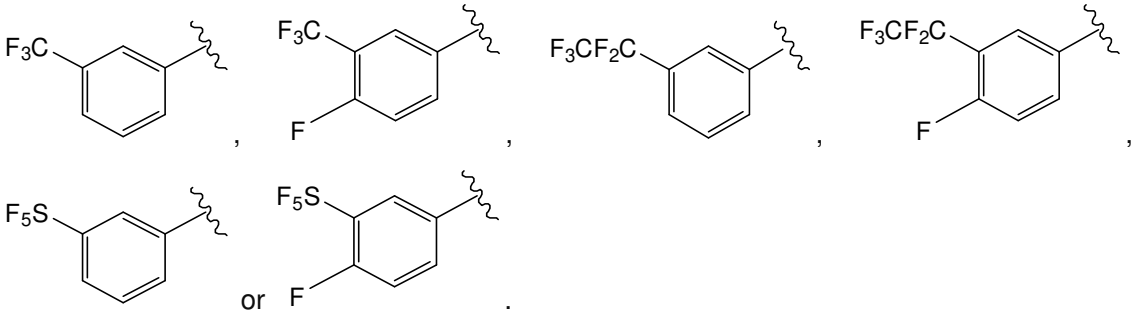


; and

R_7 and **R_8** are selected to provide the structure



or **R_7** and **R_8** are selected to provide the structure:



.

The following compounds represent specific embodiments of use in the first, second and third 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)

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

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

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

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

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

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

Example 31: 3, 5-difluoro-4-[2-methyl-6-[3-(pentafluorosulfanyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol

Example 32: 4-fluoro-5-{2-cyclopropyl-6-[4-fluoro-3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl}-1H-indazole

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

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-[4-fluoro-3-(trifluoromethyl)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

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

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

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

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

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-difluoro-phenol

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

Example 56: 4-[2-Cyclopropyl-6-(4-fluoro-3-pentafluorosulfanyl-phenyl)-imidazo[1,2-a]pyrazin-3-yl]-3,5-difluoro-phenol

Example 57: 2-Cyclopropyl-3-(4-fluoro-1H-indazol-5-yl)-6-(4-fluoro-3- pentafluorosulfanyl -phenyl)-imidazo[1,2-a]pyrazine

Example 58: 3-(4-Fluoro-1H-indazol-5-yl)-5-(4-fluoro-3-pentafluoroethyl-phenyl)-2-isopropyl-pyrazolo[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-difluoro-phenol

Example 61: 3-(4-Fluoro-1H-indazol-5-yl)-5-(4-fluoro-3-trifluoromethyl-phenyl)-2-isopropyl-pyrazolo[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-difluoro-phenyl} ester

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

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

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

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

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

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

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

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

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

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

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

The following compounds represent specific embodiments of use in the first to ninth embodiments of the invention:

Example 91: 2-methoxy-5-[2-methyl-6-[3-(trifluoromethyl)phenyl] imidazo[1,2-a]pyridin-3-yl]phenol

Example 92: 2-methoxy-5-[2-isopropyl-6-[3-(trifluoromethyl)phenyl] imidazo[1,2-a]pyridin-3-yl]phenol

Example 93: 3-fluoro-4-[2-methyl-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyridin-3-yl]phenol

Example 94: 3-fluoro-4-[2-isopropyl-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyridin-3-yl]phenol

C. Compositions

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 comprising (i) a therapeutically effective amount of a compound of formula (1e) 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. 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), (1d) and 1(e) as defined above, or a pharmaceutically acceptable salt or solvate thereof, for use in the treatment of fascioliasis. The subject to be treated can be a human or an animal.

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

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

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

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

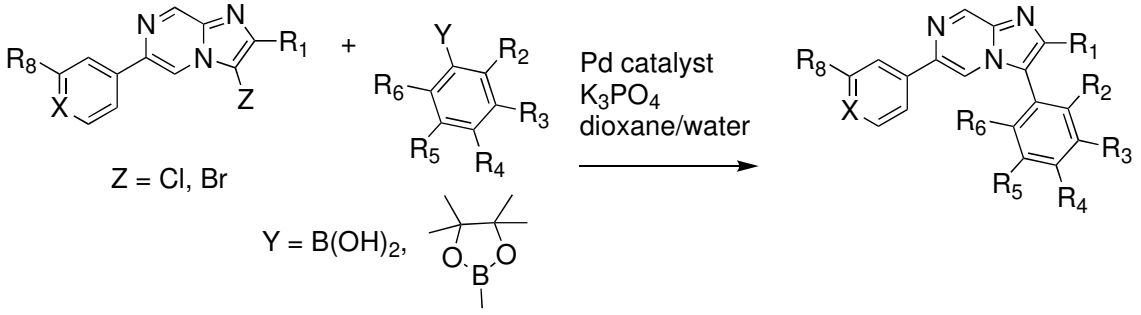
The amount of active ingredient which is required to achieve a therapeutic effect will, of course, vary with the particular compound, the route of administration, the subject under treatment, including the type, species, age, weight, sex, and medical condition of the subject and the renal and hepatic 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.

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.

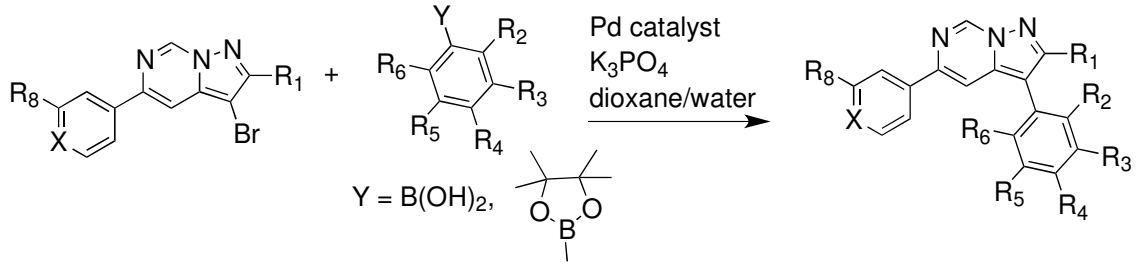
General Method 1A

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.



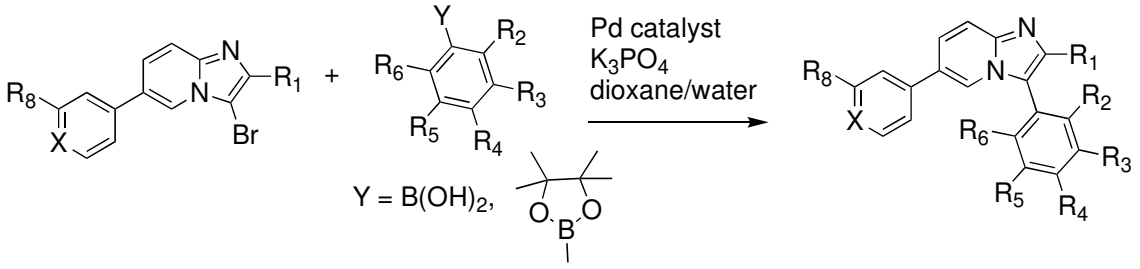
General Method 1B

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.



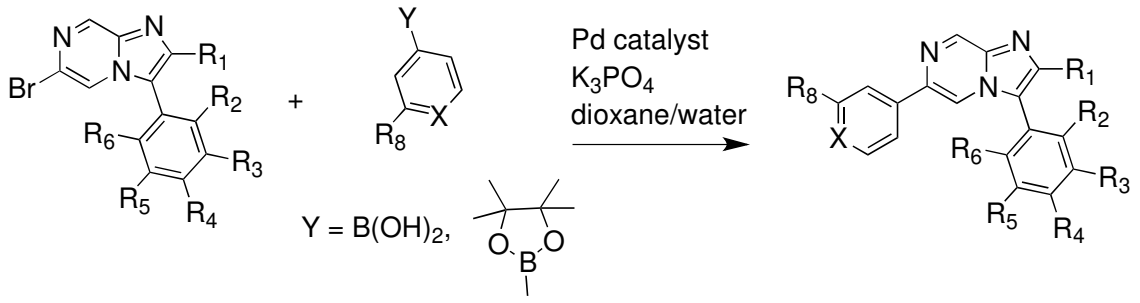
General Method 1C

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-imidazo[1,2-a]pyridine with an appropriate arylboronic acid or aryl pinacol borane under Suzuki conditions in the presence of a palladium catalyst.



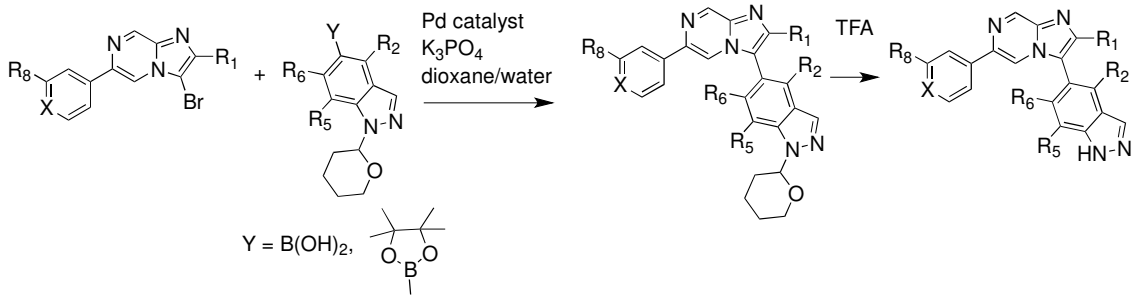
General Method 2

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_2CF_3 or SF_5. 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.



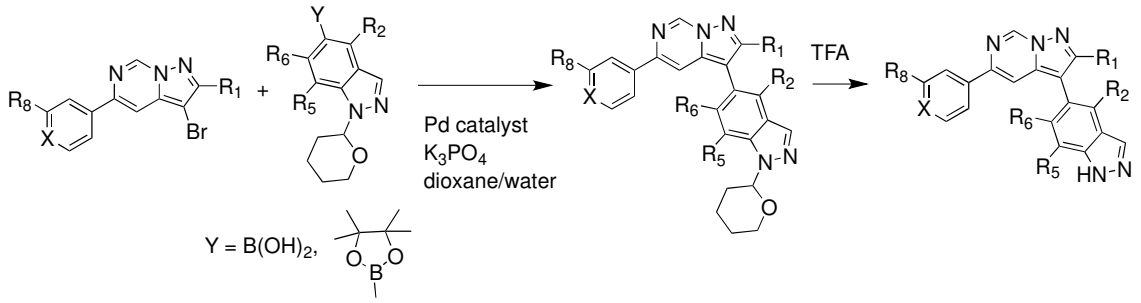
General Method 3A

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, $CH(CH_3)_2$, CH_2CF_3, OCF_3, $OCH(CH_3)_2$, $OCH_2C{\equiv}CH$, cPr, cBu or SF_5. 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.



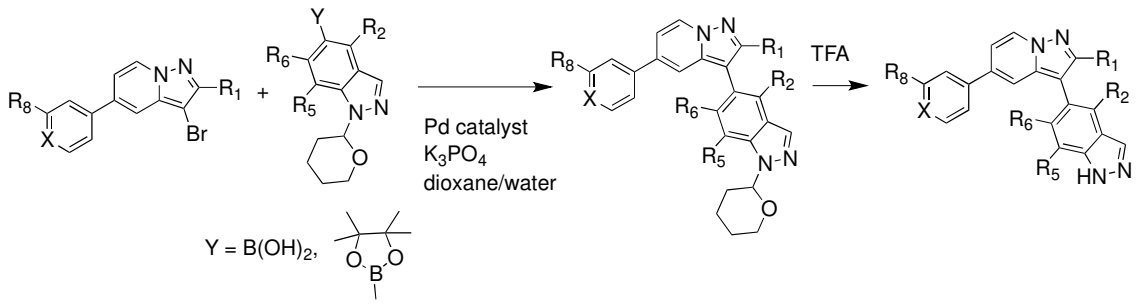
General Method 3B

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. 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.



