



(51) International Patent Classification:

C07D 471/04 (2006.01) **A61P 11/00** (2006.01)
A61K 31/4188 (2006.01) **A61P 29/00** (2006.01)

(21) International Application Number:

PCT/EP2009/062425

(22) International Filing Date:

25 September 2009 (25.09.2009)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

08165120.0 25 September 2008 (25.09.2008) EP
61/099,987 25 September 2008 (25.09.2008) US

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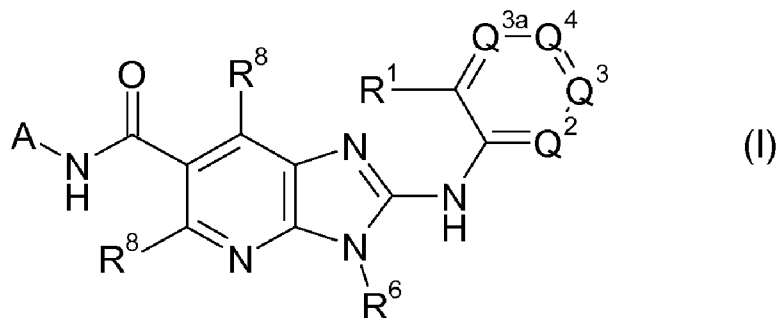
(81) **Designated States** (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE,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

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

Published:

— with international search report (Art. 21(3))

(54) **Title:** 3H-IMIDAZO [4, 5-B] PYRIDINE- 6 -CARBOXAMIDES AS ANTI -INFLAMMATORY AGENTS



(57) **Abstract:** There are provided compounds of formula (I), wherein R¹, R⁶, R⁸, Q², Q³, Q^{3a}, Q⁴, L and A have meanings given in the description, and pharmaceutically-acceptable salts thereof, which compounds are useful in the treatment of diseases in which inhibition of the activity of a member of the MAPEG family is desired and/or required, and particularly in the treatment of inflammation and/or cancer.

3H-IMIDAZO[4,5-B]PYRIDINE-6-CARBOXAMIDES AS ANTI-INFLAMMATORY AGENTS

Field of the Invention

This invention relates to novel pharmaceutically-useful compounds, which compounds are
5 useful as inhibitors of enzymes belonging to the membrane-associated proteins in the
eicosanoid and glutathione metabolism (MAPEG) family. Members of the MAPEG family
include the microsomal prostaglandin E synthase-1 (mPGES-1), 5-lipoxygenase-activating
protein (FLAP), leukotriene C₄ synthase and microsomal glutathione S-transferases (MGST1,
MGST2 and MGST3). The compounds are of potential utility in the treatment of
10 inflammatory diseases including respiratory diseases. The invention also relates to the use
of such compounds as medicaments, to pharmaceutical compositions containing them, and
to synthetic routes for their production.

Background of the Invention

15 There are many diseases/disorders that are inflammatory in their nature. One of the major
problems associated with existing treatments of inflammatory conditions is a lack of efficacy
and/or the prevalence of side effects (real or perceived).

Inflammatory diseases that affect the population include asthma, inflammatory bowel
disease, rheumatoid arthritis, osteoarthritis, rhinitis, conjunctivitis and dermatitis.

20 Inflammation is also a common cause of pain. Inflammatory pain may arise for numerous
reasons, such as infection, surgery or other trauma. Moreover, several diseases including
malignancies and cardiovascular diseases are known to have inflammatory components
adding to the symptomatology of the patients.

Asthma is a disease of the airways that contains elements of both inflammation and
25 bronchoconstriction. Treatment regimens for asthma are based on the severity of the
condition. Mild cases are either untreated or are only treated with inhaled β -agonists which
affect the bronchoconstriction element, whereas patients with more severe asthma typically
are treated regularly with inhaled corticosteroids which to a large extent are anti-inflammatory
in their nature.

30 Another common disease of the airways with inflammatory and bronchoconstrictive
components is chronic obstructive pulmonary disease (COPD). The disease is potentially
lethal, and the morbidity and mortality from the condition is considerable. At present, there is
no known pharmacological treatment capable of changing the course of the disease.

The cyclooxygenase (COX) enzyme exists in two forms, one that is constitutively expressed in many cells and tissues (COX-1), and one that in most cells and tissues is induced by pro-inflammatory stimuli, such as cytokines, during an inflammatory response (COX-2).

COXs metabolise arachidonic acid to the unstable intermediate prostaglandin H_2 (PGH₂).

- 5 PGH₂ is further metabolized to other prostaglandins including PGE₂, PGF_{2α}, PGD₂, prostacyclin and thromboxane A₂. These arachidonic acid metabolites are known to have pronounced physiological and pathophysiological activity including pro-inflammatory effects. PGE₂ in particular is known to be a strong pro-inflammatory mediator, and is also known to induce fever and pain. Consequently, numerous drugs have been developed with a view to
- 10 inhibiting the formation of PGE₂, including "NSAIDs" (non-steroidal antiinflammatory drugs) and "coxibs" (selective COX-2 inhibitors). These drugs act predominantly by inhibition of COX-1 and/or COX-2, thereby reducing the formation of PGE₂.

However, the inhibition of COXs has the disadvantage that it results in the reduction of the formation of all metabolites downstream of PGH₂, some of which are known to have

- 15 beneficial properties. In view of this, drugs which act by inhibition of COXs are therefore known/suspected to cause adverse biological effects. For example, the non-selective inhibition of COXs by NSAIDs may give rise to gastrointestinal side-effects and affect platelet and renal function. Even the selective inhibition of COX-2 by coxibs, whilst reducing such gastrointestinal side-effects, is believed to give rise to cardiovascular problems.

- 20 An alternative treatment of inflammatory diseases that does not give rise to the above-mentioned side effects would thus be of real benefit in the clinic. In particular, a drug that inhibits (preferably selectively) the transformation of PGH₂ to the pro-inflammatory mediator PGE₂ might be expected to reduce the inflammatory response in the absence of a corresponding reduction of the formation of other, beneficial arachidonic acid metabolites.

- 25 Such inhibition would accordingly be expected to alleviate the undesirable side-effects mentioned above.

PGH₂ may be transformed to PGE₂ by prostaglandin E synthases (PGES). Two microsomal prostaglandin E synthases (mPGES-1 and mPGES-2), and one cytosolic prostaglandin E synthase (cPGES) have been described.

- 30 The leukotrienes (LTs) are formed from arachidonic acid by a set of enzymes distinct from those in the COX / PGES pathway. Leukotriene B₄ is known to be a strong proinflammatory mediator, while the cysteinyl-containing leukotrienes C₄, D₄ and E₄ (CysLTs) are mainly very potent bronchoconstrictors and have thus been implicated in the pathobiology of asthma.

The biological activities of the CysLTs are mediated through two receptors designated CysLT₁ and CysLT₂. As an alternative to steroids, leukotriene receptor antagonists (LTRas) have been developed in the treatment of asthma. These drugs may be given orally, but do not control inflammation satisfactorily. The presently used LTRas are highly selective for CysLT₁. It may be hypothesised that better control of asthma, and possibly also COPD, may be attained if the activity of both of the CysLT receptors could be reduced. This may be achieved by developing unselective LTRas, but also by inhibiting the activity of proteins, e.g. enzymes, involved in the synthesis of the CysLTs. Among these proteins, 5-lipoxygenase, 5-lipoxygenase-activating protein (FLAP), and leukotriene C₄ synthase may be mentioned. A FLAP inhibitor would also decrease the formation of the proinflammatory LTB₄.

mPGES-1, FLAP and leukotriene C₄ synthase belong to the membrane-associated proteins in the eicosanoid and glutathione metabolism (MAPEG) family. Other members of this family include the microsomal glutathione S-transferases (MGST1, MGST2 and MGST3). For a review, c.f. P.-J. Jacobsson *et al* in *Am. J. Respir. Crit. Care Med.* **161**, S20 (2000). It is well known that compounds prepared as antagonists to one of the MAPEGs may also exhibit inhibitory activity towards other family members, c.f. J. H Hutchinson *et al* in *J. Med. Chem.* **38**, 4538 (1995) and D. Claveau *et al* in *J. Immunol.* **170**, 4738 (2003). The former paper also describes that such compounds may also display notable cross-reactivity with proteins in the arachidonic acid cascade that do not belong to the MAPEG family, e.g. 5-lipoxygenase.

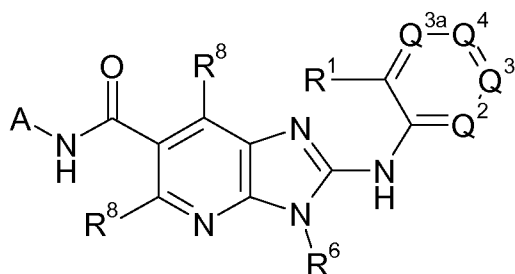
Thus, agents that are capable of inhibiting the action of mPGES-1, and thus reducing the formation of the specific arachidonic acid metabolite PGE₂, are likely to be of benefit in the treatment of inflammation. Further, agents that are capable of inhibiting the action of the proteins involved in the synthesis of the leukotrienes are also likely to be of benefit in the treatment of asthma and COPD.

In addition to their anti-inflammatory effect, mPGES-1 inhibitors are also known to be of potential use in treating or preventing a neoplasia, for example as described in international patent application WO 2007/124589. The rationale behind this may stem from the fact that the production of PGE₂ is believed to promote the formation, growth and/or metastasis of neoplasias. As mPGES-1 is often expressed with COX-2 in benign and cancerous neoplasias, the inhibition of mPGES-1 (rather than COX-2) may cause the reduction of PGE₂ and therefore mPGES-1 inhibitors may be useful the treatment of benign or malignant neoplasias. The listing or discussion of an apparently prior-published document in this specification should not necessarily be taken as an acknowledgement that the document is part of the state of the art or is common general knowledge.

The synthesis of various benzimidazoles has been disclosed by Carpenter *et al* in the *Journal of Combinatorial Chemistry* (2006), 8(6), 907-914. However, no apparent medical use has been ascribed to such compounds.

5 Disclosure of the Invention

There is provided a compound of formula I,



I

10

in which

Q^2 , Q^3 , Q^{3a} and Q^4 respectively represent $-C(R^2)=$, $-C(R^3)=$, $-C(R^{3a})=$ and $-C(R^4)=$; or

15 any one or two of Q^2 , Q^3 , Q^{3a} and Q^4 may alternatively and independently represent $-N=$;

R^1 represents halo, $-CN$, $-N(R^{y1})R^{y2}$, $-N(R^{y3})-C(O)-R^{y4}$, $-N(R^{y5})-S(O)_2-R^{y6}$, $-C(O)OR^{y7}$, $-C(O)N(R^{y8})R^{y9}$, $-OR^{y10}$, $-S(O)_m-R^{y11}$, $-S(O)_2O-R^{y12}$, $-S(O)_2N(R^{y13})R^{y14}$, $-C(O)R^{y15}$;

20 C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, cycloalkyl [which latter four groups are optionally substituted by one or more substituents selected from fluoro, $-CN$, $-N(R^{y1})R^{y2}$, $-N(R^{y3})-C(O)-R^{y4}$, $-N(R^{y5})-S(O)_2-R^{y6}$, $-C(O)OR^{y7}$, $-C(O)N(R^{y8})R^{y9}$, $-OR^{y10}$, $-S(O)_m-R^{y11}$, $-S(O)_2O-R^{y12}$, $-S(O)_2N(R^{y13})R^{y14}$ and $-C(O)R^{y15}$]; or heterocycloalkyl or heteroaryl (which latter two groups are optionally substituted by one or more substituents selected from R^9);

25

R^2 , R^3 , R^{3a} and R^4

independently represent hydrogen, halo, $-CN$, $-N(R^{y1})R^{y2}$,
 $-N(R^{y3})-C(O)-R^{y4}$, $-N(R^{y5})-S(O)_2-R^{y6}$, $-C(O)OR^{y7}$, $-C(O)N(R^{y8})R^{y9}$,
 $-OR^{y10}$, $-S(O)_m-R^{y11}$, $-S(O)_2O-R^{y12}$, $-S(O)_2N(R^{y13})R^{y14}$, $-C(O)R^{y15}$;

- 5 C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, cycloalkyl [which latter four groups are optionally substituted by one or more substituents selected from fluoro, $-CN$, $-N(R^{y1})R^{y2}$, $-N(R^{y5})-S(O)_2-R^{y6}$, $-C(O)OR^{y7}$, $-C(O)N(R^{y8})R^{y9}$, $-OR^{y10}$, $-S(O)_m-R^{y11}$, $-S(O)_2O-R^{y12}$, $-S(O)_2N(R^{y13})R^{y14}$ and $-C(O)R^{y15}$] provided that if R^3 or R^{3a} is a substituted C_1 alkyl group, then the substituent cannot be $-N(R^{y5})-S(O)_2-R^{y6}$;
- 10 or any adjacent pair of R^1 , R^2 , R^3 , R^{3a} and R^4 (i.e. R^1 and R^{3a} , R^2 and R^3 , R^3 and R^4 and R^4 and R^{3a}) may be linked together to form, along with the essential carbon atoms of the Q^2 to Q^4 -containing ring to which they are necessarily attached, a further 5- to 7-membered ring, optionally containing one to three heteroatoms, which ring may contain one or two further unsaturations and which is optionally substituted by one or more C_{1-3} alkyl and/or $=O$
- 15 substituents;

R^6 represents hydrogen;

heterocycloalkyl, aryl, heteroaryl (which latter three groups are optionally substituted by one or more substituents selected from R^9); or

- 20 C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, which latter four groups are optionally substituted by one or more substituents selected from fluoro, $-N(R^{y1})R^{y2}$, $-N(R^{y3})-C(O)-R^{y4}$, $-N(R^{y5})-S(O)_2-R^{y6}$, $-C(O)OR^{y7}$, $-C(O)N(R^{y8})R^{y9}$, $-OR^{y10}$, $-S(O)_m-R^{y11}$, $-S(O)_2N(R^{y13})R^{y14}$, $-C(O)R^{y15}$, heterocycloalkyl, cycloalkyl, aryl and heteroaryl
- 25 (which latter four groups are optionally substituted by one or more substituents selected from R^9);

each R^8 independently represents hydrogen, halo, $-N(R^{y1})R^{y2}$, $-OR^{y10}$, $-S(O)_2-R^{y11}$;

- 30 C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, $-O-C_{1-6}$ alkyl, $-O-C_{2-6}$ alkenyl, $-O-C_{2-6}$ alkynyl, $-O$ -cycloalkyl, $-O$ -heterocycloalkyl [which latter nine groups are optionally substituted by one or more substituents selected from fluoro, $-CN$, $-N(R^{y1})R^{y2}$, $-N(R^{y3})-C(O)-R^{y4}$, $-N(R^{y5})-S(O)_2-R^{y6}$, $-C(O)OR^{y7}$, $-C(O)N(R^{y8})R^{y9}$, $-OR^{y10}$, $-S(O)_m-R^{y11}$, $-S(O)_2O-R^{y12}$, $-S(O)_2N(R^{y13})R^{y14}$, $-C(O)R^{y15}$, C_{1-3} alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl (which latter four groups are optionally substituted by one or more substituents selected from R^9)];
- 35

heterocycloalkyl or heteroaryl (which latter two groups are optionally substituted by one or more substituents selected from R^9);

5 A represents aryl, heteroaryl, heterocycloalkyl, cycloalkyl, C_{1-12} alkyl, C_{2-12} alkenyl or C_{2-12} alkynyl, all of which are optionally substituted by one or more substituents selected from R^9 ;

R^9 represents, on each occasion when used herein:
 10 halo, -CN, $-N(R^{y1})R^{y2}$, $-N(R^{y3})-C(O)-R^{y4}$, $-N(R^{y5})-S(O)_2-R^{y6}$, $-C(O)OR^{y7}$,
 $-C(O)N(R^{y8})R^{y9}$, $-OR^{y10}$, $-S(O)_m-R^{y11}$, $-S(O)_2O-R^{y12}$, $-S(O)_2N(R^{y13})R^{y14}$ and
 $-C(O)R^{y15}$;
 C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, cycloalkyl, heterocycloalkyl [which latter
 15 five groups are optionally substituted by one or more substituents selected
 from fluoro, -CN, $-N(R^{y1})R^{y2}$, $-N(R^{y3})-C(O)-R^{y4}$, $-N(R^{y5})-S(O)_2-R^{y6}$, $-C(O)OR^{y7}$,
 $-C(O)N(R^{y8})R^{y9}$, $-OR^{y10}$, $-S(O)_m-R^{y11}$, $-S(O)_2O-R^{y12}$, $-S(O)_2N(R^{y13})R^{y14}$ and
 $-C(O)R^{y15}$]; or
 aryl or heteroaryl [which latter two groups are optionally substituted by one or
 more substituents selected from halo, -CN, C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl,
 20 cycloalkyl (which latter four groups are optionally substituted by one or more
 substituents selected from fluoro and $-OR^{x2}$), $-O-C_{1-7}$ alkyl, $-O-C_{2-7}$ alkenyl,
 $-O-C_{2-7}$ alkynyl and $-O$ -cycloalkyl (which latter four groups are optionally
 substituted by one or more fluoro atoms)]; or

any two R^9 substituents:

25 when attached to the adjacent atoms of the A group; and,
 in the case where the R^9 substituents are attached to a non-aromatic A group,
 when attached to the same atoms,
 may be linked together to form, together with the essential atoms of the A
 group to which the relevant R^9 substituents are necessarily attached, a further
 30 3- to 8-membered ring, optionally containing a further one or two heteroatoms,
 and which further ring optionally contains one or two unsaturations and which
 is optionally substituted by one or more C_{1-3} alkyl and/or =O substituents;

m represents 0, 1 or 2;

each R^{y4} , R^{y6} , R^{y11} and R^{y15} :

independently represent C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, cycloalkyl, which latter four groups are optionally substituted by one or more fluoro atoms;

5

each R^{x2} , R^{y1} , R^{y2} , R^{y3} , R^{y5} , R^{y7} , R^{y8} , R^{y9} , R^{y10} , R^{y12} , R^{y13} and R^{y14} :

independently represent hydrogen or C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, cycloalkyl, heterocycloalkyl, which latter five groups are optionally substituted one or more substituents selected from fluoro and $-OC_{1-3}$ alkyl; or

10 any two groups, when attached to the same nitrogen atom (i.e. R^{y1} and R^{y2} , R^{y8} and R^{y9} , and R^{y13} and R^{y14}), may, together with that nitrogen atom to which they are necessarily attached, be linked together to form a 3- to 8-membered ring, optionally containing one or two further heteroatoms and which ring optionally contains one or two unsaturations and is optionally substituted by one or more

15 C_{1-3} alkyl and/or $=O$ substituents,

or a pharmaceutically acceptable salt thereof,

which compounds are hereinafter referred to as 'the compounds of the invention'.

20

Pharmaceutically-acceptable salts include acid addition salts and base addition salts. Such salts may be formed by conventional means, for example by reaction of a free acid or a free base form of a compound of formula I with one or more equivalents of an appropriate acid or base, optionally in a solvent, or in a medium in which the salt is insoluble, followed by
25 removal of said solvent, or said medium, using standard techniques (e.g. *in vacuo*, by freeze-drying or by filtration). Salts may also be prepared by exchanging a counter-ion of a compound of the invention in the form of a salt with another counter-ion, for example using a suitable ion exchange resin.

Compounds of the invention may contain double bonds and may thus exist as *E* (*entgegen*)
30 and *Z* (*zusammen*) geometric isomers about each individual double bond. All such isomers and mixtures thereof are included within the scope of the invention.

Compounds of the invention may also exhibit tautomerism. All tautomeric forms and mixtures thereof are included within the scope of the invention. For instance, a compound containing the moiety "*1H*-benzimidazole" may be considered to be identical to a
35 corresponding compound containing a "*3H*-benzimidazole" moiety.

Compounds of the invention may also contain one or more asymmetric carbon atoms and may therefore exhibit optical and/or diastereoisomerism. Diastereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The various stereoisomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. fractional crystallisation or HPLC, techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation or epimerisation (i.e. a 'chiral pool' method), by reaction of the appropriate starting material with a 'chiral auxiliary' which can subsequently be removed at a suitable stage, by derivatisation (i.e. a resolution, including a dynamic resolution), for example with a homochiral acid followed by separation of the diastereomeric derivatives by conventional means such as chromatography, or by reaction with an appropriate chiral reagent or chiral catalyst all under conditions known to the skilled person. All stereoisomers and mixtures thereof are included within the scope of the invention.

Unless otherwise specified, C_{1-q} alkyl, and C_{1-q} alkylene, groups (where q is the upper limit of the range), defined herein may be straight-chain or, when there is a sufficient number (i.e. a minimum of two or three, as appropriate) of carbon atoms, be branched-chain. For the avoidance of doubt, such groups are fully saturated.

Unless otherwise specified, C_{2-q} alkenyl, and C_{2-q} alkenylene, groups (where q is the upper limit of the range) refer to a hydrocarbon chain (in the case of alkenylene, the chain links two moieties) containing one or more double bond. Such groups as defined herein may be straight-chain or, when there is a sufficient number (i.e. a minimum of two or three, as appropriate) of carbon atoms, be branched-chain.

Unless otherwise specified, C_{2-q} alkynyl, and C_{2-q} alkynylene, groups (where q is the upper limit of the range) refer to a hydrocarbon chain (in the case of alkynylene, the chain links two moieties) containing one or more triple bond. Such groups as defined herein may be straight-chain or, when there is a sufficient number (i.e. a minimum of three or four, as appropriate) of carbon atoms, be branched-chain.

In the instance where a 'cycloalkyl' group (e.g. C_{3-q} cycloalkyl) is specifically mentioned, such groups may be monocyclic or bicyclic non-aromatic alkyl groups, which may further be bridged (so forming, for example, fused ring systems). Such cycloalkyl groups may be saturated or unsaturated, e.g. containing one or more double bond (forming for example a C_{5-q} cycloalkenyl). Optional substituents may be attached at any point on the cycloalkyl group. Cycloalkyl groups that may be mentioned preferably include C₃₋₁₂ cycloalkyl, for instance a 3- to 7-membered monocyclic cycloalkyl group, a C₇₋₁₁ (e.g. C₈₋₁₁) bicyclic

cycloalkyl group or a C₈₋₁₂ (e.g. C₉₋₁₁) tricyclic cycloalkyl group. As stated above, cycloalkyl groups may further be bridged, so forming, for example, an adamantyl group (for example when a bicyclic cycloalkyl group is bridged). The term 'acyclic' alkyl group when used herein refers to an alkyl group that is not cyclic, but may be branched-chain or, is preferably,
5 straight-chain.

For the avoidance of doubt, the term "bicyclic", when employed in the context of cycloalkyl, refers to such groups in which the second ring is formed between two adjacent atoms of the first ring (i.e. systems of two rings share one bond formed with two adjacent carbon atoms). The term "bridged", when employed in the context of cycloalkyl groups refers to monocyclic
10 or bicyclic groups in which two non-adjacent atoms are linked by an alkylene chain.

The term "halo", when used herein, includes fluoro, chloro, bromo and iodo.

Aryl groups that may be mentioned include C₆₋₁₄ (e.g. C₆₋₁₀) aryl groups. Such groups may be monocyclic, bicyclic or tricyclic and have between 6 and 14 ring carbon atoms, in which at least one ring is aromatic. C₆₋₁₄ aryl groups include phenyl, naphthyl and the like, such as
15 1,2,3,4-tetrahydronaphthyl, indanyl, indenyl and fluorenyl. The point of attachment of aryl groups may be *via* any atom of the ring system, for instance when aryl groups are bicyclic or tricyclic, they are linked to the rest of the molecule *via* an atom of an aromatic or non-aromatic ring.

Heteroaryl groups that may be mentioned include those which have between 5 and 14 (e.g.
20 10) members. Such groups may be monocyclic, bicyclic or tricyclic, provided that at least one of the rings is aromatic and wherein at least one (e.g. one to four) of the atoms in the ring system is other than carbon (i.e. a heteroatom). Heteroaryl groups that may be mentioned include acridinyl, benzimidazolyl, benzodioxanyl, benzodioxepinyl, benzodioxolyl (including 1,3-benzodioxolyl), benzofuranyl, benzofurazanyl, benzothiazolyl, benzoxadiazolyl
25 (including 2,1,3-benzoxadiazolyl), benzoxazinyl (including 3,4-dihydro-2H-1,4-benzoxazinyl), benzoxazolyl, benzomorpholinyl, benzoselenadiazolyl (including 2,1,3-benzoselenadiazolyl), benzothiadiazolyl (including 2,1,3-benzothiadiazolyl), benzothienyl, carbazolyl, chromanyl, cinnolinyl, furanyl, imidazolyl, imidazopyridyl (including imidazo[4,5-*b*]pyridyl, imidazo[5,4-*b*]pyridyl and imidazo[1,2-*a*]pyridyl), indazolyl, indolinyl, indolyl, isobenzofuranyl, isochro-
30 manyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isothiochromanyl, isoxazolyl, naphthyridinyl (including 1,6-naphthyridinyl or, preferably, 1,5-naphthyridinyl and 1,8-naphthyridinyl), oxadiazolyl (including 1,3,4-oxadiazolyl), oxazolyl, phenazinyl, phenothiazinyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoliziny, quinoxalinyl, tetrahydroisoquinolinyl (including 1,2,3,4-
35 tetrahydroisoquinolinyl and 5,6,7,8-tetrahydroisoquinolinyl), tetrahydroquinolinyl

(including 1,2,3,4-tetrahydroquinolyl and 5,6,7,8-tetrahydroquinolyl), tetrazolyl, thiadiazolyl (including 1,3,4-thiadiazolyl), thiazolyl, oxazolopyridyl (including oxazolo[4,5-*b*]pyridyl, oxazolo[5,4-*b*]pyridyl and, in particular, oxazolo[4,5-*c*]pyridyl and oxazolo[5,4-*c*]pyridyl), thiazolopyridyl (including thiazolo[4,5-*b*]pyridyl, thiazolo[5,4-*b*]pyridyl and, in particular, thiazolo[4,5-*c*]pyridyl and thiazolo[5,4-*c*]pyridyl), thiochromanyl, thienyl, triazolyl (including 1,2,3-triazolyl and 1,2,4-triazolyl) and the like. Substituents on heteroaryl groups may, where appropriate, be located on any atom in the ring system including a heteroatom. The point of attachment of heteroaryl groups may be *via* any atom in the ring system including (where appropriate) a heteroatom (such as a nitrogen atom), or an atom on any fused carbocyclic ring that may be present as part of the ring system. When heteroaryl groups are bicyclic or tricyclic, they may be linked to the rest of the molecule *via* an atom of an aromatic or non-aromatic ring. Heteroaryl groups may also be in the *N*- or *S*- oxidised form (so forming, for example, a pyridine *N*-oxide).

Heterocycloalkyl groups that may be mentioned include non-aromatic monocyclic and bicyclic heterocycloalkyl groups (which groups may further be bridged) in which at least one (e.g. one to four) of the atoms in the ring system is other than carbon (i.e. a heteroatom), and in which the total number of atoms in the ring system is between three and twelve (e.g. between five and ten). Further, such heterocycloalkyl groups may be saturated or unsaturated containing one or more double and/or triple bonds, forming for example a C_{2-q} heterocycloalkenyl (where *q* is the upper limit of the range) or a C_{7-q} heterocycloalkynyl group. C_{2-q} heterocycloalkyl groups that may be mentioned include 7-azabicyclo-[2.2.1]heptanyl, 6-azabicyclo[3.1.1]heptanyl, 6-azabicyclo[3.2.1]-octanyl, 8-azabicyclo[3.2.1]octanyl, aziridinyl, azetidiny, dihydropyranyl, dihydropyridyl, dihydropyrrolyl (including 2,5-dihydropyrrolyl), dioxolanyl (including 1,3-dioxolanyl), dioxanyl (including 1,3-dioxanyl and 1,4-dioxanyl), dithianyl (including 1,4-dithianyl), dithiolanyl (including 1,3-dithiolanyl), imidazolidinyl, imidazoliny, morpholiny, 7-oxabicyclo[2.2.1]heptanyl, 6-oxabicyclo[3.2.1]-octanyl, oxetanyl, oxiranyl, piperazinyl, piperidinyl, pyranyl, pyrazolidinyl, pyrrolidinonyl, pyrrolidinyl, pyrroliny, quinuclidinyl, sulfolanly, 3-sulfolenyl, tetrahydropyranyl, tetrahydrofuranyl, tetrahydropyridyl (such as 1,2,3,4-tetrahydropyridyl and 1,2,3,6-tetrahydropyridyl), thietanyl, thiiranyl, thiolanyl, thiomorpholiny, trithianyl (including 1,3,5-trithianyl), tropanyl and the like. Substituents on heterocycloalkyl groups may, where appropriate, be located on any atom in the ring system including a heteroatom. Further, in the case where the substituent is another cyclic compound, then the cyclic compound may be attached through a single atom on the heterocycloalkyl group, forming a so-called "spiro"-compound.

The point of attachment of heterocycloalkyl groups may be *via* any atom in the ring system including (where appropriate) a heteroatom (such as a nitrogen atom), or an atom on any fused carbocyclic ring that may be present as part of the ring system. Heterocycloalkyl groups may also be in the *N*- or *S*- oxidised form.

- 5 Heteroatoms that may be mentioned include phosphorus, silicon, boron, tellurium, selenium and, preferably, oxygen, nitrogen and sulfur.

For the avoidance of doubt, in cases in which the identity of two or more substituents in a compound of formula I may be the same, the actual identities of the respective substituents are not in any way interdependent. For example, in case of R^8 , the respective $-C(R^8)-$ groups
10 in question may be the same or different. Similarly, when groups are substituted by more than one substituent as defined herein, the identities of those individual substituents are not to be regarded as being interdependent. For example, when an A group is substituted by two R^9 substituents, in which, in both cases, R^9 represents C_{1-7} alkyl substituted by - $N(R^{y1})R^{y2}$, then the identities of the two $-N(R^{y1})R^{y2}$ groups are not to be regarded as being
15 interdependent, i.e. the two $-N(R^{y1})R^{y2}$ moieties may be the same or different, i.e. at each occurrence, R^{y1} and R^{y2} may also be the same or different.

