(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 June 2025 (19.06.2025)

WIPO | PCT

(10) International Publication Number
WO 2025/125666 A1

(51) International Patent Classification:
C07D 233/84 (2006.01) *C07D 417/12* (2006.01)
C07D 233/90 (2006.01) *C07D 471/04* (2006.01)
C07D 401/06 (2006.01) *C07D 487/04* (2006.01)
C07D 401/12 (2006.01) *C07D 487/12* (2006.01)
C07D 403/06 (2006.01) *A61P 25/02* (2006.01)
C07D 403/12 (2006.01) *A61K 31/4178* (2006.01)
C07D 405/12 (2006.01)

(21) International Application Number:
PCT/EP2024/086450

(22) International Filing Date:
16 December 2024 (16.12.2024)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
23217117.3 15 December 2023 (15.12.2023) EP

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

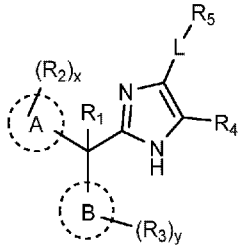
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:
— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*
— *in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE*

(54) Title: SUBSTITUTED IMIDAZOLES AS INHIBITORS OF NAV1.8

(57) Abstract: The invention relates to compounds according to general formula (I) which act as inhibitors of $Na_V1.8$ and can be used in the treatment of pain.



(I)

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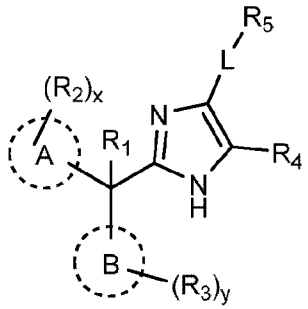
Substituted imidazoles as inhibitors of Nav1.8

The invention relates to compounds according to general formula (I)



(I)

which act as inhibitors of $Na_V1.8$ and can be used in the treatment of pain.

Normal pain sensation (nociception) serves primarily as a survival mechanism, the body's way of self-protection, alerting against (further) tissue damage and disease from noxious stimuli. For instance, acute pain can arise when the external environment (temperature, pressure, chemicals) activates modality specific receptors (nociceptors) and ion channels within the skin. The peripheral terminals of pain-signaling neurons – whose cell bodies are found in the dorsal root ganglia [DRG] and trigeminal ganglia [TG] – convert the external stimuli into electrochemical generator potentials. Specific voltage-gated sodium channels (Na_Vs) integrate and amplify these generator signals until the threshold for an action potential [AP] is reached. Thus, what starts as a noxious stimuli in the periphery eventually leads to action potential firing that travels towards the central nervous system, synapsing first onto neurons in the spinal cord and then towards the brain. Na_Vs also function to support propagation of action potentials to the central terminals within the spinal cord. At the end of its travels along the somatosensory pathway, the action potential signal is interpreted as pain by the brain (Lumpkin and Caterina, Nature (2007), Vol.445 pp 858-865; and Crawford and Caterina Toxicologic Pathology (2020) 48(1)-174; Goodwin G and McMahon S.B. Nature Reviews Neuroscience (2021) Vol 22 pp 263-274; Bennett D.L. et al. Physiol Rev 99 (2019) Vol 99 pp 1079-1151).

Abnormal persistent neuropathic pain arises as a consequence of a lesion or disease of this somatosensory pathway. In response to nerve injury or inflammation, abnormal changes in ion channel expression can cause hyper-excitability of pain-signaling neurons and their nerves/axons, thus resulting in pathological pain.

The voltage-gated $Na_V1.8$ sodium channel is a therapeutic target for analgesia because of its restricted expression profile (almost exclusive to peripheral sensory tissues), its placement along the pain pathway (free nerve endings, sciatic nerve, and DRG), prominent physiological role in pain signaling (supports upstroke of AP and facilitates repetitive AP firing), and supporting genetic/pharmaco-phenotypic evidence (human/animal studies showing changes in $Na_V1.8$ function cause parallel changes in pain sensitivity).

Regarding its expression profile along the pain pathway, because $Na_V1.8$ was first found predominantly in peripheral sensory neurons of the dorsal root ganglia (DRG) and trigeminal ganglia (TG), it was originally termed SNS (sensory neuron specific) (Akopian A.N. et al Nature (1996) Vol 379 pp 257-261) or PN3 (peripheral nerve 3)

(Sangameswaran L. et al J. Biol. Chem. (1996) Vol 271 pp 5953-5956). As well, $Na_V1.8$ is localized at free nerve endings, where pain signaling is initiated in the skin (Persson A.K. et al Mol. Pain. (2010) 6:84) and is diffusely localized along the entire length of non-myelinated axons of sciatic nerve (Rush A.M. et al. Eur.J.Neurosci (2005) Vol 22 pp 39-49).

In contrast, $Na_V1.8$ has minimal expression in nonneuronal tissue, such as heart and skeletal muscle, and in the CNS, including brain and spinal cord (9, 10, 338, 406) (Akopian A.N. op. cit.; Akopian A.N. et al. Nat. Neurosci (1999) Vol 2 pp 541-548; Novakovic S.D. et al. J. Neurosci. (1998) Vol 18, pp 2174-2187; and Sagameswaran L. op. cit.).

Regarding its physiological role, $Na_V1.8$ contributes the majority of the inward current during the rising phase of an all-or-none action potential in nociceptive sensory neurons (Blair N.T. et al. J. Neurosci. (2003) Vol 23 pp 10338-10350 and Renganathan M et al. J. Neurophysiol (2001) Vol 86 pp 629-640) – and also contributes most of the current in subsequent spikes during repetitive firing in DRG neurons (Choi J.S. J. Neurophysiol (2011) Vol 106 pp 3173-3184; and Tan Z.Y. et al. J. Neurosci. (2014) Vol 34 pp 7190-7197).

Regarding genetic and pharmacology studies, gain-of-function mutations in $Na_V1.8$ were found in patients with chronic neuropathic pain such as small fiber neuropathy (Faber C.G. et al. (2012) Ann. Neurol Vol 71 pp 26-39; Han C et al. J. Neurol Neurosurg Psychiatry (2014) Vol 85 pp 499-505; and, Kist A.M. et al. PLoS One (2016) Vol 11 e0161789); Eijkenboom I. et al J. Neurol Neurosurg Psychiatry (2019) 90 (3) pp 342-352); loss-of-function (gene knockout) studies in mice reduced pain sensitivity, notably in nociception (Laird J.M. et al. J. Neurosci (2002) J. Neurosci Vol 22 pp 8352-8356; Jarvis M.F. et al Proc Natl Acad Sci USA (2007) Vol 104 pp 8520-8525; Joshi S.K. et al Pain (2006) Vol 123 pp 75-82) and in neuropathic models (Roza C. et al J Physiol (2003) Vol 550 pp 921-926); $Na_V1.8$-selective small molecule inhibitors reduced pain in rodents, specifically in inflammatory and neuropathic models (Jarvis et al. op. cit.; Kort M.E. et al Bioorg Med Chem Lett (2010) Vol 20 pp 6812-6815; Scanio M.J. et al Bioorg Med Chem (2010) Vol 18 pp 7816-7825; Payne C.E. et al Br J Pharmacol (2015) Vol 172 pp 2654-2670).

Currently, non-selective Na_V channel inhibitors are used to treat epilepsy, cardiac arrhythmia, and chronic pain (Hille, B. J. Gen. Physiol. (1977) Vol. 69 pp. 497-515; Hille. B, Ion Channels of Excitable Membranes (1992) pp. 391-421; Sunderland, Mass., Sinauer Associates, Inc. 3rd ed.; Hondeghem L.M. and Katzung B.G. Annu. Rev. Pharmacol. Toxicol. (1984) Vol. 24. Pp. 387-423; Catterall W.A. Trends Pharmacol. Sci. (1987) Vol. 8 pp.57-65) – however, all of these analgesics have limited efficacy owing to dose-limiting adverse side-effects related to inhibiting $Na_V1.1$/$Na_V1.2$/1.6 (seizure liability), inhibiting $Na_V1.4$ (muscle weakness/paralysis), inhibiting $Na_V1.5$ (arrhythmia risk).

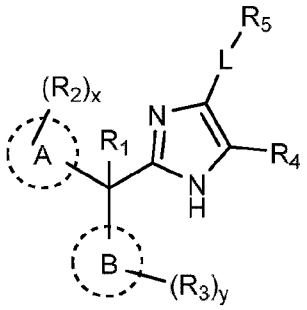
There is a need to develop a $Na_V1.8$-selective small molecule inhibitor as an effective and safe analgesic.

It was an object of the invention to provide novel compounds which are inhibitors, preferably selective inhibitors, of $Na_V1.8$, and which preferably have advantages over the compounds of the prior art. The novel compounds should in particular be suitable for use in the treatment of pain.

This object has been achieved by the subject-matter of the patent claims.

It was surprisingly found that the compounds according to the invention are highly potent and selective inhibitors of the $Na_V1.8$ channel. Further it was surprisingly found that the compounds according to the invention have advantageous properties compared to the $Na_V1.8$ inhibitors of the prior art.

The invention relates to a compound according to general formula (I)



(I)

wherein

R_1	represents H or OH;
A and B	independently from one another represent phenyl, 5 to 10-membered heteroaryl, C_{3-7}-cycloalkyl, or 4- to 10-membered heterocycloalkyl;
R_2 and R_3	independently from one another represent F, Cl, CN, C_{1-4}-alkyl, C_{3-6}-cycloalkyl, NH_2, $N(H)C_{1-4}$-alkyl, $N(C_{1-4}\text{-alkyl})_2$, OH, or $O\text{-}C_{1-4}$-alkyl;
x and y	independently from one another represent 0, 1, 2, 3, or 4;
R_4	represents H, Cl, C_{1-6}-alkyl, or C_{3-6}-cycloalkyl;
L	represents bond, C_{1-3}-alkylene or C_{1-2}-alkylene-N(H); and
R_5	represents $S(=O)R_6$, $S(=O)(=NH)R_6$, $S(=O)(=N(C_{1-4}\text{-alkyl}))R_6$, $S(=O)(=NR_6)R_6$, $S(=O)_2R_6$, $S(=O)_2NH_2$, $S(=O)_2N(H)R_6$, or $S(=O)_2N(C_{1-4}\text{-alkyl})R_6$;
R_6	represents C_{1-6}-alkyl, C_{3-7}-cycloalkyl, 4- to 10-membered heterocycloalkyl, C_{1-4}-alkylene-(C_{3-7}-cycloalkyl), or C_{1-4}-alkylene-(4- to 7-membered heterocycloalkyl);

or R_4 and R_5 together with the carbon atoms to which they are connected form 5- to 7- membered heterocycloalkyl;

wherein C_{1-6}-alkyl, C_{1-4}-alkyl, C_{1-4}-alkylene, C_{1-3}-alkylene and C_{1-2}-alkylene in each case independently from one another is linear or branched, saturated or unsaturated;

wherein C_{1-6}-alkyl, C_{1-4}-alkyl, C_{1-4}-alkylene, C_{1-3}-alkylene, C_{1-2}-alkylene, C_{3-6}-cycloalkyl, C_{5-7}-cycloalkyl, 4- to 7-membered heterocycloalkyl, 4- to 10- membered heterocycloalkyl, and 5- to 7- membered heterocycloalkyl in each case independently from one another are unsubstituted or mono- or polysubstituted with one or more substituents selected from F; Cl; CN; C_{1-6}-alkyl; C_{1-6}-alkylene-NH_2, CF_3; CF_2H; CFH_2; $C(O)\text{-}C_{1-6}$-alkyl; C(O)-OH; $C(O)\text{-}OC_{1-6}$-alkyl; $C(O)\text{-}NH_2$; $C(O)\text{-}N(H)(C_{1-6}\text{-alkyl})$; $C(O)\text{-}N(C_{1-6}\text{-alkyl})_2$; OH; =O; OCF_3; OCF_2H; $OCFH_2$; $O\text{-}C_{1-6}$-alkyl;; NH_2; $N(H)(C_{1-6}\text{-alkyl})$; $N(C_{1-6}\text{-alkyl})_2$; $N(H)\text{-}C(O)\text{-}C_{1-6}$-alkyl; and $S(O)_2\text{-}C_{1-6}$-alkyl;;

wherein phenyl, 5 to 10-membered heteroaryl and 5 or 6-membered heteroaryl in each case independently from one another are unsubstituted or mono- or polysubstituted with one or more substituents selected from F; Cl; CN;

C_{1-6}-alkyl; CF_3; CF_2H; CFH_2; OH; OCF_3; OCF_2H; $OCFH_2$; O-C_{1-6}-alkyl; NH_2; N(H)(C_{1-6}-alkyl); and N(C_{1-6}-alkyl)$_2$;

in the form of the free compound or a physiologically acceptable salt thereof.

In a preferred embodiment, the compound according to the invention is present in form of the free compound. For the purpose of specification, "free compound" preferably means that the compound according to the invention is not present in form of a salt. Methods to determine whether a chemical substance is present as the free compound or as a salt are known to the skilled artisan such as ^{14}N or ^{15}N solid state NMR, x-ray diffraction, x-ray powder diffraction, IR, Raman, XPS. ^1H-NMR recorded in solution may also be used to consider the presence of protonation.

In another preferred embodiment, the compound according to the invention is present in form of a physiologically acceptable salt. For the purposes of this specification, the term "physiologically acceptable salt" preferably refers to a salt obtained from a compound according to the invention and a physiologically acceptable acid or base.

According to the invention, the compound according to the invention may be present in any possible form including solvates, cocrystals and polymorphs. For the purposes of this specification, the term "solvate" preferably refers to an adduct of (i) a compound according to the invention and/or a physiologically acceptable salt thereof with (ii) distinct molecular equivalents of one or more solvents.

Further, the compound according to the invention may be present in form of the racemate, enantiomers, diastereomers, tautomers or any mixtures thereof. The person skilled in the art knows that imidazoles show annular tautomerism.

The compounds according to the invention may have one or more stereocenter. The person skilled in art knows by looking at a chemical structure whether the depicted compound has one or more stereocenters or not.

For some compounds according to the invention that have one or more stereocenters and which chemical structures are disclosed in the examples of the present application, the chemical structure includes bold bonds and/or hashed bonds to indicate the relative structural orientation of those substituents connected by the bold bonds and/or hashed bonds to the superior structure. If the bold bonds and/or hashed bonds are depicted in form of a wedge, the absolute stereochemical configuration of the compound is known and thereby indicated. If the bold bonds and/or hashed bonds are depicted as a straight bond (i.e. no wedge), the absolute stereochemical configuration of the compound has not been determined. In that case, the bold bonds and/or hashed bonds merely serve to indicate that this particular compound is present as one enantiomer or one diastereomer (e.g. cis-diastereomer (i.e. mixture of two cis-enantiomers) or trans-diastereomer (i.e. mixture of two trans-enantiomers)). All compounds according to the invention that have one or more stereocenters but which chemical structures disclosed in the examples of the present application do not include bold bonds and/or hashed bonds, are present as a mixture of the respective stereoisomers.

The invention also includes isotopic isomers of a compound of the invention, wherein at least one atom of the compound is replaced by an isotope of the respective atom which is different from the naturally predominantly occurring isotope, as well as any mixtures of isotopic isomers of such a compound. Preferred isotopes are ^2H

(deuterium), ^{3}H (tritium), ^{13}C and ^{14}C. Isotopic isomers of a compound of the invention can generally be prepared by conventional procedures known to a person skilled in the art.

According to the invention, the terms "C_{1-3}-alkyl", "C_{1-4}-alkyl" and "C_{1-6}-alkyl" preferably mean acyclic and preferably saturated hydrocarbon residues, which can be linear (i.e. unbranched) or branched and which can be unsubstituted or mono- or polysubstituted (e.g. di- or trisubstituted), and which contain 1 to 3 (i.e. 1, 2, or 3), 1 to 4 (i.e. 1, 2, 3 or 4) or 1 to 6 (i.e. 1, 2, 3, 4, 5 or 6) carbon atoms, respectively. Preferably, C_{1-3}-alkyl, C_{1-4}-alkyl and C_{1-6}-alkyl are saturated. Preferred C_{1-3}-alkyl groups are selected from the group consisting of methyl, ethyl, n-propyl, and 2-propyl. Preferred C_{1-4}-alkyl groups are selected from the group consisting of methyl, ethyl, n-propyl, 2-propyl, n-butyl, isobutyl, sec-butyl and tert-butyl. Preferred C_{1-6}-alkyl groups are selected from the group consisting of methyl, ethyl, n-propyl, 2-propyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, 2-pentyl, 3-pentyl, 2-methylbutyl, 3-methylbutyl, 3-methylbut-2-yl, 2-methylbut-2-yl, 2,2-dimethylpropyl, and n-hexyl.

Still further according to the invention, the terms "C_{3-7}-cycloalkyl", "C_{3-6}-cycloalkyl", and "C_{5-7}-cycloalkyl" preferably means monocyclic or polycyclic, preferably monocyclic or bicyclic, aliphatic hydrocarbons containing 3 to 7 (i.e. 3, 4, 5, 6 or 7), 3 to 6 (i.e. 3, 4, 5 or 6) or 5 to 7 (i.e. 5, 6 or 7) carbon atoms, wherein the hydrocarbons in each case can be saturated or unsaturated (but not aromatic), unsubstituted or mono- or polysubstituted.

For the purpose of this specification, "polycyclic" and "bicyclic" shall preferably mean fused, bridged or spiro cyclic systems.

Preferably, C_{3-7}-cycloalkyl, C_{3-6}-cycloalkyl, and C_{5-7}-cycloalkyl are saturated. C_{3-7}-cycloalkyl, C_{3-6}-cycloalkyl, and C_{5-7}-cycloalkyl can be bound to the respective superordinate general structure via any desired and possible ring member of the cycloalkyl group. C_{3-7}-cycloalkyl, C_{3-6}-cycloalkyl and C_{5-7}-cycloalkyl can also be fused with further saturated or (partially) unsaturated heterocycloalkyl, aromatic or heteroaromatic ring systems, preferably aromatic ring system, which can in turn be unsubstituted or mono- or polysubstituted, thereby being part of a bi- or polycyclic system having up to 14 ring members. Accordingly, the terms "C_{3-7}-cycloalkyl", "C_{3-6}-cycloalkyl", and "C_{5-7}-cycloalkyl" preferably include monocyclic or polycyclic, preferably monocyclic or bicyclic, aliphatic hydrocarbons containing 3 to 7, 3 to 6 or 5 to 7 carbon atoms; which are fused with a phenyl moiety. Preferred C_{3-7}-cycloalkyl groups are selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, spiro[2.2]pentyl, spiro[2.3]hexyl, spiro[3.3]heptyl, bicyclo[1.1.0]butyl, bicyclo[2.1.0]pentyl, bicyclo[2.1.1]hexyl, bicyclo[3.1.1]heptyl, bicyclo[2.2.1]heptyl, bicyclo[3.1.0]hexyl, bicyclo[3.2.0]heptyl, and bicyclo[4.1.0]heptyl.

Preferred C_{3-6}-cycloalkyl groups are selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, spiro[2.2]pentyl, spiro[2.3]hexyl, bicyclo[1.1.0]butyl, bicyclo[2.1.0]pentyl, bicyclo[2.1.1]hexyl, and bicyclo[3.1.0]hexyl.

Preferred C_{5-7}-cycloalkyl groups are selected from the group consisting of cyclopentyl, cyclohexyl, cycloheptyl, spiro[2.2]pentyl, spiro[2.3]hexyl, spiro[3.3]heptyl, bicyclo[2.1.0]pentyl, bicyclo[2.1.1]hexyl, bicyclo[3.1.1]heptyl, bicyclo[2.2.1]heptyl, bicyclo[3.1.0]hexyl, bicyclo[3.2.0]heptyl, and bicyclo[4.1.0]heptyl.

Further according to the present invention, the terms "C_{1-3}-alkylene" and "C_{1-2}-alkylene" relate to linear or branched, preferably linear, and preferably saturated aliphatic residues which are preferably selected from the group consisting of methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), propylene ($-CH_2CH_2CH_2-$ or $-C(CH_3)_2-$), more preferably methylene ($-CH_2-$) and ethylene ($-CH_2CH_2$).

According to the invention, C_{1-6}-alkyl, C_{1-4}-alkyl, C_{1-4}-alkylene, C_{1-3}-alkylene and C_{1-2}-alkylene in each case independently from one another is linear or branched, saturated or unsaturated. In a preferred embodiment, C_{1-6}-alkyl, C_{1-4}-alkyl, C_{1-4}-alkylene, C_{1-3}-alkylene and C_{1-2}-alkylene in each case independently from one another is linear or branched, and saturated.

According to the present invention, the terms "4 to 7-membered heterocycloalkyl", "5 to 7-membered heterocycloalkyl" and "4 to 10-membered heterocycloalkyl" preferably mean monocyclic or polycyclic, preferably monocyclic or bicyclic, heterocycloaliphatic saturated or unsaturated (but not aromatic) residues having 4 to 7 (i.e. 4, 5, 6 or 7), 5 to 7 (i.e. 5, 6 or 7) or 4 to 10 (i.e. 4, 5, 6, 7, 8, 9 or 10) ring memberswherein in each case at least one, if appropriate also two or three carbon atoms are replaced by a heteroatom or a heteroatom group each selected independently of one another from the group consisting of O, S, S(=O), $S(=O)_2$, N, NH and $N(C_{1-4}$-alkyl) such as $N(CH_3)$, wherein the carbon atoms of the ring can be unsubstituted or mono- or polysubstituted. Preferably, 4 to 7-membered heterocycloalkyl, 5 to 7-membered heterocycloalkyl and 4 to 10-membered heterocycloalkyl are saturated. The 4 to 7-membered heterocycloalkyl, the 5 to 7-membered heterocycloalkyl and the 4 to 10-membered heterocycloalkyl groups can also be fused with further saturated or (partially) unsaturated cycloalkyl, aromatic or heteroaromatic ring systems, preferably aromatic ring system, which can in turn be unsubstituted or mono- or polysubstituted, if not indicated otherwise, thereby being being part of a bi- or polycyclic system having up to 14 ring members.. In a preferred embodiment, 4 to 7-membered heterocycloalkyl, 5 to 7-membered heterocycloalkyl and 4 to 10-membered heterocycloalkyl are not fused with further ring systems. Still more preferably, 4 to 7-membered heterocycloalkyl, 5 to 7-membered heterocycloalkyl and 4 to 10-membered heterocycloalkyl are not fused with further ring systems and are saturated. In another preferred embodiment, 4 to 7-membered heterocycloalkyl, 5 to 7-membered heterocycloalkyl and 4 to 10-membered heterocycloalkyl are condensed with further ring systems, preferably phenyl. The 4 to 7-membered heterocycloalkyl, the 5 to 7-membered heterocycloalkyl and 4 to 10-membered heterocycloalkyl group can be bound to the superordinate general structure via any desired and possible ring member of the heterocycloaliphatic residue if not indicated otherwise. In a preferred embodiment, 4 to 7-membered heterocycloalkyl, 5 to 7-membered heterocycloalkyl and 4 to 10-membered heterocycloalkyl are bound to the superordinate general structure via a carbon atom. In another preferred embodiment, 4 to 7-membered heterocycloalkyl, 5 to 7-membered heterocycloalkyl and 4 to 10-membered heterocycloalkyl are bound to the superordinate general structure via a heteroatom, in particular N.

Preferred 4 to 7-membered heterocycloalkyl groups are selected from the group consisting of 1,1-dioxo tetrahydrothiophenyl, 1-oxo thiomorpholinyl, tetrahydropyranyl, oxetanyl, tetrahydrofuranyl, morpholinyl, pyrrolidinyl, pyrrolidinonyl, azetidinyl, piperazinyl, piperazinonyl, piperidinyl, thietanyl, 1,1-dioxothietanyl, 2,6-diazaspiro[3.3]heptyl, 2,5-diazabicyclo[2.2.1]heptyl, azepanyl, dioxepanyl, oxazepanyl, diazepanyl, thiazolidinyl, tetrahydrothiophenyl, tetrahydropyridinyl, thiomorpholinyl, 4-methylpiperazinyl, morpholinonyl, dithiolanyl, dihydropyrrolyl, dioxanyl, dioxolanyl, dihydropyridinyl, dihydrofuranyl, dihydroisoxazolyl, dihydrooxazolyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, pyrazolidinyl, and cromanyl.

Particularly preferred 4 to 7-membered heterocycloalkyl groups are selected from 5 to 7-membered heterocycloalkyl groups. Preferred 5 to 7-membered heterocycloalkyl groups are selected from the group consisting of 1,1-dioxo tetrahydrothiophenyl, 1-oxo thiomorpholinyl, tetrahydropyranyl, tetrahydrofuranyl, morpholinyl, pyrrolidinyl, pyrrolidinonyl, piperazinyl, piperazinonyl, piperidinyl, 2,6-diazaspiro[3.3]heptyl, 2,5-diazabicy-

clo[2.2.1]heptyl, azepanyl, dioxepanyl, oxazepanyl, diazepanyl, thiazolidinyl, tetrahydrothiophenyl, tetrahydropyridinyl, thiomorpholinyl, 4-methylpiperazinyl, morpholinonyl, dithiolanyl, dihydropyrrolyl, dioxanyl, dioxolanyl, dihydropyridinyl, dihydrofuranyl, dihydroisoxazolyl, dihydrooxazolyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, pyrazolidinyl and cromanyl.

Preferred 4 to 10-membered heterocycloalkyl groups are selected from the group consisting of tetrahydro-2H-thiopyranyl 1,1-dioxide, 1-oxo thiomorpholinyl, tetrahydropyranyl, oxetanyl, tetrahydrofuranyl, morpholinyl, pyrrolidinyl, pyrrolidinonyl, azetidinyl, piperazinyl, piperazinonyl, piperidinyl, thietanyl, 1,1-dioxothietanyl, 2,6-diazaspiro[3.3]heptyl, 2,5-diazabicyclo[2.2.1]heptyl, cromanyl, thiepanyl 1,1-dioxide, 1,2-thiazepanyl 1,1-dioxide, 2,5,6,7-tetrahydro-1,2-thiazepinyl 1,1-dioxide, 5,6-dihydro-2H-1,2-thiazinyl 1,1-dioxide, 1,1-dioxo tetrahydrothiophenyl, 2-oxaspiro[3.4]octyl, 5-oxaspiro[2.4]heptyl, 2-oxabicyclo[2.1.1]hexyl, 1,1-dioxo thietanyl, 2,3-dihydro-[1,4]dioxino[2,3-b]pyridyl, tetrahydro-1,8-naphthyridinyl, azepanyl, dioxepanyl, oxazepanyl, diazepanyl, thiazolidinyl, tetrahydrothiophenyl, tetrahydropyridinyl, thiomorpholinyl, 4-methylpiperazinyl, morpholinonyl, dithiolanyl, dihydropyrrolyl, dioxanyl, dioxolanyl, dihydropyridinyl, dihydrofuranyl, dihydroisoxazolyl, dihydrooxazolyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, pyrazolidinyl, 5,7-dihydrofuro[3,4-b]pyridinyl, and 5,7-dihydrofuro[3,4-d]pyrimidinyl, more preferably tetrahydro-2H-thiopyranyl 1,1-dioxide, 1-oxo thiomorpholinyl, tetrahydropyranyl, oxetanyl, tetrahydrofuranyl, pyrrolidinyl, pyrrolidinonyl, azetidinyl, piperazinyl, piperazinonyl, piperidinyl, 1,1-dioxothietanyl, 2,6-diazaspiro[3.3]heptyl, 2,5-diazabicyclo[2.2.1]heptyl, cromanyl, thiepanyl 1,1-dioxide, 1,2-thiazepanyl 1,1-dioxide, 2,5,6,7-tetrahydro-1,2-thiazepinyl 1,1-dioxide and 5,6-dihydro-2H-1,2-thiazinyl 1,1-dioxide.

According to the present invention, the terms “5 to 10-membered heteroaryl” and "5- to 6-membered heteroaryl“ preferably mean a 5, 6, 7, 8, 9 or 10-membered and 5 or 6-membered monocyclic or bicyclic aromatic residue, respectively, which contains at least 1, if appropriate also 2, 3, 4 or 5 heteroatoms, wherein the heteroatoms are each selected independently of one another from the group S, N and O and the heteroaryl residue can be unsubstituted or mono- or polysubstituted, if not indicated otherwise. In the case of substitution on the heteroaryl, the substituents can be the same or different and be in any desired and possible position of the heteroaryl. The binding to the superordinate general structure can be carried out via any desired and possible ring member of the heteroaryl residue if not indicated otherwise. Preferably, the 5 to 10-membered heteroaryl and 5- to 6-membered heteroaryl are bound to the suprordinate general structure via a carbon atom of the heterocycle. The heteroaryl can also be fused with further saturated or (partially) unsaturated cycloalkyl, or heterocycloalkyl ring systems, which can in turn be unsubstituted or mono- or polysubstituted, thereby being being part of a bi- or polycyclic system having up to 14 ring members.. In a preferred embodiment, the 5 to 10-membered heteroaryl and 5- to 6-membered heteroaryl are not fused with further saturated or (partially) unsaturated cycloalkyl, or heterocycloalkyl ring systems. Preferably, the 5 to 10-membered heteroaryl is selected from 5- to 6-membered heteroaryl. Preferably, the 5- to 6-membered heteroaryl is selected from the group consisting of pyridyl (i.e. 2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, furanyl, thienyl (thiophenyl), triazolyl, thiadiazolyl, 4,5,6,7-tetrahydro-2H-indazolyl, 2,4,5,6-tetrahydrocyclopenta[c]pyrazolyl, benzofuranyl, benzoimidazolyl, benzothienyl, benzothiadiazolyl, benzothiazolyl, benzotriazolyl, benzooxazolyl, benzooxadiazolyl, quinazolinyl, quinoxalinyl, carbazolyl, quinolinyl, dibenzofuranyl, dibenzothienyl, imidazothiazolyl, indazolyl, indolizinyl, indolyl, isoquinolinyl, naphthyridinyl, oxazolyl, oxadiazolyl, phenazinyl, phenothiazinyl, phthalazinyl, purinyl, phenazinyl, tetrazolyl and triazinyl. Particularly preferred 5- to 6-membered heteroaryl are selected from the group consisting of pyridyl (i.e. 2-pyridyl, 3-pyridyl, 4-pyridyl).

In connection with the terms "C_{1-6}-alkyl", "C_{1-4}-alkyl", "C_{1-4}-alkylene", "C_{1-3}-alkylene", "C_{1-2}-alkylene", "C_{3-7}-cycloalkyl", "C_{3-6}-cycloalkyl", "C_{5-7}-cycloalkyl", "4- to 7- membered heterocycloalkyl", "4- to 10- membered heterocycloalkyl" and "5- to 7- membered heterocycloalkyl" the term "substituted" refers in the sense of the invention, with respect to the corresponding residues or groups, to the single substitution (monosubstitution) or multiple substitution (polysubstitution), e.g. disubstitution, trisubstitution or tetrasubstitution; more preferably to monosubstitution, disubstitution or trisubstitution; of one or more hydrogen atoms each independently of one another by at least one substituent. In case of a multiple substitution, i.e. in case of polysubstituted residues, such as di- or trisubstituted residues, these residues may be polysubstituted either on different or on the same atoms, for example trisubstituted on the same carbon atom, as in the case of CF_3, CH_2CF_3 or disubstituted as in the case of 1,1-difluorocyclopropyl, or at various points, as in the case of 1-chloro-3-fluorocyclopropyl. The multiple substitution can be carried out using the same or using different substituents.

If a residue occurs multiply within a molecule, then this residue can have respectively different meanings for various substituents: if, for example, both R_4 and R_6 denote C_{1-6}-alkyl, then C_{1-6}-alkyl can e.g. represent methyl for R_4 and can represent 2-propyl for R_6.

According to the invention, C_{1-6}-alkyl, C_{1-4}-alkyl, C_{1-4}-alkylene, C_{1-3}-alkylene, C_{1-2}-alkylene, C_{3-7}-cycloalkyl, C_{3-6}-cycloalkyl, C_{5-7}-cycloalkyl, 4- to 7- membered heterocycloalkyl, 4- to 10- membered heterocycloalkyl and 5- to 7- membered heterocycloalkyl in each case independently from one another are unsubstituted or mono- or polysubstituted with one or more substituents selected from F; Cl; CN; C_{1-6}-alkyl; C_{1-6}-alkylene-NH_2, CF_3; CF_2H; CFH_2; C(O)-C_{1-6}-alkyl; C(O)-OH; C(O)-OC_{1-6}-alkyl; C(O)-NH_2; C(O)-N(H)(C_{1-6}-alkyl); C(O)-N(C_{1-6}-alkyl)$_2$; OH; =O; OCF_3; OCF_2H; $OCFH_2$; O-C_{1-6}-alkyl;; NH_2; N(H)(C_{1-6}-alkyl); N(C_{1-6}-alkyl)$_2$; N(H)-C(O)-C_{1-6}-alkyl; and S(O)$_2$-C_{1-6}-alkyl..

Further according to the invention, phenyl, 5 to 10-membered heteroaryl and 5 or 6-membered heteroaryl in each case independently from one another are unsubstituted or mono- or polysubstituted with one or more substituents selected from F; Cl; CN; C_{1-6}-alkyl; CF_3; CF_2H; CFH_2; OH; OCF_3; OCF_2H; $OCFH_2$; O-C_{1-6}-alkyl; NH_2; N(H)(C_{1-6}-alkyl); and N(C_{1-6}-alkyl)$_2$; preferably F; Cl; C_{1-6}-alkyl; CF_3; OH; OCF_3; and O-C_{1-6}-alkyl.

According to the invention, A and B independently from one another represent phenyl, 5 to 10-membered heteroaryl, C_{3-7}-cycloalkyl, or 4- to 10-membered heterocycloalkyl; preferably phenyl, 5 or 6-membered heteroaryl, C_{3-7}-cycloalkyl, or 4- to 7-membered heterocycloalkyl ; more preferably phenyl, 5- or 6-membered heteroaryl, or C_{3-7}-cycloalkyl; more preferably phenyl or 5- or 6-membered heteroaryl.

In a preferred embodiment, at least one of A and B represents phenyl or 5- or 6-membered heteroaryl.

In another preferred embodiment, A represents phenyl.

In still another preferred embodiment, B represents phenyl, 5- or 6-membered heteroaryl, or C_{3-7}-cycloalkyl; more preferably phenyl or 5- or 6-membered heteroaryl; most preferably phenyl or pyridyl.

In another preferred embodiment, B represents phenyl, pyridyl, thiophenyl, thiazolyl, oxazolyl, cyclobutyl, cyclopentyl, cyclohexyl, spiro[2.3]hexyl, spiro[3.3]heptyl or cromanyl.

According to the invention, R_1 represents H, or OH.

In a preferred embodiment, R_1 represents H.

According to the invention, R_2 and R_3 independently from one another represent F, Cl, CN, C_{1-4}-alkyl, C_{3-6}-cycloalkyl, NH_2, $N(H)C_{1-4}$-alkyl, $N(C_{1-4}$-alkyl$)_2$, OH, or O-C_{1-4}-alkyl; preferably wherein C_{1-4}-alkyl can in each case independently be unsubstituted, mono-, di- or trisubstituted with F.

In a preferred embodiment, R_2 represents F, Cl, OCH_3, OCF_3, or CHF_2.

In another preferred embodiment, R_3 represents F, Cl, NH_2, C_{1-4}-alkylor O-C_{1-4}-alkyl; preferably wherein C_{1-4}-alkyl can in each case independently be unsubstituted, mono-, di- or trisubstituted with F.

Particularly preferably, R_3 represents F, Cl, NH_2, CH_3, CF_3, CHF_2, OCH_3, OCF_3, $OCHF_2$ or O-CH_2-CF_3.

In a preferred embodiment, when x and y are 2, 3 or 4; the 2, 3 or 4 entities of R_2 and the 2, 3 or 4 entities of R_3 are not identical. In a particularly preferred embodiment, when x represents 2, one R_2 will represent F and one R_2 will represent Cl. In a particularly preferred embodiment, when y represents 2, one R_3 will represent F and one R_3 will represent Cl.

According to the invention, x and y independently from one another represent 0, 1, 2, 3, or 4. In a preferred embodiment, x and y independently from one another represent 1 or 2.

In another preferred embodiment, x and y independently from one another represent 0, 1, 2 or 3; more preferably 0, 1 or 2; most preferably 1 or 2 and inparticular 2.

In another preferred embodiment, x and y independently from one another represent 1, 2, 3, or 4; preferably 1, 2 or 3; more preferably 1 or 2; and most preferably 2.

According to the invention, R_4 represents H, Cl, C_{1-6}-alkyl, or C_{3-6}-cycloalkyl; preferably H, Cl, methyl, ethyl, CH_2OH, CH_2OCH_3, CF_3 or cyclopropyl. In a preferred embodiment, R_4 represents H.

According to the invention, L represents bond, C_{1-3}-alkylene or C_{1-2}-alkylene-N(H).

In a preferred embodiment, L represents bond or C_{1-3}-alkylene; more preferably bond, methylene, or ethylene.

According to the invention, R_5 represents $S(=O)R_6$, $S(=O)(=NH)R_6$, $S(=O)(=N(C_{1-4}$-alkyl$))R_6$, $S(=O)(=NR_6)R_6$, $S(=O)_2R_6$, $S(=O)_2NH_2$, $S(=O)_2N(H)R_6$, or $S(=O)_2N(C_{1-4}$-alkyl$)R_6$..

In a preferred embodiment, R_5 represents $S(=O)R_6$, $S(=O)(=NH)R_6$, $S(=O)(=N(C_{1-4}$-alkyl$))R_6$, $S(=O)_2R_6$, $S(=O)_2NH_2$, $S(=O)_2N(H)R_6$, or $S(=O)_2N(C_{1-4}$-alkyl$)R_6$.

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According to the invention, R_6 represents C_{1-6}-alkyl, C_{3-7}-cycloalkyl, 4- to 10-membered heterocycloalkyl, C_{1-4}-alkylene-(C_{3-7}-cycloalkyl), or C_{1-4}-alkylene-(4- to 7-membered heterocycloalkyl).

In a preferred embodiment, R_6 represents

(i) C_{1-6}-alkyl selected from the group consisting of methyl, ethyl, n-propyl, 2-propyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, 2-pentyl, 3-pentyl, 2-methylbutyl, 3-methylbutyl, 3-methylbut-2-yl, 2-methyl-but-2-yl, 2,2-dimethylpropyl, and n-hexyl;

(ii) C_{3-7}-cycloalkyl selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, spiro[2.2]pentyl, spiro[2.3]hexyl, spiro[3.3]heptyl, bicyclo[1.1.0]butyl, bicyclo[2.1.0]pentyl, bicyclo[2.1.1]hexyl, bicyclo[3.1.1]heptyl, bicyclo[2.2.1]heptyl, bicyclo[3.1.0]hexyl, bicyclo[3.2.0]heptyl, and bicyclo[4.1.0]heptyl;

(iii) 4- to 7-membered heterocycloalkyl selected from the group consisting of 1,1-dioxo tetrahydrothiophenyl, 1-oxo thiomorpholinyl, tetrahydropyranyl, oxetanyl, tetrahydrofuranyl, morpholinyl, pyrrolidinyl, pyrrolidinonyl, azetidinyl, piperazinyl, piperazinonyl, piperidinyl, thietanyl, 1,1-dioxothietanyl, 2,6-diazaspiro[3.3]heptyl, 2,5-diazabicyclo[2.2.1]heptyl, tetrahydro-2H-thiopyranyl 1,1-dioxide, azepanyl, dioxepanyl, oxazepanyl, diazepanyl, thiazolidinyl, tetrahydrothiophenyl, tetrahydropyridinyl, thiomorpholinyl, 4-methylpiperazinyl, morpholinonyl, dithiolanyl, dihydropyrrolyl, dioxanyl, dioxolanyl, dihydropyridinyl, dihydrofuranyl, dihydroisoxazolyl, dihydrooxazolyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, and pyrazolidinyl;

(iv) C_{1-4}-alkylene-(C_{3-7}-cycloalkyl) selected from the group consisting of $(CH_2)_{1-2}$-cyclopropyl, $(CH_2)_{1-2}$-cyclobutyl, $(CH_2)_{1-2}$-cyclopentyl, $(CH_2)_{1-2}$-cyclohexyl; $(CH_2)_{1-2}$-cycloheptyl, $(CH_2)_{1-2}$-spiro[2.2]pentyl, $(CH_2)_{1-2}$-spiro[2.3]hexyl, $(CH_2)_{1-2}$-spiro[3.3]heptyl, $(CH_2)_{1-2}$-bicyclo[1.1.0]butyl, $(CH_2)_{1-2}$-bicyclo[2.1.0]pentyl, $(CH_2)_{1-2}$-bicyclo[2.1.1]hexyl, $(CH_2)_{1-2}$-bicyclo[3.1.1]heptyl, $(CH_2)_{1-2}$-bicyclo[2.2.1]heptyl, $(CH_2)_{1-2}$-bicyclo[3.1.0]hexyl, $(CH_2)_{1-2}$-bicyclo[3.2.0]heptyl, and $(CH_2)_{1-2}$-bicyclo[4.1.0]heptyl; or

(v) C_{1-4}-alkylene-(4- to 7-membered heterocycloalkyl) selected from the group consisting of $(CH_2)_{1-2}$-(1,1-dioxo tetrahydrothiophenyl), $(CH_2)_{1-2}$-(1-oxo thiomorpholinyl), $(CH_2)_{1-2}$-tetrahydropyranyl, $(CH_2)_{1-2}$-oxetanyl, $(CH_2)_{1-2}$-tetrahydrofuranyl, $(CH_2)_{1-2}$-morpholinyl, $(CH_2)_{1-2}$-pyrrolidinyl, $(CH_2)_{1-2}$-pyrrolidinonyl, $(CH_2)_{1-2}$-azetidinyl, $(CH_2)_{1-2}$-piperazinyl, $(CH_2)_{1-2}$-piperazinonyl, $(CH_2)_{1-2}$-piperidinyl, $(CH_2)_{1-2}$-thietanyl, $(CH_2)_{1-2}$-(1,1-dioxothietanyl), $(CH_2)_{1-2}$-(2,6-diazaspiro[3.3]heptyl), $(CH_2)_{1-2}$-(2,5-diazabicyclo[2.2.1]heptyl), $(CH_2)_{1-2}$-tetrahydro-2H-thiopyranyl 1,1-dioxide, $(CH_2)_{1-2}$-azepanyl, $(CH_2)_{1-2}$-dioxepanyl, $(CH_2)_{1-2}$-oxazepanyl, $(CH_2)_{1-2}$-diazepanyl, $(CH_2)_{1-2}$-thiazolidinyl, $(CH_2)_{1-2}$-tetrahydrothiophenyl, $(CH_2)_{1-2}$-tetrahydropyridinyl, $(CH_2)_{1-2}$-thiomorpholinyl, $(CH_2)_{1-2}$-(4-methylpiperazinyl), $(CH_2)_{1-2}$-morpholinonyl, $(CH_2)_{1-2}$-dithiolanyl, $(CH_2)_{1-2}$-dihydropyrrolyl, $(CH_2)_{1-2}$-dioxanyl, $(CH_2)_{1-2}$-dioxolanyl, $(CH_2)_{1-2}$-dihydropyridinyl, $(CH_2)_{1-2}$-dihydrofuranyl, $(CH_2)_{1-2}$-dihydroisoxazolyl, $(CH_2)_{1-2}$-dihydrooxazolyl, $(CH_2)_{1-2}$-imidazolidinyl, $(CH_2)_{1-2}$-isoxazolidinyl, $(CH_2)_{1-2}$-oxazolidinyl, and $(CH_2)_{1-2}$-pyrazolidin;

wherein said methyl, ethyl, n-propyl, 2-propyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, 2-pentyl, 3-pentyl, 2-methylbutyl, 3-methylbutyl, 3-methylbut-2-yl, 2-methylbut-2-yl, 2,2-dimethylpropyl, n-hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, spiro[2.2]pentyl, spiro[2.3]hexyl, spiro[3.3]heptyl, bicyclo[1.1.0]butyl, bicyclo[2.1.0]pentyl, bicyclo[2.1.1]hexyl, bicyclo[3.1.1]heptyl, bicyclo[2.2.1]heptyl, bicyclo[3.1.0]hexyl, bicyclo[3.2.0]heptyl, and bicyclo[4.1.0]heptyl, 1,1-dioxo tetrahydrothiophenyl, 1-oxo thiomorpholinyl, tetrahydropyranyl, oxetanyl, tetrahydrofuranyl, morpholinyl, pyrrolidinyl, pyrrolidinonyl, azetidinyl, piperazinyl, piperazinonyl, piperidinyl, thietanyl, 1,1-dioxothietanyl, 2,6-diazaspiro[3.3]heptyl, 2,5-diazabicyclo[2.2.1]heptyl, tetrahydro-2H-thiopyranyl 1,1-dioxide, azepanyl, dioxepanyl, oxazepanyl, diazepanyl, thiazolidinyl, tetrahydrothiophenyl, tetrahydropyridinyl, thiomorpholinyl, 4-methylpiperazinyl, morpholinonyl, dithiolanyl, dihydropyrrolyl, dioxanyl, dioxolanyl, dihydropyridinyl, dihydrofuranyl, dihydroisoxazolyl, dihydrooxazolyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, and pyrazolidinyl in each case independently from one another are unsubstituted or mono- or polysubstituted with one or more substituents selected from F; Cl; CN; C_{1-6}-alkyl; CF_3;

CF_2H; CFH_2; C(O)-C_{1-6}-alkyl; C(O)-OH; C(O)-OC_{1-6}-alkyl; C(O)-NH_2; C(O)-N(H)(C_{1-6}-alkyl); C(O)-N(C_{1-6}-alkyl)$_2$; OH; =O; OCF_3; OCF_2H; $OCFH_2$; O-C_{1-6}-alkyl;; NH_2; N(H)(C_{1-6}-alkyl); N(C_{1-6}-alkyl)$_2$; N(H)-C(O)-C_{1-6}-alkyl; and $S(O)_2$-C_{1-6}-alkyl.

According to the invention, R_4 and R_5 can together with the carbon atoms to which they are connected form 5- to 7- membered heterocycloalkyl.

In a preferred embodiment, R_4 and R_5 together with the carbon atoms to which they are connected form thiepanyl 1,1-dioxide, 1,2-thiazepanyl 1,1-dioxide, 2,5,6,7-tetrahydro-1,2-thiazepinyl 1,1-dioxide, or 5,6-dihydro-2H-1,2-thiazinyl 1,1-dioxide,, preferably wherein the thiepanyl 1,1-dioxide, 1,2-thiazepanyl 1,1-dioxide, 2,5,6,7-tetrahydro-1,2-thiazepinyl 1,1-dioxide, or 5,6-dihydro-2H-1,2-thiazinyl 1,1-dioxide, can be unsubstituted or monosubstituted with CH_3, F, Cl, OH, CF_3, or OCH_3; more preferably CH_3,.

In another preferred embodiment, R_4 and R_5 do not form together with the carbon atoms to which they are connected 5- to 7- membered heterocycloalkyl.

According to the present invention, the compound according to the invention is preferably selected from the group consisting of

1	2-(bis(3-chloro-4-fluorophenyl)methyl)-5-(methylsulfonyl)-1H-imidazole
2	2-(bis(3-chloro-4-fluorophenyl)methyl)-5-(ethylsulfonyl)-1H-imidazole
3	2-(bis(3-chloro-4-fluorophenyl)methyl)-5-(cyclopropylsulfonyl)-1H-imidazole
4	2-(bis(3-chloro-4-fluorophenyl)methyl)-4-(isopropylsulfonyl)-1H-imidazole
5	2-(bis(3-chloro-4-fluorophenyl)methyl)-4-((tetrahydrofuran-3-yl)sulfonyl)-1H-imidazole
6	2-(bis(3-chloro-4-fluorophenyl)methyl)-4-((tetrahydro-2H-pyran-4-yl)sulfonyl)-1H-imidazole
7	2-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-4-yl)sulfonyl)ethan-1-amine
8	2-(bis(3-chloro-4-fluorophenyl)methyl)-5-chloro-4-(methylsulfonyl)-1H-imidazole
9	2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazole-5-sulfonamide
10	2-(bis(3-chloro-4-fluorophenyl)methyl)-4-methyl-1H-imidazole-5-sulfonamide
11	2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(1-(dimethylamino)propan-2-yl)-1H-imidazole-5-sulfonamide
12	2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(2-(pyrrolidin-1-yl)ethyl)-1H-imidazole-5-sulfonamide
13	1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-4-isopropylpiperazine
14	1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-4-ethylpiperazine
15	1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-4-(methylsulfonyl)piperazine
16	2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(2-hydroxyethyl)-N-methyl-1H-imidazole-5-sulfonamide
17	2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(2-methoxyethyl)-1H-imidazole-5-sulfonamide
18	2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(2-(dimethylamino)ethyl)-1H-imidazole-5-sulfonamide
19	1-(4-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)piperazin-1-yl)ethan-1-one

20 2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(2-hydroxypropyl)-1H-imidazole-5-sulfonamide

21 2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(oxetan-2-ylmethyl)-1H-imidazole-5-sulfonamide

22 1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-N,N-dimethylazetidin-3-amine

23 1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-N,N-dimethylpyrrolidin-3-amine

24 2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(2-(methylsulfonyl)ethyl)-1H-imidazole-5-sulfonamide

25 2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(2-hydroxyethyl)-1H-imidazole-5-sulfonamide

26 2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(2-hydroxy-2-methylpropyl)-1H-imidazole-5-sulfonamide

27 2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(1-methoxypropan-2-yl)-1H-imidazole-5-sulfonamide

28 2-(bis(3-chloro-4-fluorophenyl)methyl)-N-methyl-N-(2-(methylsulfonyl)ethyl)-1H-imidazole-5-sulfonamide

29 4-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)thiomorpholine 1-oxide

30 2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(3-methoxypropyl)-1H-imidazole-5-sulfonamide

31 2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(oxetan-3-ylmethyl)-1H-imidazole-5-sulfonamide

32 2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(3-(dimethylamino)propyl)-1H-imidazole-5-sulfonamide

33 1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-N,N-dimethylpiperidin-4-amine

34 ethyl ((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)glycinate

35 2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(1,1-dioxidothietan-3-yl)-1H-imidazole-5-sulfonamide

36 2-(bis(3-chloro-4-fluorophenyl)methyl)-N-((3R,4R)-4-hydroxytetrahydro-2H-pyran-3-yl)-1H-imidazole-5-sulfonamide

37 2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(1,1-dioxidotetrahydrothiophen-3-yl)-N-methyl-1H-imidazole-5-sulfonamide

38 1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)azetidin-3-ol

39 2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(2,3-dimethoxypropyl)-1H-imidazole-5-sulfonamide

40 2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(oxetan-3-yl)-1H-imidazole-5-sulfonamide

41 1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)piperazine

43 N-(2-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazole)-5-sulfonamido)ethyl)acetamide

44 N-(1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)azetidin-3-yl)acetamide

45 2-((2-(bis(3-chloro-4-fluorophenyl)methyl)-N-methyl-1H-imidazole)-5-sulfonamido)-N-methylacetamide

46	2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(3-methoxycyclobutyl)-1H-imidazole-5-sulfonamide
47	2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(3-hydroxycyclopentyl)-1H-imidazole-5-sulfonamide
48	N-(1-acetylpiperidin-4-yl)-2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazole-5-sulfonamide
49	2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(2,2-difluoroethyl)-1H-imidazole-5-sulfonamide
50	3-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazole)-5-sulfonamido)-2,2-dimethylpropanamide
51	2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(1-methylpiperidin-4-yl)-1H-imidazole-5-sulfonamide
52	methyl ((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)glycinate
53	2-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazole)-5-sulfonamido)propanamide
54	2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(cyanomethyl)-1H-imidazole-5-sulfonamide
55	2-(bis(3-chloro-4-fluorophenyl)methyl)-N-methyl-N-(2-(methylamino)ethyl)-1H-imidazole-5-sulfonamide
59	1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-3-methylpiperazine
60	1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-N-methylpyrrolidin-3-amine
61	2-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-2,6-diazaspiro[3.3]heptane
62	2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(piperidin-3-yl)-1H-imidazole-5-sulfonamide
76	2-(bis(3-chloro-4-fluorophenyl)methyl)-5-(methylsulfinyl)-1H-imidazole
77	2-(bis(3-chloro-4-fluorophenyl)methyl)-4-methyl-5-(methylsulfinyl)-1H-imidazole
78	(2-(bis(3-chloro-4-fluorophenyl)methyl)-4-methyl-1H-imidazol-5-yl)(imino)(methyl)-l6-sulfanone
79	2-(bis(3-chloro-4-fluorophenyl)methyl)-4-methyl-5-(methylsulfonyl)-1H-imidazole
80	2-(bis(3-chloro-4-fluorophenyl)methyl)-4-cyclopropyl-5-(methylsulfonyl)-1H-imidazole
81	2-(bis(3-chloro-4-fluorophenyl)methyl)-5-(methylsulfonyl)-4-(trifluoromethyl)-1H-imidazole
82	(2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)(imino)(methyl)-l6-sulfanone
87	(2-(bis(3-chloro-4-fluorophenyl)methyl)-4-(methylsulfonyl)-1H-imidazol-5-yl)methanol
88	5-((3-chloro-4-fluorophenyl)(4-(methylsulfonyl)-1H-imidazol-2-yl)methyl)-2-(2,2,2-trifluoroethoxy)pyridine
89	2-((3-chloro-4-fluorophenyl)(4-(methylsulfonyl)-1H-imidazol-2-yl)methyl)-4-fluoroaniline
91	2-(bis(3-chloro-4-fluorophenyl)methyl)-4-((methylsulfonyl)methyl)-1H-imidazole
92	2-((3-chloro-4-fluorophenyl)(4-(trifluoromethyl)cyclohexyl)methyl)-4-(methylsulfonyl)-1H-imidazole
93	3-chloro-6-((4-chlorophenyl)(4-(methylsulfonyl)-1H-imidazol-2-yl)methyl)-2-(trifluoromethyl)pyridine
94	2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-N-cyclopropyl-1H-imidazole-4-sulfonamide

95	2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-4-(pyrrolidin-1-ylsulfonyl)-1H-imidazole
96	2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-4-((3,3-difluoropyrrolidin-1-yl)sulfonyl)-1H-imidazole
97	4-((2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazol-4-yl)sulfonyl)piperazin-2-one
98	2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-N,N-dimethyl-1H-imidazole-4-sulfonamide
99	1-((2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazol-4-yl)sulfonyl)-4-methylpiperazine
102	2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-N-(tetrahydrofuran-3-yl)-1H-imidazole-4-sulfonamide
103	2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-N-(3-hydroxycyclopentyl)-1H-imidazole-4-sulfonamide
104	2-((2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazole)-4-sulfonamido)acetamide
106	2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-4-((3-methoxy-3-methylpyrrolidin-1-yl)sulfonyl)-1H-imidazole
107	2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-N-(2-methoxypropyl)-1H-imidazole-4-sulfonamide
108	4-(azetidin-3-ylsulfonyl)-2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazole
109	2-((2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazole)-4-sulfonamido)propanamide
110	2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-4-((1-methylazetidin-3-yl)sulfonyl)-1H-imidazole
111	((2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazol-4-yl)sulfonyl)glycine
112	2-((2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-N-methyl-1H-imidazole)-4-sulfonamido)acetamide
113	2-((2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazol-4-yl)sulfonyl)-2,5-diazabicyclo[2.2.1]heptane
114	1-((2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazol-4-yl)sulfonyl)piperidin-3-amine
115	(1-((2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazol-4-yl)sulfonyl)azetidin-3-yl)methanamine
116	4-((2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazol-4-yl)sulfonyl)piperidine
117	2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-4-(pyrrolidin-3-ylsulfonyl)-1H-imidazole
118	4-((2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazol-4-yl)sulfonyl)-1-methylpiperidine

119 2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-4-((1-methylpyrrolidin-3-yl)sulfonyl)-1H-imidazole

120 2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-N-(pyrrolidin-3-yl)-1H-imidazole-4-sulfonamide

121 N-(azetidin-3-yl)-2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazole-4-sulfonamide

122 N-(azetidin-3-ylmethyl)-2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazole-4-sulfonamide

123 2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-N-(2-hydroxycyclopentyl)-1H-imidazole-4-sulfonamide

124 1-((2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazol-4-yl)sulfonyl)-3,5-dimethylpiperazine

125 2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-N-(pyrrolidin-3-ylmethyl)-1H-imidazole-4-sulfonamide

126 2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-N-(2-(dimethylamino)ethyl)-5-methyl-1H-imidazole-4-sulfonamide

