Abstract:
The present invention relates to substituted imidazoi2-al]pyrazines of Formula (I) and their use as antibacterial agents.

Formula (I):

\[
\begin{align*}
R_1 & \quad \text{Substituted group} \\
R_2 & \quad \text{Substituted group} \\
R_3 & \quad \text{Substituted group}
\end{align*}
\]
The present invention relates to 2- or 3-substituted 8-amino-imidazo[1,2-a]pyrazines and derivatives thereof and methods of making such compounds. The present invention also relates to the use of these compounds as antibacterial agents and their use in methods of treating or preventing bacterial infection.

Background to the Invention

Gram-negative bacteria, such as Helicobacter pylori, Legionella pneumophilia, Brucella suis, Bartonella henselae and Bordetella pertussis, can cause serious infections in both animals and plants and many resources have been devoted to developing pharmaceutical agents to kill such bacteria. However, through natural selection these bacterial populations in a host can develop resistance to these pharmaceutical agents and survive, resulting in inefficient treatments which do not kill the bacteria in question.

These microorganisms have evolved a number of macromolecular secretion machineries to translocate proteins and nucleoprotein complexes from the bacterial cytosol to the host cell. Five types of secretion systems (I-V) have so far been identified, with a diverse range of functions including: the transfer of plasmid DNA from one cell to another (the major mechanism for the spread of antibiotic resistance genes between pathogenic bacteria); the secretion of proteins toxic to host cells; and the secretion of effector molecules required for the propagation of the microorganism within the host cell.

Type IV secretion systems (T4SS) are vital for the pathogenicity of these important gram-negative bacteria. For example, H. pylori utilizes the Type IV secretion system to translocate the toxic protein CagA into gastric epithelial cells, and in doing so induces a number of changes in the host cell. Also, T4SS mediate transfer of plasmid DNAs from one cell to another and, as such, are the primary cause for the spread of antibiotics resistance genes.
Type IV secretion systems require ATP as an energy source to drive this transport and therefore require a class of ATPases known as VirB11 ATPases, which are associated with the inner membrane.

Targeting the ATPase activity of VirB11 therefore represents an attractive approach to generating novel antibacterial agents. There has been one previous report of inhibition of the cag VirB11-type ATPase Caga (Microbiology, (2006), 152, 2919-2930).

It is therefore an object of the present invention to identify inhibitors of the VirB11 ATPase from H. pylori and its homologs in other gram-negative bacteria. These inhibitors should also be well absorbed from the gastrointestinal tract, be metabolically stable and possess favourable pharmacokinetic properties. Furthermore, the ideal drug candidate will exist in a physical form that is stable, non-hygroscopic and easily formulated.

**Summary of the Invention**

According to a first aspect of the invention there is provided a compound of Formula (I) for use in preventing or treating a bacterial infection:

$$R_1SO_2O \quad || \quad Z \quad || \quad L \quad || \quad Z \quad || \quad R_5 \quad R_4 \quad R_3\quad R_2$$

(1)

wherein:

- Z is O or NH;
- $R_1$ is selected from substituted alkyl, unsubstituted alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl or unsubstituted heteroaryl;
- one of $R_2$ and $R_3$ is H, and the other one of $R_2$ and $R_3$ is selected from substituted aryl, unsubstituted aryl, substituted heteroaryl or unsubstituted heteroaryl;
- L is a direct bond or is selected from:
wherein \( n = 0, 1, 2, 3, 4, 5 \) or 6;

\[
\text{or} \quad \begin{array}{c}
\text{N} \\
(\text{CH}_2)_n
\end{array}
\]

, each of which may optionally be substituted at one or more exocyclic positions; and wherein \( n = 0, 1, 2, 3, 4, 5 \) or 6; wherein

\[
\text{is a 5- or 6-membered nitrogen-containing heteroaryl moiety, optionally containing at least one or more further heteroatom; and}
\]

\( R_4 \) and \( R_5 \) are independently selected from H, alkyl, halo, alkoxy, alkylthio, hydroxy, cyano, amino and nitro;

or a pharmaceutically acceptable salt, solvate or prodrug thereof.

According to a second aspect of the invention there is provided a compound of Formula (I):

\[
\begin{array}{c}
R_4 \\
S\begin{array}{c}
O
\end{array}
\end{array}
\]

\[
\begin{array}{c}
Z \\
(\text{CH}_2)_n
\end{array}
\]

(1)

wherein:

\( Z \) is O or NH;

\( R_4 \) is selected from substituted alkyl, unsubstituted alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl or unsubstituted heteroaryl;

one of \( R_2 \) and \( R_3 \) is H, and the other one of \( R_2 \) and \( R_3 \) is selected from substituted aryl, unsubstituted aryl, substituted heteroaryl or unsubstituted heteroaryl;
L is a direct bond or is selected from:

\[
\text{NH} \quad \quad \quad \quad (\text{CH}_2)_n
\]

wherein \( n = 0, 1, 2, 3, 4, 5 \) or \( 6 \);

each of which may optionally be substituted at one or more exocyclic positions; and wherein \( n = 0, 1, 2, 3, 4, 5 \) or \( 6 \); wherein

\[
(\text{CH}_2)_n
\]

is a 5- or 6-membered nitrogen-containing heteroaryl moiety, optionally containing at least one or more further heteroatom; and

\( R_4 \) and \( R_5 \) are independently selected from \( \text{H}, \text{alkyl}, \text{halo}, \text{alkoxy}, \text{alkylthio}, \text{hydroxy}, \text{cyano}, \text{amino} \) and \( \text{nitro} \);
or a pharmaceutically acceptable salt, solvate or prodrug thereof.

According to a second aspect of the present invention there is also provided a compound of Formula (la):

\[
\text{R}_1 \quad \text{SO}_2 \quad \text{L} \quad \text{NH} \quad (\text{la})
\]

wherein:

\( \text{R}_1 \) is selected from substituted aryl, unsubstituted aryl, substituted heteroaryl or unsubstituted heteroaryl;

one of \( \text{R}_2 \) and \( \text{R}_3 \) is \( \text{H} \), and the other one of \( \text{R}_2 \) and \( \text{R}_3 \) is selected from substituted aryl, unsubstituted aryl, substituted heteroaryl or unsubstituted heteroaryl;
L is a direct bond or is selected from:

\[
\begin{array}{c}
\text{NH} \\
\text{OR} \\
\text{N}
\end{array}
\]

, each of which may optionally be substituted at one or more exocyclic positions; wherein

\[
\text{N}
\]

is a 5- or 6-membered nitrogen-containing heteroaryl moiety, optionally containing at least one or more further heteroatom; and

\[
\begin{array}{c}
\text{R}_4 \\
\text{R}_5
\end{array}
\]

are independently selected from H, alkyl, halo, alkoxy, alkylthio, hydroxy, cyano, amino and nitro;

or a pharmaceutically acceptable salt, solvate or prodrug thereof.

According to a third aspect of the invention there is provided a compound as defined according to the second aspect or a pharmaceutically acceptable salt thereof for use in treating or preventing bacterial infection.

According to a fourth aspect of the invention there is provided a method of treating or preventing bacterial infection in a subject by administering a therapeutically effective amount of a compound according to the second aspect or a pharmaceutically acceptable salt thereof to a patient in need thereof.

According to a fifth aspect of the invention there is provided a use of a compound of the second aspect in the manufacture of a medicament for treating or preventing bacterial infection or inhibiting the spread of antibiotic resistance genes.

The bacterial infection may be infection with *Helicobacter pylori*, *Legionella pneumophila*, *Brucella suis*, *Bartonella henselae* or *Bordetella pertussis*. Inhibition of conjugation applies to all bacterial Gram-negative pathogens.

According to a sixth aspect of the invention there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound according to
the second aspect, optionally one or more other active ingredients and a pharmaceutically acceptable carrier.

According to a seventh aspect of the invention, there is provided a method of making a compound of the second aspect which comprises reacting a compound of Formula (II):

\[
\begin{array}{c}
\text{X} \\
\text{N} \\
\text{N} \\
\text{R}_2 \\
\text{R}_3 \\
\end{array}
\]

wherein \( X \) is a leaving group, for example a halo group (eg chloro), and \( R_2 \) and \( R_3 \) are as defined above, with a compound of the formula:

\[
\begin{array}{c}
\text{R}_1 \text{SO}_2 \\
\text{O} \\
\text{L} \\
\text{Z} \\
\end{array}
\]

wherein \( R_1, L \) and \( Z \) are as above.

According to a seventh aspect of the invention, there is further provided a method of making a compound of the second aspect which comprises reacting a compound of Formula (II):

\[
\begin{array}{c}
\text{X} \\
\text{N} \\
\text{N} \\
\text{R}_2 \\
\text{R}_3 \\
\end{array}
\]

wherein \( X \) is a leaving group, for example a halo group (eg chloro), and \( R_2 \) and \( R_3 \) are as defined above, with a compound of the formula:

\[
\begin{array}{c}
\text{R}_1 \text{SO}_2 \\
\text{O} \\
\text{L} \\
\text{NH}_2 \\
\end{array}
\]

wherein \( R_1 \) and \( L \) are as above.

According to an eighth aspect of the invention there is provided a method of making a compound of the second aspect in which \( R_3 \) is substituted aryl, unsubstituted aryl, substituted heteroaryl or unsubstituted heteroaryl, comprising:
(i) reacting a compound of Formula (IV)

\[
\begin{array}{c}
\text{OH} \\
R_3 \text{--} \text{NH}_2
\end{array}
\] (IV)

with 2,3-dichloropyrazine;

(ii) oxidising the product of (i);

(iii) effecting an intramolecular cyclisation of the product of (ii); and

(iv) coupling the product of (iii) with a compound of Formula (VI)

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
R_1 \text{--} \text{SO} \text{--} \text{S} \\
\text{O} \\
\text{L---Z---H}
\end{array}
\] (VI)

wherein

\[R_1, R_3, L \text{ and } Z \text{ are as above.}\]

According to an eighth aspect of the invention there is further provided a method of making the compounds of the second aspect in which \( R_3 \) is substituted aryl, unsubstituted aryl, substituted heteroaryl or unsubstituted heteroaryl, comprising:

(i) reacting a compound of Formula (IV)

\[
\begin{array}{c}
\text{OH} \\
R_3 \text{--} \text{NH}_2
\end{array}
\] (IV)

with 2,3-dichloropyrazine;

(ii) oxidising the product of (i);

(iii) effecting an intramolecular cyclisation of the product of (ii); and

(iv) coupling the product of (iii) with a compound of Formula (III)

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
R_1 \text{--} \text{SO} \\
\text{O} \\
\text{L---NH}_2
\end{array}
\] (III)

wherein

\[R_1, R_3 \text{ and } L \text{ are as above.}\]

According to a ninth aspect there is provided a method of making a compound of the second aspect in which \( R_2 \) is substituted aryl, unsubstituted aryl, substituted heteroaryl or unsubstituted heteroaryl, comprising:

(i) reacting a compound of Formula (V)

\[
\begin{array}{c}
\text{O} \\
R_2 \text{--} \text{Br}
\end{array}
\] (V)
with 2-amino-3-chloropyrazine;

(ii) coupling the product of (i) with a compound of Formula (VI)

\[ \text{Formula (VI)} \]

wherein

R\(_1\), R\(_2\), L and Z are as above.

According to a ninth aspect there is also provided a method of making the compounds of the second aspect in which R\(_2\) is substituted aryl, unsubstituted aryl, substituted heteroaryl or unsubstituted heteroaryl, comprising:

(i) reacting a compound of Formula (V)

\[ \text{Formula (V)} \]

with 2-amino-3-chloropyrazine;

(ii) coupling the product of (i) with a compound of Formula (III)

\[ \text{Formula (III)} \]

wherein

R\(_1\), R\(_2\) and L are as above.

Definitions

The phrase "a" or "an" entity as used herein refers to one or more of that entity; for example, a compound refers to one or more compounds or at least one compound.

As such, the terms "a" (or "an"), "one or more", and "at least one" can be used interchangeably herein.

The term "alkyl" as used herein denotes an unbranched or branched chain, saturated, monovalent hydrocarbon residue containing 1 or more carbon atoms. Examples of alkyl groups include, but are not limited to, lower alkyl groups include methyl, ethyl, propyl, \(\beta\)-propyl, n-butyl, \(\beta\)-butyl, i-butyl or pentyl, isopentyl, neopentyl and hexyl. For example, alkyl may refer to lower alkyl groups of CrC\(_6\).
The term "substituted alkyi" as used herein denotes an alkyi group containing one or more substituents selected from the group consisting of alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkyldi thiocarbonyl, alkoxycarbonyl, phosphinate, phos phonato, phosphinato, cyano, amino, alkyl amino, dialkylamino, arylamino, diarylamino, alkylarylamino, acyl amino, alkylcarbonylamino, arylcarbonylamino, carbamoyl, ureido, amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfate, alkylsulfanyl, sulfonate sulfamoyl, sulfonamido, nitro, trifluoromethyl, azido, heterocyclyl, alkylaryl or an aromatic or heteroaromatic group.

The term "alkylene" as used herein means a divalent unbranched or branched saturated hydrocarbon radical consisting solely of carbon and hydrogen atoms, having 1 or more carbon atoms inclusive, for example lower alkylene groups of C1-C6, unless otherwise indicated. Examples of alkylene radicals include, but are not limited to, methylene, ethylene, propylene, 2-methylethylene, 3-methylpropylene, 2- ethylethylene, pentylene, hexylene, and the like.

The term "haloalkyl" as used herein denotes an unbranched or branched chain alkyi group as defined above wherein 1, 2, 3 or more hydrogen atoms are substituted by a halogen. Examples are 1-fluoromethyl, 1-chloromethyl, 1-bromomethyl, 1-iodomethyl, trifluoromethyl, trichloromethyl, tribromomethyl, triiodomethyl, 1-fluoroethyl, 1-chloroethyl, 1-bromoethyl, 1-idoethyl, 2-fluoroethyl, 2-chloroethyl, 2-bromoethyl, 2-idoethyl, 2,2-dichloroethyl, 3-bromopropyl or 2,2,2-trifluoroethyl. The term "fluoroalkyl" refers to a "haloalkyl" wherein the halogen is fluorine.

The term "cyloalkyl" as used herein denotes a saturated carbocyclic ring containing 3 to 7 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl. In one embodiment, the cyloalkyl group may be substituted with one or more substituents as defined above with reference to substituted alkyi.

The term "alkenyl" as used herein denotes an unsubstituted hydrocarbon chain radical having 2 or more carbon atoms, preferably 2 to 6 carbon atoms and having one or two olefinic double bonds, for example C2-C6. Examples are vinyl, 1-propenyl, 2-propenyl,
(allyl) or 2-butenyl (crotyl). In one embodiment, the alkenyl group may be substituted with one or more substituents as defined above with reference to substituted alkyl.

The term "alkynyl" as used herein denotes an unsubstituted hydrocarbon chain radical having 2 or more carbon atoms, preferably 2 to 6 carbon atoms and having one or where possible two triple bonds. Examples are ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl or 3-butynyl. In one embodiment, the alkylnyl group may be substituted with one or more substituents as defined above with reference to substituted alkyl.

The term "alkoxy" as used herein denotes an unsubstituted unbranched or branched chain alkyloxy group wherein the "alkyl" portion is as defined above such as methoxy, ethoxy, n-propoxy, i-propoxy, n-butyloxy, i-butyloxy, pentyloxy and hexyloxy including their isomers.

The term "haloalkoxy group" as used herein means an O-haloalkyl group, wherein haloalkyl is as defined above. Examples of haloalkoxy groups include, but are not limited to, 2,2,2-trifluoroethoxy, difluromethoxy and 1,1,1,3,3,3-hexafluoro-iso-propoxy.

The term "thioalkyl" or "alkylthio" as used herein refers to a group -SR where R is an alkyl group as defined herein such as methylthio, ethylthio, n-propylthio, i-propylthio and n-butylthio including their isomers.

The term "alkoxyalkyi" as used herein refers to the radical R'R"-, wherein R' is an alkoxy radical as defined herein, and R" is an alkylene radical as defined herein with the understanding that the attachment point of the alkoxyalkyi moiety will be on the alkylene radical. Examples are methoxymethyl, methoxyethyl, methoxypropyl, ethoxymethyl, ethoxyethyl, ethoxypropyl, propoxypropyl, methoxybutyl, ethoxybutyl, propoxybutyl, butyloxybutyl, i-butyloxybutyl, methoxypentyl, ethoxypentyl, propoxypropyl, butyloxybutyl, i-butyloxybutyl, methoxypentyl, ethoxypentyl, propoxypropyl including their isomers.
The terms "hydroxyalkyl" as used herein denotes the radical R'R" where R' is an hydroxy radical and R" is alkylene as defined herein and the attachment point of the hydroxyalkyl radical will be on the alkylene radical.

The term "acyl" as used herein denotes a group of formula C(=0)R ("alkylcarbonyl") wherein R is hydrogen, unbranched or branched alkyl containing 1 or more carbon atoms, for example a lower alkyl Ci-C₆ group, cycloalkyl containing 3 to 7 carbon atoms, an aryl, an alkoxy, or a NR'R" group. The term acyl includes a group of formula C(=0)OR′ ("alkoxycarbonyl") or C(=0)NR'R" ("carbamoyl") where R is an alkyl group as defined herein above.

The term "acylating agent" as used herein refers to a reagent which is capable of transferring an acyl moiety as defined previously to another functional group capable of reacting with the acylating agent. Typically an alkylcarbonyl is introduced by reaction with an anhydride or an acyl halide. The term "anhydride" as used herein refers to compounds of the general structure RC(0)-0-C(0)R wherein R is as defined in the previous paragraph. The term "acyl halide" as used herein refers to the group RC(0)X wherein X is bromo or chloro. Typically an alkoxycarbonyl is introduced by reaction with an alkoxycarbonyl chloride. The term "alkoxycarbonyl chloride" as used herein refers to compounds of the general structure ROC(=0)Cl. Typically a carbamoyl group is introduced by reaction with an isocyanate. The term "isocyanate" as used herein refers to compounds of the general structure RN=C=0.

The functional group depicted as "-XC(=Y)Z" wherein X and Y are independently O or NR' and Z is C₁₋₆ alkoxy, NR'R", alkyl or alkoxyalkyl preferably refers to "guanidines" (-NR'(=NR") NR'R"), "imidates" (-OC(=NR')alkyl), "amidines" (-NR'C(=NR')alkyl), "carbonates" (-OC(=0)OR), "carbamates" (-OC(=0) NR'R" or -NR'C(=0)OR), "ureas" (-NR'C(=0)NR'R") or "amides" (-NR'C(=0)alkyl) or "esters" (-OC(=0)alkyl) where R' and R" are alkyl groups as defined herein.

The functional group "C(=Y)Z" as used herein refers to esters, amides, imidates and amidines.
The term "heterocyclylalkyl" as used herein means a radical R'R" where R' is an alkylene radical and R" is a heterocycl radical as defined herein. Examples of heterocyclylalkyl radicals include, but are not limited to, tetrahydropyran-2-ylmethyl, 2-piperidinylmethyl, 3-piperidinylmethyl, morpholin-1-ylpropyl, and the like.

The term "alkylamo" as used herein means a radical-N R'R", wherein R' is hydrogen and R" is an alkyl radical as defined herein. The term "dialkylamino" as used herein means a radical-N R'R", wherein R' and R" are alkyl radicals as defined herein.

Examples of alkylamino radicals include, but are not limited to, methylamino, ethylamino, cyclopropylmethylamino, dicyclopentylmethylamino, dimethylamino, methylethylamino, diethylamino, di(1-methylethyl)amino, and the like.

The term "aryl" as used herein denotes an optionally substituted monocyclic or polycyclic-aromatic group comprising carbon and hydrogen atoms. Examples of suitable aryl groups include, but are not limited to, phenyl and naphthyl (e.g. 1-naphthyl or 2-naphthyl). Suitable substituents for aryl are selected from the group consisting of C1-6 alkyl, C1-6 alkenyl, C1-6 alkynyl, C1-6 haloalkyl, C1-6 alkoxy, C1-6 haloalkoxy, C1-6 alkylthio, arylthio, alkoxy carbonyl, amino, substituted amino for example alkylamino, CON R'R", carbamoyl, carbamate, ureido, amidino, imino, aryl, nitro, halogen and cyano. Optionally substituted phenyl in R1 or R2 or R3 can be for example 2-phenoxypenyl, 2-methyl-phenyl, 3-methyl-phenyl, 4-methyl-phenyl, 2,3-dimethylphenyl, 2,4-dimethylphenyl, 2,5-dimethylphenyl, 2,6-dimethylphenyl, 3,4-dimethylphenyl, 3,5-dimethylphenyl, 2,3,4,5,6-trimethylphenyl, 2,3,4,5-trimethylphenyl, 2,4-pentamethylphenyl, 2-cyano-phenyl, 3-cyano-phenyl, 4-cyano-phenyl, 2,3-dicyanophenyl, 2,4-dicyanophenyl, 2,5-dicyanophenyl, 2,6-dicyanophenyl, 3,4-dicyanophenyl, 3,5-dicyanophenyl, 3,6-dicyanophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2,3-dimethoxyphenyl, 2,4-dimethoxyphenyl, 2,5-dimethoxyphenyl, 2,6-dimethoxyphenyl, 3,4-dimethoxyphenyl, 3,5-dimethoxyphenyl, 3,6-dimethoxyphenyl. In one embodiment, aryl may be substituted with a PEG moiety.

The term "heteroaryl" or "heteroaromatic" as used herein means a monocyclic or bicyclic radical of 5 to 12 ring atoms having at least one aromatic ring containing four to eight atoms per ring, incorporating one or more N, O, or S heteroatoms, the remaining
ring atoms being carbon, with the understanding that the attachment point of said heteroaryl radical will be on said aromatic ring. As well known to those skilled in the art, heteroaryl rings have less aromatic character than their all-carbon counter parts. Thus, for the purposes of the invention, a heteroaryl group need only have some degree of aromatic character.

Examples of heteroaryl moieties include monocyclic aromatic heterocycles having 5 to 6 ring atoms and 1 to 3 heteroatoms including but not limited to, pyridinyl, pyrimidinyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, thiophenyl and oxadiazolyl which can optionally be substituted with one or more, preferably one or two substituents selected from hydroxy, cyano, alkyl, alkoxy, thio, lower haloalkoxy, alkylthio, halo, haloalkyl, alkylsulfanyl, alkylsulfonyl, halogen, amino, alkylamino, dialkylamino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, nitro, alkoxycarbonyl and carbamoyl, alkylcarbamoyl and dialkylcarbamoyl and aryloxy such as benzyloxy.

Particularly preferred examples of heteroaryl moieties include bicyclic aromatic heterocycles such as quinoxaline and quinoline.

The term "heterocyclylalkyl" as used herein means a radical \(-R'R''\) where \(R'\) is an alkylene radical and \(R''\) is a heterocyclyl radical as defined herein. Examples of heterocyclylalkyl radicals include, but are not limited to, 2-piperidinylmethy1, 3-piperidinylmethyl, morpholin-1-ylpropyl, and the like.

The term "heterocycle" or "heterocyclic" as used herein means a non-aromatic monocyclic or polycyclic ring comprising carbon and hydrogen atoms and one or more N, S, or O heteroatoms. A heterocyclic group can have one or more carbon-carbon double bonds or carbon-heteroatom double bonds in the ring as long as the ring is not rendered aromatic by their presence. Examples of heterocycloalkyl groups include pyrrolidinyl, pyrrolidinyl, piperidinyl, piperidino, piperazinyl, piperazino, morpholinyl, morpholino, thiomorpholinyl, thiomorpholino. A heterocyclic group can be unsubstituted or substituted with one to three suitable substituents selected from hydroxy, cyano, alkyl, alkoxy, thio, lower haloalkoxy, alkylthio, halo, haloalkyl, alkylsulfanyl, alkylsulfonyl, halogen, amino, alkylamino, dialkylamino, aminoalkyl, alkylaminoalkyl, and dialkylaminoalkyl, nitro, alkoxycarbonyl and carbamoyl, alkylcarbamoyl and dialkylcarbamoyl.
The terms "amino", "alkylamino" and "dialkylamino" as used herein refer to $-\text{NH}_2$, $-\text{NHR}$ and $-\text{NR}_2$ respectively and $R$ is alkyl as defined above. The two alkyl groups attached to a nitrogen in a dialkyl moiety can be the same or different. The terms "aminoalkyl", "alkylaminoalkyl" and "dialkylaminoalkyl" as used herein refer to $\text{NH}_2(\text{CH}_2)_n\cdot R\text{HN}(\text{CH}_2)_n\cdot$ and $R_2\text{N}(\text{CH}_2)_n\cdot$ respectively wherein $n$ is 1 or more and $R$ is alkyl as defined above.

The term "acyl" or "alkylcarbonyl" as used herein denotes a radical of formula $\text{C}(=\text{O})R$ wherein $R$ is hydrogen, unbranched or branched alkyl containing 1 or more carbon atoms, for example a lower alkyl $\text{CrC}_6$ group, or a phenyl group.

The term "acylamino" as used herein denotes a radical of formula $-\text{NH-C}(=\text{O})-R$ wherein $R$ is hydrogen, unbranched or branched alkyl containing 1 or more carbon atoms, for example a lower alkyl $\text{Ci-C}_6$ group, cycloalkyl containing 3 to 7 carbon atoms or an aryl.

The term "halogen" as used herein means fluorine, chlorine, bromine, or iodine. Correspondingly, the meaning of the term "halo" encompasses fluoro, chloro, bromo, and iodo.

The term "alkythio" or "thioalkyl" means an $-\text{S-alkyl group}$, wherein alkyl is as defined above such as meththio, ethylthio, $n$-propylthio, $i$-propylthio, $n$-butylthio, hexylthio, including their isomers.

The term "alkylsulfinyl" as used herein means the radical $\text{S}(0)R'$, wherein $R'$ is alkyl as defined herein. Examples of alkylaminosulfonyl include, but are not limited to methylsulfinyl and $/so$-propylsulfinyl.

The term "alkylsulfonyl" as used herein means the radical $\text{S}(0)\_2R'$, wherein $R'$ is alkyl as defined herein. Examples of alkylaminosulfonyl include, but are not limited to methylsulfonyl and $/so$-propylsulfonyl.
The term "sulfonylating agent" as used herein refers to a reagent which is capable of transferring an alkyl sulfonyl moiety as defined previously to another functional group capable of reacting with the sulfonating agent such as a sulfonyl chloride Cl-SO₂⁻R.

The prefix "carbamoyl" as used herein means the radical -CONH₂. The prefix "N-alkylcarbamoyl" and "N,N-dialkylcarbamoyl" as used herein means the radical CONHR' or CONR'R" respectively wherein the R' and R" groups are independently alkyl as defined herein.

**Detailed Description of the Invention**

As described above, the present inventors have identified compounds of Formula (I) as being inhibitors of the bacterial ATPase VirB11 and its homologs, and thus being useful as antibacterial agents. The compounds when used as antibacterial agents reduce the spread of antibiotic resistance.

In an embodiment of the compound of Formula I, R₂ is H; and R₃ is selected from substituted aryl, unsubstituted aryl, substituted heteroaryl or unsubstituted heteroaryl.

In another embodiment, R₂ is selected from substituted aryl, unsubstituted aryl, substituted heteroaryl or unsubstituted heteroaryl; and R₃ is H.

In an embodiment, R₄ and R₅ are independently selected from H, lower alkyl, halo (e.g. chloro, fluoro or bromo), alkoxy, alkylthio, hydroxy, cyano, amino and nitro. For example, R₄ and R₅ are each hydrogen.

In one embodiment, Z is NH.

In the embodiment where L is , the amino substituent may be in the ortho, meta or para position. In another embodiment, the amino substituent is in the para position.
In the embodiment where L is , the amino substituent may be in the ortho, meta or para position. In another embodiment, the amino substituent is in the para position.

In one embodiment, \( R_i \) is unsubstituted or substituted alkyl. In another embodiment, \( R_i \) is unsubstituted or substituted aryl. In another embodiment, \( R_i \) is unsubstituted or substituted heteroaryl.

In one embodiment, \( R_i \) is substituted aryl substituted with a poly(ethylene) glycol or PEG moiety. The PEG moiety may be coupled to the aryl group via a linker. In one embodiment, the linker is a carbamate linker. However, it would be clear to the skilled person that the present invention encompasses any linker, for example but not limited to an amide, ester, carbonate, imidate, alkyl, alkenyl or alkynyl linker. In one embodiment, the PEG moiety is coupled directly to the aryl group. In a further embodiment, the PEG moiety may itself be substituted. In one embodiment, the PEG moiety may be substituted with an alkenyl, alkynyl or maleido group.

The PEG moiety may comprise one or more PEG monomers, for example two PEG monomers, three PEG monomers or four PEG monomers. Thus, the PEG moiety may comprise \( \text{(PEG)}_i \), \( \text{(PEG)}_2 \), \( \text{(PEG)}_3 \) or \( \text{(PEG)}_4 \).

In an embodiment, the compound is not selected from the group consisting of:

- 4-methyl-/V-[3-(2-naphthylimidazo[1,2-a]pyrazin-8-yl]benzenesulfonamide,
- 4-methyl-/V-[3-(2-phenoxypyphenylimidazo[1,2-a]pyrazin-8-yl]benzenesulfonamide,
- /V-[3-(3,4-dimethoxyphenylimidazo[1,2-a]pyrazin-8-yl]-4-methyl-benzenesulfonamide,
- 4-methyl-/V-[3-(3,5-dimethylphenylimidazo[1,2-a]pyrazin-8-yl]benzenesulfonamide,
- 4-methyl-/V-[4-[3-(2-naphthylimidazo[1,2-a]pyrazin-8-yl]aminophenyl]benzenesulfonamide,
- 4-methyl-/V-[4-[3-(3-thienylimidazo[1,2-a]pyrazin-8-yl]amino]phenyl]benzenesulfonamide.
In an embodiment, the compound is not selected from the compounds of Table 1:

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-methyl-/V-[3-(2-naphthyl)imidazo[1,2-a]pyrazin-8-yl]benzenesulfonamide</td>
<td></td>
</tr>
<tr>
<td>4-methyl-/V-[3-(2-phenoxyphenyl)imidazo[1,2-a]pyrazin-8-yl]benzenesulfonamide</td>
<td></td>
</tr>
<tr>
<td>/V-[3-(3,4-dimethoxyphenyl)imidazo[1,2-a]pyrazin-8-yl]-4-methyl-benzenesulfonamide</td>
<td></td>
</tr>
<tr>
<td>4-methyl-/V-[3-(3,5-dimethylphenyl)imidazo[1,2-a]pyrazin-8-yl]benzenesulfonamide</td>
<td></td>
</tr>
<tr>
<td>4-methyl-/V-[4-[3-(2-naphthyl)imidazo[1,2-a]pyrazin-8-yl]aminophenyl]benzenesulfonamide</td>
<td></td>
</tr>
</tbody>
</table>

Table 1

In an embodiment, the compound is selected from the group consisting of:

5 4-methyl-/V-[3-(2-naphthyl)imidazo[1,2-a]pyrazin-8-yl]benzenesulfonamide,
4-methyl-/V-[3-(2-phenoxyphenyl)imidazo[1,2-a]pyrazin-8-yl]benzenesulfonamide,
/V-[3-(3,4-dimethoxyphenyl)imidazo[1,2-a]pyrazin-8-yl]-4-methyl-benzenesulfonamide,
4-methyl-/V-[3-(3,5-dimethylphenyl)imidazo[1,2-a]pyrazin-8-yl]benzenesulfonamide,
4-methyl-/V-[4-[3-(2-naphthyl)imidazo[1,2-a]pyrazin-8-yl]aminophenyl]benzenesulfonamide,
4-methyl-/V-[4-[3-(3-thienyl)imidazo[1,2-a]pyrazin-8-yl]amino]phenyl]benzenesulfonamide,
4-methyl-/V-[2-(2-naphthyl)imidazo[1,2-a]pyrazin-8-yl]benzenesulfonamide,
4-methyl-/V-[2-(2-phenoxyphenyl)imidazo[1,2-a]pyrazin-8-yl]benzenesulfonamide,
/V-[2-(3,4-dimethoxyphenyl)imidazo[1,2-a]pyrazin-8-yl]-4-methyl-benzenesulfonamide,
/V-[2-(3,5-dimethylphenyl)imidazo[1,2-a]pyrazin-8-yl]-4-methyl benzenesulfonamide,
4-methyl-/V-[4-[2-(naphthyl)imidazo[1,2-a]pyrazin-8-yl]aminophenyl]benzenesulfonamide,
4-methyl-/V-[4-[2-(3-thienyl)imidazo[1,2-a]pyrazin-8-yl]aminophenyl]benzenesulfonamide,
4-methyl-/V-[4-[2-(3,4-dimethoxyphenyl)imidazo[1,2-a]pyrazin-8-yl]-4-methyl-benzenesulfonamide,
4-methyl-/V-[4-[2-(3,5-dimethylphenyl)imidazo[1,2-a]pyrazin-8-yl]-4-methyl benzenesulfonamide,
4-methyl-/V-[4-(2-naphthyl)imidazo[1,2-a]pyrazin-8-yl]aminophenyl]benzenesulfonamide,
4-methyl-/V-[4-(2-(naphthalen-2-yl)imidazo[1,2-a]pyrazin-8-ylaminophenyl]benzenesulfonamide,
4-methyl-/V-(4-(2-(3-thienyl)imidazo[1,2-a]pyrazin-8-ylamino)phenyl)benzenesulfonamide,
4-methyl-/V-(4-(2-(2-phenoxyphenyl)imidazo[1,2-a]pyrazin-8-ylamino)phenyl]benzenesulfonamide,
4-methyl-/V-(4-((2-(naphthalen-2-yl)imidazo[1,2-a]pyrazin-8-ylamino)methyl)phenyl)benzenesulfonamide,
I
n an embodiment, the compound is selected from the compounds in Table 2.
In an embodiment, any one of the compounds of Table 2 may be used in treating or preventing bacterial infection.
All of the compounds of the Formula (I) can be prepared by the procedures described in the general methods presented below or by the specific methods described in the Examples section. The present invention also encompasses any one or more of these methods for preparing the compounds of Formula (I), in addition to any novel intermediates used therein. It will be clear to the skilled person that many steps in the syntheses of these compounds are analogous and where a particular step is not explicitly described that it is readily apparent from the steps that are described in relation to other compounds.

**General Synthesis**

The compounds of the present invention wherein \( Z = \text{NH} \) may be prepared, for example, as shown in the following General Method A for 3-substituted derivatives or General Method B for 2-substituted derivatives.

Unless otherwise indicated, \( R_1, R_2 \) and \( R_3 \) in the following methods are as defined above. All starting materials in the following general syntheses may be commercially available or obtained by conventional methods known to those skilled in the art.
Solvents and reagents were obtained from commercial sources and were used as received unless otherwise stated. Dry solvents were dried over anhydrous columns. Moisture levels were usually <15 ppm by Karl Fischer titration. Brine refers to a saturated solution of sodium chloride. Anhydrous magnesium sulfate (MgSO₄) or sodium sulfate (Na₂SO₄) were used as drying agents after reaction workup, as indicated. Pet Ether refers to the fraction of light petroleum ether boiling in the range 40-60 °C.

Where a solvent is specified, it will be readily understood that there is no restriction on the particular solvent to be used, provided that it has no adverse effect on the reaction or reagents involved and that it can at least partially dissolve the reagents. Examples of suitable solvents include: halogenated hydrocarbons, such as dichloromethane, chloroform, carbon tetrachloride and 1,2-dichloroethane; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran and dioxane; nitriles, such as acetonitrile and benzonitrile; aromatic hydrocarbons, such as benzene, toluene and nitrobenzene; amides, such as formamide, N,N,N,N-dimethylformamide, and N,N,N-dimethylacetamide sulfoxides, such as dimethyl sulfoxide and sulfolane; or mixed solvents thereof.

