

Novel Compounds

The present invention relates to inhibitors of the Wnt signalling pathways of general formula (I) as described and defined herein, to methods of preparing said compounds, to intermediate compounds
5 useful for preparing said compounds, to pharmaceutical compositions and combinations comprising said compounds and to the use of said compounds for manufacturing a pharmaceutical composition for the treatment or prophylaxis of a disease, in particular of a hyper-proliferative disorder, as a sole agent or in combination with other active ingredients.

10 BACKGROUND

The Wnt signaling pathways are a group of signal transduction pathways made of proteins that pass signals from outside of a cell through cell surface receptors to the inside of the cell.

Wnt proteins are secreted glycoproteins with a molecular weight in the range of 39-46 kD, whereby
15 in total 19 different members of the Wnt protein family are known (McMahon et al., Trends Genet. 8, 1992, 236 – 242). They are the ligands of so-called Frizzled receptors, which form a family of seven-transmembrane spanning receptors comprising 10 distinct subtypes. A certain Wnt ligand can thereby activate several different Frizzled receptor subtypes and vice versa a particular Frizzled receptor can be activated by different Wnt protein subtypes (Huang et al., Genome Biol. 5, 2004,
20 234.1 – 234.8).

Binding of a Wnt to its receptor can activate two different signaling cascades, one is called the non-canonical pathway, which involves CamK II and PKC (Kuhl et al., Trends Genet. 16 (7), 2000, 279 – 283). The other, the so-called canonical pathway (Tamai et al., Mol. Cell 13, 2004, 149-156) regulates the concentration of the transcription factor β -catenin.

25 In the case of non-stimulated canonical Wnt signaling, β -catenin is captured by a destruction complex consisting of adenomatous polyposis coli (APC), glycogen synthase kinase 3- β (GSK-3 β), Axin-1 or -2 and Casein Kinase 1 α . Captured β -catenin is then phosphorylated, ubiquitinated and subsequently degraded by the proteasome.

However, when a canonical Wnt activates the membrane complex of a Frizzled receptor and its
30 Lipoprotein 5 or 6 (LRP 5/6) co-receptor, this leads to the recruitment of dishevelled (Dvl) by the receptors and subsequent phosphorylation of LRP 5/6, followed by binding of Axin-1 or Axin-2 to the membrane complex as well. The deprivation of Axin from the β -catenin destruction complex leads to the disassembly of the latter and β -catenin can reach the nucleus, where it together with TCF and LEF transcription factors and other transcriptional coregulators like Pygopus, BCL9/Legless, CDK8 module

of Mediator and TRRAP initiates transcription of genes with promoters containing TCF elements (Najdi, J. Carcinogenesis 2011; 10:5).

The Wnt signaling cascade can be constitutively activated by mutations in genes involved in this pathway. This is especially well documented for mutations of the APC and axin genes, and also for mutations of the β -catenin phosphorylation sites, all of which are important for the development of colorectal and hepatocellular carcinomas (Polakis, EMBO J., 31, 2012, 2737-2746).

The Wnt signaling cascade has important physiological roles in embryonal development and tissue homeostasis the latter especially for hair follicles, bones and the gastrointestinal tract. Deregulation of the Wnt pathway can activate in a cell and tissue specific manner a number of genes known to be important in carcinogenesis. Among them are c-myc, cyclin D1, Axin-2 and metalloproteases (He et al., Science 281, 1998, 1509-1512).

Deregulated Wnt activity can drive cancer formation, increased Wnt signaling can thereby be caused through autocrine Wnt signaling, as shown for different breast, ovarian, prostate and lung carcinomas as well as for various cancer cell lines (Bafico, Cancer Cell 6, 2004, 497-506; Yee, Mol. Cancer 9, 2010, 162-176; Nguyen, Cell 138, 2009, 51-62).

For cancer stem cells (CSCs) it was shown that they have increased Wnt signaling activity and that its inhibition can reduce the formation of metastases (Vermeulen et al., Nature Cell Biol. 12 (5), 2010, 468-476; Polakis, EMBO J. 31, 2012, 2737-2746; Reya, Nature, 434, 2005, 843-850).

Furthermore, there is a lot of evidence supporting an important role of Wnt signaling in cardiovascular diseases. One aspect thereby is heart failure and cardiac hypertrophy where deletion of Dapper-1, an activator of the canonical β -catenin Wnt pathway has been shown to reduce functional impairment and hypertrophy (Hagenmueller, M. et al.: *Dapper-1 induces myocardial remodeling through activation of canonical wnt signaling in cardiomyocytes*; Hypertension, 61 (6), 2013, 1177-1183).

Additional support for a role of Wnt signaling in heart failure comes from animal experimental models and clinical studies with patients, in which it was shown, that the level of secreted frizzled related protein 3 (sFRP3) is associated with the progression of heart failure (Askevold, E.T. et al.: *The cardiokine secreted Frizzled-related protein 3, a modulator of Wnt signaling in clinical and experimental heart failure*; J. Intern Med., 2014 (doi:10.1111/joim.12175)). For cardiac remodeling and infarct healing the expression of Fzd2 receptors on myofibroblasts migrating into the infarct area

has been demonstrated (Blankesteyn, W.M. et al.: *A homologue of Drosophila tissue polarity gene frizzled is expressed in migrating myofibroblasts in the infarcted rat heart*; Nat. Med. 3, 1997, 541-544). The manifold effects of Wnt signaling in heart failure, fibrosis and arrhythmias have been recently reviewed by Dawson et al. (Dawson, K. et al.: *Role of the Wnt-Frizzled system in cardiac pathophysiology: a rapidly developing, poorly understood area with enormous potential*; J. Physiol. 591 (6), 2013, 1409-1432).

For the vasculature, effects of Wnt signaling could be shown as well, mainly in respect to restenosis via enhancement of vascular smooth muscle cell proliferation (Tsaousi, A. et al.: *Wnt4/b-catenin signaling induces VSMC proliferation and is associated with intimal thickening*; Circ. Res. 108, 2011, 427-436).

Besides the effects on heart and vasculature, dysregulated Wnt signaling is also an important component in chronic kidney disease as could be shown for upregulated Wnt activity in immune cells from corresponding patients (Al-Chaqqmaqchi, H.A. et al.: *Activation of Wnt/b-catenin pathway in monocytes derived from chronic kidney disease patients*; PLoS One, 8 (7), 2013, doi: 10.1371) and altered levels of secreted Wnt inhibitor in patient sera (de Oliveira, R.B. et al.: *Disturbances of Wnt/b-catenin pathway and energy metabolism in early CKD: effect of phosphate binders*; Nephrol. Dial. Transplant. (2013) 28 (10): 2510-2517).

In adults, mis-regulation of the Wnt pathway also leads to a variety of abnormalities and degenerative diseases. An LRP mutation has been identified that causes increased bone density at defined locations such as the jaw and palate (Boyden LM et al.: *High bone density due to a mutation in LDL-receptor-related protein 5*; N Engl J Med. 2002 May 16; 346(20):1513-21, Gong Y, et al.: *LDL receptor-related protein 5 (LRP5) affects bone accrual and eye development*; Cell 2001; 107:513-23). The mutation is a single amino-acid substitution that makes LRP5 insensitive to Dkk-mediated Wnt pathway inhibition, indicating that the phenotype results from overactive Wnt signaling in the bone.

Recent reports have suggested that Wnt signaling is an important regulator for adipogenesis or insulin secretion and might be involved in the pathogenesis of type 2 diabetes. It has been shown that expression of the Wnt5B gene was detectable in several tissues, including adipose, pancreas, and liver. Subsequent in vitro experiments identified the fact that expression of the Wnt5b gene was increased at an early phase of adipocyte differentiation in mouse 3T3-L1 cells. Furthermore, overexpression of the Wnt5b gene in preadipocytes resulted in the promotion of adipogenesis and the enhancement of adipocytokine-gene expression. These results indicate that the Wnt5B gene may contribute to conferring susceptibility to type 2 diabetes and may be involved in the pathogenesis of this disease through the regulation of adipocyte function (Kanazawa A, et al.: *Association of the gene encoding wingless-type mammary tumor virus integration-site family member 5B (Wnt5B) with type 2 diabetes*; Am J Hum Genet. 2004 Nov; 75(5):832-43)

Accordingly, identification of methods and compounds that modulate the Wnt - dependent cellular responses may offer an avenue for regulating physiological functions and therapeutic treatment of diseases associated with aberrant activity of the pathways.

Inhibitors of the Wnt signalling pathways are disclosed e.g. in US2008-0075714(A1), US2011-0189097(A1), US2012-0322717(A9), WO2010/014948(A1), WO2012/088712(A1), WO2012/140274(A2,A3) and WO2013/093508(A2).

WO 2005/084368(A2) discloses heteroalkyl-substituted biphenyl-4-carboxylic acid arylamide analogues and the use of such compounds for treating conditions related to capsaicin receptor activation, for identifying other agents that bind to capsaicin receptor, and as probes for the detection and localization of capsaicin receptors. The structural scope of the compounds claimed in claim 1 is huge, whereas the structural space spanned by the few examples is much smaller. There is no specific example which is covered by the formula (I) as described and defined herein.

WO 2000/55120(A1) and WO 2000/07991 (A1) disclose amide derivatives and their use for the treatment of cytokine mediated diseases. The few specific examples disclosed in WO 2000/55120(A1) and WO 2000/07991 (A1) are not covered by the formula (I) as described and defined herein.

WO 1998/28282 (A2) discloses oxygen or sulfur containing heteroaromatics as factor Xa inhibitors. The specific examples disclosed in WO 1998/28282 (A2) are not covered by the formula (I) as described and defined herein.

WO 2011/035321 (A1) discloses methods of treating Wnt/Frizzled-related diseases, comprising administering niclosamide compounds. According to the specification of WO 2011/035321 (A1) libraries of FDA-approved drugs were examined for their utility as Frizzled internalization modulators, employing a primary imaged-based GFP-fluorescence assay that used Frizzled1 endocytosis as the readout. It was discovered that the antihelminthic niclosamide, a drug used for the treatment of tapeworms, promotes Frizzled1 internalization (endocytosis), down regulates Dishevelled-2 protein, and inhibits Wnt3A-stimulated β -catenin stabilization and LEF/TCF reporter activity. The specific examples disclosed in WO 2011/035321 (A1) are not covered by the formula (I) as described and defined herein. Additionally, WO 2011/035321 (A1) does neither teach nor suggest the compounds

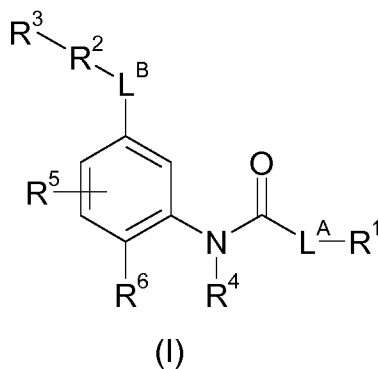
of formula (I) as described and defined herein. The same is true for the related publication WO 2004/006906 (A2) which discloses a method for treating a patient having a cancer or other neoplasm by administering to the patient a niclosamide.

JP 2010-138079 (A) relates to amide derivatives exhibiting insecticidal effects. The specific examples disclosed in JP 2010-138079 (A) are not covered by the formula (I) as described and defined herein.

WO 2004/022536 (A1) relates to heterocyclic compounds that inhibit phosphodiesterase type 4 (PDE 4) and their use for treating inflammatory conditions, diseases of the central nervous system and insulin resistant diabetes. The specific examples disclosed in WO 2004/022536 (A1) are not covered by the formula (I) as described and defined herein.

SUMMARY

The present invention relates to compounds of general formula (I) :



in which :

L^A represents a methylene or ethylene group, said methylene or ethylene group being optionally substituted, one or more times, identically or differently, with a substituent selected from:

hydroxy-, cyano-, C_1 - C_3 -alkyl-, C_1 - C_3 -alkoxy-, halo- C_1 - C_3 -alkyl-, hydroxy- C_1 - C_3 -alkyl-, halo- C_1 - C_3 -alkoxy-, C_3 - C_7 -cycloalkyl-, 3- to 10-membered heterocycloalkyl-; or, when two substituents are present at the same carbon atom, the two substituents, together with the carbon atom they are attached to, may form a C_3 - C_6 -cycloalkyl- or 3- to 6-membered heterocycloalkyl- ring; wherein said ring is optionally substituted one or more times, identically or differently, with a substituent selected from: halo-, hydroxy-, cyano-, C_1 - C_3 -alkyl-, C_1 - C_3 -alkoxy-;

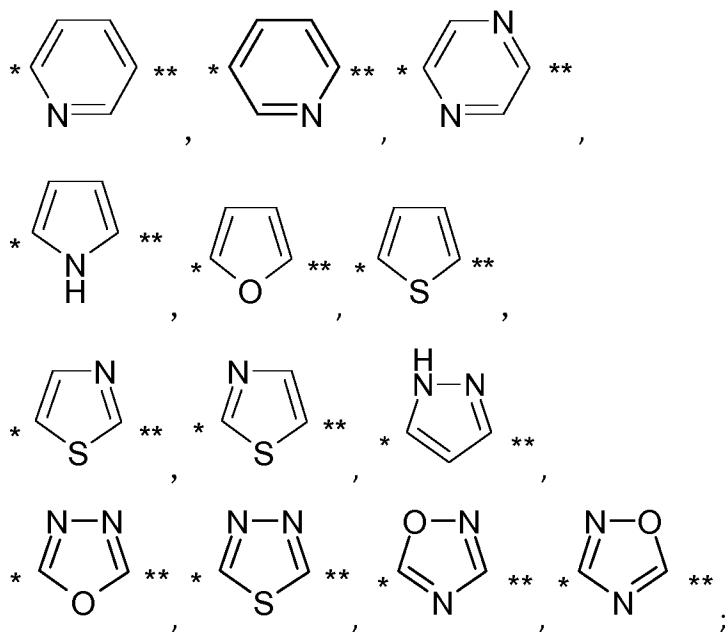
L^B represents $*N(H)-C(=O)**$ or $*C(=O)-N(H)**$;

wherein " * " indicates the point of attachment to R^2 , and " ** " indicates the point of attachment to the phenyl group;

R^1 represents a group selected from:

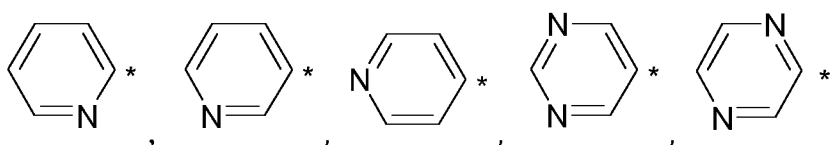
5 5- to 8-membered heterocycloalkyl-, 4- to 10-membered heterocycloalkenyl-, aryl-, heteroaryl-, and -N(R⁷)-(C₁-C₆-alkyl); wherein said 5- to 8-membered heterocycloalkyl-, 4- to 10-membered heterocycloalkenyl-, aryl-, heteroaryl-, and -N(R⁷)-(C₁-C₆-alkyl) group is optionally substituted, one or more times, identically or differently, with a substituent selected from: halo-, hydroxy-, cyano-,
10 C₁-C₃-alkyl-, C₁-C₃-alkoxy-, halo-C₁-C₃-alkyl-, hydroxy-C₁-C₃-alkyl-, halo-C₁-C₃-alkoxy-, C₃-C₇-cycloalkyl-;

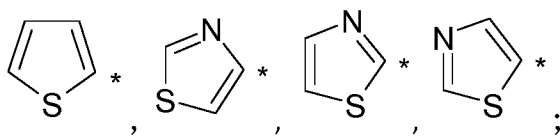
R^2 represents a group selected from:



wherein " * " indicates the point of attachment to R³, and " ** " indicates the point of attachment to L^B; wherein said group is optionally substituted, one or more times, identically or differently, with a C₁-C₃-alkyl- group;

R³ represents a group selected from:





wherein " * " indicates the point of attachment to R²;

wherein said group is optionally substituted one time with a substituent selected from:

halo-, hydroxy-, -N(R⁹)(R¹⁰), -N(H)C(=O)R⁹, cyano-, nitro-, C₁-C₃-alkyl-, C₁-C₃-alkoxy-, halo-C₁-C₃-alkyl-, hydroxy-C₁-C₃-alkyl-, amino-C₁-C₃-alkyl-, halo-C₁-C₃-alkoxy-;

R⁴ represents a hydrogen atom or a C₁-C₃-alkyl- group;

R⁵ represents a hydrogen atom or a halogen atom or a group selected from: cyano-, C₁-C₃-alkyl-, C₁-C₃-alkoxy-;

R⁶ represents a group selected from:

C₁-C₆-alkyl-, C₂-C₆-alkenyl-, C₂-C₆-alkynyl-,

C₁-C₆-alkoxy-, C₃-C₆-cycloalkoxy-, halo-, hydroxy-, cyano-, aryl-,

heteroaryl-, (3- to 10-membered heterocycloalkyl)-O-,

-N(R⁹)(R¹⁰), -C(=O)-O-C₁-C₄-alkyl, -C(=O)-N(R⁹)(R¹⁰), R⁹-S-, R⁹-S(=O)-, R⁹-S(=O)₂-;

said C₁-C₆-alkyl-, C₂-C₆-alkenyl-, C₂-C₆-alkynyl-, aryl-, heteroaryl-, and C₁-C₆-alkoxy- group being optionally substituted, one or more times, identically or differently, with a substituent selected from: halo-, cyano-, nitro-, hydroxy-, C₁-C₃-alkyl-, C₁-C₃-alkoxy-, halo-C₁-C₃-alkoxy-, hydroxy-C₁-C₃-alkoxy-, C₁-C₃-alkoxy-C₂-C₃-alkoxy-,

C₃-C₇-cycloalkyl-, C₄-C₇-cycloalkenyl-,

3- to 10-membered heterocycloalkyl-, 4- to 10-membered heterocycloalkenyl-,

aryl-, heteroaryl-, -C(=O)R⁹, -C(=O)O-(C₁-C₄-alkyl), -OC(=O)-R⁹, -N(H)C(=O)R⁹, -N(R¹⁰)C(=O)R⁹,

-N(H)C(=O)NR¹⁰R⁹, -N(R¹¹)C(=O)NR¹⁰R⁹, -N(H)R⁹, -NR¹⁰R⁹,

-C(=O)N(H)R⁹, -C(=O)NR¹⁰R⁹, R⁹-S-, R⁹-S(=O)-, R⁹-S(=O)₂-,

-N(H)S(=O)R⁹, -N(R¹⁰)S(=O)R⁹, -S(=O)N(H)R⁹, -S(=O)NR¹⁰R⁹,

-N(H)S(=O)₂R⁹, -N(R⁹)S(=O)₂R¹⁰, -S(=O)₂N(H)R⁹, -S(=O)₂NR¹⁰R⁹,

-S(=O)(=NR¹⁰)R⁹, -N=S(=O)(R¹⁰)R⁹;

R⁷ represents a hydrogen atom or a C₁-C₃-alkyl- or C₁-C₃-alkoxy-C₁-C₃-alkyl- group;

R⁹, R¹⁰, R¹¹

represent, independently from each other, a hydrogen atom or a C₁-C₃-alkyl- or C₁-C₃-alkoxy-C₁-C₃-alkyl- group;

or

- 5 R⁹R¹⁰ together with the atom or the group of atoms they are attached to, form a 3- to 10-membered heterocycloalkyl- or 4- to 10-membered heterocycloalkenyl- group;

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

- 10 The present invention further relates to a pharmaceutical composition comprising a compound of formula (I), *supra*.

The present invention further relates to the use of a compound of formula (I), *supra*, for the prophylaxis or treatment of a disease.

- The present invention further relates to the use of a compound of formula (I), *supra*, for the
15 preparation of a medicament for the prophylaxis or treatment of a disease.

The present invention further relates to methods of preparing a compound of formula (I), *supra*.

The present invention further relates to intermediate compounds useful for preparing a compound of formula (I), *supra*.

20 DETAILED DESCRIPTION

The terms as mentioned in the present text have preferably the following meanings :

- The term “halogen atom” or “halo-” is to be understood as meaning a fluorine, chlorine, bromine or
25 iodine atom.

- The term “C₁-C₆-alkyl” is to be understood as preferably meaning a linear or branched, saturated, monovalent hydrocarbon group having 1, 2, 3, 4, 5 or 6 carbon atoms, *e.g.* a methyl, ethyl, propyl, butyl, pentyl, hexyl, *iso*-propyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, *iso*-pentyl, 2-methylbutyl, 1-
30 methylbutyl, 1-ethylpropyl, 1,2-dimethylpropyl, *neo*-pentyl, 1,1-dimethylpropyl, 4-methylpentyl, 3-methylpentyl, 2-methylpentyl, 1-methylpentyl, 2-ethylbutyl, 1-ethylbutyl, 3,3-dimethylbutyl, 2,2-dimethylbutyl, 1,1-dimethylbutyl, 2,3-dimethylbutyl, 1,3-dimethylbutyl, or 1,2-dimethylbutyl group, or an isomer thereof. Particularly, said group has 1, 2, 3 or 4 carbon atoms (“C₁-C₄-alkyl”), *e.g.* a methyl, ethyl, propyl, butyl, *iso*-propyl, *iso*-butyl, *sec*-butyl, *tert*-butyl group, more particularly 1, 2 or
35 3 carbon atoms (“C₁-C₃-alkyl”), *e.g.* a methyl, ethyl, *n*-propyl- or *iso*-propyl group.

The term "halo-C₁-C₆-alkyl" is to be understood as preferably meaning a linear or branched, saturated, monovalent hydrocarbon group in which the term "C₁-C₆-alkyl" is defined *supra*, and in which one or more of the hydrogen atoms is replaced, identically or differently, by a halogen atom. Particularly, said halogen atom is F. Said halo-C₁-C₆-alkyl group is, for example, -CF₃, -CHF₂, -CH₂F, -CF₂CF₃, or -CH₂CF₃.

The term "C₁-C₆-alkoxy" is to be understood as preferably meaning a linear or branched, saturated, monovalent group of formula -O-(C₁-C₆-alkyl), in which the term "C₁-C₆-alkyl" is defined *supra*, e.g. a methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *iso*-butoxy, *tert*-butoxy, *sec*-butoxy, pentoxy, *iso*-pentoxy, or *n*-hexoxy group, or an isomer thereof.

The term "halo-C₁-C₆-alkoxy" is to be understood as preferably meaning a linear or branched, saturated, monovalent C₁-C₆-alkoxy group, as defined *supra*, in which one or more of the hydrogen atoms is replaced, identically or differently, by a halogen atom. Particularly, said halogen atom is F. Said halo-C₁-C₆-alkoxy group is, for example, -OCF₃, -OCHF₂, -OCH₂F, -OCF₂CF₃, or -OCH₂CF₃.

The term "C₁-C₆-alkoxy-C₁-C₆-alkyl" is to be understood as preferably meaning a linear or branched, saturated, monovalent C₁-C₆-alkyl group, as defined *supra*, in which one or more of the hydrogen atoms is replaced, identically or differently, by a C₁-C₆-alkoxy group, as defined *supra*, e.g. methoxyalkyl, ethoxyalkyl, propyloxyalkyl, *iso*-propoxyalkyl, butoxyalkyl, *iso*-butoxyalkyl, *tert*-butoxyalkyl, *sec*-butoxyalkyl, pentyloxyalkyl, *iso*-pentyloxyalkyl, hexyloxyalkyl group, or an isomer thereof.

The term "halo-C₁-C₆-alkoxy-C₁-C₆-alkyl" is to be understood as preferably meaning a linear or branched, saturated, monovalent C₁-C₆-alkoxy-C₁-C₆-alkyl group, as defined *supra*, in which one or more of the hydrogen atoms is replaced, identically or differently, by a halogen atom. Particularly, said halogen atom is F. Said halo-C₁-C₆-alkoxy-C₁-C₆-alkyl group is, for example, -CH₂CH₂OCF₃, -CH₂CH₂OCHF₂, -CH₂CH₂OCH₂F, -CH₂CH₂OCF₂CF₃, or -CH₂CH₂OCH₂CF₃.

The term "C₁-C₆-alkoxy-C₂-C₆-alkoxy" is to be understood as preferably meaning a saturated, monovalent C₂-C₆-alkoxy group, as defined *supra*, in which one of the hydrogen atoms is replaced by a C₁-C₆-alkoxy group, as defined *supra*, e.g. methoxyalkoxy, ethoxyalkoxy, pentoxyalkoxy, hexoxyalkoxy group or methoxyethoxy, ethoxyethoxy, *iso*-propoxyhexoxy group, in which the term "alkoxy" is defined *supra*, or an isomer thereof.

The term “C₂-C₆-alkenyl” is to be understood as preferably meaning a linear or branched, monovalent hydrocarbon group, which contains one or more double bonds, and which has 2, 3, 4, 5 or 6 carbon atoms, particularly 2 or 3 carbon atoms (“C₂-C₃-alkenyl”), it being understood that in the case in which said alkenyl group contains more than one double bond, then said double bonds may be isolated from, or conjugated with, each other. Said alkenyl group is, for example, a vinyl, allyl, (E)-2-methylvinyl, (Z)-2-methylvinyl, homoallyl, (E)-but-2-enyl, (Z)-but-2-enyl, (E)-but-1-enyl, (Z)-but-1-enyl, pent-4-enyl, (E)-pent-3-enyl, (Z)-pent-3-enyl, (E)-pent-2-enyl, (Z)-pent-2-enyl, (E)-pent-1-enyl, (Z)-pent-1-enyl, hex-5-enyl, (E)-hex-4-enyl, (Z)-hex-4-enyl, (E)-hex-3-enyl, (Z)-hex-3-enyl, (E)-hex-2-enyl, (Z)-hex-2-enyl, (E)-hex-1-enyl, (Z)-hex-1-enyl, *iso*-propenyl, 2-methylprop-2-enyl, 1-methylprop-2-enyl, 2-methylprop-1-enyl, (E)-1-methylprop-1-enyl, (Z)-1-methylprop-1-enyl, 3-methylbut-3-enyl, 2-methylbut-3-enyl, 1-methylbut-3-enyl, 3-methylbut-2-enyl, (E)-2-methylbut-2-enyl, (Z)-2-methylbut-2-enyl, (E)-1-methylbut-2-enyl, (Z)-1-methylbut-2-enyl, (E)-3-methylbut-1-enyl, (Z)-3-methylbut-1-enyl, (E)-2-methylbut-1-enyl, (Z)-2-methylbut-1-enyl, (E)-1-methylbut-1-enyl, (Z)-1-methylbut-1-enyl, 1,1-dimethylprop-2-enyl, 1-ethylprop-1-enyl, 1-propylvinyl, 1-isopropylvinyl, 4-methylpent-4-enyl, 3-methylpent-4-enyl, 2-methylpent-4-enyl, 1-methylpent-4-enyl, 4-methylpent-3-enyl, (E)-3-methylpent-3-enyl, (Z)-3-methylpent-3-enyl, (E)-2-methylpent-3-enyl, (Z)-2-methylpent-3-enyl, (E)-1-methylpent-3-enyl, (Z)-1-methylpent-3-enyl, (E)-4-methylpent-2-enyl, (Z)-4-methylpent-2-enyl, (E)-3-methylpent-2-enyl, (Z)-3-methylpent-2-enyl, (E)-2-methylpent-2-enyl, (Z)-2-methylpent-2-enyl, (E)-1-methylpent-2-enyl, (Z)-1-methylpent-2-enyl, (E)-4-methylpent-1-enyl, (Z)-4-methylpent-1-enyl, (E)-3-methylpent-1-enyl, (Z)-3-methylpent-1-enyl, (E)-2-methylpent-1-enyl, (Z)-2-methylpent-1-enyl, (E)-1-methylpent-1-enyl, (Z)-1-methylpent-1-enyl, 3-ethylbut-3-enyl, 2-ethylbut-3-enyl, 1-ethylbut-3-enyl, (E)-3-ethylbut-2-enyl, (Z)-3-ethylbut-2-enyl, (E)-2-ethylbut-2-enyl, (Z)-2-ethylbut-2-enyl, (E)-1-ethylbut-2-enyl, (Z)-1-ethylbut-2-enyl, (E)-3-ethylbut-1-enyl, (Z)-3-ethylbut-1-enyl, 2-ethylbut-1-enyl, (E)-1-ethylbut-1-enyl, (Z)-1-ethylbut-1-enyl, 2-propylprop-2-enyl, 1-propylprop-2-enyl, 2-isopropylprop-2-enyl, 1-isopropylprop-2-enyl, (E)-2-propylprop-1-enyl, (Z)-2-propylprop-1-enyl, (E)-1-propylprop-1-enyl, (Z)-1-propylprop-1-enyl, (E)-2-isopropylprop-1-enyl, (Z)-2-isopropylprop-1-enyl, (E)-1-isopropylprop-1-enyl, (Z)-1-isopropylprop-1-enyl, (E)-3,3-dimethylprop-1-enyl, (Z)-3,3-dimethylprop-1-enyl, 1-(1,1-dimethylethyl)ethenyl, buta-1,3-dienyl, penta-1,4-dienyl, hexa-1,5-dienyl, or methylhexadienyl group. Particularly, said group is vinyl or allyl.

The term “C₂-C₆-alkynyl” is to be understood as preferably meaning a linear or branched, monovalent hydrocarbon group which contains one or more triple bonds, and which contains 2, 3, 4, 5 or 6 carbon atoms, particularly 2 or 3 carbon atoms (“C₂-C₃-alkynyl”). Said C₂-C₆-alkynyl group is, for

example, ethynyl, prop-1-ynyl, prop-2-ynyl, but-1-ynyl, but-2-ynyl, but-3-ynyl, pent-1-ynyl, pent-2-ynyl, pent-3-ynyl, pent-4-ynyl, hex-1-ynyl, hex-2-ynyl, hex-3-ynyl, hex-4-ynyl, hex-5-ynyl, 1-methylprop-2-ynyl, 2-methylbut-3-ynyl, 1-methylbut-3-ynyl, 1-methylbut-2-ynyl, 3-methylbut-1-ynyl, 1-ethylprop-2-ynyl, 3-methylpent-4-ynyl, 2-methylpent-4-ynyl, 1-methylpent-4-ynyl, 2-methylpent-3-ynyl, 1-methylpent-3-ynyl, 4-methylpent-2-ynyl, 1-methylpent-2-ynyl, 4-methylpent-1-ynyl, 3-methylpent-1-ynyl, 2-ethylbut-3-ynyl, 1-ethylbut-3-ynyl, 1-ethylbut-2-ynyl, 1-propylprop-2-ynyl, 1-isopropylprop-2-ynyl, 2,2-dimethylbut-3-ynyl, 1,1-dimethylbut-3-ynyl, 1,1-dimethylbut-2-ynyl, or 3,3-dimethylbut-1-ynyl group. Particularly, said alkynyl group is ethynyl, prop-1-ynyl, or prop-2-ynyl.

The term “C₃-C₇-cycloalkyl” is to be understood as meaning a saturated, monovalent, monocyclic hydrocarbon ring which contains 3, 4, 5, 6 or 7 carbon atoms. Said C₃-C₇-cycloalkyl group is for example a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl ring. Particularly, said ring contains 3, 4, 5 or 6 carbon atoms (“C₃-C₆-cycloalkyl”).

The term “C₄-C₈-cycloalkenyl” is to be understood as preferably meaning a monovalent, monocyclic hydrocarbon ring which contains 4, 5, 6, 7 or 8 carbon atoms and one or two double bonds, in conjugation or not, as the size of said cycloalkenyl ring allows. Particularly, said ring contains 4, 5 or 6 carbon atoms (“C₄-C₆-cycloalkenyl”). Said C₄-C₈-cycloalkenyl group is for example a cyclobutenyl, cyclopentenyl, or cyclohexenyl group.

The term “C₃-C₆-cycloalkoxy” is to be understood as meaning a saturated, monovalent, monocyclic group of formula -O-(C₃-C₆-cycloalkyl), in which the term “C₃-C₆-cycloalkyl” is defined *supra*, e.g. a cyclopropyloxy, cyclobutyloxy, cyclopentyloxy or cyclohexyloxy group.

The term “3- to 10-membered heterocycloalkyl”, is to be understood as meaning a saturated, monovalent, mono- or bicyclic hydrocarbon ring which contains 2, 3, 4, 5, 6, 7, 8 or 9 carbon atoms, and one or more heteroatom-containing groups selected from C(=O), O, S, S(=O), S(=O)₂, NH ; it being possible for said heterocycloalkyl group to be attached to the rest of the molecule via any one of the carbon atoms or, if present, a nitrogen atom.

Particularly, said 3- to 10-membered heterocycloalkyl can contain 2, 3, 4, 5 or 6 carbon atoms, and one or more of the above-mentioned heteroatom-containing groups (a “3- to 7-membered heterocycloalkyl”), more particularly said heterocycloalkyl can contain 4, 5 or 6 carbon atoms, and

one or more of the above-mentioned heteroatom-containing groups (a “4- to 6-membered heterocycloalkyl”).

Particularly, without being limited thereto, said heterocycloalkyl can be a 4-membered ring, such as an azetidiny, oxetanyl, or a 5-membered ring, such as tetrahydrofuranyl, dioxolinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, pyrrolinyl, or a 6-membered ring, such as tetrahydropyranyl, piperidinyl, morpholinyl, dithianyl, thiomorpholinyl, piperazinyl, or trithianyl, or a 7-membered ring, such as a diazepanyl ring, for example.

The term “4- to 10-membered heterocycloalkenyl”, is to be understood as meaning an unsaturated, monovalent, mono- or bicyclic hydrocarbon ring which contains 3, 4, 5, 6, 7, 8 or 9 carbon atoms, and one or more heteroatom-containing groups selected from C(=O), O, S, S(=O), S(=O)₂, NH ; it being possible for said heterocycloalkenyl group to be attached to the rest of the molecule via any one of the carbon atoms or, if present, a nitrogen atom. Examples of said heterocycloalkenyl may contain one or more double bonds, *e.g.* 4*H*-pyranyl, 2*H*-pyranyl, 2,5-dihydro-1*H*-pyrrolyl, [1,3]dioxolyl, 4*H*-[1,3,4]thiadiazinyl, 2,5-dihydrofuranyl, 2,3-dihydrofuranyl, 2,5-dihydrothiophenyl, 2,3-dihydrothiophenyl, 4,5-dihydrooxazolyl, or 4*H*-[1,4]thiazinyl group.

The term “aryl” is to be understood as preferably meaning a monovalent, aromatic or partially aromatic, mono-, or bi- or tricyclic hydrocarbon ring having 6, 7, 8, 9, 10, 11, 12, 13 or 14 carbon atoms (a “C₆-C₁₄-aryl” group), particularly a ring having 6 carbon atoms (a “C₆-aryl” group), *e.g.* a phenyl group; or a ring having 9 carbon atoms (a “C₉-aryl” group), *e.g.* an indanyl or indenyl group, or a ring having 10 carbon atoms (a “C₁₀-aryl” group), *e.g.* a tetralinyl, dihydronaphthyl, or naphthyl group, or a biphenyl group (a “C₁₂-aryl” group), or a ring having 13 carbon atoms, (a “C₁₃-aryl” group), *e.g.* a fluorenyl group, or a ring having 14 carbon atoms, (a “C₁₄-aryl” group), *e.g.* an anthracenyl group. Preferably, the aryl group is a phenyl group.