127 N-(3-aminocyclobutyl)-2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazole-4-sulfonamide

128 2-(((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-4-yl)(methyl)(oxo)-l6-sulfaneylidene)amino)acetamide

129 2-amino-N-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-4-yl)(methyl)(oxo)-l6-sulfaneylidene)acetamide

130 2-((3-chloro-4-fluorophenyl)(5-chlorothiophen-2-yl)methyl)-5-methyl-4-(methylsulfonyl)-1H-imidazole

131 2-((3-chloro-4-fluorophenyl)(5-methyl-4-(methylsulfonyl)-1H-imidazol-2-yl)methyl)-5-(trifluoromethyl)thiazole

132 2-((3-chloro-4-fluorophenyl)(3,3-difluorocyclopentyl)methyl)-5-methyl-4-(methylsulfonyl)-1H-imidazole

133 azetidin-3-yl(2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)(imino)-l6-sulfanone

134 (2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)(imino)(1-methylazetidin-3-yl)-l6-sulfanone

135 2-((4-chloro-3-fluorophenyl)(chroman-3-yl)methyl)-4-methyl-5-(methylsulfonyl)-1H-imidazole

136 2-((3-chloro-4-fluorophenyl)(3,3-dimethylcyclobutyl)methyl)-5-methyl-4-(methylsulfonyl)-1H-imidazole

137 2-((3-chloro-4-fluorophenyl)(6,6-difluorospiro[3.3]heptan-2-yl)methyl)-5-methyl-4-(methylsulfonyl)-1H-imidazole

138 2-((3-chloro-4-fluorophenyl)(3-(difluoromethoxy)cyclobutyl)methyl)-5-methyl-4-(methylsulfonyl)-1H-imidazole

139 2-((3-chloro-4-fluorophenyl)(spiro[2.3]hexan-5-yl)methyl)-5-methyl-4-(methylsulfonyl)-1H-imidazole

140 (2-(bis(3-chloro-2,4-difluorophenyl)methyl)-5-methyl-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone

141 (2-(bis(3-chloro-4,5-difluorophenyl)methyl)-5-methyl-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone

142 (2-(bis(5-chloro-2,4-difluorophenyl)methyl)-5-methyl-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone

143 (2-(bis(4-chloro-2-fluorophenyl)methyl)-5-methyl-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone

144 (2-(bis(2-chloro-4-fluorophenyl)methyl)-5-methyl-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone

145 (2-(bis(4-(trifluoromethoxy)phenyl)methyl)-5-methyl-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone

146 (2-(bis(3-(trifluoromethoxy)phenyl)methyl)-5-methyl-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone

147 (2-(bis(3-fluoro-4-(trifluoromethoxy)phenyl)methyl)-5-methyl-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone

148 2-((2-(bis(3-chloro-4-fluorophenyl)methyl)-N-methyl-1H-imidazole)-5-sulfonamido)acetamide

149 1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-3-methylpiperazine

150 2-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-2,5-diazabicyclo[2.2.1]heptane

151 1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)piperidin-3-amine

152 (1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)azetidin-3-yl)methanamine

153 ((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)glycine

154 2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(4-hydroxytetrahydrofuran-3-yl)-1H-imidazole-5-sulfonamide

155 1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-3,5-dimethylpiperazine

156 N-(azetidin-3-ylmethyl)-2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazole-5-sulfonamide

157 1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-2-methylpiperazine

158 2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(pyrrolidin-3-yl)-1H-imidazole-5-sulfonamide

159 N-(azetidin-3-yl)-2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazole-5-sulfonamide

160 2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(pyrrolidin-3-ylmethyl)-1H-imidazole-5-sulfonamide

161 N-(3-aminocyclobutyl)-2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazole-5-sulfonamide

162 2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(1-hydroxy-2-methylpropan-2-yl)-1H-imidazole-5-sulfonamide

163 N-(3-aminocyclopentyl)-2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazole-5-sulfonamide

164 1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-N-methylazetidin-3-amine

165 2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(3-(methylamino)propyl)-1H-imidazole-5-sulfonamide

166 N-(3-aminopropyl)-2-(bis(3-chloro-4-fluorophenyl)methyl)-N-methyl-1H-imidazole-5-sulfonamide

167 2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(2-(methylamino)ethyl)-1H-imidazole-5-sulfonamide

168 1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)piperidin-4-amine

169 2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(2-methoxypropyl)-1H-imidazole-5-sulfonamide

170 N-(2-amino-2-methylpropyl)-2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazole-5-sulfonamide

171 2-(bis(3-chloro-4-fluorophenyl)methyl)-N,N-dimethyl-1H-imidazole-5-sulfonamide

172 2-(bis(3-chloro-4-fluorophenyl)methyl)-N-cyclopropyl-1H-imidazole-5-sulfonamide

173 2-(bis(3-chloro-4-fluorophenyl)methyl)-5-(pyrrolidin-1-ylsulfonyl)-1H-imidazole

174 2-(bis(3-chloro-4-fluorophenyl)methyl)-5-((3,3-difluoropyrrolidin-1-yl)sulfonyl)-1H-imidazole

175 2-(bis(3-chloro-4-fluorophenyl)methyl)-5-((3-methoxy-3-methylpyrrolidin-1-yl)sulfonyl)-1H-imidazole

176 4-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)piperazin-2-one

177 2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(5-oxopyrrolidin-3-yl)-1H-imidazole-5-sulfonamide

178 1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)pyrrolidin-3-ol

179 2-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazole)-5-sulfonamido)acetamide

180 2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(tetrahydrofuran-3-yl)-1H-imidazole-5-sulfonamide

181 4-(azetidin-3-ylsulfonyl)-2-[bis(3-chloro-4-fluorophenyl)methyl]-1*H*-imidazole

182 2-[bis(3-chloro-4-fluorophenyl)methyl]-4-(1-methylazetidin-3-yl)sulfonyl-1H-imidazole

183 4-[[2-[bis(3-chloro-4-fluorophenyl)methyl]-1H-imidazol-4-yl]sulfonyl]piperidine

184 2-[bis(3-chloro-4-fluorophenyl)methyl]-4-pyrrolidin-3-ylsulfonyl-1H-imidazole

185 (2-(bis(3-(difluoromethyl)-4-fluorophenyl)methyl)-5-methyl-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone

186 (2-(bis(4-chloro-2-methoxyphenyl)methyl)-5-methyl-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone

187 (2-(bis(4-chloro-3-fluorophenyl)methyl)-5-methyl-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone

188 (2-(bis(3-chloro-4-fluorophenyl)methyl)-5-(methyl-d3)-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone

189 (2-(bis(3-chloro-4-fluorophenyl)methyl)-5-cyclopropyl-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone

190 (2-(bis(3-chloro-4-fluorophenyl)methyl)-5-ethyl-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone

191 2-(bis(3-chloro-4-fluorophenyl)methyl)-5-chloro-1H-imidazole-4-sulfonamide

192	(2-(bis(3-chloro-4-fluorophenyl)methyl)-5-chloro-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone
193	2-(bis(3-chloro-4-fluorophenyl)methyl)-5-(methoxymethyl)-4-(methylsulfonyl)-1H-imidazole
194	6-(bis(3-chloro-4-fluorophenyl)methyl)-4-methyl-2,5-dihydroimidazo[4,5-e][1,2]thiazine 1,1-dioxide
195	7-(bis(3-chloro-4-fluorophenyl)methyl)-3,6-dihydro-2H-imidazo[4,5-f][1,2]thiazepine 1,1-dioxide
196	7-(bis(3-chloro-4-fluorophenyl)methyl)-3,4,5,6-tetrahydro-2H-imidazo[4,5-f][1,2]thiazepine 1,1-dioxide
197	2-(bis(3-chloro-4-fluorophenyl)methyl)-5,6,7,8-tetrahydro-1H-thiepino[2,3-d]imidazole 4,4-dioxide
198	N-((2-(bis(3-chloro-4-fluorophenyl)methyl)-4-methyl-1H-imidazol-5-yl)methyl)methanesulfonamide
199	3-chloro-6-((4-chlorophenyl)(4-(methylsulfonyl)-1H-imidazol-2-yl)methyl)-2-(trifluoromethyl)pyridine
200	(2-((5-chloro-6-(trifluoromethyl)pyridin-2-yl)(4-chlorophenyl)methyl)-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone
201	(3-chloro-4-fluorophenyl)(4-(methylsulfonyl)-1H-imidazol-2-yl)(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)methanol
202	(2-((3-chloro-4-fluorophenyl)(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)methyl)-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone
203	(2-((3-chloro-4-fluorophenyl)(5-chloro-6-(trifluoromethyl)pyridin-3-yl)methyl)-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone
204	(3-chloro-4-fluorophenyl)(3,3-difluorocyclopentyl)(4-methyl-5-(methylsulfonyl)-1H-imidazol-2-yl)methanol
205	5-((3-chloro-4-fluorophenyl)(4-methyl-5-(methylsulfonyl)-1H-imidazol-2-yl)methyl)-4-methyloxazol-2-amine

in the form of the free compound or a physiologically acceptable salt thereof.

In a preferred embodiment, the compound according to the invention is an inhibitor of $Na_V1.8$. In the sense of the invention, the term "inhibitor of $Na_V1.8$" preferably means that the respective compound exhibits in a patch clamp assay an IC50 value on $Na_V1.8$ of at most 10 µM ($10 \cdot 10^{-6}$ mol/L); more preferably at most 1 µM; still more preferably at most 500 nM (10^{-9} mol/L); even more preferably at most 100 nM; and most preferably at most 10 nM.

A preferred assay for testing compounds for their potency and method for determining an IC50 on $Na_V1.8$ is described in the experimental part down below.

In a preferred embodiment, the compound according to the invention is a selective inhibitor of $Na_V1.8$. In the sense of the invention, the term "selective inhibitor of $Na_V1.8$" preferably means that the respective compound preferably does not exhibit any inhibitory activity on $Na_V1.1$, $Na_V1.2$, $Na_V1.4$, $Na_V1.5$ and $Na_V1.6$. The skilled artisan knows

suitable ways to determine whether a compound exhibits inhibitory effects on any of $Na_V1.1$, $Na_V1.2$, $Na_V1.4$, $Na_V1.5$ and $Na_V1.6$.

The invention therefore relates to a compound according to the invention for use in the inhibition of $Na_V1.8$.

Therefore, another aspect of the invention relates to a compound according to the invention for use in the treatment of pain. Still another aspect of the invention relates to a method of treatment of pain; comprising the administration of a therapeutically effective amount of a compound according to the invention to a subject in need thereof, preferably a human.

A further aspect of the invention relates to a compound according to the invention as medicament.

Another aspect of the invention relates to a pharmaceutical dosage form comprising a compound according to the invention. Preferably, the pharmaceutical dosage form comprises a compound according to the invention and one or more pharmaceutical excipients such as physiologically acceptable carriers, additives and/or auxiliary substances; and optionally one or more further pharmacologically active ingredient. Examples of suitable physiologically acceptable carriers, additives and/or auxiliary substances are fillers, solvents, diluents, colorings and/or binders. These substances are known to the person skilled in the art (see H. P. Fiedler, Lexikon der Hilfsstoffe fur Pharmazie, Kosmetik und angrenzende Gebiete, Editio Cantor Aulendoff).

The pharmaceutical dosage form according to the invention is preferably for systemic, topical or local administration, preferably for oral administration. Therefore, the pharmaceutical dosage form can be in form of a liquid, semisolid or solid, e.g. in the form of injection solutions, drops, juices, syrups, sprays, suspensions, tablets, patches, films, capsules, plasters, suppositories, ointments, creams, lotions, gels, emulsions, aerosols or in multiparticulate form, for example in the form of pellets or granules, if appropriate pressed into tablets, decanted in capsules or suspended in a liquid, and can also be administered as such.

The pharmaceutical dosage form according to the invention is preferably prepared with the aid of conventional means, devices, methods and processes known in the art. The amount of the compound according to the invention to be administered to the patient may vary and is e.g. dependent on the patient's weight or age and also on the type of administration, the indication and the severity of the disorder. Preferably 0.001 to 100 mg/kg, more preferably 0.05 to 75 mg/kg, most preferably 0.05 to 50 mg of a compound according to the invention are administered per kg of the patient's body weight.

Therefore, another aspect of the invention relates to the pharmaceutical dosage form according to the invention for use in the treatment of pain. Still another aspect of the invention relates to a method of treatment of pain; comprising the administration of a pharmaceutical dosage form according to the invention to a subject in need thereof, preferably a human.

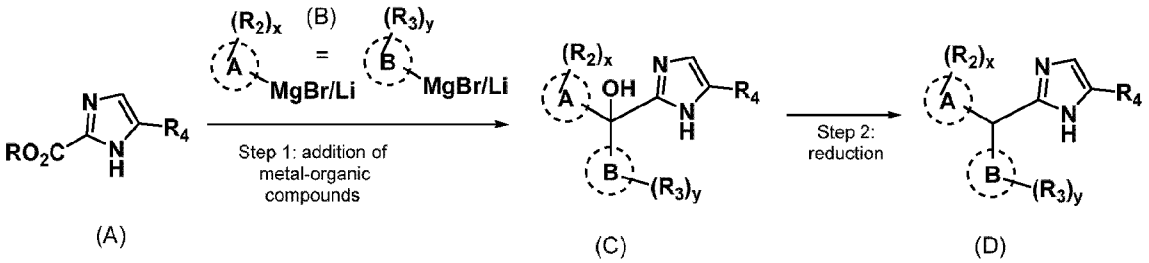
General synthesis schemes

Examples of the invention can be synthesized preferentially according to the general synthetic schemes below or using chemistry known to the person skilled in the art.

As illustrated in Scheme 1, compounds of the general formula (A) can be treated with metal-organic compounds of the general formula (B) (wherein A=B, R_2=R_3 and x=y) to afford compounds of general formula (C). Preferred metal-organic compounds include Grignard and organolithium reagents. Compounds of the general formula (C) can be converted into compounds of the general formula (D) with reactions known to the person skilled in the art.

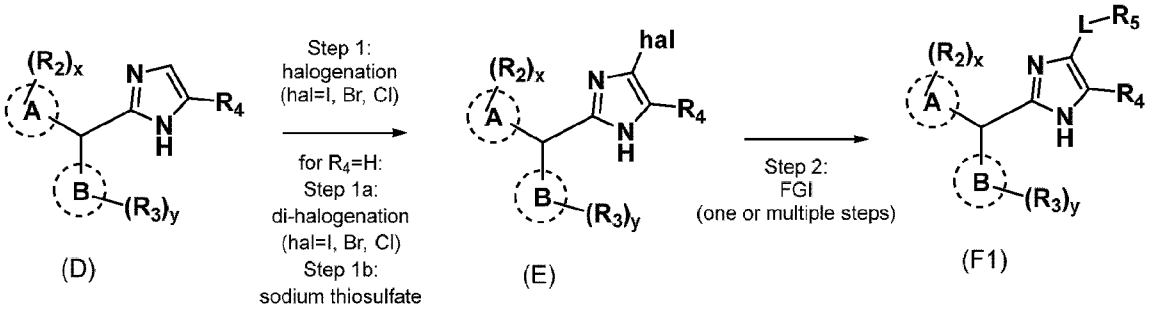
Preferred transformations include reductions to get compounds of the general formula (D) with R_1=H (preferred reagents include tin (II)chloride in acetic media).

Scheme 1: A, B, R_2, R_3, R_4, x and y are as defined in claim 1.



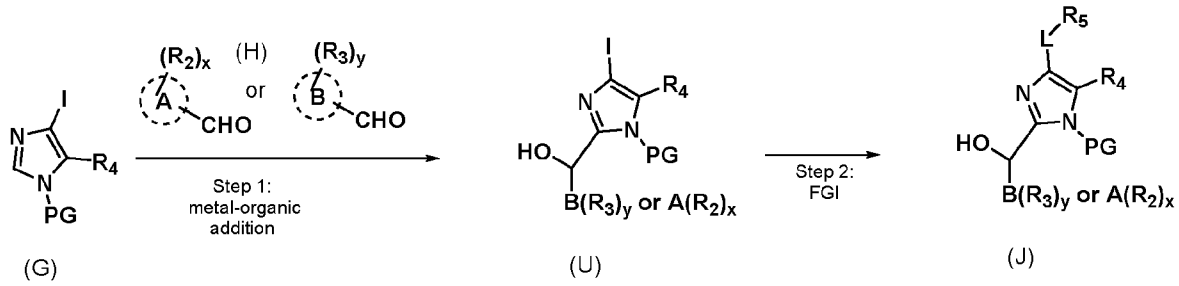
As illustrated in Scheme 2, compounds of the general formula (D) can be halogenated, preferentially iodinated using I_2 to obtain compounds of the general formula (E). These compounds can be used to install a variety of L-R_5 moieties to yield compounds of the general formula (F1). One step procedures include the formation of sulfones using sulfinate salts (*Synthesis*, **2016**, *48*, 1939–1973). Multi step procedures include thioether formation under transition metal catalysis followed by oxidation to yield sulfoxides (*Chem. Rev.* **2022**, *122*, 16110–16293) or sulfoximines (*Chem. Eur. J.* **2021**, *27*, 17293–17321). The obtained thioethers can also be converted into the corresponding sulfonylchlorides via oxidation (preferred reagents include DCDMH) and then further into sulfonamides upon treatment with nitrogen nucleophiles. In the case of R_4=H, iodination using NIS yields bis-iodinated products (hal=I, R_4=I) that are transformed into compounds of the general formula (E) with R_4=H upon treatment with sodium thiosulfate.

Scheme 2: A, B, R_2, R_3, R_4, R_5, L, x and y are as defined in claim 1. Hal=I, Br, Cl.



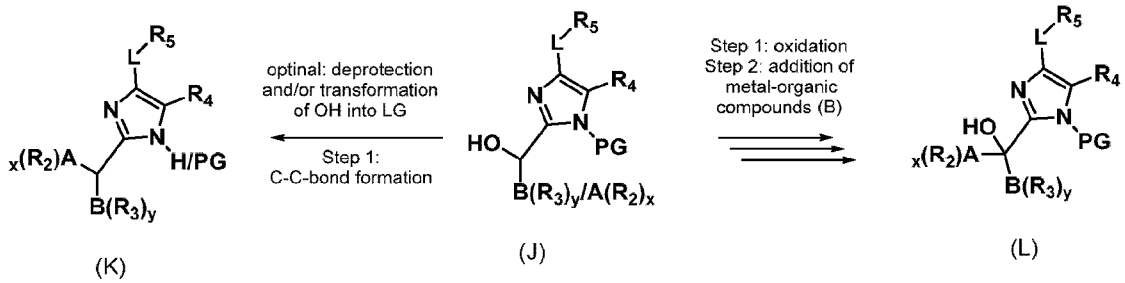
As illustrated in Scheme 3, compounds of the general formula (G) can be added to aldehydes of the general formula (H) after deprotonation (preferred bases include LDA) to yield alcohols of the general formula (U). These compounds can be used to install a variety of L-R_5 moieties as described for the transformation (E) to (F) in scheme 2 to yield compounds of the general formula (J). Suitable protecting groups are known in the literature and include e.g. SEM (T. W. Green, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, Wiley-Interscience, **2007**, 4th edition, 872-893).

Scheme 3: A, B, R_2, R_3, R_4, R_5, L, x and y are as defined in claim 1. PG=protecting group.



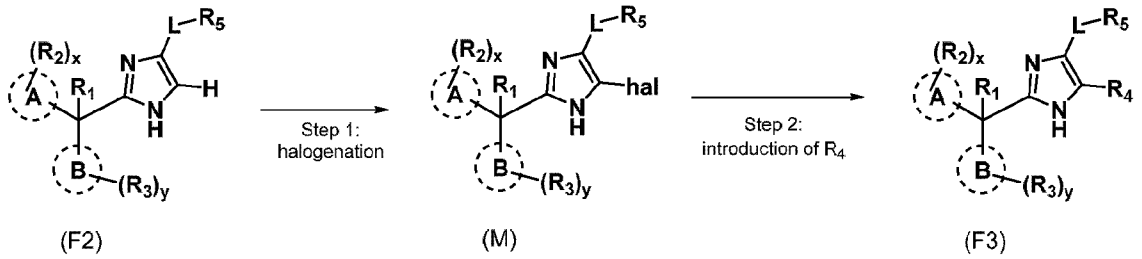
As illustrated in Scheme 4, compounds of the general formula (J) can be converted into compounds of the general formula (K) under formation of a new C-C bond. This transformation can optionally be preceded by deprotection (T. W. Green, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, Wiley-Interscience, **2007**, 4th edition, 872-893) and/or transformation of the alcohol into a suitable leaving group. Preferred methods of construction of the new C-C bond include acid-catalyzed Friedel-Crafts type reactions (e.g using pTSA/anilines). Compounds of the general formula (J) can also be formed in situ (example 205) and converted into a carbamate leaving group in step. Friedel-Crafts type reactions (e.g using BF_3/TFA and appropriate nucleophiles) can be carried out with these carbamates. Compounds of the general formula (J) can also be converted into compounds of the general formula (L) via a two-step sequence including first oxidation of the alcohol to a ketone (preferred oxidants include PCC) followed by addition of metal-organic compounds of the general formula (B). Compounds of the general formula (L) can be transformed into compounds of the general formula (F) using chemistry described for the transformation of (C) to (D) followed or preceded by deprotection (T. W. Green, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, Wiley-Interscience, **2007**, 4th edition, 872-893). For the transformations in scheme 4 the corresponding carbon-nucleophiles for the transformations (J) to (K) and (J) to (L) have to be chosen orthogonally, e.g. if a compound of the general formula (I) with the substituent $B(R_3)_y$ is used, the chosen carbon nucleophile will attach $A(R_2)_x$ and vice versa.

Scheme 4: A, B, R_2, R_3, R_4, R_5, L, x and y are as defined in claim 1. PG=protecting group.



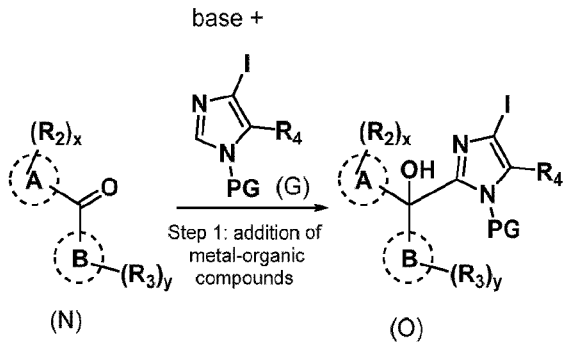
As illustrated in Scheme 5, compounds of the general formula (F2) with R_4=H can be converted into compounds of the general formula (M) using halogenation reactions, preferrable iodination using NIS. This halogen handle can be used to introduce a variety of different kinds of R_4, e.g. alkyl substituents via Suzuki-type transition metal-catalyzed cross couplings (*Chem. Soc. Rev.* **2014**, *43*, 412-443) to give compounds of the general formula (F3). Introduction of R_4 can also be carried out in multiple steps using standard functional group interconversions to build compounds with R_5/R_4 being connected as exemplified for examples 83-85.

Scheme 5: A, B, R_1, R_2, R_3, R_4, R_5, L, x and y are as defined in claim 1.



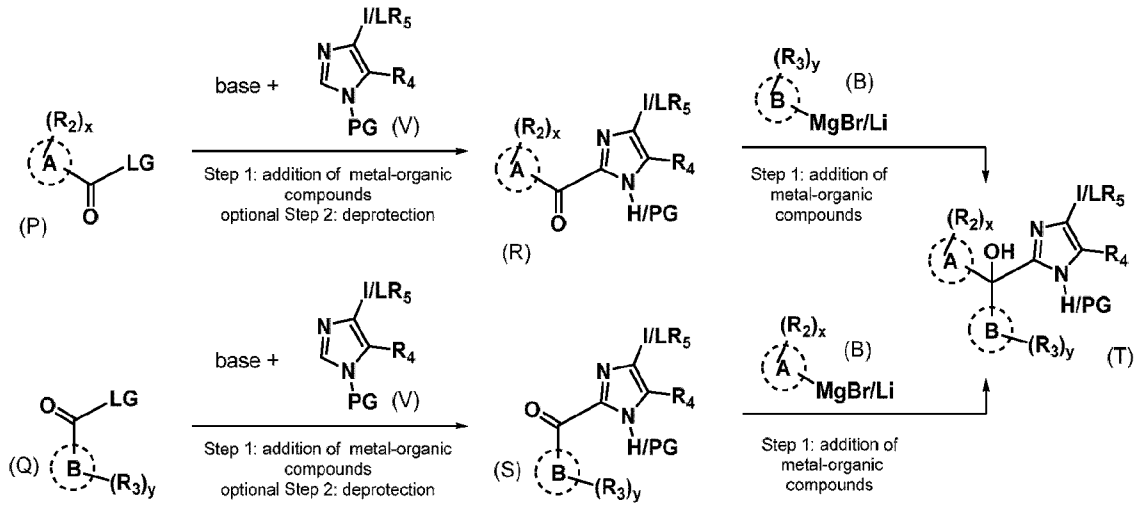
As illustrated in Scheme 6, ketones of the general formula (N) can be converted into compounds of the general formula (O) using compounds of the general structure (G) after deprotonation (preferred bases include LDA). Compounds of the general formula (O) can be converted into compound of the genera formula (F) using the transformations described for the conversion of (E) to (F) and (C) to (D) and deprotection (T. W. Green, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, Wiley-Interscience, **2007**, 4th edition, 872-893).

Scheme 6: A, B, R_2, R_3, R_4, R_5, L, x and y are as defined in claim 1.



As illustrated in Scheme 7, compounds of the general formula (P) or (Q) can be converted into ketones of the general formula (R) or (S) using compounds of the general structure (V) after deprotonation (preferred bases include LDA). Preferred leaving groups on compounds (P) or (Q) include N-methoxy-N-methyl or chloride. Ketones of the general formula (R) or (S) can be transformed into compounds of the general formula (T) using metal-organic compounds of the general formula (B). Compounds of the general formula (T) can be converted into final compounds using reactions described for the conversion of (C) to (D) and/or (E) to (F). Deprotection as indicated in scheme 7 is known in the art (T. W. Green, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, Wiley-Interscience, **2007**, 4th edition, 872-893). Synthesis of compounds of the general formula (P) or (Q) is known in the art.

Scheme 7: A, B, R_2, R_3, R_4, R_5, L, x and y are as defined in claim 1. PG= protecting group, LG= leaving group.

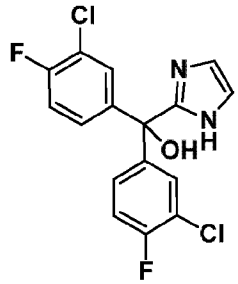


List of abbreviations

ACN= acetonitrile, ABPR= automated back pressure regulator, Boc= tert-butyloxycarbonyl, DAST= diethylaminosulfur trifluoride, dba= dibenzylideneacetone, DBU= 1,8-diazabicyclo[5.4.0]undec-7-ene, DCDMH= 1,3-dichlor-5,5-dimethylhydantoin, DCM= dichloromethane, DIBAL-H= diisobutylaluminium hydride, DIPA= diisopropylamine, DIPEA= N,N-diisopropylethylamine, DMA= dimethylacetamide, DMF= dimethylformamide, DMSO= dimethyl sulfoxide, DPPA= diphenylphosphoryl azide, dppf= 1,1′-bis(diphenylphosphino)ferrocene, EA=ethyl acetate, FGI=functional group interconversion, Grubbs catalyst, 2nd generation= (1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichlor(phenylmethylen)(tricyclohexylphosphan)ruthenium, HATU= [O-(7-Azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium-hexafluorphosphat, Hex= hexane/hexanes , HPLC= high-performance liquid chromatography, LCMS= liquid chromatography–mass spectrometry, LDA= lithium diisopropylamide, mCPBA= meta-chloroperoxybenzoic acid, Ms= mesyl, NCS= N-chlorosuccinimide, NIS= N-iodosuccinimide, NMO= N-methylmorpholine N-oxide, NMP= N-methyl-2-pyrrolidone, NMR= nuclear magnetic resonance, PCC= pyridinium chlorochromate, pet ether=petroleum ether, PG=protecting group, pTSA= *p*-toluenesulfonic acid , Rt=retention time, RVC= reticulated vitreous carbon, SEM= 2-(trimethylsilyl)ethoxymethyl, SFC= supercritical fluid chromatography, T3P= propanephosphonic acid anhydride, TEA= triethylamine, TFA= trifluoroacetic acid, THF=tetrahydrofurane, TMS= trimethylsilyl, Xantphos= (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphane).

Intermediate 1

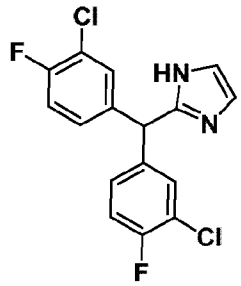
bis(3-chloro-4-fluorophenyl)(1H-imidazol-2-yl)methanol



Mg (0.86 g, 35.71 mmol) was weighted in into a two-neck flask equipped with a reflux condenser and dried under an argon atmosphere. Then THF (7.0 mL), 4-bromo-2-chloro-1-fluorobenzene (7.5 g, 35.71 mmol) and DIBAL (1M in toluene, 0.4 mL) were added to the mixture sequentially at rt. The mixture was stirred at rt for 1 h. To the freshly prepared reagent was then added a solution of ethyl 1H-imidazole-2-carboxylate (1.0 g, 7.14 mmol) in THF (33.0 mL) at 0 °C and the reaction mixture was heated to 80 °C for 3 h. The reaction mixture was cooled to rt, quenched with ammonium chloride solution and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to get the crude product which purified by CombiFlash column chromatography (SiO_2, 0-60% EtOAc/Hex) to yield the title compound (1.5 g, 59%), LCMS: m/z $[M+H]^+$ = 355.

Intermediate 2

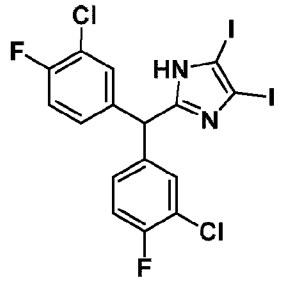
2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazole



To a solution of bis(3-chloro-4-fluorophenyl)(1H-imidazol-2-yl)methanol (intermediate 1, 1.5 g, 4.22 mmol) in acetic acid (15.0 mL) were added $SnCl_2$ (4.8 g, 25.35 mmol) and HCl (12N, 3.0 mL) at rt. The reaction mixture was heated to 120 °C under reflux conditions for 16 h, cooled to rt and concentrated under reduced pressure. The residue was neutralized with $NaHCO_3$ solution and extracted with ethyl acetate (3 × 150 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude product was purified by CombiFlash column chromatography (SiO_2, 0-80% EtOAc/Hex) to yield the title compound (1.1 g, 77%), LCMS: m/z $[M+H]^+$ = 339.

Intermediate 3

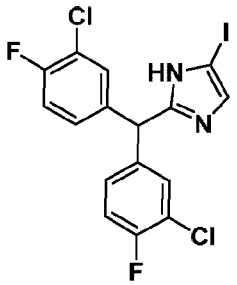
2-(bis(3-chloro-4-fluorophenyl)methyl)-4,5-diiodo-1H-imidazole



To a solution of 2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazole (intermediate 2, 1.5 g, 4.42 mmol) in DMF (20.0 mL) were added KOH (0.5 g, 8.85 mmol) and I_2 (1.7 g, 6.63 mmol) at 0 °C and the reaction mixture was stirred at rt for 2 h. The reaction mixture was quenched with sodium thiosulfate solution, the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude product was purified by CombiFlash column chromatography (SiO_2, 0-40% EtOAc/Hex) to yield the title compound (1.8 g, 69%), LCMS: m/z $[M+H]^+$ = 591.

Intermediate 4

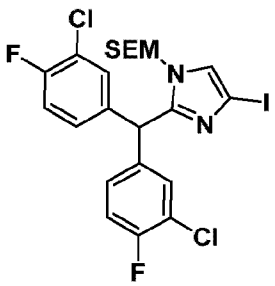
2-(bis(3-chloro-4-fluorophenyl)methyl)-4-iodo-1H-imidazole



To a stirred solution of 2-[bis(3-chloro-4-fluorophenyl)methyl]-4,5-diiodo-1H-imidazole (intermediate 3, 2.2 g, 3.72 mmol) in ethanol (25.0 mL) and water (7.0 mL) was added sodium thiosulfate (18.5 g, 74.57 mmol) at rt and the mixture was heated to 110 °C under reflux conditions for 16 h. Sodium thiosulfate (18.5 g, 74.57 mmol) was then added again to the reaction mixture and the mixture was heated to 110 °C for 4 days. The reaction mixture was cooled to rt, diluted with water and extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by CombiFlash column chromatography (SiO_2, 0-40% EtOAc/Hex) to yield the title compound (1.5 g, 86%), LCMS: m/z $[M+H]^+$ = 465.

Intermediate 5

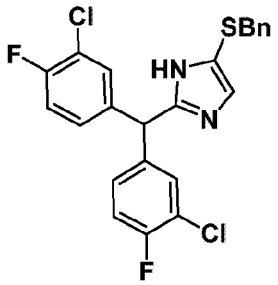
2-(bis(3-chloro-4-fluorophenyl)methyl)-4-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole and the corresponding SEM regioisomer



To a solution of 2-(bis(3-chloro-4-fluorophenyl) methyl)-4-iodo-1H-imidazole (intermediate 4, 2.0 g, 4.301 mmol) in DMF (15.0 mL) was added NaH (0.343 g, 8.602 mmol, 60% suspension) at 0 °C, the mixture was then stirred at rt for 30 minutes. Then SEM-Cl (1.14 mL, 6.452 mmol) was added after cooling the mixture to 0°C and the mixture was then stirred at rt for 16 h. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by combiflash column chromatography (SiO_2, 10% EtOAc/Hex) to yield the title compound (2.0 g, 78%), LCMS: m/z $[M+H]^+$ = 595.

Intermediate 6

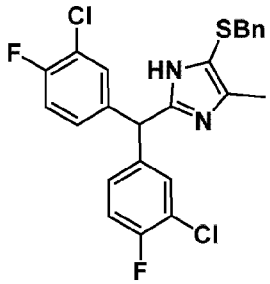
4-(benzylthio)-2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazole



To a solution of 2-(bis(3-chloro-4-fluorophenyl)methyl)-4-iodo-1H-imidazole (intermediate 4, 0.4 g, 0.862 mmol) in dioxane (10.0 mL) were added phenylmethanethiol (0.215 g, 1.724 mmol), DIPEA (0.3 mL, 1.724 mmol) and Xanthphos (0.025 g, 0.043 mmol) at rt. The reaction mixture was degassed with argon for 10 min followed by the addition of $Pd_2(dba)_3$ (0.025 g, 0.026 mmol) at rt. The reaction mixture was heated to 110 °C for 16 h in a sealed tube. The reaction mixture was cooled to rt and filtered through a celite bed. The filtrate was evaporated under reduced pressure to get the crude product, which was purified by CombiFlash column chromatography (SiO_2, 0-40% EtOAc/Hex) to yield the title compound (0.18 g, 45%), LCMS: m/z $[M+H]^+$ = 461.

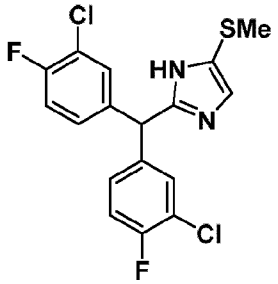
Intermediate 7

The title compound was prepared from the appropriate intermediate using an analogous method to that described for intermediate 6.

Intermediate	Name/Structure/Data
7	methyl 5-chloro-2-(4,4-difluoropiperidin-1-yl)-6-methylpyridine-3-carboxylate  Yield: 0.05 g, 52%. LCMS: m/z $[M+H]^+$ = 475.

Intermediate 8

2-(bis(3-chloro-4-fluorophenyl)methyl)-4-(methylthio)-1H-imidazole

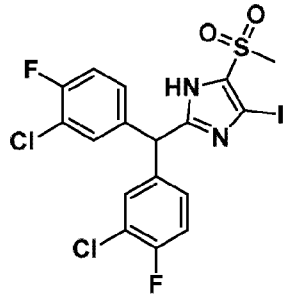


A solution of 2-(bis(3-chloro-4-fluorophenyl)methyl)-4-iodo-1H-imidazole (intermediate 4, 0.6 g, 1.29 mmol) in NMP (10 mL) was degassed with argon for 15 min followed by the addition of NaSMe (0.18 g, 2.58 mmol) and $CuCl_2$ (0.08 g, 0.64 mmol) at rt. The reaction mixture was heated to 130 °C for 16 h, was then cooled to rt and

filtered through a celite bed. The filtrate was concentrated under reduced pressure to get the crude product, which was purified by column chromatography (SiO_2, 0-60% EtOAc/Hex) to afford the title compound (0.26 g, 52%), LCMS: m/z $[M+H]^+$= 385.

Intermediate 13

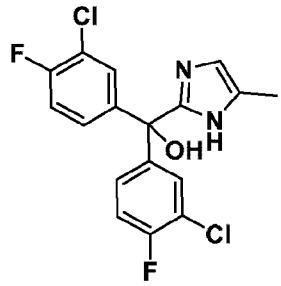
2-(bis(3-chloro-4-fluorophenyl)methyl)-4-iodo-5-(methylsulfonyl)-1H-imidazole



To a stirred solution of 2-(bis(3-chloro-4-fluorophenyl)methyl)-5-(methylsulfonyl)-1H-imidazole (example 1, 1.5 g, 3.606 mmol) in DCM (50.0 mL) was added NIS (1.3 g, 5.40 mmol) at rt. The reaction mixture was stirred at rt for 16 h. The reaction mixture was quenched with sodium thiosulfate solution, the aqueous layer was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to get a residue which was purified by CombiFlash column chromatography (SiO_2, 0-60% EtOAc/Hex) to yield the title compound (1.3 g, 66%), LCMS: m/z $[M+H]^+$ = 543.

Intermediate 14

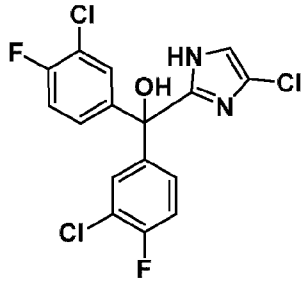
bis(3-chloro-4-fluorophenyl)(5-methyl-1H-imidazol-2-yl)methanol



Mg (3.2 g, 129.727 mmol) was taken up in a 2-necked flask equipped with a reflux condenser and dried under argon atmosphere. THF (30.0 mL), 4-bromo-2-chloro-1-fluorobenzene (15.8 mL, 129.727 mmol) and DIBAL (1M in toluene) (2.0 mL) were added to the mixture sequentially at rt. The reaction mixture was stirred at rt for 1 h. To this mixture, a solution of ethyl 4-methyl-1H-imidazole-2-carboxylate (4.0 g, 25.95 mmol) in THF (170.0 mL) was added at 0 °C and the reaction mixture was heated to 80 °C for 5 h. The reaction mixture was cooled to rt and quenched with ammonium chloride solution. The aqueous layer was filtered through a celite bed and extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to get the crude product which was purified by column chromatography (SiO_2, 0-60% EtOAc/Hex) to yield the title compound (7.1 g, 74%), LCMS: m/z $[M+H]^+$ = 369.

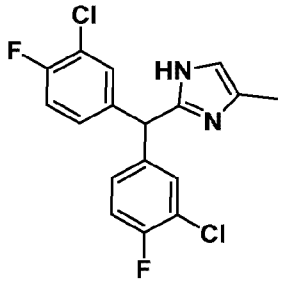
Intermediate 15

The title compound was prepared from the appropriate intermediates using an analogous method to that described for intermediate 14.

Intermediate	Name/Structure/Data
15	(5-chloro-1H-imidazol-2-yl)bis(3-chloro-4-fluorophenyl)methanol  Yield: 0.5 g, 37%, LCMS: m/z $[M+H]^+$ = 389.

Intermediate 16

2-(bis(3-chloro-4-fluorophenyl)methyl)-4-methyl-1H-imidazole

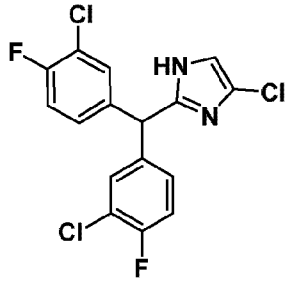


To a solution of bis(3-chloro-4-fluorophenyl)(5-methyl-1H-imidazol-2-yl)methanol (intermediate 14, 7.0 g, 19.02 mmol) in acetic acid (100.0 mL) were added $SnCl_2$ (21.6 g, 114.13 mmol) and conc. HCl (21.0 mL) at 0 °C. The reaction mixture was stirred at 120 °C under reflux conditions for 16 h. The reaction mixture was cooled to rt and concentrated under reduced pressure. The resulting crude residue was basified with Na_2CO_3 solution. The aqueous layer was filtered through a celite bed and the filtrate was extracted with ethyl acetate (3 × 200 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to get the crude product which was washed with 10% ethyl acetate in hexane to obtain the title compound (5.2 g, 77%), LCMS: m/z $[M+H]^+$ = 353.

Intermediate 17

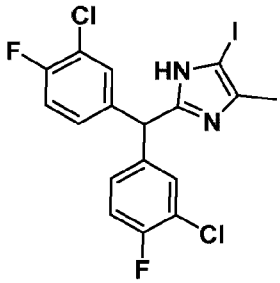
The title compound was prepared from the appropriate intermediates using an analogous method to that described for intermediate 16.

Intermediate	Name/Structure/Data
17	(5-chloro-1H-imidazol-2-yl)bis(3-chloro-4-fluorophenyl)methanol

	 Yield: 0.12 g, 50%. LCMS: m/z $[M+H]^+$ = 373.

Intermediate 18

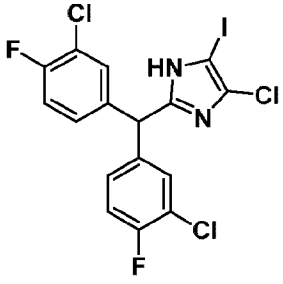
2-(bis(3-chloro-4-fluorophenyl)methyl)-5-iodo-4-methyl-1H-imidazole



To a solution of 2-[bis(3-chloro-4-fluorophenyl)methyl]-5-methyl-1H-imidazole (intermediate 16, 2.5 g, 7.102 mmol) in DMF (30.0 mL) were added KOH (0.6 g, 10.653 mmol) and I_2 (2.4 g, 9.233 mmol) at 0 °C. The reaction mixture was then stirred at rt for 1 h. The reaction mixture was quenched with sodium thiosulfate solution, the aqueous layer was extracted with ethyl acetate (2 × 150 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure to get the crude product which was purified by column chromatography (SiO_2, 0-40% EtOAc/Hex) to yield the title compound (2.2 g, 64%), LCMS: m/z $[M+H]^+$ = 479.

Intermediate 19

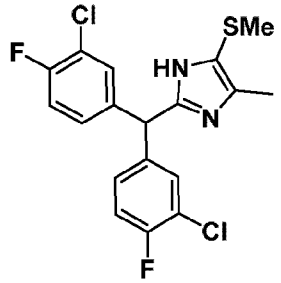
2-(bis(3-chloro-4-fluorophenyl)methyl)-4-chloro-5-iodo-1H-imidazole



To a stirred solution of 2-[bis(3-chloro-4-fluorophenyl)methyl]-5-chloro-1H-imidazole (intermediate 17, 6.0 g, 16.086 mmol) in DCM (100.0 mL) was added NIS (5.5 g, 24.129 mmol) at rt. The reaction was stirred for 16 h at rt. The reaction mixture was quenched with sodium thiosulfate solution, was diluted with water and extracted with ethyl acetate (2 × 300 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to get the crude product, which was purified by CombiFlash column chromatography (SiO_2, 0-60% EtOAc/Hex) to yield the title compound (4.2 g, 53%). LCMS: m/z $[M+H]^+$ = 499.

Intermediate 20

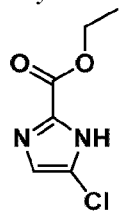
2-(bis(3-chloro-4-fluorophenyl)methyl)-5-methyl-4-(methylthio)-1H-imidazole



A solution of 2-[bis(3-chloro-4-fluorophenyl)methyl]-5-iodo-4-methyl-1H-imidazole (intermediate 18, 0.5 g, 1.046 mmol) in dioxane (30.0 mL) was degassed with argon for 10 min followed by the addition of NaSMe (0.11 g, 1.569 mmol), Xanthphos (0.091 g, 0.157 mmol) and $Pd_2(dba)_3$ (0.096 g, 0.105 mmol) at rt. The reaction mixture was heated to 110 °C for 16 h in a sealed tube. The reaction mixture was cooled to rt, diluted with ice water and extracted with ethyl acetate (3 x 80 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to get the crude product, which was purified by column chromatography (SiO_2, 0-50% EtOAc/Hex) to yield the title compound (0.23 g, 55%), LCMS: m/z $[M+H]^+$ = 399.

Intermediate 21

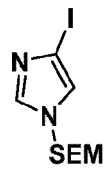
ethyl 5-chloro-1H-imidazole-2-carboxylate



To a solution of ethyl 1H-imidazole-2-carboxylate (5.0 g, 35.71 mmol) in DMF (100.0 mL) was added acetic acid (1.0 mL) at rt. To this mixture was added a solution of NCS (4.7 g, 35.71 mmol) in DMF (100.0 mL) dropwise at 0 °C. The reaction mixture was stirred at rt for 40 h. The reaction mixture was diluted with ice water and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was triturated with acetonitrile to obtain the title compound (2.3 g, 36%), LCMS: m/z $[M+H]^+$ = 175.

Intermediate 22

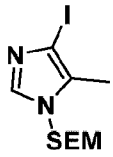
4-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole



Sodium hydride (60% dispersion in mineral oil, 0.297 g, 12.372 mmol.) was added to a solution of 4-iodo-1*H*-imidazole (2.0 g, 10.310 mmol) in DMF (20 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h followed by the addition of 2-(trimethylsilyl)ethoxymethyl chloride (1.829 mL, 10.310 mmol) at 0 °C. The reaction was stirred at

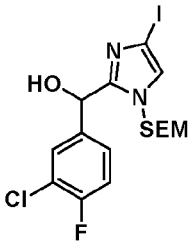
rt for 18 h. The reaction mixture was diluted with ice water (10 mL) and extracted with ethyl acetate (20 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get the crude material which was purified by flash chromatography (SiO_2, 0-50% EtOAc/Hex) to afford the title compound (1.7 g, 51%).

The title compound was prepared from the appropriate intermediates using an analogous method to that described for intermediate 22.

Intermediate	Structure	Name	Data
27		4-iodo-5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole and the corresponding SEM regioisomer	LCMS m/z = 339 $[M+H]^+$.

Intermediate 23

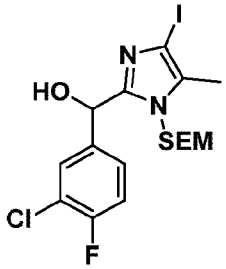
(3-chloro-4-fluorophenyl)(4-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methanol and the corresponding SEM regioisomer



LDA (2M sol. in THF/n-heptane/ethylbenzene, 12.383 mL, 24.766 mmol) was added to a solution of 4-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazole (intermediate 22, 7.3 g, 22.514 mmol) in THF at –78 °C. The reaction was stirred at –78 °C for 1 h followed by the addition of 3-chloro-4-fluorobenzaldehyde (3.570 g, 22.514 mmol). The reaction mixture was stirred at –78 °C for 1 h. The reaction was quenched with sat. NH_4Cl solution (50 mL) and extracted with ethyl acetate (100 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated to get the crude compound, which was purified by flash chromatography (SiO_2, 0-50% EtOAc/Hex) to afford the title compound (7.0 g, 64%).

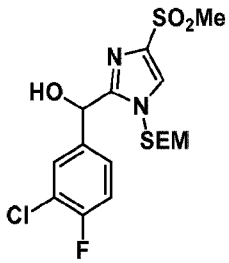
The title compound was prepared from the appropriate intermediates using an analogous method to that described for intermediate 23.

Intermediate	Structure	Name	Data

28		(3-chloro-4-fluorophenyl)(4-iodo-5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methanol and the corresponding SEM regioisomer	LCMS m/z = 497 $[M+H]^+$.

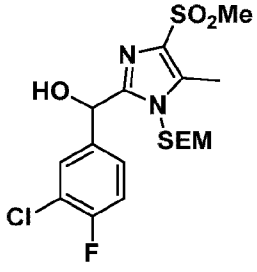
Intermediate 24

(3-chloro-4-fluorophenyl)(4-(methylsulfonyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methanol and the corresponding SEM regioisomer



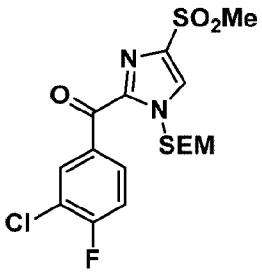
L-Proline (262.313 mg, 2.278 mmol) was added to an argon purged solution of sodium hydroxide (91.136 mg, 2.278 mmol) in DMSO (30 mL) and the mixture was stirred at rt for 30 min followed by the addition of (3-chloro-4-fluorophenyl)(4-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)methanol (mixture of regioisomers, intermediate 23, 1.1 g, 2.278 mmol), copper(I) iodide (433.922 mg, 2.278 mmol) and sodium methanesulfinate (930.318 mg, 9.114 mmol) at rt. The reaction was heated to 120 °C for 18 h. The reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (50 mL x 2). The organic layers were evaporated under reduced pressure to yield the title compound (0.65 g, crude), which was used in the next step without further purification.

The title compound was prepared from the appropriate intermediates using an analogous method to that described for intermediate 24.

Intermediate	Structure	Name	Data
29		(3-chloro-4-fluorophenyl)(5-methyl-4-(methylsulfonyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methanol and the corresponding SEM regioisomer	LCMS m/z = 449 $[M+H]^+$.

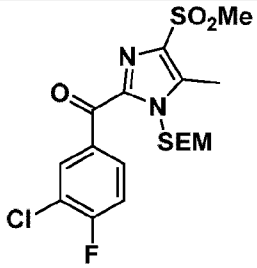
Intermediate 25

(3-chloro-4-fluorophenyl)(4-(methylsulfonyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methanone and the corresponding SEM regioisomer



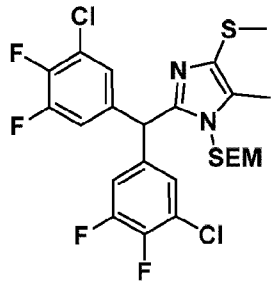
Pyridinium chlorochromate (3.964 g, 18.392 mmol) was added to a solution of (3-chloro-4-fluorophenyl)(4-(methylsulfonyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methanol (mixture of regioisomers, intermediate 24, 3.0 g, 6.897 mmol) in dichloromethane (90 mL) at 0 °C. The reaction was stirred at rt for 2 h. After completion of the reaction, the reaction mixture was diluted in water (50 mL) and extracted with DCM (2 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, 0-50% EtOAc/Hex) to afford the title compound (1.0 g, 25%).

The title compound was prepared from the appropriate intermediates using an analogous method to that described for intermediate 25.

Intermediate	Structure	Name	Data
30		(3-chloro-4-fluorophenyl)(5-methyl-4-(methylsulfonyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methanone and the corresponding SEM regioisomer	LCMS m/z = 447 $[M+H]^+$;

Intermediate 31

2-(bis(3-chloro-4,5-difluorophenyl)methyl)-5-methyl-4-(methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole and the corresponding SEM regioisomer



Step 1: Mg (1.53 g, 63.062 mmol) was taken up in a 2-necked flask equipped with a reflux condenser and dried under an argon atmosphere. THF (30.0 mL) and I_2 (0.02 g) were added. A solution of 5-bromo-1-chloro-2,3-difluorobenzene (6.64 mL, 52.551 mmol) in THF (10.0 mL) was added dropwise to the reaction mixture. The reaction mixture was stirred at room temperature for 1 h. To the freshly prepared Grignard reagent was added a solution of ethyl 5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole-2-carboxylate (mixture of regioisomers, 3.0 g, 10.51 mmol) in THF (10.0 mL) at 0 °C and the reaction mixture was stirred for 2 h. The reaction mixture was quenched with saturated NH_4Cl solution, diluted with EtOAc (150 mL) and washed with H_2O (50 mL) and brine (50 mL). The organic extract was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get the crude product, which was purified by column chromatography (SiO_2, 0-20% EtOAc/Hex) to afford bis(3-chloro-4,5-difluorophenyl)(5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methanol and the corresponding SEM regioisomer (5 g, 88%).

Step 2: To a stirred solution of bis(3-chloro-4,5-difluorophenyl)(5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methanol (mixture of refioisomers, 5.0 g, 9.321 mmol) in acetic acid (20.0 mL) and conc. HCl (10 mL) was added $SnCl_2$ (10.6 g, 55.924 mmol) at 0 °C. The reaction mixture was stirred at 120 °C for 16 h. The reaction mixture was concentrated under reduced pressure, the resulting residue was basified with Na_2CO_3 solution and filtered through a pad of celite. The filtrate was extracted with DCM (2 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford 2-[bis(3-chloro-4,5-difluorophenyl)methyl]-5-methyl-1H-imidazole (2.6 g, 71%).

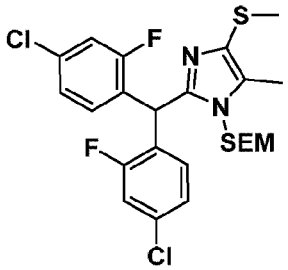
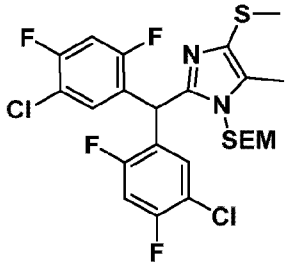
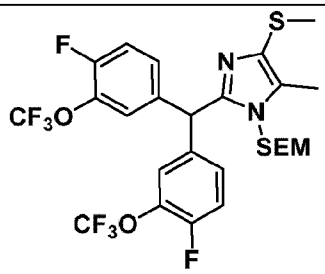
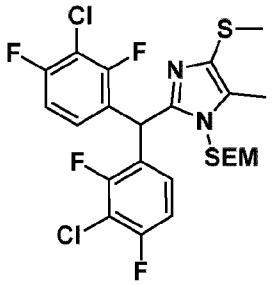
Step 3: To a solution of 2-[bis(3-chloro-4,5-difluorophenyl)methyl]-5-methyl-1H-imidazole (2.2 g, 5.653 mmol) in DMF (20.0 mL) were added KOH (0.476 g, 8.479 mmol) and I_2 (1.87 g, 7.349 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with EtOAc (150 mL) and washed with $Na_2S_2O_3$ solution (50 mL), H_2O (50 mL) and brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get the crude product, which was purified by column chromatography (SiO_2, 0-40% EtOAc/Hex) to afford 2-[bis(3-chloro-4,5-difluorophenyl)methyl]-4-iodo-5-methyl-1H-imidazole (2.1 g, 72%).

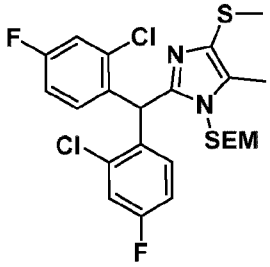
Step 4: To a stirred solution of 2-[bis(3-chloro-4,5-difluorophenyl)methyl]-4-iodo-5-methyl-1H-imidazole (0.7 g, 1.359 mmol) in DCM (14 mL) were added DIPEA (0.59 mL, 3.398 mmol) and then SEM-Cl (0.36 mL, 2.039 mmol) dropwise to the reaction mixture at 0 °C. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure to get crude product, which was purified by flash chromatography (SiO_2, 0-20% EtOAc/Hex) to afford 2-(bis(3-chloro-4,5-difluorophenyl)methyl)-4-iodo-5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole (0.72 g, 81%).

Step 5: A stirred solution of 2-(bis(3-chloro-4,5-difluorophenyl)methyl)-4-iodo-5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole (0.5 g, 0.774 mmol) in 1,4-dioxane (10.0 mL) was degassed for 5 minutes in a

sealed tube. Then NaSMe (0.108 g, 1.547 mmol), XantPhos (0.022 g, 0.039 mmol) and $Pd_2(dba)_3$ (0.028 g, 0.031 mmol) were added and the resulting mixture was stirred at 100 °C for 16 h. The reaction mixture was filtered through a pad of celite. The celite pad was washed with EtOAc (100 mL), the filtrate was concentrated under reduced pressure to get crude product. The crude product was purified by column chromatography (SiO_2, 0-30% EtOAc/Hex) to afford the title compounds (0.32 g, 73%). LCMS: m/z $[M+H]^+$ = 585.