For the avoidance of doubt, when a term such as " R^{y1} to R^{y15} " is employed herein, this will be understood by the skilled person to mean R^{y1} , R^{y2} , R^{y3} , R^{y4} , R^{y5} , R^{y6} , R^{y7} , R^{y8} , R^{y9} , R^{y10} , R^{y11} , R^{y12} , R^{y13} , R^{y14} and R^{y15} inclusively. Further, when a term such as " R^1 to R^5 " is employed
20 herein, the skilled person will understand this to mean R^1 , R^2 , R^3 , R^{3a} , R^4 and R^5 inclusively. Similarly, when the term " Q^2 to Q^4 " is employed, this will be understood to mean Q^2 , Q^3 , Q^{3a} and Q^4 inclusively.

For the avoidance of doubt, when the compound of formula I is substituted by a heterocycloalkyl or heteroaryl group, for example when R^1 or R^8 represent such substituents, then the point of
25 attachment may be *via* a carbon atom or heteroatom (e.g. nitrogen heteroatom), assuming that the valency of the heteroatom permits. Similarly, when heterocycloalkyl or heteroaryl groups are substituted with further substituents, then those substituents may be attached at any position including on a carbon atom or heteroatom (e.g. a nitrogen heteroatom), again assuming that the valency permits.

- 30 For the avoidance of doubt, where it is mentioned herein that alkyl, alkenyl, alkynyl or cycloalkyl groups may be substituted with one or more halo atoms, then those halo atoms are preferably fluoro atoms.

The skilled person will appreciate that there may be free rotation around the nitrogen-carbon bond to which the requisite phenyl ring bearing the R^1 to R^4 substituents is pending. In view of
35 this (when Q^2 to Q^4 respectively represent

12

-C(R²)=, -C(R³)=, -C(R^{3a})= and -C(R⁴)=), the R¹ and R² positions are 'identical' (as are the R³ and R^{3a} positions) relative to the point of attachment of that phenyl ring. Hence, the definitions of R¹ and R² may be interchanged (in which case the definitions of R³ and R^{3a} are also 'interchanged', relative to the definitions of R¹ and R²), in view of the fact that both R¹ and R² represent *ortho* phenyl substituents. The important aspect in relation to the R¹ to R⁴ substituents is therefore their positions relative to one another, rather than their positions relative to the point of attachment of that phenyl ring to the rest of the compound of formula I. For the avoidance of doubt, when preferred features are mentioned herein, then such features may be taken independently of others preferred features or conjunctively with other preferred features.

The skilled person will appreciate that compounds of formula I that are the subject of this invention include those that are stable. That is, compounds of the invention include those that are sufficiently robust to survive isolation from e.g. a reaction mixture to a useful degree of purity.

In one embodiment, the invention provides compounds of formula I as described above and in which

Q² represents -C(R²)=; and

any two of Q³, Q^{3a} and Q⁴ respectively represent -C(R³)=, -C(R^{3a})= and -C(R⁴)=; and the remaining one of Q³, Q^{3a} and Q⁴ represents -N=.

In another embodiment, the invention provides compounds of formula I according to any of the preceding embodiments and

in which

Q², Q³ and Q^{3a} respectively represent -C(R²)=, -C(R³)= and -C(R^{3a})=; and

Q⁴ represents -N=.

In another embodiment, the invention provides compounds of formula I according to any of the preceding embodiments and in which

Q^2 , Q^{3a} and Q^4 respectively represent $-C(R^2)=$, $-C(R^{3a})=$ and $-C(R^4)=$; and

Q^3 represents $-N=$;

5 or

Q^2 , Q^3 and Q^4 respectively represent $-C(R^2)=$, $-C(R^3)=$ and $-C(R^4)=$; and

Q^{3a} represents $-N=$.

10 In another embodiment, the invention provides compounds of formula I according to any of the preceding embodiments and

in which

R^1 represents C_{1-3} alkyl (optionally substituted by one or more fluoro atoms), C_{3-6} cycloalkyl or halo.

15

In another embodiment, the invention provides compounds of formula I according to any of the preceding embodiments and

in which

R^2 represents hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl (which latter two groups are optionally substituted by one or more atoms selected from fluoro), halo or $-O-C_{1-3}$ alkyl (optionally substituted by one or more fluoro atoms).

20

In another embodiment, the invention provides compounds of formula I according to any of the preceding embodiments and

25 in which

R^2 represents hydrogen, C_{1-3} alkyl (optionally substituted by one or more atoms selected from fluoro), C_{3-6} cycloalkyl, halo or $-O-C_{1-3}$ alkyl (optionally substituted by one or more fluoro atoms).

30 In another embodiment, the invention provides compounds of formula I according to any of the preceding embodiments and

in which

R^3 , R^{3a} and R^4 independently represent hydrogen, C_{1-4} alkyl (optionally substituted by one or more fluoro atoms) or halo.

In another embodiment, the invention provides compounds of formula I according to any of the preceding embodiments and

in which

- 5 R^3 , R^{3a} and R^4 independently represent hydrogen, C_{1-3} alkyl (optionally substituted by one or more fluoro atoms) or halo.

In another embodiment, the invention provides compounds of formula I according to any of the preceding embodiments and

in which

R^9 represents halo, -CN, $-N(R^{y1})R^{y2}$, $-N(R^{y3})-C(O)-R^{y4}$, $-N(R^{y5})-S(O)_2-R^{y6}$, $-C(O)OR^{y7}$, $-C(O)N(R^{y8})R^{y9}$, $-OR^{y10}$, $-S(O)_m-R^{y11}$, $-S(O)_2O-R^{y12}$, $-S(O)_2N(R^{y13})R^{y14}$ and/or $-C(O)R^{y15}$; or

- 15 C_{1-7} alkyl optionally substituted by one or more substituents selected from fluoro, -CN, $-N(R^{y1})R^{y2}$, $-N(R^{y3})-C(O)-R^{y4}$, $-N(R^{y5})-S(O)_2-R^{y6}$, $-C(O)OR^{y7}$, $-C(O)N(R^{y8})R^{y9}$, $-OR^{y10}$, $-S(O)_m-R^{y11}$, $-S(O)_2O-R^{y12}$, $-S(O)_2N(R^{y13})R^{y14}$ and/or $-C(O)R^{y15}$; or
 20 aryl, heteroaryl (which latter two groups are optionally substituted by one or more substituents selected from $-O-C_{1-3}$ alkyl, -CN, halo and C_{1-2} alkyl optionally substituted by one or more fluoro atoms); or
 any two R^9 groups may be linked together as defined above.

In another embodiment, the invention provides compounds of formula I according to any of the preceding embodiments and

in which

R^8 represents hydrogen, halo, C_{1-3} alkyl [optionally substituted by one or more substituents selected from fluoro, $-OR^{y10}$, $-N(R^{y1})R^{y2}$, $-N(R^{y3})-C(O)-R^{y4}$, and $-C(O)N(R^{y8})R^{y9}$], $-O-C_{1-6}$ alkyl, $-O$ -cycloalkyl, $-O$ -heterocycloalkyl [which latter three groups are optionally substituted by one or more substituents selected from fluoro, C_{1-3} alkyl, $-N(R^{y1})R^{y2}$, $-N(R^{y3})-C(O)-R^{y4}$, $-N(R^{y5})-S(O)_2-R^{y6}$, $-C(O)OR^{y7}$, $-C(O)N(R^{y8})R^{y9}$,
 30

-OR^{y10}, -S(O)_m-R^{y11}, -S(O)₂O-R^{y12}, -S(O)₂N(R^{y13})R^{y14}, -C(O)R^{y15},
cycloalkyl, heterocycloalkyl, aryl and heteroaryl (which latter four
groups are optionally substituted by one or more substituents selected
from R⁹).

In another embodiment, the invention provides compounds of formula I according to any of the
preceding embodiments and
in which

R⁶ represents hydrogen or C₁₋₆ alkyl optionally substituted by one or more
substituents selected from -N(R^{y1})R^{y2}, -N(R^{y3})-C(O)-R^{y4},
-N(R^{y5})-S(O)₂-R^{y6}, -C(O)OR^{y7}, -C(O)N(R^{y8})R^{y9}, -OR^{y10}, -S(O)₂R^{y11} and a
4- to 6-membered heterocycloalkyl group (containing two or one
heteroatom(s) selected from oxygen and nitrogen).

In another embodiment, the invention provides compounds of formula I according to any of the
preceding embodiments and
in which

R^{x2}, R^{y1}, R^{y2}, R^{y3}, R^{y5}, R^{y7}, R^{y8}, R^{y9}, R^{y10}, R^{y12}, R^{y13} and R^{y14} independently represent
hydrogen or C₁₋₄ alkyl optionally substituted by one or more fluoro atoms or -OC₁₋₂ alkyl
groups; or any pair of R^{y1} and R^{y2}, R^{y8} and R^{y9} and/or R^{y13} and R^{y14} are linked together to
form a 3- to 7-membered ring, optionally containing one further nitrogen or oxygen
heteroatom, one or two further double bonds, and which ring is optionally substituted by one
or more C₁₋₂ alkyl or =O substituents.

In another embodiment, the invention provides compounds of formula I according to any of the
preceding embodiments and
in which

R^{y4}, R^{y6}, R^{y11} and R^{y15} independently represent C₁₋₄ alkyl.

In another embodiment, the invention provides compounds of formula I according to any of the preceding embodiments and

in which

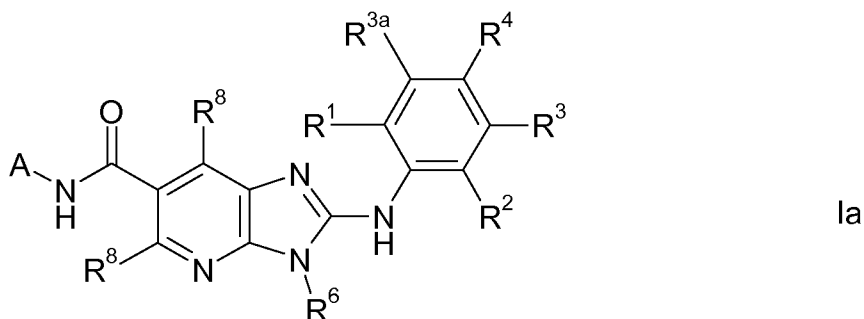
- 5 A represents C₁₋₁₂ linear or branched alkyl, aryl, heteroaryl, 5- or 6-membered heterocycloalkyl; or C₃₋₁₀ cycloalkyl, all of which groups are optionally substituted by one or more substituents selected from R⁹.

In another embodiment, the invention provides compounds of formula I according to any of the preceding embodiments and

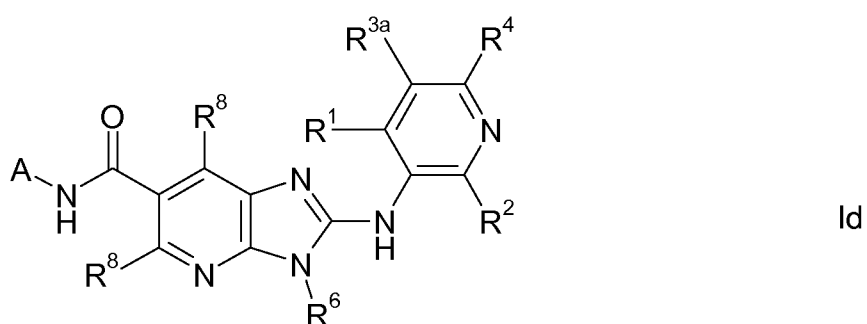
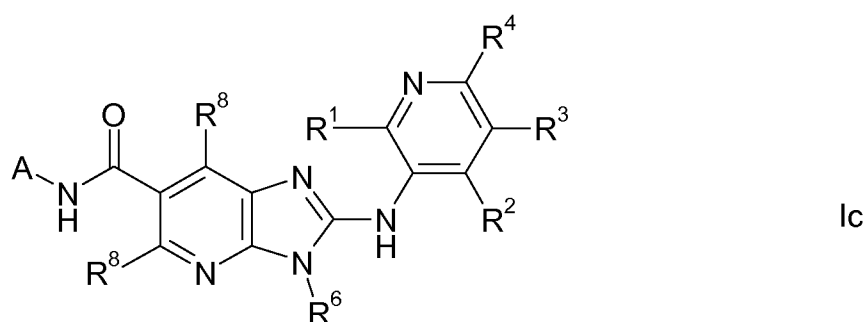
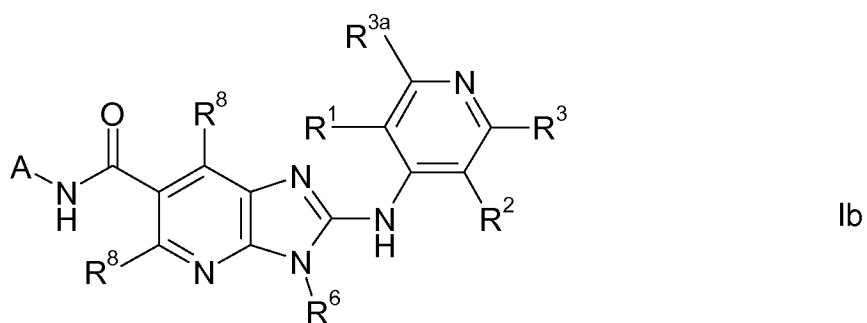
in which

- 10 A represents C₄₋₁₂ linear or branched alkyl, aryl, heteroaryl, 5- or 6-membered heterocycloalkyl; or C₃₋₇ cycloalkyl (all of which groups are optionally substituted by one or more substituents selected from R⁹); or
- 15 arylmethylene, heteroarylmethylene [which latter two groups are optionally substituted by one or more groups selected from C₁₋₇ alkyl (optionally substituted by one or more substituents selected from fluoro and -OR^{x2}), halo, -CN and/or -O-C₁₋₇ alkyl (optionally substituted by one or more fluoro atoms)].

- 20 In another embodiment, the invention provides compounds according to any of the preceding embodiments, namely compounds of formula Ia, Ib, Ic or Id



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in which

R¹ represents C₁₋₃ alkyl (optionally substituted by one or more fluoro atoms),
C₃₋₆ cycloalkyl, fluoro, chloro, bromo;

R² represents hydrogen, C₁₋₃ alkyl (optionally substituted by one or more fluoro
atoms), C₃₋₆ cycloalkyl, fluoro, chloro, bromo;

R³, R^{3a} and R⁴ independently represent hydrogen, fluoro, chloro, bromo, C₁₋₃ alkyl (optionally
substituted by one or more fluoro atoms);

R^6 represents hydrogen; C_{1-4} alkyl optionally substituted by one or more fluoro atoms;

5 R^8 independently represents hydrogen, $-O-C_{1-6}$ alkyl, $-O$ -cycloalkyl, $-O$ -heterocycloalkyl [which latter three groups are optionally substituted by one or more substituents selected from fluoro, C_{1-3} alkyl, C_{3-6} cycloalkyl, $-O-C_{1-3}$ alkyl, $-N(C_{1-3} \text{ alkyl})_2$, $-NHCO-C_{1-3}$ alkyl, $-N(C_{1-3}\text{-alkyl})CO-C_{1-3}$ alkyl, in all of which latter groups the alkyl-groups are optionally substituted by one or
10 more fluoro-atoms];

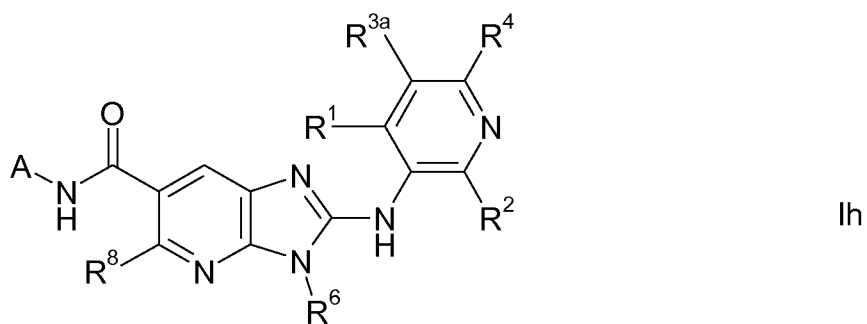
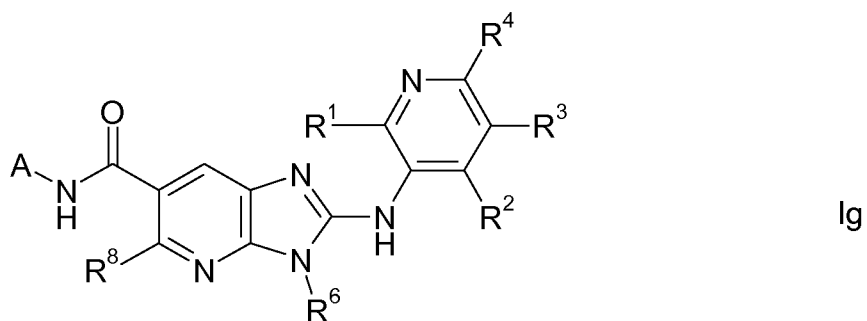
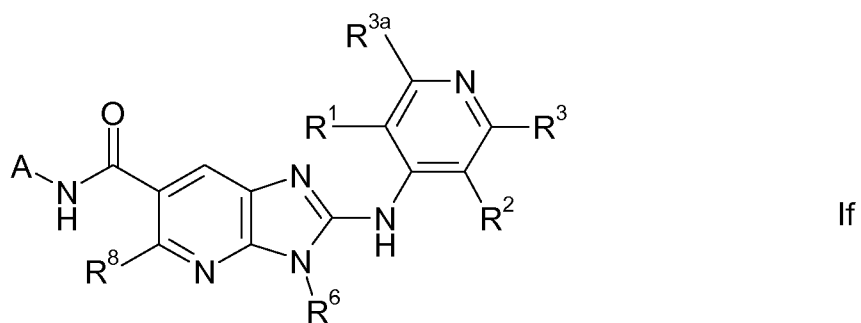
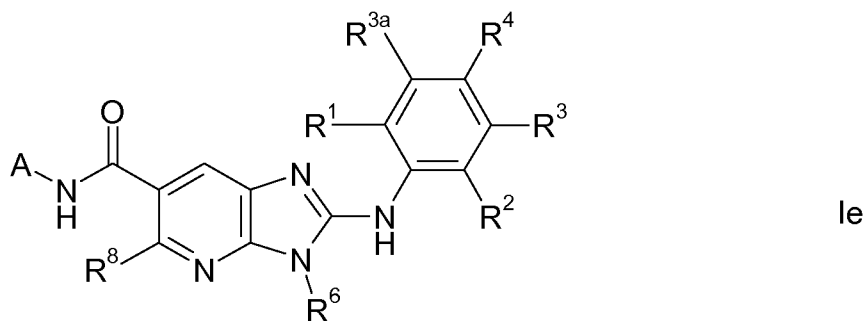
A represents phenyl, pyridyl, 5- or 6-membered heterocycloalkyl, C_{3-7} cycloalkyl, C_{5-8} linear or branched alkyl (all of which groups are optionally substituted by one or more substituents selected from R^9); or
15 benzyl, pyridylmethylene [which latter two groups are optionally substituted by one or more groups selected from C_{1-7} alkyl (optionally substituted by one or more substituents selected from fluoro and $-OR^{x2}$), halo, $-CN$ and/or $-O-C_{1-7}$ alkyl (optionally substituted by one or more fluoro atoms)];

20 R^9 represents on each occasion when used herein: halo, $-N(R^{y1})R^{y2}$, $-N(R^{y3})-C(O)-R^{y4}$, $-C(O)N(R^{y8})R^{y9}$, $-OR^{y10}$, and/or C_{1-6} alkyl optionally substituted by one or more substituents selected from fluoro, $-N(R^{y1})R^{y2}$, $-N(R^{y3})-C(O)-R^{y4}$, $-C(O)N(R^{y8})R^{y9}$, and/or $-OR^{y10}$; or any two R^9 substituents,
25 when attached to the adjacent atoms of the A group and, in the case where the R^9 substituents are attached to a non-aromatic A group, when attached to the same atoms, may be linked together to form, together with the essential atoms of the A group to which the relevant R^9 substituents are necessarily attached, a further
30 3- to 8-membered ring, optionally containing a further one or two heteroatoms, and which further ring optionally contains one or two unsaturations and which is optionally substituted by one or more C_{1-3} alkyl and/or $=O$ substituents;

and

the substituents R^{x2} , R^{y1} , R^{y2} , R^{y3} , R^{y4} , R^{y5} , R^{y6} , R^{y7} , R^{y8} , R^{y9} , R^{y10} , R^{y11} , R^{y12} , R^{y13} , R^{y14} and
35 R^{y15} have the meaning as defined in the embodiments above.

In another embodiment, the invention provides compounds according to any of the preceding embodiments, namely compounds of formula Ie, If, Ig or Ih



in which

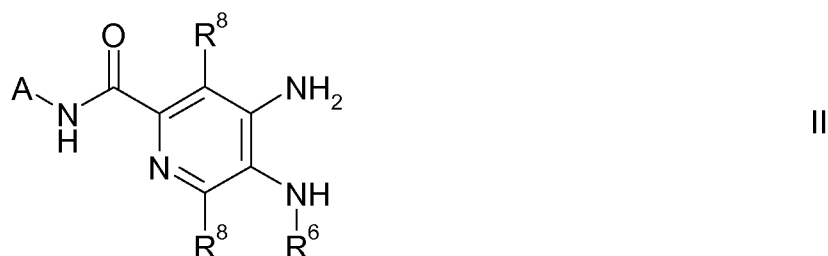
- R^1 represents chloro, bromo, fluoro, C_{1-3} alkyl (which latter alkyl group is optionally substituted by one or more fluoro-atoms);
- 5 R^2 represents hydrogen, chloro, bromo, fluoro, C_{1-3} - alkyl (which latter alkyl group is optionally substituted by one or more fluoro atoms);
- R^3 , R^{3a} and R^4 independently represent hydrogen, chloro, bromo, fluoro, C_{1-3} - alkyl (which latter alkyl group is optionally substituted by one or more fluoro atoms);
- 10 R^6 represents hydrogen; C_{1-4} alkyl optionally substituted by one or more fluoro atoms;
- R^8 independently represents hydrogen, $-O-C_{1-4}$ alkyl [optionally substituted by one or more substituents selected from fluoro, C_{1-3} alkyl, $-O-C_{1-3}$ alkyl, $-N(C_{1-3} \text{ alkyl})_2$, $-NHCO-C_{1-3}$ alkyl, $-N(C_{1-3}\text{-alkyl})CO-C_{1-3}$ alkyl], $-O-C_{3-6}$ cycloalkyl, $-O$ -oxetan-3-yl, $-O$ -tetrahydrofuran-3-yl, $-O$ -pyrrolidin-3-yl [which latter four groups are optionally substituted by one or more substituents selected from fluoro or C_{1-3} alkyl];
- 15 A represents phenyl, 2-pyridyl, 5- or 6-membered heterocycloalkyl, C_{3-7} cycloalkyl, C_{5-8} linear or branched alkyl (all of which groups are optionally substituted by one or more substituents selected from R^9); or benzyl, pyridin-2-yl-methylene [which latter two groups are optionally substituted by one or more groups selected from C_{1-7} alkyl (optionally substituted by one or more substituents selected from fluoro and $-OR^{x2}$), halo, $-CN$ and/or $-O-C_{1-7}$ alkyl (optionally substituted by one or more fluoro atoms)];
- 20 R^9 represents halo, $-O-C_{1-4}$ alkyl, C_{1-4} alkyl, C_{3-5} cycloalkyl, (which latter three groups are optionally substituted by one or more fluoro atoms).
- 25
- 30

In a further embodiment, the invention provides compounds namely those of the examples described hereinafter.

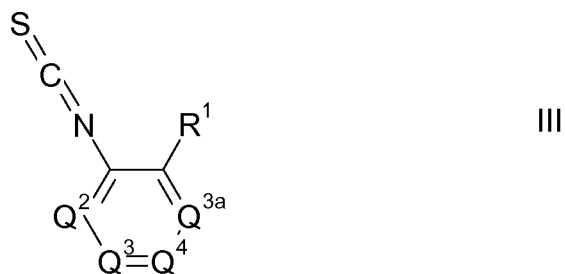
Compounds of the invention may be made in accordance with techniques that are well known to those skilled in the art, for example as described hereinafter.

According to a further aspect of the invention there is provided a process for the preparation of a compound of formula I, which process comprises:

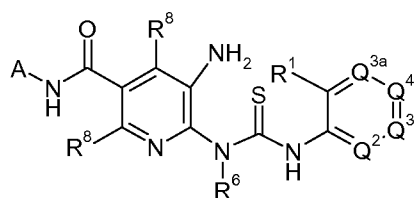
(i) for compounds of formula I, reaction of a compound of formula II,



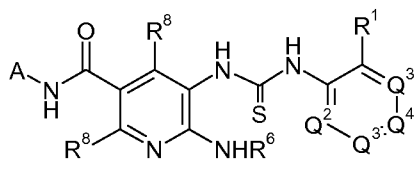
wherein: in each case, R⁶, R⁸ and A are as hereinbefore defined, with a compound of formula III,



wherein R^1 , Q^2 , Q^3 , Q^{3a} and Q^4 are as hereinbefore defined, under standard conditions known to those skilled in the art, for example in the presence of a suitable solvent (such as diethyl ether, or, preferably, dimethylformamide, dichloromethane, acetonitrile and/or tetrahydrofuran) and preferably in the presence of a suitable 'coupling' reagent (which reagent is preferably added during the course of the reaction, e.g. when there is no more starting material present and/or a thiourea intermediate has been formed) that may enhance the reactivity of any intermediate that may be formed (e.g. a thiourea intermediate such of formulae IIIA, IIIB, IIIC and/or IIID described hereinafter) between the reaction of the compound of formula II with the compound of formula III, for instance a carbodiimide based compound such as dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (or salt, e.g. hydrochloride, thereof) or, preferably *N,N*-diisopropylcarbodiimide (DIC), which reaction may proceed at any suitable temperature (e.g. one between about 0°C to about 200°C), and which may also be performed in the presence of an additive (such as 2,2,2-trifluoro-*N,O*-bis-(trimethylsilyl)-acetamide). Alternatively, this reaction may be performed in the presence of a suitable base or mixture of bases, such as those described hereinafter (process step (ii)), for example by reaction in the presence of triethylamine and/or DMAP (optionally in the presence of a suitable solvent such as dichloromethane), after which any intermediate so formed may be protected, optionally isolated and reacted in the presence of an aqueous basic solution (e.g. aqueous NaOH; optionally mixed with a further suitable solvent such as an alcoholic solvent), which reaction may take place at ambient temperature or up to reflux. The skilled person will appreciate that the reaction between compounds of formulae II and III may proceed *via* intermediates of formulae IIIA or IIIB (as appropriate),



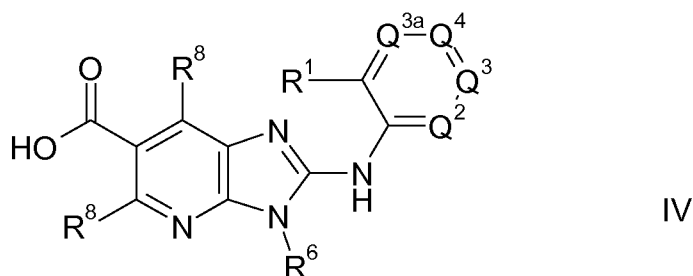
IIIA



IIIB

wherein R^1 , R^6 , R^8 , Q^2 , Q^3 , Q^{3a} , Q^4 and A are as hereinbefore defined. Such intermediates may be isolated or may be produced *in situ* in the reaction to form a compound of formula I. When such intermediates are produced separately, then they may be reacted in the presence of solvent (e.g. acetonitrile and/or methanol) and that the intermediate so formed may be then reacted under the conditions set out above;

(ii) for compounds of formula I, reaction of a compound of formula IV,



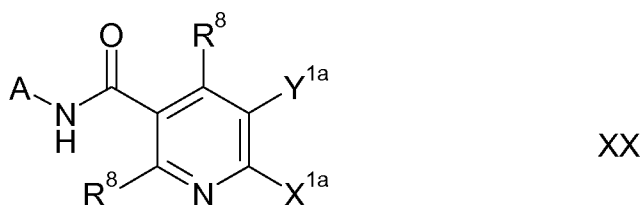
or a derivative thereof (e.g. an ester derivative, such as a methyl ester), wherein R^1 , Q^2 , Q^3 , Q^{3a} , Q^4 , R^6 and R^8 are as hereinbefore defined, with a compound of formula V,



wherein A is as hereinbefore defined, under coupling reaction conditions, for example at around room temperature or above (e.g. up to 40-180°C), optionally in the presence of a suitable base (e.g. sodium hydride, sodium bicarbonate, potassium carbonate, pyrrolidino-pyridine, pyridine, triethylamine, tributylamine, trimethylamine, dimethylaminopyridine, diisopropylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene, sodium hydroxide, *N*-ethyldiisopropylamine, *N*-(methylpolystyrene)-4-(methylamino)pyridine, butyllithium (e.g. *n*-, *s*- or *t*-butyllithium) or mixtures thereof), an appropriate solvent (e.g. tetrahydrofuran, pyridine, toluene, dichloromethane, chloroform, acetonitrile, dimethylformamide, dimethylsulfoxide,

trifluoromethylbenzene, triethylamine or water) and a suitable coupling agent (e.g. 1,1'-carbonyldiimidazole, *N,N'*-dicyclohexylcarbodiimide, *N,N'*-diisopropylcarbodiimide, 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide (or salt, e.g. hydrochloride thereof), *N,N'*-disuccinimidyl carbonate, benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate, 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, benzotriazol-1-yloxytrispyrrolidinophosphonium hexafluorophosphate, bromo-tris-pyrrolidinophosphonium hexafluorophosphate, 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluorocarbonate, 1-cyclohexyl-carbodiimide-3-propyloxymethyl polystyrene, O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetra-methyluronium hexafluorophosphate, O-pentafluorophenyl-*N,N,N',N'*-tetra-methyluronium hexafluorophosphate, O-(benzotriazol-1-yl)-*N,N,N',N'*-tetra-methyluronium tetrafluoroborate or mixtures thereof). Alternatively, compounds of formula III may first be activated by treatment with a suitable reagent (e.g. oxalyl chloride, thionyl chloride, phosphorous pentachloride, phosphorous oxychloride, (1-chloro-2-methyl-propenyl)-dimethyl-amine or the like, or mixtures thereof) optionally in the presence of an appropriate solvent (e.g. dichloromethane, THF, toluene or benzene) and a suitable catalyst (e.g. DMF), resulting in the formation of the respective acyl chloride. This activated intermediate may then be reacted with a compound of formula V under standard conditions, such as those described above. An alternative way of performing this step, includes the reaction of an ester derivative of a compound of formula IV (e.g. an ethyl or, preferably, a methyl ester) with a compound of formula V, in the presence of, e.g. trimethylaluminium, optionally in the presence of a suitable solvent (e.g. dichloromethane or tetrahydrofuran) under an inert atmosphere;

Compounds of formula II may be prepared by reduction of a compound of formula XX,

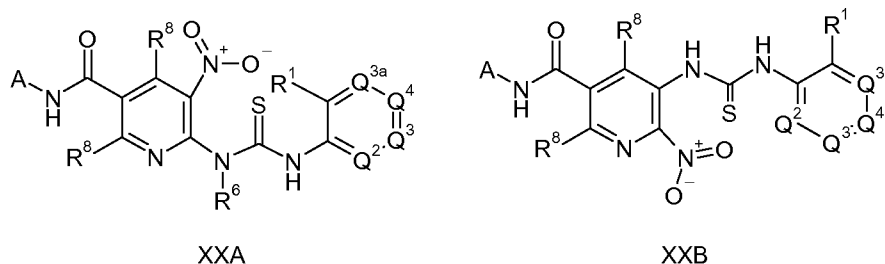


wherein Y^{1a} represents $-NO_2$ (or an azido group), and X^{1a} represents $-N(R^6)H$ or, in the case where the compound of formula II to be formed is one in which both X^1 and Y^1 represent

25

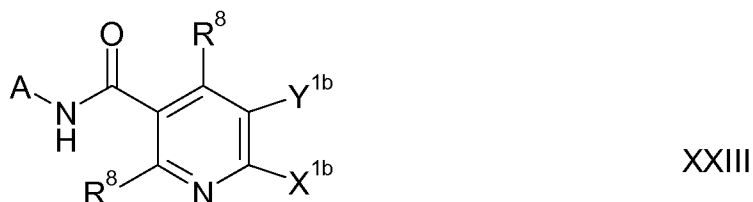
-N(H)-, then both of X^{1a} and Y^{1a} may represent $-\text{NO}_2$ (or an azido group), and R^8 and A are as hereinbefore defined, under standard conditions known to those skilled in the art, for example, under hydrogenation reaction conditions, including catalytic hydrogenation reaction conditions (e.g. employing a precious metal catalyst such as a platinum group catalyst, e.g. platinum or, preferably, palladium, which latter may be employed as 10%-20% Pd/C, or employing a non-precious metal catalyst such as one based on nickel, e.g. Raney nickel), for example in the presence of a suitable solvent such as diethyl ether or, preferably, ethyl acetate, tetrahydrofuran or an alcoholic solvent (e.g. EtOH or MeOH), or mixtures thereof. Alternatively, the reduction may be performed in the presence of other suitable conditions, such as employing a mixture of Sn/HCl or Fe powder in EtOH and/or acetic acid and NH_4Cl .