**Method A**

\[ \begin{align*}
\text{R}_3\text{CBr} & \rightarrow \text{R}_3\text{CO}_3 \text{N}_3 \quad \text{(a)} \\
\text{Cl}_{3}\text{N} & \rightarrow \text{R}_3\text{H} & \text{H} & \rightarrow \text{R}_3\text{NH}_2
\end{align*} \]

**Scheme 1** Reagents: a) NaN₃, DMSO, 0 °C to RT, 1.5h; b) NaBH₄, MeOH, 0 °C, 1h.; c) H₂, Pd/C, MeOH, RT, 3-16h; d) 3-dichloropyrazine (shown), NEt₃, dioxane, reflux, 16-20 hours; e) (COCl)₂, DMSO, NEt₃, CH₂Cl₂, -78°C, 3h; f) TFA/TFAA, toluene, room
temp. 72h; g) "sulfonamide" (shown), Pd(dba)$_2$, tBu-XPhos, K$_2$CO$_3$, tBuOH, reflux, 16-48h.

For each 3-substituted derivative, the synthesis of the amino alcohol was achieved via a-bromination of the aryl ketone with pyridinium tribromide. This was followed by substitution of the a-bromine with an azide, giving the azidoketone which was then reduced to give the corresponding azido-alcohol. Hydrogenation to give the amino alcohol was performed at atmospheric pressure, with the exception of the thiophene analogue which required 3 bar pressure to go to completion. Coupling with 2,3-dichloropyrazine in 1,4-dioxane afforded the pyrazinyl-amino alcohol in good yields. Swern oxidation to the ketone was followed by acid-induced cyclisation to form the 3-aryl-8-chloroimidazo[1,2-a]pyrazine.

In order to install the sulfonamide groups, a Buchwald-Hartwig coupling approach was used. Several different palladium catalysts and ligands were tested.

It will be understood that there are many alternative transition metal catalysts and ligands which could be used to effect this reaction. Examples of palladium catalysts which may be suitable include but are not limited to: palladium metal, palladium-carbon, palladium (II) acetate, tris(dibenzylideneacetone)dipalladiumchloroform, [1,2-bis(diphenylphosphino)ethane]palladium dichloride, bis(tri-o-tolylphosphine)palladium dichloride, bis(triphenylphosphine)palladium dichloride, tetrakis(triphenylphosphine) palladium or dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium. One preferred catalyst is Pd(dba)$_2$.

Examples 1 to 6 were prepared according to this general method.
Method B

Scheme 2 Reagents: a) 2-amino-3-chloropyrazine (shown), NaHCO₃, tBuOH, reflux 20-40h; b) Pd(dba)₂, tBu-XPhos, K₂CO₃, tBuOH, reflux, 16-48h.

Using the a-bromo aryl ketones, the key 8-chloro-2-aryl imidazo[1,2-a]pyrazine intermediates were readily prepared by condensation with 2-amino-3-chloropyrazine (Scheme 2). Again, the sulfonamide groups were introduced using Buchwald-Hartwig coupling chemistry, to give Examples 7-17 and 29 to 23 in low to moderate yields. However the coupling was very substrate dependent: for the 3,5-dimethylphenyl derivative the previous combination gave no reaction at all, and therefore Pd(dppf)Cl₂ had to be used as an alternative. It was also found that DavePhos ligand could be used in place of 'Butyl-XPhos to give the substrates in similar yields.

For compounds wherein Z = O, these can be made by a route exemplified by the synthesis of Example 18 below.

Analysis of compounds

Melting points (Mpt) were recorded on a Gallenkamp Melting Point Apparatus and are uncorrected. Proton nuclear magnetic resonance (¹H NMR) were recorded using Bruker AV400 (400 MHz), AV500 (500 MHz) and AV600 (600MHz) spectrometers as indicated. Carbon nuclear magnetic resonance (¹³C NMR) were recorded using Bruker AV400 (100 MHz), AV500 (125 MHz) and AV600 (150MHz) spectrometers as indicated. Spectra were obtained using CDCl₃, CD₃OD, CD₂Cl₂ and DMSO-c₆ as solvents and chemical shifts are quoted on the δ scale in units of ppm using TMS as an internal standard. Coupling constants (J) are reported in Hz with the following splitting abbreviations: s (singlet), d (doublet), t (triplet), dd (doublet of doublets), bs (broad singlet).
The regiochemistry of the 2- and 3-substituted imidazo[1,2-a]pyrazines was confirmed by 2D NMR.

Infra-Red (IR) spectroscopy was carried out using a PerkinElmer Spectrum 100 FT-IR Spectrometer using thin films. Absorption maxima ($\nu_{\text{max}}$) are reported in wavenumbers (cm$^{-1}$).

High Performance Liquid Chromatography (HPLC) was performed using a Varian ProStar instrument; a Chiralpak AD column for normal phase analytical HPLC; DiscoveryBIO wide pore C18-10 (25 cm x 4.6 mm, 10 $\mu$m) for reverse phase analytical HPLC; and a DiscoveryBIO wide pore C18 (25 cm x 21.2 mm, 10 $\mu$m) column for reverse phase preparative HPLC. Each solvent used contained 0.1% TFA buffer.

Liquid Chromatography Mass Spectrometry (LCMS) was carried out using SQD-Waters Acquity UPLC/SQD with C18 (50 mm x 2.1 mm, 1.7 $\mu$m) column. A total run time of 5 minutes and flow rate of 0.6 mL/min was used with gradient elution: 95% H$_2$O/5% MeCN (0 min), 5% H$_2$O/95% MeCN (3 min), 95% H$_2$O/5% MeCN (4.5 min). Each solvent contained 0.1% formic acid buffer. LRMS refers to low resolution mass spectrometry and HRMS refers to high resolution mass spectrometry. Electron Impact/Chemical Ionisation (EI/CI) MS was carried out using MAT900XP (Thermo Finnigan) instrument and electrospray ionization (ESI) accurate mass was determined using Waters LCT Premier XE instrumentation.

Thin layer chromatography (TLC) was carried out using Fluka aluminium backed sheets coated with 60F$_{254}$ silica gel. Visualisation of the silica plates was achieved using a UV lamp ($\lambda_{\text{max}} = 245$ nm) and/or potassium permanganate (KMnO$_4$ in 1M NaOH with 5% K$_2$CO$_3$). Flash chromatography was carried out using either Geduran (Merck) or ZEOprep (Apollo) Si60 40-63 $\mu$m silica gel.

Abbreviations

In addition to those specified elsewhere, the following abbreviations, designations, and formulae are used throughout:

Cs$_2$CO$_3$ = caesium carbonate
DCM = dichloromethane
DMSO = dimethylsulfoxide
Et₂O = diethyl ether
Et₃N = triethylamine
EtOAc = ethyl acetate
IPA = isopropanol
K₂CO₃ = potassium carbonate
MeCN = acetonitrile
MeOH = methanol
NaHCO₃ = sodium hydrogen carbonate
Sat. = saturated
RT = room temperature

Pharmaceutical Compositions

The present invention provides a pharmaceutical composition comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof, each as described herein, together with a pharmaceutically acceptable carrier for said compound. Also, the present invention provides a pharmaceutical composition comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof, each as described herein, further comprising other pharmacologically active agent(s).

Pharmaceutically acceptable salts of a compound of Formula (I) include the acid addition salts (including disalts) thereof.

Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, adipate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, cyclamate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzoate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, palmoate, phosphate/hydrogen phosphate/dihydrogen phosphate, pyroglutamate, saccharate, stearate, succinate, tannate, tartrate, tosylate, trifluoroacetate and xinofoate salts.
For a review on suitable salts, see “Handbook of Pharmaceutical Salts: Properties, Selection, and Use” by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002). A pharmaceutically acceptable salt of a compound of Formula (I) may be readily prepared by mixing together solutions of the compound of Formula (I) and the desired acid or base, as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionization in the salt may vary from completely ionized to almost non-ionized. Pharmaceutically acceptable salts of the compounds of the invention include both unsolvated and solvated forms. The term "solvate" is used herein to describe a molecular complex comprising a compound of the invention and one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

Pharmaceutically acceptable solvates in accordance with the invention include hydrates and solvates wherein the solvent of crystallization may be isotopically substituted, e.g. D₂O, d₆-acetone, d₆-DMSO.

Included within the scope of the invention are complexes such as clathrates, drug-host inclusion complexes wherein, in contrast to the aforementioned solvates, the drug and host are present in stoichiometric or non-stoichiometric amounts. Also included are complexes of the drug containing two or more organic and/or inorganic components which may be in stoichiometric or non-stoichiometric amounts.

The resulting complexes may be ionized, partially ionized, or non-ionized. For a review of such complexes, see J Pharm Sci. 64 (8), 1269-1288 by Halebian (August 1975). The compounds of Formula (I) may exist in one or more crystalline forms. These polymorphs, including mixtures thereof are also included within the scope of the present invention. The compounds of Formula (I) containing one or more asymmetric carbon atoms can exist as two or more stereoisomers.

Included within the scope of the present invention are all stereoisomers of the compounds of Formula (I), including compounds exhibiting more than one type of isomerism, and mixtures of one or more thereof.
Administration

Compounds of the invention intended for pharmaceutical use may be administered as crystalline or amorphous products. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze-drying, spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

They 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 pharmaceutical composition or formulation in association with one or more pharmaceutically acceptable carriers or excipients. The term "carrier" or "excipient" is used herein to describe any ingredient other than the compound(s) of the invention. The choice of carrier or excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. 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).

Oral Administration

The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the bloodstream directly from the mouth.

Formulations suitable for oral administration include solid formulations such as, for example, tablets, capsules containing particulates, liquids, or powders, lozenges (including liquid-filled), chews, multi- and nano-particulates, gels, solid solution, liposome, films (including muco-adhesive), ovules, sprays and liquid formulations.
Liquid formulations include, for example, suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

The compounds of the invention may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Expert Opinion in Therapeutic Patents. H (6), 981-986 by Liang and Chen (2001).

For tablet dosage forms, depending on dose, the drug may make up from about 1 wt% to about 80 wt% of the dosage form, more typically from about 5 wt% to about 60 wt% of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinised starch and sodium alginate. Generally, the disintegrant will comprise from about 1 wt% to about 25 wt%, preferably from about 5 wt% to about 20 wt% of the dosage form.

Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinised starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

Tablets may also optionally comprise surface-active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents may comprise from about 0.2 wt% to about 5 wt% of the tablet, and glidants may comprise from about 0.2 wt% to about 1 wt% of the tablet.
Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally comprise from about 0.25 wt% to about 10 wt%, preferably from about 0.5 wt% to about 3 wt% of the tablet.

Other possible ingredients include anti-oxidants, colourants, flavouring agents, preservatives and taste-masking agents.

Exemplary tablets contain up to about 80% drug, from about 10 wt% to about 90 wt% binder, from about 0 wt% to about 85 wt% diluent, from about 2 wt% to about 10 wt% disintegrant, and from about 0.25 wt% to about 10 wt% lubricant.

Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tabletting. The final formulation may comprise one or more layers and may be coated or uncoated; it may even be encapsulated.


Solid formulations for oral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Suitable modified release formulations for the purposes of the invention are described in US Patent No. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles are to be found in Verma et al, Pharmaceutical Technology On-line. 25(2), 1-14 (2001). The use of chewing gum to achieve controlled release is described in WO00/35298.
Parenteral Administration

The compounds of the invention may also be administered directly into the bloodstream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from about 3 to about 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

The solubility of compounds of Formula (I) used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents.

Formulations for parenteral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release. Thus compounds of the invention may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and PGLA microspheres.

Topical Administration

The compounds of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally. Typical formulations for this purpose include
gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol.

Penetration enhancers may be incorporated - see, for example, J Pharm Sci, 88 (10), 955-958 by Finnin and Morgan (October 1999).

Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (e.g. Powderject(TM), Bioject(TM), etc.) injection.

Formulations for topical administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

**Inhaled/Intranasal administration**

The compounds of the invention can also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurized container, pump, spray, atomiser (preferably an atomiser using electrohydrodynamics to produce a fine mist), or nebuliser, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin. The pressurized container, pump, spray, atomizer, or nebuliser contains a solution or suspension of the compound(s) of the invention comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilising, or extending release of the active, a propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.
Prior to use in a dry powder or suspension formulation, the drug product is micronised to a size suitable for delivery by inhalation (typically less than 5 microns). This may be achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenization, or spray drying.

Capsules (made, for example, from gelatin or HPMC), blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as /-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose.

A suitable solution formulation for use in an atomiser using electrohydrodynamics to produce a fine mist may contain from about 1µg to about 20mg of the compound of the invention per actuation and the actuation volume may vary from about 1 µl to about 100µl. A typical formulation may comprise a compound of Formula (I), propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

Suitable flavors, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium, may be added to those formulations of the invention intended for inhaled/intranasal administration. Formulations for inhaled/intranasal administration may be formulated to be immediate and/or modified release using, for example, poly(DL-lactic-coglycolic acid (PGLA). Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve which delivers a metered amount. Units in accordance with the invention are typically arranged to administer a metered dose or "puff" containing from about 1 to about 100 µg of the compound of Formula (I).

The overall daily dose will typically be in the range about 50 µg to about 20 mg which
may be administered in a single dose or, more usually, as divided doses throughout the day.

Other Technologies

The compounds of the invention may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing polymers, in order to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability for use in any of the aforementioned modes of administration.

Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, i.e. as a carrier, diluent, or solubiliser. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in W091/1 1172, WO94/02518 and W098/55148.

Kit of Parts

Inasmuch as it may be desirable to administer a combination of active compounds, for example, for the purpose of treating a particular disease or condition, it is within the scope of the present invention that two or more pharmaceutical compositions, at least one of which contains a compound in accordance with the invention, may conveniently be combined in the form of a kit suitable for coadministration of the compositions. Thus the kit of the invention comprises two or more separate pharmaceutical compositions, at least one of which contains a compound of Formula (I) in accordance with the invention, and means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of tablets, capsules and the like.

The kit of the invention is particularly suitable for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one
another. To assist compliance, the kit typically comprises directions for administration and may be provided with a so-called memory aid.

**Dosage**

For administration to human patients, the total daily dose of the compounds of the invention is typically in the range of about 0.05 mg to about 500 mg depending, of course, on the mode of administration, preferred in the range of about 0.1 mg to about 400 mg and more preferred in the range of about 0.5 mg to about 300 mg. For example, oral administration may require a total daily dose of from about 1 mg to about 300 mg, while an intravenous dose may only require from about 0.5 mg to about 100 mg. The total daily dose may be administered in single or divided doses. These dosages are based on an average human subject having a weight of about 65 kg to about 70 kg. The physician will readily be able to determine doses for subjects whose weight falls outside this range, such as infants and the elderly.

**Examples**

The following compounds of the invention were synthesized according to the general methods outlined above, with the synthesis of any required precursors using standard transformations provided.
Example 1
4-methyl-A/-[3-(2-naphthyl)imidazo[1,2-a]pyrazin-8-yl]benzenesulfonamide

Step 1
2-azido-1-(2-naphthyl)ethanone

2-(bromoacetyl)naphthalene (2.00 g, 8.03 mmol) was dissolved in DMSO (10 mL) and the mixture was cooled on ice such that the temperature was kept below 10°C. Sodium azide (0.630 g, 9.64 mmol) was added in one portion and the reaction was stirred under argon at RT for 90 min. The reaction was quenched with H₂O (20 mL), and extracted with EtOAc (3 x 30 mL). The organic layers were combined, washed with H₂O, dried (Na₂SO₄) and filtered. The solvent was removed in vacuo to give brown/orange oil (1.53 g, 7.25 mmol, 90.3%) with NMR consistent with literature values. Rf = 0.63 (5:1 Pet Ether/ EtOAc); IR (υmax/cm⁻¹, thin film): 2105 (-N=N+ = N Stretch), 1690 (C=O Stretch); ¹H NMR (600 MHz, CDCl₃): δH = 4.73 (s, 2H, 1-H), 7.61 (t, J = 7.6 Hz, 1H, 7-H), 7.66 (t, J = 7.6 Hz, 1H, 8-H), 7.91(d, J = 8.1 Hz, 1H, 9-H), 7.95(d, J = 8.6 Hz, 1H, 11-H), 7.99(m 2H, 6,12-H), 8.42 (s, 1H, 4-H); ¹³C NMR (150 MHz, CDCl₃): δc = 55.0 (C-1), 123.3 (C-12), 127.2 (C-7), 127.9 (C-9) 129.0 (C-11), 129.1 (C-8), 129.6 (C-6), 129.8 (C-4), 131.7, 132.4 (C-5,10), 136.0 (C-3), 193.2 (C-2); LRMS m/z (EI⁺): 211 [M]⁺, 155 [M-CH₂N₃]⁺, 127 [Naphthalene]⁺.
Step 2

**2-azido-1-(2-naphthyl)ethanol**

2-azido-1-(2-naphthyl)ethanone (2.11 g, 10.0 mmol) was dissolved in anhydrous MeOH (100 mL) and cooled on ice. Sodium borohydride (568 mg, 15.0 mmol) was added portion wise and the mixture was stirred on ice under argon for 1 hour until the reaction had gone to completion by TLC. The solvent was removed and the resulting residue was taken up in DCM (100 mL) and carefully washed with H₂O (2 x 60 mL) followed by brine (60 mL). The organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo to give the title compound as a brown oil (2.14 g, 10.0 mmol, 100%).

Spectroscopic data was consistent to that previously reported. *R*ᵣ = 0.65 (3:1 Pet Ether /EtOAc); IR (v max/cm⁻¹, thin film): 3398 (O-H stretch), 2100 (-N=N+=N Stretch); ¹H NMR (500 MHz, CDCl₃): δH = 2.70 (bs, 1H, 13-H), 3.46 - 3.58 (m, 2H, 1-H), 5.02 (dd, J = 8.1, 3.9 Hz, 1H, 2-H), 7.44 (dd J = 8.4, 1.6 Hz, 1H, 4-H), 7.49 - 7.52 (m, 2H, 7,8-H), 7.83 - 7.86 (m, 4H, 6,7,1,12-H); ¹³C NMR (125 MHz, CDCl₃): δC = 58.1 (C-1), 73.6 (C-2), 123.7 (C-12), 125.1 (C-7), 126.4 (C-9), 126.5 (C-11), 127.8 (C-8), 128.1 (C-6), 128.6 (C-4), 133.3 (C-5,10), 138.0 (C-3); LRMS m/z (EI⁺): 221, 157 [M-CH₂N₃⁺], 147, 129

Step 3

**2-amino-1-(2-naphthyl)ethanol**

2-azido-1-(2-naphthyl)ethanol (453 g, 2.13 mmol) was dissolved in anhydrous MeOH (10 mL) and 10% palladium on carbon (45.0 mg, 10% w/w) was added. The reaction mixture was stirred under hydrogen atmosphere until completion as determined by TLC and disappearance of N₃ peak by IR. After 3 ½ h, the hydrogen was carefully released,
and the reaction mixture was filtered through celite (pre-washed with MeOH). Solvent removal in vacuo gave the crude compound as a orange oil (383 mg, 2.05 mmol, 96.1%). Spectroscopic data was consistent with that previously reported. Flash chromatography (100% EtOAc to EtOAc/20% MeOH) afforded the title compound as a white solid (288.6 mg, 73%). \( R_f \) = 0.06 (5:1 EtOAc/MeOH); IR (\( v_{\text{max}} \)/cm\(^{-1}\), thin film): 3290 (O-H Stretch), 3054 (C-H), 2916 (N-H Stretch), 1599 (N-H Bend); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta_H \) = 2.82 (m, 2H, 1-H), 4.59-4.75 (m, 1H, 2-H), 7.36-7.40 (m, 3H, 7,8,9-H), 7.74-7.76 (m, 4H, 4,6,11,12-H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta_C \) = 49.8 (C-1), 74.3 (C-2), 123.8 (C-12), 124.5 (C-7), 125.7 (C-9), 126.0 (C-1 1), 127.5 (C-8), 128.1 (C-4), 132.8 (C-5), 133.1 (C-10), 139.7 (C-3); LRMS m/z (ESI\(^+\)): 229.2 [M+MeCN]\(^+\), 211.2 [M+Na]\(^+\), 188.1 [M+H]\(^+\), 170 [M-OH]\(^+\).

**Step 4**

2-[(3-chloropyrazin-2-yl)amino]-1-(2-naphthyl)ethanol

![Diagram](image)

2-amino-1-(2-naphthyl)ethanol (289 mg, 1.55 mmol), 2,3-dichloropyrazine (177 \( \mu \)L, 1.70 mmol) and Et\(_3\)N (301 \( \mu \)L, 2.16 mmol) were dissolved in 1,4-dioxane (3 mL) and the reaction was stirred under reflux, under argon. After 19 h, the reaction was cooled to RT, and the solvent removed in vacuo. The residue was taken up in DCM and washed with \( \text{H}_2\text{O} \) (3 x 20 mL) and brine (1 x 20 mL). The organic extracts were dried (Na\(_2\)SO\(_4\)), filtered and concentrated to give the crude product as an amber oil. Purification was carried out via flash chromatography (100% DCM - 2:1 DCM/EtOAc gradient) to afford the title compound as a yellow oil (295 mg, 0.983 mmol, 63.4%). \( R_f \) = 0.64 (2:1 DCM/EtOAc); IR (\( v_{\text{max}} \)/cm\(^{-1}\), thin film): 3419 (O-H Stretch), 3054 (C-H), 2922 (N-H Stretch), 1523 (N-H Bending); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta_H \) = 3.65-3.70 (m, 1H, 1-H), 3.88 (bs, 1H, 13-H), 3.92-3.97 (m, 1H, 1-H), 5.12 (dd, \( J = 7.5, 2.8 \) Hz, 2-H), 5.67 (t, \( J = 5.3 \) Hz, 14-H), 7.47-7.50 (m, 3H, 7,8,12-H), 7.59 (d, \( J = 2.7 \) Hz, 1H, 18-H), 7.81-7.84 (m, 3H, 6,9,11-H), 7.86 (s, 1H, 4-H), 7.91 (d, \( J = 2.7 \) Hz, 1H, 17-H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta_C \) = 49.4 (C-1), 73.9 (C-2), 123.9 (C-12), 124.8 (C-7), 126.1 (C-9), 126.4 (C-1 1), 127.8 (C-8), 128.0 (C-6), 128.4 (C-4), 131.3 (C-18), 1332. (C-5), 1383.7 (C-3).
133.3 (C-10), 135.1 (C-20), 139.4 (C-3), 140.2, (C-17), 151.5 (C-15); LRMS m/z (ESI+): 300.1 [M(35Cl)+H]+, 284.2 [M(37Cl)-OH]+, 282.2 [M(35Cl)-OH]+; HRMS m/z (ESI+): Found 298.0731 [M(35Cl)-H]-; C16H13ClN3O requires 298.0747.

Step 5

2-[(3-chloropyrazin-2-yl)amino]-1-(2-naphthyl)ethanone

DMSO (982 μL, 13.9 mmol) was dissolved in anhydrous DCM (60 mL) and the reaction mixture was cooled to and maintained at -78°C. Oxalyl chloride (586 μL, 6.93 mmol) was added drop wise and the mixture was stirred for 20 min. 2-[(3-chloropyrazin-2-yl)amino]-1-(2-naphthyl)ethanol (1.60 g, 5.33 mmol) dissolved in anhydrous DCM (40 mL) was added drop wise, and stirred for 20 min. Et3N (3.54 mL, 26.6 mmol) was added drop wise and the reaction mixture was allowed to warm to RT over a period of 2½ h. The reaction was then quenched with H2O (50 mL) and organics extracted, which were then washed with 2.0 M HCl (2 x 40 mL), sat. NaHCO3 (40 mL), H2O (40 mL) and brine (40 mL). The organic were dried (MgSO4), filtered and solvent removed to give a yellow/orange solid. Flash chromatography (100:1 to 30:1 DCM/EtOAc) afforded the title compound as a yellow solid (903 mg, 3.03 mmol, 56.9%). Mpt: 160 °C; Rf = 0.30 (30:1 DCM/EtOAc); IR (νmax/cm⁻¹, thin film): 1680 (C=O stretch); 1H NMR (500 MHz, CDCl3): δH = 5.10 (d, J = 4.3, 2H, 1-H), 6.54 (s, 1H, 13-H), 7.58-7.62 (m, 1H, 7-H), 7.64-7.67 (m, 1H, 8-H), 7.68 (d, J = 6.1 Hz, 1H, 17-H), 7.91 (d, J = 8.0 Hz, 1H, 9-H), 7.96 (d, J = 8.6 Hz, 1H, 11-H), 8.00-8.02 (m, 2H, 6,16-H), 8.10 (dd, J = 8.6, 1.8 Hz, 1H, 12-H), 8.62 (s, 1H, 4-H); 13C NMR (125 MHz, CDCl3): δC = 48.4 (C-1), 123.4 (C-12), 127.3 (C-7), 128.0 (C-9), 129.0 (C-8), 129.2 (C-11), 129.8 (C-6), 130.1 (C-4), 131.3 (C-17), 131.8 (C-5), 132.6 (C-10), 136.2 (C-3), 139.7 (C-16), 193.8 (C-2); LRMS m/z (ESI+): 300[M(35Cl)+H]+, 298 [M(37Cl)+H]+, 282[M(35Cl)-OH]+, 280[M(35Cl)-OH]+; HRMS m/z (ESI+): Found 296.0591 [M(35Cl)-H]-; C16H13ClN3O requires 296.0591; Anal. Calcd. for C16H13ClN3O: C, 64.54; H, 4.06; N, 14.11. Found C, 64.35; H, 3.94; N, 13.82%
Step 6

8-chloro-3-(2-naphthyl)imidazo[1,2-a]pyrazine

\[
\begin{align*}
\text{Cl} & \quad \text{N} \\
5 & \quad 6 \\
7 & \quad 8 \\
9 & \quad 10 \\
11 & \quad 12 \\
13 & \quad 14 \\
15 & \quad 16 \\
17 & \quad 18 \\
\end{align*}
\]

2-[(3-chloropyrazin-2-yl)amino]-1-(2-naphthyl)ethanone (903 mg, 3.03 mmol) was dissolved in anhydrous toluene (40 mL) and the mixture was cooled on ice. Trifluoroacetic acid (1.64 mL, 21.2 mmol) was added and the reaction was allowed to stir on ice for 30 min, followed by the addition of trifluoroacetic anhydride (2.95 mL, 21.2 mmol). The reaction mixture was then stirred on ice for a further 30 minutes and then at RT for 65 h. The reaction was then diluted with toluene (20 mL) and washed with NaHCO\textsubscript{3} solution (10% w/v). The organics were dried (MgSO\textsubscript{4}), filtered and concentrated to give crude amber oil. Purification was carried out via flash chromatography (DCM/\text{EtOAc} gradient - 80:1 to 10:1) to afford the title compound as an off white solid (386 mg, 1.38 mmol, 45.5%). Mpt: 166 °C; \textit{R}_{\text{f}} = 0.21 (10:1 DCM/\text{EtOAc}); \text{IR} (\nu_{\text{max}}/\text{cm}^{-1}, \text{thin film}): 3102 (w), 3052 (w), 1333; \text{HNMR} (500 MHz, CDCl\textsubscript{3}): \delta_H = 7.59 (dd, J = 6.2, 3.2 Hz, 2H, 15,16-H), 7.63 (dd, J = 8.6, 1.7 Hz, 1H, 12-H), 7.73 (d, J = 4.6 Hz, 1H, 6-H), 7.91-7.94 (m, 2H, 14,17-H), 8.00 (s, 1H, 2-H), 8.03 (d, J = 5.8 Hz, 1H, 11-H), 8.04 (s, 1H, 19-H), 8.29 (d, J = 4.6 Hz, 1H, 5-H); \text{^13C NMR} (125 MHz, CDCl\textsubscript{3}): \delta_C = 116.4 (C-5), 124.7 (C-10), 125.2 (C-12), 127.3 (C-15), 127.4 (C-16), 127.6 (C-19), 128.0 (C-17), 128.2 (C-13), 128.6 (C-6), 129.4 (C-3), 129.7 (C-1 1), 133.4 (C-13), 133.5 (C-18), 134.8 (C-2), 138.4 (C-9), 144.5 (C-8); \text{LRMS} m/z (ESI\textsuperscript{+}): 282 [M(\textsuperscript{35}Cl)+H]\textsuperscript{+}, 280 [M(\textsuperscript{37}Cl)+H]\textsuperscript{+}; \text{HRMS} m/z (ESI\textsuperscript{+}): \text{Found 280.0646} [M(\textsuperscript{37}Cl)+H]\textsuperscript{+}; \text{C}_{16}\text{H}_{10}\text{ClN}_{3} requires 280.0642; \text{Anal. Calcd for } \text{C}_{16}\text{H}_{10}\text{ClN}_{3}: \text{C, 68.70; H, 3.60; N, 15.02. Found C, 64.41 ; H, 3.31 ; N, 14.14%}
Step 7
4-methyl-A/-[3-(2-naphthyl)imidazo[1,2-a]pyrazin-8-yl]benzenesulfonamide

All glassware was evacuated and flushed with argon prior to use. 8-chloro-3-(2-naphthyl)imidazo[1,2-a]pyrazine (12.3 mg, 0.044 mmol), 4-toluene sulfonamide (9.10 mg, 0.053 mmol), K$_2$CO$_3$ (7.30 mg, 0.053 mmol), 1 mol% Pd(dba)$_2$ (0.120 mg) and 5 mol% ie/f-butyl XPhos (0.600 mg) were weighed into a 5 mL round bottom flask. BuOH (1 mL) was added and the reaction was stirred under reflux for 40 h. The reaction mixture was cooled to RT, diluted with MeOH and filtered through celite (pre-washed with MeOH). Flash chromatography (DCI W EtOAc- 10:1 to 1:1 gradient ran) afforded the target compound as a white solid (7.50 mg, 0.018 mmol, 40.9%).

Mpt: Decomposed before melting; $R_f = 0.62$ (1:1 DCM/EtOAc); IR ($\nu_{max}$/cm$^{-1}$, thin film): 3258 (w), 3112 (w), 2923 (w), 2854 (w), 1579 (s); $^1$H NMR (600 MHz, DMSO-d$_6$): $\delta$H = 2.36 (s, 3H, 26-H), 7.16 (bs, 1H, 6-H), 7.39 (d, J = 8.2 Hz, 2H, 24-H), 7.60 - 7.62 (m, 2H, 15,16-H), 7.74 (d, J = 8.9 Hz, 1H, 11-H), 7.87 (bd, J = 6.8 Hz, 1H, 5, 23-H) 7.91 (s, 1H, 2-H), 8.00 - 8.04 (m, 2H, 14,17-H), 8.1 1 (d, J = 8.2 H, 12-H), 8.21 (s, 1H, 19-H), 11.70 (s, 1H, 20-H); $^{13}$C NMR (150 MHz, DMSO-d$_6$): $\delta$C = 21.0 (C-26), 108.7 (C-5), 116.8 (C-6), 124.6 (C-10), 125.7 (C-1 1), 126.1 (C-23), 127.1 (C-15,16), 127.4 (C-19), 128.1 (C-14,17), 129.0 (C-12), 129.6 (C-24), 130.6 (C-3), 132.8 (C-13,18), 133.3 (C-2), 135.6 (C-9), 140.1 (C-22), 142.6 (C-25), 144.5 (C-8); LRMS m/z (ESI$^+$): 415 [M+H]$^+$, 260 [M-SO$_2$C$_6$H$_4$CH$_3$+H]$^+$; HRMS m/z (ESI$^+$): Found 415.1230 [M+H]$^+$; C$_{23}$H$_{18}$N$_4$O$_2$S requires 415.1229; Anal. Calcd for C$_{23}$H$_{18}$N$_4$O$_2$S: C, 66.65; H, 4.38; N, 13.52. Found C, 65.47; H, 4.72; N, 12.35%
Example 2

4-methyl-W-[3-(2-phenoxyphenyl)imidazo[1,2-a]pyrazin-8-yl]benzenesulfonamide

Step 1

2-bromo-1-(2-phenoxyphenyl)ethanone

1-(2-phenoxyphenyl)ethanone (2.00 g, 9.42 mmol) was dissolved in chloroform (60 mL) and ethanol (60 mL). Pyridinium tribromide (7.50 g, 23.6 mmol) was added and the reaction was stirred at 50°C for 16 h. The reaction mixture was cooled to RT and the solvents removed in vacuo. The resulting orange slurry was suspended in H₂O (30 mL) and extracted with EtOAc (4 x 30 mL). The combined organic extracts were washed with H₂O (2 x 20 mL) and brine (1 x 20 mL), dried (Na₂SO₄), filtered and concentrated in vacuo to give a yellow oil. Flash chromatography was carried out (100% Pet ether - 10:1 - 2:1 Pet Ether/DCM) to afford the title compound as a pale yellow oil (2.30 g, 7.90 mmol, 83.9%).

Rf = 0.68 (DCM); IR (vmax/cm⁻¹, thin film): 1677 (C=O stretch), 1598, 1574, 1475, 1446 (Aromatic C=C stretch), 1223 (C-O-C stretch);

¹H NMR (500 MHz, CDCl₃): δH = 4.65 (s, 2H, 1-H), 6.86 (d, J = 8.4 Hz, 1H, 7-H), 7.09 (d, J = 7.7 Hz, 2H, 10-H), 7.17 (t, J = 7.3 Hz, 1H, 5-H), 7.22 (t, J = 7.3 Hz, 1H, 12-H), 7.40-7.47 (m, 3H, 6,11-H), 7.92 (dd, J = 7.8, 1.5 Hz, 1H, 4-H); ¹³C NMR (125 MHz, CDCl₃): δc = 36.8 (C-1), 117.6 (C-7), 119.5 (C-10), 123.0 (C-5), 124.4 (C-12), 126.2 (C-
3), 129.9 (C-11), 131.3 (C-4), 134.2 (C-6), 155.0 (C-9), 156.5 (C-8), 191.6 (C-2); LRMS m/z (El⁺): 292 [M (81Br)⁺], 290 [M (79Br)⁺], 212 [M-Br]⁺, 197 [M-CH₂Br]⁺; HRMS m/z (El⁺): Found 289.99403 [M(79Br)⁺]; C₄H₇N₂Br₂ requires 289.99369.