The term “heteroaryl” is understood as preferably meaning a monovalent, monocyclic-, bicyclic- or tricyclic aromatic ring system having 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 ring atoms (a “5- to 14-membered heteroaryl” group), particularly 5 or 6 or 9 or 10 atoms, and which contains at least one heteroatom which may be identical or different, said heteroatom being such as oxygen, nitrogen or sulfur, and in addition in each case can be benzocondensed. Particularly, heteroaryl is selected from thienyl, furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, thia-4*H*-pyrazolyl *etc.*, and benzo derivatives thereof, such as, for example, benzofuranyl, benzothienyl, benzoxazolyl, benzisoxazolyl, benzimidazolyl, benzotriazolyl,

indazolyl, indolyl, isoindolyl, *etc.*; or pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, *etc.*, and benzo derivatives thereof, such as, for example, quinolinyl, quinazolinyl, isoquinolinyl, *etc.*; or azocinyl, indoliziny, purinyl, *etc.*, and benzo derivatives thereof; or cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthpyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, xanthenyl, or oxepinyl, *etc.*.

In general, and unless otherwise mentioned, the heteroaryl or heteroarylenic radicals include all the possible isomeric forms thereof, e.g. the positional isomers thereof. Thus, for some illustrative non-restricting example, the term pyridyl includes pyridin-2-yl, pyridin-3-yl, and pyridin-4-yl; or the term thienyl includes thien-2-yl and thien-3-yl. Preferably, the heteroaryl group is a pyridinyl group.

The term "C₁-C₆", as used throughout this text, *e.g.* in the context of the definition of "C₁-C₆-alkyl", "C₁-C₆-haloalkyl", "C₁-C₆-alkoxy", or "C₁-C₆-haloalkoxy" is to be understood as meaning an alkyl group having a finite number of carbon atoms of 1 to 6, *i.e.* 1, 2, 3, 4, 5, or 6 carbon atoms. It is to be understood further that said term "C₁-C₆" is to be interpreted as any sub-range comprised therein, *e.g.* C₁-C₆, C₂-C₅, C₃-C₄, C₁-C₂, C₁-C₃, C₁-C₄, C₁-C₅, C₁-C₆; particularly C₁-C₂, C₁-C₃, C₁-C₄, C₁-C₅, C₁-C₆; more particularly C₁-C₄; in the case of "C₁-C₆-haloalkyl" or "C₁-C₆-haloalkoxy" even more particularly C₁-C₂.

Similarly, as used herein, the term "C₂-C₆", as used throughout this text, *e.g.* in the context of the definitions of "C₂-C₆-alkenyl" and "C₂-C₆-alkynyl", is to be understood as meaning an alkenyl group or an alkynyl group having a finite number of carbon atoms of 2 to 6, *i.e.* 2, 3, 4, 5, or 6 carbon atoms. It is to be understood further that said term "C₂-C₆" is to be interpreted as any sub-range comprised therein, *e.g.* C₂-C₆, C₃-C₅, C₃-C₄, C₂-C₃, C₂-C₄, C₂-C₅; particularly C₂-C₃.

Further, as used herein, the term "C₃-C₇", as used throughout this text, *e.g.* in the context of the definition of "C₃-C₇-cycloalkyl", is to be understood as meaning a cycloalkyl group having a finite number of carbon atoms of 3 to 7, *i.e.* 3, 4, 5, 6 or 7 carbon atoms. It is to be understood further that said term "C₃-C₇" is to be interpreted as any sub-range comprised therein, *e.g.* C₃-C₆, C₄-C₅, C₃-C₅, C₃-C₄, C₄-C₆, C₅-C₇; particularly C₃-C₆.

The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

The term "optionally substituted" means that the number of substituents can be zero. Unless otherwise indicated, optionally substituted groups may be substituted with as many optional substituents as can be accommodated by replacing a hydrogen atom with a non-hydrogen substituent on any available carbon or nitrogen atom. Commonly, the number of optional substituents (when present) ranges from 1 to 3.

Ring system substituent means a substituent attached to an aromatic or nonaromatic ring system which, for example, replaces an available hydrogen on the ring system.

As used herein, the term "one or more times", *e.g.* in the definition of the substituents of the compounds of the general formulae of the present invention, is understood as meaning "one, two, three, four or five times, particularly one, two, three or four times, more particularly one, two or three times, even more particularly one or two times".

As used herein, the term "leaving group" refers to an atom or a group of atoms that is displaced in a chemical reaction as stable species taking with it the bonding electrons. Preferably, a leaving group is selected from the group comprising: halo, in particular chloro, bromo or iodo, methanesulfonyloxy, p-toluenesulfonyloxy, trifluoromethanesulfonyloxy, nonafluorobutanesulfonyloxy, (4-bromo-benzene)sulfonyloxy, (4-nitro-benzene)sulfonyloxy, (2-nitro-benzene)-sulfonyloxy, (4-isopropyl-benzene)sulfonyloxy, (2,4,6-tri-isopropyl-benzene)-sulfonyloxy, (2,4,6-trimethyl-benzene)sulfonyloxy, (4-tertbutyl-benzene)sulfonyloxy, benzenesulfonyloxy, and (4-methoxy-benzene)sulfonyloxy.

Where the plural form of the word compounds, salts, polymorphs, hydrates, solvates and the like, is used herein, this is taken to mean also a single compound, salt, polymorph, isomer, hydrate, solvate or the like.

The compounds of this invention contain one or more asymmetric centres, depending upon the location and nature of the various substituents desired. Asymmetric carbon atoms may be present in the (*R*) or (*S*) configuration. In certain instances, asymmetry may also be present due to restricted rotation about a given bond, for example, the central bond adjoining two substituted aromatic rings of the specified compounds.

Substituents on a ring may also be present in either cis or trans form. It is intended that all such configurations are included within the scope of the present invention.

Preferred compounds are those which produce the more desirable biological activity. Separated, pure or partially purified isomers and stereoisomers or racemic or diastereomeric mixtures of the compounds of this invention are also included within the scope of the present invention. The purification and the separation of such materials can be accomplished by standard techniques known in the art.

The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example, by the formation of diastereoisomeric salts using an optically active acid or base or formation of covalent diastereomers. Examples of appropriate acids are tartaric, diacetyltartaric, ditoluoyltartaric and camphorsulfonic acid. Mixtures of diastereoisomers can be separated into their individual diastereomers on the basis of their physical and/or chemical differences by methods known in the art, for example, by chromatography or fractional crystallisation. The optically active bases or acids are then liberated from the separated diastereomeric salts. A different process for separation of optical isomers involves the use of chiral chromatography (*e.g.*, chiral HPLC columns), with or without conventional derivatisation, optimally chosen to maximise the separation of the enantiomers. Suitable chiral HPLC columns are manufactured by Diacel, *e.g.*, Chiracel OD and Chiracel OJ among many others, all routinely selectable. Enzymatic separations, with or without derivatisation, are also useful. The optically active compounds of this invention can likewise be obtained by chiral syntheses utilizing optically active starting materials.

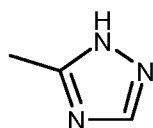
In order to limit different types of isomers from each other reference is made to IUPAC Rules Section E (Pure Appl Chem 45, 11-30, 1976).

The invention also includes all suitable isotopic variations of a compound of the invention. An isotopic variation of a compound of the invention is defined as one in which at least one atom is replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually or predominantly found in nature. Examples of isotopes that can be incorporated into a compound of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulphur, fluorine, chlorine, bromine and iodine, such as ^2H (deuterium), ^3H (tritium), ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{17}O , ^{18}O , ^{32}P , ^{33}P , ^{33}S , ^{34}S , ^{35}S , ^{36}S , ^{18}F , ^{36}Cl , ^{82}Br , ^{123}I , ^{124}I , ^{129}I and ^{131}I , respectively. Certain isotopic variations of a compound of the invention, for example, those in which one or more radioactive isotopes such as ^3H or ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution studies. Tritiated and carbon-14, *i.e.*, ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in

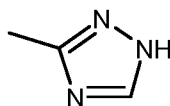
vivo half-life or reduced dosage requirements and hence may be preferred in some circumstances. Isotopic variations of a compound of the invention can generally be prepared by conventional procedures known by a person skilled in the art such as by the illustrative methods or by the preparations described in the examples hereafter using appropriate isotopic variations of suitable reagents.

The present invention includes all possible stereoisomers of the compounds of the present invention as single stereoisomers, or as any mixture of said stereoisomers, in any ratio. Isolation of a single stereoisomer, *e.g.* a single enantiomer or a single diastereomer, of a compound of the present invention may be achieved by any suitable state of the art method, such as chromatography, especially chiral chromatography, for example.

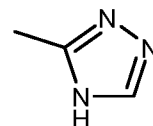
Further, the compounds of the present invention may exist as tautomers. For example, any compound of the present invention which contains a pyrazole moiety as a heteroaryl group for example can exist as a *1H* tautomer, or a *2H* tautomer, or even a mixture in any amount of the two tautomers, or a triazole moiety for example can exist as a *1H* tautomer, a *2H* tautomer, or a *4H* tautomer, or even a mixture in any amount of said *1H*, *2H* and *4H* tautomers, *viz.* :



1H-tautomer



2H-tautomer



4H-tautomer.

The present invention includes all possible tautomers of the compounds of the present invention as single tautomers, or as any mixture of said tautomers, in any ratio.

Further, the compounds of the present invention can exist as N-oxides, which are defined in that at least one nitrogen of the compounds of the present invention is oxidised. The present invention includes all such possible N-oxides.

The present invention also relates to useful forms of the compounds as disclosed herein, such as metabolites, hydrates, solvates, prodrugs, salts, in particular pharmaceutically acceptable salts, and co-precipitates.

The compounds of the present invention can exist as a hydrate, or as a solvate, wherein the compounds of the present invention contain polar solvents, in particular water, methanol or ethanol

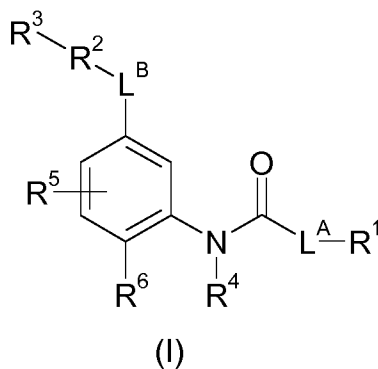
for example as structural element of the crystal lattice of the compounds. The amount of polar solvents, in particular water, may exist in a stoichiometric or non-stoichiometric ratio. In the case of stoichiometric solvates, *e.g.* a hydrate, hemi-, (semi-), mono-, sesqui-, di-, tri-, tetra-, penta- *etc.* solvates or hydrates, respectively, are possible. The present invention includes all such hydrates or solvates.

Further, the compounds of the present invention can exist in free form, *e.g.* as a free base, or as a free acid, or as a zwitterion, or can exist in the form of a salt. Said salt may be any salt, either an organic or inorganic addition salt, particularly any pharmaceutically acceptable organic or inorganic addition salt, customarily used in pharmacy.

The present invention includes all possible salts of the compounds of the present invention as single salts, or as any mixture of said salts, in any ratio.

Furthermore, the present invention includes all possible crystalline forms, or polymorphs, of the compounds of the present invention, either as single polymorphs, or as a mixture of more than one polymorphs, in any ratio.

In accordance with a first aspect, the present invention covers compounds of general formula (I) :



in which :

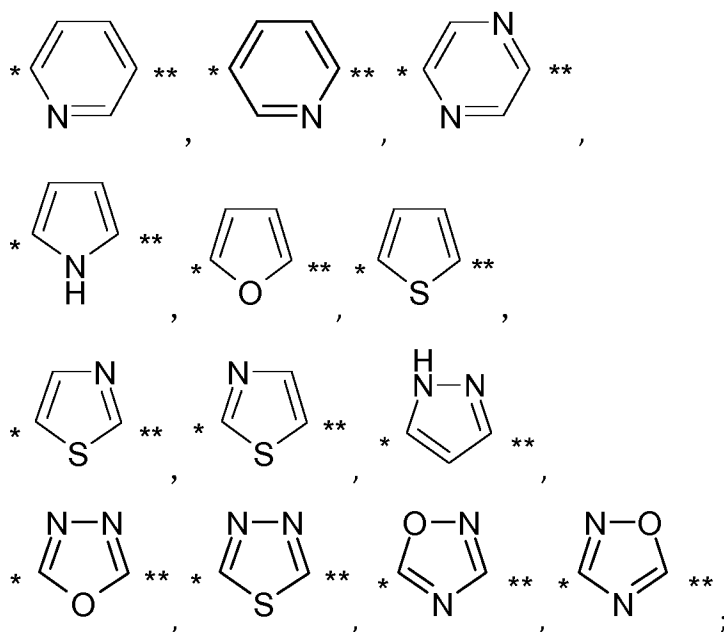
L^A represents a methylene or ethylene group, said methylene or ethylene group being optionally substituted, one or more times, identically or differently, with a substituent selected from:
hydroxy-, cyano-, C_1 - C_3 -alkyl-, C_1 - C_3 -alkoxy-, halo- C_1 - C_3 -alkyl-, hydroxy- C_1 - C_3 -alkyl-, halo- C_1 - C_3 -alkoxy-, C_3 - C_7 -cycloalkyl-, 3- to 10-membered heterocycloalkyl-;

or, when two substituents are present at the same carbon atom, the two substituents, together with the carbon atom they are attached to, may form a C₃-C₆-cycloalkyl- or 3- to 6-membered heterocycloalkyl- ring; wherein said ring is optionally substituted one or more times, identically or differently, with a substituent selected from:

^{L^B} represents *N(H)-C(=O)** or *C(=O)-N(H)**;
wherein " * " indicates the point of attachment to R², and " ** " indicates the point of attachment to the phenyl group;

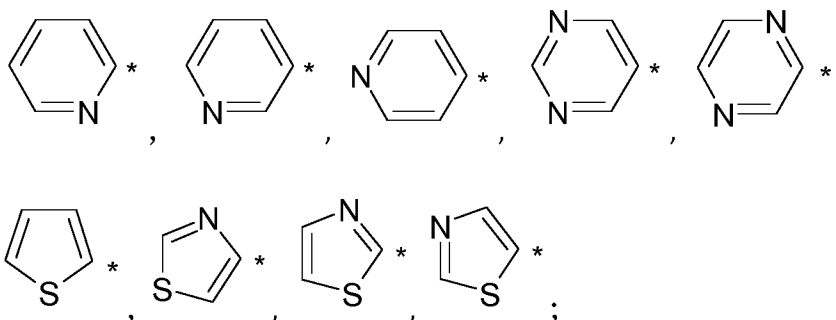
^{R¹} represents a group selected from:
5- to 8-membered heterocycloalkyl-, 4- to 10-membered heterocycloalkenyl-, aryl-, heteroaryl-, and -N(R⁷)-(C₁-C₆-alkyl);
wherein said 5- to 8-membered heterocycloalkyl-, 4- to 10-membered heterocycloalkenyl-, aryl-, heteroaryl-, and -N(R⁷)-(C₁-C₆-alkyl) group is optionally substituted, one or more times, identically or differently, with a substituent selected from: halo-, hydroxy-, cyano-, C₁-C₃-alkyl-, C₁-C₃-alkoxy-, halo-C₁-C₃-alkyl-, hydroxy-C₁-C₃-alkyl-, halo-C₁-C₃-alkoxy-, C₃-C₇-cycloalkyl-;

^{R²} represents a group selected from:



wherein " * " indicates the point of attachment to R^3 , and " ** " indicates the point of attachment to L^B ; wherein said group is optionally substituted, one or more times, identically or differently, with a C_1 - C_3 -alkyl- group;

5 R^3 represents a group selected from:



wherein " * " indicates the point of attachment to R^2 ;

wherein said group is optionally substituted one time with a substituent selected from:

10 halo-, hydroxy-, $-N(R^9)(R^{10})$, $-N(H)C(=O)R^9$, cyano-, nitro-, C_1 - C_3 -alkyl-, C_1 - C_3 -alkoxy-, halo- C_1 - C_3 -alkyl-, hydroxy- C_1 - C_3 -alkyl-, amino- C_1 - C_3 -alkyl-, halo- C_1 - C_3 -alkoxy-;

R^4 represents a hydrogen atom or a C_1 - C_3 -alkyl- group;

15

R^5 represents a hydrogen atom or a halogen atom or a group selected from:
cyano-, C_1 - C_3 -alkyl-, C_1 - C_3 -alkoxy-;

R^6 represents a group selected from:

20 C_1 - C_6 -alkyl-, C_2 - C_6 -alkenyl-, C_2 - C_6 -alkynyl-,
 C_1 - C_6 -alkoxy-, C_3 - C_6 -cycloalkoxy-, halo-, hydroxy-, cyano-, aryl-,
heteroaryl-, (3- to 10-membered heterocycloalkyl)-O-,
 $-N(R^9)(R^{10})$, $-C(=O)-O-C_1-C_4$ -alkyl-, $-C(=O)-N(R^9)(R^{10})$, R^9-S- , $R^9-S(=O)-$, $R^9-S(=O)_2-$;
said C_1 - C_6 -alkyl-, C_2 - C_6 -alkenyl-, C_2 - C_6 -alkynyl-, aryl-, heteroaryl-, and C_1 - C_6 -alkoxy- group
25 being optionally substituted, one or more times, identically or differently, with a substituent
selected from: halo-, cyano-, nitro-, hydroxy-, C_1 - C_3 -alkyl-, C_1 - C_3 -alkoxy-, halo- C_1 - C_3 -alkoxy-,
hydroxy- C_1 - C_3 -alkoxy-, C_1 - C_3 -alkoxy- C_2 - C_3 -alkoxy-,
 C_3 - C_7 -cycloalkyl-, C_4 - C_7 -cycloalkenyl-,
3- to 10-membered heterocycloalkyl-, 4- to 10-membered heterocycloalkenyl-,
30 aryl-, heteroaryl-, $-C(=O)R^9$, $-C(=O)O-(C_1-C_4$ -alkyl), $-OC(=O)-R^9$, $-N(H)C(=O)R^9$, $-N(R^{10})C(=O)R^9$,

-N(H)C(=O)NR¹⁰R⁹, -N(R¹¹)C(=O)NR¹⁰R⁹, -N(H)R⁹, -NR¹⁰R⁹,
 -C(=O)N(H)R⁹, -C(=O)NR¹⁰R⁹, R⁹-S-, R⁹-S(=O)-, R⁹-S(=O)₂-,
 -N(H)S(=O)R⁹, -N(R¹⁰)S(=O)R⁹, -S(=O)N(H)R⁹, -S(=O)NR¹⁰R⁹,
 -N(H)S(=O)₂R⁹, -N(R⁹)S(=O)₂R¹⁰, -S(=O)₂N(H)R⁹, -S(=O)₂NR¹⁰R⁹,
 5 -S(=O)(=NR¹⁰)R⁹, -N=S(=O)(R¹⁰)R⁹;

R⁷ represents a hydrogen atom or a C₁-C₃-alkyl- or C₁-C₃-alkoxy-C₁-C₃-alkyl- group;

R⁹, R¹⁰, R¹¹

10 represent, independently from each other, a hydrogen atom or a C₁-C₃-alkyl- or C₁-C₃-alkoxy-C₁-C₃-alkyl- group;

or

R⁹R¹⁰ together with the atom or the group of atoms they are attached to, form a 3- to
 15 10-membered heterocycloalkyl- or 4- to 10-membered heterocycloalkenyl- group;

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

In an embodiment, the present invention relates to compounds of the general formula (I), *supra*, in
 20 which L^A represents a methylene group, said methylene group being optionally substituted, one or more times, identically or differently, with a substituent selected from:

hydroxy-, cyano-, C₁-C₃-alkyl-, C₁-C₃-alkoxy-, halo-C₁-C₃-alkyl-, hydroxy-C₁-C₃-alkyl-,
 halo-C₁-C₃-alkoxy-, C₃-C₇-cycloalkyl-, 3- to 10-membered heterocycloalkyl-;

or, when two substituents are present at the same carbon atom, the two substituents, together with
 25 the carbon atom they are attached to, may form a C₃-C₆-cycloalkyl- or 3- to 6-membered heterocycloalkyl- ring; wherein said ring is optionally substituted one or more times, identically or differently, with a substituent selected from: halo-, hydroxy-, cyano-, C₁-C₃-alkyl-, C₁-C₃-alkoxy-.

In another embodiment, the present invention relates to compounds of the general formula (I),
 30 *supra*, in which L^A represents a methylene group, said methylene group being optionally substituted, one or more times, identically or differently, with a substituent selected from:

hydroxy-, C₁-C₃-alkyl-, C₁-C₃-alkoxy-, hydroxy-C₁-C₃-alkyl-;

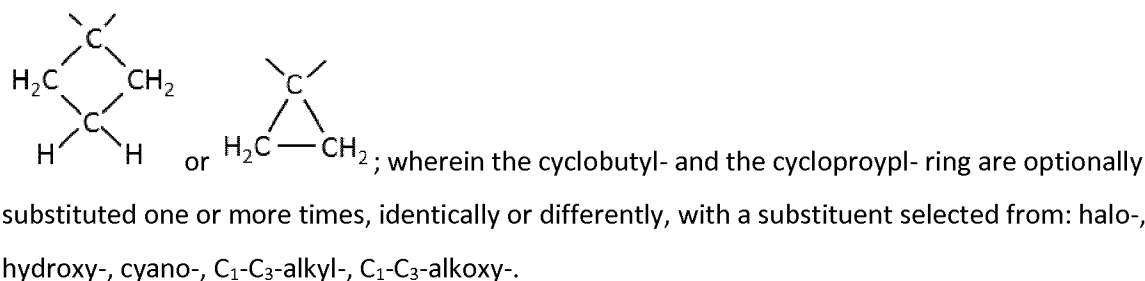
or, when two substituents are present at the same carbon atom, the two substituents, together with the carbon atom they are attached to, may form a C₃-C₆-cycloalkyl- or 3- to 6-membered

heterocycloalkyl- ring; wherein said ring is optionally substituted one or more times, identically or differently, with a substituent selected from: halo-, hydroxy-, cyano-, C₁-C₃-alkyl-, C₁-C₃-alkoxy-.

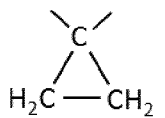
In a preferred embodiment, the present invention relates to compounds of general formula (I),

- 5 *supra*, in which L^A represents a methylene group, said methylene group being optionally substituted one or two times, identically or differently, with C₁-C₃-alkyl-, wherein, if said methylene is substituted with two C₁-C₃-alkyl- groups, these may, together with the carbon atom they are attached to, form a C₃-C₆-cycloalkyl- ring.

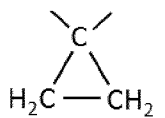
- 10 In a particularly preferred embodiment, the present invention relates to compounds of general formula (I), *supra*, in which L^A represents -CH₂-, -CH(CH₃)-, -C(CH₃)₂-, -CH(C₂H₅)-,



- 15 In another particularly preferred embodiment, the present invention relates to compounds of general formula (I), *supra*, in which L^A represents -CH₂-, -CH(CH₃)-, -C(CH₃)₂- or



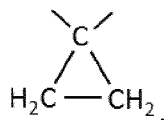
- 20 In another particularly preferred embodiment, the present invention relates to compounds of general formula (I), *supra*, in which L^A represents -CH₂-, -CH(CH₃)- or



- 25 In another particularly preferred embodiment, the present invention relates to compounds of general formula (I), *supra*, in which L^A represents -CH₂-.

In another particularly preferred embodiment, the present invention relates to compounds of general formula (I), *supra*, in which L^A represents -CH(CH₃)-.

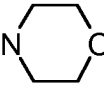
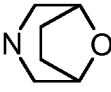
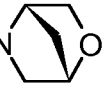
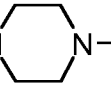
In another particularly preferred embodiment, the present invention relates to compounds of general formula (I), *supra*, in which L^A represents



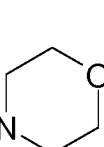
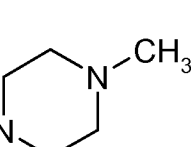
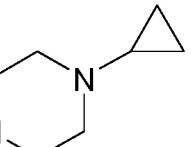
- 5 In another preferred embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which L^B represents $*N(H)-C(=O)**$; wherein " * " indicates the point of attachment to R^2 , and " ** " indicates the point of attachment to the phenyl group.

- 10 In another preferred embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which L^B represents $*C(=O)-N(H)**$; wherein " * " indicates the point of attachment to R^2 , and " ** " indicates the point of attachment to the phenyl group.

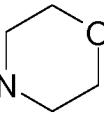
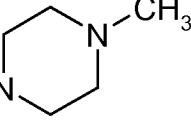
In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^1 represents a group selected from:

- 15 $*N$ , $*N$ , $*N$ , $*N$ - R^{12} ; wherein " * " indicates the point of attachment to L^A ; and wherein R^{12} represents methyl, ethyl or cyclopropyl.

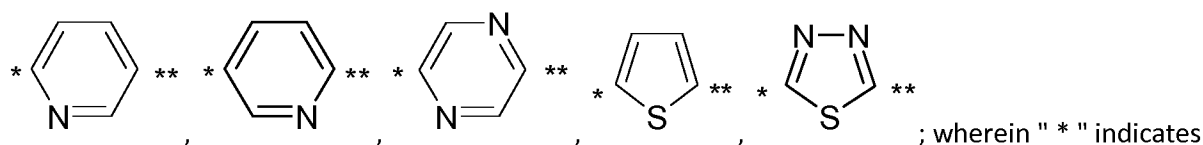
In a particularly preferred embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^1 represents a group selected from:

- 20 $*N$ , $*N$ , $*N$ ; wherein " * " indicates the point of attachment to L^A .

In a particularly preferred embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^1 represents a group selected from:

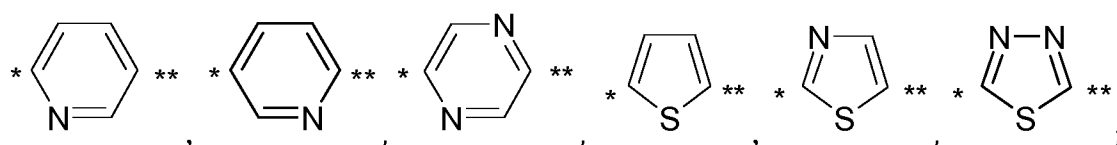
- 25 $*N$ , $*N$ ; wherein " * " indicates the point of attachment to L^A .

In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^2 represents a group selected from:



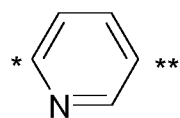
5 the point of attachment to R^3 , and " ** " indicates the point of attachment to L^B .

In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^2 represents a group selected from:



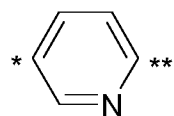
10 wherein " * " indicates the point of attachment to R^3 , and " ** " indicates the point of attachment to L^B .

In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^2 represents



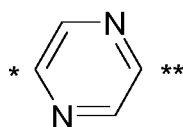
15 of attachment to L^B .

In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^2 represents



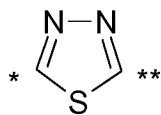
20 attachment to L^B .

In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^2 represents



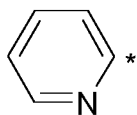
of attachment to L^B .

In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^2 represents



; wherein " * " indicates the point of attachment to R^3 , and " ** " indicates the point of attachment to L^B .

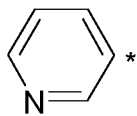
- 5 In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^3 represents



; wherein " * " indicates the point of attachment to R^2 ; and wherein said group is optionally substituted one time with a substituent selected from: halo-, hydroxy-, $-N(R^9)(R^{10})$, $-N(H)C(=O)R^9$, cyano-, nitro-, C_1 - C_3 -alkyl-, C_1 - C_3 -alkoxy-, halo- C_1 - C_3 -alkyl-,

- 10 hydroxy- C_1 - C_3 -alkyl-, amino- C_1 - C_3 -alkyl-, halo- C_1 - C_3 -alkoxy-.

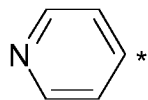
In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^3 represents



; wherein " * " indicates the point of attachment to R^2 ; and wherein said group is optionally substituted one time with a substituent selected from: halo-, hydroxy-, $-N(R^9)(R^{10})$, $-N(H)C(=O)R^9$, cyano-, nitro-, C_1 - C_3 -alkyl-, C_1 - C_3 -alkoxy-, halo- C_1 - C_3 -alkyl-, hydroxy- C_1 - C_3 -alkyl-, amino- C_1 - C_3 -alkyl-, halo- C_1 - C_3 -alkoxy-.

- 15

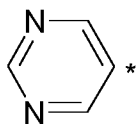
In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^3 represents



; wherein " * " indicates the point of attachment to R^2 ; and wherein said group is optionally substituted one or more time with a substituent selected from: halo-, hydroxy-, $-N(R^9)(R^{10})$, $-N(H)C(=O)R^9$, cyano-, nitro-, C_1 - C_3 -alkyl-, C_1 - C_3 -alkoxy-, halo- C_1 - C_3 -alkyl-, hydroxy- C_1 - C_3 -alkyl-, amino- C_1 - C_3 -alkyl-, halo- C_1 - C_3 -alkoxy-.

- 25

In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^3 represents

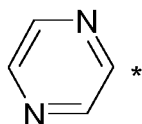


; wherein " * " indicates the point of attachment to R^2 ; and wherein said group is

optionally substituted one time with a substituent selected from: halo-, hydroxy-,
 $-N(R^9)(R^{10})$, $-N(H)C(=O)R^9$, cyano-, nitro-, C_1 - C_3 -alkyl-, C_1 - C_3 -alkoxy-, halo- C_1 - C_3 -alkyl-,
 hydroxy- C_1 - C_3 -alkyl-, amino- C_1 - C_3 -alkyl-, halo- C_1 - C_3 -alkoxy-.

5

In another embodiment, the present invention relates to compounds of the general formula (I),
supra, in which R^3 represents

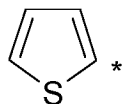


; wherein " * " indicates the point of attachment to R^2 ; and wherein said group is

optionally substituted one time with a substituent selected from: halo-, hydroxy-,
 $-N(R^9)(R^{10})$, $-N(H)C(=O)R^9$, cyano-, nitro-, C_1 - C_3 -alkyl-, C_1 - C_3 -alkoxy-, halo- C_1 - C_3 -alkyl-,
 hydroxy- C_1 - C_3 -alkyl-, amino- C_1 - C_3 -alkyl-, halo- C_1 - C_3 -alkoxy-.

10

In another embodiment, the present invention relates to compounds of the general formula (I),
supra, in which R^3 represents

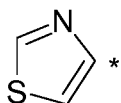


; wherein " * " indicates the point of attachment to R^2 ; and wherein said group is

optionally substituted one time with a substituent selected from: halo-, hydroxy-,
 $-N(R^9)(R^{10})$, $-N(H)C(=O)R^9$, cyano-, nitro-, C_1 - C_3 -alkyl-, C_1 - C_3 -alkoxy-, halo- C_1 - C_3 -alkyl-,
 hydroxy- C_1 - C_3 -alkyl-, amino- C_1 - C_3 -alkyl-, halo- C_1 - C_3 -alkoxy-.

15

In another embodiment, the present invention relates to compounds of the general formula (I),
supra, in which R^3 represents

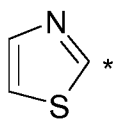


; wherein " * " indicates the point of attachment to R^2 ; and wherein said group is

optionally substituted one time with a substituent selected from: halo-, hydroxy-,
 $-N(R^9)(R^{10})$, $-N(H)C(=O)R^9$, cyano-, nitro-, C_1 - C_3 -alkyl-, C_1 - C_3 -alkoxy-, halo- C_1 - C_3 -alkyl-,
 hydroxy- C_1 - C_3 -alkyl-, amino- C_1 - C_3 -alkyl-, halo- C_1 - C_3 -alkoxy-.

25

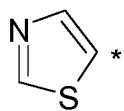
In another embodiment, the present invention relates to compounds of the general formula (I),
supra, in which R^3 represents



; wherein " * " indicates the point of attachment to R^2 ; and wherein said group is optionally substituted one time with a substituent selected from: halo-, hydroxy-, $-N(R^9)(R^{10})$, $-N(H)C(=O)R^9$, cyano-, nitro-, C_1 - C_3 -alkyl-, C_1 - C_3 -alkoxy-, halo- C_1 - C_3 -alkyl-, hydroxy- C_1 - C_3 -alkyl-, amino- C_1 - C_3 -alkyl-, halo- C_1 - C_3 -alkoxy-.

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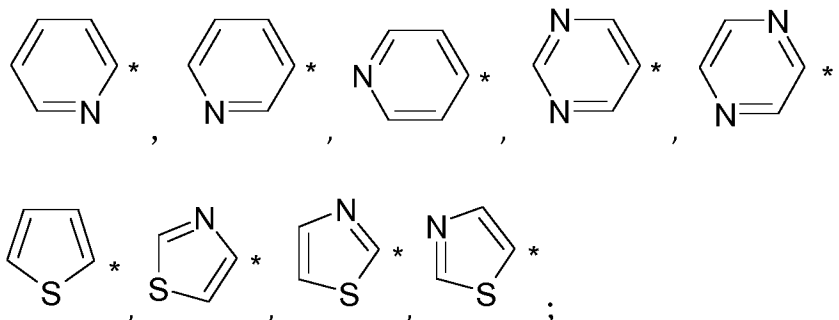
In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^3 represents



; wherein " * " indicates the point of attachment to R^2 ; and wherein said group is optionally substituted one time with a substituent selected from: halo-, hydroxy-, $-N(R^9)(R^{10})$, $-N(H)C(=O)R^9$, cyano-, nitro-, C_1 - C_3 -alkyl-, C_1 - C_3 -alkoxy-, halo- C_1 - C_3 -alkyl-, hydroxy- C_1 - C_3 -alkyl-, amino- C_1 - C_3 -alkyl-, halo- C_1 - C_3 -alkoxy-.

10

In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^3 represents a group selected from:



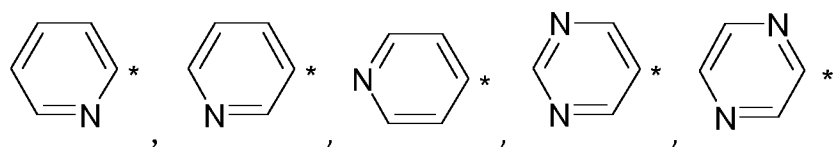
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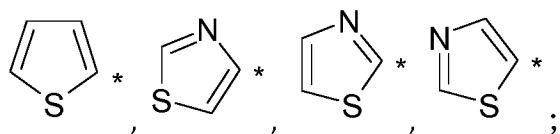
wherein " * " indicates the point of attachment to R^2 ;

wherein said group is optionally substituted one time with a substituent selected from: halo-, $-N(R^9)(R^{10})$, C_1 - C_3 -alkyl-, C_1 - C_3 -alkoxy-, halo- C_1 - C_3 -alkyl-.