Compounds of formula IIIA and IIIB (the latter with $R^6 = \text{H}$) may be prepared by reduction of a corresponding compound of formula XXA or XXB,



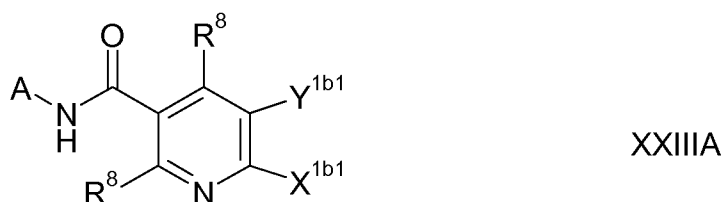
wherein R^1 , R^6 , R^8 , Q^2 , Q^3 , Q^{3a} , Q^4 and A are as hereinbefore defined, under reduction reaction conditions for example such as those hereinbefore described in respect of preparation of compounds of formula II. The skilled person will appreciate that a similar reaction may be performed on compounds in which the nitro group is replaced with an azido group.

Compounds of formula XX may be prepared by nitration of a compound of formula XXIII,



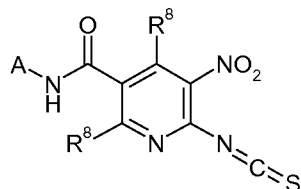
wherein X^{1b} represents $-N(R^6)H$ and Y^{1b} represents hydrogen, or X^{1b} represents hydrogen and Y^{1b} represents $-NH_2$, and R^8 and A are as hereinbefore defined, under standard nitration reaction conditions, for example in the presence of a mixture of nitric acid and sulfuric acid (e.g. conc. sulfuric acid) which may be mixed at low temperatures (e.g. at about $0^\circ C$), thereby forming a nitronium ion *in situ*, which may then react with the compound of formula XXIII.

Alternatively, compounds of formula XX in which one of X^{1a} and Y^{1a} represents $-NO_2$ and the other represents $-NH_2$ or $-N(R^6)H$ may be prepared by reaction of a compound of formula XXIIIA,

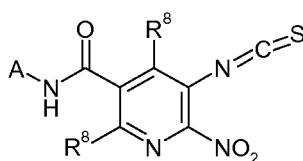


wherein one of X^{1b1} and Y^{1b1} represents $-NO_2$ and the other represents a suitable leaving group, such as hereinbefore defined in respect of L^{yb} (and preferably represents a halo group, such as chloro), and A and R^8 are as hereinbefore defined, with either: ammonia (or a suitable source thereof; for example, methanolic ammonia, or the like); or, for the introduction of the appropriate $-N(R^6)H$ (e.g. when R^6 is hydrogen), the corresponding amine R^6-NH_2 , under standard nucleophilic aromatic substitution reaction conditions.

Compounds of formula XXA and XXB in which X^1 and Y^1 preferably represent $-N(H)-$ may be prepared by reaction of a compound of formula XXIIIB or XXIIIC,



XXIIIB



XXIIIC

respectively, wherein R⁸ and A are as hereinbefore defined, with a compound of formula X as hereinbefore defined, under standard reaction conditions, for example such as those hereinbefore described in respect of preparation of compounds of formula I (process step (iv) above).

Compounds of formulae III, IIIA, IIIB, IV, V, VI, VII, VIII, X, XI, XII, XIII, XIV, XV, XVII, XVIII, XIX, XXIB, XXIC, XXII, XXIIIB, XXIIIC, XXIIIA, XXV, XXVI, XXVIA, XXVII and XXVIII are either commercially available, are known in the literature, or may be obtained either by analogy with the processes described herein, or by conventional synthetic procedures, in accordance with standard techniques, from available starting materials using appropriate reagents and reaction conditions. In this respect, the skilled person may refer to *inter alia* "Comprehensive Organic Synthesis" by B. M. Trost and I. Fleming, Pergamon Press, 1991.

The substituents R¹, Q², Q³, Q^{3a}, Q⁴, R⁵, Z¹, Z², Z³, B, E, X, Y, L and A in final compounds of formula I or relevant intermediates may be modified one or more times, after or during the processes described above by way of methods that are well known to those skilled in the art. Examples of such methods include substitutions, reductions (e.g. of double bonds to single bonds by hydrogenation), oxidations, alkylations, acylations, hydrolyses, esterifications, etherifications and nitrations. The precursor groups can be changed to a different such group, or to the groups defined in formula I, at any time during the reaction sequence. In this respect, the skilled person may also refer to "Comprehensive Organic Functional Group Transformations" by A. R. Katritzky, O. Meth-Cohn and C. W. Rees, Pergamon Press, 1995.

For example, in the case where R¹ or R² represents a halo group, such groups may be inter-converted one or more times, after or during the processes described above for the preparation of compounds of formula I. Appropriate reagents include NiCl₂ (for the conversion to a chloro group). Further, oxidations that may be mentioned include oxidations of sulfanyl groups to sulfoxide and sulfonyl groups, for example employing standard reagents (e.g. *meta*-chloroperbenzoic acid, KMnO₄ or a solution of Oxone® in ethylenediaminetetraacetic acid).

Other transformations that may be mentioned include the conversion of a halo group (preferably iodo or bromo) to a -CN or 1-alkynyl group (e.g. by reaction with a compound which is a source of cyano anions (e.g. sodium, potassium, copper (I) or zinc cyanide) or with a 1-alkyne, as appropriate). The latter reaction may be performed in the presence of a

suitable coupling catalyst (e.g. a palladium and/or a copper based catalyst) and a suitable base (e.g. a tri-(C₁₋₆ alkyl)amine such as triethylamine, tributylamine or ethyldiisopropylamine). Further, amino groups and hydroxy groups may be introduced in accordance with standard conditions using reagents known to those skilled in the art.

5

Compounds of formula I may be isolated from their reaction mixtures using conventional techniques.

10

It will be appreciated by those skilled in the art that, in the processes described above and hereinafter, the functional groups of intermediate compounds may need to be protected by protecting groups.

The protection and deprotection of functional groups may take place before or after a reaction in the above-mentioned schemes.

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Protecting groups may be removed in accordance with techniques that are well known to those skilled in the art and as described hereinafter. For example, protected compounds/intermediates described herein may be converted chemically to unprotected compounds using standard deprotection techniques.

20

The type of chemistry involved will dictate the need, and type, of protecting groups as well as the sequence for accomplishing the synthesis.

25

The use of protecting groups is fully described in "*Protective Groups in Organic Chemistry*", edited by J W F McOmie, Plenum Press (1973), and "*Protective Groups in Organic Synthesis*", 3rd edition, T.W. Greene & P.G.M. Wutz, Wiley-Interscience (1999).

Medical and Pharmaceutical Uses

Compounds of the invention are indicated as pharmaceuticals. According to a further aspect of the invention there is provided a compound of the invention, as hereinbefore defined but without the provisos for use as a pharmaceutical.

Although compounds of the invention may possess pharmacological activity as such, certain pharmaceutically-acceptable (e.g. "protected") derivatives of compounds of the invention may exist or be prepared which may not possess such activity, but may be administered parenterally or orally and thereafter be metabolised in the body to form compounds of the invention. Such compounds (which may possess some pharmacological activity, provided that such activity is appreciably lower than that of the "active" compounds to which they are metabolised) may therefore be described as "prodrugs" of compounds of the invention.

By "prodrug of a compound of the invention", we include compounds that form a compound of the invention, in an experimentally-detectable amount, within a predetermined time (e.g. about 1 hour), following oral or parenteral administration. All prodrugs of the compounds of the invention are included within the scope of the invention.

Furthermore, certain compounds of the invention may possess no or minimal pharmacological activity as such, but may be administered parenterally or orally, and thereafter be metabolised in the body to form compounds (e.g. compounds of the invention) that possess pharmacological activity as such. Such compounds (which also includes compounds that may possess some pharmacological activity, but that activity is appreciably lower than that of the "active" compounds of the invention to which they are metabolised), may also be described as "prodrugs".

Thus, the compounds of the invention are useful because they possess pharmacological activity, and/or are metabolised in the body following oral or parenteral administration to form compounds which possess pharmacological activity (e.g. similar or pronounced pharmacological activity as compared to the compounds of the invention from which they are formed).

Compounds of the invention are particularly useful because they may inhibit the activity of a member of the MAPEG family.

Compounds of the invention are particularly useful because they may inhibit (for example selectively) the activity of prostaglandin E synthases (and particularly microsomal prostaglandin E synthase-1 (mPGES-1)), i.e. they prevent the action of mPGES-1 or a complex of which the mPGES-1 enzyme forms a part, and/or may elicit a mPGES-1

modulating effect, for example as may be demonstrated in the test described below.

Compounds of the invention may thus be useful in the treatment of those conditions in which inhibition of a PGES, and particularly mPGES-1, is required.

Compounds of the invention are thus expected to be useful in the treatment of inflammation.

- 5 Further, as the compounds of the invention may be of use as mPGES inhibitors (e.g. mPGES-1 inhibitors), they may also be useful in preventing or treating benign or malignant neoplasias (as they may reduce the production of PGE₂). Hence, the compounds of the invention may also be useful in treating cancers.

- 10 The term "inflammation" will be understood by those skilled in the art to include any condition characterised by a localised or a systemic protective response, which may be elicited by physical trauma, infection, chronic diseases, such as those mentioned hereinbefore, and/or chemical and/or physiological reactions to external stimuli (e.g. as part of an allergic response). Any such response, which may serve to destroy, dilute or sequester both the injurious agent and the injured tissue, may be manifest by, for example, heat, swelling, pain,
15 redness, dilation of blood vessels and/or increased blood flow, invasion of the affected area by white blood cells, loss of function and/or any other symptoms known to be associated with inflammatory conditions.

- The term "inflammation" will thus also be understood to include any inflammatory disease, disorder or condition *per se*, any condition that has an inflammatory component associated
20 with it, and/or any condition characterised by inflammation as a symptom, including *inter alia* acute, chronic, ulcerative, specific, allergic and necrotic inflammation, and other forms of inflammation known to those skilled in the art. The term thus also includes, for the purposes of this invention, inflammatory pain, pain generally and/or fever.

- Where a condition has an inflammatory component associated with it, or a condition
25 characterised by inflammation as a symptom, the skilled person will appreciate that compounds of the invention may be useful in the treatment of the inflammatory symptoms and/or the inflammation associated with the condition.

- Accordingly, compounds of the invention may be useful in the treatment of asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, inflammatory bowel disease, irritable
30 bowel syndrome, inflammatory pain, fever, migraine, headache, low back pain, fibromyalgia, myofascial disorders, viral infections (e.g. influenza, common cold, herpes zoster, hepatitis C and AIDS), bacterial infections, fungal infections, dysmenorrhea, burns, surgical or dental procedures, malignancies (e.g. breast cancer, colon cancer, and prostate cancer), hyperprostaglandin E syndrome, classic Bartter syndrome, atherosclerosis, gout, arthritis,

osteoarthritis, juvenile arthritis, rheumatoid arthritis, rheumatic fever, ankylosing spondylitis, Hodgkin's disease, systemic lupus erythematosus, vasculitis, pancreatitis, nephritis, bursitis, conjunctivitis, iritis, scleritis, uveitis, wound healing, dermatitis, eczema, psoriasis, stroke, diabetes mellitus, neurodegenerative disorders such as Alzheimer's disease and multiple sclerosis, autoimmune diseases, allergic disorders, rhinitis, ulcers, coronary heart disease, sarcoidosis and any other disease with an inflammatory component.

Compounds of the invention may also have effects that are not linked to inflammatory mechanisms, such as in the reduction of bone loss in a subject. Conditions that may be mentioned in this regard include osteoporosis, osteoarthritis, Paget's disease and/or periodontal diseases. Compounds the invention may thus also be useful in increasing bone mineral density, as well as the reduction in incidence and/or healing of fractures, in subjects. Compounds of the invention are indicated both in the therapeutic and/or prophylactic treatment of the above-mentioned conditions.

According to a further aspect of the present invention, there is provided a method of treatment of a disease which is associated with, and/or which can be modulated by inhibition of, a member of the MAPEG family such as a PGES (e.g. mPGES-1), LTC₄ synthase and/or FLAP and/or a method of treatment of a disease in which inhibition of the activity of a member of the MAPEG family such as PGES (and particularly mPGES-1), LTC₄ synthase and/or FLAP is desired and/or required (e.g. inflammation), which method comprises administration of a therapeutically effective amount of a compound of the invention, as hereinbefore defined but without the provisos, to a patient suffering from, or susceptible to, such a condition.

"Patients" include mammalian (including human) patients.

The term "effective amount" refers to an amount of a compound, which confers a therapeutic effect on the treated patient. The effect may be objective (i.e. measurable by some test or marker) or subjective (i.e. the subject gives an indication of or feels an effect).

Compounds of the invention will normally be administered orally, intravenously, subcutaneously, buccally, rectally, dermally, nasally, tracheally, bronchially, sublingually, by any other parenteral route or *via* inhalation, in a pharmaceutically acceptable dosage form.

Compounds of the invention may be administered alone, but are preferably administered by way of known pharmaceutical formulations, including tablets, capsules or elixirs for oral administration, suppositories for rectal administration, sterile solutions or suspensions for parenteral or intramuscular administration, and the like.

Such formulations may be prepared in accordance with standard and/or accepted pharmaceutical practice.

According to a further aspect of the invention there is thus provided a pharmaceutical

- 5 formulation including a compound of the invention, as hereinbefore defined but without the provisos, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

Depending on e.g. potency and physical characteristics of the compound of the invention (i.e. active ingredient), pharmaceutical formulations that may be mentioned include those in which the active ingredient is present in at least 1% (or at least 10%, at least 30% or at least 50%)

- 10 by weight. That is, the ratio of active ingredient to the other components (i.e. the addition of adjuvant, diluent and carrier) of the pharmaceutical composition is at least 1:99 (or at least 10:90, at least 30:70 or at least 50:50) by weight.

The invention further provides a process for the preparation of a pharmaceutical formulation, as hereinbefore defined, which process comprises bringing into association a compound of

- 15 the invention, as hereinbefore defined but without the provisos, or a pharmaceutically acceptable salt thereof with a pharmaceutically-acceptable adjuvant, diluent or carrier.

Compounds of the invention may also be combined with other therapeutic agents that are useful in the treatment of inflammation (e.g. NSAIDs and coxibs).

- 20 According to a further aspect of the invention, there is provided a combination product comprising:

(A) a compound of the invention, as hereinbefore defined but without the provisos; and

(B) another therapeutic agent that is useful in the treatment of inflammation,

wherein each of components (A) and (B) is formulated in admixture with a pharmaceutically-

- 25 acceptable adjuvant, diluent or carrier.

Such combination products provide for the administration of a compound of the invention in conjunction with the other therapeutic agent, and may thus be presented either as separate formulations, wherein at least one of those formulations comprises a compound of the

- 30 invention, and at least one comprises the other therapeutic agent, or may be presented (i.e. formulated) as a combined preparation (i.e. presented as a single formulation including a compound of the invention and the other therapeutic agent).

Thus, there is further provided:

(1) a pharmaceutical formulation including a compound of the invention, as hereinbefore

5 defined but without the provisos, another therapeutic agent that is useful in the treatment of inflammation, and a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(2) a kit of parts comprising components:

(a) a pharmaceutical formulation including a compound of the invention, as hereinbefore
10 defined but without the provisos, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(b) a pharmaceutical formulation including another therapeutic agent that is useful in the treatment of inflammation in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier,

15 which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

The invention further provides a process for the preparation of a combination product as hereinbefore defined, which process comprises bringing into association a compound of the
20 invention as hereinbefore defined but without the provisos with another therapeutic agent that is useful in the treatment of inflammation, and a pharmaceutically-acceptable adjuvant, diluent or carrier.

By "bringing into association", we mean that the two components are rendered suitable for
25 administration in conjunction with each other.

Thus, in relation to the process for the preparation of a kit of parts as hereinbefore defined, by bringing the two components "into association with" each other, we include that the two components of the kit of parts may be:

(i) provided as separate formulations (i.e. independently of one another), which are
30 subsequently brought together for use in conjunction with each other in combination therapy; or

(ii) packaged and presented together as separate components of a "combination pack" for use in conjunction with each other in combination therapy.

Compounds of the invention may be administered at varying doses. Oral, pulmonary and topical dosages may range from between about 0.01 mg/kg of body weight per day

(mg/kg/day) to about 100 mg/kg/day, preferably about 0.01 to about 100 mg/kg/day, and

more preferably about 0.1 to about 25 mg/kg/day. For e.g. oral administration, the

compositions typically contain between about 0.01 mg to about 5000 mg, and preferably

between about 1 mg to about 2000 mg, of the active ingredient. Intravenously, the most

preferred doses will range from about 0.001 to about 10 mg/kg/hour during constant rate

infusion. Advantageously, compounds may be administered in a single daily dose, or the

total daily dosage may be administered in divided doses of two, three or four times daily.

In any event, the physician, or the skilled person, will be able to determine the actual dosage

which will be most suitable for an individual patient, which is likely to vary with the route of

administration, the type and severity of the condition that is to be treated, as well as the

species, age, weight, sex, renal function, hepatic function and response of the particular

patient to be treated. The above-mentioned dosages are exemplary of the average case;

there can, of course, be individual instances where higher or lower dosage ranges are

merited, and such are within the scope of this invention.

Compounds of the invention may have the advantage that they are effective, and preferably

selective, inhibitors of a member of MAPEG family, e.g. inhibitors of prostaglandin E

synthases (PGES) and particularly microsomal prostaglandin E synthase-1 (mPGES-1). The

compounds of the invention may reduce the formation of the specific arachidonic acid

metabolite PGE₂ without reducing the formation of other COX generated arachidonic acid

metabolites, and thus may not give rise to the associated side-effects mentioned

hereinbefore.

Compounds of the invention may also have the advantage that they may be more efficacious

than, be less toxic than, be longer acting than, be more potent than, produce fewer side

effects than, be more easily absorbed than, and/or have a better pharmacokinetic profile

(e.g. higher oral bioavailability and/or lower clearance) than, and/or have other useful

pharmacological, physical, or chemical properties over, compounds known in the prior art,

whether for use in the above-stated indications or otherwise.

Biological Test

Microsomes from Rosetta E.coli bacteria expressing recombinant human mPGES-1 is dissolved in 0.1 M KP_i pH 7.4 buffer containing 2,5 mM GSH. 50 µl of the enzyme is subsequently dispensed in a 384-well plate. 0,5 µl of the inhibitor dissolved in DMSO at is

thereafter added to each well and incubated for 25 minutes at room temperature.

Subsequently, 2 µl of PGH2 dissolved in an appropriate solvent is added to each well and after one minute the acidified stop solution containing FeCl₂ is added. 4 µl of the total volume is transferred to a separate plate and diluted 750-fold in two separate steps before HTRF detection of PGE₂.

The HTRf detection is performed by the use of a commercially available kit from CisBio essentially according to the manufacturer's protocol. Briefly, 10 µl of the diluted sample is transferred to a white 384-well plate. 5 µl of d2 and 5µl Eu3+-Cryptate labeled anti-PGE₂ is added to each well containing samples by the use of a Multidrop. The plate is covered with a plastic self-adhesive film, centrifuged at 1200 rpm for 1 minute and subsequently stored at +4°C over night.

After over night incubation the fluorescence is measured by the use of an appropriate microplate reader. The fluorescence of europium cryptate, and d2 are measured using the following excitation and emission wavelength, europium cryptate: $\lambda_{\max}^{\text{ex}} = 307 \text{ nm}$, $\lambda_{\max}^{\text{em}} = 620 \text{ nm}$ and d2: $\lambda_{\max}^{\text{ex}} = 620 \text{ nm}$, $\lambda_{\max}^{\text{em}} = 665 \text{ nm}$), respectively. The extent of the specific FRET is measured as a ratio of the emission intensity at 665 nm vs. that at 620 nm. A standard curve using synthetic PGE₂ is used to quantify the amount of PGE₂ in unknown samples.

Chemical Examples

Unless otherwise stated, one or more tautomeric forms of compounds of the examples described hereinafter may be prepared *in situ* and/or isolated. All tautomeric forms of compounds of the examples described hereinafter should be considered to be disclosed.

The invention is illustrated by way of the following examples, in which the following abbreviations may be employed:

AIBN	Azo-bis-isobutyronitrile
aq.	aqueous solution
Boc	<i>tert.</i> -butoxycarbonyl
DIC	diisopropyl-carbodiimide

	DIPEA	<i>N</i> -ethyl-diisopropylamine
	DMSO	dimethylsulphoxide
	DMF	<i>N,N</i> -dimethylformamide
	sat.	saturated
5	h	hour(s)
	HATU	<i>O</i> -(7-azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium-hexafluorophosphate
	HBTU	<i>O</i> -Benzotriazole-1-yl- <i>N,N,N',N'</i> -tetramethyluronium-hexafluorophosphate
	DPPA	Diphenylphosphoryl azide
	HPLC	high performance liquid chromatography
10	i. vac.	<i>in vacuo</i>
	conc.	concentrated
	min	minute(s)
	MS	mass spectrometry
	NBS	<i>N</i> -bromo-succinimide
15	NMM	<i>N</i> -methyl-morpholine
	NMP	<i>N</i> -methyl-pyrrolidin-2-one
	o	ortho
	PfTU	<i>O</i> -pentafluorophenyl- <i>N,N,N',N'</i> -tetramethyluronium-hexafluorophosphate
	PPA	propanephosphonic acid cycloanhydride
20	quant.	quantitative
	R _f	retention factor
	R _t	retention time
	mp	melting point
	rac.	Racemic
25	M	mol / L
	sat.	saturated
	TBME	<i>tert.</i> -butyl-methyl-ether
	TBTU	<i>O</i> -(benzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium tetrafluoroborate
	TEA	triethylamine
30	TFA	trifluoroacetic acid
	THF	tetrahydrofuran
	tert.	tertiary
	TLC	Thin layer chromatography
	Σ	yield over all the steps carried out analogously as described
35	KHCO ₃	potassium-hydrogen-carbonate
	K ₂ CO ₃	potassium carbonate

	Na ₂ SO ₄	sodium sulfate
	NaOH	sodium hydroxide
	HCl	hydrochloric acid
	DCC	<i>N,N'</i> -Dicyclohexylcarbodiimide
5	DIBAL-H	Diisobutylaluminium hydride
	DMAP	4-Dimethylaminopyridine
	EDC	3-(3-Dimethylaminopropyl)-1-ethyl-carbodiimide
	EDCI	3-(3-Dimethylaminopropyl)-1-ethyl-carbodiimide hydrochloride

10 The HPLC/MS data, where specified, were obtained under the following conditions:

Agilent 1100 with quaternary pump, Gilson G215 Autosampler, HP diode array detector.

The following was used as the mobile phase:

- 15 E1: water with 0.15% formic acid
 E2: acetonitrile
 E3: water with 0.1% acetic acid

Eluent gradient A (polar):

20	time in min	%E1	%E2	flow rate in mL/min
	0.0	95	5	1.6
	4.00	50	50	1.6
	4.50	10	90	1.6
	5.00	10	90	1.6
25	5.50	90	10	1.6

Eluent gradient B (standard):

	time in min	%E1	%E2	flow rate in mL/min
	0.0	95	5	1.6
30	4.50	10	90	1.6
	5.00	10	90	1.6
	5.50	90	10	1.6

Eluent gradient C (unpolar):

	time in min	%E1	%E2	flow rate in mL/min
	0.0	95	5	1.6
5	2.00	10	90	1.6
	5.00	10	90	1.6
	5.50	90	10	1.6

Eluent gradient D (ultrakurz-polar):

	time in min	%E1	%E2	flow rate in mL/min
	0.0	95	5	1.6
	2.00	50	50	1.6
	2.25	10	90	1.6
	2.5	10	90	1.6
15	2.75	95	5	1.6

Eluent gradient E (ultrakurz-standard):

	time in min	%E1	%E2	flow rate in mL/min
	0.0	95	5	1.6
20	2.25	10	90	1.6
	2.5	10	90	1.6
	2.75	95	5	1.6

Eluent gradient F (ultakurz-unpolar):

	time in min	%E1	%E2	flow rate in mL/min
	0.0	95	5	1.6
	1.00	10	90	1.6
	2.5	10	90	1.6
	2.75	95	5	1.6

Eluent gradient G :

time in min	%E3	%E2	flow rate in mL/min
0.0	95	5	3
0.3	95	5	3
2	2	98	3
2.4	2	98	3
2.45	95	5	3
2.8	95	5	3

The following was used as the stationary phase: (column temperature: constant at 25°C)

- 1: Zorbax StableBond C18, 3.5µm, 4.6x75mm
- 2: Waters Symmetry C18, 3.5µm, 4.6x75mm
- 3: Zorbax Bonus-RP C18, 3.5µm, 4.6x75mm
- 4: YMC-Pack ODS-AQ, 3µm, 4.6x75mm
- 5: XBridge C18, 3.5µm, 4.6x75mm
- 7: Zorbax Stable Bond C18, 1.8µm, 3,0x30mm
- 8: Sunfire C18, 2.5µm, 3.0x30mm
- 9: Xbridge C1, 2,5µm, 3,0x30mm
- 12: Zorbax Stable Bond C18, 3.5µm, 4.6x75mm

The following was used as the stationary phase: (column temperature: constant at 20°C)

- 10: Interchim Strategy C18, 5µm, 4,6x50mm
- 11: XRS C18, 5µm, 4,6x50mm

The method is abbreviated using the above descriptions (eg. A1 for Eluent gradient A with stationary phase 1).

The diode array detection took place in a wavelength range from 210-550 nm

Range of mass-spectrometric detection: m/z 120 to m/z 1000

Alternatively, the following method was used, abbreviated CC:

HP1100 HPLC + DAD (Wavelength range: 210nm to 500nm), and Gilson 215 Autosampler
RP-HPLC MS analyses were performed on a Waters ZQ2000 mass spectrometer

5

The following was used as the mobile phase:

E1: water with 0.1% trifluoroacetic acid

E2: acetonitrile with 0.1% trifluoroacetic acid

10 Eluent gradient:

time in min	%E1	%E2	flow rate in mL/min
0.0	95	5	1.5
2.00	0	100	1.5
2.50	0	100	1.5
2.60	95	5	1.5

15

The following was used as the stationary phase:

Sunfire C18 4.6x50mm, 3.5µm (column temperature: constant at 40°C)

20

The diode array detection took place in a wavelength range from 210-500 nm

Range of mass-spectrometric detection: m/z 120 to m/z 820.

Alternatively, the following method was used, abbreviated EX1:

25

Column: Atlantis dC18 5 mm, 2.1x50 mm.

Mobile phase: 10-95% MeCN in 0.01% TFA.

Flow rate: 0.2 mL/min.

Detection: UV 254 nm.

30

Alternatively, the following method was used, abbreviated EX2:

Column: Acquity UPLC BEH SHIELD RP18 1.7 mm, 2.1x100 mm.

