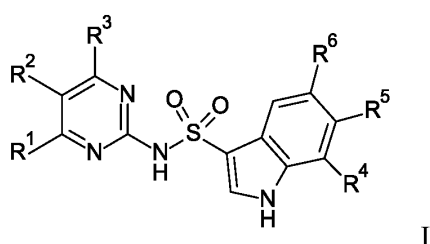


Novel 7-substituted indole sulfonamide derivatives

The present invention relates to organic compounds useful for therapy and/or prophylaxis in a mammal, and in particular to compounds that modulate GPR17 activity.

5

The present invention provides novel compounds of formula I



wherein,

R¹ is alkoxy or haloalkoxy;

10 R² is halo, alkyl, alkoxy, haloalkyl, haloalkoxy, cyanoalkyl, cyanoalkoxy or cyclopropyl optional substituted with up to two substituents independently selected from cyano and halo;

R³ is H, alkoxy or haloalkoxy;

R⁵ is H, halo, alkyl, or haloalkyl;

15 R⁶ is H or halo;

R⁴ is a C-linked aryl or a C-linked heteroaryl, wherein the C-linked aryl or C-linked heteroaryl is optionally substituted by one or more substituents independently selected from alkyl, halo, and haloalkyl; and pharmaceutically acceptable salts.

20

Furthermore, the invention includes all racemic mixtures, all their corresponding enantiomers and/or optical isomers.

Background of the Invention

25 Myelination is a process that occurs robustly during development and despite the abundant presence of oligodendrocyte precursor cells (OPCs) throughout the adult CNS, the transition to myelinating oligodendrocytes and the production of restorative myelin sheaths around denuded axons is impaired in chronic demyelinating diseases. During development,

myelination proceeds in a very orderly manner, with OPCs, characterized by expression of markers such as neural/glial antigen 2 (NG2) and platelet-derived growth factor alpha (PDGFR α), differentiating into oligodendrocytes which lose NG2 and PDGFR α expression and gain the expression of markers such as myelin basic protein (MBP) and myelin oligodendrocyte glycoprotein (MOG). The production of myelin by oligodendrocytes is a very tightly regulated process and in the CNS, this can be controlled by interactions with axons, well-understood in the peripheral but not in the central nervous system (Macklin, W.B. (2010). *Sci. Signal.* 3, pe32–pe32, “The myelin brake: When Enough Is Enough”). Myelination can also be controlled by internal brakes within oligodendrocytes themselves, through the transcription factor EB (TFEB)-PUMA axis or through GPR17 antagonism (Chen, Y., et al. (2009). *Nat Neurosci* 12, 1398–1406, “The oligodendrocyte-specific G protein-coupled receptor GPR17 is a cell-intrinsic timer of myelination”) (Sun, L.O., et al. (2018). *Cell* 175, 1811–1826.e21, “Spatiotemporal Control of CNS Myelination by Oligodendrocyte Programmed Cell Death through the TFEB-PUMA Axis”). Myelin serves not only to protect axons and facilitate neuronal transmission, but oligodendrocytes have also been shown to play an important role in metabolism of axons as well as in maintaining the electrolyte balance around axons (Schirmer, L., et al. (2014). *Ann Neurol* 75, 810–828, “Differential loss of KIR4.1 immunoreactivity in multiple sclerosis lesions”) (Simons, M., and Nave, K.-A. (2015). *Cold Spring Harb Perspect Biol.* 22, “Oligodendrocytes: Myelination and Axonal Support”).

GPR17 is a Class A orphan G protein-coupled receptor (GPCR). GPCRs are 7 domain transmembrane proteins that couple extracellular ligands with intracellular signaling via their intracellular association with small, heterotrimeric G-protein complexes consisting of G α , G β , G γ subunits. It is the coupling of the GPCR to the G α subunit that confers results in downstream intracellular signaling pathways. GPR17 is known to be coupled directly to G $\alpha_{i/o}$, which leads to inhibition of adenylate cyclase activity, resulting in a reduction in cyclic AMP production (cAMP). GPR17 has also been shown to couple to G $_{q/11}$, that targets phospholipase C. Activation of phospholipase C leads to the cleavage of phosphatidylinositol 4,5-bisphosphate which produces inositol triphosphate (IP $_3$) and diacylglycerol (DAG). IP $_3$ consequently binds to the IP $_3$ receptor on the endoplasmic reticulum and causes an increase in intracellular calcium levels (Hanlon, C.D., and Andrew, D.J. (2015). *J Cell Sci.* 128, 3533–3542, “Outside-in signaling-a brief review of GPCR signaling with a focus on the Drosophila GPCR family”) (Inoue, A., et al. (2019), *Cell* 177, 1933–1947.e25, “Illuminating G-Protein-Coupling Selectivity of GPCRs”).

The role of GPR17 in myelination was first identified in a screen of the optic nerves of *Olig1* knockout mice to identify genes regulating myelination. GPR17 expression was found to be expressed only in the myelinating cells of the CNS and absent from the Schwann cells, the peripheral nervous system's myelinating cells. The expression of GPR17 was found to be exclusively expressed in the oligodendrocyte lineage cells and was downregulated in myelinating oligodendrocyte (Chen, Y., et al. (2009)). Specifically, GPR17 expression is found to be present at low levels early on in the OPC and increases in the pre-myelinating oligodendrocyte before the expression is downregulated in the mature, myelinating oligodendrocyte (Boda, E., et al. (2011), *Glia* 59, 1958–1973, “The GPR17 receptor in NG2 expressing cells: Focus on in vivocell maturation and participation in acute trauma and chronic damage”) (Dziedzic, A., et al. (2020). *Int. J. Mol. Sci.* 21, 1852, “The gpr17 receptor—a promising goal for therapy and a potential marker of the neurodegenerative process in multiple sclerosis”) (Fumagalli, M. et al. (2011), *J Biol Chem* 286, 10593–10604, “Phenotypic changes, signaling pathway, and functional correlates of GPR17-expressing neural precursor cells during oligodendrocyte differentiation”). GPR17 knockout animals were shown to exhibit precocious myelination throughout the CNS and conversely, transgenic mice overexpressing *GPR17* in oligodendrocytes with the CNP-Cre (2', 3' - cyclic-nucleotide 3'-phosphodiesterase) promoter exhibited myelinogenesis defects, in line with what is to be expected of a cell-intrinsic brake on the myelination process (Chen, Y., et al. (2009)). Furthermore, loss of GPR17 enhances remyelination following demyelination with lysophosphatidylcholine-induced demyelination (Lu, C., Dong, et al. (2018), *Sci. Rep.* 8, 4502, “G-Protein-Coupled Receptor Gpr17 Regulates Oligodendrocyte Differentiation in Response to Lysolecithin-Induced Demyelination”). As such, antagonism of GPR17 that promotes the differentiation of oligodendrocyte lineage cells into mature, myelinating oligodendrocytes would lead to increase in myelination following demyelination.

Multiple sclerosis (MS) is a chronic neurodegenerative disease that is characterized by the loss of myelin, the protective fatty lipid layer surrounding axons, in the central nervous system (CNS). Prevention of myelin loss or remyelination of denuded axons is thought to prevent axonal degeneration and thus prevent progression of the disease (Franklin, R.J. (2002), *Nat Rev Neurosci* 3, 705–714, “Why does remyelination fail in multiple sclerosis?”). Due to the restorative impact that myelin repair has on the central nervous system, such a treatment will benefit all types of MS namely relapse-remitting, secondary progressive, primary progressive and progressive relapsing MS. Reparation of lost myelin will alleviate neurological symptoms associated with MS due to the neuroprotective effect of preserving axons.

Due to the essential role that myelination plays in functioning of the nervous system, facilitating OPC to oligodendrocyte differentiation has the potential to impact multiple diseases where white matter defects/irregularities due to either loss of myelinating oligodendrocytes or hampered differentiation of OPCs to oligodendrocytes have been observed, due to the disease
5 itself or inflammation. This is in addition to the diseases where GPR17 expression itself is altered.

The diseases that GPR17 antagonism can be thus used to yield a positive disease outcome include, but are not limited to:

Direct damage to myelin sheaths:

- 10 - Metabolic conditions that lead to destruction of central myelin such as central pontine myelinolysis, extra-pontine myelinolysis due to overly-rapid correction of hyponatremia in conditions for instance, but not limited to, alcoholism, liver disease, immunosuppression after transplantation
- Carbon monoxide poisoning where oligodendrocyte dysfunction and failure to
15 regenerate has been reported in the deep white matter layers of the brain
- Nutritional deficiency that results in myelin loss or failure to properly generate myelin during development
- Virus-induced demyelination

20 Primary demyelinating disorders

- Multiple Sclerosis (relapse-remitting, secondary progressive, primary progressive and progressive relapsing MS)
- Acute and multiphasic disseminated encephalomyelitis
- Neuromyelitis optica spectrum disorders including optic neuritis
- 25 - Transverse myelitis
- Leukodystrophies such as adrenoleukodystrophy, adrenomyeloneuropathy and other inherited leukodystrophies that result in myelin loss

CNS disorders with associated myelin loss:

- 30 - Alzheimer's Disease
- Schizophrenia
- Parkinson's Disease
- Huntington's disease

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- Amyotrophic lateral
- Ischemia due to stroke

Other diseases:

- 5 - Inflammation in the CNS for instance following encephalitis, primary angitis, meningitis

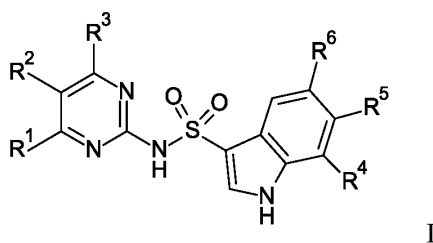
The compounds of formula I bind to and modulates GPR17 activity.

- 10 The compounds of formula I are therefore particularly useful in the treatment of diseases related to GPR17 antagonism.

- 15 The compounds of formula I are particularly useful in the treatment or prophylaxis of multiple sclerosis (MS), conditions related to direct damage to myelin sheaths such as carbon monoxide poisoning or virus induced demyelination, primary demyelinating disorders such as acute and multiphasic disseminated encephalomyelitis, and other CNS disorders associated with myelin loss such as Alzheimer's disease, schizophrenia, Parkinson's disease and Huntington's disease.

Summary of the Invention

- 20 The present invention provides novel compounds of formula I



I

wherein

- R¹ is alkoxy or haloalkoxy;
- 25 R² is halo, alkyl, alkoxy, haloalkyl, haloalkoxy, cyanoalkyl, cyanoalkoxy or cyclopropyl optional substituted with up to two substituents independently selected from cyano and halo;
- R³ is H, alkoxy or haloalkoxy;
- R⁵ is H, halo, alkyl, or haloalkyl;
- R⁶ is H or halo;

R^4 is a C-linked aryl or a C-linked heteroaryl, wherein the C-linked aryl or C-linked heteroaryl is optionally substituted by one or more substituents independently selected from alkyl, halo, and haloalkyl; and pharmaceutically acceptable salts.

5

The term “alkyl” denotes a monovalent linear or branched saturated hydrocarbon group of 1 to 6 carbon atoms. In some embodiments, if not otherwise described, alkyl comprises 1 to 6 carbon atoms (C_{1-6} -alkyl), or 1 to 4 carbon atoms (C_{1-4} -alkyl). Examples of C_{1-6} -alkyl include methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl and pentyl. Particular
10 alkyl group is methyl. When an alkyl residue having a specific number of carbons is named, all geometric isomers having that number of carbons may be encompassed. Thus, for example, “butyl” can include n-butyl, sec-butyl, isobutyl and t-butyl, and “propyl” can include n-propyl and isopropyl. Particular example of alkyl is methyl.

The term “alkoxy” denotes a group of the formula $-O-R'$, wherein R' is a C_{1-6} -alkyl group.
15 Examples of C_{1-6} -alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy and tert-butoxy. Particular example is methoxy.

The term “aryl”, alone or in combination with other groups, denotes a monovalent cyclic aromatic hydrocarbon moiety consisting of a mono- or bicyclic aromatic ring. Preferred aryl is phenyl. Aryl may be unsubstituted or substituted as described herein. Particular example of aryl
20 is phenyl.

The term “halogen”, “halide” and “halo” are used interchangeably herein and denote fluoro, chloro, bromo or iodo. Particular halogens are fluoro, chloro and bromo.

The term “haloalkyl” denotes a C_{1-6} -alkyl group wherein at least one of the hydrogen atoms of the C_{1-6} -alkyl group has been replaced by the same or different halogen atoms.
25 Particular examples are difluoroethyl and difluoromethyl.

The term “haloalkoxy” denotes a C_{1-6} -alkoxy group wherein at least one of the hydrogen atoms of the C_{1-6} -alkoxy group has been replaced by the same or different halogen atoms. Particular examples fluoroethoxy, difluoroethoxy, and difluoromethoxy.

The term “cyano” denotes a $-C\equiv N$ group.
30 “Cyanoalkyl” means a moiety of the formula $-R'-R''$, where R' is alkyl as defined herein and R'' is cyano or nitrile. An example of cyanoalkyl is cyanoethyl.

"Cyanoalkoxy" means a moiety of the formula -R'-R", where R' is alkoxy as defined herein and R" is cyano or nitrile. An example of cyanoalkoxy is cyanomethoxy.

The term "heteroaryl" denotes a monovalent aromatic mono- or bicyclic ring system of 4 to 9 ring atoms, comprising 1, 2, 3, or 4 ring heteroatoms selected from N and O, the remaining
5 ring atoms being carbon. Heteroatom may also be S. Bicyclic means consisting of two cycles having one or two ring atoms in common. Example for heteroaryl are pyrimidyl, oxazolyl, pyridazinyl, imidazolyl, pyrazinyl, and pyridyl. Other example for heteroaryl are pyrazolyl, pyrimidinyl, isoazolyl, triazolyl, oxadiazolyl, oxazolyl, pyrrolylimidazolyl, and thiazolyl.

The term "C-linked heteroaryl" means denotes a heteroaryl system up to 9 ring atoms,
10 wherein the heteroaryl system is attached to the rest of the molecule through a C-atom.

The term "pharmaceutically acceptable salts" refers to those salts which retain the biological effectiveness and properties of the free bases or free acids, which are not biologically or otherwise undesirable. The salts are formed with inorganic acids such as hydrochloric acid,
15 hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, particularly hydrochloric acid, and organic acids such as formic acid, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, N-acetylcystein. In addition these salts may be prepared from addition of an
20 inorganic base or an organic base to the free acid. Salts derived from an inorganic base include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium salts. Salts derived from organic bases include, but are not limited to salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine,
25 triethylamine, tripropylamine, ethanolamine, lysine, arginine, N-ethylpiperidine, piperidine, polyamine resins. The compound of formula I can also be present in the form of zwitterions. Particularly preferred pharmaceutically acceptable salts of compounds of formula I are the salts formed with formic acid and the salts formed with hydrochloric acid yielding a hydrochloride, dihydrochloride or trihydrochloride salt.

30 The abbreviation uM means microMolar and is equivalent to the symbol μM .

The abbreviation uL means microliter and is equivalent to the symbol μL .

The abbreviation ug means microgram and is equivalent to the symbol μg .

The compounds of formula I can contain several asymmetric centers and can be present in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates or mixtures of diastereoisomeric racemates.

5 According to the Cahn-Ingold-Prelog Convention the asymmetric carbon atom can be of the "R" or "S" configuration.

Also an embodiment of the present invention provides compounds according to formula I as described herein and pharmaceutically acceptable salts or esters thereof, in particular compounds according to formula I as described herein and pharmaceutically acceptable salts
10 thereof, more particularly compounds according to formula I as described herein.

An embodiment of the present invention provides compounds according to formula I as described herein, wherein R¹ is alkoxy.

An embodiment of the present invention provides compounds according to formula I as
15 described herein, wherein R² is halo, alkyl, haloalkyl, haloalkoxy, cyanoalkyl, cyanoalkoxy or cyclopropyl substituted with cyano.

An embodiment of the present invention provides compounds according to formula I as described herein, wherein R² is haloalkyl, haloalkoxy, or cyclopropyl substituted with cyano.

An embodiment of the present invention provides compounds according to formula I as
20 described herein, wherein R² is alkyl, haloalkoxy or haloalkyl.

An embodiment of the present invention provides compounds according to formula I as described herein, wherein R² is haloalkyl or haloalkoxy.

An embodiment of the present invention provides compounds according to formula I as described herein, wherein R³ is H or alkoxy.

25 An embodiment of the present invention provides compounds according to formula I as described herein, wherein R³ is alkoxy.

An embodiment of the present invention provides compounds according to formula I as described herein, wherein R⁵ is H, halo, or haloalkyl.

An embodiment of the present invention provides compounds according to formula I as
30 described herein, wherein R⁵ is alkyl, H, or halo.

An embodiment of the present invention provides compounds according to formula I as described herein, wherein R⁵ is H or halo.

An embodiment of the present invention provides compounds according to formula I as described herein, wherein R⁶ is H.

5 An embodiment of the present invention provides compounds according to formula I as described herein, wherein R⁴ is a C-linked aryl or a C-linked heteroaryl, wherein the C-linked aryl or C-linked heteroaryl is optionally substituted by one or more substituents independently selected from alkyl and halo.

10 An embodiment of the present invention provides compounds according to formula I as described herein, wherein R⁴ is a C-linked aryl or a C-linked heteroaryl, wherein the C-linked aryl or C-linked heteroaryl is optionally substituted by alkyl, halo, or haloalkyl.

An embodiment of the present invention provides compounds according to formula I as described herein, wherein R⁴ is selected from

- 15 i. a C-linked 6-member aryl optionally substituted with alkyl, halo or haloalkyl;
- ii. a C-linked 6-member heteroaryl comprising 1 to 3 nitrogen heteroatoms optionally substituted with alkyl, halo or haloalkyl;
- iii. a C-linked 5-member heteroaryl comprising 1-3 heteroatoms independently
20 selected from N, S and O, optionally substituted with alkyl, halo or haloalkyl; and
- iv. a C-linked 8-9 membered bicyclic heteroaryl system comprising 2 N heteroatoms.

25 An embodiment of the present invention provides compounds according to formula I as described herein, wherein R⁴ is selected from

- i. a C-linked 6-member aryl;
- ii. a C-linked 6-member heteroaryl comprising 1 to 2 nitrogen heteroatoms
 optionally substituted with alkyl or halo;
- 30 iii. a C-linked 5-member heteroaryl comprising 1-3 heteroatoms independently
 selected from N, S and O, optionally substituted with 1 to 2 substituents
 independently selected from alkyl and halo; and

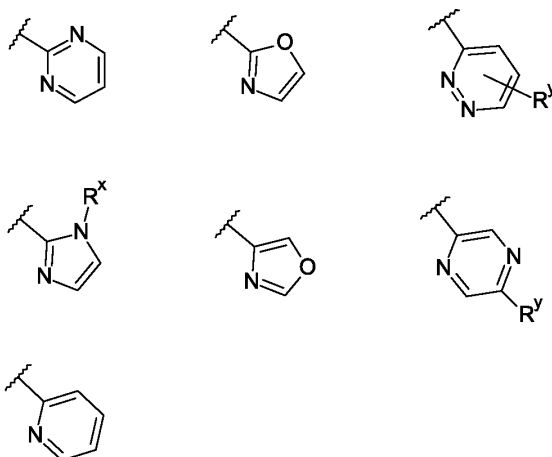
-10-

- iv. a C-linked 8-membered bicyclic heteroaryl system comprising 2 N heteroatoms.

5 An embodiment of the present invention provides compounds according to formula I as described herein, wherein R^4 is selected from

- i. a C-linked 6-member heteroaryl comprising 1 to 3 nitrogen heteroatoms optionally substituted with alkyl or halo; and
- 10 ii. a C-linked 5-member heteroaryl comprising 1-2 heteroatoms independently selected from N and O.

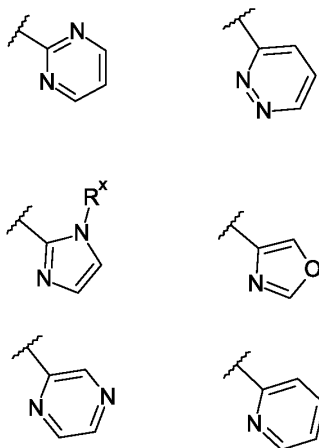
An embodiment of the present invention provides compounds according to formula I as described herein, wherein R^4 is selected from



15 wherein R^x is H or alkyl and R^y is H, alkyl or halo.

An embodiment of the present invention provides compounds according to formula I as described herein, wherein R^4 is selected from

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wherein R^x is methyl.

An embodiment of the present invention provides compounds according to formula I as
 5 described herein, wherein

R^1 is alkoxy;

R^2 is halo, alkyl, haloalkyl, haloalkoxy, cyanoalkyl, cyanoalkoxy or cyclopropyl
 substituted with cyano;

R^3 is H or alkoxy;

10 R^5 is H, halo, alkyl, or haloalkyl;

R^6 is H or halo;

R^4 is a C-linked aryl or a C-linked heteroaryl, wherein the C-linked aryl or C-linked
 heteroaryl is optionally substituted by one or more substituents independently
 selected from alkyl and halo;

15 and pharmaceutically acceptable salts.

An embodiment of the present invention provides compounds according to formula I as
 described herein, wherein

R^1 is alkoxy;

20 R^2 is halo, alkyl, haloalkyl, haloalkoxy, cyanoalkyl, cyanoalkoxy or cyclopropyl
 substituted with cyano;

R^3 is H or alkoxy;

R^5 is H, halo, alkyl, or haloalkyl;

R^6 is H or halo;

R⁴ is selected from

- i. a C-linked 6-member aryl;
- ii. a C-linked 6-member heteroaryl comprising 1 to 2 nitrogen heteroatoms optionally substituted with alkyl or halo;
- 5 iii. a C-linked 5-member heteroaryl comprising 1-3 heteroatoms independently selected from N, S and O, optionally substituted with 1 to 2 substituents independently selected from alkyl and halo; and
- iv. a C-linked 8-membered bicyclic heteroaryl system comprising 2 N heteroatoms; and pharmaceutically acceptable salts.

10

An embodiment of the present invention provides compounds according to formula I as described herein, wherein

R¹ is alkoxy or haloalkoxy;

15

R² is halo, alkyl, alkoxy, haloalkyl, haloalkoxy, cyanoalkyl, cyanoalkoxy or cyclopropyl optional substituted with up to two substituents independently selected from cyano and halo;

R³ is H, alkoxy or haloalkoxy;

R⁵ is H, halo, alkyl, or haloalkyl;

20

R⁶ is H or halo;

R⁴ is a C-linked aryl or a C-linked heteroaryl, wherein the C-linked aryl or C-linked heteroaryl is optionally substituted by alkyl, halo, or haloalkyl; and pharmaceutically acceptable salts.

25

An embodiment of the present invention provides compounds according to formula I as described herein, wherein

R¹ is alkoxy;

R² is haloalkyl, haloalkoxy, or cyclopropyl substituted with cyano;

R³ is alkoxy;

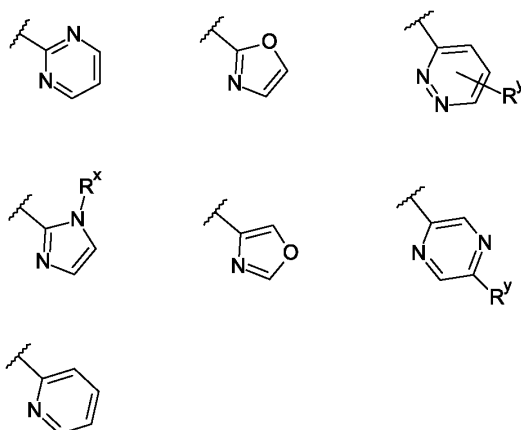
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R⁵ is H, halo, or haloalkyl;

R⁶ is H;

R⁴ is selected from

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wherein R^x is H or alkyl and R^y is H, alkyl or halo;
and pharmaceutically acceptable salts.

5

An embodiment of the present invention provides compounds according to formula I as described herein, wherein

R^1 is alkoxy;

R^2 is haloalkyl or haloalkoxy;

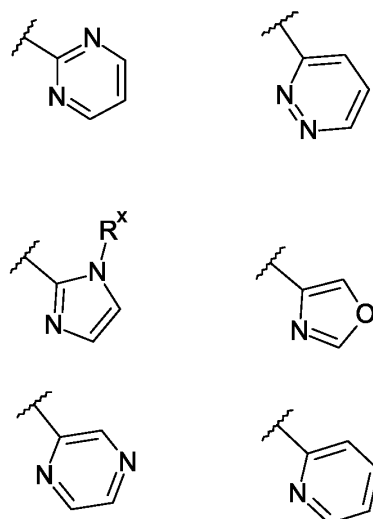
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R^3 is alkoxy;

R^5 is H or halo;

R^6 is H;

R^4 is selected from



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wherein R^x is alkyl;
and pharmaceutically acceptable salts.