5 Step 2
2-azido-1-(2-phenoxyphenyl)ethanone

2-bromo-1-(2-phenoxyphenyl)ethanone (3.07 g, 10.5 mmol) was dissolved in DMSO (15 mL) and the mixture was cooled on ice. Sodium azide (824 mg, 12.68 mmol) was added in one portion and the reaction was stirred under argon at RT for 5 h. An extra portion of sodium azide (200 mg) was added and left to stir overnight. After 15 h, the reaction was quenched with H₂O (30 mL) and extracted with EtOAc (4 x 40 mL). The combined organic layers were washed with H₂O (5 x 20 mL) and then dried (Na₂SO₄) and filtered. The solvent was removed in vacuo to give brown liquid (2.52 g, 9.96 mmol, 94.9%). Rᵣ = 0.4 (DCM); IR (ν₁max/cm⁻¹, thin film): 3071 (C-H Stretch), 2100 (-N=N+=N' stretch), 1685 (CO Stretch), 1599, 1475, 1448 (aromatic C=C stretch), 1225 (aromatic C-O-C stretch); ¹H NMR (500 MHz, CDCl₃): δ_H = 4.60 (s, 2H, 1-H), 6.87 (dd, J = 8.3, 0.9 Hz, 1H, 7-H), 7.04-7.06 (m, 2H, 10,14-H), 7.18-7.23 (m 2H, 5,12-H), 7.40-7.43 (m, 2H, 11,13-H), 7.45-7.49 (m, 1H, 6-H), 7.92 (dd, J = 7.8, 1.5 Hz, 1H, 4-H); ¹³C NMR (125 MHz, CDCl₃): δ_C = 58.9 (C-1), 118.0 (C-7), 119.2 (C-10), 123.2 (C-5), 124.4 (C-12), 126.2 (C-3), 130.0 (C-1 1), 130.8 (C-4), 134.5 (C-6), 155.0 (C-9), 157.0 (C-8), 193.6 (C-2); LRMS m/z (Cl⁺): 198 [M-CH₂N₃⁺], 85 [COCH₂N₃⁺].
Step 3

2-azido-1-(2-phenoxyphenyl)ethanol

2-azido-1-(2-phenoxyphenyl)ethanone (2.52 g, 9.96 mmol) was dissolved in anhydrous MeOH (50 mL) and cooled on ice. Sodium borohydride (565 mg, 14.9 mmol) was added portion wise and the mixture was stirred on ice under argon for 1 h until the reaction had gone to completion by TLC. The solvent was removed and the resulting residue was taken up in DCM (50 mL) and carefully washed with H₂O. An emulsion formed at the interface, and as a result, the mixture was acidified (from approximately pH 12) and the extraction continued. The combined organic extracts were dried (Na₂SO₄), filtered and concentrated in vacuo to give the title compound as a brown oil (2.47 g, 9.69 mmol, 97.3%).

f = 0.19 (DCM); IR (ν max/cm⁻¹, thin film): 3413 (O-H Stretch), 3039 (C-H Stretch), 2102 (-N=N+=N stretch), 1583, 1483, 1452 (aromatic C=C stretch), 1230 (Aromatic C-O-C stretch); ¹H NMR (500 MHz, CDCl₃): δ_H = 2.54 (bs, 1H, 15-H), 3.50 (dd, J = 12.5, 8.0 Hz, 1H, 1-H), 3.58 (dd, J = 12.5, 3.5 Hz, 1H, 1-H), 5.23 (dd, J = 8.0, 3.4 Hz, 1H, 2-H), 6.84 (dd, J = 8.2, 1.1 Hz, 1H, 7-H), 6.97-7.00 (m, 2H, 10-H), 7.13 (tt, J = 7.4, 1.1 Hz, 1H, 5-H), 7.17 (td, J = 7.5, 1.0 Hz, 1H, 12-H), 7.24-7.27 (m, 1H, 6-H), 7.34-7.37 (m, 2H, 11-H), 7.58 (dd, J = 7.7, 1.7 Hz, 1H, 4-H); ¹³C NMR (125 MHz, CDCl₃): δ_C = 56.5 (C-1), 68.7 (C-2), 118.0 (C-7), 118.3 (C-10), 123.4 (C-5), 123.5 (C-12), 127.1 (C-4), 129.6 (C-6), 129.6 (C-11), 130.8 (C-3), 153.5 (C-9), 156.3 (C-8); LRMS m/z (Cl⁺): 200 [M-CH₂N₃]⁺, 182 [M-OH,CH₂N₃]⁺.
Step 4

2-amino-1-(2-phenoxyphenyl)ethanol

2-azido-1-(2-phenoxyphenyl)ethanol (2.46 g, 9.66 mmol) was dissolved in anhydrous MeOH (50 mL) and 10% palladium on carbon (246 mg, 10% w/w) was added. The reaction mixture was stirred under hydrogen atmosphere until completion as determined by TLC and disappearance of N₃ peak by IR. After 22 h, the hydrogen was carefully released, and the reaction mixture was filtered through celite (pre-washed with MeOH). Solvent removal in vacuo gave the title compound as a brown oil (2.21 g, 9.66 mmol, 99.9%). \( R_{f} = 0.0 \) (DCM); IR (\( \nu_{\text{max}}/\text{cm}^{-1} \), thin film): 3413 (O-H Stretch), 3055 (C-H Stretch), 2983 (N-H Stretch); \(^1\)H NMR (600 MHz, CDCl₃): \( \delta_H = 2.17 \) (bs, 3H, \( 15,16-H \)), 2.84 (dd, \( J = 13.2, 7.8 \) Hz, 1H, \( 1-H \)), 3.10 (dd, \( J = 13.2, 4.2 \) Hz, 1H, \( 1-H \)), 4.99 (dd, \( J = 7.8, 3.6 \) Hz, 1H, \( 2-H \)), 6.82 (dd, \( J = 8.4, 1.2 \) Hz, 1H, \( 7-H \)), 6.95 (d, \( J = 7.8 \) Hz, 2H, \( 10-H \)), 7.08-7.11 (m, 1H, \( 12-H_j \)), 7.13-7.15 (m, 1H, \( 5-H \)), 7.21 (td, \( J = 7.8, 1.8 \) Hz, 1H, \( 6-H \)), 7.30-7.33 (m, 2H, \( 11-H \)), 7.57 (dd, \( J = 7.8, 1.2 \) Hz, 1H, \( 4-H \)); \(^{13}\)C NMR (150 MHz, CDCl₃): \( \delta_C = 47.7 \) (C-1), 69.4 (C-2), 118.2 (C-7), 118.5 (C-10), 123.4 (C-12), 123.9 (C-5), 127.5 (C-4), 128.6 (C-6), 130.0 (C-11), 133.3 (C-3), 153.8 (C-9), 157.2 (C-8); LRMS m/z (ESI\(^+\)): 230.1 [M+H\(^+\)]\(^+\), 212.1 [M-OH\(^+\)]\(^+\), 195.1 [M-OH, NH\(_2\)]\(^+\).

Step 5

2-[(3-chloropyrazin-2-yl)amino]-1-(2-phenoxyphenyl)ethanol
2-amino-1-(2-phenoxyphenyl)ethanol (2.21 g, 9.66 mmol), 2,3-dichloropyrazine (1.11 mL, 10.6 mmol) and Et₃N (1.88 mL, 13.5 mmol) were dissolved in 1,4-dioxane (22 mL) and the reaction was stirred under reflux, under argon. After 17 h, the reaction was cooled to RT, and the solvent removed in vacuo. The residue was taken up in DCM and washed with H₂O (3 x 20 mL) and brine (1 x 20 mL). The organic extracts were dried (Na₂SO₄), filtered, and concentrated to give the crude product as a brown oil. Purification was carried out via flash chromatography (100% DCM - 9:1 DCM/EtOAc gradient) to afford the title compound as an orange oil (2.09 g, 6.15 mmol, 63.7%). Rᵣ = 0.42 (9:1 DCM/EtOAc); IR (νₘₐₓ/cm⁻¹, thin film): 3423 (O-H Stretch), 3060 (C-H Stretch), 2924 (N-H Stretch); ¹H NMR (400 MHz, CDCl₃): δ_H = 3.76-3.83 (m, 1H, 1-H), 3.92-3.98 (m, 1H, 1-H), 5.31 (dd, J = 7.2, 3.2 Hz, 1H, 2-H), 5.64 (1H, 16-H), 6.87 (dd, J = 8.1, 1.1 Hz, 1H, 7-H), 6.99-7.02 (m, 2H, 10-H), 7.10-7.18 (m, 2H, 5,12-H), 7.25 (dd, J = 8.0, 1.7 Hz, 1H, 6-H), 7.33-7.38 (m, 2H, 11-H), 7.60 (d, J = 1.7 Hz, 1H, 4-H), 7.61 (d, J = 2.8 Hz, 1H, 19-H), 7.89 (d, J = 2.8 Hz, 1H, 18-H); ¹³C NMR (100 MHz, CDCl₃): δ_C = 47.9 (C-1), 69.3 (C-2), 118.2 (C-7,10), 123.2 (C-5), 123.5 (C-12), 127.2 (C-4), 128.6 (C-6), 129.6 (C-1 1), 130.8 (C-19), 132.2 (C-3), 134.8 (C-20), 139.2 (C-18), 151.0 (C-17), 153.4 (C-9), 156.6 (C-8); LRMS m/z (Cl⁺): 325 [M(³⁷Cl)-OH]⁺, 323 [M(³⁵Cl)-OH]⁺; HRMS m/z (ESI⁺): Found 340.0867 [M(³⁵Cl)-H]⁺; C₁₈H₁₅ClN₃O₂ requires 340.0853

Step 6

2-[(3-chloropyrazin-2-yl)amino]-1-(2-phenoxyphenyl)ethanone

DMSO (1.13 mL, 15.98 mmol) was dissolved in anhydrous DCM (100 mL) and the mixture was cooled to and maintained at -78°C. Oxalyl chloride (677 µL, 7.99 mmol) was added drop wise and the reaction was stirred for 20 min. 2-[(3-chloropyrazin-2-yl)amino]-1-(2-phenoxyphenyl)ethanol (2.10 g, 6.15 mmol), dissolved in DCM (20 mL), was then added drop wise and after 20 min stirring, Et₃N (4.08 mL, 30.7 mmol) was added drop wise. The reaction was then allowed to slowly warm to RT over a period of 2 ½ h. The reaction was quenched with H₂O (50 mL) and organics extracted followed by washing with 2.0 M HCl (2 x 40 mL), sat. NaHCO₃ (1 x 40 mL), H₂O (1 x 40 mL) and brine (1 x 40 mL). Drying (MgSO₄), filtration and concentration gave a brown/orange
oil. Flash chromatography was carried out (DCM/EtOAc - 50:1 to 10:1 gradient) to afford the title compound as a yellow solid (1.33 g, 3.92 mmol, 63.7%). Mpt: 76-78 °C; \( R_f = 0.74 \) (9:1 DCM/EtOAc); IR (\( \nu_{max}/\text{cm}^{-1} \), thin film): 3423 (O-H Stretch), 3060 (C-H Stretch), 2924 (N-H Stretch); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta_H = 4.95 \) (d, \( J = 4.8 \) Hz, 1H, 1-H), 6.30 (1H, 15-H), 6.90 (dd, \( J = 8.4, 0.8 \) Hz, 1H, 7-H), 7.1 - 7.13 (m, 2H, 10-H), 7.18 - 7.23 (m, 2H, 5,12-H), 7.40 - 7.44 (m, 2H, 11-H), 7.46 - 7.49 (m, 1H, 6-H), 7.59 (d, \( J = 2.7 \) Hz, 1H, 19-H), 7.88 (d, \( J = 2.7 \) Hz, 1H, 18-H), 8.01 (dd, \( J = 7.9, 1.8 \) Hz, 1H, 4-H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta_C = 52.0 \) (C-1), 118.1 (C-7) 119.4 (C-10), 123.0 (C-5), 124.3 (C-12), 126.5 (C-3), 129.9 (C-11), 130.7 (C-4), 130.8 (C-19), 134.3 (C-6), 134.8 (C-21), 140.0 (C-18), 150.2 (C-6), 155.2 (C-9), 157.2 (C-8), 194.8 (C-2); LRMS m/z (ESI\(^+\)): 342 [M\(^{35}\)Cl]+, 340 [M\(^{37}\)Cl]+, 322 [M\(^{35}\)Cl-OH]+; HRMS m/z (ESI\(^+\)): Found 340.0864 [M\(^{35}\)Cl]+; \( \text{C}_{18}\text{H}_{15}\text{ClN}_3 \) requires 340.0853; Anal. Calcd for \( \text{C}_{18}\text{H}_{14}\text{ClN}_3\text{O}_2 \): C, 63.63; H, 4.15; N, 12.37. Found C, 63.90; H, 4.26; N, 11.44%.

**Step 7**

8-chloro-3-(2-phenoxyphenyl)imidazo[1,2-a]pyrazine

2-[(3-chloropyrazin-2-yl)amino]-1-(2-phenoxyphenyl)ethanone (1.33 g, 3.92 mmol) was dissolved in anhydrous toluene (50 mL) and the mixture was cooled on ice. Trifluoroacetic acid (2.11 mL, 24.7 mmol) was added and the reaction was allowed to stir on ice for 30 min, followed by the addition of trifluoroacetic anhydride (3.81 mL, 24.7 mmol). The reaction mixture was then stirred on ice for a further 30 min and then at RT for 68 h. The reaction was then diluted with toluene (50 mL) and washed with NaHC\(_3\)O\(_3\) solution (10% w/v, 3 x 30 mL) and brine (1 x 40 mL). The organics were dried (MgSO\(_4\)), filtered and concentrated to give crude brown oil. Purification was carried out via flash chromatography (DCM/EtOAc gradient - 50:1 to 5:1) to afford the title compound as a yellow solid (1.26 g, 3.92 mmol, 99.9%). \( R_f = 0.25 \) (9:1 DCM/EtOAc); IR (\( \nu_{max}/\text{cm}^{-1} \), thin film): 1460, 1231 (Ar-O-Ar Stretch); \(^1\)H NMR (600 MHz, CDCl\(_3\)): \( \delta_H = 6.83-6.85 \) (m, 2H, 18-H), 7.05-7.10 (m, 2H, 14,20-H), 7.23-7.26 (m, 2H, 19-H), 7.29 (td, \( J = 7.8, 1.2 \) Hz, 1H, 12-H), 7.46-7.49 (m, 1H, 13-H), 7.53 (dd, \( J = 7.2, 1.2 \) Hz, 1H, 16-H), 7.64 (dd, \( J = 8.2, 1.2 \) Hz, 1H, 21-H); 194.8 (C-2); LRMS m/z (ESI\(^+\)): 342 [M\(^{35}\)Cl]+, 340 [M\(^{37}\)Cl]+, 322 [M\(^{35}\)Cl-OH]+; HRMS m/z (ESI\(^+\)): Found 340.0864 [M\(^{35}\)Cl]+; \( \text{C}_{18}\text{H}_{15}\text{ClN}_3 \) requires 340.0853; Anal. Calcd for \( \text{C}_{18}\text{H}_{14}\text{ClN}_3\text{O}_2 \): C, 63.63; H, 4.15; N, 12.37. Found C, 63.90; H, 4.26; N, 11.44%.
1.2 Hz, 1H, 11-H), 7.70 (d, J = 4.2 Hz, 1H, 6-H), 7.86 (s, 1H, 2-H), 8.01 (d, J = 4.2 Hz, 1H, 5-H); 13C NMR (150 MHz, CDCl3): δC = 118.3 (C-5), 118.5 (C-18), 118.8 (C-22), 124.2 (C-10, 12, 20), 126.1 (C-3), 130.0 (C-19), 131.5 (C-13), 132.0 (C-11), 135.6 (C-2), 138.4 (C-9), 143.9 (C-8), 155.0 (C-15), 156.0 (C-17); LRMS m/z (El⁺): 323 [M(35Cl)]⁺, 321 [M(37Cl)]⁺; HRMS m/z (El⁺): Found: 321.06586 [M(35Cl)]⁺; C18H12ClN3O requires 321.06634.

Step 8
4-methyl-W-[3-(2-phenoxyphenyl)imidazo[1,2-a]pyrazin-8-yl]benzenesulfonamide

All glassware was evacuated and flushed with argon prior to use. 8-chloro-3-(2-phenoxyphenyl)imidazo[1,2-a]pyrazine (516 mg, 1.60 mmol), 4-toluenesulfonamide (330 mg, 1.93 mmol), K2CO3 (266 mg, 1.93 mmol), 1 mol% Pd(dba)2 (5.20 mg) and 5 mol% ie/f-butyl XPhos (26.0 mg) were weighed into a 50 mL round bottom flask. 1BuOH (10 mL) was added and the reaction was stirred under reflux for 40 h. The reaction mixture was cooled to RT, diluted with MeOH and filtered through celite (pre-washed with MeOH). Flash Chromatography was carried out (10:1 DCM/EtOAc to 1:1 gradient followed by DCM/10% MeOH) to afford the title compound as yellow solid (188 mg, 0.412 mmol 25.8%). Mpt: > 200 °C; Rf = 0.18 (2:1 DCM/EtOAc); IR (νmax/cm⁻¹, thin film): 3243 (N-H), 2917 (C-H Stretch), 1588 (S=O), 1233 (Ar-O-Ar); 1H NMR (600 MHz, CDCl3): δH = 2.37 (s, 3H, 27-H), 6.85 (d, J = 7.8 Hz, 2H, 18-H), 7.04 (d, J = 8.4 Hz, 2H, 6, 14H), 7.07 (t, J = 7.2 Hz, 1H, 20H), 7.23-7.27 (m, 5H, 12, 19, 25-H), 7.43-7.46 (m, 3H, 5, 11, 13-H), 7.65 (s, 1H, 2-H), 7.94 (bs, 2H, 24-H), 11.45 (bs, 1H, 21-H); 13C NMR (150 MHz, CDCl3): δC = 21.7 (C-27), 109.5 (C-5), 115.1 (C-6), 118.6 (C-10), 118.8 (C-18), 118.9 (C-14), 124.0 (C-12), 124.2 (C-20), 126.8 (C-24), 128.1 (C-3), 129.4 (C-25), 130.0 (C-19), 131.5 (C-13), 132.1 (C-11), 134.6 (C-2), 136.0 (C-9), 139.5 (C-23), 143.2
(C-26), 146.0 (C-8), 155.0 (C-15), 155.9 (C-17); LRMS m/z (ESI+): 457 [M+H]+, 302 [M-C6H5-SO2]+. HRMS m/z (ESI+): Found: 455.1 183 [M-H]-; C25H20N4O3S requires 455.1 178; Anal. Calcd for C25H19N4O3S: C, 65.77; H, 4.42; N, 12.27. Found C, 63.37; H, 4.22; N, 11.88%

Example 3
yV-[3-(3,4-dimethoxyphenyl)imidazo[1,2-a]pyrazin-8-yl]-4-methylbenzenesulfonamide

Step 1
2-bromo-1-(3,4-dimethoxyphenyl)ethanone

3,4-dimethoxyacetophenone (1.00 g, 5.55 mmol) was dissolved in a 1:1 mixture of ethanol and chloroform (60 ml). Pyridinium tribromide (4.46 g, 13.9 mmol) was added and the mixture was stirred at 50°C for 16 h. The reaction was cooled to RT and solvents removed in vacuo to give a sticky orange solid, which was then dissolved in H2O (30 ml), and organics extracted with EtOAc (3 x 20 mL) and washed with H2O (2 x 20 mL) and brine (20 mL). The organics were dried (MgSO4), filtered and concentrated in vacuo to give an orange oil containing a mixture of mono- and di-bromated species (approx 1:5 to 1 ratio). Flash chromatography (DCM isocratic) afforded the title compound as an off-white solid (752 mg, 2.90 mmol. 52.3%). Spectroscopic data was consistent with that previously reported. Mpt: 62 °C [Lit. 67-70 °C]; Rf = 0.12 (DCM); IR
(ν\text{max}/\text{cm}^{-1}\text{ thin film)}: 2940 (C-H stretch), 1679 (C=O stretch), 1585, 1512, 1465, 1418 (Aromatic C=C stretch), 1241 (C-O-C stretch); ^1\text{H NMR} (500 MHz, CDCl\textsubscript{3}): δ\textsubscript{H} = 3.93 (s, 3H, 9-H), 3.95 (s, 3H, 10-H), 4.40 (s, 2H, 1-H), 6.90 (d, J = 8.4 Hz, 1H, 5-H), 7.53 (d, J = 2.1 Hz, 1H, 8-H), 7.60 (dd, J = 8.4, 2.1 Hz, 1H, 4-H); ^13\text{C NMR} (125 MHz, CDCl\textsubscript{3}): δ\textsubscript{C} = 30.5 (C-1), 56.1 (C-9), 56.2 (C-10), 110.2 (C-5), 110.9 (C-8), 123.9 (C-4), 127.1 (C-3), 149.4 (C-7), 154.1 (C-6), 190.2 (C-2); LRMS m/z (EI\textsuperscript{+}): 260 [M(\textsuperscript{81}Br)]\textsuperscript{+}, 258 [M(\textsuperscript{79}Br)]\textsuperscript{+}, 165 [M-CH\textsubscript{2}Br]\textsuperscript{+}; HRMS m/z (EI\textsuperscript{+}): Found 257.98872 [M(\textsuperscript{79}Br)]\textsuperscript{+}; C\textsubscript{10}HnO\textsubscript{3}Br requires 257.98861.

10 Step 2
2-azido-1-(3,4-dimethoxyphenyl)ethyl anone

2-bromo-1-(3,4-dimethoxyphenyl)ethanone (2.33 g, 8.61 mmol) was dissolved in anhydrous DMSO (10 mL) and the mixture was cooled on ice. Sodium azide (671 mg, 10.3 mmol) was added in one portion and the reaction was stirred under argon at RT for 2 h. An immediate colour change of yellow to orange was observed on addition of the sodium azide. The reaction was then quenched with H\textsubscript{2}O (30 mL), and extracted with EtOAc (4 x 40 mL). The combined organic layers were washed with H\textsubscript{2}O (5 x 20 mL) followed by brine (20 mL) and then dried (MgSO\textsubscript{4}) and filtered. The solvent was removed \textit{in vacuo} to give an orange solid (1.87 g, 8.46 mmol, 98.3%) with NMR data comparable with literature values. Mpt: ; R\textsubscript{f} = 0.22 (DCM); IR (ν\text{max}/\text{cm}^{-1}, thin film): 2106 (-N=N\textsuperscript{+}=N\textsuperscript{+} Stretch), 1682 (C=O Stretch), 1595, 1515 (aromatic C=C stretch), 1264 (Aromatic C-O-C Stretch); ^1\text{H NMR} (600 MHz, CDCl\textsubscript{3}): δ\textsubscript{H} = 3.94 (s, 3H, 9-H), 3.96 (s, 3H, 10-H), 4.52 (s, 2H, 1-H), 6.90 (d, J = 8.4 Hz, 1H, 5-H), 7.47 (dd, J = 8.5, 2.0 Hz, 1H, 4-H), 7.52 (d, J = 2.1 Hz, 1H, 8-H); ^13\text{C NMR} (150 MHz, CDCl\textsubscript{3}): δ\textsubscript{C} = 54.5 (C-1), 56.1 (C-9), 56.2 (C-10), 110.0 (C-8), 110.1 (C-5), 122.5 (C-4), 127.5 (C-3), 149.4 (C-7), 154.1 (C-6), 191.8 (C-2); LRMS m/z (Cl\textsuperscript{+}): 222 [M+H]\textsuperscript{+}, 165 [M-CH\textsubscript{2}N\textsubscript{3}]\textsuperscript{+}; HRMS m/z (Cl\textsuperscript{+}): Found 222.08777 [M+H]\textsuperscript{+}; C\textsubscript{10}H\textsubscript{12}N\textsubscript{3}O\textsubscript{3} requires 222.08787.
Step 3

2-azido-1-(3,4-dimethoxyphenyl)ethanol

![Chemical structure](image)

2-azido-1-(3,4-dimethoxyphenyl)ethanone (1.86 g, 8.40 mmol) was dissolved in anhydrous Et₂O (80 mL). Activated neutral alumina (8 g) and sodium borohydride (635 mg, 16.8 mmol) were added and the suspension was stirred at RT under argon. After 16 h the reaction mixture was filtered and washed with ether. The resulting filtrate was washed with H₂O (2 x 30 mL), followed by brine (2 x 30 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated in vacuo to give the title compound as a yellow oil (1.64 g, 7.37 mmol, 87.7 %). Rf = 0.65 (2:1 DCM/EtOAc); IR (v_max/cm⁻¹, thin film): 3497 (O-H Stretch), 2938, 2839 (C-H stretch), 2106 (-N=N+ = Stretch), 1516 (aromatic C=C stretch), 1263 (Aromatic C-O-C Stretch); ¹H NMR (500 MHz, CDCl₃): δ_H = 2.67 (bs, 1H, 11-H) 3.36 (dd, J = 12.6, 3.8 Hz, 1H, 1-H), 3.49 (dd, J = 12.6, 8.3 Hz, 1H, 1-H), 3.84 (s, 3H, 9-H), 3.85 (s, 3H, 10-H), 4.78 (dd, J = 8.3, 3.8 Hz, 1H, 2-H), 6.82 (d, J = 8.2 Hz, 1H, 5-H), 6.86 (dd, J = 8.2, 1.9 Hz, 1H, 4-H), 6.89 (d, J = 1.9 Hz, 1H, 8-H); ¹³C NMR (125 MHz, CDCl₃): δ_C = 55.6 (C-9,10), 57.7 (C-1), 72.9 (C-2), 108.6 (C-8), 110.8 (C-5), 117.9 (C-4), 132.0 (C-3), 148.6 (C-7), 148.8 (C-6); LRMS m/z (El⁺): 223 [M]+, 167 [M-CH₂N₃]⁺, 139 [M-CH(OH)CH₂N₃]⁺.

Step 4

2-amino-1-(3,4-dimethoxyphenyl)ethanol

![Chemical structure](image)

2-azido-1-(3,4-dimethoxyphenyl)ethanol (1.58 g, 7.09 mmol) was dissolved in anhydrous MeOH (30 mL) and 10% palladium on carbon (158 mg, 10% w/w) was
added. The reaction mixture was stirred under hydrogen atmosphere until completion as determined by TLC and disappearance of N₃ peak by IR. After 2 h, the hydrogen was carefully released, and the reaction mixture was filtered through celite (pre-washed with MeOH). Solvent removal in vacuo gave the crude compound as an orange oil. Flash chromatography (100% EtOAc followed by 100% MeOH), followed by redissolving in DCM and filtering to remove silica yielded the title compound as a white solid (880 mg, 4.47 mmol, 63.0%). Spectroscopic data was consistent that previously reported. Mpt: ; R_f = 0.3 (1:1 EtOAc/MeOH); IR (ν_max/cm⁻¹, thin film): 3362 (O-H Stretch), 2938, 2838 (N-H Stretch); ^{1}H NMR (500 MHz, CDCl₃): δ_H = 2.14 (bs, 3H, 11,12-H) 2.80 (dd, J = 12.7, 7.9 Hz, 1H, 1-H), 2.96 (dd, J = 12.6, 4.0 Hz, 1H, 1-H) 3.86 (s, 3H, 9-H), 3.88 (s, 3H, 10-H), 4.93 (dd, J = 7.6, 3.7 Hz, 1H, 2-H), 6.86 (dd, J = 8.5, 1.8 Hz, 1H, 4-H), 6.91 (s, 7.9 Hz, 1H, 8-H); ^{13}C NMR (125 MHz, CDCl₃): δc = 48.9 (C-1), 55.5 (C-9), 55.6 (C-10), 73.8 (C-2), 108.7 (C-8), 110.7 (C-5), 117.8 (C-4), 134.8 (C-3), 148.1 (C-7), 148.7 (C-6); LRMS m/z (El⁺): 197 [M⁺], 167 [M-CH₂NH₂]⁺; HRMS m/z (El⁺): Found: 197.10492 [M⁺]; C₁₀H₁₅NO₃ requires 197.10464

Step 5

2-[3-chloropyrazin-2-yl]amino]-1-(3,4-dimethoxyphenyl)ethanol

2-amino-1-(3,4-dimethoxyphenyl)ethanol (827 g, 4.20 mmol), 2,3-dichloropyrazine (481 μ₇, 4.62 mmol) and Et₃N (781 μ₇, 5.88 mmol) were dissolved in 1,4-dioxane (8 mL) and the reaction was stirred under reflux, under argon. After 16 h, the reaction was cooled to RT, and the solvent removed in vacuo. The residual brown oil was taken up in DCM and washed with H₂O (3 x 30 mL) and brine (1 x 20 mL). The organic extracts were dried (Na₂SO₄), filtered and concentrated to give the crude product as a brown oil. Purification was carried out via flash chromatography (100% DCM - 10:1 - 5:1 DCM/EtOAc gradient) to afford the title compound as a light orange oil (748 mg, 2.42 mmol, 57.6%). R_f = 0.27 (2:1 DCM/EtOAc); IR (ν_max/cm⁻¹, thin film): 3377 (O-H Stretch) 2934 (N-H Stretch); ^{1}H NMR (500 MHz, CDCl₃): δ_H = 3.60-3.66 (m, 1H, 1-H), 3.83-3.89 (m, 1H, 1-H) 3.88 (s, 3H, 9-H), 3.89 (s, 3H, 10-H), 4.93 (dd, J = 7.6, 3.7 Hz, 1H, 2-H),
5.61 (s, 1H, 12-H), 6.87 (d, J = 8.2 Hz, 1H, 5-H), 6.93 (d, J = 8.2 Hz, 1H, 4-H), 6.97 (s, 1H, 8-H), 7.62 (d, J = 1.0 Hz, 1H, 16-H), 7.93 (d, J = 1.0 Hz, 1H, 15-H); 13C NMR (125 MHz, CDCl3): δC = 49.0 (C-1), 55.6 (C-9,10), 73.2 (C-2), 108.6 (C-8), 110.8 (C-5), 117.8 (C-4), 130.9 (C-16) 134.1 (C-3), 134.7 (C-18), 139.6 (C-15) 148.4 (C-7), 148.8 (C-6), 150.9 (C-13); LRMS m/z (Cl+): 312 [M(37Cl)+H]+, 310 [M(35Cl)+H]+, 294 [M(35Cl)-OH]+ 292 [M(35Cl)-OH]2+; HRMS m/z (Cl+): Found 310.09562 [M(35Cl)+H]+; C14H17ClN3O3 requires 310.09584

Step 6

2-[(3-chloropyrazin-2-yl)amino]-1-(3,4-dimethoxyphenyl)ethanone

DMSO (417 µL, 5.89 mmol) was dissolved in anhydrous DCM (25 mL) and the mixture was cooled to and maintained at -78°C. Oxaly chloride (249 µL, 2.94 mmol) was added drop wise and the reaction was stirred for 15 min. 2-[(3-chloropyrazin-2-yl)amino]-1-(3,4-dimethoxyphenyl)ethanol (700 mg, 2.26 mmol), dissolved in DCM (20 mL), was then added drop wise and after 15 min stirring, Et3N (1.5 mL, 11.31 mmol) was added drop wise. The reaction was then allowed to slowly warm to RT over a period of 2 h. The reaction was quenched with H2O (20 mL) and organics extracted followed by washing with 2.0 M HCl (2 x 20 mL), sat.NaHCO3 (1 x 20 mL), H2O (1 x 20 mL) and brine (1 x 20 mL). Drying (MgSO4), filtration and concentration gave an off white solid. Flash chromatography (DCM - 50:1 to 5:1 DCM/EtOAc gradient) gave the title compound as a white solid (543 mg, 1.76 mmol, 77.9%). Mpt: 128-130 °C; Rf = 0.31 (5:1 DCM/EtOAc); IR (υmax/cm−1, thin film): 3399 (C-H Stretch), 2936 (N-H Stretch), 1677 (C=O Stretch); 1H NMR (500 MHz, CDCl3): δH = 3.96 (s, 3H, 9-H), 3.97 (s, 3H, 10-H), 4.88 (d, J = 4.2 Hz, 1H, 1-H), 6.43 (s, 1H, 12-H), 6.94 (d, J = 8.2 Hz, 1H, 5-H), 7.57 (d, J = 1.7 Hz, 1H, 8-H), 7.64 (d, J = 2.9 Hz, 1H, 16-H), 7.70 (dd, J = 8.2, 2.0 Hz, 1H, 4-H), 7.96 (d, J = 2.5 Hz, 1H, 15-H); 13C NMR (125 MHz, CDCl3): δC = 47.3 (C-1), 55.8 (C-9), 55.9 (C-10) 109.7 (C-8), 110.0 (C-5), 122.3 (C-4), 127.3 (C-3), 130.8 (C-16), 135.1 (C-18), 139.8 (C-15) 149.0 (C-7), 150.1 (C-13), 153.9 (C-6), 192.1 (C-2); LRMS m/z (Cl+): 310 [M(37Cl)+H]+, 308 [M(35Cl)+H]+; HRMS m/z (Cl+): Found
308.08143 \[\text{[M}^{35}\text{Cl}\text{]+H}^+\]; \text{C}_{14}\text{H}_{15}\text{CIN}_3\text{O}_3\text{ requires 308.08109}; \text{Anal. Calcd for C}_{14}\text{H}_{14}\text{CIN}_3\text{O}_3; \text{C, 54.64; H, 4.59; N, 13.65. Found C, 53.70; H, 4.46; N, 14.01%}

**Step 7**

5 8-chloro-3-(3,4-dimethoxyphenyl)imidazo[1,2-a]pyrazine

![Chemical structure image]

2-[(3-chloropyrazin-2-yl)amino]-1-(3,4-dimethoxyphenyl)ethanone (280 mg, 0.912 mmol) was dissolved in anhydrous toluene (20 mL) and the mixture was cooled on ice. Trifluoroacetic acid (490 \(\mu\)l, 6.39 mmol) was added and the reaction was allowed to stir on ice for 30 min, followed by the addition of trifluoroacetic anhydride (887 \(\mu\)l, 6.39 mmol). The reaction mixture was then stirred on ice for a further 30 min and then at RT for 68 h. The reaction was then diluted with toluene (50 mL) and washed with NaHCO\(_3\) solution (10% w/v, 3 x 30 mL) and brine (1 x 40 mL). The organics were dried (MgSO\(_4\)), filtered and concentrated to give crude yellow solid. Purification was carried out via flash chromatography (9:1 to 2:1 DCM/EtOAc) to afford the title compound as a white solid (46.8 mg, 0.162 mmol, 17.8%). Mpt: > 200 °C; \(R_f = 0.32\) (2:1 DCM/EtOAc); IR (\(v_{max}/\text{cm}^{-1}\), thin film): 2960 (w), 2924 (w), 1732 (w); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta_H = 3.93\) (s, 3H, 16-H), 3.96 (s, 3H, 17-H), 6.99 (d, \(J = 2.0\) Hz, 1H, 15-H), 7.03 (d, \(J = 8.2\) Hz, 1H, 12-H), 7.10 (dd, \(J = 8.3, 2.0\) Hz, 1H, 11-H), 7.67 (d, \(J = 4.6\) Hz, 1H, 6-H), 7.84 (s, 1H, 2-H), 8.15 (d, \(J = 4.6\) Hz, 1H, 5-H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta_C = 56.1\) (C-16), 56.2 (C-17), 111.4 (C-15), 111.8 (C-12), 116.3 (C-5), 119.8 (C-10), 121.0 (C-11), 128.2 (C-6), 129.2 (C-3), 134.2 (C-2), 138.0 (C-9), 144.3 (C-8), 149.8 (C-14), 150.1 (C-13); HRMS m/z (ESI\(^+\)): Found 290.0683 [M\(^{35}\text{Cl}\)+H]\(^+\); C\(_{14}\)H\(_{13}\)N\(_3\)O\(_2\)Cl requires 290.0696; Anal. Calcd for C\(_{14}\)H\(_{12}\)N\(_3\)O\(_2\)Cl: C, 58.04; H, 4.17; N, 14.50.
Step 8

*yV-[3-(3,4-dimethoxyphenyl)imidazo[1,2-a]pyrazin-8-yl]-4-methyl-
benzenesulfonamide*

All glassware was evacuated and flushed with argon prior to use. 8-chloro-3-(3,4-
dimethoxyphenyl)imidazo[1,2-a]pyrazine (95.0 mg, 0.033 mmol), 4-toluenesulfonamide
(67.5 mg, 0.039 mmol), \( \text{K}_2\text{CO}_3 \) (54.4 mg, 0.039 mmol), 1 mol% \( \text{Pd(dba)}_2 \) (0.950 mg)
and 5 mol% ie/f-butyl XPhos (4.75 mg) were weighed into a 10 mL round bottom flask.

\( \text{BuOH} \) (2 mL) was added and the reaction was stirred under reflux for 40 h. The
reaction mixture was cooled to RT, diluted with MeOH and filtered through celite (pre-
was washed with MeOH). Flash Chromatography was carried out (50:1 to 1:1 DCiW EtOAc
gradient) to afford the title compound as a yellow solid (42.3 mg, 0.010 mmol or 30.5%).