Mobile phase: 5-100% MeCN in 0.1% HCOOH.

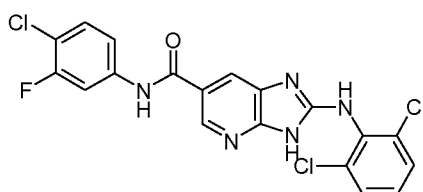
Flow rate: 0.2 mL/min.

35

Detection: UV 254 nm / 211 nm.

The following compounds are accompanied by structural drawings. The skilled person will appreciate that the rules of valency must be adhered to and hence there must be a certain number of bonds attached to each atom, which may not necessarily be depicted on the drawings. For example, in the case where a nitrogen heteroatom is depicted with only one or two bonds attached to it, the skilled person will realise that it should be attached to an additional one or two bonds (a total of three), in which such bonds are normally attached to one or two hydrogen atoms (so forming a -NH₂ or -N(H)- moiety).

Example 154



2-(2,6-Dichloro-phenylamino)-3H-imidazo[4,5-b]-pyridine-6-carboxylic acid (4-chloro-3-fluoro-phenyl)-amide

(154a) 6-Amino-5-nitro-nicotinic acid

6-Chloro-5-nitro-nicotinic acid (3.00 g, 14.8 mmol) in 100 mL conc. ammonia was stirred for 16 h. The mixture was concentrated, the residue mixed with 50 mL water, acidified with hydrochloric acid and stirred for 10 min. The precipitate was filtered off and washed with water. The solid was dried and taken up in refluxing THF. The mixture was filtered and concentrated. The residue was reacted without further purification.

Yield: 1.90 g (70%)

(154b) 6-Amino-5-nitro-nicotinoyl chloride

6-amino-5-nitro-nicotinic acid (2.50 g, 13.7 mmol) was mixed with 50 mL thionyl chloride and refluxed for 2 h. The mixture was concentrated and the residue reacted without further purification.

Yield: 2.75 g (quant.)

(154c) 6-Amino-*N*-(4-chloro-3-fluoro-phenyl)-5-nitro-nicotinamide

6-Amino-5-nitro-nicotinoyl chloride (2.70 g, 13.4 mmol) in 50 mL THF was added to a mixture of 4-chloro-3-fluoro-aniline (1.95 g, 13.4 mmol) with TEA (2.80 g, 27.7 mmol) in 50 mL THF and the mixture stirred at ambient temperature for 1 h. The mixture was poured into water, the resulting mixture was stirred, the precipitate was filtered off, washed with water and dried. The solid was stirred in 30 mL methanol for 30 min, filtered off, washed with methanol and ether and dried. The solid was reacted without further purification.

Yield: 2.00 g (48%)

mass spectrum: $(M-H)^- = 309/311$ (chlorine isotopes)

(154d) 5,6-Diamino-*N*-(4-chloro-3-fluoro-phenyl)-nicotinamide

6-Amino-*N*-(4-chloro-3-fluoro-phenyl)-5-nitro-nicotinamide (1.70 g, 5.47 mmol) in 100 mL THF was hydrogenated for 2 days at ambient temperature and 50 psi hydrogen pressure using Raney nickel. The reaction mixture was filtered and concentrated. The residue was triturated in methanol, filtered off, washed with methanol and diethylether and dried.

Yield: 0.80 g (52%)

mass spectrum: $(M+H)^+ = 281/283$ (chlorine isotopes)

(154e) 2-(2,6-Dichloro-phenylamino)-3H-imidazo[4,5-b]-pyridine-6-carboxylic acid (4-chloro-3-fluoro-phenyl)-amide

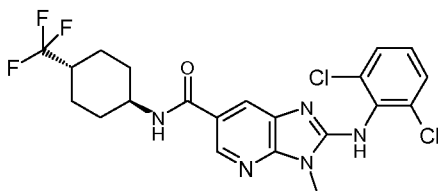
1,3-Dichloro-2-isothiocyanato-benzene (146 mg, 0.72 mmol) was added to the product obtained in (154d) in 30 mL acetonitrile with 5 mL DMF and stirred at ambient temperature for 40 h. DIC (104 mg, 0.82 mmol) was added to the mixture and stirred at 90°C for 16 h. The mixture was concentrated, the residue mixed with water and extracted with ethyl acetate.

The combined organic layers were washed with water and sat. NaCl (aq), dried and evaporated. The residue was purified by preparative HPLC.

Yield: 25 mg (7.8%)

mass spectrum: $(M+H)^+ = 450/452/454/456$ (chlorine isotopes)

R_t value: 2.91 min (C5)

Example 174

2-(2,6-Dichloro-phenylamino)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxylic acid (trans-4-trifluoromethyl-cyclohexyl)-amide

(174a) 6-Methylamino-5-nitro-nicotinic acid

Prepared analogously to example 154a from 6-chloro-5-nitro-nicotinic acid and 2 M methylamine solution in THF.

Yield: 84%

R_t value: 2.73 min (B1)

mass spectrum: $(M+H)^+ = 198$

(174b) 6-Methylamino-5-nitro-nicotinic acid ethyl ester

40 mL ethanol was added to a mixture of the product obtained in 174a (2.45 g, 12.4 mmol) and conc. sulphuric acid (1.33 mL, 25.0 mmol). The mixture was stirred for 2 days at reflux. The mixture was concentrated *i.vac.*. The residue was taken up in diluted aq. ammonia solution and ethyl acetate. The organic phase was separated, dried and concentrated *i.vac.*. The residue was purified by chromatography on silica gel (eluent: petrol ether / ethyl acetate = 1:1).

Yield: 1.92 g (69%)

mass spectrum: $(M+H)^+ = 226$

R_t value: 2.71 min (C1)

(174c) 5-Amino-6-methylamino-nicotinic acid ethyl ester

Conc. HCl (aq) (15.0 mL) was added to a stirred mixture of the product obtained at (174b) (0.80 g, 3.6 mmol) and iron powder (0.99 g, 17.8 mmol) in 30 mL ethanol. After stirring for 30 min the mixture was poured onto sat. aq. K_2CO_3 solution. The aq. phase was extracted with ethyl acetate. The organic phase was separated, dried and concentrated *i.vac.*.

Yield: quant.

R_t value: 1.73 min (C1)

(174d) 2-(2,6-Dichloro-phenylamino)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxylic acid ethyl ester

Prepared analogously to example 154e from the product obtained at (174c), 1,3-dichloro-2-thioisocyanato-benzene and DIC in acetonitrile.

5 Yield: 84%

mass spectrum: $(M+H)^+ = 365/367/369$ (chlorine isotopes)

R_t value: 2.71 min (C1)

(174e) 2-(2,6-Dichloro-phenylamino)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxylic acid

10 1 M aq. NaOH (15 mL, 15 mmol) was added to the product obtained from (174d) (1.10 g, 3.01 mmol) in 15 mL ethanol and the mixture stirred for 24 h at ambient temperature. Then the mixture was concentrated, 20 mL water were added, acidified with 1 M hydrochloric acid and stirred for 30 min. The precipitate was filtered off, washed with water and dried.

Yield: 1.00 g (99%)

15 mass spectrum: $(M+H)^+ = 337/339/341$ (chlorine isotopes)

R_t value: 2.18 min (C1)

(174f) 2-(2,6-Dichloro-phenylamino)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxylic acid (*trans*-4-trifluoromethyl-cyclohexyl)-amide

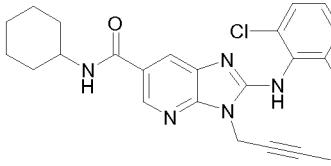
20 TBTU (116 mg, 0.36 mmol) was added to a mixture of the product obtained in (174e) with TEA (0.13 ml, 0.90 mmol) in 7 mL THF with 1 mL DMF and the mixture stirred for 30 min at ambient temperature. *trans*-4-Trifluoromethyl-cyclohexylamine hydrochloride was added and the mixture stirred for 16 h at ambient temperature. The mixture was concentrated, methanol and formic acid were added to the residue and then purified by preparative HPLC.

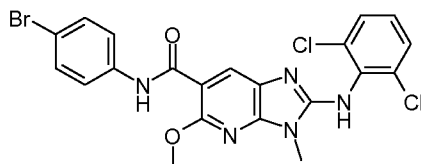
25 Yield: 86 mg (59%)

mass spectrum $(M+H)^+ = 486$

R_t value: 2.76 min (C4)

In analogy with the above described example, the following compounds were prepared:

No.	Structural formula	Yield	Mass peak(s)	R _f value or R _t
	Name			
523		Σ: 14.5%	(M+H) ⁺ = 456/458/460 (chlorine isotopes)	3.00 min (C4)
	3-(But-2-ynyl)-N-cyclohexyl-2-(2,6-dichlorophenylamino)-3H-imidazo[4,5-b]pyridine-6-carboxamide			

Example 377

N-(4-Bromophenyl)-2-(2,6-dichlorophenylamino)-5-methoxy-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide

10 (377a) 6-Methoxy-N-methyl-3-nitropyridin-2-amine

Prepared analogously to example 154a from 2-chloro-6-methoxy-3-nitropyridine and 2 N methylamine (solution in THF) in THF

Yield: 96%

mass spectrum: (M+H)⁺ = 184

15

(377b) 5-Bromo-6-methoxy-N-methyl-3-nitropyridin-2-amine

6-Methoxy-N-methyl-3-nitropyridin-2-amine (7 g, 38 mmol) in 150 mL dichloromethane and 50 mL methanol were combined with tetrabutylammonium-tri-bromide (20.3 g, 42.0 mmol).

The mixture was stirred at ambient temperature for 2h. The mixture was poured into water,

20 filtered and washed with water and ethanol and reacted without further purification.

Yield: 11 g (110%), crude

mass spectrum: (M+H)⁺ = 262

(377c) 1-(5-Bromo-6-methoxy-2-(methylamino)-pyridin-3-yl)-3-(2,6-dichloro-phenyl)-thiourea

5-Bromo-6-methoxy-N-methyl-3-nitropyridin-2-amine (0.5 g, 1.9 mmol) in THF was combined with Raney nickel (70 mg) and hydrogenated in a Parr apparatus at ambient temperature for 10 h at 3.5 bar hydrogen pressure. Then the mixture was directly filtered into a mixture of 1,3-dichloro-2-isothiocyanatobenzene (0.39 g, 1.9 mmol) in THF and stirred overnight at ambient temperature. The solvent was removed i. vac. and the residue was purified by HPLC (C18 Symmetry, 8µm, eluent: H₂O + 0.15% HCOOH + 15-100% acetonitrile).

(377d) 6-Bromo-N-(2,6-dichlorophenyl)-5-methoxy-3-methyl-3H-imidazo[4,5-b]pyridin-2-amine

DIC (0.23 mL, 1.49 mmol) was added to the product obtained in (377c) in 20 mL acetonitrile and the mixture was stirred at 70°C for 2 h. The mixture was then filtered, washed with acetonitrile and dried at ambient temperature.

Yield: 0.547 (91%)

mass spectrum: (M+H)⁺ = 401

(377e) Methyl 2-(2,6-dichlorophenylamino)-5-methoxy-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxylate

A mixture of 6-bromo-N-(2,6-dichlorophenyl)-5-methoxy-3-methyl-3H-imidazo[4,5-b]pyridin-2-amine (0.44 g, 1.09 mmol) with 1,1'-bis-(diphenylphosphino)-ferrocene (40 mg, 80 µM), palladium(II)-acetate (20 mg, 90 µM) and TEA (0.5 mL, 3.6 mmol) in 0.5 mL DMF and 30 mL methanol was stirred at 80°C under 5.2 bar carbon monoxide pressure for 15 h. Then the mixture was filtered, the filtrate concentrated, the residue mixed with water, filtered off, washed with water and dried at ambient temperature. Then the product was purified by preparative HPLC (RP Symmetry C18, 8µm; eluent gradient: (water+0.15% formic acid) / acetonitrile = 85:15 -> 0:100).

Yield: 0.43 g (quant.)

(377f) N-(4-Bromophenyl)-2-(2,6-dichlorophenylamino)-5-methoxy-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide

2 M trimethyl aluminium solution in hexane (0.35 mL, 0.35 mmol) was added to 4-bromo-aniline (50 mg, 0.31 mmol) in 3.0 mL THF and the mixture stirred at ambient temperature for 1 h. Then methyl 2-(2,6-dichlorophenylamino)-5-methoxy-3-methyl-3H-imidazo[4,5-b]

47

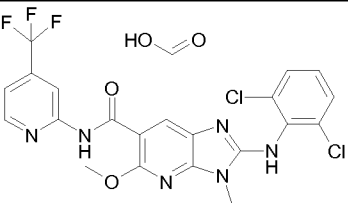
pyridine-6-carboxylate (0.10 g, 0.26 mmol) was added and the mixture stirred at 60°C for 16 h. Then methanol and acetic acid were added, the mixture poured into water. The precipitate was filtered off, washed with water and dried. Then the product was purified by preparative HPLC (RP Symmetry C18, 8µm; eluent gradient: (water+0.15% formic acid) / acetonitrile = 85:15 -> 0:100).

Yield: 62 mg (45%)

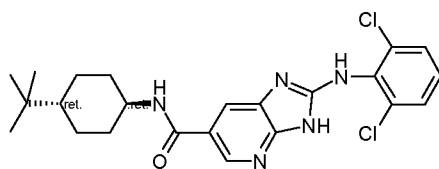
mass spectrum: (M+H)⁺ = 520/522/524/526 (bromine and chlorine isotopes)

R_t value: 3.28 min (C2)

In analogy to the above described example, the following compounds were prepared:

No.	Structural formula	Yield	Mass peak(s)	R _f value or R _t
	Name			
386		Σ: 24%	(M+H) ⁺ = 511/513/515 (chlorine isotopes)	1.61 min (F8)
	2-(2,6-Dichloro-phenylamino)-5-methoxy-3-methyl-N-(4-trifluoromethyl-pyridin-2-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide formate			

Example 379



N-((1r,4r)-4-tert.-Butylcyclohexyl)-2-(2,6-dichlorophenylamino)-3H-imidazo[4,5-b]pyridine-6-carboxamide

(379a) 6-Amino-5-nitro-nicotinic acid

Prepared analogously to example 154a from 6-chloro-5-nitro-nicotinic acid and conc. ammonia (aq).

Yield: 68%

mass spectrum: (M+H)⁺ = 184

(379b) 6-Amino-5-nitro-nicotinoyl chloride

Prepared analogously to example 154b from 6-amino-5-nitro-nicotinic acid and thionyl chloride.

Yield: quant.

5

(379c) Ethyl 6-amino-5-nitro-nicotinate

6-Amino-5-nitro-nicotinoyl chloride (5.00 g, 24.8 mmol) was refluxed in 100 mL ethanol for 3 h. Then the mixture was concentrated, conc. ammonia added and stirred for 10 min. The precipitate was filtered off, washed with water, dried and reacted without further purification.

10 Yield: 4.60 g (88%)

R_f value: 0.40 (silica gel; eluens: dichloromethane / methanol = 19:1).

(379d) Ethyl 5,6-diamino-nicotinate

Prepared analogously to example 154d by hydrogenation of ethyl 6-amino-5-nitro-nicotinate using palladium/charcoal (10%) in THF.

15

Yield: 96%

R_f value: 0.50 (silica gel; eluens: dichloromethane / methanol = 9:1).

(379e) Ethyl 6-amino-5-(3-(2,6-dichlorophenyl)-thioureido)-nicotinate

A mixture of ethyl 5,6-diamino-niconiate (1.50 g, 8.28 mmol) and 1,3-dichloro-2-isothiocyanatobenzene (1.70 g, 8.33 mmol) in 60 mL acetonitrile was stirred for 24 h at ambient temperature. The precipitate was filtered off, washed with acetonitril and diethylether, dried and reacted without further purification.

20

Yield: 1.90 g (60%)

25 mass spectrum: (M+H)⁺ = 385/387/389 (chlorine isotopes)

R_f value: 0.18 (silica gel; eluens: dichloromethane / methanol = 19:1).

(379f) Ethyl 2-(2,6-dichlorophenylamino)-3H-imidazo[4,5-b]pyridine-6-carboxylate

Prepared analogously to example 377d from ethyl 6-amino-5-(3-(2,6-dichlorophenyl)-thioureido)-nicotinate and DIC in acetonitrile

30

Yield: 92%

mass spectrum: (M+H)⁺ = 351/353/355 (chlorine isotopes)

(379g) 2-(2,6-Dichlorophenylamino)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid

Prepared analogously to example 174e from ethyl 2-(2,6-dichlorophenylamino)-3H-imidazo[4,5-b]pyridine-6-carboxylate and NaOH in ethanol and water.

Yield: 82%

5 mass spectrum: (M+H)⁺ = 323/325/327 (chlorine isotopes)

(379h) N-((1r,4r)-4-tert.-Butylcyclohexyl)-2-(2,6-dichlorophenylamino)-3H-imidazo[4,5-b]pyridine-6-carboxamide

10 Prepared analogously to example 174f from 2-(2,6-dichlorophenylamino)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid, (1r,4r)-4-tert.-butylcyclohexanamine hydrochloride, TBTU and TEA in DMF and THF.

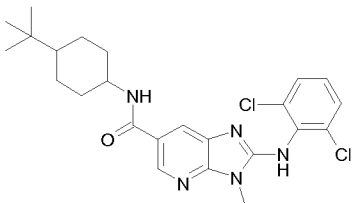
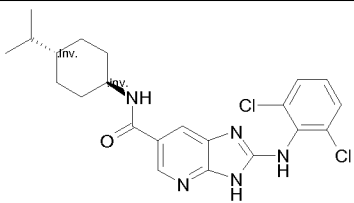
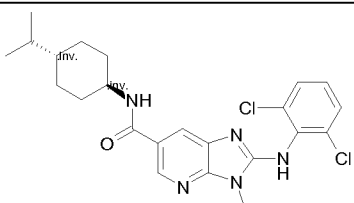
Yield: 63%

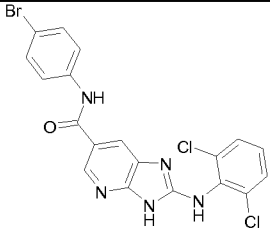
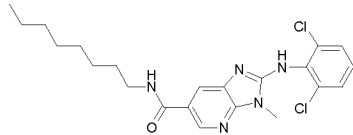
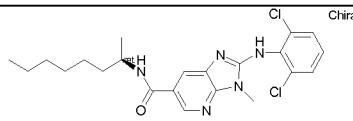
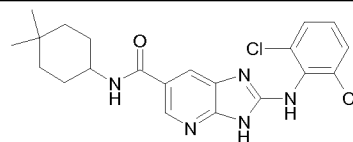
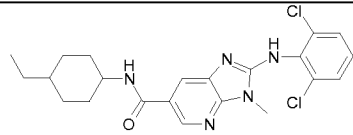
mass spectrum: (M+H)⁺ = 460/462/464 (chlorine isotopes)

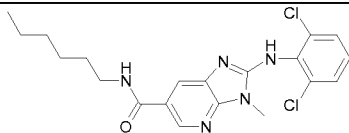
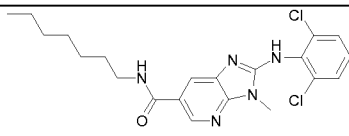
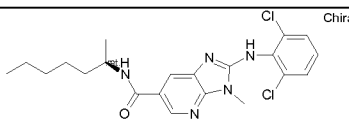
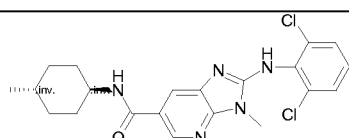
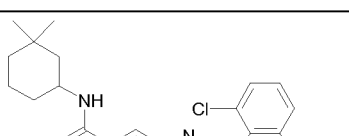
R_t value: 2.68 min (C4)

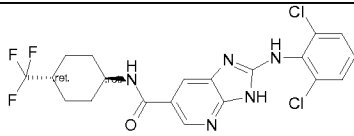
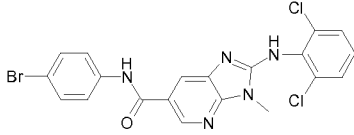
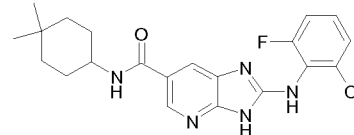
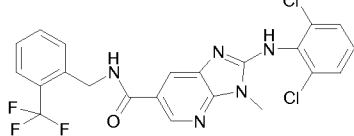
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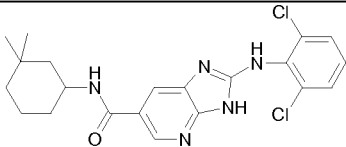
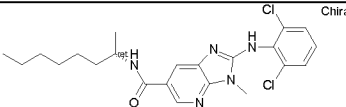
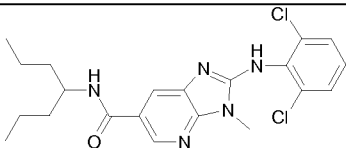
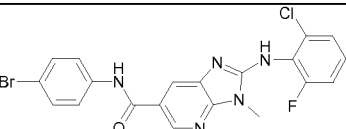
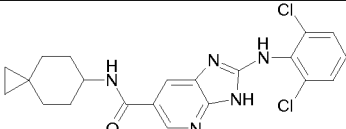
In analogy with the above described example, the following compounds were prepared:

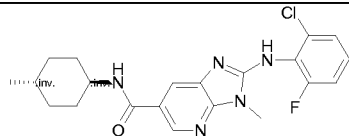
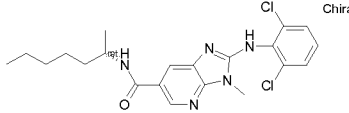
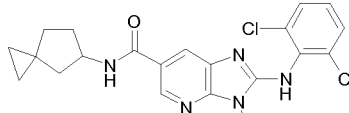
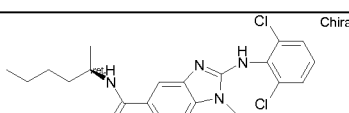
No.	Structural formula	Yield	Mass peak(s)	R _f value or R _t
	Name			
393		Σ: 18%	(M+H) ⁺ = 474/476/478 (chlorine isotopes)	2.82 min (C4)
	N-(4-tert-Butylcyclohexyl)-2-(2,6-dichlorophenylamino)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			
394		Σ: 1.5%	(M+H) ⁺ = 446/448/450 (chlorine isotopes)	2.64 min (C3)
	2-(2,6-Dichlorophenylamino)-N-((1r,4r)-4-isopropylcyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			
400		Σ: 13%	(M+H) ⁺ = 460/462/464 (chlorine isotopes)	3.06 min (C4)

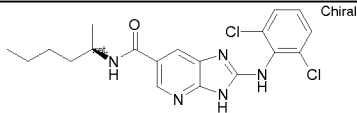
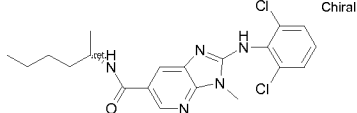
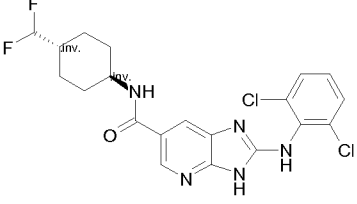
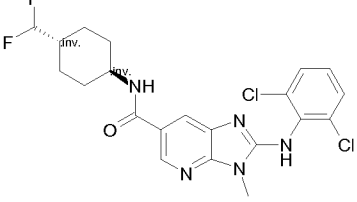
No.	Structural formula	Yield	Mass peak(s)	R _f value or R _t
	Name			
	2-(2,6-Dichlorophenylamino)-N-((1r,4r)-4-isopropylcyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			
401		Σ: 2.6%	(M+H)+ = 447/449/451(chlorine isotopes)	2.51 min (C1)
	N-(4-Bromophenyl)-2-(2,6-dichlorophenylamino)-3H-imidazo[4,5-b]pyridine-6-carboxamide			
403		Σ: 13%	(M+H)+ = 448/540/452 (chlorine isotopes)	3.14 min (C4)
	2-(2,6-Dichlorophenylamino)-3-methyl-N-octyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			
411		Σ: 13.4%	(M+H)+ = 448/450/452 (chlorine isotopes)	3.03 min (C4)
	(R)-2-(2,6-Dichlorophenylamino)-3-methyl-N-(oct-2-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			
429		Σ: 2.8%	(M+H)+ = 432/434/436 (chlorine isotopes)	2.274 min (C4)
	2-(2,6-Dichlorophenylamino)-N-(4,4-dimethylcyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			
438		Σ: 8.2%	(M+H)+ = 446/448/450 (chlorine isotopes)	2.92 min (C4)

No.	Structural formula	Yield	Mass peak(s)	R _f value or R _t
	Name			
	2-(2,6-Dichlorophenylamino)-N-(4-ethylcyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			
439		Σ : 15.3%	(M+H) ⁺ = 420/422/424 (chlorine isotopes)	2.83 min (C4)
	2-(2,6-Dichlorophenylamino)-N-hexyl-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			
448		Σ : 14.8%	(M+H) ⁺ = 434/36/38 (chlorine isotopes)	3.00 min (C4)
	2-(2,6-Dichlorophenylamino)-N-heptyl-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			
449		Σ : 16.1%	(M+H) ⁺ = 434/436/438 (chlorine isotopes)	2.88 min (C4)
	(R)-2-(2,6-Dichlorophenylamino)-N-(hept-2-yl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			
453		Σ : 14.3%	(M+H) ⁺ = 432/434/436 (chlorine isotopes)	2.81 min (C4)
	2-(2,6-Dichlorophenylamino)-3-methyl-N-((1r,4r)-4-methylcyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			
454		Σ : 10.4%	(M+H) ⁺ = 446/448/450 (chlorine isotopes)	2.86 min (C4)

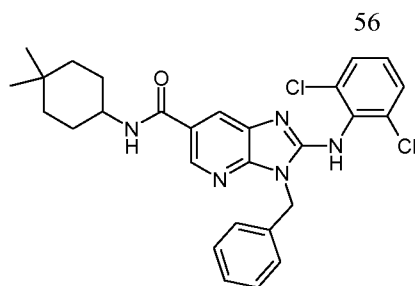
No.	Structural formula	Yield	Mass peak(s)	R _f value or R _t
	Name			
	2-(2,6-Dichlorophenylamino)-N-(3,3-dimethylcyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			
459		Σ: 9.2%	(M+H) ⁺ = 472/474/476 (chlorine isotopes)	3.43 min (B4)
	2-(2,6-Dichlorophenylamino)-N-((1r,4r)-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			
463		Σ: 3.2%	(M+H) ⁺ = 491/493/495 (chlorine isotopes)	2.9 min (C4)
	N-(4-Bromophenyl)-2-(2,6-dichlorophenylamino)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			
466		Σ: 6.9%	(M+H) ⁺ = 416/418/420 (chlorine isotopes)	2.44 min (C4)
	2-(2-Chloro-6-fluorophenylamino)-N-(4,4-dimethylcyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			
468		Σ: 16%	(M+H) ⁺ = 494/496/498 (chlorine isotopes)	2.77 min (C4)
	2-(2,6-Dichlorophenylamino)-3-methyl-N-(2-trifluoromethyl-benzyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			

No.	Structural formula	Yield	Mass peak(s)	R _f value or R _t
	Name			
469		Σ: 11%	(M+H) ⁺ = 491/493/495 (chlorine isotopes)	3.54 min (B3)
	2-(2,6-Dichlorophenylamino)-N-(3,3-dimethylcyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			
471		Σ: 9.5%	(M+H) ⁺ = 448/450/452 (chlorine isotopes)	3.03 min (C4)
	(S)-2-(2,6-Dichlorophenylamino)-3-methyl-N-(oct-2-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			
473		Σ: 13.5%	(M+H) ⁺ = 434/436/438 (chlorine isotopes)	2.87 min (C4)
	2-(2,6-Dichlorophenylamino)-N-(hept-4-yl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			
480		Σ: 9%	(M+H) ⁺ = 474/476/478 (chlorine isotopes)	2.82 min (C4)
	N-(4-Bromophenyl)-2-(2-chloro-6-fluorophenylamino)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			
485		Σ: 7.2%	(M+H) ⁺ = 430/432/434 (chlorine isotopes)	3.43 min (B3)

No.	Structural formula	Yield	Mass peak(s)	R _f value or R _t
	Name			
	2-(2,6-Dichlorophenylamino)-N-(spiro[2.5]octan-6-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			
486		Σ : 13.2%	(M+H) ⁺ = 416/418/420 (chlorine isotopes)	2.73 min (C4)
	2-(2-Chloro-6-fluorophenylamino)-3-methyl-N-((1r,4r)-4-methylcyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			
497		Σ : 10.1%	(M+H) ⁺ = 434/436/438 (chlorine isotopes)	2.88 min (C4)
	(S)-2-(2,6-Dichlorophenylamino)-N-(hept-2-yl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			
506		Σ : 17.5%	(M+H) ⁺ = 430/432/434 (chlorine isotopes)	1.84 min (G11)
	2-(2,6-Dichlorophenylamino)-3-methyl-N-(spiro[2.4]heptan-5-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			
508		Σ : 14.8%	(M+H) ⁺ = 420/422/424 (chlorine isotopes)	2.74 min (C4)
	(R)-2-(2,6-Dichlorophenylamino)-N-(hexan-2-yl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			

No.	Structural formula	Yield	Mass peak(s)	R _f value or R _t
	Name			
517		Σ: 9.2%	(M+H) ⁺ = 406/408/410 (chlorine isotopes)	3.31 min (B3)
	(R)-2-(2,6-Dichlorophenylamino)-N-(hex-2-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			
527		Σ: 14.1%	(M+H) ⁺ = 420/422/424 (chlorine isotopes)	2.75 min (C4)
	(S)-2-(2,6-Dichlorophenylamino)-N-(hex-2-yl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			
535		Σ: 3.6%	(M+H) ⁺ = 454/456/458 (chlorine isotopes)	2.20 min (C3)
	2-(2,6-Dichlorophenylamino)-N-((1r,4r)-4-(difluoromethyl)cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			
560		Σ: 8.2%	(M+H) ⁺ = 468/470/472 (chlorine isotopes)	3.98 min (B3)
	(2-(2,6-Dichlorophenylamino)-N-((1r,4r)-4-(difluoromethyl)cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			

Example 413



3-Benzyl-2-(2,6-dichlorophenylamino)-N-(4,4-dimethylcyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

5 (413a) 6-(Benzylamino)-5-nitro-nicotinic acid

6-Chloro-5-nitro-nicotinic acid (5.5 g, 27 mmol) in 250 mL THF was combined with TEA (8.5 mL, 60 mmol) and benzylamine (3 g, 28 mmol) and stirred for 7 h at ambient temperature. Half of the solvent was removed in vac.. The residue was acidified using HCl (aq). The solid formed was filtered and dried.