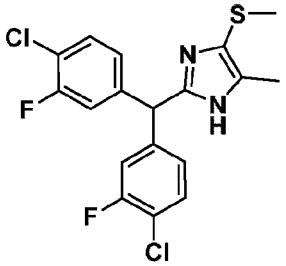
The title compounds were prepared from the appropriate intermediates using an analogous method to that described for intermediate 31.

Intermediate	Structure	Name	Data
32		2-(bis(2,4-difluorophenyl)methyl)-5-methyl-4-(methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole and the corresponding SEM regioisomer	LCMS m/z = 529 $[M+H]^+$.
33		2-(bis(5-chloro-2,4-difluorophenyl)methyl)-5-methyl-4-(methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole and the corresponding SEM regioisomer	LCMS m/z = 565 $[M+H]^+$.
34		2-(bis(4-fluoro-3-(trifluoromethoxy)phenyl)methyl)-5-methyl-4-(methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole and the corresponding SEM regioisomer	LCMS m/z = 629 $[M+H]^+$.
35		2-(bis(3-chloro-2,4-difluorophenyl)methyl)-5-methyl-4-(methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole and the corresponding SEM regioisomer	LCMS m/z = 565 $[M+H]^+$.

36		2-(bis(2-chloro-4-fluoro-phenyl)methyl)-5-methyl-4-(methylthio)-1-((2-(trime-thylsilyl)ethoxy)methyl)-1H-imidazole and the corre-sponding SEM regioisomer	LCMS m/z = 529 $[M+H]^+$.

Intermediate 37

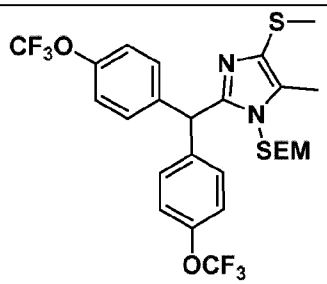
2-(bis(4-chloro-3-fluorophenyl)methyl)-5-methyl-4-(methylthio)-1H-imidazole



Step 1: Mg (2.84 g, 116.75 mmol) was heated under vacuum for 5 minutes, then cooled to room temperature. THF (50 mL) was added, followed by the addition of DIBAL-H (1.0 mL). The mixture was stirred at room temperature. 4-bromo-1-chloro-2-fluorobenzene (14.3 ml, 116.757 mmol) dissolved in THF (20 mL) and added dropwise to the reaction mixture. The reaction mixture was stirred at room temperature for 1h. The freshly prepared Grignard reagent was cooled at 0 °C, ethyl 5-methyl-1H-imidazole-2-carboxylate (3.6 g, 42.19 mmol) was added and the reaction was stirred at room temperature for 16 h. The reaction was quenched with aqueous NH_4Cl solution, extracted with EtOAc and washed with water. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get crude product which was purified by column chromatography (SiO_2, 0-60% EtOAc/Hex) to obtain bis(4-chloro-3-fluorophenyl)(5-methyl-1H-imidazol-2-yl)methanol (6.2 g, 72%). LCMS: m/z $[M+H]^+$ = 369.

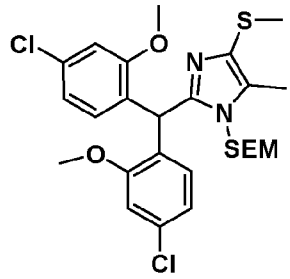
Step 2-3 was carried out in analogy to the synthesis of intermediate 31 to obtain the title compounds. LCMS: m/z $[M+H]^+$ = 399.

The title compound was prepared from the appropriate intermediates using an analogous method to that described for intermediate 37 followed by SEM protection (e.g. intermediate 31, step 4).

Intermedi-ate	Structure	Name	Data
38		2-(bis(4-(trifluorometh-oxy)phenyl)methyl)-5-me-thyl-4-(methylthio)-1-((2-(trimethylsilyl)ethoxy)me-thyl)-1H-imidazole and the corresponding SEM regioiso-mer	LCMS m/z = 593 $[M+H]^+$.

Intermediate 39

2-(bis(4-chloro-2-methoxyphenyl)methyl)-5-methyl-4-(methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazoleand the corresponding SEM regioisomer

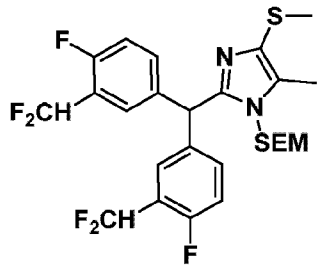


Step 1: To a stirred solution of 1-bromo-4-chloro-2-methoxybenzene (18 g, 81.08 mmol) in THF (75 mL) was added iPrMgBr (2 M in THF, 41 mL, 81.08 mmol) dropwise at 0 °C and the resulting solution was stirred at 40 °C for 16 h. To this freshly prepared Grignard reagent was added a solution of ethyl 5-methyl-1H-imidazole-2-carboxylate (2.5 g, 16.22 mmol) in THF (25 mL) at 0 °C and the reaction mixture was then heated to 80 °C for 3 h. The reaction mixture was quenched with ammonium chloride solution. The aqueous part was extracted with ethyl acetate (2 x 200 mL). The combined organic layers were washed with brine (150 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography (SiO_2, 10% EtOAc/Hex) to afford bis(4-chloro-2-methoxyphenyl)(5-methyl-1H-imidazol-2-yl)methanol. Yield: 39% (2.5 g, 6.36 mmol). LCMS: m/z $[M+H]^+$ = 393.

Step 2-4 was carried out in analogy to the synthesis of intermediate 31 to obtain the title compounds. LCMS: m/z $[M+H]^+$ = 553.

Intermediate 40

2-(bis(3-(difluoromethyl)-4-fluorophenyl)methyl)-5-methyl-4-(methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole and the corresponding SEM regioisomer



Step 1: To a stirred solution of 4-bromo-2-(difluoromethyl)-1-fluorobenzene (1 g, 14.01 mmol) in THF (20 mL) was added iPrMgBr (8 mL, 15.77 mmol) at 40 °C. The reaction mixture was stirred at the same temperature for 2 h. The mixture was cooled to 0 °C and ethyl 5-methyl-1H-imidazole-2-carboxylate (2.5 g, 3.503 mmol) in THF (5 mL) was added. The mixture was heated to 80 °C for 4 h. The reaction mixture was cooled to room temperature and quenched with ammonium chloride solution. The aqueous part was extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford bis(3-(difluoromethyl)-4-fluorophenyl)(5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methanol. Yield: Crude (1 g). LCMS: m/z $[M+H]^+$ = 531.

Step 2: To a stirred solution of bis(3-(difluoromethyl)-4-fluorophenyl)(5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methanol (4.5 g, 8.46 mmol) in acetic acid (50 mL) was added $SnCl_2$ (9.63 g, 50.79 mmol) followed by conc. HCl (12N, 10 mL) at room temperature. The reaction mixture was stirred at 110 °C for 16 h. The reaction mixture was concentrated under reduced pressure. The obtained residue was neutralized with Na_2CO_3 solution, the mixture was filtered and extracted with ethyl acetate (2 × 300 mL). The combined organic layers were washed with water (200 mL) followed by brine (200 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography (SiO_2, 10% EtOAc/Hex) to afford 5,5'-((5-methyl-1H-imidazol-2-yl)methylene)bis(2-fluorobenzaldehyde) and 5-((3-(difluoromethyl)-4-fluorophenyl)(5-methyl-1H-imidazol-2-yl)methyl)-2-fluorobenzaldehyde. Yield: 10% over 2 steps (1.8 g, 1.176 mmol). LCMS: m/z $[M+H]^+$ = 341/363.

Step 3: To a solution of 5,5'-((5-methyl-1H-imidazol-2-yl)methylene)bis(2-fluorobenzaldehyde) and 5-((3-(difluoromethyl)-4-fluorophenyl)(5-methyl-1H-imidazol-2-yl)methyl)-2-fluorobenzaldehyde (2.2 g, 3.13 mmol) in DCM (40 mL) was added DIPEA (1.4 mL, 7.83 mmol) followed by SEM-Cl (0.8 mL, 4.69 mmol) at 0 °C. The resulting reaction mixture stirred at room temperature for 16 h. The reaction mixture was poured into ice water and extracted with ethyl acetate (2 × 90 mL). The combined organic layers were washed with water (70 mL) followed by brine (60 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product. The obtained residue was purified by column chromatography (SiO_2, 10% EtOAc/Hex) to afford 5,5'-((5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methylene)bis(2-fluorobenzaldehyde), 5-((3-(difluoromethyl)-4-fluorophenyl)(5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methyl)-2-fluorobenzaldehyde and the corresponding SEM regioisomers. Yield: 97% (1.5 g, 3.049 mmol). LCMS: m/z $[M+H]^+$ = 471/493.

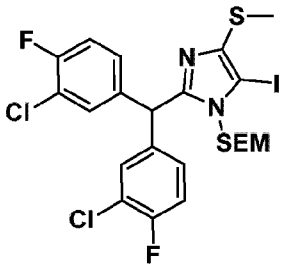
Step 4: To a stirred solution of 5,5'-((5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methylene)bis(2-fluorobenzaldehyde) and 5-((3-(difluoromethyl)-4-fluorophenyl)(5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methyl)-2-fluorobenzaldehyde (mixture of regioisomers, 1.8 g, 3.65 mmol) in DCM (24 mL) was added DAST (1.5 mL, 10.94 mmol) at 0 °C. The reaction mixture was stirred for 3 h. The reaction mixture was quenched with $NaHCO_3$ (100 mL) solution and extracted with DCM (3 × 100 mL). The combined organic layers were washed with water (100 mL) followed by brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford 2-(bis(3-(difluoromethyl)-4-fluorophenyl)methyl)-5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole and the corresponding SEM regioisomer. Yield: 37% (700 mg, 1.36 mmol). LCMS: m/z $[M+H]^+$ = 515.

Step 5: To a solution of 2-(bis(3-(difluoromethyl)-4-fluorophenyl)methyl)-5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole (mixture of regioisomers, 550 mg, 1.067 mmol) in MeCN (10 mL) was added NIS (0.312 g, 1.38 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was poured into ice water (100 mL) and quenched with sodium thiosulfate solution. The resulting aqueous layer was extracted with ethyl acetate (2 × 70 mL). The combined organic layers were washed with cold water (50 mL) followed by brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product, which was triturated with hexane to afford 2-(bis(3-(difluoromethyl)-4-fluorophenyl)methyl)-4-iodo-5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole and the corresponding SEM regioisomer. Yield: 59% (400 mg, 0.624 mmol). LCMS: m/z $[M+H]^+$ = 641.

Step 6: A stirred solution of 2-(bis(3-(difluoromethyl)-4-fluorophenyl)methyl)-4-iodo-5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole (mixture of regioisomers, 440 mg, 0.685 mmol) in 1,4-dioxane (10 mL) was degassed with argon for 10 minutes followed by the addition of NaSMe (62 mg, 0.891 mmol), Xantphos (28 mg, 0.048 mmol) and $Pd_2(dba)_3$ (31 mg, 0.0.034 mmol) at room temperature. The reaction mixture was heated to 80 °C for 16 h in a sealed tube. The reaction mixture was filtered and the filtrate was concentracted. The obtained residue was diluted with water (50 mL) and extracted with ethyl acetate (2 × 70 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography (SiO_2, 10% EtOAc/Hex) to afford the title compounds. Yield: 78% (300 mg, 0.536 mmol). LCMS: m/z $[M+H]^+$ = 571.

Intermediate 41

2-(bis(3-chloro-4-fluorophenyl)methyl)-5-iodo-4-(methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole and the corresponding SEM regioisomer

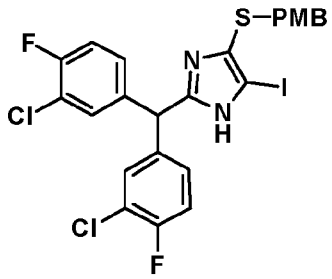


Step 1: A stirred solution of 2-(bis(3-chloro-4-fluorophenyl)methyl)-4-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole (intermediate 5, 5 g, 8.39 mmol) in 1,4-dioxane (100 mL) was degassed with argon for 10 min followed by the addition of NaSMe (0.9 g, 12.59 mmol), Xanthphos (0.73 g, 1.26 mmol) and $Pd_2(dba)_3$ (0.8 g, 0.84 mmol) at room temperature. The reaction mixture was heated to 80 °C for 16 h in a sealed tube. The reaction mixture was filtered and the filtrate was concentracted. The obtained residue was diluted with water (70 mL) and extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine (60 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography (SiO_2, 10% EtOAc/Hex) to afford 2-(bis(3-chloro-4-fluorophenyl)methyl)-5-(methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole and the corresponding SEM regioisomer (3.5 g, 81%). LCMS: m/z $[M+H]^+$ = 515.

Step 2: To a stirred solution of 2-(bis(3-chloro-4-fluorophenyl)methyl)-5-(methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole (mixture of regioisomers, 3.5 g, 6.79 mmol) in DCM (90 mL) was added NIS (2.3 g, 10.18 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was quenched with aqueous sodium thiosulfate solution (60 mL). The aqueous layer was extracted with ethyl acetate (2 × 130 mL). The combined organic layers were washed with brine (60 mL), dried over Na_2SO_4 and concentrated under reduced pressure to get the crude product, which was purified by flash column chromatography (SiO_2, 10% EtOAc/Hex) to afford the title compounds (2.5 g, 57%). LCMS: m/z $[M+H]^+$ = 641.

Intermediate 42

2-(bis(3-chloro-4-fluorophenyl)methyl)-5-iodo-4-((4-methoxybenzyl)thio)-1H-imidazole



Step 1: To a solution of ethyl 4-bromo-1H-imidazole-2-carboxylate (3.0 g, 13.699 mmol) in 1,4-dioxane (100 mL) was added DIPEA (7.2 mL, 41.096 mmol) at room temperature. The reaction mixture was degassed with argon for 10 min followed by the addition of (4-methoxyphenyl)methanethiol (5.8 mL, 41.096 mmol), Xantphos (0.8 g, 1.37 mmol) and $Pd_2(dba)_3$ (0.63 g, 0.685 mmol) at room temperature. The reaction mixture was heated to 110 °C for 30 h in a sealed tube. The reaction mixture was cooled room temperature, diluted with ethyl acetate and filtered through a celite bed. The filtrate was evaporated under reduced pressure. The resulting crude was purified by column chromatography (SiO_2, 0-50% EtOAc/Hex) to yield ethyl 4-{[(4-methoxyphenyl)methyl]sulfanyl}-1H-imidazole-2-carboxylate. Yield: 87% (3.5 g). LCMS: m/z $[M+H]^+$ = 293.

Step 2: Mg (4.6 g, 188.35 mmol) was taken up in a 2-neck flask equipped with a reflux condenser and was dried under an argon atmosphere. THF (40 mL), 4-bromo-2-chloro-1-fluorobenzene (23.0 mL, 188.35 mmol) and DIBAL-H (1M in toluene, 3.0 mL) were added to the mixture sequentially at room temperature. The reaction mixture was stirred at room temperature for 1 h. To the freshly prepared Grignard reagent was added a solution of ethyl 4-((4-methoxybenzyl)thio)-1H-imidazole-2-carboxylate (11.0 g, 37.67 mmol) in THF (260 mL) at 0 °C and the reaction mixture was heated to 80 °C for 5 h. The reaction mixture was cooled to room temperature and was quenched with ammonium chloride solution. The aqueous layer was filter through a celite bed and extracted with ethyl acetate (3 × 200 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by column chromatography (SiO_2, 0-60% EtOAc/Hex) to yield bis(3-chloro-4-fluorophenyl)(5-{[(4-methoxyphenyl)methyl]sulfanyl}-1H-imidazol-2-yl)methanol. Yield: 58% (11.0 g). LCMS: m/z $[M+H]^+$ = 507.

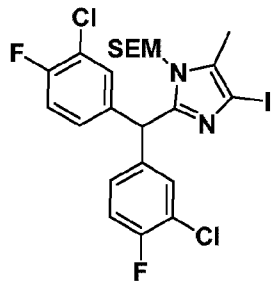
Step 3: To a solution of bis(3-chloro-4-fluorophenyl)(5-{[(4-methoxyphenyl)methyl]sulfanyl}-1H-imidazol-2-yl)methanol (10.0 g, 19.724 mmol) in acetic acid (150 mL) were added $SnCl_2$ (22.4 g, 118.343 mmol) and HCl (12N, 30 mL) at 0 °C. The reaction mixture was stirred at 120 °C for 16 h. The reaction mixture was cooled to room temperature and was concentrated under reduced pressure to get the crude compound which was basified with Na_2CO_3 solution. The aqueous layer was filter through a celite bed and was extracted with ethyl acetate (3 × 200 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, 0-60% EtOAc/Hex) to yield 2-[bis(3-chloro-4-fluorophenyl)methyl]-5-{[(4-methoxyphenyl)methyl]sulfanyl}-1H-imidazole. Yield: 41% (4.0 g). LCMS: m/z $[M+H]^+$ = 491.

Step 4 : To a stirred solution of 2-[bis(3-chloro-4-fluorophenyl)methyl]-5-{[(4-methoxyphenyl)methyl]sulfanyl}-1H-imidazole (1.0 g, 2.04 mmol) in DCM (20 mL) was added NIS (0.55 g, 2.5 mmol) at 0 °C and the mixture was stirred at for 3 h. The reaction mixture was quenched with sodium thiosulfate solution. The aqueous layer was

extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure to get the crude product, which was purified by column chromatography (SiO_2, 0-60% EtOAc/Hex) to yield the title compounds. Yield: 64% (0.8 g). LCMS: m/z $[M+H]^+$ = 617.

Intermediate 43

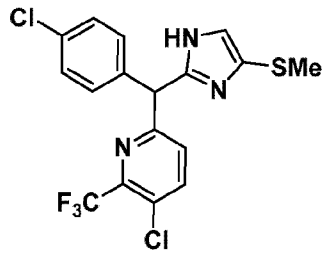
2-(bis(3-chloro-4-fluorophenyl)methyl)-4-iodo-5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole and the corresponding SEM regioisomer



To a stirred solution of 2-[bis(3-chloro-4-fluorophenyl)methyl]-4-iodo-5-methyl-1H-imidazole (12 g, 25.05 mmol) in DCM (120 mL) was added DIPEA (11 mL, 62.62 mmol) followed by SEM-Cl (6.7 mL, 37.57 mmol) dropwise at 0 °C. The resulting reaction mixture was stirred at room temperature for 16 h. The reaction mixture was quenched with cold ammonium chloride solution (100 mL) and extracted with ethyl acetate (2 × 150 mL). The combined organic layers were washed with brine (150 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography (SiO_2, 10% EtOAc/Hex) to afford the title compounds. Yield: 79% (12 g). LCMS: m/z $[M+H]^+$ = 609.

Intermediate 44

3-chloro-6-((4-chlorophenyl)(4-(methylthio)-1H-imidazol-2-yl)methyl)-2-(trifluoromethyl)pyridine



Step 1: To a solution of 3,6-dichloro-2-(difluoromethyl)pyridine (2.5 g, 11.628 mmol) in ethanol (50 mL) was added TEA (2 mL, 13.953 mmol). The mixture was degassed with nitrogen for 10 minutes, followed by the addition of potassium vinyltrifluoroborate (1.9 g, 13.953 mmol) followed by the addition of $PdCl_2$(dppf)·DCM (0.43 g, 0.581 mmol) at room temperature. The mixture was then heated to 110 °C for 3 h in a sealed flask. The reaction mixture was cooled to room temperature and filtered through a celite bed, the filtrate was evaporated at low temperature (below 40 °C) under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, Hex) to get 3-chloro-6-ethenyl-2-(trifluoromethyl)pyridine Yield: 75% (1.8 g).

Step 2: To a solution of 3-chloro-6-ethenyl-2-(trifluoromethyl) pyridine (1.8 g, 8.696 mmol) in 1,4-dioxane-water (3:1, 60 mL) was added NMO (2.6 mL, 9.565 mmol, 50% in water) followed by OsO_4 (1.2 mL, 0.174 mmol, 0.15 M in Dioxane) at room temperature. The mixture was stirred for 3 h. Then, $NaIO_4$ (19 g, 86.957 mmol) was added

and the mixture was stirred for 1 h. The mixture was quenched with saturated sodium bi-carbonate solution and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure to get 5-chloro-6-(trifluoromethyl)picolinaldehyde. Yield: 82% (1.5 g).

Step 3: To a solution of 5-chloro-6-(trifluoromethyl) picolinaldehyde (0.1 g, 0.478 mmol) in THF (4 mL), was added (4-chlorophenyl) magnesium bromide (1M in Et_2O, 0.57 mL, 0.574 mmol) slowly at 0 °C, and the mixture was stirred for 1 h. The reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to get the crude product, which was purified by column chromatography (SiO_2, 30% EtOAc/Hex) to get [5-chloro-6-(trifluoromethyl)pyridin-2-yl](4-chlorophenyl)methanol. Yield: 84% (0.13 g). LCMS: m/z $[M+H]^+$ = 322.

Step 4: To a solution of [5-chloro-6-(trifluoromethyl) pyridin-2-yl] (4-chlorophenyl) methanol (0.13 g, 0.404 mmol) in THF (5 mL) was added MnO_2 (0.18 g, 2.019 mmol) at room temperature and the mixture was stirred for 16 h. The mixture was filtered through a celite bed, which was washed with THF. The filtrate was evaporated to get the crude compound which was purified by column chromatography (SiO_2, 20% EtOAc/Hex) to get 3-chloro-6-[(4-chlorophenyl) carbonyl]-2-(trifluoromethyl)pyridine. Yield: 77% (0.1 g)

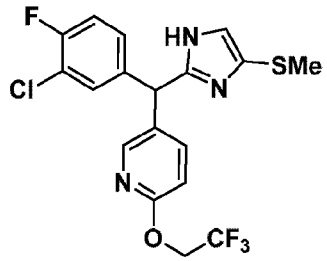
Step 5: To a solution of DIPA (0.72 mL, 5.156 mmol) in THF (10 mL) was added n-BuLi (2.3 mL, 2 M in THF, 4.688 mmol) slowly at -78 °C under a nitrogen atmosphere. The mixtue was stirred for 10 minutes at -78 °C, then at 0 °C for 30 minutes. The solution was cooled back to -78 °C, 4-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole (mixture of regioisomers, 1.3 g, 3.906 mmol) in THF (10 mL) was added. The mixture was stirred for 30 minutes, followed by the addition of 3-chloro-6-[(4-chlorophenyl)carbonyl]-2-(trifluoromethyl)pyridine (0.5 g, 1.563 mmol) in THF (10 mL) at the same temperature. Thew mixture was slowly warm up to room temperature and was stirred for 6 h. The mixture was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure to get the crude compound which was purified by column chromatography (SiO_2, 10% EtOAc/Hex) to get (5-chloro-6-(trifluoromethyl)pyridin-2-yl)(4-chlorophenyl)(4-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methanol and the corresponding SEM regioisomer. Yield: 50% (0.5 g). LCMS: m/z $[M+H]^+$ = 645.

Step 6: To a solution of (5-chloro-6-(trifluoromethyl)pyridin-2-yl)(4-chlorophenyl)(4-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methanol (mixture of regioisomers, 0.5 g, 0.776 mmol) in 1,4-dioxane (20 mL) was added NaSMe (0.1 g, 1.32 mmol) and the mixture was degassed with nitrogen for 10 minutes. Then Xantphos (0.07 g, 0.116 mmol) and $Pd_2(dba)_3$ (0.07 g, 0.078 mmol) were added at room temperature and the mixture was heated to 110 °C for 16 h in a sealed tube. The mixture was filtered through a celite bed and the celite bed was washed with EtOAc. The solvent was evaporated to get the crude compound which was purified by column cromatography (SiO_2, 10% EtOAc/Hex) to get (5-chloro-6-(trifluoromethyl)pyridin-2-yl)(4-chlorophenyl)(4-(methylsulfonyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methanol and the corresponding SEM regioisomer. Yield: 68% (0.3 g). LCMS: m/z $[M+H]^+$ = 564.

Step 7: To a solution of (5-chloro-6-(trifluoromethyl)pyridin-2-yl)(4-chlorophenyl)(4-(methylsulfonyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methanol (mixture of regioisomers, 0.32 g, 0.566 mmol) in acetic acid (5.0 mL) were added $SnCl_2$ (0.64 g, 3.398 mmol) and aqueous HCl (1 mL, 12N). The mixture was heated to 120 °C for 24 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure to get the crude compound which was basified with aqueous Na_2CO_3 solution. The mixture was filtered through a celite bed and was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to get the crude compound which was purified by combi-flash column chromatography (SiO_2, 50% EtOAc/Hex) to get the title compound. Yield: 55% (0.13 g). LCMS: m/z $[M+H]^+$ = 418.

Intermediate 45

5-((3-chloro-4-fluorophenyl)(4-(methylthio)-1H-imidazol-2-yl)methyl)-2-(2,2,2-trifluoroethoxy)pyridine



Step 1: To a solution of (3-chloro-4-fluorophenyl)(4-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methanol (intermediate 23, 4.2 g, 8.699 mmol) in dichloromethane (50 mL) was added celite (1.6 g) followed by pyridinium chlorochromate (3.750 g, 17.399 mmol) at room temperature under an argon atmosphere. The resulting reaction mixture was stirred for 16 h. The reaction mixture was filtered through a celite bed, which was washed with DCM (300 mL). The filtratre was concentrated under reduced pressure to afford the crude product. (3 g) crude. The reaction was in parallel carried out with another 0.5 g of (3-chloro-4-fluorophenyl)(4-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methanol in analogy. The two crude materials were combined and purified by column chromatography (SiO_2, 0-10% EtOAc/Hex) to afford (3-chloro-4-fluorophenyl)(4-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methanone (2.1 g, crude).

Step 2: (3-Chloro-4-fluoro phenyl)(4-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methanone (10 g, 20.800 mmol) was dissolved in HCl in 1,4-dioxane (4N, 200 mL) at 0 °C. The resulting mixture was stirred at room temperature for 5 h. The reaction mixture was concentrated under reduced pressure and was then diluted with water (5 mL) and basified with $NaHCO_3$ solution (pH=8) at 0 °C. After stirring for 10 min, the resulting precipitate was filtered off and dried under reduced pressure to afford (3-chloro-4-fluorophenyl)(4-iodo-1H-imidazol-2-yl)methanone (7.5 g, crude).

Step 3: (3-Chloro-4-fluorophenyl)(4-iodo-1H-imidazol-2-yl)methanone (3 g, 8.559 mmol) and sodium thiomethoxide (0.600 g, 8.559 mmol) were dissolved in 1,4-dioxane (30 mL) followed by the addition of cesium carbonate (8.366 g, 25.676 mmol). The mixture was then degassed with argon for 10 min. Then $Pd_2(dba)_3$ (0.784 g, 0.856 mmol) followed by Xantphos (0.495 g, 0.856 mmol) were added at room temperature. The resulting reaction mixture was heated to 120 °C for 16 h. The reaction mixture was cooled to room temperature, filtered through a celite bed and the celite bed was washed with 250 mL of ethyl acetate. The filtrate was concentrated under reduced

pressure. The crude product was purified by column chromatography (SiO_2, 13% EtOAc/pet ether) to afford (3-chloro-4-fluorophenyl)(4-(methylthio)-1H-imidazol-2-yl)methanone (0.560 g, 24%).

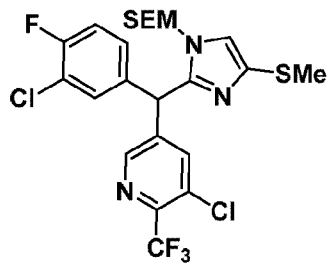
Step 4: 2-Bromo-5-(2,2,2-trifluoroethoxy)pyridine (7.944 g, 31.030 mmol) was added to a vigorous stirred solution of magnesium turnings (0.754 g, 31.030 mmol) and iodine (5.250 mg, 0.021 mmol) in anhydrous tetrahydrofuran (10 mL) at room temperature under an argon atmosphere. The resulting suspension was stirred for 1 h. The reaction mixture was cooled to 0 °C and a solution of (3-chloro-4-fluorophenyl)(4-(methylthio)-1H-imidazol-2-yl)methanone (0.56 g, 2.069 mmol) in anhydrous tetrahydrofuran (10 mL) was addeddrop wise. The resulting reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was quenched by the addition of sat. solution of NH_4Cl (20 mL) at 0 °C and extracted with ethyl acetate (2×30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2, 40% EtOAc/pet ether) to afford (3-chloro-4-fluorophenyl)(4-(methylthio)-1H-imidazol-2-yl)(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)methanol (455 mg, crude).

Step 5: Stannous chloride dihydrate (1.36 g, 6.029 mmol) was added to a stirred solution of (3-chloro-4-fluorophenyl)(4-(methylthio)-1H-imidazol-2-yl)(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)methanol (450 mg, 1.005 mmol) and conc. HCl (1 mL) in acetic acid (5.2 mL) at room temperature. The resulting reaction mixture was heated to 100 °C for 16 h. he reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was diluted with ice-cold water (20 mL), basified with solid $NaHCO_3$ (pH= 8) and diluted with EtOAc (80 mL). The resulting suspension was filtered through celite, the organic phase vwas separated, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford 5-((3-chloro-4-fluorophenyl)(4-(methylthio)-1H-imidazol-2-yl)methyl)-2-(2,2,2-trifluoroethoxy)pyridine (360 mg, crude).

Step 6: Sodium hydride (69.471 mg, 1.737 mmol) was added in a solution of 5-((3-chloro-4-fluorophenyl)(4-(methylthio)-1H-imidazol-2-yl)methyl)-2-(2,2,2-trifluoroethoxy)pyridine (300 mg, 0.695 mmol) in THF (6 mL) at 0 °C under an argon atmosphere. The reaction was stirred at 0 °C for 5 min followed by the addition of SEMCl (0.308 mL, 1.737 mmol) at 0 °C. The mixture was stirred for 15 min. The reaction was diluted with ice water (10 mL) and extracted with ethyl acetate (3×25 mL). The solvent was evaporated under reduced pressure to afford the title compound (570 mg, crude).

Intermediate 46

3-chloro-5-((3-chloro-4-fluorophenyl)(4-(methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methyl)-2-(trifluoromethyl)pyridine and the corresponding SEM regioisomer



Step 1: To a stirred solution of 2-iodo-1H-imidazole (3.0 g, 15.466 mmol) in THF (30 mL) at 0 °C was added sodium hydride (60% dispersion in mineral oil, 1.237 g, 18.559 mmol) and the mixture was stirred for 1 h followed

by addtion of SEMCl (2.743 mL, 15.466 mmol). The resulting reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with cold water (50 mL) and extracted with EtOAc (50 mL x 2). The combined organic layers were dried over sodium sulphate and the solvent was evaporated under reduced pressure to get crude compound, which was purified by column column (SiO_2, 0-50% EtOAc/Hex) to afford 2-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole and the corresponding SEM regioisomer (3.5 g, 70%).

Step 2: To a stirred solution of methyl 5,6-dichloronicotinate (4 g, 19.415 mmol) in MeCN (10 mL) at room temperature was added trimethylsilyl iodide (4.162 mL, 29.122 mmol). The resulting reaction mixture was stirred at 80 °C for 4 h. The reaction mixture was cooled to room temperature, basified with aq. sodium bicarbonate (50 mL) and extracted with EtOAc (100 mL x 2). The combined organic layers were washed with aq. sodium thiosulfate (100 mL) and concentrated under reduced pressure to get methyl 5-chloro-6-iodonicotinate (5.0 g, 86%).

Step 3: To a stirred solution of methyl 5-chloro-6-iodonicotinate (1.0 g, 3.362 mmol) and copper iodide (2.561 g, 13.446 mmol) in DMF (10.0 mL) at room temperature was added methyl 2,2-difluoro-2-(fluorosulfonyl) acetate (4.198 g, 21.851 mmol). The resulting reaction mixture was heated to 80 °C for 18 h. The reaction mixture was cooled to room temperature, diluted with water (50 mL) and extracted with EtOAc (50 mL x 2). The combined organic layers were dried over sodium sulphate and concentrated under reduced pressure to get the crude product, which was purified via column chromatography (SiO_2, 10% EtOAc/pet ether) to obtain (3-chloro-4-fluorophenyl) (4-iodo-5-methyl-1-((2-(trimethylsilyl) ethoxy) methyl)-1H-imidazol-2-yl) methyl diisopropylcarbamate (2.8 g, 93%).

Step 4: Lithium hydroxide hydrate (262.724 mg, 6.261 mmol) was added to stirred solution of methyl 5-chloro-6-(trifluoromethyl) nicotinate (500 mg, 2.087 mmol) in methanol (4 mL), THF (4 mL) and water (2 mL) at room temperature. The reaction mixture was stirred for 2 h. The solvent was removed under reduced pressure to obtain a residue, which was neutralised with 20% HCl solution (ph=3) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were evaporated under reduced pressure to obtain 5-chloro-6-(trifluoromethyl) nicotinic acid (0.4 g, crude).

Step 5: DIPEA (0.238 mL, 1.330 mmol) was added to a stirred solution of 5-chloro-6-(trifluoromethyl) nicotinic acid (100 mg, 0.443 mmol), HATU (252.867 mg, 0.665 mmol) and N, O-dimethylhydroxylamine hydrochloride (64.874 mg, 0.665 mmol) in DMF (5 mL) at room temperature. The reaction mixture was stirred for 4 h. The reaction reaction mass was diluted with water (5 mL) and extracted with ethyl acetate (10 mL x 2). The combined organic layers were dried over sodium sulphate and evaporated under reduced pressure to get the crude product, which was purified by column chromatography (SiO_2, 0-50% EtOAc/pet ether) to afford 5-chloro-N-methoxy-N-methyl-6-(trifluoromethyl) nicotinamide (0.08 g, 93%).

Step 6: 4-Bromo-2-chloro-1-fluorobenzene (19.492 g, 93.068 mmol) was added to a stirred solution of magnesium turnings (2.457 g, 102.375 mmol) and iodine (10 mg) in THF (30 mL) at room temperature. The reaction mixture was stirred for 30 min and was then cooled to 0 °C. 5-Chloro-N-methoxy-N-methyl-6-(trifluoromethyl)nicotinamide (5.0 g, 18.614 mmol) in THF (20 mL) was added and the mixture was stirred for 30 min. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (100 mL x 2). The combined organic layers were dried over sodium sulphate and evaporated under reduced pressure to get the crudecompound, which was purified

by column chromatography (SiO_2, 0-50% EtOAc/pet ether) to obtain (3-chloro-4-fluorophenyl) (5-chloro-6-(trifluoromethyl) pyridin-3-yl) methanone (2.7 g, 46%).

Step 7: To a stirred solution of 2-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole (mixture of regioisomers, 2.9 g, 8.944 mmol) in THF (30 mL) at -78 °C was added n-BuLi (1.6M solution in hexanes, 5.366 mL, 13.416 mmol) and the mixture was stirred for 30 min. Then (3-chloro-4-fluorophenyl) (5-chloro-6-(trifluoromethyl) pyridin-3-yl)methanone (1.512 g, 4.472 mmol) in THF (10 mL) was added. The resulting mixture was stirred at -78 °C for 1.5 h. The reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (50 mL x 2). The combined organic layers were dried over sodium sulphate and evaporated under reduced pressure to get the crude com pound, which was purified by column chromatography (SiO_2, 0-50% EtOAc/pet ether) to afford (3-chloro-4-fluorophenyl) (5-chloro-6-(trifluoromethyl) pyridin-3-yl) (1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methanol and the corresponding SEM regioisomer (2.7g, 56%).

Step 8: To a stirred solution of (3-chloro-4-fluorophenyl) (5-chloro-6-(trifluoromethyl) pyridin-3-yl) (1-((2-(trimethylsilyl) ethoxy) methyl)-1H-imidazol-2-yl) methanol (mixture of regioisomers, 350 mg, 0.652 mmol), acetic acid (7 mL, 0.125 mmol) and HCl (37% solution in water, 5 mL, 0.025 mmol) at room temperature was added stannous chloride dihydrate (1.472 g, 6.525 mmol). The resulting reaction mixture was stirred at 120 °C for 18 h. The reaction mixture was concentrated under reduced pressure, the residue was basified with sat solution of $NaHCO_3$ and extracted with ethyl acetate (30 mL x 2). The combined organic layers were dried over sodium sulphate and evaporated under reduced pressure to get the crude product, which was purified by column chromatography (SiO_2, 0-50% EtOAc/pet ether) to afford 3-chloro-5-((3-chloro-4-fluorophenyl) (4,5-diiodo-1H-imidazol-2-yl) methyl)-2-(trifluoromethyl) pyridine (0.25 g, 98%).

Step 9: NIS (562.240 mg, 2.499 mmol) was added to a stirred solution of 3-chloro-5-((3-chloro-4-fluorophenyl) (1H-imidazol-2-yl) methyl)-2-(trifluoromethyl) pyridine (650 mg, 1.666 mmol) in chloroform (10 mL) at 0 °C. The reaction mixture was stirred for 2 h at room temperature. The reaction mixture was diluted with water (10 mL) and extracted with DCM (20 mL x 2). The combined organic layers were dried over sodium sulphate and evaporated under reduced pressure to get the crude compound, which was purified by column chromatography (SiO_2, 0-50% EtOAc/pet ether) to afford 3-chloro-5-((3-chloro-4-fluorophenyl) (4,5-diiodo-1H-imidazol-2-yl) methyl)-2-(trifluoromethyl) pyridine (1.0 g, 93%).

Step 10: Sodium sulfite (1.963 g, 15.577 mmol) was added to a stirred solution of 3-chloro-5-((3-chloro-4-fluorophenyl) (4,5-diiodo-1H-imidazol-2-yl) methyl)-2-(trifluoromethyl) pyridine (1.0 g, 1.558 mmol) in ethanol (7 mL) and water (3 mL) at room temperature. The resulting reaction mixture was heated to 110 °C for 18 h. The reaction mixture was concentrated under reduced pressure, the obtained residue was taken up in water (10 mL) and extracted with ethyl acetate (20 mL x 2). The combined organic layers were dried over sodium sulphate and evaporated under reduced pressure to get the crude compound, which was purified by column chromatography (SiO_2, 0-50% EtOAc/pet ether) to afford 3-chloro-5-((3-chloro-4-fluorophenyl) (4-iodo-1H-imidazol-2-yl) methyl)-2-(trifluoromethyl) pyridine (0.75 g, 93%).

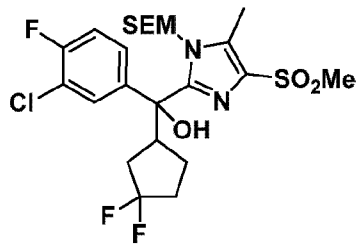
Step 11: Sodium hydride (60% dispersion in mineral oil, 51.157 mg, 1.279 mmol) was added to a stirred solution of 3-chloro-5-((3-chloro-4-fluorophenyl) (4-iodo-1H-imidazol-2-yl) methyl)-2-(trifluoromethyl) pyridine (550

mg, 1.066 mmol) in THF (5 mL) at 0 °C and the reaction mixture was stirred for 1 h. Then SEM-Cl (0.284 mL, 1.599 mmol) was added dropwise. The resulting reaction mixture was stirred for 2 h at room temperature. The reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate (20 mL x 2). The combined organic layers were dried over sodium sulphate and evaporated under reduced pressure to get the crude compound, which was purified by column chromatography (SiO_2, 0-50% EtOAc/pet ether) to afford 3-chloro-5-((3-chloro-4-fluorophenyl) (4-iodo-1-((2-(trimethylsilyl) ethoxy) methyl)-1H-imidazol-2-yl) methyl)-2-(trifluoromethyl) pyridine and the corresponding SEM regioisomer (0.4 g, 80%).

Step 12: $Pd_2(dba)_3$ (56.673 mg, 0.062 mmol) and Xantphos (71.620 mg, 0.124 mmol) were added to an argon purged solution of 3-chloro-5-((3-chloro-4-fluorophenyl) (4-iodo-1-((2-(trimethylsilyl) ethoxy) methyl)-1H-imidazol-2-yl) methyl)-2-(trifluoromethyl) pyridine (mixture of regioisomers, 800 mg, 1.238 mmol), sodium thiomethoxide (104.107 mg, 1.485 mmol) and cesium carbonate (1.210 g, 3.713 mmol) in 1,4-dioxane (10 mL) at room temperature. The reaction mixtre was stirred for 1 h under microwave irradiation at 120 °C. The reaction mixture was filtered through a pad of celite and the celite pad was washed with ethyl acetate (2 x 30 mL). The filtrate was evaporated under reduced pressure to get the crude compound, which was purified by column chromatography (SiO_2, 0-50% EtOAc/pet ether) to get the title compounds (0.7 g, crude).

Intermediate 47

(3-chloro-4-fluorophenyl)(3,3-difluorocyclopentyl)(5-methyl-4-(methylsulfonyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methanol and the corresponding SEM regioisomer



Step 1: To a stirred solution of 3,3-difluorocyclopentane-1-carboxylic acid (2.0 g, 13.322 mmol), N, O-dimethyl hydroxylamine (1.627 g, 26.644 mmol) and DIPEA (9.282 mL, 53.289 mmol) in DCM (20 mL) at 0 °C was added HATU (7.598 g, 19.983 mmol). The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was quenched with water (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL) and were then concentrated under reduced pressure to afford the crude compound, which was purified by column chromatography (SiO_2, 70% EtOAc/pet ether) afford 3,3-difluoro-N-methoxy-N-methylcyclopentane-1-carboxamide (2.1 g, 81%).

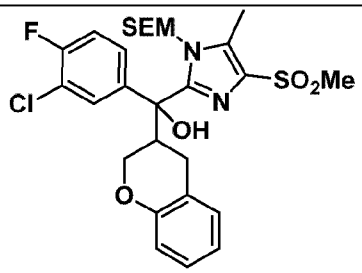
Step 2: To a stirred solution of magnesium (0.67 g, 27.91 mmol) in THF (5.0 mL) at room temperature were added 4-bromo-2-chloro-1-fluorobenzene (3.398 mL, 27.907 mmol) and DIBAL-H (1.2M solution in toluene, 0.5 mL). The mixture was stirred for 1 h. The mixture was cooled to 0 °C and 3,3-difluoro-N-methoxycyclopentane-1-carboxamide (1.0 g, 5.58 mmol) in THF (25.0 mL) was added. The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was quenched with saturated ammonium chloride solution (20 mL) and extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL) and were concentrated under reduced pressure to afford the crude compound, which was purified by column

chromatography (SiO_2, 5% EtOAc/pet ether) to afford (3-chloro-4-fluorophenyl) (3,3-difluorocyclopentyl) methanone (0.9 g, 61%).

Step 3: To a stirred solution of 4-iodo-5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole (mixture of regioisomers, intermediate 27, 1.288 g, 3.807 mmol) in THF (15 mL) at -78°C was added LDA (2M in THF, 3.807 mL, 7.615 mmol). The reaction mixture was stirred at -78°C for 1 h, then (3-chloro-4-fluorophenyl) (3,3-difluorocyclopentyl) methanone (1.0 g, 3.807 mmol) in THF (5 mL) was added. The reaction mixture was stirred at -78 °C for 2 h. The reaction mixture was quenched with saturated ammonium chloride solution (50 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with water (30 mL) and brine solution (30 mL) and were concentrated under reduced pressure to afford the crude compound, which was purified by column chromatography (SiO_2, 15% EtOAc/pet ether) and later reverse phase chromatography to afford (3-chloro-4-fluorophenyl)(3,3-difluorocyclopentyl)(4-iodo-5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methanol and the corresponding SEM regioisomer (0.8 g, 35%).

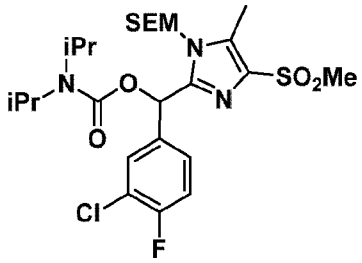
Step 4: To a stirred degassed solution of (3-chloro-4-fluorophenyl)(3,3-difluorocyclopentyl)(4-iodo-5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methanol (mixture of regioisomers, 0.9 g, 1.498 mmol), methanesulfinic acid sodium salt (0.612 g, 5.991 mmol, 4 equiv.), sodium hydroxide (0.120 g, 2.995 mmol) and L-Proline (0.172 g, 1.498 mmol) in DMSO (18 mL) at room temperature was added copper(I)iodide (0.143 g, 0.749 mmol). The reaction mixture was stirred at 80 °C for 18 h. The reaction mixture was diluted with 10% MeOH:DCM (50 mL), filtered through a celite bed, the filtrate was washed with water (2 × 30 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated under the reduced pressure to afford the crude compound. The crude was purified by column chromatography (SiO_2, 12% EtOAc/pet ether) to afford the title compounds (0.23 g, 27%).

The title compound was prepared from the inermediates using an analogous method to that described for Intermediate 47.

Intermediate	Structure	Name	Data
48		(3-chloro-4-fluorophenyl)(chroman-3-yl)(5-methyl-4-(methylsulfonyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methanol and the corresponding SEM regioisomer	LCMS m/z = 581 $[M+H]^+$.

Intermediate 49

(3-chloro-4-fluorophenyl)(5-methyl-4-(methylsulfonyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methyl diisopropylcarbamate and the corresponding SEM regioisomer

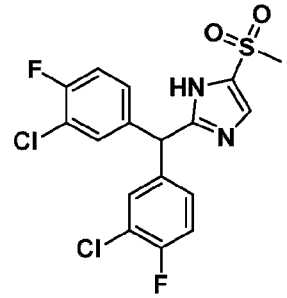


Step 1: To a solution of 4-iodo-5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole (intermediate 27, mixture of regioisomers, 12 g, 35.475 mmol) in MeCN (50 mL) were added diisopropylcarbamic chloride (6.38 g, 39.023 mmol), 3-chloro-4-fluorobenzaldehyde (8.437 g, 53.213 mmol) and DIPEA (19.61 mL, 106.4 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 16 h. The reaction mixture was diluted with water (150 mL) and extracted with ethyl acetate (2×150 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography (SiO_2, 15-20% EtOAc/pet ether) to afford 15 g (68%) of (3-chloro-4-fluorophenyl)(4-iodo-5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methyl diisopropylcarbamate (mixture of regioisomers).

Step 2: A mixture of (3-chloro-4-fluorophenyl)(4-iodo-5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methyl diisopropylcarbamate (mixture of regioisomers, 7 g, 11.218 mmol), sodium methanesulfonate (5.299 g, 44.871 mmol), cesium carbonate (3.655 g, 11.218 mmol), L-proline (1.29 g, 11.21 mmol) and copper(I) iodide (1.71 g, 8.974 mmol) in DMSO (80 mL) was stirred at 120 °C for 16 h in a sealed tube. The reaction mixture was cooled to room temperature, diluted with water (100 mL) and extracted with EtOAc (3×100 mL). The combined organic layers were washed with brine (2×80 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography (C18, MeCN/water) to afford 3.0 g of the title compounds.

Example 1

2-(bis(3-chloro-4-fluorophenyl)methyl)-5-(methylsulfonyl)-1H-imidazole

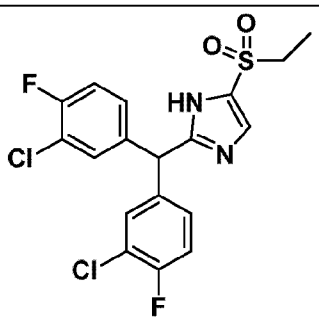
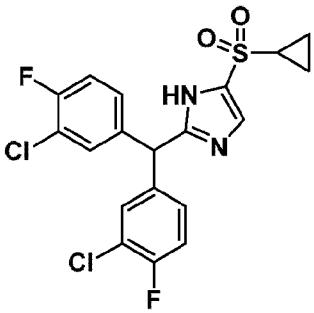
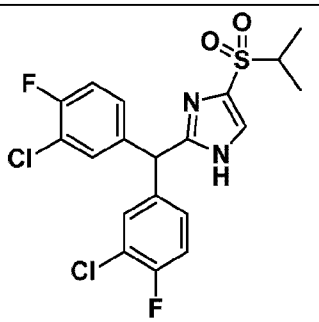


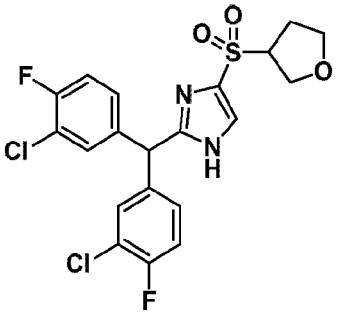
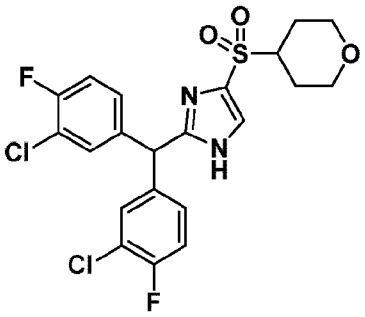
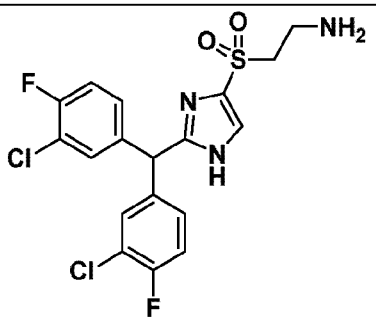
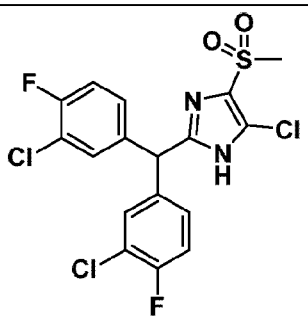
To a solution of 2-(bis(3-chloro-4-fluorophenyl)methyl)-4-iodo-1H-imidazole (intermediate 4, 0.4 g, 0.86 mmol) in DMSO (10.0 mL) were added Cs_2CO_3 (0.7 g, 2.15 mmol), L-Proline (0.08 g, 0.688 mmol) and sodium methanesulfinate (0.132 g, 1.29 mmol) at rt. The reaction mixture was degassed with argon for 10 minutes followed by the addition of CuI (0.066 g, 0.344 mmol) at rt. The reaction mixture was heated to 110 °C for 2.5 h under microwave irradiation. The reaction mixture was diluted with water and extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine, dried over sodium sulphate and concentrated under reduced pressure. The resulting crude product was purified by reverse-phase prep HPLC to yield the title compound (0.072

g, 20%). LCMS m/z = 417 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.89 (s, 1H), 7.85 (s, 1H), 7.54-7.52 (m, 2H), 7.42-7.38 (m, 2H), 7.33-7.30 (m, 2H), 5.74 (m, 1H), 3.10 (s, 3H).

Examples 2-8.

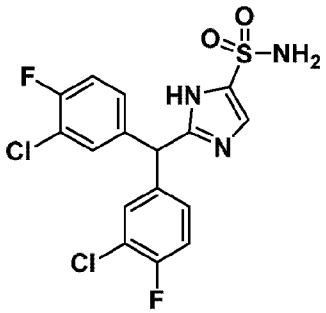
The title compounds were prepared from the appropriate intermediates and reagents using an analogous method to that described for example 1.

Example	Structure	Name	Data
2		2-(bis(3-chloro-4-fluoro-phenyl)methyl)-5-(ethyl-sulfonyl)-1H-imidazole	Yield: (0.035 g, 18%). LCMS m/z = 431 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.91 (s, 1H), 7.86 (s, 1H), 7.52-7.51 (m, 2H), 7.42-7.37 (m, 2H), 7.32-7.29 (m, 2H), 5.72 (s, 1H), 3.19-3.14 (m, 2H), 1.14-1.10 (m, 3H).
3		2-(bis(3-chloro-4-fluoro-phenyl)methyl)-5-(cyclo-propylsulfonyl)-1H-imidaz-ole	Yield: (0.035 g, 10%). LCMS m/z = 443 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.88 (bs, 1H), 7.82 (s, 1H), 7.56-7.54 (m, 2H), 7.42-7.38 (m, 2H), 7.33-7.30 (m, 2H), 5.73 (s, 1H), 2.73-2.69 (m, 1H), 1.06-3.05 (m, 2H), 1.03-0.98 (m, 2H).
4		2-(bis(3-chloro-4-fluoro-phenyl)methyl)-4-(iso-propylsulfonyl)-1H-imidaz-ole	LCMS m/z = 445 $[M+H]^+$; retention time: 7.67 min, method B

5		2-(bis(3-chloro-4-fluorophenyl)methyl)-4-((tetrahydrofuran-3-yl)sulfonyl)-1H-imidazole	LCMS m/z = 473 $[M+H]^+$; retention time: 2.96 min, method A
6		2-(bis(3-chloro-4-fluorophenyl)methyl)-4-((tetrahydro-2H-pyran-4-yl)sulfonyl)-1H-imidazole	LCMS m/z = 487 $[M+H]^+$; retention time: 3.00 min, method A
7		2-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-4-yl)sulfonyl)ethan-1-amine	LCMS m/z = 446 $[M+H]^+$; retention time: 2.61 min, method A
8		2-(bis(3-chloro-4-fluorophenyl)methyl)-5-chloro-4-(methylsulfonyl)-1H-imidazole	Yield: 82% (0.042 g, 0.093 mmol). LCMS m/z = 451 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 7.37 (d, 2H), 7.21 (d, 4H), 5.54 (s, 1H), 3.18 (s, 3H).

Example 9

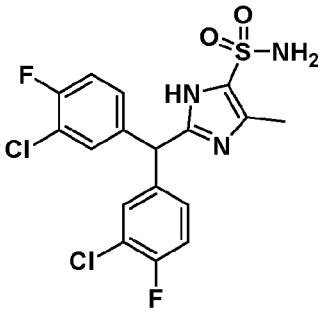
2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazole-5-sulfonamide



To a solution of 4-(benzylthio)-2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazole (intermediate 6, 0.14 g, 0.304 mmol) in MeCN (8.0 mL)-AcOH (1.0 mL)-H_2O (0.5 mL) was added DCDMH (0.12 g, 0.609 mmol) at 0 °C. The reaction was stirred at rt for 2 h. The reaction mixture was diluted with water (20.0 mL) and extracted with ethyl acetate (3 x 60 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to obtain a residue, which was dissolved in THF (12.0 mL) and cooled to 0° C followed by the addition of 30% aq NH_3 (6.0 mL) at 0 °C. The resulting mixture was stirred at rt for 16 h. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine, dried over sodium sulphate and concentrated under reduced pressure to get the crude product which was purified by reverse-phase prep HPLC to yield the title compound (0.022 g, 16% over two steps). LCMS m/z = 418 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.75 (s, 1H), 7.57 (s, 1H), 7.52 (d, 2H), 7.42-7.38 (m, 2H), 7.38-7.28 (m, 2H), 7.17 (s, 2H), 5.17 (s, 1H).

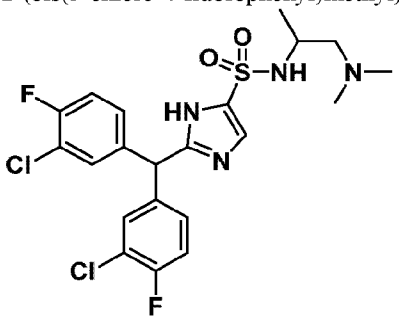
Example 10.

The title compounds were prepared from the appropriate intermediates and reagents using an analogous method to that described for example 9.