Mpt: >200 °C; \( R_f = 0.08 \) (1:1 DCM/EtOAc); IR (\( \nu_{\text{max}}/\text{cm}^{-1} \), thin film): 3244 (N-H), 3129,
2838 (C-H), 1582 (s), 1254 (Ar-O-Me); \( ^{1} \text{H NMR} \) (600 MHz, CDCl\(_3\)): \( \delta_H = 2.34 \) (s, 3H,
24-H), 3.89 (s, 3H, 16-H), 6.93 (d, \( J = 1.8 \) Hz, 1H, 15-H), 6.98 (d, \( J = 8.3 \) Hz, 1H, 12-H), 7.02 (dd, \( J = 8.2, 1.8 \) Hz, 11-H), 7.13 (bs, 1H, 6-H), 7.21 (d, \( J =
8.1 \) Hz, 2H, 22-H), 7.41 (bs, 1H, 5-H), 7.64 (s, 1H, 2-H), 7.92 (d, \( J = 8.1 \) Hz, 2H, 21-H),
11.53 (s, 1H, 18-H); \( ^{13} \text{C NMR} \) (150 MHz, CDCl\(_3\)): \( \delta_C = 21.5 \) (C-24), 56.1 (C-16), 56.2
(C-17), 108.0 (C-5), 111.5 (C-15), 111.7 (C-12), 116.1 (C-6), 119.5 (C-10), 121.2 (C-
11), 126.6 (C-21), 129.4 (C-22), 131.4 (C-3), 133.1 (C-2), 135.6 (C-9), 139.3 (C-20),
143.2 (C-23), 145.8 (C-8), 149.6 (C-14), 150.1 (C-13); LRMS m/z (ESI\(^+\)): 425 [M+H]\(^+\),
447 [M+Na]\(^+\), HRMS m/z (ESI\(^+\)) Found 423.0940 [M-H]\(^+\); \( c_{21}H_{21}N_{4}O_{4}S \) requires
423.0949; Anal. Calcd for \( c_{21}H_{20}N_{4}O_{4}S \): C, 59.42; H, 4.75; N, 13.20. Found C, 55.59; H,
4.52; N, 11.97%
Example 4
4-methyl-4-[[3-(3,5-dimethylphenyl)imidazo[1,2-a]pyrazin-8-yl]benzenesulfonamide

Step 1
2-bromo-1-(3,5-dimethylphenyl)ethanone

3,5-dimethyl acetophenone (1.00 g, 6.75 mmol) was dissolved in chloroform (40 mL) and ethanol (40 mL). Pyridinium tribromide (6.47 g, 20.2 mmol) was added and the reaction was stirred at 50°C for 17 h. The reaction mixture was cooled to RT and the solvents removed in vacuo. The resulting orange slurry was suspended in H₂O (30 mL) and extracted with EtOAc (4 x 30 mL). The combined organic extracts were washed with H₂O (2 x 20 mL) and brine (1 x 20 mL), dried (Na₂SO₄), filtered and concentrated in vacuo to give a yellow oil. Flash chromatography was carried out (100% Pet Ether - 20:1 - 2:1 Pet Ether/DCM) to afford the title compound as a pale yellow oil (760 g, 3.34 mmol 49.6%). Spectroscopic data was consistent with that previously reported. R_f = 0.31 (1:1 Pet Ether/DCM); IR (v_max/cm⁻¹, thin film): 2919 (C-H Stretch), 1683 (C=O Stretch); ¹H NMR (500 MHz. CDCl₃): δ_H = 2.38 (s, 6H, 7-H), 4.44 (s, 2H, 1-H), 7.24 (s, 1H, 6-H), 7.58 (s, 2H, 4-H); ¹³C NMR (125 MHz, CDCl₃): δ_C = 21.3 (C-7), 31.3 (C-1), 126.7 (C-4), 134.2 (C-3), 135.7 (C-6), 138.7 (C-5), 191.7 (C-2); LRMS m/z (E⁺): 228[M(³⁷Br)]⁺, 226 [M(³⁹Br)]⁺, 133 [M-CH₂Br]⁺; HRMS m/z (E⁺): Found 225.99851 [M(³⁷Br)]⁺; C₁₀H₁₁BrO requires 225.99877.
Step 2
2-azido-1-(3,5-dimethylphenyl)ethanone

2-bromo-1-(3,5-dimethylphenyl)ethanone (3.44 g, 15.1 mmol) was dissolved in anhydrous DMSO (15 mL) and the mixture was cooled on ice. Sodium azide (1.18 g, 18.2 mmol) was added in one portion and the reaction was stirred under argon at RT for 16 h. An extra portion of sodium azide (200 mg) was added and the reaction was left to stir for a further 1 h. A colour change from yellow to deep orange was observed. The reaction was then quenched with H₂O (30 mL), and extracted with EtOAc (4 x 40 mL). The combined organic layers were washed with H₂O (5 x 20 mL) followed by brine (20 mL) and then dried (MgSO₄) and filtered. The solvent was removed in vacuo to give an orange solid (2.85 g, 15.1 mmol, 99.9%). Rₛ = 0.59 (DCM); IR (ν max/cm⁻¹, thin film): 2920 (C-H Stretch), 2105 (-N=N,+ N Stretch), 1692 (C=0 Stretch), 1604 (aromatic C=C stretch); ¹H NMR (500 MHz, CDCl₃): δH = 2.35 (s, 6H, 7-H), 4.52 (s, 2H, 1-H), 7.20 (s, 1H, 6-H), 7.40 (s, 2H, 4-H); ¹³C NMR (125 MHz, CDCl₃): δC = 21.3 (C-7), 55.0 (C-1), 125.7 (C-4), 134.5 (C-3), 135.9 (C-6), 138.8 (C-5), 193.6 (C-2); LRMS m/z (Cl⁺): 132 [M-CH₂N₃]⁺

Step 3
2-azido-1-(3,5-dimethylphenyl)ethanol

2-azido-1-(3,5-dimethylphenyl)ethanone (2.85 g, 15.1 mmol) was dissolved in anhydrous MeOH (60 mL) and cooled on ice. Sodium borohydride (855 mg, 22.6 mmol) was added portion wise and the mixture was stirred on ice under argon for 1 h until the reaction had gone to completion by TLC. The solvent was removed and the resulting orange oil was taken up in DCM (60 mL) and carefully washed with 2.0 M HCl (40 mL), H₂O (30 mL) and brine (30 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated in vacuo to give the title compound as an orange oil (2.85 g, 14.9 mmol, 98.7%). Rₛ = 0.27 (DCM); IR (ν max/cm⁻¹, thin film): 3395 (O-H
2-amino-1-(3,5-dimethylphenyl)ethanol

2-azido-1-(3,5-dimethylphenyl)ethanol (2.85 g, 14.9 mmol) was dissolved in anhydrous MeOH (60 mL) and 10% palladium on carbon (285 mg, 10% w/w) was added. The reaction mixture was stirred under hydrogen atmosphere until completion as determined by TLC and disappearance of N_3 peak by IR. After 22 h, the hydrogen was carefully released, and the reaction mixture was filtered through celite (pre-washed with MeOH).Solvent removal in vacuo gave the title compound as a sticky green/brown solid (2.37 g, 14.4 mmol, 96.6%). R_f = 0.0 (DCM); IR (ν_max/cm⁻¹, thin film): 3289 (O-H Stretch), 3010 (C-H Stretch), 2916, 2861 (N-H Stretch); ¹H NMR (600 MHz, CDCl₃): δ_H = 2.31 (s, 6H, 7-H), 2.81 (dd, J = 12.6, 7.8 Hz, 1H, 1-H), 2.96 (dd, J = 13.2, 4.2 Hz, 1H, 1-H), 4.57 (dd, J = 7.8, 4.2 Hz, 1H, 2-H), 6.91 (s, 1H, 6-H), 6.96 (s, 2H, 4-H); ¹³C NMR (150 MHz, CDCl₃): δC = 21.5 (C-7), 49.3 (C-1), 74.5 (C-2), 123.8 (C-4), 130.6 (C-6), 138.1 (C-5), 142.5 (C-3); LRMS m/z (Cl⁺): 192 [M+H⁺], 132 [M-OH-N₃⁺].

Step 5

2-[(3-chloropyrazin-2-yl)amino]-1-(3,5-dimethylphenyl)ethanol

2-amino-1-(3,5-dimethylphenyl)ethanol (2.34 g, 14.2 mmol), 2,3-dichloropyrazine (1.62 mL, 15.6 mmol) and Et₃N (2.76 mL, 19.8 mmol) were dissolved in 1,4-dioxane (24 mL) and the reaction was stirred under reflux, under argon. After 16 h, the reaction was...
cooled to RT, and the solvent removed in vacuo. The residue was taken up in DCM and washed with H$_2$O (3 x 30 mL) and brine (1 x 20 mL). The organic extracts were dried (MgSO$_4$), filtered and concentrated to give the crude product as a brown oil. Purification was carried out via flash chromatography (100% DCM - 30:1 - 10:1 DCM/EtOAc gradient) to afford the title compound as a light orange oil (2.58 g, 9.37 mmol, 65.5%). $R_f$ = 0.37 (9:1 DCM/EtOAc); IR ($v_{max}$ cm$^{-1}$, thin film): 3422 (O-H Stretch), 2921 (C-H Stretch); $^1$H NMR (600 MHz, CDCl$_3$): $\delta_H$ = 2.33 (s, 6H, 7-H), 3.27 (s, 1H, 8-H) 3.61 (ddd, $J$ = 13.8, 7.8, 4.8 Hz, 1H, 1-H), 3.88 (ddd, $J$ = 13.8, 6.6, 3.6 Hz, 1H, 1-H), 4.91 (dd, $J$ = 7.9, 2.8 Hz, 1H, 2-H), 5.62 (bt, 1H, 9-H), 6.95 (s, 1H, 6-H), 7.02 (s, 2H, 4-H), 7.62 (d, $J$ = 3.0 Hz, 1H, 13-H), 7.93 (d, $J$ = 3.0 Hz, 1H, 12-H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta_C$ = 21.5 (C-7), 49.53 (C-1), 73.8 (C-2), 123.7 (C-4), 129.7 (C-6), 131.2 (C-13), 135.3 (C-15) 138.4 (C-5), 139.7 (C-12), 142.5 (C-3), 151.3 (C-10); LRMS m/z (Cl$^+$): 280 [M$^{35}Cl$]+, 278 [M$^{35}Cl$]+, 262 [M$^{37}Cl$]+, 260 [M$^{35}Cl$]+, HRMS m/z (Cl$^+$): Found 278.10589 [M$^{35}Cl$]+; C$_{14}$H$_{11}$N$_2$OCl requires 278.10601

Step 6

2-[(3-chloropyrazin-2-yl)amino]-1-(3,5-dimethylphenyl)ethanone

DMSO (1.71 mL, 24.2 mmol) was dissolved in anhydrous DCM (170 mL) and the mixture was cooled to and maintained at -78°C. Oxaly chloride (1.02 mL, 12.1 mmol) was added drop wise and the reaction was stirred for 20 min. 2-[(3-chloropyrazin-2-yl)amino]-1-(3,5-dimethylphenyl)ethanol (2.58 g, 9.30 mmol), dissolved in DCM (30 mL), was then added drop wise and after 20 min stirring, Et$_3$N (6.18 mL, 46.6 mmol) was added drop wise. The reaction was then allowed to slowly warm to RT over a period of 2 1/2 h. The reaction was quenched with H$_2$O (50 mL) and organics extracted followed by washing with 2.0 M HCl (2 x 40 mL), sat. NaHCO$_3$ (1 x 40 mL), H$_2$O (1 x 40 mL) and brine (1 x 40 mL). Drying (MgSO$_4$), filtration and concentration gave a yellow solid (2.31, 8.37 mmol, 90.0%). Mpt: Decomposed before melting; $R_f$ = 0.76 (9:1 DCM/EtOAc); IR ($v_{max}$ cm$^{-1}$, thin film): 3405 (m), 2916 (w), 1681 (s), 1578 (s), 1497 (s); $^1$H NMR (500 MHz, CDCl$_3$): $\delta_H$ = 2.40 (s, 6H, 7-H), 4.89 (d, $J$ = 4.0 Hz, 1H, 1-H), 6.43 (s, 1H, 8-H), 7.27 (s, 1H, 6-H), 7.65 (d, $J$ = 3.0 Hz, 1H, 12-H), 7.67 (s, 2H, 4-H), 7.97
(d, J = 3.0 Hz, 1H, 11-H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta_C = 20.9$ (C-7), 47.8 (C-1), 125.4 (C-4), 130.9 (C-12), 134.2 (C-3), 135.1 (C-14), 135.5 (C-6), 138.4 (C-5), 139.8 (C-11), 150.0 (C-9), 193.6 (C-2); LRMS m/z (ESI$^+$): 276 [M($^{35}$Cl)-H]$^+$, 274 [M($^{35}$Cl)-H]$^+$; HRMS m/z (ESI$^+$): Found 274.0762 [M($^{35}$Cl)-H]$^+$; $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta_C = 21.5$ (C-14), 116.6 (C-5), 125.9 (C-11), 127.4 (C-10), 128.3 (C-6), 129.6 (C-3), 131.3 (C-13), 134.5 (C-2), 138.3 (C-9), 139.5 (C-12), 144.4 (C-8); LRMS m/z (ESI$^+$): 259 [M($^{35}$Cl)]$^+$, 257 [M($^{37}$Cl)]$^+$; HRMS m/z (ESI$^+$): Found: 257.07143 [M($^{35}$Cl)]$^+$; $^{15}$N NMR (125 MHz, CDCl$_3$): $\delta_N = 274.07143$; Anal. Calcd for C$_{14}$H$_{12}$ClN$_3$: C, 65.25; H, 4.69; N, 16.30. Found C, 64.67; H, 4.57; N, 16.09%

**Step 7**

8-chloro-3-(3,5-dimethylphenyl)imidazo[1,2-a]pyrazine

2-[(3-chloropyrazin-2-yl)amino]-1-(3,5-dimethylphenyl)ethanone (2.29 g, 8.31 mmol) was dissolved in anhydrous toluene (90 mL) and the mixture was cooled on ice. Trifluoroacetic acid (4.48 mL, 58.1 mmol) was added and the reaction was allowed to stir on ice for 30 min, followed by the addition of trifluoroacetic anhydride (8.09 mL, 58.1 mmol). The reaction mixture was then stirred on ice for a further 30 min and then at RT for 68 h. The reaction was then diluted with toluene (50 mL) and washed with NaHCO$_3$ solution (10% w/v, 3 x 40 mL) and brine (1 x 40 mL). The organics were dried (MgSO$_4$), filtered and concentrated to give crude orange sticky solid. Purification was carried out via flash chromatography (40:1 DCM/EtOAc) to afford the title compound as a yellow solid (531.7 g, 2.06 mmol, 24.8%). Mpt: 178-180 °C; R$_f$ = 0.32 (9:1 DCM/EtOAc); IR (v$_{max}$/cm$^{-1}$, thin film): 2918 (C-H), 1603, 1457, 1336, 922; $^1$H NMR (600 MHz, CDCl$_3$): $\delta_H = 2.41$ (s, 6H, 14-H), 7.14 (s, 1H, 13-H), 7.16 (s, 2H, 11-H), 7.69 (d, J = 4.6 Hz, 1H, 6-H), 7.87 (s, 1H, 2-H), 8.21 (d, J = 4.6 Hz, 1H, 5-H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta_C = 21.5$ (C-14), 116.6 (C-5), 125.9 (C-11), 127.4 (C-10), 128.3 (C-6), 129.6 (C-3), 131.3 (C-13), 134.5 (C-2), 138.3 (C-9), 139.5 (C-12), 144.4 (C-8); LRMS m/z (ESI$^+$): 259 [M($^{35}$Cl)]$^+$, 257 [M($^{37}$Cl)]$^+$; HRMS m/z (ESI$^+$): Found: 257.07149 [M($^{35}$Cl)]$^+$; $^{15}$N NMR (125 MHz, CDCl$_3$): $\delta_N = 274.07143$; Anal. Calcd for C$_{14}$H$_{12}$ClN$_3$: C, 65.25; H, 4.69; N, 16.30. Found C, 64.67; H, 4.57; N, 16.09%
All glassware was evacuated and flushed with argon prior to use. 8-chloro-3-(3,5-dimethylphenyl)imidazo[1,2-a]pyrazine (93.8 mg, 0.364 mmol), 4-toluenesulfonamide (74.8 mg, 0.437 mmol), \( \text{K}_2\text{CO}_3 \) (60.4 mg, 0.437 mmol), 1 mol% \( \text{Pd(dba)}_2 \) (2.10 mg) and 5 mol% tert-butyl XPhos (7.70 mg) were weighed into a 10 mL round bottom flask.

\( \text{BuOH} \) (2 mL) was added and the reaction was stirred under reflux for 40 h. The reaction mixture was cooled to RT, diluted with MeOH and filtered through celite (pre-washed with MeOH). Flash Chromatography was carried out (9:1 to 1:1 DCM/ EtOAc gradient followed by DCM/10% MeOH) to afford the title compound as a pale yellow solid (96.2 mg, 0.245 mmol, 67.3%). Mpt: >200 °C; \( R_f = 0.5 \) (DCM/10% MeOH); IR (\( \nu_{\text{max}} / \text{cm}^{-1}, \text{thin film} \)): 3253 (w), 1591 (s); \(^1\text{H NMR} \) (600 MHz, \( \text{CD}_2\text{Cl}_2 \)) \( \delta_{\text{H}} = 2.38 \) (s, 6H, 14-H), 2.39 (s, 3H, 21-H), 6.98 (bs, 1H, 6-H), 7.11 (s, 2H, 11-H), 7.13 (s, 1H, 13-H), 7.30 (d, \( J = 8.0 \) Hz, 2H, 19-H), 7.50 (bs, 1H, 5-H), 7.64 (s, 1H, 2-H), 7.90 (bd, \( J = 6.1 \) Hz, 2H, 18-H), 11.33 (bs, 1H, 15-H); \(^{13}\text{C NMR} \) (150 MHz, \( \text{CD}_2\text{Cl}_2 \)) \( \delta_{\text{C}} = 21.4 \) (C-14), 21.7 (C-21), 108.9 (C-5), 115.8 (C-6), 125.9 (C-3), 126.4 (C-11), 126.8 (C-18), 129.8 (C-19), 131.4 (C-13), 132.2 (C-10), 133.6 (C-2), 136.1 (C-9), 139.4 (C-12), 139.7 (C-17), 143.9 (C-20), 146.2 (C-8); LRMS m/z (ESI\(^+\)): 415 [M+Na]\(^+\), 393 [M+H]\(^+\); HRMS m/z (ESI\(^+\)): Found: 393.1366 [M+H]\(^+\); \( C_{21}\text{H}_{21}\text{N}_4\text{O}_2\text{S} \) requires 393.1385; Anal. Calcd for \( C_{21}\text{H}_{20}\text{N}_4\text{O}_2\text{S} \): C, 64.27; H, 5.14; N, 14.27. Found C, 63.49; H, 5.06; N, 14.24%
Example 5
4-methyl-yV-[4-[3-(2-naphthyl)imidazo[1,2-a]pyrazin-8-yl]amino]phenyl]benzenesulfonamide

Steps 1 to 6 were carried out as per Steps 1 to 6 of Example 1.

Step 7
4-methyl-yV-[4-[3-(2-naphthyl)imidazo[1,2-a]pyrazin-8-yl]amino]phenyl]benzenesulfonamide

All glassware was evacuated and flushed with argon prior to use. 8-chloro-3-(2-naphthyl)imidazo[1,2-a]pyrazine (283 mg, 1.01 mmol), \( \text{N-(4-aminophenyl)-4-methylbenzenesulfonamide} \) (318 mg, 1.21 mmol), \( \text{K}_2\text{CO}_3 \) (167 mg, 1.21 mmol), 1 mol%
Pd(dba)$_2$ (5.80 mg) and 5 mol% ie/f-butyl XPhos (21.5 mg) were weighed into a 25 mL round bottom flask. $^1$BuOH (6 mL) was added and the reaction was stirred under reflux for 46 h. The reaction mixture was cooled to RT, diluted with MeOH (100 mL) and filtered through celite (pre-washed with MeOH). Flash chromatography (DCM/Et$_2$O 100:1 to 8:1 gradient) was carried out to give the title compound as a yellow solid (181 mg, 0.355 mmol, 35.1%). Mpt: >200 °C; $R_f$ = 0.12 (10:1 DCM/EtOAc); \(\delta_H = 2.37 \text{ (s, 3H, 31-H)}, 7.09 \text{ (d, } J = 8.9 \text{ Hz, 2H, 23-H)}, 7.17 \text{ (s, 1H, 25-H)}, 7.21 \text{ (d, } J = 8.2 \text{ Hz, 2H, 29-H)}, 7.52 \text{ (d, } J = 4.7 \text{ Hz, 1H, 6-H)}\), 7.58 (dd, \(J = 5.8, 3.1 \text{ Hz, 2H, } 15,16\text{-H)}\), 7.64 (dd, \(J = 8.3, 1.6 \text{ Hz, 1H, 11-H)}\), 7.65 (d, \(J = 8.3 \text{ Hz, 2H, 28-H)}\), 7.73 (s, 1H, 2-H), 7.79-7.80 (m, 3H, 5,22-H), 7.91 (dd, \(J = 5.9, 3.4 \text{ Hz, 2H, } 14,17\text{-H)}\), 8.00 (d, \(J = 8.6 \text{ Hz, 1H, 12-H)}\), 8.03 (s, 1H, 19-H), 8.39 (bs, 1H, 20-H); $^{13}$C NMR (150 MHz, CDCl$_3$): \(\delta_C = 21.6 \text{ (C-31)}, 109.4 \text{ (C-5)}, 120.3 \text{ (C-22)}, 123.7 \text{ (C-23)}, 125.2 \text{ (C-10)}, 125.4 \text{ (C-1 1)}, 127.1 \text{ (C-15,16)}, 127.3 \text{ (C-19,28)}, 127.9 \text{ (C-14)}, 128.1 \text{ (C-17)}, 128.9 \text{ (C-3)}, 129.0 \text{ (C-6)}, 129.3 \text{ (C-12)}, 129.7 \text{ (C-29)}, 130.4 \text{ (C-2)}, 131.2 \text{ (C-24)}, 133.1 \text{ (C-9,18)}, 133.4 \text{ (C-13)}, 136.1 \text{ (C-27)}, 137.2 \text{ (C-21)}, 143.7 \text{ (C-30)}, 146.2 \text{ (C-8)}\); LRMS m/z (ESI$^-$): 504 [M-H$^-$]; HRMS m/z (ESI$^-$): Found 504.1503 [M-H$^-$]; C$_{29}$H$_{23}$N$_5$O$_2$S requires 504.1494; Anal. Calcd for C$_{29}$H$_{23}$N$_5$O$_2$S: C, 68.89; H, 4.59; N, 13.85. Found C, 66.66; H, 4.51; N, 13.11%

Example 6

4-methyl-yV-[4-[3-(3-thienyl)imidazo[1,2-a]pyrazin-8-yl]aminophenyl]benzenesulfonamide
Step 1
2-bromo-1-(3-thienyl)-1-ethanone

1-(3-thienyl)ethanone (2.00 g, 15.9 mmol) was dissolved in chloroform (100 mL) and ethanol (100 mL). Pyridinium tribromide (10.1 g, 31.7 mmol) was added and the reaction was stirred at 50°C for 18 h. The reaction mixture was cooled to RT and the solvents removed in vacuo. The resulting orange slurry was suspended in H₂O (40 mL) and extracted with EtOAc (4 x 50 mL). The combined organic extracts were washed with H₂O (2 x 30 mL) and brine (1 x 30 mL), dried (MgSO₄), filtered and concentrated in vacuo to give an amber liquid. Flash chromatography was carried out (3:1 Pet Ether/DCM) to afford the title compound as a white solid (1.61 g, 7.81 mmol, 49.1%). Spectroscopic data was consistent with that previously reported (Laufer, S., et al Arch Pharm. Pharm. Med Chem., 1997, 330, 307-312). Mpt: 59-60 °C [Lit. 61.6 °C]; Rᵢ = 0.48 (1:1 Pet Ether/DCM); IR (v max/cm⁻¹, thin film): 3094.5 (C-H stretch), 1688.5 (C=O stretch), 1508, 1415, 1400, 1393, 1380 (Aromatic C=C stretch), 1181; ¹H NMR (600 MHz, CDCl₃): δH = 4.34 (s, 2H, 1-H), 7.36 (dd, J = 2.9, 5.2 Hz, 1H, 5-H), 7.58 (dd, J = 5.2, 1.2Hz, 1H, 4-H), 8.17 (dd, J = 2.9, 1.3 Hz, 1H, 7-H); ¹³C NMR (150 MHz, CDCl₃): δc = 31.7 (C-1), 127.0 (C-5), 127.4 (C-4), 133.9 (C-7), 138.9 (C-3), 185.7 (C-2); LRMS m/z (Cl⁺): 207 [M⁺][Br]⁺, 205 [M⁺][Br]⁺

Step 2
2-azido-1-(3-thienyl)ethanone

2-bromo-1-(3-thienyl)-1-ethanone (573 mg, 2.80 mmol) was dissolved in DMSO (3 mL) and the mixture was cooled on ice. Sodium azide (218 mg, 3.35 mmol) was added in one portion and the reaction was stirred under argon at RT for 5 h. The reaction was quenched with H₂O (20 mL), and extracted with EtOAc (3 x 30 mL). The organic layers were combined, washed with H₂O (5 x 20 mL) followed by brine (20 mL), dried (Na₂SO₄) and filtered. The solvent was removed in vacuo to give brown/orange oil (460 mg, 2.75 mmol, 98.5%). Rᵢ = 0.27 (DCM); IR (v max/cm⁻¹, thin film): 3105 (C-H stretch, 2928 (C-H stretch), 2765 (C-H stretch), 2353 (C=N stretch), 1688 (C=O stretch), 1602 (Aromatic C=C stretch), 1455 (Aromatic C=C stretch), 1375 (Aromatic C=C stretch), 1248 (Aromatic C=C stretch), 1141 (Aromatic C=C stretch), 753 (Aromatic C=C stretch), 695 (Aromatic C=C stretch), 601 (Aromatic C=C stretch), 505 (Aromatic C=C stretch), 400 (Aromatic C=C stretch), 200 (Aromatic C=C stretch), 100 (Aromatic C=C stretch), 90 (Aromatic C=C stretch), 80 (Aromatic C=C stretch), 70 (Aromatic C=C stretch), 60 (Aromatic C=C stretch), 50 (Aromatic C=C stretch), 40 (Aromatic C=C stretch), 30 (Aromatic C=C stretch), 20 (Aromatic C=C stretch), 10 (Aromatic C=C stretch), 0 (Aromatic C=C stretch).
stretch), 2097 (-N=N + =N Stretch), 1679 (C=O Stretch), 1508, 1409, 1231, 1177; H NMR (500 MHz, CDCl₃): δ H = 4.43 (s, 2H, 1-H), 7.38 (dd, J = 5.1, 2.8 Hz, 1H, 5-H), 7.55 (dd, J = 5.0, 1.2 Hz, 1H, 4-H), 8.10 (dd, J = 2.9, 1.3 Hz, 1H, 7-H); ¹³C NMR (125 MHz, CDCl₃): δC = 55.5 (C-1), 126.6 (C-5), 127.2 (C-4), 132.7 (C-7), 139.1 (C-3), 187.6 (C-2); LRMS m/z HRMS m/z (ESI⁺): Found 168.02354 [M+H]⁺; C₆H₆N₃OS requires 168.02316.

**Step 3**

2-azido-1-(3-thienyl)ethanol

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2-azido-1-(3-thienyl)ethanol (278 mg, 1.67 mmol) was dissolved in anhydrous MeOH (10 mL) and cooled on ice. Sodium borohydride (94.5 mg, 2.45 mmol) was added portion wise and the mixture was stirred on ice under argon for 1 h until the reaction had gone to completion by TLC. The solvent was removed and the resulting residue was taken up in DCM (30 mL) and carefully washed with H₂O (2 x 20 mL) followed by brine (20 mL). The organic extracts were (Na₂SO₄), filtered and concentrated in vacuo to give the title compound as a yellow oil (257 mg, 1.52 mmol 91.2%). Rf = 0.8 (1:1 Pet Ether/EtOAc); IR (ν max/cm⁻¹, thin film): 3372 (O-H stretch), 3105 (C-H stretch), 2096 (-N=N + =N Stretch); H NMR (500 MHz, CDCl₃): δ H = 3.51-3.54 (m, 2H, 1-H), 4.98 (dd, J = 4.7, 1.9 Hz, 1H, 2-H), 7.08 (dd, J = 5.0, 1.3 Hz, 1H, 4-H), 7.29-7.30 (m, 1H, 7-H), 7.34 (dd, J = 5.0, 3.0 Hz, 1H, 5-H); ¹³C NMR (125 MHz, CDCl₃): δC = 57.5 (C-1), 69.9 (C-2) 122.0 (C-7), 125.4 (C-4), 126.7 (C-5), 142.0 (C-3); LRMS m/z (Cl⁺): 152 [M-OH]⁺, 127 [M-N₃]⁺, 113 [M-CH₂N₃]⁺; HRMS m/z (Cl⁺): Found 152.02859 [M-OH]⁺; C₆H₆N₃OS requires 152.02824.

**Step 4**

2-amino-1-(3-thienyl)ethanol

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2-azido-1-(3-thienyl)ethanol (257 mg, 1.52 mmol) was dissolved in anhydrous MeOH (10 mL) and 10% palladium on carbon (25.7 mg, 10% w/w) was added. The reaction vessel was then subjected to 3 bar hydrogen for 5 h. After this period the mixture was filtered through celite and concentrated in vacuo to give a pale yellow solid (217 mg, 1.52 mmol, 99.9%). RF = 0.0 (1:1 DCM/EtOAc); νmax/cm⁻¹ (thin film): 3194 (O-H stretch), 3091 (N-H), 2921 (C-H); 1H NMR (600 MHz,CDCl₃): δH = 1.91 (bs, 3H, 8,9-H), 2.88 (dd, J = 12.6, 7.8 Hz, 1H, 1-H), 3.04 (d, J = 10.2 Hz, 1H, 1-H), 4.75 (dd, J = 6.6, 3.6 Hz, 1H, 2-H), 7.08 (d, J = 5.4 Hz, 1H, 4-H), 7.23 (d, J = 2.4 Hz, 1H, 7-H), 7.31 (dd, J = 4.8, 3.0 Hz, 1H, 5-H); 13C NMR (150 MHz, CDCl₃): δC = 48.4 (C-1), 70.9 (C-2) 121.1 (C-7), 125.6 (C-4), 126.3 (C-5), 144.0 (C-3); LRMS m/z (Cl⁺): 177, 159, 127 [M-NH₂⁺]; (El⁺): 131, 127 [M-NH₂⁺]; 119, 114

Step 5

2-[(3-chloropyrazin-2-yl)amino]-1-(3-thienyl)ethanol

2-amino-1-(3-thienyl)ethanol (232 mg, 1.63 mmol), 2,3-dichloropyrazine (183 µL, 1.79 mmol), Et₃N (316 µL, 2.27 mmol) and 1,4-dioxane (2.5 mL) were stirred under reflux, under argon for 18 h. The solvent was removed in vacuo and the residual was taken up in DCM (30 mL), washed with H₂O (5 x 10 mL) and brine (10 mL). The organics were dried (MgSO₄), filtered and solvent removed to give a brown oil. Flash chromatography (DCM followed by 2:1 DCM/EtOAc) afforded the title compound as an orange oil (193 mg, 0.753 mmol, 46.2%). RF = 0.46 (2:1 DCM/EtOAc); IR (νmax/cm⁻¹, thin film): 3420 (O-H), 3091 (N-H), 2920 (C-H), 1583, 1525; 1H NMR (600 MHz,CDCl₃): δH = 3.69-3.74 (m, 1H, 1-H), 3.96-4.00 (m, 1H, 1-H), 5.10 (dd, J = 7.2, 3.0 Hz, 1H, 2-H), 5.72 (bs, 1H, 9-H), 7.13 (dd, J = 4.8, 1.2 Hz, 1H, 4-H), 7.31-7.32 (m, 1H, 7-H), 7.35 (dd, J = 5.4, 3.0 Hz, 1H, 5-H), 7.65 (d, J = 3.0 Hz, 1H, 13-H), 7.93 (d, J = 2.4 Hz, 12-H); 13C NMR (150 MHz, CDCl₃): δC = 49.0 (C-1), 70.4 (C-2), 121.6 (C-7), 125.5 (C-4), 126.7 (C-5), 131.3 (C-13), 135.6 (C-15), 138.8 (C-12), 143.1 (C-3), 150.8 (C-10); LRMS m/z (EI⁺): 240 [M(37Cl)-OH]⁺, 238 [M(35Cl)-OH]⁺; HRMS m/z (ESI⁺): Found 254.0145 [M-H]⁻; C₁₀H₉N₂OSCl requires 254.0155.
Step 6

2-[(3-chloropyrazin-2-yl)amino]-1-(3-thienyl)ethanone

DMSO (128 µL, 1.81 mmol) was dissolved in anhydrous DCM (9 mL) and the mixture was cooled to and maintained at -78°C. Oxalyl chloride (77.0 µL, 0.906 mmol) was added drop wise and the reaction was stirred for 20 min. 2-[(3-chloropyrazin-2-yl)amino]-1-(3-thienyl)ethanol (178 mg, 0.697 mmol), dissolved in DCM (5 mL), was then added drop wise and after 20 min stirring, Et3N (463 µL, 3.48 mmol) was added drop wise. The reaction was then allowed to slowly warm to RT over a period of 2 1/2 h. The reaction was quenched with H2O (20 mL) and organics extracted followed by washing with 2.0 M HCl (2 x 10 mL), sat. NaHCO3 (1 x 10 mL), H2O (1 x 10 mL) and brine (1 x 10 mL). Drying (MgSO4), filtration and concentration gave an orange sticky solid. Flash chromatography (DCM - 50:1 to 20:1 DCM/EtOAc gradient) gave the title compound as a yellow solid (135 mg, 0.531 mmol, 76.2%). Mpt: 130-134 °C; Rf = 0.85 (2:1 DCM/EtOAc); IR (νmax/cm⁻¹, thin film): 3407 (w), 3107 (w), 2917 (w), 1682 (s), 1582 (s); 1H NMR (600 MHz,CDCl3): δH = 4.84 (d, J = 4.4 Hz, 1H, 1-H), 7.41 (dd, J = 5.0, 2.8 Hz, 1H, 5-H), 7.65 (dd, J = 5.0, 1.2 Hz, 1H, 4-H), 7.66 (d, J = 2.8 Hz, 1H, 13-H), 7.96 (d, J = 2.7 Hz, 12-H), 8.26 (dd, J = 5.4, 3.0 Hz, 1H, 7-H); 13C NMR (150 MHz, CDCl3): δc = 49.0 (C-1), 70.4 (C-2), 121.6 (C-4), 125.5 (C-7), 126.7 (C-5), 131.3 (C-13), 135.6 (C-15), 138.8 (C-12), 143.1 (C-3), 150.8 (C-10); LRMS m/z (Cl⁺): 256 [M(35Cl)+H]+, 254 [M(37Cl)+H]+; HRMS m/z (Cl⁺): Found 254.01471 [M(35Cl)+H]+; ClO3H3N3OSCI requires 254.01549; Anal. Calcd for C10H8N3OSCI: C, 47.34; H, 3.18; N, 16.56. Found C, 48.16; H, 3.41; N, 15.78%

Step 7

8-chloro-3-(3-thienyl)imidazo[1,2-a]pyrazine
2-[(3-chloropyrazin-2-yl)amino]-1-(3-thienyl)ethanone (147 mg, 0.623 mmol) was dissolved in anhydrous toluene (10 mL) and the mixture was cooled on ice. Trifluoroacetic acid (336 µL, 4.36 mmol) was added and the reaction was allowed to stir on ice for 30 minutes, followed by the addition of trifluoroacetic anhydride (606 µL, 4.36 mmol). The reaction mixture was then stirred on ice for a further 30 minutes and then at RT for 68 h. The reaction was then diluted with toluene (20 mL) and washed with NaHCO₃ solution (10% w/v, 3 x 10 mL) and brine (1 x 10 mL). The organics were dried (MgSO₄), filtered and concentrated to give crude orange oil. Purification was carried out via flash chromatography (DCM/EtOAc gradient - 20:1 to 5:1) to afford the title compound as an off white solid (39.5 mg, 0.166 mmol, 29.0%). Mpt: 178-180 °C; R₅ = 0.34 (5:1 DCM/EtOAc); IR (vₘₐₓ/cm⁻¹, thin film): 3098 (w), 1462 (s), 1341 (s); ¹H NMR (600 MHz, CDCl₃): δH = 7.34-7.36 (m, 1H, 12-H), 7.58 (s, 1H, 14-H), 7.59 (d, J = 0.7 Hz, 1H, 11-H), 7.73 (d, J = 4.6 Hz, 1H, 6-H), 7.91 (s, 1H, 2-H), 8.19 (d, J = 4.6 Hz, 1H, 5-H); ¹³C NMR (150 MHz, CDCl₃): δC = 116.7 (C-5), 124.2 (C-14), 125.0 (C-10), 126.7 (C-12), 127.7 (C-3), 128.0 (C-1), 128.6 (C-6), 134.6 (C-2), 138.1 (C-9), 144.5 (C-8); LRMS m/z (Cl⁺): 238 [M(³⁵Cl)+H]⁺, 236 [M(³⁷Cl)+H]⁺; HRMS m/z (Cl⁺): Found 236.00569 [M(³⁵Cl)+H]⁺; C₅₁H₂₇N₃SCI requires 236.00492; Anal. Calcd for ClO₆H₆N₃SCI: C, 51.0; H, 2.6; N, 17.8. Found C, ; H, ; N, %

## Step 8

4-methyl-yV-[4-[3-(3-thienyl)imidazo[1,2-a]pyrazin-8-y]aminophenyl]benzenesulfonamide

All glassware was evacuated and flushed with argon prior to use. 8-chloro-3-(3-thienyl)imidazo[1,2-a]pyrazine (35.0 mg, 0.149 mmol), y-(4-aminophenyl)-4-methylbenzenesulfonamide (47.8 mg, 0.178 mmol), K₂CO₃ (24.6 mg, 0.178 mmol), 1
mol% Pd(dba)₂ (0.900 mg) and 5 mol% ie/f-butyl XPhos (3.20 mg) were weighed into a 25 mL round bottom flask. βBuOH (2 mL) was added and the reaction was stirred under reflux for 46 h. The reaction mixture was cooled to RT, diluted with MeOH (100 mL) and filtered through celite (pre-washed with MeOH). Flash chromatography (3:2 Pet Ether/EtOAc) was carried out to give a mixture of the product and starting sulfonamide.