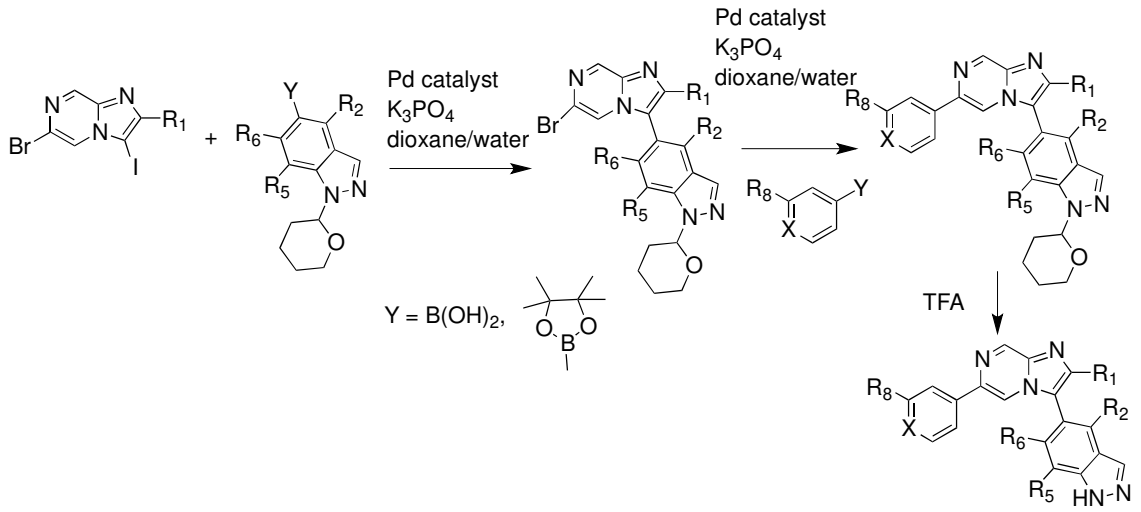
General Method 3C

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.



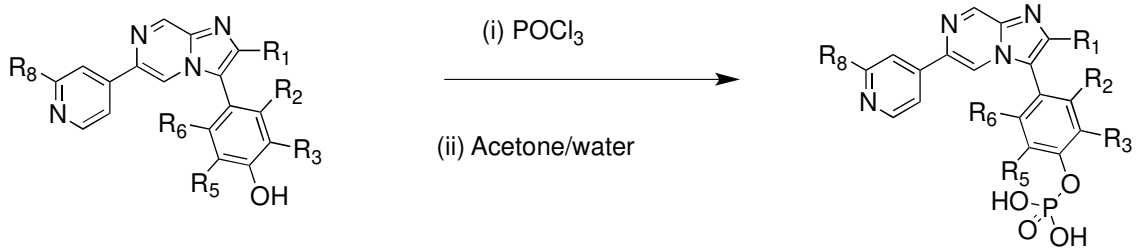
General Method 3D

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.



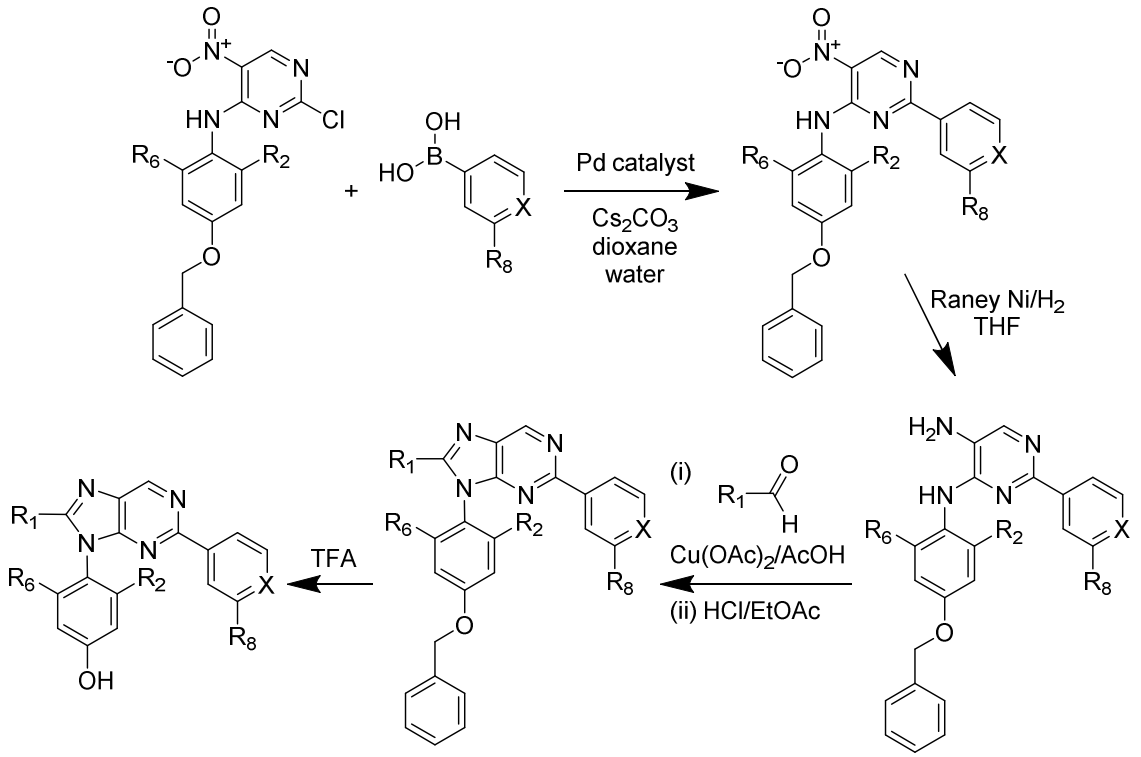
General Method 4

The invention also provides a process for the preparation of *Schistosoma* growth inhibitors where R_1, R_2 and R_5-R_8 and **X** are defined according to the invention, and R_3 or R_4 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 R_1, R_2, R_6, R_8 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

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).

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% [CH_3CN] held for 0.75 min, then to 90% [0.05% Modifier in water] and 10% [CH_3CN] in 1.0 min, further to 2% [0.05% Modifier in water] and 98% [CH_3CN] 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

Method E: (General-5 min)

Column - Zorbax C18 (50 x 4.6 mm, 5u, 130A), (mobile phase: from 90% [10 mM NH_4OAc in water] and 10% [CH_3CN] to 70% [10 mM NH_4OAc in water] and 30% [CH_3CN] in 1.5 min,

further to 10% [10 mM NH_4OAc in water] and 90% [CH_3CN] 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 ^{13}C 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 $Pd(dppf)Cl_2$.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 Na_2SO_4 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, $CDCl_3$) 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.

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

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 $Na_2S_2O_3$ (100.0 mL) at 10°C and extracted with EtOAc (2 X 100 mL). Combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 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-d_6) δ 7.09 (t, J=8.2, 1H), 6.40 (d, J=8.52, 1H), 1.98 (s, 3H).

Step 2

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 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 an off white solid. LCMS rt 3.03 min MH+214. 1H NMR (400 MHz, $CDCl_3$) δ 10.44 (brs, 1H), 8.14 (s, 1H), 7.49-7.45 (m, 1H), 7.19 (d, J=8.76, 1H).

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 $NaHCO_3$ solution and brine, combined organic layer was dried over anhydrous Na_2SO_4 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 an off white solid.

LCMS rt 3.83 min MH+299. 1H NMR (400 MHz, $CDCl_3$) 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, $CDCl_3$) 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 dissoved 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 coloumn 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-d_6) 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:H_2O (3:1, 20mL) and treated with K_3PO_4 (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 coloumn 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-d_6) 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-d_6) 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-d_6) 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-d_6) 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

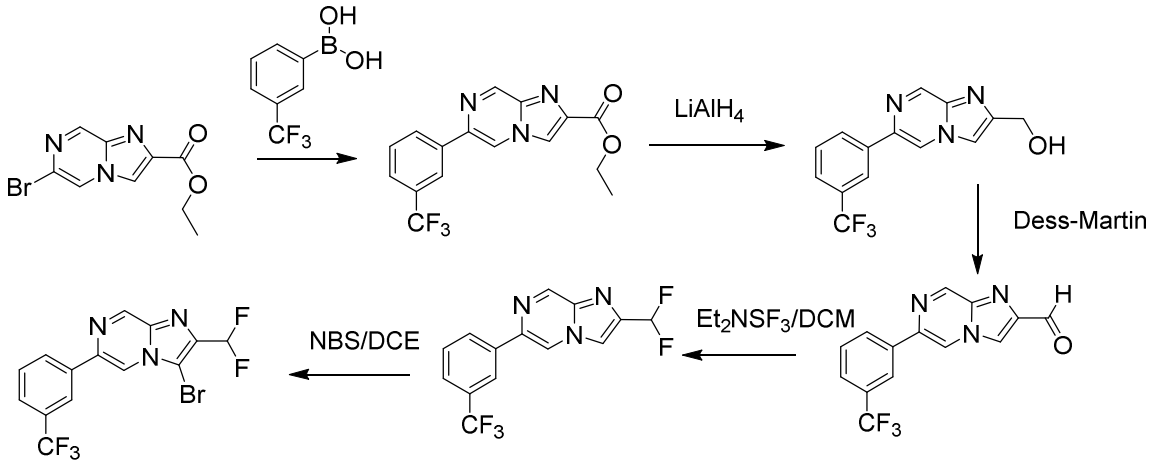
A mixture of 6-Bromo-3-chloro-2-trifluoromethyl-imidazo[1,2-a]pyrazine (800 mg, 2.67 mmol) and 2-(4-Fluoro-3-pentafluoroethyl-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (1 g, 2.93 mmol) was dissolved in 1,4-dioxane:H_2O (4:1, 15mL) and treated with K_3PO_4 (1.7 g, 8 mmol). The mixture was degassed for 20-30 min, treated with [1,1'-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-d_6) 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, 38-64

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.



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

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

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:H_2O (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 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

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 (2.5M in THF, 87 µL, 2.3mmol) in THF at 0°C and stirred for 3h. The reaction was then quenched by saturated solution of Na_2SO_4 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).