Particular examples of compounds of formula I as described herein are selected from

- 5 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-oxazol-2-yl-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;
- 10 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyridazin-3-yl-1H-indole-3-sulfonamide;
- N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylimidazol-2-yl)-1H-indole-3-sulfonamide;
- 15 6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyridazin-3-yl-1H-indole-3-sulfonamide;
- N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylimidazol-2-yl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylimidazol-2-yl)-1H-indole-3-sulfonamide;
- 20 N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-fluoro-7-(1-methylimidazol-2-yl)-1H-indole-3-sulfonamide;
- N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-6-fluoro-7-(1-methylimidazol-2-yl)-1H-indole-3-sulfonamide;

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N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyridazin-3-yl-1H-indole-3-sulfonamide;

N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyridazin-3-yl-1H-indole-3-sulfonamide;

5 N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(4-methylpyridazin-3-yl)-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-oxazol-4-yl-1H-indole-3-sulfonamide;

10 6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-1H-indole-3-sulfonamide;

N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;

15 6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyridyl)-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyridyl)-1H-indole-3-sulfonamide;

20 6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2-fluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-1H-indole-3-sulfonamide;

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6-chloro-N-[5-(2-fluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-
1H-indole-3-sulfonamide;

6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-
pyrimidyl)-1H-indole-3-sulfonamide;

5 6-chloro-N-[5-(2-cyanocyclopropyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-
pyrimidyl)-1H-indole-3-sulfonamide;

N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-1H-
indole-3-sulfonamide;

10 N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-fluoro-7-(2-
pyrimidyl)-1H-indole-3-sulfonamide;

N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-6-fluoro-7-(2-pyrimidyl)-
1H-indole-3-sulfonamide;

6-fluoro-N-[5-(2-fluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-
1H-indole-3-sulfonamide;

15 N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-fluoro-7-(2-pyrimidyl)-
1H-indole-3-sulfonamide;

N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-1H-
indole-3-sulfonamide;

20 N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-6-fluoro-7-pyrazin-2-yl-
1H-indole-3-sulfonamide;

6-fluoro-N-[5-(2-fluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-
1H-indole-3-sulfonamide;

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N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-fluoro-7-pyrazin-2-yl-1H-indole-3-sulfonamide;

N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-fluoro-7-pyrazin-2-yl-1H-indole-3-sulfonamide;

5 6-bromo-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;

6-bromo-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;

10 6-bromo-N-[5-(2-fluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;

6-bromo-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;

6-bromo-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-1H-indole-3-sulfonamide;

15 6-bromo-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-1H-indole-3-sulfonamide;

6-bromo-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-1H-indole-3-sulfonamide;

20 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(5-fluoropyrazin-2-yl)-1H-indole-3-sulfonamide;

6-bromo-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyridazin-3-yl-1H-indole-3-sulfonamide;

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6-(difluoromethyl)-N-[5-(2-fluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;

N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-fluoro-7-(1H-imidazol-2-yl)-1H-indole-3-sulfonamide; and

5 pharmaceutically acceptable salts thereof.

Further particular examples of compounds of formula I as described herein are selected from

- 10 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1,5-dimethylimidazol-4-yl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylimidazol-4-yl)-1H-indole-3-sulfonamide;
- N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-methyl-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;
- 15 N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-(difluoromethyl)-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;
- N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-(difluoromethyl)-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;
- 20 N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-6-(difluoromethyl)-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;
- N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-6-methyl-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;
- N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-methylpyrazin-2-yl)-1H-indole-3-sulfonamide;
- 25 N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-methylpyrazin-2-yl)-1H-indole-3-sulfonamide;
- N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-methyl-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;

- N-[5-(2-fluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-methyl-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;
- N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-methyl-7-pyridazin-3-yl-1H-indole-3-sulfonamide;
- 5 N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-methyl-7-pyrazin-2-yl-1H-indole-3-sulfonamide;
- N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-methyl-7-pyrazin-2-yl-1H-indole-3-sulfonamide;
- 10 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-5-fluoro-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylpyrazol-3-yl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-methylpyrimidin-4-yl)-1H-indole-3-sulfonamide;
- 15 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methylpyridazin-3-yl)-1H-indole-3-sulfonamide;
- 6-chloro-7-(3-chloropyrazin-2-yl)-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-1H-indole-3-sulfonamide;
- 20 6-chloro-7-(3-chloropyrazin-2-yl)-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-1H-indole-3-sulfonamide;
- 6-chloro-7-(3-chloropyrazin-2-yl)-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylpyrazol-3-yl)-1H-indole-3-sulfonamide;
- 25 6-chloro-N-[5-(2-fluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylpyrazol-3-yl)-1H-indole-3-sulfonamide;
- 6-bromo-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylpyrazol-4-yl)-1H-indole-3-sulfonamide;

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- 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-phenyl-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-phenyl-1H-indole-3-sulfonamide;
- 5 N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-methylpyrazin-2-yl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-methylpyrazin-2-yl)-1H-indole-3-sulfonamide;
- 10 N-(5-bromo-4,6-dimethoxy-pyrimidin-2-yl)-6-chloro-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(4-pyrimidyl)-1H-indole-3-sulfonamide;
- 15 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(4-pyrimidyl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(cyanomethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2-cyanoethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;
- 20 6-chloro-N-[5-(2-fluoroethoxy)-4-methoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-methylpyrazin-2-yl)-1H-indole-3-sulfonamide;
- 25 6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(5-methylpyrazin-2-yl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(5-methylpyrazin-2-yl)-1H-indole-3-sulfonamide;

- 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(5-methylpyrazin-2-yl)-1H-indole-3-sulfonamide;
- 6-chloro-N-(4,6-dimethoxy-5-methyl-pyrimidin-2-yl)-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;
- 5 6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methylpyrazin-2-yl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methylpyrazin-2-yl)-1H-indole-3-sulfonamide;
- 10 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methylpyrazin-2-yl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(5-pyrimidyl)-1H-indole-3-sulfonamide;
- 6-chloro-7-(5-chloropyrazin-2-yl)-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-1H-indole-3-sulfonamide;
- 15 6-chloro-7-(5-chloropyrazin-2-yl)-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methyl-2-pyridyl)-1H-indole-3-sulfonamide;
- 20 6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methyl-2-pyridyl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methyl-2-pyridyl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyridazin-4-yl-1H-indole-3-sulfonamide;
- 25 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methylpyrimidin-4-yl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-fluoropyrazin-2-yl)-1H-indole-3-sulfonamide;

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- 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-fluoropyrazin-2-yl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-fluoropyrazin-2-yl)-1H-indole-3-sulfonamide;
- 5 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-methyl-2-pyridyl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methyltriazol-4-yl)-1H-indole-3-sulfonamide;
- 10 6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-methyl-2-pyridyl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-methyl-2-pyridyl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methyl-1,2,4-triazol-3-yl)-1H-indole-3-sulfonamide;
- 15 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(5-fluoropyrimidin-2-yl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-methyltriazol-4-yl)-1H-indole-3-sulfonamide;
- 20 6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-methyltriazol-4-yl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-methyltriazol-4-yl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2-fluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-methyltriazol-4-yl)-1H-indole-3-sulfonamide;
- 25 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1,3,4-oxadiazol-2-yl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylpyrazol-4-yl)-1H-indole-3-sulfonamide;

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- 6-chloro-N-[5-(2-fluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylpyrazol-4-yl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylpyrazol-4-yl)-1H-indole-3-sulfonamide;
- 5 6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylpyrazol-4-yl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-thiazol-4-yl-1H-indole-3-sulfonamide;
- 10 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-oxazol-5-yl-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-oxazol-5-yl-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-isoxazol-4-yl-1H-indole-3-sulfonamide;
- 15 6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-isoxazol-4-yl-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-thiazol-4-yl-1H-indole-3-sulfonamide;
- 20 N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6,7-dihydro-5H-pyrrol[1,2-c]imidazol-3-yl)-1H-indole-3-sulfonamide; and
- pharmaceutically acceptable salts thereof.

Preferred examples of compounds of formula I as described herein are selected from

- 25 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;

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6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyridazin-3-yl-1H-indole-3-sulfonamide;

N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylimidazol-2-yl)-1H-indole-3-sulfonamide;

5 6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyridazin-3-yl-1H-indole-3-sulfonamide;

N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylimidazol-2-yl)-1H-indole-3-sulfonamide;

10 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylimidazol-2-yl)-1H-indole-3-sulfonamide;

N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-6-fluoro-7-(1-methylimidazol-2-yl)-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-oxazol-4-yl-1H-indole-3-sulfonamide;

15 6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-1H-indole-3-sulfonamide;

20 6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyridyl)-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyridyl)-1H-indole-3-sulfonamide;

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6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-
1H-indole-3-sulfonamide;

6-chloro-N-[5-(2-fluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-
1H-indole-3-sulfonamide;

5 6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-
pyrimidyl)-1H-indole-3-sulfonamide;

6-bromo-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-
pyrimidyl)-1H-indole-3-sulfonamide;

10 6-bromo-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-
pyrimidyl)-1H-indole-3-sulfonamide;

6-bromo-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-
1H-indole-3-sulfonamide;

6-bromo-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-
1H-indole-3-sulfonamide;

15 6-bromo-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-
yl-1H-indole-3-sulfonamide; and

pharmaceutically acceptable salts thereof.

Further preferred examples of compounds of formula I as described herein are selected
20 from

6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1,5-
dimethylimidazol-4-yl)-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-
methylimidazol-4-yl)-1H-indole-3-sulfonamide;

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N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-6-methyl-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;

N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-methylpyrazin-2-yl)-1H-indole-3-sulfonamide;

5 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylpyrazol-3-yl)-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-methylpyrimidin-4-yl)-1H-indole-3-sulfonamide;

10 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methylpyridazin-3-yl)-1H-indole-3-sulfonamide;

6-chloro-7-(3-chloropyrazin-2-yl)-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-1H-indole-3-sulfonamide;

6-chloro-7-(3-chloropyrazin-2-yl)-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-1H-indole-3-sulfonamide;

15 6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylpyrazol-3-yl)-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2-fluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylpyrazol-3-yl)-1H-indole-3-sulfonamide;

20 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-methylpyrazin-2-yl)-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-methylpyrazin-2-yl)-1H-indole-3-sulfonamide;

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6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(4-pyrimidyl)-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(4-pyrimidyl)-1H-indole-3-sulfonamide;

5 6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-methylpyrazin-2-yl)-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(5-methylpyrazin-2-yl)-1H-indole-3-sulfonamide;

10 6-chloro-N-(4,6-dimethoxy-5-methyl-pyrimidin-2-yl)-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methylpyrazin-2-yl)-1H-indole-3-sulfonamide;

6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methylpyrazin-2-yl)-1H-indole-3-sulfonamide;

15 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methylpyrazin-2-yl)-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(5-pyrimidyl)-1H-indole-3-sulfonamide;

20 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methyl-2-pyridyl)-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methyl-2-pyridyl)-1H-indole-3-sulfonamide;

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6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methyl-2-pyridyl)-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyridazin-4-yl-1H-indole-3-sulfonamide;

5 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methylpyrimidin-4-yl)-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-fluoropyrazin-2-yl)-1H-indole-3-sulfonamide;

10 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-fluoropyrazin-2-yl)-1H-indole-3-sulfonamide;

6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-fluoropyrazin-2-yl)-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-methyl-2-pyridyl)-1H-indole-3-sulfonamide;

15 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methyltriazol-4-yl)-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-methyl-2-pyridyl)-1H-indole-3-sulfonamide;

20 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-methyltriazol-4-yl)-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-methyltriazol-4-yl)-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2-fluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-methyltriazol-4-yl)-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1,3,4-oxadiazol-2-yl)-1H-indole-3-sulfonamide;

5 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-thiazol-4-yl-1H-indole-3-sulfonamide;

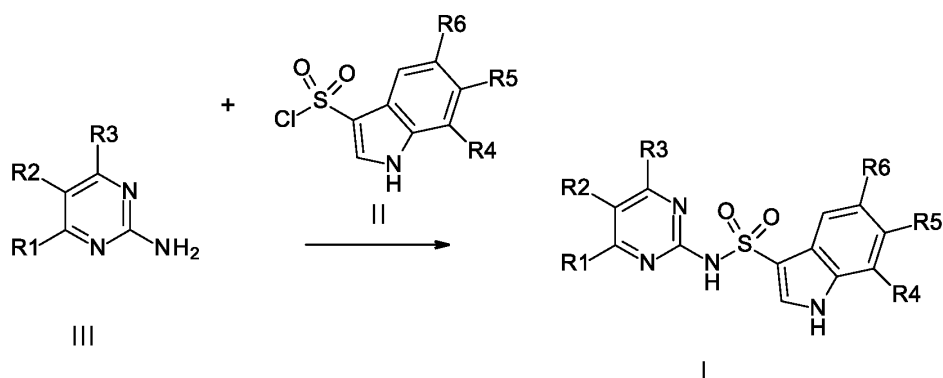
N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6,7-dihydro-5H-pyrrol[1,2-c]imidazol-3-yl)-1H-indole-3-sulfonamide;

and pharmaceutically acceptable salts thereof.

10

Processes for the manufacture of compounds of formula I as described herein are an object of the invention.

The present compounds of formula I and their pharmaceutically acceptable salts can be prepared by methods known in the art, for example, by processes described below, which process comprises reacting a compound of formula III with a compound of formula II in the presence of a base selected from N-ethyl-diisopropylamine, pyridine, potassium phosphate or sodium hydride, to provide a compound of formula I,



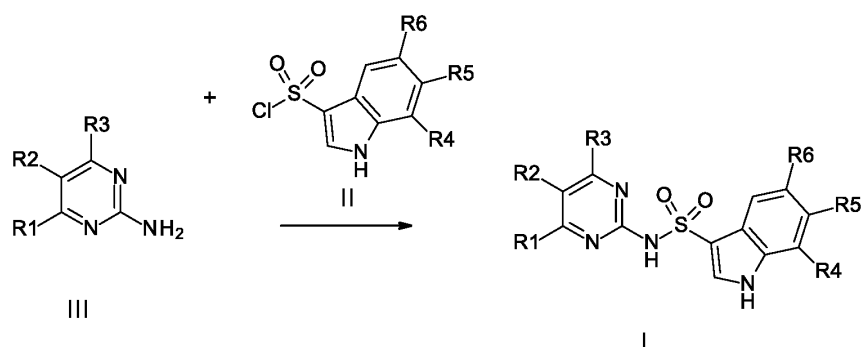
20 wherein $R^1, R^2, R^3, R^3, R^4, R^5$ and R^6 are as described above.

General Synthetic Schemes

The compounds of formula I may be prepared in accordance with the process variant described above and with the following scheme 1. The starting materials are commercially available or

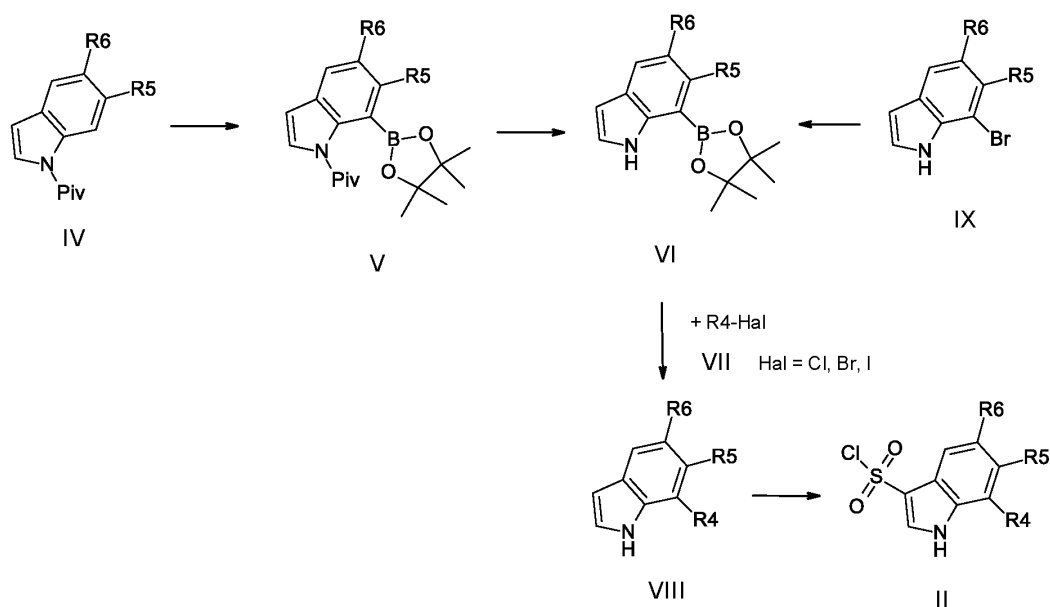
5 may be prepared in accordance with known methods.

Scheme 1



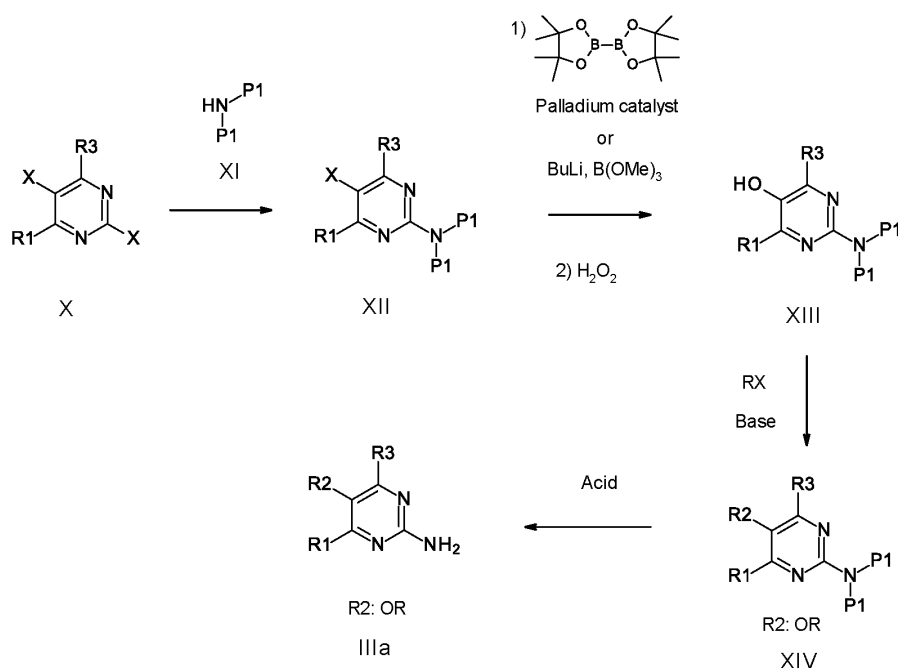
Compounds of general formula I can be prepared by reacting sulfonylchloride II with amines III
 10 in the presence of a base like N-ethyl-diisopropylamine, pyridine, potassium phosphate or sodium hydride. The starting materials are commercially available or may be prepared in accordance with known methods or methods described in the following schemes.

Scheme 2



Intermediate of formula II can be prepared by a reaction sequence as described in Scheme 2. Pivaloyl-protected indole IV can be reacted with boron tribromide followed by treatment with pinacol to form compound V, which is then deprotected by treatment with a base like trimethylamine to form intermediate VI. Alternatively, this intermediate can be obtained by
 5 reaction of bromoindole derivative IX with bis(pinacolato)diboron using palladium catalysis. Intermediate VI can then be reacted with heterocyclic compound VII to obtain compound VIII using a suitable palladium catalyst and a base. Reaction of the resulting compound VIII with a) a chlorosulfonylating agent like chlorosulfonic acid, or b) a sulfonylating agent like sulfuric acid or sulfur trioxide N,N-dimethylformamide complex, followed by chlorination of the intermediate
 10 sulfonic acid with a chlorinating agent like thionylchloride provides compound II.

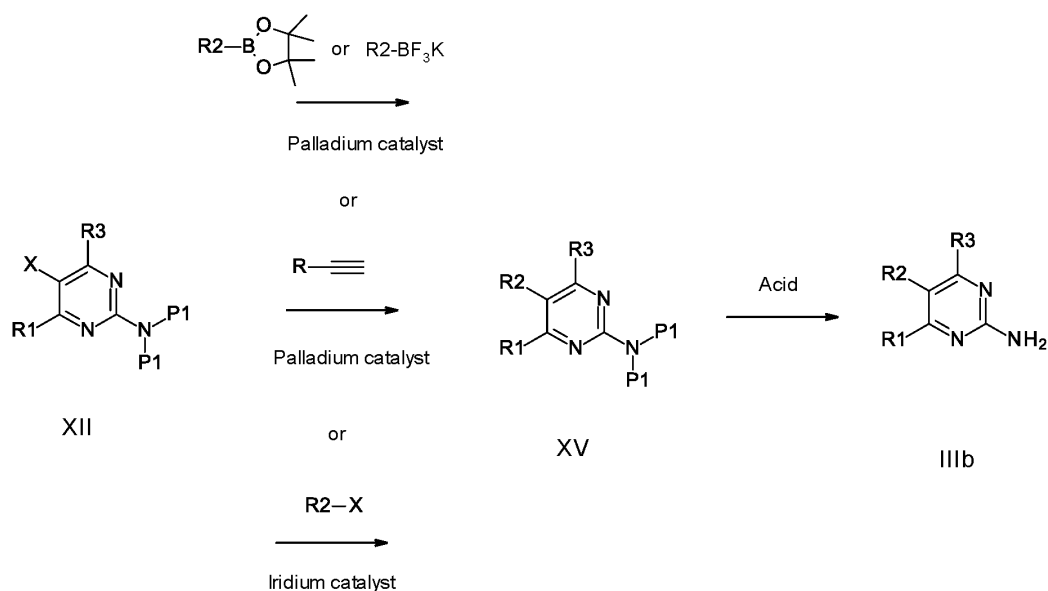
Scheme 3



2-Amino-pyrimidine of formula IIIa wherein R² is an alkoxy group can be prepared by deprotection of intermediate XIV in the presence of an acid like trifluoro acetic acid wherein P¹ is a protective group like p-methoxy-benzyl, 3,4-dimethoxybenzyl or a Boc group. XIV can be obtained by alkylation of alcohol XIII in the presence of a base like cesium- or potassium-carbonate or sodium- or potassium-hydroxide and an alkylating agent RX. Alcohol XIII can be prepared from dihalogenated starting material X, by reacting XI with a protected amine XI to
 20

provide intermediate XII which is first transformed into a boronic ester that is then oxidized in the presence of an oxidant like hydrogen peroxide.

Scheme 4

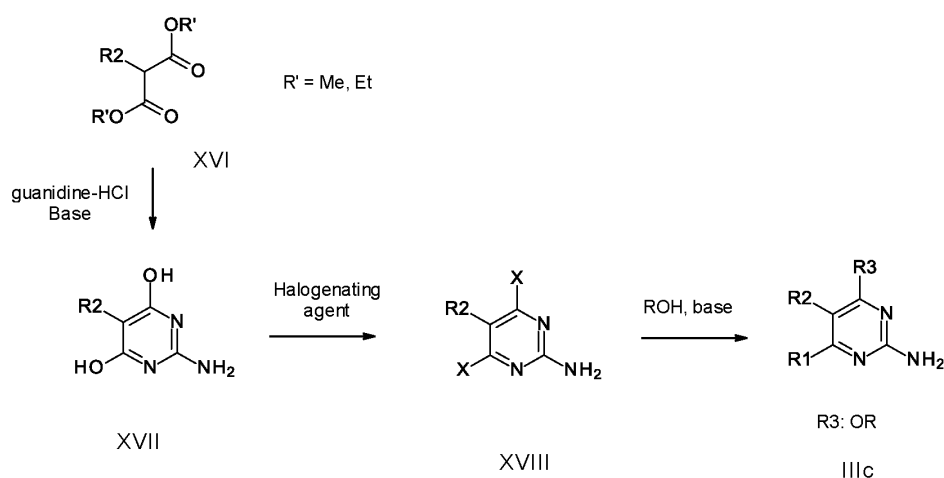


5

2-Amino-pyrimidine of formula IIIb wherein R² is an alkyl, alkenylalkyl, alkynyl, cyanoalkyl, cycloalkyl, heterocycloalkyl can be prepared by deprotection of intermediate XV in the presence of an acid like trifluoro acetic acid wherein P1 is a protective group like p-methoxy-benzyl or a Boc group. Compound XV can be obtained from intermediate XII under well known metal-catalyzed cross coupling reactions conditions.

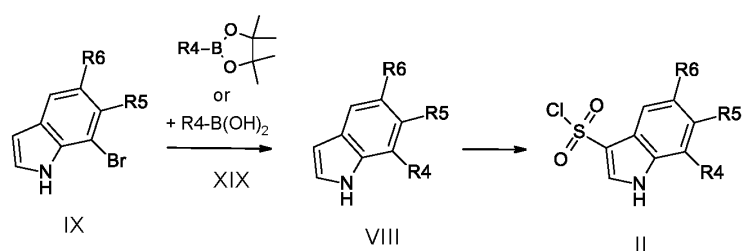
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Scheme 5



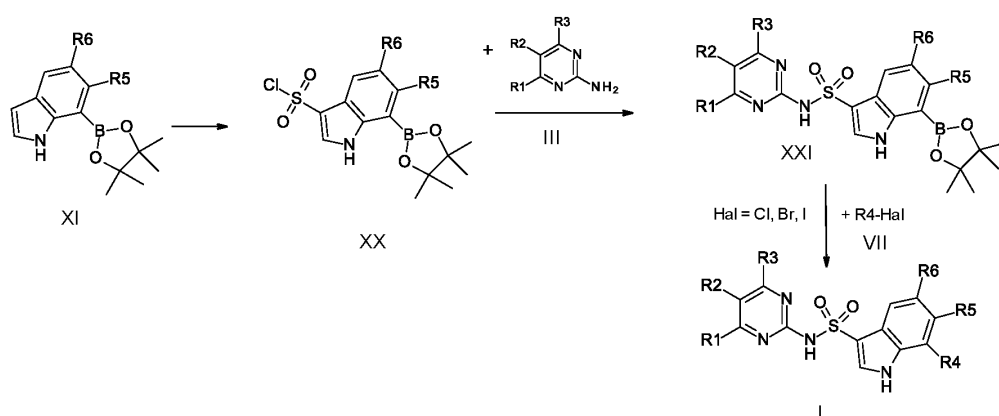
- 2-Amino-pyrimidine of formula IIIc wherein R1 and R3 is an alkoxy group can be prepared by reaction of halogenated starting material XVIII in the presence of an alcohol and a base like sodium hydride. Compound XVII can be prepared from malonester XVI by its reaction with guanidine-hydrochloride salt in the presence of a base like sodium methoxide to provide
- 5 intermediate XVII which is then reacted with a halogenating agent like phosphorus oxychloride to give halogenated starting material XVIII.