20

In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^3 represents a group selected from:



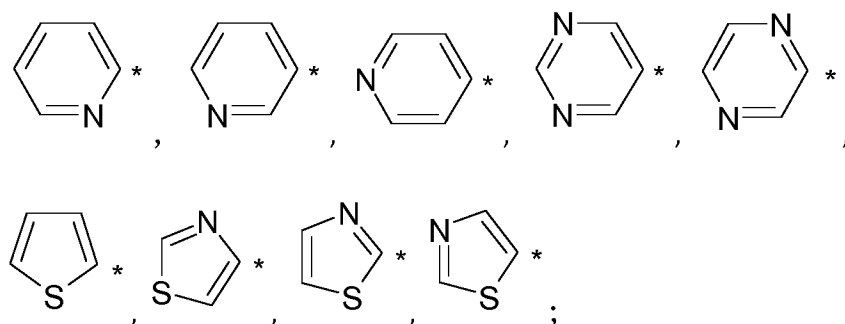


wherein " * " indicates the point of attachment to R²;

wherein said group is optionally substituted with a substituent selected from: halo-, -N(R⁹)(R¹⁰), C₁-C₃-alkyl-, C₁-C₃-alkoxy-, halo-C₁-C₃-alkyl-.

5

In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R³ represents a group selected from:



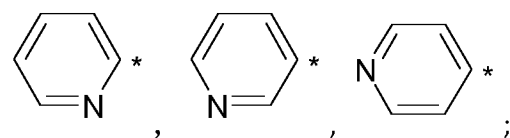
10 wherein " * " indicates the point of attachment to R²;

wherein said group is optionally substituted one time with a substituent selected from:

fluoro-, chloro-, -NH₂, H₃C-, H₃C-O-, F₃C-.

In another embodiment, the present invention relates to compounds of the general formula (I),

15 *supra*, in which R³ represents a group selected from:



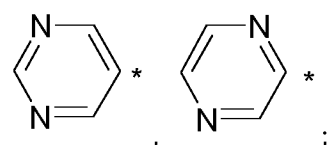
wherein " * " indicates the point of attachment to R²;

wherein said group is optionally substituted one time with a substituent selected from:

fluoro-, chloro-, -NH₂, H₃C-, H₃C-O-, F₃C-.

20

In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R³ represents a group selected from:

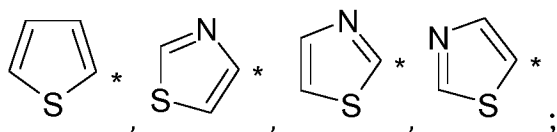


wherein " * " indicates the point of attachment to R²;

wherein said group is optionally substituted one time with a substituent selected from:

fluoro-, chloro-, -NH₂, H₃C-, H₃C-O-, F₃C-.

- 5 In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R³ represents a group selected from:

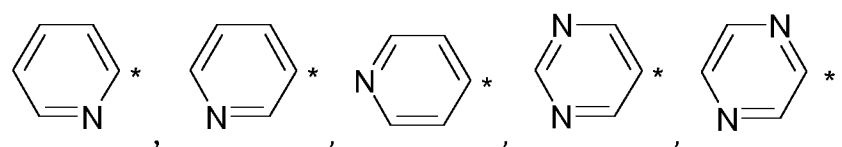
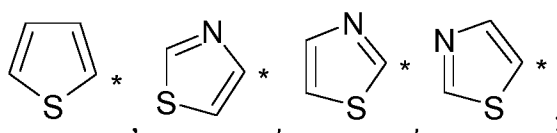


wherein " * " indicates the point of attachment to R²;

wherein said group is optionally substituted one time with a substituent selected from:

- 10 fluoro-, chloro-, -NH₂, H₃C-, H₃C-O-, F₃C-.

In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R³ represents a group selected from:



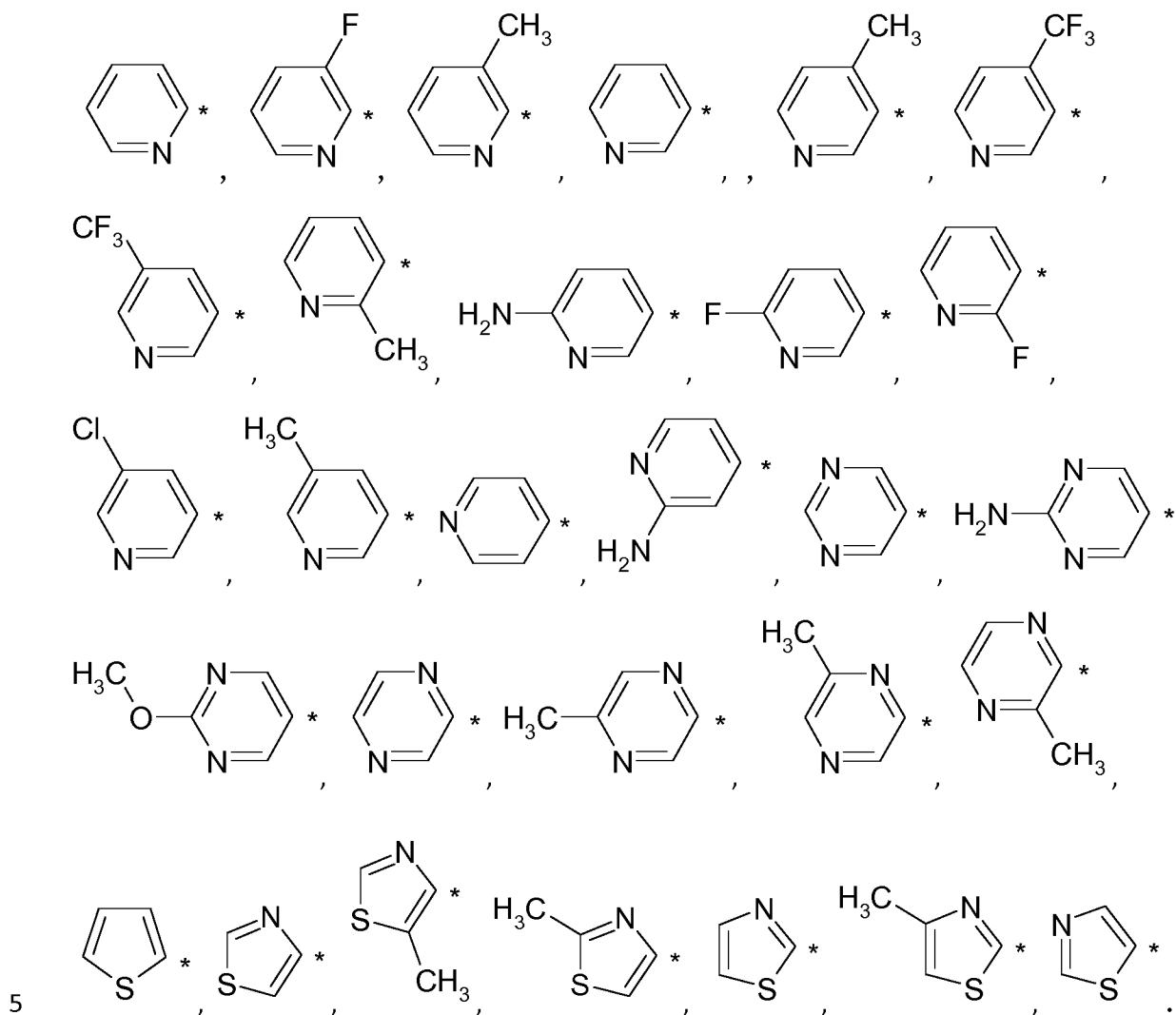
15

wherein " * " indicates the point of attachment to R²;

wherein said group is optionally substituted with one substituent selected from:

fluoro-, chloro-, -NH₂, H₃C-, H₃C-O-, F₃C-.

- 20 In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R³ represents a group selected from:



In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R⁴ represents a hydrogen atom.

10 In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R⁵ represents a hydrogen atom or a halogen atom.

In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R⁵ represents a hydrogen atom or a fluorine atom.

15

In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R⁵ represents a hydrogen atom.

In another embodiment, the present invention relates to compounds of the general formula (I),
 20 *supra*, in which R⁵ represents fluorine atom.

In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R⁶ represents a group selected from:

C₁-C₆-alkyl-, C₂-C₆-alkenyl-, C₂-C₆-alkynyl-, C₁-C₆-alkoxy-, C₃-C₆-cycloalkoxy-, halo-, hydroxy-, cyano-,
 5 aryl-, heteroaryl-, -N(R⁹)(R¹⁰), -C(=O)-O-C₁-C₄-alkyl, -C(=O)-N(R⁹)(R¹⁰), R⁹-S-, R⁹-S(=O)-, R⁹-S(=O)₂-;
 said C₁-C₆-alkyl-, C₂-C₆-alkenyl-, C₂-C₆-alkynyl-, aryl-, heteroaryl-, and C₁-C₆-alkoxy- group being
 optionally substituted, one or more times, identically or differently, with a substituent selected from:
 halo-, cyano-, nitro-, hydroxy-, C₁-C₃-alkyl-, C₁-C₃-alkoxy-, halo-C₁-C₃-alkoxy-, hydroxy-C₁-C₃-alkoxy-,
 C₁-C₃-alkoxy-C₂-C₃-alkoxy-, C₃-C₇-cycloalkyl-, C₄-C₇-cycloalkenyl-,

10 3- to 10-membered heterocycloalkyl-, 4- to 10-membered heterocycloalkenyl-, aryl-, heteroaryl-,
 -C(=O)R⁹, -C(=O)O-(C₁-C₄-alkyl), -OC(=O)-R⁹, -N(H)C(=O)R⁹, -N(R¹⁰)C(=O)R⁹, -N(H)C(=O)NR¹⁰R⁹,
 -N(R¹¹)C(=O)NR¹⁰R⁹, -N(H)R⁹, -NR¹⁰R⁹, -C(=O)N(H)R⁹, -C(=O)NR¹⁰R⁹, R⁹-S-, R⁹-S(=O)-, R⁹-S(=O)₂-,
 -N(H)S(=O)R⁹, -N(R¹⁰)S(=O)R⁹, -S(=O)N(H)R⁹, -S(=O)NR¹⁰R⁹, -N(H)S(=O)₂R⁹, -N(R⁹)S(=O)₂R¹⁰,
 -S(=O)₂N(H)R⁹, -S(=O)₂NR¹⁰R⁹, -S(=O)(=NR¹⁰)R⁹, -N=S(=O)(R¹⁰)R⁹.

15 In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R⁶ represents a group selected from:

C₁-C₆-alkyl-, C₂-C₆-alkenyl-, C₂-C₆-alkynyl-, C₁-C₆-alkoxy-, halo-, hydroxy-, halo-C₁-C₆-alkyl-,
 halo-C₁-C₆-alkoxy-, cyano-, -aryl-, -heteroaryl-, -N(R⁹)(R¹⁰), -C(=O)-O-C₁-C₄-alkyl, -C(=O)-N(R⁹)(R¹⁰);
 20 said C₁-C₆-alkyl-, C₂-C₆-alkenyl-, C₂-C₆-alkynyl-, aryl-, heteroaryl- or C₁-C₆-alkoxy- group being
 optionally substituted, one or more times, identically or differently, with a substituent selected from:
 halo-, cyano-, nitro-, hydroxy-, C₁-C₃-alkyl-, C₁-C₃-alkoxy-, halo-C₁-C₃-alkoxy-, hydroxy-C₁-C₃-alkoxy-,
 C₁-C₃-alkoxy-C₂-C₃-alkoxy-, C₃-C₇-cycloalkyl-, C₄-C₇-cycloalkenyl-,

25 3- to 10-membered heterocycloalkyl-, 4- to 10-membered heterocycloalkenyl-, aryl-, heteroaryl-,
 -C(=O)R⁹, -C(=O)O-(C₁-C₄-alkyl), -OC(=O)-R⁹, -N(H)C(=O)R⁹, -N(R¹⁰)C(=O)R⁹, -N(H)C(=O)NR¹⁰R⁹,
 -N(R¹¹)C(=O)NR¹⁰R⁹, -N(H)R⁹, -NR¹⁰R⁹, -C(=O)N(H)R⁹, -C(=O)NR¹⁰R⁹, R⁹-S-, R⁹-S(=O)-, R⁹-S(=O)₂-,
 -N(H)S(=O)R⁹, -N(R¹⁰)S(=O)R⁹, -S(=O)N(H)R⁹, -S(=O)NR¹⁰R⁹, -N(H)S(=O)₂R⁹, -N(R⁹)S(=O)₂R¹⁰,
 -S(=O)₂N(H)R⁹, -S(=O)₂NR¹⁰R⁹, -S(=O)(=NR¹⁰)R⁹, -N=S(=O)(R¹⁰)R⁹.

30 In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R⁶ represents a group selected from:

C₁-C₆-alkyl-, C₁-C₆-alkoxy-, halo-, hydroxy-, fluoro-C₁-C₆-alkyl-, fluoro-C₁-C₆-alkoxy-, phenyl-, 5- to 6-
 membered heteroaryl-, cyano-, -C(=O)-O-C₁-C₄-alkyl, -C(=O)-N(R⁹)(R¹⁰);
 said C₁-C₆-alkyl- or C₁-C₆-alkoxy- group being optionally substituted, one or more times, identically or
 35 differently, with a substituent selected from:

C₁-C₃-alkyl-, C₁-C₃-alkoxy-, halo-C₁-C₃-alkoxy-, hydroxy-C₁-C₃-alkoxy-, C₁-C₃-alkoxy-C₂-C₃-alkoxy-,
C₃-C₇-cycloalkyl-, 3- to 10-membered heterocycloalkyl-, aryl-, heteroaryl-, -C(=O)R⁹,
-C(=O)O-(C₁-C₄-alkyl), -OC(=O)-R⁹, -N(H)C(=O)R⁹, -N(R¹⁰)C(=O)R⁹, -N(H)C(=O)NR¹⁰R⁹,
-N(R¹¹)C(=O)NR¹⁰R⁹, -N(H)R⁹, -NR¹⁰R⁹, -C(=O)N(H)R⁹, -C(=O)NR¹⁰R⁹.

5

In another embodiment, the present invention relates to compounds of the general formula (I),
supra, in which R⁶ represents a group selected from:

C₁-C₆-alkyl-, C₁-C₆-alkoxy-, C₃-C₆-cycloalkoxy-, halo-, hydroxy-, fluoro-C₁-C₆-alkyl-, fluoro-C₁-C₆-alkoxy-,
phenyl-, 5- to 6-membered heteroaryl-, cyano-, -C(=O)-O-C₁-C₄-alkyl, -C(=O)-N(R⁹)(R¹⁰), R⁹-S-,
10 R⁹-S(=O)-, R⁹-S(=O)₂-;

said C₁-C₆-alkyl- or C₁-C₆-alkoxy- group being optionally substituted, one or more times, identically or
differently, with a substituent selected from: C₁-C₃-alkyl-, C₁-C₃-alkoxy-, halo-C₁-C₃-alkoxy-,

hydroxy-C₁-C₃-alkoxy-, C₁-C₃-alkoxy-C₂-C₃-alkoxy-, C₃-C₇-cycloalkyl-,

3- to 10-membered heterocycloalkyl-, aryl-, heteroaryl-, -C(=O)R⁹,

15 -C(=O)O-(C₁-C₄-alkyl), -OC(=O)-R⁹, -N(H)C(=O)R⁹, -N(R¹⁰)C(=O)R⁹, -N(H)C(=O)NR¹⁰R⁹,
-N(R¹¹)C(=O)NR¹⁰R⁹, -N(H)R⁹, -NR¹⁰R⁹, -C(=O)N(H)R⁹, -C(=O)NR¹⁰R⁹.

In another embodiment, the present invention relates to compounds of the general formula (I),
supra, in which R⁶ represents a group selected from:

20 C₁-C₆-alkyl-, C₁-C₆-alkoxy-, halo-, hydroxy-, fluoro-C₁-C₆-alkyl-, fluoro-C₁-C₆-alkoxy-, cyano-,
-C(=O)-O-C₁-C₄-alkyl, -C(=O)-N(R⁹)(R¹⁰);

said C₁-C₆-alkyl- or C₁-C₆-alkoxy- group being optionally substituted, one or more times, identically or
differently, with a substituent selected from:

C₃-C₇-cycloalkyl-, 3- to 10-membered heterocycloalkyl-, aryl-, heteroaryl-, -C(=O)R⁹,

25 -C(=O)O-(C₁-C₄-alkyl), -OC(=O)-R⁹, -N(H)C(=O)R⁹, -N(R¹⁰)C(=O)R⁹, -N(H)C(=O)NR¹⁰R⁹,
-N(R¹¹)C(=O)NR¹⁰R⁹, -N(H)R⁹, -NR¹⁰R⁹, -C(=O)N(H)R⁹, -C(=O)NR¹⁰R⁹.

In another embodiment, the present invention relates to compounds of the general formula (I),
supra, in which R⁶ represents a group selected from:

30 C₁-C₆-alkyl-, C₁-C₆-alkoxy-, C₃-C₆-cycloalkoxy-, halo-, hydroxy-, cyano-, -C(=O)-O-C₁-C₄-alkyl,
-C(=O)-N(R⁹)(R¹⁰), R⁹-S-, R⁹-S(=O)-, R⁹-S(=O)₂-;

said C₁-C₆-alkyl-, and C₁-C₆-alkoxy- group being optionally substituted, one or more times, identically
or differently, with a substituent selected from:

halo-, cyano-, nitro-, hydroxy-, C₁-C₃-alkoxy-, halo-C₁-C₃-alkoxy-, hydroxy-C₁-C₃-alkoxy-,

35 C₁-C₃-alkoxy-C₂-C₃-alkoxy-, C₃-C₇-cycloalkyl-, 3- to 10-membered heterocycloalkyl-,

-C(=O)R⁹, -C(=O)O-R⁹, -C(=O)O-(C₁-C₄-alkyl), -N(H)C(=O)R⁹, -N(R¹⁰)C(=O)R⁹,
 -N(H)C(=O)NR¹⁰R⁹, -N(R¹¹)C(=O)NR¹⁰R⁹, -N(H)R⁹, -NR¹⁰R⁹, -C(=O)N(H)R⁹, -C(=O)NR¹⁰R⁹, R⁹-S-, R⁹-S(=O)-,
 R⁹-S(=O)₂-, -N(H)S(=O)R⁹, -N(R¹⁰)S(=O)R⁹, -S(=O)N(H)R⁹, -S(=O)NR¹⁰R⁹, -N(H)S(=O)₂R⁹, -N(R⁹)S(=O)₂R¹⁰,
 -S(=O)₂N(H)R⁹, -S(=O)₂NR¹⁰R⁹, -S(=O)(=NR¹⁰)R⁹, -N=S(=O)(R¹⁰)R⁹.

5

In another embodiment, the present invention relates to compounds of the general formula (I),
supra, in which R⁶ represents a group selected from:

C₁-C₆-alkyl-, C₁-C₆-alkoxy-, C₃-C₆-cycloalkoxy-, halo-, hydroxy-, cyano-, -C(=O)-O-C₁-C₄-alkyl,
 -C(=O)-N(R⁹)(R¹⁰), R⁹-S-, R⁹-S(=O)-, R⁹-S(=O)₂-;

10 said C₁-C₆-alkyl-, and C₁-C₆-alkoxy- group being optionally substituted, one or more times, identically
 or differently, with a substituent selected from:

halo-, C₁-C₃-alkoxy-, C₁-C₃-alkoxy-C₂-C₃-alkoxy-, C₃-C₇-cycloalkyl-,
 3- to 10-membered heterocycloalkyl-, -C(=O)R⁹, -C(=O)O-R⁹, -C(=O)O-(C₁-C₄-alkyl),
 -N(H)C(=O)R⁹, -N(R¹⁰)C(=O)R⁹, -N(H)C(=O)NR¹⁰R⁹, -N(R¹¹)C(=O)NR¹⁰R⁹, -N(H)R⁹, -NR¹⁰R⁹,
 15 -C(=O)N(H)R⁹, -C(=O)NR¹⁰R⁹, R⁹-S-, R⁹-S(=O)-, R⁹-S(=O)₂-, -N(H)S(=O)R⁹, -N(R¹⁰)S(=O)R⁹,
 -S(=O)N(H)R⁹, -S(=O)NR¹⁰R⁹, -N(H)S(=O)₂R⁹, -N(R⁹)S(=O)₂R¹⁰, -S(=O)₂N(H)R⁹, -S(=O)₂NR¹⁰R⁹,
 -S(=O)(=NR¹⁰)R⁹, -N=S(=O)(R¹⁰)R⁹.

In another embodiment, the present invention relates to compounds of the general formula (I),
 20 *supra*, in which R⁶ represents a group selected from:

C₁-C₆-alkyl-, C₁-C₆-alkoxy-, C₃-C₆-cycloalkoxy-, halo-, hydroxy-, cyano-,
 -C(=O)-O-C₁-C₄-alkyl, -C(=O)-N(R⁹)(R¹⁰), R⁹-S-, R⁹-S(=O)-, R⁹-S(=O)₂-;

said C₁-C₆-alkyl-, and C₁-C₆-alkoxy- group being optionally substituted, one or more times, identically
 or differently, with a substituent selected from:

25 halo-, C₁-C₃-alkoxy-, C₁-C₃-alkoxy-C₂-C₃-alkoxy-, C₃-C₇-cycloalkyl-.

In another embodiment, the present invention relates to compounds of the general formula (I),
supra, in which R⁶ represents a group selected from:

C₁-C₃-alkyl-, C₁-C₃-alkoxy-, halo-, hydroxy-, cyano-, -N(R⁹)(R¹⁰), -C(=O)-O-C₁-C₄-alkyl,

30 -C(=O)-N(R⁹)(R¹⁰); said C₁-C₃-alkyl- and C₁-C₃-alkoxy- group being optionally substituted, one or more
 times, identically or differently, with halo-, cyano-, C₁-C₃-alkoxy-, R⁹-S(=O)₂-.

In a preferred embodiment, the present invention relates to compounds of the general formula (I),
supra, in which R⁶ represents halogen, C₁-C₄-alkyl-, fluoro-C₁-C₃-alkyl-, C₁-C₄-alkoxy- or

35 fluoro-C₁-C₃-alkoxy-.

In a preferred embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R⁶ represents chloro-, C₁-C₄-alkyl-, fluoro-C₁-C₃-alkyl-, C₁-C₄-alkoxy-, (C₁-C₂-alkoxy)-(C₁-C₃-alkoxy)-, (oxetanyl)-O-, cyclopropyloxy- or fluoro-C₁-C₃-alkoxy-.

5

In another preferred embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R⁶ represents halo, C₁-C₃-alkoxy-, halo-C₁-C₃-alkoxy- or C₃-C₆-cycloalkoxy-.

10 In another preferred embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R⁶ represents F₃C-O-, F₃C-CH₂-O-, cyclopropyloxy-, chloro- or H₃C-O-.

In another preferred embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R⁶ represents a group selected from: methoxy-, difluoromethoxy-, trifluoromethoxy-, methyl-, trifluormethyl-, tert-butyl-, chloro-, bromo-, cyano-, methoxymethyl-, -
15 C(=O)NH₂, -CH₂-S(=O)₂-CH₃.

In another preferred embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R⁶ represents halogen.

20 In another preferred embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R⁶ represents fluoro-C₁-C₃-alkyl-.

In another preferred embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R⁶ represents fluoro-C₁-C₃-alkoxy-.

25

In another preferred embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R⁶ represents C₁-C₄-alkoxy-.

30 In another preferred embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R⁶ represents cyclopropyloxy-.

In another preferred embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R⁶ represents cyclopropylmethoxy-.

In a particularly preferred embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R⁶ represents chloro, C₁-C₄-alkyl-, methoxy-, difluoromethoxy-, trifluoromethoxy-, trifluoromethyl-, -C(=O)-NH₂, -CH₂-O-CH₃ or -CH₂-S(=O)₂-CH₃.

- 5 In another particularly preferred embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R⁶ represents difluoromethoxy- or trifluoromethoxy-.

In another particularly preferred embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R⁶ represents chloro, C₁-C₄-alkyl-, methoxy-, trifluoromethoxy- or
10 trifluoromethyl-.

In another particularly preferred embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R⁶ represents chloro.

- 15 In another particularly preferred embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R⁶ represents C₁-C₄-alkyl-.

In another particularly preferred embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R⁶ represents methoxy.

20 In another particularly preferred embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R⁶ represents trifluoromethyl.

In another particularly preferred embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R⁶ represents trifluoromethoxy.
25

In a particularly preferred embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R⁶ represents difluoromethoxy-.

- 30 In another particularly preferred embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R⁶ represents *tert*-butyl.

In another particularly preferred embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R⁶ represents -C(=O)-N(R⁹)(R¹⁰).

35

In a particularly preferred embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R⁶ represents -C(=O)-NH₂.

5 In a particularly preferred embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R⁶ represents -CH₂-O-CH₃.

In a particularly preferred embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R⁶ represents -CH₂-S(=O)₂-CH₃.

10 In a particularly preferred embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R⁶ represents a group selected from: R⁹-S-, R⁹-S(=O)-, R⁹-S(=O)₂-, wherein R⁹ represents a C₁-C₃-alkyl- group, preferably a methyl- group.

15 In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R⁷ represents -H, C₁-C₃-alkyl- or C₁-C₃-alkoxy-C₁-C₃-alkyl-.

In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R⁷ represents -H or C₁-C₃-alkyl-.

20 In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R⁹ represents -H or C₁-C₃-alkyl-.

In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R⁹ represents -H.

25 In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R¹⁰ represents -H or C₁-C₃-alkyl-.

30 In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R¹⁰ represents -H.

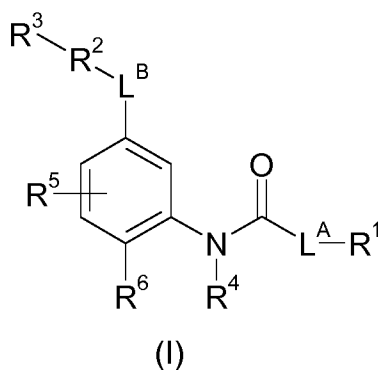
In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R¹¹ represents -H or C₁-C₃-alkyl-.

In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R¹¹ represents -H.

It is to be understood that the present invention relates also to any combination of the preferred
5 embodiments described above.

Some examples of combinations are given hereinafter. However, the invention is not limited to these combinations.

10 In a preferred embodiment, the present invention relates to compounds of the general formula (I),



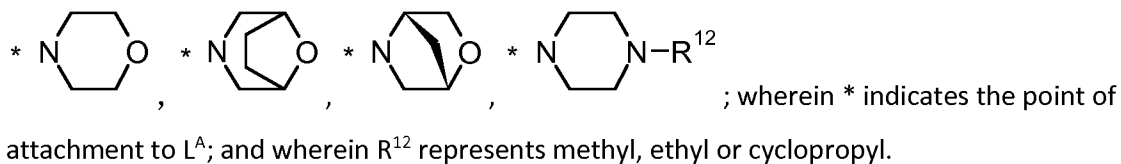
in which :

15 L^A represents -CH₂-, -CH(CH₃)-, -C(CH₃)₂-, -CH(C₂H₅)-,

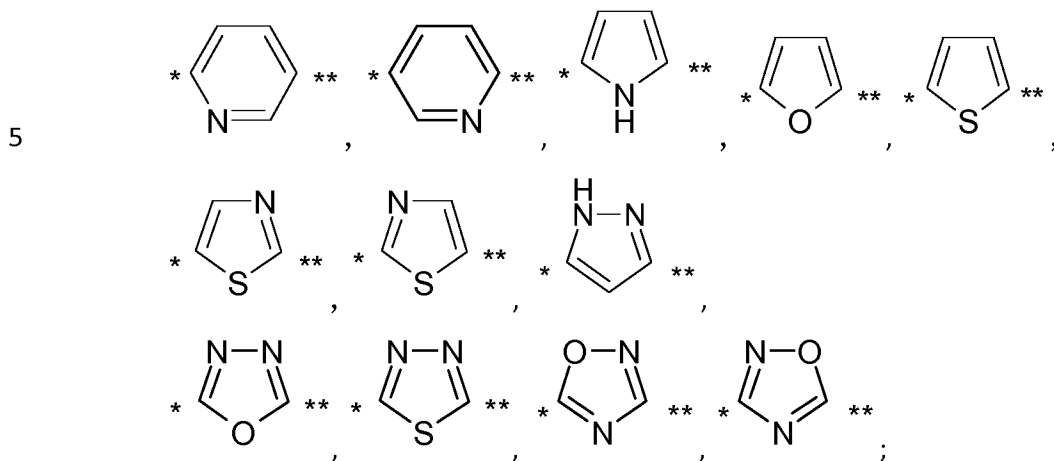
or
 ; wherein the cyclobutyl- and the cyclopropyl- ring are optionally substituted one or more times, identically or differently, with a substituent selected from: halo-, hydroxy-, cyano-, C₁-C₃-alkyl-, C₁-C₃-alkoxy-;

20 L^B represents *N(H)-C(=O)** or *C(=O)-N(H)**;
 wherein " * " indicates the point of attachment to R², and " ** " indicates the point of attachment to the phenyl group;

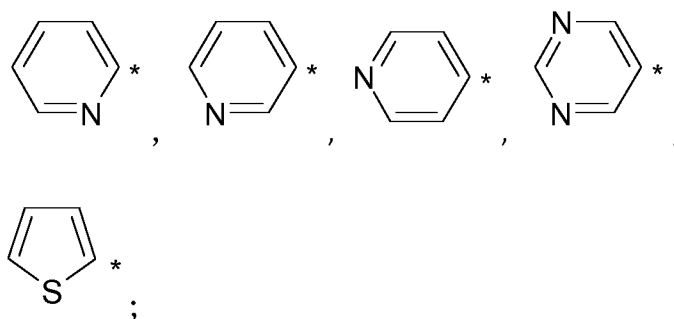
R¹ represents a group selected from:



R² represents a group selected from:



R³ represents a group selected from:



wherein " * " indicates the point of attachment to R²;

wherein said group is optionally substituted one time with a substituent selected from:

halo-, hydroxy-, -N(R⁹)(R¹⁰), -N(H)C(=O)R⁹, cyano-, nitro-, C₁-C₃-alkyl-, C₁-C₃-alkoxy-, halo-C₁-C₃-alkyl-, hydroxy-C₁-C₃-alkyl-, amino-C₁-C₃-alkyl-, halo-C₁-C₃-alkoxy-;

R⁴ represents a hydrogen atom;

R⁵ represents a hydrogen atom;

R⁶ represents a group selected from:

C₁-C₆-alkyl-, C₁-C₆-alkoxy-, C₃-C₆-cycloalkoxy-, halo-, hydroxy-, fluoro-C₁-C₆-alkyl-, fluoro-C₁-C₆-alkoxy-, phenyl-, 5- to 6-membered heteroaryl-, cyano-, -C(=O)-O-C₁-C₄-alkyl, -C(=O)-N(R⁹)(R¹⁰), R⁹-S-, R⁹-S(=O)-, R⁹-S(=O)₂-;

5 said C₁-C₆-alkyl- or C₁-C₆-alkoxy- group being optionally substituted, one or more times, identically or differently, with a substituent selected from: C₁-C₃-alkyl-, C₁-C₃-alkoxy-, halo-C₁-C₃-alkoxy-, hydroxy-C₁-C₃-alkoxy-, C₁-C₃-alkoxy-C₂-C₃-alkoxy-, C₃-C₇-cycloalkyl-, 3- to 10-membered heterocycloalkyl-, aryl-, heteroaryl-, -C(=O)R⁹, -C(=O)O-(C₁-C₄-alkyl), -OC(=O)-R⁹, -N(H)C(=O)R⁹, -N(R¹⁰)C(=O)R⁹, -N(H)C(=O)NR¹⁰R⁹,
10 -N(R¹¹)C(=O)NR¹⁰R⁹, -N(H)R⁹, -NR¹⁰R⁹, -C(=O)N(H)R⁹, -C(=O)NR¹⁰R⁹;

R⁷ represents a hydrogen atom or a C₁-C₃-alkyl- or C₁-C₃-alkoxy-C₁-C₃-alkyl- group;

R⁹, R¹⁰, R¹¹

15 represent, independently from each other, a hydrogen atom or a C₁-C₃-alkyl- or C₁-C₃-alkoxy-C₁-C₃-alkyl- group;

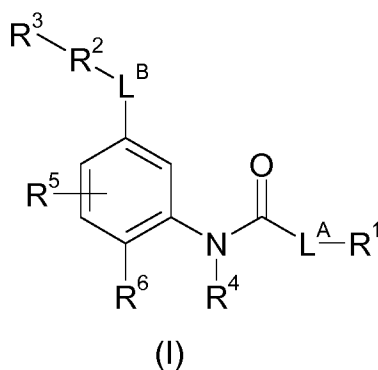
or

R⁹R¹⁰ together with the atom or the group of atoms they are attached to, form a 3- to
20 10-membered heterocycloalkyl- or 4- to 10-membered heterocycloalkenyl- group;

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

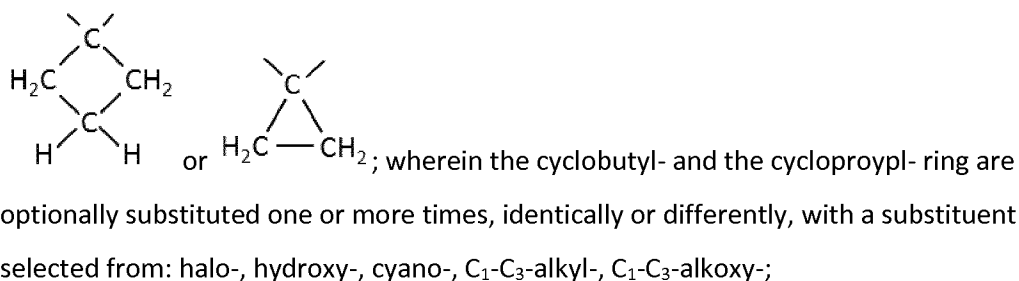
In another preferred embodiment, the present invention relates to compounds of the general

25 formula (I),



in which :