Ex-anple	Structure	Name	Data
10		2-(bis(3-chloro-4-fluoro-phenyl)methyl)-4-methyl-1H-imidazole-5-sulfona-mide	Yield: (0.013 g, 10%). LCMS m/z = 432 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.30 (s, 1H), 7.53-7.50 (m, 2H), 7.42-7.37 (m, 2H), 7.33-7.29 (m, 2H), 7.04 (s, 1H), 5.62 (s, 1H), 2.32 (s, 3H)

Example 11

2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(1-(dimethylamino)propan-2-yl)-1H-imidazole-5-sulfonamide

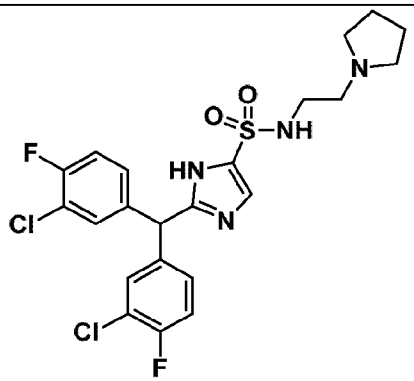


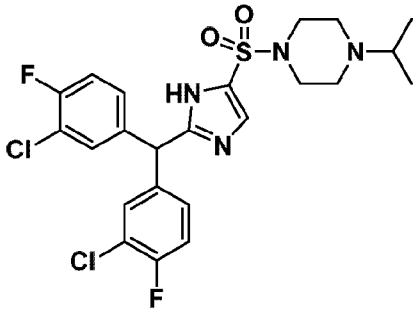
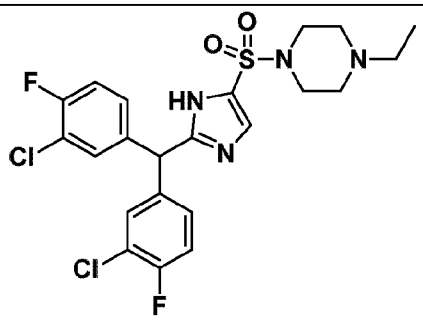
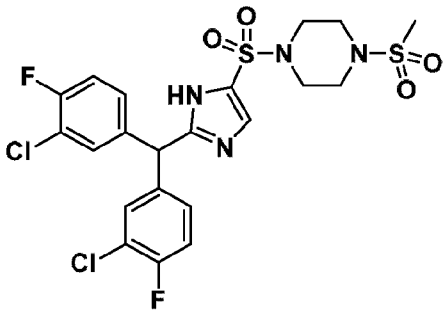
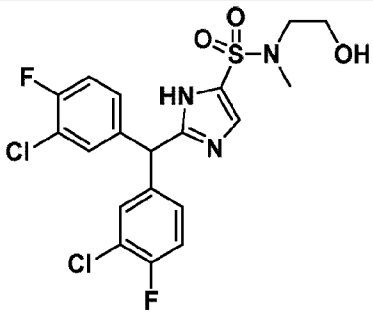
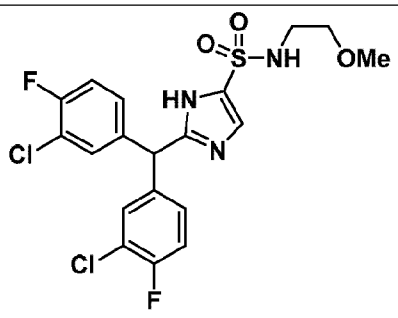
Step 1: To a stirred solution of 2-(bis(3-chloro-4-fluorophenyl)methyl)-4-((4-methoxybenzyl)thio)-1H-imidazole (0.6 g, 1.22 mmol) in MeCN (35.0 mL)-AcOH (4.0 mL)-H_2O (2.0 mL) was added DCDMH (0.5 g, 2.53 mmol) at 0 °C. The reaction was stirred at rt for 2 h.The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (3 x 80 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get the crude product, which was purified by CombiFlash column chromatography (SiO_2, 0-40% EtOAc/Hex) to afford 2-(bis(3-chloro-4-fluorophenyl) methyl)-1H-imidazole-4-sulfonyl chloride (0.35 g, 65%).

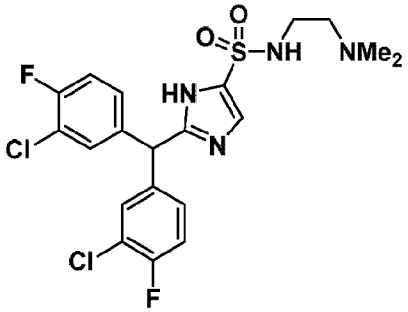
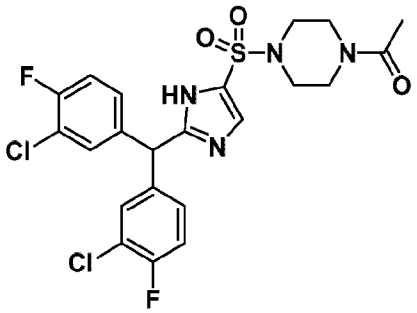
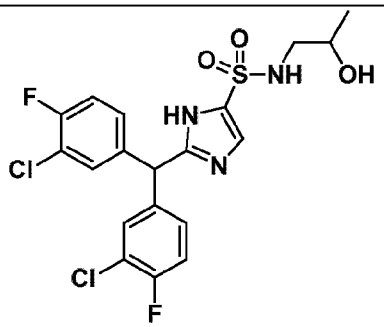
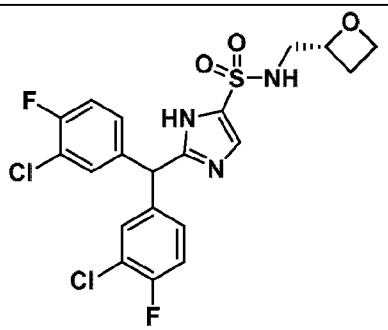
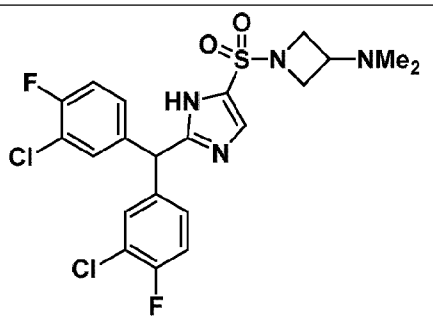
Step 2: To a stirred solution of 2-(bis(3-chloro-4-fluorophenyl) methyl)-1H-imidazole-4-sulfonyl chloride (0.1 g, 0.23 mmol) in DCM (5.0 mL) was added TEA (2.5 equiv.) at 0 °C. To it was added N1,N1-dimethylpropane-1,2-diamine (0.9 eq) at 0 °C and the reaction mixture was stirred at rt for 1.5 hours. The volatiles were removed under reduced pressure and the residue was purified via reverse-phase prep. HPLC. LCMS m/z = 503 $[M+H]^+$; retention time: 2.68 min, method A

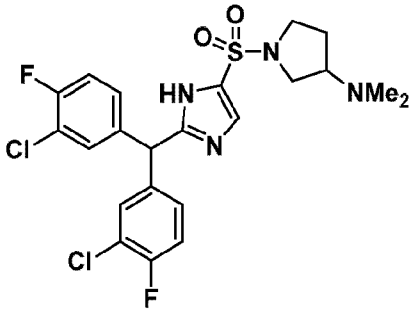
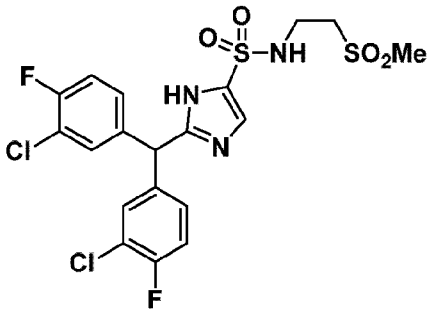
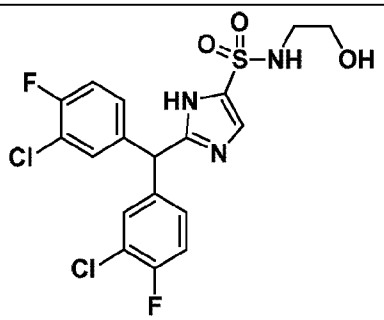
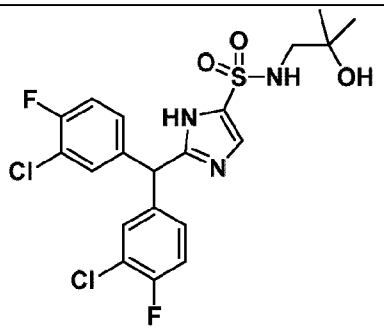
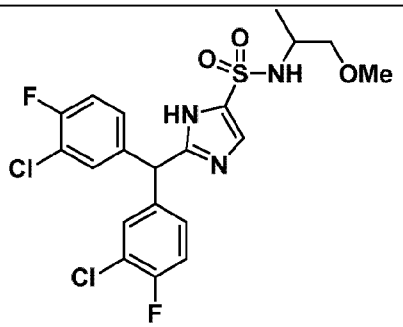
Examples 12-62, 148-184.

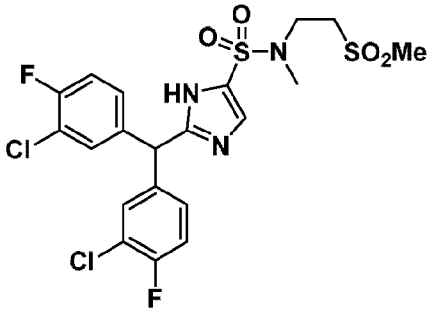
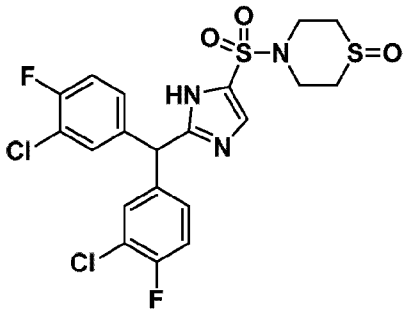
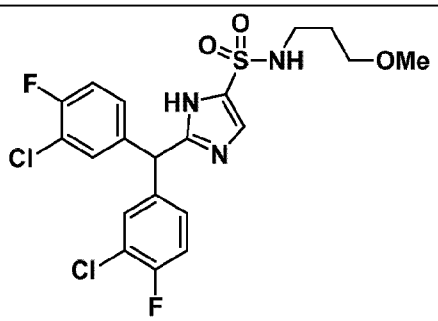
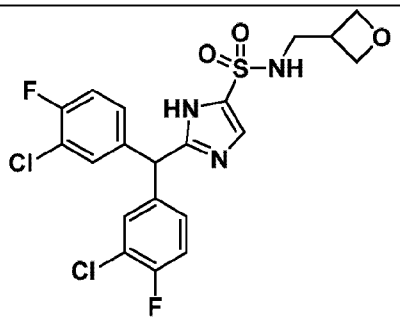
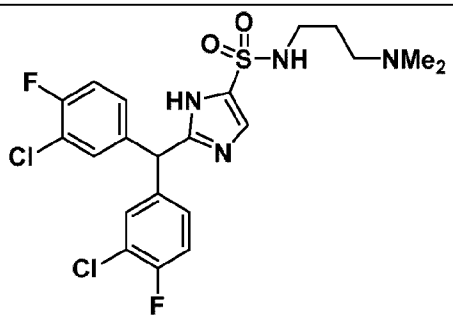
The title compounds were prepared from the appropriate intermediates and reagents using an analogous method to that described for example 11. If applicable, a Boc protecting group was deprotected in the last step using procedures known to the person skilled in the art (e.g. TFA, DCM, 0 °C). If applicable, chiral SFC was perfomed to separate enantiomers.

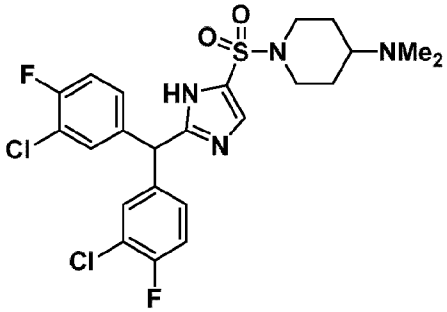
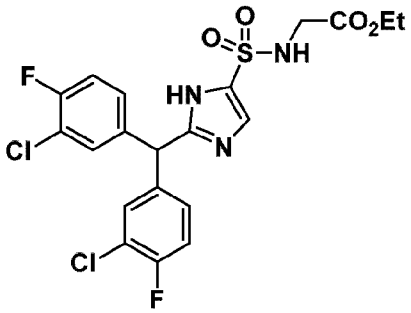
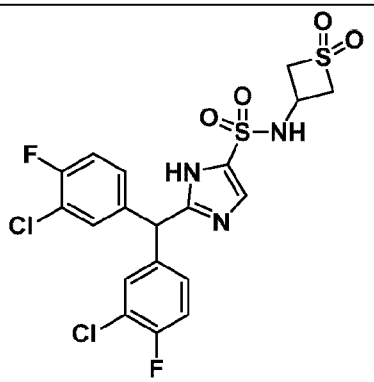
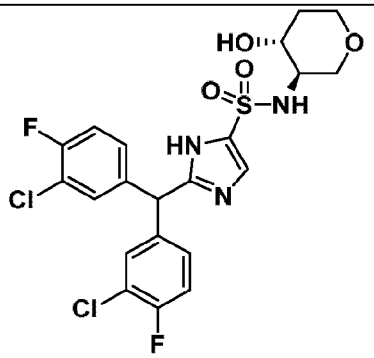
Ex-anple	Structure	Name	Data
12		2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(2-(pyrrolidin-1-yl)ethyl)-1H-imidaz-ole-5-sulfonamide	LCMS m/z = 515 $[M+H]^+$; retention time: 2.68 min, method A

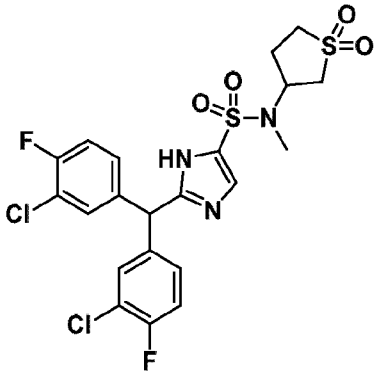
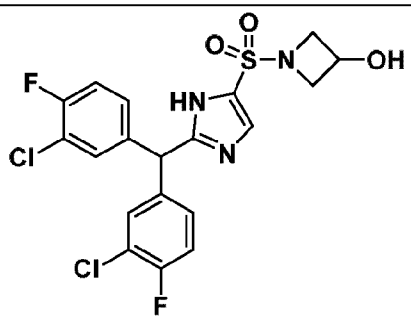
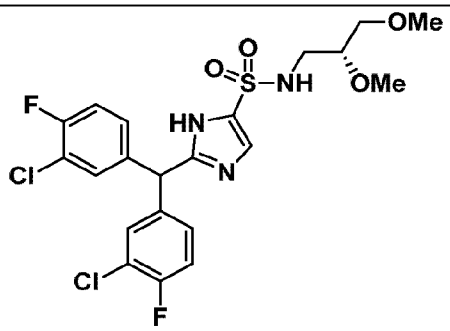
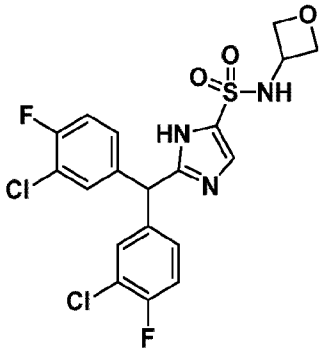
13		1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-4-isopropylpiperazine	LCMS m/z = 529 $[M+H]^+$; retention time: 3.19 min, method A
14		1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-4-ethylpiperazine	LCMS m/z = 515 $[M+H]^+$; retention time: 3.06 min, method A
15		1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-4-(methylsulfonyl)piperazine	LCMS m/z = 529 $[M+H]^+$; retention time: 5.65 min, method A
16		2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(2-hydroxyethyl)-N-methyl-1H-imidazole-5-sulfonamide	LCMS m/z = 476 $[M+H]^+$; retention time: 2.85 min, method A
17		2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(2-methoxyethyl)-1H-imidazole-5-sulfonamide	LCMS m/z = 476 $[M+H]^+$; retention time: 2.93 min, method A

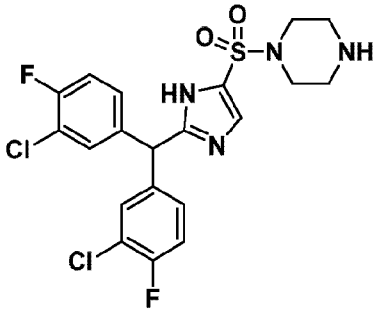
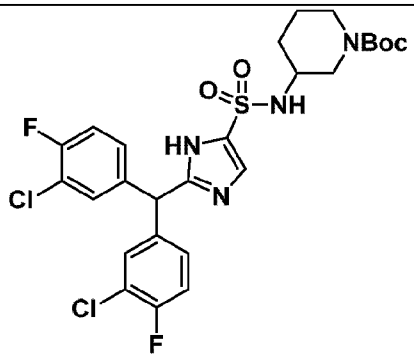
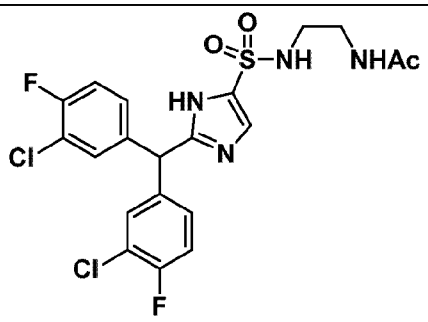
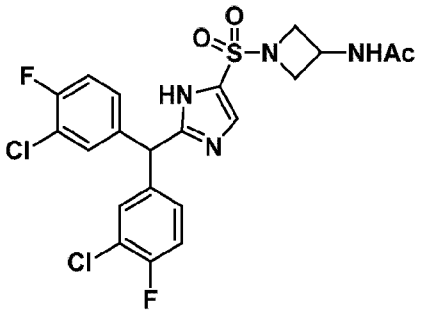
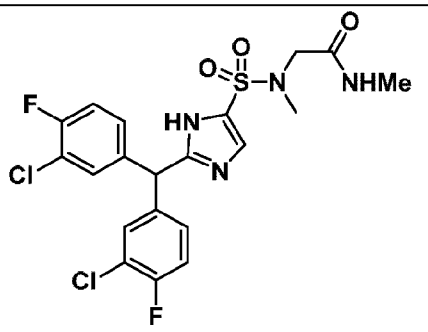
18		2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(2-(dimethylamino)ethyl)-1H-imidazole-5-sulfonamide	LCMS m/z = 489 $[M+H]^+$; retention time: 2.67 min, method A
19		1-(4-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)piperazin-1-yl)ethan-1-one	LCMS m/z = 529 $[M+H]^+$; retention time: 2.82 min, method A
20		2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(2-hydroxypropyl)-1H-imidazole-5-sulfonamide	LCMS m/z = 476 $[M+H]^+$; retention time: 2.79 min, method A
21		(R)-2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(oxetan-2-ylmethyl)-1H-imidazole-5-sulfonamide	LCMS m/z = 488 $[M+H]^+$; retention time: 2.93 min, method A
22		1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-N,N-dimethylazetidin-3-amine	LCMS m/z = 501 $[M+H]^+$; retention time: 3.08 min, method A

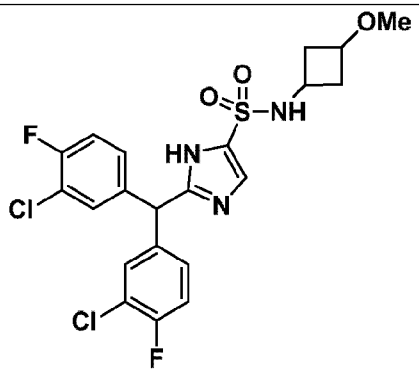
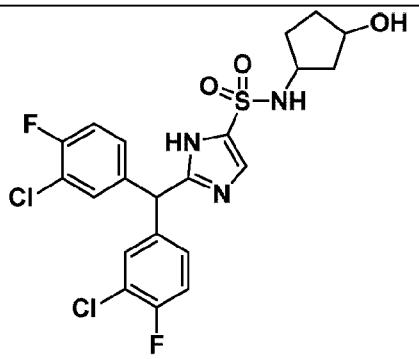
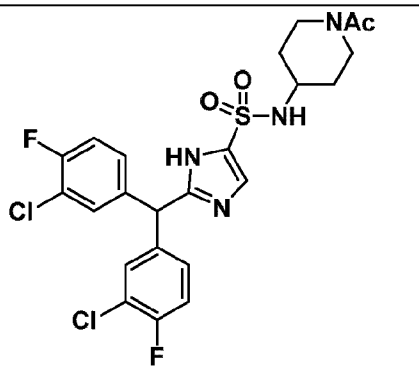
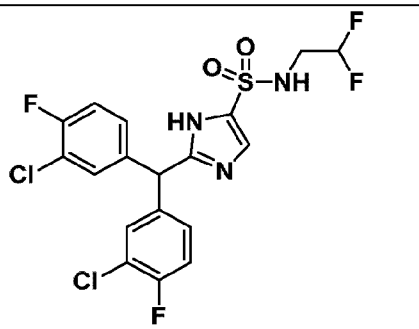
23		1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-N,N-dimethylpyrrolidin-3-amine	LCMS m/z = 515 $[M+H]^+$; retention time: 3.02 min, method A
24		2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(2-(methylsulfonyl)ethyl)-1H-imidazole-5-sulfonamide	LCMS m/z = 524 $[M+H]^+$; retention time: 2.88 min, method A
25		2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(2-hydroxyethyl)-1H-imidazole-5-sulfonamide	LCMS m/z = 462 $[M+H]^+$; retention time: 2.76 min, method A
26		2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(2-hydroxy-2-methylpropyl)-1H-imidazole-5-sulfonamide	LCMS m/z = 490 $[M+H]^+$; retention time: 2.86 min, method A
27		2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(1-methoxypropan-2-yl)-1H-imidazole-5-sulfonamide	LCMS m/z = 490 $[M+H]^+$; retention time: 3.03 min, method A

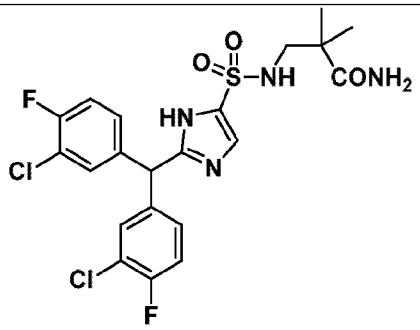
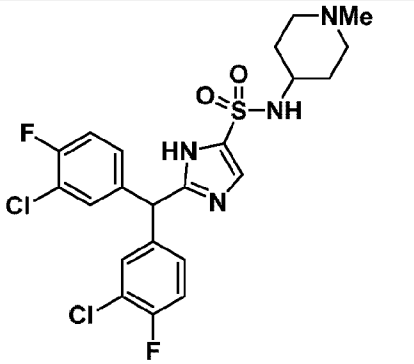
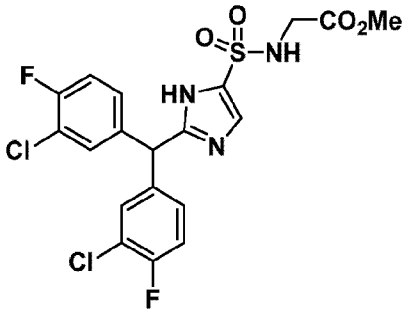
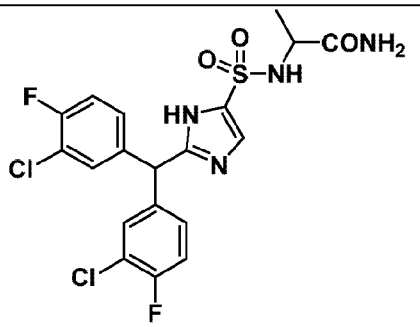
28		2-(bis(3-chloro-4-fluorophenyl)methyl)-N-methyl-N-(2-(methylsulfonyl)ethyl)-1H-imidazole-5-sulfonamide	LCMS m/z = 538 $[M+H]^+$; retention time: 2.95 min, method A
29		4-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)thiomorpholine 1-oxide	LCMS m/z = 520 $[M+H]^+$; retention time: 2.79 min, method A
30		2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(3-methoxypropyl)-1H-imidazole-5-sulfonamide	LCMS m/z = 490 $[M+H]^+$; retention time: 2.98 min, method A
31		2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(oxetan-3-ylmethyl)-1H-imidazole-5-sulfonamide	LCMS m/z = 488 $[M+H]^+$; retention time: 2.83 min, method A
32		2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(3-(dimethylamino)propyl)-1H-imidazole-5-sulfonamide	LCMS m/z = 503 $[M+H]^+$; retention time: 2.59 min, method A

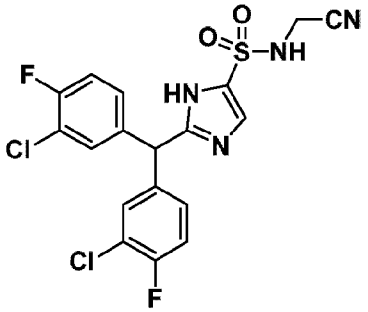
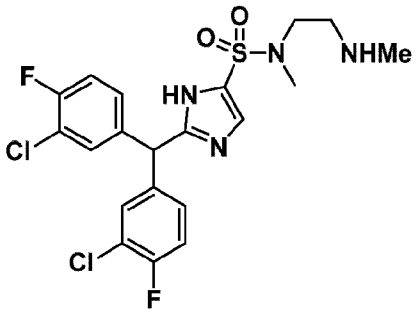
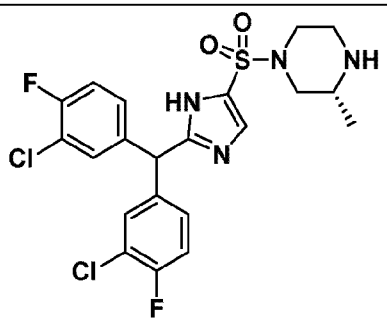
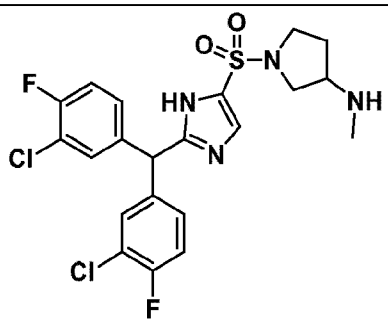
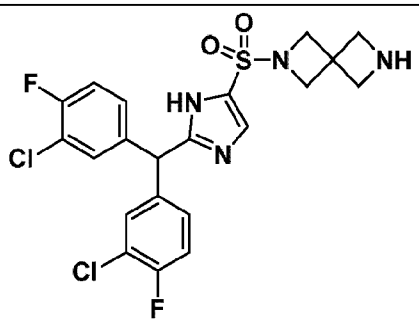
33		1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-N,N-dimethylpiperidin-4-amine	LCMS m/z = 529 $[M+H]^+$; retention time: 2.69 min, method A
34		ethyl ((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)glycinate	LCMS m/z = 504 $[M+H]^+$; retention time: 2.98 min, method A
35		2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(1,1-dioxidothietan-3-yl)-1H-imidazole-5-sulfonamide	LCMS m/z = 522 $[M+H]^+$; retention time: 2.97 min, method A
36		2-(bis(3-chloro-4-fluorophenyl)methyl)-N-((3R,4R)-4-hydroxytetrahydro-2H-pyran-3-yl)-1H-imidazole-5-sulfonamide	LCMS m/z = 518 $[M+H]^+$; retention time: 2.83 min, method A

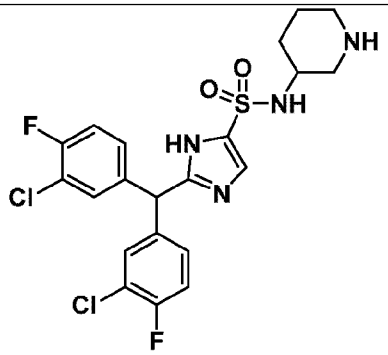
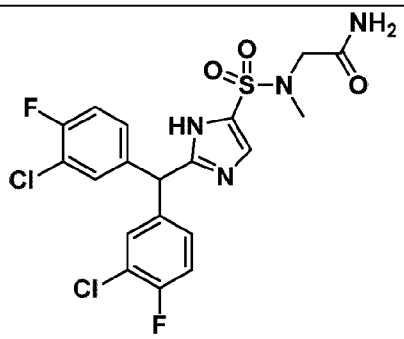
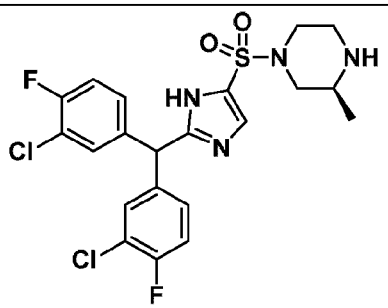
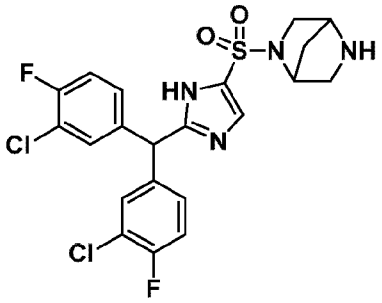
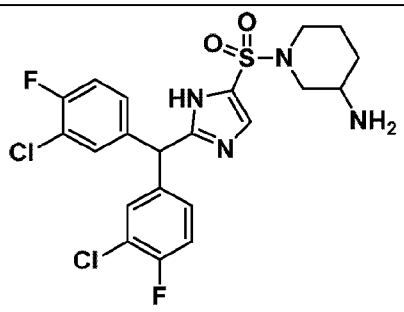
37		2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(1,1-dioxidotetrahydrothiophen-3-yl)-N-methyl-1H-imidazole-5-sulfonamide	LCMS m/z = 550 $[M+H]^+$; retention time: 2.94 min, method A
38		1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)azetidin-3-ol	LCMS m/z = 474 $[M+H]^+$; retention time: 2.85 min, method A
39		(R)-2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(2,3-dimethoxypropyl)-1H-imidazole-5-sulfonamide	LCMS m/z = 520 $[M+H]^+$; retention time: 2.98 min, method A
40		2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(oxetan-3-yl)-1H-imidazole-5-sulfonamide	LCMS m/z = 474 $[M+H]^+$; retention time: 2.82 min, method A

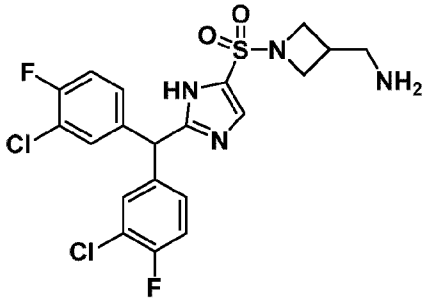
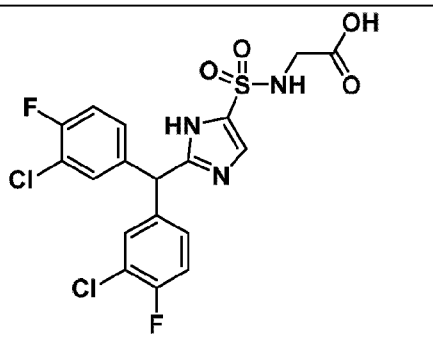
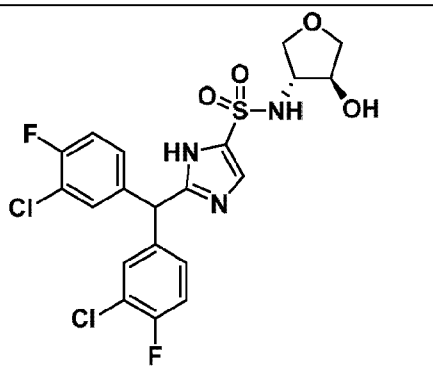
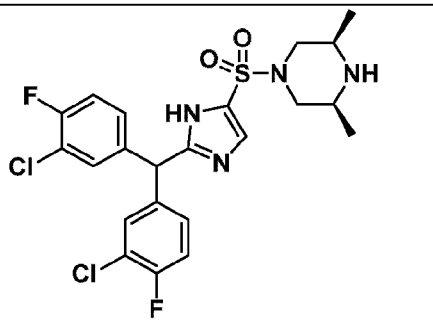
41		1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)piperazine	LCMS m/z = 487 $[M+H]^+$; retention time: 2.71 min, method A
42		tert-butyl 3-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazole)-5-sulfonamido)piperidine-1-carboxylate	LCMS m/z = 601 $[M+H]^+$; retention time: 3.26 min, method A
43		N-(2-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazole)-5-sulfonamido)ethyl)acetamide	LCMS m/z = 503 $[M+H]^+$; retention time: 2.70 min, method A
44		N-(1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)azetidin-3-yl)acetamide	LCMS m/z = 515 $[M+H]^+$; retention time: 2.79 min, method A
45		2-((2-(bis(3-chloro-4-fluorophenyl)methyl)-N-methyl-1H-imidazole)-5-sulfonamido)-N-methylacetamide	LCMS m/z = 503 $[M+H]^+$; retention time: 2.93 min, method A

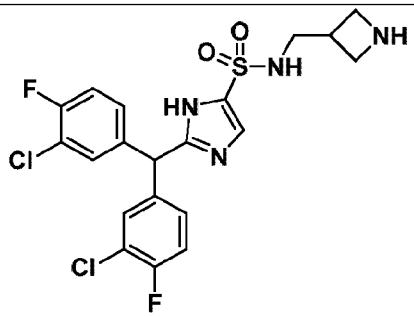
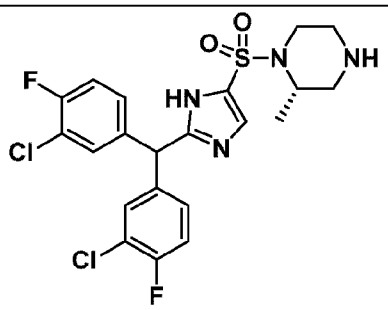
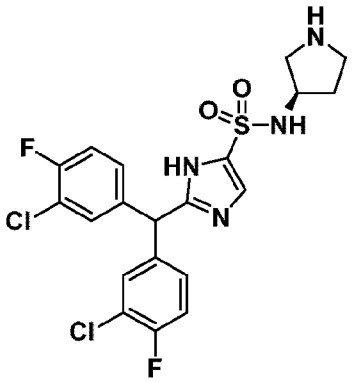
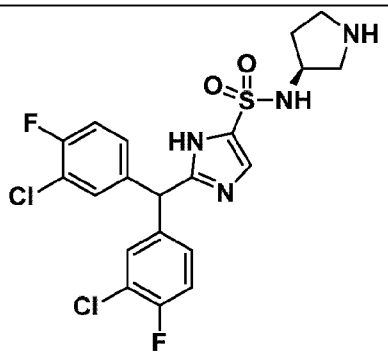
46		2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(3-methoxycyclobutyl)-1H-imidazole-5-sulfonamide	LCMS m/z = 502 $[M+H]^+$; retention time: 2.88 min, method A
47		2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(3-hydroxycyclopentyl)-1H-imidazole-5-sulfonamide	LCMS m/z = 502 $[M+H]^+$; retention time: 2.71 min, method A
48		N-(1-acetylpiperidin-4-yl)-2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazole-5-sulfonamide	LCMS m/z = 543 $[M+H]^+$; retention time: 2.76 min, method A
49		2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(2,2-difluoroethyl)-1H-imidazole-5-sulfonamide	LCMS m/z = 482 $[M+H]^+$; retention time: 3.03 min, method A

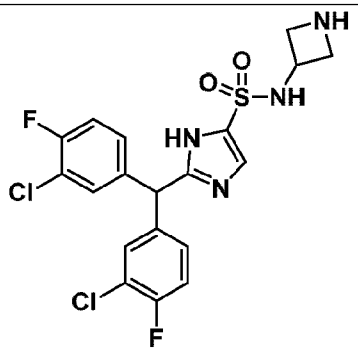
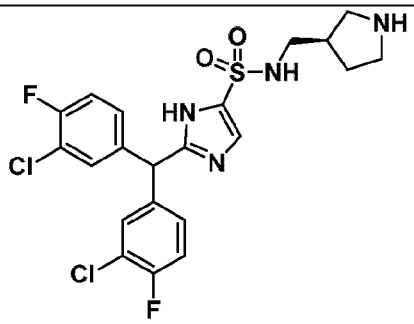
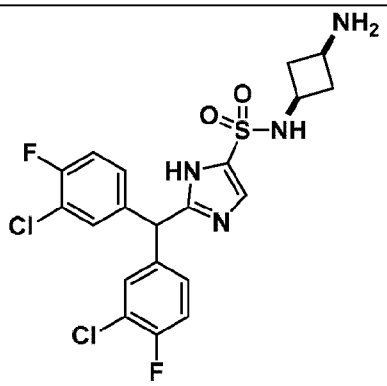
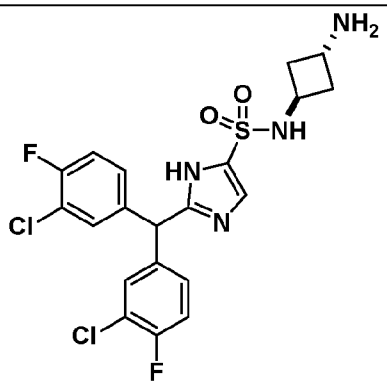
50		3-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazole)-5-sulfonamido)-2,2-dimethylpropanamide	LCMS m/z = 517 $[M+H]^+$; retention time: 2.77 min, method A
51		2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(1-methylpiperidin-4-yl)-1H-imidazole-5-sulfonamide	LCMS m/z = 515 $[M+H]^+$; retention time: 2.59 min, method A
52		methyl ((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)glycinate	LCMS m/z = 490 $[M+H]^+$; retention time: 2.95 min, method A
53		2-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazole)-5-sulfonamido)propanamide	LCMS m/z = 489 $[M+H]^+$; retention time: 2.75 min, method A

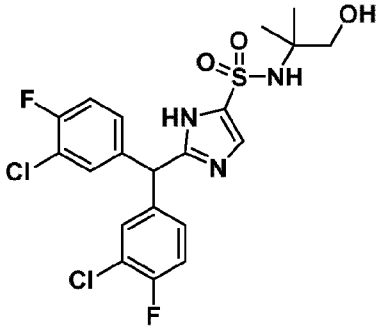
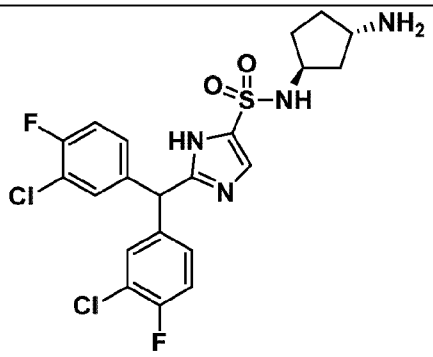
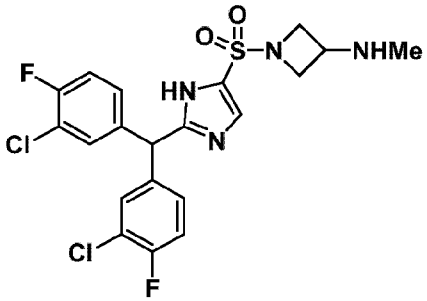
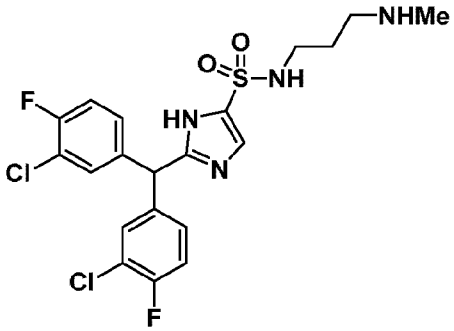
54		2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(cyanomethyl)-1H-imidazole-5-sulfonamide	LCMS m/z = 457 $[M+H]^+$; retention time: 3.01 min, method A
55		2-(bis(3-chloro-4-fluorophenyl)methyl)-N-methyl-N-(2-(methylamino)ethyl)-1H-imidazole-5-sulfonamide	LCMS m/z = 489 $[M+H]^+$; retention time: 2.71 min, method A
59		(R)-1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-3-methylpiperazine	LCMS m/z = 501 $[M+H]^+$; retention time: 2.78 min, method A
60		1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-N-methylpyrrolidin-3-amine	LCMS m/z = 501 $[M+H]^+$; retention time: 2.71 min, method A
61		2-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-2,6-diazaspiro[3.3]heptane	LCMS m/z = 499 $[M+H]^+$; retention time: 2.57 min, method A

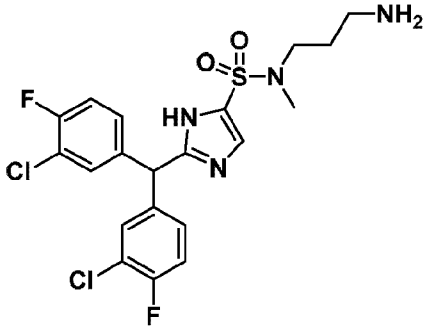
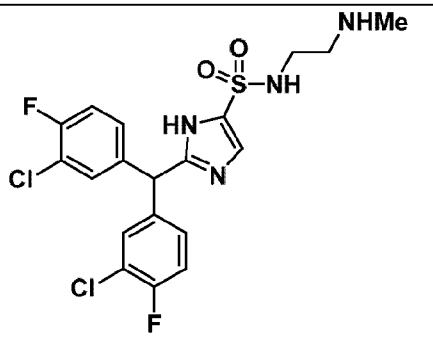
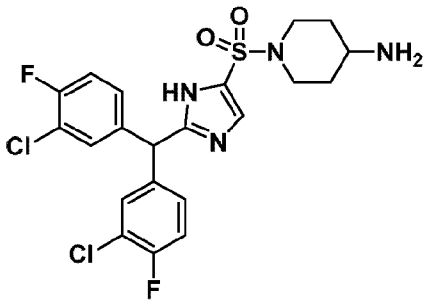
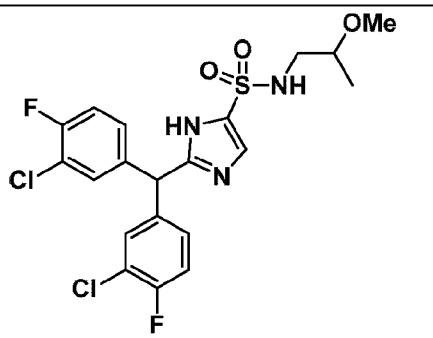
62		2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(piperidin-3-yl)-1H-imidazole-5-sulfonamide	LCMS m/z = 501 $[M+H]^+$; retention time: 2.57 min, method A
148		2-((2-(bis(3-chloro-4-fluorophenyl)methyl)-N-methyl-1H-imidazole)-5-sulfonamido)acetamide	LCMS m/z = 489 $[M+H]^+$; retention time: 2.77 min, method A
149a		(S)-1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-3-methylpiperazine	LCMS m/z = 501 $[M+H]^+$; retention time: 2.79 min, method A
150		2-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-2,5-diazabicyclo[2.2.1]heptane	LCMS m/z = 499 $[M+H]^+$; retention time: 2.62 min, method A
151		1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)piperidin-3-amine	LCMS m/z = 501 $[M+H]^+$; retention time: 2.70 min, method A

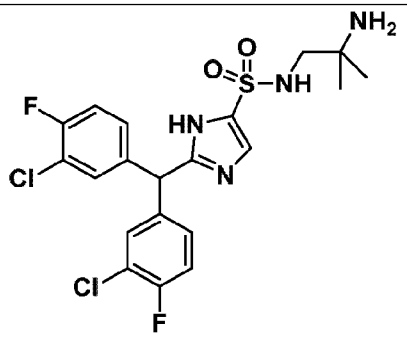
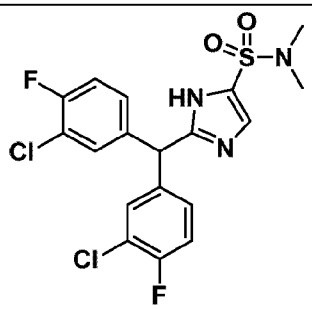
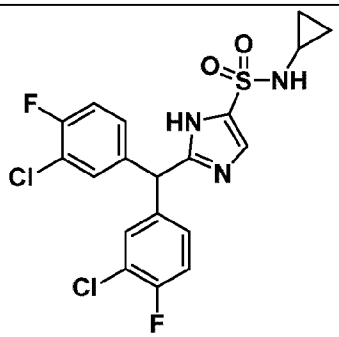
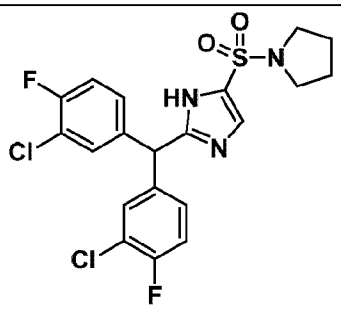
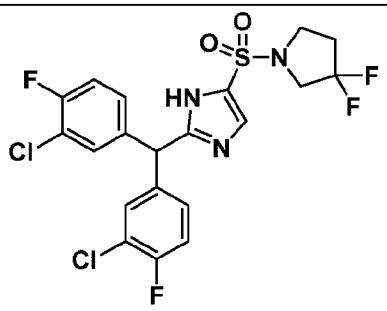
152		(1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)azetidin-3-yl)methanamine	LCMS m/z = 487 $[M+H]^+$; retention time: 2.58 min, method A
153		((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)glycine	LCMS m/z = 476 $[M+H]^+$; retention time: 2.43 min, method A
154a		2-(bis(3-chloro-4-fluorophenyl)methyl)-N-((3R,4S)-4-hydroxytetrahydrofuran-3-yl)-1H-imidazole-5-sulfonamide	LCMS m/z = 504 $[M+H]^+$; retention time: 2.63 min, method A
155a		(3S,5R)-1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-3,5-dimethylpiperazine	LCMS m/z = 515 $[M+H]^+$; retention time: 2.72 min, method A

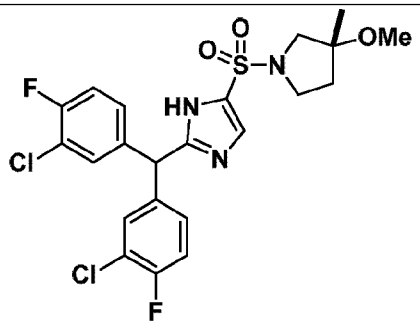
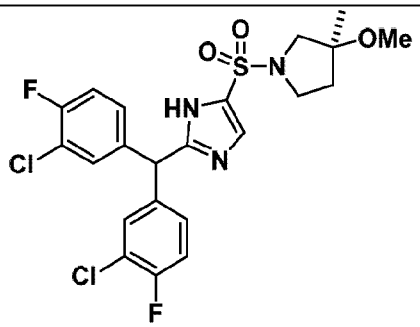
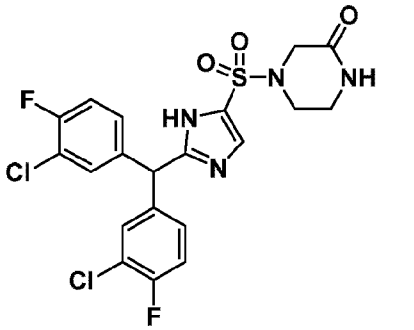
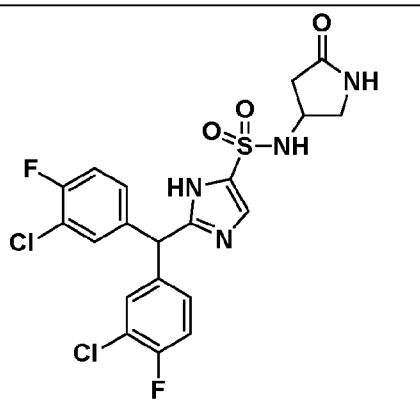
156		N-(azetidin-3-ylmethyl)-2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazole-5-sulfonamide	LCMS m/z = 487 $[M+H]^+$; retention time: 2.39 min, method A
157a		(S)-1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-2-methylpiperazine	LCMS m/z = 501 $[M+H]^+$; retention time: 2.59 min, method A
158a		(R)-2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(pyrrolidin-3-yl)-1H-imidazole-5-sulfonamide	LCMS m/z = 487 $[M+H]^+$; retention time: 2.33 min, method A
158b		(S)-2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(pyrrolidin-3-yl)-1H-imidazole-5-sulfonamide	LCMS m/z = 487 $[M+H]^+$; retention time: 2.42 min, method A

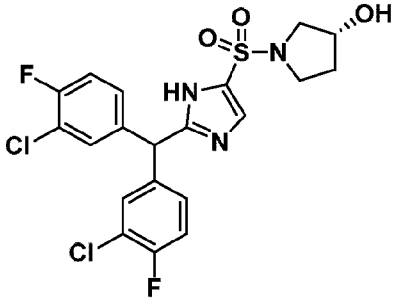
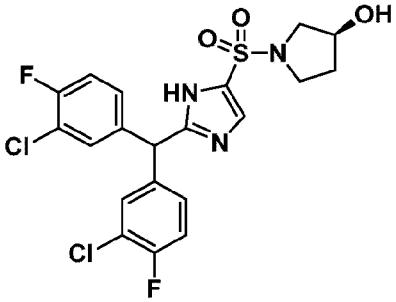
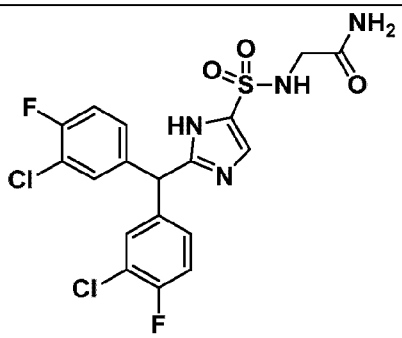
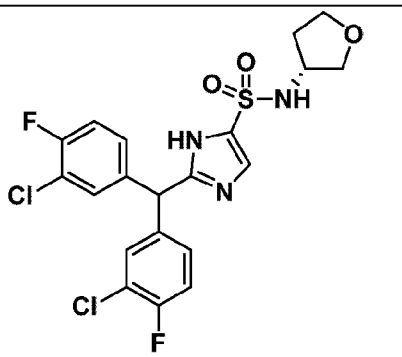
159		N-(azetidin-3-yl)-2-(bis(3-chloro-4-fluoro-phenyl)methyl)-1H-imidazole-5-sulfona-mide	LCMS m/z = 473 $[M+H]^+$; retention time: 2.37 min, method A
160a		(R)-2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(pyrrolidin-3-ylmethyl)-1H-imidazole-5-sulfonamide	LCMS m/z = 501 $[M+H]^+$; retention time: 2.42 min, method A
161a		N-((cis)-3-aminocyclobutyl)-2-(bis(3-chloro-4-fluoro-phenyl)methyl)-1H-imidazole-5-sulfona-mide	LCMS m/z = 487 $[M+H]^+$; retention time: 2.39 min, method A
161b		N-((trans)-3-aminocyclobutyl)-2-(bis(3-chloro-4-fluoro-phenyl)methyl)-1H-imidazole-5-sulfona-mide	LCMS m/z = 487 $[M+H]^+$; retention time: 2.40 min, method A

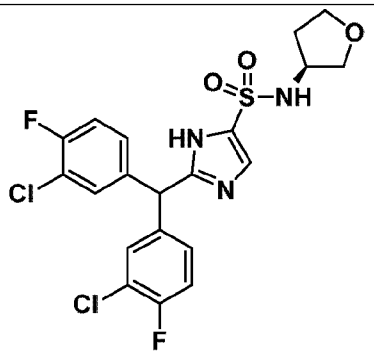
162		2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(1-hydroxy-2-methylpropan-2-yl)-1H-imidazole-5-sulfonamide	LCMS m/z = 490 $[M+H]^+$; retention time: 2.77 min, method A
163a		N-((1S,3S)-3-aminocyclopentyl)-2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazole-5-sulfonamide	LCMS m/z = 501 $[M+H]^+$; retention time: 2.39 min, method A
164		1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-N-methylazetidin-3-amine	LCMS m/z = 487 $[M+H]^+$; retention time: 2.68 min, method A
165		2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(3-(methylamino)propyl)-1H-imidazole-5-sulfonamide	LCMS m/z = 489 $[M+H]^+$; retention time: 2.40 min, method A

166		N-(3-aminopropyl)-2-(bis(3-chloro-4-fluorophenyl)methyl)-N-methyl-1H-imidazole-5-sulfonamide	LCMS m/z = 489 $[M+H]^+$; retention time: 2.46 min, method A
167		2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(2-(methylamino)ethyl)-1H-imidazole-5-sulfonamide	LCMS m/z = 475 $[M+H]^+$; retention time: 4.92 min, method B
168		1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)piperidin-4-amine	LCMS m/z = 501 $[M+H]^+$; retention time: 2.44 min, method A
169		2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(2-methoxypropyl)-1H-imidazole-5-sulfonamide	LCMS m/z = 490 $[M+H]^+$; retention time: 3.02 min, method A

170		N-(2-amino-2-methyl-propyl)-2-(bis(3-chloro-4-fluorophe-nyl)methyl)-1H-imida-zole-5-sulfonamide	LCMS m/z = 489 $[M+H]^+$; retention time: 2.44 min, method A
171		2-(bis(3-chloro-4-flu-orophenyl)methyl)-N,N-dimethyl-1H-imidazole-5-sulfona-mide	LCMS m/z = 446 $[M+H]^+$; retention time: 7.73 min, method B
172		2-(bis(3-chloro-4-flu-orophenyl)methyl)-N-cyclopropyl-1H-imidazole-5-sulfona-mide	LCMS m/z = 458 $[M+H]^+$; retention time: 7.58 min, method B
173		2-(bis(3-chloro-4-flu-orophenyl)methyl)-5-(pyrrolidin-1-ylsul-fonyl)-1H-imidazole	LCMS m/z = 472 $[M+H]^+$; retention time: 7.77 min, method B
174		2-(bis(3-chloro-4-flu-orophenyl)methyl)-5-((3,3-difluoropyrroli-din-1-yl)sulfonyl)-1H-imidazole	LCMS m/z = 507 $[M+H]^+$; retention time: 7.81 min, method B

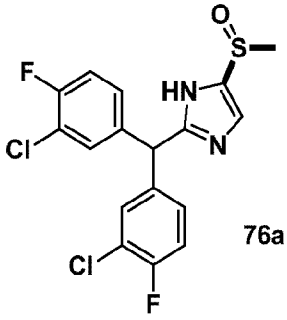
175a		2-(bis(3-chloro-4-fluorophenyl)methyl)-5-((3-methoxy-3-methylpyrrolidin-1-yl)sulfonyl)-1H-imidazole	LCMS m/z = 516 $[M+H]^+$; retention time: 3.22 min, method A, Chiral SFC: column: Chiralpak IC (4.6 x 250 mm) 5 µm; co-solvent: 0.3% $iPrNH_2$ in MeOH, flow: 4 mL/min; % of co-solvent: 45%; ABPR: 100 bar T: 35 °C; Rt = 2.58 min (first eluting).
175b		2-(bis(3-chloro-4-fluorophenyl)methyl)-5-((3-methoxy-3-methylpyrrolidin-1-yl)sulfonyl)-1H-imidazole	LCMS m/z = 516 $[M+H]^+$; retention time: 3.22 min, method A, Chiral SFC: column: Chiralpak IC (4.6 x 250 mm) 5 µm; co-solvent: 0.3% $iPrNH_2$ in MeOH, flow: 4 mL/min; % of co-solvent: 45%; ABPR: 100 bar T: 35 °C; Rt = 2.89 min (first eluting).
176		4-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)piperazin-2-one	LCMS m/z = 501 $[M+H]^+$; retention time: 7.19 min, method B
177		2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(5-oxopyrrolidin-3-yl)-1H-imidazole-5-sulfonamide	LCMS m/z = 499 $[M+H]^+$; retention time: 2.70 min, method A

178a		(R)-1-((2-(bis(3-chloro-4-fluoro-phenyl)methyl)-1H-imidazol-5-yl)sul-fonyl)pyrrolidin-3-ol	LCMS m/z = 488 $[M+H]^+$; retention time: 2.91 min, method A
178b		(S)-1-((2-(bis(3-chloro-4-fluoro-phenyl)methyl)-1H-imidazol-5-yl)sul-fonyl)pyrrolidin-3-ol	LCMS m/z = 488 $[M+H]^+$; retention time: 2.91 min, method A
179		2-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazole)-5-sul-fonamido)acetamide	LCMS m/z = 475 $[M+H]^+$; retention time: 2.68 min, method A
180a		(R)-2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(tetrahydrofuran-3-yl)-1H-imidazole-5-sulfonamide	LCMS m/z = 488 $[M+H]^+$; retention time: 7.44 min, method B

180b		(S)-2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(tetrahydrofuran-3-yl)-1H-imidazole-5-sulfonamide	LCMS m/z = 488 $[M+H]^+$; retention time: 2.95 min, method A

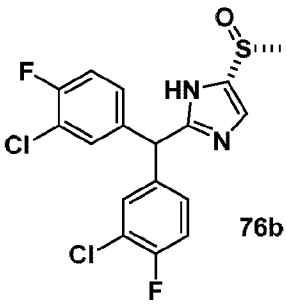
Example 76

2-(bis(3-chloro-4-fluorophenyl)methyl)-5-(methylsulfinyl)-1H-imidazole



76a

and



76b

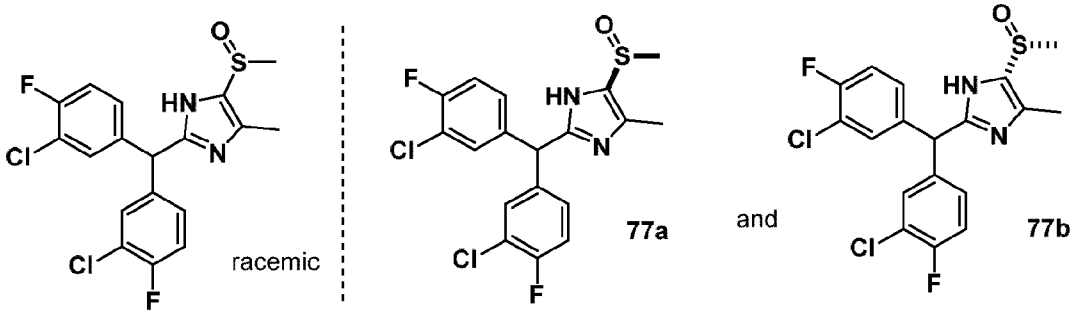
To a stirred solution of 2-(bis(3-chloro-4-fluorophenyl)methyl)-4-(methylthio)-1H-imidazole (intermediate 8, 0.22 g, 0.581 mmol) in DCM (5 ml) was added mCPBA (77% in water, 0.098 g, 0.436 mmol) at 0 °C. The reaction mixture was stirred for 20 minutes at 0 °C. The reaction mixture was diluted with water and extracted with EtOAc (3 × 60 mL). The combined organic part was washed with saturated $NaHCO_3$ solution and brine and was dried over Na_2SO_4. The organic layer was concentrated under reduced pressure to get the crude product, which was purified via column chromatography (SiO_2, 0-60% EtOAc/Hex) followed by chiral HPLC to yield the title compound.