Scheme 6



- 10 Furthermore, intermediates of formula II can be prepared by a reaction sequence as described in Scheme 6. Bromoindole IX can be reacted with boronic acid derivative XIX to obtain compound VIII using a suitable palladium catalyst and a base. Reaction of the resulting compound VIII with
- a) a chlorosulfonylating agent like chlorosulfonic acid, or b) a sulfonylating agent like sulfuric acid or sulfur trioxide N,N-dimethylformamide complex, followed by chlorination of the
- 15 intermediate sulfonic acid with a chlorinating agent like thionylchloride provides compound II.

Scheme 7



Furthermore, compounds of formula I can be prepared by a reaction sequence as described in Scheme 7. Intermediate XI can first be reacted with a chlorosulfonylating agent like

chlorosulfonic acid to provide compound XX which is then coupled with amine III in presence of a suitable base to give compound XXI. Reaction of this intermediate with heteroaryl halide VII using a palladium catalyst and a base provides compounds of formula I.

5 Another embodiment of the invention provides a pharmaceutical composition or medicament containing a compound of the invention and a therapeutically inert carrier, diluent or excipient, as well as a method of using the compounds of the invention to prepare such composition and medicament. In one example, the compound of formula I may be formulated by mixing at ambient temperature at the appropriate pH, and at the desired degree of purity, with
10 physiologically acceptable carriers, i.e., carriers that are non-toxic to recipients at the dosages and concentrations employed into a galenical administration form. The pH of the formulation depends mainly on the particular use and the concentration of compound, but preferably ranges anywhere from about 3 to about 8. In one example, a compound of formula I is formulated in an acetate buffer, at pH 5. In another embodiment, the compound of formula I is sterile. The
15 compound may be stored, for example, as a solid or amorphous composition, as a lyophilized formulation or as an aqueous solution.

 Compositions are formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the
20 cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners.

 The compounds of the invention may be administered by any suitable means, including oral, topical (including buccal and sublingual), rectal, vaginal, transdermal, parenteral, subcutaneous, intraperitoneal, intrapulmonary, intradermal, intrathecal and epidural and
25 intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration.

 The compounds of the present invention may be administered in any convenient administrative form, e.g., tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches, etc. Such compositions may contain components
30 conventional in pharmaceutical preparations, e.g., diluents, carriers, pH modifiers, sweeteners, bulking agents, and further active agents.

A typical formulation is prepared by mixing a compound of the present invention and a carrier or excipient. Suitable carriers and excipients are well known to those skilled in the art and are described in detail in, e.g., Ansel, Howard C., et al., *Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems*. Philadelphia: Lippincott, Williams & Wilkins, 2004; Gennaro, Alfonso R., et al. *Remington: The Science and Practice of Pharmacy*. Philadelphia: Lippincott, Williams & Wilkins, 2000; and Rowe, Raymond C. *Handbook of Pharmaceutical Excipients*. Chicago, Pharmaceutical Press, 2005. The formulations may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents, diluents and other known additives to provide an elegant presentation of the drug (i.e., a compound of the present invention or pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (i.e., medicament).

The compounds of formula I and their pharmaceutically acceptable salts can be processed with pharmaceutically inert, inorganic or organic adjuvants for the production of tablets, coated tablets, dragées, hard gelatin capsules, injection solutions or topical formulations. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc. can be used, for example, as such adjuvants for tablets, dragées and hard gelatin capsules.

Suitable adjuvants for soft gelatin capsules, are, for example, vegetable oils, waxes, fats, semi-solid substances and liquid polyols, etc.

Suitable adjuvants for the production of solutions and syrups are, for example, water, polyols, saccharose, invert sugar, glucose, etc.

Suitable adjuvants for injection solutions are, for example, water, alcohols, polyols, glycerol, vegetable oils, etc.

Suitable adjuvants for suppositories are, for example, natural or hardened oils, waxes, fats, semi-solid or liquid polyols, etc.

Suitable adjuvants for topical ocular formulations are, for example, cyclodextrins, mannitol or many other carriers and excipients known in the art.

Moreover, the pharmaceutical preparations can contain preservatives, solubilizers, viscosity-increasing substances, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

5 The dosage can vary in wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of oral administration a daily dosage of about 0.1 mg to 20 mg per kg body weight, preferably about 0.5 mg to 4 mg per kg body weight (e.g. about 300 mg per person), divided into preferably 1-3 individual doses, which can consist, for example, of the same amounts, should it be appropriate. In the case of topical
10 administration, the formulation can contain 0.001% to 15% by weight of medicament and the required dose, which can be between 0.1 and 25 mg in can be administered either by single dose per day or per week, or by multiple doses (2 to 4) per day, or by multiple doses per week It will, however, be clear that the upper or lower limit given herein can be exceeded when this is shown to be indicated.

15 The invention also relates in particular to:

A compound of formula I for use as therapeutically active substance;

A compound of formula I for use in the treatment of a disease modulated by GPR17;

Likewise an object of the present invention is a pharmaceutical composition comprising a compound according to formula I as described herein and a therapeutically inert carrier.

20 The use of a compound of formula I for the treatment or prophylaxis of conditions resulting from direct damage to myelin sheaths (including but not limited central pontine and extra-pontine myelinolysis, carbon monoxide poisoning, nutritional deficiency, and virus-induced demyelination), demyelinating disorders (including but not limited to multiple sclerosis, acute and multiphasic disseminated encephalomyelitis, neuromyelitis optica spectrum disorders,
25 and leukodystrophies), CNS disorders associated with myelin loss (including but not limited to Alzheimer's disease, schizophrenia, Parkinson's disease, Huntington's disease, Amyotrophic lateral sclerosis, and Ischemia due to stroke), and Inflammation in the CNS for instance following encephalitis, primary angiitis, meningitis and obesity.

An embodiment of the present invention is the use of a compound of formula I for the treatment or prophylaxis of multiple sclerosis, Alzheimer's disease, Parkinson's disease, or Huntington's disease.

5 A particular embodiment of the invention is the use of a compound of formula I for the treatment or prophylaxis of multiple sclerosis.

10 The use of a compound of formula I for the preparation of a medicament for the treatment or prophylaxis of conditions resulting from direct damage to myelin sheaths (including but not limited central pontine and extra-pontine myelinolysis, carbon monoxide poisoning, nutritional deficiency, and virus-induced demyelination), demyelinating disorders (including but not limited to multiple sclerosis, acute and multiphasic disseminated encephalomyelitis, neuromyelitis optica spectrum disorders, and leukodystrophies), CNS disorders associated with myelin loss (including but not limited to Alzheimer's disease, schizophrenia, Parkinson's disease, Huntington's disease, Amyotrophic lateral sclerosis, and Ischemia due to stroke), and Inflammation in the CNS for instance following encephalitis, primary angiitis, meningitis and obesity.

15 An embodiment of the present invention is the use of a compound of formula I for the preparation of a medicament for the treatment or prophylaxis of multiple sclerosis, Alzheimer's disease, Parkinson's disease, or Huntington's disease.

A particular embodiment of the invention is the use of a compound of formula I for the preparation of a medicament for the treatment or prophylaxis of multiple sclerosis.

20 A compound according to formula I for use in the treatment or prophylaxis of conditions resulting from direct damage to myelin sheaths (including but not limited central pontine and extra-pontine myelinolysis, carbon monoxide poisoning, nutritional deficiency, and virus-induced demyelination), demyelinating disorders (including but not limited to multiple sclerosis, acute and multiphasic disseminated encephalomyelitis, neuromyelitis optica spectrum disorders, and leukodystrophies), CNS disorders associated with myelin loss (including but not limited to Alzheimer's disease, schizophrenia, Parkinson's disease, Huntington's disease, Amyotrophic lateral sclerosis, and Ischemia due to stroke), and Inflammation in the CNS for instance following encephalitis, primary angiitis, meningitis and obesity.

25

An embodiment of the present invention is a compound of formula I for use in the treatment or prophylaxis of multiple sclerosis, Alzheimer's disease, Parkinson's disease, or Huntington's disease.

5 A particular embodiment of the invention is a compound according to formula I for use in the treatment or prophylaxis of multiple sclerosis.

10 A method for the treatment or prophylaxis of conditions resulting from direct damage to myelin sheaths (including but not limited to central pontine and extra-pontine myelinolysis, carbon monoxide poisoning, nutritional deficiency, and virus-induced demyelination), demyelinating disorders (including but not limited to multiple sclerosis, acute and multiphasic disseminated encephalomyelitis, neuromyelitis optica spectrum disorders, and leukodystrophies), CNS disorders associated with myelin loss (including but not limited to Alzheimer's disease, schizophrenia, Parkinson's disease, Huntington's disease, Amyotrophic lateral sclerosis, and Ischemia due to stroke), and Inflammation in the CNS for instance following encephalitis, primary angiitis, meningitis and obesity, which method comprises administering an effective
15 amount of a compound of formula I to a patient in need thereof.

An embodiment of the present invention is a method for the treatment or prophylaxis of multiple sclerosis, Alzheimer's disease, Parkinson's disease, or Huntington's disease, which method comprises administering an effective amount of a compound of formula I to a patient in need thereof.

20 A particular embodiment of the invention is a method for the treatment or prophylaxis of multiple sclerosis, which method comprises administering an effective amount of a compound of formula I to a patient in need thereof.

Also an embodiment of the present invention provides compounds of formula I as described herein, when manufactured according to any one of the described processes.

25

30

Assay Procedures**GPR17 cAMP Assay Protocol:**

CHO-K1 cells stably expressing vector containing untagged human GPR17 short isoform (Roche) were cultured at 37°C / 5% CO₂ in DMEM (Dulbecco's Modified Eagle Medium):F-12 (1:1) supplemented with 10% foetal bovine serum and 400 µg/ml Geneticin.

Changes in intracellular cyclic adenosine monophosphate (cAMP) levels were quantified using the Nano-TRF Detection Assay kit (Roche Diagnostics, Cat. No. 05214386001). This assay allows for direct cAMP quantification in a homogeneous solution. cAMP is detected based on time-resolved fluorescence energy transfer (TR-FRET) and competitive binding of ruthenylated cAMP and endogenous cAMP to an anti-cAMP monoclonal antibody labeled with AlexaFluor-700. The Ruthenium complex serves as the FRET donor and transfers energy to AlexaFluor-700. The FRET signal is inversely proportional to the cAMP concentration.

CHO-GPR17S cells were detached with Accutase and resuspended in assay buffer consisting of Hank's Balanced Salt Solution (HBSS), 10mM HEPES (4-(2-hydroxyethyl) piperazine-1-ethanesulfonic acid solution) and 0.1% bovine serum albumin (pH 7.4). The cells were seeded in black 384-well plates (Corning) at a density of 10'000 cells / 20µl assay buffer until the addition of compounds.

Test antagonist compounds were serially diluted in dimethyl sulfoxide (DMSO) and spotted in 384-well plates. The compounds were then diluted in HBSS buffer supplemented with an EC₈₀ concentration of MDL29,951 (3-(2-Carboxy-4,6-dichloroindol-3-yl)propionic acid) (GPR17 agonist) plus 3-Isobutyl-1-methylxanthine (IBMX) (0.5mM final concentration) and added to the cells at room temperature. Forskolin (15µM final concentration) was added 5 minutes after the test compounds and the cells were incubated at room temperature for 30 minutes. The assay was stopped by adding cAMP detection mix (containing detergents for cell lysis) for 90 minutes at room temperature.

Cellular cAMP was measured using a Paradigm reader (Molecular Devices). The raw data was used to calculate the FRET signal based on the assay's P-factor as per cAMP kit instructions. The data was normalized to the maximal activity of a reference antagonist and dose response curves were fitted to the percent activity of the test compounds using a sigmoidal dose response model (Genedata Screener).

Results in the hGPR17 cAMP assay are provided for compounds of formula I in Table 1

Table 1:

Example number	hGPR17 cAMP IC50 [μ M]	Example number	hGPR17 cAMP IC50 [μ M]
1	0.048	27	0.120
2	0.098	28	0.307
3	0.046	29	0.604
4	0.044	30	0.130
5	0.026	31	0.084
6	0.042	32	0.129
7	0.034	33	0.132
8	0.039	34	0.407
9	0.069	35	0.034
10	0.030	36	0.042
11	0.050	37	0.067
12	0.085	38	0.054
13	0.057	39	0.017
14	0.032	40	0.009
15	0.027	41	0.015
16	0.025	42	0.038
17	0.806	43	0.032
18	0.019	44	0.182
19	0.018	45	0.050
20	0.032	46	0.034
21	0.040	47	0.017
22	0.080	48	0.086
23	0.050	49	0.301
24	0.061	50	0.288
25	0.056	51	0.074
26	0.218	52	0.022

Example number	hGPR17 cAMP IC ₅₀ [μ M]
53	0.043
54	0.064
55	0.157
56	0.129
57	0.109
58	0.051
59	0.068
60	0.121
61	0.023
62	0.037
63	0.045
64	0.035
65	0.039
66	0.055
67	0.024
68	0.018
69	0.056
70	0.102
71	0.099
72	1.416
73	0.037
74	0.019
75	0.135
76	0.021
77	0.024
78	0.122
79	0.059
80	0.260
81	0.031
82	0.047

Example number	hGPR17 cAMP IC ₅₀ [μ M]
83	0.097
84	0.052
85	0.044
86	0.029
87	0.031
88	0.027
89	0.042
90	0.261
91	0.225
92	0.028
93	0.024
94	0.020
95	0.046
96	0.032
97	0.034
98	0.035
99	0.038
100	0.040
101	0.043
102	0.042
103	0.054
104	0.113
105	0.221
106	0.034
107	0.076
108	0.032
109	0.036
110	0.046
111	0.053
112	0.052

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Example number	hGPR17 cAMP IC50 [μ M]
113	0.082
114	0.055
115	0.040
116	0.059
117	0.106

Example number	hGPR17 cAMP IC50 [μ M]
118	0.063
119	0.129
120	0.149
121	0.046

The invention will now be illustrated by the following examples which have no limiting character.

- 5 In case the preparative examples are obtained as a mixture of enantiomers, the pure enantiomers can be obtained by methods described herein or by methods known to those skilled in the art, such as e.g. chiral chromatography or crystallization.

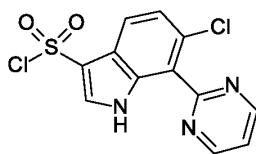
10 Examples

All examples and intermediates were prepared under nitrogen atmosphere if not specified otherwise.

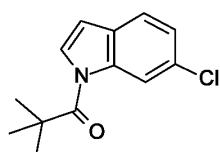
Intermediates A

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Intermediate A1: 6-chloro-7-pyrimidin-2-yl-1H-indole-3-sulfonyl chloride



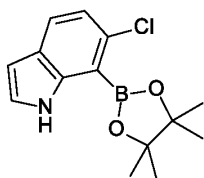
Step 1: 1-(6-chloroindol-1-yl)-2,2-dimethyl-propan-1-one



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6-Chloro-1H-indole (3.0 g, 19.8 mmol), triethylamine (3.0 g, 4.15 ml, 30 mmol) and 4-dimethylaminopyridine (242 mg, 1.98 mmol) was dissolved in dichloromethane (60 ml). Under argon, pivaloyl chloride (2.86 g, 2.9 ml, 23.8 mmol) was added at 0°C within 7 min. The solution was stirred for about 10 min and was then allowed to warm to room temperature. After 2.5 h the suspension was poured into water and extracted twice with dichloromethane. The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 5% ethyl acetate in heptane) to give 1-(6-chloroindol-1-yl)-2,2-dimethyl-propan-1-one (4.26 g, 91% yield) as a white solid. MS (ESI) m/z: 236.2 [M+H]⁺

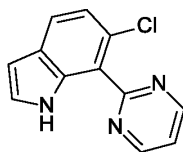
Step 2: 6-chloro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole



To a solution of 1-(6-chloroindol-1-yl)-2,2-dimethyl-propan-1-one (5.0 g, 20.2 mmol) in dichloromethane (55 ml), under argon, was added boron tribromide solution in dichloromethane (1 M, 58.7 g, 22.2 ml, 22.2 mmol) dropwise within 20 min at room temperature. The resulting suspension was stirred at room temperature for 1 h. After cooling to 0°C a solution of pinacol (4.76 g, 40.3 mmol) and pyridine (16 g, 16.3 ml, 202 mmol) in dichloromethane (25 ml) was added within 15 min. The yellow solution was allowed to warm to room temperature, then heated to 40°C for 2 h and stirred again at room temperature overnight. The mixture was concentrated in vacuo, then methanol (70 ml) and triethylamine (10.2 g, 14 ml, 100.8 mmol) were added. The orange solution was stirred at 60°C for 7 h to remove the pivaloyl group. The mixture was concentrated in vacuo, tetrahydrofuran (70 ml), pinacol (2.38 g, 20.15 mmol) and magnesium sulfate (3 spatula) were added and the suspension was stirred at room temperature overnight. Then the mixture was distributed between water and ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 5% ethyl acetate in heptane) to give 6-chloro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (1.42 g, 25% yield) as a white solid. MS (ESI) m/z: 278.2 [M+H]⁺

Step 3: 6-chloro-7-pyrimidin-2-yl-1H-indole

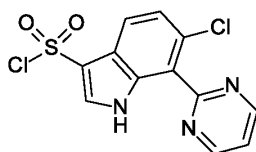
-44-



A mixture of 6-chloro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (500 mg, 1.64 mmol), cesium carbonate (1.08 g, 3.28 mmol), tetrakis(triphenylphosphine)palladium(0) (189 mg, 164 μ mol) and 2-bromopyrimidine (313 mg, 1.97 mmol) in 1,4-dioxane (10 ml) and water (2 ml) was heated in a microwave to 100°C for 30 min. The reaction mixture was poured into water and extracted twice with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 0% to 60% ethyl acetate in heptane) to provide 6-chloro-7-(2-pyrimidinyl)-1H-indole (375 mg, 99% yield) as light yellow solid. MS (ESI) m/z : 230.1 $[M+H]^+$

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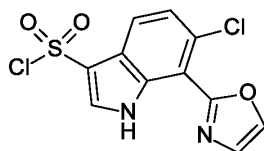
Step 4: 6-chloro-7-pyrimidin-2-yl-1H-indole-3-sulfonyl chloride



A solution of 6-chloro-7-(2-pyrimidinyl)-1H-indole (374 mg, 1.63 mmol) in acetonitrile (10 ml) was cooled to 0 °C. Chlorosulfonic acid (493 mg, 284 μ l, 4.23 mmol) was added and the reaction mixture was stirred at 0 °C for 30 min. Then phosphorus oxychloride (1.25 g, 759 μ l, 8.14 mmol) was added and the reaction mixture was stirred at 70°C for 16 h. The mixture was poured into ice/ethyl acetate and extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo. The residue was triturated with ethyl acetate, filtered through sintered glass and dried in vacuo to provide the title compound (321 mg, 60% yield) as white solid. MS (ESI) m/z : 328.0 $[M+H]^+$

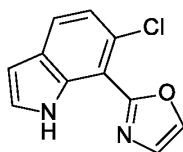
20

Intermediate A2: 6-chloro-7-oxazol-2-yl-1H-indole-3-sulfonyl chloride



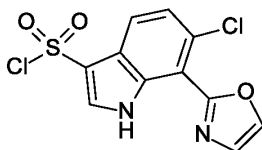
25 Step 1: 2-(6-chloro-1H-indol-7-yl)oxazole

-45-



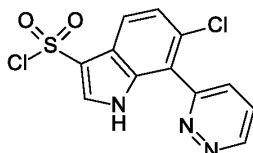
A mixture of 6-chloro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (see Intermediate A1, 100 mg, 353 μmol), potassium carbonate (99 mg, 706 μmol), 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium(II) (27 mg, 35 μmol , 0.100 eq) and 2-bromooxazole (82.5 mg, 530 μmol) in 1,4-dioxane (1.6 ml) and water (0.4 ml) was heated in a microwave at 110 °C for 30 min. The reaction mixture was poured into water and extracted with ethyl acetate twice. The organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (silica gel (0% to 10% ethyl acetate) to provide 2-(6-chloro-1H-indol-7-yl)oxazole (47 mg, 61% yield) as white solid. MS (ESI) m/z: 219.1 $[\text{M}+\text{H}]^+$

Step 2: 6-chloro-7-pyrimidin-2-yl-1H-indole-3-sulfonyl chloride



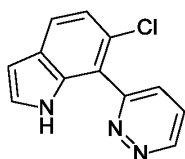
A solution of 2-(6-chloro-1H-indol-7-yl)oxazole (52 mg, 209 μmol) in acetonitrile (1.5 ml) was cooled to 0 °C. Chlorosulfonic acid (63 mg, 36 μl , 544 μmol) was added and the reaction mixture was stirred at 0 °C for 1 h at room temperature. Then phosphoryl chloride (160 mg, 98 μl , 1.05 mmol) was added. The reaction mixture was heated to 70 °C for 16 h. The mixture was poured into ice and ethyl acetate and extracted with ethyl acetate twice. The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo to provide the title compound (61 mg, 92% yield) as off-white solid. MS (ESI) m/z: 316.9 $[\text{M}+\text{H}]^+$

Intermediate A3: 6-chloro-7-pyridazin-3-yl-1H-indole-3-sulfonyl chloride



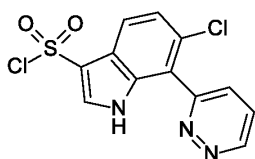
Step 1: 6-chloro-7-pyridazin-3-yl-1H-indole

-46-



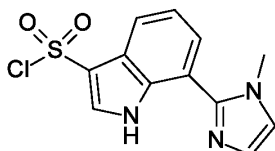
A mixture of 6-chloro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (see, Intermediate A1, 110 mg, 388 μmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) dichloride dichloromethane complex (32 mg, 39 μmol , 0.1 eq), potassium carbonate (217 mg, 1.55 mmol) and 3-chloropyridazine (56 mg, 466 μmol) in 1,4-dioxane (2.2 ml) and water (1.1 ml) was heated in microwave at 90 °C for 30 min. The reaction mixture was poured into water and extracted with ethyl acetate twice. The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 0% to 60% ethyl acetate in heptane) to provide 6-chloro-7-pyridazin-3-yl-1H-indole (69 mg, 73% yield) as light yellow solid. MS (ESI) m/z : 230.0 $[\text{M}+\text{H}]^+$

Step 2: 6-chloro-7-pyrimidin-2-yl-1H-indole-3-sulfonyl chloride



A suspension of 6-chloro-7-pyridazin-3-yl-1H-indole (68 mg, 278 μmol) in acetonitrile (2 ml) was cooled to 0 °C. Chlorosulfonic acid (84 mg, 48 μl , 723 μmol) was added and the reaction mixture was stirred at 0 °C for 1 h, then phosphorus oxychloride (213 mg, 130 μl , 1.39 mmol) was added. The reaction mixture was heated to 70 °C and stirred for 17 h. The mixture was poured into ice and ethyl acetate and extracted with ethyl acetate twice. The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo to provide the title compound (90 mg, 99% yield) as light brown solid. MS (ESI) m/z : 327.9 $[\text{M}+\text{H}]^+$

Intermediate A4: 7-(1-methylimidazol-2-yl)-1H-indole-3-sulfonyl chloride

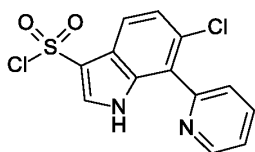


-47-

The title compound was prepared in analogy to Intermediate A1 from 2-iodo-1-methyl-imidazole instead of 2-bromopyrimidine and 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (CAS 642494-37-9) instead of 6-chloro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole in Step 3) as an orange semisolid. MS (ESI) m/z: 296.0 [M+H]⁺

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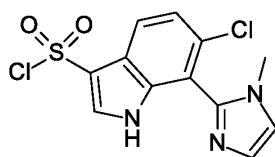
Intermediate A5: 6-chloro-7-(2-pyridyl)-1H-indole-3-sulfonyl chloride



The title compound was prepared in analogy to Intermediate A1 from 2-bromopyridine instead of 2-bromopyrimidine in Step 3) as a off-white solid. MS (ESI) m/z: 325.0 [M-H]⁻

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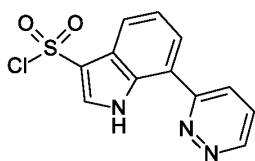
Intermediate A6: 6-chloro-7-(1-methylimidazol-2-yl)-1H-indole-3-sulfonyl chloride



The title compound was prepared in analogy to Intermediate A1 from 2-iodo-1-methyl-imidazole instead of 2-bromopyrimidine in Step 3) as off-white solid. MS (ESI) m/z: 330.0 [M+H]⁺

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Intermediate A7: 7-pyridazin-3-yl-1H-indole-3-sulfonyl chloride

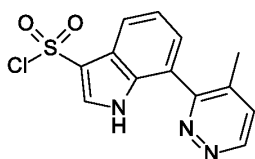


The title compound was prepared in analogy to Intermediate A3 from 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (CAS 642494-37-9) instead of 6-chloro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole as an off-white solid. MS (ESI) m/z: 294.1 [M+H]⁺

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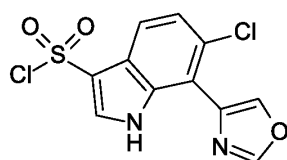
Intermediate A8: 7-(4-methylpyridazin-3-yl)-1H-indole-3-sulfonyl chloride

-48-

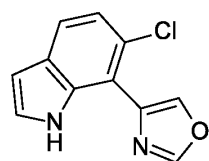


The title compound was prepared in analogy to Intermediate A3 from 3-chloro-4-methyl-pyridazine instead of 3-chloro-pyridazine and 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (CAS 642494-37-9) instead of 6-chloro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole as a light brown solid. MS (ESI) m/z: 308.1 [M+H]⁺

Intermediate A9: 6-chloro-7-oxazol-4-yl-1H-indole-3-sulfonyl chloride



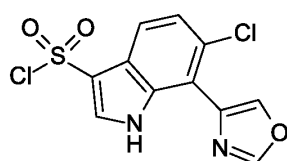
Step 1: 4-(6-chloro-1H-indol-7-yl)oxazole



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A mixture of 6-chloro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (see Intermediate A1, 400 mg, 1.31 mmol), cesium carbonate (1.29 g, 3.93 mmol), XPhos Pd G2 (CAS 1310584-14-5, 103 mg, 131 μmol, 0.10 eq) and 4-bromooxazole (245 mg, 1.57 mmol) in 1,4-dioxane (3 ml) and water (1.5 ml) was heated in a microwave at 90 °C for 30 min. The reaction mixture was poured into brine and extracted with ethyl acetate twice. The organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 0% to 30% ethyl acetate in heptan) to provide 4-(6-chloro-1H-indol-7-yl)oxazole (40 mg, 14%) as light yellow solid. MS (ESI) m/z: 219.0 [M+H]⁺

20 Step 2: 6-chloro-7-oxazol-4-yl-1H-indole-3-sulfonyl chloride

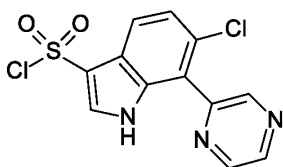


-49-

A solution of 4-(6-chloro-1H-indol-7-yl)oxazole (39 mg, 178 μmol) in acetonitrile (1.5 ml) was cooled to 0 °C. Chlorosulfonic acid (54 mg, 31 μL , 464 μmol) was added. The reaction mixture was stirred at 0 °C for 30 min and at room temperature for 3 days. Then phosphorus oxychloride (137 mg, 83 μL , 892 μmol) was added. The reaction mixture was heated to 70 °C and stirred for 10 h, then it was poured into ice and ethyl acetate and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo to provide the title compound (55 mg, 97% yield) as light brown solid.