L^A represents -CH₂-, -CH(CH₃)-, -C(CH₃)₂-, -CH(C₂H₅)-,

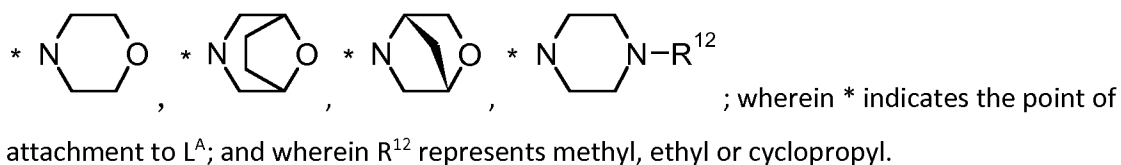


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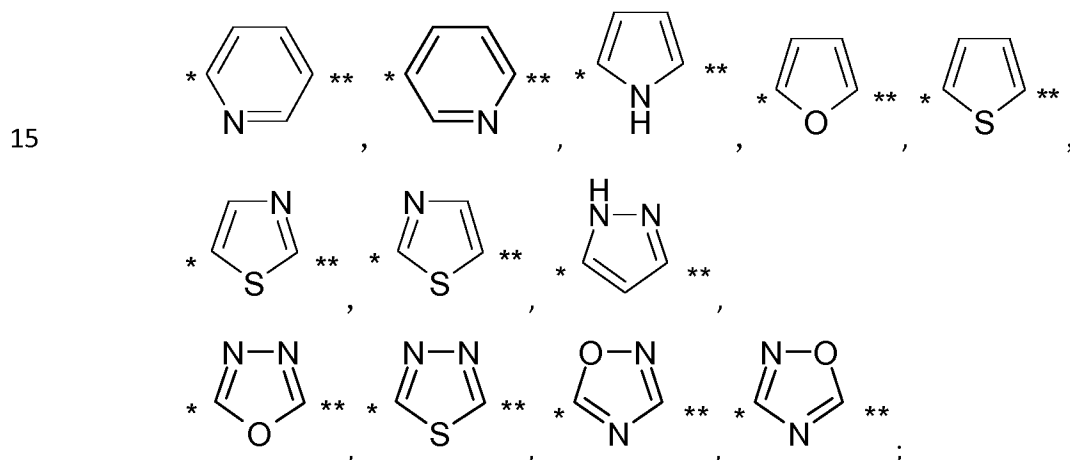
L^B represents *N(H)-C(=O)** or *C(=O)-N(H)**;

wherein " * " indicates the point of attachment to R², and " ** " indicates the point of attachment to the phenyl group;

10 R¹ represents a group selected from:

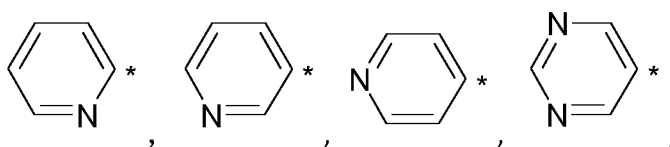


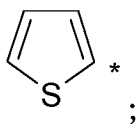
R² represents a group selected from:



wherein " * " indicates the point of attachment to R³, and " ** " indicates the point of attachment to L^B; wherein said group is optionally substituted, one or more times, identically or differently, with a C₁-C₃-alkyl- group;

R³ represents a group selected from:





wherein " * " indicates the point of attachment to R²;

wherein said group is optionally substituted one time with a substituent selected from:

halo-, hydroxy-, -N(R⁹)(R¹⁰), -N(H)C(=O)R⁹, cyano-, nitro-, C₁-C₃-alkyl-, C₁-C₃-alkoxy-,

halo-C₁-C₃-alkyl-, hydroxy-C₁-C₃-alkyl-, amino-C₁-C₃-alkyl-, halo-C₁-C₃-alkoxy-;

R⁴ represents a hydrogen atom;

R⁵ represents a hydrogen atom;

R⁶ represents a group selected from:

C₁-C₆-alkyl-, C₁-C₆-alkoxy-, C₃-C₆-cycloalkoxy-, halo-, hydroxy-, fluoro-C₁-C₆-alkyl-,
fluoro-C₁-C₆-alkoxy-, cyano-, -C(=O)-O-C₁-C₄-alkyl-, -C(=O)-N(R⁹)(R¹⁰), R⁹-S-, R⁹-S(=O)-,
R⁹-S(=O)₂-;

said C₁-C₆-alkyl- or C₁-C₆-alkoxy- group being optionally substituted, one or more times,
identically or differently, with a substituent selected from: C₁-C₃-alkyl-, C₁-C₃-alkoxy-, halo-

C₁-C₃-alkoxy-, hydroxy-C₁-C₃-alkoxy-, C₁-C₃-alkoxy-C₂-C₃-alkoxy-, C₃-C₇-cycloalkyl-,

3- to 10-membered heterocycloalkyl-, -C(=O)R⁹, -C(=O)O-(C₁-C₄-alkyl),

-OC(=O)-R⁹, -N(H)C(=O)R⁹, -N(R¹⁰)C(=O)R⁹, -N(H)C(=O)NR¹⁰R⁹,

-N(R¹¹)C(=O)NR¹⁰R⁹, -N(H)R⁹, -NR¹⁰R⁹, -C(=O)N(H)R⁹, -C(=O)NR¹⁰R⁹;

R⁷ represents a hydrogen atom or a C₁-C₃-alkyl- or C₁-C₃-alkoxy-C₁-C₃-alkyl- group;

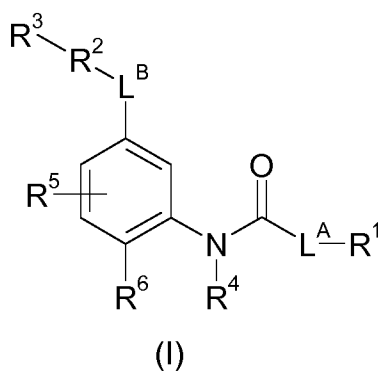
R⁹, R¹⁰, R¹¹

represent, independently from each other, a hydrogen atom or a C₁-C₃-alkyl- or

C₁-C₃-alkoxy-C₁-C₃-alkyl- group;

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

In another preferred embodiment, the present invention relates to compounds of the general formula (I),



in which :

L^A represents $-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-CH(C_2H_5)-$,

5 or H_2C-CH_2 ; wherein the cyclobutyl- and the cyclopropyl- ring are optionally substituted one or more times, identically or differently, with a substituent selected from: halo-, hydroxy-, cyano-, C_1 - C_3 -alkyl-, C_1 - C_3 -alkoxy-;

L^B represents $*N(H)-C(=O)**$ or $*C(=O)-N(H)**$;

10 wherein " * " indicates the point of attachment to R^2 , and " ** " indicates the point of attachment to the phenyl group;

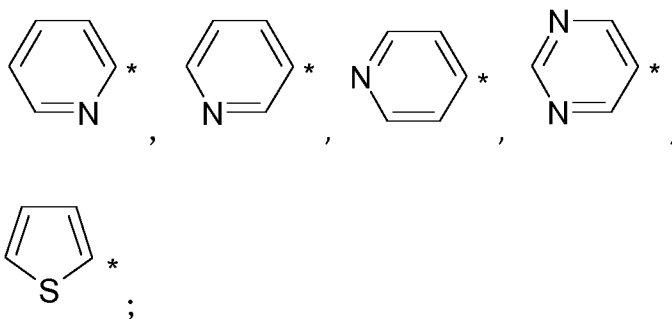
R^1 represents a group selected from:

15 ; wherein * indicates the point of attachment to L^A ; and wherein R^{12} represents methyl, ethyl or cyclopropyl.

R^2 represents a group selected from:

20 ; wherein " * " indicates the point of attachment to R^3 , and " ** " indicates the point of attachment to L^B ; wherein said group is optionally substituted, one or more times, identically or differently, with a C_1 - C_3 -alkyl- group;

R^3 represents a group selected from:



wherein " * " indicates the point of attachment to R^2 ;

wherein said group is optionally substituted one time with a substituent selected from:

- 5 halo-, hydroxy-, $-N(R^9)(R^{10})$, $-N(H)C(=O)R^9$, cyano-, nitro-, C_1 - C_3 -alkyl-, C_1 - C_3 -alkoxy-,
halo- C_1 - C_3 -alkyl-, hydroxy- C_1 - C_3 -alkyl-, amino- C_1 - C_3 -alkyl-, halo- C_1 - C_3 -alkoxy-;

R^4 represents a hydrogen atom;

10 R^5 represents a hydrogen atom;

R^6 represents a group selected from:

- C_1 - C_6 -alkyl-, C_1 - C_6 -alkoxy-, C_3 - C_6 -cycloalkoxy-, halo-, hydroxy-, fluoro- C_1 - C_6 -alkyl-,
fluoro- C_1 - C_6 -alkoxy-, phenyl-, 5- to 6-membered heteroaryl-, cyano-, $-C(=O)-O-C_1-C_4$ -alkyl,
15 $-C(=O)-N(R^9)(R^{10})$, R^9-S- , $R^9-S(=O)-$, $R^9-S(=O)_2-$;
said C_1 - C_6 -alkyl- or C_1 - C_6 -alkoxy- group being optionally substituted, one or more times,
identically or differently, with a substituent selected from: C_1 - C_3 -alkyl-, C_1 - C_3 -alkoxy-, halo-
 C_1 - C_3 -alkoxy-, hydroxy- C_1 - C_3 -alkoxy-, C_1 - C_3 -alkoxy- C_2 - C_3 -alkoxy-, C_3 - C_7 -cycloalkyl-,
3- to 10-membered heterocycloalkyl-, aryl-, heteroaryl-, $-C(=O)R^9$,
20 $-C(=O)O-(C_1-C_4$ -alkyl), $-OC(=O)-R^9$, $-N(H)C(=O)R^9$, $-N(R^{10})C(=O)R^9$, $-N(H)C(=O)NR^{10}R^9$,
 $-N(R^{11})C(=O)NR^{10}R^9$, $-N(H)R^9$, $-NR^{10}R^9$, $-C(=O)N(H)R^9$, $-C(=O)NR^{10}R^9$;

R^7 represents a hydrogen atom or a C_1 - C_3 -alkyl- or C_1 - C_3 -alkoxy- C_1 - C_3 -alkyl- group;

- 25 R^9 , R^{10} , R^{11}
represent, independently from each other, a hydrogen atom or a C_1 - C_3 -alkyl- or
 C_1 - C_3 -alkoxy- C_1 - C_3 -alkyl- group;

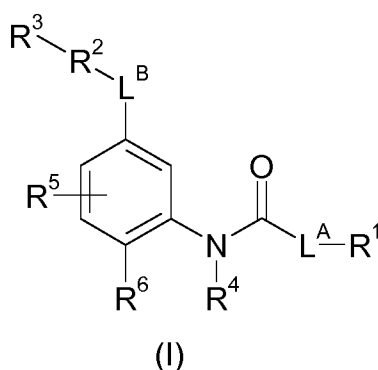
or

R^9R^{10} together with the atom or the group of atoms they are attached to, form a 3- to 10-membered heterocycloalkyl- or 4- to 10-membered heterocycloalkenyl- group;

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

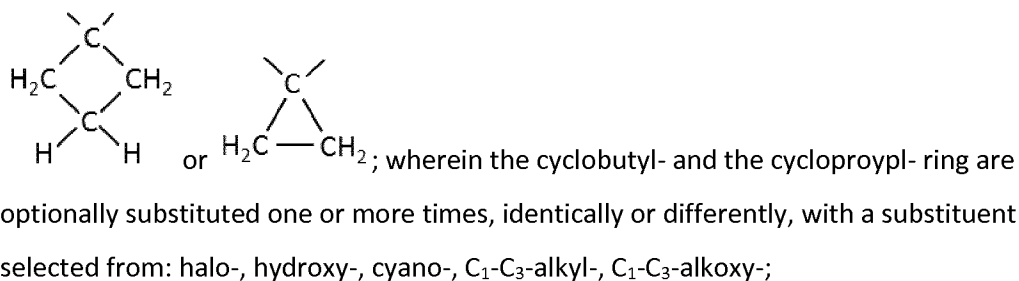
5

In another preferred embodiment, the present invention relates to compounds of the general formula (I),



10 in which :

L^A represents $-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-CH(C_2H_5)-$,

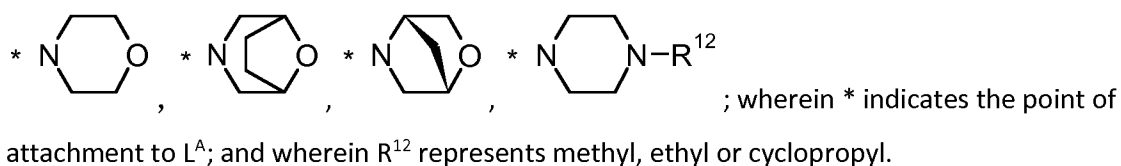


15

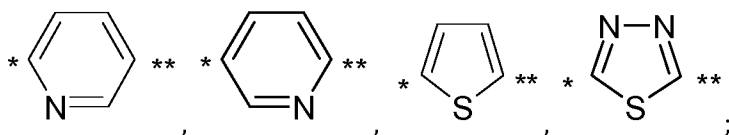
L^B represents $*N(H)-C(=O)**$ or $*C(=O)-N(H)**$;
wherein " * " indicates the point of attachment to R^2 , and " ** " indicates the point of attachment to the phenyl group;

20

R^1 represents a group selected from:

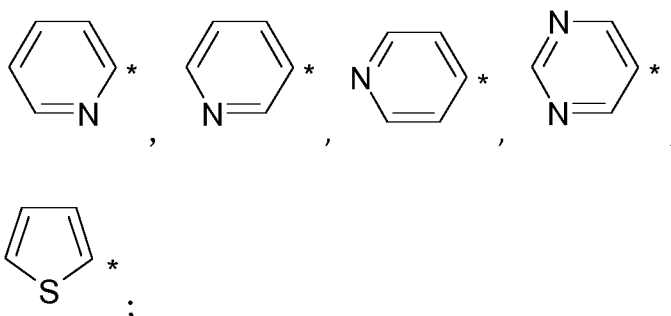


R² represents a group selected from:



wherein " * " indicates the point of attachment to R³, and " ** " indicates the point of attachment to L³; wherein said group is optionally substituted, one or more times, identically or differently, with a C₁-C₃-alkyl- group;

R³ represents a group selected from:



wherein " * " indicates the point of attachment to R²;

wherein said group is optionally substituted one time with a substituent selected from: halo-, hydroxy-, -N(R⁹)(R¹⁰), -N(H)C(=O)R⁹, cyano-, nitro-, C₁-C₃-alkyl-, C₁-C₃-alkoxy-, halo-C₁-C₃-alkyl-, hydroxy-C₁-C₃-alkyl-, amino-C₁-C₃-alkyl-, halo-C₁-C₃-alkoxy-;

R⁴ represents a hydrogen atom;

R⁵ represents a hydrogen atom;

R⁶ represents a group selected from:

C₁-C₆-alkyl-, C₁-C₆-alkoxy-, C₃-C₆-cycloalkoxy-, halo-, hydroxy-, fluoro-C₁-C₆-alkyl-, fluoro-C₁-C₆-alkoxy-, cyano-, -C(=O)-O-C₁-C₄-alkyl-, -C(=O)-N(R⁹)(R¹⁰), R⁹-S-, R⁹-S(=O)-, R⁹-S(=O)₂-;

said C₁-C₆-alkyl- or C₁-C₆-alkoxy- group being optionally substituted, one or more times, identically or differently, with a substituent selected from: C₁-C₃-alkyl-, C₁-C₃-alkoxy-, halo-

C₁-C₃-alkoxy-, hydroxy-C₁-C₃-alkoxy-, C₁-C₃-alkoxy-C₂-C₃-alkoxy-, C₃-C₇-cycloalkyl-, 3- to 10-membered heterocycloalkyl-, -C(=O)R⁹, -C(=O)O-(C₁-C₄-alkyl), -OC(=O)-R⁹, -N(H)C(=O)R⁹, -N(R¹⁰)C(=O)R⁹, -N(H)C(=O)NR¹⁰R⁹, -N(R¹¹)C(=O)NR¹⁰R⁹, -N(H)R⁹, -NR¹⁰R⁹, -C(=O)N(H)R⁹, -C(=O)NR¹⁰R⁹;

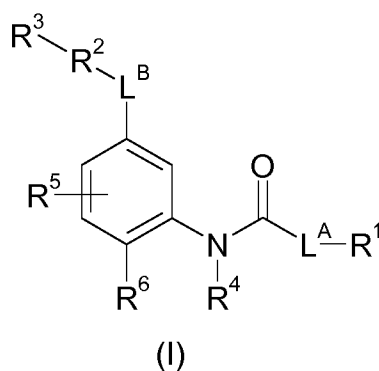
R^7 represents a hydrogen atom or a C_1 - C_3 -alkyl- or C_1 - C_3 -alkoxy- C_1 - C_3 -alkyl- group;

R^9, R^{10}, R^{11}

5 represent, independently from each other, a hydrogen atom or a C_1 - C_3 -alkyl- or C_1 - C_3 -alkoxy- C_1 - C_3 -alkyl- group;

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

10 In another preferred embodiment, the present invention relates to compounds of the general formula (I),



in which :

15

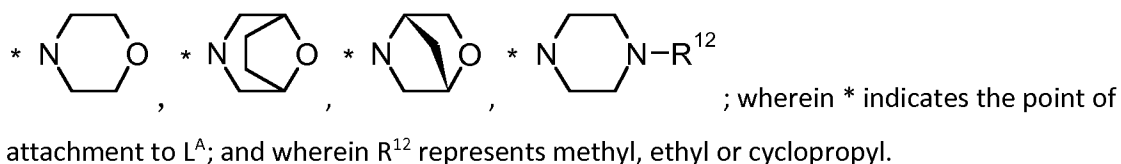
L^A represents $-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-CH(C_2H_5)-$,

or H_2C-CH_2 ; wherein the cyclobutyl- and the cyclopropyl- ring are optionally substituted one or more times, identically or differently, with a substituent selected from: halo-, hydroxy-, cyano-, C_1 - C_3 -alkyl-, C_1 - C_3 -alkoxy-;

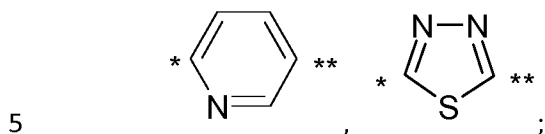
20

L^B represents $*N(H)-C(=O)**$ or $*C(=O)-N(H)**$;
 wherein " * " indicates the point of attachment to R^2 , and " ** " indicates the point of attachment to the phenyl group;

25 R^1 represents a group selected from:

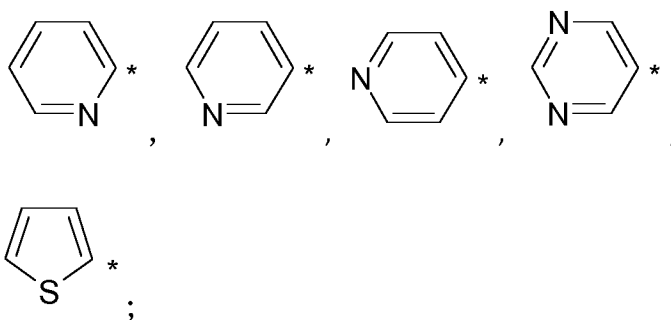


R² represents a group selected from:



wherein " * " indicates the point of attachment to R³, and " ** " indicates the point of attachment to L^B; wherein said group is optionally substituted, one or more times, identically or differently, with a C₁-C₃-alkyl- group;

10 R³ represents a group selected from:



wherein " * " indicates the point of attachment to R²;

wherein said group is optionally substituted one time with a substituent selected from:

15 halo-, hydroxy-, -N(R⁹)(R¹⁰), -N(H)C(=O)R⁹, cyano-, nitro-, C₁-C₃-alkyl-, C₁-C₃-alkoxy-, halo-C₁-C₃-alkyl-, hydroxy-C₁-C₃-alkyl-, amino-C₁-C₃-alkyl-, halo-C₁-C₃-alkoxy-;

R⁴ represents a hydrogen atom;

20 R⁵ represents a hydrogen atom;

R⁶ represents a group selected from:

C₁-C₆-alkyl-, C₁-C₆-alkoxy-, C₃-C₆-cycloalkoxy-, halo-, hydroxy-, fluoro-C₁-C₆-alkyl-,
 fluoro-C₁-C₆-alkoxy-, phenyl-, 5- to 6-membered heteroaryl-, cyano-, -C(=O)-O-C₁-C₄-alkyl,
 25 -C(=O)-N(R⁹)(R¹⁰), R⁹-S-, R⁹-S(=O)-, R⁹-S(=O)₂-;

said C₁-C₆-alkyl- or C₁-C₆-alkoxy- group being optionally substituted, one or more times, identically or differently, with a substituent selected from: C₁-C₃-alkyl-, C₁-C₃-alkoxy-, halo-C₁-C₃-alkoxy-, hydroxy-C₁-C₃-alkoxy-, C₁-C₃-alkoxy-C₂-C₃-alkoxy-, C₃-C₇-cycloalkyl-, 3- to 10-membered heterocycloalkyl-, aryl-, heteroaryl-, -C(=O)R⁹,
 5 -C(=O)O-(C₁-C₄-alkyl), -OC(=O)-R⁹, -N(H)C(=O)R⁹, -N(R¹⁰)C(=O)R⁹, -N(H)C(=O)NR¹⁰R⁹,
 -N(R¹¹)C(=O)NR¹⁰R⁹, -N(H)R⁹, -NR¹⁰R⁹, -C(=O)N(H)R⁹, -C(=O)NR¹⁰R⁹;

R⁷ represents a hydrogen atom or a C₁-C₃-alkyl- or C₁-C₃-alkoxy-C₁-C₃-alkyl- group;

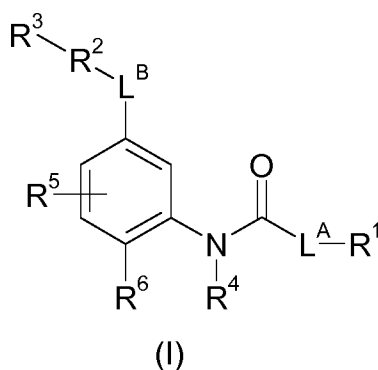
10 R⁹, R¹⁰, R¹¹
 represent, independently from each other, a hydrogen atom or a C₁-C₃-alkyl- or C₁-C₃-alkoxy-C₁-C₃-alkyl- group;

or

15 R⁹R¹⁰ together with the atom or the group of atoms they are attached to, form a 3- to 10-membered heterocycloalkyl- or 4- to 10-membered heterocycloalkenyl- group;

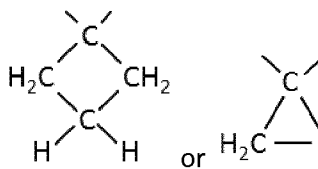
or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

20 In another preferred embodiment, the present invention relates to compounds of the general formula (I),



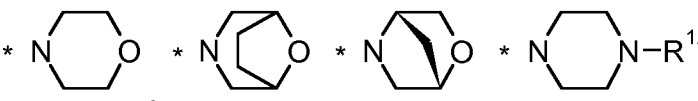
in which :

25 L^A represents -CH₂-, -CH(CH₃)-, -C(CH₃)₂-, -CH(C₂H₅)-,

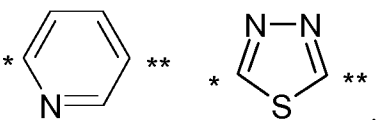

 or $\text{H}_2\text{C}-\text{CH}_2$; wherein the cyclobutyl- and the cyclopropyl- ring are optionally substituted one or more times, identically or differently, with a substituent selected from: halo-, hydroxy-, cyano-, $\text{C}_1\text{-C}_3$ -alkyl-, $\text{C}_1\text{-C}_3$ -alkoxy-;

5 L^{B} represents *N(H)-C(=O)** or *C(=O)-N(H)** ;
 wherein " * " indicates the point of attachment to R^2 , and " ** " indicates the point of attachment to the phenyl group;

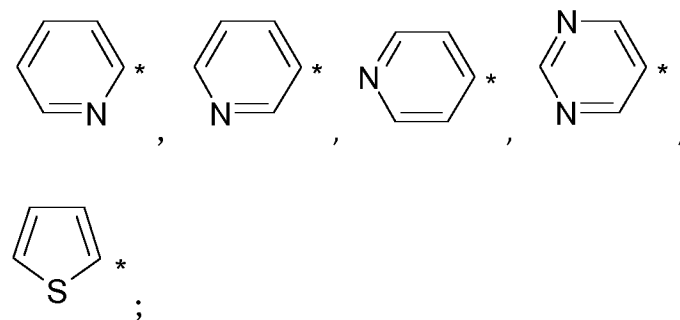
R^1 represents a group selected from:

10 
 ; wherein * indicates the point of attachment to L^{A} ; and wherein R^{12} represents methyl, ethyl or cyclopropyl.

R^2 represents a group selected from:

15 
 ;
 wherein " * " indicates the point of attachment to R^3 , and " ** " indicates the point of attachment to L^{B} ; wherein said group is optionally substituted, one or more times, identically or differently, with a $\text{C}_1\text{-C}_3$ -alkyl- group;

R^3 represents a group selected from:

20 
 ;

wherein " * " indicates the point of attachment to R^2 ;

wherein said group is optionally substituted one time with a substituent selected from:
 halo-, hydroxy-, $\text{-N(R}^9\text{)(R}^{10}\text{)}$, -N(H)C(=O)R^9 , cyano-, nitro-, $\text{C}_1\text{-C}_3$ -alkyl-, $\text{C}_1\text{-C}_3$ -alkoxy-,

halo-C₁-C₃-alkyl-, hydroxy-C₁-C₃-alkyl-, amino-C₁-C₃-alkyl-, halo-C₁-C₃-alkoxy-;

R⁴ represents a hydrogen atom;

5 R⁵ represents a hydrogen atom;

R⁶ represents a group selected from:

C₁-C₆-alkyl-, C₁-C₆-alkoxy-, C₃-C₆-cycloalkoxy-, halo-, hydroxy-, fluoro-C₁-C₆-alkyl-,
fluoro-C₁-C₆-alkoxy-, cyano-, -C(=O)-O-C₁-C₄-alkyl, -C(=O)-N(R⁹)(R¹⁰), R⁹-S-, R⁹-S(=O)-,
10 R⁹-S(=O)₂-;

said C₁-C₆-alkyl- or C₁-C₆-alkoxy- group being optionally substituted, one or more times,
identically or differently, with a substituent selected from: C₁-C₃-alkyl-, C₁-C₃-alkoxy-, halo-
C₁-C₃-alkoxy-, hydroxy-C₁-C₃-alkoxy-, C₁-C₃-alkoxy-C₂-C₃-alkoxy-, C₃-C₇-cycloalkyl-,
3- to 10-membered heterocycloalkyl-, -C(=O)R⁹, -C(=O)O-(C₁-C₄-alkyl),
15 -OC(=O)-R⁹, -N(H)C(=O)R⁹, -N(R¹⁰)C(=O)R⁹, -N(H)C(=O)NR¹⁰R⁹,
-N(R¹¹)C(=O)NR¹⁰R⁹, -N(H)R⁹, -NR¹⁰R⁹, -C(=O)N(H)R⁹, -C(=O)NR¹⁰R⁹;

R⁷ represents a hydrogen atom or a C₁-C₃-alkyl- or C₁-C₃-alkoxy-C₁-C₃-alkyl- group;

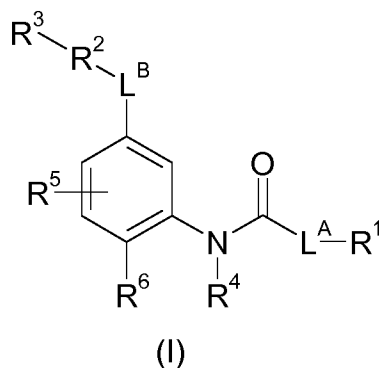
20 R⁹, R¹⁰, R¹¹

represent, independently from each other, a hydrogen atom or a C₁-C₃-alkyl- or
C₁-C₃-alkoxy-C₁-C₃-alkyl- group;

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

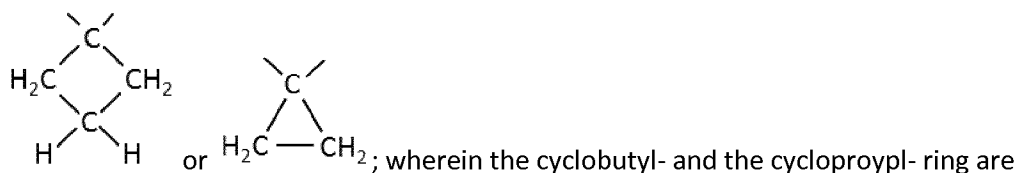
25

In another preferred embodiment, the present invention relates to compounds of the general
formula (I),



in which :

L^A represents -CH₂-, -CH(CH₃)-, -C(CH₃)₂-, -CH(C₂H₅)-,

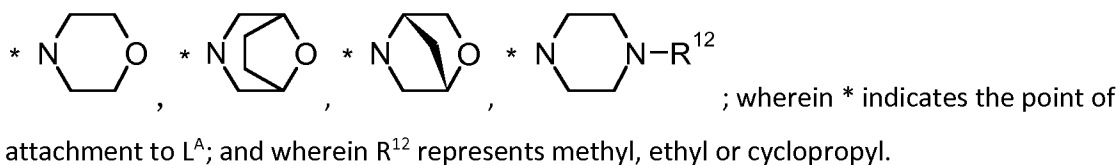


5 optionally substituted one or more times, identically or differently, with a substituent selected from: halo-, hydroxy-, cyano-, C₁-C₃-alkyl-, C₁-C₃-alkoxy-;

L^B represents *N(H)-C(=O)** or *C(=O)-N(H)**;

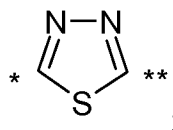
10 wherein " * " indicates the point of attachment to R², and " ** " indicates the point of attachment to the phenyl group;

R¹ represents a group selected from:



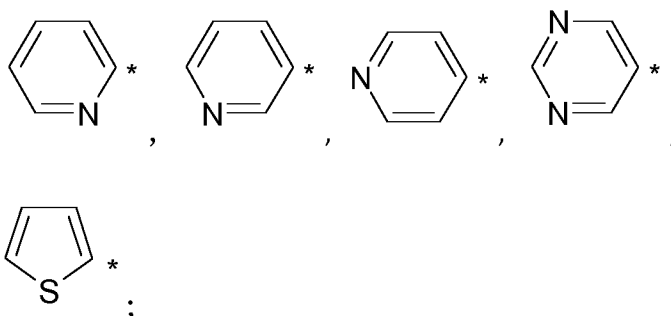
15

R² represents a group selected from:



20 wherein " * " indicates the point of attachment to R³, and " ** " indicates the point of attachment to L^B; wherein said group is optionally substituted, one or more times, identically or differently, with a C₁-C₃-alkyl- group;

R³ represents a group selected from:



wherein " * " indicates the point of attachment to R²;

wherein said group is optionally substituted one time with a substituent selected from:

halo-, hydroxy-, -N(R⁹)(R¹⁰), -N(H)C(=O)R⁹, cyano-, nitro-, C₁-C₃-alkyl-, C₁-C₃-alkoxy-, halo-C₁-C₃-alkyl-, hydroxy-C₁-C₃-alkyl-, amino-C₁-C₃-alkyl-, halo-C₁-C₃-alkoxy-;

5

R⁴ represents a hydrogen atom;

R⁵ represents a hydrogen atom;

10 R⁶ represents a group selected from:

C₁-C₆-alkyl-, C₁-C₆-alkoxy-, C₃-C₆-cycloalkoxy-, halo-, hydroxy-, fluoro-C₁-C₆-alkyl-, fluoro-C₁-C₆-alkoxy-, phenyl-, 5- to 6-membered heteroaryl-, cyano-, -C(=O)-O-C₁-C₄-alkyl, -C(=O)-N(R⁹)(R¹⁰), R⁹-S-, R⁹-S(=O)-, R⁹-S(=O)₂-;

said C₁-C₆-alkyl- or C₁-C₆-alkoxy- group being optionally substituted, one or more times,

15

identically or differently, with a substituent selected from: C₁-C₃-alkyl-, C₁-C₃-alkoxy-, halo-

C₁-C₃-alkoxy-, hydroxy-C₁-C₃-alkoxy-, C₁-C₃-alkoxy-C₂-C₃-alkoxy-, C₃-C₇-cycloalkyl-,

3- to 10-membered heterocycloalkyl-, aryl-, heteroaryl-, -C(=O)R⁹,

-C(=O)O-(C₁-C₄-alkyl), -OC(=O)-R⁹, -N(H)C(=O)R⁹, -N(R¹⁰)C(=O)R⁹, -N(H)C(=O)NR¹⁰R⁹,

-N(R¹¹)C(=O)NR¹⁰R⁹, -N(H)R⁹, -NR¹⁰R⁹, -C(=O)N(H)R⁹, -C(=O)NR¹⁰R⁹;

20

R⁷ represents a hydrogen atom or a C₁-C₃-alkyl- or C₁-C₃-alkoxy-C₁-C₃-alkyl- group;

R⁹, R¹⁰, R¹¹

represent, independently from each other, a hydrogen atom or a C₁-C₃-alkyl- or

25

C₁-C₃-alkoxy-C₁-C₃-alkyl- group;

or

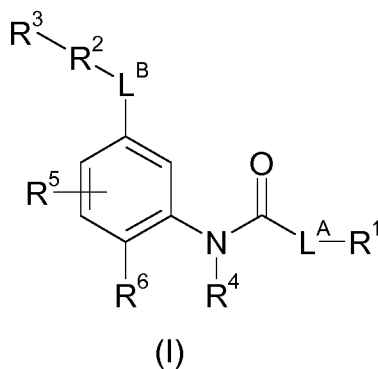
R⁹R¹⁰ together with the atom or the group of atoms they are attached to, form a 3- to 10-membered heterocycloalkyl- or 4- to 10-membered heterocycloalkenyl- group;

30

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

In another preferred embodiment, the present invention relates to compounds of the general formula (I),

35



in which :

L^A represents $-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-CH(C_2H_5)-$,

5 or H_2C-CH_2 ; wherein the cyclobutyl- and the cyclopropyl- ring are optionally substituted one or more times, identically or differently, with a substituent selected from: halo-, hydroxy-, cyano-, C_1-C_3 -alkyl-, C_1-C_3 -alkoxy-;

L^B represents $*N(H)-C(=O)**$ or $*C(=O)-N(H)**$;

10 wherein " * " indicates the point of attachment to R^2 , and " ** " indicates the point of attachment to the phenyl group;

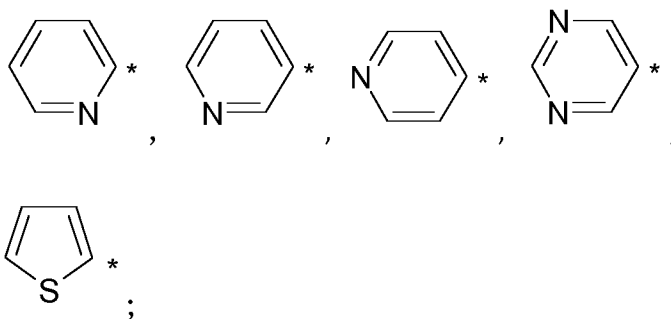
R^1 represents a group selected from:

15 ; wherein * indicates the point of attachment to L^A ; and wherein R^{12} represents methyl, ethyl or cyclopropyl.