Peak 1, example 76a: Yield: 19%, LCMS m/z = 401 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.62 (s, 1H), 7.73 (s, 1H), 7.54 (bs, 2H), 7.41-7.34 (m, 4H), 5.72 (s, 1H), 2.80 (s, 3H). Chiral HPLC: column: Chiralpak IC (4.6 x 250 mm) 5 µm, mobile phase: Hexane/DCM/EtOH/isopropylamine 50/25/25/0.1, flow rate: 1.0 mL/min, Rt = 4.63 min (first eluting).

Peak 2, example 76b: Yield: 19%, LCMS m/z = 401 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.62 (s, 1H), 7.73 (s, 1H), 7.54 (bs, 2H), 7.41-7.34 (m, 4H), 5.72 (s, 1H), 2.80 (s, 3H). Chiral HPLC: column: Chiralpak IC (4.6 x 250 mm) 5 µm, mobile phase: Hexane/DCM/EtOH/isopropylamine 50/25/25/0.1, flow rate: 1.0 mL/min, Rt = 5.61 min (first eluting).

Example 77

2-(bis(3-chloro-4-fluorophenyl)methyl)-4-methyl-5-(methylsulfinyl)-1H-imidazole



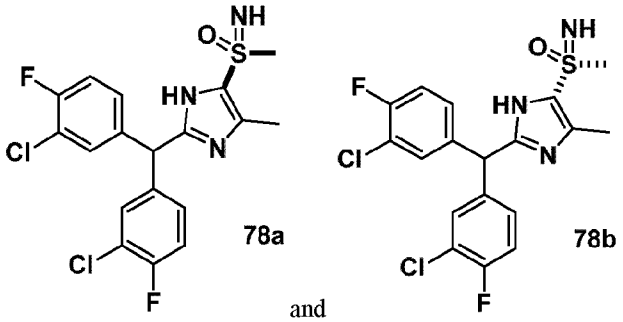
To a solution of 2-[bis(3-chloro-4-fluorophenyl)methyl]-5-methyl-4-(methylsulfanyl)-1H-imidazole (intermediate 19, 0.35 g, 0.877 mmol) in DCM (20.0 mL) was added mCPBA (70% in water; 0.148 g, 0.658 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched with a (1:1) solution of sodium sulfite and sodium bicarbonate at 0 °C. The aqueous layer was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to get the crude product. The resulting crude mixture was purified by CombiFlash column chromatography (SiO_2, 0-70% acetone/Hex) to yield the racemic title compound (0.25 g, 68%), which was separated using chiral SFC.

Peak 1, **example 77a:** Yield: 14% (0.03 g, 0.072 mmol). LCMS m/z = 415 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.39 (s, 1H), 7.57-7.53 (m, 2H), 7.42-7.34 (m, 4H), 5.65 (s, 1H), 2.78 (s, 3H), 2.29 (s, 3H). Chiral SFC: column: Chiralpak IC (4.6 x 250 mm) 5 µm; co-solvent: 0.3% $iPrNH_2$ in isopropylalcohol, flow: 3 mL/min; % of co-solvent: 30%; ABPR: 1500 psi T: 35 °C; Rt = 5.35 min (first eluting).

Peak 2, **example 77b:** Yield: 19% (0.04 g, 0.096 mmol). LCMS m/z = 415 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.38 (s, 1H), 7.57-7.53 (m, 2H), 7.42-7.34 (m, 4H), 5.65 (s, 1H), 2.78 (s, 3H), 2.29 (s, 3H). Chiral SFC: column: Chiralpak IC (4.6 x 250 mm) 5 µm; co-solvent: 0.3% $iPrNH_2$ in isopropylalcohol, flow: 3 mL/min; % of co-solvent: 30%; ABPR: 1500 psi T: 35 °C; Rt = 5.91 min (second eluting).

Example 78

(2-(bis(3-chloro-4-fluorophenyl)methyl)-4-methyl-1H-imidazol-5-yl)(imino)(methyl)-l6-sulfanone



Step 1: Iodobenzene diacetate (0.39 g, 1.205 mmol) was added to a stirred suspension of 2-[bis(3-chloro-4-fluorophenyl)methyl]-4-methanesulfinyl-5-methyl-1H-imidazole (example 77, 0.25 g, 0.602 mmol), magnesium oxide (0.105 g, 2.59 mmol), rhodium(II) acetate dimer (0.027g, 0.06 mmol) and 2,2,2-trifluoro acetamide (0.15 g, 1.325 mmol) in dioxane (10.0 mL) at 40 °C. The reaction mixture was stirred at 40 °C for 6 h. The reaction mixture was

concentrated under reduced pressure to get the crude product which was purified by CombiFlash column chromatography (SiO_2, 0-60% EtOAc/Hex) to yield N-((2-(bis(3-chloro-4-fluorophenyl)methyl)-5-methyl-1H-imidazol-4-yl)(methyl)(oxo)-l6-sulfaneylidene)-2,2,2-trifluoroacetamide (0.12 g, 37%). LCMS m/z = 526 $[M+H]^+$.

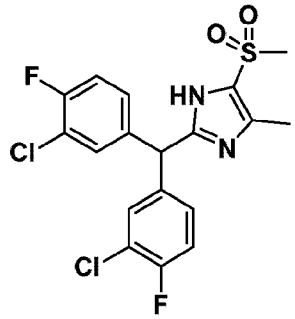
Step 2: To a stirred solution of N-((2-(bis(3-chloro-4-fluorophenyl)methyl)-5-methyl-1H-imidazol-4-yl)(methyl)(oxo)-l6-sulfaneylidene)-2,2,2-trifluoroacetamide (0.12 g, 0.229 mmol) in acetonitrile:methanol (1:1) (4.0 mL) was added K_2CO_3 (0.065 g, 0.457 mmol) at rt. The reaction mixture was stirred at rt for 6 h. The solvent was evaporated to get the crude product, which was purified by reverse-phase prep HPLC followed by the chiral separation using chiral SFC to yield the title compound.

Peak 1, example 78a: Yield: 35% (0.035 g, 0.081 mmol). LCMS m/z = 430 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.79 (s, 1H), 7.55-7.53 (m, 2H), 7.43-7.38 (m, 2H), 7.34-7.33 (m, 2H), 5.68 (s, 1H), 3.29 (s, 3H, masked with water peak), 2.39 (s, 3H). Chiral SFC: column: Chiralpak IC (4.6 x 250 mm) 5 µm; co-solvent: 0.3% $iPrNH_2$ in isopropylalcohol, flow: 3 mL/min; % of co-solvent: 30%; ABPR: 1500 psi T: 35 °C; Rt = 2.26 min (first eluting).

Peak 2, example 78b: Yield: 25% (0.035 g, 0.081 mmol). LCMS m/z = 430 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.54 (s, 1H), 7.55-7.52 (m, 2H), 7.42-7.38 (m, 2H), 7.34-7.31 (m, 2H), 5.65 (s, 1H), 3.10 (s, 3H), 2.38 (s, 3H). Chiral SFC: column: Chiralpak IC (4.6 x 250 mm) 5 µm; co-solvent: 0.3% $iPrNH_2$ in isopropylalcohol,, flow: 3 mL/min; % of co-solvent: 30%; ABPR: 1500 psi T: 35 °C; Rt = 2.89 min (second eluting).

Example 79

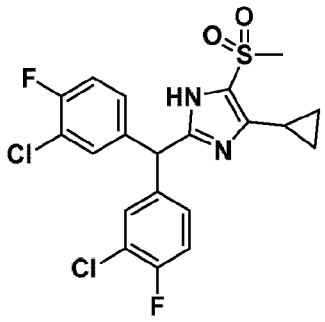
2-(bis(3-chloro-4-fluorophenyl)methyl)-4-methyl-5-(methylsulfonyl)-1H-imidazole



To a solution of 2-(bis(3-chloro-4-fluorophenyl)methyl)-4-iodo-5-(methylsulfonyl)-1H-imidazole (intermediate 13, 0.125 g, 0.23 mmol) in 1,4-dioxane (7.0 mL) was added Cs_2CO_3 (0.151 g, 0.46 mmol) at rt. The reaction mixture was degassed with argon for 10 min followed by the addition of trimethylboroxine (0.06 g, 0.46 mmol) and $PdCl_2$(dppf)·DCM (0.01 g, 0.012 mmol) at rt. The reaction mixture was heated to 100 °C for 16 h in a sealed tube. The reaction mixture was filtered through a celite bed and the filtrate was concentrated under reduced pressure to get the crude product, which was purified by reverse-phase prep HPLC to the title compound (0.035 g, 35%). LCMS m/z = 431 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.58 (s, 1H), 7.54-7.52 (m, 2H), 7.42-7.37 (m, 2H), 7.33-7.30 (m, 2H), 5.65 (s, 1H), 3.06 (s, 3H), 2.36 (s, 3H).

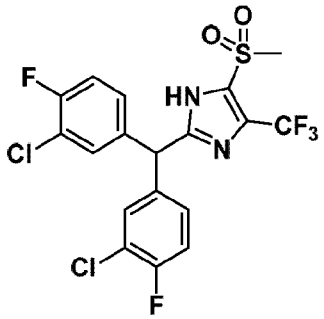
Example 80

The title compound wase prepared from the appropriate intermediates and reagents using an analogous method to that described for example 79.

Example	Name/Structure/Data
80	2-(bis(3-chloro-4-fluorophenyl)methyl)-4-cyclopropyl-5-(methylsulfonyl)-1H-imidazole  Yield: 0.05 g, 34%. LCMS m/z = 457 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.18 (bs, 1H), 7.54-7.53 (m, 2H), 7.41-7.36 (m, 2H), 7.33-7.30 (m, 2H), 5.53 (s, 1H), 3.11 (s, 3H), 2.50-2.47 (m, 1H), 1.01-0.99 (m, 2H), 0.83-0.79 (m, 2H).

Example 81

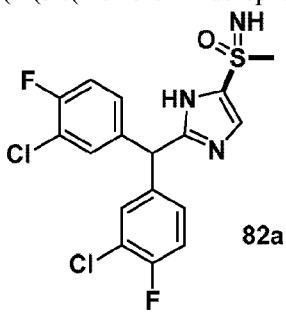
2-(bis(3-chloro-4-fluorophenyl)methyl)-5-(methylsulfonyl)-4-(trifluoromethyl)-1H-imidazole



To a solution of 2-(bis(3-chloro-4-fluorophenyl)methyl)-5-iodo-4-(methylsulfonyl)-1H-imidazole (intermediate 13, 0.5 g, 0.923 mmol) in NMP (3.0 mL) were added KF (0.27 g, 4.61 mmol) and CuI (0.36 g, 1.84 mmol) at rt. The reaction mixture was degassed with argon for 10 min followed by the dropwise addition of $TMSCF_3$ (3.0 mL, 18.45 mmol) at 0 °C over 2 minutes. The reaction mixture was heated to 110 °C in a sealed tube for 16 h. The reaction mixture was cooled to rt and was diluted with cold water (20 mL). The aqueous layer was extracted with ethyl acetate (2 × 80 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to get the crude product which was purified by RP prep HPLC to yield the title compound (0.07 g, 19%). LCMS m/z = 485 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 7.58-7.57 (m, 2H), 7.43-7.39 (m, 2H), 7.34-7.33 (m, 2H), 5.75 (s, 1H), 3.22 (s, 3H, masked with water peak).

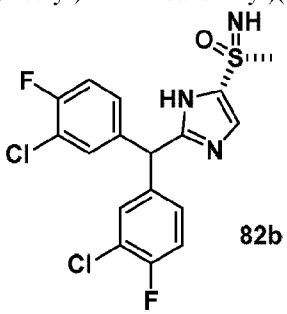
Example 82

(2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)(imino)(methyl)-l6-sulfanone



82a

and



82b

Step 1: A mixture of 2-(bis(3-chloro-4-fluorophenyl) methyl)-5-iodo-1-((2-(trimethylsilyl) ethoxy) methyl)-1H-imidazole and 2-(bis(3-chloro-4-fluorophenyl) methyl)-4-iodo-1-((2-(trimethylsilyl) ethoxy) methyl)-1H-imidazole (intermediate 5, 0.35 g, 0.58 mmol) in NMP (3 mL) was degassed with argon for 15 min followed by the addition of NaSMe (0.08 g, 1.17 mmol) and $CuCl_2$ (0.04 g, 0.29 mmol) at rt. The reaction mixture was heated to 130 °C for 16 h. The reaction mixture was cooled to rt and filtered through a celite bed. The filtrate was concentrated under reduced pressure to get the crude product, which was purified by column chromatography (silica gel; 0-60% ethyl acetate in hexane as eluent) to afford a mixture of 2-(bis(3-chloro-4-fluorophenyl) methyl)-5-(methylthio)-1-((2-(trimethylsilyl) ethoxy) methyl)-1H-imidazole and 2-(bis(3-chloro-4-fluorophenyl) methyl)-4-(methylthio)-1-((2-(trimethylsilyl) ethoxy) methyl)-1H-imidazole (0.23 g, 77%). LCMS m/z = 515 $[M+H]^+$.

Step 2: To a mixture of 2-(bis(3-chloro-4-fluorophenyl)methyl)-5-(methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole and 2-(bis(3-chloro-4-fluorophenyl)methyl)-4-(methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole (0.13 g, 0.25 mmol) in MeOH (4 mL) were added diacetoxyiodobenzene (0.65 g, 2.01 mmol) and ammonium carbonate (0.19 g, 2.01 mmol) at rt. The reaction mixture was stirred at rt for 2 h. The reaction mixture was diluted with water and extracted with EtOAc (3×100 mL). The combined organic part was washed with cold brine, dried over Na_2SO_4 and concentrated under reduced pressure to get the crude product, which was purified by column chromatography (SiO_2, 0-60% EtOAc/Hex) to afford a mixture of (2-(bis(3-chloro-4-fluorophenyl)methyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)(imino)(methyl)-l6-sulfanone and (2-(bis(3-chloro-4-fluorophenyl)methyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone (0.07 g, 51%). LCMS m/z = 546 $[M+H]^+$.

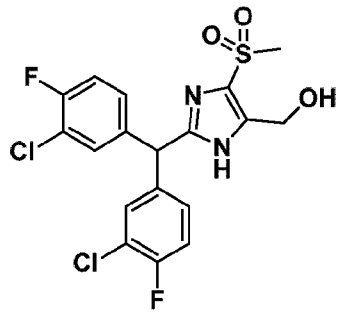
Step 3: To a mixture of (2-(bis(3-chloro-4-fluorophenyl)methyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)(imino)(methyl)-l6-sulfanone and (2-(bis(3-chloro-4-fluorophenyl)methyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone (0.18 g, 0.33 mmol, 1.0 eq.) in EtOH (5 mL) was added 4(M) HCl in 1,4-dioxane (5 mL) at 0 °C. The reaction mixture was heated to 60 °C for 3 h. The reaction mixture was concentrated under reduced pressure to get the crude title compound, which was purified by reverse-phase prep HPLC followed by chiral separation to yield the separated enantiomers.

Peak 1, **example 82a:** Yield: 0.025 g, 18%. LCMS m/z = 416 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.66 (brs, 1H), 7.65 (s, 1H), 7.53 (d, 2H), 7.40 (t, 2H), 7.34-7.31 (m, 2H), 5.71 (s, 1H), 3.96 (s, 1H), 3.00 (s, 3H). Chiral HPLC: column: Chiralpak IC (4.6 x 250 mm) 5 µm, mobile phase: Hexane/DCM/EtOH/isopropylamine 50/25/25/0.1, flow rate: 1.0 mL/min Rt = 5.31 min (first eluting).

Peak 2, **example 82b:** Yield: 0.025 g, 18%. LCMS m/z = 416 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.65 (brs, 1H), 7.66 (s, 1H), 7.53 (d, 2H), 7.40 (t, 2H), 7.34-7.31 (m, 2H), 5.72 (s, 1H), 3.96 (s, 1H), 3.00 (s, 3H). Chiral HPLC: column: Chiralpak IC (4.6 x 250 mm) 5 µm, mobile phase: Hexane/DCM/EtOH/isopropylamine 50/25/25/0.1, flow rate: 1.0 mL/min Rt = 6.51 min (second eluting).

Example 87

(2-(bis(3-chloro-4-fluorophenyl)methyl)-4-(methylsulfonyl)-1H-imidazol-5-yl)methanol



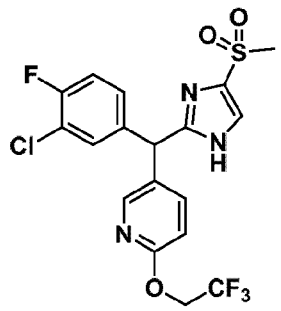
Step 1: To a solution of 2-[bis(3-chloro-4-fluorophenyl)methyl]-4-iodo-5-methanesulfonyl-1H-imidazole (intermediate 13, 0.5 g, 0.92 mmol) in 1,4-dioxane-H_2O (20.0 mL) were added K_2CO_3 (0.153 g, 1.1 mmol) and potassium vinyltrifluoroborate (0.25 g, 1.84 mmol) at rt. The reaction mixture was degassed with argon for 10 minutes. $PdCl_2$(dppf)·DCM (0.034 g, 0.046 mmol) was added to the reaction mixture at rt. The reaction mixture was heated to 110 °C for 16 h in a sealed tube. The reaction mixture was cooled to rt and filtered through a celite bed. The filtrate was evaporated under reduced pressure at low temperature to get the crude product, which was purified by CombiFlash column chromatography (SiO_2, 0-70% EtOAc/Hex) to yield 2-(bis(3-chloro-4-fluorophenyl)methyl)-4-(methylsulfonyl)-5-vinyl-1H-imidazole (0.35 g, 80%). LCMS m/z = 443 $[M+H]^+$.

Step2: To a stirred solution of 2-[bis(3-chloro-4-fluorophenyl)methyl]-5-ethenyl-4-methanesulfonyl-1H-imidazole (0.35 g, 0.79 mmol) in 1,4-dioxane (10.0 mL) and H_2O (3.0 mL) were added OsO_4 (0.16 M in H_2O; 0.15 mL, 0.024 mmol) and NMO (50%; 0.102 g, 0.869 mmol) at rt. The reaction mixture was stirred at rt for 16 h. Then, $NaIO_4$ (1.7 g ,7.90 mmol) was added at rt and the mixture was stirred for one hour. The reaction mixture was diluted with water (30.0 mL) and extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to get the crude product, which was purified by CombiFlash (SiO_2, 0-20% EtOAc/Hex) to obtain 2-[bis(3-chloro-4-fluorophenyl)methyl]-4-methanesulfonyl-1H-imidazole-5-carbaldehyde (0.12 g, 34%).

Step 3: To a stirred solution of 2-[bis(3-chloro-4-fluorophenyl)methyl]-4-methanesulfonyl-1H-imidazole-5-carbaldehyde (0.1 g, 0.225 mmol) in MeOH (8.0 mL) was added portionwise $NaBH_4$ (0.07 g, 1.12 mmol) at 0 °C and the reaction mixture was stirred at rt for 2 h. The reaction mixture was cooled to 0 °C and diluted with water. The aqueous part was extracted with ethyl acetate (2 × 30 mL). The combined organic part was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get the crude product, which was purified by reverse-phase prep HPLC to get the title compound (0.045 g, 44%). LCMS m/z = 447 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.91 (s, 1H), 7.55-7.54 (m, 2H), 7.42-7.32 (m, 4H), 5.69 (s, 1H), 5.46-5.43 (m, 1H), 4.68-4.67 (m, 2 H), 3.09 (s, 3H).

Example 88

5-((3-chloro-4-fluorophenyl)(4-(methylsulfonyl)-1H-imidazol-2-yl)methyl)-2-(2,2,2-trifluoroethoxy)pyridine



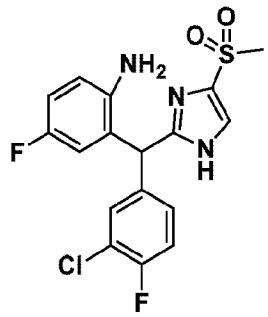
Step 1: (3-Chloro-4-fluorophenyl)(4-(methylsulfonyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methanone (intermediate 25, mixture of regioisomers, 200 mg, 0.463 mmol) was dissolved in 4 M HCl in 1,4-dioxane (5 mL) at rt and the mixture was stirred for 4 h. The mixture was concentrated under reduced pressure and the residue were taken up in ethyl acetate (20 mL) and washed with sodium bicarbonate solution (5 mL × 2). The combined organic layers were concentrated under reduced pressure to get crude (3-chloro-4-fluorophenyl)(4-(methylsulfonyl)-1H-imidazol-2-yl)methanone (0.13 g, crude) which was used in the next step without any further purification.

Step 2: 5-Bromo-2-(2,2,2-trifluoroethoxy)pyridine (1271.6 mg, 4.967 mmol) was added to a stirred solution of magnesium turnings (119.2 mg, 4.967 mmol) and iodine (10 mg) in THF (2.0 mL) at rt. The resulting reaction mixture was stirred for 30 min at rt followed by the addition of (3-chloro-4-fluorophenyl)(4-(methylsulfonyl)-1H-imidazol-2-yl)methanone (100 mg, 0.331 mmol) at 0 °C . The resulting reaction mixture was warmed to rt for 2 h. The reaction mixture was diluted with NH_4Cl solution (5 mL) and extracted with ethyl acetate (10 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, 0-50% EtOAc/PE) to afford (3-chloro-4-fluorophenyl) (4-(methylsulfonyl)-1H-imidazol-2-yl) (6-(2,2,2-trifluoroethoxy)pyridin-3-yl)methanol (0.1 g, 54%).

Step 3: To a stirred solution of (3-chloro-4-fluorophenyl)(4-(methylsulfonyl)-1H-imidazol-2-yl)(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)methanol (440 mg, 0.917 mmol), acetic acid (5.0 mL, 0.125 mmol) and fuming hydrochloric acid in water (2.0 mL, 0.025 mmol) at rt was added stannous chloride dihydrate (1241.5 mg, 5.502 mmol). The resulting reaction mixture was heated to 120 °C for 18 h. The reaction mixture was concentrated under reduced pressure, diluted with water (5 mL) and extracted with ethyl acetate (10 mL × 2). The combined organic layers were dried over sodium sulphate, filtered and concentrated under reduced pressure to get the crude product, which was purified by Prep HPLC followed by SFC to the title compound (0.03 g, 7%). LCMS m/z = 464 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.90 (s, 1H), 8.14 (d, 1H), 7.82 (s, 1H), 7.76 (dd, 1H), 7.52 (dd, 1H), 7.40 (t, 1H), 7.32-7.28 (m, 1H), 6.99 (d, 1H), 5.71 (s, 1H), 5.00-4.93 (m, 2H), 3.10 (s, 3H).

Example 89

2-((3-chloro-4-fluorophenyl)(4-(methylsulfonyl)-1H-imidazol-2-yl)methyl)-4-fluoroaniline



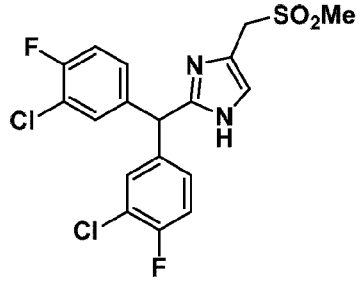
Step 1: Sodium borohydride (0.119 g, 3.234 mmol) was added to a stirred solution of (3-chloro-4-fluorophenyl) (4-(methylsulfonyl)-1-((2-(trimethylsilyl) ethoxy) methyl)-1H-imidazol-2-yl) methanone (intermediate 25, mixture of regioisomers, 0.700 g, 1.617 mmol) in methanol (10 mL) at 0 °C, and the resulting mixture was stirred at 0 °C for 1 h. The reaction mixture was concentrated under reduced pressure. The obtained crude material was purified by flash chromatography (SiO_2, 0-70% EtOAc/PE) to afford (3-chloro-4-fluorophenyl) (4-(methylsulfonyl)-1-((2-(trimethylsilyl) ethoxy) methyl)-1H-imidazol-2-yl) methanol and the corresponding SEM regioisomer (0.450 g, 64%).

Step 2: (3-Chloro-4-fluorophenyl) (4-(methylsulfonyl)-1-((2-(trimethylsilyl) ethoxy) methyl)-1H-imidazol-2-yl) methanol (mixture of regioisomers, 0.500 g, 1.14 mmol) was dissolved in 4 M HCl in 1,4-dioxane (5 mL) and the mixture was stirred at rt for 18 h. The reaction mixture was concentrated under reduced pressure. The obtained crude product was purified by Prep-HPLC to afford (3-chloro-4-fluorophenyl)(4-(methylsulfonyl)-1H-imidazol-2-yl)methanol (0.320 g, 91%).

Step 3: *p*-Toluenesulfonic acid monohydrate (0.280 g, 1.477 mmol) was added to a stirred solution of (3-chloro-4-fluorophenyl)(4-(methylsulfonyl)-1H-imidazol-2-yl)methanol (0.150 g, 0.492 mmol) and 4-fluoroaniline (0.164 g, 1.477 mmol) in toluene (10 mL) at rt and the mixture was then heated to 120 °C for 4 h. The reaction mixture was concentrated under reduced pressure. The obtained crude product was purified by Prep-HPLC to yield the title compound (0.030 g, 15%). LCMS m/z = 398 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.80 (s, 1H), 7.80 (s, 1H), 7.41 - 7.35 (m, 2H), 7.25 - 7.21 (m, 1H), 6.88 - 6.84 (m, 1H), 6.69 - 6.66 (m, 1H), 6.55 (dd, 1H), 5.69 (s, 1H), 4.92 (s, 2H), 3.09 (s, 3H).

Example 91

2-(bis(3-chloro-4-fluorophenyl)methyl)-4-((methylsulfonyl)methyl)-1H-imidazole



Step 1: To a stirred solution of methyl 2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazole-4-carboxylate (intermediate 9, 1.8 g, 4.545 mmol) in DMF (20.0 mL) was added NaH (60% in mineral oil, 0.275 g, 6.818 mmol) at 0 °C and the reaction mixture was stirred at 0 °C for 15 min. Then, SEM-Cl (1.6 mL, 9.09 mmol) was added to the reaction mixture at 0 °C and the reaction mixture was stirred at rt for 16 h. The reaction mixture was cooled to 0 °C and quenched with NH_4Cl solution. The aqueous layer was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to get the crude product, which was purified by column chromatography (SiO_2, 0-60% EtOAc/Hex) to yield methyl 2-[bis(3-chloro-4-fluorophenyl)methyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazole-4-carboxylate and methyl 2-[bis(3-chloro-4-fluorophenyl)methyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazole-5-carboxylate (1.0 g, 75%); LCMS m/z = 523 $[M+H]^+$.

Step 2: To a stirred solution of methyl 2-(bis(3-chloro-4-fluorophenyl)methyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole-5-carboxylate and methyl 2-[bis(3-chloro-4-fluorophenyl)methyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazole-5-carboxylate (1.1 g, 2.09 mmol) in THF (30.0 mL) was added $NaBH_4$ (1.0 g, 27.186 mmol) at rt and the reaction mixture was then heated to 60 °C followed by the addition of MeOH (7.0 mL) dropwise at 60 °C. The reaction mixture was then heated to 60 °C for 16 h. The reaction mixture was cooled to 0 °C, diluted with water and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get the crude product which was purified by CombiFlash column chromatography (SiO_2, 0-70% EtOAc/Hex) to yield (2-(bis(3-chloro-4-fluorophenyl)methyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)methanol and the corresponding SEM regioisomer (0.7 g, 67%); LCMS m/z = 499 $[M+H]^+$.

Step 3: To a stirred solution of (2-(bis(3-chloro-4-fluorophenyl)methyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)methanol (mixture of regioisomers, 0.4 g, 0.802 mmol) in DCM (15.0 mL) was added thionyl chloride (0.29 mL, 4.00 mmol) at 0 °C and the mixture was then stirred at rt for 2 h. The reaction mixture was concentrated and then diluted with ethyl acetate (40 mL). The organic layer was washed with sodium bicarbonate solution (15 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The resulted crude compound was dissolved in THF (15 mL) followed by the addition of TEA (0.34 mL, 2.405 mmol) and NaSMe (0.28 g, 4.0 mmol) at 0 °C. The mixture was then stirred at rt for 16 h. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by CombiFlash chromatography (SiO_2, 0-30% EtOAc/Hex) to afford 2-(bis(3-chloro-4-fluorophenyl)methyl)-5-((methylthio)methyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole and the corresponding SEM regioisomer (0.26 g, 61%); LCMS m/z = 529 $[M+H]^+$.

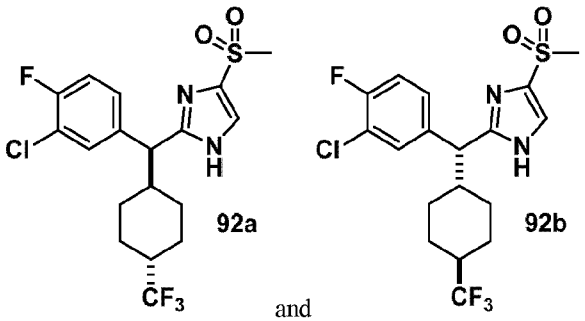
Step 4: To a stirred solution 2-(bis(3-chloro-4-fluorophenyl)methyl)-5-((methylthio)methyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole (mixture of regioisomers, 0.25 g, 0.473 mmol) in DCM (10.0 mL) was added m-CPBA (70 %, 0.232 g, 0.947 mmol) at 0 °C and the reaction mixture was stirred at rt for 3 h. To the reaction mixture was then added $NaHCO_3$ solution (10 mL) and the mixture was stirred for 30 minutes. The mixture was extracted with ethyl acetate (3 x 30 mL), the combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The crude material was purified by CombiFlash column chromatography (SiO_2, 0-70% EtOAc/PE) to yield 2-(bis(3-chloro-4-fluorophenyl)methyl)-5-((methylsulfonyl)methyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole and the corresponding SEM regioisomer (0.2 g, 42%). LCMS m/z = 561 $[M+H]^+$.

Step 5: To a stirred solution of 2-(bis(3-chloro-4-fluorophenyl)methyl)-5-((methylsulfonyl)methyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole (mixture of regioisomers, 0.13 g, 0.232 mmol) in ethanol (2 mL) was

added HCl (4M in dioxane, 2 mL) at rt and the reaction mixture was then heated to 70 °C for 5 h. The solvent was then evaporated under reduced pressure and the residue was purified by prep-HPLC to obtain the title compound (0.055 g, 55%). LCMS m/z = 431 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.1 (brs, 1H), 7.54-7.52 (m, 2H), 7.39-7.29 (m, 4H), 7.14 (s, 1H), 5.63 (s, 1H), 4.31 (s, 2H), 2.93 (s, 3H).

Example 92

2-((3-chloro-4-fluorophenyl)(4-(trifluoromethyl)cyclohexyl)methyl)-4-(methylsulfonyl)-1H-imidazole



92a and 92b

Step 1: HATU (11.630 g, 30.586 mmol) was added portionwise to a stirred solution of 4-(trifluoromethyl) cyclohexane-1-carboxylic acid (5.0 g, 25.488 mmol), N, O-dimethyl hydroxylamine hydrochloride (2.983 g, 30.586 mmol) and N, N-Diisopropylethylamine (17.430 mL, 101.953 mmol) in DMF (50 mL) at 0 °C under an argon atmosphere. The mixture was allowed to warm to rt and was stirred for 4 h. The reaction mixture was then cooled to 0 °C, quenched with a saturated aqueous solution of $NaHCO_3$ (30 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by 100-200 silica gel column chromatography (SiO_2, 25% EtOAc/PE) to afford N-methoxy-N-methyl-4-(trifluoromethyl) cyclohexane-1-carboxamide (5.6 g, 91%).

Step 2: LDA (2M in THF, 13.061 mL, 26.123 mmol) was added dropwise to a stirred solution of 4-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole (intermediate 22, mixture of regioisomers, 7.7 g, 23.748 mmol) in THF (30 mL) at –78 °C under an argon atmosphere. The resulting reaction mixture was stirred at this temperature for 1 h followed by the addition of a solution of (1s,4s)-N-methoxy-N-methyl-4-(trifluoromethyl)cyclohexane-1-carboxamide (5.681 g, 23.748 mmol) in THF (40 mL). The resulting reaction mixture was stirred for 1 h at –78 °C. The reaction mixture was quenched with saturated NH_4Cl solution (300mL), diluted with water (150 mL) and extracted with EtOAc (2 x 250 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, 0-20% EtOAc/PE) to afford (5-iodo-1-((2-(trimethylsilyl) ethoxy) methyl)-1H-imidazol-2-yl) ((trans)-4-(trifluoromethyl) cyclohexyl) methanone and the corresponding SEM regioisomer (6 g, 50%).

Step 3: 4-Bromo-2-chloro-1-fluorobenzene (2.084 g, 9.952 mmol) was added in one portion to a stirred solution of magnesium turnings (238.857 mg, 9.952 mmol) and Iodine (2 mg) in THF (7 mL) at rt under an argon atmosphere. The temperature of the reaction was raised to 60 °C. The reaction mixture was allowed to come to rt and was stirred for 1 h. The reaction mixture was cooled to 0 °C and a solution of (4-iodo-1-((2-(trimethylsilyl) ethoxy) methyl)-1H-imidazol-2-yl) ((trans)-4-(trifluoromethyl) cyclohexyl) methanone (mixture of regioisomers, 1.0 g, 1.990 mmol) in THF (33 mL) was added dropwise. The reaction mixture was warmed to rt and was stirred for 1 h.

The reaction mixture was quenched with NH_4Cl solution (150 mL) and extracted with ethyl acetate (3×150 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and then concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, 35% EtOAc/PE) afford (3-chloro-4-fluorophenyl) (4-iodo-1-((2-(trimethylsilyl) ethoxy) methyl)-1H-imidazol-2-yl) ((trans)-4-(trifluoromethyl) cyclohexyl) methanol and the corresponding SEM regioisomer (0.7 g, 55%).

Step 4: To a stirred solution of (3-chloro-4-fluorophenyl) (4-iodo-1-((2-(trimethylsilyl) ethoxy) methyl)-1H-imidazol-2-yl) ((trans)-4-(trifluoromethyl) cyclohexyl) methanol (mixture of regioisomers, 0.7 g, 1.106 mmol) and methylsulfinic acid sodium salt (451.229 mg, 4.424 mmol) dissolved in DMSO (20 mL) was added sodium hydroxide powder (44.238 mg, 1.106 mmol). The mixture was degassed with argon gas, followed by the addition of copper(I) iodide (126.377 mg, 0.664 mmol) and L-Proline (127.328 mg, 1.106 mmol). The resulting reaction mixture was heated to 150 °C for 2 h under microwave irradiation. The reaction mixture was cooled to rt, filtered through a celite bed, the celite bed was washed with 10% methanol in dichloromethane (300 mL) and the filtrate was washed with water (2×100 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, 35% EtOAc/PE) to afford (3-chloro-4-fluorophenyl) (4-(methyl sulfonyl)-1-((2-(trimethylsilyl) ethoxy) methyl)-1H-imidazol-2-yl) ((trans)-4-(trifluoromethyl) cyclohexyl) methanol and the corresponding SEM regioisomer (348 mg, 53%).

Step 5: To a solution of (3-chloro-4-fluorophenyl) (4-(methyl sulfonyl)-1-((2-(trimethylsilyl) ethoxy) methyl)-1H-imidazol-2-yl) ((trans)-4-(trifluoromethyl) cyclohexyl) methanol (mixture of regioisomers, 320 mg, 0.547 mmol) in acetic acid (5 mL) was added stannous chloride anhydrous (740.434 mg, 3.281 mmol) followed by conc. hydrochloric acid (1.6 mL) at rt. The resulting reaction mixture was heated to 120 °C for 2 h. The reaction mixture was cooled to rt, diluted with water (10 mL), basified with $NaHCO_3$ solution (pH=8) and extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford (3-chloro-4-fluorophenyl) (4-(methyl sulfonyl)-1H-imidazol-2-yl) ((trans)-4-(trifluoromethyl) cyclohexyl) methanol (430 mg, crude).

Step 6: To a solution of (3-chloro-4-fluorophenyl) (4-(methyl sulfonyl)-1H-imidazol-2-yl) ((trans)-4-(trifluoromethyl) cyclohexyl) methanol (290 mg, 0.638 mmol) in acetic acid (25 mL) was added stannous chloride dehydrate (863.181 mg, 3.825 mmol) followed by fuming hydrochloric acid (37% solution in water, 20 mL) at rt. The resulting reaction mixture was heated to 120 °C for 16 h. The reaction mixture was cooled to rt and was concentrated under reduced pressure. The residue was diluted with water (10 mL), basified with $NaHCO_3$ solution (pH=8) and then extracted with ethyl acetate (3x25 mL). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered and then concentrated under reduced pressure.

Similarly, using above experimental protocol another 0.127 mg of (3-chloro-4-fluorophenyl) (4-(methyl sulfonyl)-1H-imidazol-2-yl) ((trans)-4-(trifluoromethyl) cyclohexyl) methanol was used. The combined crudes were purified by prep HPLC to afford Peak 1 of the title compound (66 mg) and Peak 2 of the title compound (90 mg).

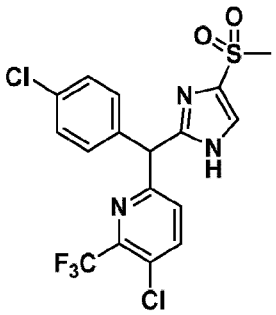
Peak 1, **example 92a:** LCMS m/z = 439 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.76 (s, 1H), 7.78 (s, 1H), 7.60 (d, 1H), 7.37 (d, 2H), 3.79 (d, 1H), 3.08 (s, 3H), 2.19-2.07 (m, 2H), 1.85-1.78 (m, 2H), 1.55-1.52 (m, 1H), 1.42-1.39 (m, 1H), 1.27-1.13 (m, 2H), 1.07-0.96 (m, 2H). Chiral SFC: column: Chiralpak AD-H (4.6 x 250 mm)

5 µm; co-solvent: 0.5% DEA in MeOH, flow: 3 mL/min; % of co-solvent: 15%; ABPR: 1500 psi T: 30 °C; Rt = 1.00 min (first eluting).

Peak 2, example 92b: LCMS m/z = 439 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.76 (s, 1H), 7.78 (s, 1H), 7.60 (d, 1H), 7.37 (d, 2H), 3.79 (d, 1H), 3.08 (s, 3H), 2.19-2.07 (m, 2H), 1.85-1.78 (m, 2H), 1.55-1.52 (m, 1H), 1.42-1.39 (m, 1H), 1.27-1.13 (m, 2H), 1.07-0.96 (m, 2H). Chiral SFC: column: Chiralpak AD-H (4.6 x 250 mm) 5 µm; co-solvent: 0.5% DEA in MeOH, flow: 3 mL/min; % of co-solvent: 15%; ABPR: 1500 psi T: 30 °C; Rt = 2.01 min (second eluting).

Example 93

3-chloro-6-((4-chlorophenyl)(4-(methylsulfonyl)-1H-imidazol-2-yl)methyl)-2-(trifluoromethyl)pyridine



Step 1: To a solution of 3,6-dichloro-2-(difluoromethyl)pyridine (2.5 g, 11.628 mmol) in ethanol (50 mL) was added TEA (2 mL, 13.953mmol) and the mixture was degassed with argon for 10 minutes. Then potassium vinyl-trifluoroborate was added (1.9 g, 13.953 mmol) followed by the addition of $PdCl_2(dppf)\cdot DCM$ (0.43 g, 0.581 mmol) at rt. The mixture was then heated to 110 °C for 3 h in a sealed tube. The reaction mixture was cooled to rt and filtered through a celite bed, the filtrate was evaporated at low temperature (~40°C) under reduced pressure. The resulting crude was purified by CombiFlash column chromatography (SiO_2, hexane) to obtain 3-chloro-6-ethenyl-2-(trifluoromethyl)pyridine (1.8 g, 75%).

Step 2: To a solution of 3-chloro-6-ethenyl-2-(trifluoromethyl) pyridine (1.8 g, 8.696 mmol) in dioxane-water (3:1, 60 mL) was added NMO (2.6 mL, 9.565 mmol, 50% in water) followed by OsO_4 (1.2 mL, 0.174 mmol, 0.15 M in dioxane) at rt. The mixture was then stirred at the same temperature for 3 h. Then $NaIO_4$ (19 g, 86.957 mmol) was added and stirring was continued at rt for 1 h. The reaction mixture was quenched with saturated sodium bi-carbonate solution and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain 5-chloro-6-(trifluoro-methyl)picolinaldehyde which was used in the next step without further purification (1.5 g, 82%).

Step 3: To a solution of 5-chloro-6-(trifluoromethyl) picolinaldehyde (0.1 g, 0.478 mmol) in THF (4 mL) was added (4-chlorophenyl) magnesium bromide (0.57 mL, 0.574 mmol, 1M in Et_2O, 1.2 eq.) slowly at 0 °C. The mixture was then stirred at the same temperature for 1 h, before being quenched with saturated aqueous ammonium chloride solution. The mixture was extracted with EtOAc (2 x 20 mL), the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude product was purified by combi-flash column chromatography (SiO_2, 30% EtOAc/Hex) to obtain [5-chloro-6-(trifluorome-thyl) pyridin-2-yl] (4-chlorophenyl) methanol (0.13 g, 84%). LCMS m/z = 322 $[M+H]^+$.

Step 4: To a solution of [5-chloro-6-(trifluoromethyl) pyridin-2-yl] (4-chlorophenyl) methanol (0.13 g, 0.404 mmol) in THF (5 mL) was added MnO_2 (0.18 g, 2.019 mmol) at rt. The mixture was then stirred at the same temperature for 16 h. The reaction mixture was filtered through celite and the celite bed was washed with THF. The solvent was evaporated under reduced pressure. The residue was purified by combi-flash column chromatography (SiO_2, 0-20% EtOAc/Hex) to obtain 3-chloro-6-[(4-chlorophenyl)carbonyl]-2-(trifluoromethyl)pyridine (0.1 g, 77%).

Step 5: To a solution of DIPA (0.72 mL, 5.156 mmol) in THF (10 mL) was added n-BuLi (2.3 mL, 2 M in THF, 4.688 mmol) slowly at –78°C under a nitrogen atmosphere. The mixture was stirred at the same temperature for 10 minutes, then allowed to warm to 0 °C for 30 minutes. The solution was again cooled to –78°C and 4-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole (intermediate 22, mixture of regioisomers, 1.3 g, 3.906 mmol) in THF (10 mL) was added. The mixture was stirred at same temperature for 30 minutes, followed by the addition of a solution of 3-chloro-6-[(4-chlorophenyl)carbonyl]-2-(trifluoromethyl)pyridine (0.5 g, 1.563 mmol) in THF (10 mL) at the same temperature. The reaction mixture was slowly warmed to rt and was stirred for 6 h. The reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude product was purified by combi-flash column chromatography (SiO_2, 0-10% EtOAc/Hex) to obtain (5-chloro-6-(trifluoromethyl)pyridin-2-yl)(4-chlorophenyl)(4-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methanol and the corresponding SEM regioisomer (0.5 g, 50%). LCMS m/z = 645 $[M+H]^+$.

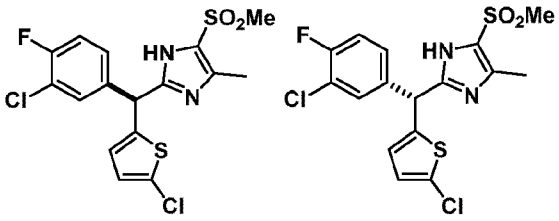
Step-6: To a solution of (5-chloro-6-(trifluoromethyl)pyridin-2-yl)(4-chlorophenyl)(4-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methanol (mixture of regioisomers, 0.5 g, 0.776 mmol) in 1,4-dioxane (20.0 mL) was added NaSMe (0.1 g, 1.32 mmol) and the mixture was degassed with argon for 10 min followed by the addition of Xantphos (0.07 g, 0.116 mmol) and $Pd_2(dba)_3$ (0.07 g, 0.078 mmol) at rt. The mixture was then heated to 110 °C for 16 h in a sealed tube. The mixture was then filtered through a celite bed and the celite bed was washed with EtOAc. The solvent was evaporated to get the crude material which was purified by CombiFlash column chromatography (SiO_2, 10% EtOAc/Hex) to get (5-chloro-6-(trifluoromethyl)pyridin-2-yl)(4-chlorophenyl)(4-(methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methanol and the corresponding SEM regioisomer (0.3 g, 68%). LCMS m/z = 564 $[M+H]^+$.

Step-7: To a solution of (5-chloro-6-(trifluoromethyl)pyridin-2-yl)(4-chlorophenyl)(4-(methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methanol (mixture of regioisomers, 0.32 g, 0.566 mmol) in acetic acid (5.0 mL) were added $SnCl_2$ (0.64 g, 3.398 mmol) and aqueous HCl (1 mL, 12 N). The mixture was heated to 120 °C for 24 h. The reaction mixture was cooled to rt and concentrated under reduced pressure to get the crude product which was basified with aqueous Na_2CO_3 solution. The mixture was filtered through a celite bed and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to get the crude material which was purified by combi-flash column chromatography (SiO_2, 50% EtOAc/Hex) to get 3-chloro-6-[(4-chlorophenyl)[4-(methylsulfanyl)-1H-imidazol-2-yl]methyl]-2-(trifluoromethyl)pyridine (0.13 g, 55%). LCMS m/z = 418 $[M+H]^+$.

Step-8: To a solution of 3-chloro-6-[(4-chlorophenyl)[4-(methylsulfanyl)-1H-imidazol-2-yl]methyl]-2-(trifluoromethyl)pyridine (0.3 g, 0.718 mmol) in DCM (5.0 mL) was added m-CPBA (70%, 0.62 g, 2.153 mmol) at rt. The mixture was stirred at rt for 3 h and was then basified with saturated Na_2SO_3 solution, stirred for 30 minutes and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to get the crude title compound which was purified by column chromatography (SiO_2, EtOAc) (0.025 g, 8%). LCMS m/z = 450 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): 12.81 (bs, 1H), 8.25 (d, 1H), 7.84 (s, 1H), 7.74 (d, 1H), 7.44 (d, 2H), 7.36 (d, 2H), 5.91 (s, 1H), 3.08 (s, 3H).

Example 130

2-((3-chloro-4-fluorophenyl)(5-chlorothiophen-2-yl)methyl)-4-methyl-5-(methylsulfonyl)-1H-imidazole



Step 1: n-butyl lithium (2.5M, 4.474 mL, 11.186 mmol) was added dropwise to a solution of 2-bromo-5-chlorothiophene (0.736 mL, 6.712 mmol) in THF (20.0 mL) at -78 °C under an argon atmosphere. The reaction was stirred at -78 °C for 15 min. After 15 min, (3-chloro-4-fluorophenyl)(5-methyl-4-(methylsulfonyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methanone (regioisomeric mixture, 2.5 g, 5.593 mmol) in THF (10.0 mL) was added dropwise at the same temperature. The reaction was stirred at room temperature for 1 h. The reaction was quenched by the addition of sat. NH_4Cl solution (50 mL) and extracted with ethyl acetate (2×50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure to get the crude compound, which was purified by column chromatography (SiO_2, 25-30% EtOAc/Hex) to afford (3-chloro-4-fluorophenyl)(5-chlorothiophen-2-yl)(5-methyl-4-(methylsulfonyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methanol (mixture of regioisomers, 0.9 g, 29%).

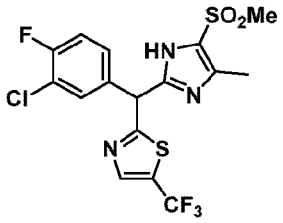
Step 2: To a solution of (3-chloro-4-fluorophenyl)(5-chlorothiophen-2-yl)(5-methyl-4-(methylsulfonyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methanol (mixture of regioisomers, 0.9 g, 1.591 mmol) in acetic acid (9.0 mL) were added stannous chloride dihydrate (2.154 g, 9.548 mmol) and conc. HCl (1.8 mL) at room temperature. The resulting reaction mixture was heated to 100 °C for 16 h. The reaction mixture was concentrated under reduced pressure to get the crude product, which was basified with sat $NaHCO_3$ solution (10 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were dried over sodium sulfate and evaporated under reduced pressure to afford the crude product which was purified by prep-HPLC to afford 100 mg of the racemic title compound.

The racemic title compound was separetad into the individual stereoisomers using chiral SFC.

LCMS m/z = 419 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.69 (brs, 1H), 7.59-7.57 (dd, 1H), 7.44-7.33 (m, 2H), 6.98 (d, 1H), 6.81 (d, 1H), 5.82 (s, 1H), 3.08 (s, 3H), 2.37 (s, 3H). Chiral SFC: column: Chiralpak IG (4.6 x 250 mm) 5 µm; co-solvent: 0.5% diethylamine in MeOH, flow: 3 mL/min; % of co-solvent: 25%; ABPR: 1500 psi T: 30 °C; (130a) Rt = 1.25 min (first eluting), (130b) Rt = 1.70 min (second eluting).

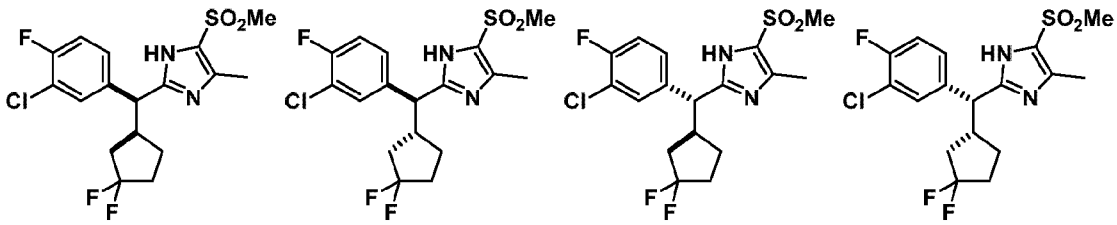
Example 131

The title compound was prepared from the appropriate intermediates and reagents using an analogous method to that described for example 130.

Example	Name/Structure/Data
131	2-((3-chloro-4-fluorophenyl)(4-methyl-5-(methylsulfonyl)-1H-imidazol-2-yl)methyl)-5-(trifluoromethyl)thiazole  LCMS m/z = 454 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.81 (brs, 1H), 8.42 (d, 1H), 7.71-7.69 (m, 1H), 7.46-7.44 (m, 2H), 6.21 (s, 1H), 3.10 (s, 3H), 2.39 (s, 3H).

Example 132

2-((3-chloro-4-fluorophenyl)(3,3-difluorocyclopentyl)methyl)-4-methyl-5-(methylsulfonyl)-1H-imidazole



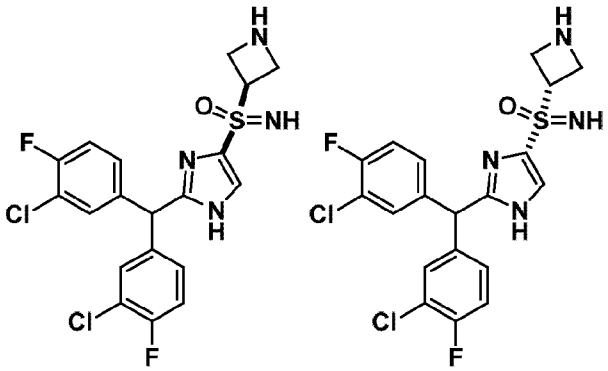
Step 1: To a stirred solution of (3-chloro-4-fluorophenyl)(3,3-difluorocyclopentyl)(5-methyl-4-(methylsulfonyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methanol (intermediate 47, mixture of regioisomers, 0.8 g, 1.446 mmol) and stannous chloride dihydrate (1.958 g, 8.678 mmol) in acetic acid (8 mL) at room temperature was added conc. HCl (1.6 mL). The reaction mixture was heated to 100 °C for 18 h. The reaction mixture was concentrated under reduced pressure, the obtained residue was basified by using sat. $NaHCO_3$ solution and extracted with EtOAC (2 x 30 mL). The combined organic layers were washed with water (30 mL) and brine (30 mL) and then concentrated under reduced pressure to afford the crude compound, which was purified by prep HPLC (column: XSelect phenyl hexyl (19 x 250 mm) 5 µm; 10 mM ammonium-bi-carbonate in water/MeCN as eluent) to yield two fractions with the desired compounds and later prep SFC to afford the title compounds.

First eluting fractions from HPLC after SFC: 132a: LCMS m/z = 407 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.52 (s, 1H), 7.58-7.56 (dd, 1H), 7.40-7.33 (m, 2H), 3.95 (d, 1H), 3.06 (s, 1H), 2.99-2.88 (m, 1H), 2.35 (s, 3H), 2.33-2.00 (m, 2H), 1.89-1.72 (m, 3H), 1.45-1.38 (m, 1H). 132b: LCMS m/z = 407 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.55 (s, 1H), 7.58-7.56 (dd, 1H), 7.40-7.34 (m, 2H), 3.95 (d, 1H), 3.06 (s, 1H), 2.99-2.88 (m, 1H), 2.35 (s, 3H), 2.33-2.00 (m, 2H), 1.89-1.72 (m, 3H), 1.45-1.38 (m, 1H). Chiral SFC: column: Chiralcel OX-H (4.6 x 250 mm) 5 µm; co-solvent: iPrOH, flow: 3 mL/min; % of co-solvent: 15%; ABPR: 1500 psi T: 30 °C; (132a) Rt = 2.82 min (first eluting), (132b) Rt = 3.63 min (second eluting).

Second eluting fractions from HPLC after SFC: 132c: LCMS m/z = 407 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.52 (s, 1H), 7.58-7.56 (dd, 1H), 7.40-7.33 (m, 2H), 3.95 (d, 1H), 3.06 (s, 1H), 2.99-2.88 (m, 1H), 2.35 (s, 3H), 2.33-2.00 (m, 2H), 1.89-1.72 (m, 3H), 1.45-1.38 (m, 1H). 132d: LCMS m/z = 407 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.55 (s, 1H), 7.58-7.56 (dd, 1H), 7.40-7.34 (m, 2H), 3.95 (d, 1H), 3.06 (s, 1H), 2.99-2.88 (m, 1H), 2.35 (s, 3H), 2.33-2.00 (m, 2H), 1.89-1.72 (m, 3H), 1.45-1.38 (m, 1H). Chiral SFC: column: Chiralcel OX-H (4.6 x 250 mm) 5 µm; co-solvent: iPrOH, flow: 3 mL/min; % of co-solvent: 15%; ABPR: 1500 psi T: 30 °C; (132c) Rt = 2.74 min (first eluting), (132d) Rt = 5.56 min (second eluting).

Example 133

azetidin-3-yl(2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-4-yl)(imino)-l6-sulfanone



Step 1: To a mixture of 2-(bis(3-chloro-4-fluorophenyl)methyl)-4-iodo-1H-imidazole (intermediate 4, 0.5 g, 1.075 mmol), tert-butyl 3-mercaptoazetidine-1-carboxylate (0.305 g, 1.613 mmol) and cesium carbonate (1.051 g, 3.225 mmol) in 1,4-dioxane (20 mL) under a nitrogen atmosphere was added slowly Xantphos, (0.062 g, 0.108 mmol) followed by $Pd_2(dba)_3$ (0.098 g, 0.108 mmol). The resulting reaction mixture was heated to 120 °C and stirred for 3 h in a sealed tube. The reaction mixture was filtered through a celite bed and the filterate was extracted with ethyl acetate (3×150 mL). The combined organic layers were were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get the crude product, which upon purification by reverse phase column chromatography 150 mg (26%) of tert-butyl 3-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-4-yl)thio)azetidine-1-carboxylate.

