

PYRIDINYL AND PYRAZINYL-(AZA)INDOLSULFONAMIDES

Background

G-protein coupled receptors (GPCRs) constitute the largest family of membrane receptors in the cell. They transduce extracellular signals to intracellular effector systems and are involved in a large variety of physiological phenomena, therefore representing the most common targets of pharmaceutical drugs although only a small percentage of GPCRs are targeted by current therapies.

GPCRs respond to a wide range of ligands. Due to the progress in human genome sequencing, for about 25% out of the more than 400 GPCRs (not including the olfactory GPCRs) that have been identified, a defined physiologically relevant ligand is still lacking. These receptors are known as "orphan GPCRs". "Deorphanization" and identification of their in vivo roles is expected to clarify novel regulatory mechanisms and, therefore, to disclose novel drug targets. Whether GPR17 is such an orphan receptor is still a matter of debate. Phylogenetically, GPR17 is closely related to the nucleotide P2Y receptors and the cysteinyleukotriene (CysLT1, CysLT2) receptors, with an amino acid sequence identity of between about 30 and about 35%, respectively.

Multiple-tissue Northern blot and RT-PCR analyses indicate a predominant expression of GPR17 in the central nervous system (CNS) (Ciana et al., 2006, EMBO J 25(19): 4615; Blasius et al., 1998, J Neurochem 70(4): 1357) and additionally in heart and kidney, i.e. organs typically undergoing ischemic damage. Two human GPR17 isoforms have been identified differing only by the length of their N-terminus. The short GPR17 isoform encodes a 339 amino acid-residue protein with typical rhodopsin type-seven transmembrane motifs. The long isoform encodes a receptor with a 28 amino acid longer N-terminus (Blasius et al., 1998). GPR17 is highly conserved among vertebrate species (~90% identity of amino acid sequence to both mouse and rat orthologs), which may constitute an advantageous feature for development of small molecule ligands and animal models in a drug discovery context.

In the original deorphaning report, GPR17 was identified as a dual receptor for uracil nucleotides and cysteinyl-leukotrienes (cysLTs) LTC₄ and LTD₄, respectively based on ³⁵SGTPyS binding and cAMP inhibition assays as well as single cell calcium imaging (Ciana et al., 2006, *ibid*). Evidence for GPR17 functionality was provided in different cellular backgrounds such as 1321N1, COS7, CHO, and HEK293 cells (Ciana et al.,

2006, *ibid*). Subsequently, an independent study confirmed activation of GPR17 by uracil nucleotides but failed to recapitulate activation by CysLTs (Benned-Jensen and Rosenkilde, 2010, *Br J Pharmacol*, 159(5): 1092). Yet recent independent reports (Qi et al., 2013, *J Pharmacol Ther* 347,1, 38; Hennen et al., 2013, *Sci Signal* 6, 298) suggested
5 lack of GPR17 responsiveness to both uracil nucleotides and CysLTs across different cellular backgrounds stably expressing GPR17 (1321N1, CHO, HEK293 cells). A novel regulatory role for GPR17 has also been proposed: GPR17 – upon coexpression with the CysLT1 receptor– rendered the CysLT1 receptor unresponsive to its endogenous lipid mediators LTC4 and LTD4. Additional investigations are required to probe GPR17
10 pharmacology and function in more depth.

Drugs modulating the GPR17 activity may have neuroprotective, anti-inflammatory and anti-ischemic effects and may thus be useful for the treatment of cerebral, cardiac and renal ischemia, and stroke (WO 2006/045476), and/or for improving the recovery from these events (Bonfanti et al, *Cell Death and Disease*, 2017, 8, e2871).

15 GPR17 modulators are also thought to be involved in food uptake, insulin and leptin responses and are thus claimed to have a role in obesity treatment (WO 2011/113032).

Moreover, there is strong evidence that GPR17 is involved in myelination processes and that negative GPR17 modulators (antagonists or inverse agonists) can be valuable drugs for the treatment or alleviation of myelination disorders such as multiple sclerosis or spinal
20 cord injury (Chen et al, *Nature neuroscience* 2009, 12(11):1398-1406; Ceruti et al; *Brain: a journal of neurology* 2009 132(Pt 8):2206-18; Hennen et al, *Sci Signal*, 6, 2013, 298; Simon et al *J Biol Chem* 291, 2016, 705; Fumagalli et al, *Neuropharmacology* 104, 2016, 82). More recently, two groups showed that adult GPR17^{-/-} knock-out mice had faster remyelination than littermate wild-type after LPC induced demyelination in the spinal cord
25 (Lu et al., *Scientific Reports*, 2018, 8:4502) or in the corpus callosum (Ou et al., *J. Neurosci.*, 2016, 36(41):10560). In contrast, activation of GPR17 has been shown to inhibit oligodendrocyte precursor cells (OPCs) maturation thus preventing effective myelination (Simon et al, *supra*). This again confirmed a potential crucial role in GPR17 in the remyelination process and as promising drug target in demyelinating diseases. The
30 identification of potent and selective GPR17 antagonists or inverse agonists would thus be of significant relevance in the treatment of myelination disorders.

Several serious myelination diseases are known to be caused by disturbances in myelination, either by a loss of myelin (usually called demyelination), and/or by a failure of the body to properly form myelin (sometimes called dysmyelination). The myelination

diseases may be idiopathic or secondary to certain trigger events like e.g. traumatic brain injury or viral infection. Myelination diseases may primarily affect the central nervous system (CNS) but may also concern the peripheral nervous system. Myelination diseases include, inter alia, multiple sclerosis, neuromyelitis optica (also known as Devic's disease),
5 leucodystrophies, Guillain-Barré syndrome, and many other diseases as described in more detail further below (see also e.g. Love, J Clin Pathol, 59, 2006, 1151, Fumagalli et al, supra). Neurodegenerative diseases such as Alzheimer's Disease, Huntington's Disease, Parkinson's Disease, amyotrophic lateral sclerosis (ALS) and multiple system atrophy (MSA) have been also strongly associated with decreased myelination recently
10 (see e.g. Etle et al, Mol Neurobiol 53, 2016, 3046; Jellinger and Welling, Movement Disorders, 31, 2016; 1767; Kang et al, Nature Neurosci 6, 2013, 571; Bartzokis, Neurochem Res (2007) 32:1655).

Multiple Sclerosis (MS) is a chronic progressive disorder. It is an inflammatory autoimmune disease causing oligodendrocyte damage, demyelination and ultimately
15 axonal loss, thus leading to a broad spectrum of signs and symptoms of a severe neurological disease, like e.g. fatigue, dizziness, mobility and walking issues, speech and swallowing difficulties, pain and others. MS takes several forms, with new symptoms either occurring in isolated attacks (relapsing forms) or building up over time (progressive forms). While certain symptoms may disappear completely between isolated attacks,
20 severe neurological problems often remain, especially as the disease advances to a more progressive form. According to the Multiple Sclerosis Association of America, approximately 400,000 individuals have been diagnosed with MS in the United States and as many as 2.5 million worldwide, with an estimated 10,000 new cases diagnosed in the United States annually. Multiple sclerosis is two to three times more common in women
25 than in men.

There is no known causal treatment or cure for multiple sclerosis, or many other myelination diseases. Treatments are usually symptomatic and try to improve function after an attack and prevent new attacks, by addressing the inflammatory component of the disease. Such immunomodulatory drugs are usually only modestly effective, in particular if
30 the disease is progressed, but can have side effects and be poorly tolerated. Moreover, most of the available drugs, like β -interferons, glatiramer acetate, or therapeutic antibodies are only available in injectable form and/or only address the inflammatory component of the disease but not demyelination directly. Other drugs, like corticosteroids, show rather unspecific anti-inflammatory and immunosuppressive effects thus potentially
35 leading to chronic side effects, such as manifested in Cushing's syndrome, for example.

A strong need therefore exists for a safe and effective drug for the treatment of myelination diseases, like MS, preferably for a drug that is suitable for oral administration. Ideally such a drug would reverse the demyelination process by decreasing demyelination and/or by promoting remyelination of the impacted neurons. A chemical compound which
5 effectively decreases the GPR17 receptor activity could fulfil these requirements.

However, only few chemical compounds are known that effectively modulate GPR17 activity.

WO 2005/103291 suggests the endogenous molecules 5 amino levulinic acid (5-ALA) and porphobilinogen (PBG) as activating ligands for GPR17, discloses analgesic effects of a
10 GPR17 agonist and proposes the use of GPR17 agonists for treating neuropathic pain and as tools in GPR17 screening assays. However, the reported affinity of 5-ALA and PBG is quite low and the amounts needed in the assays are significant, namely in the three digit micromolar range for 5-ALA or even in the mM range for PBG, which make both compounds not well suited for use in routine screening assays or even for therapy.
15 Moreover, PBG is a chemically unstable, reactive compound which rapidly decomposes after exposure to air and light, making it impractical to handle on a routine basis. Hence, these compounds do not offer a promising starting point to develop therapeutically effective negative GPR17 modulators.

Montelukast and pranlukast were originally developed as leukotriene receptor antagonists
20 and were recently found to act on the GPR17 receptor as well (Ciana et al, EMBO J. 2006, 25, 4615–4627). However, subsequent results in a functional assay were contradictory for montelukast (Hennen et al, 2013, *ibid*), while pharmacological inhibition of GPR17 with pranlukast promotes differentiation of primary mouse (Hennen et al., 2013, *ibid*) and rat (Ou et al., J. Neurosci. 36, 2016, 10560-10573) oligodendrocytes. Pranlukast
25 even phenocopies the effect of GPR17 depression in a lysolecithin model of focal demyelination because both GPR17 knock-out and pranlukast-treated wild-type mice show an earlier onset of remyelination (Ou, *ibid*). These results strongly support the hypothesis that GPR17 inhibitors offer potential for the treatment of human demyelinating diseases.

30 However, the affinity of montelukast and pranlukast to GPR17 is only in the high micromolar range (Köse et al, ACS Med. Chem. Lett. 2014, 5, 326–330). Given the high protein binding of both compounds and their poor brain penetration, it is unlikely that they could reach high enough free concentrations to bind to GPR17 receptors in amounts suitable for human therapy. In addition, results obtained in vivo with these compounds are

difficult to interpret due to their confounding high affinity for CYSLT1 receptors. Cross-reactions to other receptors further complicates using them for targeting GPR17.

- US 8,623,593 discloses certain indole-2-carboxylic acids as GPR17 agonists and their use in screening assays. However, these derivatives are all potent agonists and are not suited to down-regulate GPR17 activity as needed in the treatment of myelination disorders such as MS. Moreover, this class of GPR17 activators does not sufficiently pass the blood-brain barrier due to their easily ionizable carboxyl groups, and were thus no suitable lead compounds to develop negative GPR17 modulators. See also Baqi et al, Med. Chem. Commun., 2014, 5, 86 and Köse et al, 2014, *ibid*.
- WO 2013/167177 suggests certain phenyltriazole and benzodiazepine compounds as GPR17 antagonists. However, the disclosed compounds were selected solely based on in- silico screening results and no biological data at all was provided. The inventors of the present application were unable to confirm the GPR17 antagonist modulating activity of any of purported ligands proposed by the authors of this former patent application so far.
- A need therefore exists to identify potent modulators, preferably negative modulators, in particular inverse agonists of GPR17 which are capable of effectively decreasing the GPR17 activity, preferably upon oral administration.

Figures:

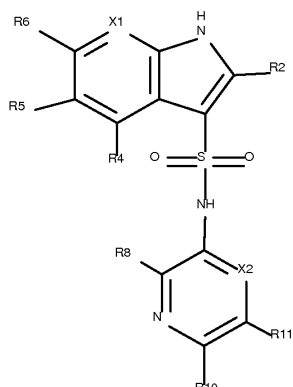
- Figure 1 shows the effect of compound I-22 on myelin expression in an oligodendrocyte/myelination assay.

Description of the Invention

- The present invention relates to compounds which act as negative modulators of the GPR17 receptor. In a preferred embodiment, the compounds act as negative agonists of the GPR17 receptor, thus inhibiting a constitutionally active GPR17.

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In one embodiment, the compounds have the structure of formula I



- wherein X1 is N or C(R7),
R2 is hydrogen or halogen, preferably hydrogen or fluoro,
- 5 R4 is hydrogen or fluoro,
R5 is hydrogen or halogen,
R6 is selected from halogen, cyano, C₃₋₅ cycloalkyl, C₃₋₅ cycloalkylmethoxy, phenyloxy, benzyloxy, benzylmethoxy, pyridinylmethoxy, C₁₋₃ alkoxy and C₁₋₃ alkyl, wherein each cycloalkyl, benzyl, pyridinyl, alkyl and alkoxy can be substituted with one or more
- 10 substituent selected from halogen, cyano, C₁₋₂alkoxy and fluoroC₁₋₂alkoxy, or
R6 together with R7 and the C-atoms to which they are attached form a five or six-membered aromatic or non-aromatic ring which may comprise one or two ring forming heteroatoms, wherein said ring is preferably a phenyl or pyridyl, and wherein said ring is unsubstituted or substituted with one to three residues R13,
- 15 R7, if present, is selected from hydrogen, halogen, cyclopropyl, cyclopropyloxy, C₁₋₃ alkoxy, and C₁₋₃ alkyl, wherein each alkyl and alkoxy can be substituted with one or more substituent selected from halogen, C₁₋₂ alkoxy, fluoro(C₁₋₂)alkoxy and cyano, or
R7 forms a ring together with R6 as described above,
R8 is selected from hydrogen, halogen, methoxy, ethoxy, fluoromethoxy and fluoroethoxy,
- 20 R10 is selected from hydrogen, cyano, halogen, C₃₋₅ cycloalkyl, C₃₋₅ cycloalkyloxy, C₃₋₅ cycloalkylmethoxy, C₁₋₄ alkoxy, and C₁₋₄ alkyl, wherein each cycloalkyl, cycloalkyloxy, alkyl and alkoxy can be substituted with one or more substituent selected from halogen, C₁₋₃ alkoxy, fluoro(C₁₋₃)alkoxy and cyano,
R11 is selected from hydrogen, fluoro and methoxy,
- 25 X2 is N or C(R12),
R12 is selected from hydrogen, methoxy and halogen,
R13, in each occurrence, is independently selected from halogen, hydroxy, cyano, methyl, methoxy, fluoromethyl and fluoromethoxy,

and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof.

In one embodiment of the compounds of Formula I, R6 forms together with R7 and the carbon atoms to which R6 and R7 are attached an unsubstituted or substituted phenyl,
5 unsubstituted or substituted pyridyl, or unsubstituted or substituted C₅₋₆ cycloalkyl, wherein each substitution, if present, of a ring formed by R6 and R7, is preferably selected from fluoro, chloro, cyano, hydroxy, methyl, fluoromethyl, methoxy and fluoromethoxy,

In each occurrence, where the compounds of the present invention contain a R6 and a R7 group, which, together with the ring forming atoms of the bicyclic ring system to which
10 they are attached, form another cycle selected from phenyl and pyridyl, this cycle together with the bicyclic moiety to which it is annulated forms a tricyclic moiety which is preferably selected from 1H-benzo[g]indol-3-yl and 1H-pyrrolo[3,2-h]quinolin-3-yl, respectively. In one embodiment, any substitution of the 1H-pyrrolo[3,2-h]quinolin-3-yl moiety is preferably in 8 position such as to result in, for example, 8-(fluoromethyl)-1H-pyrrolo[3,2-h]quinoline.

15

One embodiment relates to compounds of formula I, wherein

X1 is N or C(R7),

R2 is hydrogen or halogen, preferably hydrogen or fluoro,

R4 is hydrogen or fluoro,

20 R5 is hydrogen or halogen,

R6 is selected from halogen, cyano, cyclopropyl, benzyl, benzyloxy, pyridinylmethoxy, C₁₋₂ alkoxy and C₁₋₂ alkyl, wherein each cyclopropyl, benzyl, pyridinyl, alkyl and alkoxy can be substituted with one or more substituent selected from halogen, cyano, C₁₋₂ alkoxy and fluoroC₁₋₂alkoxy, or

25 R6 together with R7 and the C-atoms to which they are attached form a pyridyl ring, such that the pyridyl together with the bicyclic ring system to which it is annulated forms a 1H-pyrrolo[3,2-h]quinoline, wherein the pyridyl ring is substituted with one or two residues R13 or is, preferably, unsubstituted,

30 R7, if present, is selected from hydrogen, halogen, cyclopropyl, cyclopropyloxy, C₁₋₃ alkoxy, and C₁₋₃ alkyl, wherein each alkyl and alkoxy can be substituted with one or more substituent selected from halogen, C₁₋₂ alkoxy, fluoro(C₁₋₂)alkoxy and cyano, or

R7 forms a ring together with R6 as described above,

R8 is selected from hydrogen, halogen, methoxy, ethoxy, fluoromethoxy and fluoroethoxy,

35 R10 is selected from hydrogen, cyano, halogen, C₃₋₅ cycloalkyl, C₃₋₅ cycloalkyloxy, C₃₋₅ cycloalkylmethoxy, C₁₋₄ alkoxy, and C₁₋₄ alkyl, wherein each cycloalkyl, cycloalkyloxy, alkyl

- and alkoxy can be substituted with one or more substituent selected from halogen, C₁₋₃ alkoxy, fluoro(C₁₋₃)alkoxy and cyano,
R11 is selected from hydrogen, fluoro and methoxy,
X2 is N or C(R12),
- 5 R12 is selected from hydrogen, methoxy and halogen,
R13, in each occurrence, is independently selected from fluoro, chloro, cyano, hydroxy, methyl, methoxy, fluoromethyl and fluoromethoxy,
and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof.
- 10 One embodiment relates to a compound of formula I,
wherein
X1 is N or C(R7),
R2 is hydrogen or halogen, preferably hydrogen or fluoro,
R4 is hydrogen or fluoro,
- 15 R5 is hydrogen or halogen,
R6 is selected from halogen, cyano, C₃₋₅ cycloalkyl, C₃₋₅ cycloalkylmethoxy, benzyloxy, benzylmethoxy, pyridinylmethoxy, C₁₋₃ alkoxy and C₁₋₃ alkyl, wherein each cycloalkyl, benzyl, pyridinyl, alkyl and alkoxy can be substituted with one or more substituent selected from halogen, cyano, C₁₋₂alkoxy and fluoroC₁₋₂alkoxy
- 20 R7, if present, is selected from hydrogen, halogen, cyclopropyl, cyclopropyloxy, C₁₋₃ alkoxy, and C₁₋₃ alkyl, wherein each alkyl and alkoxy can be substituted with one or more substituent selected from halogen, C₁₋₂ alkoxy, fluoro(C₁₋₂)alkoxy and cyano, wherein preferably, R7 is selected from hydrogen and halogen, in particular from hydrogen and fluoro,
- 25 R8 is selected from hydrogen, halogen, methoxy, ethoxy, fluoromethoxy and fluoroethoxy,
R10 is selected from hydrogen, halogen, C₃₋₅ cycloalkyl, C₃₋₅ cycloalkyloxy, C₃₋₅ cycloalkylmethoxy, C₁₋₄ alkoxy, and C₁₋₄ alkyl, wherein each cycloalkyl, cycloalkyloxy, alkyl and alkoxy can be substituted with one or more substituent selected from halogen, C₁₋₃ alkoxy, fluoro(C₁₋₃)alkoxy and cyano,
- 30 R11 is selected from hydrogen, fluoro and methoxy,
X2 is N or C(R12),
R12 is selected from hydrogen, methoxy and halogen,
and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof.
- 35 One embodiment relates to compounds of Formula I, wherein
X1 is N or C(R7),

- R2 is hydrogen or halogen, preferably hydrogen or fluoro,
R4 is hydrogen or fluoro,
R5 is hydrogen or halogen,
R6 is selected from halogen, cyano, C₃₋₅ cycloalkyl, C₃₋₅ cycloalkylmethoxy, benzyloxy,
5 benzylmethoxy, pyridinylmethoxy, C₁₋₃ alkoxy and C₁₋₃ alkyl, wherein each cycloalkyl, benzyl, pyridinyl, alkyl and alkoxy can be substituted with one or more substituent selected from halogen, cyano, methoxy, and fluoromethoxy,
R7, if present, is selected from hydrogen, halogen, cyclopropyl, cyclopropyloxy, C₁₋₃ alkoxy, and C₁₋₃ alkyl, wherein each alkyl and alkoxy can be substituted with one or more
10 substituent selected from halogen, C₁₋₂ alkoxy, fluoro(C₁₋₂)alkoxy and cyano,
R8 is selected from hydrogen, halogen, methoxy and fluoromethoxy,
R10 is selected from hydrogen, halogen, C₃₋₅ cycloalkyl, C₃₋₅ cycloalkyloxy, C₁₋₄ alkoxy, and C₁₋₄ alkyl, wherein each cycloalkyl, cycloalkyloxy, alkyl and alkoxy can be substituted with one or more substituent selected from halogen, C₁₋₃ alkoxy, fluoro(C₁₋₃)alkoxy and
15 cyano,
R11 is selected from hydrogen, fluoro and methoxy,
X2 is N or C(R12),
R12 is selected from hydrogen, methoxy and halogen,
and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof.
20
- One embodiment relates to compounds of formula I, wherein X1 is N or C(R7),
R2, R4 and R5 are independently selected from hydrogen and fluoro, and are preferably hydrogen,
R6 is selected from halogen, cyano, C₃₋₅ cycloalkyl, benzyloxy, pyridin-3-ylmethoxy,
25 pyridin-4-ylmethoxy, C₁₋₃ alkoxy and C₁₋₃ alkyl, wherein each cycloalkyl, benzyl, pyridinyl, alkyl and alkoxy can be substituted with one or more substituent selected from halogen, methoxy, and fluoromethoxy,
R7, if present, is selected from hydrogen, halogen, cyclopropyl, cyclopropyloxy, C₁₋₂ alkoxy, and C₁₋₂ alkyl, wherein each alkyl and alkoxy can be substituted with one or more
30 substituent selected from halogen, methoxy, fluoromethoxy and cyano,
R8 is selected from hydrogen, halogen, and methoxy,
R10 is selected from halogen, C₃₋₄ cycloalkyl, C₃₋₄ cycloalkyloxy, C₁₋₃ alkoxy, and C₁₋₃ alkyl, wherein each cycloalkyl, cycloalkyloxy, alkyl and alkoxy can be substituted with one or more substituent selected from halogen, C₁₋₂ alkoxy, fluoro(C₁₋₂)alkoxy and cyano,
35 R11 is selected from hydrogen, fluoro and methoxy,
X2 is N or C(R12),

R12 is selected from hydrogen, methoxy and halogen,
and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof.

One embodiment relates to compounds of formula I, wherein

- 5 X1 is N or C(R7),
R2 is hydrogen,
R4 is hydrogen or fluoro,
R5 is hydrogen or fluoro,
R6 is selected from halogen, cyano, C₃₋₅ cycloalkyl, C₁₋₃ alkoxy, and C₁₋₃ alkyl, wherein
10 each cycloalkyl, alkyl and alkoxy can be substituted with one or more substituent selected
from halogen, methoxy, and fluoromethoxy,
R7, if present, is selected from hydrogen, halogen, cyclopropyl, cyclopropyloxy, C₁₋₂
alkoxy, and C₁₋₂ alkyl, wherein each alkyl and alkoxy can be substituted with one or more
substituent selected from halogen, C₁₋₂alkoxy, fluoro(C₁₋₂)alkoxy and cyano,
15 R8 is selected from hydrogen, halogen, methoxy and fluoromethoxy,
R10 is selected from halogen, C₃₋₄ cycloalkyl, C₃₋₄ cycloalkyloxy, C₁₋₃ alkoxy, and C₁₋₃ alkyl,
wherein each cycloalkyl, cycloalkyloxy, alkyl and alkoxy can be substituted with one or
more substituent selected from halogen, C₁₋₃ alkoxy, fluoro(C₁₋₃)alkoxy and cyano,
R11 is selected from hydrogen, fluoro and methoxy,
20 X2 is N or C(R12),
R12 is selected from hydrogen, methoxy, and fluoro,
and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof.

One embodiment relates to compound of formula I, wherein

- 25 X1 is N or C(R7),
R2 is hydrogen,
R4 is hydrogen or fluoro, preferably hydrogen
R5 is hydrogen or fluoro, preferably hydrogen,
R6 is selected from halogen, cyano, cyclopropyl, C₁₋₂ alkoxy, and C₁₋₂ alkyl, wherein each
30 alkyl and alkoxy can be substituted with one or more substituent selected from halogen,
methoxy, and fluoromethoxy,
R7, if present, is selected from hydrogen, halogen, cyclopropyl, cyclopropyloxy, C₁₋₂
alkoxy, and C₁₋₂ alkyl, wherein each alkyl and alkoxy can be substituted with one or more
substituent selected from halogen, C₁₋₂alkoxy, fluoro C₁₋₂alkoxy and cyano,
35 R8 is selected from hydrogen, halogen, methoxy and fluoromethoxy,

R10 is selected from halogen, C₃₋₄ cycloalkyl, C₃₋₄ cycloalkyloxy, C₁₋₃ alkoxy, and C₁₋₃ alkyl, wherein each cycloalkyl, cycloalkyloxy, alkyl and alkoxy can be substituted with one or more substituent selected from halogen, C₁₋₃ alkoxy, fluoro C₁₋₃ alkoxy and cyano,

R11 is selected from hydrogen, fluoro and methoxy,

5 X2 is N or C(R12),

R12 is selected from hydrogen, methoxy and fluoro,

and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof

One embodiment relates to compound of formula I, wherein

10 X1 is N or C(R7),

R2 is hydrogen

R4 and R5 are independently selected from hydrogen and fluoro,

R6 is selected from halogen, cyano, cyclopropyl, methoxy, and methyl, wherein each methoxy and methyl can be substituted with one or more substituent selected from

15 halogen, methoxy, and fluoromethoxy,

R7, if present, is selected from hydrogen, halogen, cyclopropyl, cyclopropyloxy, methoxy and methyl, wherein each methoxy and methyl can be substituted with one or more substituent selected from fluoro, methoxy, fluoromethoxy and cyano,

R8 is selected from hydrogen, halogen, methoxy and fluoromethoxy,

20 R10 is selected from halogen, C₃₋₄ cycloalkyl, C₃₋₄ cycloalkyloxy, C₁₋₂ alkoxy, and C₁₋₂ alkyl, wherein each cycloalkyl, cycloalkyloxy, alkyl and alkoxy can be substituted with one or more substituent selected from halogen, C₁₋₂ alkoxy, fluoro C₁₋₂ alkoxy and cyano,

R11 is selected from hydrogen, fluoro and methoxy,

X2 is N or C(R12),

25 R12 is selected from hydrogen, methoxy and fluoro,

and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof

One embodiment relates to compound of formula I, wherein

X1 is N or C(R7),

30 R2 is hydrogen

R4 and R5 are independently selected from hydrogen and fluoro,

R6 is selected from halogen, cyano, cyclopropyl, C₁₋₃ alkoxy and C₁₋₃ alkyl, wherein each alkoxy and alkyl can be unsubstituted or substituted with one or more halogens, preferably with one or more fluoro atoms,

35 R7, if present, is selected from hydrogen and halogen, preferably from hydrogen and fluoro,

- R8 is selected from hydrogen, halogen, methoxy, fluoromethoxy and fluoroethoxy,
R10 is selected from halogen, cycloC₃₋₅alkyl, C₁₋₃ alkoxy, and C₁₋₃ alkyl, wherein each cycloalkyl, alkyl and alkoxy can be substituted with one or more substituent selected from halogen, C₁₋₂ alkoxy and halogenated C₁₋₂ alkoxy,
- 5 R11 is selected from hydrogen, halogen and methoxy,
X2 is N or C(R12),
R12 is selected from hydrogen, methoxy and halogen,
and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof
- 10 One embodiment relates to compound of formula I, wherein
X1 is N or C(R7),
R2, R4 and R5 are all hydrogen,
R6 is selected from halogen, cyano, cyclopropyl, methoxy, methyl and isopropyl, wherein each methoxy and methyl can be unsubstituted or substituted with one or more fluoros,
- 15 R7, if present, is selected from hydrogen, fluoro, and chloro,
R8 is selected from hydrogen, fluoro, methoxy, fluoromethoxy and fluoroethoxy,
R10 is selected from halogen, methyl, cyclopropyl, cyclopropyloxy and C₁₋₃ alkoxy, wherein each alkoxy can be substituted with one or more substituent selected from fluoro, C₁₋₂ alkoxy and fluoro C₁₋₂ alkoxy,
- 20 R11 is selected from hydrogen, fluoro and methoxy,
X2 is N or C(R12),
R12 is selected from hydrogen, methoxy and fluoro,
and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof
- 25 One preferred embodiment relates to compounds of Formula I, wherein
X1 is N or C(R7),
R2, R4, and R5 are all hydrogen,
R6 is selected from halogen, cyano, methyl, fluoromethyl, methoxy and fluoromethoxy,
R7, if present, is selected from hydrogen, fluoro, chloro, cyclopropyloxy and fluoromethyl,
- 30 and preferably from hydrogen and fluoro,
R8 is selected from hydrogen, fluoro, and methoxy,
R10 is selected from halogen, cyclopropyl, and C₁₋₂ alkoxy, wherein the alkoxy can be optionally substituted with one or more substituent selected from fluoro, methoxy, ethoxy, and fluoro C₁₋₂ alkoxy,
- 35 R11 is hydrogen or fluoro
X2 is N or C(R12), and

wherein R12, if present, is selected from hydrogen, methoxy and fluoro, and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof.

One preferred embodiment relates to compounds of Formula I, wherein

- 5 R2, R4, and R5 are all hydrogen,
R6 is chloro or fluoromethyl,
X1 is N or C(R7),
R7, if present, is selected from hydrogen, fluoro, chloro, cyclopropyloxy and fluoromethyl,
R8 is selected from hydrogen, fluoro, and methoxy,
10 R10 is selected from halogen and C₁₋₂ alkoxy, wherein the alkoxy can be optionally substituted with one or more substituent selected from fluoro, cyano and fluoro C₁₋₂ alkoxy,
R11 is hydrogen or fluoro
X2 is N or C(R12), and
wherein R12, if present, is selected from hydrogen, methoxy and fluoro,
15 and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof.

One preferred embodiment relates to compounds of Formula I, wherein

- R2, R4, and R5 are all hydrogen,
R6 is selected from fluoro, chloro, cyano, methyl, methoxy, fluoromethoxy and
20 fluoromethyl,
X1 is N or C(R7),
R7, if present, is selected from hydrogen and fluoro,
R8 is selected from fluoro and methoxy,
R10 is selected from chloro, bromo, cyclopropyl and C₁₋₂ alkoxy, wherein the alkoxy is
25 substituted with either up to three fluoro atoms or with one substituent selected from methoxy, fluoromethoxy and fluoroethoxy,
R11 is hydrogen or fluoro
X2 is N or C(R12),
R12, if present, is hydrogen or fluoro, preferably hydrogen,
30 and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof.

One preferred embodiment relates to compounds of Formula I, wherein

- R2, R4, and R5 are all hydrogen,
R6 is chloro or difluoromethyl,
35 X1 is N or C(R7),

- R7, if present, is selected from hydrogen, fluoro, chloro, and fluoromethyl, preferably hydrogen,
- R8 is selected from fluoro and methoxy,
- R10 is selected from chloro, bromo and C₁₋₂ alkoxy, wherein the alkoxy is substituted with
- 5 either up to three fluoro atoms or with one fluoromethoxy,
- R11 is hydrogen or fluoro
- X2 is N or C(R12), and
- wherein R12, if present, is hydrogen or fluoro, preferably hydrogen,
- and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof.
- 10
- One preferred embodiment relates to compounds of Formula I, wherein R2 is hydrogen.
- One preferred embodiment relates to compounds of Formula I, wherein R4 is hydrogen.
- One preferred embodiment relates to compounds of Formula I, wherein R5 is hydrogen.
- One preferred embodiment relates to compounds of Formula I, wherein R5 is halogen,
- 15 preferably bromo.
- One preferred embodiment relates to compounds of Formula I, wherein R2, R4 and R5 are all hydrogen.
- One preferred embodiment relates to compounds of Formula I, wherein R6 is selected from halogen, cyano, fluoromethoxy and fluoromethyl,
- 20 One preferred embodiment relates to compounds of Formula I, wherein R6 is isopropyl.
- One preferred embodiment relates to compounds of Formula I, wherein R6 is selected from chloro or fluoromethyl, preferably from chloro and difluoromethyl,
- One preferred embodiment relates to compounds of Formula I, wherein R6 is fluoromethoxy.
- 25 One preferred embodiment relates to compounds of Formula I, wherein R6 is methoxy.
- One preferred embodiment relates to compounds of Formula I, wherein R6 is cyano.
- One preferred embodiment relates to compounds of Formula I, wherein R6 and R7 form together with the C-atoms to which they are attached a phenyl or pyridyl ring, which is either unsubstituted or substituted with one or more residues R13 as defined herein.
- 30 One preferred embodiment relates to compounds of Formula I, wherein R6 and R7 form together with the C-atoms to which they are attached an unsubstituted pyridyl ring; in one embodiment, said pyridyl ring forms together with the bicyclic system to which it is annulated, a 1H-pyrrolo[3,2-h]quinoline group.
- One preferred embodiment relates to compounds of Formula I, wherein R7 is hydrogen.
- 35 One preferred embodiment relates to compounds of Formula I, wherein R7 is selected from fluoro, chloro, cyclopropyloxy, fluoromethyl and fluoromethoxy.

One preferred embodiment relates to compounds of Formula I, wherein R7 is hydrogen or fluoro.

One preferred embodiment relates to compounds of Formula I, wherein R8 is selected from hydrogen, fluoro, methoxy and fluoromethoxy, preferably from fluoro and methoxy.

- 5 One preferred embodiment relates to compounds of Formula I, wherein R8 is methoxy.
One preferred embodiment relates to compounds of Formula I, wherein R10 is not hydrogen.

- One preferred embodiment relates to compounds of Formula I, wherein R10 is selected from halogen, C₃₋₄ cycloalkyloxy, C₁₋₃ alkoxy and C₁₋₃ alkyl, wherein each alkyl or alkoxy
10 can be substituted with one or more substituents selected from cyano, fluoro, C₁₋₂ alkoxy, and fluoro C₁₋₂ alkoxy

One preferred embodiment relates to compounds of Formula I, R10 is selected from halogen, cyclopropyl, and C₁₋₂ alkoxy, wherein the alkoxy can be optionally substituted with one or more substituent selected from fluoro, methoxy, ethoxy and fluoro C₁₋₂ alkoxy.

- 15 One preferred embodiment relates to compounds of Formula I, wherein R10 is selected from halogen, cyclopropyl, methoxy, fluoromethoxy, methoxyethoxy, fluoroethoxy and fluoroethoxymethoxy.

One preferred embodiment relates to compounds of Formula I, wherein R10 is selected from halogen, methoxy, ethoxy, fluoromethoxy, fluoroethoxy and fluoromethoxyethoxy.

- 20 One preferred embodiment relates to compounds of Formula I, wherein R10 is selected from chloro, bromo, methoxy, difluoromethoxy, monofluoroethoxy and difluoroethoxy.

One preferred embodiment relates to compounds of Formula I, wherein R11 is hydrogen or fluoro, preferably fluoro.

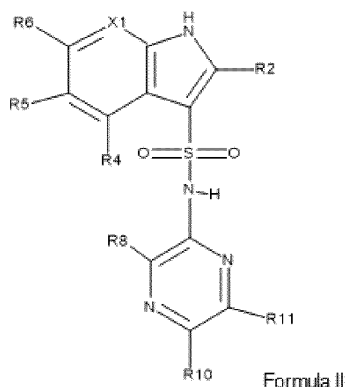
- One preferred embodiment relates to compounds of Formula I, wherein R11 is methoxy
25 and R8 is fluoro.

One preferred embodiment relates to compounds of Formula I, wherein X2 is C(R12) and R12 is hydrogen.

One preferred embodiment relates to compounds of Formula I, wherein X2 is C(R12) and R12 is hydrogen, R8 is methoxy and R11 is fluoro.

- 30 One preferred embodiment relates to compounds of Formula I, wherein X2 is C(R12) and R12 is fluoro.

One particular embodiment relates to compounds of Formula I, wherein X2 is N, thus having the structure of Formula II,



wherein all substituents are as described for Formula I hereinbefore.

5 In one embodiment, in the compounds of Formula II.

X1 is N or C(R7)

R2, R4, and R5 are all hydrogen,

R6 is selected from halogen, cyano, methyl, fluoromethyl, methoxy, fluoromethoxy and benzyloxy,

10 R7, if present, is selected from hydrogen, fluoro, chloro, cyclopropyloxy and fluoromethyl, and is preferably selected from hydrogen and fluoro,

R8 is selected from hydrogen, fluoro, and methoxy,

R10 is selected from halogen, cyclopropyl, C₁₋₂ alkyl, and C₁₋₂ alkoxy, wherein the alkyl and alkoxy can be optionally substituted with one or more substituent selected from fluoro,

15 cyano, methoxy and fluoro C₁₋₂ alkoxy,

R11 is selected from hydrogen, methoxy and fluoro, preferably from hydrogen and fluoro, and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof.

In one embodiment, in the compounds of Formula II.

20 X1 is N or C(R7)

R2, R4, and R5 are all hydrogen,

R6 is chloro or fluoromethyl,

R7, if present, is selected from hydrogen, fluoro, chloro, cyclopropyloxy and fluoromethyl,

R8 is selected from hydrogen, fluoro, and methoxy,

25 R10 is selected from halogen, C₁₋₂ alkyl, and C₁₋₂ alkoxy, wherein the alkyl and alkoxy can be optionally substituted with one or more substituent selected from fluoro, cyano and fluoro C₁₋₂ alkoxy,

R11 is selected from hydrogen, methoxy and fluoro, preferably from hydrogen and fluoro, and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof.

In one embodiment of the compounds of Formula II,

5 X1 is N or C(R7)

R2, R4 and R5 are all hydrogen,

R6 is chloro or fluoromethyl,

R7, if present, is selected from hydrogen, fluoro, chloro, fluoromethyl and cyclopropyloxy and is preferably hydrogen,

10 R8 is selected from fluoro and methoxy,

R10 is selected from chloro, bromo, methoxy, fluoromethoxy, fluoroethoxy, fluoromethoxyethoxy and fluoroethoxymethoxy,

R11 is fluoro,

and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof.

15

One preferred embodiment relates to compounds having formula II, wherein

R2, R4, and R5 are all hydrogen,

R6 is chloro or difluoromethyl,

X1 is C(R7),

20 R7 is selected from hydrogen, fluoro, chloro and fluoromethyl, and is preferably hydrogen,

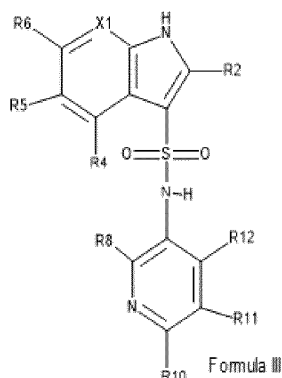
R8 is selected from fluoro and methoxy,

R10 is selected from chloro, bromo and C₁₋₂ alkoxy, wherein the alkoxy is substituted with either up to three fluoro atoms or with one fluoromethoxy or fluoroethoxy,

R11 is hydrogen or fluoro

25 and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof.

One particular embodiment relates to compounds of Formula I, wherein X2 is C(R12), thus having formula III



wherein all substituents are as described herein before for compounds of Formula I.

- 5 In one embodiment, in the compounds of Formula III,
R2, R4, and R5 are all hydrogen,
R6 is selected from halogen, cyano, methyl, methoxy, fluoromethoxy, fluoromethyl and benzyloxy,
X1 is N or C(R7),
- 10 R7, if present, is selected from hydrogen, halogen, fluoromethoxy and fluoromethyl, and is preferably hydrogen or fluoro,
R8 is selected from hydrogen, fluoro, C₁₋₂alkoxy and fluoroC₁₋₂alkoxy
R10 is selected from halogen, cyclopropyl, C₁₋₂ alkyl and C₁₋₂ alkoxy, wherein the cyclopropyl, alkyl and alkoxy can each be optionally substituted with one or more
- 15 substituent selected from fluoro, methoxy and fluoro C₁₋₂ alkoxy,
R11 is selected from hydrogen, methoxy and fluoro, preferably from hydrogen and fluoro,
R12 is selected from hydrogen, methoxy and fluoro,
and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof.
- 20 In one embodiment, in the compounds of Formula III,
R2, R4, and R5 are all hydrogen,
R6 is selected from fluoro, chloro, cyano, methyl, methoxy, fluoromethoxy and fluoromethyl,
X1 is N or C(R7),
- 25 R7, if present, is hydrogen or fluoro,
R8 is selected from hydrogen, fluoro and methoxy, preferably from fluoro and methoxy,

R10 is selected from halogen, cyclopropyl and C₁₋₂ alkoxy, wherein the alkoxy can be optionally substituted with one or more substituent selected from fluoro, methoxy and fluoro C₁₋₂ alkoxy,

R11 is selected from hydrogen, methoxy and fluoro, preferably from hydrogen and fluoro,

- 5 R12 is selected from hydrogen and fluoro, and is preferably fluoro,
and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof.

In one embodiment, in the compounds of Formula III,

R2, R4, and R5 are all hydrogen,

- 10 R6 is chloro or fluoromethyl,

X1 is N or C(R7),

R7, if present, is selected from hydrogen, fluoro, chloro, cyclopropyloxy, fluoromethoxy and fluoromethyl,

R8 is selected from hydrogen, fluoro, and methoxy,

- 15 R10 is selected from halogen C₁₋₂ alkyl and C₁₋₂ alkoxy, wherein the alkyl and alkoxy can be optionally substituted with one or more substituent selected from fluoro, cyano and fluoro C₁₋₂ alkoxy,

R11 is selected from hydrogen, methoxy and fluoro, preferably from hydrogen and fluoro,

R12 is selected from hydrogen, methoxy and fluoro,

- 20 and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof.

In a preferred embodiment, in the compounds of Formula III,

R2, R4 and R5 are all hydrogen

R6 is selected from chloro, methoxy, fluoromethoxy and fluoromethyl,

- 25 X1 is N or C(R7),

R7, if present, is selected from hydrogen and fluoro,

R8 is selected from hydrogen, fluoro and methoxy,

R10 is selected from chloro, bromo, cyclopropyl, methoxy, fluoromethoxy, fluoroethoxy, fluoromethoxyethoxy and fluoroethoxymethoxy,

- 30 R11 is hydrogen or fluoro, preferably fluoro, and

R12 is selected from hydrogen and fluoro, and is preferably hydrogen,

and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof.

In a preferred embodiment, in the compounds of Formula III,

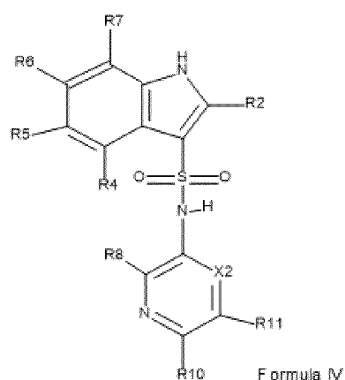
- 35 R2, R4 and R5 are all hydrogen

R6 is chloro or fluoromethyl,

- X1 is N or C(R7),
R7, if present, is selected from hydrogen, fluoro, chloro, fluoromethyl and cyclopropyloxy,
R8 is selected from fluoro and methoxy,
R10 is selected from chloro, bromo, methoxy, fluoromethoxy, fluoroethoxy,
5 fluoromethoxyethoxy and fluoroethoxymethoxy,
R11 is hydrogen or fluoro, preferably fluoro, and
R12 is selected from hydrogen, methoxy and fluoro, preferably hydrogen,
and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof.
- 10 In a preferred embodiment, in the compounds of Formula III,
R2, R4, and R5 are all hydrogen,
R6 is selected from chloro, cyano, methyl, methoxy, fluoromethoxy and fluoromethyl,
X1 is N or C(R7),
R7, if present, is selected from hydrogen, fluoro and chloro,
15 R8 is selected from fluoro and methoxy,
R10 is selected from chloro, bromo and C₁₋₂ alkoxy, wherein the alkoxy is substituted with
either up to three fluoro atoms or with one fluoromethoxy or fluoroethoxy,
R11 is hydrogen or fluoro, and
R12 is hydrogen or fluoro, preferably hydrogen,
20 and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof.

- In a preferred embodiment, in the compounds of Formula III,
R2, R4, and R5 are all hydrogen,
R6 is chloro or difluoromethyl,
25 X1 is N or C(R7),
R7, if present, is selected from hydrogen, fluoro, chloro and fluoromethyl, preferably
hydrogen,
R8 is selected from fluoro and methoxy,
R10 is selected from chloro and C₁₋₂ alkoxy, wherein the alkoxy is substituted with either
30 up to three fluoro atoms or with one fluoromethoxy,
R11 is hydrogen or fluoro, and
R12 is hydrogen or fluoro, preferably hydrogen,
and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof.

One particular embodiment relates to compounds of Formula I, wherein X1 is -C(R7)- thus having Formula IV,



5

wherein the other substituents are as described for Formula I hereinbefore.