R^2 represents a group selected from:

20 ; wherein " * " indicates the point of attachment to R^3 , and " ** " indicates the point of attachment to L^B ; wherein said group is optionally substituted, one or more times, identically or differently, with a C_1-C_3 -alkyl- group;

R^3 represents a group selected from:



wherein " * " indicates the point of attachment to R^2 ;

wherein said group is optionally substituted one time with a substituent selected from:

5 halo-, hydroxy-, $-N(R^9)(R^{10})$, $-N(H)C(=O)R^9$, cyano-, nitro-, C_1 - C_3 -alkyl-, C_1 - C_3 -alkoxy-,
halo- C_1 - C_3 -alkyl-, hydroxy- C_1 - C_3 -alkyl-, amino- C_1 - C_3 -alkyl-, halo- C_1 - C_3 -alkoxy-;

R^4 represents a hydrogen atom;

10 R^5 represents a hydrogen atom;

R^6 represents a group selected from:

C_1 - C_6 -alkyl-, C_1 - C_6 -alkoxy-, C_3 - C_6 -cycloalkoxy-, halo-, hydroxy-, fluoro- C_1 - C_6 -alkyl-,
fluoro- C_1 - C_6 -alkoxy-, cyano-, $-C(=O)-O-C_1$ - C_4 -alkyl-, $-C(=O)-N(R^9)(R^{10})$, R^9-S- , $R^9-S(=O)-$,
15 $R^9-S(=O)_2-$;
said C_1 - C_6 -alkyl- or C_1 - C_6 -alkoxy- group being optionally substituted, one or more times,
identically or differently, with a substituent selected from: C_1 - C_3 -alkyl-, C_1 - C_3 -alkoxy-, halo-
 C_1 - C_3 -alkoxy-, hydroxy- C_1 - C_3 -alkoxy-, C_1 - C_3 -alkoxy- C_2 - C_3 -alkoxy-, C_3 - C_7 -cycloalkyl-,
3- to 10-membered heterocycloalkyl-, $-C(=O)R^9$, $-C(=O)O-(C_1-C_4\text{-alkyl})$,
20 $-OC(=O)-R^9$, $-N(H)C(=O)R^9$, $-N(R^{10})C(=O)R^9$, $-N(H)C(=O)NR^{10}R^9$,
 $-N(R^{11})C(=O)NR^{10}R^9$, $-N(H)R^9$, $-NR^{10}R^9$, $-C(=O)N(H)R^9$, $-C(=O)NR^{10}R^9$;

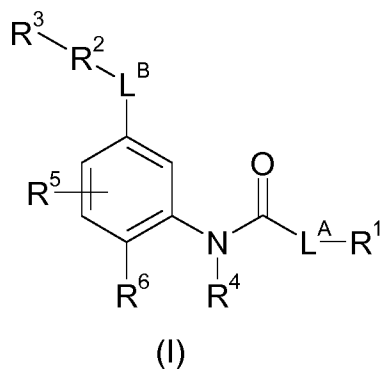
R^7 represents a hydrogen atom or a C_1 - C_3 -alkyl- or C_1 - C_3 -alkoxy- C_1 - C_3 -alkyl- group;

25 R^9 , R^{10} , R^{11}
represent, independently from each other, a hydrogen atom or a C_1 - C_3 -alkyl- or
 C_1 - C_3 -alkoxy- C_1 - C_3 -alkyl- group;

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

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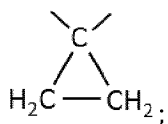
In another preferred embodiment, the present invention relates to compounds of the general formula (I),



in which :

5

L^A represents $-CH_2-$, $-CH(CH_3)-$ or

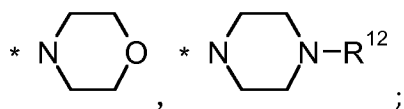


L^B represents $*N(H)-C(=O)**$ or $*C(=O)-N(H)**$;

10

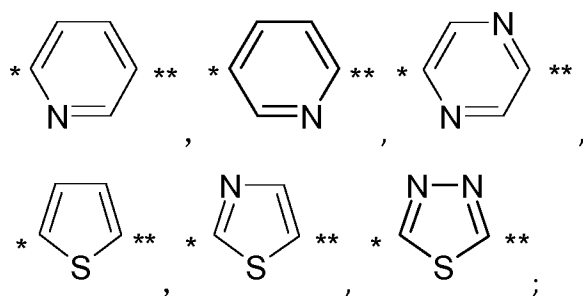
wherein " * " indicates the point of attachment to R^2 , and " ** " indicates the point of attachment to the phenyl group;

R^1 represents a group selected from:



15

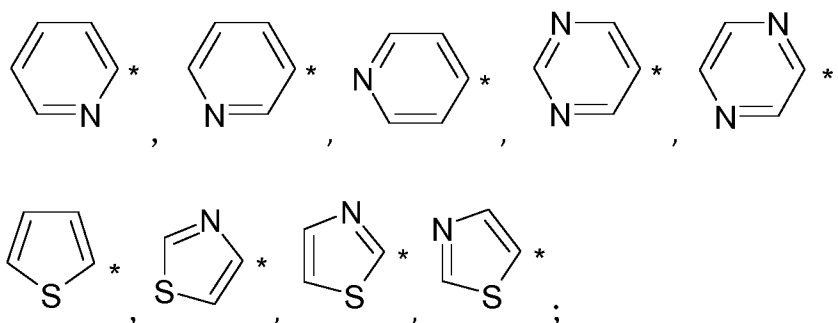
R^2 represents a group selected from:



wherein " * " indicates the point of attachment to R^3 , and " ** " indicates the point of attachment to L^B ;

20

R^3 represents a group selected from:



wherein " * " indicates the point of attachment to R^2 ;

wherein said group is optionally substituted one time with a substituent selected from:

5 fluoro-, halo-, $-NH_2$, $-CH_3$, H_3C-O- , $-CF_3$;

R^4 represents a hydrogen atom;

R^5 represents a hydrogen atom or a fluoro atom;

10

R^6 represents a group selected from:

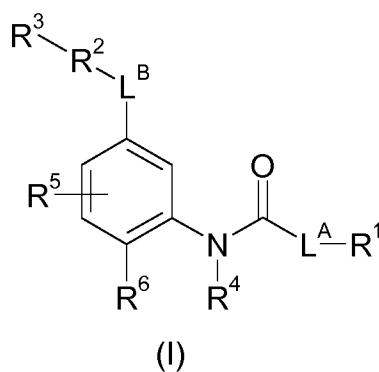
chloro-, C_1-C_4 -alkyl-, fluoro- C_1-C_3 -alkyl-, C_1-C_4 -alkoxy-, $(C_1-C_2$ -alkoxy)- $(C_1-C_3$ -alkoxy)-, (oxetanyl)-O-, cyclopropyloxy- or fluoro- C_1-C_3 -alkoxy-;

15 R^{12} represents methyl, ethyl or cyclopropyl;

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

In another preferred embodiment, the present invention relates to compounds of the general

20 formula (I),



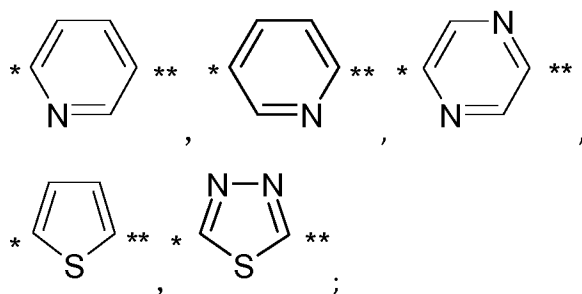
in which :

L^A represents a methylene group, said methylene group being optionally substituted, one or two times with a C₁-C₃-alkyl- group;
 or, when two C₁-C₃-alkyl- groups are present at the same carbon atom, the two substituents, together with the carbon atom they are attached to, may form a
 5 C₃-C₆-cycloalkyl- ring;

L^B represents *N(H)-C(=O)** or *C(=O)-N(H)**;
 wherein " * " indicates the point of attachment to R², and " ** " indicates the point of attachment to the phenyl group;

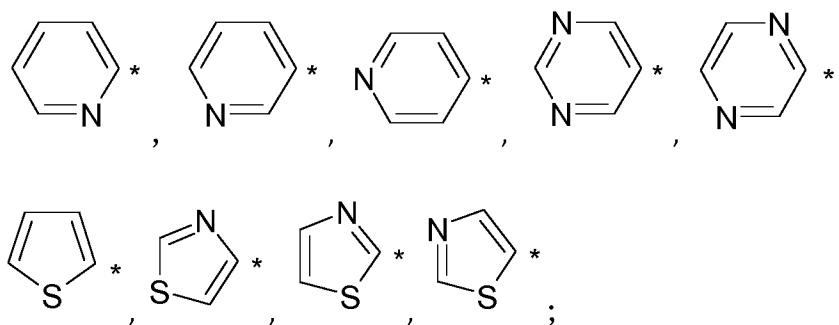
R¹ represents a group selected from:
 5- to 8-membered heterocycloalkyl-;
 wherein said 5- to 8-membered heterocycloalkyl- group is optionally substituted, one time with a C₁-C₃-alkyl- group;

R² represents a group selected from:



wherein " * " indicates the point of attachment to R³, and " ** " indicates the point of attachment to L^B;

R³ represents a group selected from:



wherein " * " indicates the point of attachment to R²;
 wherein said group is optionally substituted one time with a substituent selected from:
 halo-, -N(R⁹)(R¹⁰), C₁-C₃-alkyl-, C₁-C₃-alkoxy-, halo-C₁-C₃-alkyl-;

R⁴ represents a hydrogen atom;

R⁵ represents a hydrogen atom;

5

R⁶ represents a group selected from:

C₁-C₆-alkoxy-, C₃-C₆-cycloalkoxy-, halo-;

said C₁-C₆-alkoxy- group being optionally substituted, one or more times, identically or differently, with a halogen atom;

10

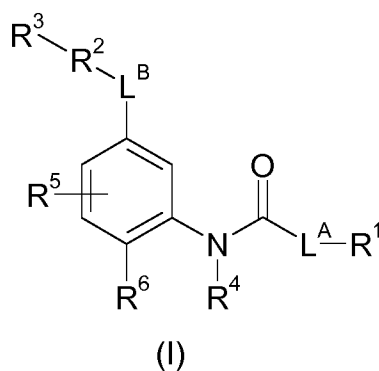
R⁹ represents a hydrogen atom;

R¹⁰ represents a hydrogen atom;

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

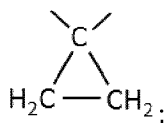
15

In another preferred embodiment, the present invention relates to compounds of the general formula (I),



20 in which :

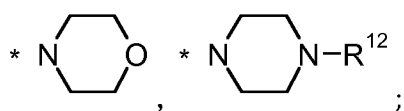
L^A represents -CH₂-, -CH(CH₃)- or



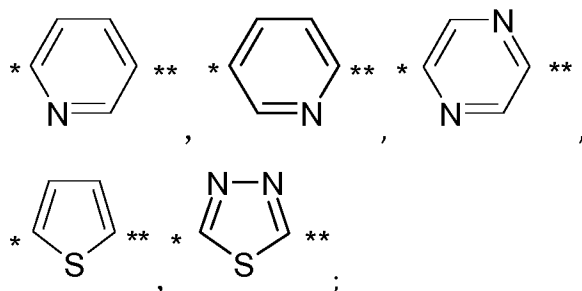
L^B represents *N(H)-C(=O)** or *C(=O)-N(H)**;

25 wherein " * " indicates the point of attachment to R², and " ** " indicates the point of attachment to the phenyl group;

R¹ represents a group selected from:

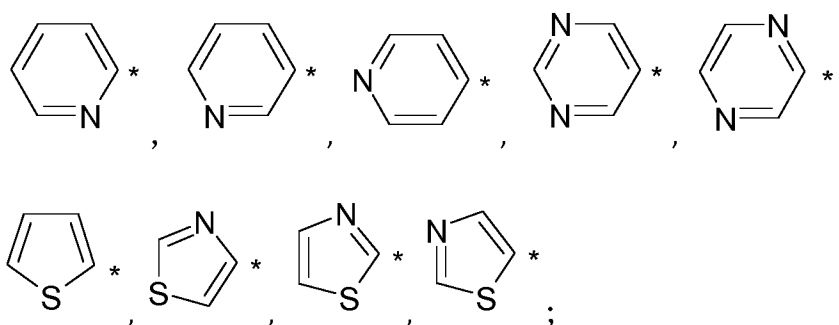


R² represents a group selected from:



wherein " * " indicates the point of attachment to R³, and " ** " indicates the point of attachment to L^B;

10 R³ represents a group selected from:



wherein " * " indicates the point of attachment to R²;

wherein said group is optionally substituted one time with a substituent selected from:

15 halo-, -N(R⁹)(R¹⁰), C₁-C₃-alkyl-, C₁-C₃-alkoxy-, halo-C₁-C₃-alkyl-;

R⁴ represents a hydrogen atom;

R⁵ represents a hydrogen atom;

20 R⁶ represents a group selected from:

C₁-C₆-alkoxy-, C₃-C₆-cycloalkoxy-, halo-;

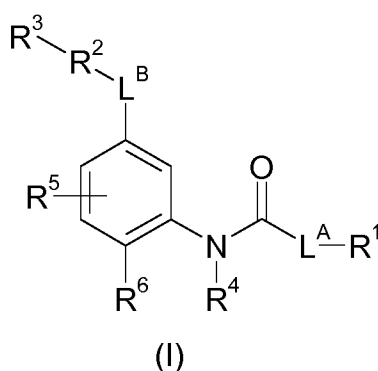
said C₁-C₆-alkoxy- group being optionally substituted, one or more times, identically or differently, with a halogen atom;

25

- R^9 represents a hydrogen atom;
 R^{10} represents a hydrogen atom;
 R^{12} represents methyl, ethyl or cyclopropyl;

5 or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

In another preferred embodiment, the present invention relates to compounds of the general formula (I),

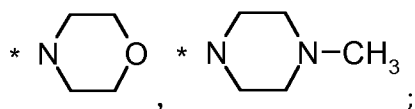


10 in which :

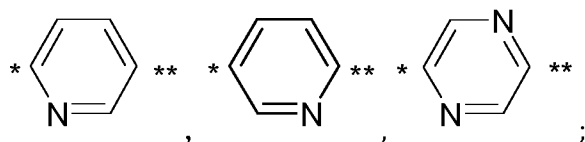
L^A represents a $-CH_2-$ or $-C(H)(CH_3)-$;

15 L^B represents $*N(H)-C(=O)**$;
 wherein " * " indicates the point of attachment to R^2 , and " ** " indicates the point of attachment to the phenyl group;

R^1 represents a group selected from:

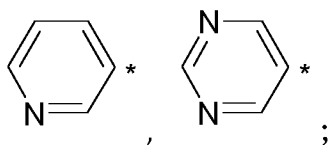


R^2 represents a group selected from:



25 wherein " * " indicates the point of attachment to R^3 , and " ** " indicates the point of attachment to L^B ;

R³ represents a group selected from:



wherein " * " indicates the point of attachment to R²;

5 wherein said group is optionally substituted one time with a substituent selected from:
halo-, -N(R⁹)(R¹⁰), C₁-C₃-alkyl-, C₁-C₃-alkoxy-, halo-C₁-C₃-alkyl-;

R⁴ represents a hydrogen atom or a C₁-C₃-alkyl- group;

10 R⁵ represents a hydrogen atom ;

R⁶ represents a group selected from:

C₁-C₆-alkoxy-, C₃-C₆-cycloalkoxy-, halo- ;

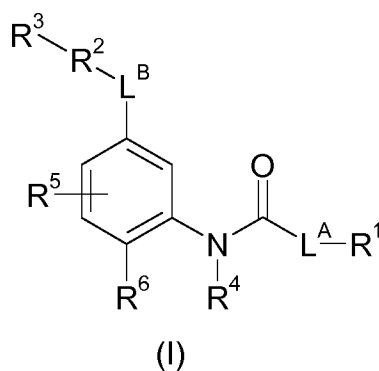
15 said C₁-C₆-alkoxy- group being optionally substituted, one or more times, identically or differently, with a substituent selected from: halo- ;

R⁹ represents a hydrogen atom;

R¹⁰ represents a hydrogen atom;

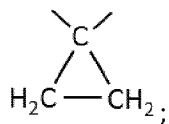
20 or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

In another preferred embodiment, the present invention relates to compounds of the general formula (I),



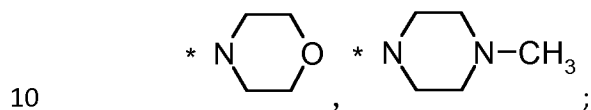
25 in which :

L^A represents -CH₂-, -C(H)(CH₃)- or

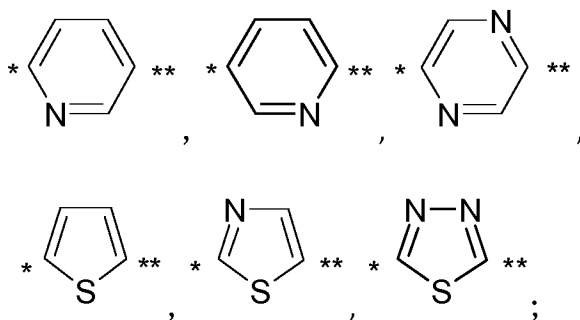


5 L^B represents *N(H)-C(=O)**;
wherein " * " indicates the point of attachment to R², and " ** " indicates the point of attachment to the phenyl group;

R¹ represents a group selected from:

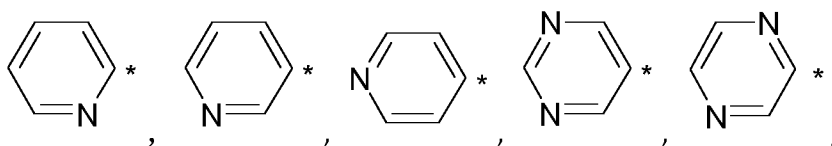


R² represents a group selected from:



15 wherein " * " indicates the point of attachment to R³, and " ** " indicates the point of attachment to L^B;

R³ represents a group selected from:



20 wherein said group is optionally substituted one time with a substituent selected from: fluoro-, chloro-, -NH₂, H₃C-, H₃C-O-, F₃C-.

R⁴ represents a hydrogen atom ;

25 R⁵ represents a hydrogen atom ;

R⁶ represents a group selected from:

chloro-, C₁-C₄-alkyl-, fluoro-C₁-C₃-alkyl-, C₁-C₄-alkoxy-,

(C₁-C₂-alkoxy)-(C₁-C₃-alkoxy)-, (oxetanyl)-O-, cyclopropyloxy- or fluoro-C₁-C₃-alkoxy-;

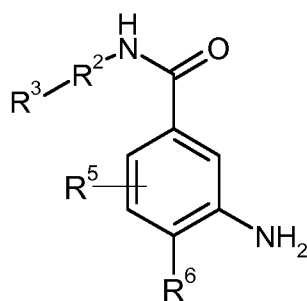
or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

It is to be understood that the present invention relates also to any combination of the preferred embodiments described above.

More particularly still, the present invention covers compounds of general formula (I) which are disclosed in the Examples section of this text, *infra*.

In accordance with another aspect, the present invention covers methods of preparing compounds of the present invention, said methods comprising the steps as described in the Experimental Section herein.

In a preferred embodiment, the present invention relates to a method of preparing a compound of general formula (I), *supra*, said method comprising the step of allowing an intermediate compound of general formula (VI):



(VI)

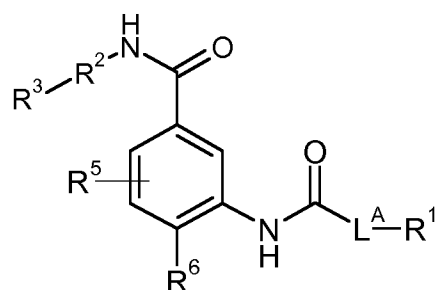
in which R², R³, R⁵, and R⁶ are as defined for general formula (I), *supra*;

to react with a carboxylic acid HO₂C-L^A-R¹ or the corresponding acyl chloride Cl-C(=O)-L^A-R¹, wherein

L^A and R¹ are as defined for the compounds of general formula (I), *supra*; or alternatively

to react with suitable reagents, such as Cl-C(=O)-L^A-LG, in which L^A is as defined for the compounds of general formula (I), and LG stands for a leaving group, preferably chloro or bromo, and subsequently with agents suitable for the introduction of R¹, exemplified by but not limited to cyclic secondary amines;

thereby giving, upon optional deprotection, a compound of general formula (Ia):

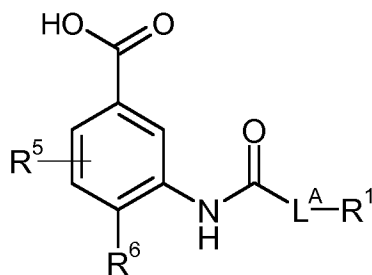


(Ia)

in which L^A , R^1 , R^2 , R^3 , R^5 , and R^6 are as defined for the compounds of general formula (I), *supra*.

5

In accordance with another embodiment, the present invention also relates to a method of preparing a compound of general formula (I), *supra*, said method comprising the step of allowing an intermediate compound of general formula (XI):



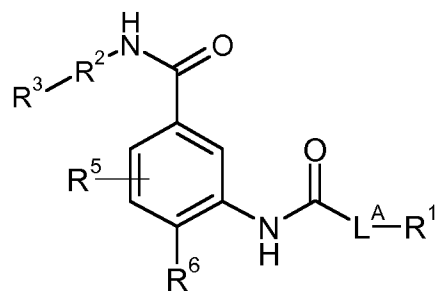
(XI)

10

in which L^A , R^1 , R^5 , and R^6 are as defined for general formula (I), *supra*;

to react with a compound of general formula $R^3R^2NH_2$, in which R^2 and R^3 are as defined for the compounds of general formula (I), *supra*;

thereby giving, upon optional deprotection, a compound of general formula (Ia):

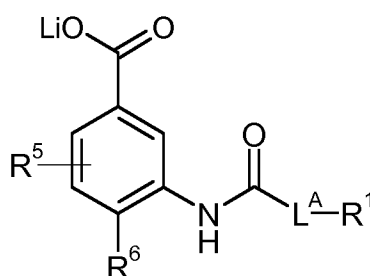


(Ia)

15

in which L^A , R^1 , R^2 , R^3 , R^5 , and R^6 are as defined for the compounds of general formula (I), *supra*.

In accordance with another embodiment, the present invention also relates to a method of preparing a compound of general formula (I), *supra*, said method comprising the step of allowing an intermediate compound of general formula (XIa):

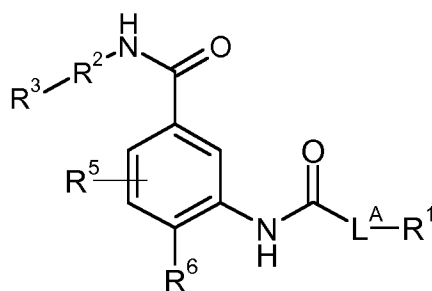


5 (XIa)

in which L^A , R^1 , R^5 , and R^6 are as defined for general formula (I), *supra*;

to react with a compound of general formula $R^3R^2NH_2$, in which R^2 and R^3 are as defined for the compounds of general formula (I), *supra*;

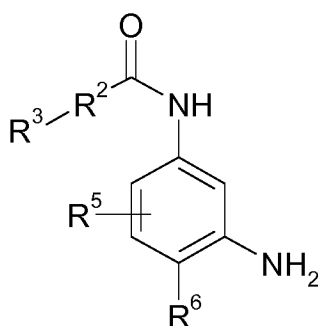
thereby giving, upon optional deprotection, a compound of general formula (Ia):



10 (Ia)

in which L^A , R^1 , R^2 , R^3 , R^5 , and R^6 are as defined for the compounds of general formula (I), *supra*.

15 In accordance with another embodiment, the present invention also relates to a method of preparing a compound of general formula (I), *supra*, said method comprising the step of allowing an intermediate compound of general formula (XVII):



(XVII)

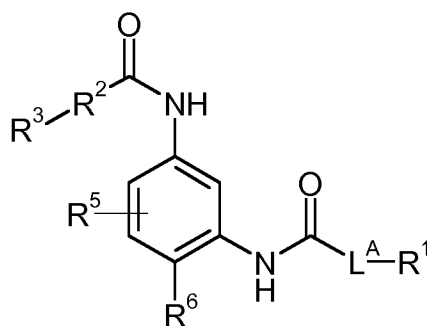
in which R^2 , R^3 , R^5 , and R^6 are as defined for general formula (I), *supra*;

to react with a carboxylic acid $\text{HO}_2\text{C}-\text{L}^{\text{A}}-\text{R}^1$ or the corresponding acyl chloride $\text{Cl}-\text{C}(=\text{O})-\text{L}^{\text{A}}-\text{R}^1$, wherein L^{A} and R^1 are as defined for the compounds of general formula (I), *supra*; or alternatively

to react with suitable reagents, such as $\text{Cl}-\text{C}(=\text{O})-\text{L}^{\text{A}}-\text{LG}$, in which L^{A} is as defined for the compounds of general formula (I), and LG stands for a leaving group, preferably chloro or bromo, and subsequently

5 with agents suitable for the introduction of R^1 , exemplified by but not limited to cyclic secondary amines;

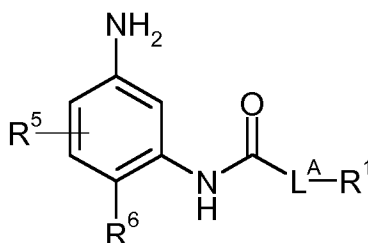
thereby giving, upon optional deprotection, a compound of general formula (Ib):



(Ib)

10 in which L^{A} , R^1 , R^2 , R^3 , R^5 , and R^6 are as defined for the compounds of general formula (I), *supra*.

In accordance with another embodiment, the present invention also relates to a method of preparing a compound of general formula (I), *supra*, said method comprising the step of allowing an intermediate compound of general formula (XXII):



(XXII)

in which L^{A} , R^1 , R^5 and R^6 are as defined for general formula (I), *supra*;

to react with a carboxylic acid $\text{HO}_2\text{C}-\text{R}^2-\text{R}^3$, wherein R^2 and R^3 are as defined for the compounds of general formula (I), *supra*; or alternatively

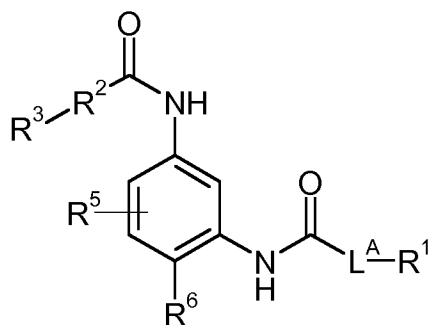
20 to react with a carboxylic acid $\text{X}-\text{R}^2-\text{CO}_2\text{H}$, in which R^2 is as defined for the compounds of general formula (I), *supra*, and subsequently subjected to a palladium catalysed coupling reaction, such as a Suzuki coupling, with $\text{R}^3-\text{X}'$, in which R^3 is as defined for the compounds of general formula (I), *supra*.

In $\text{X}-\text{R}^2-\text{CO}_2\text{H}$ and $\text{R}^3-\text{X}'$, both X and X' represent groups enabling palladium catalysed coupling reactions, such as chloro, bromo, iodo, trifluoromethylsulfonyloxy, nonafluorobutylsulfonyloxy or a

25 boronic acid or an ester thereof, with the proviso that if X represents a boronic acid or an ester

thereof, X' stands for chloro, bromo, iodo, trifluoromethylsulfonyloxy or nonafluorobutylsulfonyloxy and the like, or *vice versa*;

thereby giving, upon optional deprotection, a compound of general formula (Ib):



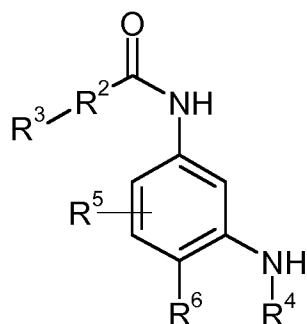
5

(Ib)

in which L^A, R¹, R², R³, R⁵, and R⁶ are as defined for the compounds of general formula (I), *supra*.

In accordance with another embodiment, the present invention also relates to a method of preparing a compound of general formula (I), *supra*, said method comprising the step of allowing an intermediate compound of general formula (XXIV):

10



(XXIV)

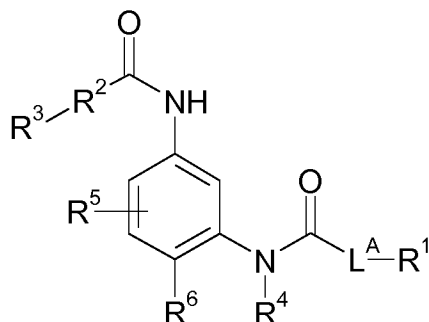
in which R², R³, R⁴, R⁵ and R⁶ are as defined for general formula (I), *supra*;

to react with a carboxylic acid HO₂C-L^A-R¹ or the corresponding acyl chloride Cl-C(=O)-L^A-R¹, wherein

15

L^A and R¹ are as defined for the compounds of general formula (I), *supra*;

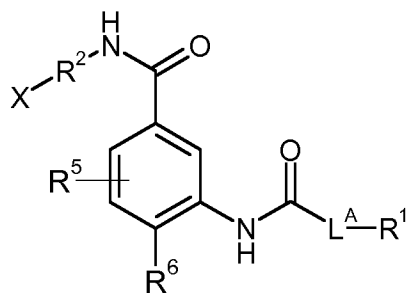
thereby giving, upon optional deprotection, a compound of general formula (Ic):



(Ic)

in which L^A , R^1 , R^2 , R^3 , R^4 , R^5 and R^6 are as defined for the compounds of general formula (I), *supra*.

In accordance with another embodiment, the present invention also relates to a method of preparing a compound of general formula (I), *supra*, said method comprising the step of allowing an
 5 intermediate compound of general formula (XXV):



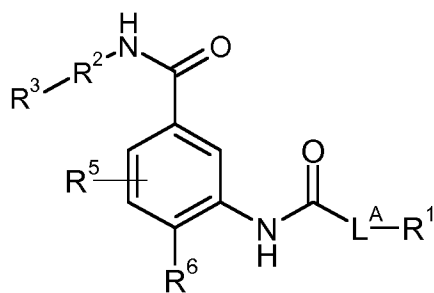
(XXV)

in which L^A , R^1 , R^2 , R^5 and R^6 are as defined for general formula (I), *supra*;

to react with a compound of general formula R^3-X' , wherein R^3 is as defined for the compounds of
 10 general formula (I), *supra*;

wherein both, X and X' represent groups enabling palladium catalysed coupling reactions, such as chloro, bromo, iodo, trifluoromethylsulfonyloxy, nonafluorobutylsulfonyloxy or a boronic acid or an ester thereof, with the proviso that if X represents a boronic acid or an ester thereof, X' stands for chloro, bromo, iodo, trifluoromethylsulfonyloxy or nonafluorobutylsulfonyloxy and the like, or *vice*
 15 *versa*.

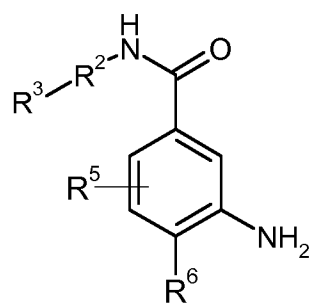
thereby giving, upon optional deprotection, a compound of general formula (Ia):



(Ia)

in which L^A , R^1 , R^2 , R^3 , R^4 , R^5 and R^6 are as defined for the compounds of general formula (I), *supra*.

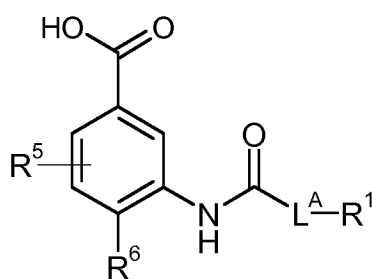
In accordance with a further aspect, the present invention covers intermediate compounds which are useful in the preparation of compounds of the present invention of general formula (I), particularly in the method described herein. In particular, the present invention covers intermediate compounds of general formula (VI):



(VI)

in which R^2 , R^3 , R^5 , and R^6 are as defined for general formula (I), *supra*.

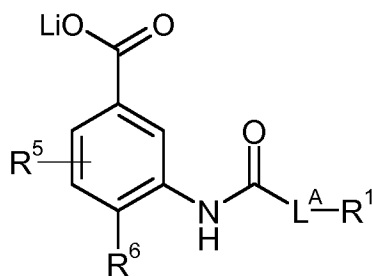
- 5 The present invention also covers intermediate compounds of general formula (XI):



(XI)

in which L^{A} , R^1 , R^5 , and R^6 are as defined for the compounds of general formula (I), *supra*.

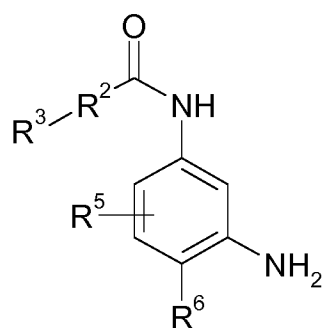
- 10 The present invention also covers intermediate compounds of general formula (XIa):



(XIa)

in which L^{A} , R^1 , R^5 , and R^6 are as defined for general formula (I), *supra*.

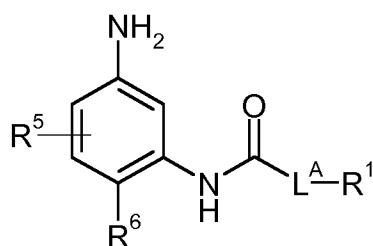
- 15 The present invention also covers intermediate compounds of general formula (XVII):



(XVII)

in which R^2 , R^3 , R^5 , and R^6 are as defined for general formula (I), *supra*.

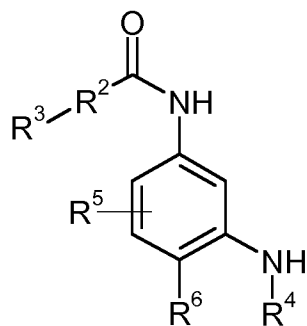
- 5 The present invention also covers intermediate compounds of general formula (XXII):



(XXII)

in which L^A , R^1 , R^5 and R^6 are as defined for general formula (I), *supra*.