Reverse phase preparative HPLC (5% MeCN - 40% 3 min - 70% 25 min - 95% 27 min, hold 2 min - 5% 30 min, hold 2 min) carried out to afford title compound as off white solid (12.4 mg, 0.027 mmol, 18.1%). Mpt: ; Rf = 0.62 (1:1 DCM/EtOAc); IR (νmax/cm⁻¹, thin film): 3112 (w), 1624 (w), 1542 (s), 1506 (s), 1159 (s); ¹H NMR (600 MHz, CD₃OD): δH = 2.38 (s, 3H, 26-H), 7.17 (d, J = 5.4 Hz, 1H, 6-H), 7.28 (d, J = 9.0 Hz, 2H, 17-H), 7.33 (d, J = 8.4 Hz, 2H, 24-H), 7.48 (d, J = 9.0 Hz, 2H, 18-H), 7.49, (dd, J = 5.4 Hz, 1.2 1H, 11-H), 7.72-7.73 (m, 3H, 12-H, 23-H), 7.92 (dd, J = 2.4, 1.2 Hz, 1H, 14-H), 7.96 (bs, 1H, 2-H), 8.02 (d, J = 5.4 Hz, 1H, 5-H); ¹³C NMR (150 MHz, CD₃OD): δC = 21.4 (C-26), 112.2 (C-5), 119.8 (C-6), 122.7 (C-17), 126.1 (C-14), 126.6 (C-18), 128.0 (C-11), 128.3 (C-10), 128.3 (C-23), 128.9 (C-12), 129.1 (C-3), 130.7 (C-24), 132.1 (C-19), 133.0 (C-9), 134.2 (C-2), 138.2 (C-22), 138.8 (C-16), 145.3 (C-25), 146.2 (C-8); ¹H NMR (600 MHz,CDCl₃): δH = 2.38 (s, 3H, 26-H), 6.69 (s, 1H, 20-H), 7.07 (d, J = 8.8 Hz, 2H, 18-H), 7.22 (d, J = 8.1 Hz, 2H, 24-H), 7.34 (dd, J = 4.0, 2.0 Hz, 1H, 11-H), 7.52 (d, J = 4.7 Hz, 1H, 6-H), 7.54 - 7.56 (m, 2H, 12,14-H), 7.63 (d, J = 8.3 Hz, 2H, 23-H), 7.64 (s, 1H, 2-H), 7.71 (d, J = 4.7 Hz, 1H, 5-H), 7.79 (d, J = 8.8 Hz, 2H, 17-H), 8.34 (bs, 1H, 15-H); ¹³C NMR (150 MHz,CDCl₃): 21.7 (C-26), 109.7 (C-5), 120.3 (C-17), 123.6 (C-12), 123.9 (C-18), 124.5 (C-10), 126.9 (C-11), 127.4 (C-14), 127.5 (C-2, 23), 128.1 (C-3), 129.1 (C-6), 129.8 (C-24), 131.2 (C-19), 132.9 (C-9), 136.2 (C-22), 137.4 (C-16), 143.9 (C-25), 146.1 (C-8); LRMS m/z (ESI⁺): 484 [M+Na]⁺, 462 [M+H]⁺; HRMS m/z (ESI⁺): Found 462.1065 [M+H]⁺; C23H20N5S2O2 requires 462.1058; Anal. Calcd for C23H19N5S2O2: C, 59.9; H, 4.1; N, 15.2. Found C, ; H, ; N, %
Example 7
4-methyl-A/-[2-(2-naphthyl)imidazo[1,2-a]pyrazin-8-yl]benzenesulfonamide

Step 1
8-chloro-2-(2-naphthyl)imidazo[1,2-a]pyrazine

2-(Bromoacetyl)naphthalene (3.14 g, 12.6 mmol), 2-amino-3-chloropyrazine (1.63 g, 12.6 mmol), NaHCO$_3$ (1.32 g, 16.7 mmol) and $^t$BuOH (60 mL) were stirred under reflux for 40 h. The reaction mixture was cooled to RT and solvent removed in vacuo. The resulting orange solid was taken up in H$_2$O (60 mL) and extracted with DCM (3x 60 mL). The combined organics were washed with H$_2$O (50 mL) and brine (40 mL), dried (MgSO$_4$), filtered and concentrated in vacuo to give crude orange solid. On addition of DCM, insoluble material filtered off to give title compound as a cream fluffy solid (1.05 g). Purification of the remaining filtrate via flash chromatography (10:1 to 2:1 Pet Ether/EtOAc gradient) afforded the title compound as a pale orange/brown solid (338 g, Total: 1.38 g, 4.95 mmol, 39.3%). Mpt: Decomposed before melting; $R_f = 0.34$ (1:1 Pet Ether/ethyl acetate); IR ($\nu_{\text{max}}$/cm$^{-1}$, thin film): 3026.3 (w), 2921.0 (w), 1495.3 (m); $^1$H NMR (600 MHz, CDCl$_3$): $\delta_\text{H} = 7.51$-7.53 (m, 2H, 15,16-H), 7.71 (d, $J = 4.5$ Hz, 1H, 6-H), 7.88 (dd, $J = 6.7, 2.2$ Hz, 1H, 14-H), 7.93 (d, $J = 8.6$, 1H, 12-H) 7.96 (dd, $J = 6.7$, 2.4 1H, 17-H), 8.06 (dd, $J = 8.6$, 1.7 Hz, 1H, 11-H) 8.08 (d, $J = 4.5$ Hz, H, 5-H), 8.14 (s, 1H, 3-H), 8.57 (s, 1H, 19-H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta_\text{C} = 111.6$ (C-3), 118.5 (C-5), 124.1 (C-11), 124.0 (C-19), 126.0/126.7 (C-15,16), 127.8 (C-14), 128.2 (C-6), 128.5 (C-17), 128.6 (C-12), 129.4 (C-10), 133.5 (C-18), 133.7 (C-13), 138.3 (C-9), 143.5 (C-8), 148.2 (C-2); LRMS m/z (ESI$^+$): 282 [M$^{[35}\text{Cl}]$+H]$^+$, 280 [M$^{[37}\text{Cl}]$+H]$^+$; HRMS m/z (Cl$^+$):
Found 280.06338 [M(35Cl)+H]⁺; C₁₆H₁₁N₃Cl requires 280.06415; Anal. Calcd for C₁₆H₁₁N₃Cl: C, 68.70; H, 3.60; N, 15.02. Found C, 67.53; H, 3.64; N, 13.97%.

Step 2

4-methyl-A/-[2-(2-naphthyl)imidazo[1,2-a]pyrazin-8-yl]benzenesulfonamide

All glassware was evacuated and flushed with argon prior to use. 8-chloro-2-(2-naphthylimidazo[1,2-a]pyrazine (50.0 mg, 0.178 mmol), 4-toluenesulfonamide (36.9 mg, 0.215 mmol), K₂CO₃ (29.7 mg, 0.215 mmol), 1 mol% Pd(dba)₂ (1.03 mg) and 5 mol% iert-butyl XPhos (3.80 mg) were weighed into a 25 mL round bottom flask. BuOH (3 mL) was added and the reaction was stirred under reflux for 24 h. The reaction mixture was cooled to RT, diluted with MeOH (100 mL) and filtered through celite (pre-washed with MeOH). Flash chromatography (silica pre-washed with 1% Et₃N, DCIW EtOAc-gradient ran) afforded the target compound as a white solid (28.0 mg, 0.068 mmol, 38.2%). Mpt: >200 °C; Rᵣ = 0.32 (1:1 DCIW EtOAc); IR (ʋmax/cm⁻¹, thin film): 1116.3, 1135.4 (S=0 Symmetric Stretch), 1360.9 (S=0 Asymmetric Stretch), 3252.8 (N-H Stretch); ¹H NMR (600 MHz, DMSO-d₆): δH = 2.37 (s, 3H, 26-H), 7.16 (bd, J = 5.2 Hz, 1H, 6-H), 7.39 (d, J = 8.2 Hz, 2H, 24-H), 7.51 - 7.54 (m, 2H, 15,16-H), 7.86 (bd, J = 5.2 Hz, 1H, 5-H), 7.89 (d, J = 8.0 Hz, 2H, 23-H), 7.92 (d, J = 7.7 Hz, 1H, 14-H), 7.98 (d, J = 8.6 Hz, 1H, 12-H), 8.01 - 8.05 (m, 2H, 11,17-H), 8.52 (s, 1H, 19-H), 8.59 (s, 1H, 3-H), 11.69 (s, 1H, NH: 20-H); ¹³C NMR (150 MHz, DMSO-d₆): δC = 21.0 (C-26), 111.0 (C-5), 115.3 (C-3), 116.8 (C-6), 123.8 (C-11), 124.2 (C-19), 126.2 (C-23), 126.3 (C15/16), 126.6 (C-15/16), 127.7 (C-14), 128.3 (C-17), 128.4 (C-12), 129.5 (C-24), 130.0 (C-10), 132.8 (C-13), 133.2 (C-18), 135.6 (C-9), 140.0 (C-22), 142.7 (C-25), 144.5 (C-8), 145.3 (C-2); LRMS m/z (ESI⁺): 415 [M+H]⁺, (ESI⁻): 413 [M-H]⁻; HRMS m/z
(ESI⁺): Found 415.1219 [M+H]⁺; C₂₃H₁₉N₄O₂S requires 415.1229; Anal. Calcd. for C₂₃H₁₉N₄O₂S: C, 66.65; H, 4.38; N, 13.52. Found C, 65.84; H, 4.38; N, 13.10%.

Example 8
4-methyl-W-[2-(2-phenoxyphenyl)imidazo[1,2-a]pyrazin-8-yl]benzenesulfonamide

\[
\begin{align*}
\text{Step 1} & \text{ was carried out as per Step 1 of Example 2} \\
\text{Step 2} & \\
8\text{-chloro-2-(2-phenoxyphenyl)imidazo[1,2-a]pyrazine (JS18)} & \\
\end{align*}
\]

2-bromo-1-(2-phenoxyphenyl)ethanone (438 mg, 1.50 mmol), 2-amino-3-chloropyrazine (195 mg, 1.50 mmol), NaHCO₃ (158 mg, 1.88 mmol) and 'BuOH (9 mL) were stirred under reflux for 48 h. The reaction was cooled to RT and solvent removed \textit{in vacuo}. The sample was taken up in DCM (25 mL) and washed with H₂O (3 x 10 mL). The combined aqueous extracts were further washed with DCM (4 x 10 mL), and the organic extracts were combined, dried (MgSO₄), filtered and solvent removed. Flash chromatography (1st column: 25:1 to 5:1 DCM/EtOAc gradient; 2nd column: 3:1 Pet Ether/EtOAc) afforded a pale yellow solid. (40.0 mg, 0.124 mmol, 29.0%). Mpt: > 200 °C; \( R_f = 0.75 \) (1:1 Pet Ether/Ethyl Acetate); IR (\( v_{max}/\text{cm}^{-1}, \text{thin film} \)): 1071 - 1225
cm⁻¹ (Ar-O-Ar Stretch); ¹H NMR (600 MHz, CDCl₃): δ₁H = 6.97 (dd, J = 1.5, 8.2 Hz, 1H, 14-H), 7.07 (d, J = 7.6 Hz, 2H, 18-H), 7.16 (t, J = 7.4 Hz, 1H, 20-H), 7.29 - 7.34 (m, 2H, 12,13-H), 7.38 (dd, J = 8.6, 7.5 Hz, 2H, 19-H), 7.65 (d, J = 4.5 Hz, 1H, 6-H), 7.99 (d, J = 4.5 Hz, 1H, 5-H), 8.31 (s, 1H, 3-H), 8.59 (dd, J = 7.6, 1.9 Hz, 1H, 11-H); ¹³C NMR (150 MHz, CDCl₃): δ = 115.3 (C-3), 118.5 (C-5), 118.8 (C-18), 119.0 (C-14), 123.7 (C-20), 123.8 (C-10), 124.1 (C-12), 127.8 (C-6), 129.7 (C-13), 129.9 (C-19), 130.1 (C-1 1), 137.1 (C-9), 143.2 (C-2), 143.3 (C-8), 154.6 (C-15), 156.5 (C-17); LRMS m/z (ESI⁺): 324 [M(³⁷Cl)+H]⁺, 322 [M(³⁵Cl)+H]⁺; HRMS m/z (Cl⁺): Found 322.075537 [M(³⁵Cl)+H]⁺; C₁₈H₁₅ClN₃O requires 322.07471; Anal. Calcd. for C₁₈H₁₅ClN₃O: C, 67.19; H, 3.76; N, 13.06. Found C, 65.36; H, 3.66; N, 12.62%.

Step 3
4-methyl-A/-[2-(2-phenoxyphenyl)imidazo[1,2-a]pyrazin-8-yl]benzenesulfonamide

All glassware was evacuated and flushed with argon prior to use. 8-chloro-2-(2-phenoxyphenyl)imidazo[1,2-a]pyrazine (130 mg, 0.405 mmol), 4-toluenesulfonamide (83.1 mg, 0.486 mmol), K₂C₅O₃ (67.1 mg, 0.127 mmol), Pd(dba)₂ (1.30 mg) and 5 mol% ie/f-butyl XPhos (6.50 mg) were weighed into a 10 mL round bottom flask. ‘BuOH (3 mL) was added and the reaction was stirred under reflux for 48 h. The reaction mixture was cooled to RT, diluted with MeOH (100 mL) and filtered through celite (pre-washed with MeOH). Flash chromatography was carried out (100% DCM to 40:1 to 30:1 to 10:1 to 1:1 DCM/EtOAc gradient) to afford the title compound as a yellow solid (23.9 mg, 0.052 mmol 12.8%). Mpt: >200 °C; Rf = 0.18 (9:1 DCM/EtOAc); IR (v_max/cm⁻¹, thin film): 3245 (N-H Stretch), 1586, 1227 (Ar-O-Ar Stretch), 1115; ¹H NMR (600 MHz, CD₂Cl₂): δ₁H = 2.43 (s, 3H, 27-H), 6.91 (bs, 1H, 6-H), 6.96 (d, J = 8.1 Hz, 1H, 14-H),
7.08 (dd, J = 8.8, 0.7 Hz, 2H, 18-H), 7.17 (t, J = 7.1 Hz, 1H, 20-H), 7.27 (t, J = 7.3 Hz, 1H, 12-H), 7.31 - 7.37 (m, 4H, 5,13,25-H), 7.38 - 7.41 (m, 2H, 19-H), 7.91 (bd, J = 5.7 Hz, 2H, 24-H), 8.12 (s, 1H, 3-H), 8.48 (dd, J = 7.8, 1.7 Hz 1H, 11-H), 11.41 (s, 1H, 21-H); $^{13}$C NMR (150 MHz, CD$_2$Cl$_2$): δ$_C$ = 21.3 (C-27), 110.2 (C-5), 115.0 (C-6), 117.7 (C-3), 118.8 (C-18), 118.9 (C-14), 123.7 (C-20), 123.8 (C-10), 123.9 (C-12), 126.2 (C-24), 129.1 (C-11), 129.5 (C-15,25), 130.0 (C-19), 134.7 (C-9), 139.4 (C-23), 142.1 (C-2), 143.5 (C-26), 145.5 (C-8), 154.3 (C-15), 156.5 (C-17); LRMS m/z (ESI$^+$): 457 [M+H]$^+$; HRMS m/z (ESI$^+$): Found 455.1 167 [M +H]$^+$; C$_{25}$H$_{20}$N$_4$O$_3$S requires 455.1 178; Anal. Calcd. for C$_{25}$H$_{20}$N$_4$O$_3$S: C, 65.77; H, 4.42; N, 12.27. Found C, 62.62; H, 4.28; N, 11.40%

**Example 9**

yV-[2-(3,4-dimethoxyphenyl)imidazo[1,2-a]pyrazin-8-yl]-4-methylbenzenesulfonamide

Step 1 was carried out as per Step 1 of Example 3.

**Step 2**

8-chloro-2-(3,4-dimethoxyphenyl)imidazo[1,2-a]pyrazine

A mixture of 2-bromo-1-(3,4-dimethoxyphenyl)ethanone (229 mg, 0.885 mmol), 2-amino-3-chloropyrazine (115 mg, 0.885 mmol) and NaHCO$_3$ (93.0 mg, 1.1 mmol) in t-BuOH (5 mL) were stirred under argon, under reflux for 40 h. After this point,
reaction mixture was cooled to RT and solvent removed in vacuo. The resulting orange solid was dissolved in DCM (30 mL) and washed with H₂O (3 x 30 mL). The aqueous layers were extracted further with DCM (2 x 20 mL) before the combined organics were washed with brine (20 mL), dried (MgSO₄), filtered and solvent removed to give a light brown solid. Flash chromatography (3:1 Pet Ether/EtOAc) was carried out to afford the title compound (155 mg, 0.536 mmol, 60.6%). Mpt: Decomposed before melting; Rₜ = 0.11 (1:1 Pet Ether/EtOAc); IR (νₛₛₒₚ/cm⁻¹, thin film): 3142 (w), 2933 (w), 2833 (w), 1498 (s); ¹H NMR (600 MHz, CDCl₃): δ_H = 3.93 (s, 3H, 16-H), 4.00 (s, 3H, 17-H), 6.93 (d, J = 8.3 Hz, 1H, 12-H), 7.48 (dd, J = 8.2, 2.1 Hz, 1H, 11-H), 7.59 (d, J = 2.1 Hz, 1H, 15-H), 7.65 (d, J = 4.5, 1H, 6-H), 7.96 (s, 1H, 3-H), 8.02 (d, J = 4.5 Hz, 1H, 5-H); ¹³C NMR (150 MHz, CDCl₃): δ_C = 56.0 (C-16), 56.1 (C-17), 109.6 (C-15), 110.6 (C-3), 111.2 (C-12), 118.3 (C-5), 119.3 (C-11), 125.2 (C-10), 128.0 (C-6), 138.0 (C-9), 143.1 (C-8), 148.3 (C-2), 149.3 (C-13), 149.9 (C-14); LRMS m/z (ESI⁺): 292 [M⁺+H⁺]+, 290 [M⁺(Cl)+H⁺]+; HRMS m/z (ESI⁺): Found 322.075537 [M⁺(Cl)+H⁺]+; C₁₄H₁₂ClN₃O₂ requires 320.0696. Anal. Calcd for C₁₄H₁₂ClN₃O₂: C, 58.04; H, 4.17; N, 14.50. Found C, 56.12; H, 4.105; N, 13.68%

**Step 3**

yV-[2-(3,4-dimethoxyphenyl)imidazo[1,2-a]pyrazin-8-yl]-4-methylbenzenesulfonamide

All glassware was evacuated and flushed with argon prior to use. 8-chloro-2-(3,4-dimethoxyphenyl)imidazo[1,2-a]pyrazine (200 mg, 0.691 mmol), 4-toluenesulfonamide (142 mg, 0.829 mmol), K₂C₀₃ (115 mg, 0.829 mmol), 1 mol% Pd(dba)₂ (2.00 mg) and 5 mol% iert-butyl XPhos (10.0 mg) were weighed into a 10 mL round bottom flask. iBuOH (4 mL) was added and the reaction was stirred under reflux for 48 h. The reaction mixture was cooled to RT, dilute with MeOH (100 mL) and filtered through
celite (pre-washed with MeOH). Flash chromatography was carried out (100% DCM to 50:1 to 1:9 DCM/EtOAc gradient followed by DCM/10% MeOH) to give the title compound as a yellow sticky solid (5.2 mg, 0.012 mmol, 1.8%). Mpt: >200 °C; \( R_f = 0.26 \) (1:1 DCM/EtOAc); IR (\( \nu_{\text{max}} \) cm\(^{-1}\), thin film): 3274, 3138, 1584; \(^1\)H NMR (600 MHz, DMSO-\( \text{d}_6 \)) : \( \delta \) \( \eta \) = 2.36 (s, 3H, 24-H), 3.78 (s, 3H, 16-H), 3.83 (s, 3H, 17-H), 7.02 (d, \( J = 8.2 \) Hz, 1H, 12-H), 7.13 (bd, \( J = 4.9 \) Hz, 1H, 6-H), 7.37 (d, \( J = 8.2 \) Hz, 1H, 22-H), 7.45 (bs, 1H, 11-H), 7.47 (bs, 1H, 15-H), 7.81 (d, \( J = 5.5 \) Hz, 1H, 5-H), 7.87 (d, \( J = 8.0 \) Hz, 2H, 21-H), 8.41 (s, 1H, 3-H), 11.63 (s, 1H, 18-H); \(^{13}\)C NMR (150 MHz, DMSO-\( \text{d}_6 \)) : \( \delta_c \) = 21.0 (C-24), 55.5 (C-16), 55.6 (C-17), 108.9 (C-15), 111.0 (C-5), 111.9 (C-12), 114.3 (C-3), 116.6 (C-6) 118.2 (C-1 1), 125.3 (C-10), 126.1 (C-21), 129.5 (C-22), 135.0 (C-9), 139.8 (C-20), 142.7 (C-23), 144.4 (C-8), 145.6 (C-2), 149.0 (C-14), 149.1 (C-13); LRMS m/z; HRMS m/z (ESI\(^+\)): Found 423.1 115 [M+H\(^+\)]; \( \text{C}_{21}\text{H}_{20}\text{N}_4\text{O}_4\text{S} \) requires 423.1 127; Anal. Calcd. for \( \text{C}_{21}\text{H}_{20}\text{N}_4\text{O}_4\text{S} \): C, 59.42; H, 4.75; N, 13.20. Found C, 58.32; H, 4.73; N, 12.52%

**Example 10**

\text{yV-[2-(3,5-dimethylphenyl)imidazo[1,2-a]pyrazin-8-yl]-4-methyl benzenesulfonamide}

![Chemical structure of yV-[2-(3,5-dimethylphenyl)imidazo[1,2-a]pyrazin-8-yl]-4-methyl benzenesulfonamide]

Step 1 was carried out as per Step 1 of Example 4
Step 2

8-chloro-2-(3,5-dimethylphenyl)imidazo[1,2-a]pyrazine

A mixture of 2-bromo-1-(3,5-dimethylphenyl)ethanone (271 mg, 1.19 mmol), 2-amino-3-chloropyrazine (155 mg, 1.19 mmol) and NaHCO$_3$ (125 mg, 1.49 mmol) in t-BuOH (5 mL) were stirred under argon, under reflux for 40 h. After this point, the reaction mixture was cooled to RT and solvent removed in vacuo. The resulting orange solid was dissolved in DCM (30 mL) and washed with H$_2$O (3 x 30 mL). The aqueous layers were extracted further with DCM (2 x 20 mL) before the combined organics were washed with brine (20 mL), dried (MgSO$_4$), filtered and solvent removed to give crude orange solid. Flash chromatography (100% DCM to 19:1 DCM/EtOAc) was carried out to afford the title compound (103 mg, 0.400 mmol, 33.6%). Mpt: 158-162 °C; $R_f = 0.68$ (2:1 DCM/EtOAc); IR ($\nu_{\text{max}}$/cm$^{-1}$, thin film): 2920 (C-H), 1365; $^1$H NMR (500 MHz, CDCl$_3$): $\delta_1 = 2.38$ (s, 6H, 14-H), 7.05 (s, 1H, 13-H), 7.62 (s, 2H, 11-H), 7.66 (d, $J = 4.5$ Hz, 1H, 6-H), 7.99 (s, 1H, 3-H), 8.02 (d, $J = 4.5$ Hz, 1H, 5-H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta_2 = 21.3$ (C-14), 111.3 (C-3), 118.4 (C-5), 124.5 (C-1 1), 128.0 (C-6), 131.1 (C-13), 132.1 (C-10), 138.2 (C-9), 138.6 (C-12), 143.4 (C-8), 148.6 (C-2); LRMS m/z; HRMS m/z (El$^+$): Found 257.07184 [M($^{35}$Cl)]$^+$; C$_{14}$H$_{12}$ClN$_3$ requires 257.07142; Anal. Calcd. for C$_{14}$H$_{12}$ClN$_3$: C, 65.25; H, 4.69; N, 16.30. Found C, 64.02; H, 4.63; N, 15.76%

Step 3

yV-[2-(3,5-dimethylphenyl)imidazo[1,2-a]pyrazin-8-yl]-4-methyl benzenesulfonamide
With Pd(dDDF)₂Cl₂:

A mixture of 8-chloro-2-(3,5-dimethylphenyl)imidazo[1,2-a]pyrazine (100 mg, 0.388 mmol), 4-toluenesulfonamide (79.8 mg, 0.466 mmol), 2 mol% Pd(dppf)Cl₂ (6.30 mg) and Cs₂CO₃ (152 mg, 0.466 mmol) in anhydrous toluene (3 mL) were stirred under reflux, under argon. After 21 h, the reaction was cooled to RT, diluted with toluene and washed with H₂O and brine. Further extraction of the aqueous layers was carried out using DCM. The combined organics were dried (MgSO₄), filtered and solvent removed in vacuo. Flash chromatography (19:1 DCM/EtOAc) afforded the title compound as a yellow solid (43.4 mg, 0.111 mmol, 28.6%). Mpt: >200 °C; Rf = 0.37 (2:1 DCM/EtOAc);

IR (v_max/cm⁻¹, thin film): 2928 (C-H Stretch), 1595; ¹H NMR (600 MHz, DMSO-d₆): δ_H = 2.31 (s, 6H, 14-H), 2.36 (s, 3H, 21-H), 6.97 (s, 1H, 13-H), 7.13 (t, J = 5.6 Hz, 1H, 6-H), 7.38 (d, J = 8.1 Hz, 2H, 19-H), 7.54 (s, 2H, 11-H), 7.81 (d, J = 5.3 Hz, 1H, 5-H), 7.87 (d, J = 8.0 Hz, 2H, 18-H), 8.42 (s, 1H, 3-H), 11.63 (d, J = 5.2 Hz, 1H, 15-H); ¹³C NMR (150 MHz, DMSO-d₆): δ_C = 21.0 (C-14,21), 111.0 (C-5), 114.8 (C-3), 116.7 (C-6), 123.3 (C-11), 126.1 (C-18), 129.5 (C-19), 129.8 (C-13), 132.4 (C-10), 135.2 (C-9), 137.9 (C-12), 139.9 (C-17), 142.6 (C-20), 144.5 (C-8), 145.5 (C-2); LRMS m/z (ESI⁺): 393 [M+H]⁺,

for C₁₉H₁₉N₄O₂: C, 64.27; H, 5.14; N, 14.27. Found: C, 63.08; H, 5.18; N, 13.52%

With XPhos:

All glassware was evacuated and flushed with argon prior to use. 8-chloro-2-(3,5-dimethylphenyl)imidazo[1,2-a]pyrazine (21.5 mg, 0.0835 mmol), 4-toluenesulfonamide (17.2 mg, 0.100 mmol), K₂CO₃ (13.8 mg, 0.100 mmol), 1 mol% Pd(dba)₂ (0.2 mg) and 5 mol% tert-butyl XPhos (1.1 mg) were weighed into a 10 mL round bottom flask.

¹BuOH (1 mL) was added and the reaction was stirred under reflux for 48 h. The reaction mixture was cooled to RT, diluted with MeOH (100 mL) and filtered through celite (pre-washed with MeOH). Flash chromatography was carried out (100% DCM to 30:1 DCM/EtOAc gradient), but contamination of the pure product was evident by NMR with not enough sample to re-purify.
Example 11
4-methyl-4-N-[4-[2-(2-naphthyl)imidazo[1,2-a]pyrazin-8-
yl]aminophenyl]benzenesulfonamide

\[
\text{Step 1}
\]
8-chloro-2-(2-naphthyl)imidazo[1,2-a]pyrazine

2-(Bromoacetyl)naphthalene (3.14 g, 12.6 mmol), 2-amino-3-chloropyrazine (1.63 g, 12.6 mmol), NaHCO\(_3\) (1.32 g, 16.7 mmol) and iBuOH (60 mL) were stirred under reflux for 40 h. The reaction mixture was cooled to RT and solvent removed in vacuo. The resulting orange solid was taken up in H\(_2\)O (60 mL) and extracted with DCM (3x 60 mL). The combined organics were washed with H\(_2\)O (50 mL) and brine (40 mL), dried (MgSO\(_4\)), filtered and concentrated in vacuo to give crude orange solid. On addition of DCM, insoluble material filtered off to give title compound as a cream fluffy solid (1.05 g). Purification of the remaining filtrate via flash chromatography (10:1 to 2:1 Pet Ether/EtOAc gradient) afforded the title compound as a pale orange/brown solid (338 g, Total: 1.38 g, 4.95 mmol, 39.3%). Mpt: Decomposed before melting; R\(_f\) = 0.34 (1:1 Pet Ether/ethyl acetate); IR (v\(_{max}\)/cm\(^{-1}\), thin film): 3026.3 (w), 2921.0 (w), 1495.3 (m); \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\)\(_H\) = 7.51-7.53 (m, 2H, 15,16-H), 7.71 (d, J = 4.5 Hz, 1H, 6-H), 7.88 (dd, J = 6.7, 2.2 Hz, 1H, 14-H), 7.93 (d, J = 8.6, 1H, 12-H) 7.96 (dd, J = 6.7, 2.4 1H, 17-H), 8.06 (dd, J = 8.6, 1.7 Hz, 1H, 11-H) 8.08 (d, J = 4.5 Hz, H, 5-H), 8.14 (s,
1H, 3-H), 8.57 (s, 1H, 19-H); 13C NMR (150 MHz, CDCl₃): δC = 111.6 (C-3), 118.5 (C-5), 124.1 (C-11), 126.0 (C-19), 126.6/126.7 (C-15,16), 127.8 (C-14), 128.2 (C-6), 128.5 (C-17), 128.6 (C-12), 129.4 (C-10), 133.5 (C-13), 133.7 (C-18), 138.3 (C-9), 143.5 (C-8), 148.2 (C-2); LRMS m/z (ESI⁺): 282 [M(37Cl)+H]⁺, 280 [M(35Cl)+H]⁺; HRMS m/z (Cl⁺): Found 280.06338 [M(37Cl)+H]⁺; C₁₅H₁₆N₃Cl requires 280.06415; Anal. Calcd for C₁₅H₁₆N₃Cl: C, 68.70; H, 3.60; N, 15.02. Found C, 67.53; H, 3.64; N, 13.97%.

Step 2

4-methyl-4-(2-(2-naphthylimidazo[1,2-a]pyrazin-8-yl)aminophenyl]benzenesulfonamide

All glassware was evacuated and flushed with argon prior to use. 8-chloro-2-(2-naphthylimidazo[1,2-a]pyrazine (50.0 mg, 0.178 mmol), 3-V-(4-aminophenyl)-4-methylbenzenesulfonamide (56.3 mg, 0.215 mmol), K₂CO₃ (29.7 mg, 0.215 mmol), 1 mol% Pd(db)₂ (1.03 mg) and 5 mol% iert-buty1 XPhos (3.80 mg) were weighed into a 25 mL round bottom flask. tBuOH (3 mL) was added and the reaction was stirred under reflux for 24 h. The reaction mixture was cooled to RT, diluted with MeOH (100 mL) and filtered through celite (pre-washed with MeOH). LCMS indicated the correct product mass was present, and flash chromatography (numerous attempts: 2:1 Pet Ether/ EtoAc, 20:1 DCM/ EtoAc, 10:1 DCM/ EtoAc, 5:1 DCM/Et₂O ) followed by reverse phase preparative HPLC (0 min: 10% IPA, 90% H₂O; 30 min: 90% IPA, 10% H₂O; 36 min: 90% IPA, 10% H₂O; 39 min: 10% IPA, 90% H₂O) to give the title compound (12.4 mg, 0.025 mmol, 14.0%). Mpt: decomposed before melting; Rₓ = 0.50
(1:1 Pet Ether/EtOAc); IR ($\nu_{\text{max}}$/cm$^{-1}$, thin film): 1143 (S=0 symmetric stretch); $^1$H NMR (600 MHz, CD$_3$OD): $\delta_H = 2.42$ (s, 3H, 31-H), 7.20 (d, $J = 5.2$ Hz, 1H, 6-H), 7.29 (d, $J = 6.8$ Hz, 2H, 22-H), 7.36 (d, $J = 8.0$ Hz, 2H, 29-H), 7.52 - 7.56 (m, 2H, 15, 16-H), 7.58 (d, $J = 8.8$ Hz, 2H, 23-H), 7.75 (d, $J = 8.3$ Hz, 2H, 28-H), 7.92 (d, $J = 7.1$, 1H, 17-H), 7.96 - 7.99 (m, 3H, 5-H, 12-H, 14-H), 8.13 (dd, $J = 1.7$, 8.5 Hz, 1H, 11-H), 8.53 (s, 1H, 3-H), 8.56 (s, 1H, 19-H); $^{13}$C NMR (150 MHz, CD$_3$OD): $\delta_C = 21.4$ (C-31), 113.9 (C-5), 115.9 (C-3), 115.9 (C-6) 122.9 (C-22), 124.9 (C-11), 125.8 (C-23), 126.1 (C-19), 127.6/127.7 (C-15,16), 128.4 (C-28), 128.9 (C-17), 129.3 (C-14), 129.7 (C-12), 130.7 (C-29), 131.0 (C-10), 133.5 (C-9, 24), 135.0 (C-13,18), 137.7 (C-21) 138.2 (C-27), 145.2 (C-30), 146.1 (C-8), 148.1 (C-2); LRMS m/z (ESI$^+$): 506 [M+H]$^+$, (ESI$^-$): 504 [M-H]$^-$; HRMS m/z (ESI$^+$): Found 506.1651 [M+H]$^+$; $C_{29}H_{24}N_5O_2S$ requires 506.1651; Anal. Calcd. For $C_{29}H_{24}N_5O_2S$: C, 68.89; H, 4.59; N, 13.85. Found C, 68.59; H, 4.94; N, 13.25.