In one embodiment, in the compounds of Formula IV,

R2, R4, and R5 are all hydrogen,

10 R6 is selected from halogen, cyano, methyl, methoxy, fluoromethoxy, fluoromethyl and benzyloxy,

R7 is selected from hydrogen, halogen, fluoromethoxy and fluoromethyl, and is preferably hydrogen or fluoro,

X2 is N or C(R12),

15 R8 is selected from hydrogen, fluoro, C₁₋₂alkoxy and fluoroC₁₋₂alkoxy

R10 is selected from halogen, cyclopropyl, C₁₋₂ alkyl and C₁₋₂ alkoxy, wherein the cyclopropyl, alkyl and alkoxy can each be optionally substituted with one or more substituent selected from fluoro, methoxy and fluoro C₁₋₂ alkoxy,

R11 is selected from hydrogen, methoxy and fluoro, preferably from hydrogen and fluoro,

20 R12, if present, is selected from hydrogen, methoxy and fluoro,

and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof.

In one embodiment, in the compounds of Formula IV,

R2, R4, and R5 are all hydrogen,

R6 is chloro or fluoromethyl,

25 R7 is selected from hydrogen, fluoro, chloro, cyclopropyloxy, cyclopropyl, fluoromethoxy and fluoromethyl,

R8 is selected from hydrogen, fluoro, and methoxy,

R10 is selected from halogen C₁₋₂ alkyl and C₁₋₂ alkoxy, wherein the alkyl and alkoxy can be optionally substituted with one or more substituent selected from fluoro, cyano and fluoro C₁₋₂ alkoxy,

R11 is selected from hydrogen, methoxy and fluoro, preferably from hydrogen and fluoro,

5 X2 is N or C(R12),

R12, if present, is selected from hydrogen, methoxy and fluoro,

and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof.

One preferred embodiment relates to compounds of formula IV, wherein

10 R2, R4 and R5 are all hydrogen

R6 is selected from chloro, cyano, methoxy, fluoromethoxy, methyl and fluoromethyl,

R7 is selected from hydrogen, halogen, fluoromethyl and fluoromethoxy, and is preferably hydrogen or fluoro,

R8 is selected from fluoro and methoxy,

15 R10 is selected from halogen, cyclopropyl, methoxy, fluoromethoxy, fluoroethoxy, fluoromethoxyethoxy and fluoroethoxymethoxy,

R11 is hydrogen or fluoro, and

X2 is N or C(R12),

R12, if present, is hydrogen, methoxy or fluoro, preferably hydrogen,

20 and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof.

One preferred embodiment relates to compounds of formula IV, wherein

R2, R4 and R5 are all hydrogen

R6 is chloro or fluoromethyl,

25 R7 is selected from hydrogen, fluoro, chloro, fluoromethyl and cyclopropyloxy,

R8 is selected from fluoro and methoxy,

R10 is selected from chloro, bromo, methoxy, fluoromethoxy, fluoroethoxy, fluoromethoxyethoxy and fluoroethoxymethoxy,

R11 is hydrogen or fluoro, and

30 X2 is N or C(R12),

R12, if present, is hydrogen, methoxy or fluoro, preferably hydrogen,

and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof.

One preferred embodiment relates to compounds of formula IV, wherein

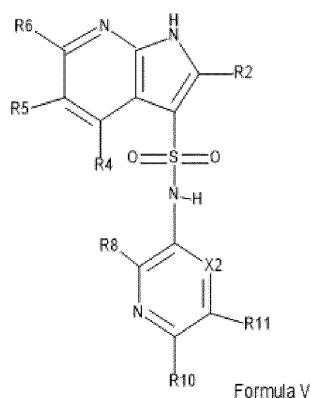
35 R2, R4, and R5 are all hydrogen,

R6 is selected from chloro, methoxy, fluoromethoxy, methyl or fluoromethyl,

- R7 is selected from hydrogen, fluoro, chloro and fluoromethyl, and is preferably hydrogen,
R8 is selected from fluoro and methoxy,
R10 is selected from chloro, bromo and C₁₋₂ alkoxy, wherein the alkoxy is optionally and preferably substituted with one to three fluoro atoms or with one fluoromethoxy,
5 R11 is hydrogen or fluoro, preferably fluoro,
X2 is N or C(R12), and
wherein R12, if present, is hydrogen or fluoro, preferably hydrogen,
and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof.
- 10 One preferred embodiment relates to compounds of formula IV, wherein
R2, R4, and R5 are all hydrogen,
R6 is chloro or difluoromethyl,
R7 is selected from hydrogen, fluoro, chloro and fluoromethyl, preferably hydrogen,
R8 is selected from fluoro and methoxy,
15 R10 is selected from chloro and C₁₋₂ alkoxy, wherein the alkoxy is substituted with either
up to three fluoro atoms or with one fluoromethoxy,
R11 is hydrogen or fluoro
X2 is N or C(R12), and
wherein R12, if present, is hydrogen or fluoro, preferably hydrogen,
20 and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof.

One preferred embodiment relates to compounds of Formula I, II, III or IV, wherein R7 is hydrogen.

- 25 One embodiment relates to compounds of Formula I, wherein X1 is N thus having
Formula V



wherein all substituents are as described for Formula I hereinbefore.

- In one embodiment, in the compounds of Formula V,
- 5 R2, R4, and R5 are all hydrogen,
R6 is selected from halogen, cyano, methyl, methoxy, fluoromethoxy, fluoromethyl and benzyloxy,
X2 is N or C(R12),
R8 is selected from hydrogen, fluoro, C₁₋₂alkoxy and fluoroC₁₋₂alkoxy
- 10 R10 is selected from halogen, cyclopropyl, C₁₋₂ alkyl and C₁₋₂ alkoxy, wherein the cyclopropyl, alkyl and alkoxy can each be optionally substituted with one or more substituent selected from fluoro, methoxy and fluoro C₁₋₂ alkoxy,
R11 is selected from hydrogen, methoxy and fluoro, preferably from hydrogen and fluoro,
R12, if present, is selected from hydrogen, methoxy and fluoro,
- 15 and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof.

- In one embodiment, in the compounds of Formula V,
- R2, R4, and R5 are all hydrogen,
R6 is chloro or fluoromethyl,
- 20 R8 is selected from hydrogen, fluoro, and methoxy,
R10 is selected from halogen C₁₋₂ alkyl and C₁₋₂ alkoxy, wherein the alkyl and alkoxy can be optionally substituted with one or more substituent selected from fluoro, cyano and fluoro C₁₋₂ alkoxy,
R11 is selected from hydrogen, methoxy and fluoro, preferably from hydrogen and fluoro,
- 25 X2 is N or C(R12),
R12 is selected from hydrogen, methoxy and fluoro,
and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof.

- 30 One preferred embodiment relates to compounds of Formula V, wherein
R2, R4 and R5 are all hydrogen
R6 is selected from chloro, cyano, methoxy, fluoromethoxy, methyl and fluoromethyl,
R8 is selected from fluoro and methoxy,
R10 is selected from halogen, cyclopropyl, methoxy, fluoromethoxy, fluoroethoxy,
- 35 fluoromethoxyethoxy and fluoroethoxymethoxy,
R11 is hydrogen or fluoro, and

X2 is N or C(R12),

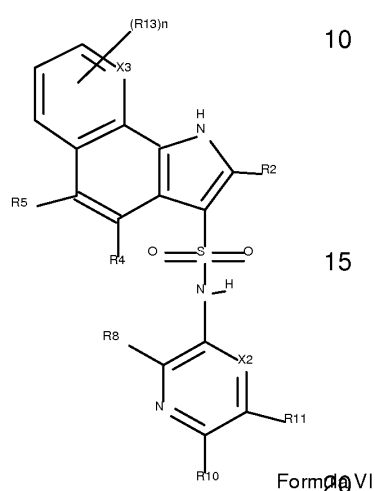
R12, if present, is hydrogen, methoxy or fluoro, preferably hydrogen, and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof.

- 5 One preferred embodiment relates to compounds of Formula V, wherein
R2, R4 and R5 are all hydrogen
R6 is chloro or fluoromethyl,
R8 is methoxy,
R10 is selected from chloro, bromo, methoxy, fluoromethoxy, fluoroethoxy,
10 fluoromethoxyethoxy and fluoroethoxymethoxy,
R11 is hydrogen or fluoro, preferably fluoro,
X2 is N or C(R12),
wherein R12, if present, is selected from hydrogen, methoxy and fluoro
and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof.
- 15 One preferred embodiment relates to compounds of formula V, wherein
R2, R4, and R5 are all hydrogen,
R6 is selected from chloro, methoxy, fluromethoxy and fluoromethyl,
R8 is selected from fluoro and methoxy,
20 R10 is selected from chloro, bromo and C₁₋₂ alkoxy, wherein the alkoxy is optionally and
preferably substituted with one to three fluoro atoms or with one fluoromethoxy or
fluoroethoxy,
R11 is hydrogen or fluoro, preferably fluoro,
X2 is C(R12) wherein R12 is hydrogen,
25 and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof.
- One preferred embodiment relates to compounds of formula V, wherein
R2, R4, and R5 are all hydrogen,
R6 is chloro or difluoromethyl, preferably chloro,
30 R8 is selected from fluoro and methoxy,
R10 is selected from chloro and C₁₋₂ alkoxy, wherein the alkoxy is substituted with either
up to three fluoro atoms or with one fluoromethoxy,
R11 is hydrogen or fluoro
X2 is C(R12) wherein R12 is selected from hydrogen, methoxy and fluoro,
35 and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof.

- In one preferred embodiment of the compounds of Formula I, II, III, IV or V,
 R₂, R₄ and R₅ are all hydrogen,
 R₈ is hydrogen or fluoro, preferably fluoro,
 R₁₁ is methoxy, X₂ is C(R₁₂) and R₁₂ is hydrogen,
 5 and X₁, R₆ and R₁₀ are as defined in the embodiments hereinbefore.

One embodiment relates to compounds of formula I, wherein R₆ and R₇ together with the C-atoms to which they are attached form a 5 or 6 membered ring as depicted in Formula

VI:



wherein

- n is 0 to 3, preferably 0 or 1,
 X₃ is CH or N,
 25 R₂ is hydrogen or halogen, preferably hydrogen or fluoro,
 R₄ is hydrogen or fluoro,
 R₅ is hydrogen or halogen,
 R₈ is selected from hydrogen, halogen, methoxy, ethoxy, fluoromethoxy and fluoroethoxy,
 R₁₀ is selected from hydrogen, halogen, C₃₋₅ cycloalkyl, C₃₋₅ cycloalkyloxy, C₃₋₅
 30 cycloalkylmethoxy, C₁₋₄ alkoxy, and C₁₋₄ alkyl, wherein each cycloalkyl, cycloalkyloxy, alkyl
 and alkoxy can be substituted with one or more substituent selected from halogen, C₁₋₃
 alkoxy, fluoro(C₁₋₃)alkoxy and cyano,
 R₁₁ is selected from hydrogen, fluoro and methoxy,
 X₂ is N or C(R₁₂),
 35 R₁₂ is selected from hydrogen, methoxy and halogen,

R13, in each occurrence, is independently selected from halogen, cyano, hydroxy, methyl, methoxy, fluoromethyl and fluoromethoxy, and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof.

- 5 One embodiment relates to compound of formula VI, wherein
n is 0
X3 is N or CH,
R2 is hydrogen,
R4 is hydrogen,
- 10 R5 is hydrogen or halogen, preferably hydrogen,
R8 is selected from hydrogen, fluoro and methoxy,
R10 is selected from halogen, cyclopropyl, and C₁₋₂ alkoxy, wherein the alkoxy can be optionally substituted with one or more substituent selected from fluoro, methoxy, ethoxy, and fluoro C₁₋₂ alkoxy,
- 15 R11 is hydrogen or fluoro
X2 is N or C(R12), and
R12, if present, is selected from hydrogen, methoxy and fluoro,
and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof.
- 20 One embodiment relates to compound of formula VI, wherein
n is 0, 1 or 2, preferably 0 or 1,
X3 is N,
R2, R4 and R5 are all hydrogen,
R8 is selected from hydrogen, fluoro and methoxy,
- 25 R10 is selected from halogen, cyclopropyl, and C₁₋₂ alkoxy, wherein the alkoxy can be optionally substituted with one or more substituent selected from fluoro, methoxy, ethoxy, and fluoro C₁₋₂ alkoxy,
R11 is hydrogen or fluoro
X2 is N,
- 30 R13 in each occurrence is selected from halogen, hydroxy, methoxy, fluoromethoxy, methyl and fluoromethyl,
and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof.

In one particular embodiment of the compounds of formula VI, n is 0, and X3 is N.

In one preferred embodiment of the compounds of Formula I, II, III, IV, V or VI, R11 is selected from hydrogen and fluoro.

In one preferred embodiment of the compounds of Formula I, II, III, IV, V or VI, R11 is fluoro.

- 5 In one preferred embodiment of the compounds of Formula I, II, III, IV, V or VI, R8 is methoxy, R11 is fluoro and R12, if present, is hydrogen.

In one particularly preferred embodiment of the compounds of Formula I, II, III, IV, V or VI, R2, R4 and R5 are all hydrogen, R8 is methoxy, R11 is fluoro and R12, if present, is hydrogen, and the other substituents are as described herein.

- 10 In one particularly preferred embodiment of the compounds of Formula I, II, III, IV or V, R2, R4, R5 and R7, if present, are all hydrogen, R8 is methoxy, R11 is fluoro and R12, if present, is hydrogen, and the other substituents are as described herein.

In one embodiment of the compounds of Formula I, II, III, IV, V or VI, R12 is methoxy, R8 is fluoro and R11 is selected from hydrogen and fluoro.

- 15 In one preferred embodiment of the compounds of Formula I, II, III, IV, V or VI, R12 is hydrogen.

One embodiment relates to any specific GPR17 modulator disclosed herein, including but not limited to those described in the experimental part and in Table 7 herein.

20

One preferred embodiment relates to a compound selected from

6-chloro-N-[6-(2,2-difluoroethoxy)-2,5-difluoropyridin-3-yl]-1H-indole-3-sulfonamide

- 25 N-[6-(difluoromethoxy)-5-fluoro-2-methoxypyridin-3-yl]-1H-pyrrolo[3,2-h]quinoline-3-sulfonamide

N-[6-(2,2-difluoroethoxy)-5-fluoro-2-methoxypyridin-3-yl]-1H-pyrrolo[3,2-h]quinoline-3-sulfonamide

5-bromo-6-chloro-N-[6-(2,2-difluoroethoxy)-5-fluoro-2-methoxypyridin-3-yl]-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide

- 30 6-chloro-N-[6-(2,2-difluoroethoxy)-5-fluoro-2-methoxypyridin-3-yl]-7-fluoro-1H-indole-3-sulfonamide

6-cyano-N-[6-(2,2-difluoroethoxy)-5-fluoro-2-methoxypyridin-3-yl]-1H-indole-3-sulfonamide

N-[6-(2,2-difluoroethoxy)-5-fluoro-2-methoxypyridin-3-yl]-6-(difluoromethoxy)-1H-indole-3-sulfonamide

- N-[6-[2-(difluoromethoxy)ethoxy]-5-fluoro-2-methoxypyridin-3-yl]-6-(difluoromethyl)-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide
6-chloro-N-[6-[2-(difluoromethoxy)ethoxy]-5-fluoro-2-methoxypyridin-3-yl]-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide
- 5 N-[6-(2,2-difluoroethoxy)-5-fluoro-2-methoxypyridin-3-yl]-6-(difluoromethyl)-1H-indole-3-sulfonamide
6-chloro-N-(6-cyclopropyl-5-fluoro-2-methoxypyridin-3-yl)-1H-indole-3-sulfonamide
6-chloro-N-(5-fluoro-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide
N-[6-(difluoromethoxy)-5-fluoro-2-methoxypyridin-3-yl]-6-methoxy-1H-indole-3-sulfonamide
- 10 N-[6-(2,2-difluoroethoxy)-5-fluoro-2-methoxypyridin-3-yl]-6-methoxy-1H-indole-3-sulfonamide
6-chloro-N-[6-[2-(difluoromethoxy)ethoxy]-5-fluoro-2-methoxypyridin-3-yl]-1H-indole-3-sulfonamide
- 15 N-[6-(difluoromethoxy)-5-fluoro-2-methoxypyridin-3-yl]-6-methyl-1H-indole-3-sulfonamide
6-cyano-N-[6-(difluoromethoxy)-5-fluoro-2-methoxypyridin-3-yl]-1H-indole-3-sulfonamide
6-(difluoromethyl)-N-(2,5-difluoro-6-methylpyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide
6-(difluoromethyl)-N-(5-fluoro-2,6-dimethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide
- 20 6-(difluoromethyl)-N-[5-fluoro-6-(2-fluoroethoxy)-2-methoxypyridin-3-yl]-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide
6-chloro-N-(6-cyclopropyl-2,5-difluoropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide
6-chloro-N-[6-(2,2-difluoroethoxy)-5-fluoro-2-methoxypyridin-3-yl]-1H-indole-3-sulfonamide
- 25 6-chloro-N-(6-cyclopropyl-2,5-difluoropyridin-3-yl)-1H-indole-3-sulfonamide
N-[6-(2,2-difluoroethoxy)-5-fluoro-2-methoxypyridin-3-yl]-6-(difluoromethyl)-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide
6-chloro-N-[6-(2,2-difluoroethoxy)-5-fluoro-2-methoxypyridin-3-yl]-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide
- 30 N-[6-(2,2-difluoroethoxy)-2-methoxypyridin-3-yl]-6-(difluoromethyl)-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide
6-chloro-N-[6-(2,2-difluoroethoxy)-2-methoxypyridin-3-yl]-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide
- 35 N-[6-(2,2-difluoroethoxy)-2,5-difluoropyridin-3-yl]-6-(difluoromethyl)-1H-indole-3-sulfonamide
6-chloro-N-[6-(difluoromethoxy)-4-methoxypyridin-3-yl]-1H-indole-3-sulfonamide

- 6-chloro-N-[6-(2,2-difluoroethoxy)-2-methoxypyridin-3-yl]-1H-indole-3-sulfonamide
6-chloro-N-[2-(2,2-difluoroethoxy)-6-methoxypyridin-3-yl]-1H-indole-3-sulfonamide
N-[6-(difluoromethoxy)-5-fluoro-2-methoxypyridin-3-yl]-6-(difluoromethyl)-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide
- 5 6-chloro-N-[6-(difluoromethoxy)-2-methoxy-3-pyridyl]-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide
N-(6-chloro-5-fluoro-2-methoxypyridin-3-yl)-6-(difluoromethyl)-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide
6-chloro-N-[6-(2-fluoroethoxy)-2-methoxypyridin-3-yl]-1H-indole-3-sulfonamide
- 10 6-chloro-N-[5-fluoro-6-(2-fluoroethoxy)-2-methoxypyridin-3-yl]-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide
6-chloro-N-[5-fluoro-6-(2-fluoroethoxy)-2-methoxypyridin-3-yl]-1H-indole-3-sulfonamide
N-[6-(difluoromethoxy)-5-fluoro-2-methoxypyridin-3-yl]-6-(difluoromethyl)-1H-indole-3-sulfonamide
- 15 6-chloro-N-[6-(difluoromethoxy)-5-fluoro-2-methoxypyridin-3-yl]-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide
6-chloro-N-(5-chloro-3-methoxypyrazin-2-yl)-1H-indole-3-sulfonamide
6-chloro-N-[6-(difluoromethoxy)-5-fluoro-2-methoxypyridin-3-yl]-1H-indole-3-sulfonamide
N-(5-bromo-3-methoxypyrazin-2-yl)-6-chloro-1H-indole-3-sulfonamide
- 20 6-chloro-N-(2,5-difluoro-6-methylpyridin-3-yl)-1H-indole-3-sulfonamide
6-chloro-N-(5-fluoro-2,6-dimethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide
6-chloro-N-(6-chloro-5-fluoro-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide
6-chloro-N-(5-fluoro-2,6-dimethoxypyridin-3-yl)-1H-indole-3-sulfonamide
- 25 6-chloro-N-(2,5-difluoro-6-methoxypyridin-3-yl)-1H-indole-3-sulfonamide
6-chloro-N-(6-chloro-5-fluoro-2-methoxypyridin-3-yl)-1H-indole-3-sulfonamide
6-chloro-N-(6-chloro-2,5-difluoropyridin-3-yl)-1H-indole-3-sulfonamide
6-chloro-N-(6-iodopyridin-3-yl)-1H-indole-3-sulfonamide
6-chloro-N-(6-chloro-4-fluoropyridin-3-yl)-1H-indole-3-sulfonamide
- 30 and pharmaceutically acceptable salts, solvates, isotopes and co-crystals thereof.

Another preferred embodiment relates to compounds having a structure of Formula I, II, III, IV, V or VI as defined herein, or any compound individually disclosed herein, in particular any one of Compounds I-1 to I-72, and comprising at least one ¹⁸F isotope, preferably in the position of a fluorine atom as indicated in one of the compounds disclosed herein. By way of non-limiting example, in the compound 6-chloro-N-(6-chloro-2,5-difluoropyridin-3-yl)-1H-indole-3-sulfonamide, disclosed herein, at least one of the two

fluorines may be represented by a ^{18}F isotope. This applies likewise to other fluorine containing compounds described herein. These ^{18}F containing compounds can preferably be used as PET tracers.

Another preferred embodiment relates to compounds having a structure of Formula
5 Formula I, II, III, IV, V or VI as defined herein, or any compound individually disclosed herein, in particular any one of Compounds I-1 to I-72, and comprising at least one ^{11}C isotope, preferably in the position of a carbon atom as indicated herein. These ^{11}C containing compounds can preferably be used as PET tracers.

Another preferred embodiment relates to compounds having a structure of Formula
10 Formula I, II, III, IV, V or VI as defined herein, or any compound individually disclosed herein, in particular any one of Compounds I-1 to I-72, and comprising at least one ^{123}I , ^{125}I or ^{131}I isotope, preferably in the position of an iodine atom as indicated herein. By way of non-limiting example, in the compound 6-chloro-N-(6-iodopyridin-3-yl)-1H-indole-3-sulfonamide, disclosed herein, the iodine may be represented by a ^{123}I , ^{125}I or ^{131}I isotope.
15 ^{123}I , ^{125}I or ^{131}I containing compounds can preferably be used as SPECT tracers.

Therapeutic and Diagnostic Application

In one aspect, the invention relates to anyone of the compounds described herein, for use in therapy or diagnosis, particularly in the therapy of animals, in particular humans.

Because of their GPR17 modulating properties, the compounds of the present invention
20 can be used as medicine, and may be used for the treatment and/or prevention of various diseases of the CNS system.

One embodiment of the present disclosure is thus a compound as described herein for use as a medicine, in particular for use as a medicine for the treatment and/or prevention of a GPR17-associated disease.

25 A GPR17 associated disease or disorder is disease which is associated with a dysfunction of the GPR17 signaling system such as, for example, an overexpression and/or overactivity of GPR17 receptors. Without wished to be bound by any theory, the activity of GPR17 may be increased, extended or otherwise altered in certain tissues, for example in oligodendrocyte progenitor cells (OPCs) or during maturation of oligodendrocytes,
30 potentially due to activating endogenous stimuli such as, for example, inflammation factors. High activity of GPR17 may prevent the differentiation of oligodendrocytes and an efficient myelination, thus promoting the emergence or further development of a

myelination disease (see Chen et al, supra). Negative GPR17 modulators may thus promote myelination by decreasing or turning off GPR17 activity and by supporting OPC maturation into myelin-producing oligodendrocytes (see e.g. Simon et al, supra).

In one preferred aspect, the invention relates to anyone of the compounds described
5 herein, for use in therapy or diagnosis for use in the prevention, or treatment of a disorder or syndrome selected from and/or associated with a myelination disorder, in particular a demyelination disorder, such as of the central nervous system. In one embodiment, the compounds of the present invention are for use in promoting, stimulating and/or accelerating remyelination in an animal in need thereof. In one embodiment, the
10 remyelination associated with the administration of a compound of the present invention will prevent or treat a demyelination disease such as, but not limited to, multiple sclerosis.

Compounds of the present invention can also be useful in the treatment or prevention of a disorder or syndrome associated with brain tissue damage, a cerebrovascular disorder, and certain neurodegenerative diseases.

15 Neurodegenerative disorders have been recently associated strongly with a loss of myelination. Accordingly, it is believed that preserved oligodendroglial and myelin functionality is a crucial prerequisite for the prevention of axonal and neuronal degeneration (see e.g. Etle et al, supra). Negative GPR17 modulators may thus represent an excellent treatment option for any neurodegenerative disease associated
20 with demyelination and/or impacted myelination such as e.g. ALS, MSA, Alzheimer's disease, Huntington Disease or Parkinson's Disease.

In a particular preferred aspect, the compounds of the present invention can thus be used in the prevention and/or treatment of a peripheral or central myelination disorder, in particular of a myelination disorder of the central nervous system. In one aspect, the
25 compounds of the present invention are use in the treatment and/or prevention and/or diagnosis of a myelination disorder by oral administration. In a preferred embodiment, the myelination disorder to be treated with the compounds of the present invention is a demyelination disorder.

Examples of such myelination disorders to be treated and/or prevented by the presently
30 disclosed compounds are, in particular,

- multiple sclerosis (MS) including its various subforms,
- neuromyelitis optica (also known as Devic's disease),

- chronic relapsing inflammatory optic neuritis, acute disseminated encephalomyelitis,
- acute haemorrhagic leucoencephalitis (AHL),
- periventricular leukomalacia
- 5 - demyelination due to viral infections, e.g. by HIV or progressive multifocal leucoencephalopathy,
- central pontine and extrapontine myelinolysis,
- demyelination due to traumatic brain tissue damage, including compression-induced demyelination, e.g. by tumors
- 10 - demyelination in response to hypoxia, stroke or ischaemia or other cardiovascular diseases,
- demyelination due to exposure to carbon dioxide, cyanide, or other CNS toxins
- Schilder's disease,
- Baló concentric sclerosis,
- 15 - Perinatal encephalopathy, and
- Neurodegenerative Diseases including, in particular,
 - o Amyotrophic lateral sclerosis (ALS).
 - o Alzheimer's disease (AD).
 - o Multiple system atrophy
 - 20 o Parkinson's Disease
 - o Spinocerebellar ataxia (SCA), also known as spinocerebellar atrophy
 - o Huntington's Disease
- psychiatric disorders such as schizophrenia and bipolar disorder).
- peripheral myelination diseases such as leukodystrophies, peripheral
- 25 demyelinating neuropathies, Dejerine-Sottas syndrome or Charcot-Marie-Tooth disease

The treatment or prevention of a CNS disease such as a demyelination disease, also includes the treatment of the signs and symptoms associated with such a disease.

- For example, the use of the compounds of the present invention for the treatment and/or
- 30 prevention of MS also includes the treatment and/or prevention of the signs and symptoms associated with MS such as negative effects on optic nerves (vision loss, double vision), dorsal columns (loss of sensation), corticospinal tract (spastic weakness), cerebellar pathways (incoordination, dysarthria, vertigo, cognitive impairment), medial longitudinal fasciculus (double vision on lateral gaze), spinal trigeminal tract (face
- 35 numbness or pain), muscle weakness (impaired swallowing, control of the bladder or gut,

spasms), or psychological effects associated with the underlying disease such as depression, anxiety or other mood disorders, general weakness or sleeplessness.

Hence, the compounds of the present invention are for use in treating signs and symptoms of a myelination disease, in particular a demyelination disease such as multiple sclerosis; such signs and symptoms of MS include but are not limited to the group of vision loss, vision impairment, double vision, loss or impairment of sensation, weakness such as spastic weakness, motor incoordination, vertigo, cognitive impairment, face numbness, face pain, impaired swallowing, impaired speech, impaired control of bladder and/or gut, spasms, depression, anxiety, mood disorders, sleeplessness, and fatigue.

10 In one preferred embodiment, the compounds of the present invention are for use in treating multiple sclerosis. MS is a heterogeneous myelination disease and can manifest itself in a variety of different forms and stages, including but not limited to Relapsing-Remitting MS, Secondary-Progressive MS, Primary Progressive MS, Progressive Relapsing MS, each depending on activity and disease progression. Hence, in one
15 embodiment, the compounds of the present invention are for use in treating multiple sclerosis in its various stages and forms, as described herein.

In one aspect, the compounds of the present invention are for use in the treatment/or prevention of Neuromyelitis optica (also known as Devic's disease or Devic's syndrome). Neuromyelitis optica is a complex disorder characterized by inflammation and
20 demyelination of the optic nerve and the spinal cord. Many of the associated symptoms are similar to MS and include muscle weakness, in particular of the limbs, reduced sensation and loss of bladder control.

In one aspect, the compounds of the present invention are for use in prevention and/or treating ALS. ALS has been associated recently with oligodendrocyte degeneration and
25 increased demyelination, suggesting ALS as a target disease for negative GPR17 modulators (Kang et al, supra; Fumagalli et al, Neuropharmacology 104, 2016, 82).

In one aspect, the compounds of the present invention are for use in prevention and/or treating Huntington Disease. Huntington is well described to be associated with impacted myelination, (Bartzokis et al, supra; Huang et al, Neuron 85, 2015, 1212).

30 In one aspect, the compounds of the present invention are for use in prevention and/or treating multiple system atrophy. MSA was associated strongly with demyelination recently (Ettle supra, Jellinger supra) suggesting remyelination strategies to treat or prevent MSA.

In one aspect, the compounds of the present invention are for use in prevention and/or treating Alzheimer's Disease. AD has been recently observed to be associated with increased cell death of oligodendroneocytes and focal demyelination and to represent a pathological process in AD (Mitew et al, Acta Neuropathol 119, 2010, 567),

- 5 One aspect of the present invention relates to a method of treatment of anyone of the diseases or disorders described herein, in particular of a myelination disease such as MS, Neuromyelitis optica, ALS, Chorea Huntington, Alzheimer's Disease or others, by administering to a subject in need thereof, including a human patient, a therapeutically effective amount of a compound of the present invention.
- 10 In another aspect, the compound of the present invention may be used in the prevention and treatment of a spinal cord injury, perinatal encephalopathy, stroke, ischemia, or a cerebrovascular disorder.

- In one aspect, the invention relates to a method for the prevention and/or treatment of a syndrome or disorder associated with a myelination disorder, or with a disorder or
- 15 syndrome associated with a brain tissue damage, which comprises administering to a patient in need thereof a therapeutically effective amount of a compound as described herein. A patient in need of such a treatment can be any patient who suffered brain tissue damage such as by mechanical, chemical, viral, or other trauma.

- In one aspect, the invention relates to a method for the prevention and/or treatment of a
- 20 syndrome or disorder associated with a myelination disorder, or with a disorder or syndrome associated with stroke or other brain ischemia, which comprises administering to a patient in need thereof a therapeutically effective amount of a compound as described herein. A patient in need thereof may be any patient that recently experienced a cerebral ischemia/stroke which may have been caused, for example, by the occlusion of a cerebral
- 25 artery either by an embolus or by local thrombosis.

- GPR17 has been also associated with food uptake, insulin control and obesity recently. According to various reports, negative modulators of GPR17 may be helpful for controlling food uptake and for treating obesity (see e.g. Ren et al, Diabetes 64, 2015; 3670.) Hence, one embodiment of the present invention relates to the use of the compounds herein for
- 30 the prevention and/or treatment of obesity, and methods of treating obesity.

Moreover, the compounds of the present invention may be used for the treatment of prevention of tissues where GPR17 is expressed, such as e.g. heart, lung or kidney. In

one embodiment, the compounds of the present invention can be used to treat or prevent ischaemic disorders of the kidney and/or the heart.

GPR17 has been also associated with pulmonary inflammation and asthma such as, for example, induced by house dust mite (Maekawa, J Immunol 2010, 185(3), 1846-1854).

- 5 Hence, the compounds of the present invention may be used for the treatment of asthma or other pulmonary inflammation.

- The treatment according to the present invention may comprise the administration of one of the presently disclosed compounds as "stand alone" treatment of a CNS disease, in particular of a myelination disease or disorder such as MS or ALS. Alternatively, a
10 compound disclosed herein may be administered together with other useful drugs in a combination therapy.

In a non-limiting example, a compound according to the present invention is combined with another medicament for treating a myelination disease, such as MS, having a different mode of action, such as e.g. an anti-inflammatory or immunosuppressive drug.

- 15 Such compounds include but are not limited to: (i) corticosteroids such as prednisone, methylprednisone or dexamethasone, (ii) beta interferons such as interferon beta-1a, interferon beta-1b or peginterferon beta-1a, (iii) anti-CD20 antibodies such as ocrelizumab, rituximab and ofatumumab, (iv) glatiramer salts such as glatiramer acetate, (v) dimethyl fumarate, (vi) fingolimod and other sphingosine-1-phosphate receptor modulators such as
20 ponesimod, siponimod, ozanimod or laquinimod, (vii) dihydro-orotate dehydrogenase inhibitors such as teriflunomide or leflunomide, (viii) anti-integrin alpha4 antibodies such as natalizumab, (ix) anti CD52 antibodies such as alemtuzumab, (x) mitoxantrone, (xi) anti Lingo1 antibodies such as opicinumab, or (xii) other immunomodulatory therapies such as masitinib.

- 25 Likewise, a compound of the present invention can be combined with an analgesic drug if a painful myelination condition is to be treated. Also, a compound of the present disclosure may be used in combination with an antidepressant to co-treat psychological effects associated with the underlying myelination disease to be treated.

- In combination therapies the two or more active principles may be provided via the same
30 Formulation or as a "kit of parts", i.e. in separate galenic units. Also, the two or more active principles, including the compounds of the present invention, may be administered to the patient at the same time or subsequently, e.g. in an interval therapy. The additional drug may be administered by the same mode or a different mode of administration. For

example, the GPR17 modulator of the present invention may be administered orally, while the second medicament may be administered by subcutaneous injection.

In one aspect, the compounds of the present invention may be used for the diagnosis and/or monitoring of a GPR17- related disease, as further described herein, in particular
5 of a demyelinating disease, as disclosed herein, preferably in the diagnosis and monitoring of multiple sclerosis.

In one aspect, the compounds of the present invention can be used to diagnose and/or monitor the expression, distribution and/or activation of the GPR17 receptor either *in-vivo*, e.g. directly in a subject, such as using molecular imaging techniques, or *in-vitro*, such as
10 e.g. by examining any samples such as body fluids or tissues taken from a subject. Any such determination of the GPR17 activity, expression and/or distribution may be used to predict, diagnose and/or monitor (a) the status and progression of a GPR17-associated disease as described herein, in particular a myelination disease including but not limited to, for example, multiple sclerosis, and (b) the efficacy and/or applicability and/or proper
15 dosing of a treatment associated with any such GPR17-associated disease.

In one aspect, the compounds of the present invention may be used as PET or SPECT tracers, as further disclosed herein, in order to perform *in-vivo* diagnosis and/or disease monitoring. By this, the expression, activation and/or distribution of a GPR17 receptor may be directly measured in a subject, e.g. by imaging of a human patient after the
20 administration of a GPR17 PET or SPECT tracer of the present invention. This may facilitate a proper diagnosis of the disease, can help to determine applicable treatment options and/or may be used to monitor disease progression and/or to monitor or predict the success of a medical intervention, including the selection and proper administration and/or dosing of a therapeutic drug.

25 In one embodiment, the PET or SPECT tracers of the present invention may be used in conjunction with a therapeutic drug, i.e. as a Companion Diagnostic, in order to monitor and/or predict the efficacy and/or safety of said therapeutic drug in a particular subject, or to estimate a drug's proper dosage.

One embodiment relates to a PET or SPECT tracer of the present invention for use as a
30 Companion Drug in conjunction with a therapeutic drug. The therapeutic drug to be used with the PET or SPECT tracer of the present invention may be selected from the group of (a) an unlabeled compound of the present invention, (b) a GPR17 modulating compound which is different from the compounds of the present invention and (c) a drug for the

treatment of a myelination disease, including but not limited to a drug for use in multiple sclerosis treatment, which is not a GPR17 modulator, as further described herein.

One embodiment relates to a kit comprising

- 5 (a) as a first component, a PET or SPECT tracer of the present invention, in particular a PET or PET tracer based on a compound having a structure according to anyone of Formula I, II, III, IV, V or VI, as further defined herein, or having a structure of any one of the compounds disclosed herein, but having incorporated at least one radionuclide which is suitable for PET or SPECT imaging, preferably a radionuclide selected from ^{18}F , ^{11}C , ^{123}I , ^{125}I and ^{131}I ,
- 10 (b) as a second component, a therapeutic drug selected from among
- i. a compound of the present invention having a structure according to anyone of Formula I, II, III, IV, V or VI, as further defined herein, or having a structure of anyone of the individual compounds disclosed herein, and having no radionuclide incorporated,
- 15 ii. a GPR17 modulating compound which is different from the compounds of the present invention as defined in (i), and
- iii. a drug for the treatment of a myelination disease, including but not limited to a drug for use in multiple sclerosis treatment, but having no GPR17 modulating activity; such compounds are known to a person skilled in the art including those examples further described above.
- 20

Alternatively, the compounds of the present invention may be used in an in-vitro diagnostic assay, for example for the examination of suitable body fluids of a subject such as e.g. blood, plasma, urine, saliva, or cerebrospinal fluid for any level of GPR17 expression, activity and/or distribution.

- 25 One embodiment relates to a method of treating a GPR17 associated disease, in particular a myelination disease including but not limited to multiple sclerosis, wherein said method includes the steps of (a) determining the expression, activity and/or distribution of the GPR17 receptor of a subject, (b) comparing the expression, activity and/or distribution of the GPR17 receptor in said subject with the expression, activity and/or distribution of
- 30 the GPR17 receptor in one or more healthy subjects or a population, (c) determining the need for medical treatment or prophylaxis of said subject based on a deviation of

expression, activity and/or distribution of GPR17 of said subject from healthy subjects or a population and (d) treating the subject with the deviation of expression, activity and/or distribution of the GPR17 receptor by administering a therapeutic drug to said individual, which drug is suitable for the treatment of GPR17 associated diseases or disorders, in particular by administering a GPR17 modulator, preferably by administering one of more of the compounds of the present invention. In one embodiment, the determination (a) of the GPR17 expression, activity and/or distribution will be conducted using one of the compounds of the present invention, in particular with a PET or SPECT tracer, or by an *in vitro* examination of body fluids or tissue of said subject using a PET or SPECT tracer of the present invention.

In one preferred aspect, the invention relates to a pharmaceutical composition comprising a compound as described herein, and a pharmaceutical acceptable carrier.

For the administration as a medicinal drug, the compounds may be used in pharmaceutical composition comprising a compound of the present disclosure, and a pharmaceutically acceptable carrier, as further defined herein. Such a pharmaceutical composition can be adapted for example for oral, intravenous, intramuscular, subcutaneous, nasal, rectal, intracranial, ophthalmic, buccal or transdermal administration and may comprise pharmaceutically acceptable carriers, adjuvants, diluents, stabilizers and the like.

For instance, the compounds of the present invention may be dissolved in oils, propylene glycol or other solvents which are commonly used to produce an injection. Suitable examples of the carriers include, but not limited to, physiological saline, polyethylene glycol, ethanol, vegetable oils, isopropyl myristate, etc. The compounds of the present invention may be formulated into injections by dissolving, suspending or emulsifying in water-soluble solvent such as saline and 5% dextrose, or in water-insoluble solvents such as vegetable oils, synthetic fatty acid glyceride, higher fatty acid esters and propylene glycol. The formulations of the invention may include any of conventional additives such as dissolving agents, isotonic agents, suspending agents, emulsifiers, stabilizers and preservatives.

In one embodiment, the compounds of the present invention may be administered orally, e.g. in the form of a tablet, a capsule, a dragee, a powder, a granulate, or in form of a liquid or a semi-solid, including e.g. syrups, suspensions, emulsions or solutions, by way of non-limiting example.

Oral formulations may contain, without limitation, sustained release agents, disintegrants, fillers, lubricants, stabilizers, antioxidants, flavours, dispersion agents, electrolytes, buffers, dyes, or conservation agents. Suitable excipients and formulations are known to those skilled in the art and are disclosed in standard monographs, such as Remington
5 (“The science and practice of pharmacy”, Lippincott, Williams & Wilkins, 2000) or disclosed in other sources well known to persons skilled in the art.

A tablet can, for example, be prepared by mixing at least one compound of the present invention with at least one non-toxic pharmaceutically acceptable excipient, such as e.g. binder, filler/diluents, disintegrant agents, plastisizer, and the like, and an optional solvent
10 (aqueous or non aqueous), and by subsequent processing the mixture to a tablet by a process including but not limited to dry compression, dry granulation, wet granulation, spray drying, or melt extrusion. A tablet can either be uncoated, or coated by known techniques to either mask the bad taste of an unpleasant tasting drug, or delay disintegration and absorption of the active ingredient in the gastrointestinal tract.

15 A tablet may provide an immediate release or sustained release of the compounds of the present invention.

Typical sustained release agents are for example those that swell upon contact with water such as polyvinylpyrrolidone, hydroxyethylcellulose, hydroxypropylcellulose, other cellulose ethers, starch, pregelatinised starch, polymethacrylate, polyvinylacetate,
20 microcrystalline cellulose, dextrans, and mixtures of these. Non-limiting examples of disintegrants include pregelatinised starch, sodium starch glycolate, microcrystalline cellulose, carboxymethylcellulose sodium (CMC-Na), cross-linked CMC-Na, and low-substituted hydroxypropylcellulose, as well as mixtures thereof. Suitable fillers and binders include without limitation microcrystalline cellulose, powdered cellulose, lactose
25 (anhydrous or monohydrate), compressible sugar, starch (e.g. corn starch or potato starch), pregelatinised starch, fructose, sucrose, dextrose, dextrans, other sugars such as mannitol, maltitol, sorbitol, lactitol and saccharose, siliconised microcrystalline cellulose, calcium hydrogen phosphate, calcium hydrogen phosphate dihydrate, dicalciumphosphate dihydrate, tricalciumphosphate, calcium lactate or mixtures thereof. Lubricants,
30 antiadherents and/or glidants include stearic acid, magnesium stearate, calcium stearate, sodium lauryl sulphate, hydrogenated vegetable oil, hydrogenated castor oil, sodium stearyl fumarate, macrogols, glycerol dibehenate, talc, corn starch, silicon dioxide, and the like, including mixtures.

The compound of the present invention may also be formulated for parenteral administration by injection, e.g. by bolus injection or infusion. The compositions for injection may be provided ready to use and may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain excipients such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water or saline, before use.

For nasal administration or administration by inhalation, the compounds according to the present invention may be conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of a suitable propellant, e.g. dichlorodifluoromethane, fluorotrichloromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

For ophthalmic administration the compounds of use in the present invention may be conveniently formulated as micronized suspensions in isotonic, pH-adjusted sterile saline, either with or without a preservative such as a bactericidal or fungicidal agent, for example phenylmercuric nitrate, benzylalkonium chloride or chlorhexidine acetate. Alternatively, for ophthalmic administration compounds may be formulated in an ointment such as petrolatum.

For rectal administration the compounds of use in the present invention may be conveniently formulated as suppositories. These can be prepared by mixing the active component with a suitable non-irritating excipient which is solid at room temperature but liquid at rectal temperature and so will melt in the rectum to release the active component. Such materials include, for example, cocoa butter, beeswax and polyethylene glycols.

In one embodiment, the compounds may be administered transdermally. This mode of administration prevents the so-called 1st pass effect of oral administration and moreover allows providing more constant plasma levels which is of particular advantage in some instances. The design of transdermal forms such as ointments or creams or other transdermal systems such as e.g. patches or electrophoretic devices is generally known from the art, see e.g. Venkatraman and Gale, *Biomaterials* 1998, Vol 19, p1119; Prausnitz and Langer, *Nat Biotechnology* 2008, Vol 26.11 p1261; WO 2001/47503; WO2009/000262; WO99/49852; WO 07/094876.

The preferable dose level of the compounds according to the present invention depends upon a variety of factors including the condition and body weight of the patient, severity of

the particular disease, dosage form, and route and period of administration, but may appropriately be chosen by those skilled in the art. In various embodiments, the compounds are administered in an amount ranging from 0.001 to 10 mg/kg of body weight per day, or from 0.03 to 1 mg/kg of body weight per day. Individual doses may range from about 0.1 to 1000 mg of active ingredient per day, from about 0.2 to 750 mg/day, from about 0.3 to 500 mg/day, from 0.5 to 300 mg/day, or from 1 to 100 mg/day. Doses may be administered once a day, or several times a day with each divided portions.

Another aspect of the present invention is a Kit comprising a medicine or a pharmaceutical composition as described herein, and instructions for its use.

- 10 Another aspect of the present invention is a package comprising at least one unit of a medicine or a pharmaceutical composition comprising at least one compound as described herein, and instructions for its use.

DEFINITIONS

- 15 Any reference to a compound according to the present invention also includes pharmaceutically acceptable salts, solvates, isotopes and co-crystals of such compounds unless expressly indicated otherwise.