Step 2: To a solution of tert-butyl 3-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-4-yl)thio)azetidine-1-carboxylate (0.4 g, 0.760 mmol) in methanol (4.0 mL) at 0 °C was added ammonium carbonate (0.146 g, 1.52 mmol) followed by (diacetoxyiodo)benzene (0.441 g, 1.368 mmol). The resulting reaction mixture was stirred for 6 h at room temperature. The reaction mixture was concentrated under reduced pressure to obtain a residue, which was taken up in water (10 mL) and extracted with ethyl acetate (2×30 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get the crude product, which after reveres phase column chromatography afforded 280 mg of tert-butyl 3-(2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazole-5-sulfonimidoyl)azetidine-1-carboxylate.

Step 3: To a solution of tert-butyl 3-(2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazole-5-sulfonimidoyl)azetidine-1-carboxylate (0.19 g, 0.341 mmol) in DCM (1.9 mL) at 0 °C was added trifluoroacetic acid (0.95 mL). The resulting reaction mixture was stirred for 2 h at room temperature. The reaction mixture was quenched with sodium bicarbonate solution, diluted with ice water (20 mL) and adjusted the pH to 7.0 with sodium bicarbonate solution.

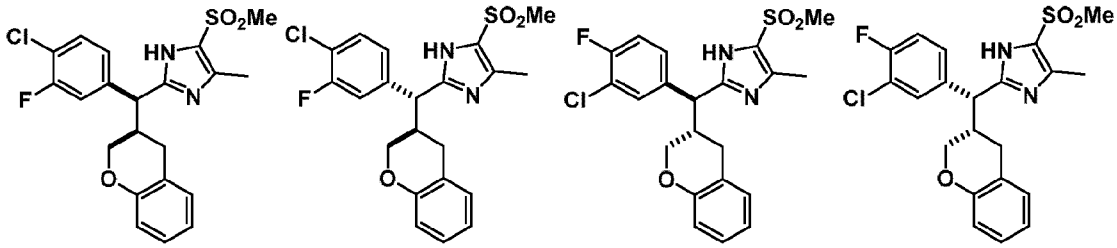
The mixture was then extracted with 10% MeOH in DCM (2×50 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get the crude product, which upon reverse phase column chromatography followed by prep HPLC gave 45 mg of the racemic title compound.

The racemic compound was separetad in the individual enantiomers using chiral SFC.

LCMS m/z = 457 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.56 (brs, 1H), 7.67 (s, 1H), 7.55-7.52 (m, 2H), 7.41-7.36 (m, 2H), 7.34-7.30 (m, 2H), 5.68 (s, 1H), 4.23-4.16 (m, 1H), 4.05-3.96 (brs, 2H), 3.80-3.74 (m, 2H), 3.52-3.45 (m, 2H). Chiral SFC: column: Chiralcel OX-H (4.6 x 250 mm) 5 µm; co-solvent: 0.5% $iPrNH_2$ in iPrOH, flow: 3 mL/min; % of co-solvent: 35%; ABPR: 1500 psi T: 30 °C; (133a) Rt = 7.18 min (first eluting), (133b) Rt = 9.00 min (second eluting).

Example 135

2-((4-chloro-3-fluorophenyl)(chroman-3-yl)methyl)-4-methyl-5-(methylsulfonyl)-1H-imidazole



Step 1: A solution of ((3-chloro-4-fluorophenyl)(chroman-3-yl)(5-methyl-4-(methylsulfonyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methanol (intermediate 48, mixture of intermediates, 300 mg, 0.516 mmol) in 1,4-dioxane (5 mL) was added to 4 M HCl in 1,4-dioxane (5 mL). The resulting reaction mixture was stirred for 6 h at room temperature. Excess voltiles were removed under reduced pressure and azeotroped with toluene (2×5 mL) to afford (4-chloro-3-fluorophenyl)(chroman-3-yl)(5-methyl-4-(methylsulfonyl)-1H-imidazol-2-yl)methanol (300 mg, crude).

Step 2: To a solution of (4-chloro-3-fluorophenyl)(chroman-3-yl)(5-methyl-4-(methylsulfonyl)-1H-imidazol-2-yl)methanol (250 mg, 0.554 mmol) in acetic acid (5 mL) was added tin(II) chloride (630.726 mg, 3.327 mmol). The resulting reaction mixture was stirred at 100 °C for 6 h. Excess voltiles were removed under reduced pressure, the residue was quenched with saturated $NaHCO_3$ solution (10 mL), diluted with water (10 mL) and extracted with ethyl acatate (3x20 mL). The combined organic layers were washed with brine (20 mL) and water (20 ml), dried over anhydrous sodium sulphate, filtered and the filtrate was concentrated under reduced pressure to get the crude product, which was purified by chiral prep-HPLC (column: XBridge C8 (19 x 250 mm) 5 µm; 0.1% formnic acid in water/(MeCN/MeOH 1:1) as eluent) to afford the title compounds as two fractions of two stereoisomers each. First eluting fraction: 9 mg, 2%, over 3 steps; second eluting fraction: 7 mg, 5%.

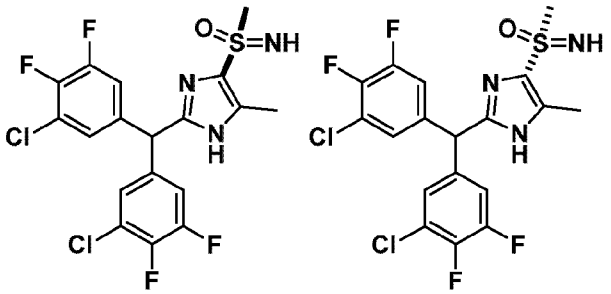
First eluting fraction from chiral HPLC: 135a: LCMS m/z = 435 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 11.97 (bs, 1H) ,7.59 (t, 1H), 7.43 (dd, 1H), 7.24 (dd, 1H), 7.09–7.01 (m, 2H), 6.83–6.75 (m, 2H), 3.97 (d, 1H), 3.88 (d, 1H), 3.71–3.67 (m, 1H), 3.08 (s, 3H), 2.90–2.80 (m, 2H), 2.48-2.46 (m, 1H), 2.35 (s, 3H). Chiral SFC: column:

Chiralpak IK (4.6 x 150 mm) 5 µm; co-solvent: iPrOH, flow: 3 mL/min; % of co-solvent: 15%; ABPR: 1500 psi T: 30 °C; (135a) Rt = 4.64 min (first eluting).

Second eluting fraction from chiral HPLC: 135b: LCMS m/z = 435 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 10.95 (bs, 1H) ,7.57 (t, 1H), 7.38 (dd, 1H), 7.17 (dd, 1H), 7.09–7.04 (m, 1H), 6.96 (d, 1H), 6.81– 6.74 (m, 2H), 4.11 (d, 1H), 3.95 (d, 1H), 3.79 –3.84 (m, 1H), 3.09 (s, 3H), 2.94–2.85 (m, 1H), 2.52–2.41 (m, 2H), 2.36 (s, 3H); Chiral SFC: column: Chiralpak IK (4.6 x 150 mm) 5 µm; co-solvent: iPrOH, flow: 3 mL/min; % of co-solvent: 15%; ABPR: 1500 psi T: 30 °C; (135b) Rt = 6.22 min (second eluting).

Example 141

(2-(bis(3-chloro-4,5-difluorophenyl)methyl)-5-methyl-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone



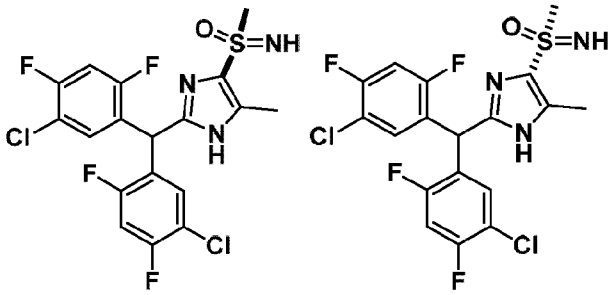
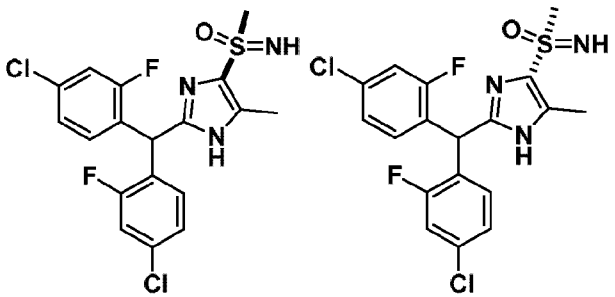
Step 1: To a stirred solution of 2-(bis(3-chloro-4,5-difluorophenyl)methyl)-5-methyl-4-(methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole (intermediate 31, mixture of regioisomers, 0.5 g, 0.883 mmol) in MeOH (10 mL) were added $(NH_4)_2CO_3$ (0.254 g, 2.648 mmol) and diacetoxyiodobenzene (0.853 g, 2.648 mmol). The reaction mixture was stirred at room temperature for 16 h. Thee reaction mixture was concentrated under reduced pressure to get the crude product, which was purified by column chromatography (SiO_2, 0-40% EtOAc/Hex) to afford {2-[bis(3-chloro-4,5-difluorophenyl)methyl]-5-methyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazol-4-yl}(imino)methyl-λ^6-sulfanone and the corresponding SEM regioisomer (0.32 g, 60%). LCMS m/z = 596 $[M+H]^+$.

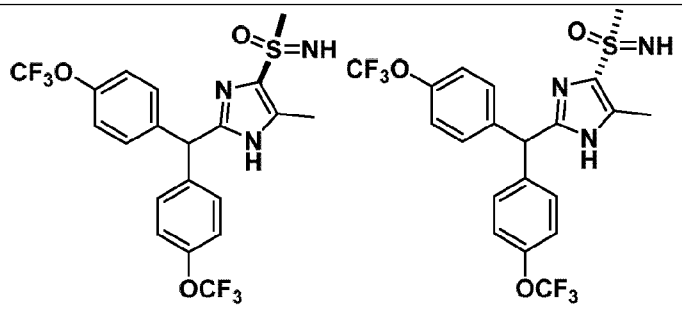
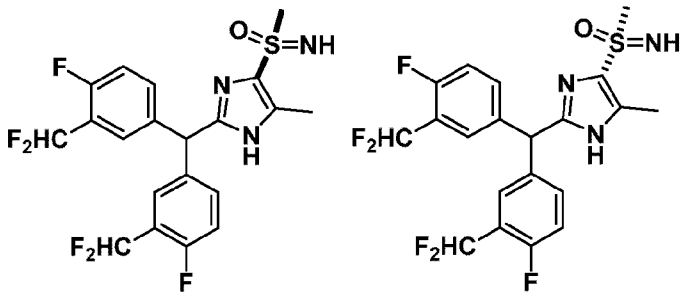
Step 2: To a stirred solution of {2-[bis(3-chloro-4,5-difluorophenyl)methyl]-5-methyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazol-4-yl}(imino)methyl-λ^6-sulfanone (mixture of regioisomers, 0.29 g, 0.485 mmol) in DCM (7.0 mL) was added TFA (0.744 mL, 9.706 mmol) at 0 °C and the mixture was then stirred at rom temperature for 2 h. The reaction mixture was poured into ice cold $NaHCO_3$ solution and extracted with DCM (2 × 50 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4 solution, filtered and concentrated under reduced pressure to get the crude product, which was purified by prep-HPLC to afford 2-[bis(3-chloro-4,5-difluorophenyl)methyl]-4-[imino(methane)sulfinyl]-5-methyl-1H-imidazole (0.075 g, 33%).

LCMS m/z = 466 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.38 (s, 1H), 7.45-7.50 (m, 4H), 5.63 (s, 1H), 3.93 (s, 1H), 2.99 (s, 3H), 2.37 (s, 3H). Chiral HPLC: column: Chiralpak IC (4.6 x 250 mm) 5 µm, mobile phase: Hexane/EtOH/$iPrNH_2$ 80/20/0.1, flow rate: 1.0 mL/min; 141a: Rt = 7.56 min (first eluting), 141b: Rt = 9.30 min (second eluting).

Example 142-145, 185.

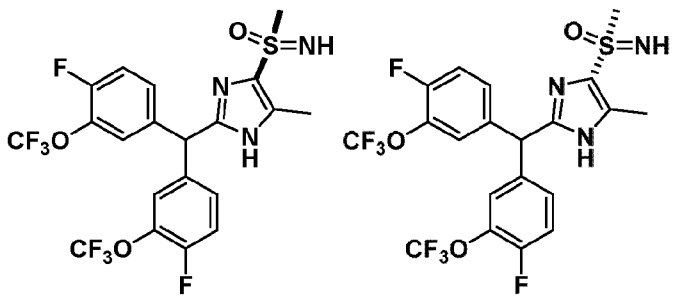
The title compounds were prepared from the appropriate intermediates and reagents using an analogous method to that described for example 141.

Example	Name/Structure/Data
142a, 142b	(2-(bis(5-chloro-2,4-difluorophenyl)methyl)-5-methyl-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone  LCMS m/z = 466 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.49 (s, 1H), 7.60 (t, 2H), 7.45-7.40 (m, 2H), 5.90 (s, 1H), 3.94 (s, 1H), 2.96 (s, 3H), 2.38 (s, 3H). Chiral SFC: column: Chiralpak IC (4.6 x 250 mm) 5 µm; co-solvent: 0.3% $iPrNH_2$ in iPrOH, flow: 3 mL/min; % of co-solvent: 40%; ABPR: 100 bar; T: 35 °C; (142a) Rt = 2.08 min (first eluting), (142b) Rt = 2.99 min (second eluting).
143a, 143b	(2-(bis(4-chloro-2-fluorophenyl)methyl)-5-methyl-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone  LCMS m/z = 430 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.48 (s, 1H), 7.46 (d, 2H), 7.30 (d, 2H), 7.18 (q, 2H), 5.89 (s, 1H), 3.87 (s, 1H), 2.95 (s, 3H), 2.37 (s, 3H). Chiral HPLC: column: Chiralpak IC (4.6 x 250 mm) 5 µm, mobile phase: Hexane/EtOH/$iPrNH_2$ 70/30/0.1, flow rate: 1.0 mL/min; 143a: Rt = 6.62 min (first eluting), 143b: Rt = 8.45 min (second eluting).
145a, 145b	(2-(bis(4-(trifluoromethoxy)phenyl)methyl)-5-methyl-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone

	 LCMS m/z = 494 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.40 (s, 1H), 7.43 (d, 4H), 7.35 (d, 4H), 5.65 (s, 1H), 3.86 (s, 1H), 2.98 (s, 3H), 2.37 (s, 3H). Chiral SFC: column: Chiralpak IC (4.6 x 250 mm) 5 µm; co-solvent: 0.3% $iPrNH_2$ in iPrOH, flow: 3 mL/min; % of co-solvent: 30%; ABPR: 100 bar; T: 35 °C; (145a) Rt = 1.65 min (first eluting), (145b) Rt = 2.03 min (second eluting).
185a, 185b	(2-(bis(3-(difluoromethyl)-4-fluorophenyl)methyl)-5-methyl-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone  LCMS m/z = 462 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.1 (s, 1H), 7.60-7.51 (m, 4H), 7.38-7.05 (m, 4H), 5.74 (s, 1H), 3.87 (s, 1H), 2.97 (s, 3H), 2.31 (s, 3H). Chiral SFC: column: Chiralpak IC (4.6 x 250 mm) 5 µm; co-solvent: 0.3% $iPrNH_2$ in iPrOH, flow: 3 mL/min; % of co-solvent: 40%; ABPR: 100 bar; T: 35 °C; (185a) Rt = 1.64 min (first eluting), (185b) Rt = 2.04 min (second eluting).

Example 147

(2-(bis(4-fluoro-3-(trifluoromethoxy)phenyl)methyl)-5-methyl-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone



Step 1: To a stirred solution of 2-(bis(3-fluoro-4-(trifluoromethoxy)phenyl)methyl)-5-methyl-4-(methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole (intermediate 34, mixture of regioisomers, 1 g, 1.59 mmol) in

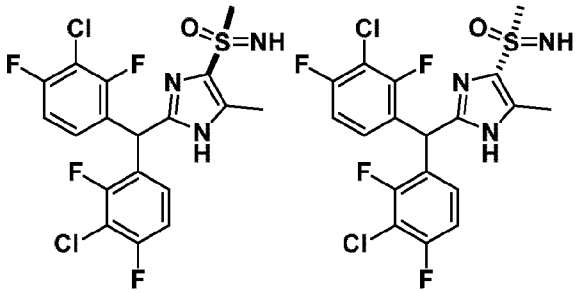
MeOH (18 mL) were added diacetoxyiodobenzene (1.5 g, 4.77 mmol) and ammonium carbonate (0.5 g, 4.77 mmol) at room temperature. The resulting solution was stirred at room temperature for 3 h. The reaction mixture was diluted with ethyl acetate (60 mL), washed with water (30 mL) and brine (20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography (SiO_2, 40% EtOAc/Hex) to afford (2-(bis(3-fluoro-4-(trifluoromethoxy)phenyl)methyl)-5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone and the corresponding SEM regioisomer. Yield: 57% (0.6 g). LCMS m/z = 660 $[M+H]^+$.

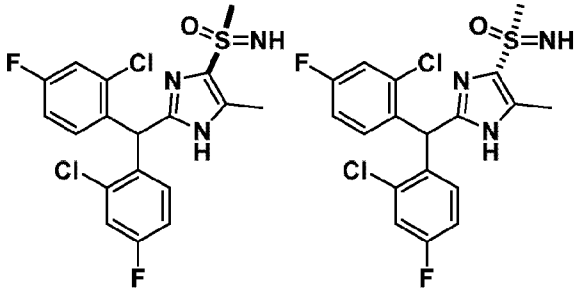
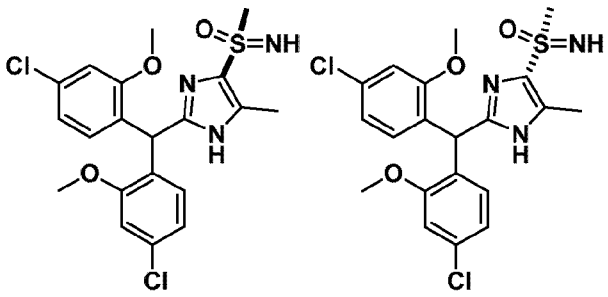
Step 2: To a stirred solution of (2-(bis(3-fluoro-4-(trifluoromethoxy)phenyl)methyl)-5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone (mixture of regioisomers, 500 mg, 0.76 mmol) in DCM (5 mL) was added 4 M HCl in dioxane (10 mL) at 0 °C. The resulting solution was stirred at room temperature for 5 h. The reaction mixture was concentrated, the obtained residue was diluted with water (20 mL), basified using aqueous $NaHCO_3$ solution and extracted with ethylacetate (2 × 30 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude compound, which was purified by reverse phase prep-HPLC to afford the title compound. Yield: 51% (210 mg).

LCMS m/z = 530 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.43 (bs, 1H), 7.58-7.54 (m, 2H), 7.51-7.48 (m, 2H), 7.30-7.28 (m, 2H), 5.71 (s, 1H), 3.89 (m, 1H), 2.99 (s, 3H), 2.37 (s, 3H). Chiral SFC: column: Chiralpak IC (4.6 x 250 mm) 5 µm; co-solvent: 0.3% $iPrNH_2$ in iPrOH, flow: 3 mL/min; % of co-solvent: 40%; ABPR: 100 bar; T: 35 °C; (147a) Rt = 2.44 min (first eluting), (147b) Rt = 3.39 min (second eluting).

Example 140, 144, 186.

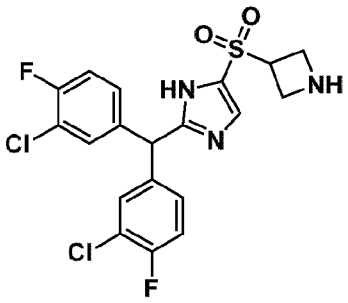
The title compounds were prepared from the appropriate intermediates and reagents using an analogous method to that described for example 147.

Example	Name/Structure/Data
140a, 140b	(2-(bis(3-chloro-2,4-difluorophenyl)methyl)-5-methyl-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone  LCMS m/z = 466 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.49 (bs, 1H), 7.36-7.22 (m, 4H), 5.98 (s, 1H), 3.90 (s, 1H), 2.96 (s, 3H), 2.38 (s, 3H). Chiral SFC: column: Chiralpak IC (4.6 x 250 mm) 5 µm; co-solvent: 0.3% $iPrNH_2$ in iPrOH, flow: 3 mL/min; % of co-solvent: 40%; ABPR: 100 bar; T: 35 °C; (140a) Rt = 2.13 min (first eluting), (140b) Rt = 3.08 min (second eluting).

144a, 144b	(2-(bis(2-chloro-4-fluorophenyl)methyl)-5-methyl-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone  LCMS m/z = 430 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.54 (bs, 1H), 7.52-7.49 (m, 2H), 7.24-7.20 (m, 2H), 7.01-6.95 (m, 2H), 6.03 (s, 1H), 3.87 (m, 1H), 2.94 (s, 3H), 2.37 (s, 3H). Chiral SFC: column: Chiralpak IC (4.6 x 250 mm) 5 µm; co-solvent: 0.3% $iPrNH_2$ in iPrOH, flow: 3 mL/min; % of co-solvent: 40%; ABPR: 100 bar; T: 35 °C; (144a) Rt = 2.53 min (first eluting), (144b) Rt = 3.79 min (second eluting).
186a, 186b	(2-(bis(4-chloro-2-methoxyphenyl)methyl)-5-methyl-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone  LCMS m/z = 454 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.23 (bs, 1H), 7.06 (s, 2H), 6.95-6.94 (m, 2H), 6.87-6.84 (m, 2H), 5.93 (s, 1H), 3.78 (m, 1H), 3.73 (s, 6H), 2.92 (s, 3H), 2.34 (s, 3H). Chiral SFC: column: Chiralpak IC (4.6 x 250 mm) 5 µm; co-solvent: 0.3% $iPrNH_2$ in iPrOH, flow: 3 mL/min; % of co-solvent: 40%; ABPR: 100 bar; T: 35 °C; (186a) Rt = 2.25 min (first eluting), (186b) Rt = 2.66 min (second eluting).

Example 181

4-(azetidin-3-ylsulfonyl)-2-[bis(3-chloro-4-fluorophenyl)methyl]-1*H*-imidazole



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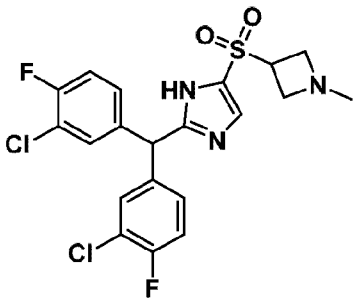
Step 1: To a stirred solution of 2-(bis(3-chloro-4-fluorophenyl) methyl)-4-iodo-1H-imidazole (intermediate 4, 0.4 g, 0.86 mmol) in 1,4-dioxane (12 mL) was added tert-butyl 3-mercaptoazetidine-1-carboxylatetert-butyl 3-mercaptoazetidine-1-carboxylate (0.196 g, 1.032 mmol) and the mixture was degassed with argon gas for 10 min. $Pd_2(dba)_3$(0.08 g, 0.086 mmol), Xantphos (0.1 g, 0.172 mmol) and DIPEA (0.45 mL, 2.58 mmol) were added and the reaction mixture was heated for 16 h at 100 °C in a sealed tube. The reaction mixture was diluted with water (15 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure. The crude material was purified by column chromatography (SiO_2, 0-40% EtOAc/Hex) to obtain tert-butyl 3-({2-[bis(3-chloro-4-fluorophenyl) methyl]-1H-imidazol-4-yl}sulfanyl)azetidine-1-carboxylate (0.24 g, 53%). LCMS m/z = 526 $[M+H]^+$.

Step 2: To a solution of tert-butyl 3-({2-[bis(3-chloro-4-fluorophenyl) methyl]-1H-imidazol-4-yl}sulfanyl)azetidine-1-carboxylate (0.31 g, 0.589 mmol) in DCM (15.0 mL) was added m-CPBA (70% in water; 0.435 g, 1.767 mmol) at 0 °C and the mixture was stirred at room temperature for 5 h. The reaction mixture was cooled to 0 °C and quenched with an aqueous solution of sodium sulfite and sodium bicarbonate (1:1). The aqueous layer was extracted with ethyl acetate (3 × 60 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, 0-50% EtOAc/Hex) to yield (3-{2-[bis(3-chloro-4-fluorophenyl)methyl]-1H-imidazole-4-sulfonyl}azetidin-1-yl) tert-butyl formate (0.15 g, 45%). LCMS m/z = 502 $[M+H]^+$.

Step 3: To a stirred solution of (3-{2-[bis(3-chloro-4-fluorophenyl)methyl]-1H-imidazole-4-sulfonyl}azetidin-1-yl) tert-butyl formate (0.15 g, 0.269 mmol) was added TFA (0.21 mL, 2.686 mmol) in DCM (10.0 mL) at 0 °C and the mixture was then stirred at room temperature for 16 h. The reaction mixture was neutralized with bicarbonate solution and extracted with ethyl acetate (2 x 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by reverse phase prep HPLC to obtain the title compound (0.024 g, 19%). LCMS m/z = 458 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): 7.85 (s, 1H), 7.49-7.47 (m, 2H), 7.38-7.28 (m, 4H), 5.68 (s, 1H), 4.33-4.29 (m, 1H), 3.78-3.74 (m, 2H), 3.60-3.56 (m, 2H).

Example 182

2-[bis(3-chloro-4-fluorophenyl)methyl]-4-(1-methylazetidin-3-yl)sulfonyl-1*H*-imidazole

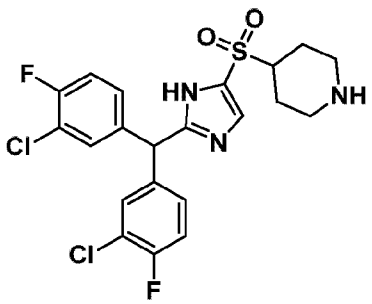


Step 1: To a stirred solution of 4-(azetidin-3-ylsulfonyl)-2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazole (example 181, 0.17 g, 0.371 mmol) in methanol (10 mL) was added formaldehyde (37 %, 0.07 mL, 1.855 mmol) followed by addition of sodium cyanoborohydride (0.07 g, 1.113 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 hours, quenched with a saturated aqueous solution of ammonium chloride and then

extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reveres phase prep HPLC to obtain the title compound (0.045 g, 26%). LCMS m/z = 472 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): 13.01 (bs, 1H), 7.94 (s, 1H), 7.53-7.52 (m, 2H), 7.42-7.37 (m, 2H), 7.31-7.30 (m, 2H), 5.73 (s, 1H), 4.18-4.14 (m, 1H), 3.53-3.49 (m, 2H), 3.44-3.42 (m, 2H), 2.19 (s, 3H).

Example 183

4-[[2-[bis(3-chloro-4-fluorophenyl)methyl]-1*H*-imidazol-4-yl]sulfonyl]piperidine



Step 1: To the stirred solution of 2-[bis(3-chloro-4-fluorophenyl)methyl]-4-iodo-1H-imidazole (intermediate 4, 1.0 g, 2.15 mmol) in dioxane (30 mL) was added tert-butyl 4-sulfanylpiperidine-1-carboxylate (0.6 g, 2.58 mmol) and the mixture was degassed with argon gas for 10 min. To the mixture $Pd_2(dba)_3$ (0.2 g, 0.21 mmol), Xantphos (0.3 g, 0.43 mmol) and DIPEA (1.1 mL, 6.45 mmol) were added and the mixture was heated at 100 °C in a sealed tube for 16 h. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (3 × 150 mL). The combined organic layers were washed with brine (50 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure. The obtained crude was purified by column chromatography (SiO_2, 0-100% EtOAc/Hex)) to get tert-butyl 4-({2-[bis(3-chloro-4-fluorophenyl)methyl]-1H-imidazol-4-yl}sulfanyl)piperidine-1-carboxylate (1.0 g, 83%). LCMS m/z = 554 $[M+H]^+$.

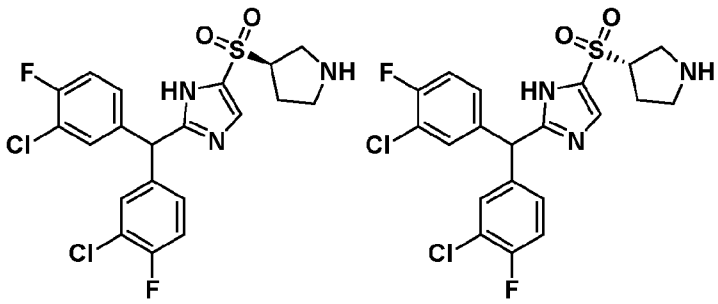
Step 2: To a solution of tert-butyl 4-({2-[bis(3-chloro-4-fluorophenyl)methyl]-1H-imidazol-4-yl}sulfanyl)piperidine-1-carboxylate (1.0 g, 1.8 mmol) in DCM (50.0 mL) was added m-CPBA (77%, 1.3 g, 5.41 mmol) at 0 °C and the reaction mixture was stirred at 0 °C for 3 h. The reaction mixture was quenched with a mixture of sodium sulfite and sodium bicarbonate (1:1) at 0 °C. The aqueous layer was extracted with ethyl acetate (3 × 200 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified through column chromatography (SiO_2, 0-100% EtOAc/Hex) to get tert-butyl 4-({2-[bis(3-chloro-4-fluorophenyl)methyl]-1H-imidazol-4-yl}sulfonyl)piperidine-1-carboxylate (0.7 g, 66%). LCMS m/z = 586 $[M+H]^+$.

Step3: To a stirred solution of tert-butyl 4-({2-[bis(3-chloro-4-fluorophenyl)methyl]-1H-imidazol-4-yl}sulfonyl)piperidine-1-carboxylate (0.2 g, 0.34 mmol) in DCM (10 mL) was added 4M HCl in dioxane (5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then concentrated under reduced pressure. The residue was basified with saturated $NaHCO_3$ solution and was extracted with ethyl acetate (3 × 80 mL). The combined organic layers were washed with cold brine and dried over Na_2SO_4. The organic layer was concentrated under reduced pressure to get the crude product which was purified by reveres phase prep HPLC to obtain the title compound (0.048 g, 29%). LCMS m/z = 486 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): 7.80 (s, 1H), 7.55-7.53

(m, 2H), 7.41-7.30 (m, 4H), 5.70 (s, 1H), 3.14-3.11 (m, 1H), 3.00-2.97 (m, 2H), 2.44-2.41 (m, 2H), 1.78-1.75 (m, 2H), 1.42-1.38 (m, 2H).

Example 184

2-[bis(3-chloro-4-fluorophenyl)methyl]-4-pyrrolidin-3-ylsulfonyl-1*H*-imidazole



Step 1: In analogy to step 1 of example 183 2-[bis(3-chloro-4-fluorophenyl) methyl]-4-iodo-1H-imidazole (intermediate 4, 1.0 g, 2.15 mmol) in dioxane (10 mL) and tert-butyl 3-sulfanylpyrrolidine-1-carboxylate (0.525 g, 2.58 mmol) were reacted to yield tert-butyl 3-({2-[bis(3-chloro-4-fluorophenyl) methyl]-1H-imidazol-4-yl} sulfanyl) pyrrolidine-1-carboxylate (0.75 g, 64%). LCMS m/z = 540 $[M+H]^+$.

Step 2: To a solution of tert-butyl 3-({2-[bis(3-chloro-4-fluorophenyl) methyl]-1H-imidazol-4-yl} sulfanyl) pyrrolidine-1-carboxylate (0.6 g, 1.11 mmol) in DCM (20 mL) was added mCPBA (70% in water, 0.575 g, 3.33 mmol) at 0 °C and the reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched with a mixture of sodium sulfite and sodium bicarbonate (1:1) at 0 °C. The aqueous layer was extracted with ethyl acetate (2 × 200 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The resultant crude product was purified through column chromatography (SiO_2, 0-100% EtOAc/Hex) and then chiral SFC purification (column: Chiralpak IG (30 x 250 mm) 5 µm; co-solvent: Hex/MeOH/iPrOH (60/30/10), flow: 100 mL/min; % of co-solvent: 25%; ABPR: 100 bar; T: 35 °C) to yield the individual enantiomers of tert-butyl 3-({2-[bis(3-chloro-4-fluorophenyl)methyl]-1H-imidazol-4-yl}sulfonyl)pyrrolidine-1-carboxylate.

Step 3: To a stirred solution of tert-butyl-3-({2-[bis(3-chloro-4-fluorophenyl)methyl]-1H-imidazol-4-yl}sulfonyl)pyrrolidine-1-carboxylate (first eluting enantiomer from SFC, 0.13 g, 0.22 mmol) in DCM (10 mL) was added HCl in 1,4-dioxane (4M, 10 mL) at 0 °C and the mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, the crude material was quenched with $NaHCO_3$ solution (30 ml) and extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified through reverse phase prep HPLC to obtain the title compound as a single enantiomer (184b). Yield: 37% (0.04 g).

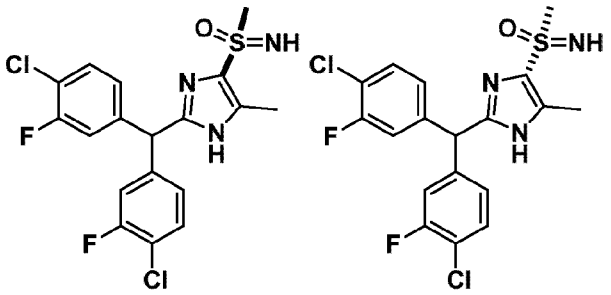
Example 184a was prepared in analogy to step 3 described above, using the second eluting enantiomer from SFC as described in step 2.

LCMS m/z = 472 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): 7.94 (s, 1H), 7.53-7.52 (m, 2H), 7.40-7.38 (m, 2H), 7.32-7.28 (m, 2H), 5.74 (s, 1H), 3.91 (bs, 1H), 3.24-3.22 (m, 2H), 2.94-2.89 (m, 2H), 2.17-2.14 (m, 1H), 2.07-2.05 (m, 1H). Chiral SFC: column: Chiralpak OX-H (4.6 x 250 mm) 5 µm; co-solvent: 0.3% $iPrNH_2$ in MeOH, flow: 3

mL/min; % of co-solvent: 40%; ABPR: 100 bar; T: 35 °C; (184a) Rt = 2.36 min (first eluting), (184b) Rt = 2.63 min (second eluting).

Example 187

(2-(bis(4-chloro-3-fluorophenyl)methyl)-5-methyl-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone



Step 1: To a solution of 2-[bis(4-chloro-3-fluorophenyl)methyl]-5-methyl-4-(methylsulfanyl)-1H-imidazole (intermediate 37, 1 g, 2.504 mmol) in DCM (20.0 mL) was added mCPBA (70% in water, 0.494 g, 2.004 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched with aq. sodium bicarbonate solution at 0 °C. The aqueous layer was extracted with ethyl acetate (100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to get the crude product, which was . Resulting crude was purified by column chromatography (SiO_2, 0-40% EtOAc/Hex) to yield 2-[bis(4-chloro-3-fluorophenyl)methyl]-4-methanesulfinyl-5-methyl-1H-imidazole (0.75 g, 72%). LCMS m/z = 415 $[M+H]^+$.

Step 2: Iodobenzene diacetate (0.39 g, 1.205 mmol) was added to a stirred suspension of 2-[bis(4-chloro-3-fluorophenyl)methyl]-4-methanesulfinyl-5-methyl-1H-imidazole (0.25 g, 0.602 mmol), magnesium oxide (0.105 g, 2.59 mmol), rhodium(II) acetate dimer (0.027g, 0.06 mmol) and 2,2,2-trifluoro acetamide (0.15 g, 1.325 mmol) in 1,4-dioxane (10.0 mL) at 40 °C. The reaction mixture was stirred at 40 °C for 6 h. The reaction mixture was concentrated under reduced pressure to get the crude compound which was purified by column chromatography (SiO_2, 0-60% EtOAc/Hex) to yield N-{2-[bis(4-chloro-3-fluorophenyl)methyl]-5-methyl-1H-imidazole-4-(methane)sulfinylidene}-2,2,2-trifluoroacetamide (0.2 g, 63%). LCMS m/z = 526 $[M+H]^+$.

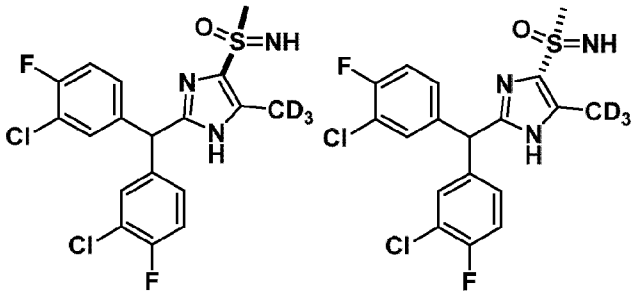
Step 3: To a stirred solution of N-{2-[bis(4-chloro-3-fluorophenyl)methyl]-5-methyl-1H-imidazole-4-(methane)sulfinylidene}-2,2,2-trifluoroacetamide (0.6 g, 1.14 mmol) in CH_3CN:MeOH (1:1, v/v) (10 mL) was added K_2CO_3 (0.315 g, 2.28 mmol) at room temperature. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated and diluted with ethyl acetate (50 ml). The organic layer was washed with water (20 ml) and brine (20 ml), dried over anhydrous sodium sulfate and concentrated under reduced pressure to get the crude compound which was purified by prep-HPLC to get the title compound (0.17 g, 35%).

The racemic compound was separeted in the individual enantiomers using chiral HPLC.

LCMS m/z = 430 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.38 (s, 1H), 7.56 (t, 2H), 7.37 (d, 2H), 7.18 (d, 2H), 5.64 (s, 1H) 3.89 (s, 1 H), 2.98 (s, 3H), 2.37 (s, 3H). Chiral HPLC: column: Chiralpak IC (4.6 x 250 mm) 5 µm, mobile phase: Hexane/EtOH/$iPrNH_2$ 70/30/0.1, flow rate: 1.0 mL/min; 187a: Rt = 6.39 min (first eluting), 187b: Rt = 7.64 min (second eluting).

Example 188

(2-(bis(3-chloro-4-fluorophenyl)methyl)-5-(methyl-d3)-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone



Step 1: A mixture of 2-[bis(3-chloro-4-fluorophenyl)methyl]-4-iodo-5-(methylsulfanyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazole (intermediate 41, mixture of regioisomers, 0.84 g, 1.31 mmol) in 1,4-dioxane (8.0 mL) and water (2.0 mL) was degassed with argon for 10 min. Then, methylboranediol-D_3 (0.824 g, 13.1 mmol), K_3PO_4 (0.556 g, 2.62 mmol) and Pd(dppf)Cl_2·DCM (0.107 g, 0.13 mmol) was added at room temperature. The reaction mixture was heated to 110 °C for 16 h in a sealed tube. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulphate and evaporated under reduced pressure to get the crude product, which was purified by column chromatography (SiO_2, 0-5% MeOH/DCM) to afford 2-[bis(3-chloro-4-fluorophenyl)methyl]-4-methyl-5-(methylsulfanyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazole and the corresponding SEM regioisomer (0.12 g, 17%). LCMS m/z = 532 $[M+H]^+$.

Step 2: To a stirred solution of 2-[bis(3-chloro-4-fluorophenyl)methyl]-4-methyl-5-(methylsulfanyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazole (mixture of regioisomers, 0.15 g, 0.282 mmol) in MeOH (5.0 mL) were added $(NH_4)_2CO_3$ (0.135 g, 1.40 mmol) and diacetoxyiodobenzene (0.45 g, 1.40 mmol). The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure to get the crude product, which was purified by column chromatography (SiO_2, 0-50% EtOAc/Hex) to afford 2-[bis(3-chloro-4-fluorophenyl)methyl]-5-[imino(methane)sulfinyl]-4-methyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazole and the corresponding SEM regioisomer (0.12 g, 75%). LCMS m/z = 563 $[M+H]^+$.

Step 3: To a stirred solution of 2-[bis(3-chloro-4-fluorophenyl)methyl]-5-[imino(methane)sulfinyl]-4-methyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazole (mixture of regioisomers, 0.4 g, 0.71 mmol) in DCM (5.0 mL) was added TFA (2.0 mL) at 0 °C and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was evaporated under reduced pressure, the residue was treated with $NaHCO_3$ solution (10 mL). The aqueous part was extracted with EtOAc (50 mL), the organic layer was washed with H_2O (2 × 10 mL) and brine (2 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get the crude product, which was purified by column chromatography (SiO_2, 0-60% EtOAc:EtOH (3:1)/Hex) to afford the racemic racemic title compound.

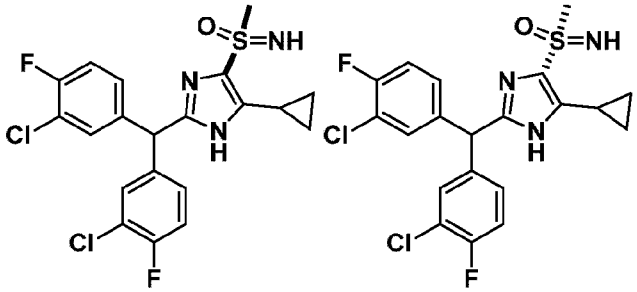
The racemic compound was separeted in the individual enantiomers using chiral SFC.

LCMS m/z = 433 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.38 (s, 1H), 7.53 (d, 2H), 7.39 (t, 2H), 7.33-7.30 (m, 2H), 5.62 (s, 1H), 3.89 (s, 1H), 2.97 (s, 3H). Chiral SFC: column: Chiralpak IC (4.6 x 250 mm) 5 µm; co-

solvent: 0.3% $iPrNH_2$ in MeOH, flow: 3 mL/min; % of co-solvent: 40%; ABPR: 100 bar; T: 35 °C; (188a) Rt = 1.72 min (first eluting), (188b) Rt = 1.88 min (second eluting).

Example 189

(2-(bis(3-chloro-4-fluorophenyl)methyl)-5-cyclopropyl-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone



Step 1: A solution of 2-(bis(3-chloro-4-fluorophenyl)methyl)-4-iodo-5-(methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole (intermediate 41, mixture of regioisomers, 500 mg, 0.78 mmol) in dioxane: water (10 mL) was degassed with nitrogen for 5 min followed by the addition of cyclopropylboronic acid (336 mg, 3.89 mmol), K_3PO_4 (500 mg, 2.34 mmol) and $PdCl_2(dppf)\cdot DCM$ (66 mg, 0.078 mmol) at room temperature. The resulting reaction mixture was heated to 100 °C for 16 h in a sealed tube. The reaction mixture was diluted with ethyl acetate (40 mL), washed with water (30 mL) and brine (20 mL). The organic layer was concentrated under reduced pressure to afford the crude product, which was purified by column chromatography (SiO_2, 10% EtOAc/Hex) to afford 2-(bis(3-chloro-4-fluorophenyl)methyl)-4-cyclopropyl-5-(methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole and the corresponding SEM regioisomer. Yield: 69% (300 mg). LCMS m/z = 555 $[M+H]^+$.

Step 2: To a stirred solution of 2-(bis(3-chloro-4-fluorophenyl)methyl)-4-cyclopropyl-5-(methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole (mixture of regioisomers, 700 mg, 1.26 mmol) in MeOH (18 mL) were added diacetoxyiodobenzene (1.2 g, 3.78 mmol) and ammonium carbonate (370 mg, 3.78 mmol) at room temperature. The resulting solution was stirred at room temperature for 3 h. The reaction mixture was diluted with ethyl acetate (40 mL), washed with water (30 mL) and brine (20 mL). The organic layer was concentrated under reduced pressure to afford (2-(bis(3-chloro-4-fluorophenyl)methyl)-4-cyclopropyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)(imino)(methyl)-l6-sulfanone and the corresponding SEM regioisomer. Yield: Crude (700 mg). LCMS m/z = 586 $[M+H]^+$.

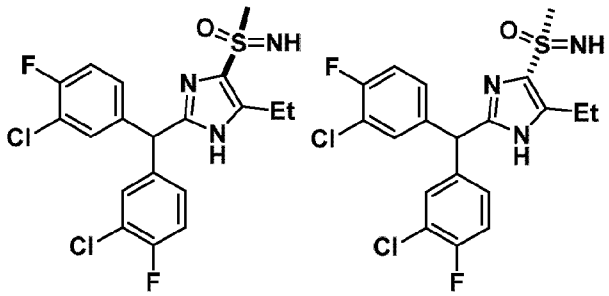
Step 3: To a stirred solution of (2-(bis(3-chloro-4-fluorophenyl)methyl)-4-cyclopropyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)(imino)(methyl)-l6-sulfanone (mixture of regioisomers, 700 mg, 1.19 mmol) in DCM (7 mL) was added 4 M HCl in 1,4-dioxane (14 mL) at 0 °C. The resulting solution was stirred at room temperature for 5 h. The reaction mixture was concentrated, the obtained residue was diluted with water (20 mL), basified using aqueous $NaHCO_3$ solution and extracted with ethylacetate (2 × 30 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude compound, which was purified by reverse phase Prep-HPLC to afford (2-(bis(3-chloro-4-fluorophenyl)methyl)-4-cyclopropyl-1H-imidazol-5-yl)(imino)(methyl)-l6-sulfanone. Yield: 21% over 2 steps (120 mg).

The recamic compound was separetad in the individual enantiomers using chiral SFC.

LCMS m/z = 456 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 11.82 (bs, 1H), 7.53 (m, 2H), 7.33 (m, 4H), 5.53 (s, 1H), 3.64 (m, 1H), 3.06 (s, 3H), 2.59 (m, 1H), 0.94 (m, 2H), 0.82 (m, 2H). Chiral SFC: column: Chiralpak IC (4.6 x 250 mm) 5 µm; co-solvent: 0.3% $iPrNH_2$ in iPrOH, flow: 3 mL/min; % of co-solvent: 40%; ABPR: 100 bar; T: 35 °C; (189a) Rt = 2.22 min (first eluting), (189b) Rt = 3.61 min (second eluting).

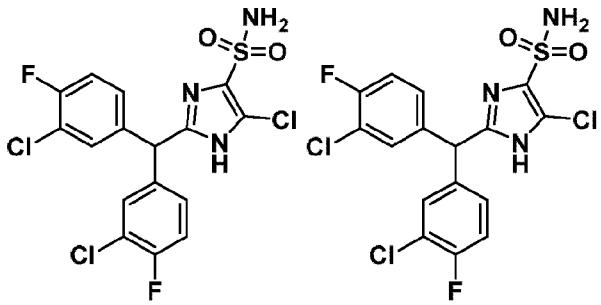
Example 190.

The title compound was prepared from the appropriate intermediates and reagents using an analogous method to that described for example 189.

Example	Name/Structure/Data
190a, 190b	(2-(bis(3-chloro-4-fluorophenyl)methyl)-5-ethyl-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone  LCMS m/z = 442 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.40 (bs, 1H), 7.56-7.54 (m, 2H), 7.42-7.34 (m, 4H), 5.62 (s, 1H), 3.91 (m, 1H), 2.99 (s, 3H), 2.88-2.82 (m, 2H), 1.15-1.11 (m, 3H). Chiral SFC: column: Chiralpak IC (4.6 x 250 mm) 5 µm; co-solvent: 0.3% $iPrNH_2$ in iPrOH, flow: 3 mL/min; % of co-solvent: 40%; ABPR: 1500 psi; T: 35 °C; (190a) Rt = 2.41 min (first eluting), (190b) Rt = 3.13 min (second eluting).

Example 191

2-(bis(3-chloro-4-fluorophenyl)methyl)-5-chloro-1H-imidazole-4-sulfonamide



Step 1: To a solution of 2-[bis(3-chloro-4-fluorophenyl)methyl]-5-chloro-4-iodo-1H-imidazole (intermediate 19, 0.5 g, 1.002 mmol) in 1,4-dioxane (10.0 mL) was added DIPEA (0.52 mL, 3.006 mmol) at room temperature. The reaction mixture was degassed with argon for 10 min, followed by the addition of (4-methoxyphenyl)methanethiol (0.42 mL, 3.006 mmol), Xantphos (0.06 g, 0.1 mmol) and $Pd_2(dba)_3$ (0.05 g, 0.05 mmol) at room temperature. The

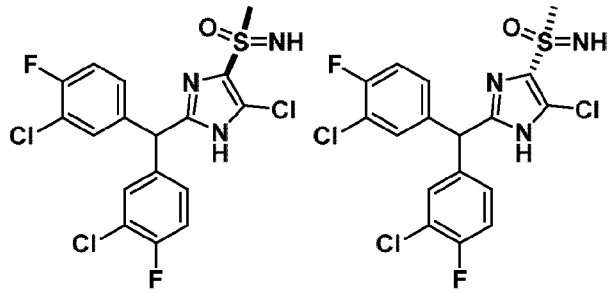
reaction mixture was heated to 110 °C for 16 h in a sealed tube. The reaction mixture was cooled to room temperature and filtered through a celide bed. The filtrate was evaporated under reduced pressure to get the crude product, which was purified by column chromatography (SiO_2, 0-50% acetone/Hex) to afford 2-(bis(3-chloro-4-fluorophenyl)methyl)-5-chloro-4-((4-methoxybenzyl)thio)-1H-imidazole. Yield: 72% (0.38 g). LCMS m/z =525 $[M+H]^+$.

Step 2: To a solution of 2-(bis(3-chloro-4-fluorophenyl)methyl)-5-chloro-4-((4-methoxybenzyl)thio)-1H-imidazole (0.3 g, 0.573 mmol) in MeCN (10.0 mL) were added H_2O (1.5 mL), AcOH (1.5 mL) and DCDMH (0.225 g, 1.145 mmol) at 0 °C. The reaction was stirred at 0 °C for 3 h. The reaction mixture was quenched with $NaHCO_3$ solution and extracted with EtOAc. The combined organic layers were washed with water, brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure to get the crude intermediate. The residue was dissolved in THF (10.0 mL) and 25% aq NH_3 (0.5 mL) was added to the reaction mixture. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was evaporated under reduced pressure to get the crude product, which was purified by prep HPLC to afford the title compound. Yield: 6% (0.015 g).

LCMS m/z = 452 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 13.48 (bs, 1H), 7.62 (bs, 2H), 7.51 (d, 2H), 7.39 (t, 2H), 7.33-7.30 (m, 2H), 5.62 (s, 1H).

Example 192

(2-(bis(3-chloro-4-fluorophenyl)methyl)-5-chloro-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone



Step 1: To a solution of 2-[bis(3-chloro-4-fluorophenyl)methyl]-4-chloro-5-iodo-1H-imidazole (intermediate 19, 1.4 g, 2.8 mmol) in 1,4-dioxane (60.0 mL) was added NaSMe (0.393 g, 5.611 mmol) at room temperature. The mixture was degassed with argon for 10 min followed by the addition of Xantphos (0.243 g, 0.421 mmol) and $Pd_2(dba)_3$ (0.257 g, 0.281 mmol) at room temperature. The reaction mixture was heated to 110 °C for 16 h in a sealed tube. The reaction mixture was cooled to room temperature and diluted with ice water. The aqueous part was extracted with ethyl acetate (3 × 80 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to get the crude product, which was purified by column chromatography (SiO_2, 0-50% EtOAc/Hex) to yield 2-[bis(3-chloro-4-fluorophenyl)methyl]-4-chloro-5-(methylsulfanyl)-1H-imidazole. Yield: 59% (0.7 g). LCMS m/z = 419 $[M+H]^+$.

Step 2: To a solution of 2-[bis(3-chloro-4-fluorophenyl)methyl]-4-chloro-5-(methylsulfanyl)-1H-imidazole (0.6 g, 1.439 mmol) in DMF (10.0 mL) was added NaH (60% in mineral oil, 0.087 g, 2.15 mmol) at 0 °C and the mixture was stirred for 15 min. Then SEM-Cl (0.383 mL, 2.15 mmol, 1.5 equiv.) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with ice water and extracted with EA (2 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over sodium sulfate

and evaporated under reduced pressured to get the crude product, which was purified by column chromatography (SiO_2, 0-50% EtOAc/Hex) to yield 2-[bis(3-chloro-4-fluorophenyl)methyl]-4-chloro-5-(methylsulfanyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazole and the corresponding SEM regioisomer. Yield: 59% (0.47 g).

Step 3: To a stirred solution of 2-(bis(3-chloro-4-fluorophenyl)methyl)-4-chloro-5-(methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole (mixture of regioisomers, 0.6 g, 1.09 mmol) in MeOH (15.0 mL) were added diacetoxyiodobenzene (1.75 g, 5.45 mmol) and ammonium carbonate (0.53 g, 5.45 mmol) at room temperature. The reaction mixture was diluted with EtOAc (100 mL). The mixture was diluted with ice water and extracted with EA (2 × 100 mL). The combined organic part was washed with cold brine and dried over Na_2SO_4. The organic layer was concentrated under reduced pressure to get the crude product, which was purified by column chromatography (SiO_2, 0-100% EtOAc/Hex) to get (2-(bis(3-chloro-4-fluorophenyl)methyl)-4-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)(imino)(methyl)-l6-sulfanone and the corresponding SEM regioisomer. Yield: 58% (0.370 g, 0.63 mmol). LCMS m/z = 580 $[M+H]^+$.

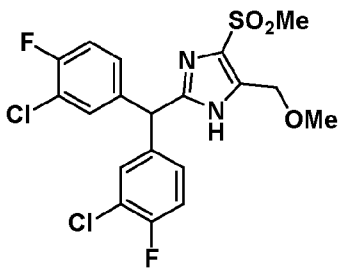
Step 4: To a stirred solution of {2-[bis(3-chloro-4-fluorophenyl)methyl]-4-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazol-5-yl}(imino)methyl-λ^6-sulfanone (mixture of regioisomers, 0.4 g, 0.688 mmol) in ethyl acetate (10.0 mL) was added 4M HCl in dioxane (12.0 mL) at room temperature. The reaction mixture was stirred at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure to obtain a residue, which was diluted with water and neutralized with $NaHCO_3$ solution. The aqueous part was extacted with ethyl acetate. The combined organic layers were washed with cold brine, dried over Na_2SO_4 and concentrated under reduced pressure to get the crude product, which was purified by column chromatography (SiO_2, 0-100% EtOAc/Hex) to yield the racemic title compound.

The racemic compound was separetad in the individual enantiomers using chiral SFC.

Yield: 192a = 15% (0.047 g), 192b = 9% (0.029 g). LCMS m/z = 450 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 13.42 (s, 1H), 7.55-7.52 (m, 2H), 7.42-7.34 (m, 4H), 5.64 (s, 1H), 4.74 (s, 1H), 3.12 (s, 3H). Chiral SFC: column: Chiralcel OX-H (4.6 x 250 mm) 5 µm; co-solvent: 0.3% $iPrNH_2$ in MeCN/iPrOH (1:1), flow: 3 mL/min; % of co-solvent: 40%; ABPR: 1000 psi; T: 35 °C; (192a) Rt = 1.67 min (first eluting), (192b) Rt = 2.25 min (second eluting).

Example 193

2-(bis(3-chloro-4-fluorophenyl)methyl)-5-(methoxymethyl)-4-(methylsulfonyl)-1H-imidazole



Step 1: To a solution of 2-[bis(3-chloro-4-fluorophenyl)methyl]-4-iodo-5-methanesulfonyl-1H-imidazole (intermediate 13, 0.4 g, 0.737 mmol) in DCM (15 mL) was added DIPEA (0.5 g, 2.94 mmol) at room temperature and the mixture was stirred for 15 min. Then SEM-Cl (0.4 mL, 2.21 mmol) was added dropwise to reaction mixture.