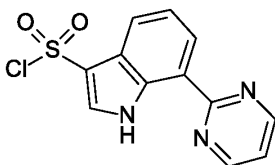
MS (ESI) m/z : 315.0 $[\text{M}-\text{H}]^-$

10 **Intermediate A10:** 6-chloro-7-pyrazin-2-yl-1H-indole-3-sulfonyl chloride



The title compound was prepared in analogy to Intermediate A1 from 2-bromopyrazine instead of 2-bromopyrimidine in Step 3) as light yellow solid. MS (ESI) m/z : 328.0 $[\text{M}+\text{H}]^+$

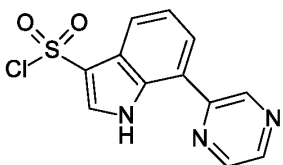
15 **Intermediate A11:** 7-pyrimidin-2-yl-1H-indole-3-sulfonyl chloride



The title compound was prepared in analogy to Intermediate A1 from 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (CAS 642494-37-9) instead of 6-chloro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole in Step 3) as light yellow solid. MS (ESI) m/z :

20 294.0 $[\text{M}+\text{H}]^+$

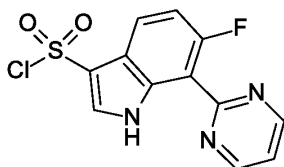
Intermediate A12: 7-pyrazin-2-yl-1H-indole-3-sulfonyl chloride



The title compound was prepared in analogy to Intermediate A1 from 2-bromopyrazine instead of 2-bromopyrimidine and 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (CAS 642494-37-9) instead of 6-chloro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole in Step 3) as yellow solid. MS (ESI) m/z: 294.1 [M+H]⁺

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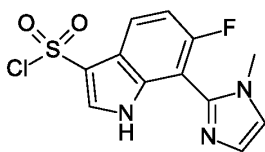
Intermediate A13: 6-fluoro-7-pyrimidin-2-yl-1H-indole-3-sulfonyl chloride



The title compound was prepared in analogy to Intermediate A1 from 6-fluoro-1H-indole instead of 6-chloro-1H-indole as light yellow solid. MS (ESI) m/z: 312.1 [M+H]⁺

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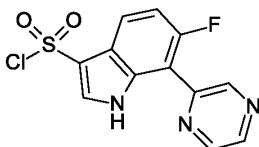
Intermediate A14: 6-fluoro-7-(1-methylimidazol-2-yl)-1H-indole-3-sulfonyl chloride



The title compound was prepared in analogy to Intermediate A1 from 6-fluoro-1H-indole instead of 6-chloro-1H-indole in Step 1) and from 2-iodo-1-methyl-imidazole instead of 2-

15
bromopyrimidine in Step 3) as light brown oil which was directly used in the next step.

Intermediate A15: 6-fluoro-7-pyrazin-2-yl-1H-indole-3-sulfonyl chloride

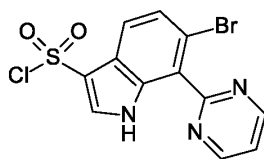


The title compound was prepared in analogy to Intermediate A1 from 6-fluoro-1H-indole instead of 6-chloro-1H-indole in Step 1) and from 2-bromopyrazine instead of 2-bromopyrimidine in Step 3) as yellow solid, MS (ESI) m/z: 312.1 [M+H]⁺

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Intermediate A16: 6-bromo-7-pyrimidin-2-yl-1H-indole-3-sulfonyl chloride

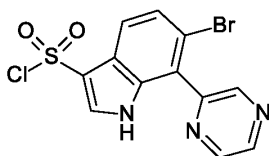
-51-



The title compound was prepared in analogy to Intermediate A1 from 6-bromo-1H-indole instead of 6-chloro-1H-indole in Step 1) as yellow solid, MS (ESI) m/z: 374.0 [M+H]⁺

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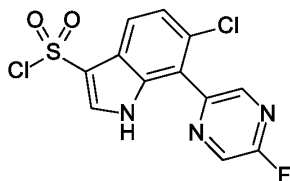
Intermediate A17: 6-bromo-7-pyrazin-2-yl-1H-indole-3-sulfonyl chloride



The title compound was prepared in analogy to Intermediate A1 from 6-bromo-1H-indole instead of 6-chloro-1H-indole in Step 1) and from 2-bromopyrazine instead of 2-bromopyrimidine in Step 3) as orange solid, MS (ESI) m/z: 374.0 [M+H]⁺

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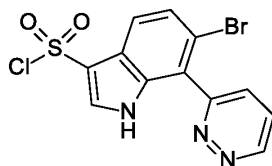
Intermediate A18: 6-chloro-7-(5-fluoropyrazin-2-yl)-1H-indole-3-sulfonyl chloride



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The title compound was prepared in analogy to Intermediate A1 from 2-bromo-5-fluoro-pyrazine instead of 2-bromopyrimidine in Step 3) as light brown solid, MS (ESI) m/z: 344.0 [M-H]⁻

Intermediate A19: 6-bromo-7-pyridazin-3-yl-1H-indole-3-sulfonyl chloride

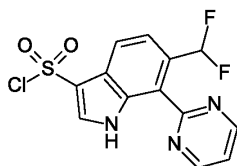


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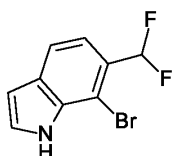
The title compound was prepared in analogy to Intermediate A1 from 6-bromo-1H-indole instead of 6-chloro-1H-indole in Step 1) and from 3-chloropyridazine instead of 2-bromopyrimidine in Step 3) as brown gum, MS (ESI) m/z: 374.0 [M+H]⁺

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Intermediate A20: 6-(difluoromethyl)-7-pyrimidin-2-yl-1H-indole-3-sulfonyl chloride

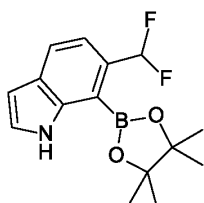


Step 1: 7-bromo-6-(difluoromethyl)-1H-indole



- 10 To the stirred solution of 2-bromo-1-(difluoromethyl)-3-nitro-benzene (CAS 1261819-77-5, 24.6 g, 97.6 mmol) in dry tetrahydrofuran (1000 ml) at -40°C was added vinylmagnesium bromide (1M solution in THF, 488 mL, 488 mmol) and mixture was stirred at -40°C for further 30 min. The mixture was quenched with ammonium chloride solution (500 ml) and extracted with ethyl acetate twice. The combined organic layers were washed with brine (300 ml), dried
- 15 over sodium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (silica gel, 0-30 % ethyl acetate in heptane) to afford 7-bromo-6-(difluoromethyl)-1H-indole (10.2 g, 42% yield) as light brown solid. MS (ESI) m/z: 245.8 [M-H]⁻

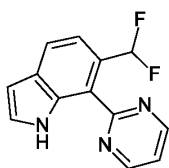
20 Step 2: 6-(difluoromethyl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole



A mixture of 7-bromo-6-(difluoromethyl)-1H-indole (2 g, 8.12 mmol), bis(pinacolato)diboron (3.10 g, 12.2 mmol), potassium acetate (2.39 g, 24.4 mmol) and XPhos Pd(crotyl)Cl (CAS

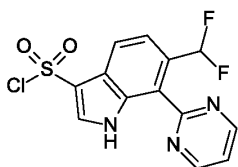
1798782-02-1, 273 mg, 0.41 mmol, 5 mol%) in methanol (70 ml) was stirred and heated to 40°C for 4 h. After cooling the mixture was filtered, the solid washed with methanol and the solution was concentrated in vacuo. The crude material was purified by flash chromatography (silica gel, 0 % to 30 % ethyl acetate in heptane) to afford 6-(difluoromethyl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (1.2 g, 50% yield) as dark brown oil. MS (ESI) m/z: 294.2 [M+H]⁺

Step 3: 6-(difluoromethyl)-7-pyrimidin-2-yl-1H-indole



10 A mixture of 6-(difluoromethyl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (729 mg, 2.49 mmol), 2-bromopyrimidine (475 mg, 2.98 mmol), tetrakis(triphenylphosphine)palladium(0) (288 mg, 249 μmol, 0.1 eq) and cesium carbonate (1.62 g, 4.97 mmol) in 1,4-dioxane (10 ml) and water (2.5 ml) was heated in microwave at 100 °C for 30 min. The mixture was poured into water and extracted with ethyl acetate twice. The combined organic
15 layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (SiliaSep Amine silicagel, 0% to 80% ethyl acetate in heptane) to provide 6-(difluoromethyl)-7-pyrimidin-2-yl-1H-indole (193 mg, 32% yield) as white semisolid. MS (ESI) m/z: 246.1 [M+H]⁺

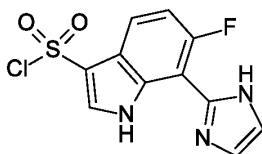
20 Step 4: 6-(difluoromethyl)-7-pyrimidin-2-yl-1H-indole-3-sulfonyl chloride



To a solution of 6-(difluoromethyl)-7-(2-pyrimidinyl)-1H-indole (195 mg, 795 μmol) in acetonitrile (5 ml) was added chlorosulfonic acid (139 mg, 80 μl, 1.19 mmol) at 0°C. The ice bath was removed and the reaction mixture was stirred 2 h at room temperature. Phosphorus
25 oxychloride (488 mg, 297 μl, 3.18 mmol) was added and the reaction mixture was stirred at 70°C overnight. The mixture was poured into ice/water and extracted with ethyl acetate twice. The combined organic layers were washed with ice and brine, dried over Na2SO4, filtered and

concentrated in vacuo to the title compound (207 mg, 76% yield) as brown solid. MS (ESI) m/z: 344.1 [M+H]⁺

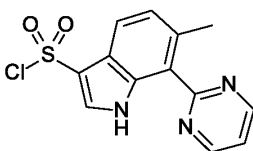
Intermediate A21: 6-fluoro-7-(1H-imidazol-2-yl)-1H-indole-3-sulfonyl chloride



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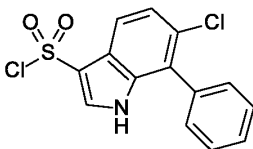
The title compound was prepared in analogy to Intermediate A1 from 6-fluoro-1H-indole instead of 6-chloro-1H-indole in Step 1) and from 2-iodoimidazole instead of 2-bromopyrimidine in Step 3) as light brown solid which was used directly for the next step.

10 **Intermediate A22:** 6-methyl-7-pyrimidin-2-yl-1H-indole-3-sulfonyl chloride

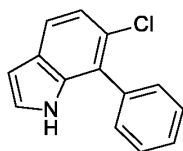


The title compound was prepared in analogy to Intermediate A1 from 6-methyl-1H-indole instead of 6-chloro-1H-indole in Step 1) as light brown foam. MS (ESI) m/z: 308.1 [M+H]⁺.

15 **Intermediate A23:** 6-chloro-7-phenyl-1H-indole-3-sulfonyl chloride



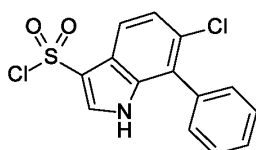
Step 1: 6-chloro-7-phenyl-1H-indole



A mixture of 7-bromo-6-chloro-1H-indole (CAS 1427439-04-0, 220 mg, 0.955 mmol),
20 phenylboronic acid (151 mg, 1.24 mmol), triphenylphosphine (50 mg, 191 umol, 0.20 eq) and
palladium(II) acetate (21 mg, 95 umol, 0.100 eq) in 1,2-dimethoxyethane (6.6 ml) and 2 M
Na₂CO₃ solution (1.57 ml, 3.15 mmol) was heated in the microwave at 90 °C for 2 h. The

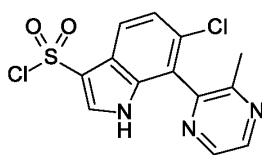
reaction mixture was poured into water and extracted with ethyl acetate. The organic layers were washed with brine, dried over MgSO₄, filtered through Celite and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 0% to 35% ethyl acetate in heptane) to provide 6-chloro-7-phenyl-1H-indole (204 mg, 89% yield) as yellow oil, MS (ESI) m/z: 228.0 [M+H]⁺.

Step 2: 6-chloro-7-phenyl-1H-indole-3-sulfonyl chloride



A stirred solution of 6-chloro-7-phenyl-1H-indole (198 mg, 826 μmol) was cooled to 0°C, then chlorosulfonic acid (250 mg, 143 μl, 2.15 mmol) was added dropwise. The reaction mixture was stirred for 1 h at 0°C. The reaction mixture was warmed to room temperature and stirred for another 2 h. Phosphoryl chloride (507 mg, 308 μl, 3.3 mmol) was added in one portion. The reaction mixture was warmed to 60°C and stirred for 16 h. The reaction mixture was poured into ice / ethyl acetate and extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo to provide 6-chloro-7-phenyl-1H-indole-3-sulfonyl chloride (282 mg, 89% yield) as brown viscous oil, MS (ESI) m/z: 324.0 [M+H]⁺.

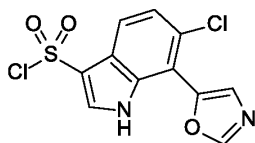
Intermediate A24: 6-chloro-7-(3-methylpyrazin-2-yl)-1H-indole-3-sulfonyl chloride



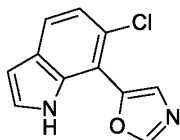
The title compound was prepared in analogy to Intermediate A1 from 2-bromo-3-methylpyrazine instead of 2-bromopyrimidine in Step 3) as off-white foam, MS (ESI) m/z: 342.0 [M+H]⁺.

Intermediate A25: 6-chloro-7-oxazol-5-yl-1H-indole-3-sulfonyl chloride

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Step 1: 5-(6-chloro-1H-indol-7-yl)oxazole

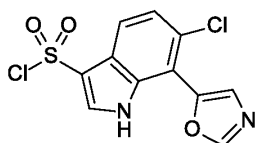


5

To a solution of 7-bromo-6-chloro-1H-indole (CAS 1427439-04-0, 1.18 g, 5.13 mmol) in tetrahydrofuran (20 ml) was added 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazole (CAS 942070-84-0, 1.0 g, 5.13 mmol), K₃PO₄ (3.26 g, 15.38 mmol) and cataCXium A Pd G3 (CAS 1651823-59-4, 373 mg, 0.51 mmol, 0.10 eq) at room temperature under nitrogen in a glove box, then the mixture was stirred at 60°C for 12 h under nitrogen. The reaction mixture was diluted with water (20 ml) and extracted with ethyl acetate (30 ml x 3). The combined organic layers were washed with brine (10 ml), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 0~17% ethyl acetate / petroleum ether) followed by preparative HPLC (column: Phenomenex luna C18, 150 * 40 mm * 15 um, water with formic acid / acetonitrile) to give 5-(6-chloro-1H-indol-7-yl)oxazole (806 mg, 68% yield) as a white solid, MS (ESI) m/z: 218.9 [M+H]⁺.

15

Step 2: 6-chloro-7-oxazol-5-yl-1H-indole-3-sulfonyl chloride



A stirring solution of 5-(6-chloro-1H-indol-7-yl)oxazole (250 mg, 1.07 mmol) was cooled to 0 °C and chlorosulfonic acid (325 mg, 186 ul, 2.79 mmol) was added dropwise. A white precipitate formed. The reaction was stirred for 30 min at 0°C. Phosphoryl chloride (824 mg, 500 ul, 5.37 mmol) was added in one portion and the reaction was heated to 70°C for 18 h. The reaction mixture was poured into ice / ethyl acetate and extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried with Na₂SO₄, filtered and

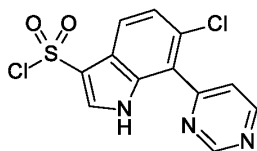
20

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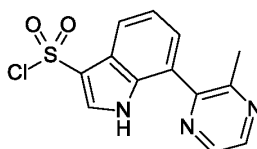
concentrated in vacuo to give 6-chloro-7-oxazol-5-yl-1H-indole-3-sulfonyl chloride (301 mg, 88% yield) as light yellow solid, MS (ESI) m/z: 316.9 [M+H]⁺.

Intermediate A26: 6-chloro-7-pyrimidin-4-yl-1H-indole-3-sulfonyl chloride



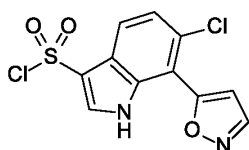
The title compound was prepared in analogy to Intermediate A2 from 4-chloropyrimidine hydrochloride instead of 2-bromooxazole in Step 1) as light yellow solid, MS (ESI) m/z: 328.0 [M+H]⁺.

Intermediate A27: 7-(3-methylpyrazin-2-yl)-1H-indole-3-sulfonyl chloride



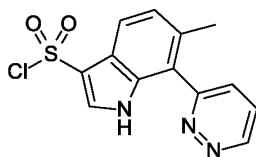
The title compound was prepared in analogy to Intermediate A1 from 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (CAS 642494-37-9) instead of 6-chloro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole and 2-bromo-3-methyl-pyrazine instead of 2-bromopyrimidine in Step 3) as yellow foam. MS (ESI) m/z: 306.1 [M-H]⁻.

Intermediate A28: 6-chloro-7-isoxazol-5-yl-1H-indole-3-sulfonyl chloride



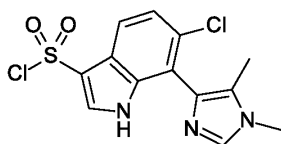
The title compound was prepared in analogy to Intermediate A25 from 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole (CAS 928664-98-6) instead of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazole in Step 1) as brown solid, MS (ESI) m/z: 314.9 [M-H]⁻.

Intermediate A29: 6-methyl-7-pyridazin-3-yl-1H-indole-3-sulfonyl chloride



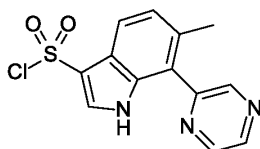
The title compound was prepared in analogy to Intermediate A3 from 2,2-dimethyl-1-[6-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indol-1-yl]propan-1-one (CAS 2376879-97-7) instead of 6-chloro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole as a light brown solid. MS (ESI) m/z: 308.1 [M+H]⁺.

Intermediate A30: 6-chloro-7-(1,5-dimethylimidazol-4-yl)-1H-indole-3-sulfonyl chloride



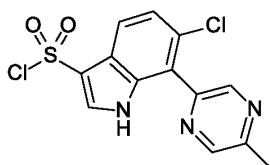
The title compound was prepared in analogy to Intermediate A2 from 4-bromo-1,5-dimethylimidazole (CAS 158585-81-0) instead of 2-bromooxazole in Step 1) as off-white foam, MS (ESI) m/z: 344.1 [M+H]⁺.

Intermediate A31: 6-methyl-7-pyrazin-2-yl-1H-indole-3-sulfonyl chloride



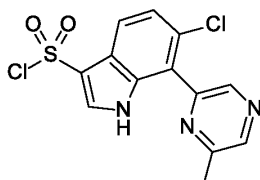
The title compound was prepared in analogy to Intermediate A3 from 2,2-dimethyl-1-[6-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indol-1-yl]propan-1-one (CAS 2376879-97-7) instead of 6-chloro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole and 2-bromopyrazine instead of 3-chloropyridazine in step 1) as a light brown solid.

Intermediate A32: 6-chloro-7-(5-methylpyrazin-2-yl)-1H-indole-3-sulfonyl chloride



The title compound was prepared in analogy to Intermediate A1 from 2-bromo-5-methylpyrazine instead of 2-bromopyrimidine in Step 3) as yellow foam. MS (ESI) m/z: 342.0 [M+H]⁺.

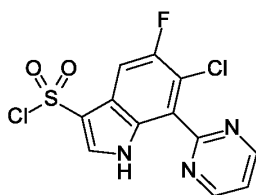
5 **Intermediate A33:** 6-chloro-7-(6-methylpyrazin-2-yl)-1H-indole-3-sulfonyl chloride



The title compound was prepared in analogy to Intermediate A1 from 2-bromo-6-methylpyrazine instead of 2-bromopyrimidine in Step 3) as off-white solid. MS (ESI) m/z: 342.0 [M+H]⁺.

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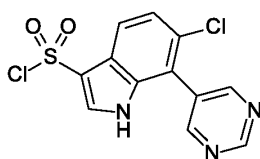
Intermediate A34: 6-chloro-5-fluoro-7-pyrimidin-2-yl-1H-indole-3-sulfonyl chloride



The title compound was prepared in analogy to Intermediate A1 from 6-chloro-5-fluoro-1H-indole instead of 6-chloro-1H-indole in Step 1) as light yellow solid. MS (ESI) m/z: 346.0

15 [M+H]⁺.

Intermediate A35: 6-chloro-7-pyrimidin-5-yl-1H-indole-3-sulfonyl chloride

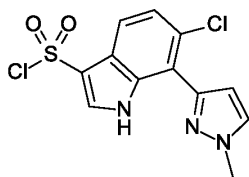


The title compound was prepared in analogy to Intermediate A1 from 5-bromopyrimidine instead of 2-bromopyrimidine in Step 3) as white solid. MS (ESI) m/z: 328.0 [M+H]⁺.

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Intermediate A36: 6-chloro-7-(1-methylpyrazol-3-yl)-1H-indole-3-sulfonyl chloride

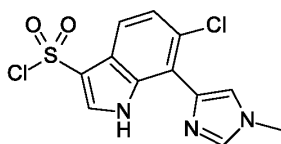
-60-



The title compound was prepared in analogy to Intermediate A1 from 3-iodo-1-methyl-pyrazole (CAS 92525-10-5) instead of 2-bromopyrimidine in Step 3) as off-white solid. MS (ESI) m/z: 330.1 [M+H]⁺.

5

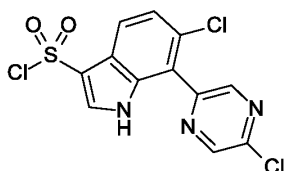
Intermediate A37: 6-chloro-7-(1-methylimidazol-4-yl)-1H-indole-3-sulfonyl chloride



The title compound was prepared in analogy to Intermediate A1 from 4-iodo-1-methyl-imidazole CAS (71759-87-0) instead of 2-bromopyrimidine in Step 3) as light brown foam. MS (ESI) m/z:

10 330.1 [M+H]⁺.