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 $SOBr_2$ (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 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 mmol) in DCM (2 mL) at -10 °C was added 1-(3-trifluoromethylphenyl)-1-tosyl methyl

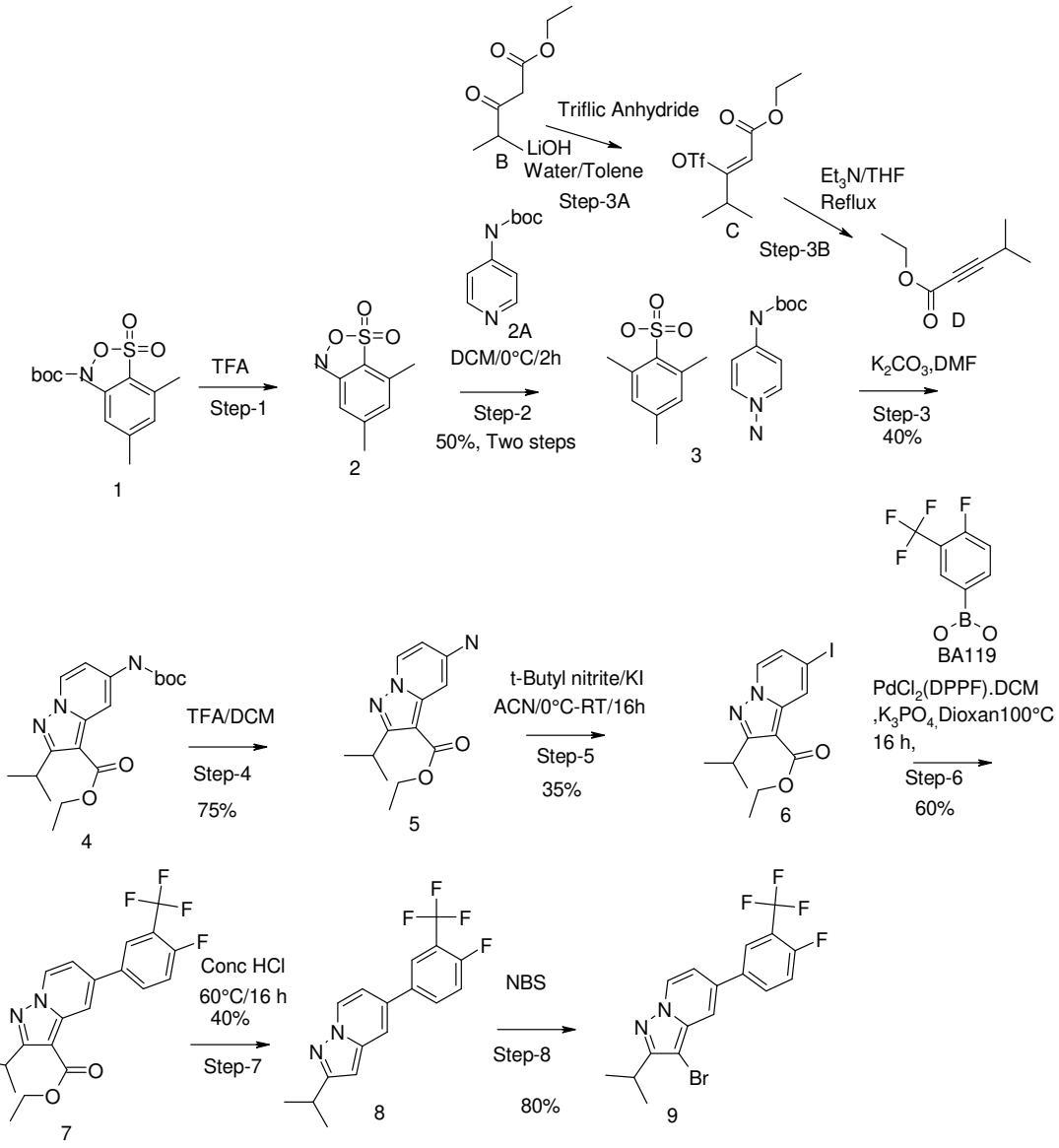
isocyanide (120mg, 0.36 mmol) and benzyl triethylammonium chloride (16mg, 0.07 mmol) and then added drop wise a solution of of 30%-NaOH in water (2 mL). The resultant reaction mixture was maintained at -10 °C for 3 h. The mixture was extracted into DCM, the organic layer was dried and concentrated under 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-d_6) 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).

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. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.93 (1H, br. s), 8.54 (2H, d, *J*=6.9 Hz), 7.85 (2H, d, J=6.8Hz s), 6.73 (2H, s), 2.16 (3H, s), 1.51 (9H, s) [possibly $SO_3\underline{H}$ 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.

^{1}H NMR (400 MHz, DMSO-d_6) 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.

^{1}H NMR (400 MHz, DMSO-d_6) 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-d_6) 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 an off white solid (0.9 g, 75%). LCMS rt 3.34 min MH^+ 248. ^1H NMR (400 MHz, DMSO-d_6) 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-d_6) 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-trifluoromethylphenylboronic 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 coloumn 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)

^{1}H 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.

^{1}H 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

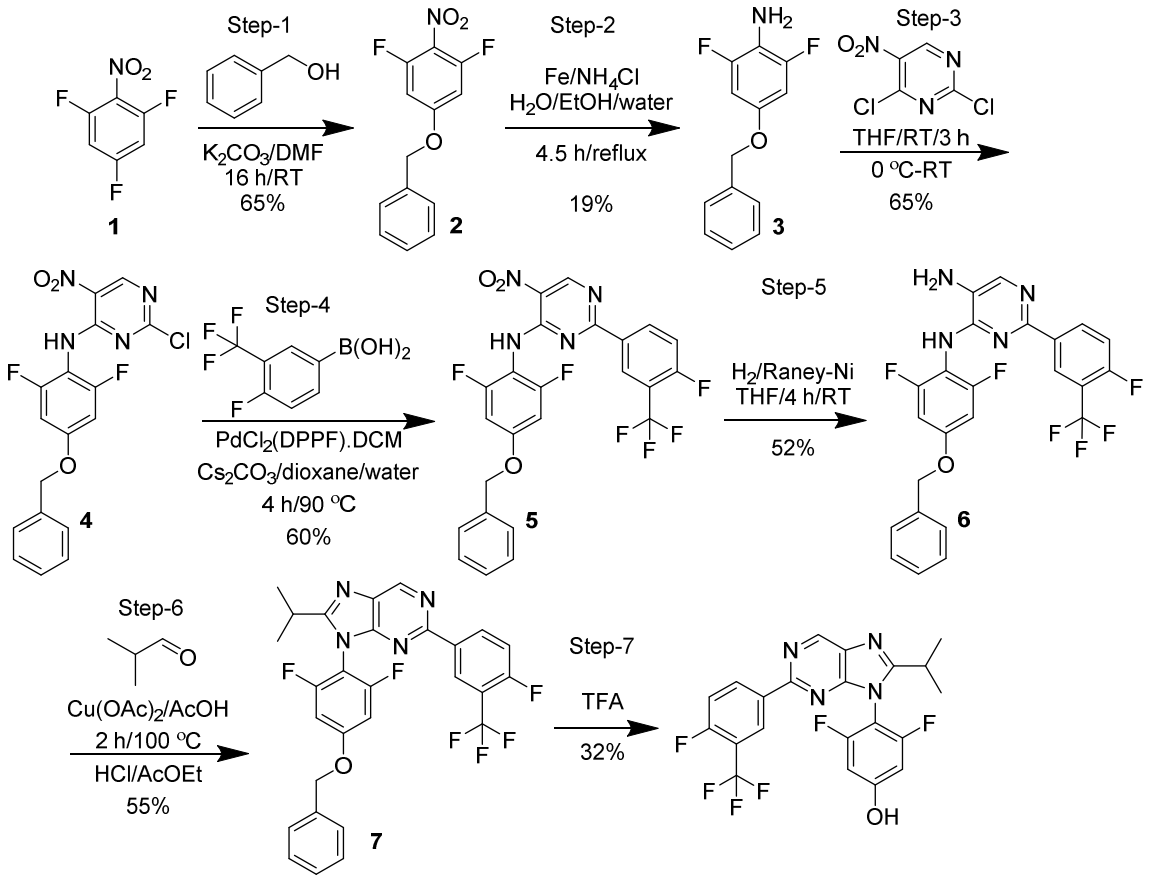
3-bromo-5-[4-fluoro-3-(trifluoromethyl)phenyl]-2-(propan-2-yl)pyrazolo[1,5-a]pyridine

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

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

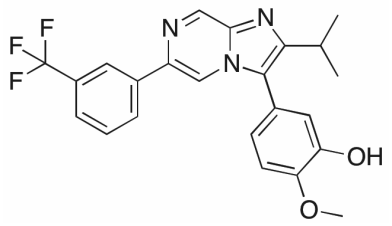


Internediates 63 and 64

Were prepared using a similar route to Intermediate 1 from 2-aminopyridine and an appropriate haloketone, followed by Suzuki coupling with 3-trifluoromethylphenylboronic acid

Preparation of Examples 1-94

Example 1



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

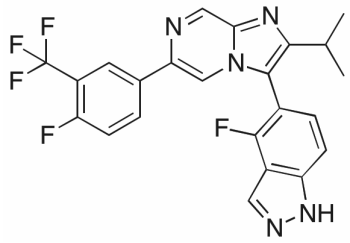
3-bromo-2-(propan-2-yl)-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazine (1.5g, 3.9mmol) and 2-methoxy-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenol (1.46g, 5.9mmol) were dissolved in dioxane/water (4:1, 30mL) and treated with K_3PO_4 (2.48g, 11.7mmol. The solution was degassed 20-30 min 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 coloumn 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.

^{1}H NMR (400 MHz, DMSO-d_6) 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 K_3PO_4 (791 mg, 3.73 mmol. The solution was degassed with argon for 5 min before 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

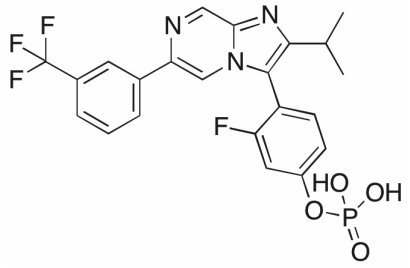
acetate and water. The organic layer was dried over sodium sulphate and concentrated under reduced pressure. The crude product was purified by column chromatography (100-200 mesh silica gel, by elution with 20% ethyl acetate in DCM). Fractions containing the desired product were combined and evaporated 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

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 dicholoromethane, washed successively with sodium bicarbonate solution, 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 (125 mg, 25%). UPLC rt 3.5 min MH^+ 458.

^1H NMR (400 MHz, DMSO-d_6) 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).

Example 3



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

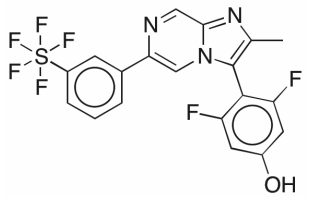
A solution of 3-fluoro-4-[2-(propan-2-yl)-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol (Example 9 600 mg, 1.45 mmol) in DCM (10 mL) was cooled to 0°C and treated with pyridine (4 mL) followed by dropwise addition of phosphorous oxychloride (4 mL) solution in DCM (10mL). The reaction mixture was stirred for 5 h at RT. Two further charges of pyridine and $POCl_3$ were added at 0°C to drive the reaction to completion over 3 days. The 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 reveres-phase prep-HPLC to give the title compound (104mg, 15%).

UPLC rt 2.6 min MH^+ 496.

^1H NMR (400 MHz, DMSO-d_6) 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).

Example 31

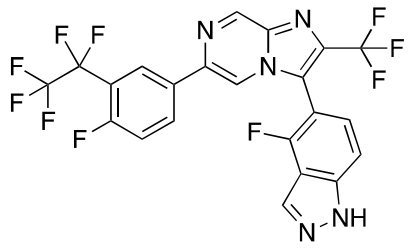


3, 5-difluoro-4-[2-methyl-6-[3-(pentafluorosulfanyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol

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 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 dicholoromethane, 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%).