The reaction mixture was stirred at 40 °C for 16 h. The reaction mixture was diluted with ice water and extracted with ethyl acetate (2 × 100 mL). The comined organic layers were washed with brine (50 mL), dried over sodium sulfate and evaporated under reduced pressure to get the crude compound, which was purified by column chromatography (SiO_2, 0-50% EtOAc/Hex) to yield 2-[bis(3-chloro-4-fluorophenyl)methyl]-4-iodo-5-methanesulfonyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazole and the corresponding SEM regioisomer. Yield: 54% (0.27 g)

Step 2: To a solution of 2-[bis(3-chloro-4-fluorophenyl)methyl]-5-iodo-4-methanesulfonyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazole (mixture of regioisomers, 0.3 g, 0.445 mmol) in 1,4-dioxane-H_2O (20 mL) were added K_2CO_3 (0.123 g, 0.891 mmol) and potassium vinyltrifluoroborate (0.120 g, 0.891 mmol) at room temperature. The reaction mixture was degassed with argon for 10 minutes. Then $PdCl_2$(dppf) (0.033 g, 0.045 mmol) was added and the mixture was heated to 110 °C for 16 h in a sealed tube. The mixture was cooled down to room temperature. The reaction mixture was extracted with ethyl acetate (2 × 100 mL). The Combined organic layerS were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to get crude product, which was purified by column chromatography (SiO_2, 0-60% EtOAc/Hex) to yield 2-[bis(3-chloro-4-fluorophenyl)methyl]-5-ethenyl-4-methanesulfonyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazole and the corresponding SEM regioisomer. Yield: 39% (0.12 g). LCMS m/z = 573 $[M+H]^+$.

Step 3: To a stirred solution of 2-[bis(3-chloro-4-fluorophenyl)methyl]-5-ethenyl-4-methanesulfonyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazole (mixture of regioisomers, 0.8 g, 1.39 mmol) in dioxane (15 mL) and H_2O (5 mL) were added 0.16 M OsO_4 in H_2O (0.3 mL, 0.042 mmol) and NMO (50%, 0.360 g, 1.53 mmol) at room temperature. The reaction was stirred at room temperature for 16 h. Then $NaIO_4$ (3.0 g, 13.94 mmol) was added to the reaction mixture and the mixtue was stirred at room temperature for 1 h. The reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (3×100 mL). The combined organic layers were dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to get crude product, which was purified by column chromatography (SiO_2, 0-70% EtOAc/Hex) to get 2-[bis(3-chloro-4-fluorophenyl)methyl]-4-methanesulfonyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazole-5-carbaldehyde and the corresponding SEM regioisomer. Yield: 49% (0.400 g).

Step 4: To a stirred solution of 2-[bis(3-chloro-4-fluorophenyl)methyl]-4-methanesulfonyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazole-5-carbaldehyde (mixture of regioisomers, 0.45 g, 0.782 mmol) in MeOH (8 mL) was added $NaBH_4$ (0.149 g, 3.909 mmol) portionwise at 0 °C. The reaction mixture was stirred at room temperature for 4 h. The reaction mixture was cooled to 0 °C and diluted with water. The aqueous part was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine and dried over anhyd. Na_2SO_4. The organic layer was concentrated under reduced pressure to get the crude product, which was purified by column chromatography (SiO_2, 0-70% EtOAc/Hex) to get {2-[bis(3-chloro-4-fluorophenyl)methyl]-4-methanesulfonyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazol-5-yl}methanol and the corresponding SEM regioisomer. Yield: 55% (0.25 g).

Step 5: To a solution of {2-[bis(3-chloro-4-fluorophenyl)methyl]-4-methanesulfonyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazol-5-yl}methanol (mixture of regioisomers, 0.13 g, 0.225 mmol) in THF (2.0 mL) were added Ag_2O (0.107 g, 0.45 mmol) and MeI (4.0 mL) at room temperature. The reaction mixture was heated to 50 °C for 16 h in a sealed vial. The reaction mixture was diluted with ethyl acetate and filtered through a celite bed. The filtrate was evaporated under reduced pressure, the obtained residue was purified by column chromatography

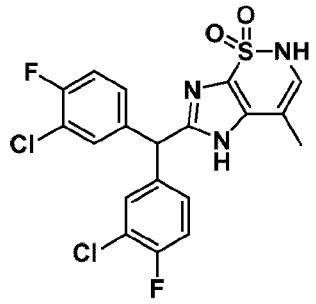
(SiO_2, 0-50% EtOAc/Hex) to get 2-[bis(3-chloro-4-fluorophenyl)methyl]-4-methanesulfonyl-5-(methoxymethyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazole and the corresponding SEM regioisomer. Yield: 52% (0.07 g). LCMS m/z = 591 $[M+H]^+$.

Step 6: A solution of 2-[bis(3-chloro-4-fluorophenyl)methyl]-4-methanesulfonyl-5-(methoxymethyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazole (mixture of regioisomers, 0.1 g, 0.169 mmol) in acetic acid (0.5 mL) and H_2O (0.2 mL) was heated to 50 °C for 4 h. The reaction mixture was diluted with water and neutralized with aq. $NaHCO_3$ solution. The aqueous part was extacted with ethyl acetate (2 x 20 mL). The combined organic laxers were washed with cold brine, dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by reverse phase prep HPLC to get the title compound. Yield: 37% (0.029 g).

LCMS m/z = 461 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 13.03 (s, 1H), 7.54 (m, 2H), 7.42-7.38 (m, 2H), 7.33 (s, 2H), 5.69 (s, 1H), 4.60 (s, 2 H), 3.32-3.27 (m, 3H), 3.11 (s, 3H).

Example 194

6-(bis(3-chloro-4-fluorophenyl)methyl)-4-methyl-2,5-dihydroimidazo[4,5-e][1,2]thiazine 1,1-dioxide



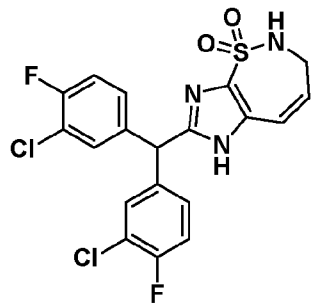
Step 1: To a solution of 2-[bis(3-chloro-4-fluorophenyl)methyl]-5-iodo-4-{[(4-methoxyphenyl)methyl]sulfanyl}-1H-imidazole (intermediate 42, 1.0 g, 1.62 mmol) in MeCN (10.0 mL), AcOH (0.8 mL) and H_2O (0.4 mL) was added DCDMH (0.64 g, 3.25 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1.5 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure to get the crude product. The crude product was dissolved in DCM (10 mL) followed by the addition of TEA (0.7 mL, 4.87 mmol) and allyl amine (0.6 mL, 8.11 mmol) at 0 °C. Reaction mixture was stirred for 1.5 h at room temperature. The reaction mixture was quenched with ice water and extracted with ethyl acetate (3× 50 mL). The combined organic layers were dried over anhydrous sodium sulphate and evaporated under reduced presure to get the crude product, which was purified by column chromatography (SiO_2, 0-60% EtOAc/Hex) to yield N-allyl-2-(bis(3-chloro-4-fluorophenyl)methyl)-5-iodo-1H-imidazole-4-sulfonamide. Yield: 42% (0.4 g). LCMS m/z = 584 $[M+H]^+$.

Step 2: To a stirred solution of N-allyl-2-(bis(3-chloro-4-fluorophenyl)methyl)-5-iodo-1H-imidazole-4-sulfonamide (0.4 g, 0.68 mmol) in DMF (5 mL) was added TEA (0.3 mL, 2.06 mmol) and the mixture was degassed with argon for 10 min. Then bis(tri-tert-butylphosphine)palladium(0) (0.035 g, 0.069 mmol) was added to the reaction mixture at room temperature. The reaction mixture was heated to 100 °C in a sealed tube for 16 h. The reaction mixture was filtered through a celite bed. The filtrate was evaporated under reduced pressure to get the crude product, which was purified by prep HPLC to yield 6-(bis(3-chloro-4-fluorophenyl)methyl)-4-methyl-2,5-dihydroimidazo[4,5-e][1,2]thiazine 1,1-dioxide. Yield: 5% (0.015 g).

LCMS m/z = 456 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.90 (s, 1H), 10.76 (s, 1H), 7.55 (d, 2H), 7.43-7.39 (m, 2H), 7.33 (bs, 2H), 6.49 (s, 1H), 5.73 (s, 1H), 2.10 (s, 3H).

Example 195

7-(bis(3-chloro-4-fluorophenyl)methyl)-3,6-dihydro-2H-imidazo[4,5-f][1,2]thiazepine 1,1-dioxide



Step 1: To a solution of 2-(bis(3-chloro-4-fluorophenyl)methyl)-5-iodo-4-((4-methoxybenzyl)thio)-1H-imidazole (intermediate 42, 1.5 g, 2.43 mmol) in 1,4-dioxane-H_2O (10:1, 75 mL) were added K_2CO_3 (0.675 g, 4.86 mmol) and potassium vinyltrifluoroborate (0.655 g, 4.86 mmol) at room temperature. The reaction mixture was degassed with argon for 10 min, followed by the addition of $PdCl_2$(dppf) (0.18 g, 0.243 mmol) at room temperature. The reaction mixture was heated to 110 °C for 16 h in a sealed tube. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and filtered through a celite bed. The filtrate was evaporated under reduced pressure, the resulting residue was purified by column chromatography (SiO_2, 0-50% EtOAc/Hex) to yield 2-(bis(3-chloro-4-fluorophenyl)methyl)-4-((4-methoxybenzyl)thio)-5-vinyl-1H-imidazole. Yield: 55% (0.7 g). LCMS m/z = 517 $[M+H]^+$.

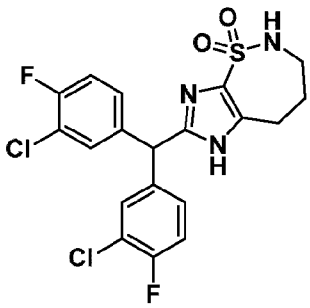
Step 2: To a solution of 2-(bis(3-chloro-4-fluorophenyl)methyl)-4-((4-methoxybenzyl)thio)-5-vinyl-1H-imidazole (0.7 g, 1.353 mmol) in MeN (18.0 mL)-AcOH (1.5 mL)-H_2O (0.9 mL) was added DCDMH (0.535 g, 2.706 mmol) at 0 °C. The reaction was stirred at 0 °C for 2 h. The reaction mixture was diluted with ethyl acetate and quenched with cold sat. $NaHCO_3$ solution. The organic layer was separated, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to get crude product. The crude product was dissolved in DCM (15.0 mL). To the solution were added TEA (0.6 mL, 4.056 mmol) and prop-2-en-1-amine (0.21 mL, 2.704 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with ice water and extracted with ethyl acetate (2 x 80 mL). The combined organic layers were washed with brine, dried over sodium sulphate and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (SiO_2, 0-50% EtOAc/Hex) to yield N-allyl-2-(bis(3-chloro-4-fluorophenyl)methyl)-5-vinyl-1H-imidazole-4-sulfonamide. Yield: 42% (0.28 g) over two steps. LCMS m/z = 484 $[M+H]^+$.

Step 3: A stirred solution of N-allyl-2-(bis(3-chloro-4-fluorophenyl)methyl)-5-vinyl-1H-imidazole-4-sulfonamide (0.48 g, 0.991 mmol) in DCM (60 mL) was degassed with argon gas for 5 minutes, followed by the addition of Grubbs catalyst, 2nd generation (0.59 g, 0.694 mmol) at room temperature. The reaction mixture was stirred at room temperature for 3 days in a sealed tube. The reaction mixture was concentrated under reduced pressure, the residue was purified by reveres phase prep HPLC to yield the title compound. Yield: 3% (0.013 g).

LCMS m/z = 456 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.66 (s, 1H), 7.65-7.54 (m, 1H), 7.53-7.51 (m, 2H), 7.42 (t, 2H), 7.32-7.29 (m, 2H), 6.43 (d, 1H), 6.00-5.91 (m, 1H), 5.70 (s, 1H), 3.89-3.86 (m, 2H).

Example 196

7-(bis(3-chloro-4-fluorophenyl)methyl)-3,4,5,6-tetrahydro-2H-imidazo[4,5-f][1,2]thiazepine 1,1-dioxide



Step 1: To a solution of 2-[bis(3-chloro-4-fluorophenyl)methyl]-5-ethenyl-N-(prop-2-en-1-yl)-1H-imidazole-4-sulfonamide (0.04 g, 0.826 mmol) in DCM (15.0 mL) was added DIPEA (0.45 mL, 2.478 mmol) followed by the dropwise addition of SEM-Cl (0.2 mL, 1.074 mmol) at 0 °C. The reaction mixture was stirred at 40 °C for 16 h. The reaction mixture was quenched with saturated ammonium chloride and extracted with DCM (2 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude product, which was purified by column chromatography (SiO_2, 0-40% EtOAc/Hex) to obtain N-allyl-2-(bis(3-chloro-4-fluorophenyl)methyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-5-vinyl-1H-imidazole-4-sulfonamide and the corresponding SEM regioisomer. Yield: 49% (0.25 g). LCMS m/z = 614 $[M+H]^+$.

Step 2: A solution of N-allyl-2-(bis(3-chloro-4-fluorophenyl)methyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-5-vinyl-1H-imidazole-4-sulfonamide (mixture of regioisomers, 0.25 g, 0.407 mmol) in DCM (100 mL) was degassed with argon gas for 10 minutes followed by the addition of Grubbs catalyst, 2nd gen (0.245 g, 0.285 mmol) at room temperature. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure, the resulting crude was purified by column chromatography (SiO_2, 0-50% EtOAc/Hex) to obtain 7-(bis(3-chloro-4-fluorophenyl)methyl)-6-((2-(trimethylsilyl)ethoxy)methyl)-3,6-dihydro-2H-imidazo-[4,5-f][1,2]thiazepine 1,1-dioxide (mixture of regioisomers). Yield: 49% (0.238 g). LCMS m/z = 586 $[M+H]^+$.

Step 3: A solution of 7-(bis(3-chloro-4-fluorophenyl)methyl)-6-((2-(trimethylsilyl)ethoxy)methyl)-3,6-dihydro-2H-imidazo[4,5-f][1,2]thiazepine 1,1-dioxide (mixture of regioisomers, 0.238 g, 0.406 mmol) in MeOH (15.0 mL) was degassed with nitrogen gas for 5 min followed by the addition of PtO_2 (0.06 g) at room temperature. The reaction mixture was stirred at room temperature for 4 h under H_2 balloon pressure. The reaction mixture was filtered through a celite bed and the filtrate was concentrated under reduced pressure to obtain 7-(bis(3-chloro-4-fluorophenyl)methyl)-6-((2-(trimethylsilyl)ethoxy)methyl)-3,4,5,6-tetrahydro-2H-imidazo[4,5-f][1,2]thiazepine 1,1-dioxide (mixture of regioisomers). Yield: 96% (0.23 g). LCMS m/z = 588 $[M+H]^+$.

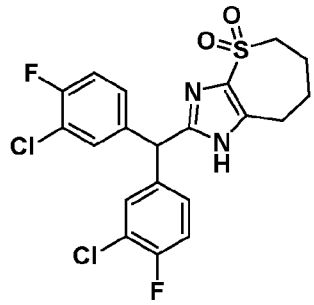
Step 4: To a stirred solution of 7-(bis(3-chloro-4-fluorophenyl)methyl)-6-((2-(trimethylsilyl)ethoxy)methyl)-3,4,5,6-tetrahydro-2H-imidazo[4,5-f][1,2]thiazepine 1,1-dioxide (mixture of regioisomers) (0.230 g, 0.391 mmol) in DCM (5.0 mL) was added 4(M) HCl in dioxane (10.0 mL) at 0 °C. The reaction mixture was stirred at room temperature for 6 h. The reaction mixture was concentrated under reduced pressure, the resulting residue was neutralized with $NaHCO_3$ solution and extracted with ethyl acetate (2×100 mL). The combined organic layera were

washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by reverse phase prep HPLC to yield the title compound. Yield: 30% (0.055 g).

LCMS m/z = 456 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.40 (bs, 1H), 7.52 (d, 2H),7.43-7.38 (m, 3H), 7.37-7.27 (m, 2H), 5.61 (s, 1H), 3.27-2.25 (m, 2H), 2.79-2.76 (m, 2H), 1.77-1.76 (m, 2H).

Example 197

2-(bis(3-chloro-4-fluorophenyl)methyl)-5,6,7,8-tetrahydro-1H-thiepino[2,3-d]imidazole 4,4-dioxide



Step 1: A solution of 2-(bis(3-chloro-4-fluorophenyl)methyl)-5-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole (intermediate 5, mixture of regioisomers) (1.4 g, 2.348 mmol) and but-3-yn-1-ol (1.32 g, 18.781 mmol) in DMSO (20 mL) was degassed with argon for 10 minutes followed by the addition of diethyl amine (1.5 mL, 14.086 mmol), CuI (0.09 g, 0.47 mmol) and $Pd(PPh_3)_4$ (0.271 g, 0.235 mmol) at room temperature. The reaction mixture was heated to 90 °C for 16 h in a sealed tube. The mixture was colled to ropom temperature and filtered through celite. The filtrate was concentrated under reduced pressure, the resulting crude was purified by column chromatography (SiO_2, 0-50% EtOAc/Hex) to get 4-(2-(bis(3-chloro-4-fluorophenyl)methyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)but-3-yn-1-ol (mixture of regioisomers). Yield: 87% (1.1 g). LCMS m/z = 537 $[M+H]^+$.

Step 2: To a solution of 4-(2-(bis(3-chloro-4-fluorophenyl)methyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)but-3-yn-1-ol (mixture of regioisomers, 1.3 g, 2.414 mmol) in methanol (30 mL) was added PtO_2 (0.26 g). The reaction mixture was stirred at room temperature under H_2-balloon pressure for 5 h. The reaction mixture was filtered through a celite bed, the celite bed was washed with methanol and the filtrate was concentrated under reduced pressure to afford 4-(2-(bis(3-chloro-4-fluorophenyl)methyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)butan-1-ol (mixture of regioisomers). Yield: 92% (1.2 g). LCMS m/z = 541 $[M+H]^+$.

Step 3: To a stirred solution of 4-(2-(bis(3-chloro-4-fluorophenyl)methyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)butan-1-ol (mixture of regioisomers, 1.45 g, 2.673 mmol) in DMF (30 mL) was added NIS (2.4 g, 10.69 mmol). The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was quenched with saturated sodium thiosulphate solution and extracted with EtOAc (3 x 300 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by coloumn chromatography (SiO_2, 0-40% EtOAc/Hex) to yield 4-(2-(bis(3-chloro-4-fluorophenyl)methyl)-4-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)butan-1-ol (mixture of regioisomers). Yield: 67% (1.2 g). LCMS m/z = 667 $[M+H]^+$.

Step 4: To a solution of 4-(2-(bis(3-chloro-4-fluorophenyl)methyl)-4-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)butan-1-ol (mixture of regioisomers, 1.0 g, 1.496 mmol) in DCM (50 mL) were added TEA (0.7 mL, 4.488 mmol) and MsCl (0.2 mL, 2.244 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with ice water and the resulting mixture was extracted with DCM (2 × 300 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford 4-(2-(bis(3-chloro-4-fluorophenyl)methyl)-4-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)butyl methanesulfonate (mixture of regioisomers). Yield: Crude (1.1 g). LCMS m/z = 745 $[M+H]^+$.

Step 5: To a solution 4-(2-(bis(3-chloro-4-fluorophenyl)methyl)-4-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)butyl methanesulfonate (mixture of regioisomers, 1.0 g, 1.34 mmol) in MeCN (20 mL) was added 1-(potassiosulfanyl)ethan-1-one (0.306 g, 2.679 mmol) at room temperature and the reaction was stirred at room temperature for 16 h. The reaction mixture was diluted with water and extracted with EtOAc (2 x 300 mL). The combined organic layers were washed with brine, dried over sodium sulphate and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (SiO_2, 0-30% EtOAc/Hex) to obtain S-(4-(2-(bis(3-chloro-4-fluorophenyl)methyl)-4-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)butyl) ethanethioate (mixture of regioisomers). Yield: 49% (0.48 g). LCMS m/z = 725 $[M+H]^+$.

Step 6: To a solution of S-(4-(2-(bis(3-chloro-4-fluorophenyl)methyl)-4-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)butyl) ethanethioate (mixture of regioisomers, 0.3 g, 0.413 mmol) in MeOH (20 mL) was added NaSMe (0.03 g, 0.413 mmol) at 0 °C and the reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was diluted with ice cold water and extracted with EtOAc (2 x 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, 0-40% EtOAc/Hex) to obtain 4-(2-(bis(3-chloro-4-fluorophenyl)methyl)-4-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)butane-1-thiol (mixture of regioisomers). Yield: 36% (0.18 g). LCMS m/z = 683 $[M-H]^-$.

Step 7: A solution of 4-(2-(bis(3-chloro-4-fluorophenyl)methyl)-4-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)butane-1-thiol (mixture of regioisomers, 0.18 g, 0.263 mmol) in 1,4-dioxane (3 mL) was degassed with argon gas for 10 min followed by the addition of $Pd_2(dba)_3$ (0.025 g, 0.026 mmol), Xantphos (0.031 g, 0.053 mmol) and DIPEA (0.15 mL, 0.789 mmol) at room temperature. The mixture was then heated to 80 °C for 16 h. The reaction mixture was diluted with water and extracted with EtOAc (2x 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (SiO_2, 0-15% EtOAc/Hex) to obtain 2-(bis(3-chloro-4-fluorophenyl)methyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-5,6,7,8-tetrahydro-1H-thiepino[2,3-d]imidazole (mixture of regioisomers). Yield: 47% (0.07 g). LCMS m/z = 553 $[M+H]^+$.

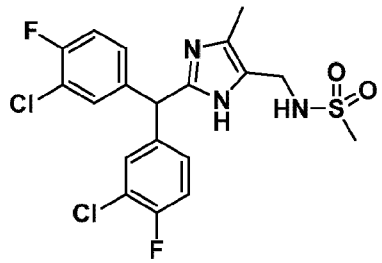
Step 8: To a solution of 2-(bis(3-chloro-4-fluorophenyl)methyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-5,6,7,8-tetrahydro-1H-thiepino[2,3-d]imidazole (mixture of regioisomers, 0.07 g, 0.126 mmol) in DCM (15 mL) was added mCPBA (0.045 g, 0.252 mmol) at room temperature and the mixture was stirred at room temperature for 3 h.The reaction mixture was quenched with sat. aqueous sodium thiosulphate solution and stirred for 30 min. The layers were separated, the organic layer was dried over Na_2SO_4 and concentrated to get the crude compound, which was purified by column chromatography (SiO_2, 0-30% EtOAc/Hex) to obtain 2-(bis(3-chloro-4-fluorophenyl)methyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-5,6,7,8-tetrahydro-1H-thiepino[2,3-d]imidazole 4,4-dioxide (mixture of regioisomers). Yield: 68 % (0.05 g). LCMS m/z = 587 $[M-H]^-$.

Step 9: To a solution of 2-(bis(3-chloro-4-fluorophenyl)methyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-5,6,7,8-tetrahydro-1H-thiepino[2,3-d]imidazole 4,4-dioxide (mixture of regioisomers, 0.05 g, 0.085 mmol) in DCM (5 mL) was added 4M HCl in 1,4-dioxane (1 mL) at room temperature and the mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under redued pressure, the obtained residue was purified by reverse phase prep HPLC to obtain the title compound. Yield: 33% (0.013 g)

LCMS m/z = 457 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.55 (bs, 1H), 7.54-7.51 (m, 2H), 7.42-7.38 (m, 2H), 7.33-7.21 (m, 2H), 5.63 (s, 1H), 3.28-3.27 (m, 2H), 2.78-2.75 (m, 2H), 2.07 (m, 2H), 1.74 (m, 2H).

Example 198

N-((2-(bis(3-chloro-4-fluorophenyl)methyl)-4-methyl-1H-imidazol-5-yl)methyl)methanesulfonamide



Step 1: To a solution of 2-(bis(3-chloro-4-fluorophenyl)methyl)-4-iodo-5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole (intermediate 43, mixture of regioisomers, 9 g, 14.77 mmol) in MeOH (120 mL) was added TEA (5.1 mL, 36.93 mmol) at room temperature. The reaction mixture was degassed with argon for 10 min followed by the addition of $PdCl_2$(dppf)·DCM (0.6 g, 0.74 mmol). The resulting reaction mixture was heated to 90°C under 10 bar pressure of CO gas for 16 h. The reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (2 × 160 mL). The combined organic layers were washed with brine (90 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography (SiO_2, 30% EtOAc/Hex) to afford methyl 2-(bis(3-chloro-4-fluorophenyl)methyl)-5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole-4-carboxylate and the corresponding SEM regioisomer. Yield: 78% (6.2 g). LCMS m/z = 541 $[M+H]^+$.

Step 2: To a stirred solution of methyl 2-(bis(3-chloro-4-fluorophenyl)methyl)-5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole-4-carboxylate (mixture of regioisomers, 3 g, 5.54 mmol) in THF (30 mL) was added $LiBH_4$ (2 M in THF, 16.6 mL, 33.24 mmol) dropwise at 0 °C. The resulting reaction mixture was stirred at room temperature for 16 h. The reaction mixture was quenched with ammonium chloride (120 mL) and was extracted with ethyl acetate (2 × 150 mL). The combined organic layers were washed with brine (90 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography (SiO_2, 50% EtOAc/Hex) to afford (2-(bis(3-chloro-4-fluorophenyl)methyl)-5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-4-yl)methanol and the corresponding SEM regioisomer. Yield: 70% (2 g). LCMS m/z = 513 $[M+H]^+$.

Step 3: To a stirred solution of (2-(bis(3-chloro-4-fluorophenyl)methyl)-5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-4-yl)methanol (mixture of regioisomers, 1 g, 1.95 mmol) in toluene (25 mL) was added DPPA (0.6 mL, 2.92 mmol) followed by DBU (0.45 mL, 2.92 mmol) at room temperature. The resulting reaction mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with cold water (60 mL) and

extracted with ethyl acetate (2 × 70 mL). The combined organic layers were washed with brine (70 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography (SiO_2, 10% EtOAc/Hex) to afford 4-(azidomethyl)-2-(bis(3-chloro-4-fluorophenyl)methyl)-5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole and the corresponding SEM regioisomer. Yield: 66% (0.7 g). LCMS m/z = 538 $[M+H]^+$.

Step 4: To a stirred solution of 4-(azidomethyl)-2-(bis(3-chloro-4-fluorophenyl)methyl)-5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole (mixture of regioisomers, 0.7 g, 1.29 mmol) in THF:water (25 mL, 4:1) was added PPh_3 (0.5 g, 1.95 mmol) at 0 °C. The resulting reaction mixture was stirred at room temperature for 16 h. The mixture was quenched with cold water (20 mL) and was extracted with ethyl acetate (2 × 80 mL). The combined organic layers were washed with brine (60 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography (SiO_2, 5% MeOH/DCM) to afford (2-(bis(3-chloro-4-fluorophenyl)methyl)-5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-4-yl)methanamine and the corresponding SEM regioisomer. Yield: 76% (0.5 g). LCMS m/z = 512 $[M+H]^+$.

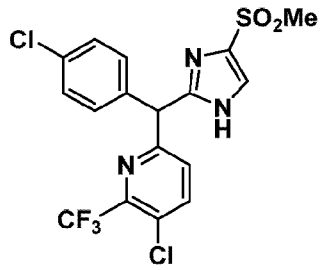
Step 5: To a stirred solution of (2-(bis(3-chloro-4-fluorophenyl)methyl)-5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-4-yl)methanamine (mixture of regioisomers, 0.4 g, 0.78 mmol) in DCM (8 mL) was added TEA (0.27 mL, 1.95 mmol) followed by mesyl chloride (0.07 mL, 0.94 mmol) at 0 °C. The resulting reaction mixture was stirred at room temperature for 2 h. Ther reaction mixture was quenched with cold water (20 mL) and was extracted with DCM (2 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography (SiO_2, 30% EtOAc/Hex) to afford N-((2-(bis(3-chloro-4-fluorophenyl)methyl)-5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-4-yl)methyl)methanesulfonamide and the corresponding SEM regioisomer . Yield: 65% (0.3 g). LCMS m/z = 590 $[M+H]^+$.

Step 6: To a stirred solution of N-((2-(bis(3-chloro-4-fluorophenyl)methyl)-5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-4-yl)methyl)methanesulfonamide (mixture of regioisomers, 0.3 g, 0.51 mmol) in DCM (3 mL) was added TFA (6 mL) at 0 °C. The resulting solution was stirred at room temperature for 16 h. The reactionmixture was concentrated, the obtained residue was diluted with water, basified using $NaHCO_3$ solution and extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product, which was purified by reverse phase prep-HPLC to afford the title compound. Yield: 43% (0.1 g).

LCMS m/z = 460 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 11.43 (s, 1H), 7.50-7.48 (m, 2H), 7.31-7.29 (m, 4H), 6.80 (bs, 1H), 5.52 (s, 1H), 4.03 (m, 2H), 2.87 (s, 3H), 2.14 (s, 3H).

Example 199

3-chloro-6-((4-chlorophenyl)(4-(methylsulfonyl)-1H-imidazol-2-yl)methyl)-2-(trifluoromethyl)pyridine

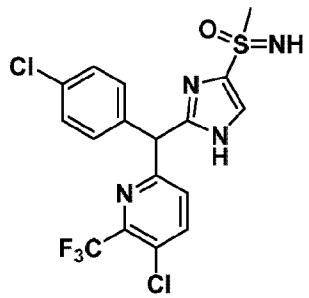


To a solution of 3-chloro-6-[(4-chlorophenyl) [4-(methylsulfanyl)-1H-imidazol-2-yl] methyl]-2-(trifluoromethyl) pyridine (intermediate 44, 0.3 g, 0.718 mmol) in DCM (5.0 mL) was added mCPBA (77%, 0.482 g, 2.153 mmol) at room temperature. The reaction mixture was stirred for 3 h. The reaction mixture was basified with saturated Na_2SO_3 solution, stirred for 30 minutes and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to get the crude product, which was purified by column chromatography (SiO_2, EtOAc) ans later HPLC to get the title compound. Yield: 5% (0.016 g).

LCMS m/z = 450 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 8.25 (d, 1H), 7.82 (s, 1H), 7.75 (d, 1H), 7.43 (d, 2H), 7.36 (d, 2H), 5.90 (s, 1H), 3.07 (s, 3H).

Example 200

(2-((5-chloro-6-(trifluoromethyl)pyridin-2-yl)(4-chlorophenyl)methyl)-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone



Step 1: To a solution of 3-chloro-6-[(4-chlorophenyl)[4-(methylsulfanyl)-1H-imidazol-2-yl]methyl]-2-(trifluoromethyl)pyridine (intermediate 44, 300 mg, 0.717 mmol) in DMF (10 mL) was added NaH (57 mg, 1.435 mmol) at 0 °C. The mixture was stirred at room temperature for 30 min. Then SEM-Cl (0.18 g, 1.076 mmol) was added at 0 °C, the mixture was then stirred at room temperature overnight. The mixture was then quenched with crushed ice and extracted with ethyl acetate (3x 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and cocentrated under reduced pressure to get the crude product which was purified by column chromatography (SiO_2, 5% EtOAc/Hex) to get 3-chloro-6-[(4-chlorophenyl)[4-(methylsulfanyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazol-2-yl]methyl]-2-(trifluoromethyl)pyridine and the corresponding SEM regioisomer. Yield: 33% (0.13 g). LCMS m/z = 548 $[M+H]^+$.

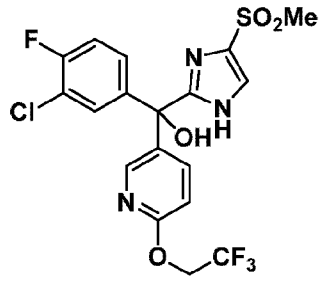
Step 2: To a stirred solution of 3-chloro-6-[(4-chlorophenyl)[4-(methylsulfanyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazol-2-yl]methyl]-2-(trifluoromethyl)pyridine (mixture of regioisomers, 0.22 g, 0.401 mmol) in MeOH (3 mL) were added diacetoxyiodobenzene (0.65 g, 2.005 mmol) and ammonium carbonate (0.19 g, 2.005 mmol) at room temperature. The mixcture was then stirred for 2 h. The solvent was evaporated under reduced pressure (without heating) to get the crude product, which was purified by column chromatography to get 3-chloro-6-[(4-chlorophenyl)({4-[imino(methane)sulfinyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazol-2-yl})methyl]-2-(trifluoromethyl)pyridine and the corresponding SEM regioisomer. Yield: Crude (0.12 g, 0.21 mmol)

Step 3: To a stirred solution of 3-chloro-6-[(4-chlorophenyl)({4-[imino(methane)sulfinyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazol-2-yl})methyl]-2-(trifluoromethyl)pyridine (mixture of regioisomers, 0.12 g, 0.207 mmol) in DCM (2 mL) was added 4M HCl in dioxane (0.5 mL, 2.071 mmol) at 0 °C. The mixture was then stirred at room temperature for 4 h. The solvent was evaporated to get the crude product which was purified by reverse prep-HPLC to get the title compound. Yield: 16% (0.015 g)

LCMS m/z = 449[M+H]$^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 11.39 (bs, 1H), 8.25 (d, 1H), 7.76-7.73 (m, 1H), 7.63 (s, 1H), 7.43-7.41 (m, 2H), 7.36-7.34 (m, 2H), 5.88 (s, 1H), 3.96 (bs, 1H), 2.98 (s, 3H).

Example 201

(3-chloro-4-fluorophenyl)(4-(methylsulfonyl)-1H-imidazol-2-yl)(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)methanol



Step 1: 3-Chloro-4-fluorophenyl)(4-(methylsulfonyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methanone (intermediate 25, mixture of regioisomers, 340 mg, 0.785 mmol) was dissolved in HCl in 1,4-dioxane (4M, 10 mL) at 0 °C. The resulting reaction mixture was stirred at rt for 5 h. The reaction mixture was concentrated under reduced pressure, the residue was taken up in water (5 mL) and basified with $NaHCO_3$ (5 mL). The precipitated solid was filtered off and dried under vacuum to afford (3-chloro-4-fluorophenyl)(4-(methylsulfonyl)-1H-imidazol-2-yl)methanone (200 mg, 84%).

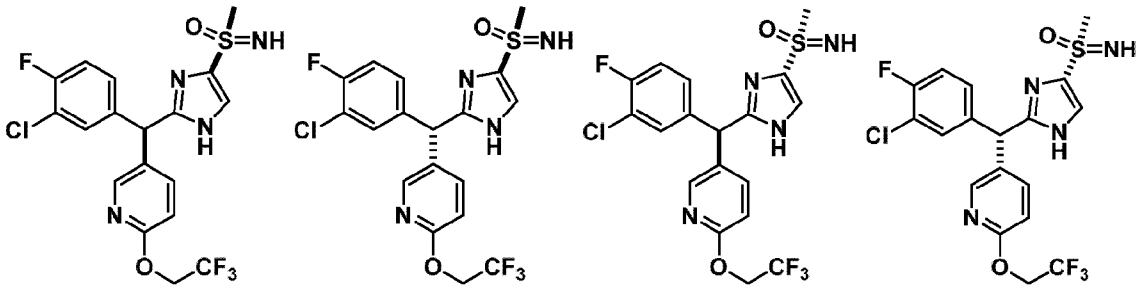
Step 2: 5-Bromo-2-(2,2,2-trifluoroethoxy) pyridine (2.537 g, 9.911 mmol) was added in one portion to a stirred solution of a mixture of magnesium turnings (237.856 mg, 9.911 mmol) and iodine (2 mg) in THF (1.4 mL) at room temperature under an argon atmosphere. The temperature rose to about 60 °C after formation of the Grignard reagent. The reaction mixture was allowed to cool to room temperature and was stirred for 1 h. The reaction mixture was cooled to 0 °C and a solution of (3-chloro-4-fluorophenyl)(4-(methylsulfonyl)-1H-imidazol-2-yl)methanone (200 mg, 0.661 mmol) in THF (6.6 mL) was added dropwise. The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was cooled to 0 °C, quenched with NH_4Cl Sat. solution (15 mL) and extracted with ethyl acetate (3×30 mL). The combined organic layers were washed with brine (10 mL), dried

over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by prep-HPLC to afford the title compound (90 mg, 28%).

LCMS m/z = 480[M+H]$^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 13.00 (s, 1H), 8.12 (dd, 1H), 7.78 (s, 1H), 7.73 (dd, 1H), 7.58 (dd, 1H), 7.42-7.37 (m, 2H), 7.35-7.31 (m, 1H), 6.97 (dd, 1H), 4.98 (q, 2H), 3.10 (s, 3H).

Example 202

(2-((3-chloro-4-fluorophenyl)(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)methyl)-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone



Step 1: Sodium hydride (69.471 mg, 1.737 mmol) was added to a solution of 5-((3-chloro-4-fluorophenyl)(4-(methylthio)-1H-imidazol-2-yl)methyl)-2-(2,2,2-trifluoroethoxy)pyridine (intermediate 45, 300 mg, 0.695 mmol) in THF (6 mL) at 0 °C under an argon atmosphere. The reaction mixture was stirred at 0 °C for 5 min followed by the addition of SEM-Cl (0.308 mL, 1.737 mmol) at 0 °C and stirring for 15 min. The reaction mixture was diluted with ice water (10 mL) and extracted with ethyl acetate (3×25 mL). The solvent was evaporated under reduced pressure to afford 5-((3-chloro-4-fluorophenyl)(4-(methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methyl)-2-(2,2,2-trifluoroethoxy)pyridine and the corresponding SEM regioisomer (570 mg, crude).

Step 2: 5-((3-chloro-4-fluorophenyl)(4-(methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methyl)-2-(2,2,2-trifluoroethoxy)pyridine (mixture of regioisomers, 570 mg, 1.014 mmol) was dissolved in methanol (10 mL) at room tempereature followed by the addition of phenyl-l3-iodanediyl diacetate (979.882 mg, 3.042 mmol) and ammonium carbonate (478.019 mg, 3.042 mmol) at room temperature. The resulting reaction mixture was stirred at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure, the residue was taken up in with water (10 mL) and extracted with ethyl acetate (3×30 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and evaporated to afford (2-((3-chloro-4-fluorophenyl)(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)methyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone and the corresponding SEM regioisomer (750 mg, crude).

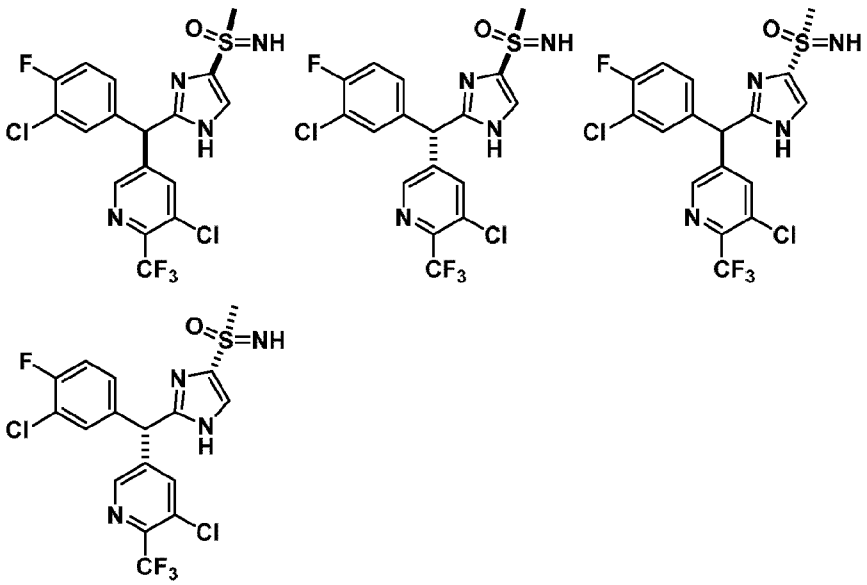
Step 3: (2-((3-chloro-4-fluorophenyl)(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)methyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone (mixture of regioisomers, 0.75 g, 1.265 mmol) was added to HCl in 1,4-dioxane (4N, 30 mL) at 0 °C. The resulting reaction mixture was stirred at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure, basified with $NaHCO_3$ solution (pH= 7-8) and extracted with ethyl acetate (3×80 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was washed with diethyl ether (10 mL) and purified by prep-HPLC to afford the title compound (mixture of isomers) (80 mg).

The title compound (mixture of isomers) was separetad into the individual stereoisomers using two subsequent chiral SFC runs.

202a: LCMS m/z = 463 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.68 (br s, 1H), 8.15 (d, 1H), 7.77 (dd, 1H), 7.63 (s, 1H), 7.52 (dd, 1H), 7.41-7.37 (m, 1H), 7.33-7.29 (m, 1H), 6.97 (d, 1H), 5.69 (s, 1H), 4.96 (q, 2H), 3.95 (br s, 1H), 3.00 (s, 3H). 202b: LCMS m/z = 463 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.67 (s, 1H), 8.15 (d, 1H), 7.77 (dd, 1H), 7.64 (s, 1H), 7.52 (dd, 1H), 7.42-7.37 (m, 1H), 7.32-7.29 (m, 1H), 6.97 (d, 1H), 5.69 (s, 1H), 4.96 (q, 2H), 3.95 (br s, 1H), 3.00 (s, 3H). 202c: LCMS m/z = 463 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.67 (s, 1H), 8.15 (d, 1H), 7.78 (dd, 1H), 7.64 (s, 1H), 7.52 (dd, 1H), 7.42-7.37 (m, 1H), 7.32-7.29 (m, 1H), 6.97 (d, 1H), 5.69 (s, 1H), 4.96 (q, 2H), 3.95 (br s, 1H), 3.00 (s, 3H). 202d: LCMS m/z = 463 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.68 (s, 1H), 8.15 (d, 1H), 7.77 (dd, 1H), 7.67 (d, 1H), 7.52 (dd, 1H), 7.42-7.37 (m, 1H), 7.33-7.29 (m, 1H), 6.98 (d, 1H), 5.71 (s, 1H), 4.96 (q, 2H), 4.22 (br s, 1H), 3.02 (s, 3H). Chiral SFC: column: Chiralcel OX-H (4.6 x 250 mm) 5 µm; co-solvent: iPrOH, flow: 3 mL/min; % of co-solvent: 25%; ABPR: 1500 psi T: 35 °C; (202a) Rt = 5.82 min (first eluting), (202b) Rt = 6.47 min (second eluting), (202c) Rt = 9.13 min (third eluting), (202d) Rt = 10.48 min (fourth eluting).

Example 203

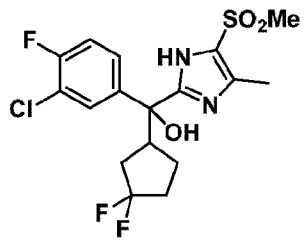
The title compound was prepared from the appropriate intermediates and reagents using an analogous method to that described for example 202.

Example	Name/Structure/Data
203a, 203b, 203c, 203d	(2-((3-chloro-4-fluorophenyl)(5-chloro-6-(trifluoromethyl)pyridin-3-yl)methyl)-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone  Without step 1, from intermediate 46. 203a: LCMS m/z = 467 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.73 (s, 1H), 8.72 (d, 1H), 8.23 (s, 1H), 7.70 (s, 1H), 7.61 (dd, 1H), 7.45-7.40 (m, 1H), 7.36 (dd, 1H), 5.92 (s, 1H),

	3.98 (s, 1H), 3.02 (s, 3H). 203b: LCMS m/z = 467 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.73 (s, 1H), 8.72 (d, 1H), 8.23 (s, 1H), 7.70 (s, 1H), 7.61 (dd, 1H), 7.45-7.40 (m, 1H), 7.36 (dd, 1H), 5.92 (s, 1H), 3.98 (s, 1H), 3.02 (s, 3H). 203c: LCMS m/z = 467 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.73 (s, 1H), 8.72 (d, 1H), 8.23 (s, 1H), 7.70 (s, 1H), 7.61 (dd, 1H), 7.45-7.40 (m, 1H), 7.36 (dd, 1H), 5.92 (s, 1H), 3.98 (s, 1H), 3.02 (s, 3H). 203d: LCMS m/z = 467 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.73 (s, 1H), 8.72 (d, 1H), 8.23 (s, 1H), 7.70 (s, 1H), 7.61 (dd, 1H), 7.45-7.40 (m, 1H), 7.36 (dd, 1H), 5.92 (s, 1H), 3.98 (s, 1H), 3.02 (s, 3H). Chiral SFC: column: Chiralcel IC (4.6 x 250 mm) 5 µm; co-solvent: iPrOH, flow: 3 mL/min; % of co-solvent: 20%; ABPR: 1500 psi; T: 35 °C; (203a) Rt = 5.88 min (first eluting), (203b) Rt = 6.91 min (second eluting), (203c) Rt = 9.92 min (third eluting), (203d) Rt = 12.47 min (fourth eluting).

Example 204

(3-chloro-4-fluorophenyl)(3,3-difluorocyclopentyl)(4-methyl-5-(methylsulfonyl)-1H-imidazol-2-yl)methanol

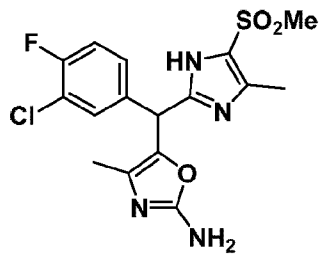


Step 1: (3-Chloro-4-fluorophenyl)(3,3-difluorocyclopentyl)(5-methyl-4-(methylsulfonyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methanol (intermediate 47, mixture of regioisomers, 0.1 g, 0.181 mmol) was added to a stirred solution of HCl in 1,4-dioxane (4N, 3.0 mL) at room temperature and the mixture was stirred for 4 h. The reaction mixture was concentrated under reduced pressure to afford the crude compound, which was purified by prep HPLC to afford the title compound (40 mg, 52%).

LCMS m/z = 421 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.47 (s, 1H), 7.71-7.68 (m, 1H), 7.45-7.35 (m, 2H), 6.44-6.42 (m, 1H), 3.31-3.24 (m, 1H), 3.07 (s, 3H), 2.49-2.33 (m, 3H), 2.22-1.90 (m, 4H), 1.81-1.61 (m, 1H), 1.58-1.50 (m, 1H), 1.32-1.23 (m, 1H).

Example 205

5-((3-chloro-4-fluorophenyl)(4-methyl-5-(methylsulfonyl)-1H-imidazol-2-yl)methyl)-4-methyloxazol-2-amine



Step 1: To a solution of (3-chloro-4-fluorophenyl)(5-methyl-4-(methylsulfonyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methyl diisopropylcarbamate (intermediate 49, 1 g, 1.736 mmol) in THF (20 mL) was

added 4-methyloxazol-2-amine (0.341 g, 3.471 mmol) followed by boron trifluoride etherate (0.369 mL, 2.603 mmol) and trifluoroacetic acid (0.396 mL, 3.471 mmol) at room temperature. Then reaction mixture was heated to 50 °C for 1 h. The reaction mixture was concentrated under reduced pressure to get the crude compound, which upon purification by column chromatography (C18, 0.1% formic acid in water/acetonitrile) followed by prep-HPLC afforded 5 mg (1%) of the title compound.

LCMS m/z = 399 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): 12.48 (s, 1H), 7.51 (dd, 1H), 7.41 (t, 1H), 7.33-7.20 (m, 1H), 6.46 (br s, 2H), 5.69 (s, 1H), 3.02 (s, 3H), 2.37 (s, 3H), 1.75 (s, 3H).

LCMS Methods

Method A:

Waters Acquity H Class UPLC attached with Waters SQD 2 mass spectrometer; Ionisation method: Electro spray Capillary (kV) 3.50, Cone (V) 25.00, Source Temperature (°C) 150, Desolvation Temperature (°C) 400, Cone Gas Flow (L/Hr) -50, Desolvation Gas Flow (L/Hr) -750; Mass range:100 to 900 Da; DAD Wavelength range (nm): 200 to 400; Solvent A: 5 mM NH_4OAc in water and Solvent B: 5 mM NH_4OAc in ACN: Water (90:10); Flow rate: 1.20 ml/min; (mobile phase: 95% [5 mM NH_4OAc in water] and 5% [5 mM NH_4OAc in ACN: Water (90:10)] held for 0.75 min, then 85% [5 mM NH_4OAc in water] and 15% [5 mM NH_4OAc in ACN: Water (90:10)] in 1.25 min further 70% [5 mM NH_4OAc in water] and 30% [5 mM NH_4OAc in ACN: Water (90:10)] in 2.50 min, and finally 2% [5 mM NH_4OAc in water] and 98% [5 mM NH_4OAc in ACN: Water (90:10)] in 3.75 min, held this mobile phase composition up to 4.25 min and finally back to initial condition in 4.50 min and held this composition up to 5.10 min).

TIME	**Flow Rate (ml/min)**	**%A** (5 mM NH4OAc in water)	**% B** (5 mM NH4OAc in ACN: Water (90:10))
0.00	**1.20**	**95**	**5**
0.75	**1.20**	**95**	**5**
1.25	**1.20**	**85**	**15**
2.50	**1.20**	**70**	**30**
3.75	**1.20**	**2**	**98**
4.25	**1.20**	**2**	**98**
4.50	**1.20**	**95**	**5**
5.10	**1.20**	**95**	**5**

Column Used: Xbridge C18 column (3.5 µm, 50 x 3 mm); Column Temperature: 40°C.

Method B

Waters Acquity H Class UPLC attached with Waters SQD 2 mass spectrometer; Ionisation method: Electro spray; Capillary (kV) 3.50, Cone (V) 25.00, Source Temperature (°C) 150, Desolvation Temperature (°C) 400, Cone Gas Flow (L/Hr) -50, Desolvation Gas Flow (L/Hr) -750;Mass range:100 to 900 Da; DAD Wavelength range (nm):

200 to 400; Solvent A: 5 mM NH_4OAc in water and Solvent B: 5 mM NH_4OAc in ACN: Water (90:10); Flow rate: 1.00 ml/min; (mobile phase: from 98% [5 mM NH_4OAc in water] and 2% [5 mM NH_4OAc in ACN: Water (90:10)] to 85% [5 mM NH_4OAc in water] and 15% [5 mM NH_4OAc in ACN: Water (90:10)] in 1.00 min, then 60% [5 mM NH_4OAc in water] and 40% [5 mM NH_4OAc in ACN: Water (90:10)] in 6.50 min, and finally 2% [5 mM NH_4OAc in water] and 98% [5 mM NH_4OAc in ACN: Water (90:10)] in 8.00 min, held this mobile phase composition up to 10.00 min and finally back to initial condition in 11.00 min and held this composition up to 12.00 min).

TIME	**Flow Rate (ml/min)**	**%A** (5 mM NH4OAc in water)	**% B** (5 mM NH4OAc in ACN: Water (90:10))
0.00	**1.00**	**98**	**2**
1.00	**1.00**	**85**	**15**
6.50	**1.00**	**60**	**40**
8.00	**1.00**	**2**	**98**
10.00	**1.00**	**2**	**98**
11.00	**1.00**	**98**	**2**
12.00	**1.00**	**98**	**2**

Column Used: Xbridge C18 column (3.5 µm, 50 x 3 mm); Column Temperature: 40°C.

Method B (K91-5-min)

Waters Acquity H Class UPLC attached with Waters SQD 2 mass spectrometer; Ionisation method: Electro spray; Capillary (kV) 3.50, Cone (V) 25.00, Source Temperature (°C) 150, Desolvation Temperature (°C) 400, Cone Gas Flow (L/Hr) -50, Desolvation Gas Flow (L/Hr) -750; Mass range:100 to 900 Da; DAD Wavelength range (nm): 200 to 400; Solvent A: 5 mM NH_4OAc in water and Solvent B: 5 mM NH_4OAc in ACN: Water (90:10); Flow rate: 1.20 ml/min; (mobile phase: 95% [5 mM NH_4OAc in water] and 5% [5 mM NH_4OAc in ACN: Water (90:10)] held for 0.75 min, then 85% [5 mM NH_4OAc in water] and 15% [5 mM NH_4OAc in ACN: Water (90:10)] in 1.25 min further 70% [5 mM NH_4OAc in water] and 30% [5 mM NH_4OAc in ACN: Water (90:10)] in 2.50 min, and finally 2% [5 mM NH_4OAc in water] and 98% [5 mM NH_4OAc in ACN: Water (90:10)] in 3.75 min, held this mobile phase composition up to 4.25 min and finally back to initial condition in 4.50 min and held this composition up to 5.10 min).

TIME	**Flow Rate (ml/min)**	**%A** (5 mM NH4OAc in water)	**% B** (5 mM NH4OAc in ACN: Water (90:10)
0.00	**1.20**	**95**	**5**
0.75	**1.20**	**95**	**5**
1.25	**1.20**	**85**	**15**
2.50	**1.20**	**70**	**30**
3.75	**1.20**	**2**	**98**

4.25	**1.20**	**2**	**98**
4.50	**1.20**	**95**	**5**
5.10	**1.20**	**95**	**5**

Column Used: Xbridge C18 column (3.5 µm, 50 x 3 mm); Column Temperature: 40°C.

Method C (K91-12-min)

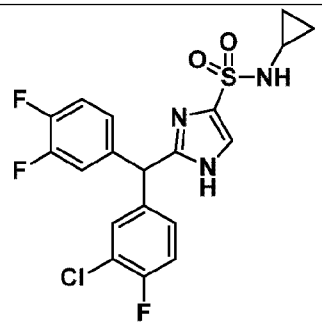
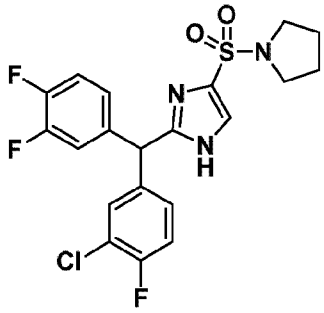
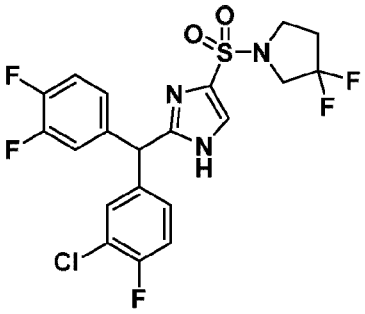
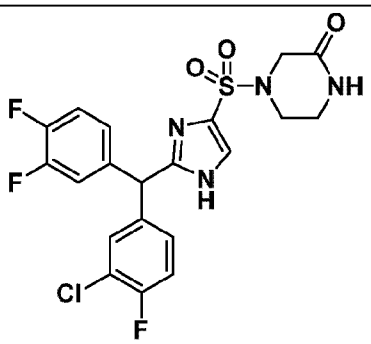
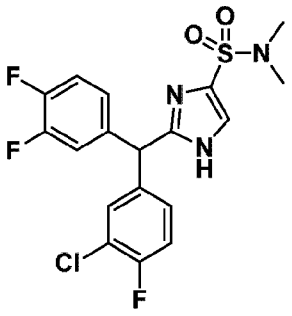
Waters Acquity H Class UPLC attached with Waters SQD 2 mass spectrometer; Ionisation method: Electro spray; Capillary (kV) 3.50, Cone (V) 25.00, Source Temperature (°C) 150, Desolvation Temperature (°C) 400, Cone Gas Flow (L/Hr) -50, Desolvation Gas Flow (L/Hr) -750; Mass range:100 to 900 Da; DAD Wavelength range (nm): 200 to 400; Solvent A: 5 mM NH4OAc in water and Solvent B: 5 mM NH_4OAc in ACN: Water (90:10); Flow rate: 1.00 ml/min; (mobile phase: from 98% [5 mM NH_4OAc in water] and 2% [5 mM NH_4OAc in ACN: Water (90:10)] to 85% [5 mM NH_4OAc in water] and 15% [5 mM NH_4OAc in ACN: Water (90:10)] in 1.00 min, then 60% [5 mM NH_4OAc in water] and 40% [5 mM NH_4OAc in ACN: Water (90:10)] in 6.50 min, and finally 2% [5 mM NH_4OAc in water] and 98% [5 mM NH_4OAc in ACN: Water (90:10)] in 8.00 min, held this mobile phase composition up to 10.00 min and finally back to initial condition in 11.00 min and held this composition up to 12.00 min).