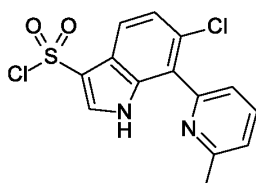
Intermediate A38: 6-chloro-7-(5-chloropyrazin-2-yl)-1H-indole-3-sulfonyl chloride



The title compound was prepared in analogy to Intermediate A2 from 2-bromo-5-chloro-

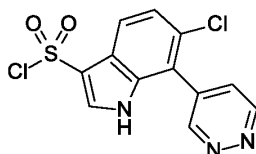
15 pyrazine instead of 2-bromooxazole in Step 1) as off-white solid, MS (ESI) m/z: 362.0 [M-H]⁻

Intermediate A39: 6-chloro-7-(6-methyl-2-pyridyl)-1H-indole-3-sulfonyl chloride



The title compound was prepared in analogy to Intermediate A1 from 2-bromo-6-methylpyridine instead of 2-bromopyrimidine in Step 3) as off-white solid. MS (ESI) m/z: 341.1 [M+H]⁺.

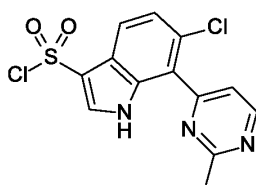
5 **Intermediate A40:** 6-chloro-7-pyridazin-4-yl-1H-indole-3-sulfonyl chloride



The title compound was prepared in analogy to Intermediate A1 from 4-bromopyridazine hydrobromide instead of 2-bromopyrimidine in Step 3) as light yellow solid. MS (ESI) m/z: 328.0 [M+H]⁺.

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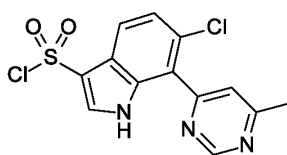
Intermediate A41: 6-chloro-7-(2-methylpyrimidin-4-yl)-1H-indole-3-sulfonyl chloride



The title compound was prepared in analogy to Intermediate A1 from 4-chloro-2-methylpyrimidine instead of 2-bromopyrimidine in Step 3) as light yellow solid. MS (ESI) m/z: 342.0 [M+H]⁺.

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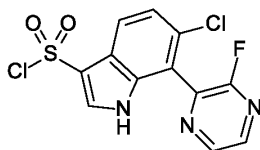
Intermediate A42: 6-chloro-7-(6-methylpyrimidin-4-yl)-1H-indole-3-sulfonyl chloride



The title compound was prepared in analogy to Intermediate A1 from 4-bromo-6-methylpyrimidine instead of 2-bromopyrimidine in Step 3) as light yellow solid. MS (ESI) m/z: 342.0 [M+H]⁺.

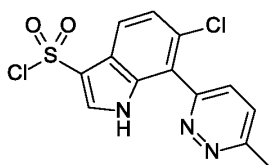
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Intermediate A43: 6-chloro-7-(3-fluoropyrazin-2-yl)-1H-indole-3-sulfonyl chloride



The title compound was prepared in analogy to Intermediate A1 from 2-bromo-3-fluoro-pyrazine instead of 2-bromopyrimidine in Step 3) as light brown solid. MS (ESI) m/z: 346.0 [M+H]⁺.

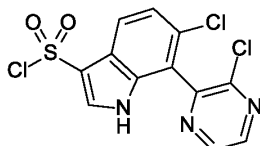
5 **Intermediate A44:** 6-chloro-7-(6-methylpyridazin-3-yl)-1H-indole-3-sulfonyl chloride



The title compound was prepared in analogy to Intermediate A2 from 3-chloro-6-methyl-pyridazine instead of 2-bromooxazole in Step 1) as off-white solid, MS (ESI) m/z: 342.0 [M+H]⁺.

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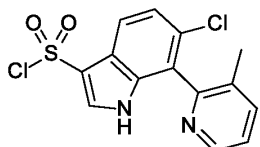
Intermediate A45: 6-chloro-7-(3-chloropyrazin-2-yl)-1H-indole-3-sulfonyl chloride



The title compound was prepared in analogy to Intermediate A2 from 2,3-dichloropyrazine instead of 2-bromooxazole in Step 1) as light brown solid, MS (ESI) m/z: 362.0 [M+H]⁺.

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Intermediate A46: 6-chloro-7-(3-methyl-2-pyridyl)-1H-indole-3-sulfonyl chloride

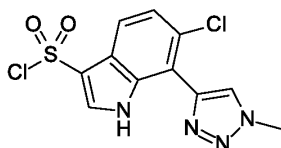


The title compound was prepared in analogy to Intermediate A1 from 2-bromo-3-methyl-pyridine instead of 2-bromopyrimidine in Step 3) as off-white solid. MS (ESI) m/z: 341.1 [M+H]⁺.

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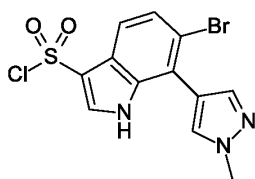
Intermediate A47: 6-chloro-7-(1-methyltriazol-4-yl)-1H-indole-3-sulfonyl chloride

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The title compound was prepared in analogy to Intermediate A2 from 4-bromo-1-methyl-triazole instead of 2-bromooxazole in Step 1) as off-white solid, MS (ESI) m/z : 331.0 $[M+H]^+$.

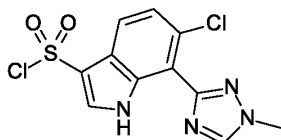
5 **Intermediate A48:** 6-bromo-7-(1-methylpyrazol-4-yl)-1H-indole-3-sulfonyl chloride



The title compound was prepared in analogy to Intermediate A1 from 6-bromo-1H-indole instead of 6-chloro-1H-indole in Step 1) and from 4-iodo-1-methyl-pyrazole instead of 2-bromopyrimidine in Step 3) as off-white solid, MS (ESI) m/z : 375.9 $[M+H]^+$

10

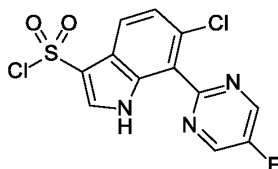
Intermediate A49: 6-chloro-7-(1-methyl-1,2,4-triazol-3-yl)-1H-indole-3-sulfonyl chloride



The title compound was prepared in analogy to Intermediate A1 from 3-bromo-1-methyl-1,2,4-triazole instead of 2-bromopyrimidine in Step 3) as white solid. MS (ESI) m/z : 233.1 $[M+H]^+$.

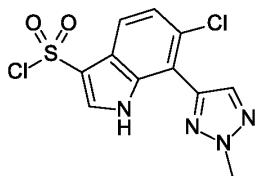
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Intermediate A50: 6-chloro-7-(5-fluoropyrimidin-2-yl)-1H-indole-3-sulfonyl chloride



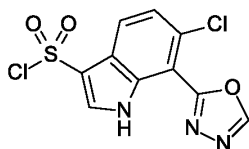
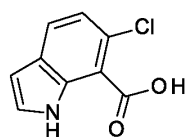
The title compound was prepared in analogy to Intermediate A1 from 2-bromo-5-fluoropyrimidine instead of 2-bromopyrimidine in Step 3) as light green solid. MS (ESI) m/z : 346.0

20 $[M+H]^+$.

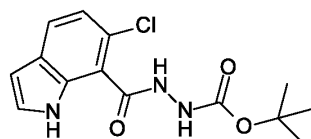
Intermediate A51: 6-chloro-7-(2-methyltriazol-4-yl)-1H-indole-3-sulfonyl chloride

The title compound was prepared in analogy to Intermediate A2 from 4-bromo-2-methyl-triazole instead of 2-bromooxazole in Step 1) as pink solid, MS (ESI) m/z : 331.0 $[M+H]^+$.

5

Intermediate A52: 6-chloro-7-(1,3,4-oxadiazol-2-yl)-1H-indole-3-sulfonyl chloride**Step 1:** 6-chloro-1H-indole-7-carboxylic acid

- 10 To a mixture of 6-chloro-1H-indole-7-carbonitrile (CAS 1427391-07-8, 1.5 g, 8.49 mmol) in ethanol (15 ml) was added a solution of potassium hydroxide (2.38 g, 42.5 mmol) in water (2.5 ml). The mixture was stirred at 80 °C for 48 h. The mixture was adjusted to pH 4 with 1N aqueous hydrochloric acid, then extracted with ethyl acetate (20 ml $\times$ 2). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure.
- 15 The residue was purified by column chromatography (silica gel, petroleum ether / ethyl acetate = 1:0 to 1:1) to give 6-chloro-1H-indole-7-carboxylic acid (1.3 g, 78% yield) as a brown solid, MS (ESI) m/z : 194.1 $[M-H]^-$.

Step 2: tert-butyl N-[(6-chloro-1H-indole-7-carbonyl)amino]carbamate

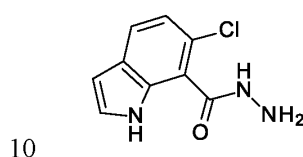
20

To a solution of 6-chloro-1H-indole-7-carboxylic acid (1.30 g, 6.65 mmol) and tert-butyl carbazate (1.32 g, 9.97 mmol) in dimethylformamide (20 ml) were added N-ethyl

-65-

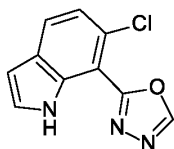
diisopropylamine (2.31 ml, 13.3 mmol) and HATU (1.88 g, 7.98 mmol) and the mixture was stirred at 20 °C for 16 h. The reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (20 ml × 2). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, petroleum ether / ethyl acetate = 1:0 to 5:1) to give tert-butyl N-[(6-chloro-1H-indole-7-carbonyl)amino]carbamate (900 mg, 44% yield) as a white solid, MS (ESI) m/z: 308.2 [M-H]⁻.

Step 3: 6-chloro-1H-indole-7-carbohydrazide



A mixture of tert-butyl N-[(6-chloro-1H-indole-7-carbonyl)amino]carbamate (900 mg, 2.91 mmol) and HCl in dioxane (4M, 18.0 ml, 72.0 mmol) was stirred at 20 °C for 1 h. Then the pH of the mixture was adjusted to 7 with saturated NaHCO₃ solution and the mixture was extracted with ethyl acetate (20 ml × 2). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure to give 6-chloro-1H-indole-7-carbohydrazide (600 mg, 98% yield) as a yellow solid, MS (ESI) m/z: 208.1 [M-H]⁻.

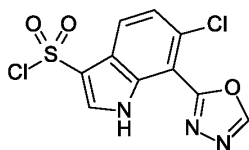
Step 4: 2-(6-chloro-1H-indol-7-yl)-1,3,4-oxadiazole



20 A solution of 6-chloro-1H-indole-7-carbohydrazide (600 mg, 2.86 mmol) and ammonium chloride (152 mg, 2.86 mmol) in triethyl orthoformate (15 ml, 98.28 mmol) was stirred at 145 °C for 1 h. The mixture was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel, petroleum ether / ethyl acetate = 1:0 to 5:1) to give 2-(6-chloro-1H-indol-7-yl)-1,3,4-oxadiazole (425 mg, 62% yield) as a white solid. MS (ESI) m/z: 220.2 [M+H]⁺.

Step 5: 6-chloro-7-(1,3,4-oxadiazol-2-yl)-1H-indole-3-sulfonyl chloride

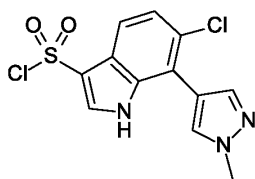
-66-



A stirred suspension of 2-(6-chloro-1H-indol-7-yl)-1,3,4-oxadiazole (100 mg, 0.414 mmol) in acetonitrile (5 ml) was cooled to 0 °C and chlorosulfonic acid (125 mg, 72 μ l, 1.08 mmol) was added dropwise. The reaction mixture was stirred at 0°C for 30 min. Phosphoryl chloride (318 mg, 193 μ l, 2.07 mmol) was added in one portion. The reaction mixture was heated to 60 °C for 22 h. The reaction mixture was poured into ice / ethyl acetate and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated to give the title compound (81 mg, 54% yield) as pink solid. MS (ESI) m/z: 318.0 [M+H]⁺.

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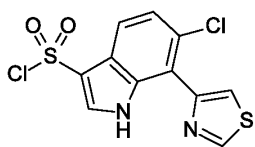
Intermediate A53: 6-chloro-7-(1-methylpyrazol-4-yl)-1H-indole-3-sulfonyl chloride



The title compound was prepared in analogy to Intermediate A1 from 4-iodo-1-methyl-pyrazole instead of 2-bromopyrimidine in Step 3) as light yellow solid, MS (ESI) m/z: 330.1 [M+H]⁺.

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Intermediate A54: 6-chloro-7-thiazol-4-yl-1H-indole-3-sulfonyl chloride



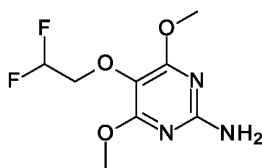
The title compound was prepared in analogy to Intermediate A2 from 4-bromothiazole instead of 2-bromooxazole in Step 1) as white solid, MS (ESI) m/z: 332.8 [M+H]⁺.

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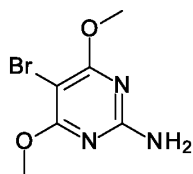
Intermediates B

Intermediate B1: 5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-amine

-67-

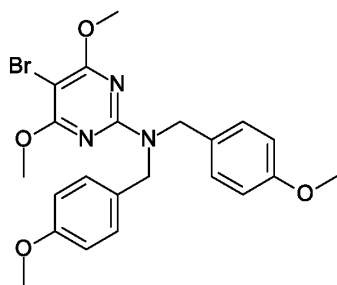


Step 1: 5-bromo-4,6-dimethoxy-pyrimidin-2-amine



To a stirred solution of (4,6-dimethoxypyrimidin-2-yl)amine (7 g, 44.22 mmol, CAS: 36315-01-2) in acetonitrile (100 mL) was added a solution of N-bromosuccinimide (10.33 g, 57.48 mmol) in acetonitrile (100 mL) dropwise at room temperature. The reaction mixture was stirred at room temperature for 30 min. The resulting white suspension was diluted with ethyl acetate and washed with water. The organic layer was dried over sodium sulfate, filtered, diluted with heptane and concentrated in vacuo. The precipitate was filtered off and washed with heptane to provide the title compound as a white solid (9.26 g, 87 % yield). MS (ESI) m/z = 234.1 $[M+H]^+$

Step 2: 5-bromo-4,6-dimethoxy-N,N-bis[(4-methoxyphenyl)methyl]pyrimidin-2-amine

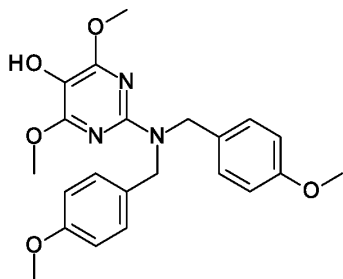


A solution of 5-bromo-4,6-dimethoxy-pyrimidin-2-amine (517 mg, 2.21 mmol) in N,N-dimethylacetamide (9 mL) was cooled to 0 °C. Sodium hydride (265.05 mg, 6.63 mmol) was added portionwise (3 x 88 mg). The stirring was continued at 0 °C for 30 min. 4-methoxybenzyl chloride (706. mg, 608.62 uL, 4.42 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature, stirred for 1 hour, carefully quenched with a saturated ammonium chloride solution, poured into water and extracted twice with ethyl acetate. The organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography over silica gel using a gradient ethylacetate/heptane 0-

-68-

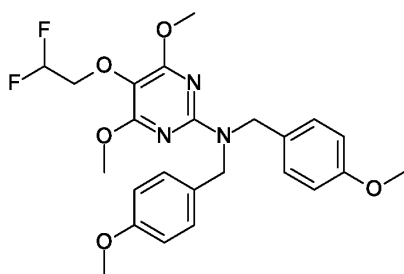
20% to provide the title compound as a white solid (1.11 g, 100 % yield). MS (ESI) m/z = 476.2 $[M+H]^+$

Step 3: 2-[bis[(4-methoxyphenyl)methyl]amino]-4,6-dimethoxy-pyrimidin-5-ol



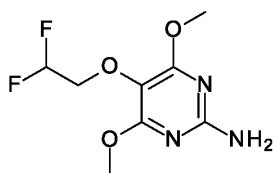
- 5 To a colorless solution of 5-bromo-4,6-dimethoxy-N,N-bis[(4-methoxyphenyl)methyl]-pyrimidin-2-amine (500 mg, 1 mmol) in tetrahydrofuran (3.5 mL) was added a 1.6 M n-butyllithium solution in hexanes (699.71 mg, 813.61 uL, 1.3 mmol) dropwise at -78 °C. The resulting yellow solution was stirred at -78 °C for 30 min. Trimethyl borate (156.08 mg, 167.47 uL, 1.5 mmol) was added dropwise and the stirring was continued at -78 °C for 1.5 hours. The
- 10 reaction mixture was allowed to warm to 0 °C and acetic acid (120.27 mg, 114.62 uL, 2 mmol) was added dropwise, followed by hydrogen peroxide 35% (145.98 mg, 131.51 uL, 1.5 mmol). The stirring was continued at 0 °C for 1.5 hours. The resulting pink suspension was poured into a 0.1 N sodium thiosulfate solution and extracted twice with ethyl acetate. The organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo. The residue
- 15 was purified by flash chromatography over silica gel using a gradient ethylacetate/heptane 0-30% to provide the title compound as a light yellow viscous oil (194 mg, 47 % yield). MS (ESI) m/z = 412.3 $[M+H]^+$

Step 4: 5-(2,2-difluoroethoxy)-4,6-dimethoxy-N,N-bis[(4-methoxyphenyl)methyl]pyrimidin-2-amine



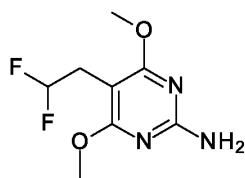
To a solution of 2-[bis[(4-methoxyphenyl)methyl]amino]-4,6-dimethoxy-pyrimidin-5-ol (100 mg, 0.214 mmol) in N,N-dimethylformamide (1.75 mL) was added potassium carbonate (88.68 g, 0.642 mmol) and 1,1-difluoro-2-iodoethane (123.16 mg, 56.5 μ L, 0.642 mmol). The reaction mixture was stirred at 80 °C for 1.5 hours, cooled to room temperature, poured into water and extracted twice with ethyl acetate. The organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography over silica gel using a gradient ethylacetate/heptane 0-20% to provide the title compound as an off-white solid (92 mg, 85 % yield). MS (ESI) m/z = 476.2 $[M+H]^+$

10 Step 5: 5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-amine



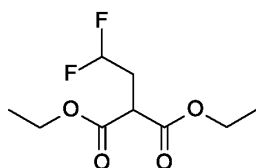
To a stirred solution of 5-(2,2-difluoroethoxy)-4,6-dimethoxy-N,N-bis[(4-methoxyphenyl)methyl]pyrimidin-2-amine (92 mg, 0.193 mmol) in dichloromethane (0.340 mL) was added trifluoroacetic acid (1.34 g, 897.97 μ L, 11.61 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 18 hours and at 50 °C for 4 hours. The resulting red solution was concentrated in vacuo, poured into sat. NaHCO_3 and extracted twice with ethyl acetate. The organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography over silica gel using a gradient ethylacetate/heptane 0-30% to provide the title compound as a light yellow solid (41 mg, 87 % yield). MS (ESI) m/z = 236.2 $[M+H]^+$

Intermediate B2: 5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-amine



Step 1: diethyl 2-(2,2-difluoroethyl)propanedioate

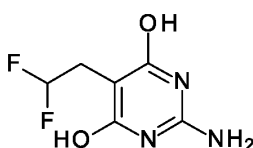
-70-



Diethyl malonate (75.8 ml, 500 mmol) was combined with tetrahydrofuran (450 ml). Sodium ethoxide (prepared from ethanol (150 mL) and sodium (11.48 g, 500 mmol)) was added at room temperature and the reaction mixture was stirred 15 min at room temperature. A solution of 2,2-difluoroethyl trifluoromethanesulfonate (76 ml, 500 mmol) in tetrahydrofuran (10 ml) was added slowly. The reaction mixture was stirred for 18 hours at 20 °C, then cooled to 0 °C, quenched with a saturated ammonium chloride solution and extracted twice with ethyl acetate. The organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo to provide the title compound (100.5 g, 90 % yield). MS (ESI) m/z = 225.0 $[M+H]^+$

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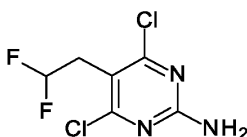
Step 2: 2-amino-5-(2,2-difluoroethyl)pyrimidine-4,6-diol



To a stirred solution of diethyl 2-(2,2-difluoroethyl)propanedioate (46.8 g, 209 mmol) in ethanol (5 mL) was added guanidine hydrochloride (19.9 g, 208 mmol), followed by sodium ethoxide (prepared from ethanol and sodium (14.38 g, 625 mmol)). The resulting orange suspension was heated to 80 °C and stirred for 4 hours. The reaction mixture was concentrated by half, 50 ml of water was added, followed by acetic acid (42.57 g, 709 mmol). The mixture was heated to 80 °C and stirred for 10 min, then cooled to room temperature. The solid product was filtered off, washed successively with water, ethanol and methyl tert-butyl ether to provide the title compound (22.3 g, 50 % yield). MS (ESI) m/z = 192.0 $[M+H]^+$

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Step 3: 4,6-dichloro-5-(2,2-difluoroethyl)pyrimidin-2-amine

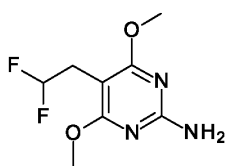


2-amino-5-(2,2-difluoroethyl)pyrimidine-4,6-diol (13.2 g, 69.1 mmol) was suspended in phosphorus oxychloride (80.5 ml, 863 mmol). The reaction mixture was heated to 100 °C and

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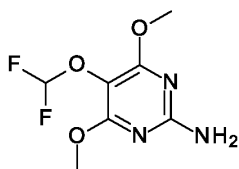
- stirred for 18 hours and concentrated in vacuo. The residue was diluted with ethyl acetate and carefully poured into ice / saturated sodium bicarbonate solution. The resulting biphasic mixture was stirred at room temperature for 5 min and extracted twice with ethyl acetate. The organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was
- 5 purified by flash chromatography over silica gel to provide the title compound (7.35 g, 47 % yield). MS (ESI) $m/z = 227.8$ $[M+H]^+$

Step 4: 5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-amine

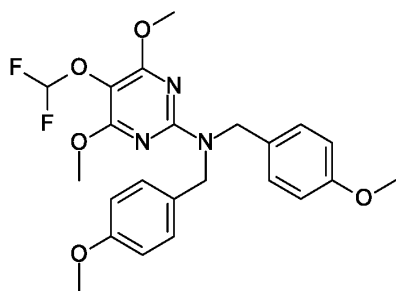


- 10 In a sealed tube, a mixture of 4,6-dichloro-5-(2,2-difluoroethyl)pyrimidin-2-amine (7.6 g, 33.33 mmol) and sodium methylate (prepared from sodium (7.66 g, 333.29 mmol) in methanol (50 ml)) was heated to 75 °C and stirred for 18 hours. The reaction mixture was quenched with water and extracted twice with ethyl acetate. The organic layers were dried over sodium sulfate,
- 15 % yield). MS (ESI) $m/z = 220.0$ $[M+H]^+$

Intermediate B3: 5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-amine



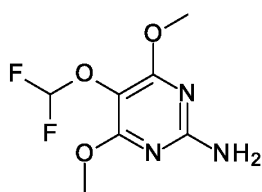
- 20 Step 1: 5-(difluoromethoxy)-4,6-dimethoxy-N,N-bis[(4-methoxyphenyl)methyl]pyrimidin-2-amine



-72-

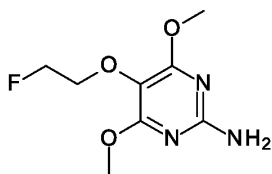
To a solution of 2-[bis[(4-methoxyphenyl)methyl]amino]-4,6-dimethoxy-pyrimidin-5-ol (130 mg, 0.316 mmol, intermediate B1, step 3) in acetonitrile (5 mL) was added a 5 M potassium hydroxide solution (1.26 mL, 6.32 mmol) dropwise at 0 °C, followed by addition of bromodifluoromethyl diethylphosphonate (168.72 mg, 112.26 uL, 0.632 mmol) in acetonitrile (1 mL) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 10 min. The resulting light yellow biphasic mixture was poured into water and extracted twice with ethyl acetate. The organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography over silica gel using a gradient ethylacetate/heptane 0-30% to provide the title compound as a white solid (57 mg, 39 % yield). MS (ESI) m/z = 462.3 [M+H]⁺

Step 2: 5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-amine

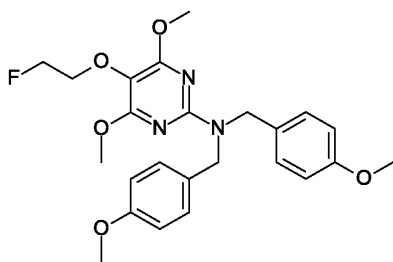


To a stirred solution of 5-(difluoromethoxy)-4,6-dimethoxy-N,N-bis[(4-methoxyphenyl)methyl]pyrimidin-2-amine (56 mg, 0.121 mmol) in dichloromethane (100 uL) was added trifluoroacetic acid (838.62 mg, 563.21 uL, 7.28 mmol). The reaction mixture was stirred at room temperature for 40 hours, at 50 °C for 6 hours and concentrated in vacuo. The residue was poured into sat. NaHCO₃ and extracted twice with ethyl acetate. The organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography over silica gel using a gradient ethylacetate/heptane 0-100% to provide the title compound as a white solid (24 mg, 89 % yield). MS (ESI) m/z = 222.1 [M+H]⁺