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



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

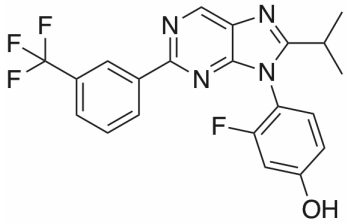
A mixture of 3-Chloro-6-(4-fluoro-3-pentafluoroethyl-phenyl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine (620 mg, 1.43 mmol) and 4-Fluoro-1-(tetrahydro-pyran-2-yl)-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-indazole (1 g, 2.9 mmol) was dissolved in 1,4-dioxane:H_2O (4:1, 15mL) and treated with 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-d_6) 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

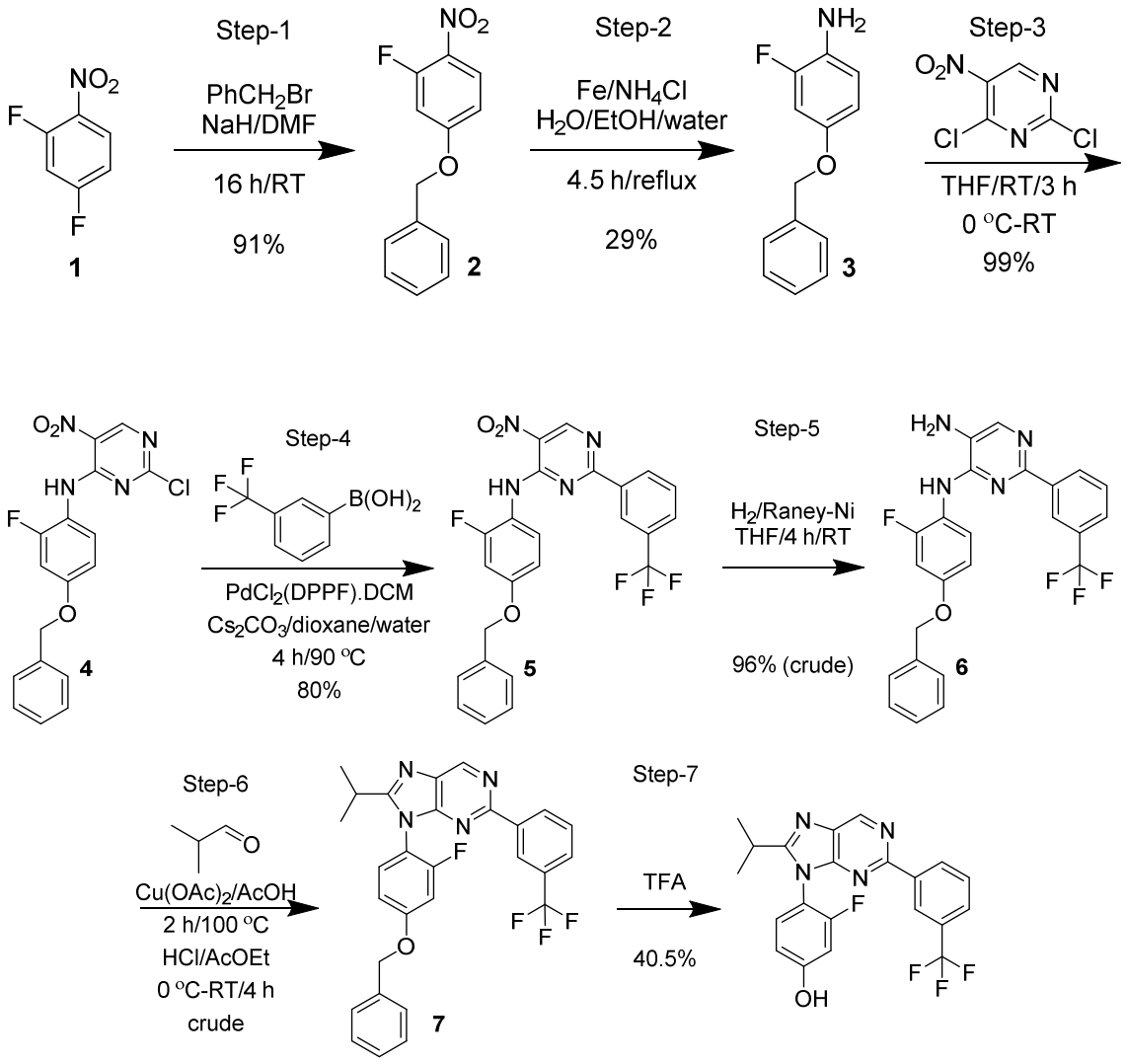
3-(4-Fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-pentafluoroethyl-phenyl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine

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, 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-d_6) δ 13.73 (s, 1H), 9.47 (s, 1H) 8.44-8.38 (m, 3H), 7.64-7.53 (m, 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, $CDCl_3$) 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, $CDCl_3$) δ 7.38-7.29 (m, 5H), 6.72-6.-6.59 (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, $CDCl_3$) δ 10.10 (brs,1H),9.16 (s, 1H), 7.93-7.89 (m, 1H), 7.43-7.34 (m, 6H), 6.85-6.-6.82 (m, 2H), 5.07 (s, 2H).

Step-4

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

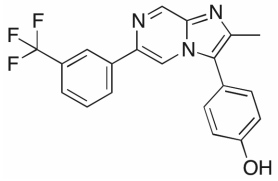
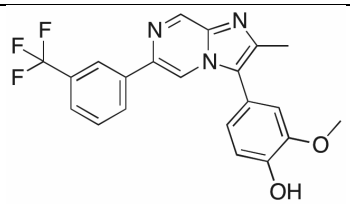
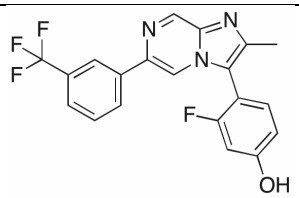
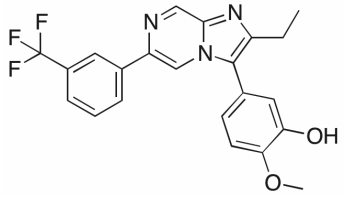
N-[4-(benzyloxy)-2-fluorophenyl]-2-chloro-5-nitropyrimidin-4-amine (4) (2.4 g, 6.41 mmol) and 3-trifluoromethylphenylboronic acid (1.81 g, 9.62 mmol) were dissolved in dioxane/water (4:1, 40 mL) and treated with Cs_2CO_3 (4.17 g, 12.83 mmol). The solution was degassed 20-30 min before addition of $PdCl_2$(dppf).DCM 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 coloumn 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

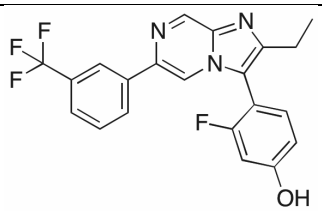
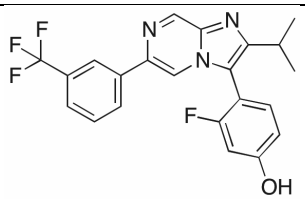
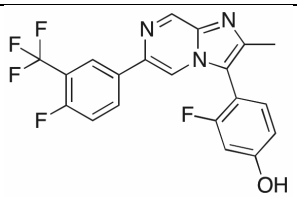
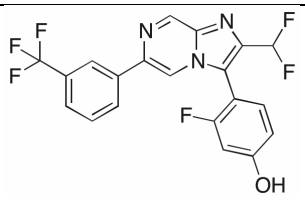
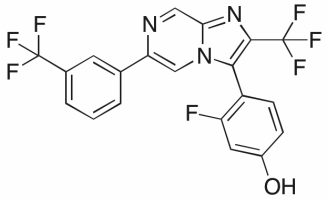
^1H NMR (400 MHz, DMSO-d_6) δ 9.98 (s, 1H), 9.4 (s, 1H), 8.64 (s, 1H), 8.52-8.51 (m, 1H) 7.89-7.57 (m, 3H), 7.47-7.37 (m, 5H), 6.9-6.71 (m, 3H), 5.11 (s, 2H).

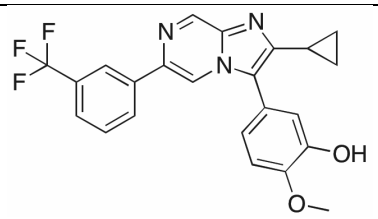
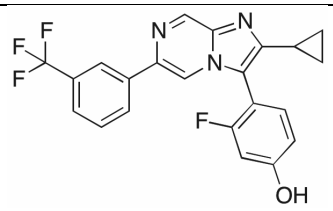
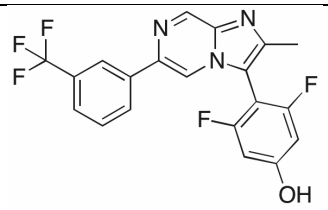
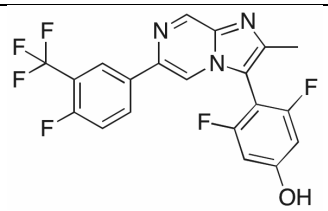
Step 5

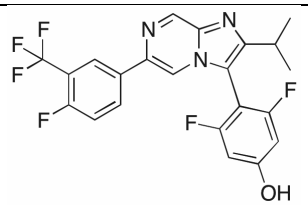
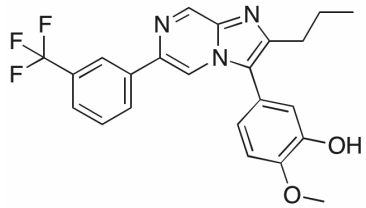
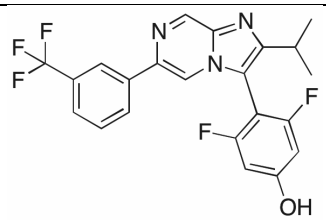
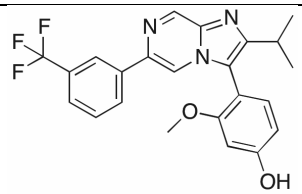
4-N-[4-(benzyloxy)-2-fluorophenyl]-2-[3-(trifluoromethyl)phenyl]pyrimidine-4,5-diamine (6)
To a stirred solution of 4 N-[4-(benzyloxy)-2-fluorophenyl]-5-nitro-2-[3-(trifluoromethyl)phenyl]pyrimidin-4-amine (5) (220 mg, 0.455 mmol) in THF(10 mL) was added Raney nickel (100 mg). The reaction vessel was 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
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 µL,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 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
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 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-d_6) 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), 1.31-1.22 (m, 6H).

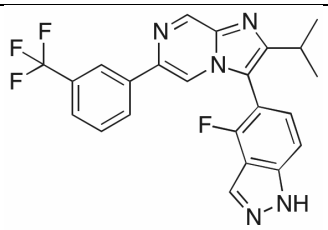
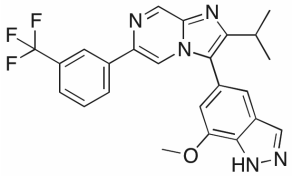
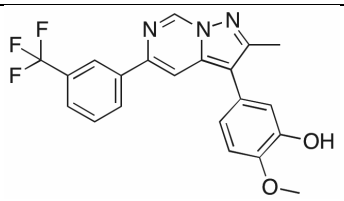
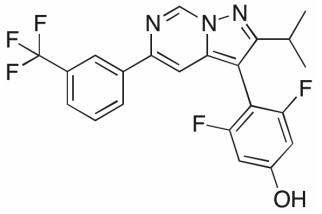
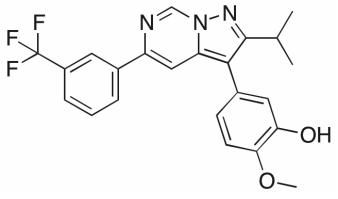
The following compounds were made by analogous methods:

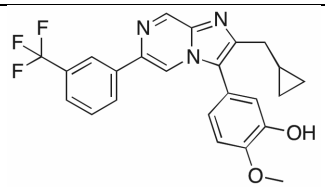
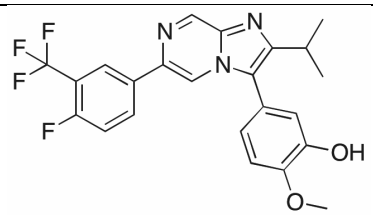
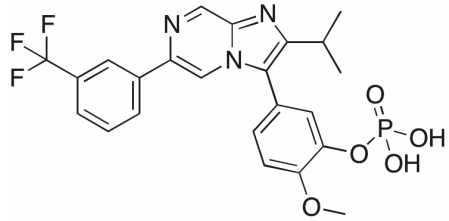
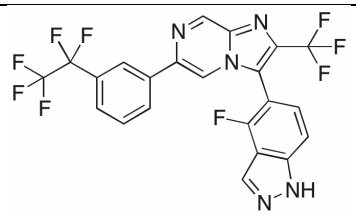
Ex No	Structure	General method	Interm-ediate Nº	Yield	Characterisation
4	 4-[2-methyl-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol	1A	2	24 mg, 29 %	UPLC rt 2.92 min, MH^+ 370
5	 2-methoxy-4-(2-methyl-6-(3-(trifluoromethyl)phenyl)imidazo[1,2-a]pyrazin-3-yl)phenol	1A	2	22 mg, 25%	UPLC 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

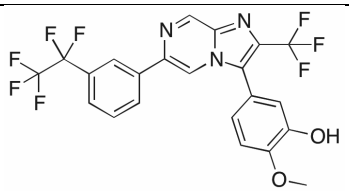
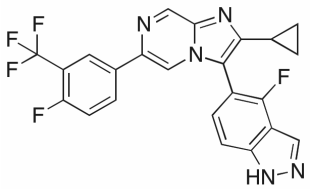
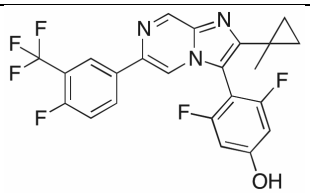
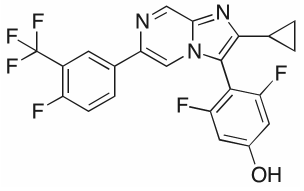
8	 3-fluoro-4-[2-ethyl-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol	1A	3	8 mg, 11 %	UPLC rt 1.84 min (3 min Run) MH^+ 402
9	 3-fluoro-4-[2-(propan-2-yl)-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol	1A	1	5 mg, 7 %	UPLC rt 3.11 min, MH^+ 416
10	 3-fluoro-4-[2-methyl-6-[4-fluoro-3-(trifluoromethyl)phenyl] 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		1B	6	25 mg, 20 %	UPLC rt 1.65 min (3 min Run) MH^+ 442

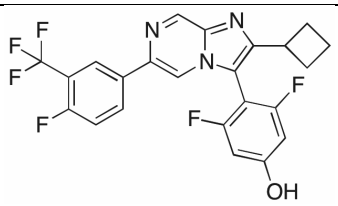
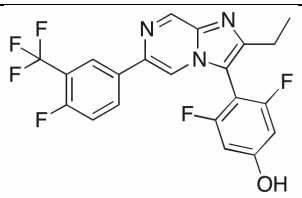
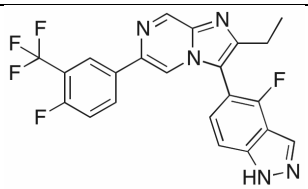
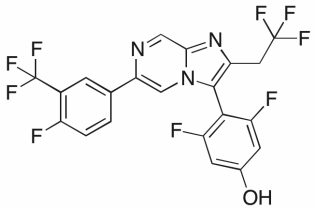
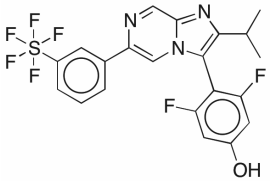
	3-fluoro-4-[2-trifluoromethyl-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol				
13	 2-methoxy-5-[2-cyclopropyl-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol	1B	7	25 mg, 37 %	UPLC rt 1.69 min (3 min Run) MH^+ 426
14	 3-fluoro-4-[2-cyclopropyl-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol	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

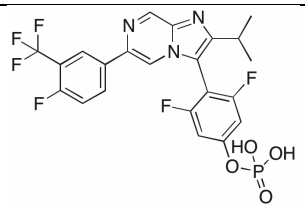
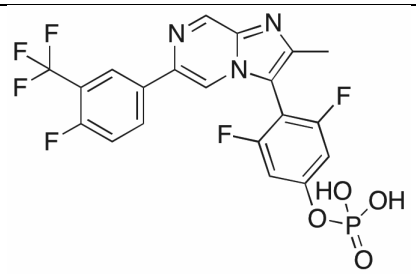
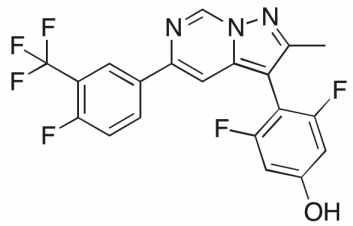
17	 3, 5-difluoro-4-[2-(propan-2-yl)-6-[4-fluoro-3-(trifluoromethyl) phenyl] imidazo[1,2-a]pyrazin-3-yl]phenol	1B	8	14 mg, 12.5 %	UPLC rt 2.60 min, MH^+ 452
18	 2-methoxy-5-[2-(propan-1-yl)-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol	1B	9	10 mg, 14 %	UPLC rt 1.89 min(3 min Run) MH^+ 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

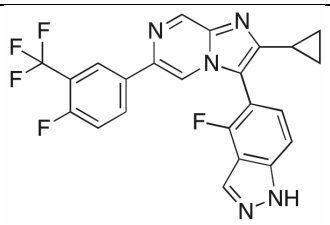
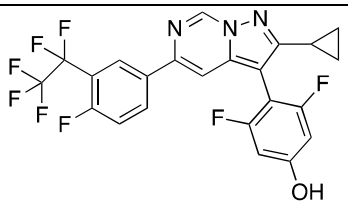
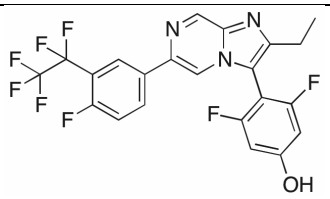
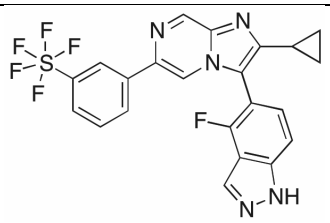
21	 4-fluoro -5-{2-propan-2-yl-6-[3-trifluoromethylphenyl]imidazo[1,2-a]pyrazin-3-yl}- 1H-indazole	2	1	5 mg, 62 %	UPLC rt 3.20 min, MH^+ 440
22	 7-methoxy-5-{2-(propan-2-yl)-6-[3-trifluoromethylphenyl]imidazo[1,2-a]pyrazin-3-yl}-1H-indazole	2	1	12 mg, 51 %	UPLC rt1.89 min (3 min Run) MH^+ 452
23	 2-methoxy-5-(2-methyl-5-(3-(trifluoromethyl)phenyl)pyrazolo[1,5-c]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		1B	11	37 mg, 42 %	UPLC rt 3.46 min, MH^+ 428

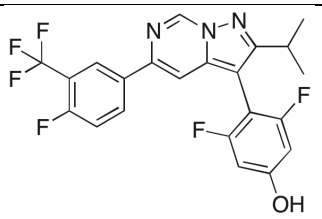
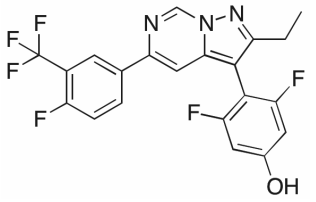
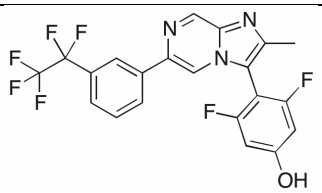
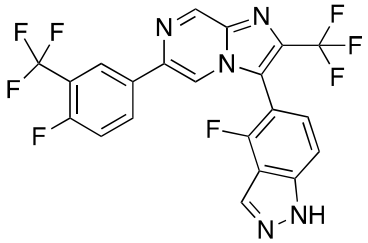
	5-(2-isopropyl-5-(3-(trifluoromethyl)phenyl)pyrazolo[1,5-c]pyrimidin-3-yl)-2-methoxyphenol				
26	 2-methoxy-5-[2-(cyclopropylmethyl)-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol	1B	12	20 mg, 25 %	UPLC rt 3.17 min, MH^+ 440
27	 2-methoxy-5-[2-(propan-2-yl)-6-[4-fluoro-3-(trifluoromethyl)phenyl] 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

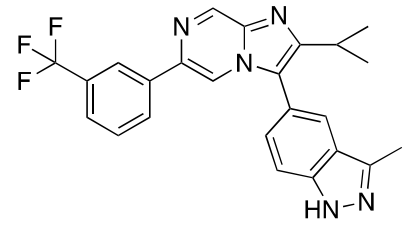
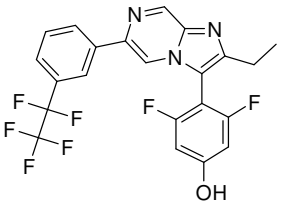
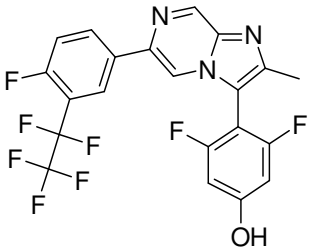
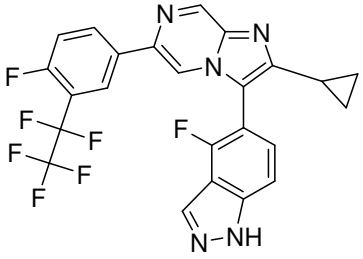
30	 2-methoxy-5-[2-(trifluoromethyl)-6-[3-(pentafluoroethyl)phenyl] imidazo[1,2-a]pyrazin-3-yl]phenol	1B	14	30 mg, 47 %	UPLC rt 3.38 min, MH^+ 502
32	 4-fluoro-5-{2-cyclopropyl-6-[4-fluoro-3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl}-1H-indazole	2	17	125 mg, 21%	UPLC rt 3.09 min, MH^+ 456
33	 3, 5-difluoro-4-[2-(1-methyl-cycloprop-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

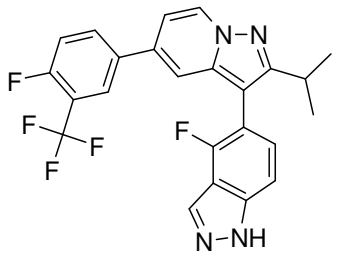
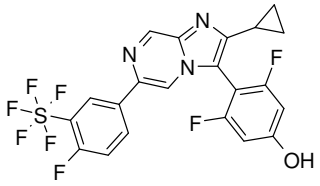
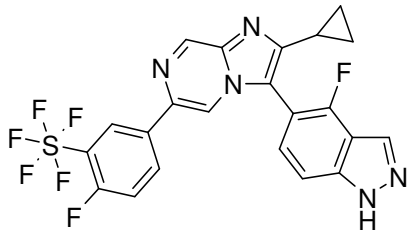
35	 4-(2-cyclobutyl-6-(4-fluoro-3-(trifluoromethyl)phenyl)imidazo[1,2-a]pyrazin-3-yl)-3,5-difluorophenol	1B	18	72 mg, 64 %	UPLC rt 3.37 min, MH^+ 464
36	 3, 5-difluoro-4-[2-ethyl-6-[4-fluoro-3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol	1B	19	20 mg, 17 %	UPLC rt 3.09 min, MH^+ 438
37	 4-fluoro-5-{2-ethyl-6-[4-fluoro-3-(trifluoromethyl)phenyl]imidazo[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		4	21	14 mg, 15 %	UPLC rt 3.36 min, MH^+ 492