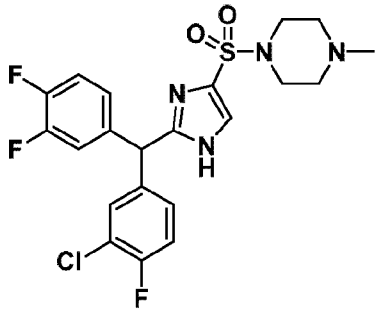
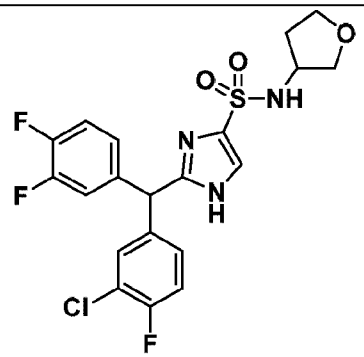
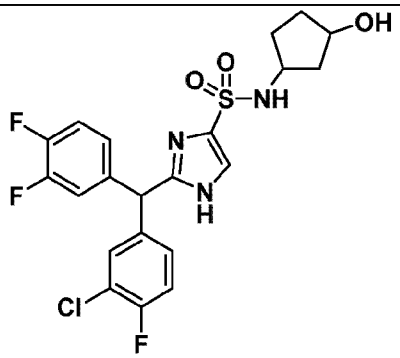
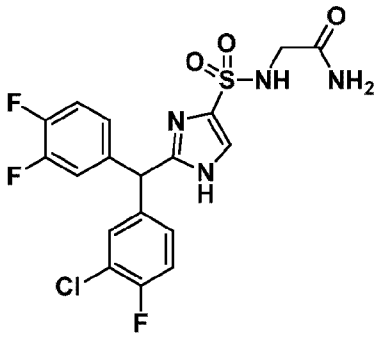
TIME	**Flow Rate (ml/min)**	**%A** (5 mM NH4OAc in water)	**% B** (5 mM NH4OAc in ACN: Water (90:10)
0.00	**1.00**	**98**	**2**
1.00	**1.00**	**85**	**15**
6.50	**1.00**	**60**	**40**
8.00	**1.00**	**2**	**98**
10.00	**1.00**	**2**	**98**
11.00	**1.00**	**98**	**2**
12.00	**1.00**	**98**	**2**

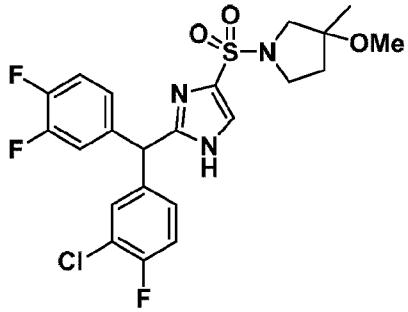
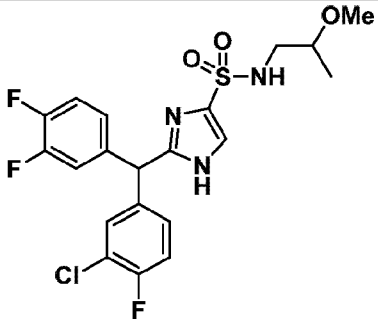
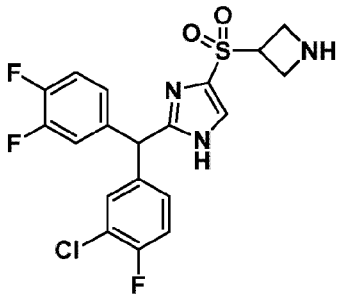
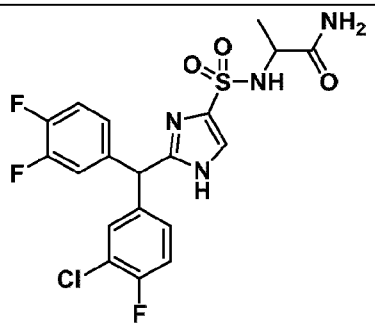
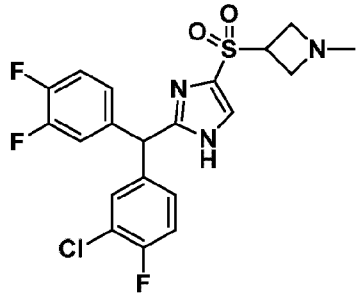
Column Used: Xbridge C18 column (3.5 µm, 50 x 3 mm); Column Temperature: 40°C.

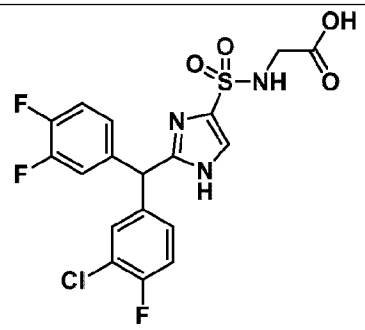
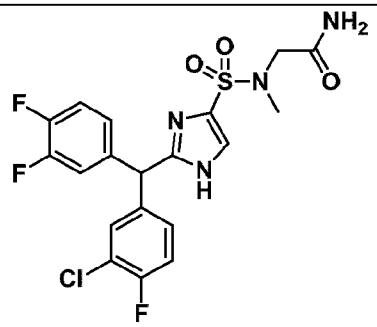
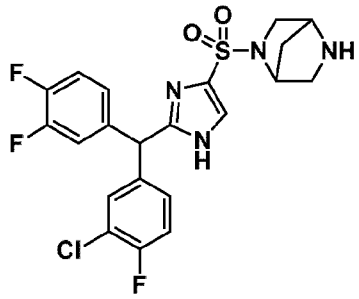
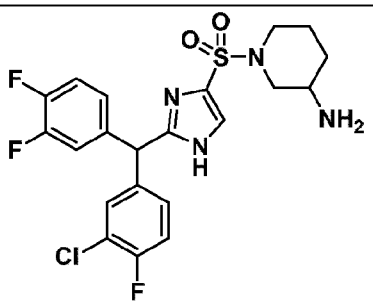
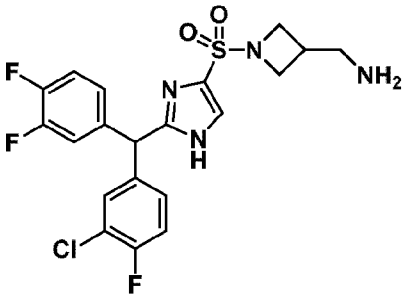
The following prophetic examples could be synthesized according to the general schemes and by analogy to the synthetic procedures described above:

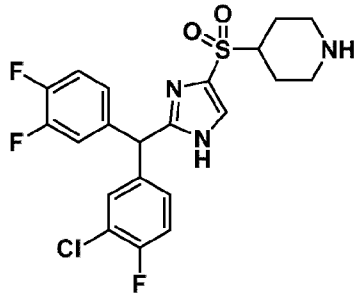
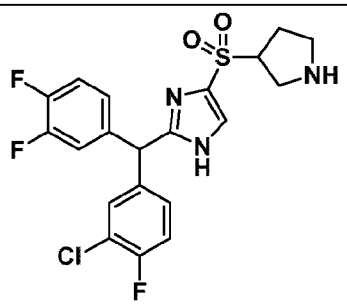
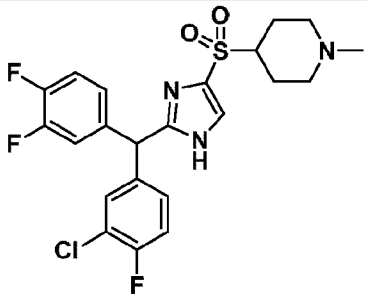
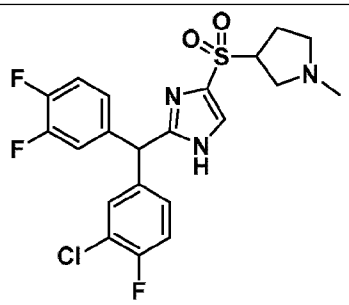
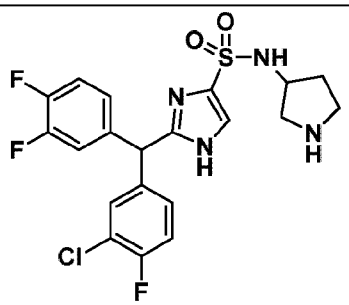
Structure	Prophetic example number	Chemical name

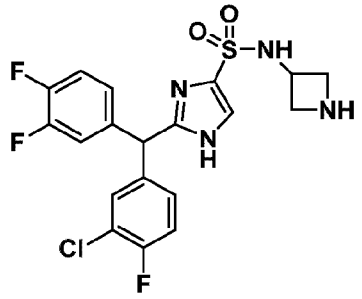
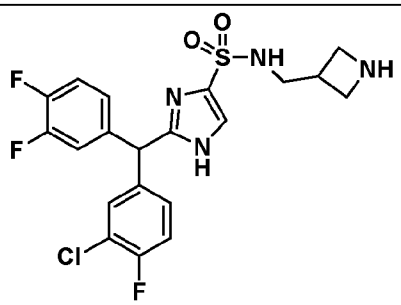
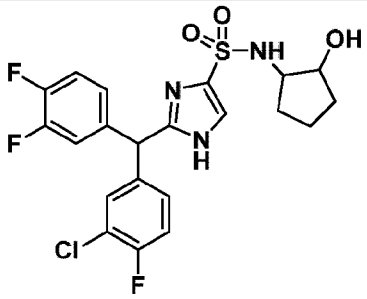
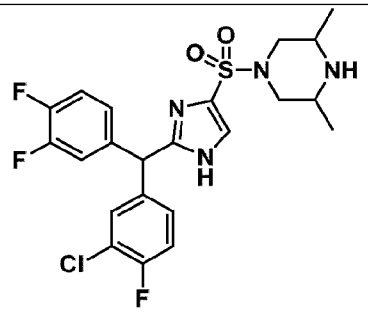
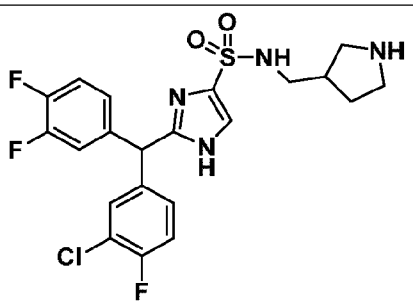
	94	2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-N-cyclopropyl-1H-imidazole-4-sulfonamide
	95	2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-4-(pyrrolidin-1-ylsulfonyl)-1H-imidazole
	96	2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-4-((3,3-difluoropyrrolidin-1-yl)sulfonyl)-1H-imidazole
	97	4-((2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazol-4-yl)sulfonyl)piperazin-2-one
	98	2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-N,N-dimethyl-1H-imidazole-4-sulfonamide

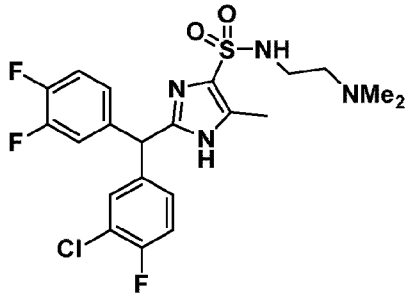
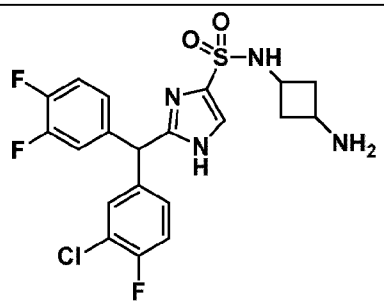
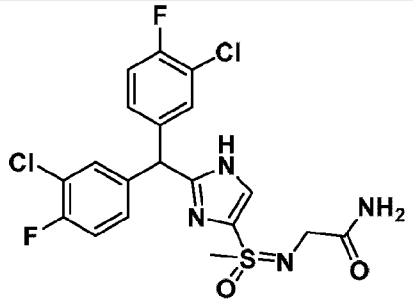
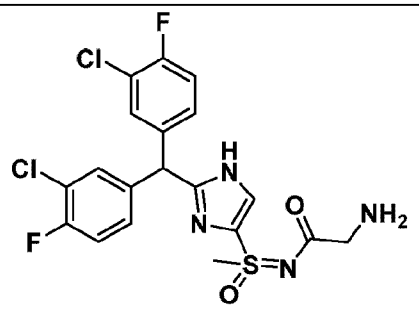
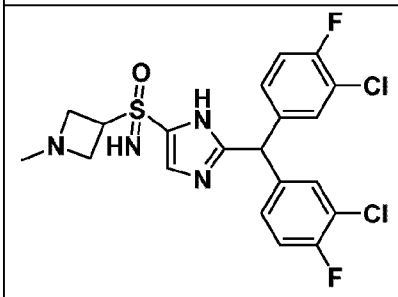
	99	1-((2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazol-4-yl)sulfonyl)-4-methylpiperazine
	102	2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-N-(tetrahydrofuran-3-yl)-1H-imidazole-4-sulfonamide
	103	2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-N-(3-hydroxycyclopentyl)-1H-imidazole-4-sulfonamide
	104	2-((2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazole)-4-sulfonamido)acetamide

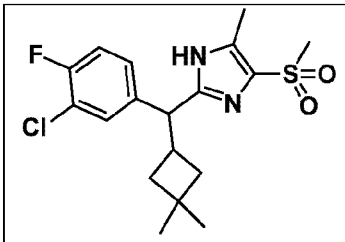
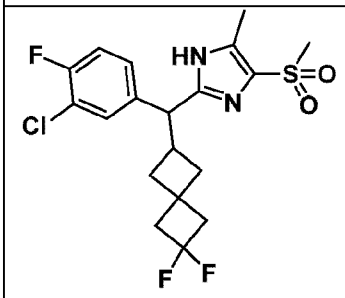
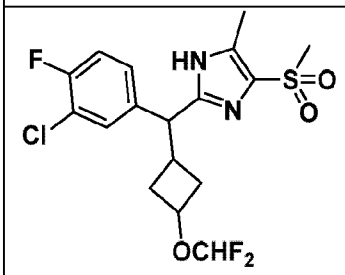
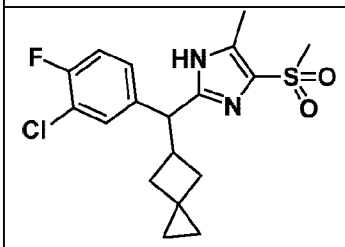
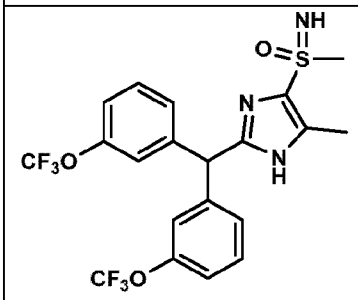
	106	2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-4-((3-methoxy-3-methylpyrrolidin-1-yl)sulfonyl)-1H-imidazole
	107	2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-N-(2-methoxypropyl)-1H-imidazole-4-sulfonamide
	108	4-(azetidin-3-ylsulfonyl)-2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazole
	109	2-((2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazole)-4-sulfonamido)propanamide
	110	2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-4-((1-methylazetidin-3-yl)sulfonyl)-1H-imidazole

	111	((2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazol-4-yl)sulfonyl)glycine
	112	2-((2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-N-methyl-1H-imidazole)-4-sulfonamido)acetamide
	113	2-((2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazol-4-yl)sulfonyl)-2,5-diazabicyclo[2.2.1]heptane
	114	1-((2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazol-4-yl)sulfonyl)piperidin-3-amine
	115	(1-((2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazol-4-yl)sulfonyl)azetidin-3-yl)methanamine

	116	4-((2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazol-4-yl)sulfonyl)piperidine
	117	2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-4-(pyrrolidin-3-ylsulfonyl)-1H-imidazole
	118	4-((2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazol-4-yl)sulfonyl)-1-methylpiperidine
	119	2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-4-((1-methylpyrrolidin-3-yl)sulfonyl)-1H-imidazole
	120	2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-N-(pyrrolidin-3-yl)-1H-imidazole-4-sulfonamide

	121	N-(azetidin-3-yl)-2-((3-chloro-4-fluorophenyl)(3,4-difluoro-phenyl)methyl)-1H-imidazole-4-sulfonamide
	122	N-(azetidin-3-ylmethyl)-2-((3-chloro-4-fluorophenyl)(3,4-difluoro-phenyl)methyl)-1H-imidazole-4-sulfonamide
	123	2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-N-(2-hydroxycyclopentyl)-1H-imidazole-4-sulfonamide
	124	1-((2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazol-4-yl)sulfonyl)-3,5-dimethylpiperazine
	125	2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-N-(pyrrolidin-3-ylmethyl)-1H-imidazole-4-sulfonamide

	126	2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-N-(2-(dimethylamino)ethyl)-5-methyl-1H-imidazole-4-sulfonamide
	127	N-(3-aminocyclobutyl)-2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazole-4-sulfonamide
	128	2-(((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-4-yl)(methyl)(oxo)-l6-sulfaneylidene)amino)acetamide
	129	2-amino-N-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-4-yl)(methyl)(oxo)-l6-sulfaneylidene)acetamide
	134	(2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)(imino)(1-methylazetidin-3-yl)-l6-sulfanone

	136	2-((3-chloro-4-fluorophenyl)(3,3-dimethylcyclobutyl)methyl)-5-methyl-4-(methylsulfonyl)-1H-imidazole
	137	2-((3-chloro-4-fluorophenyl)(6,6-difluorospiro[3.3]heptan-2-yl)methyl)-5-methyl-4-(methylsulfonyl)-1H-imidazole
	138	2-((3-chloro-4-fluorophenyl)(3-(difluoromethoxy)cyclobutyl)methyl)-5-methyl-4-(methylsulfonyl)-1H-imidazole
	139	2-((3-chloro-4-fluorophenyl)(spiro[2.3]hexan-5-yl)methyl)-5-methyl-4-(methylsulfonyl)-1H-imidazole
	146	(2-(bis(3-(trifluoromethoxy)phenyl)methyl)-5-methyl-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone

Electrophysiology: Voltage-Clamp recordings

The following $Na_V1.8$ recombinant cell line was used for recordings: HEK-$Na_V1.8$ (NM_006514.1) with b3 (NM_018400.3).

Sodium currents were measured using the patch clamp technique in the whole-cell configuration using the Qube384 (Sophion A/S, Copenhagen, Denmark) automated voltage clamp platform. "Multi hole" plates were used

for the cell line expressing $Na_V1.8$ while "single or multi hole" plates were used for the recombinant cell lines expressing the other subtypes. Appropriate filters (for minimum seal resistance and minimum current size) and series resistance compensation (for high quality sodium channel recordings) were applied. Data was collected at ambient room temperature or 19 °C.

The recording extracellular solution contained (in mM): NaCl 145 mM, KCl 4 mM, $CaCl_2$ 2 mM, $MgCl_2$ 1 mM, HEPES 10 mM, Glucose 10 mM, pH 7.4 (NaOH). The intracellular recording solution contained (in mM): CsF 120 mM, CsCl 20 mM, NaCl 10 mM, EGTA 10 mM, HEPES 10 mM, pH 7.2 (CsOH). Currents were recorded at 25 kHz sampling frequency and filtered at 5 kHz. Series resistance compensation was applied at 65%.

Vehicle (VEH) is the control condition where cells are exposed to 0.3% DMSO without compound. All runs include VEH controls being exposed to the same voltage protocols to assess non-compound related phenomena such as run down and then used to isolate compound dependent effects on currents.

To check for *state-dependent inhibition*, the following voltage-sequence was applied every 20 seconds:

From a resting membrane potential of -120 mV, the first test pulse (P1; 20 ms to -10 mV) was applied to check for channels in the Resting State followed by a brief recovery (100 ms to -120 mV), then holding the membrane voltage to $V_{1/2}$ (4 seconds at voltage to obtain half the channel at Rest and half Inactivated) with a subsequent second test pulse (P2; 20 ms to -10 mV) to check for channels in the Inactivated State, followed by another brief recovery (20 ms to -120 mV) and a final third test pulse (P3; 20 ms to -10 mV) to check for recovered channels.

To check for *frequency-dependent inhibition*, a 10 Hz protocol and a 20 Hz protocol were applied; namely,

From a resting membrane potential of -120 mV, 40-pulses (10 ms to -10 mV) was applied at 10 Hz (at 100 ms between pulses) and then at 20 Hz (at 50 ms between pulses).

Each parameter was recorded (P1, P2, P3, P40 from 10Hz and P40 from 20Hz) during a control period (lasting ~ 5 minutes) when establishing the baseline and during compound period (lasting ~ 12 minutes) when test compound (or vehicle) was applied. For each parameter, the value at the end of the compound period was normalized to the vehicle baseline; as follows

$$Normalized\ Inhibition\ (Norm_{CPD}) = \frac{CPD\ Value_{end\ CPD\ period}}{VEH\ Value_{end\ Control\ Period}}$$

To adjust for any variance in the Na^+ current signal during the compound period (owing to cumulative inactivation independent of compound or shifts in biophysics over time), a dedicated segment of the recording wells in each 384 plate were dedicated to having only vehicle exposure. These vehicle-only recordings were used to correct for any apparent "run-up" or "run-down" in the experiment.

$$Normalized\ Inhibition\ (Norm_{VEH}) = \frac{VEH\ Value_{end\ CPD\ period}}{VEH\ Value_{end\ Control\ Period}}$$

The adjusted inhibition was calculated as follows:

$$\%\ Inhibition_{corrected} = 100 \times \frac{Norm_{CPD} - Norm_{VEH}}{100 - Norm_{VEH}}$$

Percent inhibition was determined and IC_{50} values were calculated using a 4 parameter logistic model within XLFit Software (IDBS, Boston MA):

$$\%\ Inhibition_{corrected} = A + \frac{(B - A)}{(1 + \left(\frac{x}{C}\right)^{D}}$$

where A and B are the maximal and minimum inhibition respectively, C is the IC_{50} concentration and D is the (Hill) slope.

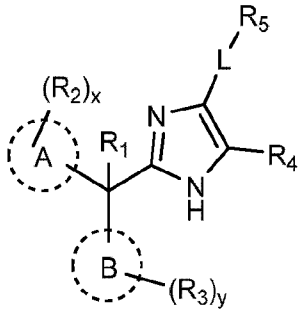
The potency data of the example compounds are summarized in the table below (category **A**: human NaV1.8 $IC_{50} \leq 0.1$ µM; category **B**: 0.1 µM < human NaV1.8 $IC_{50} \leq 1$ µM; category **C**: 1 µM < human NaV1.8 $IC_{50} \leq 10$ µM; "n.d.": not determined):

Example	Potency category	Example	Potency category	Example	Potency category
1	A	80	A	175b	C
2	A	81	B	176	n.d.
3	A	82a	A	177	A
4	A	82b	A	178a	B
5	A	87	A	178b	A
6	B	88a	A	179	A
7	A	88b	B	180a	B
8	B	89	B	180b	A
9	A	91	A	181	A
10	A	92a	A	182	A
11	A	92b	B	183	A
12	A	93	A	184a	A
13	B	130a	A	184b	A
14	A	130b	A	185a	A
15	B	131	B	185b	A
16	A	132a	A	186a	A
17	A	132b	B	186b	A
18	A	132c	A	187a	A
19	B	132d	B	187b	A
20	A	133a	A	188a	A
21	A	133b	A	188b	A
22	B	135a	B	189a	A
23	A	135b	A	189b	A
24	A	140a	A	190a	A
25	A	140b	A	190b	A
26	B	141a	A	191	A
27	A	141b	A	192a	B
28	A	142a	A	192b	B
29	B	142b	A	193	A
30	B	143a	A	194	A
31	A	143b	A	195	A
32	A	144a	A	196	A
33	A	144b	A	197	A
34	B	145a	A	198	A
35	A	145b	A	199	A
36	A	148	A	200	A
37	B	149a	A	201	C
38	A	150	A	202a	B
39	B	151	A	202b	A
40	A	152	A	202c	B
41	A	153	B	202d	B
43	A	154a	A	203a	B
44	B	155a	A	203b	B
45	A	156	A	203c	B
46	B	157a	A	203d	B
47	A	158a	A	204	B

48	n.d.		158b	A		205	C
49	n.d.		159	A			
50	n.d.		160a	A			
51	n.d.		161a	A			
52	n.d.		161b	A			
53	n.d.		162	B			
54	n.d.		163a	A			
55	A		164	A			
59	A		165	A			
60	A		166	A			
61	A		167	A			
62	n.d.		168	A			
76a	A		169	B			
76b	A		170	A			
77a	A		171	n.d.			
77b	A		172	A			
78a	A		173	B			
78b	A		174	C			
79	A		175a	C			

CLAIMS

1. A compound according to general formula (I)



(I)

wherein

R_1 represents H or OH;

A and B independently from one another represent phenyl, 5 to 10-membered heteroaryl, C_{3-7}-cycloalkyl, or 4- to 10-membered heterocycloalkyl;

R_2 and R_3 independently from one another represent F, Cl, CN, C_{1-4}-alkyl, C_{3-6}-cycloalkyl, NH_2, $N(H)C_{1-4}$-alkyl, $N(C_{1-4}\text{-alkyl})_2$, OH, or $O\text{-}C_{1-4}$-alkyl;

x and y independently from one another represent 0, 1, 2, 3, or 4;

R_4 represents H, Cl, C_{1-6}-alkyl, or C_{3-6}-cycloalkyl;

L represents bond, C_{1-3}-alkylene or C_{1-2}-alkylene-N(H); and

R_5 represents $S(=O)R_6$, $S(=O)(=NH)R_6$, $S(=O)(=N(C_{1-4}\text{-alkyl}))R_6$, $S(=O)(=NR_6)R_6$, $S(=O)_2R_6$, $S(=O)_2NH_2$, $S(=O)_2N(H)R_6$, or $S(=O)_2N(C_{1-4}\text{-alkyl})R_6$;

R_6 represents C_{1-6}-alkyl, C_{3-7}-cycloalkyl, 4- to 10-membered heterocycloalkyl, C_{1-4}-alkylene-(C_{3-7}-cycloalkyl), or C_{1-4}-alkylene-(4- to 7-membered heterocycloalkyl);

or R_4 and R_5 together with the carbon atoms to which they are connected form 5- to 7- membered heterocycloalkyl;

wherein C_{1-6}-alkyl, C_{1-4}-alkyl, C_{1-4}-alkylene, C_{1-3}-alkylene and C_{1-2}-alkylene in each case independently from one another is linear or branched, saturated or unsaturated;

wherein C_{1-6}-alkyl, C_{1-4}-alkyl, C_{1-4}-alkylene, C_{1-3}-alkylene, C_{1-2}-alkylene, C_{3-6}-cycloalkyl, C_{5-7}-cycloalkyl, 4- to 7- membered heterocycloalkyl, 4- to 10- membered heterocycloalkyl, and 5- to 7- membered heterocycloalkyl in each case independently from one another are unsubstituted or mono- or polysubstituted with one or more substituents selected from F; Cl; CN; C_{1-6}-alkyl; C_{1-6}-alkylene-NH_2, CF_3; CF_2H; CFH_2; $C(O)\text{-}C_{1-6}$-alkyl; C(O)-OH; $C(O)\text{-}OC_{1-6}$-alkyl; $C(O)\text{-}NH_2$; $C(O)\text{-}N(H)(C_{1-6}\text{-alkyl})$; $C(O)\text{-}N(C_{1-6}\text{-alkyl})_2$; OH; =O; OCF_3; OCF_2H; $OCFH_2$; $O\text{-}C_{1-6}$-alkyl; NH_2; $N(H)(C_{1-6}\text{-alkyl})$; $N(C_{1-6}\text{-alkyl})_2$; $N(H)\text{-}C(O)\text{-}C_{1-6}$-alkyl; and $S(O)_2\text{-}C_{1-6}$-alkyl;

wherein phenyl, 5 to 10-membered heteroaryl and 5 or 6-membered heteroaryl in each case independently from one another are unsubstituted or mono- or polysubstituted with one or more substituents selected from

F; Cl; CN; C_{1-6}-alkyl; CF_3; CF_2H; CFH_2; OH; OCF_3; OCF_2H; $OCFH_2$; O-C_{1-6}-alkyl; NH_2; N(H)(C_{1-6}-alkyl); and N(C_{1-6}-alkyl)$_2$;

in the form of the free compound or a physiologically acceptable salt thereof.

2. The compound according to claim 1, wherein
R_1 represents H.

3. The compound according to claim 1 or 2, wherein
x and y independently from one another represent 1 or 2.

4. The compound according to any of the preceding claims, wherein at least one of A and B represents phenyl or 5- or 6-membered heteroaryl.

5. The compound according to any of the preceding claims, wherein A represents phenyl.

6. The compound according to any of the preceding claims, wherein B represents phenyl, 5- or 6-membered heteroaryl, or C_{3-7}-cycloalkyl.

7. The compound according to any of the preceding claims, wherein
R_2 represents F, Cl, OCH_3, OCF_3, or CHF_2.

8. The compound according to any of the preceding claims, wherein
R_3 represents F, Cl, NH_2, CH_3, CF_3, CHF_2, OCH_3, OCF_3, $OCHF_2$ or O-CH_2-CF_3.

9. The compound according to any of the preceding claims, wherein
L represents bond or C_{1-3}-alkylene.

10. The compound according to any of the preceding claims, wherein
R_5 represents S(=O)R_6, S(=O)(=NH)R_6, S(=O)(=N(C_{1-4}-alkyl))R_6, S(=O)$_2R_6$, S(=O)$_2NH_2$, S(=O)$_2$N(H)R_6, or S(=O)$_2$N(C_{1-4}-alkyl)R_6.

11. The compound according to any of the preceding claims, wherein
R_6 represents

(vi) C_{1-6}-alkyl selected from the group consisting of methyl, ethyl, n-propyl, 2-propyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, 2-pentyl, 3-pentyl, 2-methylbutyl, 3-methylbutyl, 3-methylbut-2-yl, 2-methylbut-2-yl, 2,2-dimethylpropyl, and n-hexyl;

(vii) C_{3-7}-cycloalkyl selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, spiro[2.2]pentyl, spiro[2.3]hexyl, spiro[3.3]heptyl, bicyclo[1.1.0]butyl, bicyclo[2.1.0]pentyl, bicyclo[2.1.1]hexyl, bicyclo[3.1.1]heptyl, bicyclo[2.2.1]heptyl, bicyclo[3.1.0]hexyl, bicyclo[3.2.0]heptyl, and bicyclo[4.1.0]heptyl;

(viii) 4- to 10-membered heterocycloalkyl selected from the group consisting of 1,1-dioxo tetrahydrothiophenyl, 1-oxo thiomorpholinyl, tetrahydropyranyl, oxetanyl, tetrahydrofuranyl, morpholinyl, pyrrolidinyl, pyrrolidinonyl, azetidinyl, piperazinyl, piperazinonyl, piperidinyl, thietanyl, 1,1-dioxothietanyl, 2,6-diazaspiro[3.3]heptyl, 2,5-diazabicyclo[2.2.1]heptyl, tetrahydro-2H-thiopyranyl 1,1-dioxide, azepanyl, dioxepanyl, oxazepanyl, diazepanyl, thiazolidinyl, tetrahydrothiophenyl, tetrahydropyridinyl, thiomorpholinyl, 4-methylpiperazinyl, morpholinonyl, dithiolanyl, dihydropyrrolyl, dioxanyl, dioxolanyl, dihydropyridinyl, dihydrofuranyl, dihydroisoxazolyl, dihydrooxazolyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, and pyrazolidinyl;

(ix) C_{1-4}-alkylene-(C_{3-7}-cycloalkyl) selected from the group consisting of $(CH_2)_{1-2}$-cyclopropyl, $(CH_2)_{1-2}$-cyclobutyl, $(CH_2)_{1-2}$-cyclopentyl, $(CH_2)_{1-2}$-cyclohexyl; $(CH_2)_{1-2}$-cycloheptyl, $(CH_2)_{1-2}$-spiro[2.2]pentyl, $(CH_2)_{1-2}$-spiro[2.3]hexyl, $(CH_2)_{1-2}$-spiro[3.3]heptyl, $(CH_2)_{1-2}$-bicyclo[1.1.0]butyl, $(CH_2)_{1-2}$-bicyclo[2.1.0]pentyl, $(CH_2)_{1-2}$-bicyclo[2.1.1]hexyl, $(CH_2)_{1-2}$-bicyclo[3.1.1]heptyl, $(CH_2)_{1-2}$-bicyclo[2.2.1]heptyl, $(CH_2)_{1-2}$-bicyclo[3.1.0]hexyl, $(CH_2)_{1-2}$-bicyclo[3.2.0]heptyl, and $(CH_2)_{1-2}$-bicyclo[4.1.0]heptyl; or

(x) C_{1-4}-alkylene-(4- to 7-membered heterocycloalkyl) selected from the group consisting of $(CH_2)_{1-2}$-(1,1-dioxo tetrahydrothiophenyl), $(CH_2)_{1-2}$-(1-oxo thiomorpholinyl), $(CH_2)_{1-2}$-tetrahydropyranyl, $(CH_2)_{1-2}$-oxetanyl, $(CH_2)_{1-2}$-tetrahydrofuranyl, $(CH_2)_{1-2}$-morpholinyl, $(CH_2)_{1-2}$-pyrrolidinyl, $(CH_2)_{1-2}$-pyrrolidinonyl, $(CH_2)_{1-2}$-azetidinyl, $(CH_2)_{1-2}$-piperazinyl, $(CH_2)_{1-2}$-piperazinonyl, $(CH_2)_{1-2}$-piperidinyl, $(CH_2)_{1-2}$-thietanyl, $(CH_2)_{1-2}$-(1,1-dioxothietanyl), $(CH_2)_{1-2}$-(2,6-diazaspiro[3.3]heptyl), $(CH_2)_{1-2}$-(2,5-diazabicyclo[2.2.1]heptyl), $(CH_2)_{1-2}$-tetrahydro-2H-thiopyranyl 1,1-dioxide, $(CH_2)_{1-2}$-azepanyl, $(CH_2)_{1-2}$-dioxepanyl, $(CH_2)_{1-2}$-oxazepanyl, $(CH_2)_{1-2}$-diazepanyl, $(CH_2)_{1-2}$-thiazolidinyl, $(CH_2)_{1-2}$-tetrahydrothiophenyl, $(CH_2)_{1-2}$-tetrahydropyridinyl, $(CH_2)_{1-2}$-thiomorpholinyl, $(CH_2)_{1-2}$-(4-methylpiperazinyl), $(CH_2)_{1-2}$-morpholinonyl, $(CH_2)_{1-2}$-dithiolanyl, $(CH_2)_{1-2}$-dihydropyrrolyl, $(CH_2)_{1-2}$-dioxanyl, $(CH_2)_{1-2}$-dioxolanyl, $(CH_2)_{1-2}$-dihydropyridinyl, $(CH_2)_{1-2}$-dihydrofuranyl, $(CH_2)_{1-2}$-dihydroisoxazolyl, $(CH_2)_{1-2}$-dihydrooxazolyl, $(CH_2)_{1-2}$-imidazolidinyl, $(CH_2)_{1-2}$-isoxazolidinyl, $(CH_2)_{1-2}$-oxazolidinyl, and $(CH_2)_{1-2}$-pyrazolidin;

wherein said methyl, ethyl, n-propyl, 2-propyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, 2-pentyl, 3-pentyl, 2-methylbutyl, 3-methylbutyl, 3-methylbut-2-yl, 2-methylbut-2-yl, 2,2-dimethylpropyl, n-hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, spiro[2.2]pentyl, spiro[2.3]hexyl, spiro[3.3]heptyl, bicyclo[1.1.0]butyl, bicyclo[2.1.0]pentyl, bicyclo[2.1.1]hexyl, bicyclo[3.1.1]heptyl, bicyclo[2.2.1]heptyl, bicyclo[3.1.0]hexyl, bicyclo[3.2.0]heptyl, and bicyclo[4.1.0]heptyl, 1,1-dioxo tetrahydrothiophenyl, 1-oxo thiomorpholinyl, tetrahydropyranyl, oxetanyl, tetrahydrofuranyl, morpholinyl, pyrrolidinyl, pyrrolidinonyl, azetidinyl, piperazinyl, piperazinonyl, piperidinyl, thietanyl, 1,1-dioxothietanyl, 2,6-diazaspiro[3.3]heptyl, 2,5-diazabicyclo[2.2.1]heptyl, tetrahydro-2H-thiopyranyl 1,1-dioxide, azepanyl, dioxepanyl, oxazepanyl, diazepanyl, thiazolidinyl, tetrahydrothiophenyl, tetrahydropyridinyl, thiomorpholinyl, 4-methylpiperazinyl, morpholinonyl, dithiolanyl, dihydropyrrolyl, dioxanyl, dioxolanyl, dihydropyridinyl, dihydrofuranyl, dihydroisoxazolyl, dihydrooxazolyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, and pyrazolidinyl in each case independently from one another are unsubstituted or mono- or polysubstituted with one or more substituents selected from F; Cl; CN; C_{1-6}-alkyl; CF_3; CF_2H; CFH_2; C(O)-C_{1-6}-alkyl; C(O)-OH; C(O)-OC_{1-6}-alkyl; C(O)-NH_2; C(O)-N(H)(C_{1-6}-alkyl); C(O)-N(C_{1-6}-alkyl)$_2$; OH; =O;

OCF_3; OCF_2H; $OCFH_2$; O-C_{1-6}-alkyl;; NH_2; N(H)(C_{1-6}-alkyl); N(C_{1-6}-alkyl)$_2$; N(H)-C(O)-C_{1-6}-alkyl; and $S(O)_2$-C_{1-6}-alkyl.

12. The compound according to any of claims 1 to 9, wherein
R_4 and R_5 together with the carbon atoms to which they are connected form thiepanyl 1,1-dioxide, 1,2-thiazepanyl 1,1-dioxide, 2,5,6,7-tetrahydro-1,2-thiazepinyl 1,1-dioxide, or 5,6-dihydro-2H-1,2-thiazinyl 1,1-dioxide.

13. The compound according to any of the preceding claims selected from the group consisting of

1	2-(bis(3-chloro-4-fluorophenyl)methyl)-5-(methylsulfonyl)-1H-imidazole
2	2-(bis(3-chloro-4-fluorophenyl)methyl)-5-(ethylsulfonyl)-1H-imidazole
3	2-(bis(3-chloro-4-fluorophenyl)methyl)-5-(cyclopropylsulfonyl)-1H-imidazole
4	2-(bis(3-chloro-4-fluorophenyl)methyl)-4-(isopropylsulfonyl)-1H-imidazole
5	2-(bis(3-chloro-4-fluorophenyl)methyl)-4-((tetrahydrofuran-3-yl)sulfonyl)-1H-imidazole
6	2-(bis(3-chloro-4-fluorophenyl)methyl)-4-((tetrahydro-2H-pyran-4-yl)sulfonyl)-1H-imidazole
7	2-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-4-yl)sulfonyl)ethan-1-amine
8	2-(bis(3-chloro-4-fluorophenyl)methyl)-5-chloro-4-(methylsulfonyl)-1H-imidazole
9	2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazole-5-sulfonamide
10	2-(bis(3-chloro-4-fluorophenyl)methyl)-4-methyl-1H-imidazole-5-sulfonamide
11	2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(1-(dimethylamino)propan-2-yl)-1H-imidazole-5-sulfonamide
12	2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(2-(pyrrolidin-1-yl)ethyl)-1H-imidazole-5-sulfonamide
13	1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-4-isopropylpiperazine
14	1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-4-ethylpiperazine
15	1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-4-(methylsulfonyl)piperazine
16	2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(2-hydroxyethyl)-N-methyl-1H-imidazole-5-sulfonamide
17	2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(2-methoxyethyl)-1H-imidazole-5-sulfonamide
18	2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(2-(dimethylamino)ethyl)-1H-imidazole-5-sulfonamide
19	1-(4-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)piperazin-1-yl)ethan-1-one
20	2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(2-hydroxypropyl)-1H-imidazole-5-sulfonamide
21	2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(oxetan-2-ylmethyl)-1H-imidazole-5-sulfonamide
22	1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-N,N-dimethylazetidin-3-amine
23	1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-N,N-dimethylpyrrolidin-3-amine

24	2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(2-(methylsulfonyl)ethyl)-1H-imidazole-5-sulfonamide
25	2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(2-hydroxyethyl)-1H-imidazole-5-sulfonamide
26	2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(2-hydroxy-2-methylpropyl)-1H-imidazole-5-sulfonamide
27	2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(1-methoxypropan-2-yl)-1H-imidazole-5-sulfonamide
28	2-(bis(3-chloro-4-fluorophenyl)methyl)-N-methyl-N-(2-(methylsulfonyl)ethyl)-1H-imidazole-5-sulfonamide
29	4-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)thiomorpholine 1-oxide
30	2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(3-methoxypropyl)-1H-imidazole-5-sulfonamide
31	2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(oxetan-3-ylmethyl)-1H-imidazole-5-sulfonamide
32	2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(3-(dimethylamino)propyl)-1H-imidazole-5-sulfonamide
33	1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-N,N-dimethylpiperidin-4-amine
34	ethyl ((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)glycinate
35	2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(1,1-dioxidothietan-3-yl)-1H-imidazole-5-sulfonamide
36	2-(bis(3-chloro-4-fluorophenyl)methyl)-N-((3R,4R)-4-hydroxytetrahydro-2H-pyran-3-yl)-1H-imidazole-5-sulfonamide
37	2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(1,1-dioxidotetrahydrothiophen-3-yl)-N-methyl-1H-imidazole-5-sulfonamide
38	1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)azetidin-3-ol
39	2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(2,3-dimethoxypropyl)-1H-imidazole-5-sulfonamide
40	2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(oxetan-3-yl)-1H-imidazole-5-sulfonamide
41	1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)piperazine
43	N-(2-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazole)-5-sulfonamido)ethyl)acetamide
44	N-(1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)azetidin-3-yl)acetamide
45	2-((2-(bis(3-chloro-4-fluorophenyl)methyl)-N-methyl-1H-imidazole)-5-sulfonamido)-N-methylacetamide
46	2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(3-methoxycyclobutyl)-1H-imidazole-5-sulfonamide
47	2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(3-hydroxycyclopentyl)-1H-imidazole-5-sulfonamide
48	N-(1-acetylpiperidin-4-yl)-2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazole-5-sulfonamide
49	2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(2,2-difluoroethyl)-1H-imidazole-5-sulfonamide

50	3-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazole)-5-sulfonamido)-2,2-dimethylpropanamide
51	2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(1-methylpiperidin-4-yl)-1H-imidazole-5-sulfonamide
52	methyl ((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)glycinate
53	2-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazole)-5-sulfonamido)propanamide
54	2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(cyanomethyl)-1H-imidazole-5-sulfonamide
55	2-(bis(3-chloro-4-fluorophenyl)methyl)-N-methyl-N-(2-(methylamino)ethyl)-1H-imidazole-5-sulfonamide
59	1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-3-methylpiperazine
60	1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-N-methylpyrrolidin-3-amine
61	2-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-2,6-diazaspiro[3.3]heptane
62	2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(piperidin-3-yl)-1H-imidazole-5-sulfonamide
76	2-(bis(3-chloro-4-fluorophenyl)methyl)-5-(methylsulfinyl)-1H-imidazole
77	2-(bis(3-chloro-4-fluorophenyl)methyl)-4-methyl-5-(methylsulfinyl)-1H-imidazole
78	(2-(bis(3-chloro-4-fluorophenyl)methyl)-4-methyl-1H-imidazol-5-yl)(imino)(methyl)-l6-sulfanone
79	2-(bis(3-chloro-4-fluorophenyl)methyl)-4-methyl-5-(methylsulfonyl)-1H-imidazole
80	2-(bis(3-chloro-4-fluorophenyl)methyl)-4-cyclopropyl-5-(methylsulfonyl)-1H-imidazole
81	2-(bis(3-chloro-4-fluorophenyl)methyl)-5-(methylsulfonyl)-4-(trifluoromethyl)-1H-imidazole
82	(2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)(imino)(methyl)-l6-sulfanone
87	(2-(bis(3-chloro-4-fluorophenyl)methyl)-4-(methylsulfonyl)-1H-imidazol-5-yl)methanol
88	5-((3-chloro-4-fluorophenyl)(4-(methylsulfonyl)-1H-imidazol-2-yl)methyl)-2-(2,2,2-trifluoroethoxy)pyridine
89	2-((3-chloro-4-fluorophenyl)(4-(methylsulfonyl)-1H-imidazol-2-yl)methyl)-4-fluoroaniline
91	2-(bis(3-chloro-4-fluorophenyl)methyl)-4-((methylsulfonyl)methyl)-1H-imidazole
92	2-((3-chloro-4-fluorophenyl)(4-(trifluoromethyl)cyclohexyl)methyl)-4-(methylsulfonyl)-1H-imidazole
93	3-chloro-6-((4-chlorophenyl)(4-(methylsulfonyl)-1H-imidazol-2-yl)methyl)-2-(trifluoromethyl)pyridine
94	2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-N-cyclopropyl-1H-imidazole-4-sulfonamide
95	2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-4-(pyrrolidin-1-ylsulfonyl)-1H-imidazole
96	2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-4-((3,3-difluoropyrrolidin-1-yl)sulfonyl)-1H-imidazole
97	4-((2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazol-4-yl)sulfonyl)piperazin-2-one

98	2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-N,N-dimethyl-1H-imidazole-4-sulfonamide
99	1-((2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazol-4-yl)sulfonyl)-4-methylpiperazine
102	2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-N-(tetrahydrofuran-3-yl)-1H-imidazole-4-sulfonamide
103	2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-N-(3-hydroxycyclopentyl)-1H-imidazole-4-sulfonamide
104	2-((2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazole)-4-sulfonamido)acetamide
106	2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-4-((3-methoxy-3-methylpyrrolidin-1-yl)sulfonyl)-1H-imidazole
107	2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-N-(2-methoxypropyl)-1H-imidazole-4-sulfonamide
108	4-(azetidin-3-ylsulfonyl)-2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazole
109	2-((2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazole)-4-sulfonamido)propanamide
110	2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-4-((1-methylazetidin-3-yl)sulfonyl)-1H-imidazole
111	((2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazol-4-yl)sulfonyl)glycine
112	2-((2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-N-methyl-1H-imidazole)-4-sulfonamido)acetamide
113	2-((2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazol-4-yl)sulfonyl)-2,5-diazabicyclo[2.2.1]heptane
114	1-((2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazol-4-yl)sulfonyl)piperidin-3-amine
115	(1-((2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazol-4-yl)sulfonyl)azetidin-3-yl)methanamine
116	4-((2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazol-4-yl)sulfonyl)piperidine
117	2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-4-(pyrrolidin-3-ylsulfonyl)-1H-imidazole
118	4-((2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazol-4-yl)sulfonyl)-1-methylpiperidine
119	2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-4-((1-methylpyrrolidin-3-yl)sulfonyl)-1H-imidazole
120	2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-N-(pyrrolidin-3-yl)-1H-imidazole-4-sulfonamide
121	N-(azetidin-3-yl)-2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazole-4-sulfonamide

122 N-(azetidin-3-ylmethyl)-2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazole-4-sulfonamide

123 2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-N-(2-hydroxycyclopentyl)-1H-imidazole-4-sulfonamide

124 1-((2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazol-4-yl)sulfonyl)-3,5-dimethylpiperazine

125 2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-N-(pyrrolidin-3-ylmethyl)-1H-imidazole-4-sulfonamide

126 2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-N-(2-(dimethylamino)ethyl)-5-methyl-1H-imidazole-4-sulfonamide

127 N-(3-aminocyclobutyl)-2-((3-chloro-4-fluorophenyl)(3,4-difluorophenyl)methyl)-1H-imidazole-4-sulfonamide

128 2-(((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-4-yl)(methyl)(oxo)-l6-sulfaneylidene)amino)acetamide

129 2-amino-N-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-4-yl)(methyl)(oxo)-l6-sulfaneylidene)acetamide

130 2-((3-chloro-4-fluorophenyl)(5-chlorothiophen-2-yl)methyl)-5-methyl-4-(methylsulfonyl)-1H-imidazole

131 2-((3-chloro-4-fluorophenyl)(5-methyl-4-(methylsulfonyl)-1H-imidazol-2-yl)methyl)-5-(trifluoromethyl)thiazole

132 2-((3-chloro-4-fluorophenyl)(3,3-difluorocyclopentyl)methyl)-5-methyl-4-(methylsulfonyl)-1H-imidazole

133 azetidin-3-yl(2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)(imino)-l6-sulfanone

134 (2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)(imino)(1-methylazetidin-3-yl)-l6-sulfanone

135 2-((4-chloro-3-fluorophenyl)(chroman-3-yl)methyl)-4-methyl-5-(methylsulfonyl)-1H-imidazole

136 2-((3-chloro-4-fluorophenyl)(3,3-dimethylcyclobutyl)methyl)-5-methyl-4-(methylsulfonyl)-1H-imidazole

137 2-((3-chloro-4-fluorophenyl)(6,6-difluorospiro[3.3]heptan-2-yl)methyl)-5-methyl-4-(methylsulfonyl)-1H-imidazole

138 2-((3-chloro-4-fluorophenyl)(3-(difluoromethoxy)cyclobutyl)methyl)-5-methyl-4-(methylsulfonyl)-1H-imidazole

139 2-((3-chloro-4-fluorophenyl)(spiro[2.3]hexan-5-yl)methyl)-5-methyl-4-(methylsulfonyl)-1H-imidazole

140 (2-(bis(3-chloro-2,4-difluorophenyl)methyl)-5-methyl-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone

141 (2-(bis(3-chloro-4,5-difluorophenyl)methyl)-5-methyl-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone

142 (2-(bis(5-chloro-2,4-difluorophenyl)methyl)-5-methyl-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone

143 (2-(bis(4-chloro-2-fluorophenyl)methyl)-5-methyl-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone

144 (2-(bis(2-chloro-4-fluorophenyl)methyl)-5-methyl-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone

145 (2-(bis(4-(trifluoromethoxy)phenyl)methyl)-5-methyl-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone

146 (2-(bis(3-(trifluoromethoxy)phenyl)methyl)-5-methyl-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone

147 (2-(bis(3-fluoro-4-(trifluoromethoxy)phenyl)methyl)-5-methyl-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone

148 2-((2-(bis(3-chloro-4-fluorophenyl)methyl)-N-methyl-1H-imidazole)-5-sulfonamido)acetamide

149 1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-3-methylpiperazine

150 2-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-2,5-diazabicyclo[2.2.1]heptane

151 1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)piperidin-3-amine

152 (1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)azetidin-3-yl)methanamine

153 ((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)glycine

154 2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(4-hydroxytetrahydrofuran-3-yl)-1H-imidazole-5-sulfonamide

155 1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-3,5-dimethylpiperazine

156 N-(azetidin-3-ylmethyl)-2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazole-5-sulfonamide

157 1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-2-methylpiperazine

158 2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(pyrrolidin-3-yl)-1H-imidazole-5-sulfonamide

159 N-(azetidin-3-yl)-2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazole-5-sulfonamide

160 2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(pyrrolidin-3-ylmethyl)-1H-imidazole-5-sulfonamide

161 N-(3-aminocyclobutyl)-2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazole-5-sulfonamide

162 2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(1-hydroxy-2-methylpropan-2-yl)-1H-imidazole-5-sulfonamide

163 N-(3-aminocyclopentyl)-2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazole-5-sulfonamide

164 1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)-N-methylazetidin-3-amine

165 2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(3-(methylamino)propyl)-1H-imidazole-5-sulfonamide

166 N-(3-aminopropyl)-2-(bis(3-chloro-4-fluorophenyl)methyl)-N-methyl-1H-imidazole-5-sulfonamide

167 2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(2-(methylamino)ethyl)-1H-imidazole-5-sulfonamide

168 1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)piperidin-4-amine

169 2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(2-methoxypropyl)-1H-imidazole-5-sulfonamide

170 N-(2-amino-2-methylpropyl)-2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazole-5-sulfonamide

171 2-(bis(3-chloro-4-fluorophenyl)methyl)-N,N-dimethyl-1H-imidazole-5-sulfonamide

172 2-(bis(3-chloro-4-fluorophenyl)methyl)-N-cyclopropyl-1H-imidazole-5-sulfonamide

173 2-(bis(3-chloro-4-fluorophenyl)methyl)-5-(pyrrolidin-1-ylsulfonyl)-1H-imidazole

174 2-(bis(3-chloro-4-fluorophenyl)methyl)-5-((3,3-difluoropyrrolidin-1-yl)sulfonyl)-1H-imidazole

175 2-(bis(3-chloro-4-fluorophenyl)methyl)-5-((3-methoxy-3-methylpyrrolidin-1-yl)sulfonyl)-1H-imidazole

176 4-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)piperazin-2-one

177 2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(5-oxopyrrolidin-3-yl)-1H-imidazole-5-sulfonamide

178 1-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazol-5-yl)sulfonyl)pyrrolidin-3-ol

179 2-((2-(bis(3-chloro-4-fluorophenyl)methyl)-1H-imidazole)-5-sulfonamido)acetamide

180 2-(bis(3-chloro-4-fluorophenyl)methyl)-N-(tetrahydrofuran-3-yl)-1H-imidazole-5-sulfonamide

181 4-(azetidin-3-ylsulfonyl)-2-[bis(3-chloro-4-fluorophenyl)methyl]-1*H*-imidazole

182 2-[bis(3-chloro-4-fluorophenyl)methyl]-4-(1-methylazetidin-3-yl)sulfonyl-1H-imidazole

183 4-[[2-[bis(3-chloro-4-fluorophenyl)methyl]-1H-imidazol-4-yl]sulfonyl]piperidine

184 2-[bis(3-chloro-4-fluorophenyl)methyl]-4-pyrrolidin-3-ylsulfonyl-1H-imidazole

185 (2-(bis(3-(difluoromethyl)-4-fluorophenyl)methyl)-5-methyl-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone

186 (2-(bis(4-chloro-2-methoxyphenyl)methyl)-5-methyl-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone

187 (2-(bis(4-chloro-3-fluorophenyl)methyl)-5-methyl-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone

188 (2-(bis(3-chloro-4-fluorophenyl)methyl)-5-(methyl-d3)-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone

189 (2-(bis(3-chloro-4-fluorophenyl)methyl)-5-cyclopropyl-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone

190 (2-(bis(3-chloro-4-fluorophenyl)methyl)-5-ethyl-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone

191 2-(bis(3-chloro-4-fluorophenyl)methyl)-5-chloro-1H-imidazole-4-sulfonamide

192 (2-(bis(3-chloro-4-fluorophenyl)methyl)-5-chloro-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone

193 2-(bis(3-chloro-4-fluorophenyl)methyl)-5-(methoxymethyl)-4-(methylsulfonyl)-1H-imidazole

194 6-(bis(3-chloro-4-fluorophenyl)methyl)-4-methyl-2,5-dihydroimidazo[4,5-e][1,2]thiazine 1,1-dioxide

195 7-(bis(3-chloro-4-fluorophenyl)methyl)-3,6-dihydro-2H-imidazo[4,5-f][1,2]thiazepine 1,1-dioxide

196 7-(bis(3-chloro-4-fluorophenyl)methyl)-3,4,5,6-tetrahydro-2H-imidazo[4,5-f][1,2]thiazepine 1,1-dioxide

197 2-(bis(3-chloro-4-fluorophenyl)methyl)-5,6,7,8-tetrahydro-1H-thiepino[2,3-d]imidazole 4,4-dioxide

198 N-((2-(bis(3-chloro-4-fluorophenyl)methyl)-4-methyl-1H-imidazol-5-yl)methyl)methanesulfonamide

199 3-chloro-6-((4-chlorophenyl)(4-(methylsulfonyl)-1H-imidazol-2-yl)methyl)-2-(trifluoromethyl)pyridine

200 (2-((5-chloro-6-(trifluoromethyl)pyridin-2-yl)(4-chlorophenyl)methyl)-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone

201 (3-chloro-4-fluorophenyl)(4-(methylsulfonyl)-1H-imidazol-2-yl)(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)methanol

202 (2-((3-chloro-4-fluorophenyl)(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)methyl)-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone

203 (2-((3-chloro-4-fluorophenyl)(5-chloro-6-(trifluoromethyl)pyridin-3-yl)methyl)-1H-imidazol-4-yl)(imino)(methyl)-l6-sulfanone

204 (3-chloro-4-fluorophenyl)(3,3-difluorocyclopentyl)(4-methyl-5-(methylsulfonyl)-1H-imidazol-2-yl)methanol

205 5-((3-chloro-4-fluorophenyl)(4-methyl-5-(methylsulfonyl)-1H-imidazol-2-yl)methyl)-4-methyloxazol-2-amine

in the form of the free compound or a physiologically acceptable salt thereof.

14. A pharmaceutical dosage form comprising a compound according to any of claims 1 to 13.

15. The compound according to any of claims 1 to 13 for use in the treatment of pain.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2024/086450

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D233/84 C07D233/90 C07D401/06 C07D401/12 C07D403/06
C07D403/12 C07D405/12 C07D417/12 C07D471/04 C07D487/04
C07D487/12 A61P25/02 A61K31/4178

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2022/263498 A1 (GRUENENTHAL GMBH [DE]) 22 December 2022 (2022-12-22)	1-12,14, 15
A	claims 1, 15	13

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 March 2025	08/04/2025

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Gutke, Hans-Jürgen

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2024/086450

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2022263498 A1	22-12-2022	EP 4355733 A1	24-04-2024
		TW 202317520 A	01-05-2023
		US 2023025025 A1	26-01-2023
		WO 2022263498 A1	22-12-2022