The term "*pharmaceutically acceptable salts*" relates to any salts that the compounds may form and which are suitable for administration to subjects, in particular human subjects, according to the present invention. Such salts include but are not limited to acid addition salts, formed either with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl) benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, and muconic acid. Other salts include 2,2-dichloroacetate, adipate, alginate, ascorbate, aspartate, 2-

acetamidobenzoate, caproate, caprate, camphorate, cyclamate, laurylsulfate, edisilate, esylate, isethionate, formate, galactarate, gentisate, gluceptate, glucuronate, oxoglutarate, hippurate, lactobionate, napadisilate, xinafoate, nicotinate, oleate, orotate, oxalate, palmitate, embonate, pidolate, p-aminosalicylate, sebacate, tannate, rhodanide, undecylenate, and the like; or salts formed when an acidic proton present in the parent compound is replaced, such as with ammonia, arginine, benethamine, benzathine, calcium, choline, deanol, diethanolamine, diethylamine, ethanolamine, ethylenediamine, meglumine, glycine, hydrabamine, imidazole, lysine, magnesium, hydroxyethylmorpholine, piperazine, potassium, epolamine, sodium, trolamine, tromethamine or zinc.

- 10 The present invention includes within its scope solvates of the compounds as defined herein. "*Solvates*" are crystals formed by an active compound and a second component (solvent) which, in isolated form, is liquid at room temperature. Such solvates may be formed with common organic solvents, e.g. hydrocarbon solvents such as benzene or toluene; chlorinated solvents such as chloroform or dichloromethane; alcoholic solvents
- 15 such as methanol, ethanol or isopropanol; ethereal solvents such as diethyl ether or tetrahydrofuran; or ester solvents such as ethyl acetate. Alternatively, the solvates of the compounds herein may be formed with water, in which case they will be hydrates.

- The present invention also includes co-crystals within its scope. The term "*co-crystal*" is used to describe the situation where neutral molecular components are present within a crystalline compound in a definite stoichiometric ratio. The preparation of pharmaceutical co-crystals enables modifications to be made to the crystalline form of an active pharmaceutical ingredient, which in turn can alter its physicochemical properties without compromising its intended biological activity. Examples of co-crystal formers, which may be present in the co-crystal alongside the active pharmaceutical ingredient, include L-
- 20 ascorbic acid, citric acid, glutaric acid, cinnamic acid, mandelic acid, urea and nicotinamide.

- The invention also includes all suitable isotopic variations of a compound of the invention. An "*isotopic variation*", or shortly "*isotope*" of a compound of the invention is defined as one in which at least one atom is replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature with the most abundant isotope(s) being preferred. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, sulphur, fluorine and chlorine such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{17}O , ^{18}O , ^{35}S , ^{18}F , and ^{36}Cl , respectively. Certain isotopic variations of the invention, for example, those in which
- 30

a radioactive isotope such as ^3H or ^{14}C is incorporated, are useful in drug and/or substrate tissue distribution studies. Tritiated, i.e., ^3H , and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with isotopes such as deuterium, i.e., ^2H , may afford certain therapeutic advantages
5 resulting from greater metabolic stability, for example, increased in vivo half-life, reduced dosage requirements and hence may be preferred in some circumstances. Isotopic variations of the compounds of the invention can generally be prepared by conventional procedures using appropriate isotopic variations of suitable reagents.

Also part of the invention are those compounds wherein at least one atom has been
10 replaced by a radioactive isotope (radioisotope) of the same or a different atom that can be used in vivo imaging techniques such as single-photon emission computed tomography (SPECT) or positron emission tomography (PET).

Examples for such isotopic variations of GPR17 modulators usable in SPECT studies (such compounds herein "SPECT tracers") are compounds wherein a $^{99\text{m}}\text{Tc}$, ^{111}In , ^{82}Rb ,
15 ^{137}Cs , ^{123}I , ^{125}I , ^{131}I , ^{67}Ga , ^{192}Ir or ^{201}Tl , and preferably ^{123}I has been introduced. For example, in order for the compounds of the present invention to be used as SPECT tracers, an ^{123}I isotope may be introduced into a GPR17 modulator as disclosed herein. By way of a non-limiting example, in order for a compound to be used as SPECT tracer, a radionuclide selected from ^{123}I , ^{125}I and ^{131}I may be introduced into a compound of the
20 present invention. In one embodiment, a SPECT tracer of the present invention may be based on the structure of a halogen-containing GPR17 modulator disclosed herein, wherein one of the radionuclides ^{123}I , ^{125}I and ^{131}I has been introduced into the position of a halogen, preferably, a iodine atom.

Accordingly, the term "*SPECT tracer of the present invention*", relates to compounds as
25 described in the present patent application and having a structure according to anyone of Formula I, II, III, IV, V or VI as further defined herein, or as otherwise individually disclosed herein, wherein at least one radioisotope has been introduced which is suitable for SPECT imaging. This includes but is not limited to $^{99\text{m}}\text{Tc}$, ^{111}In , ^{82}Rb , ^{137}Cs , ^{123}I , ^{125}I , ^{131}I , ^{67}Ga , ^{192}Ir or ^{201}Tl .

30 Examples for GPR17 modulator derivatives usable in PET applications (herein "PET tracers") are compounds wherein ^{11}C , ^{13}N , ^{15}O , ^{18}F , ^{76}Br or ^{124}I have been introduced. For example, in order for a compound to be used as a PET tracer, an ^{18}F isotope may be introduced into a compound of the present invention. In one embodiment, a PET tracer may be based on the structure of a fluorine-containing GPR17 modulator disclosed

herein, wherein the respective radionuclide ^{18}F has been introduced into the position of the fluorine atom. This likewise applies to the introduction of at least one ^{11}C , ^{13}N , ^{15}O , ^{76}Br or ^{124}I , instead of an "unlabelled" carbon, nitrogen, oxygen, bromine, or iodine atom, respectively (see e.g. Pimlott and Sutherland, Chem Soc Rev 2011, 40, 149; van der Born
5 et al, Chem Soc Rev 2017, 46, 4709).

Accordingly, the term "*PET tracer of the present invention*", relates to compounds as described in the present patent application and having a structure according to anyone of Formula I, II, III, IV, V or VI as further defined herein, or as otherwise individually disclosed herein, wherein at least one radioisotope has been introduced which is suitable for PET
10 imaging. This includes but is not limited to ^{11}C , ^{13}N , ^{15}O , ^{18}F , ^{76}Br or ^{124}I .

The present invention includes within its scope prodrugs of the compounds of the present invention. In general, such prodrugs will be functional derivatives of the compounds described herein which are readily convertible in vivo, e.g. by endogenous enzymes in the gut or the blood, into the required GPR17 modulating compounds described herein.
15 Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in Design of Prodrugs, ed. H. Bundgaard, Elsevier, 1985.

Depending on its substitution pattern, the compounds of the present invention may or may not have one or more optical stereocenters, and may or may not exist as different enantiomers or diastereomers. Any such enantiomers, diastereomers or other optical
20 isomers are encompassed by the scope of the invention.

The compound of the present invention may also exist in different crystal forms, i.e. as polymorphs, all of which are encompassed by the present invention.

The compounds of the present invention may be included in a pharmaceutical composition which may also include a pharmaceutically acceptable carrier.
25 "*Pharmaceutically acceptable carrier*" refers to a diluent, adjuvant, excipient, or carrier, or other ingredient with which a compound of the invention is administered and which a person of skilled in the art would understand to be pharmaceutically acceptable.

The compounds of the present invention are useful in the prevention and/or treatment of certain diseases or disorders in animals, in particular in humans, as described herein.

30 "*Preventing*" or "*prevention*" refers to a reduction in risk of acquiring a disease or disorder (i. e., causing at least one of the clinical symptoms of the disease not to develop in a subject, in particular a human subject, that may be exposed to or predisposed to the

disease but does not yet experience or display symptoms of the disease).

"*Treating*" or "*treatment*" of any disease or disorder includes, in one embodiment, to improve the disease or disorder (i. e., arresting or reducing the development of the disease or at least reducing one of the clinical symptoms of the disease). In another embodiment "treating" or "treatment" refers to improve at least one physical parameter, which may or may not be discernible by the subject, in particular a human subject, but which is based on or associated with the disease or disorder to be treated. In yet another embodiment, "treating" or "treatment" refers to modulating or alleviating the disease or disorder, either physically (e. g. stabilization of a discernible on non-discernible symptom), physiologically (e. g. stabilization of a physiological parameter), or both. In yet another embodiment, "treating" or "treatment" refers to delaying the onset or progression of the disease or disorder. Accordingly, "*treating*" or "*treatment*" includes any causal treatment of the underlying disease or disorder (i.e. disease modification), as well as any treatment of signs and symptoms of the disease or disorder (whether with or without disease modification), as well as any alleviation or amelioration of the disease or disorder, or its signs and symptoms.

"*Diagnosis*", "*diagnoses*" or "*diagnosing*" of a disease or disorder include, in one embodiment, the identification and measurement of signs and symptoms which are associated with said disease. "Diagnosis", "diagnoses" or "diagnosing" include but are not limited to the detection and/or measurement of decreased, increased, or otherwise incorrectly (e.g. as to time or place) expressed, activated, or distributed GPR17 receptors as indicator of a GPR17-related disease or disorder, as compared to healthy subjects. In one example, GPR17 ligands may be used in the form of PET or SPECT tracers for such a diagnosis, including a diagnosis for a myelination disease.

The terms "*disease(s)*" and "*disorder(s)*" are used largely interchangeably herein.

"*Monitoring*" refers to the observation of a disease, condition or at least one medical parameter over a certain period of time. "Monitoring" also includes the observations of the effects of a therapeutic drug with the assistance of a "*Companion Drug*".

"*Companion Diagnostic*" as used herein refers to a compound that can be used in conjunction to a therapeutic drug with the aim to determine the applicability (e.g. in terms of safety and efficacy) of said therapeutic drug to a specific patient. The use of a "Companion Diagnostic" may include diagnostic and monitoring steps.

The term "*animal(s)*" and "*subject(s)*" includes humans. The terms "*human*," "*patient*" and "*human subject*" are typically used interchangeably herein, unless clearly indicated.

The invention also relates to methods of treating an animal disease or disorder, as described in more detail herein, in particular a human disease or disorder, which includes
5 the administration of the compounds of the present invention in therapeutically effective amounts. "*Therapeutically effective amount*" means the amount of a compound that, when administered to a subject, in particular a human subject, for treating a disease, is sufficient to effect such treatment for the disease. The "therapeutically effective amount" can vary depending on the compound, the disease and its severity, and the condition, age, weight,
10 gender etc. of the subject, in particular a human subject, to be treated.

The term "*multiple sclerosis*" as used herein refers to the disease as classified in Section G35 of the ICD-10-CM diagnosis code of the 2018 American edition.

The term "*GPR17 modulators*" as used herein are meant to describe compounds that are capable of modulating the activity of the GPR17 receptor, in particular compounds that are
15 capable of decreasing the GPR17 activity. Such "negative GPR17 modulators" include GPR17 antagonists which are capable of blocking the effects of GPR17 agonists, as well as GPR17 inverse agonists which are also capable of inhibiting constitutional active GPR17 receptors or receptor variants. Preferred GPR17 modulators of the present invention are inverse GPR17 agonists.

20 Whenever numbers appear in subscript following a "C", these numbers (whether in brackets or not) refer to the range of carbon atoms comprised by the respective group directly following the numbers. For example, "C₁₋₃" and "(C₁₋₃)" both refer to a group, as further specified herein, which comprises between 1 and 3 C-Atoms.

"*Alkyl*" includes saturated aliphatic hydrocarbonyl groups. The hydrocarbon chain may be
25 either straight-chained or branched. Examples of "alkyl" include those with 1-5 carbon atoms ("C₁₋₅ alkyl"), 1-4 carbon atoms ("C₁₋₄ alkyl"), 1-3 carbon atoms ("C₁₋₃ alkyl"), or 1-2 carbon atoms ("C₁₋₂ alkyl"). This term is exemplified by groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, t-amyl, and the like. Any numbers of C atoms in alkyls or other groups may be indicated herein in brackets or without
30 brackets.

"*Alkyloxy*" and "*alkoxy*", as used interchangeably herein (together *alk(yloxy)*), include the group -OR wherein R is "alkyl" as defined and exemplified further herein. Particular

alk(yl)oxy groups include, by way of example, meth(yl)oxy, eth(yl)oxy, n-prop(yl)oxy, isoprop(yl)oxy, n-but(yl)oxy, tert-but(yl)oxy, sec-but(yl)oxy, isobut(yl)oxy, and the like.

"Halogen" includes fluorine, chlorine, bromine, and iodine atoms.

"Cyano" refers to $\text{-C}\equiv\text{N}$.

- 5 The term "*fluoroalkyl*" as used refers to an "*alkyl*" as described herein, which is substituted with one or more fluorine atoms. Representative examples of fluoro(C_{1-3})alkyl groups include, but are not limited to -CF_3 , -CHFCHF_2 and $\text{-CH}_2\text{CF}_3$. A particularly preferred fluoroalkyl group is difluoromethyl -CHF_2 .

- The terms "*fluoroalkyloxy*" or "*fluoroalkoxy*" as interchangeably used herein refer to an
10 "*alk(yl)oxy*" as described herein, which is substituted with one or more fluorine atoms. Representative examples of fluoro(C_{1-3})alk(yl)oxy groups include, but are not limited to -OCF_3 , $\text{-OCHFCH}_2\text{F}$ and $\text{-OCH}_2\text{CF}_3$.

- The term "*fluoromethoxy*" as used herein refers to a methoxy group which is substituted with one to three fluorine atoms. The term "*monofluoromethoxy*" refers to a methoxy group
15 which is substituted with one fluoro atom. The term "*difluoromethoxy*" as used herein refers to a methoxy group which is substituted with two fluorine atoms. The term "*trifluoromethoxy*" refers to a methoxy group which is substituted with three fluorine atoms.

- The term "*fluoroethoxy*" as used herein refers to an ethoxy group which is substituted with one to three fluorine atoms. The term "*monofluoroethoxy*" as used herein refers to an
20 ethoxy group which is substituted with one fluorine atom. A particularly preferred monofluoroethoxy is the group $\text{-OCH}_2\text{CH}_2\text{F}$. The term "*difluoroethoxy*" as used herein refers to an ethoxy group which is substituted with two fluorine atoms. A particularly preferred difluoroethoxy is the group $\text{-OCH}_2\text{CHF}_2$. The term "*trifluoroethoxy*" refers to an ethoxy group which is substituted with three fluorine atoms. A preferred trifluoroethoxy
25 group is the group $\text{-OCH}_2\text{CF}_3$.

The term "*fluoromethoxyethoxy*" refers to a terminal *fluoromethoxy* group as further defined herein which is attached to an ethoxy group. A preferred "*fluoromethoxyethoxy*" is difluoromethoxyethoxy, which is represented by $\text{-OCH}_2\text{CH}_2\text{OCHF}_2$.

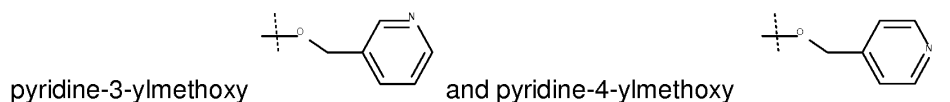
- The term "*cycloalkyl*" as used herein refers to a monovalent group derived from a
30 saturated hydrocarbon, which may be unsubstituted or substituted with one or more substituents as further indicated herein. The "cycloalkyl" is comprised of at least three up

to, for example, 5 ring forming carbon atoms ("*C₃₋₅ cycloalkyl*"), or 4 ring forming atoms ("*C₃₋₄ cycloalkyl*"). Suitable cycloalkyl groups include cyclopropyl, cyclobutyl, and cyclopentyl.

The terms "benzyloxy" or "phenylmethoxy" as used herein refers to a group, wherein a phenylring is linked to a methoxy to represent the group -O-CH₂-phenyl.

The terms "benzylmethoxy" as used herein refers to a phenylethoxy group wherein a phenylring is linked to an ethoxy group to represent the group -O-CH₂-CH₂-phenyl.

The term "pyrid(in)ylmethoxy" refers to a group wherein a pyrid(in)yl group is linked to a methoxy to represent the group -O-CH₂-pyridyl, wherein the pyridyl can be any pyridyl group. Preferred pyridylmethoxy groups in connection with the present invention are



Experimental Part:

A. CHEMISTRY

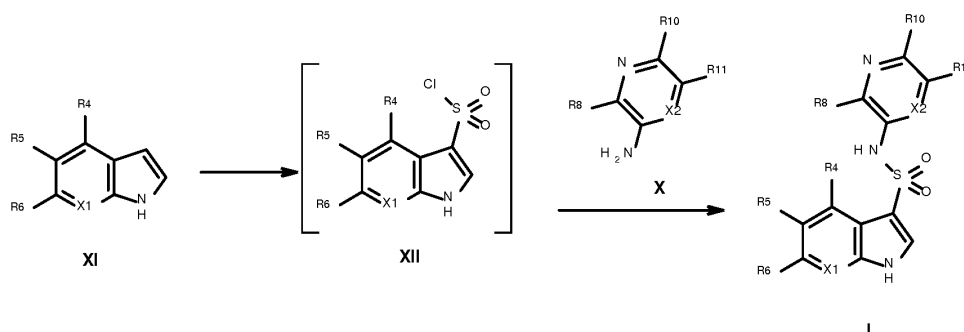
The compounds of the present invention and their synthetic routes are described in more details below.

A-I General methods of making the compounds

The compounds of Formula I according to the invention can be prepared analogously to conventional methods as understood by the person skilled in the art of synthetic organic chemistry.

Any reference to the synthesis of compounds of general Formula I herein likewise apply to the applicable compounds of the subgeneric Formula II, III, IV and V, and the specific Example compounds disclosed herein.

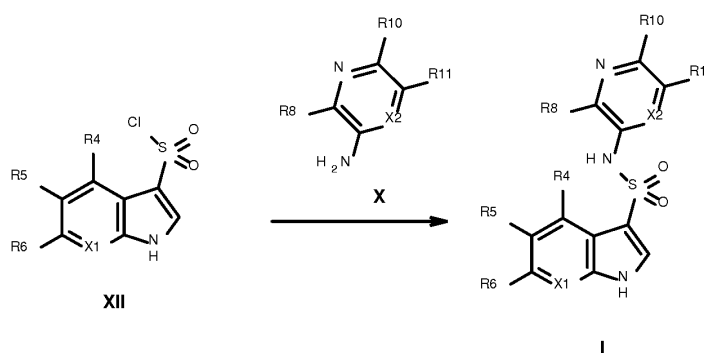
According to one embodiment, some compounds of general Formula I may be prepared by reaction of a compound of Formula XI with an aniline of Formula X according to the equation:



This reaction may be performed with chlorosulfonic acid to form the non-isolated sulfonyl chloride intermediate **XII** at a temperature ranging from 60 to 120°C in a polar solvent such as acetonitrile. Intermediate **XII** is then directly reacted with an aniline **X** in the presence of a base such as pyridine with or without a catalytic amount of 4-dimethylaminopyridine (DMAP), in a polar solvent such as acetonitrile at a temperature preferably ranging from 60 to 80°C.

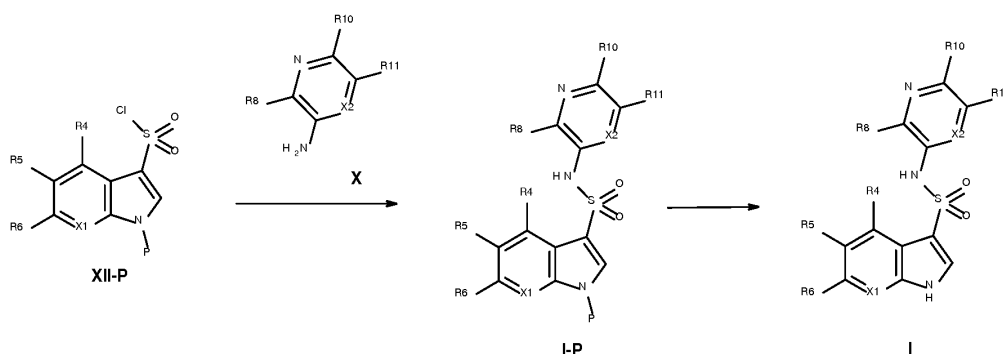
Alternatively, the sulfonyl chloride intermediate **XII** may be formed starting from compound **XI**, in the presence of pyridine-sulfur trioxide complex in pyridine, at reflux temperature. The intermediate sulfonic acid salt may be chlorinated in the presence of a chlorinating agent such as triphenylphosphine/trichloroacetonitrile in a solvent such as dichloromethane at reflux temperature.

Alternatively, some compounds of general Formula **I** may be prepared by reaction of a sulfonyl chloride of Formula **XII** with an aniline of Formula **X** according to the equation:



This reaction may be performed in the presence of a base such as pyridine used as solvent at room temperature.

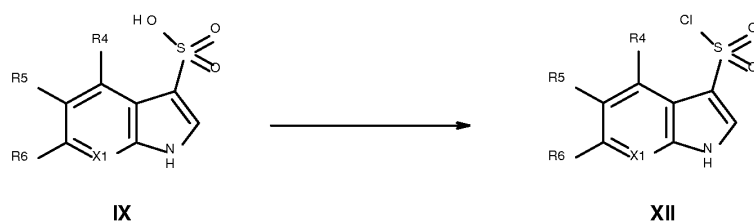
Alternatively, some compounds of general Formula I may be prepared by deprotection of a compound of Formula I-P wherein P is a protecting group such as phenylsulfonyl (PhSO₂) according to the equation:



- 5 This reaction may be performed in the presence of a weak base such as potassium carbonate or cesium carbonate in a polar solvent mixture such as methanol or dioxane and water at room temperature or under heating at a temperature preferably ranging from 80 to 120°C. This reaction may be performed in the presence of tetrabutylammonium fluoride in a solvent such as THF under heating at a temperature preferably ranging from 60 to 90°C.

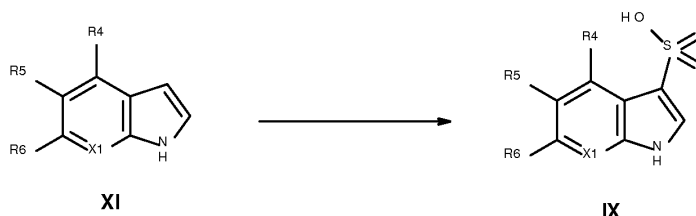
Compounds of Formula I-P may be prepared by reaction of a sulfonyl chloride of Formula XII-P with an aniline of Formula X. This reaction may be performed in the presence of a base such as pyridine used as solvent at room temperature.

- 15 Compounds of Formula XII may be prepared by chlorination of a compound of Formula IX according to the equation:



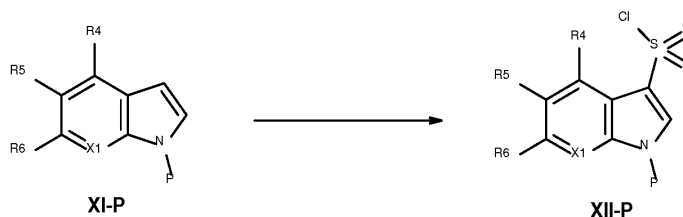
- 20 This reaction may be performed in the presence of a chlorinating agent such as phosphorus oxychloride in a polar solvent such as acetonitrile at a temperature ranging from 50 to 100°C.

Compounds of Formula **IX** wherein may be prepared by sulfonylation of a compound of Formula **XI** according to the equation:



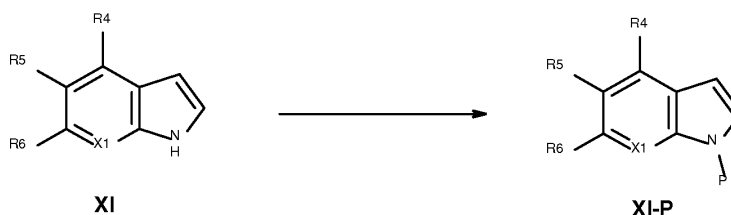
This reaction may be performed in the presence of a sulfonylating agent such as pyridine-sulfur trioxide complex in the presence of a base such as pyridine used as a solvent at reflux temperature.

Compounds of Formula **XII-P** wherein P is a protecting group such as phenylsulfonyl may be prepared by chlorosulfonylation of a compound of Formula **XI-P** according to the equation:



This reaction may be performed in the presence of chlorosulfonic acid in a polar solvent such as acetonitrile at room temperature.

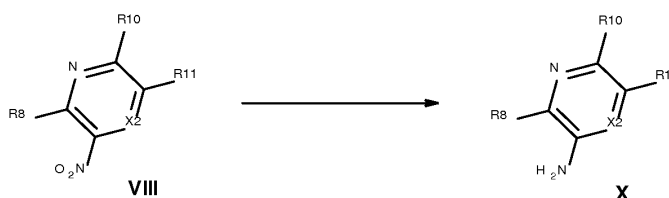
Compounds of Formula **XI-P** wherein P is a protecting group such as phenylsulfonyl may be prepared by protection of a compound of Formula **XI** according to the equation:



This reaction may be performed according to any method known to the person skilled in the art.

Anilines of Formula **X** are commercially available or may be prepared according to any method known to the person skilled in the art or using procedures described in literature.

Alternatively, some anilines of Formula **X** may be prepared by reduction of a compound **VIII** according to the equation:



- 5 This reaction may be performed using any reducing agent such as iron in the presence of an acid such as acetic acid or hydrogen in the presence of a catalytic amount of palladium on charcoal in a polar solvent such as ethyl acetate or methanol or according to any method known to the person skilled in the art.

Compounds of Formula **VIII** are commercially available or may be prepared according to literature procedures or or any other methods known to the person skilled in the art.

- 10 Compounds of Formula **XI** are commercially available or may be prepared by suitable methods well known by the person skilled in the art.

A-II. Abbreviations/recurrent reagents

Ac: acetyl

- 15 ACN: Acetonitrile

AcOH: Acetic acid

Brine: Saturated aqueous sodium chloride solution

Boc: tert-butoxycarbonyl

*n*Bu: n-butyl

- 20 *t*Bu: tert-butyl

Cy: Cyclohexyl

DAST: Diethylaminosulfur fluoride

dba: dibenzylideneacetone

- DCM: Dichloromethane
- DMAP: 4-dimethylaminopyridine
- DMF: *N,N*-Dimethylformamide
- DMSO: Dimethylsulfoxide
- 5 Dppf: 1,1'- bis(diphenylphosphanyl) ferrocene
- ES⁺: Electrospray Positive Ionization
- ES⁻: Electrospray Negative Ionization
- ESI: Electrospray Ionization
- EtOAc: Ethyl acetate
- 10 h: Hour
- LC: Liquid Chromatography
- LCMS: Liquid Chromatography Mass Spectrometry
- Me: Methyl
- MeOH: Methanol
- 15 min.: minutes
- mw: microwave oven
- NBS: N-Bromosuccinimide
- NCS: N-Chlorosuccinimide
- NMR: Nuclear magnetic resonance
- 20 rt: room temperature
- TBAHSA: Tetrabutylammonium hydrogen sulfate
- TBAF: Tetrabutylammonium fluoride
- TEA: Triethylamine
- TFAA: Trifluoroacetic anhydride

THF: Tetrahydrofuran

TLC: Thin Layer Chromatography

Xantphos: 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

5 **A-III. Analytical methods**

Commercial solvents and reagents were generally used without further purification, including anhydrous solvents when appropriate (generally Sure-Seal™ products from Aldrich Chemical Company or AcroSeal™ from ACROS Organics). In general reactions were followed by thin layer chromatography or Liquid Chromatography Mass

10 Spectrometry analyses.

Mass spectrometric measurements in LCMS mode are performed using different methods and instruments as follows:

- *Basic LCMS Method 1:*

15 A QDA Waters simple quadrupole mass spectrometer is used for LCMS analysis. This spectrometer is equipped with an ESI source and an UPLC Acquity Hclass with diode array detector (200 to 400 nm). Data are acquired in a full MS scan from m/z 70 to 800 in positive/negative mode with a basic elution. The reverse phase separation is carried out at 45°C on a Waters Acquity UPLC BEH C18 1.7 µm (2.1 x 50 mm) column for basic elution. Gradient elution is done with water/ACN/ammonium formate (95/5/63 mg/L) (solvent A) and ACN/water/ammonium formate (95/5/63 mg/L) (solvent B) according to table 1.
20 Injection volume: 1 µL. Full flow in MS.

Table 1:

Time (min)	A (%)	B (%)	Flow (mL/min)
0	99	1	0.4
0.3	99	1	0.4
3.2	0	100	0.4
3.25	0	100	0.5
4	0	100	0.5
4.1	99	1	0.4
4.8	99	1	0.4

- *Basic LCMS Method 2:*

Mass spectrometry (MS) spectra were recorded on an LCMS-2010EV mass spectrometer (Shimadzu) with electrospray ionization (ESI) coupled to an HPLC modular Prominence (Shimadzu) using Xbridge C18-2.1x30mm, 2.5 μ m (Waters) column. A volume of 3 μ L of sample solution with a concentration of approx. 1mg/mL was injected. The mobile phase for basic conditions was a mixture of A) 5mM ammonium formate +0.1% ammonia in water B) 5% mobile phase A+ 0.1% ammonia in acetonitrile. The gradient used was as follows-5:95(B/A) to 95:5(B/A) in 4min and hold 95:5(B/A) for next 1min.

- *Neutral LCMS Method 3:*

Mass spectrometry (MS) spectra were recorded on an LCMS instrument (Applied Biosystems API 2000 LC/MS/MS, HPLC Agilent 1100) using the following procedure: dissolving of the compounds at a concentration of 1.0 mg mL⁻¹ in ACN (Solvent A) or water (containing 2 mM ammonium acetate) : MeOH 90:10 (Solvent B), and if necessary sonicated until completely dissolved. Then, 10 μ L of the solution was injected into a Phenomenex Luna C18 HPLC column (50 $\times$ 2.00 mm, particle size 3 μ m) and elution was performed with a gradient of water : ACN (Gradient A) or water : MeOH (Gradient B) from 90 : 10 to 0 : 100 within 10 min, starting the gradient after 1 min, followed by elution in

pure organic solvent for 10 min at a flow rate of 300 $\mu\text{L min}^{-1}$. UV absorption was detected from 220 to 400 nm using a diode array detector (DAD).

- *Acidic LCMS Method 4:*

- HPLC-MS was performed on an Agilent 1200-6120 LC-MS system coupled to UV
 5 Detection (230 to 400 nm and 215 nm) and Mass Spec Detection Agilent 6120 Mass Spectrometer (ES) m/z 120 to 800 using an X-Bridge C18 Waters 2.1 x 20 mm, 2.5 μM column. Elution was performed with a gradient depicted in Table 2 of Mobile Phase A (10 mM Ammonium formate in water + 0.1% Formic acid) and Mobile Phase B (Acetonitrile + 5% water + 0.1% Formic acid) with a flow rate of 1 mL/min

10 Table 2:

Time (min)	A (%)	B (%)
0	94	6
1.5	5	95
2.25	5	95
2.50	94	6

Crude materials could be purified by normal phase chromatography, (acidic or basic) reverse phase chromatography or recrystallization.

- Normal phase chromatography was performed using silica gel columns (100:200 mesh
 15 silica gel or cartridges for flash chromatography systems such as Isolera™ Four from Biotage® or Teledyne Isco CombiFlash®).

Preparative reverse phase chromatography was performed with two different instruments and according to the methods as follows:

- *Basic prep LCMS Method 1:*

- 20 LCMS purification is using an SQD or QM Waters single quadrupole mass spectrometer for MS detection. This spectrometer is equipped with an ESI source, Waters 2525 binary pump coupled with 2767 sample Manager and with a diode array detector (210 to 400 nm).

MS parameters: ESI capillary voltage 3 kV. Cone and Extractor voltage 10. Source block temperature 120°C. Desolvation temperature 300°C. Cone gas flow 30 L/h (Nitrogen), Desolvation Gas flow 650 L/h. Data are acquired in a full MS scan from m/z 100 to 850 in positive/negative mode.

- 5 *LC parameters:* The reverse phase separation is carried out at rt on an XBridge prep OBD C18 column (5 µm, 30 x 50 mm). Gradient elution is done with solvent A1 (H₂O + NH₄HCO₃ 10mM + 50µl/L NH₄OH) and solvent B1 (100% ACN) (pH ~8.5). HPLC flow rate : 35ml/min to 45 ml/min , injection volume : 990 µl. The splitting ratio is set at +/- 1/6000 to MS (table 3).

- 10 Table 3:

Time (min)	A1 (%)	B1 (%)	Flow (mL/min)
0	95	5	35
1	95	5	35
7	10	90	35
7.5	5	95	35
9	5	95	35
9.1	5	95	45
12	5	95	45

- *Neutral RP- HPLC Method 2:*

- 15 HPLC purification of final products was performed on a Knauer Smartline 1050 HPLC system using a RP-HPLC column (Knauer 20 mm i.d., Eurospher-100 C18). The product was dissolved in methanol (20 mg per 8 mL) and subjected to reversed-phase HPLC applying a gradient of methanol/water (70:30 to 100:0 over 24 min).

NMR spectra were recorded on different instruments:

- a BRUKER AVANCEIII 400 MHz-Ultrashield NMR Spectrometer fitted with a Windows 7 Professional workstation running Topspin 3.2 software and a 5 mm Double Resonance

Broadband Probe (PABBI 1H/19F-BB Z-GRD Z82021/0075) or a 1 mm Triple Resonance Probe (PATXI 1H/ D-13C/15N Z-GRD Z868301/004).

- a Varian 400 MHz NMR spectrometer with acquisition time (at) =2.0 sec, relaxation delay (d1) = 2.0 sec and line broadening (lb)=0.5 Hz.

5 - a Bruker Avance DRX 500 MHz NMR spectrometer

- a Bruker Avance III 600 MHz NMR spectrometer

Chemical shifts are referenced to signals deriving from residual protons of the deuterated solvents (DMSO-*d*₆, Benzene-*d*₆ or CDCl₃). Chemical shifts are given in parts per million (ppm) and coupling constants (J) in Hertz (Hz). Spin multiplicities are given as broad (br),
10 singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m).

Products were generally dried under vacuum before final analyses and submission to biological testing.

A-IV: EXAMPLE COMPOUNDS AND SYNTHESIS

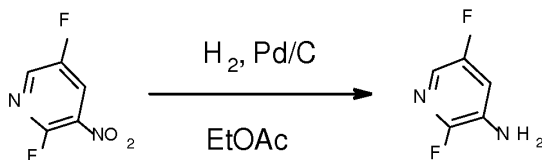
15 The names of the following compounds are IUPAC names generated by Biovia Draw Version 16.1 for Intermediates of Formula X, XI, XII and by Pipeline Pilot 2018 using OpenEye oemetachem version 1.4.5 for Example compounds of Formula I.

Intermediates

When commercially available, starting materials are identified by their CAS Register
20 Numbers.

A. Synthesis of intermediates of Formula X

A.1. Synthesis of 2,5-difluoropyridin-3-amine X-1:



CAS: 179558-82-8

X-1

To a solution of 2,5-difluoro-3-nitro-pyridine (0.30 g, 1.87 mmol) in EtOAc (40 mL) was added Pd/C (0.13 g, 1.27 mmol) and the reaction mixture was stirred at room temperature for 8h under hydrogen pressure. Progress of the reaction was monitored by TLC and LCMS. After completion, the reaction mixture was filtered through celite, washed with EtOAc (40 mL) and the filtrate was concentrated under vacuum to afford 2,5-difluoropyridin-3-amine **X-1** (0.19 g) as a yellow solid.

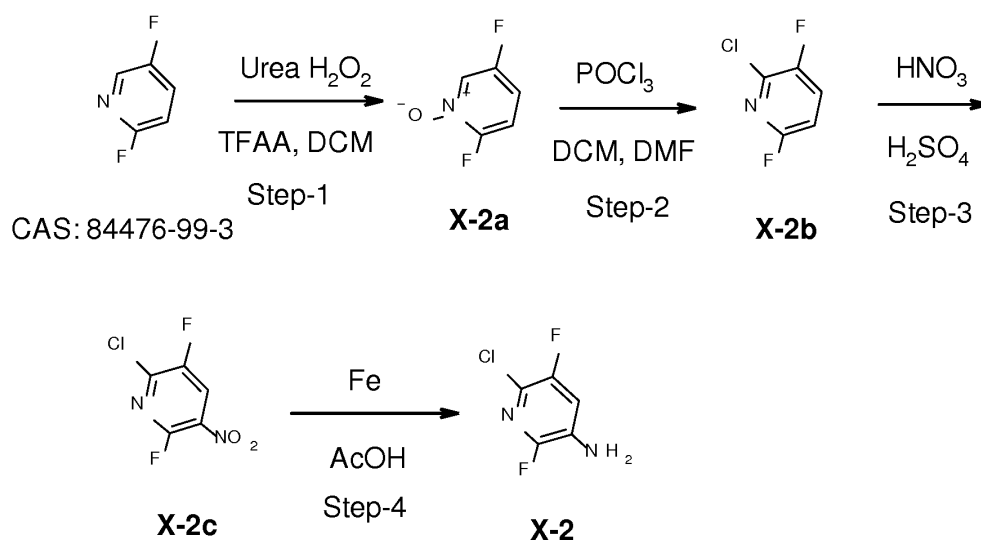
This compound was used as such for the next reaction without further purification.

Yield: 71%.

Basic LCMS Method 2 (ES⁺): 131 (M+H)⁺, 90% purity.

¹H NMR (400 MHz, DMSO-*d*₆) δ 5.81 (brs, 2H), 6.94-6.98 (m, 1H), 7.23 (t, J=2.69 Hz, 1H)

A.2. Synthesis of 6-chloro-2,5-difluoro-pyridin-3-amine **X-2**:



Step-1: Synthesis of 2,5-difluoro-1-oxido-pyridin-1-ium **X-2a**:

To a solution of 2,5-difluoropyridine (3.00 g, 26.1 mmol) in DCM (120 mL) was added Urea hydrogen peroxide (7.36 g, 78.2 mmol) and the reaction mixture was stirred at room temperature for 10 min. The reaction mixture was cooled at 0 °C followed by drop wise addition of trifluoroacetic anhydride (12 mL). The reaction mixture was stirred at room temperature for 4h. Progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with aqueous NaHCO₃ (120 mL) and extracted with DCM (3 × 80 mL). The organic layer was separated, dried over anhydrous Na₂SO₄ and

concentrated under vacuum to afford 2,5-difluoro-1-oxido-pyridin-1-ium **X-2a** (1.00 g) as an off-white solid.

This compound was used as such for the next reaction without further purification.

Yield: 29%.

- 5 ^1H NMR (400 MHz, DMSO- d_6) δ 7.39-7.47 (m, 1H), 7.50 (m, 1H), 8.48-8.57 (m, 1H).

Step-2: Synthesis of 2-chloro-3,6-difluoro-pyridine **X-2b**:

- To a solution of 2,5-difluoro-1-oxido-pyridin-1-ium **X-2a** (0.95 g, 7.25 mmol) in DCM (30 mL) was added POCl_3 (1.33 mL, 14.5 mmol) drop wise at 0 °C. The reaction mixture was stirred at same temperature for 5 min followed by addition of DMF (0.60 mL). The reaction mixture was stirred at room temperature for 6h. Progress of the reaction was monitored by TLC. After completion, the reaction mixture was quenched with saturated NaHCO_3 (50 mL) solution and extracted with EtOAc (2 $\times$ 50 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford 2-chloro-3,6-difluoro-pyridine **X-2b** (0.65 g) as a pale brown liquid. This compound was used as such for the next reaction without further purification.

Yield: 60%.

^1H NMR (400 MHz, DMSO- d_6) δ 7.35-7.39 (m, 1H), 8.15-8.23 (m, 1H).

Step-3: Synthesis of 2-chloro-3,6-difluoro-5-nitro-pyridine **X-2c**:

- To a solution of 2-chloro-3,6-difluoro-pyridine **X-2b** (0.60 g, 4.01 mmol) in fuming HNO_3 (4.19 mL, 100 mmol) was added concentrated H_2SO_4 (3.21 mL, 60.2 mmol) drop wise maintaining a temperature below 40 °C. The reaction mixture was then heated at 60 °C for 30 min. Progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled and poured into crushed ice and extracted with DCM (2 $\times$ 50 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude obtained was purified by column chromatography (silica, 100-200 mesh, 10% EtOAc in hexane) to afford 2-chloro-3,6-difluoro-5-nitro-pyridine **X-2c** (0.185 g) as a pale yellow liquid.

Yield: 24%.

^1H NMR (400 MHz, DMSO- d_6) δ 9.10-9.14 (m, 1H).

- 30 Step-4: Synthesis of 6-chloro-2,5-difluoro-pyridin-3-amine **X-2**:

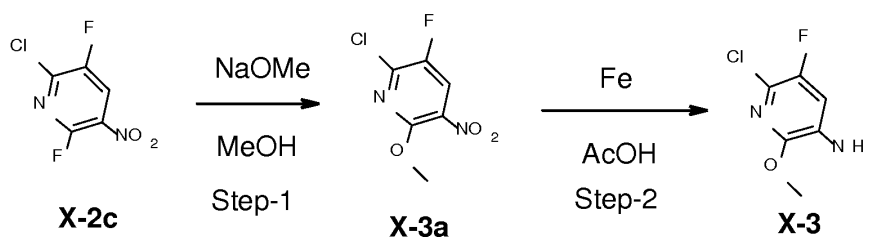
To a solution of 2-chloro-3,6-difluoro-5-nitro-pyridine **X-2c** (0.18 g, 0.93 mmol) in acetic acid (9 mL) was added iron (0.05 g, 0.93 mmol) and the reaction mixture was heated at 80 °C for 2h. Progress of the reaction was monitored by TLC and LCMS. After completion, the reaction mixture was concentrated under vacuum. The residue was diluted with EtOAc (40 mL) and washed with saturated NaHCO₃ (25 mL). The organic layer was separated, dried over anhydrous Na₂SO₄ and concentrated under vacuum to 6-chloro-2,5-difluoro-pyridin-3-amine **X-2** (0.28 g) as a pale brown solid.

This compound was used as such for the next reaction without further purification.

Yield: 42%.

Basic LCMS Method 2 (ES⁻): 163 (M-H)⁻, 23% purity.

A.3. Synthesis of 6-chloro-5-fluoro-2-methoxy-pyridin-3-amine **X-3**:



Step-1: Synthesis of 2-chloro-3-fluoro-6-methoxy-5-nitro-pyridine **X-3a**:

To a solution of 2-chloro-3,6-difluoro-5-nitro-pyridine **X-2c** (0.67 g, 3.44 mmol) in MeOH (10 mL) was added NaOMe (0.82 mL, 3.79 mmol) drop wise at -40 °C and the reaction mixture was stirred at same temperature for 20 min. Progress of reaction was monitored by TLC. After completion, the reaction mixture was poured into ice cold 1N HCl (10 mL) and extracted with hexane (2 × 15 mL). The organic layer was separated, dried over anhydrous Na₂SO₄ and concentrated under vacuum to obtain 2-chloro-3-fluoro-6-methoxy-5-nitro-pyridine **X-3a** (0.40 g) as a yellow solid.

This compound was used as such for next reaction without further purification.

Yield: 56%.

¹H NMR (400 MHz, DMSO-*d*₆) δ 4.03 (s, 3H), 8.82 (d, J=7.83 Hz, 1H).

Step-2: Synthesis of 6-chloro-5-fluoro-2-methoxy-pyridin-3-amine **X-3**:

To a stirred solution of 2-chloro-3-fluoro-6-methoxy-5-nitro-pyridine **X-3a** (0.20 g, 0.97 mmol) in acetic acid (4 mL) was added iron (0.22 g, 3.87 mmol) at 0 °C. The reaction

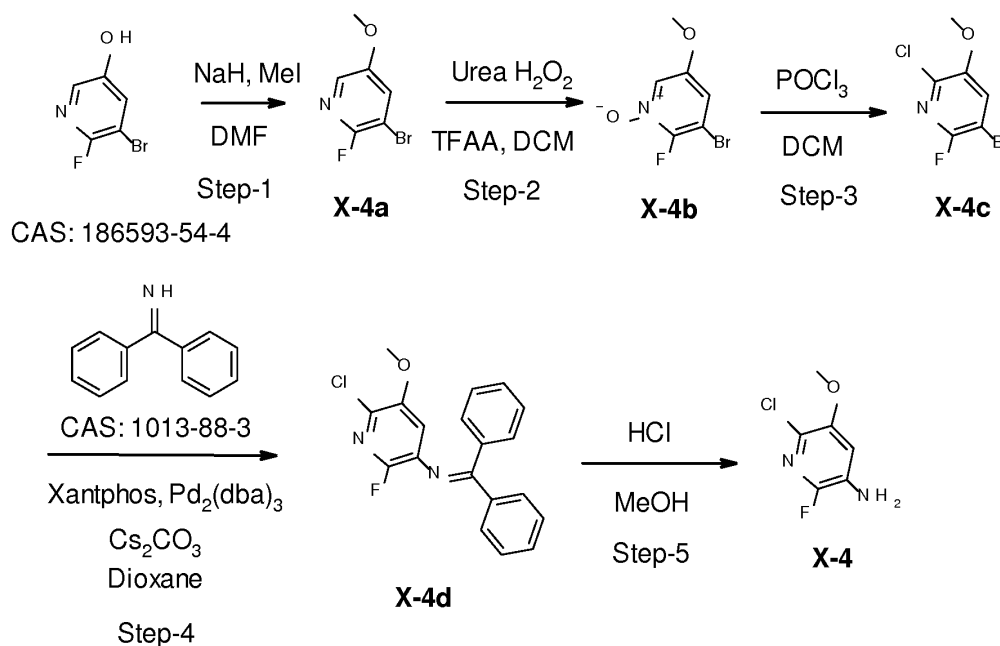
- 5 mixture was stirred at room temperature for 2h. Progress of reaction was monitored by TLC and LCMS. After completion, reaction mixture was poured in to ice cold saturated NaHCO_3 (25 mL). The reaction mixture was filtered through a pad of celite, washed with EtOAc (2×15 mL) and the aqueous layer was extracted with EtOAc (2×15 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude obtained was purified by column chromatography (silica, 100-200 mesh, 4% EtOAc in hexane) to afford 6-chloro-5-fluoro-2-methoxy-pyridin-3-amine **X-3** (0.11 g, 63%) as an off white solid.