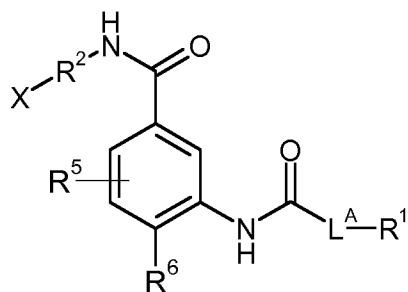
- 10 The present invention also covers intermediate compounds of general formula (XXIV):



(XXIV)

in which R^2 , R^3 , R^4 , R^5 and R^6 are as defined for general formula (I), *supra*.

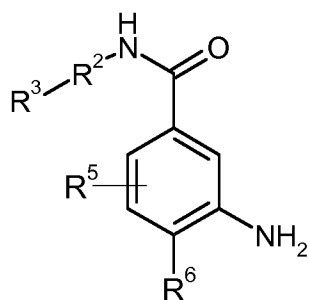
- 15 The present invention also covers intermediate compounds of general formula (XXV):



(XXV)

in which L^A , R^1 , R^2 , R^5 and R^6 are as defined for general formula (I), *supra*, and X represents a group enabling palladium catalysed coupling reactions, such as chloro, bromo, iodo, trifluoromethylsulfonyloxy, nonafluorobutylsulfonyloxy or a boronic acid or an ester thereof.

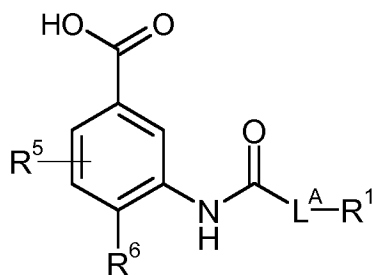
In accordance with yet another aspect, the present invention covers the use of the intermediate compounds of general formula (VI) :



(VI)

in which R^2 , R^3 , R^5 , and R^6 are as defined for general formula (I) *supra*, for the preparation of a compound of general formula (I) as defined *supra*.

In accordance with yet another aspect, the present invention covers the use of the intermediate compounds of general formula (XI) :

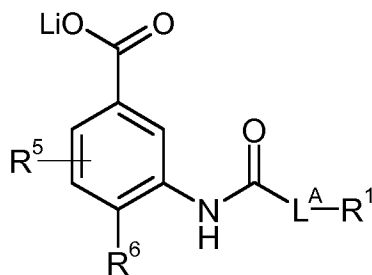


(XI)

in which L^A , R^1 , R^5 , and R^6 are as defined for the compounds of general formula (I) *supra*,

for the preparation of a compound of general formula (I) as defined *supra*.

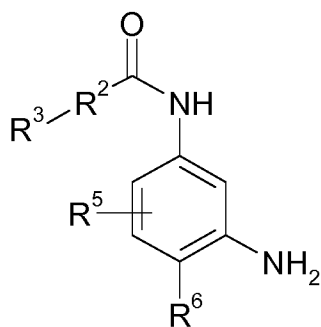
In accordance with yet another aspect, the present invention covers the use of the intermediate compounds of general formula (XIa) :



(XIa)

in which L^A , R^1 , R^5 , and R^6 are as defined for general formula (I) *supra*,
for the preparation of a compound of general formula (I) as defined *supra*.

- 10 In accordance with yet another aspect, the present invention covers the use of the intermediate compounds of general formula (XVII) :

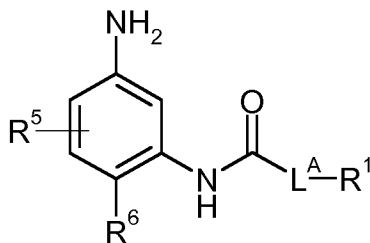


(XVII)

in which R^2 , R^3 , R^5 , and R^6 are as defined for general formula (I) *supra*,

- 15 for the preparation of a compound of general formula (I) as defined *supra*.

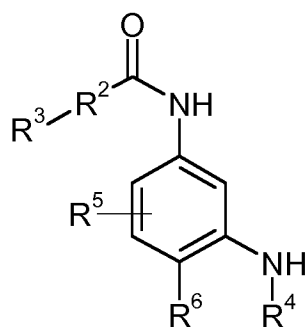
In accordance with yet another aspect, the present invention covers the use of the intermediate compounds of general formula (XXII) :



(XXII)

in which L^A , R^1 , R^5 and R^6 are as defined for general formula (I) *supra*,
for the preparation of a compound of general formula (I) as defined *supra*.

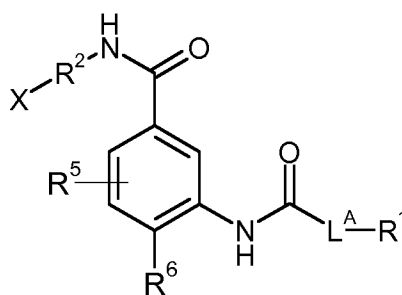
- 5 In accordance with yet another aspect, the present invention covers the use of the intermediate compounds of general formula (XXIV) :



(XXIV)

- in which R^2 , R^3 , R^4 , R^5 and R^6 are as defined for general formula (I) *supra*,
10 for the preparation of a compound of general formula (I) as defined *supra*.

In accordance with yet another aspect, the present invention covers the use of the intermediate compounds of general formula (XXV) :

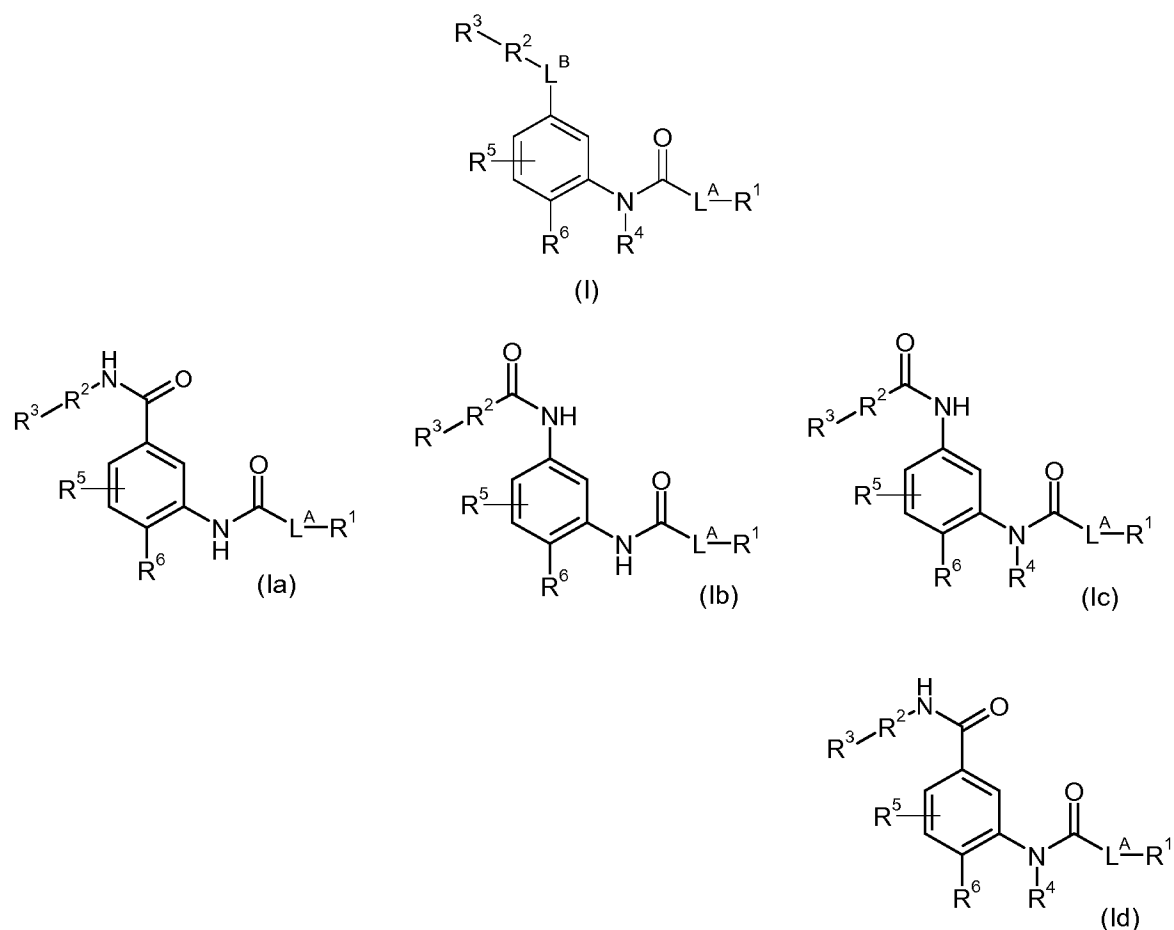


(XXV)

- in which L^A , R^1 , R^2 , R^5 and R^6 are as defined for general formula (I), *supra*, and X represents a group enabling palladium catalysed coupling reactions, such as chloro, bromo, iodo, trifluoromethylsulfonyloxy, nonafluorobutylsulfonyloxy or a boronic acid or an ester thereof;
15
20 for the preparation of a compound of general formula (I) as defined *supra*.

GENERAL SYNTHESIS OF THE COMPOUNDS OF THE INVENTION

The following paragraphs outline a variety of synthetic approaches suitable to prepare compounds of formulae (Ia), (Ib), (Ic), and (Id), in which L^A , R^1 , R^2 , R^3 , R^5 and R^6 are as defined for the compounds of general formula (I), *supra*. Formulae (Ia) and (Ib), in which R^4 represents hydrogen, both constitute subsets of formula (I) in that they feature different orientations of the amide linker L^B , which stands for $-NH-C(=O)-$ in formula (Ia) whilst representing $-C(=O)-NH-$ in formula (Ib), as shown in Scheme A. In formula (Ic), L^B represents $-C(=O)-NH-$, alike formula (Ib), and R^4 is as defined for the compounds of general formula (I), *supra*, but different from hydrogen. In formula (Id), L^B represents $-NH-C(=O)-$, alike formula (Ia), and R^4 is as defined for the compounds of general formula (I), *supra*, but different from hydrogen.



Scheme A: Formulae (I), (Ia), (Ib), (Ic), and (Id).

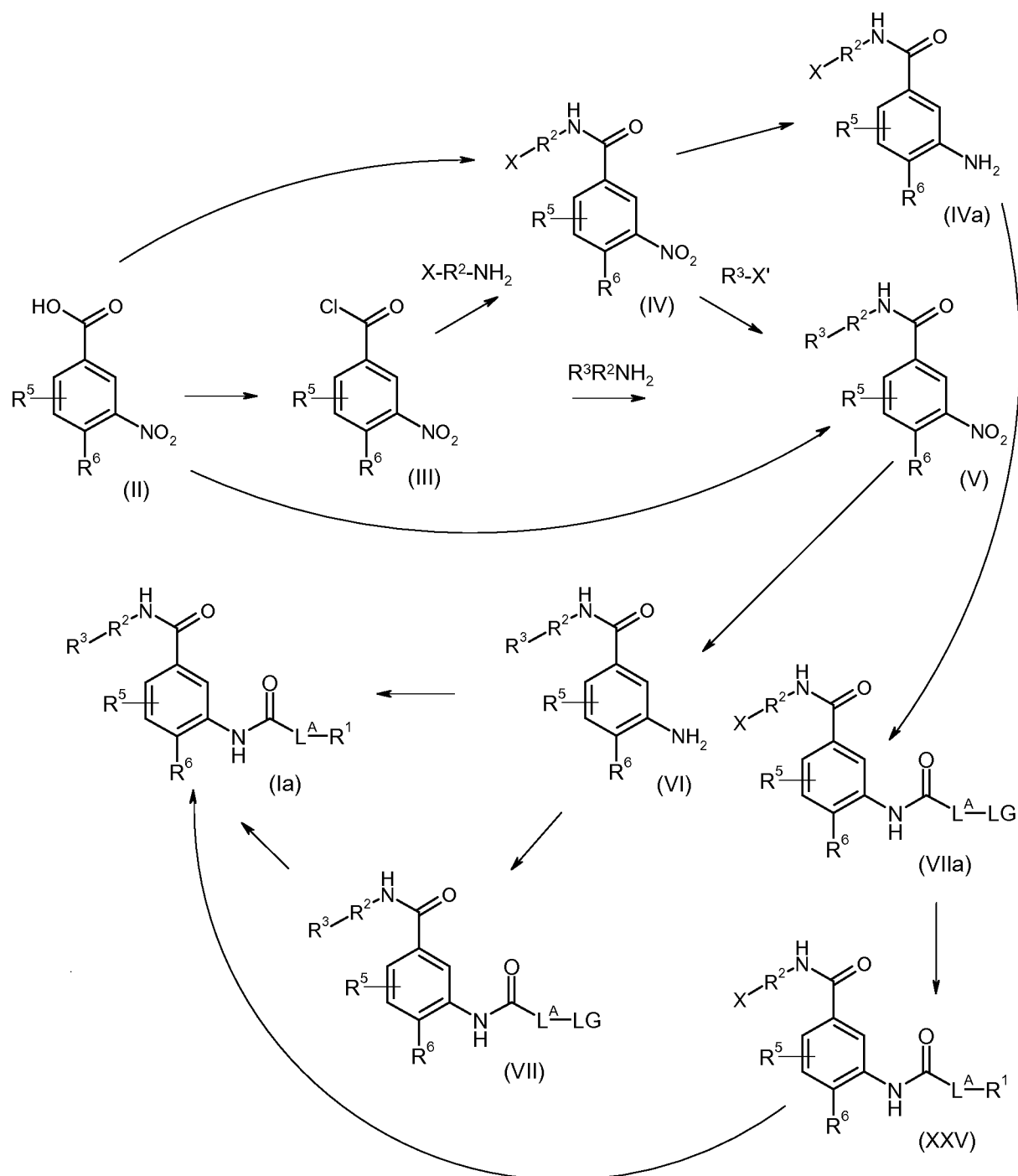
In addition to the routes described below, also other routes may be used to synthesise the target compounds, in accordance with common general knowledge of a person skilled in the art of organic synthesis. The order of transformations exemplified in the following Schemes is therefore not

intended to be limiting, and suitable synthesis steps from various schemes can be combined to form additional synthesis sequences. In addition, interconversion of any of the substituents R^1 , R^2 , R^3 , R^4 , R^5 and/or R^6 , can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protective groups, cleavage of protective groups, reduction or oxidation of functional groups, halogenation, metallation, metal catalysed coupling reactions, substitution or other reactions known to a person skilled in the art. These transformations include those which introduce a functionality allowing for further interconversion of substituents. Appropriate protective groups and their introduction and cleavage are well-known to a person skilled in the art (see for example T.W. Greene and P.G.M. Wuts in *Protective Groups in Organic Synthesis*, 3rd edition, Wiley 1999). Specific examples are described in the subsequent paragraphs. Further, it is possible that two or more successive steps may be performed without work-up being performed between said steps, *e.g.* in a "one-pot" reaction, as it is well-known to a person skilled in the art.

Scheme B outlines the preparation of compounds of the formula (Ia), in which L^A , R^1 , R^2 , R^3 , R^5 , and R^6 are as defined for the compounds of general formula (I), *supra*, starting from *meta*-nitrobenzoic acid derivatives (II), in which R^5 and R^6 are as defined for the compounds of general formula (I), which can be converted into the corresponding benzoyl chlorides (III), by treatment with a suitable chlorinating agent, such as oxalyl chloride. Benzoic acid derivatives of the formula (II) are well known to the person skilled in the art, and are often commercially available. Said benzoyl chlorides of the formula (III) can be subsequently converted into amides of the general formula (V), *e.g.* directly by aminolysis with amines R^3 - R^2 -NH₂, in which R^2 and R^3 are as defined for the compounds of general formula (I). Alternatively, amides of the formula (V) can be accomplished in two steps by aminolysis of (III) using an amine X - R^2 -NH₂, in which R^2 is as defined for the compounds of general formula (I), giving rise to amides of the formula (IV). Said amides can be subsequently coupled with R^3 - X' , in which R^3 is as defined for the compounds of general formula (I), in a palladium catalysed coupling reaction such as a Suzuki coupling to furnish amides of general formula (V). In X - R^2 -NH₂ and R^3 - X' , both X and X' represent groups enabling palladium catalysed coupling reactions, such as chloro, bromo, iodo, trifluoromethylsulfonyloxy, -O-S(=O)₂C₄F₉ (nonafluorobutylsulfonyloxy) or a boronic acid or an ester thereof, with the proviso that if X represents a boronic acid or an ester thereof, X' stands for chloro, bromo, iodo, trifluoromethylsulfonyloxy or nonafluorobutylsulfonyloxy and the like, or *vice versa*.

The nitro group present in said amides (V) is then reduced by treatment with a suitable reducing agent, such as titanium(III)chloride, or hydrogenation in the presence of a suitable catalyst, *e.g.* palladium on charcoal, to give anilines of the formula (VI). Said anilines of the formula (VI) are then elaborated into compounds of the formula (Ia). This can be accomplished directly by reacting a compound of the formula (VI) with a carboxylic acid HO₂C- L^A - R^1 , wherein L^A and R^1 are as defined for

the compounds of general formula (I), in an amide coupling reaction, for example in the presence of a tertiary aliphatic amine, such as *N,N*-diisopropylethylamine, and 2,4,6-tripropyl-1,3,5,2,4,6-trioxaphosphinane 2,4,6-trioxide (also known as T3P), in a suitable solvent such as *N,N*-dimethylformamide. Alternatively, the transformation of anilines (VI) into compounds of the formula (Ia) can be performed by reaction of anilines (VI) with suitable reagents such as $\text{Cl-C(=O)-L}^{\text{A}}\text{-R}^1$, or, in a two step synthesis firstly with $\text{Cl-C(=O)-L}^{\text{A}}\text{-LG}$, in which L^{A} is as defined for the compounds of general formula (I), and LG stands for a leaving group, preferably chloro or bromo, to give the corresponding compounds of formula (VII), which are subsequently reacted with agents suitable for the introduction of R^1 , exemplified by but not limited to cyclic secondary amines, to give compounds of the formula (Ia). As depicted in Scheme B there are more synthetic routes to compounds of formula (Ia). Benzoyl chlorides (III) can be reacted in an amide coupling reaction, as describe *supra*, with $\text{X-R}^2\text{-NH}_2$, X and R^2 are defined as *supra*, giving compound of formula (IV), which can be reduced by treatment with a suitable reducing agent, such as titanium(III)chloride, to compounds of formula (IVa). Additionally, compounds of the formula (IV) can be prepared directly from meta-nitrobenzoic acids of formula (II) in a amide coupling reaction, as described *supra*, R^2 , R^5 , R^6 , X are as defined as *supra*. The anilines of formula (IVa) can be reacted with $\text{Cl-C(=O)-L}^{\text{A}}\text{-LG}$, in which L^{A} and LG are as defined as *supra*, giving compounds of the formula (VIIa), which are subsequently reacted with agents suitable for the introduction of R^1 , defined as *supra*, leading to compounds of formula (XXV). Afterwards, compounds of the general formula (XXV) can be reacted in a palladium catalysed coupling reaction, described as *supra*, to give compounds of the formula (Ia). The compounds of formula (V) can be coupled directly with $\text{R}^3\text{-R}^2\text{-NH}_2$, R^2 and R^3 are as defined as *supra*, in an amide coupling reaction, described *supra*, starting from compounds of formula (II).



Scheme B: Preparation of compounds of the formula (Ia) from *meta*-nitrobenzoic acid derivatives of formula (II)

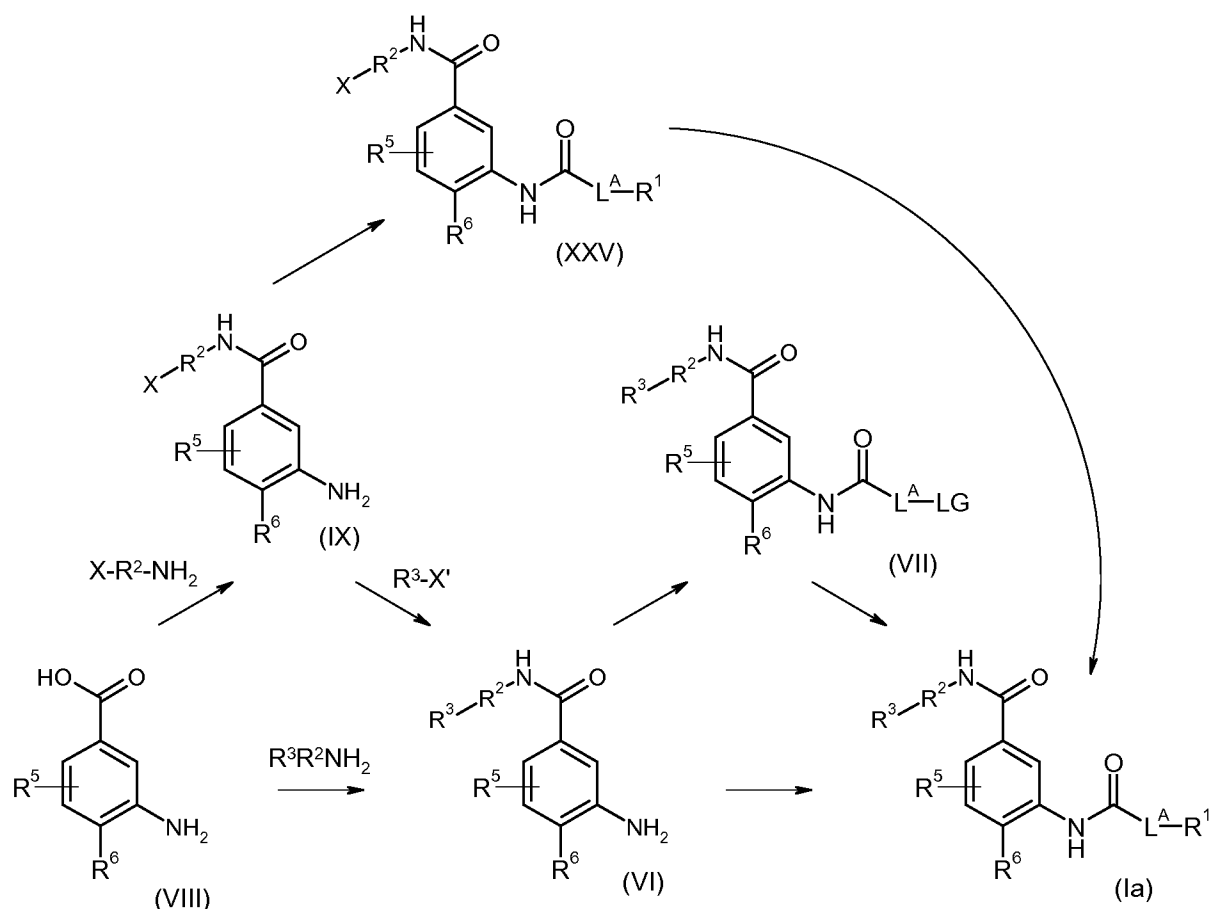
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Alternatively, compounds of the formula (Ia) can be prepared starting from *meta*-aminobenzoic acid derivatives of formula (VIII), in which R^5 and R^6 are as defined for the compounds of general formula (I), *supra*, as outlined in Scheme C. Said *meta*-aminobenzoic acid derivatives of formula (VIII) are well known to the person skilled in the art and are commercially available in many cases. Compounds of formula (VIII) can be reacted with an amine $R^3R^2NH_2$, in which R^2 and R^3 are as defined for the

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compounds of general formula (I), *supra*, in a standard amide coupling reaction, described in context with Scheme B, to give amide derivatives of formula (VI). Said compounds of formula (VI) can also be obtained by coupling the aforementioned acids of formula (VIII) with an amine $X-R^2-NH_2$, in which R^2 is as defined for the compounds of general formula (I), *supra*, giving rise to amides of the formula (IX).

- 5 These are subsequently subjected to a palladium catalysed coupling reaction, such as a Suzuki coupling, with R^3-X' , in which R^3 is as defined for the compounds of general formula (I), in order to furnish amides of general formula (VI), respectively. In $X-R^2-NH_2$ and R^3-X' , both X and X' represent groups enabling palladium catalysed coupling reactions, such as chloro, bromo, iodo, trifluoromethylsulfonyloxy, nonafluorobutylsulfonyloxy or a boronic acid or an ester thereof, with
- 10 the proviso that if X represents a boronic acid or an ester thereof, X' stands for chloro, bromo, iodo, trifluoromethylsulfonyloxy or nonafluorobutylsulfonyloxy and the like, or *vice versa*. Amides of the formula (VI) are subsequently converted into compounds of formula (Ia) as described *supra* in context with Scheme B. As depicted in Scheme C there are more synthetic routes to the compounds of formula (Ia). The compounds of formula (IX) can be coupled with a carboxylic acid $HOOC-L^A-R^1$, L^A
- 15 and R^1 are as defined for the compounds of general formula (I), *supra*, in an amide coupling reaction, as described *supra* in context with Scheme B, to afford compounds of the formula (XXV), which are reacted in a palladium catalysed coupling reaction, as described in context with Scheme B, *supra*, to yield compounds of the formula (Ia).

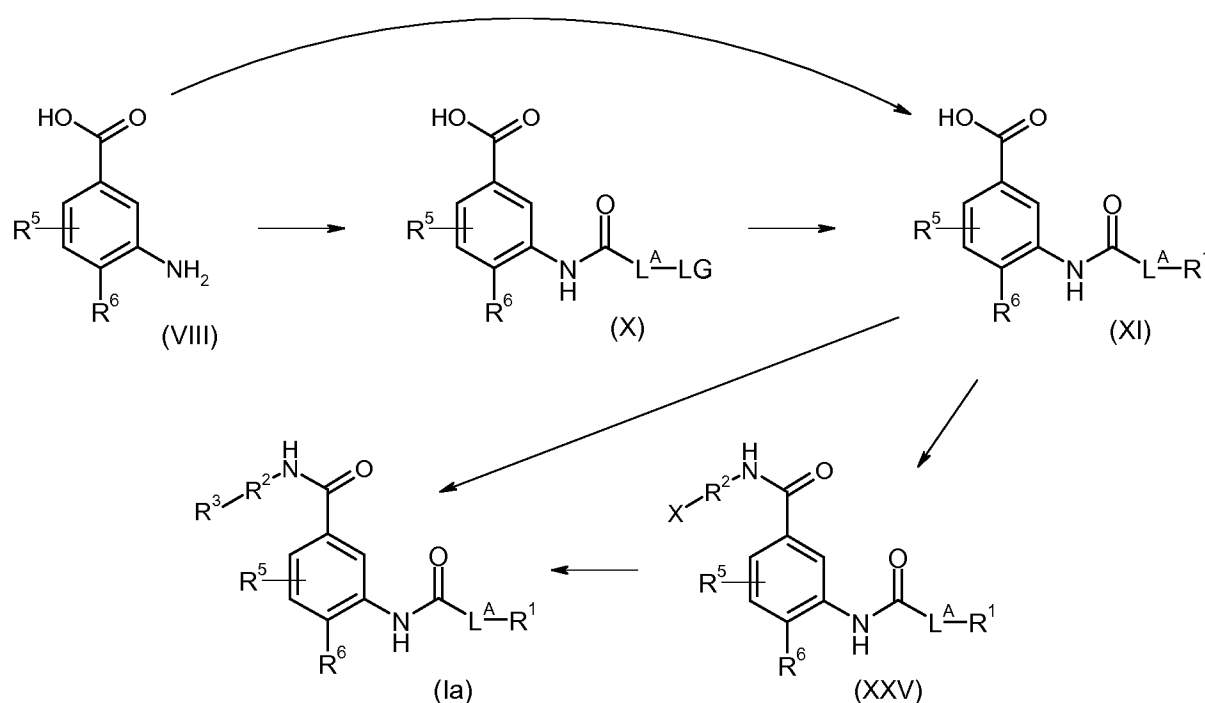


Scheme C: Preparation of compounds of the formula (Ia) from *meta*-aminobenzoic acid derivatives of formula (VIII)

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The sequence of synthetic steps can be varied as outlined in Scheme D, in order to convert *meta*-aminobenzoic acid derivatives of formula (VIII), in which R⁵ and R⁶ are as defined for the compounds of general formula (I), into compounds of the formula (Ia). Said benzoic acid derivatives of the formula (VIII) can be converted into compounds of the formula (X), in which LG stands for a leaving group, preferably chloro or bromo, followed e.g. by aminolysis of compounds of the formula (X) using reagents suitable for the introduction of R¹, exemplified by but not limited to suitable cyclic secondary amines, to give compounds of the formula (XI). Compounds of the formula (XI) can be synthesised directly from *meta*-aminobenzoic acids of formula (VIII) by reacting with carboxylic acids of the formula HOOC-L^A-R¹, L^A and R¹ are as defined for the compounds of general formula (I), *supra*, in a standard amide coupling reaction, as described in the context with Scheme B, or with the corresponding carboxylic acid chloride Cl(C=O)-L^A-R¹, R¹ and L^A are defined as *supra*. Subsequently, the carboxy group present in compounds of the formula (XI) can be coupled with an amine R³R²NH₂, in which R² and R³ are as defined for the compounds of general formula (I), *supra*, in an amide coupling reaction, for example in the presence of a tertiary aliphatic amine, such as *N,N*-

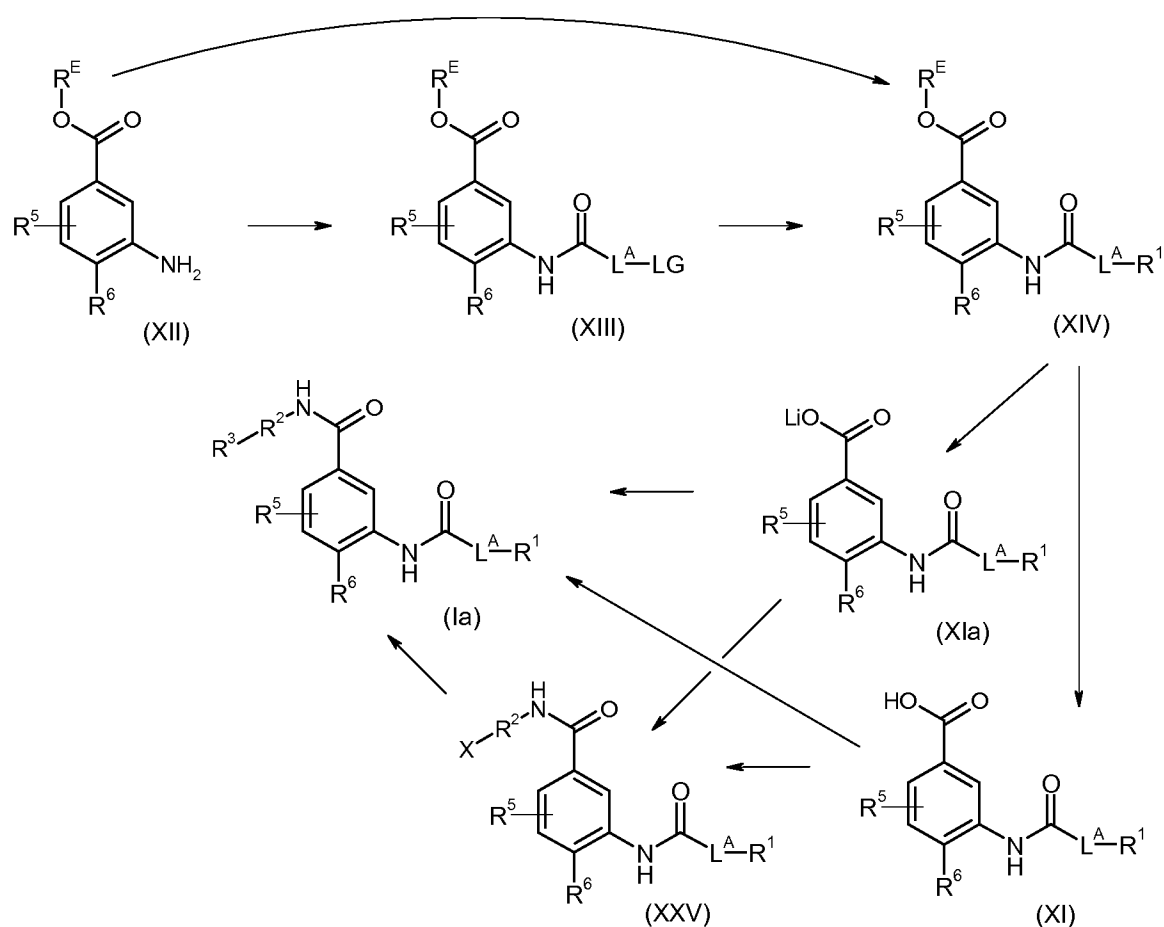
diisopropylethylamine, and 2,4,6-tripropyl-1,3,5,2,4,6-trioxaphosphinane 2,4,6-trioxide (also known as T3P), in a suitable solvent such as *N,N*-dimethylformamide, to afford compounds of the formula (Ia). Additionally, compounds of the formula (XI) can be reacted with amines of the formula $X-R^2-NH_2$, X and R^2 are as defined as described in the context with Scheme B, *supra*, in an amide coupling reaction, as described *supra*, to yield compounds of the formula (XXV), which can be transformed by a palladium catalysed coupling reaction, as described in context with Scheme B, affording the compounds of formula (Ia).