Example 12

4-methyl-A/-[4-[2-(3-thienyl)imidazo[1,2-a]pyrazin-8-yl]aminophenyl]benzenesulfonamide

![Chemical Structure Image]
Step 1
2-bromo-1-(3-thienyl)-1-ethanone

1-(3-thienyl)ethanone (2.00 g, 15.9 mmol) was dissolved in chloroform (100 mL) and ethanol (100 mL). Pyridinium tribromide (10.1 g, 31.7 mmol) was added and the reaction was stirred at 50°C for 18 h. The reaction mixture was cooled to RT and the solvents removed in vacuo. The resulting orange slurry was suspended in H₂O (40 mL) and extracted with EtOAc (4 x 50 mL). The combined organic extracts were washed with H₂O (2 x 30 mL) and brine (1 x 30 mL), dried (MgSO₄), filtered and concentrated in vacuo to give an amber liquid. Flash chromatography was carried out (3:1 Pet Ether/DCM) to afford the title compound as a white solid (1.61 g, 7.81 mmol, 49.1%). Spectroscopic data was consistent with that previously reported. Mpt: 59-60 °C [Lit. 61.6 °C]; R_f = 0.48 (1:1 Pet Ether/DCM); IR (ν_max/cm⁻¹, thin film): 3094.5 (C-H stretch), 1688.5 (C=O stretch), 1508, 1415, 1400, 1393, 1380 (Aromatic C=C stretch), 1181; ¹H NMR (600 MHz, CDCl₃): δ_H = 4.34 (s, 2H, 1-H), 7.36 (dd, J = 2.9, 5.2 Hz, 1H, 5-H), 7.58 (dd, J = 5.2, 1.2Hz, 1H, 4-H), 8.17 (dd, J = 2.9, 1.3 Hz, 1H, 7-H); ¹³C NMR (150 MHz, CDCl₃): δ_c = 31.7 (C-1), 127.0 (C-5), 127.4 (C-4), 133.9 (C-7), 138.9 (C-3), 185.7 (C-2); LRMS m/z (Cl⁺): 207 [M⁺]⁺, 205 [M⁺]⁺

Step 2
8-chloro-2-(3-thienyl)imidazo[1,2-a]pyrazine

2-bromo-1-(3-thienyl)-1-ethanone (293 mg, 1.43 mmol), 2-amino-3-chloropyrazine (185 mg, 1.43 mmol), NaHCO₃ (150 mg, 1.79 mmol) and BuOH (6 mL) were stirred under reflux for 41 h. The reaction was cooled to RT and solvent removed in vacuo. The sample was taken up in water (15 mL) and extracted with DCM (2 x 20 mL). The combined organics were washed with H₂O (2 x 15 mL) and brine (15 mL) before they were dried (MgSO₄), filtered and concentrated to give a pale yellow liquid. Flash chromatography (2:1 Pet Ether/Ethyl acetate) afforded a pale yellow solid. Mpt: decomposed before melting; R_f = 0.33 (1:1 Pet Ether/Ethyl acetate); m/z: 207 [M⁺]⁺, 205 [M⁺]⁺
Acetate); IR (ν<sub>max</sub>/cm<sup>-1</sup>, thin film): 1240 - 1480 (Thiophene Stretch); <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> = 7.44 (dd, <i>J</i> = 5.0, 3.0 Hz, 1H, 12-H), 7.58 (dd, <i>J</i> = 5.0, 1.3 Hz, 1H, 11-H), 7.69 (d, <i>J</i> = 4.4 Hz, 1H, 6-H), 7.93 (s, 1H, 3-H), 7.96 (dd, <i>J</i> = 3.0, 1.3 Hz, 1H 14-H), 8.04 (d, <i>J</i> = 4.4 Hz, 1H, 5-H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> = 121.1 (C-3), 118.4 (C-5), 123.6 (C-14), 126.0 (C-12), 126.6 (C-1 1), 128.1 (C-6), 134.1 (C-10), 138.0 (C-9), 143.3 (C-8), 144.3 (C-2); LRMS m/z (ESI<sup>+</sup>) 238 [M<sup>(35</sup>Cl)+H]<sup>+</sup>, 236 [M<sup>(35</sup>Cl)+H]<sup>+</sup>; HRMS m/z (ESI<sup>+</sup>): Found: 236.0056 [M<sup>(35</sup>Cl)+H]<sup>+</sup>; R<sub>Calcd</sub> = 236.0049; Anal. Calcd. for C<sub>10</sub>H<sub>7</sub>CIN<sub>3</sub>S requires 236.0049; C, 47.14; H, 2.66; N, 15.26%.

Step 3

4-methyl-W-[4-[2-(3-thienyl)imidazo[1,2-a]pyrazin -8-yl]aminophenyl]benzenesulfonamide

All glassware was evacuated and flushed with argon prior to use. 8-chloro-2-(3-thienyl)imidazo[1,2-a]pyrazine (128 mg, 0.540 mmol), V-(4-aminophenyl)-4-methylbenzenesulfonamide (171 mg, 0.650 mmol), K<sub>2</sub>C<sub>3</sub>O<sub>4</sub> (90.1 mg, 0.652 mmol), 1 mol% Pd(dba)<sub>2</sub> (3.12 mg) and 5 mol% ie/f-butyl XPhos (1.15 mg) were weighed into a 25 mL round bottom flask. <sup>1</sup>BuOH (5 mL) was added and the reaction was stirred under reflux for 40 h. The reaction mixture was cooled to RT, diluted with MeOH (100 mL) and filtered through celite (pre-washed with MeOH). LCMS indicated the correct product mass was present, and flash chromatography (1:1 Pet Ether/ EtOAc) was carried to give the title compound as a yellow solid (19.2 mg, 0.042 mmol, 7.8%). Mpt: 158-164 °C; <i>R</i><sub>f</sub> = 0.57 (1:1 DCM/Et<sub>2</sub>O); IR (ν<sub>max</sub>/cm<sup>-1</sup>, thin film): 1140 cm<sup>-1</sup> (S=0 symmetric stretch); <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>OD): δ<sub>H</sub> = 2.41 (s, 3H, 26-H), 7.17 (d, <i>J</i> =
4.5 Hz, 1H, 6-H), 7.29 (d, J = 8.8 Hz, 2H, 17-H), 7.35 (d, J = 8.0 Hz, 2H, 24-H), 7.53 (d, J = 8.8, 2H, 18-H), 7.57 (dd, J = 4.9, 2.9 Hz, 1H, 12-H), 7.66 (dd, J = 4.9, 1.1 Hz, 1H, 11-H), 7.75 (d, J = 8.4, 2H, 23-H), 7.96 (d, J = 5.4, 1H, 5-H), 7.98 (dd, J = 1.1, 2.8 Hz, 1H, 14-H), 8.30 (s, 1H, 3-H); 13C NMR (150 MHz, CD3OD): δC = 20.0 (C-26), 112.6 (C-5), 114.3 (C-3), 118.8 (C-6), 121.4 (C-17), 122.3 (C-14), 122.6, 124.8 (C-18), 125.5 (C-11), 126.5 (C-12), 127.0 (C-23), 129.3, (C-24), 131.4 (C-16), 134.0 (C-9 + C-10), 136.8 (C-19 + C-22), 143.2 (C-2), 143.8 (C-25), 144.4 (C-8); LRMS m/z (ESI+) 462 [M+H]+; HRMS m/z (ESI+) : Found 462.1047 [M+H]+; C23H19N2O5S2 requires 462.1058; Anal. Calcd. for C23H19N2O5S2: C, 59.85; H, 4.15; N, 15.17. Found C, 53.48; H, 3.74; N, 12.89%.

Example 13

4-Methyl-yV- (4-(2-(2-phenoxyphenyl)imidazo [1,2-a]pyrazin -8-ylamino)phenyl)benzenesulfonamide (HK007)

Steps 1 and 2 were carried out as per Steps 1 and 2 of Example 8 to give compound JS18.

Step 3

4-Methyl-yV-(4-(2-(2-phenoxyphenyl)imidazo [1,2-a]pyrazin -8-ylamino)phenyl)benzenesulfonamide (HK007)
Tris(dibenzylideneacetone)dipalladium(0) (~ 1 mg, 1.1 \( \mu \text{mol} \)), 2-Dicyclohexylphosphino-2'-(\(N,N\)-dimethylamino)biphenyl (~ 1 mg, 2.5 \( \mu \text{mol} \)) and Sodium-i//t-butoxide (~ 12.5 mg, 130 \( \mu \text{mol} \)) were added to a flask and dissolved in 5 ml anhydrous toluene. 8-chloro-2-(2-phenoxyphenyl)imidazo[1,2-a]pyrazine (JS18, 30 mg, 93.4 \( \mu \text{mol} \)) and \(N\)-(4-aminophenyl)-4-methylbenzenesulfonamide (29 mg, 112 \( \mu \text{mol} \)) were added under argon atmosphere. The reaction was stirred under reflux (121 °C) for 24 hours. The reaction was cooled to room temperature and solvent removed in vacuo. The product was taken up in dichloromethane (2 ml) and filtered. The filtrate was washed with water (3 x 1 ml), the combined aqueous extracts were further washed with dichloromethane (2 x 1 ml). The solvent was removed in vacuo. Flash chromatography (3:1 Petroleum ether / ethyl acetate) was performed. Solvent was removed from the product fraction in vacuo. The product was taken up in dichloromethane and further purified by a second plastic-free flash chromatography in a Pasteur pipette column (dichloromethane to ethyl acetate gradient). Solvent was removed in vacuo (repeated coevaporation with dichloromethane), and the product was dried under high vacuum. 4.8 mg (8.8 \( \mu \text{mol} \), yield: 9%) of a yellow, sticky solid were obtained as final product. Mpt: decomposed before melting; \(R_f = 0.14 \) (3:1 Petroleum ether / ethyl acetate); IR (\( \nu_{\text{max}}/\text{cm}^{-1} \), thin film): 1229 (C-O-C-stretch), 1489-1542 (Ar-ringvibration); \(^1\text{H} \text{NMR} \) (600 MHz, CDCI3), \( \delta _{\text{H}} \) (ppm): 2.38 (s, 3H, CH3: 32-H), 6.36 (bs, 1H, NH: 21-H), 6.96 (dd, \( J = 6.7, 2.3 \) Hz, 1H, CH: 14-H), 7.06 (d, \( J = 7.5 \) Hz, 2H, CH: 18-H), 7.07 (d, \( J = 8.6 \) Hz, 1H, CH: 24-H), 7.14 (t, \( J = 7.2 \) Hz, 1H, CH: 20-H), 7.22 (d, \( J = 8.3 \) Hz, 2H, CH: 30-H), 7.21-7.31 (m, 2H, CH: 12-H, CH: 13-H), 7.35-7.38 (m, 3H, CH: 6-H, CH: 19-H), 7.48 (d, \( J = 4.5 \) Hz, 1H, CH: 5-H), 7.62 (d, \( J = 8.2 \) Hz, 2H, CH: 29-H), 7.79 (d, \( J = 8.3 \) Hz, 2H, CH: 23-H), 8.05 (s, 1H, CH: 3-H), 8.45 (dd, \( J = 6.2, 2.2 \) Hz, 1H, CH: 11-H); \(^{13}\text{C} \text{NMR} \) (125 MHz, CDCI3), \( \delta _{\text{C}} \) (ppm): 21.7 (C-32), 111.9 (C-5), 115.0 (C-3), 118.8 (C-18), 119.4 (C-14), 120.1 (C-23), 123.7 (C-20), 124.1 (C-24), 124.2 (C-12), 124.8 (C-10), 127.4 (C-29), 127.8 (C-6), 85
129.1 (C-1), 129.3 (C-13), 129.7 (C-30), 130.1 (C-19), 130.8 (C-25), 132.6 (C-9), 136.1 (C-28), 137.6 (C-22), 140.0 (C-2), 143.9 (C-8), 145.9 (C-31), 154.3 (C-15);
LRMS m/z (ES+): 548 [M+H]+; HRMS m/z (ES+): Found 548.1733 [M+H]+;
C31H26N5O2S requires 548.1756; analysis calculated for C31H26N5O2S: C, 67.99; H, 4.60; N, 12.79; Found C, 65.37; H, 4.57; N, 11.38%

Example 14

4-methyl-Y-(4-(2-(quinoxalin-2-yl)imidazo[1,2-a]pyrazin-8-ylamino)phenyl)benzenesulfonamide (JS1 17)

Step 1

1-(quinoxalin-2-yl)ethanone (JS1 10)

Quinoxaline (1.1864 g, 9.11 mmol), Pyruvic acid (1.90 ml, 27.3 mmol), AgN03 (0.124 g, 0.73 mmol), N2H5S2O8 (3.12 g, 13.67 mmol) and H2SO4 (0.49 ml, 9.11 mmol) were stirred in 1:1 CH2Cl2/H2O (150 ml) at 40 °C for 2 ½ h. The solution was then basified via the addition of NaOH and the organics extracted (3x) and washed brine, dried (MgSO4), filtered and solvent removed. Flash chromatography (Pet Ether; 3:1 Pet Ether/EtOAc) afforded the title compound as a yellow solid (617.5 mg, 3.91 mmol, 42.9%). Mpt: 70-74 °C [Lit. (J. Org. Chem., 1991, 56, 2866-2869) 76-97 °C]; Rf = 0.24 (3:1 Pet Ether/EtOAc); IR (vmax/cm⁻¹, thin film): 1689 (CO stretch), 1357; ¹H NMR (500 MHz, CDCl3): δH = 2.84 (s, 3H, 12-H), 7.82-7.90 (m, 2H, 7,8-H), 8.14-8.21 (m, 2H, 6,9-H), 9.47 (s, 1H, 3-H); ¹3C NMR (125 MHz, CDCl3): δC = 25.6 (C-12), 129.5 (C-6), 130.5 (C-8), 130.8 (C-9), 132.3 (C-7), 141.1 (C-10), 143.1 (C-3), 143.9 (C-5), 146.6 (C-
2), 199.8 (C-1 1); LRMS m/z (El\(^+\)): 172 [M\(^+\)], 130 [M-Ac\(^+\)], 86; HRMS m/z (El\(^+\)): Found 172.06372; C\textsubscript{10}H\textsubscript{8}N\textsubscript{2}O requires 172.0631 1; Anal. Calcd. for C\textsubscript{10}H\textsubscript{8}N\textsubscript{2}O: C, 69.76; H, 4.68; N, 16.27. Found C, 69.28; H, 4.56; N, 16.00%.

Step 2

2-bromo-(quinoxalin-2-yl)ethanone (JS1 11)

Pyridinium tribromide (2.935 g, 9.18 mmol) was added to a stirred solution of JS1 10 (580 mg, 3.67 mmol) in 1:1 CHCl\textsubscript{3}/EtOH (60 ml) and the mixture was heated at 50 °C for 16 h. Removal of the solvent in vacuo was followed by addition of H\textsubscript{2}O and extraction with EtOAc (3x). The combined organic extracts were further washed with H\textsubscript{2}O and brine, dried (MgSO\textsubscript{4}), filtered and concentrated in vacuo. Flash chromatography (CH\textsubscript{2}Cl\textsubscript{2} isocractic) afforded the title compound as a brown solid (656 mg, 2.61 mmol, 71.2%). Mpt: Decomposed before melting [Lit. (Pharmazie 1983, 38(12), 829-32) 112-114 °C]; \(R_f = 0.26\) (CH\textsubscript{2}Cl\textsubscript{2}); IR (\(\nu_{\text{max}}\) cm\(^{-1}\), thin film): 1708 (CO stretch), 1392, 762 (C-Br Stretch); \(^1\)H NMR (600 MHz, CDCl\textsubscript{3}): \(\delta_\text{H} = 4.96\) (s, 2H, 12-H), 7.88-7.90 (m, 1H, 8-H), 7.93-7.96 (m, 1H, 7-H), 8.20-8.21 (m, 2H, 6,9-H), 9.53 (s, 1H, 3-H); \(^{13}\)C NMR (150 MHz, CDCl\textsubscript{3}): \(\delta_\text{C} = 31.3\) (C-12), 129.7 (C-6), 130.6 (C-9), 131.3 (C-8), 133.0 (C-7), 141.0 (C-10), 143.4 (C-3), 144.3 (C-5), 144.7 (C-2), 192.4 (C-11); LRMS m/z (El\(^+\)): 252 [M\(^{48\text{Br}}\)\(^+\)], 250 [M\(^{79\text{Br}}\)\(^+\)], 142, 115 \([^{6\text{Br}}\]), 113 \([^{7\text{Br}}\]); HRMS m/z (El\(^+\)): Found 249.97396; C\textsubscript{10}H\textsubscript{2}BrN\textsubscript{2}O requires 249.97363; Anal. Calcd. for C\textsubscript{10}H\textsubscript{2}BrN\textsubscript{2}O: C, 47.84; H, 2.81; N, 11.16. Found C, 47.70; H, 2.68; N, 10.86%.

Step 3

2-(8-chloroimidazo[1,2-a]pyrazin-2-yl)quinoxaline (JS1 14)

JS1 11 (648 mg, 2.58 mmol), 2-amino-3-chloropyrazine (334.4 mg, 2.58 mmol) and NaHC\textsubscript{3}O\textsubscript{3} (271.0 mg, 3.23 mmol) in i/e-f-butanol (15 ml) were stirred under reflux for 40
h. The solvent was removed and the resulting residual was taken up in CH₂Cl₂ and washed H₂O and brine, dried (MgSO₄). filtered and solvent removed. Flash chromatography (Pet Ether; 3:1 to 1:1 to 1:3 Pet Ether/EtOAc) afforded the title compound as an orange solid (341.9 mg, 1.21 mmol, 47.1%). Mpt: >200 °C; Rᵣ = 0.1 1

1:1 Pet Ether/EtOAc: IR (νmax/cm⁻¹, thin film): 2924, 1675, 1495, 1354, 1200; ¹H NMR (600 MHz, DMSO-d6): δ H = 2.34 (s, 3H, 31-H), 7.05

Step 4
4-methyl-yV-(4-(2-(quinoxalin-2-yl)imidazo[1,2-a]pyrazin-8-ylamino)phenyl)benzenesulfonamide (JS1 17)

JS1 14 (100 mg, 0.355 mmol), /V-(4-aminophenyl)-4-methylbenzenesulfonamide (111.8 mg, 0.426 mmol), Pd(dba)₂ (2.0 mg, 1 mol%), DavePhos (4.2 mg, 3 mol%) and Cs₂CO₃ (162.0 mg, 0.497 mmol) were stirred in anhydrous 1,4-dioxane under reflux for 40 h. After LCMS confirmed the presence of the product mass, the reaction was cooled to RT and solvent removed. The resulting residue was taken up in CH₂Cl₂ and washed with sat. aq. NaHCO₃, H₂O and brine, dried (MgSO₄), filtered and solvent removed. Flash chromatography (Toluene; 0% to 50% EtOAc) afforded the title compound as a light yellow solid (12.3 mg, 0.024 mmol, 6.8%). Mpt: Decomposed before melting; Rᵣ = 0.49 (1:1 CH₂Cl₂/EtOAc); IR (νmax/cm⁻¹, thin film): 3135, 3061 (Aromatic C-H Stretch), 1495, 1291, 1201, 936; ¹H NMR (600 MHz, DMSO-d6): δ H = 2.34 (s, 3H, 31-H), 7.05
(d, J = 8.9 Hz, 2H, 23-H), 7.35 (d, J = 8.2 Hz, 2H, 29-H), 7.44 (d, J = 4.6 Hz, 1H, 6-H), 7.64 (d, J = 8.3 Hz, 2H, 28-H), 7.84-7.86 (m, 1H, 15-H), 7.88-7.90 (m, 3H, 14, 22-H), 8.03 (d, J = 4.6 Hz, 1H, 5-H), 8.10-8.14 (m, 2H, 13,16-H), 8.80 (s, 1H, 3-H), 9.61 (s, 1H, 20-H), 9.78 (s, 1H, 19-H), 10.06 (bs, 1H, 25-H); 13C NMR (150 MHz, DMSO-d6): δC = 21.0 (C-31), 112.5 (C-5), 115.9 (C-3), 121.1 (C-23), 121.2 (C-22), 126.8 (C-28), 128.2 (C-6), 128.8 (C-13), 129.1 (C-16), 129.7 (C-29), 129.9 (C-15), 130.9 (C-14), 132.1 (C-24), 133.4 (C-9), 136.6 (C-21), 136.7 (C-27), 141.2 (C-10), 141.4 (C-17), 141.5 (C-12), 143.1 (C-30), 143.7 (C-19), 146.1 (C-8), 147.0 (C-2) ; LRMS m/z (ES+): 508 [M+H]+, 530 [M+Na]+; HRMS m/z (ES+): Found 508.1565; C27H21N7O2S requires 508.1556; Anal. Calcd. for C27H21N7O2S: C, 63.89; H, 4.17; N, 19.32. Found C, 63.82; H, 4.23; N, 18.30%.

Example 15
4-methyl-W-(4-(2-(quinolin-2-yl)imidazo[1,2-a]pyrazin-8-ylamino)phenyl)benzenesulfonamide (HK01 0)

Step 1
1-(quinolin-2-yl)ethanone (HK003)

1.177g Quinoline (9.1 1 mol), 150 ml dichloromethane / water (1:1), pyruvic acid (0.64 ml, 9.1 1 mmol), 0.49 ml H2SO4 (9.1 1 mmol), 3.12 g N2H8S2O8 (13.7 mmol) and 0.13 g AgN03 (0.73 mmol) were added to a flask and stirred for 4 hours at 50 °C; the solution turned from yellow to brown. The solution was neutralized with KOH, and the organic phase separated. The aqueous phase was extracted 4x (2x) with dichloromethane; the united organic phases were washed with basic brine (with KOH) and dried with MgSO4. The solvent was removed in vacuo, and flash chromatography (Gradient petroleum
ether to petroleum ether / ethyl acetate 10:1) was performed. The product was dried under high vacuum after final solvent removal in vacuo; it was liquid until induction of crystallization by movement of the product containing flask. A yellow solid was obtained as a final product (HK003: 0.193 g, 1.13 mmol, yield: 12%, 1H-NMR identical to HK001). Mpt: 37.5 °C; $R_f = 0.40$ (10:1 Petroleum ether / ethyl acetate); IR ($\nu_{\text{max}}$/cm$^{-1}$, thin film): 1688 (C=O-stretch); $^1$H NMR (600 MHz, CDCl$_3$), $\delta_H$ (ppm): 2.86 (s, 3H, CH$_3$: 12-H), 7.63 (ddd, $J = 8.0$, 7.0, 1.0 Hz, 1H, CH: 7-H), 7.77 (ddd, $J = 8.4$, 7.0, 1.3 Hz, 1H, CH: 8-H), 7.85 (d, $J = 8.1$ Hz, 1H, CH: 6-H), 8.11 (d, $J = 8.0$ Hz, CH: 6-H), 8.15 (d, $J = 8.6$ Hz, CH: 3-H), 8.24 (d, $J = 8.5$ Hz, 1H, CH: 9-H), 8.24 (d, $J = 8.5$ Hz, 1H, CH: 4-H); $^{13}$C-NMR (125 MHz, CDCl$_3$), $\delta_C$ (ppm): 25.7 (C-12), 118.1 (C-3), 127.8 (C-6), 128.7 (C-7), 129.7 (C-5), 130.1 (C-8), 130.7 (C-9), 137 (C-4), 147.3 (C-10), 153.3 (C-2), 200.8 (C-1 1); HRMS m/z (ES+): Found 171.0675 [M($^{79}$Br)$^+$]; C$_{n}$H$_{9}$NO requires 171.06786; analysis calculated for C$_{n}$H$_{9}$NO: C, 77.17; H, 5.30; N, 8.18. Found C, 76.85; H, 5.24; N, 8.08%.

**Step 2**

**2-bromo-1-(quinolin-2-yl)ethanone** (HK005)

1-(quinolin-2-yl)ethanone (HK001 & HK003, 0.25 g, 1.46 mmol) was dissolved in chloroform (7.5 ml) and ethanol (7.5 ml). Pyridinium tribromide (0.94 g, 2.94 mmol) was added and the reaction was stirred at 50 °C overnight. The reaction mixture was cooled to room temperature and the solvents removed in vacuo (in a fumehood, Br$_2$!). The resulting mixture was suspended in 25 ml water and extracted with 3 x 25 ml ethyl acetate. The combined organic phases were washed with 2 x 15 ml water and 15 ml brine, dried with MgSO$_4$ and solvent was removed in vacuo. Flash chromatography was carried out for purification (Petroleum ether / dichloromethane, gradient 6:1 to 1:1). The final product was obtained as a white solid with grease as an impurity (0.27 g, 1.1mmol, yield: 75%). Mpt: decomposed before melting; $R_f = 0.60$ (1:1 Petroleum ether / dichloromethane); IR ($\nu_{\text{max}}$/cm$^{-1}$, thin film): 1712 (C=O-stretch), 2853 (‘grease’-CH$_2$-asymmetric stretch), 2923 (‘grease’-CH$_2$-symmetric stretch); $^1$H NMR (600 MHz, Acetone), $\delta_H$ (ppm): 7.80 (ddd, $J = 6.5$, 5.0, 0.6 Hz, 1H, CH: 7-H), 7.93 (ddd, $J = 8.6$, 7.1 , 1.5 Hz, 1H, CH: 8-H), 8.1 1 (d, $J = 8.0$ Hz, CH: 6-H), 8.15 (d, $J = 8.6$ Hz, CH: 3-H), 9.35 (s, 1H, CH=N).
8.23 (d, J = 8.6 Hz, CH: 9 -H), 8.59 (d, J = 8.6 Hz, CH: 4 -H); 13C-NMR (125 MHz, d8-Acetone), δc (ppm): 53.6 (C-12), 117.6 (C-3), 127.6 (C-6), 128.7 (C-7), 129.4 (C-5), 129.7 (C-8), 130.1 (C-9), 137.3 (C-4), 146.5 (C-10), 150.7 (C-2), 169.5 (C-11); HRMS m/z (ES+): Found 248.97860 [M(79Br)]+; CnH8BrNO requires 248.97838.

Step 3

2-(8-chlorimidazo[1,2-a]pyrazin-2-yl)quinoline (HK006)

0.26 g (1.04 mmol) 2-bromo-1-(quinolin-2-yl)ethanone (HK005), 0.17 g (0.90 mmol) 2-amino-3-chloropyrazine, 0.094 g (1.12 mmol) NaHCO3 and 5.4 ml i.e/f-Butanol were added to a flask and stirred under reflux (105 °C) for 48 hours. The sample was taken up in 15 ml chloromethane and washed with 3 x 10 ml water. The aqueous phases were washed with 3 x 7.5 ml dichloromethane. The combined organic phases were dried with MgSO4 and filtered. Flash chromatography (Petroleum ether / ethyl acetate 5:1 to 1:4), solvent evaporation and drying under high vacuum afforded a white solid with grease as an impurity (50 mg, 0.18 mmol, yield 17%). Mpt: decomp. before melting; Rf = 0.19 (1:1 Dichloromethane / Ethyl acetate); IR (νmax/cm⁻¹, thin film): 804 (s), 996 (s), 1287 (s), 1600 (Ar-ring-vib.), 2852 ("grease"-CH2-asymmetric stretch), 2922 ("grease"-CH2-symmetric stretch); 1H NMR (600 MHz, CD2Cl2), δH (ppm): 7.57 (t, J = 7.4 Hz, 1H, CH: 16-H), 7.70 (d, J = 4.3 Hz, 1H, CH: 12-H), 7.75 (dd, J = 8.3, 6.8 Hz, 1H, CH: 15-H), 7.89 (d, J = 8.5 Hz, 1H, CH: 17-H), 8.10 (d, J = 8.2 Hz, 1H, CH: 14-H), 8.17 (d, J = 4.4 Hz, 1H, CH: 11-H), 8.33 (d, J = 8.1 Hz, 1H, CH: 5-H), 8.44 (d, J = 8.8 Hz, 1H, CH: 6-H), 8.64 (s, 1H, CH: 3-H); 13C-NMR (125 MHz, CD2Cl2), δc (ppm): 115 (C-11), 119.4 (C-3), 119.6 (C-16), 127.1 (C-12), 128.2 (C-17), 128.6 (C-13), 128.7 (C-14), 129.6 (C-5), 130.2 (C-15), 137.3 (C-6), 138.5 (C-9), 144 (C-2), 148.2 (C-10), 148.5 (C-18), 152.2 (C-8); HRMS m/z (ES+): Found 280.0516 [M(35Cl)]+; C15H8ClN4 requires 280.05103.
Step 4
4-methyl-4-V-(4-(2-(quinolin-2-yl)imidazo[1,2-a]pyrazin-8-ylamino)phenyl)benzenesulfonamide (HK01 0)

Step 4
4-methyl-4-V-(4-(2-(quinolin-2-yl)imidazo[1,2-a]pyrazin-8-ylamino)phenyl)benzenesulfonamide (HK01 0)

Tris(dibenzylideneacetone)dipalladium(0) (~ 2 mg, 2.2 µmol), 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (~ 3 mg, 7.6 µmol) and sodium-tertbutoxide (~ 7 mg, 73 µmol) were added to a flask and dissolved in 5 ml anhydrous toluene. 2-(8-chloroimidazo[1,2-a]pyrazin-2-yl)quinoline (HK006, 15 mg, 53 µmol) and N-(4-aminophenyl)-4-methylbenzenesulfonamide (15 mg, 57 µmol) were added under argon atmosphere. The reaction was stirred under reflux (121 °C) for 24 (21) hours. The reaction was cooled to room temperature and solvent removed in vacuo. The product was taken up in 2 ml acetonitrile / water / methanol (2:2:1) and < 1 % trifluoroacetic acid. Preparative HPLC was performed: x% H2O + y% MeCN + 0.1% TFA, x+y = 100; x = 98 (0 min), 65 (4 min), 60 (5 min), 50 (20 min), 2 (21 min), 2 (24 min), 98 (25 min), 98 (29 min). The main fraction was collected in three split subfractions; only the first subfraction was furtherly used; 1H-NMR, but not LCMS showed that the other subfractions were not appropriate. This HPLC procedure was repeated with this first subfraction: conditions and time points see above, but x = 95, 65, 62, 47, 2, 2, 98, 98. The product was dried under high vacuum after evaporation of the solvent (coevaporation with dichloromethane). 0.8 mg (1.6 µmol, yield: 3%) of the solid product were obtained with minor to moderate impurities and characterized by 1H-NMR and an IC50 assay. Further characterization of the product was impeded by problems to dissolve the compound, occurrence of new relatively significant impurities and the small amount of the sample. Rf = 0.35 (1:1 Petroleum ether / ethyl acetate); 1H NMR (600 MHz, DMSO-d6), δH (ppm): 0.8 (m, "grease"), 1.29 (brm, "grease"), 2.34 (s, 3H, CH3; 31-H), 2.50 (s, solvent peak), 3.32 (s, DHO), 3.35 (s, H2O), 7.04 (d, J = 9.42 Hz, "2H), 7.35 (d, J = 8.28 Hz, ≈2H), 7.42 (d, J = 4.56 Hz, "1H), 7.61 (d, J = 7.32 Hz, "1H), 7.64 (t, J = 8.1 Hz, ≈1H), 7.68 (m, 5 - 5.5H, impurity?, ≈ toluene?), 7.72 (m, 5 - 5.5H,
impurity? (≈ toluene?), 7.80 (t, $J = 8.0$ Hz, $^1H$), 7.90 (d, $J = 8.82$ Hz, $^2H$), 8.00 (d, $J = 7.98$ Hz, $^1H$), 8.04 (m, 2H), 8.43 (d, $J = 8.8$ Hz, $^1H$), 8.51 (d, $J = 8.8$ Hz, $^1H$), 8.71 (s, $^1H$), 9.49 (s, $^1H$), 10.04 (s, $^1H$); LRMS m/z (both HK008 and HK010, ES+): 530, 529 [M+Na]+, 508, 507 [M+H]+; HRMS m/z (only HK008, ES+): Found 507.1617 [M+H]+ (and an impurity); C$_{28}$H$_{23}$N$_6$O$_2$S requires 507.1603.

**Example 16**

$yV-(4-(2-(naphthalen-2-yl)imidazo[1,2-a]pyrazin-8-ylamino)phenyl)methanesulfonamide$ (JS1 19)

**Step 1**

A/-(4-aminophenyl)methanesulfonamide JS1 13

Benzene-1,4-diamine (3.14 g, 29.0 mmol), was dissolved in anhydrous CH$_2$Cl$_2$ (100 ml), triethylamine (1.62 ml, 11.61 mmol) added and the mixtures cooled on ice. MeSO$_2$Cl (0.449 ml, 5.81 mmol) was added drop wise and the reaction was stirred at RT for 16 h. The mixture was then diluted with CH$_2$Cl$_2$ and washed sat. aq. NaHC0$_3$. The aqueous layer was then extracted with CH$_2$Cl$_2$ (4x) as well as EtOAc (4x). Each of the organic extracts were washed with brine, dried (MgSO$_4$), filtered and concentrated in vacuo. Flash chromatography (CH$_2$Cl$_2$: 1% to 2% to 5% MeOH) afforded the title compound as a white solid (843.9 mg, 4.54 mmol, 78.1%). Mpt: 89 °C [Lit: Synthetic Commun., 2008, 38: 1909-1916]; $R_f = 0.53$ (10% MeOH/CH$_2$Cl$_2$); IR (v$_{max}$/cm$^{-1}$, thin film): 3459, 3375, 3330 (N-H Stretch), 1625, 1518, 1309, 1152; $^1$H NMR
(600 MHz, CD$_3$OD): $\delta_H$ = 2.87 (s, 3H, 8-H), 6.71-6.73 (m, 2H, 3-H), 7.02-7.05 (m, 2H, 4-H); $^{13}$C NMR (150 MHz, CD$_3$OD): $\delta_C$ = 36.8 (C-8), 115.4 (C-3), 124.4 (C-4), 127.5 (C-5), 145.8 (C-2); LRMS m/z (CI): 187 [M+H]$^+$, 107; HRMS m/z (CI): Found 187.05387; C$_7$H$_{11}$N$_2$O$_2$S requires 187.05412; Anal. Calcd. for C$_7$H$_{10}$N$_2$O$_2$S: C, 45.15; H, 5.41; N, 15.04. Found C, 43.53; H, 5.05; N, 13.90%.