Yield: 63%.

- 10 Basic LCMS Method 2 (ES^+): 177 ($\text{M}+\text{H}$) $^+$, 98% purity.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 3.84 (s, 3H), 5.49 (brs, 2H), 6.90 (d, $J=9.78$ Hz, 1H).

A.4. Synthesis of 6-chloro-2-fluoro-5-methoxy-pyridin-3-amine **X-4**:



Step-1: Synthesis of 3-bromo-2-fluoro-5-methoxy-pyridine **X-4a**:

- 15 To a solution of 5-bromo-6-fluoro-pyridin-3-ol (0.80 g, 4.17 mmol) and NaH (0.33 g, 8.33 mmol) in DMF (15 mL) was added CH_3I (0.31 mL, 5.00 mmol) drop wise at 0 °C. The reaction mixture was stirred at room temperature for 4h. Progress of reaction was monitored by TLC and LCMS. After completion, the reaction mixture was poured into cold H_2O (20 mL) and extracted with EtOAc (2×30 mL). The organic layer was separated,

washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude obtained was purified by combi-flash column chromatography (30% EtOAc in hexane) to afford 3-bromo-2-fluoro-5-methoxy-pyridine **X-4a** (0.80 g) as a pale yellow solid.

5 Yield: 93%.

Basic LCMS Method 2 (ES^+): 206 ($\text{M}+\text{H}$) $^+$, 99% purity.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 3.85 (s, 3H), 7.92 (t, $J=2.20$ Hz, 1H), 7.99 (dd, $J=7.34$, 2.20 Hz, 1H).

Step-2: Synthesis of 3-bromo-2-fluoro-5-methoxy-1-oxido-pyridin-1-ium **X-4b**:

10 To a solution of 3-bromo-2-fluoro-5-methoxy-pyridine **X-4a** (0.30 g, 1.35 mmol) in DCM (15 mL) was added urea hydrogen peroxide (0.38 g, 4.05 mmol) at 0 °C and the reaction mixture was stirred for 10 min. Trifluoroacetic anhydride (0.96 mL, 6.76 mmol) was added drop wise at 0 °C and the reaction mixture was stirred at room temperature for 16h. Progress of reaction was monitored by TLC and LCMS. After completion, the reaction
15 mixture was poured in to ice cold H_2O (15 mL), basified with saturated NaHCO_3 (15 mL) up to pH 8 and extracted with DCM (2 $\times$ 15 mL). The organic layer was separated, washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford 3-bromo-2-fluoro-5-methoxy-1-oxido-pyridin-1-ium **X-4b** (0.16 g, 37%) as an off white solid.

20 This compound was used as such for the next reaction without further purification.

Yield: 93%.

Basic LCMS Method 2 (ES^+): 222 ($\text{M}+\text{H}$) $^+$, 69% purity.

Step-3: Synthesis of 5-bromo-2-chloro-6-fluoro-3-methoxy-pyridine **X4-c**:

To a solution of 3-bromo-2-fluoro-5-methoxy-1-oxido-pyridin-1-ium **X-4b** (0.40 g, 1.45
25 mmol) in DCM (10 mL) was added POCl_3 (0.35 mL, 3.88 mmol) followed by addition of DMF (0.1 mL) at 0 °C and the reaction mixture was stirred at room temperature for 16h. Progress of reaction was monitored by TLC. After completion, the reaction mixture was concentrated under vacuum. The residue was poured in to ice cold H_2O (15 mL), basified with saturated NaHCO_3 (15 mL) up to pH 8 and extracted with EtOAc (2 $\times$ 15 mL). The
30 organic layer was separated, washed with brine (15 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude obtained was purified by combi-flash column

chromatography (30% EtOAc in hexane) to afford 5-bromo-2-chloro-6-fluoro-3-methoxy-pyridine **X4-c** (0.26 g) as a pale yellow solid.

Yield: 74%.

^1H NMR (400 MHz, DMSO- d_6) δ 3.93 (s, 3H), 8.16 (d, $J=6.85$ Hz, 1H).

5 Step-4: Synthesis of N-(6-chloro-2-fluoro-5-methoxy-3-pyridyl)-1,1-diphenyl-methanimine **X4-d**:

To a solution of 5-bromo-2-chloro-6-fluoro-3-methoxy-pyridine **X4-c** (0.25 g, 1.04 mmol), benzophenone imine (0.21 g, 1.14 mmol) in dioxane (15 mL) was added Cs_2CO_3 (1.02 g, 3.12 mmol) and Xantphos (0.12 g, 0.21 mmol). The reaction mixture was purged with
10 argon for 20 min followed by addition of $\text{Pd}_2(\text{dba})_3$ (0.10 g, 0.10 mmol). The reaction mixture was heated at 100 °C for 16h. Progress of the reaction was monitored by TLC and LCMS. After completion, the reaction mixture was diluted with EtOAc (15 mL), filtered through a pad of celite, washed with EtOAc (2 × 15 mL). The organic later was separated, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude obtained was
15 purified by combi-flash column chromatography (30 % EtOAc in hexane) to afford N-(6-chloro-2-fluoro-5-methoxy-3-pyridyl)-1,1-diphenyl-methanimine **X4-d** (0.25 g, 50%) as an off-white solid.

Yield: 93%.

Basic LCMS Method 2 (ES^+): 341 ($\text{M}+\text{H}$) $^+$, 71% purity.

20 Step-5: Synthesis of 6-chloro-2-fluoro-5-methoxy-pyridin-3-amine **X-4**:

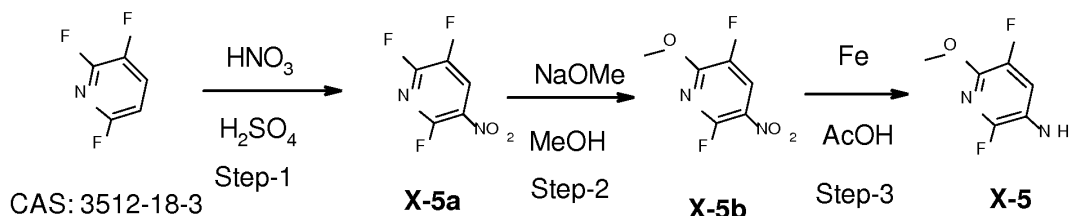
To a solution of N-(6-chloro-2-fluoro-5-methoxy-3-pyridyl)-1,1-diphenyl-methanimine **X4-d** (0.24 g, 0.51 mmol) in MeOH (15 mL) was added 1N HCl (0.5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 3h. Progress of reaction was monitored by TLC and LCMS. After completion, the reaction mixture was poured into H_2O (15 mL) and
25 extracted with DCM (2 × 20 mL). The organic layer was separated, washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude obtained was purified by combi-flash column chromatography (30% EtOAc in hexane) to afford 6-chloro-2-fluoro-5-methoxy-pyridin-3-amine **X-4** (0.06 g) as an off-white solid.

Yield: 62%.

30 Basic LCMS Method 2 (ES^+): 177 ($\text{M}+\text{H}$) $^+$, 93% purity.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 3.79 (s, 3H), 5.64 (s, 2H), 6.99 (d, $J=8.80$ Hz, 1H)

A.5. Synthesis of 2,5-difluoro-6-methoxy-pyridin-3-amine **X-5**:



Step-1: Synthesis of 2,3,6-trifluoro-5-nitropyridine **X-5a**:

- 5 To a stirred solution of 2,3,6-trifluoropyridine (2.00 g, 15.0 mmol) in fuming HNO_3 (12.5 mL, 301 mmol) was added concentrated H_2SO_4 (12.0 mL, 225 mmol) drop wise at 0°C . The reaction mixture was heated at 60°C for 1h. Progress of reaction was monitored by TLC. After completion, reaction mixture was poured on crushed ice (40 mL) and extracted with hexane (2×30 mL). The organic layer was separated, washed with saturated
- 10 NaHCO_3 (40 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford 2,3,6-trifluoro-5-nitropyridine **X-5a** (1.20 g) as a yellow oil.

This compound was used as such for next reaction without further purification.

Yield: 45%.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.20-9.26 (m, 2H).

- 15 Step-2: Synthesis of 2,5-difluoro-6-methoxy-3-nitropyridine **X-5b**:

- To a stirred solution of 2,3,6-trifluoro-5-nitropyridine **X-5a** (0.20 g, 1.12 mmol) in MeOH (10 mL) was added NaOMe (0.93 mL, 4.32 mmol) dropwise at -78°C and the reaction mixture was stirred at same temperature for 2h. Progress of reaction was monitored by TLC. After completion, reaction mixture was quenched with saturated HCl (10 mL) at -78°C
- 20 $^\circ\text{C}$ and extracted with hexane (2×15 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford 2,5-difluoro-6-methoxy-3-nitropyridine **X-5b** (0.136 g) as a pale yellow solid.

This compound was used as such for next reaction without further purification.

Yield: 64%.

- 25 ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 4.06 (s, 3H), 8.76 (dd, $J=8.80, 7.34$ Hz, 1H).

Step-3: Synthesis of 2,5-difluoro-6-methoxy-pyridin-3-amine **X-5**:

- To a stirred solution of 2,5-difluoro-6-methoxy-3-nitro-pyridine **X-5b** (0.13 g, 0.68 mmol) in acetic acid (4 mL) was added iron (0.15 g, 2.74 mmol) in portions at 0 °C. The reaction mixture was stirred at room temperature for 1h. Progress of reaction was monitored by TLC and LCMS. After completion, the reaction mixture was quenched with saturated
- 5 NaHCO_3 (25 mL) and extracted with EtOAc (2×25 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford 2,5-difluoro-6-methoxy-pyridin-3-amine **X-5** (0.104 g, 94%) as a brown solid.

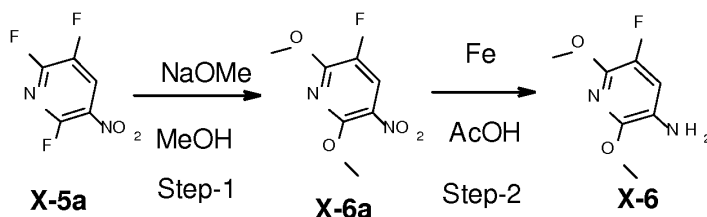
This compound was used as such for next reaction without further purification.

Yield: 62%.

- 10 Basic LCMS Method 2 (ES^+): 161 ($\text{M}+\text{H}$) $^+$, 99% purity.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 3.77 (s, 3H), 5.04 (brs, 2H), 7.17 (dd, $J=10.76, 8.31$, 1H).

A.6. Synthesis of 5-fluoro-2,6-dimethoxy-pyridin-3-amine **X-6**:



Step-1: Synthesis of 3-fluoro-2,6-dimethoxy-5-nitro-pyridine **X-6a**:

- 15 To a stirred solution of 2,3,6-trifluoro-5-nitro-pyridine **X-5a** (0.30 g, 1.68 mmol) in MeOH (4 mL) was added NaOMe (0.36 mL, 1.68 mmol) dropwise at -40 °C and the reaction mixture was stirred at same temperature for 2h. Progress of reaction was monitored by TLC. After completion, reaction mixture was quenched with 2 N HCl (6 mL) at 0 °C and extracted with hexane (2×10 mL). The organic layer was separated, dried over anhydrous Na_2SO_4
- 20 and evaporated under vacuum to afford 3-fluoro-2,6-dimethoxy-5-nitro-pyridine **X-6a** (0.32 g, 94%) as a pale yellow solid.

This compound was used as such for next reaction without further purification.

Yield: 94%.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 4.06 (s, 3H), 4.09 (s, 3H), 8.52 (d, $J=9.29$ Hz, 1H).

- 25 Step-2: Synthesis of 5-fluoro-2,6-dimethoxy-pyridin-3-amine **X-6**:

- To a stirred solution of 3-fluoro-2,6-dimethoxy-5-nitro-pyridine **X-6a** (0.25 g, 1.24 mmol) in acetic acid (8 mL) was added iron (0.28 g, 4.95 mmol) in portions at 0 °C. The reaction mixture was stirred at room temperature for 1 h. Progress of reaction was monitored by TLC and LCMS. After completion, the reaction mixture was poured on ice cold saturated
- 5 NaHCO_3 (25 mL) and extracted with EtOAc (2 × 20 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford 5-fluoro-5-fluoro-2,6-dimethoxy-pyridin-3-amine **X-6** (0.19 g) as a brown solid.

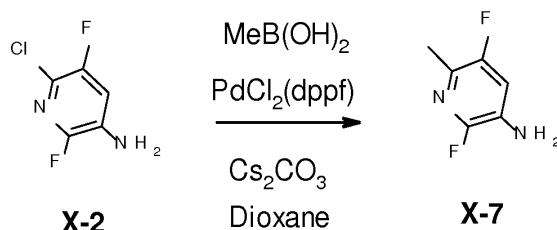
This compound was used as such for next reaction without further purification.

Yield: 89%.

- 10 Basic LCMS Method 2 (ES^+): 173 ($\text{M}+\text{H}$)⁺, 99% purity.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 3.82 (s, 3H), 3.85 (s, 3H), 4.58 (brs, 2H), 6.92 (d, $J=11.25$ Hz, 1H).

A.7. Synthesis of 2,5-difluoro-6-methyl-pyridin-3-amine **X-7**:



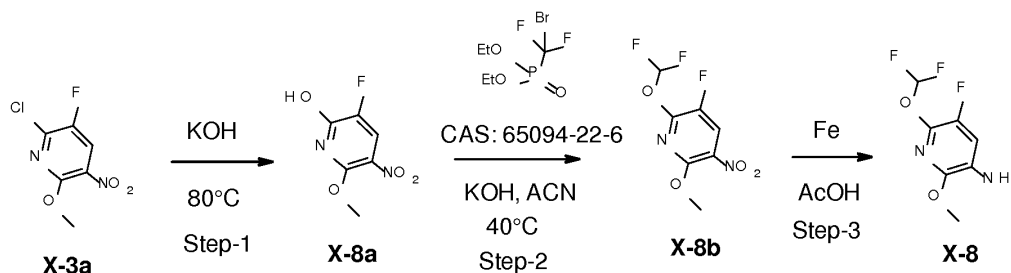
- 15 To a solution of 6-chloro-2,5-difluoro-pyridin-3-amine **X-2** (0.24 g, 1.38 mmol) in dioxane (12 mL) were added methyl boronic acid (0.25 g, 4.15 mmol) and Cs_2CO_3 (1.13 g, 3.46 mmol) solution in H_2O (4 mL) at room temperature and the reaction mixture was purged with argon for 20 min. $\text{PdCl}_2(\text{dppf})$ (0.10 g, 0.14 mmol) was added and the reaction mixture was purged with argon for 10 min. The reaction mixture was heated at 120 °C for
- 20 6h. Progress of the reaction was monitored by TLC and LCMS. After completion, the reaction mixture was cooled to room temperature, filtered through a pad of celite, washed with EtOAc (2 × 60 mL) and filtrate was concentrated under vacuum. The residue was diluted with H_2O (60 mL) and extracted with EtOAc (3 × 40 mL). The organic layer was separated, washed with brine (70 mL), dried over anhydrous Na_2SO_4 and concentrated
- 25 under vacuum to afford 2,5-difluoro-6-methyl-pyridin-3-amine **X-7** (0.32 g) as pale brown liquid.

This compound was used as such for the next reaction without further purification.

Yield: 51%.

Basic LCMS Method 2 (ES⁺): 145 (M+H)⁺, 31% purity.

A.8. Synthesis of 6-(difluoromethoxy)-5-fluoro-2-methoxy-pyridin-3-amine **X-8**:



5 Step-1: Synthesis of 3-fluoro-6-methoxy-5-nitro-pyridin-2-ol **X-8a**:

To a solution of 2-chloro-3-fluoro-6-methoxy-5-nitro-pyridine **X-3a** (0.90 g, 4.36 mmol) in H₂O (6 mL) was added KOH (0.61 g, 10.9 mmol) and the reaction mixture was heated at 80 °C for 16h. Progress of reaction was monitored by TLC. After completion, the reaction mixture was diluted with H₂O (100 mL) and extracted with EtOAc (3 × 80 mL). The organic layer was separated, dried over anhydrous Na₂SO₄ and concentrated under vacuum to afford 3-fluoro-6-methoxy-5-nitro-pyridin-2-ol **X-8a** (0.30 g crude) as a pale yellow solid.

This compound was used as such for the next reaction without further purification.

¹H NMR (400 MHz, DMSO-*d*₆) δ 3.99 (s, 3H), 8.42 (d, J=9.60 Hz, 1H), 12.12 (s, 1H).

Step-2: Synthesis of 2-(difluoromethoxy)-3-fluoro-6-methoxy-5-nitro-pyridine **X-8b**:

To a solution of 3-fluoro-6-methoxy-5-nitro-pyridin-2-ol **X-8a** (0.29 g, 1.54 mmol) in CH₃CN (4 mL) was added KOH (0.87 g, 15.4 mmol) solution in H₂O (1 mL) and bromodifluoromethyl diethylphosphonate (2.74 mL, 15.4 mmol) at 40 °C and the reaction mixture was stirred at same temperature for 4h. Progress of reaction was monitored by TLC. After completion, the reaction mixture was diluted with H₂O (50 mL) and extracted with EtOAc (3 × 40 mL). The organic layer was separated, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude obtained was purified by flash chromatography (2 to 5% EtOAc in hexane) to afford 2-(difluoromethoxy)-3-fluoro-6-methoxy-5-nitro-pyridine **X-8b** (0.24 g) as a pale yellow liquid.

This compound was used as such for the next reaction without further purification.

Yield: 65%.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 4.04 (s, 3H), 7.90 (t, $J=70.8$ Hz, 1H), 8.80 (d, $J=9.60$ Hz, 1H).

Step-3: Synthesis of 6-(difluoromethoxy)-5-fluoro-2-methoxy-pyridin-3-amine **X-8**:

To a solution of 2-(difluoromethoxy)-3-fluoro-6-methoxy-5-nitro-pyridine **X-8b** (0.23 g, 0.97 mmol) in CH_3COOH (8 mL) was added Fe (0.27 g, 4.83 mmol) slowly at 0 °C and the reaction mixture was stirred at room temperature for 4h. Progress of reaction was monitored by TLC and LCMS. After completion, the reaction mixture was filtered through a pad of celite, washed with EtOAc (80 mL) and filtrate was concentrated under vacuum. The residue was poured in to aqueous saturated NaHCO_3 (80 mL) solution and extracted with EtOAc (2 $\times$ 70 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford 6-(difluoromethoxy)-5-fluoro-2-methoxy-pyridin-3-amine **X-8** (0.18 g) as a brown liquid.

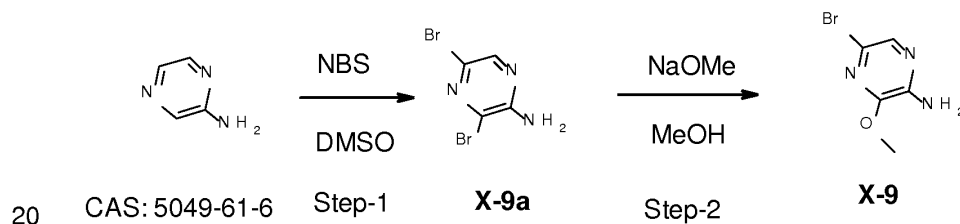
This compound was used as such for the next reaction without further purification.

Yield: 77%.

Basic LCMS Method 2 (ES^-): 207 ($\text{M}-\text{H}$) $^-$, 85% purity.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 3.84 (s, 3H), 5.18 (brs, 2H), 6.95 (d, $J=10.8$ Hz, 1H), 7.39 (t, $J=74$ Hz, 1H).

A.9. Synthesis of 5-bromo-3-methoxy-pyrazin-2-amine **X-9**:



Step-1: Synthesis of 3,5-dibromopyrazin-2-amine **X-9a**:

To a solution of pyrazin-2-amine (0.50 g, 5.26 mmol) in DMSO (10 mL) and H_2O (0.3 mL) was added NBS (1.97 g, 11.0 mmol) portion wise below 15 °C over a period of 10 min. The reaction was stirred in absence of light at room temperature for 5h. Progress of the reaction was monitored by TLC and LCMS. The reaction mixture was poured into iced H_2O (60 mL) and extracted with EtOAc (2 $\times$ 70 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude obtained was

purified by column chromatography (silica, 100-200 mesh, 5% EtOAc in hexane) to afford 3,5-dibromopyrazin-2-amine **X-9a** (0.612 g) as an off-white solid.

Yield: 46%.

Basic LCMS Method 2 (ES⁺): 252 (M+H)⁺, 100% purity.

5 ¹H NMR (400 MHz, DMSO-*d*₆) δ 6.97 (brs, 2H), 8.13 (s, 1H).

Step-2: Synthesis of 5-bromo-3-methoxy-pyrazin-2-amine **X-9**:

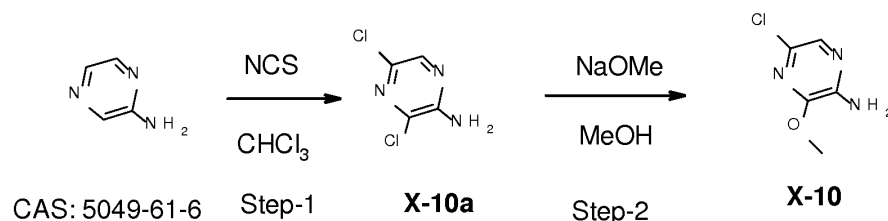
A solution of 3,5-dibromopyrazin-2-amine **X-9a** (0.60 g, 2.37 mmol) and NaOMe (0.15 g, 2.78 mmol) in MeOH (15 mL) was heated to reflux for 1h. Progress of the reaction was monitored by TLC and LCMS. After completion, the reaction mixture was cooled to room
 10 temperature. The precipitated solid was purified by column chromatography (silica, 100-200 mesh, 10% EtOAc in hexane) to afford 5-bromo-3-methoxy-pyrazin-2-amine **X-9** (0.295 g) as a white solid.

Yield: 61%.

Basic LCMS Method 2 (ES⁺): 204 (M+H)⁺, 100% purity.

15 ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.87 (s, 3H), 6.52 (brs, 2H), 7.57 (s, 1H)

A.10. Synthesis of 5-chloro-3-methoxypyrazin-2-amine **X-10**:



Step-1: Synthesis of 3,5-dichloropyrazin-2-amine **X-10a**:

To a stirred solution of pyrazin-2-amine (2.00 g, 21.0 mmol) in CHCl₃ (25 mL) was added
 20 NCS (3.65 g, 27.3 mmol) portionwise and the reaction mixture was stirred at room temperature for 6h. Progress of reaction was monitored by TLC. After completion, the reaction mixture was poured in to ice cold H₂O (20 mL) and extracted with EtOAc (2 × 40 mL). The organic layer was separated, washed with brine (25 mL), dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude obtained was purified by combi flash
 25 chromatography (20% EtOAc in hexane) to afford 3,5-dichloropyrazin-2-amine **X-10a** (1.50 g) as an off-white solid.

Yield: 37%.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.02 (brs, 2H), 8.06 (s, 1H).

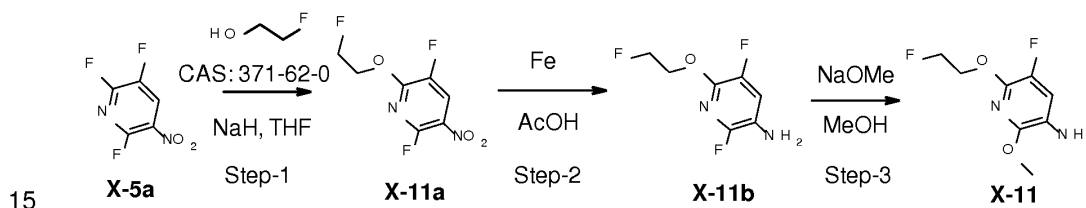
Step-2: Synthesis of 5-chloro-3-methoxypyrazin-2-amine **X-10**:

To a stirred solution of 3,5-dichloropyrazin-2-amine **X-10a** (0.80 g, 4.15 mmol) in MeOH (20 mL) was added NaOMe (0.90 g, 16.6 mmol) at room temperature. The reaction mixture was heated at 70 °C for 16h. Progress of reaction was monitored by TLC. After completion, the reaction mixture was concentrated under vacuum. The residue was diluted with H_2O (15 mL) and extracted with EtOAc (3 $\times$ 25 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude obtained was purified by combi flash chromatography (20% EtOAc in hexane) to afford 5-chloro-3-methoxypyrazin-2-amine **X-10** (0.53 g) as an off-white solid.

Yield: 69%.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 3.89 (s, 3H), 6.52 (brs, 2H), 7.53 (s, 1H).

A.11. Synthesis of 5-fluoro-6-(2-fluoroethoxy)-2-methoxy-pyridin-3-amine **X-11**:



Step-1: Synthesis of 2,5-difluoro-6-(2-fluoroethoxy)-3-nitropyridine **X-11a**:

To a stirred solution of 2-fluoroethanol (1.19 g, 18.5 mmol) in THF (30 mL) was added NaH (0.81 g, 20.2 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 1h. The reaction mixture was cooled at -78 °C followed by slow addition of 2,3,6-trifluoro-5-nitropyridine **X-5a** (3.00 g, 16.8 mmol) at same temperature and the reaction mixture was stirred at -78 °C for 2h. Progress of the reaction was monitored by TLC. After completion, the reaction mixture was quenched with ice cold H_2O (50 mL) and extracted with EtOAc (2 $\times$ 100 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford 2,5-difluoro-6-(2-fluoroethoxy)-3-nitropyridine **X-11a** (3.10 g) as a brown gummy liquid.

This compound was used as such for the next reaction without further purification.

Yield: 83%.

^1H NMR (400 MHz, DMSO- d_6) δ 4.64-4.69 (m, 1H) 4.73-4.76 (m, 2H) 4.86-4.89 (m, 1H) 8.79-8.83 (m, 1H).

Step-2: Synthesis of 2,5-difluoro-6-(2-fluoroethoxy)pyridin-3-amine **X-11b**:

To a solution of 2,5-difluoro-6-(2-fluoroethoxy)-3-nitropyridine **X-11a** (2.70 g, 12.2 mmol) in CH_3COOH (25 mL) was added Fe (6.79 g, 122 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 2h. Progress of the reaction was monitored by TLC and LCMS. After completion, the reaction mixture was filtered through a pad of celite and washed with Et_2O (500 mL) and the filtrate was concentrated under vacuum. The residue was poured in to aqueous saturated NaHCO_3 solution (380 mL) and extracted with Et_2O (2 $\times$ 500 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford 2,5-difluoro-6-(2-fluoroethoxy)pyridin-3-amine **X-11b** (2.00 g) as a brown solid.

This compound was used as such for the next reaction without further purification.

Yield: 70%.

Basic LCMS Method 2 (ES^+): 193 ($\text{M}+\text{H}$) $^+$, 82% purity.

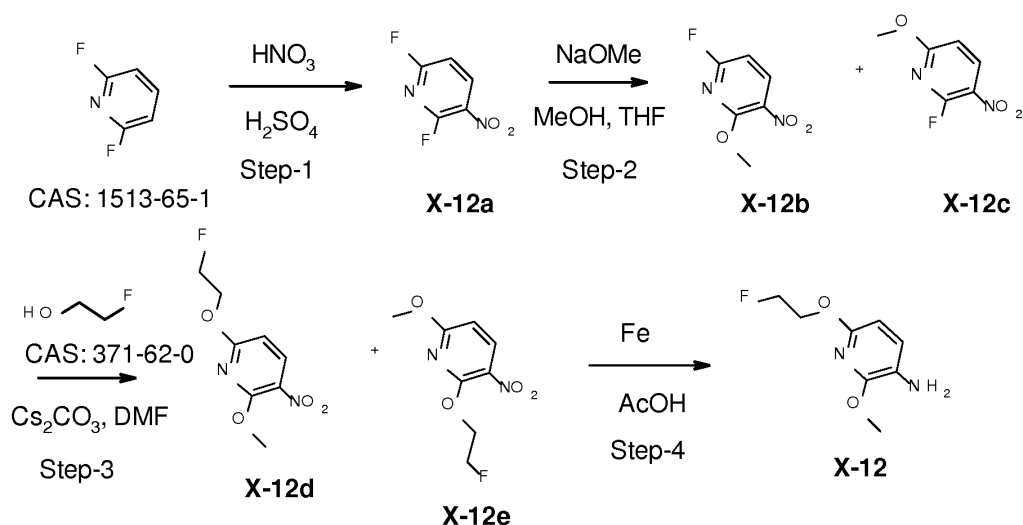
Step-3: Synthesis of 5-fluoro-6-(2-fluoroethoxy)-2-methoxy-pyridin-3-amine **X-11**

To a solution of 2,5-difluoro-6-(2-fluoroethoxy)pyridin-3-amine **X-11b** (1.00 g, 4.27 mmol) in MeOH (10 mL) was added NaOMe (25% solution in MeOH, 1.85 mL, 8.55 mmol) slowly at 0 °C and the reaction mixture was heated at 100 °C for 16h. Progress of the reaction was monitored by TLC and LCMS. After completion, the reaction mixture was quenched with aqueous ice cold 1 N HCl solution (50 mL) and extracted with hexane (2 $\times$ 500 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude obtained was purified by prep HPLC to afford 5-fluoro-6-(2-fluoroethoxy)-2-methoxy-pyridin-3-amine **X-11** (0.46 g) as a brown solid.

Yield: 50%.

Basic LCMS Method 2 (ES^+): 205 ($\text{M}+\text{H}$) $^+$, 97% purity.

^1H NMR (400 MHz, DMSO- d_6) δ 3.83 (s, 3H) 4.41-4.43 (m, 1H) 4.48-4.50 (m, 1H) 4.65 (brs, 3H) 4.76-4.78 (m, 1H) 6.90-6.98 (m, 1H).

A.12. Synthesis of 6-(2-fluoroethoxy)-2-methoxypyridin-3-amine X-12:**Step-1: Synthesis of 2,6-difluoro-3-nitropyridine X-12a:**

To a solution of 2,6-difluoropyridine (5.00 g, 43.4 mmol) in Conc. HNO_3 (36.3 mL, 869 mmol) was added concentrated H_2SO_4 (34.7 mL, 652 mmol) slowly at 0 °C and the reaction mixture was heated at 60 °C for 3h. Progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled at room temperature, poured into crushed ice (120 mL) and extracted with DCM (2 × 100 mL). The organic layer was separated, washed with an aqueous saturated NaHCO_3 solution (120 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford 2,6-difluoro-3-nitropyridine X-12a (3.20 g crude) as a yellow oil.

This compound was used as such for the next reaction without further purification.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.47 (dd, $J=8.80, 2.45$ Hz, 1H) 8.91-9.00 (m, 1H).

Step-2: Synthesis of 6-fluoro-2-methoxy-3-nitropyridine X-12b and 2-fluoro-6-methoxy-3-nitropyridine X-12c:

To a solution of 2,6-difluoro-3-nitropyridine X-12a (2.90 g, 18.1 mmol) in THF (25 mL) was added NaOMe (25% solution in MeOH, 4.31 mL, 19.9 mmol) slowly at -78 °C and the reaction mixture was stirred at same temperature for 1h. Progress of the reaction was monitored by TLC. After completion, the reaction mixture was quenched with ice cold H_2O (60 mL) and extracted with Et₂O (2 × 100 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford 6-fluoro-2-methoxy-3-

nitropyridine **X-12b** and 2-fluoro-6-methoxy-3-nitropyridine **X-12c** (2.51 g, mixture of two regio isomers) as a brown liquid.

This compound was used as such for the next reaction without further purification.

¹H NMR (400 MHz, DMSO-*d*₆, ¹H NMR showed mixture of regio isomers) δ 3.97 (s, 3H),
5 4.02 (s, 3H) 6.97-7.00 (m, 2H) 8.58-8.71 (m, 2H).

Step-3: Synthesis of 6-(2-fluoroethoxy)-2-methoxy-3-nitropyridine **X-12d** and 2-(2-fluoroethoxy)-6-methoxy-3-nitropyridine **X-12e**:

To a solution of 2-fluoroethanol (1.12 g, 17.5 mmol) in DMF (40 mL) was added Cs₂CO₃ (9.51 g, 29.2 mmol) and 6-fluoro-2-methoxy-3-nitropyridine **X-12b** and 2-fluoro-6-methoxy-3-nitropyridine **X-12c** mixture (2.51 g, 14.6 mmol, mixture of two regio isomers). The
10 reaction mixture was heated at 100 °C for 16h. Progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with cold H₂O (80 mL) and extracted with EtOAc (2 × 80 mL). The organic layer was separated, washed with cold H₂O (2 × 50 mL), dried over anhydrous Na₂SO₄ and concentrated under vacuum. The
15 crude obtained was purified by column chromatography (silica, 100-200 mesh, 5 to 12% EtOAc in hexane) and repurified by prep HPLC to afford 6-(2-fluoroethoxy)-2-methoxy-3-nitropyridine **X-12d** (0.98 g) as an off-white solid and 2-(2-fluoroethoxy)-6-methoxy-3-nitropyridine **X-12e** (1.10 g) as an off-white solid.

6-(2-fluoroethoxy)-2-methoxy-3-nitropyridine **X-12d**:

20 Yield: 31%.

¹H NMR (400 MHz, CDCl₃) δ 4.12 (s, 3H) 4.63 (t, J=4 Hz, 1H) 4.69-4.74 (m, 2H) 4.84 (t, J=4 Hz, 1H) 6.47 (d, J=8.8 Hz, 1H) 8.39 (d, J=8.8 Hz, 1H).

2-(2-fluoroethoxy)-6-methoxy-3-nitropyridine **X-12e**:

Yield: 35%.

25 ¹H NMR (400 MHz, CDCl₃) δ 4.01 (s, 3H) 4.75-4.78 (m, 2H) 4.80-4.84 (m, 1H) 4.85-4.91 (m, 1H) 6.43 (d, J=8.8 Hz, 1H) 8.37 (d, J=8.8 Hz, 1H)

Step-4: Synthesis of 6-(2-fluoroethoxy)-2-methoxypyridin-3-amine **X-12**:

To a solution of 6-(2-fluoroethoxy)-2-methoxy-3-nitropyridine **X-12d** (0.97 g, 4.49 mmol) in CH₃COOH (15 mL) was added Fe (1.25 g, 22.4 mmol) slowly and the reaction mixture
30 was stirred at room temperature for 6h. Progress of the reaction was monitored by TLC

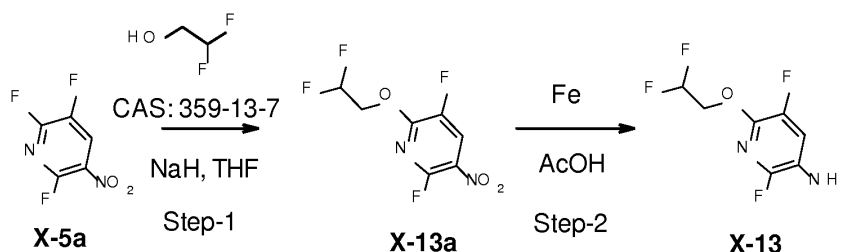
and LCMS. The reaction mixture was filtered through a pad of celite, washed with EtOAc (80 mL) and filtrate was concentrated under vacuum. The residue was diluted with a saturated NaHCO_3 solution (150 mL) and extracted with EtOAc (2×100 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude obtained was purified by flash chromatography (10 to 20% EtOAc in hexane) to afford 6-(2-fluoroethoxy)-2-methoxypyridin-3-amine **X-12** (0.67 g) as a pale brown liquid.

Yield: 79%.

Basic LCMS Method 2 (ES^+): 187 ($\text{M}+\text{H}$) $^+$, 97% purity.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 3.84 (s, 3H) 4.28-4.34 (m, 1H) 4.36 (s, 2H) 4.38-4.41 (m, 1H) 4.62-4.66 (m, 1H) 4.73-4.80 (m, 1H) 6.20 (d, $J=8.31$ Hz, 1H) 6.96 (d, $J=7.83$ Hz, 1H).

A.13. Synthesis of 2,5-difluoro-6-methoxy-pyridin-3-amine **X-13**:



Step-1: Synthesis of 2-(2,2-difluoroethoxy)-3,6-difluoro-5-nitropyridine **X-13a**:

To a stirred solution of 2,2-difluoroethanol (0.79 g, 11.2 mmol) in THF (20 mL) was added NaH (1.35 g, 33.7 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 1h. The reaction mixture was cooled at -78 °C followed by slow addition of 2,3,6-trifluoro-5-nitropyridine **X-5a** (2.00 g, 11.2 mmol) at same temperature and the reaction mixture was stirred at -78 °C for 2h. Progress of the reaction was monitored by TLC. After completion, the reaction mixture was quenched with ice cold H_2O (50 mL) and extracted with EtOAc (2×100 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude material was purified by column chromatography (silica, 100-200 mesh, 2% EtOAc in hexane) to afford 2-(2,2-difluoroethoxy)-3,6-difluoro-5-nitropyridine **X-13a** (0.86 g) as a brown liquid.

Yield: 32%.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 4.78 (td, $J=14.92, 2.93$ Hz, 2 H), 6.32 - 6.62 (m, 1 H), 8.87 (dd, $J=8.80, 7.34$ Hz, 1 H).

Step-2: Synthesis of 6-(2,2-difluoroethoxy)-2,5-difluoro-pyridin-3-amine **X-13**:

To a solution of 2-(2,2-difluoroethoxy)-3,6-difluoro-5-nitro-pyridine **X-13a** (0.85 g, 3.5 mmol) in CH₃COOH (17 mL) was added Fe (1.98 g, 35 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 2h. Progress of the reaction was monitored by
 5 TLC and LCMS. After completion, the reaction mixture was filtered through a pad of celite and washed with Et₂O (500 mL) and the filtrate was concentrated under vacuum. The residue was poured in to aqueous saturated NaHCO₃ solution (380 mL) and extracted with Et₂O (2 × 500 mL). The organic layer was separated, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude material was washed with pentane to afford
 10 6-(2,2-difluoroethoxy)-2,5-difluoro-pyridin-3-amine **X-13** (0.51 g) as a brown solid.

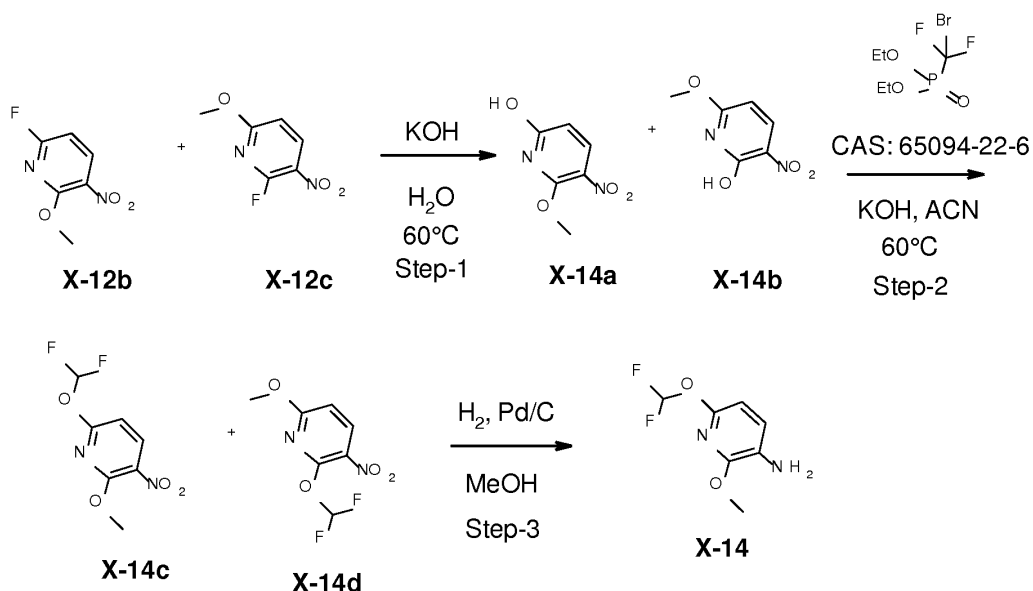
This compound was used as such for the next reaction without further purification.

Yield: 67%.

Basic LCMS Method 2 (ES⁺): 211 (M+H)⁺, 99% purity.

¹H NMR (400 MHz, DMSO-*d*₆) δ 4.43 (td, J=14.92, 3.42 Hz, 2 H), 5.20 (s, 2 H), 6.20 - 6.50
 15 (m, 1 H), 7.21 (dd, J=10.76, 8.31 Hz, 1 H).

A.14. Synthesis of 6-(difluoromethoxy)-2-methoxy-pyridin-3-amine X-14:



Step-1: Synthesis of 6-methoxy-5-nitro-pyridin-2-ol **X-14a** and 6-methoxy-3-nitro-pyridin-2-ol **X-14b**:

To a solution of 6-fluoro-2-methoxy-3-nitropyridine **X-12b** and 2-fluoro-6-methoxy-3-nitropyridine **X-12c** mixture (0.60 g, 3.5 mmol, mixture of two regio isomers) in water (20 mL) was added KOH (0.78 g, 13.9 mmol). The reaction mixture was heated at 60 °C for 3h. Progress of the reaction was monitored by TLC. After completion, the reaction mixture
5 was cooled to 0 °C and acidified to pH 4-5 with HCl 1N (6 mL). The precipitated solid was filtered and dried under vacuum to afford 6-methoxy-5-nitro-pyridin-2-ol **X-14a** and 6-methoxy-3-nitro-pyridin-2-ol **X-14b** mixture (0.45 g, mixture of two regio isomers) as a yellow solid.

Yield: 29%.

10 Basic LCMS Method 2 (ES⁺): 171 (M+H)⁺, 99% purity (40/60 mixture).

Step-2: Synthesis of 6-(difluoromethoxy)-2-methoxy-3-nitro-pyridine **X-14c** and 2-(difluoromethoxy)-6-methoxy-3-nitro-pyridine **X-14d**:

To a solution of 6-methoxy-5-nitro-pyridin-2-ol **X-14a** and 6-methoxy-3-nitro-pyridin-2-ol **X-14b** mixture (1.2 g, 5.06 mmol, mixture of two regio isomers) in CH₃CN (32 mL) and
15 water (8 mL) was added KOH (1.42 g, 25.3 mmol) and bromodifluoromethyl diethylphosphonate (6.75 g, 25.3 mmol) and the reaction mixture was stirred at 60 °C for 4h. Progress of reaction was monitored by TLC. After completion, the reaction mixture was diluted with H₂O (60 mL) and extracted with EtOAc (3 × 40 mL). The organic layer was separated, washed with brine (2 × 50 mL) and dried over anhydrous Na₂SO₄ and
20 concentrated under vacuum. The crude obtained was purified by flash chromatography (2% EtOAc in hexane) to afford 6-(difluoromethoxy)-2-methoxy-3-nitro-pyridine **X-14c** (0.24 g) and 2-(difluoromethoxy)-6-methoxy-3-nitro-pyridine **X-14d** (0.07 g) as off-white solids.

6-(difluoromethoxy)-2-methoxy-3-nitro-pyridine **X-14c**

25 Yield: 22%.

¹H NMR (400 MHz, DMSO-*d*₆) δ 4.12 (s, 3 H), 6.60 (d, J=8.80 Hz, 1 H), 7.41 (t, J=72 Hz, 1 H), 8.47 (d, J=8.80 Hz, 1 H).

2-(difluoromethoxy)-6-methoxy-3-nitro-pyridine **X-14d**

Yield: 7%.

30 ¹H NMR (400 MHz, DMSO-*d*₆) δ 4.03 (s, 3 H), 6.65 (d, J=9.29 Hz, 1 H), 7.51 (t, J=72 Hz, 1 H), 8.41 (d, J=9.29 Hz, 1 H).

Step-3: Synthesis of 6-(difluoromethoxy)-2-methoxy-pyridin-3-amine **X-14**:

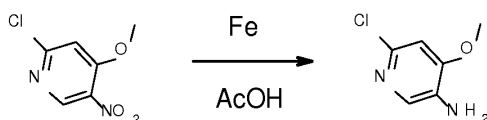
To a solution of 6-(2-fluoroethoxy)-2-methoxy-3-nitropyridine **X-12d** (50 mg, 0.22 mmol) in MeOH (3 mL) was added Pd/C (10 mg) and the reaction mixture was stirred at room temperature for 2h under hydrogen pressure. Progress of the reaction was monitored by
5 TLC and LCMS. After completion, the reaction mixture was filtered through celite, washed with MeOH (2 × 30 mL) and the filtrate was concentrated under vacuum to afford 6-(difluoromethoxy)-2-methoxy-pyridin-3-amine **X-14** (30 mg) as a brown liquid.