Scheme D: Alternative preparation of compounds of the formula (Ia) from *meta*-aminobenzoic acid derivatives of formula (VIII)

Instead of said benzoic acid derivatives of formula (VIII), also the corresponding ester analogues of formula (XII), in which R^5 and R^6 are as defined for the compounds of general formula (I), and in which R^E stands for a C_1 - C_6 -alkyl group, preferably methyl or ethyl, can be employed in a similar fashion in order to prepare compounds of the formula (Ia), as outlined in Scheme E. Esters of the formula (XII) are well known to the person skilled in the art, and are commercially available in many cases. Elaboration of said benzoic acid esters of formula (XII) into compounds of formula (XIV), in which L^A and R^1 are as defined for the compounds of general formula (I), *supra*, can proceed *via* compounds of formula (XIII), in which LG stands for a leaving group, preferably chloro or bromo, and can be performed analogously as described in context with Scheme D. Alternatively, conversion of (XII) into (XIV) can be performed *via* standard amide coupling reactions, as described in context with

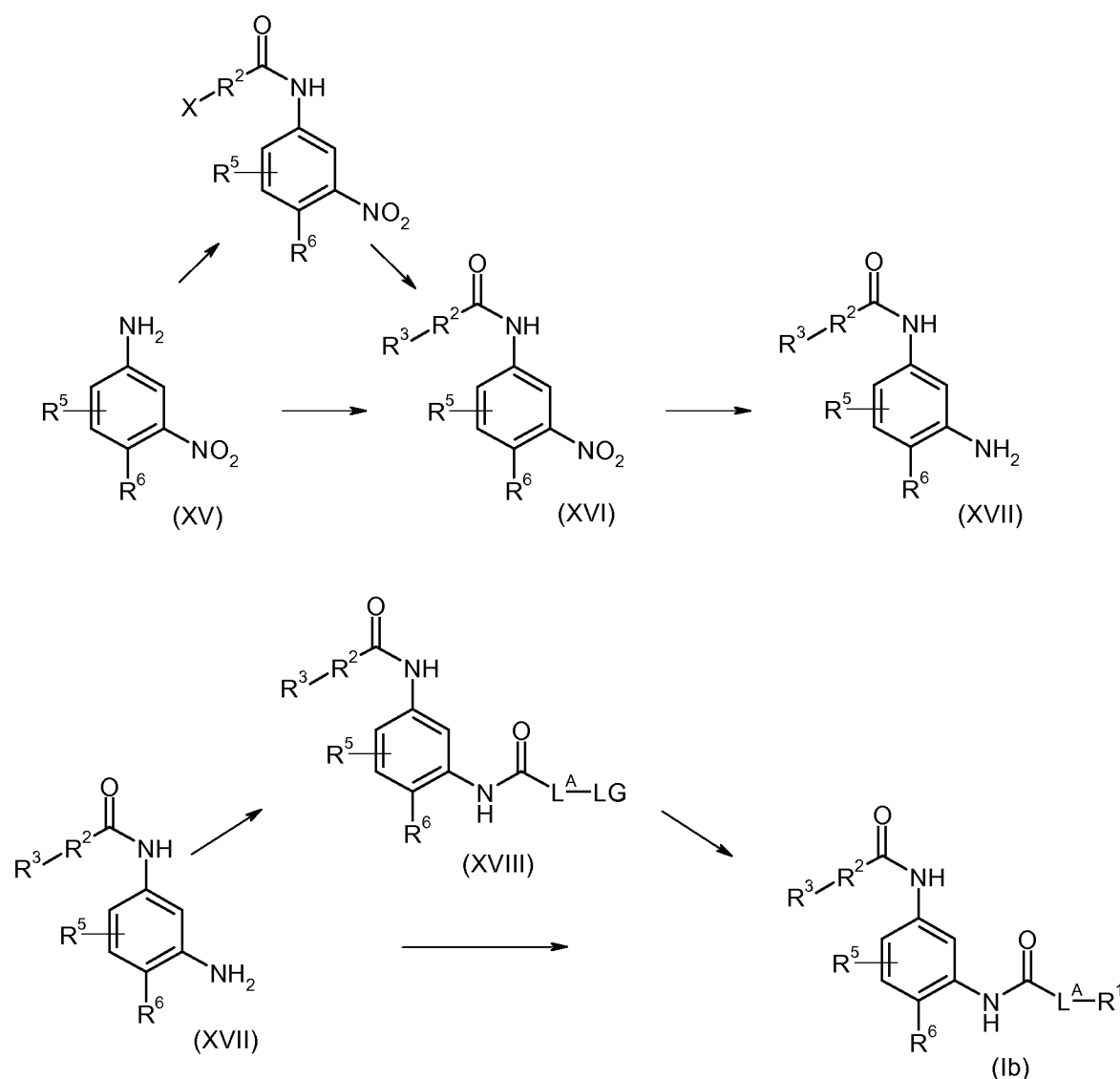
Scheme D, *supra*, of carboxylic acids of the formula R^1-L^A-COOH , R^1 and L^A are as defined for the compounds in general formula (I), *supra*. Subsequently, the ester group present in compounds of formula (XIV) can be saponified by reaction with e.g. lithium hydroxide to yield the lithium salt of the formula (XIa). Said lithium salt of formula (XIa) or the corresponding carboxylic acid of formula (XI) is then converted into compounds of formula (Ia), R^2 and R^3 are as defined for the compounds of general formula (I), *supra*. This can be performed in different ways as described in the context with Scheme D, *supra*, starting with compounds of formula (XI).



Scheme E: Preparation of compounds of the formula (Ia) from *meta*-aminobenzoic acid esters of formula (XII)

A first approach to compounds of the formula (Ib) from *meta*-nitroaniline derivatives of formula (XV), in which R^5 and R^6 are as defined for the compounds of general formula (I), *supra*, is outlined in Scheme F. Said *meta*-nitroaniline derivatives of formula (XV) are well known to the person skilled in the art, and are often commercially available. They can be converted into amide derivatives of formula (XVI) e.g. by a reacting with a carboxylic acid chloride $R^3-R^2-C(=O)Cl$, in which R^2 and R^3 are as defined for the compounds of general formula (I), *supra*, in the presence of a suitable base, such as

potassium carbonate, and in a suitable solvent, such as acetonitrile. Basic solvents, such as pyridine, can take over both the role of a base and of a solvent, respectively. Alternatively, conversion of (XV) into (XVI) can be performed *via* standard amide coupling reactions. In addition, nitro compounds of formula (XV) can be converted into compounds of the formula (XVI) in a two step sequence. This can be performed *via* amide coupling reactions, methods are described in the context with Scheme B, *supra*, of (XV) with $X-R^2-NH_2$, R^2 is as defined for the compounds of general formula (I) and X is as defined as described in context with Scheme B for performing a palladium catalysed coupling reaction, which can be performed in the subsequent step with R^3-X' , R^3 is as defined for the compounds of general formula (I), and X' is as defined as described in context with Scheme B for performing the palladium catalysed coupling reaction. After the palladium catalysed coupling reaction, the nitro group present in amides of the formula (XVI) can be subsequently reduced *e.g.* by hydrogenation in the presence of a suitable catalyst, *e.g.* palladium on charcoal, to give the corresponding aniline derivatives of formula (XVII). Said anilines of the formula (XVII) can then be elaborated into compounds of the formula (Ib). This can be accomplished directly by reacting a compound of the formula (XVII) with a carboxylic acid $HO_2C-L^A-R^1$, wherein L^A and R^1 are as defined for the compounds of general formula (I), in an amide coupling reaction, for example in the presence of a tertiary aliphatic amine, such as *N,N*-diisopropylethylamine, and 2,4,6-tripropyl-1,3,5,2,4,6-trioxaphosphinane 2,4,6-trioxide (also known as T3P), in a suitable solvent such as *N,N*-dimethylformamide. Alternatively, the transformation of anilines (XVII) into compounds of the formula (Ib) can be performed by reaction of anilines (XVII) with suitable reagents, such as $Cl-C(=O)-L^A-LG$, in which L^A is as defined for the compounds of general formula (I), and LG stands for a leaving group, preferably chloro or bromo, to give the corresponding compounds of formula (XVIII), which are subsequently reacted with agents suitable for the introduction of R^1 , exemplified by but not limited to cyclic secondary amines, to give compounds of the formula (Ib).



Scheme F: Preparation of compounds of the formula (Ib) from *meta*-nitroaniline derivatives of formula (XV)

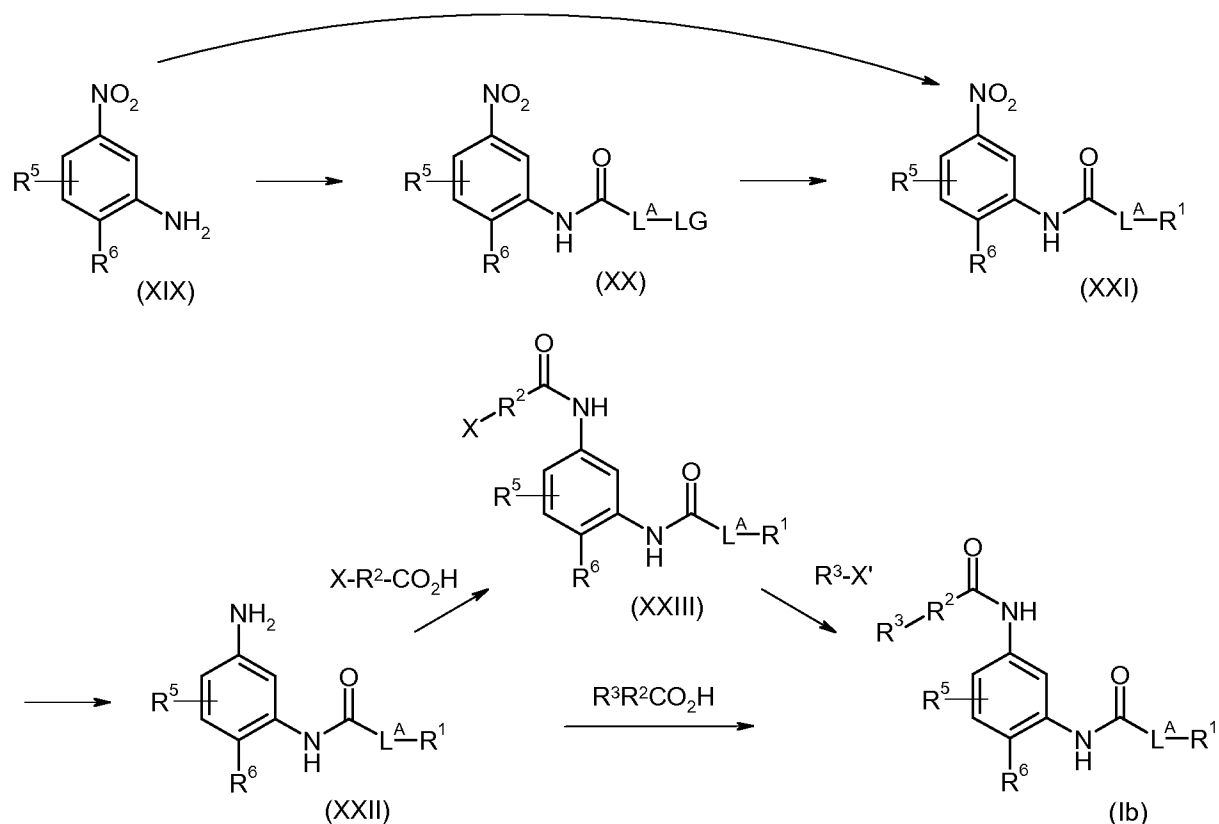
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Scheme G outlines an approach complementary to Scheme F as an alternative synthesis route for compounds of the formula (Ib), from *meta*-nitroaniline derivatives of formula (XIX), in which R^5 and R^6 are as defined for the compounds of general formula (I), *supra*, and which differ from the compounds of formula (XV) by the inverse arrangement of their nitro and amino groups, respectively. Said *meta*-nitroaniline derivatives of formula (XIX) are well known to the person skilled in the art, and are often commercially available. They can be converted into amide derivatives of formula (XX), in which L^A is as defined for the compounds of general formula (I), *supra*, and in which LG stands for a leaving group, preferably chloro or bromo, by reacting with a carboxylic acid $LG-L^A-CO_2H$, in a standard amide coupling reaction. Said amides of the formula (XX) can be subsequently converted into compounds of the formula (XXI), in which R^1 is as defined for the compounds of

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general formula (I), *supra*, using reagents suitable for the introduction of R^1 , exemplified by but not limited to cyclic secondary amines. Alternatively, converting compounds (XIX) into compounds of formula (XXI) can be accomplished directly by reacting compounds of the formula R^1-L^A-COOH , wherein R^1 and L^A are as defined for the compounds of general formula (I), *supra*, or the corresponding carboxylic acid chloride in an amide coupling reaction, *supra*. The nitro group present in amides of the formula (XXI) is then reduced *e.g.* by hydrogenation in the presence of a suitable catalyst, *e.g.* palladium on charcoal, to give the corresponding aniline derivatives of formula (XXII). Compounds of formula (XXII) can be reacted with a carboxylic acid $R^3R^2CO_2H$, wherein R^2 and R^3 are as defined for the compounds of general formula (I), *supra*, in an amide coupling reaction, *supra*, to give compounds of the formula (Ib). The compounds of formula (Ib) can also be obtained by coupling the aforementioned anilines of formula (XXII) with a carboxylic acid $X-R^2-CO_2H$, in which R^2 is as defined for the compounds of general formula (I), *supra*, giving rise to amides of the formula (XXIII). These can be subsequently subjected to a palladium catalysed coupling reaction, such as a Suzuki coupling, with R^3-X' , in which R^3 is as defined for the compounds of general formula (I), in order to furnish compounds of the formula (Ib), respectively. In $X-R^2-CO_2H$ and R^3-X' , both X and X' represent groups enabling palladium catalysed coupling reactions, such as chloro, bromo, iodo, trifluoromethylsulfonyloxy, nonafluorobutylsulfonyloxy or a boronic acid or an ester thereof, with the proviso that if X represents a boronic acid or an ester thereof, X' stands for chloro, bromo, iodo, trifluoromethylsulfonyloxy or nonafluorobutylsulfonyloxy and the like, or *vice versa*.



Scheme G: Preparation of compounds of the formula (Ib) from *meta*-nitroaniline derivatives of formula (XIX)

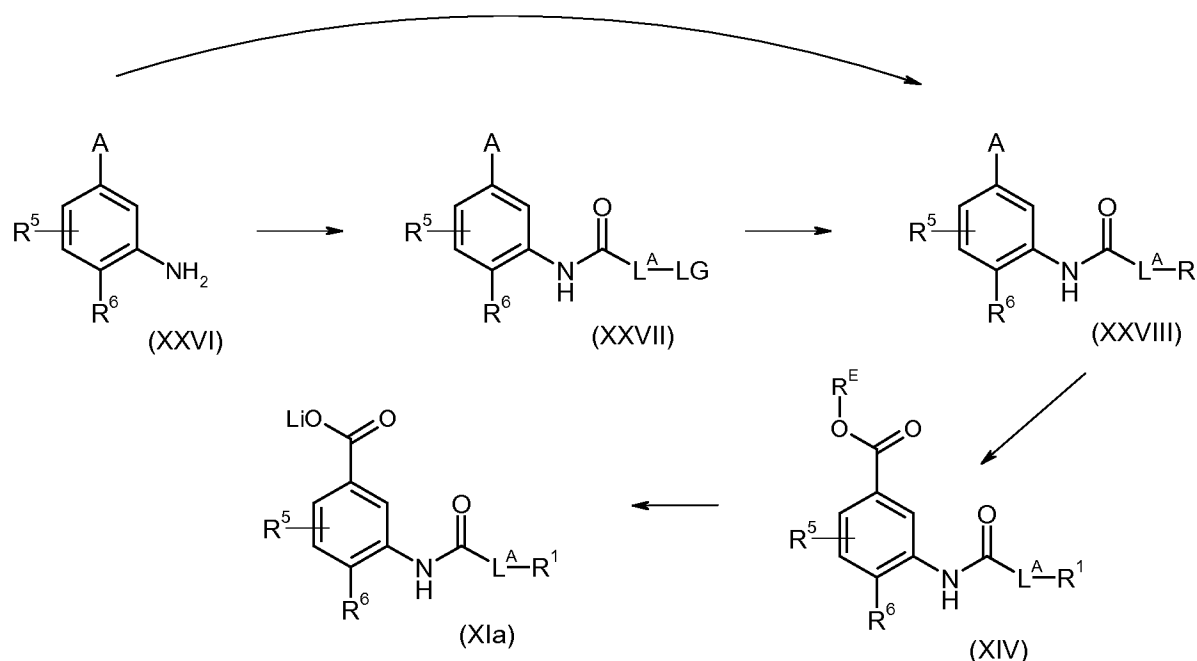
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Instead of benzoic acid ester derivatives of formula (XII), as depicted in Scheme E, also the corresponding *meta*-substituted analogues of formula (XXVI), in which R^5 and R^6 are as defined for the compounds of general formula (I), and in which A stands for a chloro, bromo, iodo, trifluoromethylsulfonyloxy, nonafluorobutylsulfonyloxy, preferably bromo, can be employed in a similar fashion in order to prepare compounds of the formula (XIa), as outlined in Scheme H.

Compounds of the formula (XXVI) are well known to the person skilled in the art, and are commercially available in many cases. Elaboration of said compounds of formula (XXVI) into compounds of formula (XXVIII), in which L^A and R^1 are as defined for the compounds of general formula (I), *supra*, can proceed *via* compounds of formula (XXVII), in which LG stands for a leaving group, preferably chloro or bromo, and can be performed analogously as described in context with Scheme D. Alternatively, conversion of (XXVI) into (XXVIII) can be performed *via* standard amide coupling reactions, as described *supra*, of carboxylic acids of the formula R^1-L^A-COOH , R^1 and L^A are as defined for the general formula (I), *supra*. The compounds of formula (XXVIII) are transformed into the corresponding esters of the formula (XIV), wherein R^E stands for a C_1 - C_6 -alkyl, preferably methyl or ethyl. This kind of reaction can be performed under palladium catalysis, for example dichloropalladium-propane-1,3-diylbis(diphenylphosphine), in an alcohol R^E-OH , R^E is as defined as

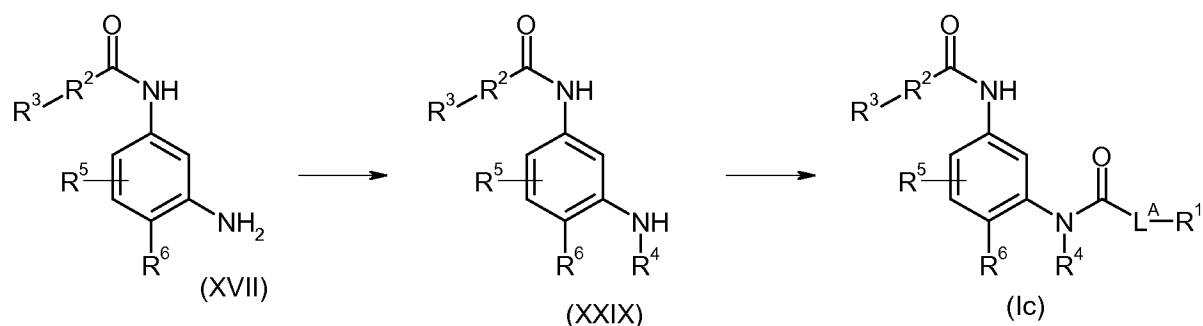
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supra, e.g. ethanol, with an aliphatic amine, e.g. triethylamine, at elevated temperatures ranging from 50-150 °C, e.g. 100 °C, and with pressurised carbon monoxide, e.g. 10-20 bar, affording compounds of the formula (XIV). Subsequently, the ester group present in compounds of formula (XIV) can be saponified by reaction with e.g. lithium hydroxide to yield the lithium salt of the formula (Xla).



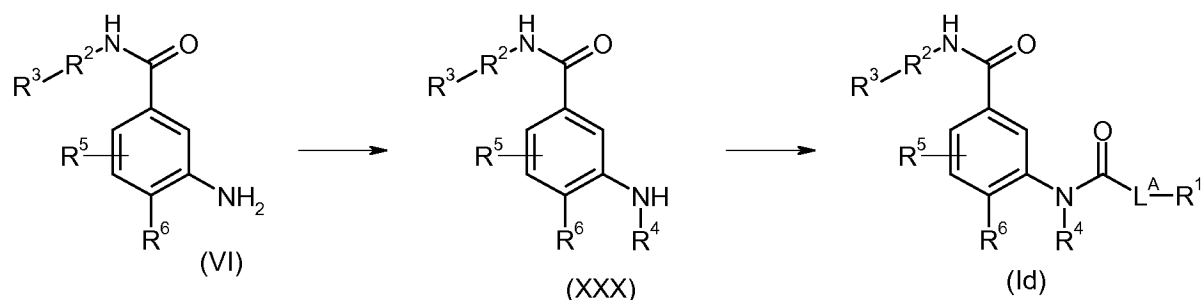
Scheme H: Preparation of compounds of the formula (Xla) from *meta*-aminobromobenzene derivatives of formula (XXVI)

Scheme I illustrates the introduction of R⁴ groups different from hydrogen. In order to do so, primary anilines of the formula (XVII), in which R², R³, R⁵, and R⁶ are as defined for the compounds of general formula (I), *supra*, and which can be prepared for example according to Scheme F, can be converted into secondary anilines of the formula (XXIX), in which R⁴ is as defined for the compounds of general formula (I), *supra*, but different from hydrogen. This can be accomplished by various methods known to the person skilled in the art, such as a reductive amination with an aldehyde suitable to confer R⁴, e.g. benzaldehyde for R⁴ = benzyl, in the presence of a suitable borohydride reagent, such as sodium triacetoxyborohydride, and in the presence of a suitable acid, such as acetic acid, in a suitable solvent, such as a chlorinated hydrocarbon, preferably dichloromethane. The resulting compounds of the formula (XXIX) are subsequently elaborated into compounds of the formula (Ic), in which L^A, R¹, R², R³, R⁴, R⁵ and R⁶ are as defined for the compounds of general formula (I), *supra*, with the proviso that R⁴ is different from hydrogen.



Scheme I: Preparation of compounds of the formula (Ic) from compounds of the general formula (XVII)

- 5 Scheme J illustrates the introduction of R^4 groups different from hydrogen. In order to do so, primary anilines of the formula (VI), in which R^2 , R^3 , R^5 , and R^6 are as defined for the compounds of general formula (I), *supra*, and which can be prepared for example according to Scheme C, can be converted into secondary anilines of the formula (XXX), in which R^4 is as defined for the compounds of general formula (I), *supra*, but different from hydrogen. This can be accomplished by various methods known
- 10 to the person skilled in the art, such as a reductive amination with an aldehyde suitable to confer R^4 , e.g. benzaldehyde for R^4 = benzyl, in the presence of a suitable borohydride reagent, such as sodium triacetoxyborohydride, and in the presence of a suitable acid, such as acetic acid, in a suitable solvent, such as a chlorinated hydrocarbon, preferably dichloromethane. The resulting compounds of the formula (XXX) are subsequently elaborated into compounds of the formula (Id), in which L^A , R^1 ,
- 15 R^2 , R^3 , R^4 , R^5 and R^6 are as defined for the compounds of general formula (I), *supra*, with the proviso that R^4 is different from hydrogen.



20 **Scheme J:** Preparation of compounds of the formula (Id) from compounds of the general formula (VI)

Further details (reaction conditions, suitable solvents etc.) can be obtained from the experimental section below.

In the present text, in particular in the Experimental Section, for the synthesis of intermediates and of examples of the present invention, when a compound is mentioned as a salt form with the corresponding base or acid, the exact stoichiometric composition of said salt form, as obtained by the respective preparation and/or purification process, is, in most cases, unknown.

5

Unless specified otherwise, suffixes to chemical names or structural formulae such as "hydrochloride", "trifluoroacetate", "sodium salt", or "x HCl", "x CF₃COOH", "x Na⁺", for example, are to be understood as not a stoichiometric specification, but solely as a salt form.

- 10 This applies analogously to cases in which synthesis intermediates or example compounds or salts thereof have been obtained, by the preparation and/or purification processes described, as solvates, such as hydrates with (if defined) unknown stoichiometric composition.

EXPERIMENTAL SECTION

15

The following table lists the abbreviations used in this paragraph, and in the examples section.

Abbreviation	Meaning
anh	anhydrous
br.	broad signal (in NMR data)
d	day(s)
DAD	Diode Array Detector
DCM	dichloromethane
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
ELSD	Evaporative Light Scattering Detector
ESI	electrospray ionisation
EtOAc	ethyl acetate
h	hour
HPLC, LC	high performance liquid chromatography
m/z	mass-to-charge ratio (in mass spectrum)
mc	multiplet centred
MeOH	methanol
min	Minute

MPLC	medium pressure liquid chromatography
MS	mass spectroscopy
neg	negative
NMR	nuclear magnetic resonance
PE	petroleum ether
pos	positive
ppm	Chemical shift δ in parts per million
PYBOP	(1H-benzotriazol-1-yloxy)(tripyrrolidin-1-yl)phosphonium hexafluorophosphate
R _t	retention time
rt	room temperature
THF	tetrahydrofuran
TLC	thin layer chromatography

Methods:**Method 1:**

Instrument: Waters Acquity UPLC-MS SQD; column: Acquity UPLC BEH C18 1.7 50x2.1mm; Eluent A:
 5 water + 0.05% vol. formic acid (98%), Eluent B: acetonitrile + 0.05% vol. formic acid (98%); gradient:
 0-1.6 min 1-99% B, 1.6-2.0 min 99% B; rate 0.8 mL/min; temperature: 60 °C; DAD scan: 210-400 nm;
 ELSD.

Method 2:

Instrument: Waters Autopurificationsystem SQD; column: Waters XBridge C18 5 μ 100x30mm; water
 10 + 0.1% vol. formic acid (99%) / acetonitrile gradient; temperature: room temperature; injection: 2500
 μ L; DAD scan: 210-400 nm.

Method 3:

Instrument: Waters Acquity UPLC-MS SQD; column: Acquity UPLC BEH C18 1.7 50x2.1mm; Eluent A:
 water + 0.2% vol. ammonia (32%), Eluent B: acetonitrile; gradient: 0-1.6 min 1-99% B, 1.6-2.0 min
 15 99% B; rate 0.8 mL/min; temperature: 60 °C; DAD scan: 210-400 nm; ELSD.

Method 4:

Instrument: Waters Acquity UPLC-MS SQD; column: Acquity UPLC BEH C18 1.7 50x2.1mm; Eluent A:
 water + 0.1% vol. formic acid (99%), Eluent B: acetonitrile; gradient: 0-1.6 min 1-99% B, 1.6-2.0 min
 99% B; rate 0.8 mL/min; temperature: 60 °C; DAD scan: 210-400 nm; ELSD.

Method 5:

Instrument: Waters Autopurificationsystem SQD; column: Waters XBridge C18 5 μ 100x30mm; water + 0.2% vol. ammonia (32%) / acetonitrile gradient; temperature: room temperature; injection: 2500 μ L; DAD scan: 210-400 nm.

5 **Method 6:**

Instrument: JASCO P2000 Polarimeter; wavelength 589 nm; temperature: 20 °C; integration time 10 s; path length 100 mm.

Method 7:

Instrument: Acquity UPLC from Waters; mass detector: LCT from Micromass (now Waters); column: 10 Kinetex C18 from Phenomenex, 50 x 2.1 mm, 2.6 μ m particle, 60 °C; solvent: A: water + 0.05% formic acid; B: acetonitrile + 0.05% formic acid; injection: 0.5 μ L; rate: 1.3 mL/min; gradient 99% A, 1% B until 1.9 min linear to 1% A, 99% B; 1.9 - 2.10 min unchanged; until 2.20 min back to 99% A, 1% B.

15 The ^1H -NMR data of selected examples are listed in the form of ^1H -NMR peaklists. For each signal peak the δ value in ppm is given, followed by the signal intensity, reported in round brackets. The δ value-signal intensity pairs from different peaks are separated by commas. Therefore, a peaklist is described by the general form: δ_1 (intensity₁), δ_2 (intensity₂), ... , δ_i (intensity_i), ... , δ_n (intensity_n).

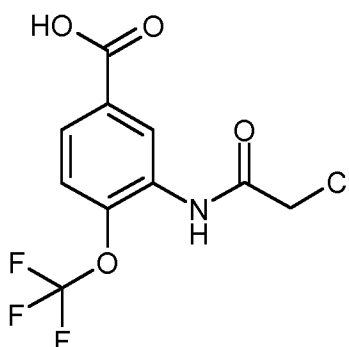
20 The intensity of a sharp signal correlates with the height (in cm) of the signal in a printed NMR spectrum. When compared with other signals, this data can be correlated to the real ratios of the signal intensities. In the case of broad signals, more than one peak, or the center of the signal along with their relative intensity, compared to the most intense signal displayed in the spectrum, are shown. A ^1H -NMR peaklist is similar to a classical ^1H -NMR readout, and thus usually contains all the peaks listed in a classical NMR interpretation. Moreover, similar to classical ^1H -NMR printouts, 25 peaklists can show solvent signals, signals derived from stereoisomers of target compounds (also the subject of the invention), and/or peaks of impurities. The peaks of stereoisomers, and/or peaks of impurities are typically displayed with a lower intensity compared to the peaks of the target compounds (e.g., with a purity of >90%). Such stereoisomers and/or impurities may be typical for the particular manufacturing process, and therefore their peaks may help to identify the reproduction of 30 our manufacturing process on the basis of "by-product fingerprints". An expert who calculates the peaks of the target compounds by known methods (MestReC, ACD simulation, or by use of empirically evaluated expectation values), can isolate the peaks of target compounds as required, optionally using additional intensity filters. Such an operation would be similar to peak-picking in

classical ^1H -NMR interpretation. A detailed description of the reporting of NMR data in the form of peaklists can be found in the publication "Citation of NMR Peaklist Data within Patent Applications" (cf. Research Disclosure Database Number 605005, 2014, 01 Aug 2014, or <http://www.researchdisclosure.com/searching-disclosures>). In the peak picking routine, as described in the Research Disclosure Database Number 605005, the parameter "MinimumHeight" can be adjusted between 1% and 4%. Depending on the chemical structure and/or depending on the concentration of the measured compound it may be reasonable to set the parameter "MinimumHeight" <1%.

10 Intermediates

Intermediate 1

3-[(chloroacetyl)amino]-4-(trifluoromethoxy)benzoic acid



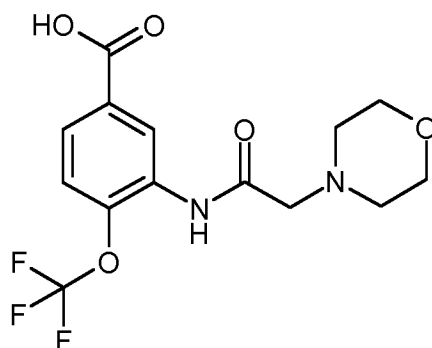
To a solution of 3-amino-4-(trifluoromethoxy)benzoic acid (2.50 g, 11.3 mmol) and pyridine (1.92 mL, 23.7 mmol, 2.1 equiv) in CH_2Cl_2 (50 mL) at 0°C was added chloroacetyl chloride (0.95 mL, 11.9 mmol, 1.05 equiv) dropwise. The resulting mixture was allowed to warm to room temperature and was stirred at that temperature for 5 h. The resulting solution was treated with a CH_2Cl_2 / isopropanol mixture (4:1, 50 mL). The resulting solution was washed with an aqueous 1N HCl solution (50 mL), dried (MgSO_4 anhydrous), and concentrated under reduced pressure to give impure 3-[(chloroacetyl)amino]-4-(trifluoromethyl)benzoic acid (3.52 g). This material was used in subsequent reactions without further purification.

^1H -NMR (300 MHz, $\text{DMSO}-d_6$): δ [ppm] = 4.35 (s, 2H), 7.52 (ddm, $J=1.5, 8.7$ Hz, 1H), 7.80 (dd, $J=2.1, 8.7$ Hz, 1H), 8.47 (d, $J=2.1$ Hz, 1H), 10.17 (s, 1H), 13.28 (br. s, 1H).

LC-MS (Method 3): R_t = 0.95 min; MS (ESIpos): m/z = 298 ($[\text{M}+\text{H}]^+$, 100%); MS (ESIneg): m/z = 296 ($[\text{M}-\text{H}]^-$, 100%), 593 ($[\text{2M}-\text{H}]^-$, 100%).

Intermediate 2

3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzoic acid



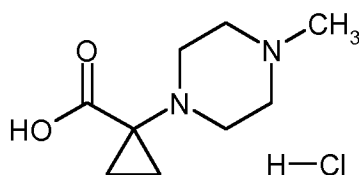
To a solution of 3-[(chloroacetyl)amino]-4-(trifluoromethoxy)benzoic acid (prepared in a manner analogous to that described in intermediate 1, 3.52 g, 11.8 mmol) in DMF (50 mL) was added morpholine (2.2 mL, 24.8 mmol, 2.1 equiv), triethylamine (3.5 mL, 24.8 mmol, 2.1 equiv) and potassium iodide (0.30 g, 1.83 mmol, 0.16 equiv). The reaction mixture was stirred at room temperature for 16 h. The resulting mixture was diluted with water (75 mL). The aqueous solution was extracted with a CH₂Cl₂ / isopropanol solution (4:1, 5 x 50 mL). The combined organic phases were washed with saturated brine (50 mL), dried (Na₂SO₄ anhydrous), and concentrated under reduced pressure to give impure 3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzoic acid (2.87 g). This material was used in subsequent reactions without further purification.

¹H-NMR (300 MHz, DMSO-d₆): δ [ppm] = 2.54-2.59 (m, 4H), 3.20 (s, 2H), 3.61-3.66 (m, 4H), 7.49-7.54 (m, 1H), 7.76 (dd, J=2.1, 8.6 Hz, 1H), 8.80 (d, J=2.1 Hz, 1H), 9.81 (s, 1H).

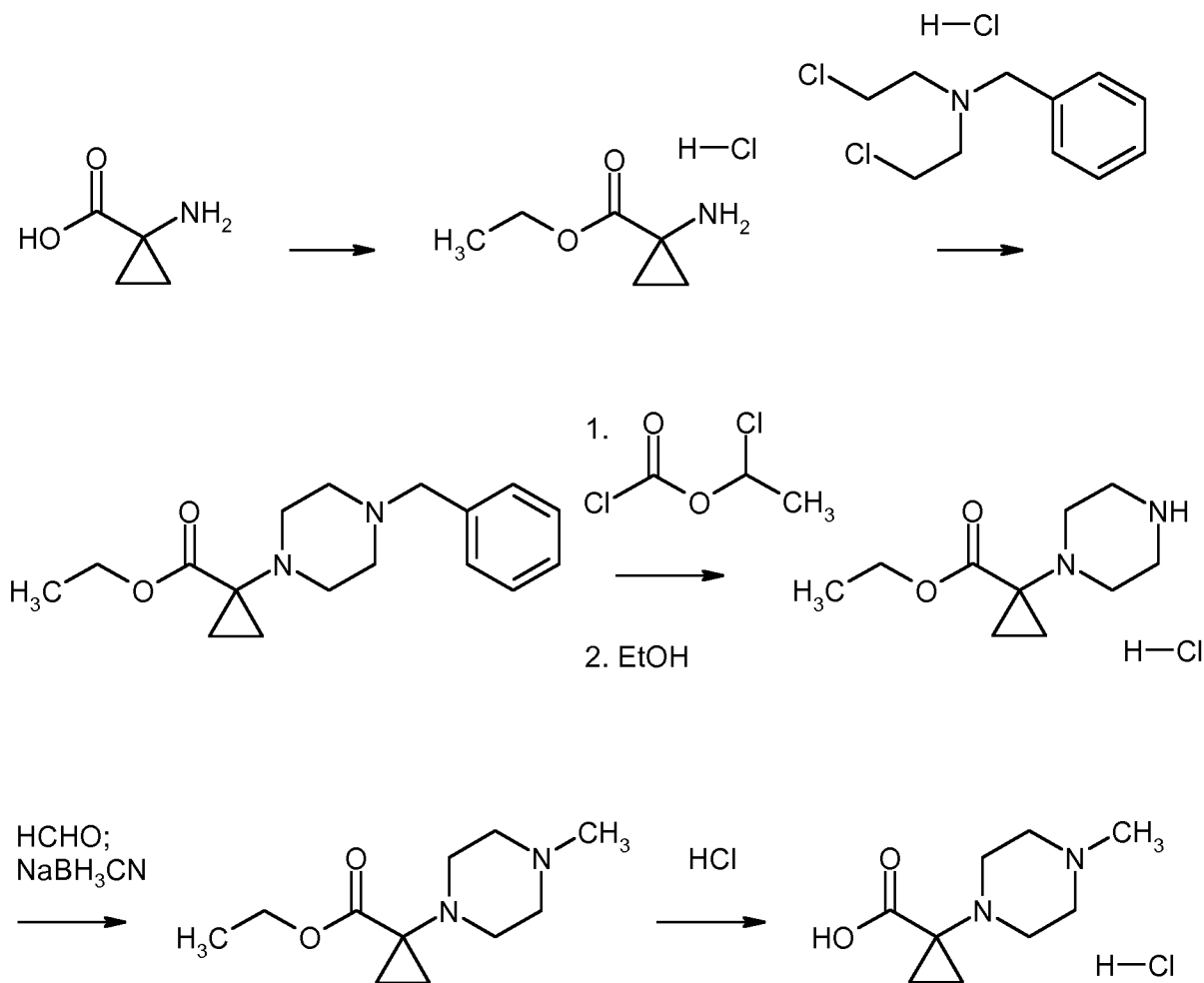
LC-MS (Method 3): R_t = 0.58 min; MS (ESIpos): m/z = 349 ([M+H]⁺, 100%); MS (ESIneg): m/z = 347 ([M-H]⁻, 100%).