Step 2

yV-(4-(2-(naphthalen-2-yl)imidazo[1,2-a]pyrazin-8-ylamino)phenyl)methanesulfonamid (JS1 19)

All glassware was dried and purged with argon prior to use. Pd$_2$(dba)$_3$ (1.6 mg, 1 mol%), DavePhos (2.1 mg, 3 mol%) and sodium i.e./f-butoxide (24.1 mg, 0.250 mmol) were dissolved in anhydrous toluene. JS1 1 (50 mg, 0.179 mmol) and JS1 13 (39.9 mg, 0.215 mmol) were added and the reaction was stirred under reflux, under argon for 20 h. The reaction was cooled to RT and solvent removed, before the residue was taken up in CH$_2$Cl$_2$ and washed with NaHCO$_3$, H$_2$O and brine, dried (MgSO$_4$), filtered and concentrated in vacuo. Flash chromatography (Toluene; 2:1 Toluene/EtOAc) afforded the title compound as an off white solid (5.2 mg, 0.012 mmol, 6.8%). $R_f$ = 0.32 (1:1 Toluene/EtOAc); IR ($\nu_{max}$/cm$^{-1}$, thin film): 3248, 3056, 2926, 2854 (Aromatic C-H and N-H stretch), 1624, 1543, 1508, 1326, 1152; $^1$H NMR (600 MHz, CDCl$_3$): $\delta_H$ = 3.01 (s, 3H, 27-H), 6.39 (s, 1H, 25-H), 7.28 (ap.d, $J$ = 8.8 Hz, 2H, 13-H), 7.47 (d, $J$ = 4.6 Hz, 1H, 6-H), 7.49-7.54 (m, 2H, 15,16-H), 7.60 (d, $J$ = 4.6 Hz, 1H, 5-H), 7.87 (d $J$ = 7.8 Hz, 1H, 14-H), 7.92-7.95 (m, 5H, 3,12,17,22-H), 8.02 (dd, $J$ = 8.5, 1.6 Hz, 1H, 11-H), 8.18 (s, 1H, 20-H), 8.48 (s, 1H, 19-H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta_C$ = 39.3 (C-27), 111.2 (C-3), 111.9 (C-5), 120.8 (C-22), 123.3 (C-23), 124.1 (C-11), 125.0 (C-19), 126.4 (C-15), 126.6 (C-16), 127.9 (C-14), 128.2 (C-17), 128.8 (C-12), 130.4 (C-10), 131.1 (C-24), 133.4 (C-13), 133.7 (C-9,18), 137.7 (C-21), 145.1 (C-2), 146.1 (C-8); LRMS m/z
(ES⁺): 430 [M+H]⁺; HRMS m/z (ES⁺): Found 430.1324; C₂₃H₂₀N₅O₂S requires 430.1338;

Example 17

4-methyl-yV-(4-((2-(naphthalen-2-yl)imidazo[1,2-a]pyrazin-8-ylamino)methyl)phenyl)benzenesulfonamide (JS173)

Step 1

A-/-(4-aminobenzyl)-2-(naphthalen-2-yl)imidazo[1,2-a]pyrazin-8-amine (JS1 69)

All glassware was dried and purged with argon prior to use. Pd₂(dba)₃ (1.6 mg, 1 mol%), DavePhos (2.1 mg, 3 mol%) and sodium ie/f-butoxide (24.1 mg, 0.250 mmol) were dissolved in anhydrous toluene. JS1 1 (see Step 1 of Example 7) (50 mg, 0.179 mmol) and 4-(aminomethyl)aniline (24.3 μl, 0.215 mmol) were added and the reaction was stirred under reflux, under argon for 20 h. The reaction was cooled to RT and solvent removed, before the residue was taken up in CH₂Cl₂ and washed with NaHCO₃, H₂O and brine, dried (MgSO₄), filtered and concentrated in vacuo. Flash
Step 2

4-methyl-yV-(4-((2-(naphthalen-2-yl)imidazo[1,2-a]pyrazin-8-ylamino)methyl)phenyl)benzenesulfonamide (JS1 73)

JS169 (18 mg, 0.049 mmol) was dissolved in anhydrous pyridine (1 ml) and the mixture was cooled on ice. 4-methylbenzene-1-sulfonyl chloride (11.3 mg, 0.059 mmol) was added and the deep yellow/orange solution was stirred under Ar at RT for 16 h. The solvent was then removed and the crude material was purified via flash chromatography (CH₂Cl₂; 10% to 20% EtOAc) to afford the title compound as an off white solid (8.2 mg, 0.016 mmol, 32.2%).; \( R_f = 0.44 \) (20% EtOAc/CH₂Cl₂); IR (\( \nu_{\text{max}}/\text{cm}^{-1} \), thin film): 3326 (Aromatic C-H stretch), 1619, 1544, 1519; \(^1\)H NMR (600 MHz, CD₃OD): \( \delta_{\text{H}} = 4.58 \) (s, 2H, 21-H), 6.73 (d, \( J = 10.9 \) Hz, 2H, 23-H), 7.19 (d, \( J = 8.4 \) Hz, 2H, 24-H), 7.25 (d, \( J = 4.7 \) Hz, 1H, 6-H), 7.44-7.49 (m, 2H, 15,16-H), 7.65 (d, \( J = 4.7 \) Hz, 1H, 5-H), 7.82-7.84 (m, 2H, 12,17-H), 7.94 (dd, \( J = 8.5 \) Hz, 1H, 3-H), 8.16 (s, 1H, 11-H), 8.34 (s, 1H, 19-H); \(^1^3\)C NMR (150 MHz, CD₃OD): \( \delta_{\text{C}} = 45.5 \) (C-21), 111.5 (C-5), 113.1 (C-3), 116.7 (C-24), 124.9 (C-11), 125.5 (C-19), 127.2 (C-15), 127.5 (C-16), 128.7 (C-14), 129.1 (C-6), 129.2 (C-17), 129.2 (C-22), 129.5 (C-12), 129.9 (C-23), 131.7 (C-10), 134.6 (C-9,13), 135.0 (C-18), 145.4 (C-2), 148.1 (C-25), 149.8 (C-8); LRMS m/z (ES⁺): 366 [M+H]⁺, 273 [M-aniline]⁺, 261 [M-CH₂-aniline]⁺; HRMS m/z (ES⁺): Found 366.1716; C₂₃H₂₀N₅ requires 366.1719;
thin film): 3240, 3050 (Aromatic C-H stretches), 2923, 2823 (C-H and N-H stretches), 1544, 1509, 1136; ¹H NMR (600 MHz, CDCl₃): δ_H = 2.47 (s, 3H, 32-H), 4.76 (bs, 2H, 21-H), 6.49 (bs, 1H, 20-H), 6.73 (bs, 1H, 26-H), 7.03 (d, J = 8.5 Hz, 2H, 24-H), 7.22 (d, J = 8.1 Hz, 2H, 30-H), 7.29 (d, J = 8.4 Hz, 2H, 23-H), 7.35 (d, J = 4.5 Hz, 1H, 6-H), 7.46-7.51 (m, 3H, 5,15,16-H), 7.64 (d, J = 8.3 Hz, 2H, 29-H), 7.83-7.85 (m, 1H, 14-H), 7.87-7.90 (m, 3H, 3,12,17-H), 7.95 (dd, J = 8.6, 1.2 Hz, 1H, 11-H), 8.40 (s, 1H, 19-H);
¹³C NMR (150 MHz, CDCl₃): δ_C = ; LRMS m/z (ES⁺): 518 [M-H]⁺; HRMS m/z (ES⁺): Found 518.1658; C₃₀H₂₄N₅O₂S requires 518.1651.

Example 18

4-methyl-6V-(4-(2-(naphthalen-2-yl)imidazo[1,2-a]pyrazin-8-yloxy)phenyl)benzenesulfonamide (JS1 75)

Step 1

8-(methylthio)-2-(naphthalen-2-yl)imidazo[1,2-a]pyrazine (JS1 30)

JS1 1 (See Step 1 of Example 7) (1.12 g, 4.01 mmol) was dissolved in anhydrous DMSO (16 ml). NaSMe (337 mg, 4.81 mmol) was added portion wise and the reaction was stirred at 100 °C for 16 h. The mixture was then cooled to RT, diluted with brine and extracted with CH₂Cl₂. The organic layer was washed with H₂O (5x) and brine (1x), dried (MgSO₄), filtered and solvent removed in vacuo. Flash chromatography (CH₂Cl₂; 0% to 1% to 2% EtOAc) afforded the title compound as an off white/yellow solid (989.3 mg, 3.40 mmol, 84.8%). Mpt: 168 °C; Rᶠ = 0.47 (5% EtOAc/CH₂Cl₂); IR (ν_max/cm⁻¹, thin
film): 3055 (aromatic C-H stretch), 1470, 1432, 1368; 1H NMR (600 MHz, CDCl$_3$): $\delta_1$ = 2.71 (s, 3H, 21-H), 7.47-7.52 (m, 2H, 15,16-H), 7.72 (d, $J = 4.5$ Hz, 1H, 6-H), 7.82 (d, $J = 4.5$ Hz, 1H, 5-H), 7.85 (ap.d, $J = 7.4$ Hz, 1H, 17-H), 7.90 (d, $J = 8.5$ Hz, 1H, 12-H), 7.94 (ap.d, $J = 7.4$ Hz, 1H, 14-H), 7.98 (s, 1H, 3-H), 8.04 (dd, $J = 8.4$, 1.6 Hz, 1H, 11-H), 8.55 (s, 1H, 19-H); 13C NMR (150 MHz, CDCl$_3$): $\delta_C$ =12.3 (C-21), 110.3 (C-3), 115.1 (C-5), 124.3 (C-1 1), 125.6 (C-19), 126.4 (C-15,16), 126.5 (C-15,16), 127.9 (C-17), 128.5 (C-12), 128.6 (C-14), 129.0 (C-6), 130.2 (C-10), 133.5 (C-18), 138.9 (C-9), 146.4 (C-2), 154.4 (C-8); LRMS m/z (ES$^+$): 292 [M+H]$^+$; HRMS m/z (ES$^+$): Found 292.0909; C$_{17}$H$_{15}$N$_3$S requires 292.0908; Anal. Calcd. for C$_{17}$H$_{15}$N$_3$S: C, 70.08; H, 4.50; N, 14.42. Found C, 69.85; H, 4.28; N, 14.42%.

Step 2
8-(methylsulfonyl)-2-(naphthalen-2-yl)imidazo[1,2-a]pyrazine  (JS132)

JS130 (1.7662 g, 6.07 mmol) was dissolved in anhydrous CH$_2$C$_2$ (50 ml) and the mixture was cooled on ice. mCPBA (5.231 g, 30.3 mmol) was added in one portion and the reaction continued to stir at RT for 5 h. The reaction was partitioned with NaHCO$_3$ and extracted with CH$_2$C$_2$ (3x); the combined organic extracts were then washed with brine, dried (MgSO$_4$), filtered and concentrated in vacuo. Flash chromatography (CH$_2$C$_2$; 2% to 5% EtOAc) afforded the title compound as a yellow solid (1.098 g, 3.398 mmol, 56.0%). Mpt: >200 °C; $R_f = 0.22$ (10% EtOAc/CH$_2$C$_2$); IR ($\nu_{max}$/cm$^{-1}$, thin film): 3121,3010 (aromatic C-H stretch), 1312, 1138; 1H NMR (600 MHz, CDCl$_3$): $\delta_1$ = 3.84 (s, 3H, 21-H), 7.51-7.54 (m, 2H, 15,16-H), 7.86-7.87 (m,1H, 14-H), 7.92 (d, $J = 8.5$ Hz, 1H, 12-H), 7.95-7.96 (m, 1H, 17-H), 8.02 (d, $J = 4.3$ Hz, 1H, 6-H), 8.08 (dd, $J = 8.5$, 1.4 Hz, 1H, 11-H), 8.26 (s, 1H, 3-H), 8.32 (d, $J = 4.3$ Hz, 1H, 5-H), 8.59 (s, 1H, 19-H); 13C NMR (150 MHz, CDCl$_3$): $\delta_C$ = 41.7 (C-21), 110.9 (C-3), 122.1 (C-5), 124.3 (C-1 1), 126.7 (C-19), 126.8 (C-16), 127.0 (C-15), 127.9 (C-14), 128.1 (C-6), 128.7 (C-17), 128.8 (C-12), 129.1 (C-10), 133.5 (C-18), 134.0 (C-13), 136.3 (C-9), 98
148.6 (C-8), 149.8 (C-2); LRMS m/z (El⁺): 323 [M]⁺; HRMS m/z (El⁺): Found 323.07266; C₁₇H₁₃N₃O₂S requires 323.07230; Anal. Calcd. for C₁₇H₁₃N₃O₂S: C, 63.14; H, 4.05; N, 12.99. Found C, 61.27; H, 3.84; N, 12.48%.

5  
Step 3

yV-(4-hydroxyphenyl)-4-methylbenzenesulfonamide (JS1 68)

A solution of 4-aminophenol (500 mg, 4.58 mmol) in anhydrous pyridine (9 ml) was cooled on ice and 4-methylbenzene-1-sulfonyl chloride (1.048 g, 5.50 mmol) was added portionwise. The resulting red solution was stirred under Argon at RT for 18 h, before diluting with Et₂0 and washing with H₂O, 5% HCl, H₂O, and brine; drying (MgSO₄) m filtering and concentrating in vacuo. Flash chromatography (Toluene; 5:1 to 4:1 toluene/Et₂0) afforded the title compound as a pale yellow solid (933.8 mg, 3.55 mmol, 77.5%). Mpt: 134-136 °C [Lit (Ref: Org Lett, 2005, 7, 1215-1218) 148.5 °C]; f = 0.33 (2:1 Toluene/Et₂0); IR (vₘₐₓ/cm⁻¹, thin film): 3445 (O-H stretch), 3234 (Aromatic C-H stretch), 1509, 1263, 1153, 1090; ¹H NMR (600 MHz, DMSO-d₆): δ H = 2.38 (s, 3H, 12-H), 6.58 (ap.d, J = 8.8 Hz, 2H, 3-H), 6.82 (ap.d, J = 8.8 Hz, 2H, 4-H), 7.31 (d, J = 8.0 Hz, 2H, 10-H), 7.53 (d, J = 8.2 Hz, 2H, 9-H), 9.29 (s, 1H, 1-H), 9.66 (bs, 1H, 6-H); ¹³C NMR (150 MHz, DMSO-d₆): δC = 21.0 (C-12), 115.5 (C-3), 123.9 (C-4), 126.8 (C-9), 129.5 (C-10), 136.7 (C-8), 142.8 (C-11), 154.8 (C-2); LRMS m/z (ES⁺): 262 [M-H]⁺, 308 [M+Formic Acid]⁺; HRMS m/z (ES⁺): Found 262.0545; C₁₃H₁₂N₂O₂S requires 262.0538; Anal. Calcd. for C₁₃H₁₂N₂O₂S: C, 59.30; H, 4.98; N, 5.32. Found C, 59.01; H, 4.73; N, 5.26%.

Step 4

4-methyl-yV-(4-(2-(naphthalen-2-yl)imidazo[1,2-a]pyrazin-8-yloxy)phenyl)benzenesulfonamide (JS1 75)
NaH was pre-activated by stirring NaH (60% in Mineral Oil; 12.4 mg, 0.310 mmol) in anhydrous hexanes (3 ml) for 20 min, removing the solvent using a syringe and drying the contents under high vacuum. DMF (0.5 ml) was added followed by JS168 (81.4 mg, 0.310 mmol) in DMF (1 ml) and the mixture was stirred at RT for 20 min. JS132 (50 mg, 0.155 mmol) in DMF (1.5 ml) was added and the resulting deep red solution was heated at 100 °C under Argon for 16 h. The mixture was then diluted with EtOAc and washed with NH₄Cl (Aq. Sat) and H₂O (5x). The combined aqueous layers were then re-extracted with EtOAc (2x), followed by washing the combined organics with brine, drying (MgSO₄), filtering and concentrating in vacuo. The crude material was purified via flash chromatography (Toluene; 25% EtOAc/Toluene) to give the title compound as an off white-pink solid (36.4 mg, 0.072 mmol, 46.6%). Mpt: 128 °C; Rf = 0.21 (2:1 Toluene/EtOAc); 1R (νmax/cm⁻¹, thin film): 3568, 3049 (Aromatic C-H stretch), 1488, 1330, 1153; 1H NMR (600 MHz, DMSO-de): δ_H = 2.39 (s, 3H, 31-H), 7.16 (ap.d, J = 8.9 Hz, 2H, 23-H), 7.22 (ap.d, J = 8.9 Hz, 2H, 22-H), 7.33 (d, J = 4.5 Hz, 1H, 6-H), 7.39 (d, J = 8.1 Hz, 2H, 29-H), 7.52-7.56 (m, 2H, 15,16-H), 7.70 (d, J = 8.3 Hz, 2H, 28-H), 7.94 (d, J = 7.6 Hz, 1H, 17-H), 8.01-8.04 (m, 2H, 12,14-H), 8.15 (dd, J = 8.5, 1.6 Hz, 1H, 11-H), 8.32 (d, J = 4.6 Hz, 1H, 5-H), 8.61 (s, 1H, 19-H), 8.74 (s, 1H, 3-H), 10.34 (s, 1H, 25-H); 13C NMR (150 MHz, DMSO-de): δ_C = 21.0 (C-31), 112.9 (C-3), 116.9 (C-5), 121.3 (C-23), 122.7 (C-22), 124.0 (C-1 1), 124.5 (C-19), 125.5 (C-6), 126.4 (C-16), 126.6 (C-15), 126.8 (C-28), 127.7 (C-17), 128.3 (C-14), 128.5 (C-12), 129.9 (C-29), 130.4 (C-10), 132.8 (C-9), 132.9 (C-13), 133.2 (C-18), 135.0 (C-24), 136.7 (C-27), 143.4 (C-30), 145.1 (C-2), 148.7 (C-21), 153.1 (C-8); LRMS m/z (ES⁻): 505 [M-H]; HRMS m/z (ES⁻): Found 505.1323; C₂₉H₂₃N₄O₃S requires 505.1334; Anal. Calcd. for C₂₉H₂₃N₄O₃S: C, 68.76; H, 4.38; N, 4.06. Found C, 65.16; H, 4.38; N, 10.17%.
Example 19
4-methyl-2-(2-(naphthalen-2-yl)imidazo[1,2-a]pyrazin-8-ylamino)ethyl)benzenesulfonamide (JS209)

Step 1
A/-)(2-aminoethyl)-4-methylbenzenesulfonamide (8TP27)

1,2-Diaminoethane (2.0 g, 33 mmol) and triethylamine (6.7 g, 66 mmol) were dissolved in a 2/1 solvent mixture of CH2Cl2/THF (50 mL). The resulting solution was stirred at room temperature and 4-methylbenzenesulfonyl chloride (3.2 g, 17 mmol) was added portion-wise over 2 h. The reaction was quenched by addition of 1 M HCl (50 mL). The biphasic mixture was extracted with 1 M HCl (20 mL x 2). The combined aqueous layers were basified with 2 M NaOH (50 mL) and extracted with CH2Cl2 (50 mL x 3). The organic layers were combined, dried (MgSO4), filtered and concentrated in vacuo to give a colourless solid (2.1 g, 58% yield) suitably pure for subsequent synthetic steps. \( R_f = 0.22 \) (15% MeOH in CH2Cl2); \(^1^H\) NMR (600 MHz, CD3OD): \( \delta_H = 2.42 \) (s, 3H, \( CH_3 \)), 2.65 (t, J = 6.2 Hz, 2H, \( CH_2NH_2 \)), 2.89 (t, J = 6.2 Hz, 2H, \( NHCH_2 \)), 7.38 (d, J = 8.2 Hz, 2H, 3-H and 5-H), 7.73 (d, J = 8.2 Hz, 2H, 2-H and 6-H); \(^13^C\) NMR (150 MHz, CD3OD): \( \delta_C = 21.4 \) (CH3), 42.2 (CH2NH2), 46.4 (NHCH2), 128.0 (C-2 and C-6), 130.8 (C-3 and C-5), 138.8 (C-1), 144.7 (C-4);
Step 2

4-methyl-4-V-(2-(2-(naphthalen-2-yl)imidazo[1,2-a]pyrazin-8-ylamino)ethyl)benzenesulfonamide (JS209)

To a solution of 8TP27 (65.9 mg, 0.310 mmol) in anhydrous DMF (2 ml) was added DIPEA (53.9 µL, 0.310 mmol) followed by JS132 (50 mg, 0.155 mmol) and the reaction mixture was stirred at 100 °C for 16 h. Cooling to RT and removal of the solvent was followed by flash chromatography (Toluene; 2:1 Toluene/EtOAc), which yielded the title compound as a white solid (15 mg, 0.0328 mmol, 21.9%). Mpt: Decomposed before melting; $R_f = 0.26$ (3:1 EtOAc/Pet Ether); IR $\nu_{max}$/cm$^{-1}$, thin film): 3412, 3029, 2924, 2853 (C-H stretch), 1621, 1538, 1327, 1158; $^1$H NMR (600 MHz, CDCl$_3$): $\delta_H = 2.24$ (s, 3H, 29-H), 3.32 (ap.d, $J = 4.7$ Hz, 2H, 22-H), 3.71 (ap.q, $J = 5.6$ Hz, 2H, 21-H), 6.32 (bs, 1H, 20-H), 6.55 (bs, 1H, 23-H), 7.10 (d, $J = 8.0$ Hz, 2H, 23-H), 7.29 (d, $J = 4.6$ Hz, 1H, 5-H), 7.45 (d, $J = 4.6$ Hz, 1H, 6-H), 7.48-7.52 (m, 2H, 15,16-H), 7.73 (d, $J = 8.1$ Hz, 2H, 26-H), 7.85-7.86 (m, 2H, 3,14-H), 7.88-7.91 (m, 2H, 12,17-H), 7.94 (ap.d, $J = 8.4$ Hz, 1H, 11-H), 8.37 (s, 1H, 19-H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta_C = 21.6$ (C-29), 40.7 (C-21), 45.0 (C-22), 110.6 (C-5), 111.0 (C-3), 124.0 (C-1 1), 124.8 (C-19), 126.4 (C-15), 126.6 (C-16), 127.0 (C-26), 127.9 (C-6,14), 128.4 (C-17), 128.7 (C-12), 129.5 (C-27), 130.4 (C-10), 133.2 (C-9), 133.4 (C-13), 133.7 (C-18), 137.0 (C-25), 143.3 (C-28), 144.9 (C-2), 149.5 (C-8); LRMS m/z (ES$^+$): 458 [M+H]$^+$;
Example 20

4-methyl-Y-(3-(2-(naphthalen-2-yl)imidazo[1,2-a]pyrazin-8-ylamino)propyl)benzenesulfonamide (JS210)

Step 1

yV-(3-aminopropyl)-4-methylbenzenesulfonamide (8TP28)

1,3-Diaminopropane (2.0 g, 27 mmol) and triethylamine (5.5 g, 54 mmol) were dissolved in a 2/1 solvent mixture of CH2Cl2/THF (50 mL). The resulting solution was stirred at room temperature and 4-methylbenzenesulfonyl chloride (2.5 g, 13 mmol) was added portion-wise over 2 h. The reaction was quenched by addition of 1 M HCl (50 mL). The biphasic mixture was extracted with 1 M HCl (20 mL x 2). The combined aqueous layers were basified with 2 M NaOH (50 mL) and extracted with CH2Cl2 (50 mL x 3). The organic layers were combined, dried (MgSO4), filtered and concentrated in vacuo to give a colourless solid (1.45 g, 49% yield) suitably pure for subsequent synthetic steps. 

Rf = 0.25 (15% MeOH in CH2Cl2); 1H NMR (600 MHz, CD3OD): δH = 1.58 (app. qt, J = 6.9 Hz, 2H, NHCH2CH2), 2.43 (s, 3H, CH3), 2.62 (t, J = 6.2 Hz, 2H, CH2NH2), 2.87 (t, J = 6.2 Hz, 2H, NHCH2), 7.38 (d, J = 8.2 Hz, 2H, 3-H and 5-H), 7.72 (d, J = 8.2 Hz, 2H, 2-H and 6-H); 13C NMR (150 MHz, CD3OD): δC = 21.4 (CH3), 42.2
Step 2

4-methyl-1-(3-(2-(naphthalen-2-yl)imidazo[1,2-a]pyrazin-8-ylamino)propyl)benzenesulfonamide (JS210)

To a solution of 8TP28 (73.1 mg, 0.322 mmol) in anhydrous DMF (2 ml) was added DIPEA (56.1 µl, 0.322 mmol) followed by JS132 (52 mg, 0.161 mmol) and the reaction mixture was stirred at 100 °C for 16 h. Cooling to RT and removal of the solvent was followed by flash chromatography (Toluene; 2:1 Toluene/EtOAc), which yielded the title compound as a white solid (24.9 mg, 0.0529 mmol, 32.8%). Mpt: Decomposed before melting; \( R_f = 0.26 \) (3:1 EtOAc/Pet Ether); IR (\( v_{\text{max}}/\text{cm}^{-1} \), thin film): 3023, 2971, 1740, 1548, 1370, 1217; \( ^1\text{H} \) NMR (600 MHz, CDC\textsubscript{3}): \( \delta_H = 1.80 \) (ap.quint, \( J = 5.9 \) Hz, 2H, 22-H), 2.35 (s, 3H, 23-H), 3.00 (ap.d, \( J = 5.4 \) Hz, 2H, 23-H), 3.68 (ap.d, \( J = 5.8 \) Hz, 2H, 21-H), 6.27 (bs, 1H, 20-H), 7.02 (bs, 1H, 24-H), 7.21 (d, \( J = 8.1 \) Hz, 2H, 28-H), 7.33 (d, \( J = 4.7 \) Hz, 1H, 6-H), 7.43 (d, \( J = 4.6 \) Hz, 1H, 5-H), 7.46-7.51 (m, 2H, 15,16-H), 7.72 (d, \( J = 8.2 \) Hz, 2H, 27-H), 7.84-7.85 (m, 1H, 14-H), 7.86 (s, 1H, 3-H), 7.88-7.90 (m, 2H, 12,17-H), 7.95 (dd, \( J = 8.5 \), 1.6 Hz, 1H, 11-H), 8.38 (s, 1H, 19-H); \( ^{13}\text{C} \) NMR (150 MHz, CDC\textsubscript{3}): \( \delta_C = 21.6 \) (C-30), 30.3 (C-22), 38.3 (C-21), 39.7 (C-23), 110.2 (C-5), 111.1 (C-3), 124.0 (C-1 1), 124.7 (C-19), 126.3 (C-15), 126.6 (C-16), 127.1 (C-27), 127.9 (C-14), 128.1 (C-6), 128.4 (C-17), 128.7 (C-12), 129.7 (C-28), 130.5 (C-10), 133.3 (C-9,13), 134.0 (C-24), 134.7 (C-24), 140.0 (C-20), 142.4 (C-20), 144.7 (C-4);
133.7 (C-18), 137.6 (C-16), 143.1 (C-29), 144.8 (C-2), 149.7 (C-8); LRMS \textit{m/z} (ES$^+$): 472 [M+H]$^+$. 

\textit{Example 21}

\begin{center}
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2-(prop-2-ynyloxy)ethyl-4-(yV-(2-(naphthalen-2-yl)imidazo[1,2-a]pyrazin-8-yl)sulfamoyl)phenylcarbamate (JS208)

10 \textbf{Step 1}

2-(prop-2-ynyloxy)ethanol (JS206)

15 Ethylene glycol (5 ml, 0.089 mol) was cooled on ice and NaH (60\% in mineral oil; 0.894 g, 0.022 mol) was added slowly to form a viscous white paste. Propargyl bromide (80\% solution in toluene; 2.49 ml, 0.022 mol) was added drop wise and the reaction mixture was stirred at 45 \degree C for 3h. The reaction was carefully quenched with H$_2$O and extracted with CHCl$_3$ (3x) and CH$_2$Cl$_2$ (5x). The combined organic extracts were dried (MgSO$_4$), filtered and concentrated \textit{in vacuo}. Flash chromatography (Pet Ether; 10\% to 50\% EtOAc/Pet Ether) afforded the title compound as a light yellow oil (1.0316 g, 0.0103 mmol, 46.9\%). \textit{Rf} = 0.39 (1:1 Pet Ether/EtOAc); \textit{IR} ($\nu_{\max}$/cm$^{-1}$, thin film): 3390 (O-H stretch), 3286, 2936, 2668 (C-H stretch), 1354, 1105, 1065, 1027; $^1$H NMR (600 MHz, CDCls): $\delta_H = 2.06$ (bs, 1H, 1-H), 2.46 (J = 2.4 Hz, 1H, 7-H), 2.65 (ap.t, J = 4.7 Hz, 2H, 3-H), 3.77 (ap.t, J = 4.3 Hz, 2H, 2-H), 4.20 (d, J = 2.3 Hz, 2H, 5-H); $^{13}$C NMR (150 MHz, CDCls):
MHz, CDCl₃): δc = 58.5 (C-5), 61.8 (C-2), 71.3 (C-3), 74.9 (C-7), 79.6 (C-6); LRMS m/z (Cl⁺): 101 [M+H]⁺; HRMS m/z (Cl⁺): Found 101.06094; C₅H₉O₂ requires 101.06025;

Step 2

5 2-(prop-2-ynyloxy)ethyl 4-sulfamoylphenylcarbamate (JS207)

JS206 (556.5 mg, 5.57 mmol) was dissolved in anhydrous toluene (140 ml). JS129 (see Example 23) (1.509 g, 6.68 mmol) and molecular sieves (4A, 10 sieves) were added and the reaction was stirred under reflux for 16 h. The solvent was removed and the reaction purified via flash chromatography (Toluene; 2:1 Toluene/EtOAc) to afford the title compound as a white solid (663 mg, 2.22 mmol, 39.9%). Mpt: 100-102 °C; Rf = 0.17 (2:1 Toluene/EtOAc); IR (νmax/cm⁻¹, thin film): 3350, 3273, 1704 (C=O Stretch), 1595, 1533, 1314, 1234, 1152; ¹H NMR (600 MHz, DMSO-d₆): δΗ = 3.48 (t, J = 2.3 Hz, 1H, 15-H), 3.69-3.70 (m, 2H, 11-H), 4.20 (d, J = 2.3 Hz, 2H, 13-H), 4.24-4.26 (m, 2H, 10-H), 7.23 (s, 2H, 1-H), 7.61 (ap.d, J = 8.8 Hz, 2H, 5-H), 7.72 (ap.d, J = 8.8 Hz, 2H, 4-H), 10.18 (s, 1H, 7-H); ¹³C NMR (150 MHz, DMSO-d₆): δC =57.5 (C-13), 63.6 (C-10), 67.3 (C-11), 77.5 (C-15), 80.1 (C-14), 117.6 (C-5), 126.8 (C-4), 137.6 (C-3), 142.2 (C-6), 1533.3 (C-8); LRMS m/z (El⁺): 298 [M]+, 243 [M-OCH₂C≡CH]⁺, 216 [M-CH₂CH₂OCH₂C≡CH]⁺, 183 [M-C(O)OCH₂CH₂OCH₂C≡CH]⁺; HRMS m/z (El⁺): Found 298.06247; C₁₂H₁₄N₂O₅S requires 298.06179; Anal. Calcd. for C₁₂H₁₄N₂O₅S: C, 48.31; H, 4.73; N, 9.39. Found C, 48.60; H, 4.66; N, 9.12%.
Step 3

2-(prop-2-ynyloxy)ethyl-4-(yV-(2-(naphthalen-2-yl)imidazo[1,2-a]pyrazin-8-yI)sulfamoyl)phenylcarbamate (JS208)

NaH was pre-activated by stirring NaH (60% in Mineral Oil; 88.7 mg, 2.215 mmol) in anhydrous hexanes (25 ml) for 20 min, removing the solvent using a syringe and drying the contents under high vacuum. DMF (6 ml) was added followed by JS207 (660 mg, 2.215 mmol) in DMF (8 ml) and the mixture was stirred at RT for 20 min. JS132 (357.7 mg, 1.107 mmol) in DMF (20 ml) was added and the resulting dark brown solution was heated at 100 °C under Argon for 18 h. The solvent was removed and the resulting residue was then taken up in EtOAc and washed with NH₄Cl (Aq. Sat) and H₂O (5x). The combined aqueous layers were then re-extracted with EtOAc (2x), followed by washing the combined organics with brine, drying (MgSO₄), filtering and concentrating in vacuo. Flash chromatography (Pet Ether; 1:1 to 1:2 to 1:4 to 1:9 Pet Ether/EtOAc) afforded the title compound as a yellow/orange solid (380.3 mg, 0.703 mmol, 63.5%). Mpt: 184-186 °C; R₇ = 0.32 (EtOAc/Pet Ether); IR (νmax/cm⁻¹, thin film): 3227, 1719, 1582, 1532, 1391, 1222, 1141, 1112; ¹H NMR (600 MHz, DMSO-d₆): δH = 3.46 (t, J = 2.4 Hz, 1H, 34-H), 3.67-3.69 (m, 2H, 30-H), 4.18 (d, J = 2.4 Hz, 2H, 32-H), 4.23-4.25 (m, 2H, 29-H), 7.16 (t, J = 5.5 Hz, 1H, 6-H), 7.51-7.54 (m, 2H, 15,16-H), 7.65 (d, J = 8.9 Hz, 2H 24-H), 7.86 (d, J = 5.6 Hz, 1H, 5-H), 7.92-7.93 (m, 3H, 14,23-H), 7.98 (ap,d, J = 8.6 Hz, 1H, 12-H), 8.02-8.05 (m, 2H, 11,17-H), 8.52 (s, 1H, 19-H), 8.59 (s, 1H, 3-H), 10.22 (s, 1H, 26-H), 11.63 (bd, J = 4.7 Hz, 7/20-H); ¹³C NMR (150 MHz, DMSO-d₆): δC = 57.5 (C-32), 63.7 (C-29), 67.3 (C-30), 77.5 (C-34), 80.1 (C-33), 110.9 (C-3), 115.3 (C-3), 116.8 (C-6), 117.7 (C-24), 123.8 (C-11), 124.2 (C-19), 126.3 (C-15/16), 126.6 (C-15/16), 127.4 (C-23), 127.7 (C-14), 128.3 (C-17), 128.4 (C-12), 130.0 (C-10), 132.8 (C-13), 133.2 (C-18), 135.6 (C-9), 136.9 (C-22), 142.9 (C-25), 148.3 (C-9), 150.7 (C-19), 153.5 (C-15), 158.4 (C-17), 162.6 (C-12), 176.2 (C-19).
Example 22

2-(allyloxy)ethyl-4-(yV-(2-(naphthalen-2-yl)imidazo[1,2-a]pyrazin-8-yl)sulfamoyl)phenylcarbamate (JS1 52)

Step 1

2-(allyloxy)ethyl 4-sulfamoylphenylcarbamate (JS121)

To a suspension of 4-sulfamoylbenzoic acid (2.01 g, 10.0 mmol) in anhydrous toluene (15 ml) was added triethylamine (1.63 ml, 11.7 mmol). Diphenyphosphoryl azide (2.52 ml, 11.7 mmol) in anhydrous toluene (10 ml) was added drop wise to the reaction mixture and stirred at RT for 30 min followed by heating at 90 °C for 30 min. 2-(allyloxy)ethanol (1.28 ml, 12.0 mmol) in anhydrous DMF (6 ml) was then added and the reaction temperature was increased to 90 °C for 16 h. The reaction was cooled to RT and solvent removed in vacuo. The crude material was taken up in EtOAc and washed with bicarb (1x), H2O (3x) and brine (1x); dried (MgSO4), filtered and concentrated in vacuo to give an orange/brown sticky solid. Flash chromatography (Pet Ether; 2:1 to 1:1 Pet Ether/EtOAc) afforded the title compound as a white solid.
(689.0 mg, 2.30 mmol, 23.0%). Mpt: 128 °C; \( R_f = 0.41 \) (2:1 EtOAc/Pet Ether); IR
\( (\nu_{\text{max}}/\text{cm}^{-1}, \text{thin film}): \) 3356, 3298, 3193, 3110, 2908 (C-H and N-H stretches), 1734
(C=0 stretch), 1596, 1529, 1336, 1314, 1216, 1151, 1099, 1055; \(^1\)H NMR (600 MHz, DMSO-\( d_6 \)): \( \delta_H = 3.63-3.64 \) (m, 2H, 5-H), 3.98 - 3.99 (m, 2H, 3-H), 4.24-4.25 (m, 2H, 6-H), 5.16 (ap.dd, \( J = 10.4, 1.7 \) Hz, 1H, 1-H), 5.27 (ap.dd, \( J = 17.3, 1.8 \) Hz, 1H, 1-Ha
\( \delta_C = 63.9 \) (C-6), 67.7 (C-5), 71.0 (C-3), 116.7 (C-11), 117.7 (C-1), 126.8 (C-12), 135.0 (C-2), 137.6 (C-13), 142.3 (C-10), 153.4 (C-8); LRMS m/z (El\(^+\)): 300 [M]+, 243 [M-OCH\(_2\)CH=CH\(_2\)]; HRMS m/z (El\(^+\)): Found 300.07810; \( C_{12}H_{16}N_2O_5S \) requires 300.07744;
Anal. Calcd. for \( C_{12}H_{16}N_2O_5S \): C, 47.99; H, 5.37; N, 9.33. Found C, 48.24; H, 5.27; N, 9.57%.

Step 2

2-(allyloxy)ethyl-4-(yV-(2-(naphthalen-2-yl)imidazo[1,2-a]pyrazin-8-yl)sulfamoyl)phenylcarbamate (JS1 52)

NaH was pre-activated by stirring NaH (60% in Mineral Oil; 70.6 mg, 1.765 mmol) in
anhydrous hexanes (50 ml) for 20 min, removing the solvent using a syringe and drying
the contents under high vacuum. DMF (5 ml) was added followed by JS121 (529 mg, 1.765 mmol) in DMF (7 ml) and the mixture was stirred at RT for 20 min. JS132 (285 mg, 0.882 mmol) in DMF (13 ml) was added and the resulting dark brown solution was
heated at 100 °C under Argon for 16 h. The mixture was then diluted with EtOAc and
washed with \( \text{NH}_4\text{Cl} \) (Aq. Sat) and \( \text{H}_2\text{O} \) (5x). The combined aqueous layers were then
re-extracted with EtOAc (2x), followed by washing the combined organics with brine,
drying (MgSO₄), filtering and concentrating in vacuo. Flash chromatography (CH₂Cl₂; 10% to 20% to 33% EtOAc/CH₂Cl₂) afforded the title compound as a light yellow solid (214.4 mg, 0.395 mmol, 44.7%). Mpt: >200 °C; Rᵣ = 0.25 (1:1 CH₂Cl₂/EtOAc); IR (νmax/cm⁻¹, thin film): 3223 (Aromatic C-H stretch), 1720 (C=O stretch), 1583, 1112; ¹H NMR (600 MHz, DMSO-d₆): δ_H = 3.62 (ap.t, J = 5.6 Hz, 2H, 30-H), 3.97 (ap.d, J = 6.7 Hz, 2H, 32-H), 4.23 (ap.t, J = 4.4 Hz, 2H, 29-H), 5.14 (dd, J = 10.5, 1.5 Hz, 1H, 34-H), 5.25 (dd, J = 17.3, 1.6 Hz, 1H, 34-Ha, Ha), 5.84-5.91 (m, 1H, 33-H), 7.16 (d, J = 4.9 Hz, 1H, 6-H), 7.50-7.55 (m, 2H, 15,16-H), 7.65 (d, J = 8.7 Hz, 2H, 24-H), 7.68 (d, J = 5.5 Hz, 1H, 5-H), 7.92 (d, J = 8.5 Hz, 3H, 14,23-H), 7.98 (d, J = 8.5 Hz, 1H, 12-H), 8.03 (t, J = 8.9 Hz, 2H, 11,17-H), 8.52 (s, 1H, 19-H), 8.59 (s, 1H, 3-H), 10.21 (s, 1H, 26-H), 11.63 (s, 1H, 20-H); ¹³C NMR (150 MHz, DMSO-d₆): δ_C = 63.9 (C-29), 67.7 (C-30), 71.0 (C-32), 110.9 (C-5), 115.3 (C-3), 116.7 (C-6,34), 117.6 (C-24), 123.8 (C-11), 124.2 (C-19), 126.3 (C-15), 126.6 (C-16), 127.4 (C-23), 127.7 (C-14), 128.3 (C-17), 128.4 (C-12), 132.8 (C-13), 133.2 (C-18), 135.0 (C-33), 153.3 (C-27); LRMS m/z (ES⁺): 544 [M+H⁺]; HRMS m/z (ES⁺): Found 544.1631; C₉₂H₇₅N₅O₅S requires 544.1655; Anal. Calcd. for C₉₂H₇₅N₅O₅S: C, 61.87; H, 4.64; N, 12.88. Found C, 61.61; H, 4.32; N, 12.85.