Intermediate B4: 5-(2-fluoroethoxy)-4,6-dimethoxy-pyrimidin-2-amine

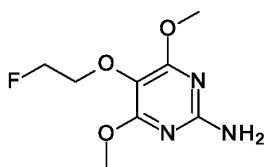


Step 1: 5-(2-fluoroethoxy)-4,6-dimethoxy-N,N-bis[(4-methoxyphenyl)methyl]pyrimidin-2-amine



A suspension of 2-bis[(4-methoxyphenyl)methyl]amino-4,6-dimethoxy-pyrimidin-5-ol (2 g, 4.52 mmol, intermediate B1, step 3), potassium carbonate (1.89 g, 13.56 mmol) and 1-bromo-2-fluoroethane (1.76 g, 1.03 mL, 13.56 mmol) in N,N-dimethylformamide (45 mL) was heated to 80 °C and stirred for 2.5 hours. The reaction mixture was poured into brine and extracted twice with ethyl acetate. The organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography over silica gel using a gradient ethylacetate/heptane 0-30% to provide the title compound as a white solid (1.79 g, 85 % yield). MS (ESI) $m/z = 458.3$ $[M+H]^+$

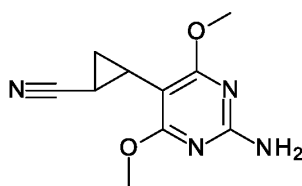
Step 2: 5-(2-fluoroethoxy)-4,6-dimethoxy-pyrimidin-2-amine



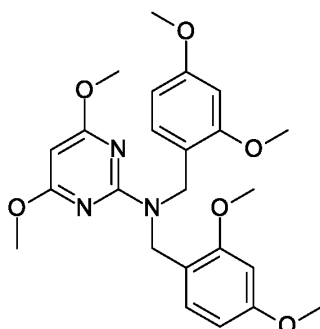
To a stirred solution of 5-(2-fluoroethoxy)-4,6-dimethoxy-N,N-bis[(4-methoxyphenyl)methyl]pyrimidin-2-amine (1.79 g, 3.83 mmol) in dichloromethane (4 mL) was added trifluoroacetic acid (26.23 g, 17.62 mL, 230.06 mmol). The reaction mixture was stirred at 50 °C for 3 hours, at room temperature for 15 hours and concentrated in vacuo. The residue was poured into sat. NaHCO₃ and extracted twice with ethyl acetate. The organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography over silica gel using a gradient ethylacetate/heptane 0-60% to provide the title compound as an off-white solid (885 mg, 100 % yield). MS (ESI) $m/z = 218.1$ $[M+H]^+$

Intermediate B5: 2-(2-amino-4,6-dimethoxy-pyrimidin-5-yl)cyclopropanecarbonitrile

-74-

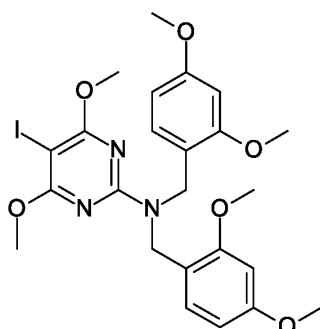


Step 1: N,N-bis[(2,4-dimethoxyphenyl)methyl]-4,6-dimethoxy-pyrimidin-2-amine



- To a solution of 2-chloro-4,6-dimethoxypyrimidine (5.0 g, 28.6 mmol) and 1-(2,4-
- 5 dimethoxyphenyl)-N-[(2,4-dimethoxyphenyl)methyl]methanamine (10.9 g, 34.37 mmol) in N-methylpyrrolidone (100 ml) was added cesium carbonate (18.7 g, 57.3 mmol) and the reaction mixture was stirred at 120 °C for 16 h. The mixture was diluted with water (500 ml) and extracted with ethyl acetate (100 ml × 2). The combined organic layers were washed with brine (100 ml × 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue
- 10 was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 1:0 to 5:1) to give N-bis[(2,4-dimethoxyphenyl)methyl]-4,6-dimethoxy-pyrimidin-2-amine (12.0 g, 89% yield) as a white solid. MS (ESI) m/z= 456.3 [M+H]⁺

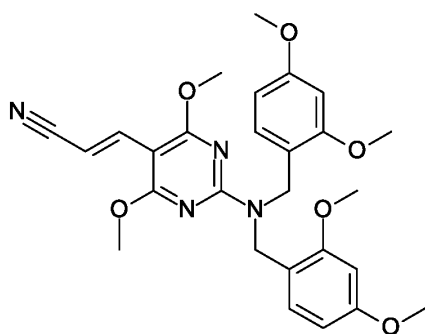
Step 2: N,N-bis[(2,4-dimethoxyphenyl)methyl]-5-iodo-4,6-dimethoxy-pyrimidin-2-amine



To a solution of N,N-bis[(2,4-dimethoxyphenyl)methyl]-4,6-dimethoxy-pyrimidin-2-amine (12.0 g, 26.3 mmol) in acetonitrile (150 ml) was added N-iodosuccinimide (7.11 g, 31.6 mmol) in portions at 20 °C and the mixture was stirred at 20 °C for 2 h. The reaction mixture was quenched by pouring into saturated sodium hydrogencarbonate solution (300 ml) and extracted with ethyl acetate (100 ml × 2). The combined organic layers were washed with brine (100 ml × 2), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, petroleum ether / ethyl acetate = 1:0 to 3:1) to give N,N-bis[(2,4-dimethoxyphenyl)methyl]-5-iodo-4,6-dimethoxy-pyrimidin-2-amine (12.0 g, 78% yield) as a yellow solid. MS (ESI) m/z= 582.2 [M+H]⁺

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Step 3: (E)-3-[2-[bis[(2,4-dimethoxyphenyl)methyl]amino]-4,6-dimethoxy-pyrimidin-5-yl]prop-2-enenitrile



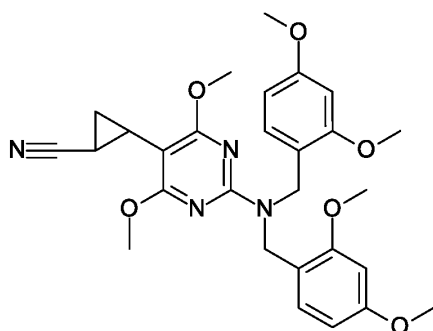
To a mixture of N,N-bis[(2,4-dimethoxyphenyl)methyl]-5-iodo-4,6-dimethoxy-pyrimidin-2-amine (9.0 g, 15.5 mmol) and acrylonitrile (6.0 ml, 90.5 mmol) in 1,4-dioxane (90 ml) was added cesium carbonate (10.8 g, 33.1 mmol) and bis(triphenylphosphine)palladium chloride (681 mg, 1.55 mmol) under nitrogen atmosphere and the reaction mixture was stirred in a sealed tube at 100 °C for 16 h. The mixture was concentrated under reduced pressure.

The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 1:0 to 5:1) to give (E)-3-[2-[bis[(2,4-dimethoxyphenyl)methyl]amino]-4,6-dimethoxy-pyrimidin-5-yl]prop-2-enenitrile (7.5 g, 96% yield) as a brown solid. MS (ESI) m/z= 507.3 [M+H]⁺

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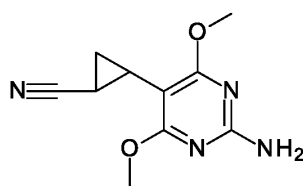
Step 4: 2-[2-[bis[(2,4-dimethoxyphenyl)methyl]amino]-4,6-dimethoxy-pyrimidin-5-yl]cyclopropanecarbonitrile

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To a mixture of trimethylsulfoxonium iodide (6.52 g, 29.6 mmol) in dimethylsulfoxide (50 ml) was added sodium hydride (60% in mineral oil, 1.18 g, 29.6 mmol) in portions at 30 °C and the mixture was stirred at 30 °C for 0.5 h. The above mixture was added to a mixture of (E)-3-[2-
 5 [bis[(2,4-dimethoxyphenyl)methyl]amino]-4,6-dimethoxy-pyrimidin-5-yl]prop-2-enenitrile (5.0 g, 9.87 mmol) in dimethylsulfoxide (50 ml) at 30 °C and the mixture was stirred at 30 °C for 16 hr. The reaction mixture was diluted with water (300 ml) and extracted with ethyl acetate (100 ml × 2). The combined organic layers were washed with brine (100 ml × 2), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column
 10 chromatography (silica gel, petroleum ether/ethyl acetate = 1:0 to 3:1) to give 2-[2-[bis[(2,4-dimethoxyphenyl)methyl]amino]-4,6-dimethoxy-pyrimidin-5-yl]cyclopropanecarbonitrile (3.0 g, 54% yield) as yellow oil. MS (ESI) m/z = 521.3 $[M+H]^+$

Step 5: 2-(2-amino-4,6-dimethoxy-pyrimidin-5-yl)cyclopropanecarbonitrile



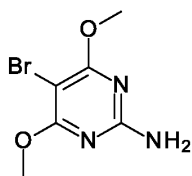
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To a solution of 2-[2-[bis[(2,4-dimethoxyphenyl)methyl]amino]-4,6-dimethoxy-pyrimidin-5-yl]cyclopropanecarbonitrile (3.0 g, 5.76 mmol) in dichloromethane (10 ml) was added trifluoroacetic acid (15 ml, 197 mmol) dropwise at 10 °C and the mixture was stirred at 10 °C for 4 h. The reaction mixture was diluted with water (100 ml) and adjusted pH to 7 with saturated
 20 sodium bicarbonate solution at 0-10 °C. The mixture was extracted with ethyl acetate (50 ml × 2). The combined organic layers were washed with brine (50 ml × 2), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was triturated with ethyl acetate (4

-77-

ml) and filtered. The filter cake was dried under reduced pressure to give the title compound (907 mg, 70 % yield) as a white solid. MS (ESI) $m/z = 221.1$ $[M+H]^+$

Intermediate B6: 5-bromo-4,6-dimethoxy-pyrimidin-2-amine

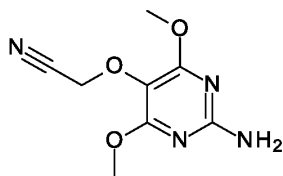


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To a stirred solution of (4,6-dimethoxypyrimidin-2-yl)amine (7 g, 44.2 mmol, CAS: 36315-01-2) in acetonitrile (100 ml) was added a solution of N-bromosuccinimide (10.3 g, 57.5 mmol) in acetonitrile (100 ml) dropwise at room temperature. The reaction mixture was stirred at room temperature for 30 min. The resulting white suspension was diluted with ethyl acetate and washed with water. The organic layer was dried over sodium sulfate, filtered, diluted with heptane and concentrated in vacuo. The precipitate was filtered off and washed with heptane to provide the title compound as a white solid (9.26 g, 87% yield). MS (ESI) $m/z = 234.1$ $[M+H]^+$.

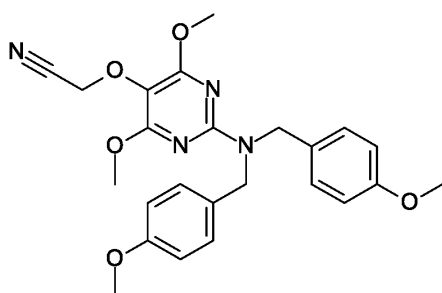
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Intermediate B7: 2-(2-amino-4,6-dimethoxy-pyrimidin-5-yl)oxyacetonitrile



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Step 1: 2-[2-[bis[(4-methoxyphenyl)methyl]amino]-4,6-dimethoxy-pyrimidin-5-yl]oxyacetonitrile



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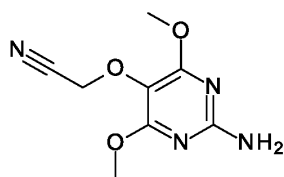
A mixture of 2-[bis[(4-methoxyphenyl)methyl]amino]-4,6-dimethoxy-pyrimidin-5-ol (1 g, 2.43 mmol, see Intermediate B1, step 3), iodoacetonitrile (1.22 g, 529 μ l, 7.29 mmol) and potassium carbonate (1.01 g, 7.29 mmol) in N,N-dimethylformamide (16 ml) was stirred at 80°C overnight.

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The reaction mixture was poured into water and extracted twice with ethyl acetate. The organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, ethyl acetate / heptane 0-20%) to provide the title compound as a white solid (855 mg, 77 % yield). MS (ESI) $m/z = 451.3$ $[M+H]^+$.

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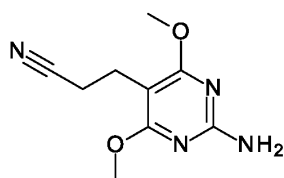
Step 2: 2-(2-amino-4,6-dimethoxy-pyrimidin-5-yl)oxyacetonitrile



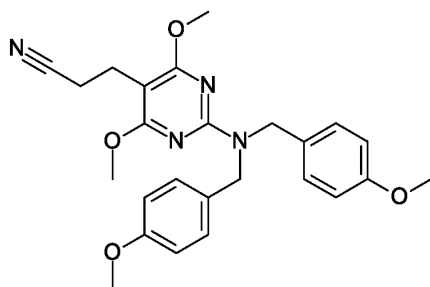
A mixture of 2-[2-[bis[(4-methoxyphenyl)methyl]amino]-4,6-dimethoxy-pyrimidin-5-yl]oxyacetonitrile (855 mg, 1.9 mmol) and trifluoroacetic acid (6.49 g, 4.39 ml, 56.94 mmol) in dichloromethane (6 ml) was stirred at 50 °C overnight. The reaction mixture was concentrated in vacuo, poured into saturated NaHCO₃ solution and extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, ethyl acetate / heptane 0-39%) to provide the title compound as an off-white solid (406 mg, 92 % yield). MS (ESI) $m/z = 211.1$ $[M+H]^+$.

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Intermediate B8: 3-(2-amino-4,6-dimethoxy-pyrimidin-5-yl)propanenitrile



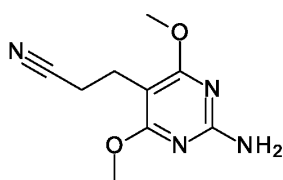
Step 1: 3-[2-[bis[(4-methoxyphenyl)methyl]amino]-4,6-dimethoxy-pyrimidin-5-yl]propanenitrile



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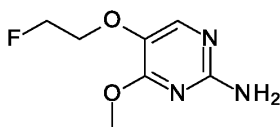
To a solution of 5-bromo-4,6-dimethoxy-N,N-bis[(4-methoxyphenyl)methyl]pyrimidin-2-amine (5.0 g, 10.54 mmol, intermediate B1, step 2) in methoxycyclopentane (75.0 ml) was added 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanenitrile (2.29 g, 12.6 mmol), cesium carbonate (10.3 g, 31.62 mmol) and cataCXium® A Pd G3 (768 mg, 1.05 mmol, CAS: 1651823-59-4) under nitrogen. The mixture was purged three times with nitrogen, stirred at 90 °C for 12 h under nitrogen, poured into NaHCO₃ solution and extracted three times with ethyl acetate. The combined organic layers were washed with dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, ethyl acetate / petroleum ether 0-30%) to provide the title compound as a yellow solid (2.9 g, 61 % yield). MS (ESI) m/z= 449.0 [M+H]⁺.

Step 2: 3-(2-amino-4,6-dimethoxy-pyrimidin-5-yl)propanenitrile

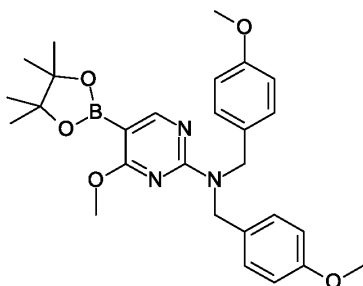


A mixture of 3-[2-[bis[(4-methoxyphenyl)methyl]amino]-4,6-dimethoxy-pyrimidin-5-yl]propanenitrile (2300 mg, 5.13 mmol) in trifluoroacetic acid (23 ml) was stirred at 25 °C for 48 h, quenched with ice/saturated NaHCO₃ solution and extracted three times with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, ethyl acetate / petroleum ether 0-100%) to provide the title compound as a yellow solid (1000 mg, 89 % yield). MS (ESI) m/z= 209.0 [M+H]⁺.

Intermediate B9: 5-(2-fluoroethoxy)-4-methoxy-pyrimidin-2-amine

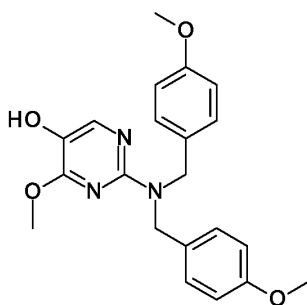


Step 1: [4-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-yl]-bis(p-anisyl)amine



A suspension of (5-bromo-4-methoxy-pyrimidin-2-yl)-bis(p-anisyl)amine (500 mg, 1.13 mmol, see Intermediate B3 step 1), bis(pinacolato)diboron (354 mg, 1.35 mmol) and potassium acetate (335 mg, 3.38 mmol) in 1,4-dioxane (10 ml) was purged with argon for 5 min. dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct (92 mg, 0.113 mmol) was added. The reaction mixture was heated to 90°C and stirred for 16 h. The resulting dark suspension was poured into ethyl acetate and washed once with brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel using a gradient ethyl acetate / heptane 0-30% to provide the title compound as a colorless viscous oil (157 mg, 29% yield). MS (ESI): $m/z = 492.4$ $[M+H]^+$

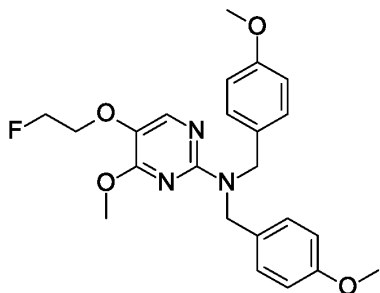
Step 2: 2-[bis(p-anisyl)amino]-4-methoxy-pyrimidin-5-ol



A solution of [4-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-yl]-bis(p-anisyl)amine (130 mg, 0.265 mmol) in tetrahydrofuran (2.5 ml) was cooled to 0°C. Hydrogen peroxide 35% (500 μ l, 5.71 mmol) was added. The reaction mixture was stirred at 0°C for 15 min, allowed to warm to room temperature and stirred for 3 h. The reaction mixture was poured into cold 0.1 N sodium sulfite solution and extracted twice with ethyl acetate. The organic layers were washed twice with brine, dried over sodium sulfate, filtered and concentrated in vacuo to

provide the title compound as a light yellow viscous oil (103 mg, 100 % yield). MS (ESI): m/z = 382.3 $[M+H]^+$

Step 3: [5-(2-fluoroethoxy)-4-methoxy-pyrimidin-2-yl]-bis(p-anisyl)amine

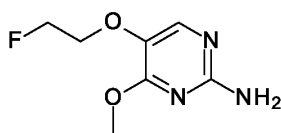


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A suspension of 2-[bis(p-anisyl)amino]-4-methoxy-pyrimidin-5-ol (100 mg, 0.236 mmol), potassium carbonate (98.8 mg, 0.708 mmol) and 1-bromo-2-fluoroethane (61 mg, 36 μ l, 0.472 mmol) in acetonitrile (2.5 ml) was stirred at room temperature for 15 min and at 80°C for 6 h. The reaction mixture was poured into water and extracted twice with ethyl acetate. The organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, ethyl acetate / heptane 0-30%) to provide the title compound as a colorless viscous oil (22 mg, 22 % yield). MS (ESI): m/z = 428.3 $[M+H]^+$

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Step 4: [5-(2-fluoroethoxy)-4-methoxy-pyrimidin-2-yl]amine

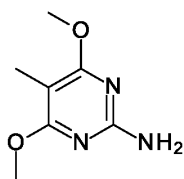


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A solution of [5-(2-fluoroethoxy)-4-methoxy-pyrimidin-2-yl]-bis(p-anisyl)amine (87 mg, 0.204 mmol) in dichloromethane (500 μ l) was cooled to 0 °C. Trifluoroacetic acid (1.41 g, 945 μ l, 12.2 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 16 h and at 55°C for two additional hours. The resulting purple solution was poured into a saturated aqueous sodium bicarbonate solution and extracted twice with ethyl acetate. The organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, ethyl acetate / heptane 0-100%) to provide the title compound as an off-white solid (27 mg, 71 % yield). MS (ESI): m/z = 188.1 $[M+H]^+$

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25 Intermediate B10: 4,6-dimethoxy-5-methyl-pyrimidin-2-amine

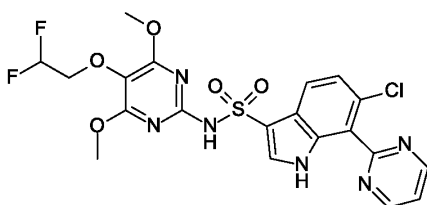


Intermediate B10 is known (CAS 341009-90-3).

Examples

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Example 1: 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide



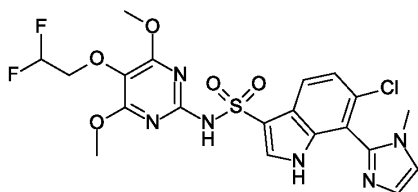
A suspension of 6-chloro-7-(2-pyrimidyl)-1H-indole-3-sulfonyl chloride (Intermediate A1, 50 mg, 117 μmol), [5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]amine (Intermediate B1, 25 mg, 106 μmol) and potassium phosphate tribasic (33 mg, 148 μmol) in acetonitrile (1.5 ml) was stirred at room temperature for 30 min. n-Ethyl diisopropylamine (21 mg, 28 μl , 159 μmol) was added and stirring was continued at room temperature for 10 min. The reaction mixture was poured into water and extracted with ethyl acetate twice. The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 0% to 70% ethyl acetate in heptane) to provide the title compound (14 mg, 25% yield) as off-white solid. MS (ESI) m/z : 527.0 $[\text{M}+\text{H}]^+$

The following **Examples 2-7** were prepared in analogy to Example 1 by coupling the indicated sulfonylchloride intermediates A and amine intermediates B.

Ex.	Structure	Name	Int. A	Int. B	MS (ESI): m/z

2		6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-oxazol-2-yl-1H-indole-3-sulfonamide	A2	B1	516.1 [M+H] ⁺
3		6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide	A1	B2	511.0 [M+H] ⁺
4		6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyridazin-3-yl-1H-indole-3-sulfonamide	A3	B1	527.1 [M+H] ⁺
5		N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylimidazol-2-yl)-1H-indole-3-sulfonamide	A4	B2	478.1 [M+H] ⁺
6		6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyridazin-3-yl-1H-indole-3-sulfonamide	A3	B2	511.1 [M+H] ⁺
7		N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylimidazol-2-yl)-1H-indole-3-sulfonamide	A4	B1	495.2 [M+H] ⁺

Example 8: 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylimidazol-2-yl)-1H-indole-3-sulfonamide

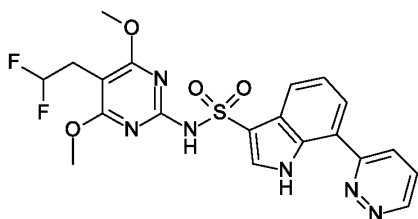


A solution of [5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]amine (Intermediate B1, 30 mg, 128 μmol) in pyridine (1.2 ml) was heated to 80 °C. 6-Chloro-7-(1-methylimidazol-2-yl)-1H-indole-3-sulfonyl chloride (Intermediate A6, 43 mg, 128 μmol) was added in 5 portions within 15 min. The reaction mixture was stirred for 5 min at 80 °C. The reaction mixture was concentrated in vacuo and the residue was poured into water and extracted with ethyl acetate twice. The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 0% to 100% ethyl acetate in heptane) to provide the title compound (17 mg, 25%) as white solid. MS (ESI) m/z : 529.2 $[\text{M}+\text{H}]^+$

The following **Examples 9-10** were prepared in analogy to Example 8 by coupling the indicated sulfonylchloride intermediates A and amine intermediates B.

Ex.	Structure	Name	Int. A	Int. B	MS (ESI): m/z
9		N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-fluoro-7-(1-methylimidazol-2-yl)-1H-indole-3-sulfonamide	A14	B1	511.4 $[\text{M}-\text{H}]^-$
10		N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-6-fluoro-7-(1-methylimidazol-2-yl)-1H-indole-3-sulfonamide	A14	B2	497.3 $[\text{M}+\text{H}]^+$

Example 11: N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyridazin-3-yl-1H-indole-3-sulfonamide

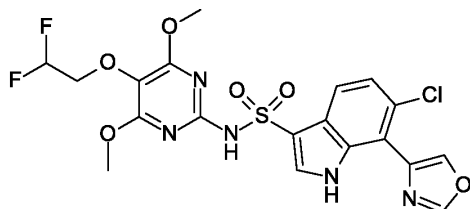


To a stirred solution of [5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]amine (Intermediate B2, 40 mg, 182 μ mol) and N-ethyl diisopropylamine (48 mg, 64 μ l, 365 μ mol) in dichloromethane (1.2 ml) was added 7-pyridazin-3-yl-1H-indole-3-sulfonyl chloride (Intermediate A7, 62 mg, 201 μ mol) portionwise at room temperature. The reaction mixture was stirred at room temperature for 3 days. The reaction mixture was poured into water and extracted with ethyl acetate twice. The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 0% to 100% ethyl acetate in heptane) to provide the title compound (11 mg, 13% yield) as white solid. MS (ESI) m/z: 477.2 [M+H]⁺

The following **Examples 12-13** were prepared in analogy to Example 11 by coupling the indicated sulfonylchloride intermediates A and amine intermediates B.