This compound was used as such for the next reaction without further purification.

Yield: 68%.

10 Basic LCMS Method 2 (ES⁺): 191 (M+H)⁺, 97% purity.

A.15. Synthesis of 6-chloro-4-methoxy-pyridin-3-amine X-15:



CAS: 607373-83-1

X-15

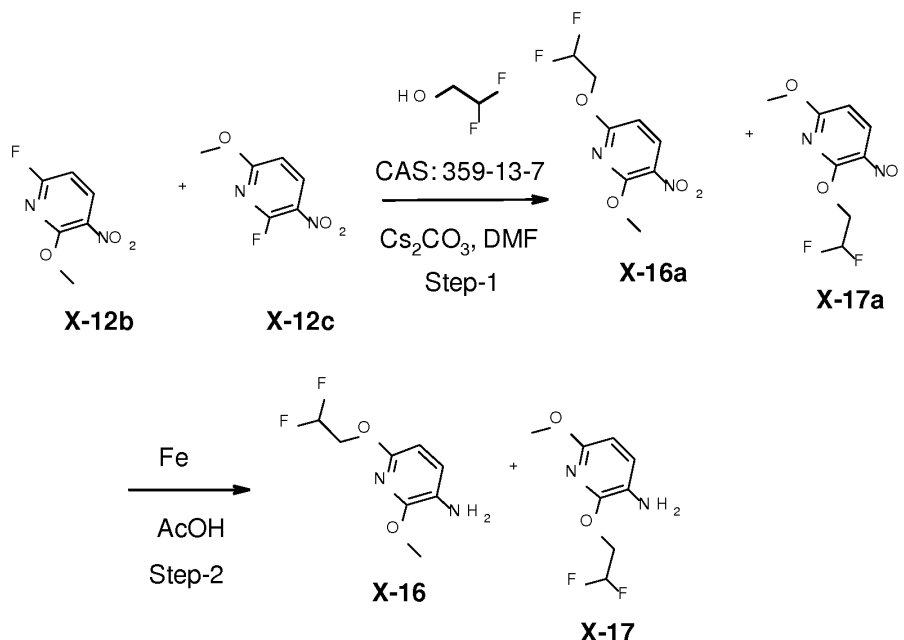
To a solution of 2-chloro-4-methoxy-5-nitropyridine (2.0 g, 10.6 mmol) in CH₃COOH (15 mL) was added Fe (2.96 g, 53 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 3h. Progress of the reaction was monitored by TLC and LCMS. After
15 completion, the reaction mixture was filtered through a pad of celite and washed with EtOAc (2 × 30 mL) and the filtrate was concentrated under vacuum. The residue was poured into aqueous saturated NaHCO₃ solution (100 mL) and extracted with EtOAc (2 × 60 mL). The organic layer was separated, dried over anhydrous Na₂SO₄ and concentrated
20 under vacuum. The crude material was washed with ether to afford 6-chloro-4-methoxy-pyridin-3-amine **X-15** (0.95 g) as an off-white solid.

Yield: 55%.

Basic LCMS Method 2 (ES⁺): 159 (M+H)⁺, 100% purity.

¹H NMR (400 MHz, DMSO-*d*₆) δ 3.85 (s, 3 H), 5.01 (s, 2 H), 6.88 (s, 1 H), 7.60 (s, 1 H).

A.16. Synthesis of 6-(2,2-difluoroethoxy)-2-methoxypyridin-3-amine **X-16 and 2-(2,2-difluoroethoxy)-6-methoxypyridin-3-amine **X-17**:**



Step-1: Synthesis of 6-(2,2-difluoroethoxy)-2-methoxy-3-nitropyridine **X-16a** and 2-(2,2-difluoroethoxy)-6-methoxy-3-nitropyridine **X-17a**:

To a solution of 6-fluoro-2-methoxy-3-nitropyridine **X-12b** and 2-fluoro-6-methoxy-3-nitropyridine **X-12c** mixture (4.00 g, 23.2 mmol, mixture of two regio isomers) in DMF (40 mL) was added Cs_2CO_3 (15.1 g, 46.5 mmol) and 2-fluoroethanol (1.79 g, 27.9 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16h. Progress of the reaction was monitored by TLC. After completion, the reaction mixture was quenched with ice cold H_2O (50 mL) and extracted with EtOAc (2 × 300 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under vacuum to 6-(2,2-difluoroethoxy)-2-methoxy-3-nitropyridine **X-16a** and 2-(2,2-difluoroethoxy)-6-methoxy-3-nitropyridine **X-17a** (4.20 g crude, mixture of two regio isomers) as a brown gummy liquid.

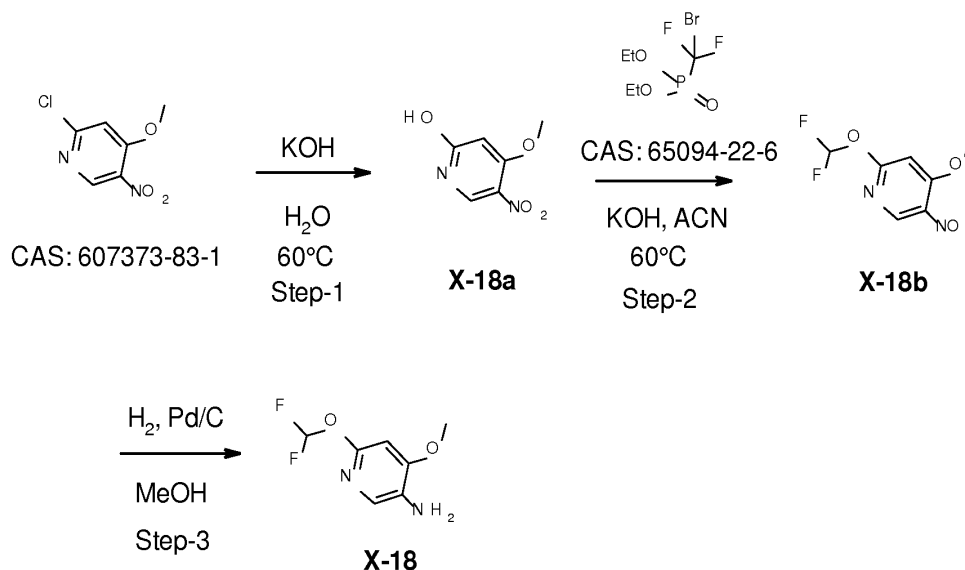
^1H NMR (400 MHz, DMSO- d_6 , 1H NMR showed mixture of regio isomers) δ 3.99 (s, 3H) 4.69-4.76 (m, 2H) 6.64-6.68 (m, 1H) 8.46 (d, $J=3.91$ Hz, 1H) 8.48 (d, $J=3.91$ Hz, 1H).

Step-2: Synthesis of 6-(2,2-difluoroethoxy)-2-methoxypyridin-3-amine **X-16** and 2-(2,2-difluoroethoxy)-6-methoxypyridin-3-amine **X-17**:

To a solution of 6-(2,2-difluoroethoxy)-2-methoxy-3-nitropyridine **X-16a** and 2-(2,2-difluoroethoxy)-6-methoxy-3-nitropyridine **X-17a** (0.50 g, 2.14 mmol, mixture of two regio

- isomers) in CH₃COOH (10 mL) was added iron (1.19 g, 21.4 mmol) slowly at 0 °C and the reaction mixture was stirred at room temperature for 2h. Progress of the reaction was monitored by TLC. The reaction mixture was filtered through a pad of Celite®, washed with EtOAc (500 mL) and the filtrate was concentrated under vacuum. The residue was
- 5 poured into aqueous saturated NaHCO₃ solution (380 mL) and extracted with EtOAc (2 × 500 mL). The organic layer was separated, dried over anhydrous Na₂SO₄ and concentrated under vacuum to afford of 6-(2,2-difluoroethoxy)-2-methoxypyridin-3-amine **X-16** and 2-(2,2-difluoroethoxy)-6-methoxypyridin-3-amine **X-17** (0.32 g crude, mixture of two regio isomers) as a brown solid.
- 10 ¹H NMR (400 MHz, DMSO-d₆, 1H NMR showed mixture of regio isomers) δ 3.99 (s, 3H) 4.69-4.76 (m, 2H) 6.64-6.68 (m, 1H) 8.46 (d, J=3.91 Hz, 1H) 8.48 (d, J=3.91 Hz, 1H). (NH₂ protons are not seen).

A.17. Synthesis of 6-chloro-4-methoxy-pyridin-3-amine **X-15**:



15 Step-1: Synthesis of 4-methoxy-5-nitropyridin-2-ol **X-18a**:

- To a solution of 2-chloro-4-methoxy-5-nitropyridine (1.00 g, 5.30 mmol) in H₂O (25 mL) was added KOH (1.49 g, 26.5 mmol) and the reaction mixture was heated at 60 °C for 3h. Progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled at room temperature, poured in to ice H₂O (100 mL), acidified with 1 N HCl (8
- 20 mL) up to pH 4 at 0 °C and extracted with EtOAc (3 × 70 mL). The organic layer was separated, dried over anhydrous Na₂SO₄ and concentrated under vacuum to afford 4-methoxy-5-nitropyridin-2-ol **X-18a** (0.71 g) as a pale yellow solid.

This compound was used as such for the next reaction without further purification.

Yield: 61%.

Basic LCMS Method 2 (ES⁺): 171 (M+H)⁺, 77% purity.

¹H NMR (400 MHz, DMSO-*d*₆) δ 3.83 (s, 3H) 5.87 (s, 1H) 8.48 (s, 1H) 12.17 (brs, 1H).

5 Step-2: Synthesis of 2-(difluoromethoxy)-4-methoxy-5-nitropyridine **X-18b**:

To a solution of 4-methoxy-5-nitropyridin-2-ol **X-18a** (0.60 g, 2.73 mmol) in CH₃CN (20 mL) and H₂O (5 mL) was added KOH (0.77 g, 13.6 mmol) and bromodifluoromethyl diethylphosphonate (3.64 g, 13.6 mmol) slowly at room temperature and the reaction mixture was heated at 60 °C for 4h. Progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with H₂O (60 mL) and extracted with EtOAc (3 × 40 mL). The organic layer was separated, washed with brine (2 × 50 mL), dried over anhydrous Na₂SO₄ and concentrated under vacuum. The reaction mixture was repeated on 2.70 g and the crude obtained from 2 reactions was clubbed and dissolved in DCM (150 mL) and the crude obtained was purified by column chromatography (silica, 100-200 mesh, 10% EtOAc in hexane) to afford 2-(difluoromethoxy)-4-methoxy-5-nitropyridine **X-18b** (1.55 g, 36%) as a pale yellow liquid.

Yield: 36%.

Basic LCMS Method 2 (ES⁺): 221 (M+H)⁺, 82% purity.

¹H NMR (400 MHz, CDCl₃) δ 4.05 (s, 3H) 6.53 (s, 1H) 7.52 (t, J=72 Hz, 1H) 8.76 (s, 1H).

20 Step-3: Synthesis of 6-(difluoromethoxy)-4-methoxypyridin-3-amine **X-18**:

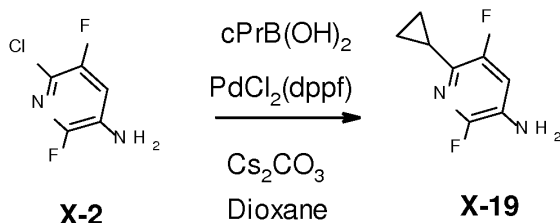
To a solution of 2-(difluoromethoxy)-4-methoxy-5-nitropyridine **X-18b** (1.50 g, 5.62 mmol) in MeOH (50 mL) was added 20% Pd/C (50% moisture, 0.18 g) at room temperature and the reaction mixture was stirred at room temperature for 4h under hydrogen pressure. Progress of the reaction was monitored by TLC and LCMS. After completion, the reaction mixture was filtered through a pad of Celite®, washed with MeOH (2 × 60 mL) and the filtrate was concentrated under vacuum. The crude obtained was purified by column chromatography (silica, 100-200 mesh, 30% EtOAc in hexane) to afford 6-(difluoromethoxy)-4-methoxypyridin-3-amine **X-18** (0.805 g, 75%) as a white solid.

Yield: 36%.

30 Basic LCMS Method 2 (ES⁺): 191 (M+H)⁺, 96% purity.

¹H NMR (400 MHz, DMSO-*d*₆) δ 3.85 (s, 3H) 4.72 (s, 2H) 6.56 (s, 1H) 7.44 (s, 1H) 7.49 (t, J= 74 Hz, 1H).

A.18. Synthesis of 6-cyclopropyl-2,5-difluoropyridin-3-amine X-19:

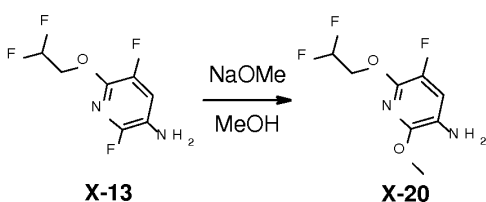


- 5 To a solution of 6-chloro-2,5-difluoro-pyridin-3-amine **X-2** (0.25 g, 1.52 mmol) in dioxane (8 mL) was added cyclopropyl boronic acid (0.27 g, 3.18 mmol) and Cs₂CO₃ (1.24 g, 3.80 mmol) in solution in H₂O (2 mL) at room temperature and the reaction mixture was
- 10 purged with argon for 10 min. PdCl₂(dppf) (0.11 g, 0.15 mmol) was added and the reaction mixture was heated at 120 °C for 18h. Progress of the reaction was monitored by TLC and
- LCMS. After completion, the reaction mixture was cooled to room temperature, filtered through a pad of celite, washed with EtOAc (2 × 60 mL) and filtrate was concentrated under vacuum. The residue was diluted with H₂O (60 mL) and extracted with EtOAc (3 × 40 mL). The organic layer was separated, washed with brine (70 mL), dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude obtained was purified by
- 15 column chromatography (silica, 100-200 mesh, 8% EtOAc in hexane) to afford 6-cyclopropyl-2,5-difluoropyridin-3-amine **X-19** (0.10 g) as colorless liquid.

Yield: 37%.

Basic LCMS Method 2 (ES⁺): 171 (M+H)⁺, 95% purity.

A.19. Synthesis of 6-(2,2-difluoroethoxy)-5-fluoro-2-methoxypyridin-3-amine X-20:



20

To a solution of 6-(2,2-difluoroethoxy)-2,5-difluoropyridin-3-amine **X-13** (1.00 g, 4.76 mmol) in THF (15 mL) was added NaOMe (25% in MeOH, 1.13 g, 5.23 mmol) slowly at 0 °C and the reaction mixture was heated at 80 °C for 16h. Progress of the reaction was monitored by TLC and LCMS. After completion, the reaction mixture was quenched with

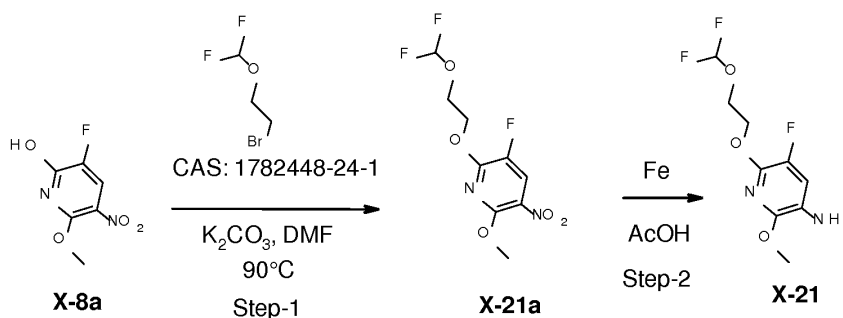
ice cold H₂O (50 mL) and extracted with EtOAc (2 × 100 mL). The organic layer was separated, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude obtained was purified by column chromatography (silica, 100-200 mesh, 5 to 10% EtOAc in hexane) to afford 6-(2,2-difluoroethoxy)-5-fluoro-2-methoxypyridin-3-amine **X-20** (0.55 g) as a brown liquid.

Yield: 50%.

Basic LCMS Method 2 (ES⁺): 223 (M+H)⁺, 91% purity.

¹H NMR (400 MHz, DMSO-*d*₆) δ 3.85 (s, 3H) 4.50 (td, J=14.89, 3.69 Hz, 2H) 4.74 (s, 2H) 6.23-6.54 (m, 1H) 6.96 (d, J=11.32 Hz, 1H).

10 A.20. Synthesis of 6-(difluoromethoxy)-5-fluoro-2-methoxy-pyridin-3-amine **X-21**:



Step-1: Synthesis of 2-(2-(difluoromethoxy)ethoxy)-3-fluoro-6-methoxy-5-nitropyridine **X-21a**:

To a solution of 3-fluoro-6-methoxy-5-nitro-pyridin-2-ol **X-8a** (0.10 g, 0.53 mmol) in DMF (4 mL) was added K₂CO₃ (0.22 g, 1.59 mmol) and 1-bromo-2-(difluoromethoxy)ethane (0.09 g, 0.53 mmol) at room temperature and the reaction mixture was heated in a microwave at 90 °C for 2h. Progress of reaction was monitored by TLC. After completion, the reaction mixture was cooled at room temperature, poured into H₂O (50 mL) and extracted with EtOAc (3 × 40 mL). The organic layer was separated, washed with brine (2 × 50 mL), dried over anhydrous Na₂SO₄ and concentrated under vacuum to afford 2-(2-(difluoromethoxy)ethoxy)-3-fluoro-6-methoxy-5-nitropyridine **X-21a** (0.09 g) as a brown liquid.

This compound was used as such for the next reaction without further purification.

Yield: 64%.

¹H NMR (400 MHz, DMSO-*d*₆) δ 4.05 (s, 3H) 4.22-4.27 (m, 2H) 4.70-4.76 (m, 2H) 6.75 (t, J=74 Hz, 1H) 8.57 (d, J=9.78 Hz, 1H).

Step-2: Synthesis of 6-(2-(difluoromethoxy)ethoxy)-5-fluoro-2-methoxypyridin-3-amine **X-21**:

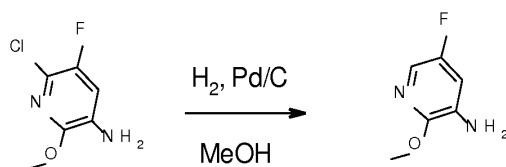
- 5 To a solution of 2-(2-(difluoromethoxy)ethoxy)-3-fluoro-6-methoxy-5-nitropyridine **X-21a** (0.09 g, 0.32 mmol) in CH₃COOH (2 mL) was added iron (0.18 g, 3.19 mmol) slowly at 0 °C and the reaction mixture was stirred at room temperature for 2h. Progress of reaction was monitored by TLC and LCMS. After completion, the reaction mixture was filtered through a pad of celite, washed with EtOAc (50 mL) and the filtrate was concentrated under vacuum. The residue was poured into an aqueous saturated NaHCO₃ solution (10 mL) and extracted with EtOAc (2 × 50 mL). The organic layer was separated, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude obtained was purified by washing with pentane (3 × 70 mL) to afford 6-(2-(difluoromethoxy)ethoxy)-5-fluoro-2-methoxypyridin-3-amine **X-21** (0.08 g, 77%) as a brown solid.
- 10
- 15 This compound was used as such for the next reaction without further purification.

MS (ESI) m/e [M+H]⁺/ Rt/%: 253.00/1.72/77.7%

Yield: 77%.

Basic LCMS Method 2 (ES⁺): 253 (M+H)⁺, 78% purity.

A.21. Synthesis of 6-chloro-4-methoxy-pyridin-3-amine **X-22**:



20

X-3

X-22

- To a solution of 6-chloro-5-fluoro-2-methoxy-pyridin-3-amine **X-3** (2.0 g, 11.33 mmol) in MeOH (38 mL) was added Pd/C (20%, 0.43 g) under argon atmosphere for 5 min and the reaction mixture was stirred at room temperature for 16h under hydrogen atmosphere. Progress of the reaction was monitored by TLC and LCMS. After completion, the reaction mixture was filtered through a pad of celite and washed with EtOAc (3 × 100 mL). The filtrate was concentrated under vacuum. The crude obtained was purified by column
- 25

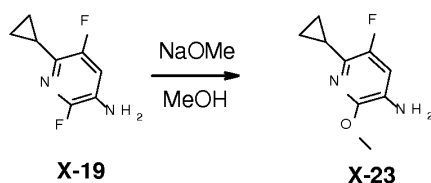
chromatography (silica, 100-200 mesh, 4 to 10% EtOAc in hexane) to afford 5-fluoro-2-methoxy-pyridin-3-amine **X-22** (0.48 g) as a brown solid.

Yield: 30%.

Basic LCMS Method 2 (ES⁺): 143 (M+H)⁺, 96% purity.

- 5 ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.83 (s, 3H) 5.32 (br s, 2H) 6.72 (dd, J=2.8, 9.6 Hz, 1H) 7.24 (d, J=2.8 Hz, 1H).

A.22. Synthesis of 6-cyclopropyl-5-fluoro-2-methoxypyridin-3-amine **X-23**:



- To a solution of 6-cyclopropyl-2,5-difluoropyridin-3-amine **X-19** (1.50 g, 8.75 mmol) in
10 MeOH (20 mL) was added NaOMe (25% in MeOH, 3.78 mL, 17.5 mmol) at room
temperature and the reaction mixture was heated at 100 °C for 24h. Progress of the
reaction was monitored by TLC and LCMS. After completion, the reaction mixture was
concentrated under vacuum. The residue was diluted with H₂O (20 mL) and extracted with
EtOAc (3 × 25 mL). The organic layer was separated, dried over anhydrous Na₂SO₄ and
15 concentrated under vacuum. The crude obtained was purified by combi-flash
chromatography (20% EtOAc in hexane) to afford 6-cyclopropyl-5-fluoro-2-
methoxypyridin-3-amine **X-23** (1.10 g) as a brown oil.

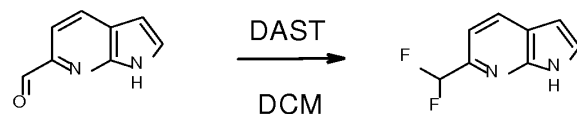
Yield: 69%.

Basic LCMS Method 2 (ES⁺): 183 (M+H)⁺, 99% purity.

- 20 ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.76 - 0.86 (m, 4H) 1.94-2.03 (m, 1H) 3.75 (s, 3H) 4.94
(s, 2H) 6.68 (d, J=10.76 Hz, 1H).

B. Synthesis of intermediates of Formula XI

B.1. Synthesis of 6-(difluoromethyl)-1H-pyrrolo[2,3-b]pyridine **XI-1**:



CAS: 22049-95-2

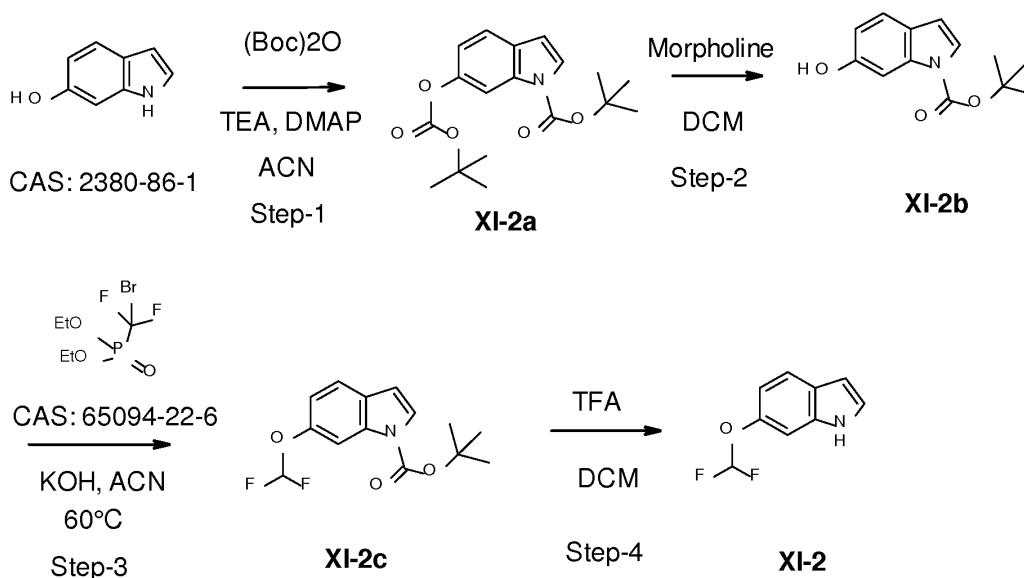
XI-1

- To a solution of 1H-pyrrolo[2,3-b]pyridine-6-carbaldehyde (196 mg, 1.26 mmol) in dichloromethane (4 mL) was added, at 0 °C, diethylaminosulfur trifluoride (260 μ L, 1.91 mmol). The reaction mixture was stirred 4h at room temperature. Pour the reaction on a mixture of ice and NaHCO₃ and extract 3 times with DCM. Dry the organic phase on Na₂SO₄ and concentrate the solvents to get 6-(difluoromethyl)-1H-pyrrolo[2,3-b]pyridine **XI-1** (96 mg) as a brown solid

Yield: 45%.

Basic LCMS Method 1 (ES⁺): 169 (M+H)⁺, 82% purity.

10 B.2. Synthesis of 6-(difluoromethoxy)-1H-indole XI-2:

Step-1: Synthesis of tert-butyl 6-((tert-butoxycarbonyl)oxy)-1H-indole-1-carboxylate **XI-2a**:

- To a solution of 1H-indol-6-ol (5.00 g, 37.6 mmol) in CH₃CN (50 mL) was added Di-tert-butyl dicarbonate (25.9 mL, 113 mmol), DMAP (2.29 g, 18.8 mmol) and Triethylamine (15.7 mmol, 113 mmol). The reaction mixture was stirred at 25 °C for 16h. Progress of the reaction was monitored by TLC and LCMS. After completion, the reaction mixture was

concentrated under vacuum. The crude obtained was purified by column chromatography (silica, 100-200 mesh, 20% EtOAc in hexane) to afford tert-butyl 6-((tert-butoxycarbonyl)oxy)-1H-indole-1-carboxylate **XI-2a** (10.0 g) as a pale yellow liquid.

Yield: 80%.

- 5 Basic LCMS Method 2 (ES⁻): 332 (M-H)⁻, 99% purity.

Step-2: Synthesis of tert-butyl 6-hydroxy-1H-indole-1-carboxylate **XI-2b**:

- To a solution of tert-butyl 6-((tert-butoxycarbonyl)oxy)-1H-indole-1-carboxylate **XI-2a** (9.90 g, 29.6 mmol) in DCM (100 mL) was added morpholine (51.8 mL, 592 mmol) and the reaction mixture was stirred at room temperature for 16h. Progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with H₂O (200 mL) and extracted with EtOAc (3 × 100 mL). The organic layer was separated, washed with brine (2 × 100 mL), dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude obtained was purified by column chromatography (silica, 100-200 mesh, 15% EtOAc in hexane) to afford tert-butyl 6-hydroxy-1H-indole-1-carboxylate **XI-2b** (6.70 g) as a colorless oil.

Yield: 97%.

¹H NMR (400 MHz, DMSO-*d*₆) δ 1.61 (s, 9H) 6.55 (d, J=3.94 Hz, 1H) 6.71 (dd, J=8.37, 1.97 Hz, 1H) 7.36 (d, J=8.86 Hz, 1H) 7.43 (d, J=3.45 Hz, 1H) 7.51 (s, 1H) 9.41 (s, 1H).

Step-3: Synthesis of tert-butyl 6-(difluoromethoxy)-1H-indole-1-carboxylate **XI-2c**:

- To a solution of tert-butyl 6-hydroxy-1H-indole-1-carboxylate **XI-2b** (2.00 g, 8.57 mmol) in CH₃CN (20 mL) and H₂O (20 mL) was added KOH (9.62 g, 171 mmol) and bromodifluoromethyl diethylphosphonate (3.05 mL, 17.1 mmol) slowly at -78 °C. After 15 min, the reaction mixture was stirred at 0 °C for 3h. Progress of the reaction was monitored by TLC and LCMS. After completion, the reaction mixture was diluted with H₂O (200 mL) and extracted with EtOAc (2 × 200 mL). The organic layer was separated, washed with brine (2 × 30 mL), dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude obtained was purified by column chromatography (silica, 100-200 mesh, 15% EtOAc in hexane) to afford tert-butyl 6-(difluoromethoxy)-1H-indole-1-carboxylate **XI-2c** (0.68 g) as a yellow oil.

- 30 Yield: 21%.

Basic LCMS Method 2 (ES⁻): 282 (M-H)⁻, 74% purity.

¹H NMR (400 MHz, DMSO-*d*₆) δ 1.63 (s, 9H) 6.73 (d, J=3.91 Hz, 1H) 7.09 (dd, J=8.80, 1.47 Hz, 1H) 7.23 (t, J=76 Hz, 1H) 7.66 (d, J=8.31 Hz, 1H) 7.69 (d, J=3.42 Hz, 1H) 7.86 (s, 1H).

Step-4: Synthesis of 6-(difluoromethoxy)-1H-indole **XI-2** :

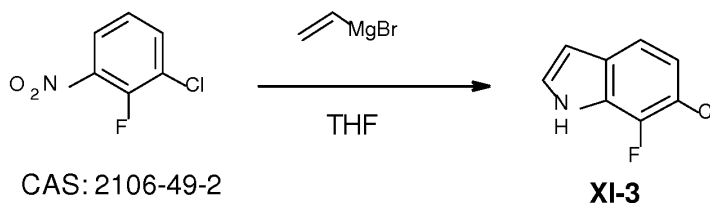
- 5 To a solution of tert-butyl 6-(difluoromethoxy)-1H-indole-1-carboxylate **XI-2c** (0.67 g, 1.76 mmol) in DCM (25 mL) was added TFA (40 mL) at 0 °C and the reaction mixture was stirred at same temperature for 5 min, then at room temperature for 1h. Progress of the reaction was monitored by TLC. After completion, the reaction mixture was concentrated under vacuum. The residue was diluted with H₂O (100 mL), saturated NaHCO₃ (50 mL)
- 10 and extracted with EtOAc (2 × 200 mL). The organic layer was separated, dried over anhydrous Na₂SO₄ and concentrated under vacuum to afford 6-(difluoromethoxy)-1H-indole **XI-2** (0.31 g) as a brown oil.

Yield: 76%.

Basic LCMS Method 2 (ES⁻): 182 (M-H)⁻, 79% purity.

- 15 ¹H NMR (400 MHz, DMSO-*d*₆) δ 6.42-6.44 (m, 1H) 6.83 (dd, J=8.56, 1.71 Hz, 1H) 7.14 (t, J=74 Hz, 1H) 7.18 (s, 1H) 7.37 (t, J=2.45 Hz, 1H) 7.54 (d, J=8.80 Hz, 1H) 11.17 (brs, 1H).

B.3. Synthesis of 6-chloro-7-fluoro-1H-indole **XI-3**:

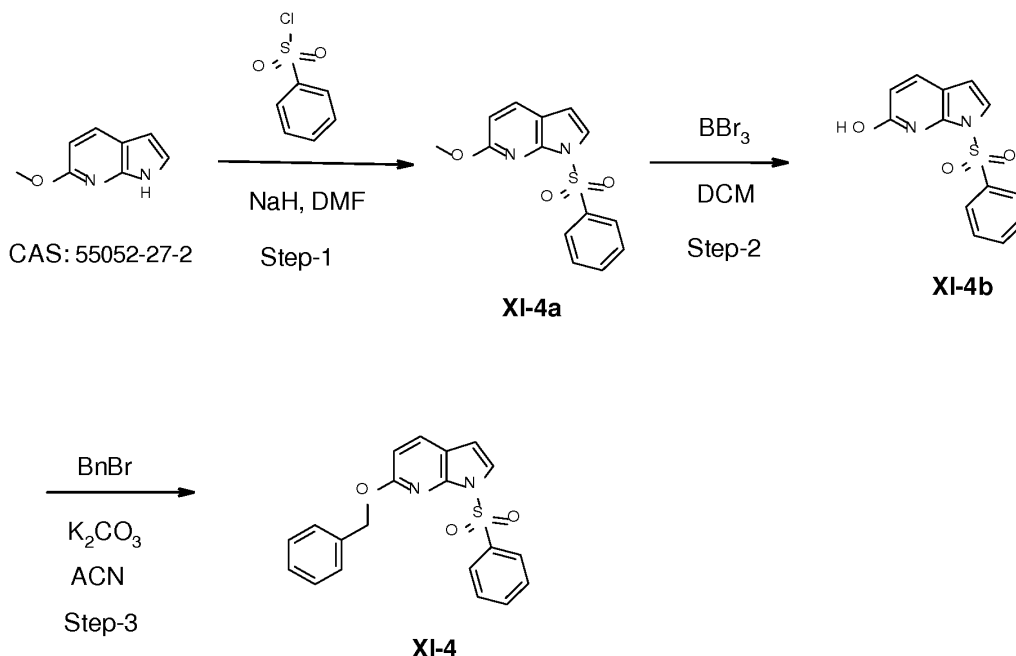


- To a solution of 1-chloro-2-fluoro-3-nitro-benzene (2.50 g, 14.2 mmol) in THF (50 mL) was added vinyl magnesium bromide (5.61 g, 42.7 mmol) at -78 °C and the reaction mixture was stirred at same temperature for 1h. Progress of the reaction was monitored by TLC and LCMS. After completion, the reaction mixture was quenched with saturated NH₄Cl (100 mL), diluted with H₂O (400 mL) and extracted with EtOAc (500 mL). The organic layer was separated, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The
- 20 crude obtained was purified by column chromatography (silica, 100-200 mesh, 5% EtOAc in hexane) to afford 6-chloro-7-fluoro-1H-indole **XI-3** (0.60 g) as a red liquid.
- 25

Yield: 17%

Basic LCMS Method 2 (ES⁻): 168.00 (M-H)⁻, 66 % purity.

B.4. Synthesis of 1-(benzenesulfonyl)-6-benzyloxy-pyrrolo[2,3-b]pyridine **XI-4**:



Step-1: Synthesis of 1-(benzenesulfonyl)-6-methoxy-pyrrolo[2,3-b]pyridine **XI-4a**

- 5 A solution of 6-methoxy-1H-pyrrolo[2,3-b]pyridine (998 mg, 5.4 mmol) in 10 mL of DMF was treated with sodium hydride (60% in paraffin, 238 mg, 6 mmol) and stirred for 1 h at room temperature. Subsequently benzenesulfonic acid chloride (0.8 mL, 6.5 mmol) was added. The reaction mixture was stirred 18 h at room temperature, water (100 mL) was added and the suspension was extracted with ethyl acetate (3 x 30 mL). The combined
- 10 organic extracts were dried over MgSO₄, filtered and concentrated under reduced pressure. The resulting material was purified by column chromatography on silica gel using (petroleum ether : ethyl acetate 80 : 20). The collected fractions were evaporated to give 980 mg of 1-(benzenesulfonyl)-6-methoxy-pyrrolo[2,3-b]pyridine **XI-4a** as a white powder.
- 15 Yield: 63%

Neutral LCMS Method 3 (ES⁺): 289 (M+H)⁺, 100% purity.

¹H NMR (600 MHz, DMSO-*d*₆) δ 3.89 (s, 3H), 6.71 (dd, *J* = 6.2, 2.3 Hz, 2H), 7.67 – 7.61 (m, 3H), 7.75 – 7.70 (m, 1H), 7.91 (d, *J* = 8.5 Hz, 1H), 8.13 (dd, *J* = 8.5, 1.3 Hz, 2H).

Step-2: Synthesis of 1-(benzenesulfonyl)pyrrolo[2,3-b]pyridin-6-ol **XI-4b**

To a solution of 1-(benzenesulfonyl)-6-methoxy-pyrrolo[2,3-b]pyridine **XI-4a** (800 mg, 2.7 mmol) in dichloromethane (35 mL), boron tribromide solution 1.0 M in dichloromethane (5 mL, 5 mmol) was added at 0 °C then warmed up to room temperature and stirred for 95 h at the same temperature. The reaction mixture was hydrolyzed by addition of a saturated NaHCO₃-solution (40 mL). Water was added and the aqueous phase was extracted with ethyl acetate (3 x 35 mL). The combined organic extracts were dried over MgSO₄, filtered and concentrated under reduced pressure. The resulting material was purified by column chromatography on silica gel using (petroleum ether : ethyl acetate 80 : 20). The collected fractions were evaporated to give 580 mg of 1-(benzenesulfonyl)pyrrolo[2,3-b]pyridin-6-ol **XI-4b** as a white powder.

Yield: 79%

Neutral LCMS Method 3 (ES⁺): 275 (M+H)⁺, 93% purity.

¹H NMR (600 MHz, DMSO-*d*₆) δ 6.58 (d, J = 8.4 Hz, 1H), 6.66 (d, J = 4.0 Hz, 1H), 7.55 (d, J = 4.0 Hz, 1H), 7.64 – 7.58 (m, 2H), 7.75 – 7.69 (m, 1H), 7.84 (d, J = 8.4 Hz, 1H), 8.20 – 8.14 (m, 2H), 10.92 (s, 1H).

Step-3: Synthesis of 1-(benzenesulfonyl)-6-benzyloxy-pyrrolo[2,3-b]pyridine **XI-4**

A mixture of 1-(benzenesulfonyl)pyrrolo[2,3-b]pyridin-6-ol **XI-4b** (767 mg, 2.8 mmol), benzylbromide (0.29 mL, 205 mmol, 0.89 equiv) and potassium carbonate (967.2 mg, 7 mmol, 2.5 equiv) in dry acetonitrile (20 mL) was heated at 50 °C for 22 h under argon atmosphere. After cooling, the reaction mixture was filtered to remove unreacted potassium carbonate and washed thoroughly with ethyl acetate (100 mL). After evaporation of the organic solvent, 1-(benzenesulfonyl)-6-benzyloxy-pyrrolo[2,3-b]pyridine **XI-4** was obtained as a white solid (600 mg).

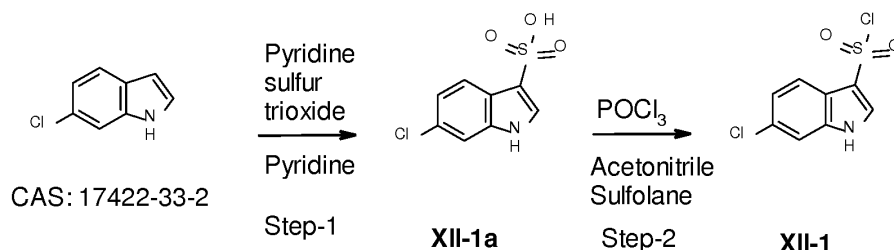
This compound was used as such for the next reaction without further purification.

Yield: 59%

Neutral LCMS Method 3 (ES⁺): 365 (M+H)⁺ crude.

C. Synthesis of intermediates of Formula XII

C.1. Synthesis of 6-chloro-1H-indole-3-sulfonyl chloride XII-1



Step-1: Synthesis of 6-chloro-1H-indole-3-sulfonic acid **XII-1a**:

- 5 To a solution of 6-chloroindole (1.00 g, 6.62 mmol) in pyridine (10 mL) was added pyridine sulfur trioxide complex (1.57 g, 9.93 mmol) and the reaction mixture was heated to reflux for 16h. Progress of the reaction was monitored by TLC and LCMS. After completion, the reaction mixture was diluted with H₂O (100 mL) and extracted with Et₂O (250 mL). The aqueous layer was separated and concentrated under vacuum. The crude obtained was
- 10 co-evaporated with toluene to afford 6-chloro-1H-indole-3-sulfonic acid **XII-1a** (2.30 g crude) as a brown semi solid.

This compound was used as such for the next reaction without further purification.

Basic LCMS Method 2 (ES⁻): 230 (M-H)⁻, 98% purity.

- ¹H NMR (400 MHz, DMSO-*d*₆) δ 6.98-7.04 (m, 1H), 7.12 - 7.26 (m, 1H), 7.44 (s, 1H), 7.69
- 15 - 7.75 (m, 1H), 11.13 (brs, 1H).

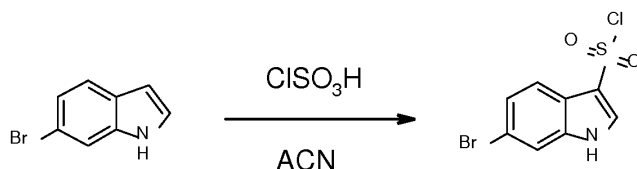
Step-2: Synthesis of 6-chloro-1H-indole-3-sulfonyl chloride **XII-1**:

- To a solution of 6-chloro-1H-indole-3-sulfonic acid **XII-1a** (2.00 g, 6.45 mmol) in sulfolane (5 mL) and CH₃CN (5 mL) was added POCl₃ (1.30 mL, 14.2 mmol) drop wise at 0 °C and the reaction mixture was heated at 70 °C for 3h. Progress of the reaction was monitored
- 20 by TLC and LCMS. After completion, the reaction mixture was quenched with ice cold H₂O (100 mL) and extracted with EtOAc (2 x 50 mL). The organic layer was separated, washed with brine (50 mL), dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude obtained was purified by column chromatography (silica, 100-200 mesh, 30% EtOAc in hexane) to afford 6-chloro-1H-indole-3-sulfonyl chloride **XII-1** (1.00
- 25 g) as a light pink solid.

Yield: 62%.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.32 (dd, $J=8.56, 1.22$ Hz, 1H), 7.71 (s, 1H), 8.03 (d, $J=8.80$ Hz, 1H), 8.45 (d, $J=2.93$ Hz, 1H), 12.38 (brs, 1H).

C.2. Synthesis of 6-bromo-1H-indole-3-sulfonyl chloride XII-2:



CAS: 52415-29-9

XII-2

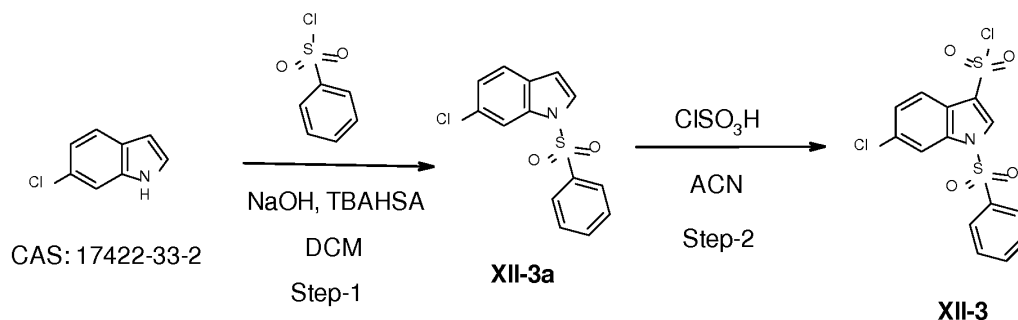
- 5 To a solution of 6-bromo-1H-indole (5 g, 25.5 mmol) in CH_3CN (60 mL) was added ClSO_3H (1 mL) at 0°C and the reaction mixture was stirred at room temperature for 12h. Progress of the reaction was monitored by TLC. After completion, the reaction mixture was poured into ice cold H_2O (200 mL) and stirred for 30 minutes. A solid precipitated out, was filtered and dried under vacuum to afford 6-bromo-1H-indole-3-sulfonyl chloride **XII-2** 10 (5 g) as a brown solid.

This compound was used as such for the next reaction without further purification.

Yield: 66%

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.38-7.48 (m, 1H) 7.85 (s, 1H) 7.97 (d, $J=8.37$ Hz, 1H) 8.44 (d, $J=3.45$ Hz, 1H) 12.55 (brs, 1H).

15 C.3. Synthesis of 1-(benzenesulfonyl)-6-chloro-indole-3-sulfonyl chloride XII-3



Step-1: Synthesis of 1-(benzenesulfonyl)-6-chloro-indole **XII-3a**

- A suspension of finely powdered sodium hydroxide (24.5 g, 613 mmol) in dichloromethane (300 mL) was stirred in an ice bath and 6-chloroindole (30 g, 197 mmol) was added in one 20 portion followed by tetrabutylammonium hydrogen sulfate (1.75 g, 5.15 mmol). Then benzenesulfonyl chloride (2.2 mL, 218 mmol) was added dropwise over 20 min and the

reaction mixture was stirred at 0 °C for 1h. The ice bath was then removed and the mixture was stirred for a further 1h at room temperature. When LC/MS showed completion of reaction, the reaction mixture was filtered through a celite pad and the latter was washed with DCM, combined filtrate and washings were evaporated to dryness. The product was triturated in ether, filtered, washed with small amount of ether then hexane and dried, the filtrate was concentrated to give a second crop with a total of 50.54 g of 1-(benzenesulfonyl)-6-chloro-indole **XII-3a** as light brown solid.

Yield: 88%.