10 Yield: 5.7 g (77%)

mass spectrum: $(M+H)^+ = 274$

R_f value: 0.5 (silica gel; dichloromethane / methanol = 9:1)

(413b) 6-(Benzylamino)-N-(4,4-dimethylcyclohexyl)-5-nitro-nicotinamide

15 Prepared analogously to example 174f from 6-(benzylamino)-5-nitronicotinic acid and 4,4-dimethylcyclohexanamine hydrochloride with TBTU and TEA in DMF and THF.

Yield: 52%

mass spectrum: $(M+H)^+ = 483$

R_f value: 0.85 (silica gel; dichloromethane / methanol = 19:1)

20

(413c) 5-Amino-6-(benzylamino)-N-(4,4-dimethylcyclohexyl)-nicotinamide

Prepared analogously to example 154d by hydrogenation of 6-(benzylamino)-N-(4,4-dimethylcyclohexyl)-5-nitro-nicotinamide using Raney nickel in THF.

Yield: 99%

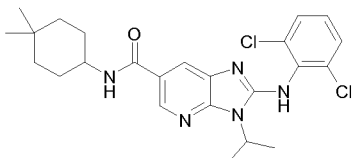
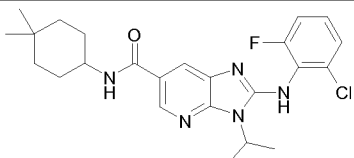
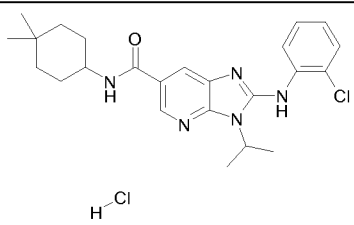
 R_f value: 0.25 (silica gel; dichloromethane / methanol = 19:1)

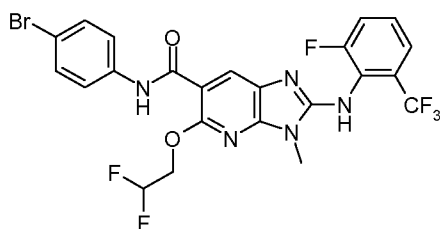
(413d) 3-Benzyl-2-(2,6-dichlorophenylamino)-N-(4,4-dimethylcyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

Prepared analogously to example 154e from 5-amino-6-(benzylamino)-N-(4,4-dimethylcyclohexyl)-nicotinamide, 1,3-dichloro-2-isothiocyanatobenzene and DIC in acetonitrile.

Yield: 21%; mass spectrum: $(M+H)^+ = 522/24/26$ (chlorine isotopes); R_t value: 3.31 min (C4)

In analogy with the above described example, the following compounds were prepared:

No.	Structural formula	Yield	Mass peak(s)	R_f value or R_t
	Name			
505		Σ : 20%	$(M+H)^+ =$ 474/476/478 (chlorine isotopes)	3.25 min (C4)
	2-(2,6-Dichlorophenylamino)-N-(4,4-dimethylcyclohexyl)-3-isopropyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			
511		Σ : 18%	$(M+H)^+ =$ 458/460/462 (chlorine isotopes)	3.10 min (C4)
	2-(2-Chloro-6-fluorophenylamino)-N-(4,4-dimethylcyclohexyl)-3-isopropyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			
541		Σ : 23%	$(M+H)^+ =$ 440/442/444 (chlorine isotopes)	3.14 min (C4)
	2-(2-Chlorophenylamino)-N-(4,4-dimethylcyclohexyl)-3-isopropyl-3H-imidazo[4,5-b]pyridine-6-carboxamide hydrochloride			

Example 771

N-(4-Bromophenyl)-2-(2-fluoro-6-trifluoromethylphenylamino)-5-(2,2-difluoro-ethoxy)-3-
methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide

(771a) 6-Chloro-2-(2,2-difluoro-ethoxy)-nicotinic acid

2,2-Difluoro-ethanol (20 mL, 316 mmol) in 100 mL dichloromethane is added to sodium hydride (16 g, 55%, 367 mmol) in 300 mL dichloromethane under stirring at 0°C. Then 2,6-dichloro-nicotinic acid (15 g, 78 mmol) was added, followed by 100 mL dichloromethane and 100 mL THF, and the mixture was stirred at ambient temperature for 16 h. 100 mL water were added, stirred for 5 min, and concentrated *i. vac.*. The aqueous residue was extracted with diethylether, the combined organic layers extracted with water. 30 mL formic acid were added to the combined aqueous layers, the precipitate filtered off, washed with water and dried.

Yield: 15.3 g (83%)

mass spectrum: (M+H)+ = 238/240 (chlorine isotopes)

(771b) Methyl 6-chloro-2-(2,2-difluoroethoxy)-nicotinate

Trimethylsilyl-diazomethane solution (2N in hexane) (44.7 mL, 85.4 mmol) were added to the product obtained from (771a) in 200 mL dichloromethane with 100 mL methanol and the mixture stirred at ambient temperature for 5 h. Then 50 mL water and 1 mL acetic acid were added, the mixture concentrated *i. vac.* and the aqueous residue poured into 350 mL water at 0°C. The precipitate was filtered off, washed with water and dried.

Yield: 15.5 g (96%)

mass spectrum: (M+H)+ = 252/254 (chlorine isotopes)

R_f value: 0.78 (silica gel; eluens: cyclohexane / ethyl acetate = 6:4)

(771c) Methyl 6-chloro-2-(2,2-difluoroethoxy)-5-nitro-nicotinate

Nitric acid (100%, 45 mL, 1.1 mol) was added to a mixture of the product obtained from (771b) (14.5 g, 57.6 mmol) in 90 mL conc. sulphuric acid at 10°C and stirred at ambient temperature for 20 min. The mixture was poured into water, the precipitate was filtered off,
5 washed with water and dried.

Yield: 17.0 g (quant.)

mass spectrum: (M+Na)+ = 319/321 (chlorine isotopes)

R_f value: 0.40 (silica gel; eluens: cyclohexane / ethyl acetate = 8:2)

10 (771d) Methyl 2-(2,2-difluoroethoxy)-6-methylamino-5-nitro-nicotinate

Prepared analogously to example 154a from the product obtained in (771c) and 2 N methylamine (solution in THF) in THF.

Yield: 94%

mass spectrum: (M+H)+ = 292

15 R_f value: 0.21 (silica gel; eluens: cyclohexane / ethyl acetate = 8:2)

(771e) 2-(2,2-Difluoroethoxy)-6-methylamino-5-nitro-nicotinic acid

Prepared analogously to example 174a from the product obtained in (771d) and 1 N NaOH (aq) in water and THF.

20 Yield: 62%

mass spectrum: (M+H)+ = 278

R_f value: 0.22 (silica gel; eluens: petrolether / ethyl acetate = 1:1)

(771f) N-(4-Bromo-phenyl)-2-(2,2-difluoroethoxy)-6-methylamino-5-nitro-nicotinic amide

25 (1-Chloro-2-methyl-propenyl)-dimethylamine (1.54 mL, 5.6 mmol) was added to a mixture of the product obtained from (771e) and 15 mL dichloromethane and 15 mL THF. The mixture was stirred at ambient temperature for 30 min. Then pyridine (607 µL, 7.7 mmol) and 4-bromo-aniline (752 mg, 5.6 mmol) were added at ambient temperature and the mixture stirred for 1 h. Then the mixture was concentrated *i. vac.* and water added to the residue.

30 The mixture was concentrated, the precipitate filtered off, washed with water and dried.

Yield: 1.27 g (57%)

R_t value: 1.58 min (F7)

(771g) N-(4-Bromo-phenyl)-2-(2,2-difluoroethoxy)-6-methylamino-5-amino-nicotinic amide

Prepared analogously to example 154d by hydrogenation of the product obtained in (771f) using Raney nickel in THF.

Yield: 97%

5 R_t value: 2.07 min (E9)

(771h) N-(4-Bromo-phenyl)-2-(2-fluoro-6-trifluoromethyl-phenylamino)-5-(2,2-difluoroethoxy)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide

Prepared analogously to example 154e from the product obtained in (771g) with 1-fluoro-2-isothiocyanato-3-trifluoromethyl-benzene and using DIC in acetonitrile and THF.

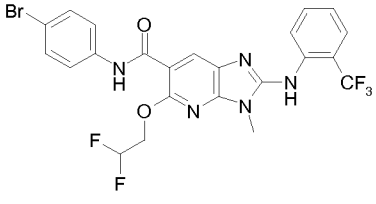
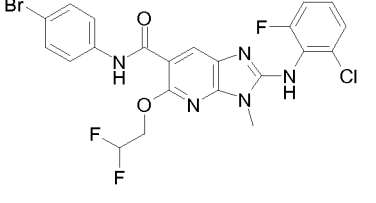
10 Yield: 60%

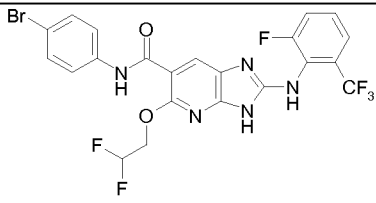
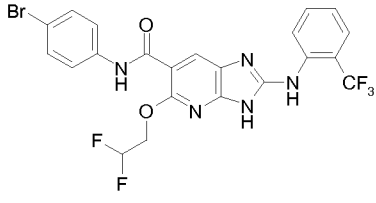
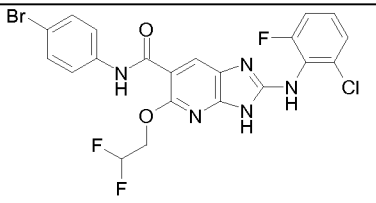
Yield: 60%

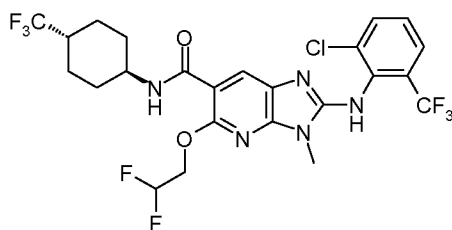
mass spectrum: (M+H)⁺ = 588/590 (bromine isotopes)

R_t value: 2.44 min (E9)

15 In analogy to the above described example, the following compounds were prepared:

No.	Structural formula	Yield	Mass peak(s)	R_f value or R_t
	Name			
772		Σ : 18%	(M+H) ⁺ = 570/572 (bromine isotopes)	2.36 min (E9)
	N-(4-Bromo-phenyl)-2-(2-trifluoromethyl-phenylamino)-5-(2,2-difluoroethoxy)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			
773		Σ : 15%	(M+H) ⁺ = 554/556/558 (bromine and chlorine isotopes)	2.30 min (E9)
	N-(4-Bromo-phenyl)-2-(2-fluoro-6-chloro-phenylamino)-5-(2,2-difluoroethoxy)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			

No.	Structural formula	Yield	Mass peak(s)	R _f value or R _t
	Name			
774		Σ : 24%	(M+H) ⁺ = 574/576 (bromine isotopes)	2.22 min (E9)
	N-(4-Bromo-phenyl)-2-(2-fluoro-6-trifluoromethyl-phenylamino)-5-(2,2-difluoroethoxy)-3H-imidazo[4,5-b]pyridine-6-carboxamide			
775		Σ : 21%	(M+H) ⁺ = 556/558 (bromine isotopes)	2.29 min (E9)
	N-(4-Bromo-phenyl)-2-(2-trifluoromethyl-phenylamino)-5-(2,2-difluoroethoxy)-3H-imidazo[4,5-b]pyridine-6-carboxamide			
776		Σ : 24%	(M+H) ⁺ = 540/542/544 (bromine and chlorine isotopes)	2.17 min (E9)
	N-(4-Bromo-phenyl)-2-(2-fluoro-6-chloro-phenylamino)-5-(2,2-difluoroethoxy)-3H-imidazo[4,5-b]pyridine-6-carboxamide			

Example 777

2-(2-Chloro-6-trifluoromethyl-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide

(777a) 2,6-Dichloro-N-(trans-4-trifluoromethyl-cyclohexyl)-nicotinamide

Prepared analogously to a sequence of examples 154b and 154c from 2,6-dichloro-nicotinic acid with thionylchloride and DMF, and from trans-4-trifluoromethyl-cyclohexylamine and TEA in THF and dichloromethane.

5 Yield: 93%

(777b) 6-Chloro-2-(2,2-difluoroethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-nicotinamide

2,2-Difluoroethanol (1.4 mL, 22.2 mmol) was added to potassium tert.-butylate (2.50 g, 21.2 mmol) in 75 mL THF and the mixture stirred for 5 min at ambient temperature. Then the
10 product obtained in (777a) (6.95 g, 19.4 mmol) in 75 mL dichloromethane was added and stirred for 15 min at ambient temperature. Water was added and the mixture concentrated *i. vac.*. The residue was triturated with water and filtered off. The solid was washed with water and dried.

Yield: 7.21 g (96%)

15 mass spectrum: (M+H)+ = 387/389 (chlorine isotopes)

(777c) 6-Chloro-2-(2,2-difluoroethoxy)-5-nitro-N-(trans-4-trifluoromethyl-cyclohexyl)-nicotinamide

Prepared analogously to example 771c from the product obtained in (777b) with nitric acid
20 (100%) and conc. sulphuric acid.

Yield: 7.74g (96%)

mass spectrum: (M+H)+ = 432/434 (chlorine isotopes)

(777d) 2-(2,2-Difluoroethoxy)-6-methylamino-5-nitro-N-(trans-4-trifluoromethyl-cyclohexyl)-nicotinamide

Prepared analogously to example 154a from the product obtained in (777c) and 2 N methylamine (solution in THF) in THF.

Yield: 92%

mass spectrum: (M+H)+ = 427

30 R_f value: 0.58 (silica gel; eluens: petrolether / ethyl acetate = 1:1)

(777e) 5-Amino-2-(2,2-difluoroethoxy)-6-methylamino-N-(trans-4-trifluoromethyl-cyclohexyl)-nicotinic acid

Prepared analogously to example 154d by hydrogenation of the product obtained in (777d)
35 using Raney nickel in THF and methanol.

Yield: 97%

 R_f value: 0.55 (silica gel; eluens: dichloromethane / methanol = 9:1)

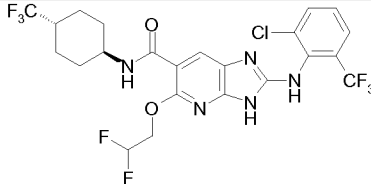
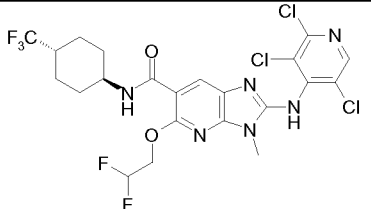
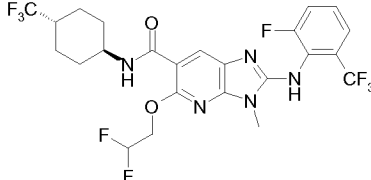
(777f) 2-(2-Chloro-6-trifluoromethyl-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide

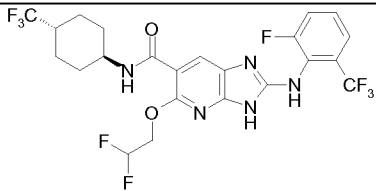
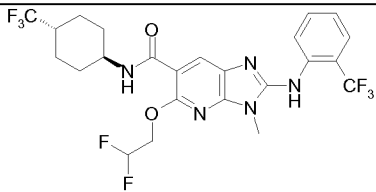
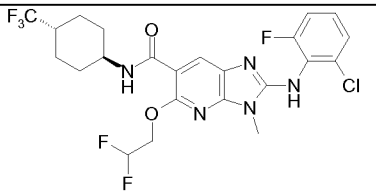
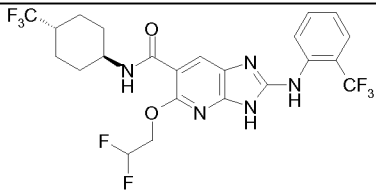
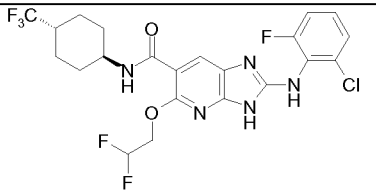
Prepared analogously to example 154e from the product obtained in (777e) with 1-chloro-2-isothiocyanato-3-trifluoromethyl-benzene and using DIC in acetonitrile.

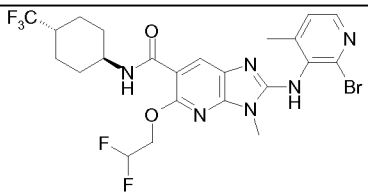
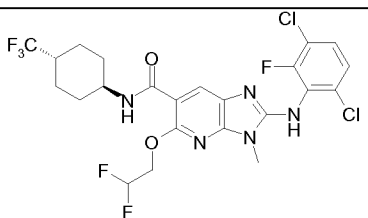
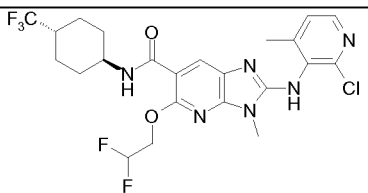
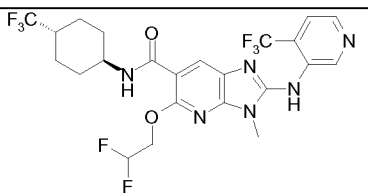
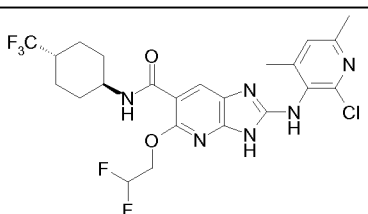
Yield: 56%

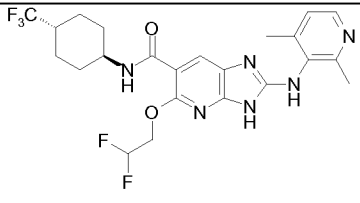
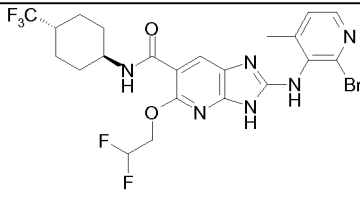
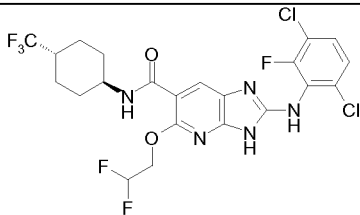
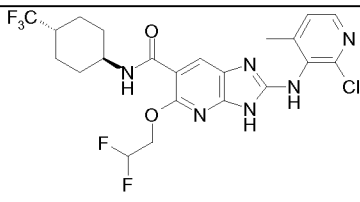
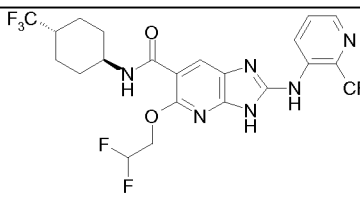
mass spectrum: (M+H)⁺ = 600/602 (chlorine isotopes) R_t value: 2.40 min (E9)

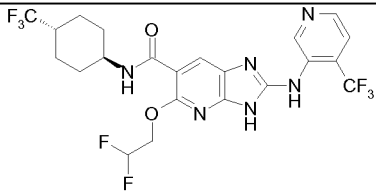
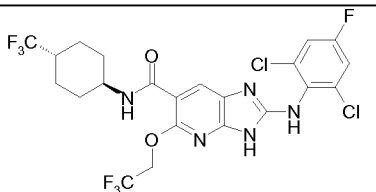
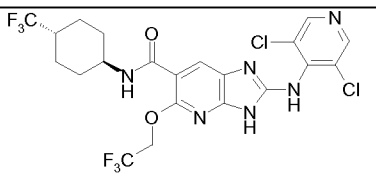
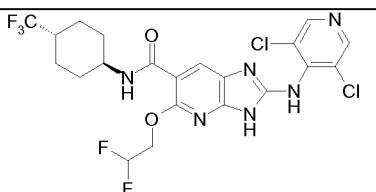
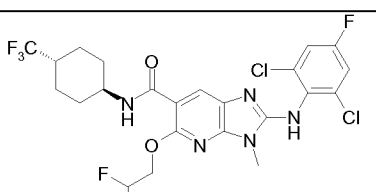
In analogy to the above described example, the following compounds were prepared:

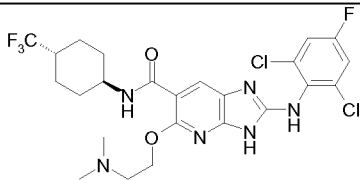
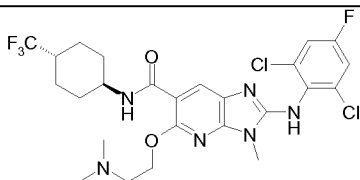
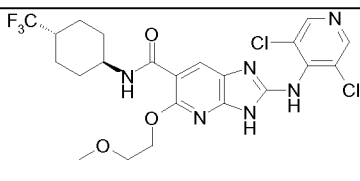
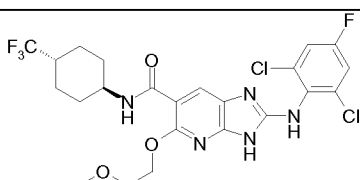
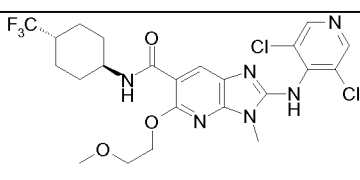
No.	Structural formula	Yield	Mass peak(s)	R _f value or R _t
	Name			
778		Σ : 45%	(M+H) ⁺ = 586/588 (chlorine isotopes)	2.14 min (E9)
	<u>2-(2-Chloro-6-trifluoromethyl-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide</u>			
779		Σ : 41%	(M+H) ⁺ = 601/603/605/607 (chlorine isotopes)	2.49 min (E9)
	<u>2-(2,3,5-Trichloro-pyridin-4-yl-amino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide</u>			
780		Σ : 36%	(M+H) ⁺ = 584	1.55 min (F7)
	<u>2-(2-Fluoro-6-trifluoromethyl-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide</u>			

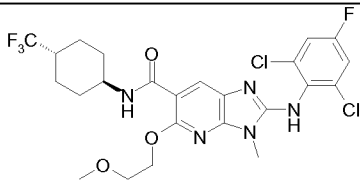
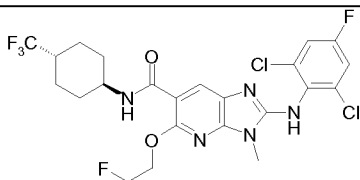
No.	Structural formula	Yield	Mass peak(s)	R _f value or R _t
Name				
781		Σ : 32%	(M+H) ⁺ = 570	1.43 min (F7)
<u>2-(2-Fluoro-6-trifluoromethyl-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide</u>				
782		Σ : 50%	(M+H) ⁺ = 566	1.49 min (F8)
<u>2-(2-Trifluoromethyl-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide</u>				
783		Σ : 56%	(M+H) ⁺ = 550/552	1.47 min (F8)
<u>2-(2-Chloro-6-fluoro-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide</u>				
784		Σ : 62%	(M+H) ⁺ = 552	1.49 min (F8)
<u>2-(2-Trifluoromethyl-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide</u>				
785		Σ : 70%	(M+H) ⁺ = 536/538	1.42 min (F8)
<u>2-(2-Chloro-6-fluoro-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide</u>				

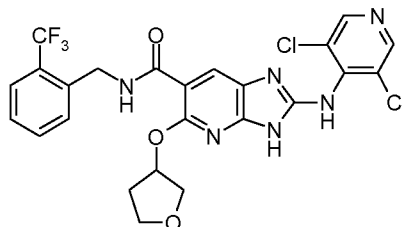
No.	Structural formula	Yield	Mass peak(s)	R _f value or R _t
	Name			
786		Σ : 54%	(M+H) ⁺ = 591/593 (bromine isotopes)	2.03 min (E9)
	<u>2-(2-Bromo-4-methyl-pyridin-3-ylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide</u>			
787		Σ : 54%	(M+H) ⁺ = 584/586/588 (chlorine isotopes)	2.37 min (E9)
	<u>2-(3,6-Dichloro-2-fluoro-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide</u>			
788		Σ : 54%	(M+H) ⁺ = 547/549 (chlorine isotopes)	2.01 min (E9)
	<u>2-(2-Chloro-4-methyl-pyridin-3-ylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide</u>			
789		Σ : 58%	(M+H) ⁺ = 567	2.19 min (E9)
	<u>2-(4-Trifluoromethyl-pyridin-3-ylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide</u>			
793		Σ : 41%	(M+H) ⁺ = 547/549 (chlorine isotopes)	1.96 min (E9)
	<u>2-(2-Chloro-4,6-dimethyl-pyridin-3-ylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide</u>			

No.	Structural formula	Yield	Mass peak(s)	R _f value or R _t
Name				
794		Σ : 40%	(M+H) ⁺ = 513	1.52 min (E8)
<u>2-(2,4-Dimethyl-pyridin-3-ylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide</u>				
795		Σ : 52%	(M+H) ⁺ = 577/579 (bromine isotopes)	1.94 min (E9)
<u>2-(2-Bromo-4-methyl-pyridin-3-ylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide</u>				
796		Σ : 26%	(M+H) ⁺ = 598/600/602 (chlorine isotopes)	2.17 min (E9)
<u>2-(3,6-Dichloro-2-fluoro-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide</u>				
797		Σ : 44%	(M+H) ⁺ = 533/535 (chlorine isotopes)	1.93 min (E9)
<u>2-(2-Chloro-4-methyl-pyridin-3-ylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide</u>				
798		Σ : 50%	(M+H) ⁺ = 553	2.09 min (E9)
<u>2-(2-Trifluoromethyl-pyridin-3-ylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide</u>				

No.	Structural formula	Yield	Mass peak(s)	R _f value or R _t
	Name			
799		Σ : 47%	(M+H) ⁺ = 553	2.02 min (E9)
	<u>2-(4-Trifluoromethyl-pyridin-3-ylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide</u>			
827		Σ : 20%	(M+H) ⁺ = 588/590/592 (chlorine isotopes)	4.68 min (B5)
	<u>2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2,2-trifluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide</u>			
859		Σ : 31%	(M+H) ⁺ = 571/573/575 (chlorine isotopes)	2.12 min (E9)
	<u>2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2,2-trifluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide</u>			
862		Σ : 43%	(M+H) ⁺ = 553/555/557 (chlorine isotopes)	2.03 min (E9)
	<u>2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide</u>			
863		Σ : 60%	(M+H) ⁺ = 584/586/588 (chlorine isotopes)	2.33 min (E9)
	<u>2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide</u>			

No.	Structural formula	Yield	Mass peak(s)	R _f value or R _t
	Name			
864		Σ : 29%	(M+H) ⁺ = 577/579/581 (chlorine isotopes)	1.80 min (E9)
	<u>2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2-dimethylamino-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide</u>			
865		Σ : 35%	(M+H) ⁺ = 591/593/595 (chlorine isotopes)	1.82 min (E9)
	<u>2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2-dimethylamino-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide</u>			
866		Σ : 12.0%	(M+H) ⁺ = 547/549/551 (chlorine isotopes)	1.96 min (E9)
	<u>2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2-methoxy-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide</u>			
867		Σ : 8.8%	(M+H) ⁺ = 564/566/568 (chlorine isotopes)	2.09 min (E9)
	<u>2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2-methoxy-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide</u>			
868		Σ : 47%	(M+H) ⁺ = 561/563/565 (chlorine isotopes)	2.27 min (E9)
	<u>2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2-methoxy-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide</u>			

No.	Structural formula	Yield	Mass peak(s)	R _f value or R _t
	Name			
869		Σ : 37%	(M+H) ⁺ = 578/580/582 (chlorine isotopes)	2.27 min (E9)
	<u>2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2-methoxy-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide</u>			
870		Σ : 39%	(M+H) ⁺ = 566/568/570 (chlorine isotopes)	2.27 min (E9)
	<u>2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2-fluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide</u>			

Example 790

5

2-(3,5-Dichloro-pyridin-4-ylamino)-5-(tetrahydrofuran-3-yl-oxy)-N-((2-trifluoromethyl-phenyl)-methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

(790a) 2-Amino-3-nitro-6-(tetrahydrofuran-3-yl-oxy)-pyridine

10 Prepared analogously to example 777b from 2-amino-6-chloro-3-nitro-pyridine and 3-hydroxy-tetrahydrofurane with potassium tert.-butylate in THF.

Yield: 56%

R_f value: 0.23 (silica gel; eluens: petrolether / ethyl acetate = 7:3)

(790b) 2-Amino-3-(3-(3,5-dichloro-pyridin-4-yl)-thioureido)-6-(tetrahydrofuran-3-yl-oxy)-pyridine

Prepared analogously to example 377c by a sequence of hydrogenation of the product obtained in (790a) using palladium on charcoal in THF and methanol followed by reaction with 3,5-dichloro-4-isothiocyanato-pyridine in THF.

Yield: quant.

R_f value: 0.65 (silica gel; eluens: petrolether / ethyl acetate = 2:8)

(790c) 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(tetrahydrofuran-3-yl-oxy)-3H-imidazo[4,5-b]pyridine

Prepared analogously to example 377d from the product obtained in (790b) with DIC in acetonitrile.

Yield: 88%

mass spectrum: (M+H)⁺ = 366/368/370 (chlorine isotopes)

R_f value: 0.50 (silica gel; eluens: petrolether / ethyl acetate = 2:8)

(790d) 6-Bromo-2-(3,5-dichloro-pyridin-4-ylamino)-5-(tetrahydrofuran-3-yl-oxy)-3H-imidazo[4,5-b]pyridine

Prepared analogously to example 377b from the product obtained in (790c) with pyridinium tribromide in dichloromethane and methanol.