Ex.	Structure	Name	Int. A	Int. B	MS (ESI): m/z
12		N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyridazin-3-yl-1H-indole-3-sulfonamide	A7	B1	493.2 [M+H] ⁺
13		N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(4-methylpyridazin-3-yl)-1H-indole-3-sulfonamide	A8	B1	507.2 [M+H] ⁺

Example 14: 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-oxazol-4-yl-1H-indole-3-sulfonamide

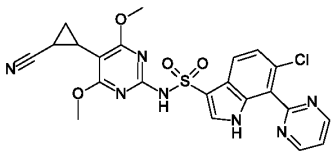
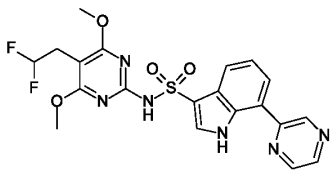
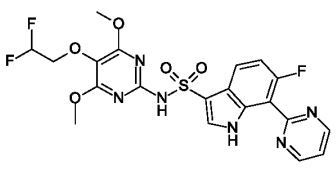
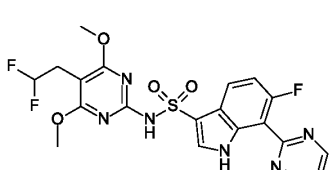
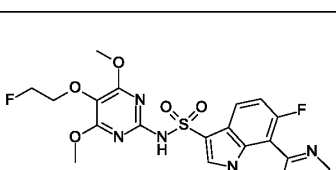
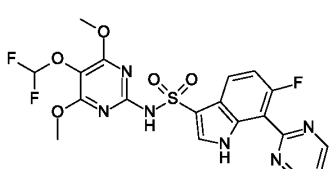


To a stirred solution of [5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]amine
 5 (Intermediate B1, 36 mg, 153 μmol) and N-ethyl diisopropylamine (40 mg, 53 μl , 306 μmol) in dichloromethane (1 ml) was added a solution of 6-chloro-7-oxazol-4-yl-1H-indole-3-sulfonyl chloride (Intermediate A9, 56 mg, 168 μmol) in ethyl acetate (1 ml) dropwise at room temperature. The reaction mixture was stirred at room temperature for 15 min. The mixture was poured into water and extracted with ethyl acetate twice. The combined organic layers were
 10 dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (silica gel (12 g, 0% to 60% ethyl acetate in heptane) to provide the title compound (38 mg, 49% yield) as off-white solid. MS (ESI) m/z : 516.2 $[\text{M}+\text{H}]^+$

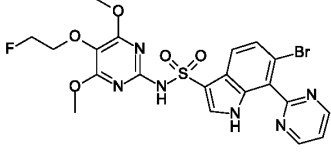
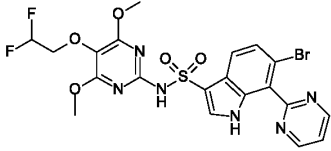
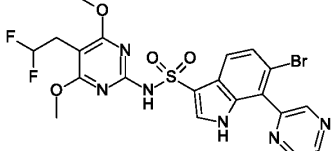
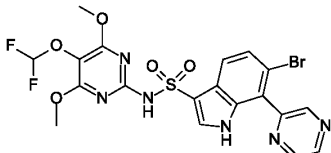
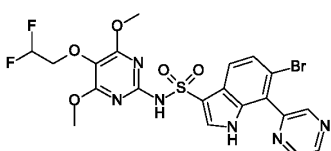
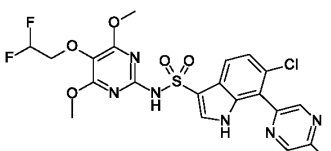
The following **Examples 15-33** were prepared in analogy to Example 14 by coupling the indicated
 15 sulfonylchloride intermediates A and amine intermediates B.

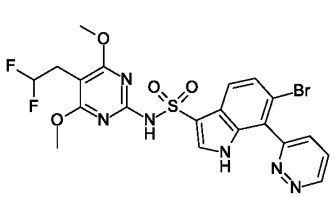
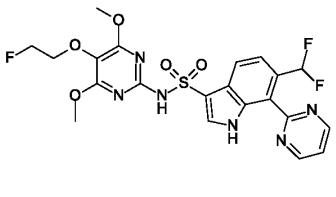
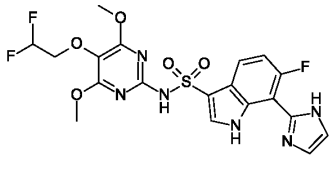
Ex.	Structure	Name	Int. A	Int. B	MS (ESI): m/z
15		6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-1H-indole-3-sulfonamide	A10	B2	493.2 $[\text{M}+\text{H}]^+$
16		6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-1H-indole-3-sulfonamide	A10	B1	527.1 $[\text{M}+\text{H}]^+$

17		N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide	A11	B2	477.2 [M+H] ⁺
18		6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyridyl)-1H-indole-3-sulfonamide	A5	B2	510.2 [M+H] ⁺
19		6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyridyl)-1H-indole-3-sulfonamide	A5	B1	526.2 [M+H] ⁺
20		6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-1H-indole-3-sulfonamide	A10	B3	513.2 [M+H] ⁺
21		6-chloro-N-[5-(2-fluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-1H-indole-3-sulfonamide	A10	B4	509.2 [M+H] ⁺
22		6-chloro-N-[5-(2-fluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide	A1	B4	509.2 [M+H] ⁺
23		6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide	A1	B3	513.2 [M+H] ⁺

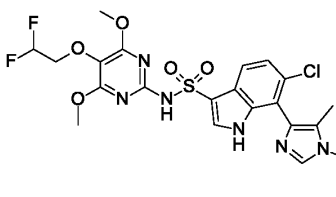
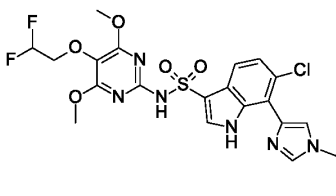
		7-(2-pyrimidyl)-1H-indole-3-sulfonamide			
24		6-chloro-N-[5-(2-cyanocyclopropyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide	A1	B5	512.3 [M+H] ⁺
25		N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-1H-indole-3-sulfonamide	A12	B2	477.2 [M+H] ⁺
26		N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-fluoro-7-(2-pyrimidyl)-1H-indole-3-sulfonamide	A13	B1	511.3 [M+H] ⁺
27		N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-6-fluoro-7-(2-pyrimidyl)-1H-indole-3-sulfonamide	A13	B2	495.3 [M+H] ⁺
28		6-fluoro-N-[5-(2-fluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide	A13	B4	493.3 [M+H] ⁺
29		N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-fluoro-7-(2-pyrimidyl)-1H-indole-3-sulfonamide	A13	B3	497.5 [M+H] ⁺

30		N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-1H-indole-3-sulfonamide	A12	B1	493.3 [M+H] ⁺
31		N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-6-fluoro-7-pyrazin-2-yl-1H-indole-3-sulfonamide	A15	B2	495.3 [M+H] ⁺
32		6-fluoro-N-[5-(2-fluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-1H-indole-3-sulfonamide	A15	B4	493.3 [M+H] ⁺
33		N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-fluoro-7-pyrazin-2-yl-1H-indole-3-sulfonamide	A15	B1	511.3 [M+H] ⁺
34		N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-fluoro-7-pyrazin-2-yl-1H-indole-3-sulfonamide	A15	B3	497.3 [M+H] ⁺
35		6-bromo-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide	A16	B2	557.1 [M+H] ⁺
36		6-bromo-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide	A16	B3	559.0 [M+H] ⁺

37		6-bromo-N-[5-(2-fluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide	A16	B4	555.1 [M+H] ⁺
38		6-bromo-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide	A16	B1	573.0 [M+H] ⁺
39		6-bromo-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-1H-indole-3-sulfonamide	A17	B2	557.1 [M+H] ⁺
40		6-bromo-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-1H-indole-3-sulfonamide	A17	B3	559.1 [M+H] ⁺
41		6-bromo-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-1H-indole-3-sulfonamide	A17	B1	573.1 [M+H] ⁺
42		6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(5-fluoropyrazin-2-yl)-1H-indole-3-sulfonamide	A18	B1	545.1 [M+H] ⁺

43		6-bromo-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyridazin-3-yl-1H-indole-3-sulfonamide	A19	B2	557.1 [M+H] ⁺
44		6-(difluoromethyl)-N-[5-(2-fluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide	A20	B4	525.1 [M+H] ⁺
45		N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-fluoro-7-(1H-imidazol-2-yl)-1H-indole-3-sulfonamide	A21	B1	499.3 [M+H] ⁺

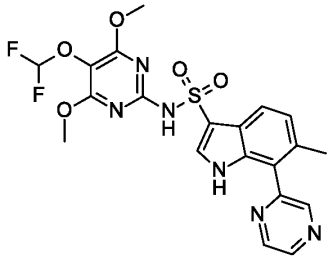
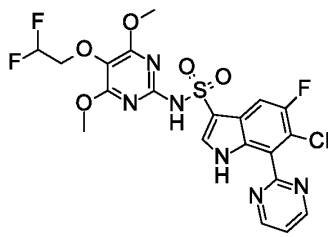
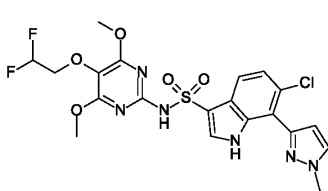
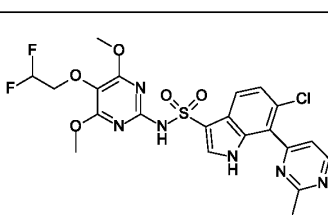
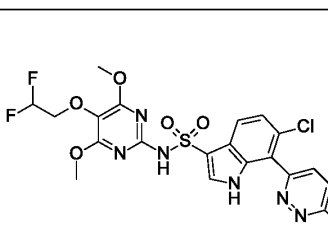
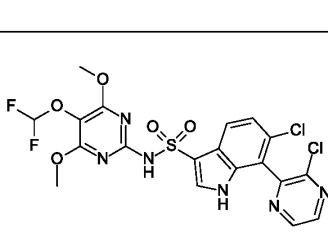
The following **Examples 46-47** were prepared in analogy to Example 8 by coupling the indicated sulfonylchloride intermediates A and amine intermediates B.

Ex.	Structure	Name	Int. A	Int. B	MS (ESI): m/z
46		6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1,5-dimethylimidazol-4-yl)-1H-indole-3-sulfonamide	A30	B1	543.2 [M+H] ⁺
47		6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylimidazol-4-yl)-1H-indole-3-sulfonamide	A37	B1	529.2 [M+H] ⁺

The following **Examples 48-71** were prepared in analogy to Example 14 by coupling the indicated sulfonylchloride intermediates A and amine intermediates B.

Ex.	Structure	Name	Int. A	Int. B	MS (ESI): m/z
48		N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-methyl-7-(2-pyrimidyl)-1H-indole-3-sulfonamide	A22	B1	507.3 [M+H] ⁺
49		N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-(difluoromethyl)-7-(2-pyrimidyl)-1H-indole-3-sulfonamide	A20	B1	543.2 [M+H] ⁺
50		N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-(difluoromethyl)-7-(2-pyrimidyl)-1H-indole-3-sulfonamide	A20	B3	529.1 [M+H] ⁺
51		N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-6-(difluoromethyl)-7-(2-pyrimidyl)-1H-indole-3-sulfonamide	A20	B2	527.1 [M+H] ⁺
52		N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-6-methyl-7-(2-pyrimidyl)-1H-indole-3-sulfonamide	A22	B2	491.3 [M+H] ⁺

53		N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-methylpyrazin-2-yl)-1H-indole-3-sulfonamide	A27	B2	491.3 [M+H] ⁺
54		N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-methylpyrazin-2-yl)-1H-indole-3-sulfonamide	A27	B1	507.3 [M+H] ⁺
55		N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-methyl-7-(2-pyrimidyl)-1H-indole-3-sulfonamide	A22	B3	493.3 [M+H] ⁺
56		N-[5-(2-fluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-methyl-7-(2-pyrimidyl)-1H-indole-3-sulfonamide	A22	B4	489.3 [M+H] ⁺
57		N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-methyl-7-pyridazin-3-yl-1H-indole-3-sulfonamide	A29	B1	507.3 [M+H] ⁺
58		N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-methyl-7-pyrazin-2-yl-1H-indole-3-sulfonamide	A31	B1	507.3 [M+H] ⁺

59		N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-methyl-7-pyrazin-2-yl-1H-indole-3-sulfonamide	A31	B3	493.3 [M+H] ⁺
60		6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-5-fluoro-7-(2-pyrimidyl)-1H-indole-3-sulfonamide	A34	B1	545.2 [M+H] ⁺
61		6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylpyrazol-3-yl)-1H-indole-3-sulfonamide	A36	B1	529.3 [M+H] ⁺
62		6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-methylpyrimidin-4-yl)-1H-indole-3-sulfonamide	A41	B1	541.1 [M+H] ⁺
63		6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methylpyridazin-3-yl)-1H-indole-3-sulfonamidemide	A44	B1	539.2 [M-H] ⁻
64		6-chloro-7-(3-chloropyrazin-2-yl)-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-1H-indole-3-sulfonamide	A45	B3	547.2 [M+H] ⁺

65		6-chloro-7-(3-chloropyrazin-2-yl)-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-1H-indole-3-sulfonamide	A45	B2	545.2 [M+H] ⁺
66		6-chloro-7-(3-chloropyrazin-2-yl)-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-1H-indole-3-sulfonamide	A45	B1	561.2 [M+H] ⁺
67		6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylpyrazol-3-yl)-1H-indole-3-sulfonamide	A36	B3	515.1 [M+H] ⁺
68		6-chloro-N-[5-(2-fluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylpyrazol-3-yl)-1H-indole-3-sulfonamide	A36	B4	511.2 [M+H] ⁺
69		6-bromo-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylpyrazol-4-yl)-1H-indole-3-sulfonamide	A48	B1	575.1 [M+H] ⁺
70		6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-phenyl-1H-indole-3-sulfonamide	A23	B1	525.1 [M+H] ⁺

71		6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-phenyl-1H-indole-3-sulfonamide	A23	B2	509.1 [M+H] ⁺
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The following **Examples 72-117** were prepared in analogy to Example 11 by coupling the indicated sulfonylchloride intermediates A and amine intermediates B.

Ex.	Structure	Name	Int. A	Int. B	MS (ESI): m/z
72		N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide	A11	B1	493.2 [M+H] ⁺
73		6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-methylpyrazin-2-yl)-1H-indole-3-sulfonamide	A24	B1	541.2 [M+H] ⁺
74		6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-methylpyrazin-2-yl)-1H-indole-3-sulfonamide	A24	B2	525.2 [M+H] ⁺
75		N-(5-bromo-4,6-dimethoxy-pyrimidin-2-yl)-6-chloro-7-(2-pyrimidyl)-1H-indole-3-sulfonamide	A1	B6	527.0 [M+H] ⁺

76		6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(4-pyrimidyl)-1H-indole-3-sulfonamide	A26	B2	511.1 [M+H] ⁺
77		6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(4-pyrimidyl)-1H-indole-3-sulfonamide	A26	B1	527.1 [M+H] ⁺
78		6-chloro-N-[5-(cyanomethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide	A1	B7	502.2 [M+H] ⁺
79		6-chloro-N-[5-(2-cyanoethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide	A1	B8	500.3 [M+H] ⁺
80		6-chloro-N-[5-(2-fluoroethoxy)-4-methoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide	A1	B9	479.2 [M+H] ⁺
81		6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-methylpyrazin-2-yl)-1H-indole-3-sulfonamide	A24	B3	527.2 [M+H] ⁺

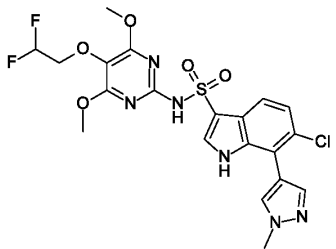
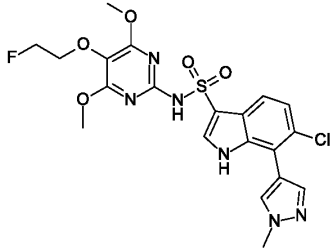
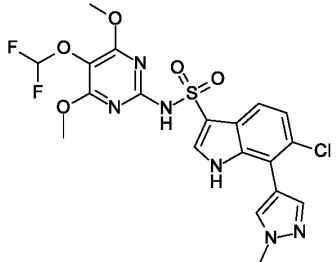
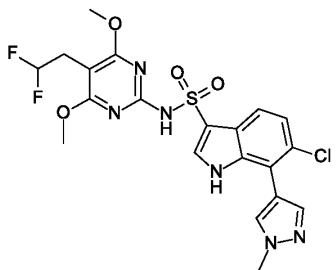
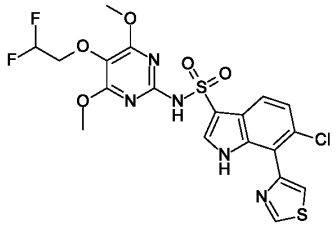
82		6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(5-methylpyrazin-2-yl)-1H-indole-3-sulfonamide	A32	B2	525.2 [M+H] ⁺
83		6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(5-methylpyrazin-2-yl)-1H-indole-3-sulfonamide	A32	B3	527.2 [M+H] ⁺
84		6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(5-methylpyrazin-2-yl)-1H-indole-3-sulfonamide	A32	B1	541.2 [M+H] ⁺
85		6-chloro-N-(4,6-dimethoxy-5-methyl-pyrimidin-2-yl)-7-(2-pyrimidyl)-1H-indole-3-sulfonamide	A1	B10	461.2 [M+H] ⁺
86		6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methylpyrazin-2-yl)-1H-indole-3-sulfonamide	A33	B2	525.2 [M+H] ⁺
87		6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methylpyrazin-2-yl)-1H-indole-3-sulfonamide	A33	B3	527.1 [M+H] ⁺

88		6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methylpyrazin-2-yl)-1H-indole-3-sulfonamide	A33	B1	541.1 [M+H] ⁺
89		6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(5-pyrimidyl)-1H-indole-3-sulfonamide	A35	B1	527.2 [M+H] ⁺
90		6-chloro-7-(5-chloropyrazin-2-yl)-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-1H-indole-3-sulfonamide	A38	B1	561.2 [M+H] ⁺
91		6-chloro-7-(5-chloropyrazin-2-yl)-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-1H-indole-3-sulfonamide	A38	B2	545.2 [M+H] ⁺
92		6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methyl-2-pyridyl)-1H-indole-3-sulfonamide	A39	B1	538.2 [M-H] ⁻
93		6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methyl-2-pyridyl)-1H-indole-3-sulfonamide	A39	B2	524.2 [M+H] ⁺

94		6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methyl-2-pyridyl)-1H-indole-3-sulfonamide	A39	B3	524.1 [M-H] ⁻
95		6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyridazin-4-yl-1H-indole-3-sulfonamide	A40	B1	527.2 [M+H] ⁺
96		6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methylpyrimidin-4-yl)-1H-indole-3-sulfonamide	A42	B1	541.1 [M+H] ⁺
97		6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-fluoropyrazin-2-yl)-1H-indole-3-sulfonamide	A43	B2	529.2 [M+H] ⁺
98		6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-fluoropyrazin-2-yl)-1H-indole-3-sulfonamide	A43	B1	545.2 [M+H] ⁺
99		6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-fluoropyrazin-2-yl)-1H-indole-3-sulfonamide	A43	B3	529.2 [M-H] ⁻

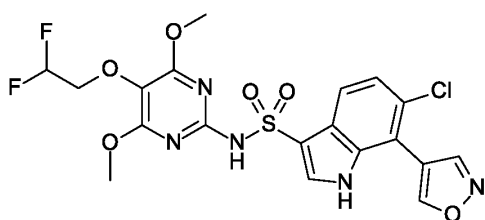
100		6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-methyl-2-pyridyl)-1H-indole-3-sulfonamide	A46	B1	540.2 [M+H] ⁺
101		6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methyl-1,2,4-triazol-4-yl)-1H-indole-3-sulfonamide	A47	B1	530.2 [M+H] ⁺
102		6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-methyl-2-pyridyl)-1H-indole-3-sulfonamide	A46	B2	524.2 [M+H] ⁺
103		6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-methyl-2-pyridyl)-1H-indole-3-sulfonamide	A46	B3	526.3 [M+H] ⁺
104		6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methyl-1,2,4-triazol-3-yl)-1H-indole-3-sulfonamide	A49	B1	530.2 [M+H] ⁺
105		6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(5-fluoropyrimidin-2-yl)-1H-indole-3-sulfonamide	A50	B1	545.1 [M+H] ⁺

106		6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-methyltriazol-4-yl)-1H-indole-3-sulfonamide	A51	B1	530.2 [M+H] ⁺
107		6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-methyltriazol-4-yl)-1H-indole-3-sulfonamide	A51	B3	516.2 [M+H] ⁺
108		6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-methyltriazol-4-yl)-1H-indole-3-sulfonamide	A51	B2	514.2 [M+H] ⁺
109		6-chloro-N-[5-(2-fluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-methyltriazol-4-yl)-1H-indole-3-sulfonamide	A51	B4	512.2 [M+H] ⁺
110		6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1,3,4-oxadiazol-2-yl)-1H-indole-3-sulfonamide	A52	B1	517.1 [M+H] ⁺

111		6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylpyrazol-4-yl)-1H-indole-3-sulfonamide	A53	B1	529.2 [M+H] ⁺
112		6-chloro-N-[5-(2-fluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylpyrazol-4-yl)-1H-indole-3-sulfonamide	A53	B4	511.1 [M+H] ⁺
113		6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylpyrazol-4-yl)-1H-indole-3-sulfonamide	A53	B3	515.1 [M+H] ⁺
114		6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylpyrazol-4-yl)-1H-indole-3-sulfonamide	A53	B2	513.2 [M+H] ⁺
115		6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-thiazol-4-yl-1H-indole-3-sulfonamide	A54	B1	532.1 [M+H] ⁺

116		6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-oxazol-5-yl-1H-indole-3-sulfonamide	A25	B1	516.0 [M+H] ⁺
117		6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-oxazol-5-yl-1H-indole-3-sulfonamide	A25	B3	502.1 [M+H] ⁺

Example 118: 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-isoxazol-4-yl-1H-indole-3-sulfonamide



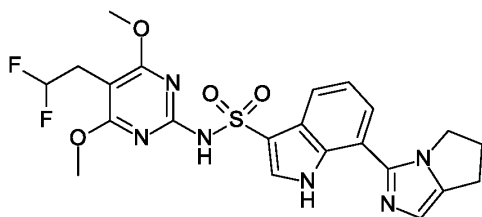
- 5 To a solution of [5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]amine (Intermediate B1, 5 mg, 21 μ mol) in acetonitrile (100 μ l) was added pyridine (100 μ l) and 6-chloro-7-isoxazol-4-yl-1H-indole-3-sulfonyl chloride (Intermediate A28, 10 mg, 25.5 μ mol) and the resulting mixture was stirred for 7 h at room temperature. Water was added and the mixture was extracted two times with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered and then concentrated. The residue was purified by chromatography (silica gel, methanol in dichloromethane 0% to 15%) to give the title compound (49 mg, 55% yield) as white solid, MS (ESI) m/z: 516.0 [M+H]⁺.

- 15 The following **Examples 119-120** were prepared in analogy to Example 118 by coupling the indicated sulfonylchloride intermediates A and amine intermediates B.

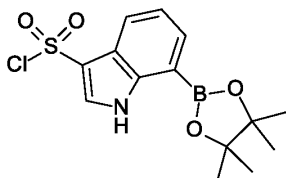
Ex.	Structure	Name	Int. A	Int. B	MS (ESI): m/z
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119		6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-isoxazol-4-yl-1H-indole-3-sulfonamide	A28	B3	502.0 [M+H] ⁺
120		6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-thiazol-4-yl-1H-indole-3-sulfonamide	A54	B3	518.0 [M+H] ⁺

Example 121: N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6,7-dihydro-5H-pyrrol[1,2-c]imidazol-3-yl)-1H-indole-3-sulfonamide



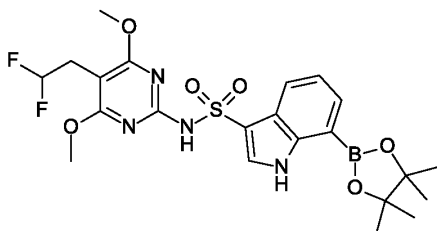
5 Step 1: 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-3-sulfonyl chloride



A solution of 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (CAS 642494-37-9, 200 mg, 0.80 mmol) in acetonitrile (3 ml) was cooled to 0 °C. Chlorosulfonic acid (242 mg, 140 µl, 2.07 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 2 h, then poured into ice/ethyl acetate and extracted with ethyl acetate twice. The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo to provide 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-3-sulfonyl chloride (204 mg, 56% yield) as light red gum. MS (ESI) m/z: 340.2 [M-H]⁻.