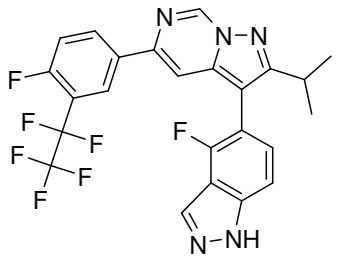
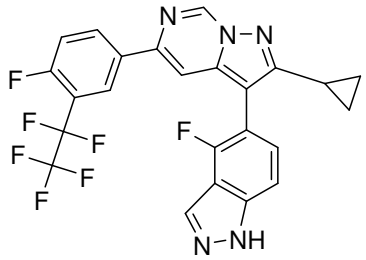
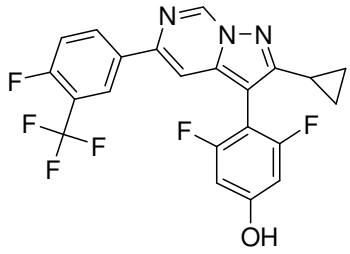
	3, 5-difluoro-4-[2-(propan-2-yl)-6-[3-(pentafluorosulfanyl)phenyl]imidazo[1,2-a]pyrazin-3-yl]phenol				
40	 3,5-difluoro-4-{6-[4-fluoro-3-(trifluoromethyl)phenyl]-2-(propan-2-yl)imidazo[1,2-a]pyrazin-3-yl}phenoxyphosphonic acid	3	Ex 17	13 mg, 28 %	UPLC rt 2.27 min, MH^+ 532
41	 3,5-difluoro-4-{6-[4-fluoro-3-(trifluoromethyl)phenyl]-2-methyl-imidazo[1,2-a]pyrazin-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

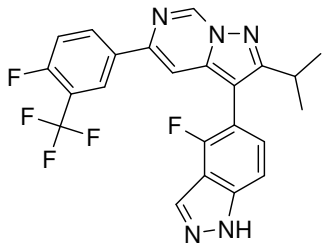
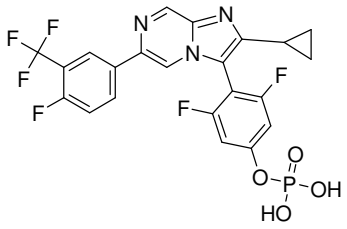
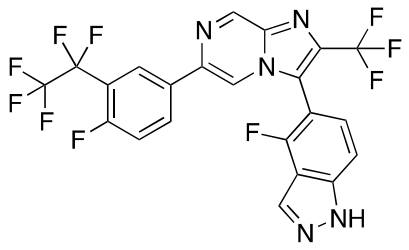
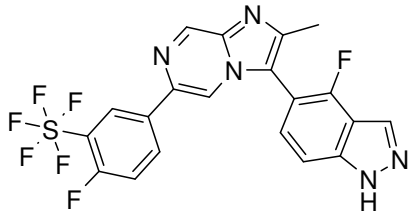
43	 2-cyclopropyl-3-(4-fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-(trifluoromethyl)phenyl)imidazo[1,2-a]pyrazine	2	17	5 mg,55 %	UPLC rt 2.73 min, MH^+ 456
44	 4-[2-Cyclopropyl-6-(4-fluoro-3-pentafluoroethyl-phenyl)-imidazo[1,2-a]pyrazin-3-yl]-3,5-difluoro-phenol	2	23	7 mg, 14 %	UPLC rt 2.66 min, MH^+ 500
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

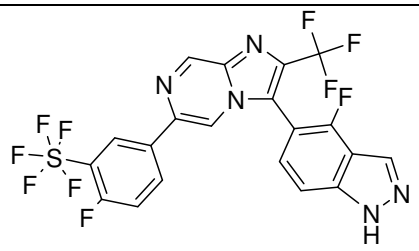
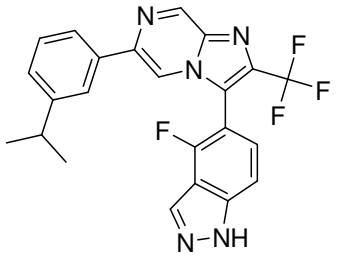
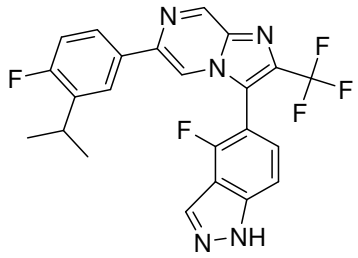
47	 3,5-difluoro-4-(5-(4-fluoro-3-(trifluoromethyl)phenyl)-2-(propan-2-yl)-pyrazolo[1,5-c]pyrimidin-3-yl)phenol	1B	26	10 mg, 17%	UPLC rt 3.57 min, $[M-H]^-$ 450
48	 4-(2-ethyl-5-(4-fluoro-3-(trifluoromethyl)phenyl)pyrazolo[1,5-c]pyrimidin-3-yl)-3,5-difluorophenol	1B	27	7 mg, 12%	UPLC rt 3.43 min, MH^+ 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

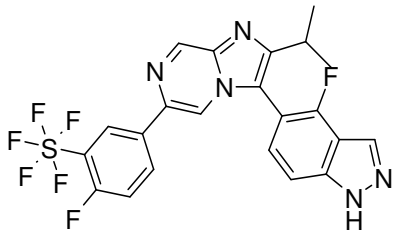
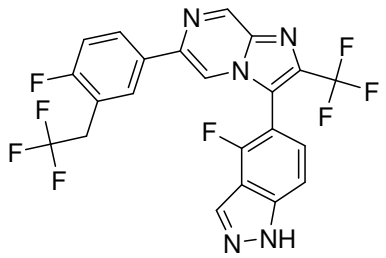
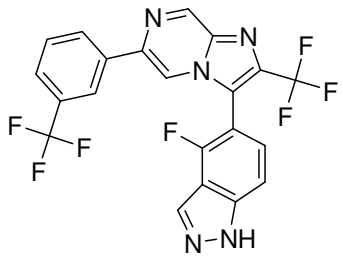
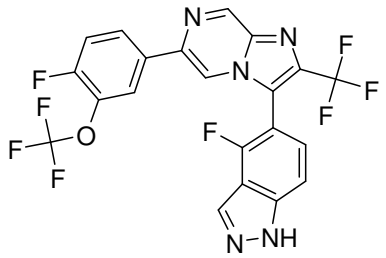
51	 2-Isopropyl-3-(3-methyl-1H-indazol-5-yl)-6-(3-trifluoromethyl-phenyl)-imidazo[1,2-a]pyrazine	3A	1	33 mg, 39%	UPLC rt 2.02 min (3 min Run) MH^+ 436
52	 4-[2-Ethyl-6-(3-pentafluoroethyl-phenyl)-imidazo[1,2-a]pyrazin-3-yl]-3,5-difluoro-phenol	1A	30	75 mg, 67%	HPLC rt 11.49 min, MH^- 468
53	 3,5-Difluoro-4-[6-(4-fluoro-3-pentafluoroethyl-phenyl)-2-methyl-imidazo[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

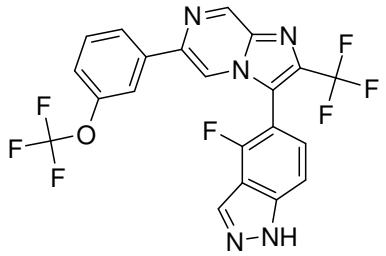
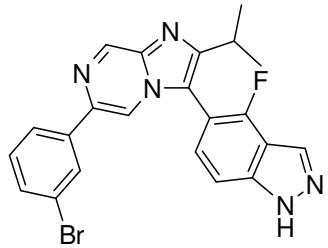
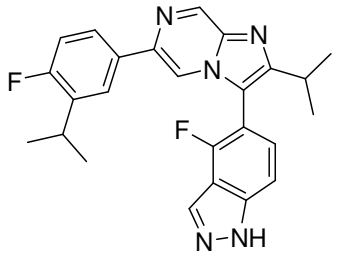
55	 4-Fluoro-5-[5-(4-fluoro-3-trifluoro methyl-phenyl)-2-isopropylpyrazolo[1,5-a]pyridin-3-yl]-1H-indazole	3C	32	15 mg, 17.75%	UPLC rt 3.32 min, MH^- 455
56	 4-[2-Cyclopropyl-6-(4-fluoro-3-pentafluorosulfanyl-phenyl)-imidazo[1,2-a]pyrazin-3-yl]-3,5-difluoro-phenol	2	33	3 mg, 2.81%	UPLC rt 1.82 min (3 min Run), MH^+ 508
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

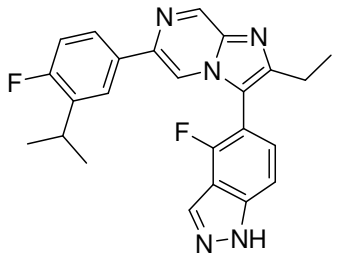
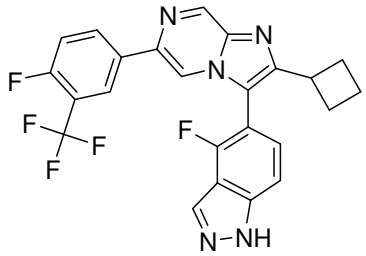
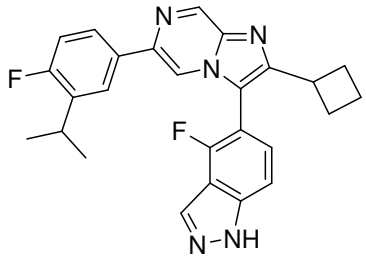
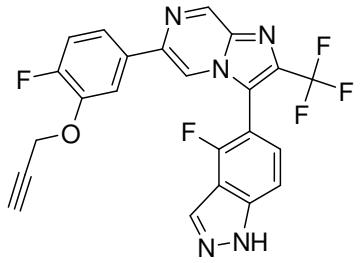
58	 3-(4-Fluoro-1H-indazol-5-yl)-5-(4-fluoro-3-pentafluoroethyl-phenyl)-2-isopropyl-pyrazolo[1,5-c]pyrimidine	3B	34	22 mg, 65.05%	UPLC rt 1.92 min (3 min Run), MH^+ 508
59	 2-Cyclopropyl-3-(4-fluoro-1H-indazol-5-yl)-5-(4-fluoro-3-pentafluoroethyl-phenyl)-pyrazolo[1,5-c]pyrimidine	3B	35	17 mg, 23.07%	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-difluoro-phenol	1B	35	34 mg, 43.24%	UPLC rt 3.57 min, MH^- 448

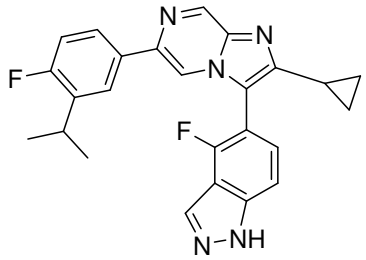
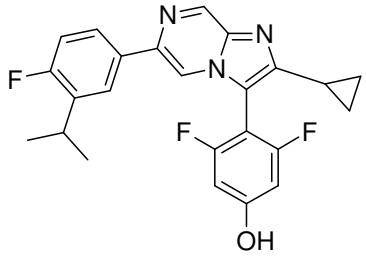
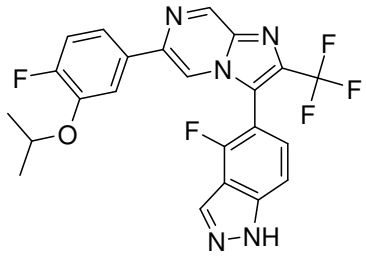
61	 3-(4-Fluoro-1H-indazol-5-yl)-5-(4-fluoro-3-trifluoromethyl-phenyl)-2-isopropyl-pyrazolo[1,5-c]pyrimidine	3B	36	33 mg, 39.03%	UPLC rt 3.58 min, MH^- 456
62	 Phosphoric acid mono-{4-[2-cyclopropyl-6-(4-fluoro-3-trifluoromethyl-phenyl)-imidazo[1,2-a]pyrazin-3-yl]-3,5-difluoro-phenyl} ester	4	Example 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		3D	38	12 mg, 10.81%	UPLC rt 3.03 min, MH^- 486