Yield: 72%

mass spectrum: (M+H)⁺ = 444/446/448/450 (bromine and chlorine isotopes)

R_f value: 0.43 (silica gel; eluens: dichloromethane / ethanol = 9:1)

(790e) Methyl 2-(3,5-dichloro-pyridin-4-ylamino)-5-(tetrahydrofuran-3-yl-oxy)-3H-imidazo[4,5-b]pyridine-6-carboxylate

Prepared analogously to example 377e by carbonylation of the product obtained in (790d) using 1,1'-bis-(diphenylphosphino)-ferrocene, palladium-II-acetate and TEA in NMP and methanol.

Yield: 94%

R_f value: 0.35 (silica gel; eluens: petrolether / ethyl acetate = 2:8)

(790f) 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(tetrahydrofuran-3-yl-oxy)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid

Prepared analogously to example 174e from the product obtained in (790e) using 2 N NaOH (aq) in ethanol.

5 Yield: 16%

R_t value: 1.06 (F9)

(790g) 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(tetrahydrofuran-3-yl-oxy)-N-((2-trifluoromethyl-phenyl)-methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

10 Prepared analogously to example 174f from the product obtained in (790f) and 2-trifluoromethyl-benzylamine with HATU and NMM in NMP.

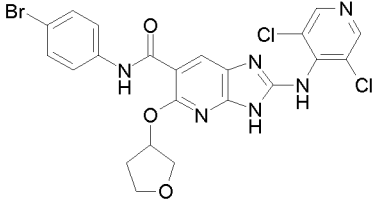
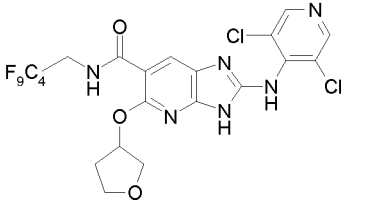
Yield: 14%

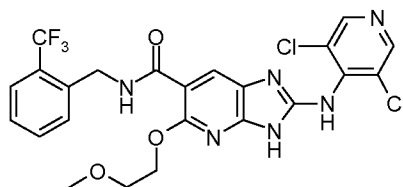
mass spectrum: (M+H)⁺ = 567/569/571 (chlorine isotopes)

R_t value: 1.33 min (F9)

15

In analogy to the above described example, the following compounds were prepared:

No.	Structural formula	Yield	Mass peak(s)	R _f value or R _t
	Name			
791		Σ: 1.2%	(M+H) ⁺ = 563/565/567/569 (bromine and chlorine isotopes)	1.38 min (F9)
	2-(3,5-Dichloro-pyridin-4-ylamino)-5-(tetrahydrofuran-3-yl-oxy)-N-(4-bromophenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			
792		Σ: 0.75%	(M+H) ⁺ = 641/643/645 (chlorine isotopes)	1.39 min (F9)
	2-(3,5-Dichloro-pyridin-4-ylamino)-5-(tetrahydrofuran-3-yl-oxy)-N-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			

Example 800

2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2-methoxy-ethoxy)-N-((2-trifluoromethyl-phenyl)-methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

(800a) 6-Chloro-2-(2-methoxy-ethoxy)-nicotinic acid

Prepared analogously to example 771a from 2,6-dichloro-nicotinic acid and 2-methoxy-ethanol with sodium hydride (55%) in dichloromethane.

Yield: 38%

R_f value: 0.2 (RP8; eluens: 5% NaCl (aq) / acetonitrile = 3:2)

(800b) Methyl 6-chloro-2-(2-methoxy-ethoxy)-nicotinate

Prepared analogously to example 771b from the product obtained in (790a) with trimethylsilyl-diazomethane (2 M in diethylether) in methanol and dichloromethane.

Yield: 97%

mass spectrum: (M+H)⁺ = 246/248 (chlorine isotopes)

R_t value: 1.82 min (E9)

(800c) Methyl 6-chloro-2-(2-methoxy-ethoxy)-5-nitro-nicotinate

Prepared analogously to example 771c from the product obtained in (800b) with nitric acid (100%) in sulphuric acid.

Yield: quant.

R_f value: 0.65 (silica gel; eluens: petrolether / ethyl acetate = 6:4)

R_t value: 1.89 min (E9)

(800d) Methyl 6-amino-2-(2-methoxy-ethoxy)-5-nitro-nicotinate

Prepared analogously to example 154a from the product obtained in (800c) with conc. ammonia in THF.

Yield: 82%

R_f value: 0.30 (silica gel; eluens: petrolether / ethyl acetate = 1:1)

(800e) Methyl 5,6-diamino-2-(2-methoxy-ethoxy)-nicotinate

Prepared analogously to example 154d by hydrogenation of the product obtained in (800d) using palladium on charcoal in THF and methanol.

Yield: 87%

5 mass spectrum: (M+H)⁺ = 242

R_t value: 0.79 min (E9)

(800f) Methyl 6-amino-2-(2-methoxy-ethoxy)-5-(3-(3,5-dichloropyridin-4-yl)-thioureido)-nicotinate

10 Prepared analogously to example 379e from the product obtained in (800e) and 3,5-dichloro-4-isothiocyano-pyridine with TEA in acetonitrile.

Yield: 23%

mass spectrum: (M+H)⁺ = 446/448/450 (chlorine isotopes)

R_t value: 1.54 min (F9)

15

(800g) Methyl 2-(3,5-dichloro-pyridin-4-ylamino)-5-(2-methoxy-ethoxy)-3H-imidazo[4,5-b]pyridine-6-carboxylate

Prepared analogously to example 377d from the product obtained in (800f) with DIC in acetonitrile.

20 Yield: quant

mass spectrum: (M+H)⁺ = 412/414/416 (chlorine isotopes)

R_t value: 1.12 min (F9)

(800h) 2-(3,5-dichloro-pyridin-4-ylamino)-5-(2-methoxy-ethoxy)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid

25

Prepared analogously to example 174e from the product obtained in (800g) with 2N NaOH (aq) in ethanol.

Yield: 80%

mass spectrum: (M+H)⁺ = 398/400/402 (chlorine isotopes)

30 R_t value: 1.06 min (F9)

(800i) 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2-methoxy-ethoxy)-N-((2-trifluoromethyl-phenyl)-methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

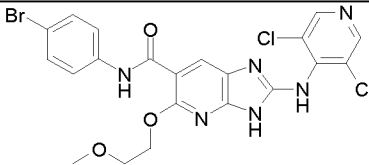
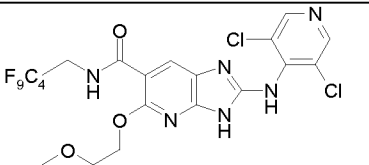
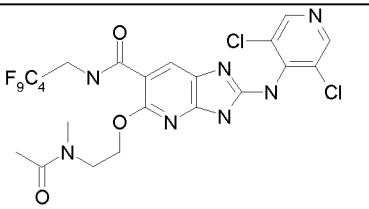
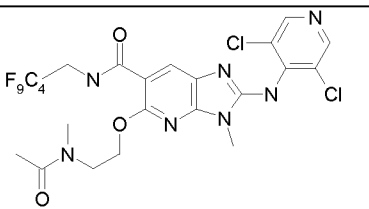
Prepared analogously to example 174f from the product obtained in (800h) and 2-

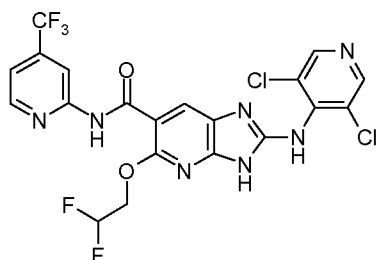
35 trifluoromethyl-benzylamine with TBTU and NMM in NMP.

Yield: 41%

mass spectrum: (M+H)⁺ = 555/557/559 (chlorine isotopes)R_t value: 1.35 min (F9)

5 In analogy to the above described example, the following compounds were prepared:

No.	Structural formula	Yield	Mass peak(s)	R _f value or R _t
	Name			
801		Σ: 2.4%	(M+H) ⁺ = 551/553/555/557 (bromine and chlorine isotopes)	1.41 min (F9)
	2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2-methoxy-ethoxy)-N-(4-bromo-phenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			
802		Σ: 2.6%	(M+H) ⁺ = 629/631/633 (chlorine isotopes)	1.41 min (F9)
	2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2-methoxy-ethoxy)-N-(2,2,3,3,4,4,5,5,5-nonafluoro-pentyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			
809		Σ: 8.7%	(M+H) ⁺ = 670/672/674 (chlorine isotopes)	1.96 min (E9)
	2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2-(acetyl-methyl-amino)-ethoxy)-N-(2,2,3,3,4,4,5,5,5-nonafluoro-pentyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			
811		Σ: 46%	(M+H) ⁺ = 684/686/688 (chlorine isotopes)	2.15 min (E9)
	2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2-(acetyl-methyl-amino)-ethoxy)-N-(2,2,3,3,4,4,5,5,5-nonafluoro-pentyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			

Example 803

5 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2-difluoro-ethoxy)-N-(4-trifluoromethyl-pyridin-2-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

(803a) Methyl 6-amino-2-(2,2-difluoro-ethoxy)-5-nitro-nicotinate

Prepared analogously to example 154a from the product obtained in (771c) (by a synthetic
10 sequence in analogy to 771a – 771c) with conc. ammonia in THF.

Yield: 94%

R_t value: 1.74 min (E9)

(803b) Methyl 5,6-diamino-2-(2,2-difluoro-ethoxy)-nicotinate

15 Prepared analogously to example 154d by hydrogenation of the product obtained in (803a) using Raney nickel in THF and methanol.

Yield: 97%

20 (803c) Methyl 2-(3,5-dichloro-pyridin-4-ylamino)-5-(2,2-difluoro-ethoxy)-3H-imidazo[4,5-b]pyridine-6-carboxylate

Prepared analogously to example 154e from the product obtained in (803b) and 3,5-dichloro-4-isothiocyanato-pyridine with DIC in acetonitrile and methanol.

Yield: 56%

mass spectrum: (M+H)⁺ = 418/420/422 (chlorine isotopes)

25 R_t value: 1.63 min (E9)

76

(803d) 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2-difluoro-ethoxy)-N-(4-trifluoromethyl-pyridin-2-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

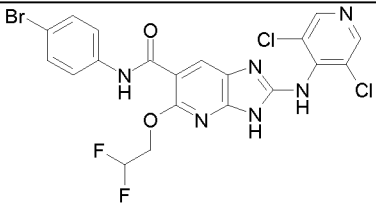
Prepared analogously to example 377f from the product obtained in (803c) and 2-amino-4-trifluoro-pyridine with trimethylaluminium (1 N in heptane) in dioxane.

5 Yield: 47%

mass spectrum: (M+H)⁺ = 548/550/552 (chlorine isotopes)

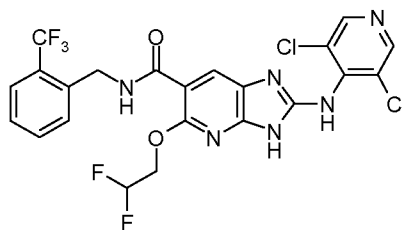
R_t value: 2.07 min (E9)

In analogy to the above described example, the following compounds were prepared:

No.	Structural formula	Yield	Mass peak(s)	R _f value or R _t
	Name			
804		Σ: 15%	(M+H) ⁺ = 557/559/561/563 (bromine and chlorine isotopes)	2.11 min (E9)
	2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2-difluoro-ethoxy)-N-(4-bromo-phenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			

10

Example 805



2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2-difluoro-ethoxy)-N-((2-trifluoromethyl-phenyl)-methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

15

(805a) 2-(3,5-dichloro-pyridin-4-ylamino)-5-(2,2-difluoro-ethoxy)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid

Prepared analogously to example 174e from the product obtained in (803c) (by a synthetic sequence in analogy to 803a – 803c) with 2 M NaOH (aq) in ethanol.

20 Yield: 91%

R_t value: 1.42 min (E9)

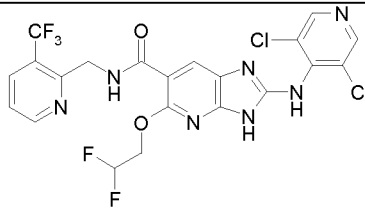
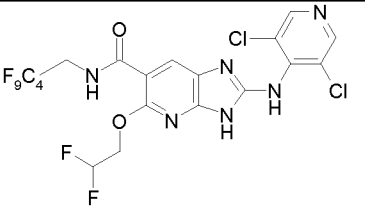
(805b) 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2-difluoro-ethoxy)-N-((2-trifluoromethyl-phenyl)-methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

Prepared analogously to example 174f from the product obtained in (805a) and 2-trifluoromethyl-benzylamine with TBTU and TEA in DMF.

5 Yield: 62%

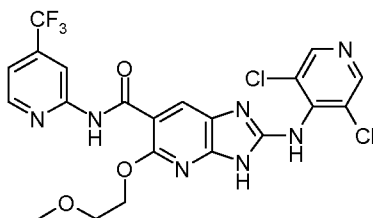
R_t value: 2.01 min (E9)

In analogy to the above described example, the following compounds were prepared:

No.	Structural formula	Yield	Mass peak(s)	R _f value or R _t
	Name			
806		Σ: 42%	(M+H) ⁺ = 562/564/566 (chlorine isotopes)	1.89 min (E9)
	2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2-difluoro-ethoxy)-N-((3-trifluoromethyl-pyridin-2-yl)-methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			
807		Σ: 42%	(M+H) ⁺ = 635/637/639 (chlorine isotopes)	2.15 min (E9)
	2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2-difluoro-ethoxy)-N-(2,2,3,3,4,4,5,5,5-nonafluoro-pentyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			

10

Example 808



2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2-methoxy-ethoxy)-N-(4-trifluoromethyl-pyridin-2-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

15

78

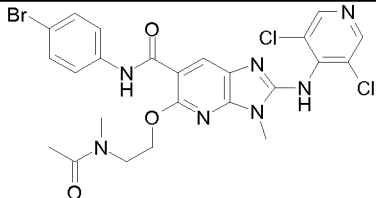
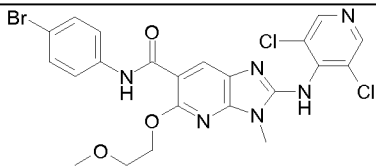
Prepared analogously to example 377f from the product obtained in (800g) (by a synthetic sequence in analogy to 800a – 800g) and 2-amino-4-trifluoromethyl-pyridine with trimethylaluminium (1 N in heptane) in dioxane.

Yield: 20%

5 mass spectrum: (M+H)⁺ = 542/544/546 (chlorine isotopes)

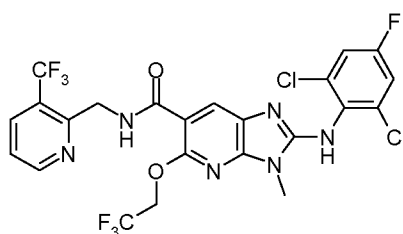
R_t value: 1.38 min (F9)

In analogy to the above described example, the following compounds were prepared:

No.	Structural formula	Yield	Mass peak(s)	R _f value or R _t
	Name			
810		Σ: 44%	(M+H) ⁺ = 606/608/610/612 (bromine and chlorine isotopes)	2.01 min (E9)
	2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2-(acetyl-methyl-amino)-ethoxy)-N-(4-bromo-phenyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			
812		Σ: 35%	(M+H) ⁺ = 565/567/569/571 (bromine and chlorine isotopes)	1.62 min (F9)
	2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2-methoxy-ethoxy)-N-(4-bromo-phenyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			

10

Example 813



2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2,2-trifluoro-ethoxy)-N-((3-trifluoromethyl-pyridin-2-yl)-methyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide

(813a) 6-Chloro-2-methylamino-3-nitro-pyridine

- 5 Prepared analogously to example 154a from 2,6-dichloro-3-nitro-pyridine and methylamine (40% in water) in ethanol.

Yield: 69%

mass spectrum: (M+H)+ = 188/190 (chlorine isotopes)

R_t value: 1.88 min (E9)

10

(813b) 2-Methylamino-3-nitro-6-(2,2,2-trifluoro-ethoxy)-pyridine

Prepared analogously to example 777b from the product obtained in (813a) and 2,2,2-trifluoro-ethanol with potassium tert.-butylate in THF.

Yield: quant.

- 15 mass spectrum: (M+H)+ = 252

R_t value: 2.10 min (E9)

(813c) 5-Bromo-2-methylamino-3-nitro-6-(2,2,2-trifluoro-ethoxy)-pyridine

- 20 Prepared analogously to example 377b from the product obtained in (813b) with pyridinium tribromide in dichloromethane and methanol.

Yield: 99%

mass spectrum: (M+H)+ = 330

R_t value: 2.26 min (E9)

- 25 (813d) 3-Amino-5-bromo-2-methylamino-6-(2,2,2-trifluoro-ethoxy)-pyridine

Prepared analogously to example 154d by hydrogenation of the product obtained in (813c) using Raney nickel in THF.

Yield: 82%

R_f value: 0.40 (silica gel; eluens: petrolether / ethyl acetate = 3:2 + 1% NH₃ (conc.))

30

(813e) 6-Bromo-2-(2,6-dichloro-4-fluoro-phenylamino)-5-(2,2,2-trifluoro-ethoxy)-3-methyl-3H-imidazo[4,5-b]pyridine

Prepared analogously to example 154e from the product obtained in (813d) and 2,6-dichloro-4-fluoro-1-isothiocyanato-benzene with DIC and TEA in acetonitrile.

- 35 Yield: 50%

mass spectrum: (M+H)⁺ = 487/489/491/493 (bromine and chlorine isotopes)

R_f value: 0.72 (silica gel; eluens: cyclohexane / ethyl acetate = 3:2 + 1% NH₃ (conc.))

(813f) Methyl 2-(2,6-dichloro-4-fluoro-phenylamino)-5-(2,2,2-trifluoro-ethoxy)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxyate

Prepared analogously to example 377e by carbonylation of the product obtained in (813e) using 1,1'-bis-diphenylphosphino-ferrocene, palladium-II-acetate and TEA in methanol and DMF.

Yield: 70%

R_t value: 2.98 min (C2)

(813g) 2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2,2-trifluoro-ethoxy)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxylic acid

Prepared analogously to example 174e from the product obtained in (813f) with 4 N NaOH (aq) in methanol.

Yield: quant.

mass spectrum: (M+H)⁺ = 453/455/457 (chlorine isotopes)

R_f value: 0.42 (silica gel; eluens: dichloromethane / methanol = 9:1)

(813h) 2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2,2-trifluoro-ethoxy)-N-((3-trifluoromethyl-pyridin-2-yl)-methyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide

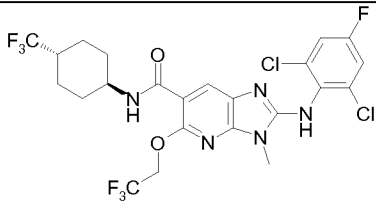
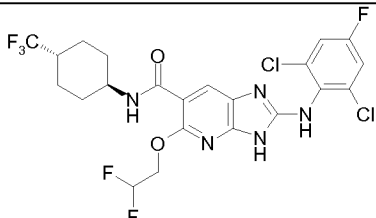
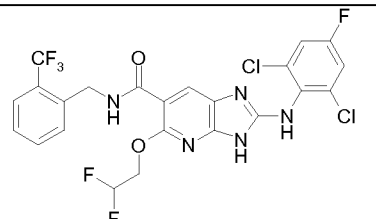
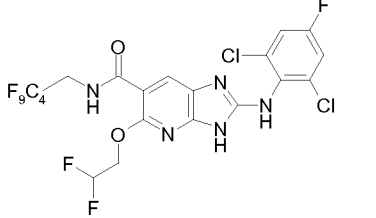
Prepared analogously to example 174f from the product obtained in (813g) and (3-trifluoromethyl-pyridin-2-yl-methyl)-amine with TBTU and TEA in DMF.

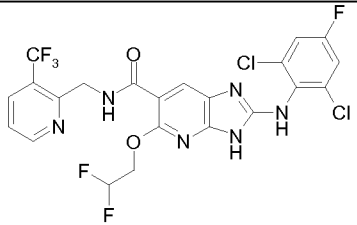
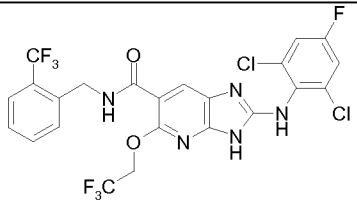
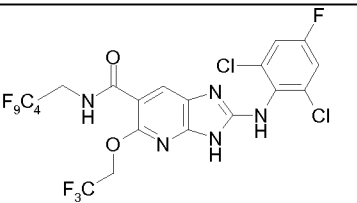
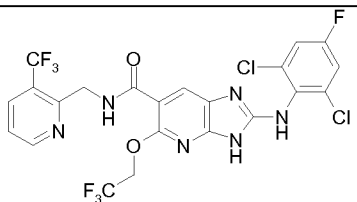
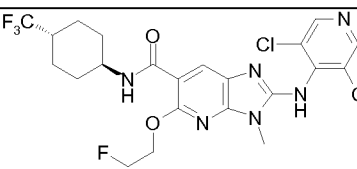
Yield: 52%

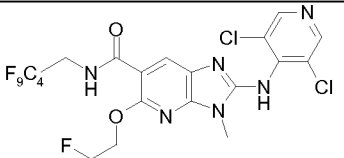
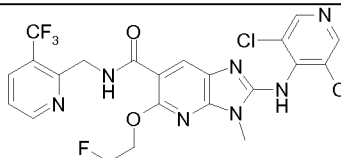
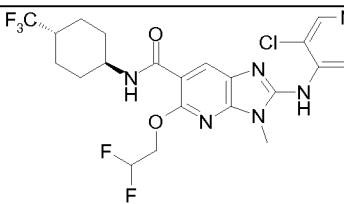
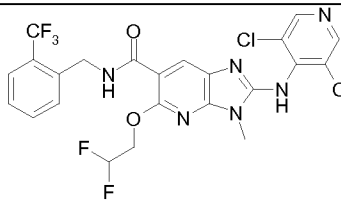
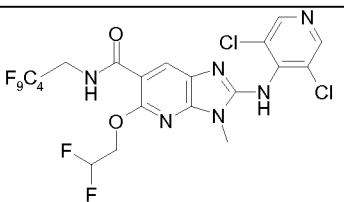
mass spectrum: (M+H)⁺ = 611/613/615 (chlorine isotopes)

R_t value: 1.55 min (F8)

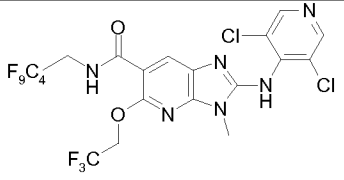
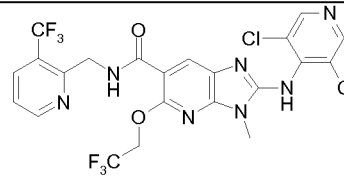
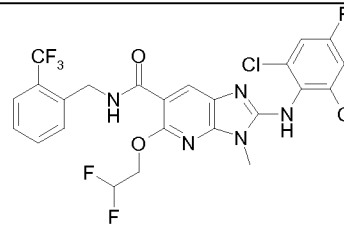
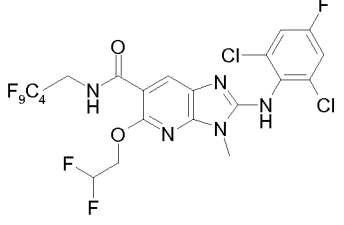
In analogy to the above described example, the following compounds were prepared:

No.	Structural formula	Yield	Mass peak(s)	R _f value or R _t
	Name			
814		Σ : 8.0%	(M+H) ⁺ = 602/604/606 (chlorine isotopes)	1.62 min (F8)
	2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2,2-trifluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			
823		Σ : 18%	(M+H) ⁺ = 570/572/574 (chlorine isotopes)	4.40 min (B5)
	2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			
824		Σ : 19%	(M+H) ⁺ = 578/580/582 (chlorine isotopes)	4.41 min (B5)
	2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(2-trifluoromethyl-benzyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			
825		Σ : 12.6%	(M+H) ⁺ = 652/654/656 (chlorine isotopes)	4.70 min (B5)
	2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			

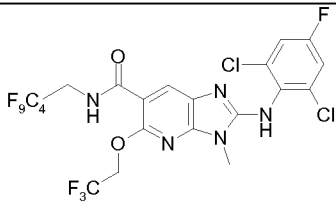
No.	Structural formula	Yield	Mass peak(s)	R _f value or R _t
	Name			
826		Σ: 20%	(M+H) ⁺ = 579/581/583 (chlorine isotopes)	4.14 min (B5)
	2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2-difluoro-ethoxy)-N-((3-trifluoromethyl-pyridin-2-yl)-methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			
828		Σ: 7.6%	(M+H) ⁺ = 596/598/600 (chlorine isotopes)	4.63 min (B5)
	2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2,2-trifluoro-ethoxy)-N-(2-trifluoromethyl-benzyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			
829		Σ: 6.8%	(M+H) ⁺ = 670/672/674 (chlorine isotopes)	4.91 min (B5)
	2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2,2-trifluoro-ethoxy)-N-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			
830		Σ: 8.9%	(M+H) ⁺ = 597/599/601 (chlorine isotopes)	4.36 min (B5)
	2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2,2-trifluoro-ethoxy)-N-((3-trifluoromethyl-pyridin-2-yl)-methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			
833		Σ: 8.0%	(M+H) ⁺ = 549/551/553 (chlorine isotopes)	2.23 min (E9)
	2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2-fluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			

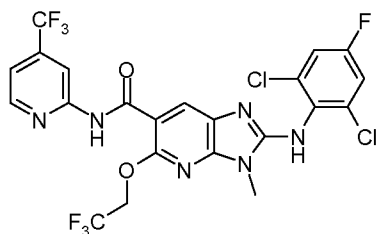
No.	Structural formula	Yield	Mass peak(s)	R _f value or R _t
	Name			
834		Σ : 6.3%	(M+H) ⁺ = 631/633/635 (chlorine isotopes)	2.35 min (E9)
	2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2-fluoro-ethoxy)-N-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			
835		Σ : 9.3%	(M+H) ⁺ = 558/560/562 (chlorine isotopes)	2.09 min (E9)
	2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2-fluoro-ethoxy)-N-((3-trifluoromethyl-pyridin-2-yl)-methyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			
838		Σ : 21%	(M+H) ⁺ = 567/569/571 (chlorine isotopes)	2.28 min (E9)
	2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			
839		Σ : 23%	(M+H) ⁺ = 575/577/579 (chlorine isotopes)	2.28 min (E9)
	2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2-difluoro-ethoxy)-N-(2-trifluoromethyl-benzyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			
840		Σ : 19%	(M+H) ⁺ = 649/651/653 (chlorine isotopes)	2.40 min (E9)
	2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2-difluoro-ethoxy)-N-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			

No.	Structural formula	Yield	Mass peak(s)	R _f value or R _t
	Name			
841		Σ: 24%	(M+H)+ = 576/578/580 (chlorine isotopes)	2.17 min (E9)
	2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2-difluoro-ethoxy)-N-((3-trifluoromethyl-pyridin-2-yl)-methyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			
846		Σ: 7.7%	(M+H)+ = 573/575/577 (chlorine isotopes)	1.62 min (F9)
	2-(3,5-Dichloro-pyridin-4-ylamino)-5-(tetrahydrofuran-3-yl-oxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			
847		Σ: 5.9%	(M+H)+ = 582/584/586 (chlorine isotopes)	1.59 min (F9)
	2-(3,5-Dichloro-pyridin-4-ylamino)-5-(tetrahydrofuran-3-yl-oxy)-N-((3-trifluoromethyl-pyridin-2-yl)-methyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			
848		Σ: 1.3%	(M+H)+ = 577/579/581/583 (bromine and chlorine isotopes)	1.73 min (F9)
	2-(3,5-Dichloro-pyridin-4-ylamino)-5-(tetrahydrofuran-3-yl-oxy)-N-(4-bromo-phenyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			
849		Σ: 4.5%	(M+H)+ = 655/657/659 (chlorine isotopes)	1.69 min (F9)
	2-(3,5-Dichloro-pyridin-4-ylamino)-5-(tetrahydrofuran-3-yl-oxy)-N-((4-fluorophenyl)-methyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			

No.	Structural formula	Yield	Mass peak(s)	R _f value or R _t
	Name			
	2-(3,5-Dichloro-pyridin-4-ylamino)-5-(tetrahydrofuran-3-yl-oxy)-N-(2,2,3,3,4,4,5,5,5-nonafluoro-pentyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			
850		Σ : 11.6%	(M+H) ⁺ = 667/669/671 (chlorine isotopes)	2.50 min (F9)
	2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2,2-trifluoro-ethoxy)-N-(2,2,3,3,4,4,5,5,5-nonafluoro-pentyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			
851		Σ : 22%	(M+H) ⁺ = 594/596/598 (chlorine isotopes)	2.27 min (E9)
	2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2,2-trifluoro-ethoxy)-N-((3-trifluoromethyl-pyridin-2-yl)-methyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			
871		Σ : 4.3%	(M+H) ⁺ = 592/594/596 (chlorine isotopes)	1.55 min (F8)
	2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(2-trifluoromethyl-benzyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			
872		Σ : 0.33%	(M+H) ⁺ = 666/668/670 (chlorine isotopes)	1.60 min (F9)
	2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			

86

No.	Structural formula	Yield	Mass peak(s)	R _f value or R _t
	Name			
873		Σ : 9.0%	(M+H) ⁺ = 684/686/688 (chlorine isotopes)	1.69 min (F8)
	2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2,2-trifluoro-ethoxy)-N-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			

Example 815

5

2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2,2-trifluoro-ethoxy)-N-(4-trifluoromethyl-pyridin-2-yl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide

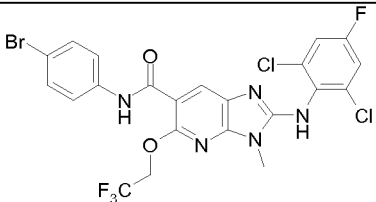
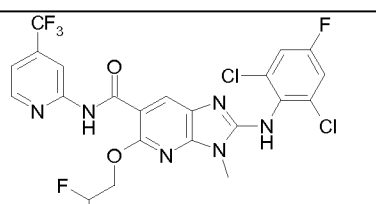
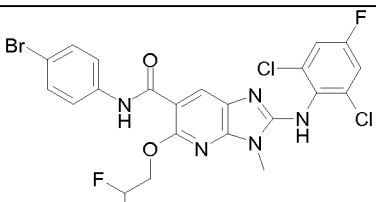
Prepared analogously to example 377f from the product obtained in (813f) (by a synthetic sequence in analogy to 813a – 813f) and 2-amino-4-trifluoromethyl-pyridine with trimethylaluminium (2 N in toluene) in dioxane.