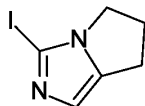
15 Step 2: N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-3-sulfonamide

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To a stirred solution of [5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]amine (Intermediate B2, 88 mg, 0.40 mmol) and N-ethyldiisopropylamine (159 mg, 210 μ l, 1.2 mmol) in dichloromethane (3 ml) was added a solution of 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-3-sulfonyl chloride (201 mg, 0.44 mmol) dropwise at room temperature. The reaction mixture was stirred at room temperature for 15 h. The reaction mixture was poured into brine and extracted twice with ethyl acetate. The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 0% to 45% ethyl acetate in heptane) to provide N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-3-sulfonamide (53 mg, 25% yield) as white solid. MS (ESI) m/z: 525.3 [M+H]⁺.

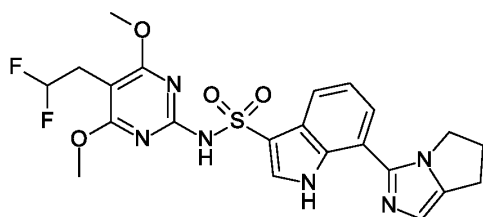
Step 3: 3-iodo-6,7-dihydro-5H-pyrrolo[1,2-c]imidazole



To the stirred solution of 6,7-dihydro-5H-pyrrolo[1,2-c]imidazole (CAS 52237-16-8, 500 mg, 4.62 mmol) in dry tetrahydrofuran (8 ml) n-butyllithium solution (2.5 M in hexanes, 2.2 ml, 5.55 mmol) was added at -78°C and the mixture was stirred at this temperature for 40 min. Then a solution of molecular iodine (1.52 g, 6.01 mmol) in dry tetrahydrofuran (4 ml) was slowly added and mixture was stirred at -78°C for 40 min. The mixture was quenched with ammonium chloride solution (15 ml) and extracted with ethyl acetate (25 ml). The organic layer was washed with aqueous sodium thiosulfate solution (15 ml) and brine, dried over Na₂SO₄ and evaporated. The residue was purified by flash chromatography (silica gel, 0% to 30% ethyl acetate in heptane) to give 3-iodo-6,7-dihydro-5H-pyrrolo[1,2-c]imidazole (600 mg, 55% yield) as white solid, MS (ESI) m/z: 235.0 [M+H]⁺.

Step 4: N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-3-yl)-1H-indole-3-sulfonamide

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A mixture of N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-3-sulfonamide (51 mg, 97 μmol), 3-iodo-6,7-dihydro-5H-pyrrol[1,2-c]imidazole (25 mg, 107 μmol), cesium carbonate (64 mg, 194 μmol) and
 5 tetrakis(triphenylphosphine)palladium(0) (11 mg, 10 μmol , 0.10 eq) in 1,4-dioxane (500 μl) and water (250 μl) was heated to 110 $^{\circ}\text{C}$ and stirred for 15 h. The reaction mixture was poured into brine and extracted twice with ethyl acetate. The organic layers were dried over Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 0% to 100% ethyl acetate in heptane) followed by another flash chromatography (column C18 RediSep
 10 Rf Gold, 10% to 60% acetonitrile in water) to provide the title compound (4.5 mg, 9% yield) as white solid, MS (ESI) m/z : 503.2 $[\text{M}-\text{H}]^-$.

Example A

15 A compound of formula I can be used in a manner known per se as the active ingredient for the production of tablets of the following composition:

	<u>Per tablet</u>
Active ingredient	200 mg
Microcrystalline cellulose	155 mg
20 Corn starch	25 mg
Talc	25 mg
Hydroxypropylmethylcellulose	<u>20 mg</u>
	425 mg

25

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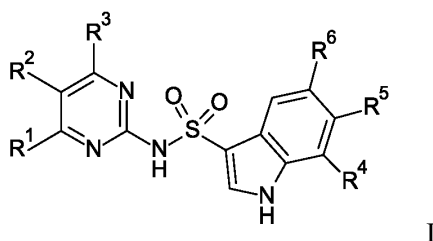
Example B

A compound of formula I can be used in a manner known per se as the active ingredient for the production of capsules of the following composition:

5		<u>Per capsule</u>
	Active ingredient	100.0 mg
	Corn starch	20.0 mg
	Lactose	95.0 mg
	Talc	4.5 mg
10	Magnesium stearate	<u>0.5 mg</u>
		220.0 mg

Claims

1. Compounds of formula I



5 wherein

R¹ is alkoxy or haloalkoxy;

R² is halo, alkyl, alkoxy, haloalkyl, haloalkoxy, cyanoalkyl, cyanoalkoxy or cyclopropyl
optional substituted with up to two substituents independently selected from cyano
and halo;

10 R³ is H, alkoxy or haloalkoxy;

R⁵ is H, halo, alkyl, or haloalkyl;

R⁶ is H or halo;

R⁴ is a C-linked aryl or a C-linked heteroaryl, wherein the C-linked aryl or C-linked
heteroaryl is optionally substituted by one or more substituents independently
15 selected from alkyl, halo, and haloalkyl;

and pharmaceutically acceptable salts.

2. A compound according to claim 1, wherein R¹ is alkoxy.

20 3. A compound according to claim 1 or claim 2, wherein R² is halo, alkyl, haloalkyl,
haloalkoxy, cyanoalkyl, cyanoalkoxy or cyclopropyl substituted with cyano.

4. A compound according to any of claims 1 to 3, wherein R² is alkyl, haloalkyl or
haloalkoxy.

25 5. A compound according to any of claims 1 to 4, wherein R³ is H or alkoxy.

6. A compound according to any of claims 1 to 5, wherein R⁵ is alkyl, H, or halo.

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7. A compound according to any of claims 1 to 6, wherein R⁵ is H or halo.
8. A compound according to any of claims 1 to 7 wherein R⁶ is H.
- 5 9. A compound according to any of claims 1 to 8, wherein R⁴ is a C-linked aryl or a C-linked heteroaryl, wherein the C-linked aryl or C-linked heteroaryl is optionally substituted by one or more substituents independently selected from alkyl and halo.
- 10 10. A compound according to any of claims 1 to 9, wherein R⁴ is selected from
- v. a C-linked 6-member aryl;
 - vi. a C-linked 6-member heteroaryl comprising 1 to 2 nitrogen heteroatoms optionally substituted with alkyl or halo;
 - vii. a C-linked 5-member heteroaryl comprising 1-3 heteroatoms independently selected from N, S and O, optionally substituted with 1 to 2 substituents
 - 15 independently selected from alkyl and halo; and
 - viii. a C-linked 8-membered bicyclic heteroaryl system comprising 2 N heteroatoms.
- 20 11. A compound according to claim 1, wherein
- R¹ is alkoxy;
 - R² is halo, alkyl, haloalkyl, haloalkoxy, cyanoalkyl, cyanoalkoxy or cyclopropyl substituted with cyano;
 - R³ is H or alkoxy;
 - 25 R⁵ is H, halo, alkyl, or haloalkyl;
 - R⁶ is H or halo;
 - R⁴ is a C-linked aryl or a C-linked heteroaryl, wherein the C-linked aryl or C-linked heteroaryl is optionally substituted by one or more substituents independently selected from alkyl and halo;
 - 30 and pharmaceutically acceptable salts.
12. A compound according to claim 1, wherein
- R¹ is alkoxy;

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R² is halo, alkyl, haloalkyl, haloalkoxy, cyanoalkyl, cyanoalkoxy or cyclopropyl substituted with cyano;

R³ is H or alkoxy;

R⁵ is H, halo, alkyl, or haloalkyl;

5 R⁶ is H or halo;

R⁴ is selected from

- i. a C-linked 6-member aryl;
- ii. a C-linked 6-member heteroaryl comprising 1 to 2 nitrogen heteroatoms optionally substituted with alkyl or halo;
- 10 iii. a C-linked 5-member heteroaryl comprising 1-3 heteroatoms independently selected from N, S and O, optionally substituted with 1 to 2 substituents independently selected from alkyl and halo; and
- iv. a C-linked 8-membered bicyclic heteroaryl system comprising 2 N heteroatoms;

15 and pharmaceutically acceptable salts

13. A compound according to any of claims 1 to 12, selected from

6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;

20

6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-oxazol-2-yl-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;

25

6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyridazin-3-yl-1H-indole-3-sulfonamide;

N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylimidazol-2-yl)-1H-indole-3-sulfonamide;

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6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyridazin-3-yl-1H-indole-3-sulfonamide;

N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylimidazol-2-yl)-1H-indole-3-sulfonamide;

5 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylimidazol-2-yl)-1H-indole-3-sulfonamide;

N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-fluoro-7-(1-methylimidazol-2-yl)-1H-indole-3-sulfonamide;

10 N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-6-fluoro-7-(1-methylimidazol-2-yl)-1H-indole-3-sulfonamide;

N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyridazin-3-yl-1H-indole-3-sulfonamide;

N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyridazin-3-yl-1H-indole-3-sulfonamide;

15 N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(4-methylpyridazin-3-yl)-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-oxazol-4-yl-1H-indole-3-sulfonamide;

20 6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-1H-indole-3-sulfonamide;

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N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyridyl)-1H-indole-3-sulfonamide;

5 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyridyl)-1H-indole-3-sulfonamide;

6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-1H-indole-3-sulfonamide;

10 6-chloro-N-[5-(2-fluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2-fluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;

6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;

15 6-chloro-N-[5-(2-cyanocyclopropyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;

N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-1H-indole-3-sulfonamide;

20 N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-fluoro-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;

N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-6-fluoro-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;

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6-fluoro-N-[5-(2-fluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-
1H-indole-3-sulfonamide;

N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-fluoro-7-(2-pyrimidyl)-
1H-indole-3-sulfonamide;

5 N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-1H-
indole-3-sulfonamide;

N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-6-fluoro-7-pyrazin-2-yl-
1H-indole-3-sulfonamide;

10 6-fluoro-N-[5-(2-fluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-
1H-indole-3-sulfonamide;

N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-fluoro-7-pyrazin-2-
yl-1H-indole-3-sulfonamide;

N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-fluoro-7-pyrazin-2-yl-
1H-indole-3-sulfonamide;

15 6-bromo-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-
pyrimidyl)-1H-indole-3-sulfonamide;

6-bromo-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-
pyrimidyl)-1H-indole-3-sulfonamide;

20 6-bromo-N-[5-(2-fluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-
1H-indole-3-sulfonamide;

6-bromo-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-
pyrimidyl)-1H-indole-3-sulfonamide;

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6-bromo-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-1H-indole-3-sulfonamide;

6-bromo-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-1H-indole-3-sulfonamide;

5 6-bromo-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(5-fluoropyrazin-2-yl)-1H-indole-3-sulfonamide;

10 6-bromo-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyridazin-3-yl-1H-indole-3-sulfonamide;

6-(difluoromethyl)-N-[5-(2-fluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;

N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-fluoro-7-(1H-imidazol-2-yl)-1H-indole-3-sulfonamide; and

15 pharmaceutically acceptable salts thereof.

14. A compound according to any one of claims 1 to 12 selected from

20 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1,5-dimethylimidazol-4-yl)-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylimidazol-4-yl)-1H-indole-3-sulfonamide;

25 N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-methyl-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;

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- N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-(difluoromethyl)-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;
- N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-(difluoromethyl)-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;
- 5 N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-6-(difluoromethyl)-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;
- N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-6-methyl-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;
- 10 N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-methylpyrazin-2-yl)-1H-indole-3-sulfonamide;
- N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-methylpyrazin-2-yl)-1H-indole-3-sulfonamide;
- N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-methyl-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;
- 15 N-[5-(2-fluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-methyl-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;
- N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-methyl-7-pyridazin-3-yl-1H-indole-3-sulfonamide;
- N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-methyl-7-pyrazin-2-yl-1H-indole-3-sulfonamide;
- 20 N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-6-methyl-7-pyrazin-2-yl-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-5-fluoro-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;
- 25 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylpyrazol-3-yl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-methylpyrimidin-4-yl)-1H-indole-3-sulfonamide;

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- 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methylpyridazin-3-yl)-1H-indole-3-sulfonamide;
- 6-chloro-7-(3-chloropyrazin-2-yl)-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-1H-indole-3-sulfonamide;
- 5 6-chloro-7-(3-chloropyrazin-2-yl)-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-1H-indole-3-sulfonamide;
- 6-chloro-7-(3-chloropyrazin-2-yl)-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-1H-indole-3-sulfonamide;
- 10 6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylpyrazol-3-yl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2-fluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylpyrazol-3-yl)-1H-indole-3-sulfonamide;
- 6-bromo-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylpyrazol-4-yl)-1H-indole-3-sulfonamide;
- 15 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-phenyl-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-phenyl-1H-indole-3-sulfonamide;
- N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;
- 20 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-methylpyrazin-2-yl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-methylpyrazin-2-yl)-1H-indole-3-sulfonamide;
- 25 N-(5-bromo-4,6-dimethoxy-pyrimidin-2-yl)-6-chloro-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(4-pyrimidyl)-1H-indole-3-sulfonamide;

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- 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(4-pyrimidyl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(cyanomethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;
- 5 6-chloro-N-[5-(2-cyanoethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2-fluoroethoxy)-4-methoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;
- 10 6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-methylpyrazin-2-yl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(5-methylpyrazin-2-yl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(5-methylpyrazin-2-yl)-1H-indole-3-sulfonamide;
- 15 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(5-methylpyrazin-2-yl)-1H-indole-3-sulfonamide;
- 6-chloro-N-(4,6-dimethoxy-5-methyl-pyrimidin-2-yl)-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;
- 20 6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methylpyrazin-2-yl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methylpyrazin-2-yl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methylpyrazin-2-yl)-1H-indole-3-sulfonamide;
- 25 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(5-pyrimidyl)-1H-indole-3-sulfonamide;
- 6-chloro-7-(5-chloropyrazin-2-yl)-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-1H-indole-3-sulfonamide;

- 6-chloro-7-(5-chloropyrazin-2-yl)-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methyl-2-pyridyl)-1H-indole-3-sulfonamide;
- 5 6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methyl-2-pyridyl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methyl-2-pyridyl)-1H-indole-3-sulfonamide;
- 10 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyridazin-4-yl-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methylpyrimidin-4-yl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-fluoropyrazin-2-yl)-1H-indole-3-sulfonamide;
- 15 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-fluoropyrazin-2-yl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-fluoropyrazin-2-yl)-1H-indole-3-sulfonamide;
- 20 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-methyl-2-pyridyl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methyltriazol-4-yl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-methyl-2-pyridyl)-1H-indole-3-sulfonamide;
- 25 6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-methyl-2-pyridyl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methyl-1,2,4-triazol-3-yl)-1H-indole-3-sulfonamide;

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- 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(5-fluoropyrimidin-2-yl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-methyltriazol-4-yl)-1H-indole-3-sulfonamide;
- 5 6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-methyltriazol-4-yl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-methyltriazol-4-yl)-1H-indole-3-sulfonamide;
- 10 6-chloro-N-[5-(2-fluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-methyltriazol-4-yl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1,3,4-oxadiazol-2-yl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylpyrazol-4-yl)-1H-indole-3-sulfonamide;
- 15 6-chloro-N-[5-(2-fluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylpyrazol-4-yl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylpyrazol-4-yl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylpyrazol-4-yl)-1H-indole-3-sulfonamide;
- 20 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-thiazol-4-yl-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-oxazol-5-yl-1H-indole-3-sulfonamide;
- 25 6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-oxazol-5-yl-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-isoxazol-4-yl-1H-indole-3-sulfonamide;

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6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-isoxazol-4-yl-1H-indole-3-sulfonamide;

6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-thiazol-4-yl-1H-indole-3-sulfonamide;

- 5 N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6,7-dihydro-5H-pyrrol[1,2-c]imidazol-3-yl)-1H-indole-3-sulfonamide; and
pharmaceutically acceptable salts thereof.

- 10 15. A compound according to any one of claims 1 to 13, selected from

6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;

- 15 6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyridazin-3-yl-1H-indole-3-sulfonamide;

N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylimidazol-2-yl)-1H-indole-3-sulfonamide;

- 20 6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyridazin-3-yl-1H-indole-3-sulfonamide;

N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylimidazol-2-yl)-1H-indole-3-sulfonamide;

- 25 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylimidazol-2-yl)-1H-indole-3-sulfonamide;

N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-6-fluoro-7-(1-methylimidazol-2-yl)-1H-indole-3-sulfonamide;

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- 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-oxazol-4-yl-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-1H-indole-3-sulfonamide;
- 5 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyridyl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyridyl)-1H-indole-3-sulfonamide;
- 10 6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2-fluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-1H-indole-3-sulfonamide;
- 15 6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;
- 6-bromo-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;
- 6-bromo-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;
- 20 6-bromo-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-1H-indole-3-sulfonamide;
- 6-bromo-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-1H-indole-3-sulfonamide;

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6-bromo-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyrazin-2-yl-1H-indole-3-sulfonamide; and
pharmaceutically acceptable salts thereof.

5

16. A compound according to claim 1 to 12, or claim 14 selected from

6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1,5-dimethylimidazol-4-yl)-1H-indole-3-sulfonamide;

10

6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylimidazol-4-yl)-1H-indole-3-sulfonamide;

N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-6-methyl-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;

N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-methylpyrazin-2-yl)-1H-indole-3-sulfonamide;

15

6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylpyrazol-3-yl)-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-methylpyrimidin-4-yl)-1H-indole-3-sulfonamide;

20

6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methylpyridazin-3-yl)-1H-indole-3-sulfonamide;

6-chloro-7-(3-chloropyrazin-2-yl)-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-1H-indole-3-sulfonamide;

6-chloro-7-(3-chloropyrazin-2-yl)-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-1H-indole-3-sulfonamide;

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- 6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylpyrazol-3-yl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2-fluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methylpyrazol-3-yl)-1H-indole-3-sulfonamide;
- 5 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-methylpyrazin-2-yl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-methylpyrazin-2-yl)-1H-indole-3-sulfonamide;
- 10 6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(4-pyrimidyl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(4-pyrimidyl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-methylpyrazin-2-yl)-1H-indole-3-sulfonamide;
- 15 6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(5-methylpyrazin-2-yl)-1H-indole-3-sulfonamide;
- 6-chloro-N-(4,6-dimethoxy-5-methyl-pyrimidin-2-yl)-7-(2-pyrimidyl)-1H-indole-3-sulfonamide;
- 20 6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methylpyrazin-2-yl)-1H-indole-3-sulfonamide;
- 6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methylpyrazin-2-yl)-1H-indole-3-sulfonamide;

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6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methylpyrazin-2-yl)-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(5-pyrimidyl)-1H-indole-3-sulfonamide;

5 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methyl-2-pyridyl)-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methyl-2-pyridyl)-1H-indole-3-sulfonamide;

10 6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methyl-2-pyridyl)-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-pyridazin-4-yl-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6-methylpyrimidin-4-yl)-1H-indole-3-sulfonamide;

15 6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-fluoropyrazin-2-yl)-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-fluoropyrazin-2-yl)-1H-indole-3-sulfonamide;

20 6-chloro-N-[5-(difluoromethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-fluoropyrazin-2-yl)-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-methyl-2-pyridyl)-1H-indole-3-sulfonamide;

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6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1-methyltriazol-4-yl)-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(3-methyl-2-pyridyl)-1H-indole-3-sulfonamide;

5 6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-methyltriazol-4-yl)-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-methyltriazol-4-yl)-1H-indole-3-sulfonamide;

10 6-chloro-N-[5-(2-fluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(2-methyltriazol-4-yl)-1H-indole-3-sulfonamide;

6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-(1,3,4-oxadiazol-2-yl)-1H-indole-3-sulfonamide;

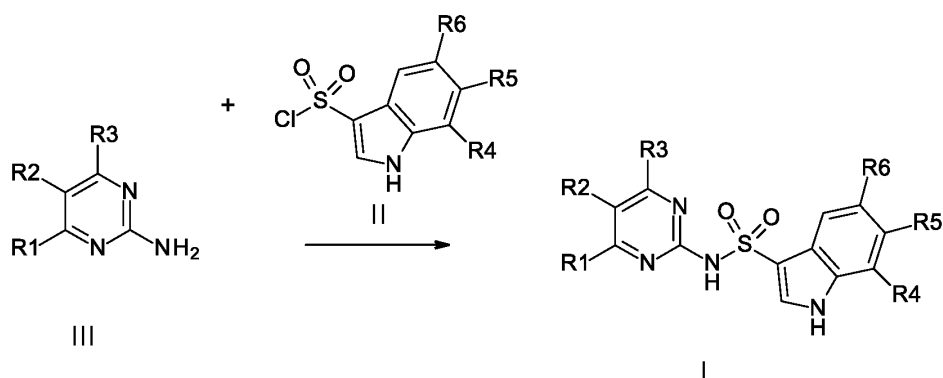
6-chloro-N-[5-(2,2-difluoroethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-7-thiazol-4-yl-1H-indole-3-sulfonamide;

15 N-[5-(2,2-difluoroethyl)-4,6-dimethoxy-pyrimidin-2-yl]-7-(6,7-dihydro-5H-pyrrol[1,2-c]imidazol-3-yl)-1H-indole-3-sulfonamide;

and pharmaceutically acceptable salts thereof.

- 20 17. A process to prepare a compound according to any one of claims 1 to 16 comprising the reacting a compound of formula III with a compound of formula II in the presence of a base selected from N-ethyl-diisopropylamine, pyridine, potassium phosphate or sodium hydride, to provide a compound of formula I,

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wherein R¹, R², R³, R⁴, R⁵ and R⁶ are as described above.

18. A compound according to any one of claims 1 to 16 for use as therapeutically active
5 substance.

19. A compound according to any one of claims 1 to 16 for use in the treatment of a disease
modulated by GPR17.

10 20. A pharmaceutical composition comprising a compound according to any one of claims 1
to 16 and a therapeutically inert carrier.

21. The use of a compound according to any one of claims 1 to 16 for the treatment or
prophylaxis of conditions resulting from direct damage to myelin sheaths (including but not
15 limited central pontine and extra-pontine myelinolysis, carbon monoxide poisoning, nutritional
deficiency, and virus-induced demyelination), demyelinating disorders (including but not limited
to multiple sclerosis, acute and multiphasic disseminated encephalomyelitis, neuromyelitis optica
spectrum disorders, and leukodystrophies), CNS disorders associated with myelin loss (including
but not limited to Alzheimer's disease, schizophrenia, Parkinson's disease, Huntington's disease,
20 Amyotrophic lateral sclerosis, and Ischemia due to stroke), and inflammation in the CNS for
instance following encephalitis, primary angiitis, meningitis and obesity.

22. The use of a compound according to any one of claims 1 to 16 for the treatment or
prophylaxis of multiple sclerosis.

25

23. The use of a compound according to any one of claims 1 to 16 for the preparation of a medicament for the treatment or prophylaxis of conditions resulting from direct damage to myelin sheaths (including but not limited central pontine and extra-pontine myelinolysis, carbon monoxide poisoning, nutritional deficiency, and virus-induced demyelination), demyelinating disorders (including but not limited to multiple sclerosis, acute and multiphasic disseminated encephalomyelitis, neuromyelitis optica spectrum disorders, and leukodystrophies), CNS disorders associated with myelin loss (including but not limited to Alzheimer's disease, schizophrenia, Parkinson's disease, Huntington's disease, Amyotrophic lateral sclerosis, and Ischemia due to stroke), and inflammation in the CNS for instance following encephalitis, primary angiitis, meningitis and obesity.

24. A compound according to any one of claims 1 to 16 for use in the treatment or prophylaxis of conditions resulting from direct damage to myelin sheaths (including but not limited central pontine and extra-pontine myelinolysis, carbon monoxide poisoning, nutritional deficiency, and virus-induced demyelination), demyelinating disorders (including but not limited to multiple sclerosis, acute and multiphasic disseminated encephalomyelitis, neuromyelitis optica spectrum disorders, and leukodystrophies), CNS disorders associated with myelin loss (including but not limited to Alzheimer's disease, schizophrenia, Parkinson's disease, Huntington's disease, Amyotrophic lateral sclerosis, and Ischemia due to stroke), and inflammation in the CNS for instance following encephalitis, primary angiitis, meningitis and obesity.

25. A compound according to any one of claims 1 to 16 for use in the treatment or prophylaxis of multiple sclerosis.

26. A method for the treatment or prophylaxis of conditions resulting from direct damage to myelin sheaths (including but not limited central pontine and extra-pontine myelinolysis, carbon monoxide poisoning, nutritional deficiency, and virus-induced demyelination), demyelinating disorders (including but not limited to multiple sclerosis, acute and multiphasic disseminated encephalomyelitis, neuromyelitis optica spectrum disorders, and leukodystrophies), CNS disorders associated with myelin loss (including but not limited to Alzheimer's disease, schizophrenia, Parkinson's disease, Huntington's disease, Amyotrophic lateral sclerosis, and Ischemia due to stroke), and inflammation in the CNS for instance following encephalitis,

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primary angiitis, meningitis and obesity, which method comprises administering an effective amount of a compound according to any one of claims 1 to 16 to a patient in need thereof.

27. A method for the treatment or prophylaxis of multiple sclerosis, which method comprises
5 administering an effective amount of a compound according to any one of claims 1 to 16 to a patient in need thereof.

28. A compound according to any one of claims 1 to 16, when manufactured according to a
process of claim 18.
10

29. The invention as hereinbefore described.

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