Example 23

2-(2-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)ethoxy)ethyl-4-(N-(2-(naphthalen-2-yl)imidazo[1,2-a]pyrazin-8-yl)sulfamoyl)phenylcarbamate (JS199)
Step 1
4-sulfamoylbenzoyl azide (JS129)

4-sulfamoylbenzoic acid (1.00 g, 4.97 mmol), triphenylphosphine (2.61 g, 9.94 mmol) and sodium azide (0.388 g, 5.96 mmol) were suspended in anhydrous acetone (10 ml). To this milky white suspension was added trichloroacetonitrile (0.997 ml, 9.94 mmol) drop wise and the reaction was left to stir at RT for 18 h. The solvent was removed in vacuo and the resulting dark yellow slurry was diluted with CH₂Cl₂ and washed with H₂O and brine, dried (MgSO₄), filtered, concentrated in vacuo. Flash chromatography (Pet Ether; 3:1 to 2:1 to 1:1 Pet Ether/EtOAc) afforded the title compound as a white solid (906.9 mg, 4.01 mmol, 80.7%). Mpt: 118 °C; R_f = 0.23 (1:1 Pet Ether/EtOAc); IR (ν_max/cm⁻¹, thin film): 3362 (aromatic C-H stretch), 3258 (N-H stretch), 2137 (N=N=N stretch), 1687 (CO stretch), 1339 (S=O stretch, asymmetrical), 1238, 1155 (S=O Symmetrical stretch), 1'H NMR (600 MHz, CD₃OD): δ_H = 8.02 (ap.d, J = 6.9 Hz, 2H, 4-H), 8.18 (ap.d, J = 6.8 Hz, 2H, 3-H); 13C NMR (150 MHz, CD₃OD): δ_C = 127.6 (C-4), 131.0 (C-3), 134.9 (C-2), 150.2 (C-5), 172.8 (C-1); LRMS/HRMS m/z (ES⁺): no product mass present; Anal. Calcd. for C₇H₆N₄O₃S: C, 37.17; H, 2.67; N, 24.77. Found C, 37.27; H, 2.49; N, 24.40%.

Step 2
ferf-butyl 2-(2-hydroxyethoxy)ethylcarbamate (JS136)

To a solution of 2-(2-aminoethoxy)ethanol (2 ml, 19.9 mmol) in CHCl₃ (20 ml) cooled on ice, was added (Boc)₂O (4.35 g, 19.9 mmol) in CHCl₃ (20 ml). The reaction was stirred at RT for 90 min, followed by diluting with H₂O and then extracting with CHCl₃ (3x). The combined organics were dried (MgSO₄), filtered, concentrated in vacuo, and then...
purified via flash chromatography (CH$_2$Cl$_2$; 2% to 5% to 10% MeOH) to afford the title compound as a colourless oil (3.93 g, 19.2 mmol, 96.4%). $R_f = 0.83$ (10% MeOH/CH$_2$Cl$_2$); IR (v$_{max}$/cm$^{-1}$, thin film): 3353 (O-H stretch), 2976, 2931, 2871 (C-H and N-H Stretches), 1687 (C-O stretch), 1520, 1366, 1169, 1123; $^1$H NMR (500 MHz, CDCl$_3$): $\delta_{HH} = 1.43$ (s, 9H, 11-H), 2.16 (bs, 1H, 1-H), 3.32 (t, J = 5.1 Hz, 2H, 6-H), 3.53-3.57 (m, 4H, 3,5-H), 3.72-3.74 (m, 2H, 2-H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta_c = 28.5$ (C-1), 40.5 (C-6), 61.8 (C-2), 70.4 (C-5), 72.3 (C-3), 79.5 (C-10), 156.2 (C-8); LRMS m/z (Cl$^+$): 206 [M+H]$^+$, 150 [M-3Bu]$^+$; HRMS m/z (Cl$^+$): Found 206.1976; C$_3$H$_2$NO$_4$ requires 206.13923.

Step 3
(JS138)

JS136 (993 mg, 4.39 mmol) was dissolved in anhydrous toluene (92 ml). JS129 (750.6 mg, 3.66 mmol) was added and the reaction was stirred under reflux for 16 h. The reaction was cooled to RT and adsorbed onto silica and purification via flash chromatography (Pet Ether; 2:1 to 1:1 to 1:2 Pet Ether/EtOAc) afforded the title compound as a white solid (1.1306 g, 2.81 mmol, 76.7%). Mpt: 94-95 °C; $R_f = 0.35$ (1:3 Pet Ether/EtOAc); IR (v$_{max}$/cm$^{-1}$, thin film): 3368, 3332 (Aromatic C-H stretch), 3201, 3101, 2976, 2919 (C-H, N-H Stretches), 1703, 1676 (C=O Stretches), 1522, 1156; $^1$H NMR (600 MHz, CD$_3$OD): $\delta_{HH} = 1.41$ (s, 9H, 19-H), 3.22 (t, J = 5.6 Hz, 2H, 14-H), 3.53 (t, J = 5.7 Hz, 2H, 13-H), 3.71 (t, J = 4.7 Hz, 2H, 11-H), 4.29 (t, J = 4.6 Hz, 2H, 10-H), 7.60 (d, J = 8.8 Hz, 2H, 5-H), 7.81 (ap.d, J = 8.8 Hz, 2H, 4-H); $^{13}$C NMR (150 MHz, CD$_3$OD): $\delta_c = 28.8$ (C-19), 41.3 (C-14), 65.4 (C-10), 70.2 (C-11), 71.0 (C-13), 80.2 (C-18), 119.0 (C-5), 128.3 (C-4), 138.7 (C-3), 144.1 (C-6), 155.4 (C-8), 158.2 (C-16); LRMS m/z (ES$^+$): 426 [M+Na]$^+$, 370 [M-3Bu+Na]$^+$; HRMS m/z (ES$^+$): Found 426.1306; C$_{16}$H$_{25}$N$_3$O$_7$NaS requires 426.131 1; Anal. Calcd. for C$_{16}$H$_{25}$N$_3$O$_7$S: C, 47.63; H, 6.25; N, 10.42. Found C, 47.78; H, 6.46; N, 10.20%
Step 4
(JS179)

NaH was pre-activated by stirring NaH (60% in Mineral Oil; 71.0 mg, 1.774 mmol) in anhydrous hexanes (25 ml) for 20 min, removing the solvent using a syringe and drying the contents under high vacuum. DMF (5 ml) was added followed by JS138 (715 mg, 1.774 mmol) in DMF (8 ml) and the mixture was stirred at RT for 20 min. JS132 (286.5 mg, 0.887 mmol) in DMF (17 ml) was added and the resulting dark brown solution was heated at 100 °C under Argon for 16 h. The solvent was then removed and the residue was diluted with EtOAc and washed with NH₄Cl (Aq. Sat) and H₂O (3x). The combined aqueous layers were then re-extracted with EtOAc (2x), followed by washing the combined organics with brine, drying (MgSO₄), filtering and concentrating in vacuo. Flash chromatography (Pet Ether; 1:1 to 1:2 to 1:3 to 1:4 to 1:5 Pet Ether/EtOAc) afforded the title compound as a light yellow solid (327.6 mg, 0.507 mmol, 57.2%). Mpt: >200 °C; Rf = 0.21 (9:1 EtOAc/Pet Ether); IR (νmax/cm⁻¹, thin film): 3230 (C-H stretch), 2972 (N-H Stretch), 1697 (C=O Stretch), 1584, 1530, 1221, 1114; ¹H NMR (600 MHz, DMSO-d₆): δH = 1.34 (s, 9H, 38-H), 3.06 (ap.q, J = 5.9 Hz, 2H, 33-H), 3.47 (ap.t, J = 5.0 Hz, 2H, 32-H), 3.62 (ap.t, J = 4.4 Hz, 2H, 30-H), 4.20 (ap.t, J = 4.1 Hz, 2H, 29-H), 6.80 (ap.t, J = 5.6 Hz, 1H, 34-H), 7.16 (bs, 1H, 6-H), 7.50-7.55 (m, 2H, 15,16-H), 7.65 (d, J = 8.8 Hz, 2H, 24-H), 7.86 (bd, J = 4.6 Hz, 1H, 5-H), 7.92 (d, J = 7.4 Hz, 3H, 14,23-H), 7.98 (d, J = 8.6 Hz, 1H, 12-H), 8.02-8.05 (m, 2H, 11,17-H), 8.52 (s, 1H, 19-H), 8.59 (s, 1H, 3-H), 10.22 (s, 1H, 26-H), 11.63 (bs, 1H, 7/20-H); ¹³C NMR (150 MHz, DMSO-d₆): δC = 28.3 (C-38), 40.0 (C-33), 63.9 (C-29), 68.2 (C-30), 69.1 (C-32), 77.7 (C-37), 110.9 (C-5), 115.3 (C-3), 116.8 (C-6), 117.6 (C-24), 123.8 (C-11), 124.2 (C-19), 126.3 (C-15/16), 126.6 (C-15/16), 127.4 (C-23), 127.7 (C-14), 128.3 (C-
12), 128.4 (C-17), 130.0 (C-10), 132.8 (C-13), 133.2 (C-18), 135.6 (C-9), 135.8 (C-22), 142.9 (C-25), 145.2 (C-2), 153.3 (C-27), 155.6 (C-35); LRMS m/z (EI\(^{+}\)): 647 [M+H\(^{+}\)], 591 [M–Bu\(^{+}\)]; (ES\(^{-}\)): 645 [M-H\(^{-}\)], 691 [M+Formic Acid\(^{-}\)]. HRMS m/z (ES\(^{-}\)): Found 645.2140; \(\text{C}_{32}\text{H}_{33}\text{N}_{6}\text{O}_{7}\text{S}\) requires 645.2131; Anal. Calcd. for \(\text{C}_{32}\text{H}_{34}\text{N}_{6}\text{O}_{7}\text{S}\): C, 59.43; H, 5.30; N, 12.99; Found: C, 58.35; H, 5.39; N, 12.34%.

Step 5

2-(2-aminoethoxy)ethyl-4-(yV-(2-(naphthalen-2-yl)imidazo[1,2-a]pyrazin-8-y1)sulfamoyl)phenylcarbamate (JS178)

JS179 (317.9 mg, 0.492 mmol) was dissolved in anhydrous \(\text{CH}_{2}\text{Cl}_{2}\) (15 ml) and cooled on ice. TFA (15 ml) was added and the reaction was stirred at RT for 3 h. Removal of the solvent, with the aid of toluene, followed by flash chromatography (\(\text{CH}_{2}\text{Cl}_{2}\); 5% to 10% MeOH/\(\text{CH}_{2}\text{Cl}_{2}\)). Mpt: >200 °C; \(R_t = 0.26\) (20% MeOH/\(\text{CH}_{2}\text{Cl}_{2}\)); IR (\(v_{\max}\); cm\(^{-1}\), thin film): 1726, 1675, 1200, 1120, 1071; \(^{1}\text{H}\) NMR (400 MHz, DMSO-\(\text{d}_{6}\)): \(\delta = 2.99\) (t, \(J = 5.3\) Hz, 2H, 33-H), 3.62 (t, \(J = 5.2\) Hz, 2H, 32-H), 3.70 (t, \(J = 4.7\) Hz, 2H, 30-H), 4.25 (t, \(J = 4.4\) Hz, 2H, 29-H), 7.11 (d, \(J = 5.0\) Hz, 1H, 6-H), 7.48-7.56 (m, 4H, 15,16,24-H), 7.74 (d, \(J = 5.0\) Hz, 1H, 5-H), 7.88 (d, \(J = 8.8\) Hz, 2H, 23-H), 7.92 (ap.d, \(J = 7.4\) Hz, 1H, 14-H), 7.97 (d, \(J = 8.6\) Hz, 1H, 12-H), 8.00 (ap.d, \(J = 7.4\) Hz, 1H, 17-H), 8.06 (dd, \(J = 8.5\), 1.6 Hz, 1H, 11-H), 8.42 (s, 1H, 3-H), 8.52 (s, 1H, 19-H), 9.98 (bs, 1H, 20-H); \(^{13}\text{C}\) NMR (150 MHz, DMSO-\(\text{d}_{6}\)): \(\delta_{c} = 38.6\) (C-33), 63.6 (C-29), 66.7 (C-32), 68.5 (C-30), 114.5 (C-3), 116.5 (C-6), 118.4 (C-24), 123.9 (C-1,119), 126.5 (C-15), 126.6 (C-16) 127.7 (C-14,23), 128.2 (C-17), 128.3 (C-12), 132.7 (C-13,18), 133.3 (C-10,22), 142.0 (C-25), 144.1 (C-2) 153.4 (C-27); LRMS m/z (ES\(^{+}\)): 547 [M+H\(^{+}\)]; HRMS m/z (ES\(^{+}\)): 547.2140.
Found 547.1757; C_{27}H_{27}N_{6}O_{5}S requires 547.1764; Anal. Calcd. for C_{35}H_{30}F_{12}N_{6}O_{13}S (4x TFA): C, 41.92; H, 3.02; N, 8.38. Found C, 41.14; H, 2.98; N, 8.71%.

Step 6

5 2-(2-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)ethoxy)ethyl-4-([/V-(2-(naphthalen-2-yl)imidazo[1,2-a]pyrazin-8-yl)sulfamoyl]phenyl carbamate (JS199)

10 3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanoic acid (62.7 mg, 0.371 mmol) and HBTU (21.09 mg, 0.556 mmol) were dissolved in anhydrous DMF (15 ml) and the mixture was purged with Argon. DIPEA (197.4 µl, 1.11 mmol) was added and a colourless to orange colour change was observed after stirring at RT for 20 min. JS178 (367 mg, 0.556 mmol) in anhydrous DMF (5 ml) was added and the reaction was stirred at RT for 16 h. Removal of the solvent was followed by diluting with EtOAc and washing with H_{2}O (4x) and brine, drying (MgSO_{4}), filtering and concentrating in vacuo. Flash chromatography (CH_{2}Cl_{2}; 2% to 3% to 4% MeOH/CH_{2}Cl_{2}) afforded the title compound as an off white solid (146.2 mg, 0.210 mmol, 56.5%). Mpt: >200 °C; R_{f} = 0.43 (10% MeOH/CH_{2}Cl_{2}); IR (ν_{max}/cm^{-1}, thin film): 3254 (aromatic C-H stretch), 2925 (C-H and N-H Stretches), 1706 (C=O stretch), 1589, 1527, 1405, 1224, 1140; {^1}H NMR (600 MHz, CD_{3}CN): δ_{H} = 2.38 (t, J = 7.1 Hz, 2H, 36-H), 3.27 (q, J = 5.5 Hz, 2H, 33-H), 3.48 (t, J = 5.6 Hz, 2H, 32-H), 3.64-3.67 (m, 4H, 20,37-H), 4.24-4.26 (m, 2H, 29-H), 6.58 (bs, 1H, 34-H), 6.72 (s, 2H, 40-H), 7.06 (bd, J = 5.4 Hz, 1H, 6-H), 7.51-7.56 (m, 2H, 15,16-H), 7.62-7.65 (m, 3H, 5,24-H), 7.91-7.93 (m, 3H, 14,23-H), 7.95-7.98 (m, 2H, 12,17-H), 8.03 (dd, J = 8.5, 1.6 Hz, 1H, 11-H), 8.20 (s, 1H, 3-H), 8.31 (bs, 1H, 20-H),
8.49 (s, 1 H, 19-H); 13C NMR (150 MHz, CD3CN): δC = 33.8 (C-37), 33.9 (C-36), 38.4 (C-33), 64.0 (C-29), 68.3 (C-30), 68.9 (C-32), 110.3 (C-5) 114.5 (C-3), 115.8 (C-6) 117.6 (C-24), 123.4 (C-11), 124.2 (C-19), 126.1 (C-15), 126.2 (C-16), 127.1 (C-23), 127.3 (C-14), 127.9 (C-17), 128.2 (C-12), 129.4 (C-10) 132.9 (C-13), 133.2 (C-18), 133.9 (C-40), 135.4 (C-9), 135.8 (C-22), 145.2 (C-2), 142.5 (C-25), 144.7 (C-8) 153.1 (C-27), 169.8 (C-35), 170.5 (C-39); LRMS m/z (ES+): 698 [M+H]+; HRMS m/z (ES+): Found 698.2010; C24H22N7O8S requires 698.2033.

VirB11 protein production and ATPase assay.

The VirB11 protein was produced in the E. coli strain BL21 Star(DE3) (Invitrogen) as described previously. The protein concentration was estimated spectroscopically using a NanoDrop (Thermo Scientific) and a calculated extinction coefficient at 280 nm, based on the amino acid composition. The ATPase activity of VirB11 was measured, with and without a specific amount of compound present, using an in vitro ATPase colorimetric assay kit (Innova Biosciences). The assay was performed in 96-well ELISA microplates (Greiner Bio-One), using a multipipett/robot. All measurements were made in duplicate.

A volume of 49 μL of a substrate buffer solution (200 mM tris(hydroxymethyl)aminomethane (TRIS), pH 7.5; 5 mM MgCl2; 250 μM ATP; and 10% DMSO) was added to each assigned well, followed by the addition of 1 μL of compound (at 0.5; 5 or 50 μM to achieve the final concentrations of 5; 50 and 500 μM in the reaction, respectively) in DMSO (or 1 μL DMSO to controls). The solutions were mixed carefully by pipetting. The reaction was started by the addition of 50 μL of 0.106 μM VirB11 to each well (except the negative control, see text below), and the reaction plate was directly transferred to 37 °C for 30 min of incubation. The reaction was stopped by the addition of the Gold mix according to the standard protocol of the kit.

The absorbance at 620 nm was measured after 30 min at room temperature. For each compound, the percentage of absorbance relative non-inhibited VirB11 was calculated, after subtracting the absorbance value of the negative control. In the negative control, the protein was added after the Gold mix, as described in the standard protocol of the
kit, which when used as a blank corrects for all free P, not produced by the enzyme during the 30 min incubation at 37 °C.

A known inhibitor of VirB11 (Microbiology, (2006), 152, 2919-2930, denoted CHIR02) was used as a control inhibitor. A selection of the compounds were assayed as above at additional concentrations ranging between 5 and 200 µM from which IC50 values were calculated, assuming a linear relationship between Pi production and absorbance. IC50 was defined as the concentration of compound that produces 50% inhibition.

Evaluation of compounds as VirB11 ATPase inhibitors

The VirB11 protein was produced recombinantly in Escherichia coli and purified to high purity as described previously. The ATPase activity of VirB11 was measured by monitoring the release of inorganic phosphate (Pi) using an in vitro ATPase assay.

The inhibitory effects of Examples 1 to 12 were evaluated by performing the ATPase assay with and without compound present at concentrations of 500 µM (or 250 µM), 50 µM and 5 µM (Fig. 1). At the highest concentration, precipitation appeared in the reaction wells of compounds 1, 2, 5, 8, 9 and 11, which interfered with the measurements. Despite this, a clear inhibitory effect could be seen of the compounds 1, 3, 4, 5, 6, 11 and 12 of which 4, 5, 8, 11 and 12 clearly reduced the ATPase activity at 50 µM. IC50 values, logP and logS values were then measured for a selection of the compounds 1 to 23 (Table 3).
<table>
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<tr>
<th>Compound</th>
<th>Structure</th>
<th>IC50/μM</th>
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<tbody>
<tr>
<td>Example 1</td>
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<tr>
<td>JS33</td>
<td>LogP = 4.4 LogS = -6.7</td>
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<td>Example 2</td>
<td><img src="image2" alt="Structure" /></td>
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<tr>
<td>JS60</td>
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<td>Example 3</td>
<td><img src="image3" alt="Structure" /></td>
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<td>JS56</td>
<td>LogP = 3.1 LogS = -5.4</td>
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<td>Example 4</td>
<td><img src="image4" alt="Structure" /></td>
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<tr>
<td>JS63</td>
<td>LogP = 4.1 LogS = 6.1</td>
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Molecular Weight: 414.48
Molecular Weight: 456.52
Molecular Weight: 424.47
Molecular Weight: 392.47
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<th>Example 5</th>
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<th>LogP = 5.9</th>
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<td>Example 6</td>
<td>JS68</td>
<td>LogP = 4.5</td>
<td>LogS = -6.3</td>
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<td>Example 7</td>
<td>JS15</td>
<td>LogP = 4.5</td>
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<td>Example 8</td>
<td>JS24</td>
<td>LogP = 4.7</td>
<td>LogS = -7.1</td>
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<td>Example 9</td>
<td>JS49</td>
<td>LogP = 3.1</td>
<td>LogS = -5.4</td>
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<td>Example</td>
<td>Compound Structure</td>
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<td>Example 10</td>
<td><img src="image1.png" alt="Molecular Structure" /></td>
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<td>Example 11</td>
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<td>Example 13</td>
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<td>HK010</td>
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<td>LogP = 5.2</td>
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<td>JS173</td>
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<th>Example 18</th>
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<td>JS175</td>
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<td>LogP = 5.9</td>
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<td>LogS = -8.1</td>
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<td><img src="image" alt="Molecular Weight: 506.57" /></td>
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</table>
| Example 19 | JS209 | LogP = 4.4  
|           |       | LogS = -6.4 |
|           | ![Molecular Structure](image) | 6.7 |

| Example 20 | JS210 | LogP = 4.8  
|           |       | LogS = -6.6 |
|           | ![Molecular Structure](image) | 153 |

| Example 21 | JS208 | LogP = 3.9  
|           |       | LogS = -7.1 |
|           | ![Molecular Structure](image) | 53.9 |

Molecular Weight: 457.55

Molecular Weight: 471.57

Molecular Weight: 541.58
Table 3. IC₅₀ values

<table>
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<th>Example 22</th>
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<th>LogP = 4.2</th>
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<th>Molecular Weight: 543.59</th>
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<td>Example 23</td>
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<td>LogP = 3.7</td>
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Claims

1. A compound of Formula (I) for use in preventing or treating a bacterial infection:

   \[
   \begin{align*}
   & R_1 - O - Z - L - O - N - N - C - R_2 \\
   & R_3 - R_4 - R_5 - R_6
   \end{align*}
   \]  

   wherein:

   \( Z \) is O or NH;

   \( R_1 \) is selected from substituted alkyl, unsubstituted alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl or unsubstituted heteroaryl;

   one of \( R_2 \) and \( R_3 \) is H, and the other one of \( R_2 \) and \( R_3 \) is selected from substituted aryl, unsubstituted aryl, substituted heteroaryl or unsubstituted heteroaryl;

   \( L \) is a direct bond or is selected from:

   \[
   \begin{align*}
   & \text{NH} \\
   & (\text{CH}_2)_n
   \end{align*}
   \]

   wherein \( n \) = 0, 1, 2, 3, 4, 5 or 6;

   or

   \[
   \begin{align*}
   & \text{NH} \\
   & (\text{CH}_2)_n
   \end{align*}
   \]

   or

   \[
   \begin{align*}
   & (\text{CH}_2)_n
   \end{align*}
   \]

   each of which may optionally be substituted at one or more exocyclic positions and wherein \( n \) = 0, 1, 2, 3, 4, 5 or 6; wherein

   \[
   \begin{align*}
   & \text{NH} \\
   & (\text{CH}_2)_n
   \end{align*}
   \]

   is a 5- or 6-membered nitrogen-containing heteroaryl moiety, optionally containing at least one or more further heteroatom; and

   \( R_4 \) and \( R_5 \) are independently selected from H, alkyl, halo, alkoxy, alkylthio, hydroxy, cyano, amino and nitro;

   or a pharmaceutically acceptable salt, solvate or prodrug thereof.

2. The compound for use as claimed in claim 1, wherein
Z is O or NH;
R₂ is H;
R₃ is selected from substituted aryl, unsubstituted aryl, substituted heteroaryl or unsubstituted heteroaryl; and
L is a direct bond.

3. The compound for use as claimed in claim 1, wherein
Z is O or NH;
R₂ is selected from substituted aryl, unsubstituted aryl, substituted heteroaryl or unsubstituted heteroaryl;
R₃ is H; and
L is a direct bond.

4. The compound for use as claimed in claim 1, wherein
Z is O or NH;
R₂ is H;
R₃ is selected from substituted aryl, unsubstituted aryl, substituted heteroaryl or unsubstituted heteroaryl; and
L is selected from:

- NH
- (CH₂)ₙ

wherein n = 0, 1, 2, 3, 4, 5 or 6;

or

each of which may optionally be substituted at one or more exocyclic positions and wherein n = 0, 1, 2, 3, 4, 5 or 6; wherein

is a 5- or 6-membered nitrogen-containing heteroaryl moiety, optionally containing at least one or more further heteroatom.

5. The compound for use as claimed in claim 1, wherein:
Z is O or NH;
\[ R_2 \text{ is selected from substituted aryl, unsubstituted aryl, substituted heteroaryl or unsubstituted heteroaryl; } \]
\[ R_3 \text{ is } H; \text{ and } \]
\[ L \text{ is selected from: } \]
\[ \text{NH} \]
\[ (\text{CH}_2)_n \]
\[ \text{, wherein } n = 0, 1, 2, 3, 4, 5 \text{ or } 6; \]
\[ \text{or} \]
\[ \text{NH} \]
\[ (\text{CH}_2)_n \]
\[ \text{or} \]
\[ (\text{CH}_2)_n \]
\[ \text{each of which may optionally be substituted at one or more exocyclic positions, and wherein } n = 0, 1, 2, 3, 4, 5 \text{ or } 6; \text{ wherein } \]
\[ (\text{CH}_2)_n \]
\[ \text{is a 5- or 6-membered nitrogen-containing heteroaryl moiety, optionally containing at least one or more further heteroatom. } \]

6. The compound for use as claimed in any one of claims 1, 3 or 5, wherein \( R_2 \) is 2-naphthyl.

7. The compound for use as claimed in any one of claims 1, 2 or 4, wherein \( R_3 \) is 2-naphthyl.

8. The compound for use as claimed in any one of the preceding claims, wherein \( R_4 \) is H.

9. The compound for use as claimed in any one of the preceding claims, wherein \( R_5 \) is H.

10. The compound for use as claimed in any one of the preceding claims, wherein \( R_1 \) is substituted aryl.
11. The compound for use as claimed in any one of the preceding claims, wherein 
   \( R_1 \) is substituted aryl substituted with a poly(ethylene) glycol moiety.

12. The compound for use as claimed in claim 11, wherein the poly(ethylene) glycol moiety is coupled to the aryl group via a linker.

13. The compound for use as claimed in claim 12, wherein the linker comprises a carbamate moiety.

14. The compound for use as claimed in any one of claims 1 to 11, wherein \( R_1 \) is substituted aryl directly substituted with a poly(ethylene) glycol moiety.

15. The compound for use as claimed in any one of the preceding claims, wherein the bacterial infection is infection with *Helicobacter pylori*, *Legionella pneumophilia*, *Brucella suis*, *Bartonella henselae* or *Bordetella pertussis*.

16. A compound of Formula (I):

\[
\begin{align*}
\text{R}_1 \backslash \text{S} & \text{O} \\
\text{O} & \text{L} \backslash \\
\text{Z} & \text{N} \\
\text{N} & \text{R}_6 \\
\text{R}_4 & \text{R}_3 \\
\text{R}_2 & \text{H}
\end{align*}
\]

wherein:

- \( Z \) is \( O \) or \( NH \);
- \( R_1 \) is selected from substituted alkyl, unsubstituted alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl or unsubstituted heteroaryl;
- one of \( R_2 \) and \( R_3 \) is \( H \), and the other one of \( R_2 \) and \( R_3 \) is selected from substituted aryl, unsubstituted aryl, substituted heteroaryl or unsubstituted heteroaryl;
- \( L \) is a direct bond or is selected from:

\[
\text{NH} \quad \text{or} \quad (\text{CH}_2)_n
\]

wherein \( n = 0, 1, 2, 3, 4, 5 \) or \( 6 \).
17. The compound of claim 16, wherein
   
   Z is O or NH;
   
   R₂ is H;
   
   R₃ is selected from substituted aryl, unsubstituted aryl, substituted heteroaryl or unsubstituted heteroaryl; and
   
   L is a direct bond.

18. The compound of claim 16, wherein
   
   Z is O or NH;
   
   R₂ is selected from substituted aryl, unsubstituted aryl, substituted heteroaryl or unsubstituted heteroaryl;
   
   R₃ is H; and
   
   L is a direct bond.

19. The compound of claim 16, wherein
   
   Z is O or NH;
   
   R₂ is H;
   
   R₃ is selected from substituted aryl, unsubstituted aryl, substituted heteroaryl or unsubstituted heteroaryl; and
L is selected from:

\[
\text{NH} \quad \text{(CH}_2\text{)}_n
\]

wherein \( n = 0, 1, 2, 3, 4, 5 \text{ or } 6 \); each of which may optionally be substituted at one or more exocyclic positions, and wherein \( n = 0, 1, 2, 3, 4, 5 \text{ or } 6 \); wherein \( \text{(CH}_2\text{)}_n \) is a 5- or 6-membered nitrogen-containing heteroaryl moiety, optionally containing at least one or more further heteroatom.

20. The compound of claim 16, wherein:

- \( Z \) is O or NH;
- \( R_2 \) is selected from substituted aryl, unsubstituted aryl, substituted heteroaryl or unsubstituted heteroaryl;
- \( R_3 \) is H; and
- \( L \) is selected from:

\[
\text{NH} \quad \text{(CH}_2\text{)}_n
\]

wherein \( n = 0, 1, 2, 3, 4, 5 \text{ or } 6 \); each of which may optionally be substituted at one or more exocyclic positions, and wherein \( n = 0, 1, 2, 3, 4, 5 \text{ or } 6 \); wherein
is a 5- or 6-membered nitrogen-containing heteroaryl moiety, optionally containing at least one or more further heteroatom.

21. The compound of any one of claims 16 to 20 as defined by Formula (la):

wherein:

- $R_1$ is selected from substituted aryl, unsubstituted aryl, substituted heteroaryl or unsubstituted heteroaryl;
- one of $R_2$ and $R_3$ is H, and the other one of $R_2$ and $R_3$ is selected from substituted aryl, unsubstituted aryl, substituted heteroaryl or unsubstituted heteroaryl;
- $L$ is selected from:

\[ \text{or} \quad \text{wherein each of which may optionally be substituted at one or more exocyclic positions; wherein} \]

is a 5- or 6-membered nitrogen-containing heteroaryl moiety, optionally containing at least one or more further heteroatom; and

- $R_4$ and $R_5$ are independently selected from H, alkyl, halo, alkoxy, alkylthio, hydroxy, cyano, amino and nitro;
- or a pharmaceutically acceptable salt, solvate or prodrug thereof.

22. The compound as claimed in any one of claims 16, 18, 20, or 21, wherein $R_2$ is 2-naphthyl.
23. The compound as claimed in any one of claims 16, 17, 19, or 21, wherein \( R_3 \) is 2-naphthyl.

24. The compound as claimed in any one of claims 16 to 23, wherein \( R_4 \) is H.

25. The compound as claimed in any one of claims 16 to 24, wherein \( R_5 \) is H.

26. The compound of any one of claims 16 to 25, wherein \( R_1 \) is substituted aryl.

27. The compound of claim 26, wherein \( R_1 \) is substituted aryl substituted with a poly(ethylene) glycol moiety.

28. The compound of claim 27, wherein the poly(ethylene) glycol moiety is coupled to the aryl group via a linker.

29. The compound of claim 28, wherein the linker comprises a carbamate moiety.

30. The compound as claimed in any one of claims 16 to 26, wherein \( R_1 \) is substituted aryl directly substituted with a poly(ethylene) glycol moiety.

31. A method of treating or preventing bacterial infection in a subject by administering a therapeutically effective amount of a compound of any one of claims 16 to 30 or a pharmaceutically acceptable salt thereof to a patient in need thereof.

32. The method of claim 31, wherein the bacterial infection is infection with *Helicobacter pylori*, *Legionella pneumophila*, *Brucella suis*, *Bartonella henselae* or *Bordetella pertussis*.

33. Use of a compound of any one of claims 16 to 30 in the manufacture of a medicament for treating or preventing bacterial infection.
34. The use of the compound of claim 33, wherein the bacterial infection is infection with *Helicobacter pylori*, *Legionella pneumophila*, *Brucella suis*, *Bartonella henselae* or *Bordetella pertussis*.

35. A pharmaceutical composition comprising a therapeutically effective amount of a compound as defined in any one of claims 16 to 30, optionally one or more other active ingredients and a pharmaceutically acceptable carrier.

36. A method of making a compound as claimed in claim 16 which comprises reacting a compound of Formula (II):

\[
\begin{array}{c}
\text{N} \\
\text{R}_5 \\
\text{N} \\
\text{R}_4 \\
\text{R}_2 \\
X \\
\text{R}_3 \\
\end{array}
\]  
(II)

wherein X is a leaving group, for example a halo group, and R_2, R_3, R_4 and R_5 are as defined in claim 16, with a compound of the formula:

\[
\begin{array}{c}
\text{S} \\
\text{O} \\
\text{L} \\
\text{Z} \\
\text{H} \\
\text{R}_1 \\
\end{array}
\]  
(VI)

wherein R_1, L and and Z are as defined in claim 16.

37. A method of making the compounds of claims 17, 19 or 21, comprising:

(i) reacting a compound of Formula (IV)

\[
\begin{array}{c}
\text{OH} \\
\text{R}_3 \\
\text{NH}_2 \\
\end{array}
\]  
(IV)

with 2,3-dichloropyrazine;

(ii) oxidising the product of (i);

(iii) effecting an intramolecular cyclisation of the product of (ii); and

(iv) coupling the product of (iii) with a compound of Formula (VI)

\[
\begin{array}{c}
\text{S} \\
\text{O} \\
\text{L} \\
\text{Z} \\
\text{H} \\
\text{R}_1 \\
\end{array}
\]  
(VI)

wherein R_1, R_3, L and Z are as defined in claim 16.
38. The method of claim 37, wherein step (iv) is carried out in the presence of a palladium catalyst.

39. A method of making the compounds of claims 18, 20 or 21, comprising:
   (i) reacting a compound of Formula (V)

   
   \[
   \text{OH} \\
   \text{R}_2 \text{NH}_2
   \]

   (IV)

   with 2-amino-3-chloropyrazine;
   (ii) coupling the product of (i) with a compound of Formula (VI)

   
   \[
   \text{R}_1 \text{SO}_3^\text{O} \\
   \text{LZ} \text{H}
   \]

   (VI)

   wherein

   \[ \text{R}_1, \text{R}_2, \text{L} \text{ and } \text{Z} \text{ are as defined in claim 16.} \]

40. The method of claim 39, wherein step (iv) is carried out in the presence of a palladium catalyst.
### INTERNATIONAL SEARCH REPORT

**International application No:**  PCT/GB2012/051303

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**A. CLASSIFICATION OF SUBJECT MATTER**

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**ADD.**

According to International Patent Classification (IPC) or to both national classification and IPC

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**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

- C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal

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**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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* Further documents are listed in the continuation of Box C. *X* See patent family annex.

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**Name and mailing address of the ISA:***

- European Patent Office, P.B. 5818 Patentlaan 2
- NL - 2280 HV Rijswijk
- Tel. (+31-70) 340-2040,
- Fax: (+31-70) 340-3016

**Authorized officer:***

- Sarakinos, Georgios
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