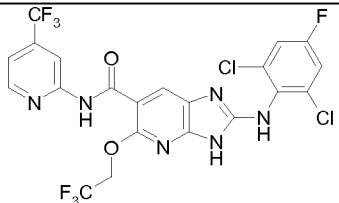
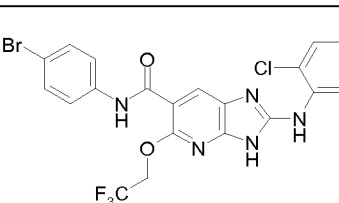
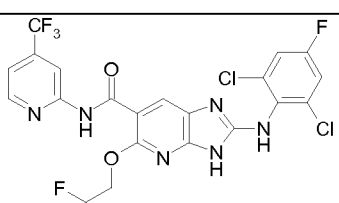
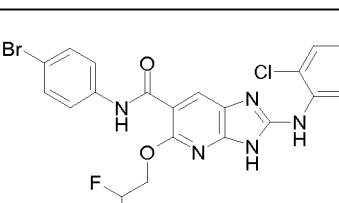
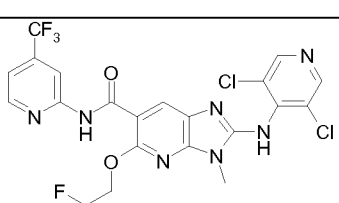
Yield: 37%

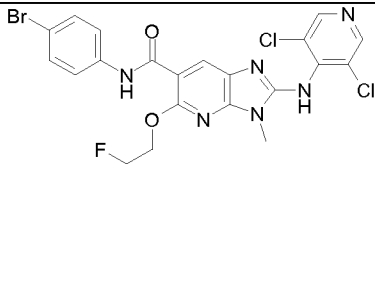
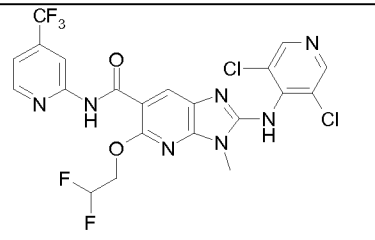
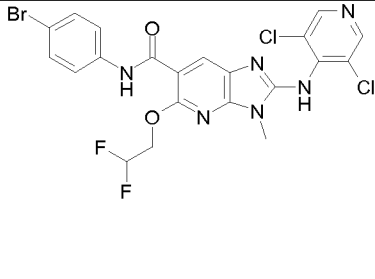
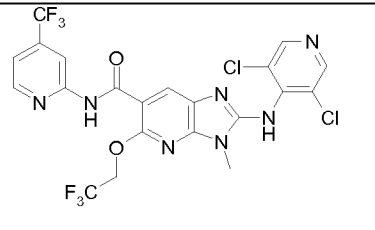
5 mass spectrum: (M+H)⁺ = 597/599/601 (chlorine isotopes)

R_t value: 1.61 min (F9)

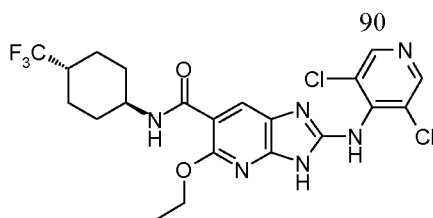
In analogy to the above described example, the following compounds were prepared:

No.	Structural formula	Yield	Mass peak(s)	R _f value or R _t
	Name			
816		64%	(M+H) ⁺ = 606/608/610/612 (bromine and chlorine isotopes)	1.63 min (F9)
	2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2,2-trifluoro-ethoxy)-N-(4-bromophenyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			
817		29%	(M+H) ⁺ = 579/581/583 (chlorine isotopes)	1.55 min (F9)
	2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(4-trifluoromethylpyridin-2-yl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			
818		49%	(M+H) ⁺ = 588/590/592/594 (bromine and chlorine isotopes)	1.55 min (F9)
	2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(4-bromophenyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			

No.	Structural formula	Yield	Mass peak(s)	R _f value or R _t
	Name			
819		66%	(M+H) ⁺ = 583/585/587 (chlorine isotopes)	2.30 min (E9)
	2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2,2-trifluoro-ethoxy)-N-(4-trifluoromethyl-pyridin-2-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			
820		80%	(M+H) ⁺ = 592/594/596/598 (bromine and chlorine isotopes)	2.34 min (E9)
	2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2,2-trifluoro-ethoxy)-N-(4-bromophenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			
821		58%	(M+H) ⁺ = 565/567/569 (chlorine isotopes)	4.61 min (B5)
	2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(4-trifluoromethyl-pyridin-2-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			
822		72%	(M+H) ⁺ = 574/576/578/580 (bromine and chlorine isotopes)	4.69 min (B5)
	2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(4-bromophenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			
831		8%	(M+H) ⁺ = 544/546/548 (chlorine isotopes)	2.31 min (E9)
	2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2-fluoroethoxy)-N-(4-trifluoromethyl-pyridin-2-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			

No.	Structural formula	Yield	Mass peak(s)	R _f value or R _t
	Name			
	2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2-fluoro-ethoxy)-N-(4-trifluoromethyl-pyridin-2-yl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			
832		8%	(M+H) ⁺ = 553/555/557/559 (bromine and chlorine isotopes)	2.36 min (E9)
	2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2-fluoro-ethoxy)-N-(4-bromo-phenyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			
836		38%	(M+H) ⁺ = 562/564/566 (chlorine isotopes)	2.35 min (E9)
	2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2-difluoro-ethoxy)-N-(4-trifluoromethyl-pyridin-2-yl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			
837		17%	(M+H) ⁺ = 571/573/575/577 (bromine and chlorine isotopes)	2.39 min (E9)
	2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2-difluoro-ethoxy)-N-(4-bromo-phenyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			
852		53%	(M+H) ⁺ = 580/582/584 (chlorine isotopes)	2.47 min (E9)
	2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2,2-trifluoro-ethoxy)-N-(4-trifluoromethyl-pyridin-2-yl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide			

Example 842



2-(3,5-Dichloro-pyridin-4-ylamino)-5-ethoxy-N-(trans-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

5

(842a) 2-Amino-5-bromo-6-ethoxy-3-nitro-pyridine

Prepared analogously to example 377b from 2-amino-6-ethoxy-3-nitro-pyridine with pyridinium tribromide in dichloromethane and methanol.

Yield: 96%

10 mass spectrum: (M+H)⁺ = 262/264 (bromine isotopes)

R_t value: 1.61 min (F7)

(842b) 5-Bromo-2,3-diamino-6-ethoxy-pyridine

Prepared analogously to example 154d by hydrogenation of the product obtained in (842a)

15 using Raney nickel in THF.

Yield: 95%

(842c) 2-Amino-3-Boc-amino-5-bromo-6-ethoxy-pyridine

Boc₂O (2.45 g, 11.2 mmol) was added to the product obtained in (842b) (2.27 g, 9.8 mmol) in 50 mL THF and the mixture was stirred at 45°C for 16 h. After concentration the residue was triturated with diethylether, filtered and the filtrate evaporated to dryness.

5 Yield: quant. (slightly contaminated)

mass spectrum: (M+H)⁺ = 332/334 (bromine isotopes)

(842d) Methyl 6-amino-5-Boc-amino-2-ethoxy-nicotinate

Prepared analogously to example 377e by carbonylation of the product obtained in (842c) using 1,1'-bis-diphenylphosphino-ferrocene, palladium-II-acetate and TEA in methanol and DMF.

Yield: 96% (slightly contaminated)

(842e) Methyl 5,6-diamino-2-ethoxy-nicotinate

15 Hydrochloric acid (4 M in dioxane) (22.9 mL, 91.5 mmol) was added to the product obtained in (842d) in 50 mL dioxane and the mixture stirred for 2 h at ambient temperature. The solid is filtered off, washed with dioxane and dried.

Yield: 2.00 g (88%) (slightly contaminated)

mass spectrum: (M+H)⁺ = 212

20 R_t value: 0.15 min (F8)

(842f) Methyl 2-(3,5-dichloro-pyridin-4-ylamino)-5-ethoxy-3H-imidazo[4,5-b]pyridine-6-carboxylate

Prepared analogously to example 154e from the product obtained in (842e) and 3,5-dichloro-4-isothiocyanto-pyridine with DIC and TEA in acetonitrile.

Yield: 47%

mass spectrum: (M+H)⁺ = 382/384/386 (chlorine isotopes)

R_t value: 1.22 min (F8)

30 (842g) 2-(3,5-Dichloro-pyridin-4-ylamino)-5-ethoxy-3H-imidazo[4,5-b]pyridine-6-carboxylic acid

Prepared analogously to example 174e from the product obtained in (842f) with 2 N NaOH (aq) in ethanol.

Yield: 97%

35 mass spectrum: (M+H)⁺ = 368/370/372 (chlorine isotopes)

R_f value: 0.47 (silica gel; eluens: dichloromethane / methanol = 9:1)

(842h) 2-(3,5-Dichloro-pyridin-4-ylamino)-5-ethoxy-N-(trans-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

- 5 Prepared analogously to example 174f from the product obtained in (842g) and trans-4-trifluoromethyl-cyclohexylamine with TBTU and TEA in DMF.

Yield: 52%

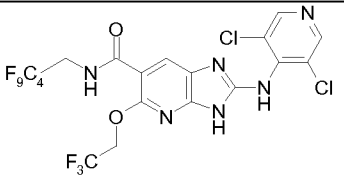
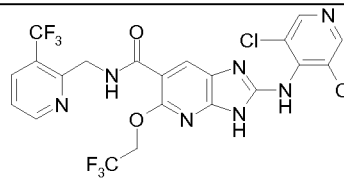
mass spectrum: (M+H)⁺ = 517/519/521 (chlorine isotopes)

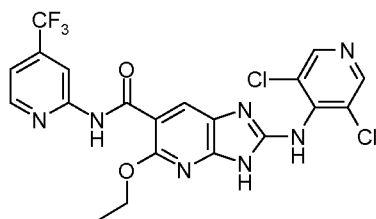
R_t value: 1.39 min (F9)

10

In analogy to the above described example, the following compounds were prepared:

No.	Structural formula	Yield	Mass peak(s)	R _f value or R _t
	Name			
843		Σ: 20%	(M+H) ⁺ = 526/528/530 (chlorine isotopes)	1.32 min (F9)
	2-(3,5-Dichloro-pyridin-4-ylamino)-5-ethoxy-N-((3-trifluoromethyl-pyridin-2-yl)-methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			
844		Σ: 13.3%	(M+H) ⁺ = 599/601/603 (chlorine isotopes)	1.46 min (F9)
	2-(3,5-Dichloro-pyridin-4-ylamino)-5-ethoxy-N-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			
853		Σ: 5.1%	(M+H) ⁺ = 579/581/583 (chlorine isotopes)	2.10 min (E9)
	2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2,2-trifluoroethoxy)-N-(2-trifluoromethyl-benzyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			

No.	Structural formula	Yield	Mass peak(s)	R _f value or R _t
	Name			
854		Σ : 2.5%	(M+H) ⁺ = 653/655/657 (chlorine isotopes)	2.22 min (E9)
	2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2,2-trifluoro-ethoxy)-N-(2,2,3,3,4,4,5,5,5-nonafluoro-pentyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			
855		Σ : 4.2%	(M+H) ⁺ = 580/582/584 (chlorine isotopes)	2.16 min (E7)
	2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2,2-trifluoro-ethoxy)-N-((3-trifluoromethyl-pyridin-2-yl)-methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			

Example 845

5

2-(3,5-Dichloro-pyridin-4-ylamino)-5-ethoxy-N-(4-trifluoromethyl-pyridin-2-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

Prepared analogously to example 377f from the product obtained in (842f) (by a synthetic sequence in analogy to 842a – 842f) and 2-amino-4-trifluoromethyl-pyridine with trimethylaluminium (1 M in heptane) in dioxane.

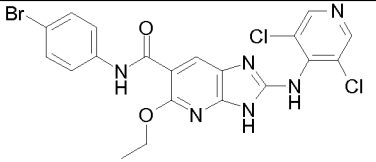
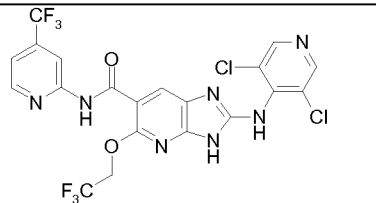
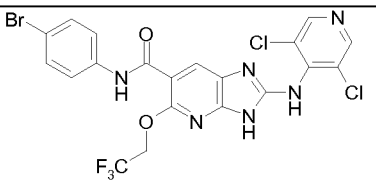
Yield: 45%

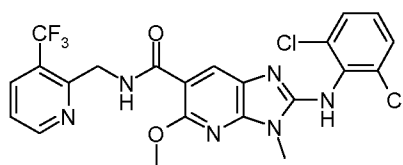
mass spectrum: (M+H)⁺ = 512/514/516 (chlorine isotopes)

R_t value: 1.65 min (F9)

15

In analogy to the above described example, the following compounds were prepared:

No.	Structural formula	Yield	Mass peak(s)	R _f value or R _t
	Name			
856		45%	(M+H) ⁺ = 521/523/525/527 (bromine and chlorine isotopes)	1.45 min (F9)
	2-(3,5-Dichloro-pyridin-4-ylamino)-5-ethoxy-N-(4-bromo-phenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			
857		43%	(M+H) ⁺ = 566/568/570 (chlorine isotopes)	2.18 min (E9)
	2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2,2-trifluoro-ethoxy)-N-(4-trifluoromethyl-pyridin-2-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			
858		44%	(M+H) ⁺ = 575/577/579/581 (bromine and chlorine isotopes)	2.22 min (E9)
	2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2,2-trifluoro-ethoxy)-N-(4-bromo-phenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide			

Example 860

2-(2,6-Dichloro-phenylamino)-5-methoxy-N-((3-trifluoromethyl-pyridin-2-yl)-methyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide

(860a) 2-(2,6-Dichloro-phenylamino)-5-methoxy-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxylic acid

Prepared analogously to example 174e from the product obtained in (377e) (by a synthetic sequence in analogy to 377a – 377e) with 4 M NaOH (aq) in methanol.

5 Yield: 76%

mass spectrum: (M+H)+ = 367/369/371 (chlorine isotopes)

R_t value: 1.19 min (F8)

(860b) 2-(2,6-Dichloro-phenylamino)-5-methoxy-N-((3-trifluoromethyl-pyridin-2-yl)-methyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide

10

Prepared analogously to example 174f from the product obtained in (860a) and (3-trifluoromethyl-pyridin-2-yl)-methylamine with TBTU and TEA in DMF.

Yield: 86%

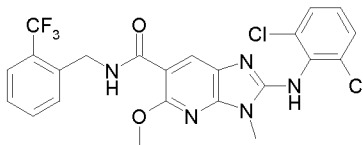
mass spectrum: (M+H)+ = 525/527/529 (chlorine isotopes)

15

R_t value: 2.73 min (C2)

R_f value: 0.49 (silica gel; eluens: dichloromethane / methanol = 9:1)

In analogy to the above described example, the following compounds were prepared:

No.	Structural formula	Yield	Mass peak(s)	R _f value or R _t
	Name			
861		Σ : 49%	(M+H)+ = 524/526/528 (chlorine isotopes)	3.01 min (C2)
2-(2,6-Dichloro-phenylamino)-5-methoxy-N-(2-trifluoromethyl-benzyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide				

Biological Data

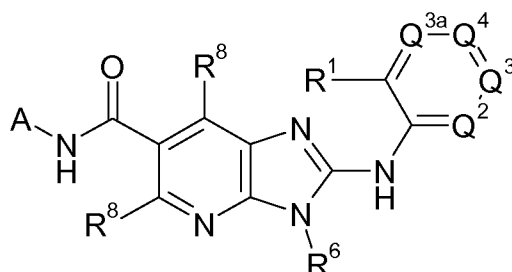
Title compounds of the examples were tested in the biological test described above and were found to exhibit 50% inhibition of mPGES-1 at a concentration of 10 μ M or below. For example, the following representative compounds of the examples exhibited the following percentage inhibitions at 10 μ M (unless otherwise specified):

example	% inhib.	example	% inhib.	example	% inhib.	example	% inhib.
154	91	463	97	771	100 (1 μ M)	791	89
174	99	466	100	772	100 (1 μ M)	792	96
377	100	468	98	773	100 (1 μ M)	793	94
379	100	469	100	774	100 (1 μ M)	794	100
386	99	471	99	775	95 (1 μ M)	795	98
393	99	473	99	776	100 (1 μ M)	796	96
394	100	480	100	777	98 (1 μ M)	797	100
400	97	485	98	778	98 (1 μ M)	798	87
401	100	486	100	779	96 (1 μ M)	799	99
403	100	497	98	780	100 (1 μ M)	800	98
411	100	505	100	781	99 (1 μ M)	801	96
413	100	506	100	782	100	802	96
429	97	508	94	783	100	803	99
438	100	511	96	784	97	804	98
439	91	517	100	785	100	805	98
448	100	523	96	786	92	806	98
449	98	527	96	787	98	807	90
453	98	535	100	788	98	808	100
454	99	541	74	789	95	809	100
459	100	560	93	790	97	810	96

example	% inhib.	example	% inhib.	example	% inhib.	example	% inhib.
811	94 (1µM)	831	100	851	98	871	100
812	97	832	100	852	95	872	100
813	99	833	100	853	100	873	100
814	97	834	99	854	96		
815	100	835	95	855	100		
816	97	836	100	856	93		
817	96	837	96	857	99		
818	99	838	94	858	100		
819	96	839	98	859	89		
820	99	840	99	860	100		
821	90	841	99	861	100		
822	100	842	92	862	99		
823	91	843	99	863	82		
824	100	844	100	864	91		
825	98	845	99	865	92		
826	100	846	100	866	100		
827	100	847	100	867	100		
828	98	848	100	868	100		
829	100	849	98	869	100		
830	98	850	99	870	100		

Claims

1. Compounds of formula I,



I

in which

Q^2 , Q^3 , Q^{3a} and Q^4 respectively represent $-C(R^2)=$, $-C(R^3)=$, $-C(R^{3a})=$ and $-C(R^4)=$;

or

any one or two of Q^2 , Q^3 , Q^{3a} and Q^4 may alternatively and independently represent $-N=$;

R^1 represents halo, $-CN$, $-N(R^{y1})R^{y2}$, $-N(R^{y3})-C(O)-R^{y4}$, $-N(R^{y5})-S(O)_2-R^{y6}$, $-C(O)OR^{y7}$, $-C(O)N(R^{y8})R^{y9}$, $-OR^{y10}$, $-S(O)_m-R^{y11}$, $-S(O)_2O-R^{y12}$, $-S(O)_2N(R^{y13})R^{y14}$, $-C(O)R^{y15}$;

C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, cycloalkyl [which latter four groups are optionally substituted by one or more substituents selected from fluoro, $-CN$, $-N(R^{y1})R^{y2}$, $-N(R^{y3})-C(O)-R^{y4}$, $-N(R^{y5})-S(O)_2-R^{y6}$, $-C(O)OR^{y7}$, $-C(O)N(R^{y8})R^{y9}$, $-OR^{y10}$, $-S(O)_m-R^{y11}$, $-S(O)_2O-R^{y12}$, $-S(O)_2N(R^{y13})R^{y14}$ and $-C(O)R^{y15}$]; or

heterocycloalkyl or heteroaryl (which latter two groups are optionally substituted by one or more substituents selected from R^9);

R^2 , R^3 , R^{3a} and R^4

independently represent hydrogen, halo, $-CN$, $-N(R^{y1})R^{y2}$, $-N(R^{y3})-C(O)-R^{y4}$, $-N(R^{y5})-S(O)_2-R^{y6}$, $-C(O)OR^{y7}$, $-C(O)N(R^{y8})R^{y9}$, $-OR^{y10}$, $-S(O)_m-R^{y11}$, $-S(O)_2O-R^{y12}$, $-S(O)_2N(R^{y13})R^{y14}$, $-C(O)R^{y15}$;

C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, cycloalkyl [which latter four groups are optionally substituted by one or more substituents selected from fluoro, $-CN$, $-N(R^{y1})R^{y2}$, $-N(R^{y5})-S(O)_2-R^{y6}$, $-C(O)OR^{y7}$, $-C(O)N(R^{y8})R^{y9}$, $-OR^{y10}$, $-S(O)_m-R^{y11}$, $-S(O)_2O-R^{y12}$, $-S(O)_2N(R^{y13})R^{y14}$ and $-C(O)R^{y15}$] provided that if R^3 or R^{3a} is a substituted C_1 alkyl group, then the substituent cannot be $-N(R^{y5})-S(O)_2-R^{y6}$;

or any adjacent pair of R^1 , R^2 , R^3 , R^{3a} and R^4 (i.e. R^1 and R^{3a} , R^2 and R^3 , R^3 and R^4 and R^4 and R^{3a}) may be linked together to form, along with the essential carbon atoms of the Q^2 to Q^4 -containing ring to which they are necessarily attached, a further 5- to 7-membered ring,
 5 optionally containing one to three heteroatoms, which ring may contain one or two further unsaturations and which is optionally substituted by one or more C_{1-3} alkyl and/or =O substituents;

R^6 represents hydrogen;

10 heterocycloalkyl, aryl, heteroaryl (which latter three groups are optionally substituted by one or more substituents selected from R^9); or
 C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, which latter four groups are optionally substituted by one or more substituents selected from fluoro,
 $-N(R^{y1})R^{y2}$, $-N(R^{y3})-C(O)-R^{y4}$,
 15 $-N(R^{y5})-S(O)_2-R^{y6}$, $-C(O)OR^{y7}$, $-C(O)N(R^{y8})R^{y9}$, $-OR^{y10}$, $-S(O)_m-R^{y11}$,
 $-S(O)_2N(R^{y13})R^{y14}$, $-C(O)R^{y15}$, heterocycloalkyl, cycloalkyl, aryl and heteroaryl
 (which latter four groups are optionally substituted by one or more substituents selected from R^9);

20 each R^8 independently represents hydrogen, halo, $-N(R^{y1})R^{y2}$, $-OR^{y10}$,
 $-S(O)_2-R^{y11}$;
 C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, $-O-C_{1-6}$ alkyl, $-O-C_{2-6}$ alkenyl,
 $-O-C_{2-6}$ alkynyl, $-O$ -cycloalkyl, $-O$ -heterocycloalkyl [which latter nine groups are
 25 optionally substituted by one or more substituents selected from fluoro, $-CN$,
 $-N(R^{y1})R^{y2}$, $-N(R^{y3})-C(O)-R^{y4}$, $-N(R^{y5})-S(O)_2-R^{y6}$, $-C(O)OR^{y7}$, $-C(O)N(R^{y8})R^{y9}$,
 $-OR^{y10}$, $-S(O)_m-R^{y11}$, $-S(O)_2O-R^{y12}$, $-S(O)_2N(R^{y13})R^{y14}$, $-C(O)R^{y15}$, C_{1-3} alkyl,
 cycloalkyl, heterocycloalkyl, aryl and heteroaryl (which latter four groups are
 30 optionally substituted by one or more substituents selected from R^9);
 heterocycloalkyl or heteroaryl (which latter two groups are optionally substituted by one or more substituents selected from R^9);

A represents aryl, heteroaryl, heterocycloalkyl, cycloalkyl, C_{1-12} alkyl,
 C_{2-12} alkenyl or C_{2-12} alkynyl, all of which are optionally substituted by one or
 more substituents selected from R^9 ;

R^9 represents, on each occasion when used herein:
halo, $-CN$, $-N(R^{y1})R^{y2}$, $-N(R^{y3})-C(O)-R^{y4}$, $-N(R^{y5})-S(O)_2-R^{y6}$, $-C(O)OR^{y7}$,
 $-C(O)N(R^{y8})R^{y9}$, $-OR^{y10}$, $-S(O)_m-R^{y11}$, $-S(O)_2O-R^{y12}$, $-S(O)_2N(R^{y13})R^{y14}$ and
 $-C(O)R^{y15}$;
 C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, cycloalkyl, heterocycloalkyl [which latter
five groups are optionally substituted by one or more substituents selected
from fluoro, $-CN$, $-N(R^{y1})R^{y2}$, $-N(R^{y3})-C(O)-R^{y4}$, $-N(R^{y5})-S(O)_2-R^{y6}$, $-C(O)OR^{y7}$,
 $-C(O)N(R^{y8})R^{y9}$, $-OR^{y10}$, $-S(O)_m-R^{y11}$, $-S(O)_2O-R^{y12}$, $-S(O)_2N(R^{y13})R^{y14}$ and
 $-C(O)R^{y15}$]; or
aryl or heteroaryl [which latter two groups are optionally substituted by one or
more substituents selected from halo, $-CN$, C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl,
cycloalkyl (which latter four groups are optionally substituted by one or more
substituents selected from fluoro and $-OR^{x2}$), $-O-C_{1-7}$ alkyl, $-O-C_{2-7}$ alkenyl,
 $-O-C_{2-7}$ alkynyl and $-O$ -cycloalkyl (which latter four groups are optionally
substituted by one or more fluoro atoms)]; or
any two R^9 substituents:
when attached to the adjacent atoms of the A group; and,
in the case where the R^9 substituents are attached to a non-aromatic A group,
when attached to the same atoms,
may be linked together to form, together with the essential atoms of the A
group to which the relevant R^9 substituents are necessarily attached, a further
3- to 8-membered ring, optionally containing a further one or two heteroatoms,
and which further ring optionally contains one or two unsaturations and which
is optionally substituted by one or more C_{1-3} alkyl and/or $=O$ substituents;
m represents 0, 1 or 2;
each R^{y4} , R^{y6} , R^{y11} and R^{y15} :
independently represent C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, cycloalkyl, which
latter four groups are optionally substituted by one or more fluoro atoms;
each R^{x2} , R^{y1} , R^{y2} , R^{y3} , R^{y5} , R^{y7} , R^{y8} , R^{y9} , R^{y10} , R^{y12} , R^{y13} and R^{y14} :
independently represent hydrogen or C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl,
cycloalkyl, heterocycloalkyl, which latter five groups are optionally substituted
one or more substituents selected from fluoro and $-OC_{1-3}$ alkyl; or

any two groups, when attached to the same nitrogen atom (i.e. R^{y1} and R^{y2} , R^{y8} and R^{y9} , and R^{y13} and R^{y14}), may, together with that nitrogen atom to which they are necessarily attached, be linked together to form a 3- to 8-membered ring, optionally containing one or two further
5 heteroatoms and which ring optionally contains one or two unsaturations and is optionally substituted by one or more

C_{1-3} alkyl and/or =O substituents,

or a pharmaceutically acceptable salt thereof.

10

2. Compounds according to claim 1, wherein

Q^2 represents $-C(R^2)=$; and

any two of Q^3 , Q^{3a} and Q^4 respectively represent $-C(R^3)=$, $-C(R^{3a})=$ and $-C(R^4)=$; and

15 the remaining one of Q^3 , Q^{3a} and Q^4 represents $-N=$.

3. Compounds according to any one of the preceding claims, wherein

Q^2 , Q^3 and Q^{3a} respectively represent $-C(R^2)=$, $-C(R^3)=$ and $-C(R^{3a})=$; and

20 Q^4 represents $-N=$.

4. Compounds according to any one of the claims 1 or 2, wherein

Q^2 , Q^{3a} and Q^4 respectively represent $-C(R^2)=$, $-C(R^{3a})=$ and $-C(R^4)=$; and

25 Q^3 represents $-N=$;

or wherein

Q^2 , Q^3 and Q^4 respectively represent $-C(R^2)=$, $-C(R^3)=$ and $-C(R^4)=$; and

Q^{3a} represents $-N=$.

30

5. Compounds according to any one of the preceding claims, wherein

R^1 represents C_{1-3} alkyl (optionally substituted by one or more fluoro atoms),
 C_{3-6} cycloalkyl or halo.

6. Compounds according to any one of the preceding claims, wherein

R^2 represents hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl (which latter two groups are optionally substituted by one or more atoms selected from fluoro), halo or
5 $-O-C_{1-3}$ alkyl (optionally substituted by one or more fluoro atoms).

7. Compounds according to any one of the preceding claims, wherein:

R^3 , R^{3a} and R^4 independently represent hydrogen, C_{1-4} alkyl (optionally substituted by one or more fluoro atoms) or halo.

8. Compounds according to any one of the preceding claims, wherein

R^9 represents halo, $-CN$, $-N(R^{y1})R^{y2}$, $-N(R^{y3})-C(O)-R^{y4}$, $-N(R^{y5})-S(O)_2-R^{y6}$,
 $-C(O)OR^{y7}$, $-C(O)N(R^{y8})R^{y9}$, $-OR^{y10}$, $-S(O)_m-R^{y11}$, $-S(O)_2O-R^{y12}$,
 $-S(O)_2N(R^{y13})R^{y14}$ and/or $-C(O)R^{y15}$; or

15 C_{1-7} alkyl optionally substituted by one or more substituents selected from fluoro, $-CN$, $-N(R^{y1})R^{y2}$, $-N(R^{y3})-C(O)-R^{y4}$, $-N(R^{y5})-S(O)_2-R^{y6}$,
 $-C(O)OR^{y7}$, $-C(O)N(R^{y8})R^{y9}$, $-OR^{y10}$, $-S(O)_m-R^{y11}$, $-S(O)_2O-R^{y12}$,
 $-S(O)_2N(R^{y13})R^{y14}$ and/or $-C(O)R^{y15}$; or

20 aryl, heteroaryl (which latter two groups are optionally substituted by one or more substituents selected from $-O-C_{1-3}$ alkyl, $-CN$, halo and C_{1-2} alkyl optionally substituted by one or more fluoro atoms); or
any two R^9 groups may be linked together as defined in claim 1.