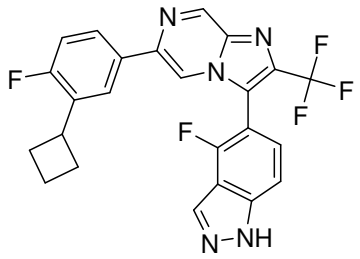
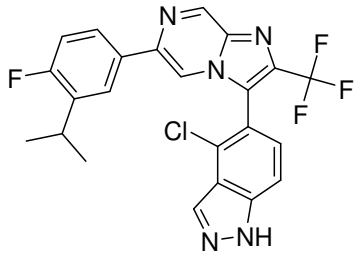
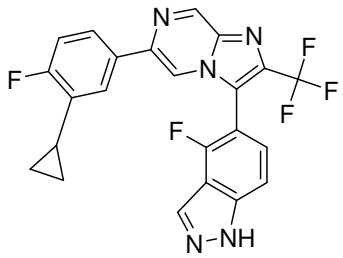
	3-(4-Fluoro-1H-indazol-5-yl)-6-(4-fluoro-3- pentafluorosulfanyl-phenyl)-2-methyl-imidazo[1,2-a]pyrazine				
65	 3-(4-Fluoro-1H-indazol-5-yl)-6-(4-fluoro-3- pentafluorosulfanyl -phenyl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine	3A	39	10 mg, 6.79%	UPLC rt 3.26 min, MH^- 540
66	 3-(4-Fluoro-1H-indazol-5-yl)-6-(3-isopropyl-phenyl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine	3A	40	46 mg, 45.63%	UPLC rt 2.59 min, MH^+ 440
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

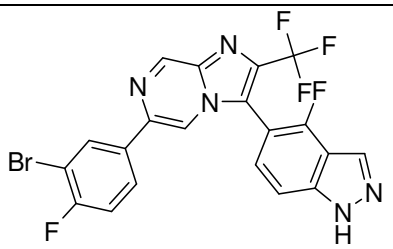
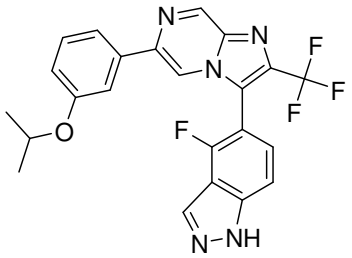
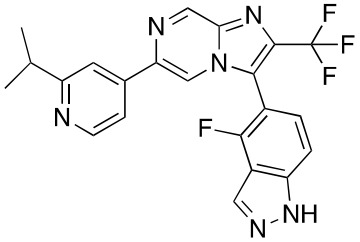
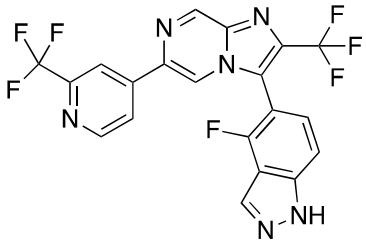
68	 3-(4-Fluoro-1H-indazol-5-yl)-6-(4-fluoro-3- pentafluorosulfanyl-phenyl)-2-isopropyl-imidazo[1,2-a]pyrazine	3D	42	35 mg, 21.54%	UPLC rt 2.66 min, MH^+ 516
69	 3-(4-Fluoro-1H-indazol-5-yl)-6-[4-fluoro-3-(2,2,2-trifluoro-ethyl)-phenyl]-2-trifluoromethyl-imidazo[1,2-a]pyrazine	3A	43	3 mg, 2.34%	UPLC 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		3A	45	35 mg, 25.54%	UPLC rt 1.79 min (3 min Run), MH^+ 500

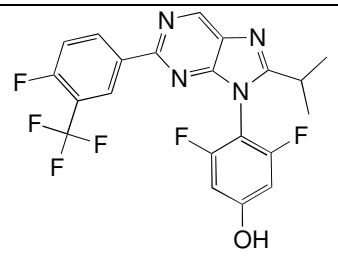
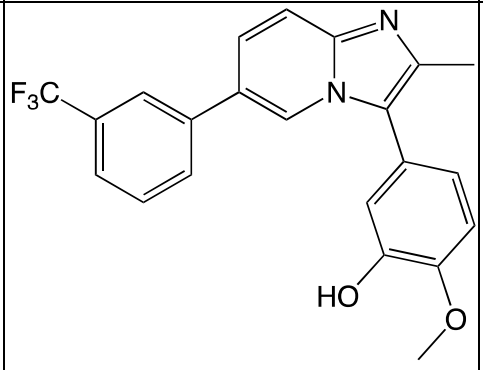
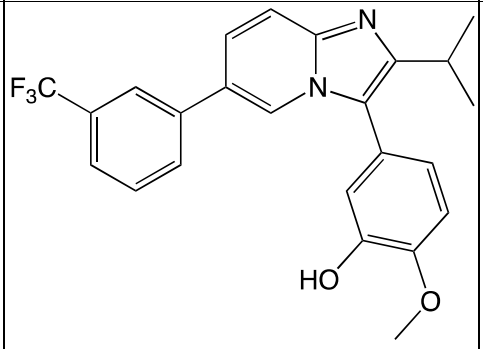
	3-(4-Fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-trifluoromethoxy-phenyl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine				
72	 3-(4-Fluoro-1H-indazol-5-yl)-6-(3-trifluoromethoxy-phenyl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine	3A	46	80 mg, 37.56%	UPLC rt 1.78 min (3 min Run), MH^+ 482
73	 6-(3-Bromo-phenyl)-3-(4-fluoro-1H-indazol-5-yl)-2-isopropyl-imidazo[1,2-a]pyrazine	3D	47	10 mg, 14.82%	UPLC rt 1.82 min (3 min Run), MH^+ 450
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

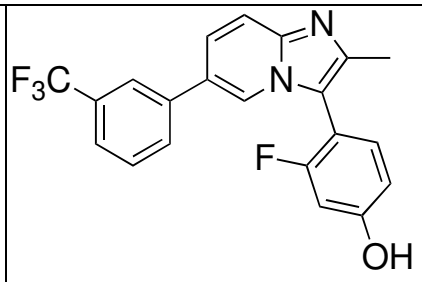
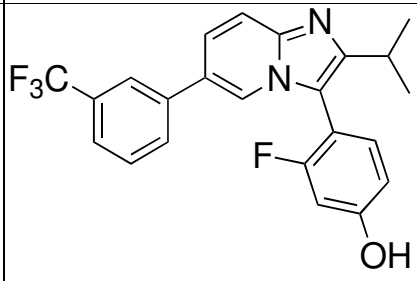
75	 2-Ethyl-3-(4-fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-isopropyl-phenyl)-imidazo[1,2-a]pyrazine	3A	49	50 mg, 13.79%	HPLC rt 13.19 min, MH^+ 418
76	 2-Cyclobutyl-3-(4-fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-trifluoromethyl-phenyl)-imidazo[1,2-a]pyrazine	3A	50	50 mg, 34.65%	UPLC rt 1.93 min (3 min Run), 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		3A	52	10 mg, 5.89%	UPLC rt 1.81 min (3 min Run), MH^+ 470

	3-(4-Fluoro-1H-indazol-5-yl)-6-(4-fluoro-3-prop-2-ynyloxy-phenyl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine				
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	 4-[2-Cyclopropyl-6-(4-fluoro-3-isopropyl-phenyl)-imidazo[1,2-a]pyrazin-3-yl]-3,5-difluoro-phenol	1A	53	3 mg, 4.32%	UPLC rt 2.78 min, MH^+ 424
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-(2-isopropyl-pyridin-4-yl)-2-trifluoromethyl-imidazo[1,2-a]pyrazine	3A	60	10 mg, 12%	UPLC rt 2.86 min, MH^+ 441
88		3A	61	60 mg, 34.52%	UPLC rt 1.70 min (3 min Run), MH^- 465

	3-(4-Fluoro-1H-indazol-5-yl)-2-trifluoromethyl-6-(2-trifluoromethyl-pyridin-4-yl)-imidazo[1,2-a]pyrazine				
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
91	 2-methoxy-5-[2-methyl-6-[3-(trifluoromethyl)phenyl] imidazo[1,2-a]pyridin-3-yl]phenol	1C	63	20mg 23.8%	UPLC rt 1.59 min (3 min Run), MH^+ 399
92	 2-methoxy-5-[2-isopropyl-6-[3-(trifluoromethyl)phenyl] imidazo[1,2-a]pyridin-3-yl]phenol	1C	64	25mg, 25.9%	UPLC rt 1.65 min (3 min Run), MH^+ 427

93	 3-fluoro-4-[2-methyl-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyridin-3-yl]phenol	1C	63	20mg, 42%	UPLC rt 1.58 min (3 min Run), MH^+ 387
94	 3-fluoro-4-[2-isopropyl-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyridin-3-yl]phenol	1C	64	25mg, 30.8%	UPLC rt 3.01 min, MH^+ 415

In vitro testing

The routine biological assays using adult liver fluke are described in Alessandra Crusco, Cinzia Bordoni, Anand Chakroborty, Kezia C.L. Whatley, Helen Whiteland, Andrew D. Westwell, Karl F. Hoffmann, "*Design, synthesis and anthelmintic activity of 7-keto-sempervirol analogues*", European Journal of Medicinal Chemistry, Volume 152, 2018, Pages 87-100.

The routine biological assays using adult or juvenile S. mansoni worms and cytotoxicity assays using MRC-5 cells have been disclosed previously in Mansour, N. R., et al. (2016). "*High 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) F. hepatica adult fluke motility score tested at 5µM. Motility is scored as per the table below:

Good movement Score 1

(Curled, sticking on wall, movement on petri plate or conical flask)

Moderate movement Score 2

(Less vigor but more than 10 seconds pulses or peristaltic waves)

Resting Score 3

(Less than 10 second pulses in head and body)

Apathetic Score 4

(Head and body with less than 2 second pulses)

Faint movement of suckers Score 5

(Movement of oral or ventral suckers only, whole body paralyzed)

Inert Score 6

(No movement at all or dead)

(b) *S. mansoni* adult worms

(c) *S. mansoni* juvenile worms

(d) *S. haemotobium* adult worms

(e) Cytotoxicity against human MRC-5 cell line

(f) Cytotoxicity against human HepG2 cell lines

Example Number	(a) F.hepatica motility score after 24, 48, 72h	(b) S.mansoni Adult (μM)	(c) S.mansoni Juvenile (μM)	(d) *S.haemotobium* (μM)	(e) Cytotox MRC-5 (μM)	(f) Cytotox HepG2 (μM)
Triclabe-ndazole	(3, 6, 6) at 40μM					
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	(6, 6, 6) at 5μM	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	(6, 6, 6) at 5μM	0.022	0.027			8.9
48		0.011	0.032			9.8
49		0.034	0.035			9.3
50	(6, 6, 6) at 5μM		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	(6, 6, 6) at 5μM	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	(6, 6, 6) at 5µM	0.071	0.128			4.8
90		0.077	0.468			9.3
91			0.53			
92			0.36			
93			0.83			
94	(6, 6, 6) at 5µM		0.25			10.6

Two compounds (example 17 and 50) were tested at different doses and motility recorded as shown below:

	Mean motility score of *F hepatica* assessed at 24, 48 and 72h treated with named compound		
Concentration of compound	Triclabendazole	Example 17	Example 50
0.04 µM		1, 1, 1	1, 1, 1
0.2 µM		3, 3, 6	2, 2, 2.5
1 µM		6, 6, 6	6, 6, 6
5 µM		6, 6, 6	6, 6, 6
40 µM	2, 3.5, 6		

More of the compounds have been tested against *S. mansoni* worms than *F. hepatica*. However, there appears to be a strong association between activity against *S. mansoni* and activity against *F. hepatica*. In total, nine compounds of the chemical class described herein have been tested against *F. hepatica*. All 6 of those with an IC_{50} against *S. mansoni* juvenile worms below 1 µM scored 6 against *F. hepatica* on motility assessment at 5 µM after 72h (see results above), whereas all 3 of those with an IC50 against *S. mansoni* juvenile worms greater than 1 µM scored 1 against *F. hepatica* on motility assessment at 5 µM after 72h (data not

shown because these 3 compounds are not within the scope of the claims). This association is statistically significant.