¹H NMR (400 MHz, CDCl₃) δ 8.04 (dd, *J* = 1.8, 0.9 Hz, 1H), 7.91 (t, *J* = 1.4 Hz, 1H), 7.89 (t, *J* = 1.8 Hz, 1H), 7.67–7.54 (m, 2H), 7.53–7.48 (m, 2H), 7.48–7.42 (m, 1H), 7.23 (dd, *J* = 8.4, 1.9 Hz, 1H), 6.65 (dd, *J* = 3.7, 0.9 Hz, 1H).

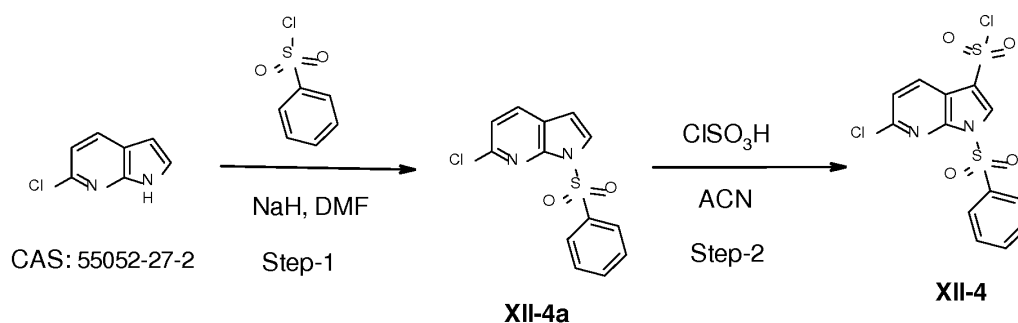
Step-2: Synthesis of 1-(benzenesulfonyl)-6-chloro-indole-3-sulfonyl chloride **XII-3**

A solution of 1-(benzenesulfonyl)-6-chloro-indole **XII-3a** (50 g, 171.4 mmol) in acetonitrile (500 mL) was stirred in an ice bath and chlorosulfonic acid (100.8 g, 856.8 mmol) was added dropwise over 20 min and the reaction mixture was stirred for 5 days at room temperature. It was then slowly poured with stirring into ice-water (2.2L) for 20 min, filtered, washed several times with water and dried by suction to give 63.77g of 1-(benzenesulfonyl)-6-chloro-indole-3-sulfonyl chloride **XII-3** as light brown solid.

Yield: 95%.

¹H NMR (400 MHz, CDCl₃) δ 8.36 (s, 1H), 8.07 (d, *J* = 1.8 Hz, 1H), 8.04 (t, *J* = 1.3 Hz, 1H), 8.02 (d, *J* = 1.5 Hz, 1H), 7.91 (d, *J* = 8.6 Hz, 1H), 7.79–7.70 (m, 1H), 7.68–7.59 (m, 2H), 7.47 (dd, *J* = 8.6, 1.8 Hz, 1H).

C.4. Synthesis of 1-(benzenesulfonyl)-6-chloro-pyrrolo[2,3-b]pyridine-3-sulfonyl chloride **XII-4**



Step-1: Synthesis of 1-(benzenesulfonyl)-6-chloro-pyrrolo[2,3-b]pyridine **XII-4a**

To a solution of 6-chloro-1H-pyrrolo[2,3-b]pyridine (1.37 g, 8.97 mmol) in DMF (100 mL), sodium hydride (60 % in paraffin, 1 g, 41 mmol) was added. The solution was stirred for 30 min being allowed to warm up from 0 °C to rt. Subsequently, benzenesulfonic acid chloride (1.5 mL, 11.8 mmol) was added dropwise. The suspension was stirred 3 h at room temperature and hydrolyzed with ice water. The resulting solid was filtered off under reduced pressure, washed thoroughly with water (75 mL) and finally with petroleum ether (15 mL). The resulting material was dried at 60 °C and purified by column chromatography (eluent: pure dichloromethane) yielding 856 mg of 1-(benzenesulfonyl)-6-chloro-pyrrolo[2,3-b]pyridine **XII-4a** as a brownish solid.

Yield: 32%

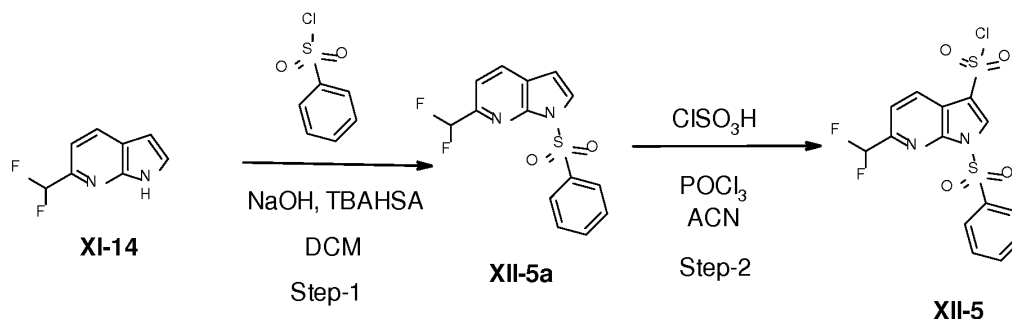
Step-2: Synthesis of 1-(benzenesulfonyl)-6-chloro-pyrrolo[2,3-b]pyridine-3-sulfonyl chloride **XII-4**

The obtained 1-(benzenesulfonyl)-6-chloro-pyrrolo[2,3-b]pyridine **XII-4a** (150 mg, 0.51 mmol) was dissolved in acetonitrile (5 mL) and treated with chlorosulfonic acid (2 mL, 2.91 mmol) dropwise. The mixture was refluxed for 3 h, cooled to room temperature, hydrolyzed with ice water (50 mL) and neutralized with a saturated solution of sodium hydrogen carbonate. The crude product was extracted with dichloromethane (3 times, 50 mL each). The combined organic extracts were dried over MgSO₄, filtered and concentrated. The resulting material was purified by column chromatography (eluent: pure dichloromethane) yielding 163 mg of 1-(benzenesulfonyl)-6-chloro-pyrrolo[2,3-b]pyridine-3-sulfonyl chloride **XII-4** as a yellowish solid.

Yield: 81%

¹H NMR (600 MHz, CDCl₃) δ: 8.48 (s, 1H), 8.32 (d, J = 7.8 Hz, 2H), 8.18 (d, J = 8.3 Hz, 1H), 7.71 (t, J = 7.5 Hz, 1H), 7.60 (t, J = 7.9 Hz, 2H), 7.41 (d, J = 8.4 Hz, 1H).

C.5. Synthesis of 1-(benzenesulfonyl)-6-(difluoromethyl)pyrrolo[2,3-b]pyridine-3-sulfonyl chloride XII-5



Step-1: Synthesis of 1-(benzenesulfonyl)-6-(difluoromethyl)pyrrolo[2,3-b]pyridine XII-5a

- 5 A suspension of sodium hydroxide (76 mg, 1.88 mmol) in dichloromethane (1 mL) was stirred in an ice bath and 6-(difluoromethyl)-1H-pyrrolo[2,3-b]pyridine **XI-14** (125 mg, 0.74 mmol) was added followed by tetrabutylammonium hydrogen sulfate (7.5 g, 0.022 mmol). Then benzenesulfonyl chloride (105 μL , 0.81 mmol) was added dropwise and the reaction mixture was stirred at room temperature overnight. After completion of reaction, the
- 10 mixture was filtered through a celite pad and the latter was washed with DCM, combined filtrate and washings were evaporated to dryness. The crude product was purified by chromatography (SiO_2 , elution with dichloromethane) to afford 1-(benzenesulfonyl)-6-(difluoromethyl)pyrrolo[2,3-b]pyridine **XII-5a** (200mg) as a light brown solid.

Yield: 70%.

- 15 Basic LCMS Method 1 (ES^+): 309 ($\text{M}+\text{H}^+$), 100% purity.

Step-2: Synthesis of 1-(benzenesulfonyl)-6-(difluoromethyl)pyrrolo[2,3-b]pyridine-3-sulfonyl chloride XII-5

- A solution of 1-(benzenesulfonyl)-6-(difluoromethyl)pyrrolo[2,3-b]pyridine **XII-5a** (76 mg, 0.24 mmol) in acetonitrile (10 mL) was stirred in an ice bath and chlorosulfonic acid (54 μL , 0.78 mmol) was added dropwise and the reaction mixture was stirred for 4 days at 50
- 20 $^{\circ}\text{C}$. Then, phosphorous oxychloride (100 μL , 1.06 mmol) was added and the reaction mixture was heated at 70 $^{\circ}\text{C}$ overnight. After cooling, it was then slowly poured into ice-water and extracted with chloroform (3x). The organic layers were dried over magnesium sulfate and evaporated to dryness to give 1-(benzenesulfonyl)-6-chloro-indole-3-sulfonyl
- 25 chloride **XII-5** (100 mg) as a solid.

The crude product was used for next reaction without further purification.

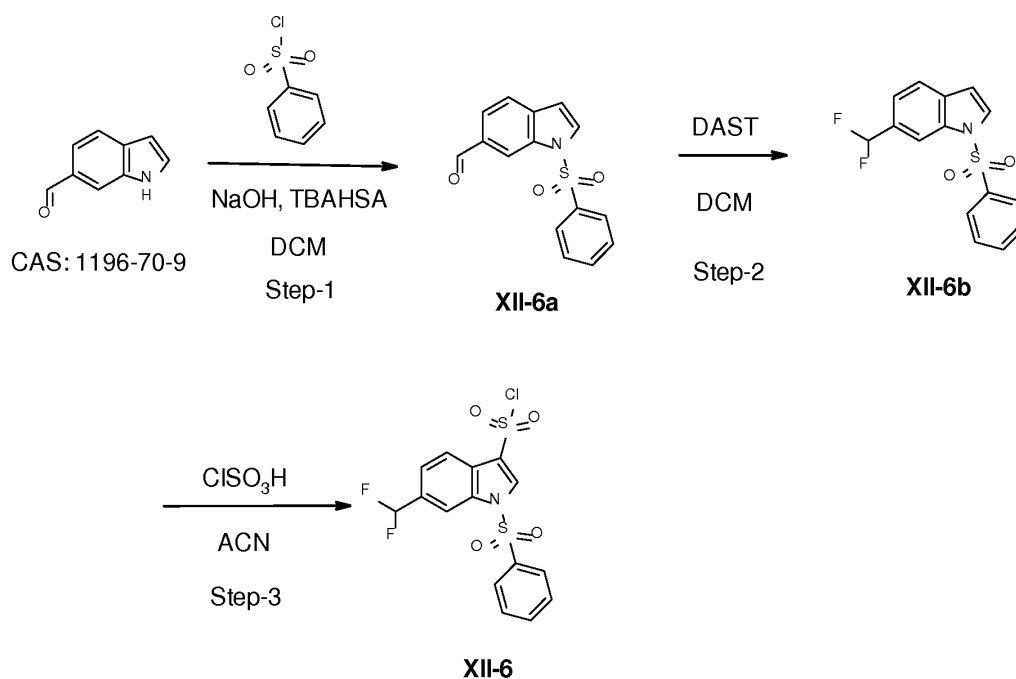
Yield: 95%.

Basic LCMS Method 1 (ES⁻): 387 (M-H)⁻ (corresponding sulfonic acid mass), 88% purity.

C.6. Synthesis of 1-(benzenesulfonyl)-6-(difluoromethyl)indole-3-sulfonyl chloride

5

XII-6



Step-1: Synthesis of 1-(benzenesulfonyl)indole-6-carbaldehyde **XII-6a**

To a stirred suspension of finely powdered sodium hydroxide (8.26 g, 206.7 mmol) in dichloromethane (130 mL) previously cooled on top of an ice bath was added 1H-indole-6-carbaldehyde (10.0 g, 68.89 mmol) as a single portion followed by tetrabutylammonium hydrogen sulfate (1.754 g, 5.17 mmol). Stirring was continued for a further 10 minutes then a solution of benzenesulfonyl chloride (9.67 mL, 75.78 mmol, 1.1 eq.) in dichloromethane (20 mL) was added dropwise over 20 min and the reaction mixture was stirred at 0 °C for 1h. The cooling bath was removed and the mixture was stirred for a further 1 hour at ambient temperature. The reaction mixture was filtered over a pad of Kieselguhr, rinsing the filter cake with dichloromethane (2 x 100 mL) and the filtrate concentrated under vacuum. The residue was then triturated in diethyl ether (100 mL) and the solid collected by filtration, rinsing the filter cake with diethyl ether (2 x 50 mL). The

solid was then dried under vacuum to afford 17.5 g of the title compound (contaminated with tetrabutylammonium hydrogen sulfate, ~8% w/w). The solid was dissolved in ethyl acetate (350 mL) and the solution washed with water (150 mL) and brine (100 mL), dried over anhydrous sodium sulfate, filtered and the solvent concentrated under vacuum to afford 1-(benzenesulfonyl)indole-6-carbaldehyde **XII-6a** (15.29 g) as a dark beige solid.

Yield: 70%.

Acidic LCMS Method 4 (ES⁺): 286 (M+H)⁺, 84% purity.

¹H NMR (400 MHz, CDCl₃) δ 6.74 (dd, J = 3.6, 0.7 Hz, 1H), 7.52 – 7.44 (m, 2H), 7.60 – 7.53 (m, 1H), 7.66 (d, J = 8.2 Hz, 1H), 7.81 – 7.75 (m, 2H), 7.98 – 7.88 (m, 2H), 8.54 – 8.45 (m, 1H), 10.09 (s, 1H).

Step-2: Synthesis of 1-(benzenesulfonyl)-6-(difluoromethyl)indole **XII-6b**

To a stirred solution of 1-(benzenesulfonyl)indole-6-carbaldehyde **XII-6a** (3.58 g, 12.55 mmol) in dichloromethane (55 mL) was added Diethylaminosulfur fluoride (7.5 mL, 56.77 mmol) dropwise. Stirring was continued at ambient temperature for 21 hours. The reaction mixture was quenched with saturated aqueous sodium hydrogencarbonate (100 mL) and then extracted with dichloromethane (2 x 150 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and the solvent concentrated under vacuum. The residue was purified using flash chromatography (340 g KP-SIL column) using a gradient of ethyl acetate in heptane (5% to 30%) to afford 1-(benzenesulfonyl)-6-(difluoromethyl)indole **XII-6b** (2.91 g) as an off-white solid.

Yield: 75%.

Acidic LCMS Method 4 (ES⁺): 308 (M+H)⁺, 100% purity.

¹H NMR (400 MHz, CDCl₃) δ 6.70 (dd, J = 3.7, 0.7 Hz, 1H), 6.76 (t, J = 56.5 Hz, 1H), 7.39 (dd, J = 8.2, 0.8 Hz, 1H), 7.50 – 7.42 (m, 2H), 7.59 – 7.51 (m, 1H), 7.64 – 7.59 (m, 1H), 7.66 (d, J = 3.7 Hz, 1H), 7.93 – 7.85 (m, 2H), 8.17 (d, J = 0.8 Hz, 1H).

Step-3: Synthesis of 1-(benzenesulfonyl)-6-(difluoromethyl)indole-3-sulfonyl chloride **XII-6**

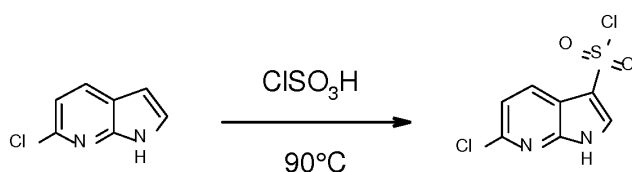
To a stirred solution of 1-(benzenesulfonyl)-6-(difluoromethyl)indole **XII-6b** (5.7 g, 18.55 mmol) in acetonitrile (57 mL) previously cooled on top of an ice batch, was added chlorosulfonic acid (10.8 g, 92.74 mmol) dropwise over 20 minutes and the reaction mixture was stirred for 3 days at ambient temperature. The reaction mixture was slowly poured with stirring into ice-water (220 mL) over 20 minutes. The precipitated solid was

collected by filtration, rinsing the filter cake with icy water (3 x 25 mL). The filter cake was then dried under a flow of nitrogen for 1 hour, rinsed with cyclohexane (25 mL) and dried under a flow of nitrogen for a further 2 hours to afford 1-(benzenesulfonyl)-6-(difluoromethyl)indole-3-sulfonyl chloride **XII-6** (7.51 g) as an off-white solid.

5 Yield: 99%.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.20 (t, $J = 55.9$ Hz, 1H), 7.51 (d, $J = 8.3$ Hz, 1H), 7.75 – 7.57 (m, 3H), 7.76 (s, 1H), 7.91 (d, $J = 8.2$ Hz, 1H), 8.11 – 8.01 (m, 2H), 8.14 (s, 1H).

C.7. Synthesis of 6-chloro-1H-pyrrolo[2,3-b]pyridine-3-sulfonyl chloride **XII-7**:



CAS: 55052-27-2

XII-7

10 A mixture of 6-chloro-1H-pyrrolo[2,3-b]pyridine (0.50 g, 3.28 mmol) in ClSO_3H (10 mL) was heated at 90°C for 16h. Progress of reaction was monitored by TLC and LCMS. After completion, the reaction mixture was quenched with ice H_2O (30 mL), filtered, washed with H_2O (30 mL) and dried under vacuum to afford 6-chloro-1H-pyrrolo[2,3-b]pyridine-3-sulfonyl chloride **XII-7** (0.45 g) as an off-white solid.

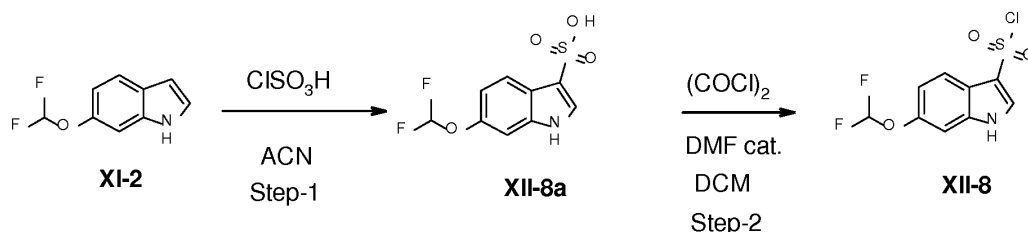
15 This compound was used as such for the next reaction without further purification.

Yield: 55%

Basic LCMS Method 2 (ES^-): 230 ($\text{M}-\text{H}^-$) (corresponding sulfonic acid), 98 % purity.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.16 (d, $J=7.98$ Hz, 1H) 7.50 (d, $J=2.99$ Hz, 1H) 8.08 (d, $J=8.48$ Hz, 1H) 11.88 (brs, 1H)

20 C.8. Synthesis of 6-(difluoromethoxy)-1H-indole-3-sulfonyl chloride **XII-8**:



Step-1: Synthesis of 6-(difluoromethoxy)-1H-indole-3-sulfonic acid **XII-8a**:

To a solution of 6-(difluoromethoxy)-1H-indole **XI-2** (0.30 g, 1.30 mmol) in CH₃CN (15 mL) was added ClSO₃H (0.13 mL, 1.95 mmol) slowly at 0 °C and the reaction mixture was stirred at room temperature for 2h. Progress of the reaction was monitored by TLC and LCMS. After completion, the reaction mixture was poured in to iced cold H₂O (50 mL) and extracted with EtOAc (100 mL). The organic layer was separated, washed with brine (20 mL) and concentrated under vacuum to afford 6-(difluoromethoxy)-1H-indole-3-sulfonic acid **XII-8a** (0.33 g crude) as a brown semi solid.

Basic LCMS Method 2 (ES⁻): 262 (M-H)⁻, 75% purity.

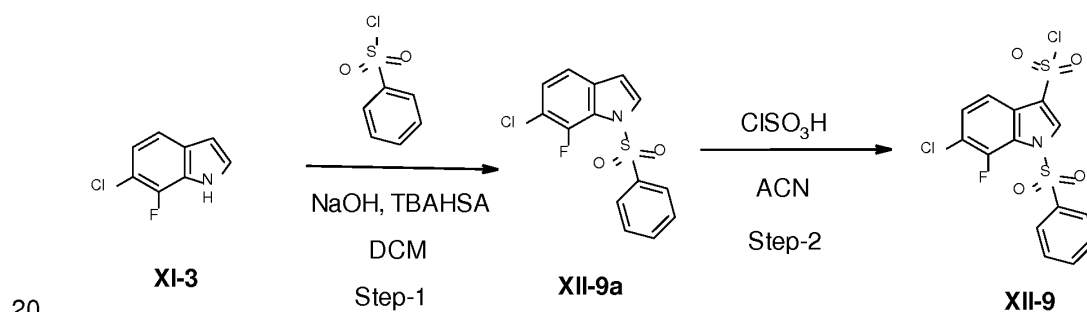
Step-2: Synthesis of 6-(difluoromethoxy)-1H-indole-3-sulfonyl chloride **XII-8**:

To a solution of 6-(difluoromethoxy)-1H-indole-3-sulfonic acid **XII-8a** (0.15 g, 0.43 mmol) in DCM (5 mL) was added oxalyl chloride (0.15 mL, 1.70 mmol) at 0 °C followed by addition of DMF (0.007 mL, 0.09 mmol) and the reaction mixture was stirred at room temperature for 3h. Progress of the reaction was monitored by TLC and LCMS. After completion, the reaction mixture was concentrated under vacuum to afford 6-(difluoromethoxy)-1H-indole-3-sulfonyl chloride **XII-8** (0.13 g crude) as a brown semi solid.

This compound was used as such for the next reaction without further purification.

Basic LCMS Method 2 (ES⁻): 262 (M-H)⁻ (corresponding sulfonic acid), 80% purity.

C.9. Synthesis of 1-(benzenesulfonyl)-6-chloro-7-fluoro-indole-3-sulfonyl chloride **XII-9**



Step-1: Synthesis of 1-(benzenesulfonyl)-6-chloro-7-fluoro-indole **XII-9a**

To a stirred suspension of finely powdered sodium hydroxide (3.54 g, 0.088 mol) in dichloromethane (60 mL) previously cooled on top of an ice bath was added 6-chloro-7-fluoro-1H-indole **XI-3** (5 g, 0.029 mol) as a single portion followed by tetrabutylammonium hydrogen sulfate (0.501 g, 0.001 mol). Stirring was continued for a further 10 minutes then a solution of benzenesulfonyl chloride (4.2 mL, 0.033 mol) in dichloromethane (15 mL)

25

was added dropwise over 20 minutes and the reaction mixture was stirred at 0 °C for 1 hour. The ice bath was removed and the mixture was stirred for a further 1 hour at ambient temperature. The reaction mixture was filtered over a pad of Kieselguhr, rinsing the filter cake with dichloromethane (2 x 50 mL). The filtrate was washed with water (4 x 50 mL), and brine (50 mL), dried over anhydrous sodium sulfate, filtered and the solvent concentrated under vacuum to afford 1-(benzenesulfonyl)-6-chloro-7-fluoro-indole **XII-9a** (8.57 g) as a dark beige solid.

Yield: 90%.

¹H NMR (400 MHz, DMSO-*d*₆) δ 6.95 (dd, J = 3.7, 2.3 Hz, 1H), 7.37 (dd, J = 8.4, 6.2 Hz, 1H), 7.48 (d, J = 8.6 Hz, 1H), 7.66 (tt, J = 6.9, 1.9 Hz, 2H), 7.80 – 7.71 (m, 1H), 7.98 – 7.91 (m, 2H), 7.99 (d, J = 3.7 Hz, 1H).

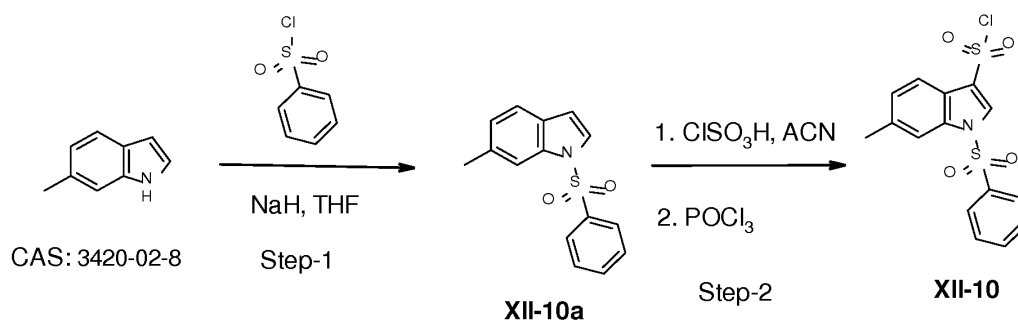
Step-2: Synthesis of 1-(benzenesulfonyl)-6-chloro-7-fluoro-indole-3-sulfonyl chloride **XII-9**

To a stirred solution of 1-(benzenesulfonyl)-6-chloro-7-fluoro-indole **XII-9a** (8.50 g, 0.027 mol) in acetonitrile (85 mL) previously cooled on top of an ice batch, was added chlorosulfonic acid (9.12 mL, 0.137 mol) dropwise over 20 min and the reaction mixture was stirred for 16 hours at ambient temperature. The reaction mixture was slowly poured with stirring into ice-water (340 mL) over 20 minutes. The precipitated solid was collected by filtration, rinsing the filter cake with icy water (3 x 50 mL) and cyclohexane (50 mL). The filter cake was then dried under a flow of nitrogen for 2 hours and then in a vacuum oven at 40 °C for 16 hours to afford 1-(benzenesulfonyl)-6-chloro-7-fluoro-indole-3-sulfonyl chloride **XII-9** (7.82 g) as a light pink solid.

Yield: 66%.

Acidic LCMS Method 4 (ES⁺): 388 (M+H)⁺, 95% purity.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.44 (dd, J = 8.5, 6.3 Hz, 1H), 7.72 – 7.61 (m, 3H), 7.80 – 7.72 (m, 1H), 7.81 (s, 1H), 8.05 – 7.98 (m, 2H).

C.10. Synthesis of 1-(benzenesulfonyl)-6-methyl-indole-3-sulfonyl chloride XII-10**Step-1: Synthesis of 1-(benzenesulfonyl)-6-methyl-indole XII-10a**

To a solution of 6-methyl-1H-indole (1g, 7.39 mmol) in THF (20 mL), sodium hydride (60 % in paraffin, 0.35 g, 8.9 mmol) was added at 0 °C. The solution was stirred for 30 min being allowed to warm up from 0 °C to rt. Subsequently, benzenesulfonic acid chloride (1.1 mL, 8.9 mmol) was added dropwise. The reaction mixture was stirred at room temperature overnight and hydrolyzed with water. It was then extracted with EtOAc. The organic layer was separated, washed with brine, dried over MgSO₄ and concentrated under vacuum. The residue was purified by column chromatography (eluent: 25-40% AcOEt in heptane) yielding 1.97 g of 1-(benzenesulfonyl)-6-methyl-indole **XII-10a** as a colourless oil.

Yield: 70%

Basic LCMS Method 1 (ES⁻): 270 (M-H)⁻, 71% purity.

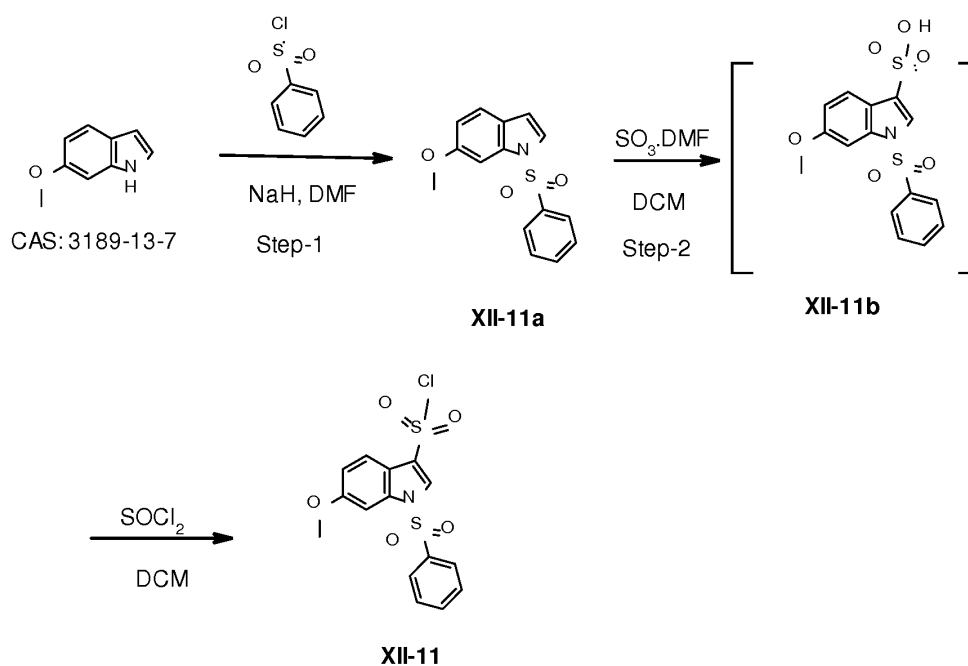
Step-2: Synthesis of 1-(benzenesulfonyl)-6-methyl-indole-3-sulfonyl chloride XII-10

The obtained 1-(benzenesulfonyl)-6-methyl-indole **XII-10a** (0.9 g, 3.15 mmol) was diluted in acetonitrile (9 mL) and treated with chlorosulfonic acid (0.32 mL, 4.72 mmol) dropwise. After 2 h, phosphorous oxychloride (0.65 mL, 6.93 mmol) was added and the reaction mixture was heated at 70 °C overnight. After cooling to room temperature and dilution with chloroform, the organic layer was separated and washed with water then brine. The combined organic extracts were dried over MgSO₄, filtered and concentrated under vacuum to afford 1.4 g of 1-(benzenesulfonyl)-6-methyl-indole-3-sulfonyl chloride **XII-10** as a brownish solid.

This compound was used as such for the next reaction without further purification.

Basic LCMS Method 1 (ES⁻): 419 (M-H)⁻, after quenching aliquot with morpholine prior to the analysis

C.11. Synthesis of 1-(benzenesulfonyl)-6-methoxy-indole-3-sulfonyl chloride XII-11



5

Step-1: Synthesis of 1-(benzenesulfonyl)-6-methoxy-indole **XII-11a**

To a solution of 6-methoxyindole (2.5 g, 17 mmol) in DMF (50 mL), sodium hydride (60 % in paraffin, 1.7 g, 71 mmol) was added at 0 °C. The suspension was stirred for 30 min then warmed up to room temperature. Subsequently, the solution was treated with benzenesulfonyl chloride (2.8 mL, 3.70 g, 22 mmol) dropwise under stirring. After stirring at room temperature for 2.5 h, ice water was added to the reaction mixture under vigorous stirring. The resulting precipitate was filtered off under reduced pressure, washed thoroughly with water (100 mL) and subsequently with petroleum ether (10 mL). After drying at 60 °C, 1-(benzenesulfonyl)-6-methoxy-indole **XII-11a** was obtained as a colorless solid (3.2 g).

Yield: 65%

¹H NMR (600 MHz, CDCl₃) δ: 7.87-7.81 (m, 2H), 7.53-7.48 (m, 2H), 7.45-7.39 (m, 3H), 7.36 (d, J = 8.5 Hz, 1H), 6.84 (dd, J = 8.6/2.3 Hz, 1H), 6.56 (dd, J = 3.7/0.9 Hz, 1H), 3.85 (s, 3H).

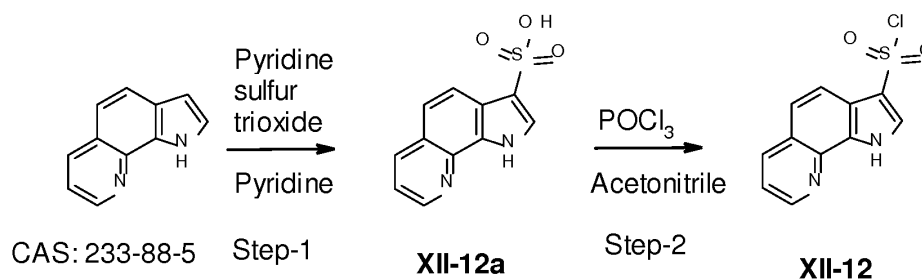
Step-2: Synthesis of 1-(benzenesulfonyl)-6-methoxy-indole-3-sulfonyl chloride **XII-11**

A solution of 1-(benzenesulfonyl)-6-methoxyindole **XII-11a** (500 mg, 1.74 mmol) in dichloromethane (15 mL) was treated with SO₃-DMF complex (1.2 g, 7.8 mmol) and stirred at room temperature for 2 h (TLC control). The expected intermediate
 5 indolesulfonic acid was not isolated. Subsequently, thionyl chloride (1 mL, 14 mmol) was added and the mixture was stirred for 16 h at room temperature. The mixture was hydrolyzed with a saturated solution of NaHCO₃ (50 mL) and extracted with dichloromethane (3 times, 50 mL each). The combined organic extracts were dried over MgSO₄, filtered and concentrated by vacuum evaporation. The residue was purified by
 10 column chromatography (silica gel 60, eluent, dichloromethane/petroleum ether = 1:1) leading to 1-(benzenesulfonyl)-6-methoxy-indole-3-sulfonyl chloride **XII-11** as a colorless solid (504 mg).

Yield: 75%

¹H NMR (600 MHz, CDCl₃) δ: 8.23 (s, 1H), 8.00 – 7.93 (m, 2H), 7.80 (d, J = 8.8 Hz, 1H),
 15 7.70 – 7.63 (m, 1H), 7.59 – 7.53 (m, 2H), 7.47 (d, J = 2.2 Hz, 1H), 7.06 (dd, J = 8.8, 2.2 Hz, 1H), 3.89 (s, 3H).

C.12. Synthesis of 1H-pyrrolo[3,2-h]quinoline-3-sulfonyl chloride XII-12



Step-1: Synthesis of 1H-pyrrolo[3,2-h]quinoline-3-sulfonic acid **XII-12a**

20 To a solution of 1H-pyrrolo[3,2-H]quinoline (400 mg, 2.3 mmol) in pyridine (6 mL) at 0°C, was added pyridine-sulfur trioxide complex (1.2 g, 3.5 mmol). The reaction mixture was then heated at 120°C under stirring for 2h, cooled to room temperature and evaporated to dryness. The beige solid was dissolved in water and the aqueous phase washed with chloroform (3x). A precipitate formed on standing in the aqueous fraction and was filtered,
 25 rinsed with water and dried under vacuum at 35°C to afford 470 mg of 1H-pyrrolo[3,2-H]quinoline-3-sulfonic acid **XII-12a** as a beige solid.

Yield: 79%.

Basic LCMS Method 1 (ES^+): 249 ($\text{M}+\text{H}$) $^+$, 100 % purity.

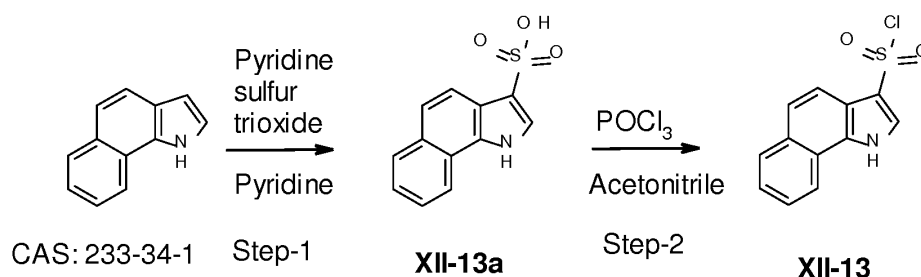
Step 2: Synthesis of 1H-pyrrolo[3,2-h]quinoline-3-sulfonyl chloride **XII-12**

To a solution of 1H-pyrrolo[3,2-h]quinoline-3-sulfonic acid **XII-12a** (855 mg, 3.44 mmol) in acetonitrile (8.5 mL), under Argon, cooled to 0°C, was added dropwise phosphorus
5 oxychloride (1.06 g, 6.88 mmol). The reaction mixture was then heated to 70°C under stirring overnight. After cooling to room temperature, ice water was carefully added under vigorous stirring. A solid precipitated and was filtered, rinsed with water and dried under vacuum at 35°C, affording 284 mg of 1H-pyrrolo[3,2-h]quinoline-3-sulfonyl chloride **XII-12** as a beige solid.

10 Yield: 27%.

Basic LCMS Method 1 (ES^+): 275 ($\text{M}+\text{H}$) $^+$, after quenching aliquot with ethylamine prior to the analysis

C.13. Synthesis of 1H-benzo[g]indole-3-sulfonyl chloride XII-13



15 Step-1: Synthesis of 1H-benzo[g]indole-3-sulfonic acid **XII-13a**

To a solution of 1H-benzo[g]indole (1 g, 5.8 mmol) in pyridine (16 mL) at 0°C, was added pyridine-sulfur trioxide complex (1.38 g, 8.7 mmol). The reaction mixture was then heated at 125°C under stirring for 5h, cooled to room temperature and evaporated to dryness.
20 The brown oil was diluted in water. Upon standing, a precipitate was formed and filtered, rinsed with water and dried under vacuum at 35°C to afford 1.4 g of 1H-benzo[g]indole-3-sulfonic acid **XII-13a** as a beige solid.

Yield: 98%.

Basic LCMS Method 1 (ES^-): 246 ($\text{M}-\text{H}$) $^-$

Step 2: Synthesis of 1H-benzo[g]indole-3-sulfonyl chloride **XII-13**

To a solution of 1H-benzo[g]indole-3-sulfonic acid **XII-13a** (100 mg, 0.4 mmol) in acetonitrile (1 mL), under Argon, cooled to 0°C, was added dropwise phosphorus oxychloride (76 μ L, 0.8 mmol). The reaction mixture was then heated to 70°C for 1h. After cooling to room temperature, ice water was carefully added under vigorous stirring. A solid
 5 precipitated and was filtered, rinsed with water and dried under vacuum at 35°C, affording 65 mg of 1H-benzo[g]indole-3-sulfonyl chloride **XII-13** as a brown solid.

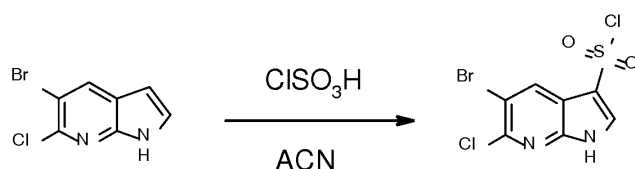
Yield: 60%.

Basic LCMS Method 1 (ES^-): 246 (M-H^-) (corresponding sulfonic acid)

C.14. Synthesis of 5-bromo-6-chloro-1H-pyrrolo[2,3-b]pyridine-3-sulfonyl chloride

10

XII-14:



CAS: 1190321-59-5

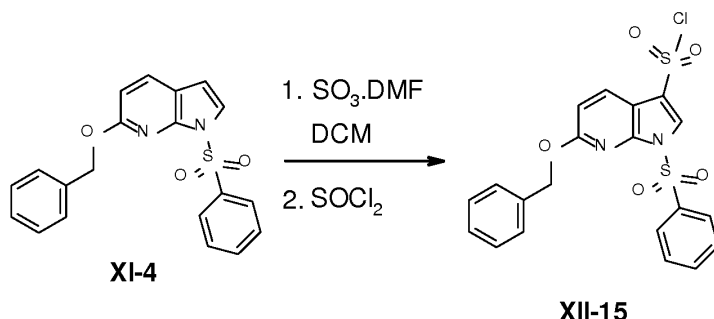
XII-14

To a solution of 5-bromo-6-chloro-1H-pyrrolo[2,3-b]pyridine (0.50 g, 2.16 mmol) in CH_3CN (10 mL) was added ClSO_3H (5 mL) at 0°C and the reaction mixture was heated at 80°C for 12h. Progress of the reaction was monitored by TLC and LCMS. After completion, the
 15 reaction mixture was poured in to ice- H_2O (150 mL), the precipitate was filtered and dried in vacuum to afford 5-bromo-6-chloro-1H-pyrrolo[2,3-b]pyridine-3-sulfonyl chloride (0.605 g crude) as a brown solid.

This compound was used as such for the next reaction without further purification.

Basic LCMS Method 2 (ES^-): 309 (M-H^-) (corresponding sulfonic acid), 97 % purity.

C.15. Synthesis of 1-(benzenesulfonyl)-6-benzyloxy-pyrrolo[2,3-b]pyridine-3-sulfonyl chloride XII-15:



A solution of 1-(benzenesulfonyl)-6-benzyloxy-pyrrolo[2,3-b]pyridine **XI-4** (570 mg, 2 mmol) in dichloromethane was treated with sulfur trioxide/DMF complex (1224 mg, 8 mmol). The mixture was stirred at room temperature for 0.5 h (TLC control showed no further starting material but a complete conversion to the expected sulfonic acid, eluent: pure dichloromethane). Subsequently thionyl chloride (1.4 mL, 20 mmol) were added and the formed suspension was stirred at room temperature for 22 h. The resulting clear solution was controlled by TLC (one spot for the expected product was observed, eluent: petroleum ether : ethyl acetate 80 : 20). The mixture was hydrolyzed with a saturated aqueous solution of NaHCO₃ (75 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were dried over MgSO₄, filtered and concentrated under reduced pressure to give 920 mg of 1-(benzenesulfonyl)-6-benzyloxy-pyrrolo[2,3-b]pyridine-3-sulfonyl chloride **XII-15**.

This compound was used as such for the next reaction without further purification.

Yield: 64%

¹H NMR (600 MHz, DMSO-*d*₆) δ 5.42 (s, 2H), 6.82 (d, J = 8.5 Hz, 1H), 7.42 – 7.31 (m, 3H), 7.49 (d, J = 9.1 Hz, 3H), 7.55 (t, J = 7.9 Hz, 2H), 7.70 (t, J = 7.5 Hz, 1H), 8.01 – 7.96 (m, 1H), 8.07 (dd, J = 8.5, 1.1 Hz, 2H).

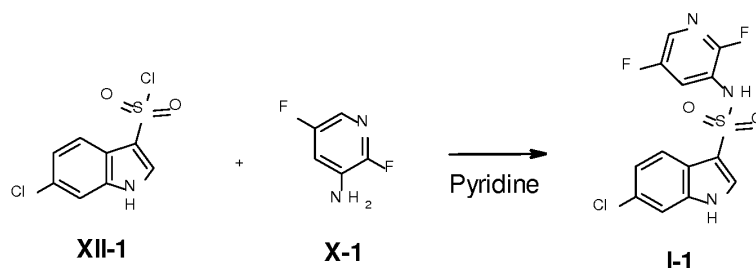
EXAMPLE COMPOUNDS

D. Synthesis of compounds of general Formula I

All compounds of the present invention specifically disclosed herein are designated "I-x" wherein any "x" refers to a number identifying the individual compounds. Accordingly, the

Example compounds are designated I-1, I-2, I-3 etc. This is irrespective of whether any compound could also be described by any subgeneric Formula herein, e.g. by Formula II, III or IV, and the like.

D.1. Method A. Synthesis of 6-chloro-N-(2,5-difluoropyridin-3-yl)-1H-indole-3-sulfonamide I-1



To a solution of **XII-1** (0.50 g, 1.97 mmol) in pyridine (10 mL) was added **X-1** (0.18 g, 1.25 mmol) and DMAP (0.012 g, 0.09 mmol). The reaction mixture was heated at 80 °C for 16h. Progress of the reaction was monitored by TLC and LCMS. After completion, the reaction mixture was concentrated under vacuum. The residue was diluted with H₂O (100 mL), 1 N HCl (50 mL) and extracted with EtOAc (100 mL). The organic layer was separated, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude obtained was purified by column chromatography (silica, 100-200 mesh, 40% EtOAc in hexane) to afford 6-chloro-N-(2,5-difluoropyridin-3-yl)-1H-indole-3-sulfonamide **I-1** (0.05 g) as an off-white solid.

Yield: 7%.

Basic LCMS Method 1 (ES⁻): 342 (M-H)⁻, 97% purity.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.25 (dd, J=8.31, 1.47 Hz, 1H), 7.54 (s, 1H), 7.71-7.81 (m, 2H), 7.89 (s, 1H), 8.16 (d, J=2.93 Hz, 1H), 10.73 (brs, 1H), 12.22 (brs, 1H).

The following compounds in Table 4 may be synthesized according to a method analogous to Method A.