9. Compounds according to any one of the preceding claims, wherein

25 R^8 represents hydrogen, halo, C_{1-3} alkyl [optionally substituted by one or more substituents selected from fluoro, $-OR^{y10}$, $-N(R^{y1})R^{y2}$,
 $-N(R^{y3})-C(O)-R^{y4}$, and $-C(O)N(R^{y8})R^{y9}$], $-O-C_{1-6}$ alkyl, $-O$ -cycloalkyl,
 $-O$ -heterocycloalkyl [which latter three groups are optionally substituted by one or more substituents selected from fluoro, C_{1-3} alkyl, $-N(R^{y1})R^{y2}$,
30 $-N(R^{y3})-C(O)-R^{y4}$, $-N(R^{y5})-S(O)_2-R^{y6}$, $-C(O)OR^{y7}$, $-C(O)N(R^{y8})R^{y9}$,
 $-OR^{y10}$, $-S(O)_m-R^{y11}$, $-S(O)_2O-R^{y12}$, $-S(O)_2N(R^{y13})R^{y14}$, $-C(O)R^{y15}$,
cycloalkyl, heterocycloalkyl, aryl and heteroaryl (which latter four groups are optionally substituted by one or more substituents selected from R^9)].

10. Compounds according to any one of the preceding claims, wherein

R^6 represents hydrogen or C_{1-6} alkyl optionally substituted by one or more substituents selected from $-N(R^{y1})R^{y2}$, $-N(R^{y3})-C(O)-R^{y4}$,
 5 $-N(R^{y5})-S(O)_2-R^{y6}$, $-C(O)OR^{y7}$, $-C(O)N(R^{y8})R^{y9}$, $-OR^{y10}$, $-S(O)_2R^{y11}$ and a 4- to 6-membered heterocycloalkyl group (containing two or one heteroatom(s) selected from oxygen and nitrogen).

11. Compound according to any one of the preceding claims, wherein

10 R^{x2} , R^{y1} , R^{y2} , R^{y3} , R^{y5} , R^{y7} , R^{y8} , R^{y9} , R^{y10} , R^{y12} , R^{y13} and R^{y14} independently represent hydrogen or C_{1-4} alkyl optionally substituted by one or more fluoro atoms or $-OC_{1-2}$ alkyl groups; or any pair of R^{y1} and R^{y2} , R^{y8} and R^{y9} and/or R^{y13} and R^{y14} are linked together to form a 3- to 7-membered ring, optionally containing one further nitrogen or oxygen
 15 heteroatom, one or two further double bonds, and which ring is optionally substituted by one or more C_{1-2} alkyl or $=O$ substituents.

12. Compounds according to any one of the preceding claims, wherein

R^{y4} , R^{y6} , R^{y11} and R^{y15} independently represent C_{1-4} alkyl.

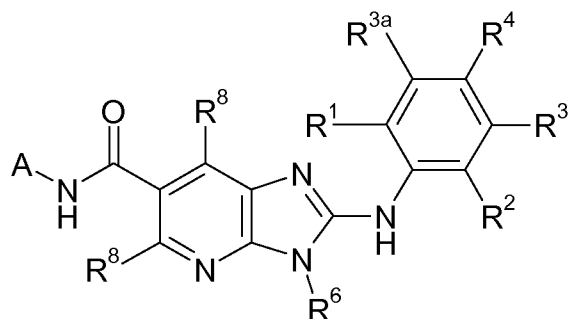
13. Compound according to any one of the preceding claims, wherein

A represents C_{1-12} linear or branched alkyl, aryl, heteroaryl, 5- or 6-membered heterocycloalkyl; or C_{3-10} cycloalkyl, all of which groups are optionally
 25 substituted by one or more substituents selected from R^9 .

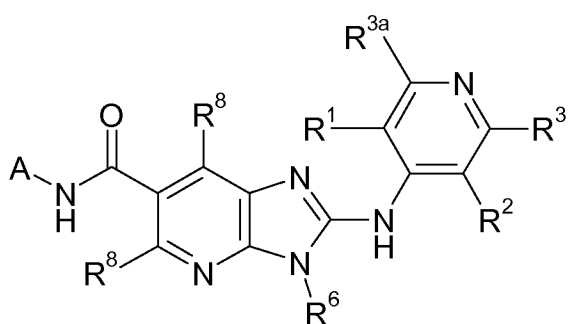
14. Compound according to any one of the preceding claims, wherein

A represents C_{4-12} linear or branched alkyl, aryl, heteroaryl, 5- or 6-membered heterocycloalkyl; or C_{3-7} cycloalkyl (all of which groups are optionally
 30 substituted by one or more substituents selected from R^9); or arylmethylene, heteroarylmethylene [which latter two groups are optionally substituted by one or more groups selected from C_{1-7} alkyl (optionally substituted by one or more substituents selected from fluoro and $-OR^{x2}$), halo, $-CN$ and/or $-O-C_{1-7}$ alkyl (optionally substituted by one or more fluoro atoms)].

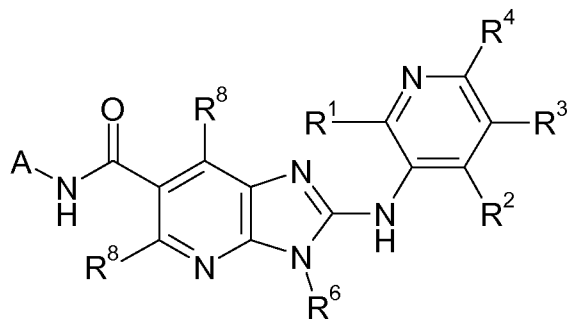
15. Compounds of formula Ia, Ib, Ic or Id



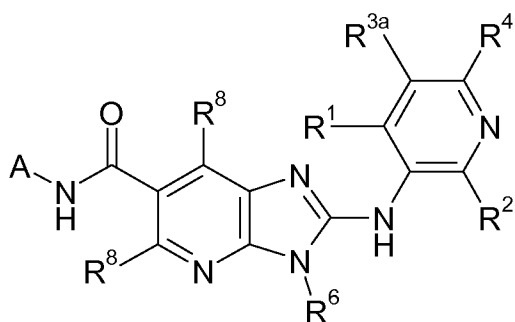
Ia



Ib



Ic



Id

in which

- 10 R^1 represents C_{1-3} alkyl (optionally substituted by one or more fluoro atoms), C_{3-6} cycloalkyl, fluoro, chloro, bromo;

R^2 represents hydrogen, C_{1-3} alkyl (optionally substituted by one or more fluoro atoms), C_{3-6} cycloalkyl, fluoro, chloro, bromo;

5 R^3 , R^{3a} and R^4 independently represent hydrogen, fluoro, chloro, bromo, C_{1-3} alkyl (optionally substituted by one or more fluoro atoms);

R^6 represents hydrogen; C_{1-4} alkyl optionally substituted by one or more fluoro atoms;

10

R^8 independently represents hydrogen, $-O-C_{1-6}$ alkyl, $-O$ -cycloalkyl, $-O$ -heterocycloalkyl [which latter three groups are optionally substituted by one or more substituents selected from fluoro, C_{1-3} alkyl, C_{3-6} cycloalkyl, $-O-C_{1-3}$ alkyl, $-N(C_{1-3} \text{ alkyl})_2$, $-NHCO-C_{1-3}$ alkyl, $-N(C_{1-3}\text{-alkyl})CO-C_{1-3}$ alkyl, in
15 all of which latter groups the alkyl-groups are optionally substituted by one or more fluoro-atoms];

15

A represents phenyl, pyridyl, 5- or 6-membered heterocycloalkyl, C_{3-7} cycloalkyl, C_{5-8} linear or branched alkyl (all of which groups are optionally substituted by
20 one or more substituents selected from R^9); or
benzyl, pyridylmethylene [which latter two groups are optionally substituted by one or more groups selected from C_{1-7} alkyl (optionally substituted by one or more substituents selected from fluoro and $-OR^{x2}$), halo, $-CN$ and/or $-O-C_{1-7}$ alkyl (optionally substituted by one or more fluoro atoms)];

25

R^9 represents on each occasion when used herein: halo, $-N(R^{y1})R^{y2}$, $-N(R^{y3})-C(O)-R^{y4}$, $-C(O)N(R^{y8})R^{y9}$, $-OR^{y10}$, and/or C_{1-6} alkyl optionally substituted by one or more substituents selected from fluoro, $-N(R^{y1})R^{y2}$, $-N(R^{y3})-C(O)-R^{y4}$, $-C(O)N(R^{y8})R^{y9}$, and/or $-OR^{y10}$; or

30

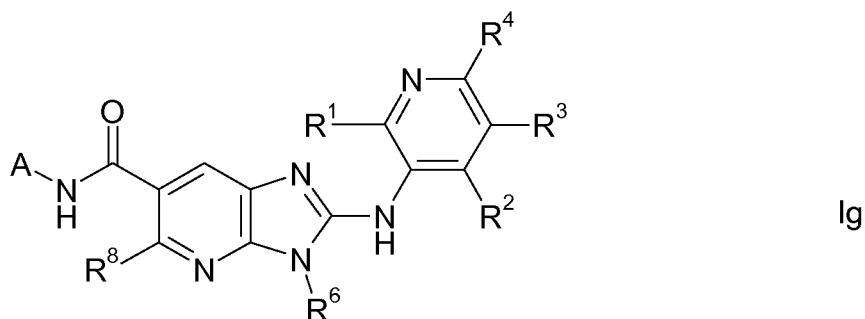
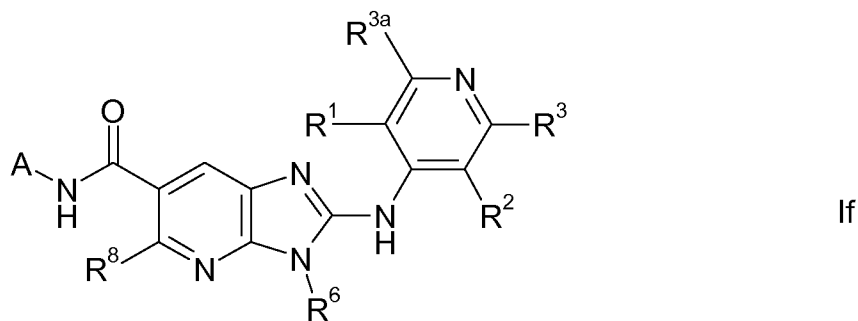
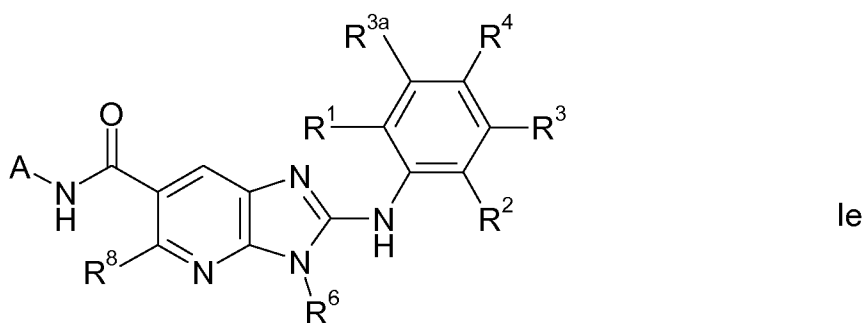
any two R^9 substituents,
when attached to the adjacent atoms of the A group and,
in the case where the R^9 substituents are attached to a non-aromatic A group,
when attached to the same atoms,

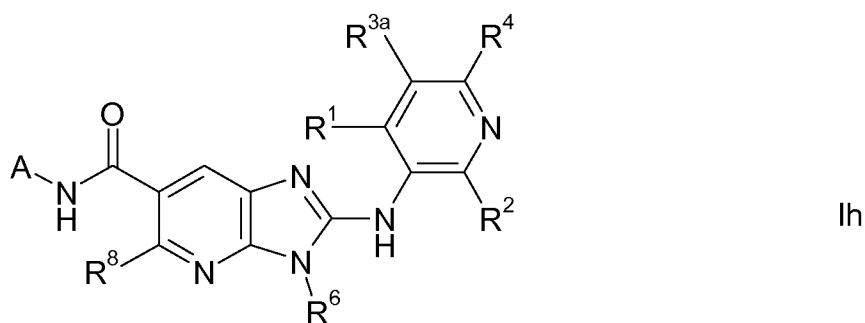
may be linked together to form, together with the essential atoms of the A group to which the relevant R^9 substituents are necessarily attached, a further 3- to 8-membered ring, optionally containing a further one or two heteroatoms, and which further ring optionally contains one or two unsaturations and which is optionally substituted by one or more C_{1-3} alkyl and/or =O substituents;

and

the substituents R^{x2} , R^{y1} , R^{y2} , R^{y3} , R^{y4} , R^{y5} , R^{y6} , R^{y7} , R^{y8} , R^{y9} , R^{y10} , R^{y11} , R^{y12} , R^{y13} , R^{y14} and R^{y15} have the meaning as defined in claims 1, 11 or 12.

16. Compounds compounds of formula le, lf, lg or lh:





in which

- 5 R^1 represents chloro, bromo, fluoro, C_{1-3} alkyl (which latter alkyl group is optionally substituted by one or more fluoro-atoms);
- R^2 represents hydrogen, chloro, bromo, fluoro, C_{1-3} alkyl (which latter alkyl group is optionally substituted by one or more fluoro atoms);
- 10 R^3 , R^{3a} and R^4 independently represent hydrogen, chloro, bromo, fluoro, C_{1-3} alkyl (which latter alkyl group is optionally substituted by one or more fluoro atoms);
- R^6 represents hydrogen; C_{1-4} alkyl optionally substituted by one or more fluoro atoms;
- 15 R^8 independently represents hydrogen, $-O-C_{1-4}$ alkyl [optionally substituted by one or more substituents selected from fluoro, C_{1-3} alkyl, $-O-C_{1-3}$ alkyl, $-N(C_{1-3} \text{ alkyl})_2$, $-NHCO-C_{1-3}$ alkyl, $-N(C_{1-3}\text{-alkyl})CO-C_{1-3}$ alkyl],
- 20 $-O-C_{3-6}$ cycloalkyl, $-O$ -oxetan-3-yl, $-O$ -tetrahydrofuran-3-yl, $-O$ -pyrrolidin-3-yl [which latter four groups are optionally substituted by one or more substituents selected from fluoro or C_{1-3} alkyl];
- A represents phenyl, 2-pyridyl, 5- or 6-membered heterocycloalkyl,
- 25 C_{3-7} cycloalkyl, C_{5-8} linear or branched alkyl (all of which groups are optionally substituted by one or more substituents selected from R^9); or

benzyl, pyridin-2-yl-methylene [which latter two groups are optionally substituted by one or more groups selected from C₁₋₇ alkyl (optionally substituted by one or more substituents selected from fluoro and -OR^{x2}), halo, -CN and/or -O-C₁₋₇ alkyl (optionally substituted by one or more fluoro atoms)];

R⁹ represents halo, -O-C₁₋₄ alkyl, C₁₋₄ alkyl, C₃₋₅ cycloalkyl, (which latter three groups are optionally substituted by one or more fluoro atoms.

17. Compounds according to any one of the preceding claims, namely
- 2-(2,6-Dichloro-phenylamino)-3H-imidazo[4,5-b]-pyridine-6-carboxylic acid (4-chloro-3-fluoro-phenyl)-amide;
- 2-(2,6-Dichloro-phenylamino)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxylic acid (trans-4-trifluoromethyl-cyclohexyl)-amide;
- N-(4-Bromophenyl)-2-(2,6-dichlorophenylamino)-5-methoxy-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- N-((1r,4r)-4-tert.-Butylcyclohexyl)-2-(2,6-dichlorophenylamino)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 2-(2,6-Dichloro-phenylamino)-5-methoxy-3-methyl-N-(4-trifluoromethyl-pyridin-2-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide formate;
- N-(4-tert-Butylcyclohexyl)-2-(2,6-dichlorophenylamino)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 2-(2,6-Dichlorophenylamino)-N-((1r,4r)-4-isopropylcyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 2-(2,6-Dichlorophenylamino)-N-((1r,4r)-4-isopropylcyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- N-(4-Bromophenyl)-2-(2,6-dichlorophenylamino)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 2-(2,6-Dichlorophenylamino)-3-methyl-N-octyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- (R)-2-(2,6-Dichlorophenylamino)-3-methyl-N-(oct-2-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 3-Benzyl-2-(2,6-dichlorophenylamino)-N-(4,4-dimethylcyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;

- 429 2-(2,6-Dichlorophenylamino)-N-(4,4-dimethylcyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 438 2-(2,6-Dichlorophenylamino)-N-(4-ethylcyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 439 2-(2,6-Dichlorophenylamino)-N-hexyl-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 448 2-(2,6-Dichlorophenylamino)-N-heptyl-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 449 (R)-2-(2,6-Dichlorophenylamino)-N-(hept-2-yl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 453 2-(2,6-Dichlorophenylamino)-3-methyl-N-((1r,4r)-4-methylcyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 454 2-(2,6-Dichlorophenylamino)-N-(3,3-dimethylcyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 459 2-(2,6-Dichlorophenylamino)-N-((1r,4r)-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 463 N-(4-Bromophenyl)-2-(2,6-dichlorophenylamino)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 466 2-(2-Chloro-6-fluorophenylamino)-N-(4,4-dimethylcyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 468 2-(2,6-Dichlorophenylamino)-3-methyl-N-(2-trifluoromethyl-benzyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 469 2-(2,6-Dichlorophenylamino)-N-(3,3-dimethylcyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 471 (S)-2-(2,6-Dichlorophenylamino)-3-methyl-N-(oct-2-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 473 2-(2,6-Dichlorophenylamino)-N-(hept-4-yl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 480 N-(4-Bromophenyl)-2-(2-chloro-6-fluorophenylamino)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 485 2-(2,6-Dichlorophenylamino)-N-(spiro[2.5]octan-6-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 486 2-(2-Chloro-6-fluorophenylamino)-3-methyl-N-((1r,4r)-4-methylcyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 497 (S)-2-(2,6-Dichlorophenylamino)-N-(hept-2-yl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;

- 505 2-(2,6-Dichlorophenylamino)-N-(4,4-dimethylcyclohexyl)-3-isopropyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 506 2-(2,6-Dichlorophenylamino)-3-methyl-N-(spiro[2.4]heptan-5-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 508 (R)-2-(2,6-Dichlorophenylamino)-N-(hexan-2-yl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 511 2-(2-Chloro-6-fluorophenylamino)-N-(4,4-dimethylcyclohexyl)-3-isopropyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 517 (R)-2-(2,6-Dichlorophenylamino)-N-(hex-2-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 523 3-(But-2-ynyl)-N-cyclohexyl-2-(2,6-dichlorophenylamino)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 527 (S)-2-(2,6-Dichlorophenylamino)-N-(hex-2-yl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 535 2-(2,6-Dichlorophenylamino)-N-((1r,4r)-4-(difluoromethyl)cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 541 2-(2-Chlorophenylamino)-N-(4,4-dimethylcyclohexyl)-3-isopropyl-3H-imidazo[4,5-b]pyridine-6-carboxamide hydrochloride;
- 560 (2-(2,6-Dichlorophenylamino)-N-((1r,4r)-4-(difluoromethyl)cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 771 N-(4-Bromophenyl)-2-(2-fluoro-6-trifluoromethylphenylamino)-5-(2,2-difluoro-ethoxy)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 772 N-(4-Bromo-phenyl)-2-(2-trifluoromethyl-phenylamino)-5-(2,2-difluoroethoxy)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 773 N-(4-Bromo-phenyl)-2-(2-fluoro-6-chloro-phenylamino)-5-(2,2-difluoroethoxy)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 774 N-(4-Bromo-phenyl)-2-(2-fluoro-6-trifluoromethyl-phenylamino)-5-(2,2-difluoroethoxy)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 775 N-(4-Bromo-phenyl)-2-(2-trifluoromethyl-phenylamino)-5-(2,2-difluoroethoxy)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 776 N-(4-Bromo-phenyl)-2-(2-fluoro-6-chloro-phenylamino)-5-(2,2-difluoroethoxy)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 777 2-(2-Chloro-6-trifluoromethyl-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 778 2-(2-Chloro-6-trifluoromethyl-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;

- 779 2-(2,3,5-Trichloro-pyridin-4-yl-amino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 780 2-(2-Fluoro-6-trifluoromethyl-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 781 2-(2-Fluoro-6-trifluoromethyl-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 782 2-(2-Trifluoromethyl-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 783 2-(2-Chloro-6-fluoro-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 784 2-(2-Trifluoromethyl-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 785 2-(2-Chloro-6-fluoro-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 786 2-(2-Bromo-4-methyl-pyridin-3-ylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 787 2-(3,6-Dichloro-2-fluoro-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 788 2-(2-Chloro-4-methyl-pyridin-3-ylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 789 2-(4-Trifluoromethyl-pyridin-3-ylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 790 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(tetrahydrofuran-3-yl-oxy)-N-((2-trifluoromethyl-phenyl)-methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 791 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(tetrahydrofuran-3-yl-oxy)-N-(4-bromo-phenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 792 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(tetrahydrofuran-3-yl-oxy)-N-(2,2,3,3,4,4,5,5,5-nonafluoro-pentyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 793 2-(2-Chloro-4,6-dimethyl-pyridin-3-ylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 794 2-(2,4-Dimethyl-pyridin-3-ylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 795 2-(2-Bromo-4-methyl-pyridin-3-ylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 796 2-(3,6-Dichloro-2-fluoro-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;

- 797 2-(2-Chloro-4-methyl-pyridin-3-ylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 798 2-(2-Trifluoromethyl-pyridin-3-ylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 799 2-(4-Trifluoromethyl-pyridin-3-ylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 800 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2-methoxy-ethoxy)-N-((2-trifluoromethyl-phenyl)-methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 801 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2-methoxy-ethoxy)-N-(4-bromo-phenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 802 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2-methoxy-ethoxy)-N-(2,2,3,3,4,4,5,5,5-nonafluoro-pentyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 803 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2-difluoro-ethoxy)-N-(4-trifluoromethyl-pyridin-2-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 804 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2-difluoro-ethoxy)-N-(4-bromo-phenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 805 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2-difluoro-ethoxy)-N-((2-trifluoromethyl-phenyl)-methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 806 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2-difluoro-ethoxy)-N-((3-trifluoromethyl-pyridin-2-yl)-methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 807 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2-difluoro-ethoxy)-N-(2,2,3,3,4,4,5,5,5-nonafluoro-pentyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 808 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2-methoxy-ethoxy)-N-(4-trifluoromethyl-pyridin-2-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 809 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2-(acetyl-methyl-amino)-ethoxy)-N-(2,2,3,3,4,4,5,5,5-nonafluoro-pentyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 810 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2-(acetyl-methyl-amino)-ethoxy)-N-(4-bromo-phenyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 811 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2-(acetyl-methyl-amino)-ethoxy)-N-(2,2,3,3,4,4,5,5,5-nonafluoro-pentyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 812 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2-methoxy-ethoxy)-N-(4-bromo-phenyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 813 2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2,2-trifluoro-ethoxy)-N-((3-trifluoromethyl-pyridin-2-yl)-methyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;

- 814 2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2,2-trifluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 815 2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2,2-trifluoro-ethoxy)-N-(4-trifluoromethyl-pyridin-2-yl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 816 2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2,2-trifluoro-ethoxy)-N-(4-bromo-phenyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 817 2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(4-trifluoromethyl-pyridin-2-yl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 818 2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(4-bromo-phenyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 819 2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2,2-trifluoro-ethoxy)-N-(4-trifluoromethyl-pyridin-2-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 820 2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2,2-trifluoro-ethoxy)-N-(4-bromo-phenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 821 2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(4-trifluoromethyl-pyridin-2-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 822 2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(4-bromo-phenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 823 2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 824 2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(2-trifluoromethyl-benzyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 825 2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 826 2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2-difluoro-ethoxy)-N-((3-trifluoromethyl-pyridin-2-yl)-methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 827 2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2,2-trifluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 828 2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2,2-trifluoro-ethoxy)-N-(2-trifluoromethyl-benzyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 829 2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2,2-trifluoro-ethoxy)-N-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 830 2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2,2-trifluoro-ethoxy)-N-((3-trifluoromethyl-pyridin-2-yl)-methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 831 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2-fluoro-ethoxy)-N-(4-trifluoromethyl-pyridin-2-yl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;

- 832 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2-fluoro-ethoxy)-N-(4-bromo-phenyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 833 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2-fluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 834 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2-fluoro-ethoxy)-N-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 835 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2-fluoro-ethoxy)-N-((3-trifluoromethyl-pyridin-2-yl)-methyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 836 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2-difluoro-ethoxy)-N-(4-trifluoromethyl-pyridin-2-yl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 837 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2-difluoro-ethoxy)-N-(4-bromo-phenyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 838 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 839 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2-difluoro-ethoxy)-N-(2-trifluoromethyl-benzyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 840 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2-difluoro-ethoxy)-N-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 841 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2-difluoro-ethoxy)-N-((3-trifluoromethyl-pyridin-2-yl)-methyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 842 2-(3,5-Dichloro-pyridin-4-ylamino)-5-ethoxy-N-(trans-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 843 2-(3,5-Dichloro-pyridin-4-ylamino)-5-ethoxy-N-((3-trifluoromethyl-pyridin-2-yl)-methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 844 2-(3,5-Dichloro-pyridin-4-ylamino)-5-ethoxy-N-(2,2,3,3,4,4,5,5,5-nonafluoro-pentyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 845 2-(3,5-Dichloro-pyridin-4-ylamino)-5-ethoxy-N-(4-trifluoromethyl-pyridin-2-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 846 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(tetrahydrofuran-3-yl-oxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 847 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(tetrahydrofuran-3-yl-oxy)-N-((3-trifluoromethyl-pyridin-2-yl)-methyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 848 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(tetrahydrofuran-3-yl-oxy)-N-(4-bromo-phenyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 849 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(tetrahydrofuran-3-yl-oxy)-N-(2,2,3,3,4,4,5,5,5-nonafluoro-pentyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;

- 850 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2,2-trifluoro-ethoxy)-N-(2,2,3,3,4,4,5,5,5-nonafluoro-pentyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 851 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2,2-trifluoro-ethoxy)-N-((3-trifluoromethyl-pyridin-2-yl)-methyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 852 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2,2-trifluoro-ethoxy)-N-(4-trifluoromethyl-pyridin-2-yl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 853 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2,2-trifluoro-ethoxy)-N-(2-trifluoromethyl-benzyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 854 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2,2-trifluoro-ethoxy)-N-(2,2,3,3,4,4,5,5,5-nonafluoro-pentyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 855 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2,2-trifluoro-ethoxy)-N-((3-trifluoromethyl-pyridin-2-yl)-methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 856 2-(3,5-Dichloro-pyridin-4-ylamino)-5-ethoxy-N-(4-bromo-phenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 857 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2,2-trifluoro-ethoxy)-N-(4-trifluoromethyl-pyridin-2-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 858 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2,2-trifluoro-ethoxy)-N-(4-bromo-phenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 859 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2,2-trifluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 860 2-(2,6-Dichloro-phenylamino)-5-methoxy-N-((3-trifluoromethyl-pyridin-2-yl)-methyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 861 2-(2,6-Dichloro-phenylamino)-5-methoxy-N-(2-trifluoromethyl-benzyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 862 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 863 2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 864 2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2-dimethylamino-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 865 2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2-dimethylamino-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 866 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2-methoxy-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 867 2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2-methoxy-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;

- 868 2-(3,5-Dichloro-pyridin-4-ylamino)-5-(2-methoxy-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 869 2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2-methoxy-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 870 2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2-fluoro-ethoxy)-N-(trans-4-trifluoromethyl-cyclohexyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 871 2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(2-trifluoromethyl-benzyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 872 2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2-difluoro-ethoxy)-N-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 873 2-(2,6-Dichloro-4-fluoro-phenylamino)-5-(2,2,2-trifluoro-ethoxy)-N-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide.

18. Compounds according to any one of the preceding claims or a pharmaceutically-acceptable salt thereof, for use as a pharmaceutical.

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19. Compounds according to any one of the preceding claims or a pharmaceutically-acceptable salt thereof, for use in the treatment of asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, inflammatory bowel disease, irritable bowel syndrome, pain, inflammatory pain, fever, migraine, headache, low back pain, fibromyalgia, a myofascial disorder, a viral infection, a bacterial infection, a fungal infection, dysmenorrhea, a burn, a surgical or dental procedure, a malignancy, hyperprostaglandin E syndrome, classic Bartter syndrome, atherosclerosis, gout, arthritis, osteoarthritis, juvenile arthritis, rheumatoid arthritis, rheumatic fever, ankylosing spondylitis, Hodgkin's disease, systemic lupus erythematosus, vasculitis, pancreatitis, nephritis, bursitis, conjunctivitis, iritis, scleritis, uveitis, wound healing, dermatitis, eczema, psoriasis, stroke, diabetes mellitus, a neurodegenerative disorder, an autoimmune disease, an allergic disorder, rhinitis, an ulcer, coronary heart disease, sarcoidosis, any other disease with an inflammatory component, osteoporosis, osteoarthritis, Paget's disease, a periodontal disease or a cancer.

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2009/062425

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D471/04 A61K31/4188 A61P11/00 A61P29/00

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

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 practical, search terms used)

EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	R. D. CARPENTER ET AL.: "Carbodiimide-based benzimidazole library method" JOURNAL OF COMBINATORIAL CHEMISTRY, vol. 8, no. 6, 27 October 2006 (2006-10-27), pages 907-914, XP002557183 * Scheme 4: Compounds of formula 10e & Figure 1 *	1-19
A	WO 00/68213 A (AVENTIS PHARMA LTD.) 16 November 2000 (2000-11-16) claims 1-30; tables 1-3 ----- -/--	1-19



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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- "E" earlier document but published on or after the international filing date
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- "O" document referring to an oral disclosure, use, exhibition or other means
- "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

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"&" document member of the same patent family

Date of the actual completion of the international search

26 November 2009

Date of mailing of the international search report

10/12/2009

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INTERNATIONAL SEARCH REPORT

International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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