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 Na_2HPO_4 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)

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.

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/kgl	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		

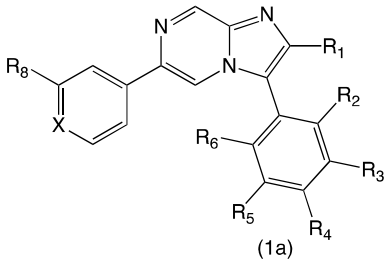
Age of infection (worms)	Compound Example No (Formulation)	Oral Dose	Mean worm recovery	Percent worm reduction	P value
	67 (F3)	50mg/kg	0	100	0.0008

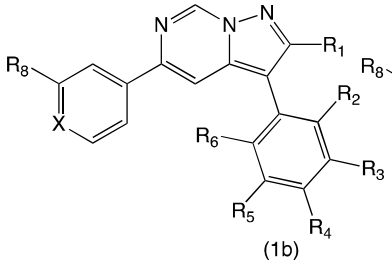
Preferred compounds are those which by inspection show a statistically significant (P value < 0.05) reduction in worm numbers of at least 50% when administered orally in the mouse model of infection as described above. For example, compounds 2, 17, 29, 50, 63 and 67.

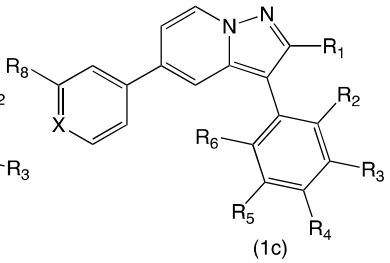
More preferred compounds are those which show a statistically significant (P value < 0.05) reduction in worm numbers of at least 50% when administered orally in the mouse model of infection as described above in a single dose of 25mg/kg or less. For example, compounds 2, 29, 50 and 63.

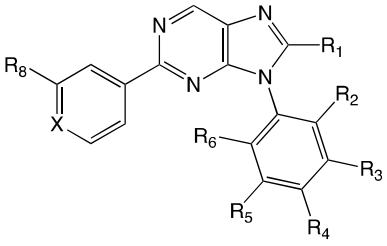
Claims

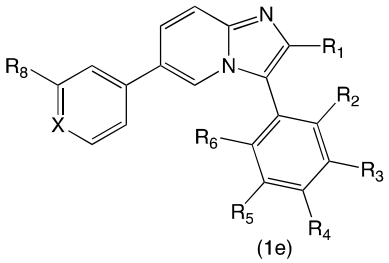
1. Use of a compound of formula (1a), (1b), (1c), (1d) or (1e) or a pharmaceutically acceptable salt or solvate thereof,


(1a)


(1b)


(1c)


(1d)


(1e)

wherein:

R_1 is C_1-C_4 alkyl optionally substituted with up to five F atoms, C_3-C_6 cycloalkyl optionally substituted with one methyl group, or C_4-C_7 cycloalkylmethyl;

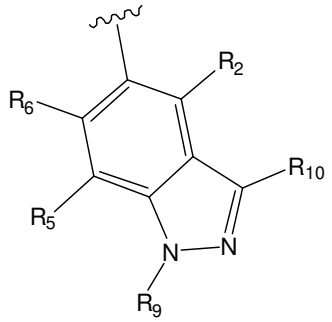
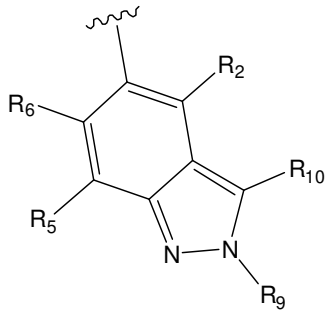
R_2 is H, F, Cl or OMe;

R_3 is H, OH, OMe, OPO(OH)OH or $OCH_2OPO(OH)OH$;

R_4 is H, OH, OMe, OPO(OH)OH or $OCH_2OPO(OH)OH$;

provided that **R_3** and **R_4** cannot both be H;

or **R_3** and **R_4** combine, together with the phenyl ring to which they are attached, to form an indazole group as shown below


or


R_5 is H, F, Cl or OMe;

R_6 is H, F, Cl or OMe;

X is N or C-**R_7**, wherein **R_7** is H or F;

R_8 is SF_5, Br, C_1-C_3 alkyl optionally substituted with up to seven F atoms, C_3-C_4 cycloalkyl, $OCH_2C{\equiv}CH$ or OC_1-C_3 alkyl optionally substituted with up to seven F atoms;
R_9 is H; and
R_{10} is H, F or Me
for the manufacture of a medicament for the treatment or prevention of fascioliasis.

2. A compound of formula (1e)**,** or a pharmaceutically acceptable salt or solvate thereof, wherein **R_1**, **R_2**, **R_3**, **R_4**, **R_5**, **R_6**, **X**, **R_7**, **R_8**, **R_9**,and **R_{10}** are as defined in claim 1 above.

3. The use of a compound according to claim 1, or a compound according to claim 2 wherein **R_1** is methyl, ethyl, n-propyl, isopropyl, cyclopropyl optionally substituted with one methyl group, cyclobutyl, cyclopropylmethyl, CHF_2, CF_3 or CH_2CF_3.

4. The use of a compound according to claim 3, or a compound according to claim 3 wherein **R_1** is ethyl, isopropyl, cyclopropyl, cyclobutyl, CF_3 or CH_2CF_3.

5. The use of a compound according to any one of claims 1, 3 or 4, or a compound according to any one of claims 2, 3 or 4 wherein **R_2** is H, F or Cl.

6. The use of a compound according to claim 5, or a compound according to claim 5 wherein **R_2** is F or Cl.

7. The use of a compound according to any one of claims 1 or 3 to 6, or a compound according to any one of claims 2 or 3 to 6 wherein **R_3** is H, OH, OMe or OPO(OH)OH.

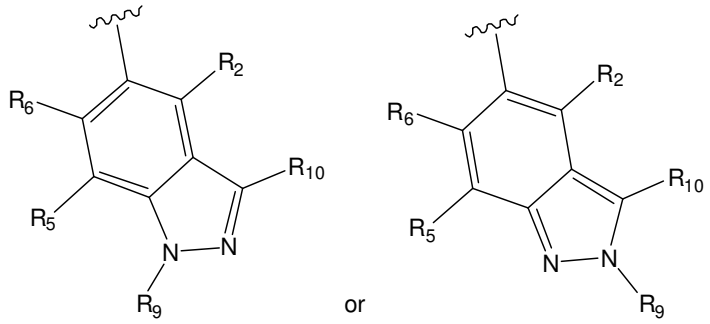
8. The use of a compound according to claim 7, or a compound according to claim 7 wherein **R_3** is H.

9. The use of a compound according to any one of claims 1 or 3 to 8, or a compound according to any one of claims 2 or 3 to 8 wherein **R_4** is H, OH, OMe or OPO(OH)OH.

10. The use of a compound according to claim 9, or a compound according to claim 9 wherein **R_4** is OH.

11. The use of a compound according to any one of claims 1 or 3 to 10, or a compound according to any one of claims 2 or 3 to 10 wherein substituents **R_3** and **R_4** combine,

together with the phenyl ring to which they are attached, to form an indazole group as shown below



wherein **R_9** and **R_{10}** are both H.

12. The use of a compound according to any one of claims 1 or 3 to 11, or a compound according to any one of claims 2 or 3 to 11 wherein **R_5** is H or OMe.

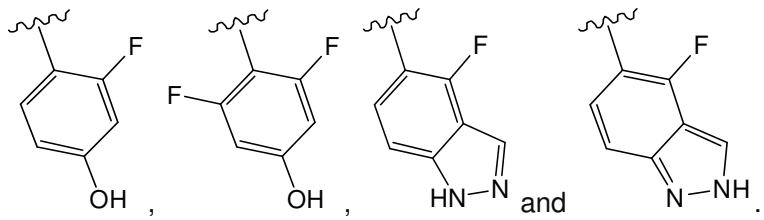
13. The use of a compound according to claim 12, or a compound according to claim 12 wherein **R_5** is H.

14. The use of a compound according to any one of claims 1 or 3 to 13, or a compound according to any one of claims 2 or 3 to 13 wherein **R_6** is H or F.

15. The use of a compound according to any one of claims 1 or 3 to 14, or a compound according to any one of claims 2 or 3 to 14 wherein **X** is C-**R_7** wherein **R_7** is H or F.

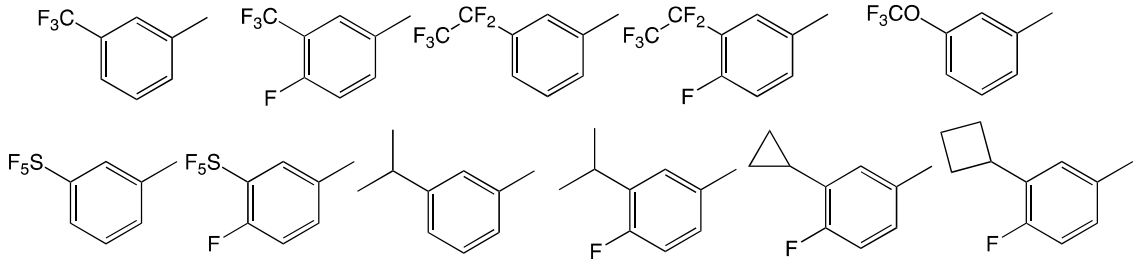
16. The use of a compound according to any one of claims 1 or 3 to 15, or a compound according to any one of claims 2 or 3 to 15 wherein **R_8** is CF_3, CF_2CF_3, CH_2CF_3, $CH(CH_3)_2$, OCF_3, $OCH(CH_3)_2$, cyclopropyl, cyclobutyl or SF_5.

17. The use of a compound according to any one of claims 1 or 3 to 16, or a compound according to any one of claims 2 or 3 to 16 wherein substituents **R_2** to **R_6** are chosen so as to provide the sub-structures:



and .

18. The use of a compound according to any one of claims 1 or 3 to 17, or a compound according to any one of claims 2 or 3 to 17 wherein substituents **R_7** and **R_8** are chosen so as to provide the sub-structures:



19. A compound of formula (1e) as defined in any one of claims 2 to 18, or a pharmaceutically acceptable salt or solvate thereof, for use in therapy.

20. A compound of formula (1e) as defined in any one of claims 2 to 18, or a pharmaceutically acceptable salt or solvate thereof, for use in the treatment of schistosomiasis.

21. Use of a compound of formula (1e) as defined in any one of claims 2 to 18, or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment of schistosomiasis.

22. A pharmaceutical composition comprising (i) a therapeutically effective amount of a compound of formula (1e) as defined in any one of claims 2 to 18, or a pharmaceutically acceptable salt or solvate thereof; and (ii) a pharmaceutically acceptable excipient.