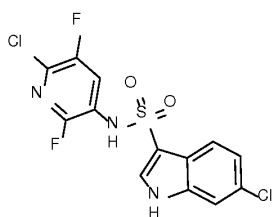
Table 4:

N°	Sulfonyl chlorides XII	Amines X	Conditions, Time	Purification conditions	Yield (%)
I-2	XII-1	X-2	80 °C, 16h	30% EtOAc/Hexane	24
I-3	XII-1	X-3	90 °C, 16h	Basic prep LCMS Method 1	34
I-4	XII-1	X-4	90 °C, 16h	30% EtOAc/Hexane	38
I-5	XII-1	X-5	90 °C, 16h	30% EtOAc/Hexane	15
I-6	XII-1	X-6	90 °C, 16h	Basic prep LCMS Method 1	18
I-7	XII-1	X-7	90 °C, 16h	40-55% EtOAc/Hexane	10
I-8	XII-1	34392-85-3	80 °C, 16h	1/2 EtOAc/Petroleum Ether	8
I-9	XII-1	X-8	80 °C, 16h	40-55% EtOAc/Hexane	15
I-10	XII-1	X-9	DMAP cat., 80 °C, 16h	40% EtOAc/Hexane	12
I-11	XII-1	X-10	DMAP cat., 90 °C, 24h	Basic prep LCMS Method 1	4
I-12	XII-1	X-11	DMAP cat., 100 °C, 30h	40% EtOAc/Hexane	13
I-13	XII-1	X-12	80 °C, 16h	40%-55% EtOAc/Hexane	35
I-14	XII-1	X-15	DMAP cat., 90 °C, 16h	20% EtOAc/Hexane	24
I-33	XII-4	X-5	rt, overnight	DCM/MeOH 98/2	38
I-34	XII-4	X-6	rt, overnight	DCM/MeOH 98/2	56

N°	Sulfonyl chlorides XII	Amines X	Conditions, Time	Purification conditions	Yield (%)
I-35	XII-4	914222-86-9	rt, overnight	Basic prep LCMS Method 1	25
I-36	XII-4	X-11	rt, 1h	EtOAc/Heptane 50/50 to 80/20	57
I-37	XII-4	X-14	rt, 2h	DCM/isopropanol 98/2	86
I-38 I-39	XII-1	X-16 X-17	DMAP cat., 100 °C, 16h	30% EtOAc/Hexane	10 11
I-40	XII-1	X-18	DMAP cat., 90 °C, 20h	25% EtOAc/Hexane	23
I-41	XII-1	X-19	DMAP cat., 100 °C, 18h	30% EtOAc/Hexane	25
I-42	XII-1	X-20	DMAP cat., 80 °C, 16h	70% EtOAc/Hexane	46
I-43	XII-1	X-21	DMAP cat., 100 °C, 18h	30% EtOAc/Hexane	37
I-44	XII-7	X-13	rt, 16h	Basic prep LCMS Method 1	26
I-45	XII-7	X-16	rt, 2h	Basic prep LCMS Method 1	49
I-46	XII-7	X-20	rt, 16h	Basic prep LCMS Method 1	47
I-47	XII-7	X-19	rt, 16h	Basic prep LCMS Method 1	14
I-48	XII-7	X-21	rt, 16h	Basic prep LCMS Method 1	27

N°	Sulfonyl chlorides XII	Amines X	Conditions, Time	Purification conditions	Yield (%)
I-49	XII-7	X-22	rt, 16h	Basic prep LCMS Method 1	2
I-50	XII-1	X-23	DMAP cat., 90 °C, 16h	20% EtOAc/Hexane	27
I-51	XII-8	X-20	DMAP cat., 90 °C, 16h	30% EtOAc/Hexane	24
I-68	XII-12	X-8	DMAP cat., 70°C, 16h	EtOAc/Heptane 90/10	35
I-69	XII-12	X-20	DMAP cat., 70°C, 16h	EtOAc/Heptane 40/60 to 100/0	12
I-70	XII-13	28020-37-3	80°C, 5h	60/40 EtOAc/Petroleum Ether	30
I-71	XII-14	X-20	DMAP cat., 90°C, 2h	20-30% EtOAc/Hexane	19

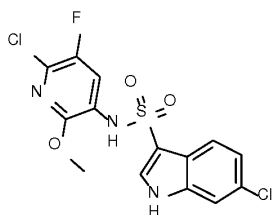
6-chloro-N-(6-chloro-2,5-difluoropyridin-3-yl)-1H-indole-3-sulfonamide **I-2**



Basic LCMS Method 2 (ES⁺): 378 (M+H)⁺, 98% purity.

- 5 ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.25 (d, J=8.31 Hz, 1H), 7.54 (s, 1H), 7.75-7.84 (m, 1H), 7.94 (t, J=7.58 Hz, 1H), 8.16 (brs, 1H), 10.86 (brs, 1H), 12.22 (brs, 1H).

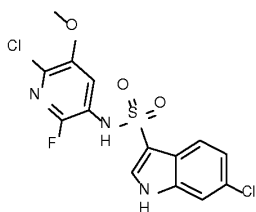
6-chloro-N-(6-chloro-5-fluoro-2-methoxypyridin-3-yl)-1H-indole-3-sulfonamide **I-3**



Basic LCMS Method 2 (ES⁻): 388 (M-H)⁻, 99% purity.

¹H NMR (400 MHz, DMSO-*d*₆) δ 3.53 (s, 3H), 7.23 (dd, J= 8.56, 1.71 Hz, 1H), 7.52 (d, J= 1.96 Hz, 1H), 7.71 (d, J= 9.29 Hz, 1H), 7.82 (d, J= 8.80 Hz, 1H), 8.08 (d, J= 2.93 Hz, 1H),
5 10.14 (brs, 1H), 12.12 (brs, 1H).

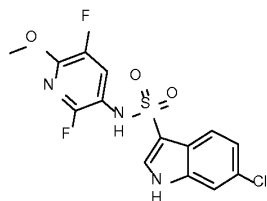
6-chloro-N-(6-chloro-2-fluoro-5-methoxypyridin-3-yl)-1H-indole-3-sulfonamide **I-4**



Basic LCMS Method 2 (ES⁻): 388 (M-H)⁻, 94% purity.

¹H NMR (400 MHz, DMSO-*d*₆) δ 3.82 (s, 3H), 7.22-7.28 (m, 1H), 7.51-7.59 (m, 2H), 7.76
10 (d, J=8.80 Hz, 1H), 8.06 (d, J=2.93 Hz, 1H), 10.51 (s, 1H), 12.17 (brs, 1H).

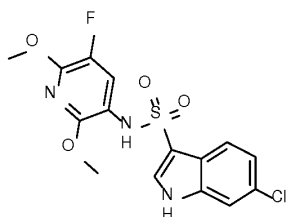
6-chloro-N-(2,5-difluoro-6-methoxypyridin-3-yl)-1H-indole-3-sulfonamide **I-5**



Basic LCMS Method 2 (ES⁻): 372 (M-H)⁻, 99% purity.

¹H NMR (400 MHz, DMSO-*d*₆) δ 3.79 (s, 3H), 7.19 (d, J=8.80 Hz, 1H), 7.55-7.60 (m, 2H),
15 7.61-7.65 (m, 1H), 7.84 (s, 1H), 10.02 (s, 1H), 12.09 (brs, 1H).

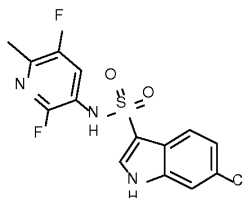
6-chloro-N-(5-fluoro-2,6-dimethoxypyridin-3-yl)-1H-indole-3-sulfonamide **I-6**



Basic LCMS Method 2 (ES⁻): 384 (M-H)⁻, 99% purity.

¹H NMR (400 MHz, DMSO-*d*₆) δ 3.24 (s, 3H), 3.82 (s, 3H), 7.19 (dd, *J*=8.56, 1.71 Hz, 1H),
 7.47 (d, *J*=10.27 Hz, 1H), 7.51 (d, *J*=1.47 Hz, 1H), 7.68 (d, *J*=8.31 Hz, 1H), 7.78 (s, 1 H),
 5 9.44 (s, 1H), 11.95 (brs, 1H).

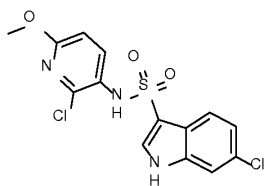
6-chloro-N-(2,5-difluoro-6-methylpyridin-3-yl)-1H-indole-3-sulfonamide **I-7**



Basic LCMS Method 2 (ES⁻): 356 (M-H)⁻, 99% purity.

¹H NMR (400 MHz, DMSO-*d*₆) δ 2.24 (d, *J*=2.8 Hz, 3H), 7.24 (dd, *J*= 8.8 Hz, 1.6 Hz, 1H),
 10 7.53 (d, *J*=2.4 Hz, 1H), 7.64 (t, *J*=8.8Hz, 1H), 7.77 (d, *J*=8.8 Hz, 1H), 8.05 (d, *J*=2.4 Hz,
 1H), 10.50 (s, 1H), 12.15 (brs, 1H).

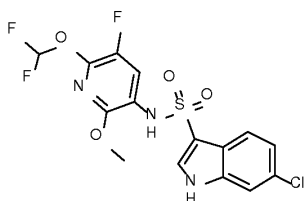
6-chloro-N-(2-chloro-6-methoxypyridin-3-yl)-1H-indole-3-sulfonamide **I-8**



Neutral LCMS Method 3 (ES⁺): 372 (M+H)⁺, 95% purity.

15 ¹H NMR (500 MHz, DMSO-*d*₆) δ 3.75 (s, 3H), 6.77 (d, *J*=8.51 Hz, 1H), 7.18 (dd,
J=1.89, 8.51 Hz, 1H), 7.48-7.56 (m, 2H), 7.65 (d, *J*=8.51 Hz, 1H), 7.77 (d, *J*=1.89
 Hz, 1H), 10.90 (s, 1H), 12.10 (brs, 1H).

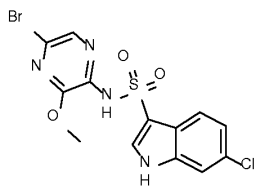
6-chloro-N-[6-(difluoromethoxy)-5-fluoro-2-methoxypyridin-3-yl]-1H-indole-3-sulfonamide **I-9**



Basic LCMS Method 2 (ES^-): 420 (M-H) $^-$, 96% purity.

- 5 ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 3.39 (s, 3H), 7.22 (dd, $J=1.2, 8.4$ Hz, 1H), 7.52 (d, $J=1.6$ Hz, 1H), 7.58 (t, $J=72.8$ Hz, 1H), 7.70-7.77 (m, 2H), 7.94 (d, $J=2.4$ Hz, 1H), 9.85 (brs, 1H), 12.06 (brs, 1H).

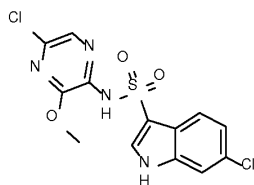
N-(5-bromo-3-methoxypyrazin-2-yl)-6-chloro-1H-indole-3-sulfonamide **I-10**



- 10 Basic LCMS Method 2 (ES^+): 417 (M+H) $^+$, 98% purity.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 3.84 (s, 3H), 7.21 (dd, $J=8.37, 1.97$ Hz, 1H), 7.54 (d, $J=1.48$ Hz, 1H), 7.82 (s, 1H), 7.89 (d, $J=8.37$ Hz, 1H), 8.09 (s, 1H), 10.93 (brs, 1H), 12.14 (brs, 1H).

6-chloro-N-(5-chloro-3-methoxypyrazin-2-yl)-1H-indole-3-sulfonamide **I-11**

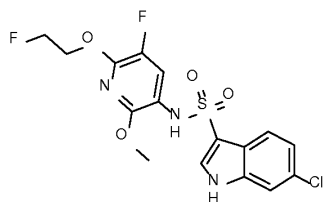


15

Basic LCMS Method 2 (ES^+): 373 (M+H) $^+$, 99% purity.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 3.89 (s, 3H), 7.24 (dd, $J=8.56, 1.71$ Hz, 1H), 7.53 (d, $J=1.47$ Hz, 1H), 7.82 (s, 1H), 7.95 (d, $J=8.31$ Hz, 1H), 8.14 (d, $J=2.94$ Hz, 1H), 10.97 (s, 1H), 12.15 (brs, 1H).

5 **12** 6-chloro-N-[5-fluoro-6-(2-fluoroethoxy)-2-methoxypyridin-3-yl]-1H-indole-3-sulfonamide **I-12**

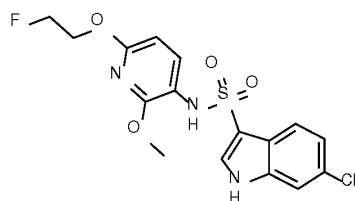


Basic LCMS Method 2 (ES^-): 416 ($\text{M}-\text{H}$) $^-$, 99% purity.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 3.24 (s, 3H), 4.42-4.46 (m, 1H), 4.50-4.55 (m, 1H), 4.62-4.66 (m, 1H), 4.75-4.78 (m, 1H), 7.20 (dd, $J=8.80, 1.96$ Hz, 1H), 7.49-7.54 (m, 2H), 7.68 (d, $J=8.31$ Hz, 1H), 7.81 (d, $J=2.45$ Hz, 1H), 9.48 (s, 1H), 11.97 (brs, 1H).

10

6-chloro-N-[6-(2-fluoroethoxy)-2-methoxypyridin-3-yl]-1H-indole-3-sulfonamide **I-13**

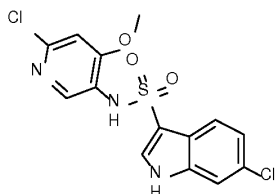


Basic LCMS Method 2 (ES^+): 400 ($\text{M}+\text{H}$) $^+$, 97% purity.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 3.24 (s, 3H), 4.31-4.36 (m, 1H), 4.40-4.43 (m, 1H), 4.60-4.63 (m, 1H), 4.71-4.76 (m, 1H), 6.34 (d, $J=8.31$ Hz, 1H), 7.17 (dd, $J=8.56, 1.71$ Hz, 1H), 7.44 (d, $J=8.31$ Hz, 1H), 7.51 (s, 1H), 7.65 (d, $J=8.31$ Hz, 1H), 7.72 (s, 1H), 9.21 (s, 1H), 11.92 (brs, 1H).

15

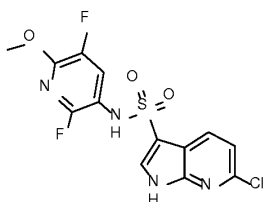
6-chloro-N-(6-chloro-4-methoxypyridin-3-yl)-1H-indole-3-sulfonamide **I-14**



Basic LCMS Method 2 (ES⁺): 372 (M+H)⁺, 98% purity.

- ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.01 (s, 1 H), 7.21 (d, J=8.31 Hz, 1 H), 7.52 (s, 1 H), 7.72 (d, J=8.31 Hz, 1 H), 7.86 (s, 1 H), 8.04 (s, 1 H), 9.68 (br s, 1 H), 12.04 (br s, 1 H) (3H's merged in solvent peak).

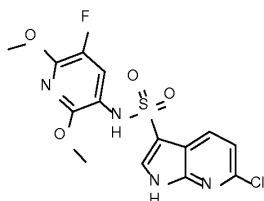
6-chloro-N-(2,5-difluoro-6-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide **I-33**



Basic LCMS Method 1 (ES⁻): 373 (M-H)⁻, 99% purity.

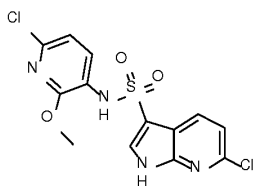
- ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.84 (s, 3H), 7.37 (d, J = 8.3 Hz, 1H), 7.70 (dd, J = 9.9, 7.4 Hz, 1H), 8.05 (d, J = 2.7 Hz, 1H), 8.10 (d, J = 8.3 Hz, 1H), 10.12 (s, 1H), 12.83 (s, 1H).

6-chloro-N-(5-fluoro-2,6-dimethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide **I-34**



- ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.24 (s, 3H), 3.85 (s, 3H), 7.36 (d, J = 8.3 Hz, 1H), 7.53 (d, J = 10.4 Hz, 1H), 7.95 (s, 1H), 8.11 (d, J = 8.4 Hz, 1H), 9.59 (s, 1H), 12.69 (s, 1H).

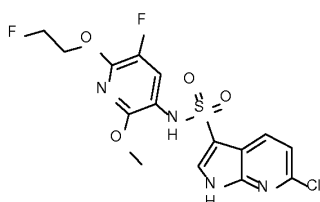
6-chloro-N-(6-chloro-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide **I-35**



Basic LCMS Method 1 (ES⁻): 371 (M-H)⁻, 99% purity.

¹H NMR (400 MHz, DMSO-*d*₆) δ 3.44 (s, 3H), 7.03 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 8.3 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 8.05 (s, 1H), 8.19 (d, J = 8.3 Hz, 1H), 9.88 (s, 1H), 12.78 (s, 1H).

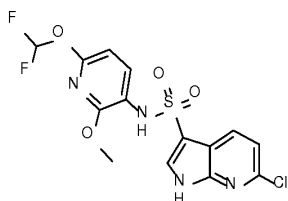
6-chloro-N-[5-fluoro-6-(2-fluoroethoxy)-2-methoxypyridin-3-yl]-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide **I-36**



Basic LCMS Method 1 (ES⁻): 417 (M-H)⁻, 99% purity.

¹H NMR (400 MHz, DMSO-*d*₆) δ 3.24 (d, J = 1.4 Hz, 3H), 4.45 (t, J = 4.4 Hz, 1H), 4.53 (t, J = 4.1 Hz, 1H), 4.68 – 4.62 (m, 1H), 4.80 – 4.74 (m, 1H), 7.35 (dd, J = 8.3, 1.4 Hz, 1H), 7.56 (dd, J = 10.4, 1.4 Hz, 1H), 7.96 (d, J = 1.4 Hz, 1H), 8.10 (dd, J = 8.4, 1.4 Hz, 1H), 9.8 (s, 1H), 12.6 (s, 1H).

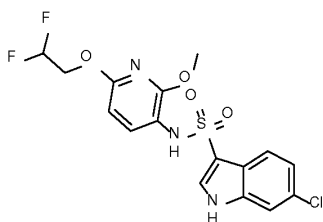
6-chloro-N-[6-(difluoromethoxy)-2-methoxy-3-pyridyl]-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide **I-37**



Basic LCMS Method 1 (ES⁻): 403 (M-H)⁻, 98% purity.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 3.34 (s, 3H), 6.58 (d, $J = 8.2$ Hz, 1H), 7.36 (d, $J = 8.3$ Hz, 1H), 7.58 (t, 1H), 7.65 (d, $J = 8.2$ Hz, 1H), 7.96 (s, 1H), 8.13 (d, $J = 8.3$ Hz, 1H), 9.68 (s, 1H), 12.72 (s, 1H).

6-chloro-N-[6-(2,2-difluoroethoxy)-2-methoxypyridin-3-yl]-1H-indole-3-sulfonamide **I-38**

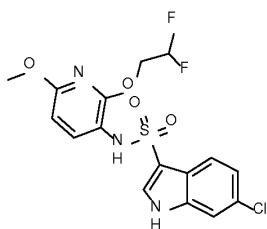


5

Basic LCMS Method 2 (ES^+): 418 ($\text{M}+\text{H}$) $^+$, 94% purity.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 3.28 (s, 3H) 4.43 (td, $J=14.92$, 3.91 Hz, 2H) 6.17-6.46 (m, 1H) 6.39 (d, $J=8.31$ Hz, 1H) 7.18 (dd, $J=8.56$, 1.71 Hz, 1H) 7.46 (d, $J=8.31$ Hz, 1H) 7.51 (d, $J=1.96$ Hz, 1H) 7.66 (d, $J=8.80$ Hz, 1H) 7.74 (s, 1H) 9.28 (brs, 1H) 11.93 (brs, 1H).

10 6-chloro-N-[2-(2,2-difluoroethoxy)-6-methoxypyridin-3-yl]-1H-indole-3-sulfonamide **I-39**

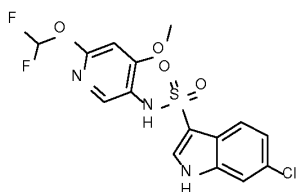


Basic LCMS Method 2 (ES^+): 418 ($\text{M}+\text{H}$) $^+$, 96% purity.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 3.74 (s, 3H) 4.05 (td, $J=14.31$, 4.16 Hz, 2H) 5.61-5.95 (m, 1H) 6.39 (d, $J=8.31\text{Hz}$, 1H) 7.12-7.21 (m, 1H) 7.48 (d, $J=8.31$ Hz, 1H) 7.52 (s, 1H) 7.65 (d, $J=8.80$ Hz, 1H) 7.77 (s, 1H) 9.36 (brs, 1H) 11.95 (brs, 1H).

15

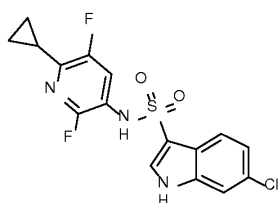
6-chloro-N-[6-(difluoromethoxy)-4-methoxypyridin-3-yl]-1H-indole-3-sulfonamide **I-40**



Basic LCMS Method 2 (ES⁺): 404 (M+H)⁺, 99% purity.

¹H NMR (400 MHz, DMSO-*d*₆) δ 3.28 (s, 3H) 6.56 (s, 1H) 7.20 (dd, J=8.61, 1.72 Hz, 1H) 7.52 (d, J=1.48 Hz, 1H) 7.63 (t, J=74 Hz, 1H) 7.69 (d, J=8.37 Hz, 1H) 7.79 (d, J=2.46 Hz, 1H) 7.85 (s, 1H) 9.49 (s, 1H) 11.99 (brs, 1H).

5 6-chloro-N-(6-cyclopropyl-2,5-difluoropyridin-3-yl)-1H-indole-3-sulfonamide **I-41**

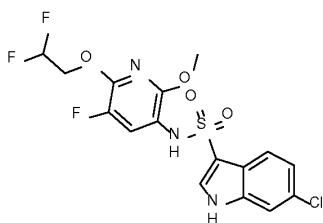


Basic LCMS Method 2 (ES⁺): 384 (M+H)⁺, 97% purity.

¹H NMR (400 MHz, DMSO-*d*₆) δ 0.77-0.79 (m, 2H) 0.93-1.00 (m, 2H) 2.11-2.14 (m, 1H) 7.22 (d, J=8.31 Hz, 1H) 7.53 (s, 1H) 7.59-7.65 (m, 1H) 7.73 (d, J=8.31 Hz, 1H) 8.04 (d, J=2.93 Hz, 1H) 10.40 (s, 1H) 12.16 (brs, 1H).

10

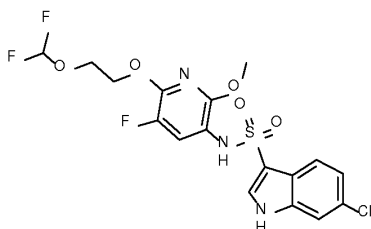
6-chloro-N-[6-(2,2-difluoroethoxy)-5-fluoro-2-methoxypyridin-3-yl]-1H-indole-3-sulfonamide **I-42**



Basic LCMS Method 2 (ES⁺): 436 (M+H)⁺, 94% purity.

15 ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.30 (s, 3H) 4.54 (td, J=14.92, 3.42 Hz, 2H) 6.20-6.51 (m, 1H) 7.20 (dd, J=8.31, 1.96 Hz, 1H) 7.52 (d, J=1.96 Hz, 1H) 7.55 (d, J=10.27 Hz, 1H) 7.70 (d, J=8.31 Hz, 1H) 7.83 (s, 1H) 9.55 (brs, 1H) 11.99 (brs, 1H).

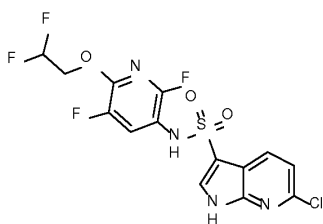
6-chloro-N-[6-[2-(difluoromethoxy)ethoxy]-5-fluoro-2-methoxypyridin-3-yl]-1H-indole-3-sulfonamide **I-43**



Basic LCMS Method 2 (ES^+): 466 ($\text{M}+\text{H}$) $^+$, 95% purity.

- ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 3.23 (s, 3H) 4.09-4.15 (m, 2H) 4.37-4.44 (m, 2H) 6.68 (t, $J=76$ Hz, 1H) 7.18 (dd, $J=8.37$, 1.48 Hz, 1H) 7.45-7.51 (m, 2H) 7.66 (d, $J=8.86$ Hz, 1H) 7.80 (s, 1H) 9.54 (brs, 1H) 11.96 (brs, 1H).

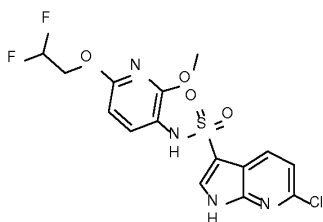
6-chloro-N-[6-(2,2-difluoroethoxy)-2,5-difluoropyridin-3-yl]-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide **I-44**



Basic LCMS Method 1 (ES^-): 423 ($\text{M}-\text{H}$) $^-$, 96% purity.

- ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 4.52 (td, $J = 15.0$, 3.3 Hz, 2H), 6.36 (tt, $J = 54.1$, 3.3 Hz, 1H), 7.37 (d, $J = 8.3$ Hz, 1H), 7.79 (dd, $J = 9.8$, 7.4 Hz, 1H), 8.21 – 7.92 (m, 2H), 10.24 (s, 1H), 12.85 (s, 1H).

6-chloro-N-[6-(2,2-difluoroethoxy)-2-methoxypyridin-3-yl]-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide **I-45**

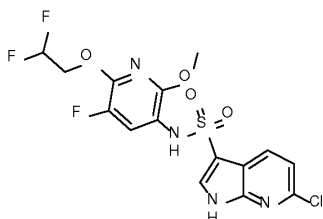


15

Basic LCMS Method 1 (ES^-): 417 ($\text{M}-\text{H}$) $^-$, 99% purity.

^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 3.28 (s, 3H), 4.45 (td, J = 14.9, 3.6 Hz, 2H), 6.51 – 6.12 (m, 2H), 7.34 (d, J = 8.3 Hz, 1H), 7.51 (d, J = 8.2 Hz, 1H), 7.90 (s, 1H), 8.08 (d, J = 8.3 Hz, 1H), 12.66 (s, 1H), 9.47 (s, 1H).

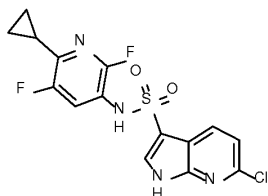
- 5 6-chloro-N-[6-(2,2-difluoroethoxy)-5-fluoro-2-methoxypyridin-3-yl]-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide **I-46**



Basic LCMS Method 1 (ES^-): 435 (M-H^-), 97% purity.

- 10 ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 3.28 (s, 3H), 4.56 (td, J = 14.8, 3.5 Hz, 2H), 6.37 (t, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.62 (d, J = 10.2 Hz, 1H), 7.99 (s, 1H), 8.13 (d, J = 8.3 Hz, 1H), 9.71 (s, 1H), 12.72 (s, 1H).

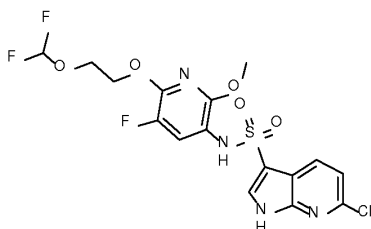
- 6-chloro-N-(6-cyclopropyl-2,5-difluoropyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide **I-47**



Basic LCMS Method 1 (ES^-): 383 (M-H^-), 95% purity.

- 15 ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 1.12 – 0.64 (m, 4H), 2.24 – 2.02 (m, 1H), 7.38 (d, J = 8.4 Hz, 1H), 7.66 (dd, J = 9.5, 7.5 Hz, 1H), 8.25 – 8.11 (m, 2H), 10.46 (s, 1H), 12.89 (s, 1H).

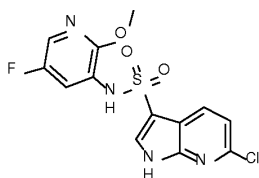
- 6-chloro-N-[6-[2-(difluoromethoxy)ethoxy]-5-fluoro-2-methoxypyridin-3-yl]-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide **I-48**



Basic LCMS Method 1 (ES^-): 465 (M-H) $^-$, 94% purity.

^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 3.24 (s, 3H), 4.30 (d, $J = 122.2$ Hz, 4H), 6.71 (s, 1H), 8.25 – 7.18 (m, 4H), 9.65 (s, 1H), 12.63 (s, 1H).

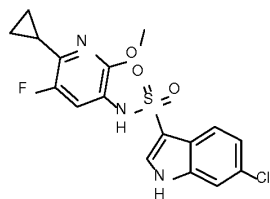
5 6-chloro-N-(5-fluoro-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide **I-49**



Basic LCMS Method 1 (ES^-): 355 (M-H) $^-$, 99% purity.

^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 3.51 (s, 3H), 7.38 (d, $J = 8.3$ Hz, 1H), 7.57 (dd, $J = 9.4$, 2.8 Hz, 1H), 7.85 (d, $J = 2.8$ Hz, 1H), 8.31 – 8.16 (m, 2H), 10.07 (s, 1H), 12.83 (s, 1H).

10 6-chloro-N-(6-cyclopropyl-5-fluoro-2-methoxypyridin-3-yl)-1H-indole-3-sulfonamide **I-50**

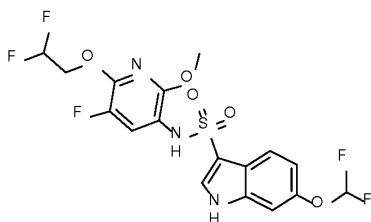


Basic LCMS Method 2 (ES^+): 396 (M+H) $^+$, 99% purity.

^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 0.81-0.87 (m, 2H) 0.89-0.94 (m, 2H) 2.08-2.10 (m, 1H) 3.36 (s, 3H) 7.20 (dd, $J=8.80$, 1.47 Hz, 1H) 7.41 (d, $J=10.27$ Hz, 1H) 7.51 (s, 1H) 7.75 (d, $J=8.80$ Hz, 1H) 7.95 (d, $J=2.45$ Hz, 1H) 9.68 (s, 1H) 12.04 (brs, 1H).

15 N-[6-(2,2-difluoroethoxy)-5-fluoro-2-methoxypyridin-3-yl]-6-(difluoromethoxy)-1H-indole-3-sulfonamide **I-51**

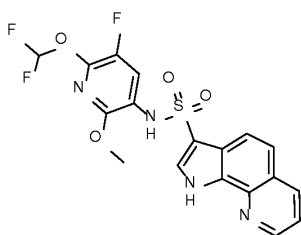
N-[6-(2,2-difluoroethoxy)-5-fluoro-2-methoxypyridin-3-yl]-6-(difluoromethoxy)-1H-indole-3-sulfonamide **I-51**



Basic LCMS Method 2 (ES^+): 468 ($\text{M}+\text{H}$) $^+$, 99% purity.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 3.29 (s, 3H) 4.50-4.60 (m, 2H) 6.22-6.52 (m, 1H) 7.00-7.05 (m, 1H) 7.20 (t, $J=74$, 1H) 7.25 (s, 1H) 7.55 (d, $J=10.34$ Hz, 1H) 7.71 (d, $J=8.86$ Hz, 1H) 7.83 (d, $J=2.46$ Hz, 1H) 9.54 (s, 1H) 11.95 (brs, 1H).

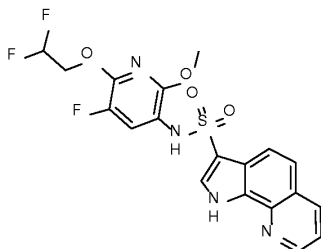
N-[6-(difluoromethoxy)-5-fluoro-2-methoxypyridin-3-yl]-1H-pyrrolo[3,2-h]quinoline-3-sulfonamide **I-68**



Basic LCMS Method 1 (ES^-): 437 ($\text{M}-\text{H}$) $^-$, 96% purity.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 3.32 (s, 3H) under solvent peak, 8.04 – 7.30 (m, 6H), 8.45 (d, $J = 8.2$ Hz, 1H), 8.92 (d, $J = 4.5$ Hz, 1H), 9.91 (s, 1H), 13.17 (s, 1H).

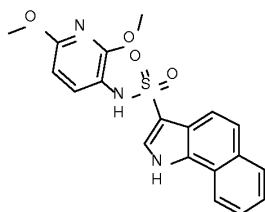
N-[6-(2,2-difluoroethoxy)-5-fluoro-2-methoxypyridin-3-yl]-1H-pyrrolo[3,2-h]quinoline-3-sulfonamide **I-69**



Basic LCMS Method 1 (ES^-): 451 ($\text{M}-\text{H}$) $^-$, 94% purity.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 3.25 (s, 3H), 4.51 (td, $J = 14.8, 3.5$ Hz, 2H), 6.33 (t, $J = 3.5$ Hz, 1H), 7.71 – 7.54 (m, 3H), 7.80 (s, 1H), 7.89 (d, $J = 8.7$ Hz, 1H), 8.45 (dd, $J = 8.3, 1.6$ Hz, 1H), 8.92 (dd, $J = 4.3, 1.6$ Hz, 1H), 9.63 (s, 1H), 13.10 (s, 1H).

N-(2,6-dimethoxypyridin-3-yl)-1H-benzo[g]indole-3-sulfonamide **I-70**

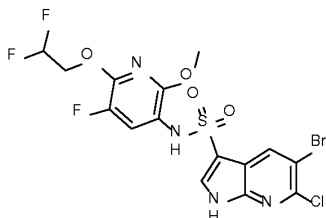


5

Neutral LCMS Method 3 (ES^+): 384 ($\text{M}+\text{H}$) $^+$, 98% purity.

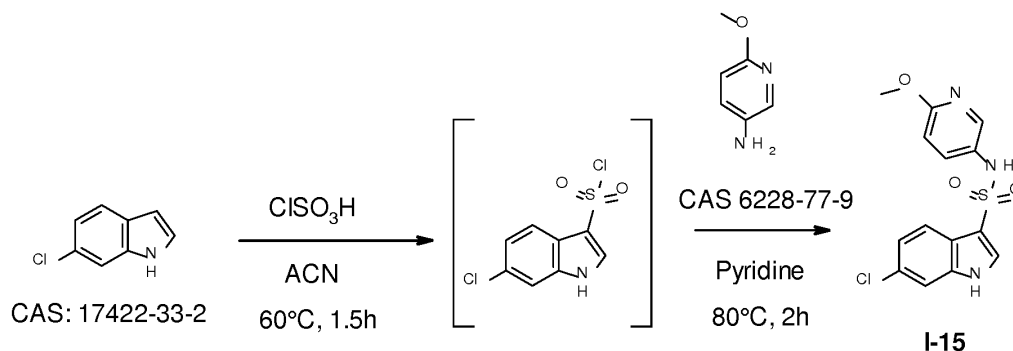
^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 3.21 (s, 3H), 3.70 (s, 3H), 6.28 (d, $J = 8.3$ Hz, 1H), 7.52 – 7.38 (m, 2H), 7.65 – 7.54 (m, 2H), 7.83 – 7.69 (m, 2H), 8.01 – 7.86 (m, 1H), 8.45 – 8.32 (m, 1H), 9.13 (s, 1H), 12.71 (s, 1H).

10 5-bromo-6-chloro-N-[6-(2,2-difluoroethoxy)-5-fluoro-2-methoxypyridin-3-yl]-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide **I-71**



Basic LCMS Method 2 (ES^+): 515 ($\text{M}+\text{H}$) $^+$, 94% purity.

15 ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 3.29 (s, 3H) 4.55 (td, $J=14.80, 3.18$ Hz, 2H) 6.22 - 6.54 (m, 1H) 7.64 (d, $J=10.27$ Hz, 1H) 8.08 (s, 1H) 8.47 (s, 1H) 9.80 (brs, 1H) 12.90 (brs, 1H).

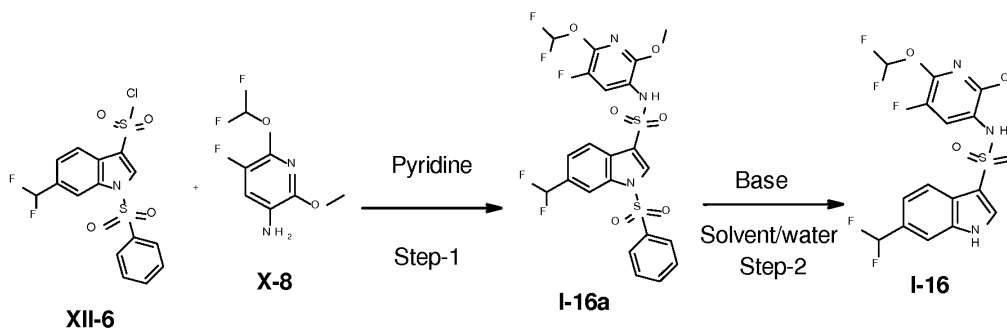
D.2. Synthesis of 6-chloro-N-(6-methoxypyridin-3-yl)-1H-indole-3-sulfonamide I-15

In a vial, a solution of 6-chloro-indole (630 mg, 4.1 mmol) in acetonitrile (25.2 mL) was stirred in an ice-bath and chlorosulfonic acid (714 μL , 10.7 mmol) was added dropwise and the reaction mixture was stirred for 30 min. The ice-bath was removed and the reaction mixture was heated to 60°C for 1.5h. After cooling to room temperature, pyridine (54.6 mL) was added and the solution turned yellow. In a second sealed vial, 6-methoxypyridin-3-amine (37.2 mg, 0.3 mmol) was weighed and an aliquot of the preceding solution was added (2.8 mL, 0.15 mmol). The reaction mixture was stirred at 80°C for 2h, then evaporated in a centrifugal evaporator. The residue was purified by reverse phase chromatography in basic mode with MS detection to afford 21.8 mg of 6-chloro-N-(6-methoxypyridin-3-yl)-1H-indole-3-sulfonamide **I-15**.

Yield: 42%.

Basic LCMS Method 1 (ES^-): 336 (M-H) $^-$, 100% purity.

15

D.3. Method B. Synthesis of N-[6-(difluoromethoxy)-5-fluoro-2-methoxypyridin-3-yl]-6-(difluoromethyl)-1H-indole-3-sulfonamide I-16

Step-1: Synthesis of 1-(benzenesulfonyl)-N-[6-(difluoromethoxy)-5-fluoro-2-methoxy-3-pyridyl]-6-(difluoromethyl)indole-3-sulfonamide **I-16a**

In a sealed vial, 6-(difluoromethoxy)-5-fluoro-2-methoxy-pyridin-3-amine **X-8** (150 mg, 0.49 mmol) was dissolved in pyridine (3 mL) under argon. 1-(benzenesulfonyl)-6-(difluoromethyl)indole-3-sulfonyl chloride **XII-6** (290 mg, 0.71 mmol) was added at 0 °C then stirred at room temperature overnight. The reaction mixture was poured into water and extracted with ethyl acetate (three times). The organic phases were dried over MgSO₄ and evaporated. The residue was purified by flash chromatography on silica (eluting with a gradient of DCM and methanol from 100/0 to 95/5) to provide 310 mg of 1-(benzenesulfonyl)-N-[6-(difluoromethoxy)-5-fluoro-2-methoxy-3-pyridyl]-6-(difluoromethyl)indole-3-sulfonamide **I-16a** as a white solid.

Yield: 75%.

Basic LCMS Method 1 (ES⁻): 576 (M-H)⁻, 100% purity.

Step-2: Synthesis of N-[6-(difluoromethoxy)-5-fluoro-2-methoxypyridin-3-yl]-6-(difluoromethyl)-1H-indole-3-sulfonamide **I-16**

In a sealed tube, 1-(benzenesulfonyl)-N-[6-(difluoromethoxy)-5-fluoro-2-methoxy-3-pyridyl]-6-(difluoromethyl)indole-3-sulfonamide **I-16a** (310 mg, 0.54 mmol) was dissolved in THF (4 mL). Tetrabutylammonium fluoride (1.3 mL, 1M solution in water, 1.3 mmol) was added and the reaction mixture was stirred at 90 °C overnight. The reaction mixture was poured into water and extracted with ethyl acetate (three times). The organic phases were dried over MgSO₄ and evaporated. The residue was purified by flash chromatography on silica (eluting with DCM/methanol 95/5) to provide 170 mg of N-[6-(difluoromethoxy)-5-fluoro-2-methoxypyridin-3-yl]-6-(difluoromethyl)-1H-indole-3-sulfonamide **I-16** as a bright yellow solid.

Yield: 58%.

Basic LCMS Method 1 (ES⁻): 436 (M-H)⁻, 97% purity.

¹H NMR (400 MHz, DMSO-*d*₆) δ 3.37 (s, 3H), 7.12 (t, J = 56.0 Hz, 1H), 7.80 – 7.32 (m, 4H), 7.89 (d, J = 8.3 Hz, 1H), 8.04 (s, 1H), 9.84 (s, 1H), 12.22 (s, 1H).

The following compounds in Table 5 may be synthesized according methods analogous to Method B.

Table 5:

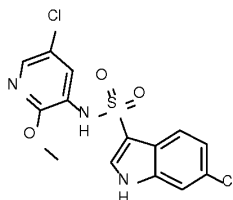
N°	Sulfonyl chlorides XII	Amines X	Conditions, Time (Step-1)	Yield (%)	Conditions, Time (Step-2)	Purification conditions	Yield (%)
I-17	XII-3	886373-70-2	DMAP cat., 16h, rt	crude	K ₂ CO ₃ , MeOH, rt, overnight	Basic prep LCMS Method 1	24
I-18	XII-3	59489-71-3	48h, 50 °C	11	K ₂ CO ₃ , Dioxane, 100 °C, 2 days	Basic prep LCMS Method 1	63
I-19	XII-3	55338-73-3	48h, 50 °C	27	K ₂ CO ₃ , Dioxane, 100 °C, 2 days	Basic prep LCMS Method 1	77
I-20	XII-3	13534-97-9	48h, 50 °C	87	K ₂ CO ₃ , Dioxane, 100 °C, 2 days	Basic prep LCMS Method 1	64
I-21	XII-3	29958-12-1	48h, 50 °C	69	K ₂ CO ₃ , Dioxane, 100 °C, 2 days	Basic prep LCMS Method 1	65
I-22	XII-4	X-8	16h, rt	60	TBAF, THF, 100 °C, 16h	DCM/MeOH 95/5	73
I-23	XII-3	1256806-83-3	2h, 80 °C	crude	Cs ₂ CO ₃ , MeOH, rt, 2h	DCM/EtOAc 95/5	31
I-24	XII-3	5350-93-6	2h, 80 °C	crude	Cs ₂ CO ₃ , MeOH, rt, 2h	DCM/EtOAc 95/5	40
I-25	XII-3	1256811-74-1	2h, 80 °C	crude	Cs ₂ CO ₃ , MeOH, rt, 2h	DCM/EtOAc 95/5	3
I-26	XII-3	7321-93-9	2h, 80 °C	crude	Cs ₂ CO ₃ , MeOH, rt, 2h	DCM/EtOAc 95/5	32

N°	Sulfonyl chlorides XII	Amines X	Conditions, Time (Step-1)	Yield (%)	Conditions, Time (Step-2)	Purification conditions	Yield (%)
I-27	XII-6	914222- 86-9	3h, rt	80	TBAF, THF, 65 °C, 2days	Basic prep LCMS Method 1	49
I-28	XII-5	914222- 86-9	1h, rt	39	TBAF, THF, 65 °C, 18h	EtOAc/Hepta ne	51
I-29	XII-5	X-3	2h, rt	29	TBAF, THF, 65 °C, 24h	Basic prep LCMS Method 1	13
I-30	XII-5	X-13	16h, rt	25	TBAF, THF, 65 °C, 21h	Basic prep LCMS Method 1	18
I-31	XII-5	X-8	16h, rt	22	TBAF, THF, 65 °C, 18h	DCM/MeOH 95/5	36
I-52	XII-6	X-13	16h, rt	59	TBAF, THF, 75 °C, 18h	Basic prep LCMS Method 1	42
I-53	XII-5	X-16	16h, rt	53	TBAF, THF, 65 °C, 18h	DCM/EtOH 95/5	18
I-54	XII-5	X-20	16h, rt	19	TBAF, THF, 65 °C, 18h	Basic prep LCMS Method 1	77
I-55	XII-5	X-11	16h, rt	34	TBAF, THF, 65 °C, 2h	Basic prep LCMS Method 1	27

N°	Sulfonyl chlorides XII	Amines X	Conditions, Time (Step-1)	Yield (%)	Conditions, Time (Step-2)	Purification conditions	Yield (%)
I-56	XII-5	X-6	16h, rt	47	TBAF, THF, 65 °C, 18h	Basic prep LCMS Method 1	24
I-57	XII-5	X-7	16h, rt	40	TBAF, THF, 65 °C, 18h	DCM/EtOH 95/5	29
I-58	XII-5	X-21	16h, rt	44	TBAF, THF, 70 °C, 18h	Basic prep LCMS Method 1	49
I-59	XII-9	X-20	16h, rt	54	TBAF, THF, 70 °C, 18h	Basic prep LCMS Method 1	66
I-60	XII-10	X-8	16h, rt	43	TBAF, THF, 80 °C, 18h	DCM/MeOH 98/8	67
I-61	XII-3	28020-37- 3	2h, 80 °C	crude	Cs ₂ CO ₃ , MeOH, rt, 2h	DCM/EtOAc 95/5	19
I-62	XII-6	X-20	2h, rt	86	TBAF, THF, 100 °C, 7 days	DCM/MeOH 99/1	40
I-63	XII-11	X-8	18h, rt	78	TBAF, THF, 100 °C, 5 days	DCM/isoprop anol 99/1	35
I-64	XII-11	X-20	18h, rt	70	TBAF, THF, 100 °C, 5 days	DCM/isoprop anol 99/1	53

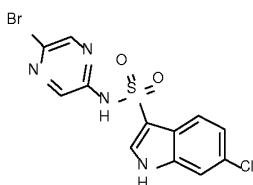
N°	Sulfonyl chlorides XII	Amines X	Conditions, Time (Step-1)	Yield (%)	Conditions, Time (Step-2)	Purification conditions	Yield (%)
I-67	XII-3	X-13	2h, rt	68	TBAF, THF, 65°C, 2h	Basic prep LCMS Method 1	85
I-72	XII-15	X-3	12h, rt	crude	TBAF, THF, 80°C, 8h	1/4 EtOAc/Petroleum Ether	39

6-chloro-N-(5-chloro-2-methoxypyridin-3-yl)-1H-indole-3-sulfonamide I-17



Basic LCMS Method 1 (ES⁻): 370 (M-H)⁻, 100% purity.

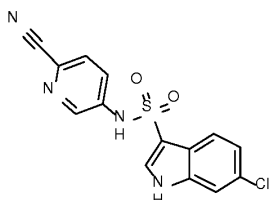
N-(5-bromopyrazin-2-yl)-6-chloro-1H-indole-3-sulfonamide I-18



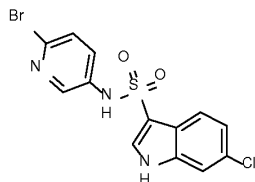
5

Basic LCMS Method 1 (ES⁻): 385 (M-H)⁻, 98% purity.

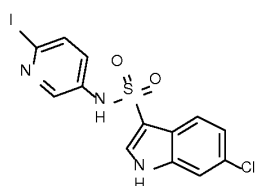
6-chloro-N-(6-cyanopyridin-3-yl)-1H-indole-3-sulfonamide I-19



Basic LCMS Method 1 (ES⁻): 331 (M-H)⁻, 98% purity.

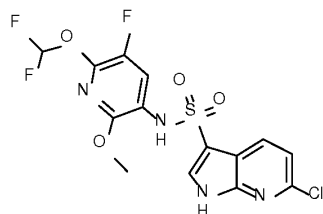
N-(6-bromopyridin-3-yl)-6-chloro-1H-indole-3-sulfonamide **I-20**

Basic LCMS Method 1 (ES^-): 384 (M-H^-), 98% purity.

6-chloro-N-(6-iodopyridin-3-yl)-1H-indole-3-sulfonamide **I-21**

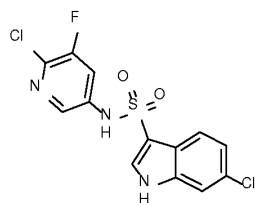
5

Basic LCMS Method 1 (ES^-): 432 (M-H^-), 100% purity.

6-chloro-N-[6-(difluoromethoxy)-5-fluoro-2-methoxypyridin-3-yl]-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide **I-22**

10 Basic LCMS Method 1 (ES^-): 421 (M-H^-), 97% purity.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 3.37 (s, $J = 1.2$ Hz, 3H), 7.37 (d, $J = 8.4, 1.2$ Hz, 1H), 7.77 – 7.40 (t, 1H), 7.77 (d, $J = 4.1$ Hz, 1H), 8.09 (s, $J = 2.1$ Hz, 1H), 8.18 (d, $J = 8.3, 1.2$ Hz, 1H), 9.95 (s, 1H), 12.77 (s, 1H).

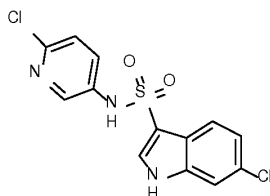
6-chloro-N-(6-chloro-5-fluoropyridin-3-yl)-1H-indole-3-sulfonamide **I-23**

15

Neutral LCMS Method 3 (ES⁺): 360 (M+H)⁺, 99% purity.

¹H NMR (500 MHz, DMSO-*d*₆) δ 7.25 (dd, J = 1.93, 8.53 Hz, 1H), 7.52 (d, J = 1.83 Hz, 1H), 7.54 (dd, J = 2.38, 10.09 Hz, 1H), 7.78 (d, J = 8.62 Hz, 1H), 7.97 (d, J = 2.38 Hz, 1H), 8.22 (d, J = 2.93 Hz, 1H), 10.97 (br s, 1H), 12.22 (br s, 1H).

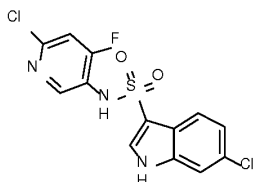
5 6-chloro-N-(6-chloropyridin-3-yl)-1H-indole-3-sulfonamide **I-24**



Neutral LCMS Method 3 (ES⁺): 342 (M+H)⁺, 95% purity.

¹H NMR (500 MHz, DMSO-*d*₆) δ 7.23 (dd, J = 1.83, 8.62 Hz, 1H), 7.33 (d, J = 8.62 Hz, 1H), 7.46 - 7.57 (m, 2H), 7.76 (d, J = 8.44 Hz, 1H), 8.01 - 8.14 (m, 2H), 10.62 (br s, 1H), 12.15 (br s, 1H).

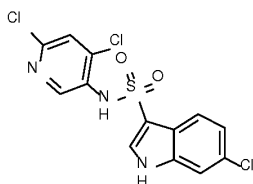
10 6-chloro-N-(6-chloro-4-fluoropyridin-3-yl)-1H-indole-3-sulfonamide **I-25**



Neutral LCMS Method 3 (ES⁺): 360 (M+H)⁺, 97% purity.

¹H NMR (500 MHz, DMSO-*d*₆) δ 7.22 (dd, J = 1.93, 8.53 Hz, 1H), 7.53 (d, J = 1.83 Hz, 1H), 7.54 (d, J = 9.54 Hz, 1H), 7.69 (d, J = 8.62 Hz, 1H), 7.96 (d, J = 2.75 Hz, 1H), 8.22 (d, J = 9.90 Hz, 1H), 10.35 (br. s., 1H), 12.14 (br. s., 1H).

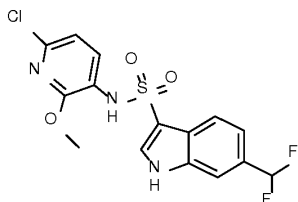
15 6-chloro-N-(4,6-dichloropyridin-3-yl)-1H-indole-3-sulfonamide **I-26**



Neutral LCMS Method 3 (ES⁺): 376 (M+H)⁺, 96% purity.

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.19 (d, J = 8.4 Hz, 1H), 7.65 (d, J = 8.6 Hz, 1H), 7.53 (s, 1H), 7.68 (s, 1H), 7.90 (d, J = 4.0 Hz, 1H), 8.22 (s, 1H), 10.17 (s, 1H), 12.13 (s, 1H).

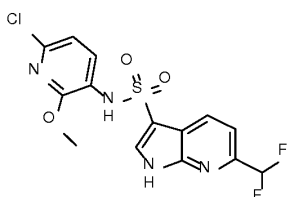
N-(6-chloro-2-methoxypyridin-3-yl)-6-(difluoromethyl)-1H-indole-3-sulfonamide **I-27**



5 Basic LCMS Method 1 (ES^-): 386 ($\text{M}-\text{H}$) $^-$, 99% purity.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.26 – 6.95 (m, 2H), 7.40 – 7.33 (m, 1H), 3.43 (s, 3H), 7.61 (d, J = 8.1 Hz, 1H), 7.69 (d, J = 1.5 Hz, 1H), 7.90 (dd, J = 8.4, 0.8 Hz, 1H), 8.00 (s, 1H), 9.78 (s, 1H), 12.21 (s, 1H).

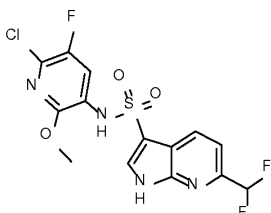
10 N-(6-chloro-2-methoxypyridin-3-yl)-6-(difluoromethyl)-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide **I-28**



Basic LCMS Method 1 (ES^-): 387 ($\text{M}-\text{H}$) $^-$, 97% purity.

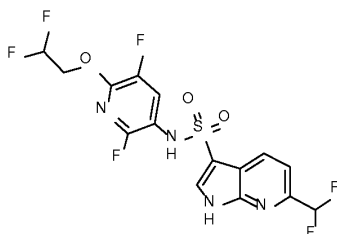
^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 3.40 (s, 3H), 7.27 – 6.63 (m, 2H), 7.77 – 7.35 (m, 2H), 8.27 (d, J = 73.6 Hz, 2H), 9.90 (s, 1H), 12.89 (s, 1H).

15 N-(6-chloro-5-fluoro-2-methoxypyridin-3-yl)-6-(difluoromethyl)-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide **I-29**



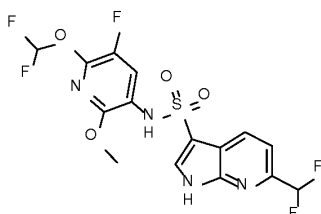
Basic LCMS Method 1 (ES^-): 405 ($\text{M}-\text{H}$) $^-$, 97% purity.

N-[6-(2,2-difluoroethoxy)-2,5-difluoro-3-pyridyl]-6-(difluoromethyl)-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide **I-30**



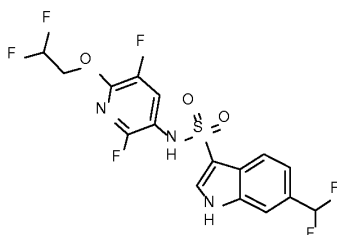
Basic LCMS Method 1 (ES⁻): 439 (M-H)⁻, 99% purity.

- 5 N-[6-(difluoromethoxy)-5-fluoro-2-methoxypyridin-3-yl]-6-(difluoromethyl)-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide **I-31**



Basic LCMS Method 1 (ES⁻): 437 (M-H)⁻, 99% purity.

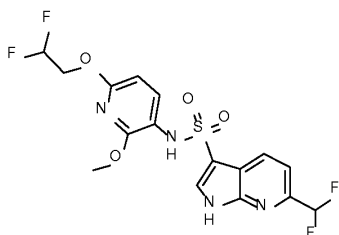
- 10 N-[6-(2,2-difluoroethoxy)-2,5-difluoropyridin-3-yl]-6-(difluoromethyl)-1H-indole-3-sulfonamide **I-52**



Basic LCMS Method 1 (ES⁻): 438 (M-H)⁻, 96% purity.

- 15 ¹H NMR (400 MHz, DMSO-*d*₆) δ 4.51 (td, J = 15.1, 3.3 Hz, 2H), 6.53 – 6.17 (m, 1H), 7.14 (t, J = 56.1 Hz, 1H), 7.38 (d, J = 8.4 Hz, 1H), 7.80 – 7.65 (m, 2H), 7.83 (d, J = 8.3 Hz, 1H), 8.04 (d, J = 2.9 Hz, 1H), 10.17 (s, 1H), 12.31 (s, 1H).

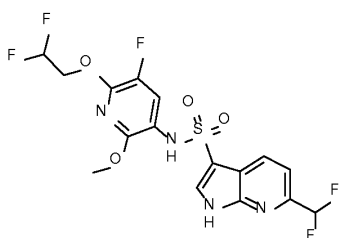
N-[6-(2,2-difluoroethoxy)-2-methoxypyridin-3-yl]-6-(difluoromethyl)-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide **I-53**



Basic LCMS Method 1 (ES⁻): 433 (M-H)⁻, 100% purity.

¹H NMR (400 MHz, DMSO-*d*₆) δ 3.21 (s, 3H), 4.43 (td, J = 14.9, 3.6 Hz, 2H), 6.48 – 6.13 (m, 2H), 7.10 (d, J = 55.1 Hz, 1H), 7.53 (dd, J = 14.9, 8.2 Hz, 2H), 8.03 (s, 1H), 8.21 (d, J = 8.2 Hz, 1H), 9.46 (s, 1H), 12.77 (s, 1H).

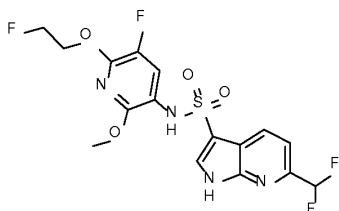
N-[6-(2,2-difluoroethoxy)-5-fluoro-2-methoxypyridin-3-yl]-6-(difluoromethyl)-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide **I-54**



Basic LCMS Method 1 (ES⁻): 451 (M-H)⁻, 95% purity.

¹H NMR (400 MHz, DMSO-*d*₆) δ 3.23 (s, 3H), 4.54 (td, J = 14.8, 3.5 Hz, 2H), 6.36 (tt, J = 54.5, 3.6 Hz, 1H), 7.04 (t, J = 55.1 Hz, 1H), 7.60 (dd, J = 17.0, 9.2 Hz, 2H), 8.13 (s, 1H), 8.27 (d, J = 8.2 Hz, 1H), 9.72 (s, 1H), 12.83 (s, 1H).

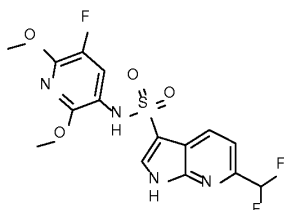
6-(difluoromethyl)-N-[5-fluoro-6-(2-fluoroethoxy)-2-methoxypyridin-3-yl]-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide **I-55**



15

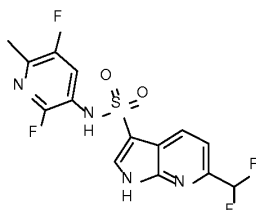
Basic LCMS Method 1 (ES⁻): 433 (M-H)⁻, 99% purity.

6-(difluoromethyl)-N-(5-fluoro-2,6-dimethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide **I-56**



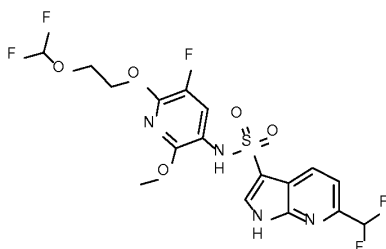
Basic LCMS Method 1 (ES⁻): 401 (M-H)⁻, 100% purity.

- 5 6-(difluoromethyl)-N-(2,5-difluoro-6-methylpyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide **I-57**



Basic LCMS Method 1 (ES⁻): 373 (M-H)⁻, 98% purity.

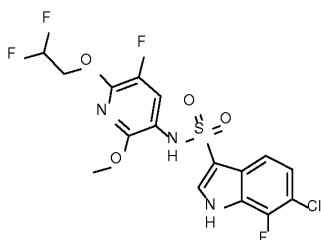
- 10 N-[6-[2-(difluoromethoxy)ethoxy]-5-fluoro-2-methoxypyridin-3-yl]-6-(difluoromethyl)-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide **I-58**



Basic LCMS Method 1 (ES⁻): 481 (M-H)⁻, 99% purity.

- 15 ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.18 (s, 3H), 4.28 (d, J = 120.0 Hz, 4H), 7.24 – 6.35 (m, 2H), 7.57 (d, J = 9.2 Hz, 2H), 8.11 (s, 1H), 8.24 (d, J = 8.1 Hz, 1H), 9.66 (s, 1H), 12.81 (s, 1H).

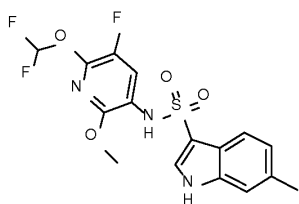
6-chloro-N-[6-(2,2-difluoroethoxy)-5-fluoro-2-methoxypyridin-3-yl]-7-fluoro-1H-indole-3-sulfonamide **I-59**



Basic LCMS Method 1 (ES^-): 452 (M-H^-), 95% purity.

- ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 3.31 (s, 3H), 4.78 – 4.42 (m, 2H), 6.60 – 6.09 (m, 1H), 7.30 (t, $J = 7.6$ Hz, 1H), 7.58 (dt, $J = 22.5, 9.7$ Hz, 2H), 7.92 (s, 1H), 9.76 (s, 1H), 12.7 (s, 1H).

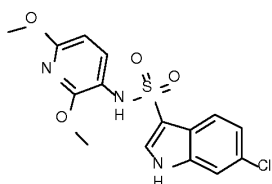
N-[6-(difluoromethoxy)-5-fluoro-2-methoxypyridin-3-yl]-6-methyl-1H-indole-3-sulfonamide **I-60**



Basic LCMS Method 1 (ES^-): 400 (M-H^-), 98% purity.

- ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 2.39 (s, 3H), 3.45 (s, 3H), 7.00 (d, $J = 8.1$ Hz, 1H), 7.25 (s, 1H), 7.74-7.56 (m, 3H), 7.84 (d, $J = 2.9$ Hz, 1H), 9.71 (s, 1H), 11.82 (s, 1H).

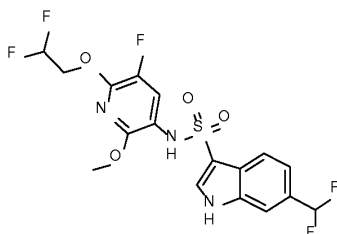
6-chloro-N-(2,6-dimethoxypyridin-3-yl)-1H-indole-3-sulfonamide **I-61**



Neutral LCMS Method 3 (ES^+): 368 (M+H^+), 99% purity.

- ^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ 3.24 (s, 3H), 3.73 (s, 3H), 6.28 (d, $J = 8.3$ Hz, 1H), 7.17 (dd, $J = 8.6, 1.9$ Hz, 1H), 7.41 (d, $J = 8.3$ Hz, 1H), 7.51 (d, $J = 1.9$ Hz, 1H), 7.66 (d, $J = 8.6$ Hz, 1H), 7.69 (s, 1H), 9.16 (s, 1H), 11.89 (s, 1H).

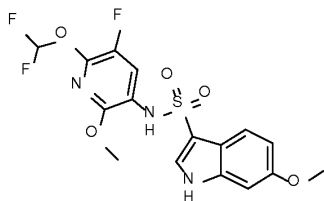
N-[6-(2,2-difluoroethoxy)-5-fluoro-2-methoxypyridin-3-yl]-6-(difluoromethyl)-1H-indole-3-sulfonamide **I-62**



Basic LCMS Method 1 (ES⁻): 450 (M-H)⁻, 99% purity.

- 5 ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.25 (s, 3H), 4.52 (td, J = 14.8, 3.6 Hz, 2H), 6.35 (tt, J = 54.5, 3.5 Hz, 1H), 7.12 (t, J = 56.1 Hz, 1H), 7.86 – 7.29 (m, 4H), 7.95 (d, J = 2.2 Hz, 1H), 9.56 (s, 1H), 12.17 (s, 1H).

N-[6-(difluoromethoxy)-5-fluoro-2-methoxypyridin-3-yl]-6-methoxy-1H-indole-3-sulfonamide **I-63**



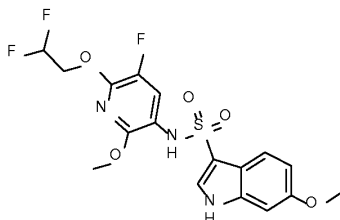
10

Basic LCMS Method 1 (ES⁻): 414 (M-H)⁻, 95% purity.

¹H NMR (400 MHz, DMSO-*d*₆) δ 3.45 (s, 3H), 3.77 (s, 3H), 6.87 – 6.76 (m, 1H), 6.93 (s, 1H), 7.76 – 7.33 (m, 3H), 7.78 (d, J = 2.9 Hz, 1H), 9.73 (s, 1H), 11.74 (s, 1H).

N-[6-(2,2-difluoroethoxy)-5-fluoro-2-methoxypyridin-3-yl]-6-methoxy-1H-indole-3-sulfonamide **I-64**

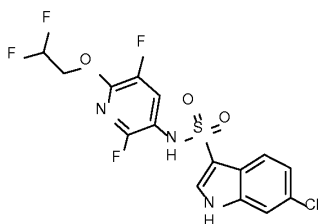
15



Basic LCMS Method 1 (ES⁻): 430 (M-H)⁻, 95% purity.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 3.36 (s, 3H), 3.77 (s, 3H), 4.54 (td, J = 14.9, 3.6 Hz, 2H), 6.36 (t, J = 3.5 Hz, 1H), 6.80 (dd, J = 8.8, 2.3 Hz, 1H), 6.93 (d, J = 2.3 Hz, 1H), 7.53 (dd, J = 19.8, 9.6 Hz, 2H), 7.66 (d, J = 2.8 Hz, 1H), 9.42 (s, 1H), 11.67 (s, 1H).

6-chloro-N-[6-(2,2-difluoroethoxy)-2,5-difluoropyridin-3-yl]-1H-indole-3-sulfonamide **I-67**

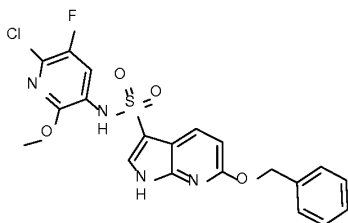


5

Basic LCMS Method 1 (ES^-): 422 ($\text{M}-\text{H}$) $^-$, 99% purity.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 4.49 (t, J = 14.8 Hz, 2H), 6.34 (t, J = 54.4 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 7.52 (s, 1H), 7.70 (d, J = 8.5 Hz, 2H), 7.88 (s, 1H), 10.14 (s, 1H), 12.03 (s, 1H).

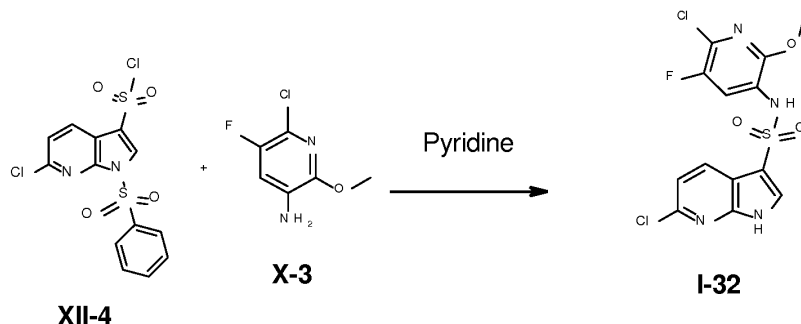
10 N-(6-chloro-5-fluoro-2-methoxypyridin-3-yl)-6-phenylmethoxy-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide **I-72**



Neutral LCMS Method 3 (ES^+): 463 ($\text{M}+\text{H}$) $^+$, 96% purity.

15 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 3.56 (s, 3H), 5.36 (s, 2H), 6.79 (d, J = 8.6 Hz, 1H), 7.30 (t, J = 7.3 Hz, 1H), 7.36 (t, J = 7.3 Hz, 2H), 7.45 (d, J = 6.9 Hz, 2H), 7.70 (d, J = 9.2 Hz, 1H), 7.90 (d, J = 2.7 Hz, 1H), 8.11 (d, J = 8.5 Hz, 1H), 10.07 (s, 1H), 12.40 (s, 1H).

D.4. Synthesis of 6-chloro-N-(6-chloro-5-fluoro-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide 1-32



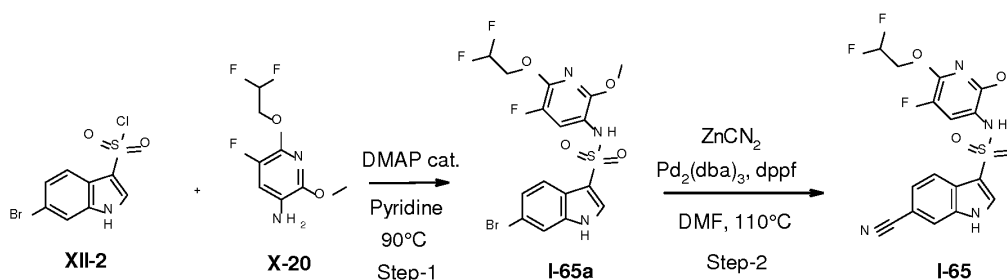
In a sealed vial, 1-(benzenesulfonyl)-6-chloro-pyrrolo[2,3-b]pyridine-3-sulfonyl chloride **XI-4** (100 mg, 0.26 mmol) was dissolved in pyridine (4 mL). 6-chloro-5-fluoro-2-methoxypyridin-3-amine **X-3** (67 mg, 0.38 mmol) was added then stirred at 70 °C for 2h. The reaction mixture was poured into water and extracted with ethyl acetate (twice). The organic phases were dried over MgSO₄ and evaporated. The residue was purified by basic prep LCMS Method 1 to provide 11 mg of 6-chloro-N-(6-chloro-5-fluoro-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide **I-32** as a pale yellow solid.

Yield: 11%.

Basic LCMS Method 1 (ES⁻): 389 (M-H)⁻, 96% purity.

¹H NMR (400 MHz, DMSO-*d*₆) δ 3.63 (s, 3H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.98 (d, *J* = 9.0 Hz, 1H), 8.29 (dd, *J* = 18.4, 5.6 Hz, 2H), 11.17 (s, 1H), 12.87 (s, 1H).

15 **D.5. Synthesis of 6-cyano-N-[6-(2,2-difluoroethoxy)-5-fluoro-2-methoxypyridin-3-yl]-1H-indole-3-sulfonamide I-65**



Step-1: Synthesis of 6-bromo-N-(6-(2,2-difluoroethoxy)-5-fluoro-2-methoxypyridin-3-yl)-1H-indole-3-sulfonamide **I-65a**

To a solution of 6-(2,2-difluoroethoxy)-5-fluoro-2-methoxypyridin-3-amine **X-20** (0.30 g, 1.34 mmol) in pyridine (8 mL) was added 6-bromo-1H-indole-3-sulfonyl chloride **XII-2** (1.58 g, 5.35 mmol) portion wise at 0 °C for 10 min followed by addition of DMAP (0.02 g, 0.13 mmol) at 0 °C and the reaction mixture was heated at 90 °C for 20h. Progress of the reaction was monitored by TLC and LCMS. After completion, the reaction mixture was concentrated under vacuum. The residue was triturated with 2 N HCl (10 mL), diluted with H₂O (70 mL) and extracted with EtOAc (3 × 35 mL). The organic layer was separated, washed with brine (2 × 60 mL), dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude obtained was purified by column chromatography (silica, 100-200 mesh, 30% EtOAc in hexane) to afford 6-bromo-N-(6-(2,2-difluoroethoxy)-5-fluoro-2-methoxypyridin-3-yl)-1H-indole-3-sulfonamide **I-65a** (0.42 g) as an off-white solid.

Yield: 62%.

Basic LCMS Method 2 (ES⁺): 481 (M+H)⁺, 95% purity.

Step-2: Synthesis of 6-cyano-N-[6-(2,2-difluoroethoxy)-5-fluoro-2-methoxypyridin-3-yl]-1H-indole-3-sulfonamide **I-65**

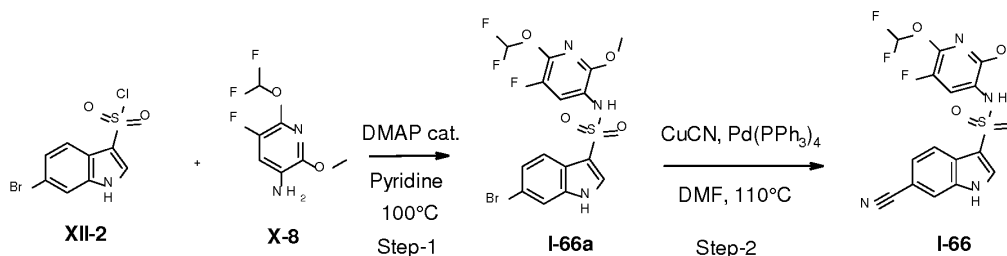
To a solution of 6-bromo-N-(6-(2,2-difluoroethoxy)-5-fluoro-2-methoxypyridin-3-yl)-1H-indole-3-sulfonamide **I-65a** (0.20 g, 0.40 mmol) in DMF (6 mL) was added Zn(CN)₂ (0.14 g, 1.19 mmol) and the reaction mixture was purged with argon for 15 min. Pd₂(dba)₃ (0.02 g, 0.02 mmol) and 1,1'-bis(diphenylphosphanyl) ferrocene (0.02 g, 0.04 mmol) were added and the reaction mixture was heated in microwave at 110 °C for 3h. Progress of the reaction was monitored by TLC and LCMS. After completion, the reaction mixture was diluted with H₂O (80 mL) and extracted with EtOAc (3 × 40 mL). The organic layer was separated, washed with brine (2 × 60 mL), dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude obtained was purified by column chromatography (silica, 100-200 mesh, 35% EtOAc in hexane) to afford 6-cyano-N-[6-(2,2-difluoroethoxy)-5-fluoro-2-methoxypyridin-3-yl]-1H-indole-3-sulfonamide **I-65** (0.077 g, 45%) as an off-white solid.

Yield: 45%.

Basic LCMS Method 2 (ES⁻): 425 (M-H)⁻, 99% purity.

¹H NMR (400 MHz, DMSO-*d*₆) δ 3.21 (s, 3H) 4.53 (td, J=14.67, 3.42 Hz, 2H) 6.20-6.50 (m, 1H) 7.54 (dd, J=8.31, 0.98 Hz, 1H) 7.59 (d, J=10.27 Hz, 1H) 7.86 (d, J=8.31 Hz, 1H) 7.99 (s, 1H) 8.04 (s, 1H) 9.68 (brs, 1H) 12.41 (brs, 1H).

D.6. Synthesis of 6-cyano-N-[6-(difluoromethoxy)-5-fluoro-2-methoxypyridin-3-yl]-1H-indole-3-sulfonamide I-66



Step-1: Synthesis of 6-bromo-N-[6-(difluoromethoxy)-5-fluoro-2-methoxypyridin-3-yl]-1H-indole-3-sulfonamide **I-66a** :

- To a solution of 6-(difluoromethoxy)-5-fluoro-2-methoxy-pyridin-3-amine **X-8** (0.10 g, 0.47 mmol) in pyridine (2 mL) was added 6-bromo-1H-indole-3-sulfonyl chloride **XII-2** (0.44 g, 1.50 mmol) portion wise at 0 °C for 20 min followed by addition of DMAP (0.006 g, 0.05 mmol) at same temperature and the reaction mixture was heated at 100 °C for 18h.
- Progress of the reaction was monitored by TLC and LCMS. After completion, the reaction mixture was concentrated under vacuum. The residue was triturated with 2 N HCl (5 mL), diluted with H₂O (10 mL) and extracted with EtOAc (3 × 25 mL). The organic layer was separated, washed with brine (2 × 30 mL), dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude obtained was purified by column chromatography (silica, 100-200 mesh, 40% EtOAc in hexane) to afford 6-bromo-N-[6-(difluoromethoxy)-5-fluoro-2-methoxypyridin-3-yl]-1H-indole-3-sulfonamide **I-66a** (0.15 g) as an off-white solid.

Yield: 63%.

Basic LCMS Method 2 (ES⁻): 46 (M-H)⁻, 92% purity.

Step-2: Synthesis of 6-cyano-N-[6-(difluoromethoxy)-5-fluoro-2-methoxypyridin-3-yl]-1H-indole-3-sulfonamide **I-66**:

- To a solution of 6-bromo-N-[6-(difluoromethoxy)-5-fluoro-2-methoxypyridin-3-yl]-1H-indole-3-sulfonamide **I-66a** (0.09 g, 0.18 mmol) in DMF (2 mL) was added CuCN (0.03 g, 0.36 mmol) and the reaction mixture was purged with argon for 20 min followed by addition of Pd(PPh₃)₄ (0.02 g, 0.02 mmol). The reaction mixture was purged with argon for 5 min and heated at 110 °C for 16h. Progress of the reaction was monitored by TLC and LCMS. After completion, the reaction mixture was diluted with H₂O (20 mL) and EtOAc (20 mL), filtered through a pad of celite. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed

with brine (2 × 20 mL), dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude obtained was purified by column chromatography (silica, 100-200 mesh, 50% EtOAc in hexane) to afford 6-cyano-N-[6-(difluoromethoxy)-5-fluoro-2-methoxypyridin-3-yl]-1H-indole-3-sulfonamide **I-66** (0.025 g) as an off-white solid.

5 Yield: 33%.

Basic LCMS Method 2 (ES⁻): 411 (M-H)⁻, 96% purity.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.53-7.55 (m, 1H) 7.55 (t, J=72 Hz, 1H) 7.73-7.77 (m, 1H) 7.91 (d, J=8.31Hz, 1H) 7.99 (s, 1H) 8.13 (s, 1H) 9.94 (brs, 1H) 12.45 (brs, 1H) (3H's merged in solvent peak).

10

Examples were tested and activities in Ca²⁺ and cAMP assays are reported in the Table 6 further below.

B. BIOLOGY/PHARMACOLOGY :

15 B-I. Cell cultures

GPR17 Recombinant cell line:

Flp-In T-REx CHO cells stably expressing human GPR17 receptor (CHO hGPR17) from Evi Kostenis' lab (Bonn University, Germany) were cultured at 37 °C in a humidified atmosphere of 5% CO₂. Cells were grown in DMEM with Nutrient Mixture F-12
20 supplemented with hygromycin B (500 µg/ml) and blasticidin (30 µg/ml). Expression from the Flp-In locus was induced by treatment with doxycycline (1 µg/ml) for 16-20 h prior assays.

Primary oligodendrocytes:

Primary oligodendrocyte progenitor cells (OPCs) were isolated from the forebrains of
25 Wistar rat pups at postnatal day 0 to 2. Cerebra were mechanically dissociated with a syringe and two different hollow needles (first 1.2 x 40 and then 0.60 x 30). Clump-free cell suspension was filtered through a 70-µm cell strainer and plated into poly-D-lysine-coated 75-cm² culture flasks in DMEM supplemented with 10% (v/v) heat-inactivated fetal calf serum, penicillin (100 units/ml), and streptomycin (0.1 mg/ml) with medium exchanged

every second day. After 8 to 11 days at 37 °C in a humidified atmosphere of 5% CO₂, mixed cultures were shaken at 240 rpm for 14–24 h to detach OPCs from astrocytes and microglia. To further enrich for OPCs, the suspension was plated onto uncoated Petri dishes for 45 min. Then, OPCs were seeded into poly-L-ornithine-coated plates and maintained at 37 °C in a humidified atmosphere of 5% CO₂ in proliferating Neurobasal medium supplemented with 2% (v/v) B27, 2 mM GlutaMAX, 100 units/ml penicillin, 0.1 mg/ml streptomycin, 10 ng/ml PDGF-AA, and 10 ng/ml basic FGF changing the medium every second day.

10 B-II: Functional in vitro GPR17 assays

B-II-A: Calcium mobilization functional assay

GPR17 is a G-protein coupled receptor. GPR17 activation triggers Gq-type G-protein signaling resulting in endoplasmic reticulum calcium (Ca²⁺) stores release in cytosol which can be measured using Calcium 5 dye, a fluorescent indicator dye of cytosolic Ca²⁺ levels.

15 The compounds of the present invention were assessed either in the Ca²⁺ assay or in the GPR17 cAMP assay, described further below. Some representative examples were measured in both activity tests as indicated in Table 6, below.

Description of Ca²⁺ assay:

20 CHO hGPR17 were defrosted and seeded at a density of 20,000 cells per well into black 384-well plates with clear bottom. Cells were incubated overnight at 37 °C in a humidified atmosphere of 5% CO₂. Sixteen to twenty hours after seeding, CHO hGPR17 were loaded for 60 min with Calcium 5 dye, a cytosolic Ca²⁺ indicator fluorescent dye, according to

25 manufacturer's instructions. Fluorescent signal relative to cytosolic Ca²⁺ concentration was recorded over time at room temperature in FLIPR Tetra reader. Cells were first incubated for 30 minutes at room temperature in HBSS Hepes buffer pH 7.4 containing increasing concentrations of test compounds (typically 10⁻¹¹M to 10⁻⁶M). Then, 50 nM MDL29,951, a GPR17 agonist, was added to the cells. Inhibitory effects of varying

30 concentrations test compounds were measured and resulting pIC₅₀s were determined. All incubations were performed in duplicate and results were compared to a concentration response curve of GPR17 agonist and antagonist reference compounds. Analysis and curve fitting were performed in ActivityBase XE using XLfit 4-parameter logistic equation y

= $A + ((B-A)/(1+((C/x)^D)))$ where A, B, C and D stand for minimum y, maximum y, IC_{50} and slope, respectively.

Results of Ca^{2+} assay:

- 5 When tested in Ca^{2+} mobilization assay, compounds of the Examples typically exhibit values of pIC_{50} greater than or equal to 6.5; more preferably greater than or equal to 7.5, and even more preferably greater than or equal to 8.5. The activities of the Example compounds tested are depicted in the table 6 in Section B-IIB below. The activity ranges A, B and C refer to pIC_{50} values in the Ca^{2+} assay as follows: "A": $pIC_{50} 6.5 \leq x < 7.5$, "B":
10 $pIC_{50} 7.5 \leq x < 8.5$, "C": $8.5 \leq pIC_{50}$

B-IIB. cAMP accumulation functional assay

- GPR17 activation can also recruit Gi-type G-protein signaling, resulting in a decrease of intracellular cyclic adenosine monophosphate (cAMP). Intracellular cAMP changes can be measured using the HTRF cAMP dynamic assay kit from CisBio (Codolet, France). Using
15 homogenous time-resolved fluorescence technology (HTRF), the assay is based on competition between native cAMP produced by cells and cAMP labelled with the dye d2. The tracer binding was determined by an anti-cAMP antibody labeled with cryptate.

Description of cAMP assay

- CHO hGPR17 were detached with PBS containing EDTA and dispatched in black 384-
20 well plates with 5,000 cells per well. Cells were first incubated for 30 minutes at room temperature in HBSS Hepes (pH 7.4) containing vehicle or varying concentrations of test GPR17 antagonist/inverse agonist compounds. Then, a dose response curve of MDL29,951 GPR17 agonist (typically from $10^{-5}M$ to $10^{-10}M$) was added on vehicle and on each test GPR17 antagonist/inverse agonist compound concentration in a final volume of
25 20 μL HBSS Hepes buffer (pH 7.4) containing 1 % DMSO, 5 μM forskolin and 0.1 mM IBMX. After 60 minutes incubation at room temperature, the reaction is terminated and the cells lysed by adding the d2 detection reagent and the cryptate reagent in 10 μL lysis buffer each according to manufacturer's instructions. After 60 minutes incubation,
30 changes in cAMP concentrations are measured according to manufacturer's instructions using an Envision plate reader with laser excitation. All incubations were performed in duplicate. Data was analyzed using GraphPad Prism software using the 4-parameter logistic equation to measure MDL29,951 pEC_{50} s in absence and presence of GPR17 antagonist/inverse agonist test compounds. Dose ratio (DR) were plotted against

antagonist concentrations and Schild analysis provided estimated affinity pA_2 of GPR17 antagonist/inverse agonist test compounds.

Results of cAMP assay:

- 5 When tested in cAMP assay, compounds of the Examples typically exhibit values of pA_2 greater than or equal to 6.5; preferably greater than or equal to 7.5; more preferably greater than or equal to 8.5. The activities of the Example compounds tested are depicted in the table below. The activity ranges A, B and C refer to pA_2 values in the cAMP assay as follows: "A": pA_2 $6.5 \leq x < 7.5$, "B": pA_2 $7.5 \leq x < 8.5$, "C": $8.5 \leq pA_2$.

10

The following table 6 shows the pIC_{50} and pA_2 values of the Example compounds tested in the Ca_{2+} and the cAMP assay. Blanks in the pA_2 or the Ca_{2+} assay columns indicate that the respective compound was not yet tested in the respective assay, or that the result was not yet available.

15

Table 6:

Ex N°	Ca ²⁺ assay pIC_{50}	cAMP assay pA_2	Ex N°	Ca ²⁺ assay pIC_{50}	cAMP assay pA_2	Ex N°	Ca ²⁺ assay pIC_{50}	cAMP assay pA_2
I-1	A		I-2	C	B	I-3	B	C
I-4	A		I-5	B	B	I-6	C	C
I-7	B	B	I-8	A		I-9		C
I-10	C	C	I-11		C	I-12		C
I-13		B	I-14			I-15	A	A
I-16		C	I-17	A		I-18	A	A
I-19	A		I-20	A		I-21	A	B
I-22		C	I-23	A		I-24	A	
I-25	B	C	I-26		A	I-27		A
I-28		A	I-29		B	I-30		A
I-31			I-32	C	C	I-33	A	A
I-34	B	B	I-35		A	I-36		C
I-37		B	I-38		C	I-39		B
I-40		B	I-41		B	I-42		C
I-43		C	I-44		A	I-45		B

Ex N°	Ca ²⁺ assay pIC ₅₀	cAMP assay pA ₂	Ex N°	Ca ²⁺ assay pIC ₅₀	cAMP assay pA ₂	Ex N°	Ca ²⁺ assay pIC ₅₀	cAMP assay pA ₂
I-46		C	I-47		B	I-48		C
I-49		A	I-50		C	I-51		C
I-52		B	I-53		B	I-54		C
I-55		B	I-56		B	I-57		B
I-58		C	I-59			I-60		C
I-61		A	I-62		C	I-63		C
I-64		C	I-65		B	I-66		C
I-67		C	I-68		C	I-69		C
I-70	A		I-71		C	I-72		A

B-IIIC: Oligodendrocyte maturation/myelination assays

The effects of negative modulators of GPR17 on primary oligodendrocytes maturation/myelination can be assessed *in vitro* by immunoassays using antibodies directed against Myelin Basic Protein (MBP), as marker for mature oligodendrocytes.

5 Description of MBP western blot/oligodendrocyte/myelination assay

After 3-4 days in proliferation medium, rat primary OPCs were seeded at 25,000 cells per cm² in 12-well tissue culture plates and switched to growth factor-free Neurobasal medium to induce spontaneous *in vitro* differentiation and GPR17 protein expression. For terminal differentiation and quantification analyses of protein expression, after 24-48 h the growth factor-free medium was supplemented with 0.20 ng/mL triiodothyronine (T3) and 10 ng/mL ciliary neurotrophic factor together with 1 μM GPR17 antagonist/inverse agonists test compounds or vehicle for additional 3 days. Following compound treatment, cells were washed twice with ice-cold PBS and lysed in ice-cold lysis buffer (25 mM Tris, pH 7.4, 150 mM NaCl, 1 mM EDTA, 1% Triton X-100, 1% IGEPAL) supplemented with protease inhibitor mixture. Lysates were rotated 20 min at 4 °C and centrifuged at 15,000 x g at 4 °C for 10 min. Protein concentration was determined using the Pierce BCA Protein Assay according to manufacturer's instructions. 7.5–15 μg of protein were separated by 10% SDS-polyacrylamide gel electrophoresis and transferred to nitrocellulose membrane by electroblotting. After washing, membranes were blocked with Roti-Block for 1 h at room temperature and incubated overnight at 4 °C in Roti-Block with MBP antibody (1:5000, LifeSpan BioSciences). Membranes were washed 3 times with PBS containing 0.1% Tween and then incubated for 1 h at room temperature with a

horseradish peroxidase-conjugated goat anti-mouse IgG antibody in Roti-Block. The immunoreactive proteins were visualized by chemiluminescence using Amersham Biosciences ECL Prime Western blotting detection reagent and quantified by densitometry using Gelscan software. To normalize for equal loading and protein transfer, membranes
5 were reprobed with an antibody against β -actin (1:2500, BioLegend; secondary antibody goat anti-rabbit IgG antibody HRP (ABIN)). Changes in MBP expression level in the presence of test compounds were compared to MBP expression in control conditions.

The result of the addition of 1 μ M of compound I-22 (6-chloro-N-[6-(difluoromethoxy)-5-fluoro-2-methoxypyridin-3-yl]-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide) on myelin
10 expression is shown in Figure 1 (n=4, mean and SD).

Description of MBP fiber plates/oligodendrocyte maturation/myelination assay

The activity of the compounds of the present invention can be also tested in the fiber plate assay as follows:

OPCs are seeded at 16,000-22,000 cells per cm^2 in Mimetix Aligned 96-well fiber plates
15 (Electrospinning company). After 2 days in proliferation medium and 2 days in growth factor-free Neurobasal medium to induce spontaneous *in vitro* differentiation and GPR17 protein expression, vehicle or 1 μ M antagonist/ inverse agonist test compounds are added in terminal differentiation medium supplemented with 0.20 ng/mL triiodothyronine and 10 ng/mL ciliary neurotrophic factor for 6 days, changing the medium after 3 days. Then cells
20 are fixed in 4% paraformaldehyde, followed by PBS washes, permeabilization in 0.1% TritonX-100 in PBS and blocking with 10% goat serum and 1% bovine serum albumin in phosphate-buffered saline. MBP antibody will be diluted in blocking buffer (1:2000) and incubated for 1 h at 37 °C. Cells are washed in PBS again and incubated 1 h with Cy2-conjugated secondary antibodies against mouse IgG (Millipore, 1:500). After PBS washes,
25 cells will be stained with 0.2 μ g/mL DAPI, washed again and mounted with Mowiol. Fluorescent images are taken by using a Zeiss AxioObserver.Z1 microscope with ApoTome Imaging System and a Plan-Apochromat 20x/0.8 objective, with an eGFP filter (excitation 470/40 nm; emission 525/50 nm) and DAPI filter (excitation 365 nm; emission 445/50 nm). At least 15 random areas for control (terminal differentiation medium with
30 0.1% DMSO) and for test compounds are imaged using the same settings processed with Zeiss ZEN2.3 software. Changes in number myelinated fibers can be reported by group of fiber lengths (0 to 40 μ m, 41 to 60 μ m, 61 to 80, 81 to 100, 101 to 120 and >120 μ m)) in the absence or presence of the GPR17 negative modulators disclosed herein.