Intermediate 3

1-(4-methylpiperazin-1-yl)cyclopropanecarboxylic acid hydrochloride (1:1)



The title compound was prepared according to the following scheme:

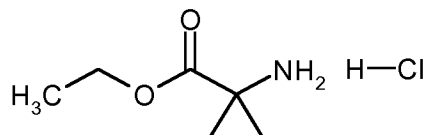


LC-MS methods for intermediates 3 and 4:

MS instrument type: Agilent 1956A; HPLC instrument type: Agilent 1200 Series; UV DAD; column: Agilent TC-C18, 2.1 x 50 mm, 5 µm; mobile phase A: 0.0375% TFA in water, mobile phase B: 0.0188% TFA in acetonitrile; gradient: 0.0 min 100% A -> 1.0 min 100% A -> 3.4 min 20% A -> 3.9 min 0% A -> 3.91 min 100% A -> 4.0 min 100% A -> 4.5 min 100% A; flow rate: 0.0 min 0.6 mL/min -> 1.0 min/3.4 min/3.9 min/3.91 min 0.6 mL/min -> 4.0 min/4.5 min 1.0 mL/min; column temp: 40 °C; UV detection: 220 nm.

Step 1:

- 10 ethyl 1-aminocyclopropanecarboxylate hydrochloride (1:1)



- 15 Thionyl chloride (150 mL, 2.056 mol) was added slowly below 0 °C to a suspension of 1-aminocyclopropanecarboxylic acid (100 g, 0.989 mol) in anhydrous ethanol (1 L). The mixture was stirred at 70 °C for 20 h. TLC (methanol, R_f = 0.4) showed that most of the starting material was consumed. Then the solution was concentrated to give 210 g of crude product. The residue was dissolved in water and adjusted to a pH between 9 and 10 with potassium carbonate. The aqueous

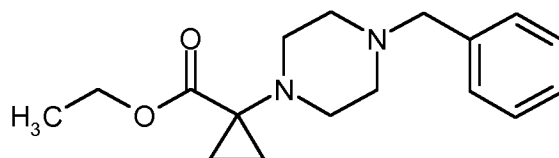
layer was extracted with dichloromethane (1 L x 3). The combined organic layers were concentrated to dryness. The residue was dissolved in ethyl acetate (300 mL) and hydrochloride in ethyl acetate (250 mL, 4M) was added slowly to the solution below -30 °C. It was stirred for 30 min at 0 °C. A solid precipitated and it was filtered under nitrogen atmosphere to give ethyl 1-aminocyclopropanecarboxylate hydrochloride (132 g, 80.6% yield) as a white solid.

The following ¹H-NMR is from the free amine.

¹H-NMR (400MHz, chloroform-d₁): δ [ppm] = 0.91-1.02 (m, 2H), 1.15-1.30 (m, 5H), 2.17 (s, 2H), 4.10 (d, 2H).

Step 2:

ethyl 1-(4-benzylpiperazin-1-yl)cyclopropanecarboxylate

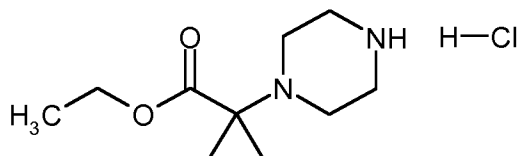


A mixture of ethyl 1-aminocyclopropanecarboxylate hydrochloride (120 g, 0.725 mol), N,N-diisopropylethylamine (942 g, 7.29 mol), N-benzyl-2-chloro-N-(2-chloroethyl)ethanamine hydrochloride (213 g, 0.793 mol) in anhydrous ethanol (1.6 L) was stirred under reflux for 16 h. TLC (PE:EtOAc = 5:1, R_f = 0.4) showed that most of the starting material was consumed. Then the mixture was concentrated. The residue was partitioned between dichloromethane (1 L) and water (0.5 L). The layers were separated and the aqueous layer was extracted with dichloromethane (0.5 L x 2). The combined organic layers were concentrated. The residue was purified by chromatography on silica gel (PE:EtOAc = 20:1 to 10:1) to give ethyl 1-(4-benzylpiperazin-1-yl)cyclopropanecarboxylate (100 g, 47.8%) as a light yellow oil.

¹H-NMR (400MHz, chloroform-d₁): δ [ppm] = 0.88-0.97 (m, 2H), 1.23-1.36 (m, 5H), 2.37 (br. s, 4H), 2.98 (br. s, 4H), 3.51 (s, 2H), 4.15 (q, 2H), 7.23-7.36 (m, 5H).

Step 3:

ethyl 1-(piperazin-1-yl)cyclopropanecarboxylate hydrochloride (1:1)



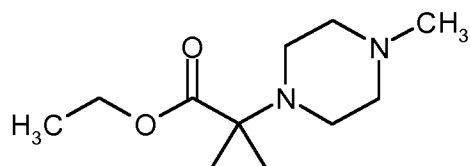
To a solution of ethyl 1-(4-benzylpiperazin-1-yl)cyclopropanecarboxylate (83 g, 0.288 mol) in anhydrous dichloromethane (700 mL) 1-chloroethyl carbonochloridate (60.4 g, 0.422 mol) was slowly added below 0 °C. After the addition, the mixture was stirred at 18 °C for 1 h. TLC (PE:EtOAc = 4:1, R_f = 0.85) showed that the reaction was complete. Then it was concentrated to dryness. The residue was dissolved in ethanol (700 mL). It was stirred under reflux for 16 h. TLC (PE:EtOAc = 4:1, R_f = 0) showed the reaction was complete. Then it was concentrated to dryness. The residue was stirred with

ethanol:methyl-tert-butylether = 5:1 to give ethyl 1-(piperazin-1-yl)cyclopropanecarboxylate hydrochloride (1:1) (62 g, 92%) as a white solid.

¹H-NMR (400MHz, methanol-d₄): δ [ppm] = 1.27 (t, 3H), 1.50-1.65 (m, 4H), 3.50 (mc, 4H), 3.65-3.85 (m, 4H), 4.21 (q, 2H).

5 Step 4:

ethyl 1-(4-methylpiperazin-1-yl)cyclopropanecarboxylate

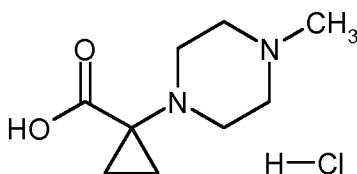


To a solution of ethyl 1-(piperazin-1-yl)cyclopropanecarboxylate hydrochloride (25 g, 0.107 mol) in water (250 mL) was added solid sodium hydrogen carbonate (10 g, 0.119 mol) so that a pH of 7-8 was reached. Then formaldehyde (13.5 g, 0.166 mol, 37% in water) and sodium cyanoborohydride (17.3 g, 0.275 mol) were added below 10 °C. The mixture was stirred 18 h at 18 °C. TLC (PE:EtOAc = 1:1, R_f = 0.1) showed that most of the starting material was consumed. Then it was extracted with DCM (50 mL x 3). The combined organic phases were concentrated to dryness. The residue was purified by chromatography on silica gel (PE:EtOAc = 3:1 to dichloromethane:methanol = 15:1) to give ethyl 1-(4-methylpiperazin-1-yl)cyclopropanecarboxylate (12 g, 53%).

¹H-NMR (400MHz, methanol-d₄): δ [ppm] = 0.98-1.04 (m, 2H), 1.24 (t, 3H), 1.26-1.31 (m, 2H), 2.70 (s, 3H), 2.97 (mc, 4H), 3.20 (mc, 4H), 4.11 (q, 2H).

Step 5:

1-(4-methylpiperazin-1-yl)cyclopropanecarboxylic acid hydrochloride (1:1)



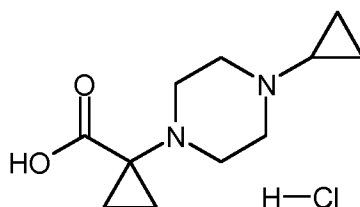
To a round bottom flask containing ethyl 1-(4-methylpiperazin-1-yl)cyclopropanecarboxylate (14 g, 65.9 mmol) was added aqueous hydrochloric acid (6M, 100 mL) slowly below 20 °C. After the addition, the mixture was stirred at 100-140 °C for 24 h. TLC (dichloromethane:methanol = 8:1, R_f=0.0) showed that the reaction was complete. Then the reaction mixture was concentrated to dryness. The residue was stirred in ethanol and the solid was filtered off to give 1-(4-methylpiperazin-1-yl)cyclopropanecarboxylic acid hydrochloride (1:1) (6.4 g, 44%) as a white solid.

¹H-NMR (400MHz, water-d₂): δ [ppm] = 1.27-1.37 (m, 2H), 1.45-1.56 (m, 2H), 2.88 (d, 3H), 3.08-3.23 (m, 2H), 3.45-3.53 (m, 2H), 3.55-3.68 (m, 2H), 3.72-3.87 (m, 2H).

ELSD: M/Z= 211.1 (M+H⁺).

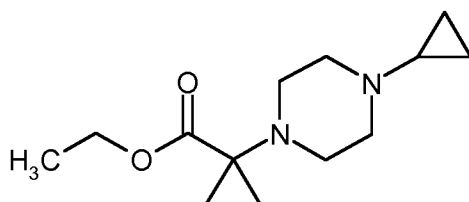
Intermediate 4

1-(4-cyclopropylpiperazin-1-yl)cyclopropanecarboxylic acid hydrochloride (1:1)



Step 1:

5 ethyl 1-(4-cyclopropylpiperazin-1-yl)cyclopropanecarboxylate

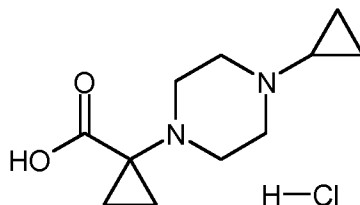


To a solution of ethyl 1-(piperazin-1-yl)cyclopropanecarboxylate hydrochloride (12.8 g, 54.5 mmol) in a mixture of anhydrous THF (68 mL) and methanol (68 mL) (1-ethoxycyclopropoxy)trimethylsilane (21.9 mL, 108.9 mmol) and acetic acid (10 mL) were added. Then sodium cyanoborohydride (5.14 g, 81.8 mmol) was added in portions. After the addition, the mixture was stirred at 60 °C for 16 h. TLC (dichloromethane:methanol = 4:1, R_f = 0.9) showed that the reaction was complete. It was cooled to 18 °C and quenched with water (5 mL). It was concentrated to dryness and the residue was partitioned between dichloromethane (100 mL) and aqueous saturated sodium hydrogen carbonate (20 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (100 mL). The combined organic layers were washed with water (15 mL) and concentrated to dryness. The residue was purified by column chromatography on silica gel (PE:EtOAc = 20:1 to 8:1) to give ethyl 1-(4-cyclopropylpiperazin-1-yl)cyclopropanecarboxylate (12 g, 92%) as a light yellow oil.

$^1\text{H-NMR}$ (400MHz, methanol- d_4): δ [ppm] = 0.40-0.45 (m, 4H), 0.91-0.97 (m, 2H), 1.19-1.28 (m, 5H), 1.58-1.66 (m, 1H), 2.40-2.70 (m, 4H), 2.87-3.09 (m, 4H), 4.10 (q, 2H).

20 Step 2:

1-(4-cyclopropylpiperazin-1-yl)cyclopropanecarboxylic acid hydrochloride (1:1)



To a round bottom flask containing ethyl 1-(piperazin-1-yl)cyclopropanecarboxylate (12 g, 50.4 mmol) was added aqueous hydrochloric acid (6M, 100 mL) below 0 °C. After the addition, the mixture was stirred at 100 °C for 16h. TLC (dichloromethane:methanol = 10:1, R_f = 0.4) showed that the reaction

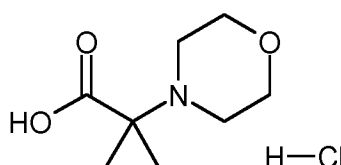
was complete. Then the reaction mixture was concentrated under reduced pressure and the residue was stirred in ethanol (40 mL). The solid was filtered off to give 1-(4-cyclopropylpiperazin-1-yl)cyclopropanecarboxylic acid hydrochloride (1:1) (10.2 g, 82%) as a white solid.

¹H-NMR (400MHz, water-d₂): δ [ppm] = 0.87-0.98 (m, 4H), 1.25-1.33 (m, 2H), 1.45-1.53 (m, 2H), 2.77-2.85 (m, 1H), 3.28-3.78 (m, 8H).

ELSD: M/Z= 211.1 (M+H⁺).

Intermediate 5

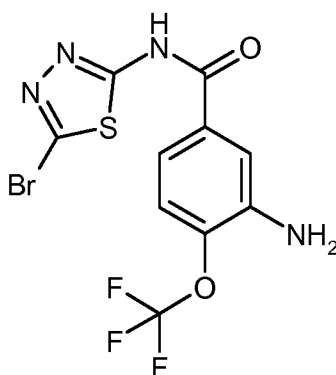
1-(morpholin-4-yl)cyclopropanecarboxylic acid hydrochloride (1:1)



The title compound is known from WO2010/136778.

Intermediate 6

3-amino-N-(5-bromo-1,3,4-thiadiazol-2-yl)-4-(trifluoromethoxy)benzamide



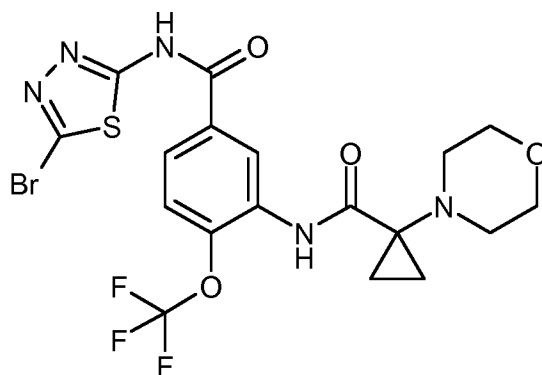
To a solution of 3-amino-4-(trifluoromethoxy)benzoic acid (known from WO2007/31791, 2.00 g, 9.04 mmol) and 5-bromo-1,3,4-thiadiazol-2-amine (2.77 g, 15.4 mmol) in DMF (20 mL) was added (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, 9.41 g, 18.1 mmol) and diisopropylethylamine (7.9 mL, 45.2 mmol). The resulting mixture was stirred at room temperature over night, was concentrated under reduced pressure, was then triturated with water, and was extracted with ethyl acetate. The combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. The remaining solids were then triturated with ethanol (50 mL) and water (50 mL), and the resulting mixture was stirred for 15 minutes. The remaining solids were removed by filtration, washed with water, and were dried at 50 °C under reduced pressure. The residue was purified using MPLC (Biotage Isolera; silica gel; hexane / EtOAc gradient). 310 mg (9% of theory) of the title compound were obtained.

¹H-NMR (400 MHz, DMSO-d₆): δ [ppm] = 5.74 (s, 2H), 7.27 (dd, 1H), 7.32 (dd, 1H), 7.49 (d, 1H), 13.29 (s, 1H).

LC-MS (Method 1): R_t = 1.14 min; MS (ESIpos): m/z = 383 [M+H]⁺.

5 **Intermediate 7**

N-(5-bromo-1,3,4-thiadiazol-2-yl)-3-({[1-(morpholin-4-yl)cyclopropyl]carbonyl}amino)-4-(trifluoromethoxy)benzamide



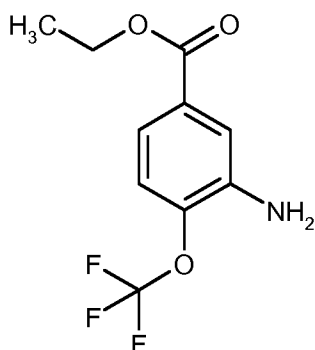
415 mg (2.00 mmol) of 1-(morpholin-4-yl)cyclopropanecarboxylic acid hydrochloride (1:1) (intermediate 5) were stirred in 10 mL of dichloromethane at room temperature. 0.015 mL (0.20 mmol) of DMF and 0.35 mL (4.00 mmol) of oxalyl chloride were added, and the mixture was stirred for additional 2 h at 50 °C after the gas formation had stopped. After concentration, 440 mg of raw material were obtained. 266 mg (1.17 mmol) of this material were added to a solution of 300 mg (0.78 mmol) of the compound of intermediate 6 and 0.55 mL (3.92 mmol) of triethylamine in a mixture of 5 mL of dichloromethane and 5 mL of THF. The resulting mixture was stirred at room temperature over night, ethyl acetate was added, and the mixture was washed with water and a saturated, aqueous ammonium chloride solution, was dried over sodium sulfate and concentrated under reduced pressure. The remaining solids were then triturated with ethanol, and the remaining solids were removed by filtration and were dried at 50 °C under reduced pressure to give the title compound (194 mg, 45% of theory).

¹H-NMR (300 MHz, DMSO-d₆): δ [ppm] = 1.10 - 1.18 (m, 2H), 1.24 - 1.33 (m, 2H), 2.38 - 2.47 (m, 4H), 3.60 - 3.76 (m, 4H), 7.66 (dd, 1H), 7.96 (dd, 1H), 9.05 (d, 1H), 10.56 (s, 1H), 13.59 (s, 1H).

LC-MS (Method 1): R_t = 1.30 min; MS (ESIpos): m/z = 536 [M+H]⁺.

25 **Intermediate 8**

ethyl 3-amino-4-(trifluoromethoxy)benzoate



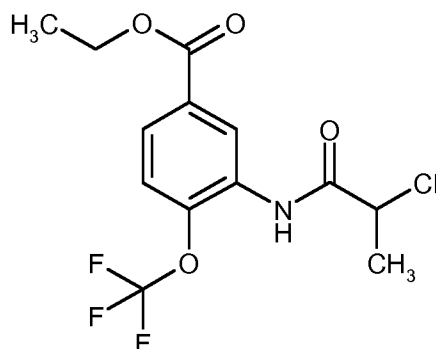
3-Amino-4-(trifluoromethoxy)benzoic acid (20.0 g, 90.4 mmol) were treated carefully under argon with thionyl chloride (38.0 mL, 520 mmol). The resulting suspension was stirred for 15 min at room temperature. Ethanol (136 mL, 2.33 mol) was added dropwise at 0 °C to the mixture. The reaction mixture was stirred for 30 min at 0 °C, over night at room temperature and subsequently 5 h under reflux. After cooling to room temperature the mixture was concentrated, the residue was diluted with water and extracted three times with ethyl acetate. The combined organic layers were washed with saturated NaHCO₃-solution, dried over MgSO₄ and the solvent was removed under reduced pressure to provide the desired compound 8 (25.7 g, quant.) as crude product which was used without further purification.

¹H-NMR (400 MHz, DMSO-d₆): δ [ppm] = 1.30 (t, 3H), 4.28 (q, 2H), 5.68 (s, 2H), 7.11 - 7.16 (m, 1H), 7.19 - 7.23 (m, 1H), 7.45 (d, 1H).

LC-MS (Method 4): R_t = 1.22 min; MS (ESIpos): m/z = 250 [M+H]⁺.

15 Intermediate 9

ethyl 3-[(2-chloropropanoyl)amino]-4-(trifluoromethoxy)benzoate



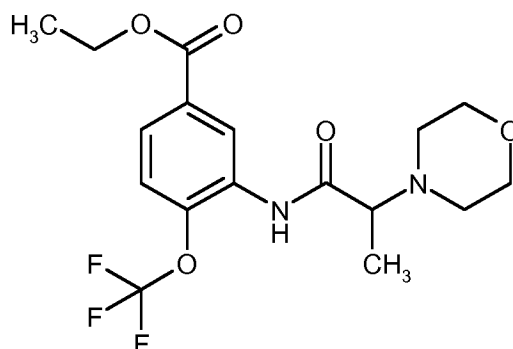
A solution of the compound of intermediate 8 (25.5 g, 102 mmol) in toluene (513 mL) was treated with 2-chloropropionyl chloride (20.5 mL, 205 mmol). The resulting mixture was stirred for 2 h at 100 °C and concentrated after cooling to room temperature under reduced pressure to provide the desired compound 9 as crude product (34.9 g, 97%) which was used without further purification.

¹H-NMR (300 MHz, DMSO-d₆): δ [ppm] = 1.32 (t, 3H), 1.62 (d, 3H), 4.34 (q, 2H), 4.89 (q, 1H), 7.59 (dd, 1H), 7.88 (dd, 1H), 8.46 (d, 1H), 10.28 (s, 1H).

LC-MS (Method 1): R_t = 1.30 min; MS (ESIpos): m/z = 340 [M+H]⁺.

Intermediate 10

ethyl 3-[[2-(morpholin-4-yl)propanoyl]amino]-4-(trifluoromethoxy)benzoate



- 5 To a solution of the compound of intermediate 9 (34.9 g, 103 mmol) in DMF (442 mL) morpholine (13.4 mL, 154 mmol), potassium iodide (2.64 g, 15.9 mmol) and triethylamine (21.4 mL, 154 mmol) were added. The mixture was stirred over night at room temperature and for 7 h at 90 °C. After cooling to room temperature the mixture was poured into water and extracted three times with ethyl acetate. The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The obtained desired product 10 (36.3 g, 80%) was used in the next step without further purification.

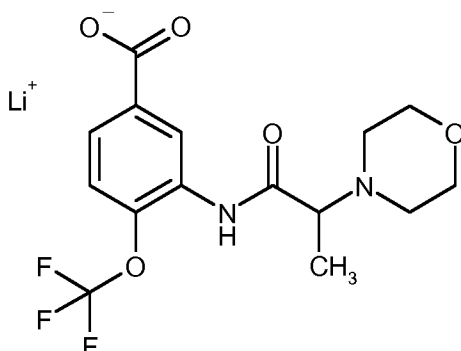
¹H-NMR (300 MHz, DMSO-d₆) δ [ppm] = 1.21 (d, 3H), 1.32 (t, 3H), 2.52 - 2.58 (m, 4H), 3.40 (d, 1H), 3.61 - 3.68 (m, 4H), 4.34 (q, 2H), 7.59 (dd, 1H), 7.80 (dd, 1H), 8.81 (d, 1H), 10.05 (s, 1H).

LC-MS (Method 1): R_t = 1.05 min; MS (ESIpos): m/z = 391 [M+H]⁺.

15

Intermediate 11

lithium 3-[[2-(morpholin-4-yl)propanoyl]amino]-4-(trifluoromethoxy)benzoate



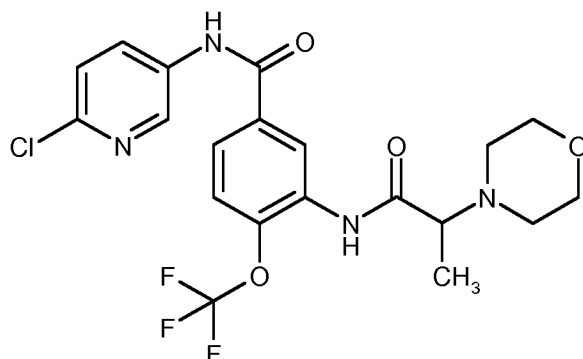
- 20 A solution of the compound of intermediate 10 (4.38 g, 11.2 mmol) in a mixture of THF/methanol (93 mL/24 mL) was treated with a 1M aqueous lithium hydroxide solution (13.5 mL, 13.5 mmol) and was stirred for 2.5 h at room temperature. The mixture was concentrated under reduced pressure to provide the desired compound 11 as 85% pure material (4.76 g, 98%).

¹H-NMR (400 MHz, DMSO-d₆): δ [ppm] = 1.18 - 1.22 (m, 3H), 2.51 - 2.59 (m, 4H), 3.63 - 3.68 (m, 4H), 7.25 (dd, 1H), 7.67 (dd, 1H), 8.50 (d, 1H), 9.73 (s, 1H). One proton under the solvent signal.

LC-MS (Method 4): R_t = 0.76 min; MS (ESIpos): m/z = 363 [M-Li⁺ + H⁺+H]⁺.

5 **Intermediate 12**

N-(6-chloropyridin-3-yl)-3-[[2-(morpholin-4-yl)propanoyl]amino]-4-(trifluoromethoxy)benzamide



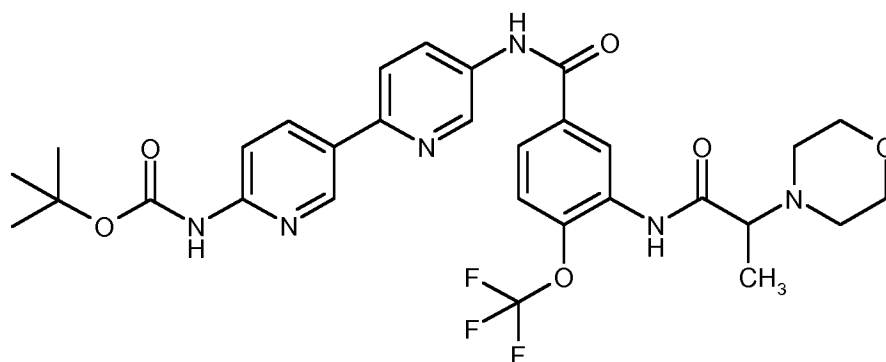
To a solution of the compound of intermediate 11 (13.5 g, 37.2 mmol) and 5-amino-2-chloropyridine (9.57 g, 74.4 mmol) in DMF (273 mL) were added (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, 29.0 g, 55.8 mmol) and diisopropylethylamine (19.4 mL, 112 mmol). The reaction mixture was stirred over night at 60 °C. After cooling to room temperature the mixture was added dropwise into water. The water was removed by decantation. The residue was dissolved in ethanol and was added dropwise into water. After stirring over night at room temperature, the precipitate was collected by filtration and dried at 60 °C under reduced pressure. The title compound 12 was obtained 93% pure (12.9 g, 25.3 mmol, 68%).

¹H-NMR (300 MHz, DMSO-d₆) δ [ppm] = 1.22 (d, 3H), 2.53 - 2.57 (m, 4H), 3.35 - 3.44 (m, 1H), 3.63 - 3.68 (m, 4H), 7.54 (d, 1H), 7.62 - 7.68 (m, 1H), 7.82 (m, 1H), 8.20 - 8.28 (m, 1H), 8.75 (dd, 2H), 10.05 (s, 1H), 10.73 (s, 1H).

LC-MS (Method 4): R_t = 0.99 min; MS (ESIpos): m/z = 473 [M+H]⁺.

Intermediate 13

tert-butyl (5-[[3-[[2-(morpholin-4-yl)propanoyl]amino]-4-(trifluoromethoxy)benzoyl]amino]-2,3'-bipyridin-6'-yl)carbamate



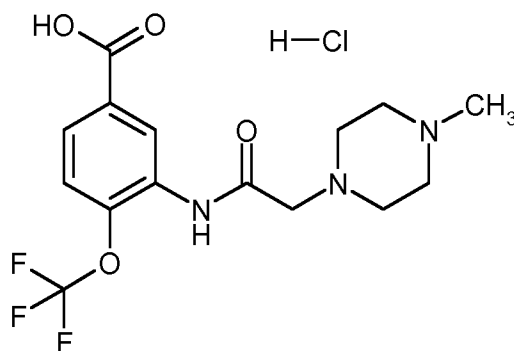
Argon was bubbled through a suspension of intermediate 12 (150 mg, 317 μ mol), {6-[(tert-butoxycarbonyl)amino]pyridin-3-yl}boronic acid (113 mg, 476 μ mol) and potassium carbonate (87.7 mg, 634 μ mol) in 1,2-dimethoxyethane (2.47 mL) and water (429 μ L) for several minutes. Afterwards

5 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride (116 mg, 159 μ mol) was added to the mixture, the tube was sealed and the reaction mixture was stirred over night at 90 °C. After cooling to room temperature, the mixture was filtered over a pad of celite. The filtrate was concentrated under reduced pressure and the residue was purified by preparative HPLC (method 5) to yield the title compound 13 (52.4 mg, 26%).

10 LC-MS (Method 4): R_t = 1.19 min; MS (ESI^{neg}): m/z = 629 [M-H]⁻.

Intermediate 14

3-[[[4-methylpiperazin-1-yl]acetyl]amino]-4-(trifluoromethoxy)benzoic acid hydrochloride (1:1)



15 To a solution of intermediate 1 (1.50 g, 5.04 mmol) in DMF (45 mL) was added triethylamine (1.05 mL, 7.56 mmol), potassium iodide (126 mg, 0.76 mmol) and 1-methylpiperazine (0.84 mL, 7.56 mmol). The reaction mixture was stirred over night at room temperature. The mixture was concentrated. The remaining residue was triturated with water, and a 1M aqueous solution of hydrogen chloride was added until a pH of 4 was achieved. The mixture was saturated with sodium

20 chloride and extracted three times with a mixture of DCM/isopropanol 4:1. The combined organic phases were dried over sodium sulfate and concentrated to yield the desired crude material (1.62 g, 69%), which was used in the next step without further purification.

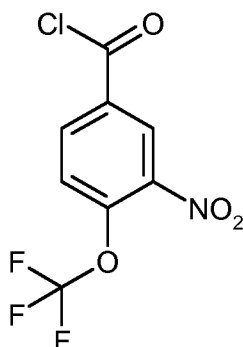
¹H-NMR (300 MHz, DMSO-d₆) δ [ppm] = 2.60 (s, 3H), 2.70 - 2.85 (m, 4H), 2.90 - 3.03 (m, 4H), 3.31 (s, 2H), 7.50 - 7.60 (m, 1H), 7.81 (dd, 1H), 8.67 (d, 1H), 9.83 (s, 1H). Säure- und Ammonium-H nicht

25 sichtbar

LC-MS (Method 4): R_t = 0.58 min; MS (ESIpos): m/z = 362 $[M-HCl+H]^+$.

Intermediate 15

3-nitro-4-(trifluoromethoxy)benzoyl chloride



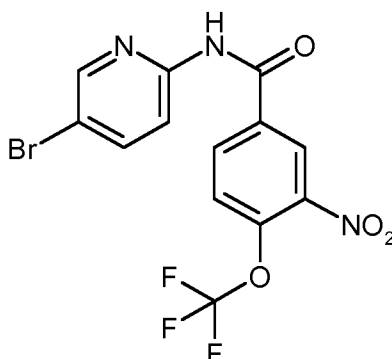
5

5.00 g (19.9 mmol) of 3-nitro-4-(trifluoromethoxy)benzoic acid were stirred in 90 mL of dichloromethane at room temperature. 0.15 mL (1.99 mmol) of DMF and 2.08 mL (23.9 mmol) of oxalyl chloride were added, and the mixture was stirred for additional 5 h at 50 °C after the gas formation had stopped. After concentration, 5.37 g of raw material were obtained, which were used without further purification.

10

Intermediate 16

N-(5-bromopyridin-2-yl)-3-nitro-4-(trifluoromethoxy)benzamide



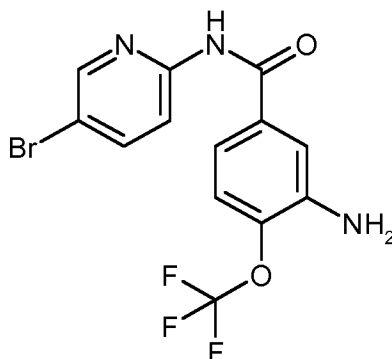
15 5.37 g of the compound of intermediate 15 were added to a suspension of 5.17 g (29.9 mmol) of 5-bromopyridin-2-amine and 13.9 mL (99.6 mmol) of triethylamine in a mixture of 75 mL of dichloromethane and 75 mL of THF. The resulting mixture was stirred at room temperature over night, water was added, and the mixture was extracted with dichloromethane. The combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. The residue was
20 purified using MPLC (Biotage Isolera; silica gel; hexane / EtOAc gradient) to give 4.60 g of the title compound.

$^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ [ppm] = 7.89 (dd, 1H), 8.11 (dd, 1H), 8.17 (d, 1H), 8.43 (dd, 1H), 8.55 (d, 1H), 8.78 (d, 1H), 11.42 (s, 1H).

LC-MS (Method 4): $R_t = 1.34$ min; MS (ESIpos): $m/z = 406$ $[M+H]^+$.

Intermediate 17

3-amino-N-(5-bromopyridin-2-yl)-4-(trifluoromethoxy)benzamide



5

To a solution of the compound of intermediate 16 (4.60 g, 11.3 mmol) in 140 mL of tetrahydrofuran was added a 15% solution of titanium(III) chloride in 10% hydrogen chloride dropwise (96 mL, 113 mmol, 10 equiv) at 0 °C. The reaction mixture was allowed to warm up to room temperature and was stirred for 4 h. The pH of the mixture was adjusted under stirring with solid sodium bicarbonate to 7. The suspension was saturated with solid sodium chloride and stirred with 200 mL of a mixture of tetrahydrofuran/ethyl acetate for 2 h. The suspension was filtered and the filtrate was washed with brine, dried over sodium sulfate and concentrated under reduced pressure. 4.27 g (100% of theory) of the title compound were obtained, which were used without further purification.

10

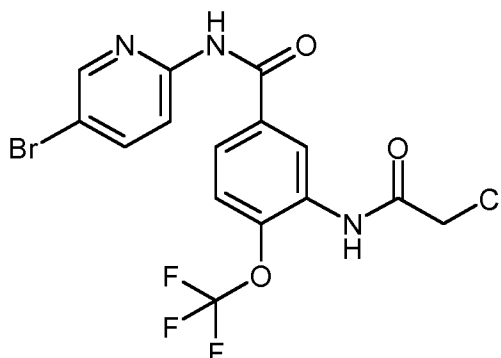
$^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ [ppm] = 5.64 (s, 2H), 7.20 (s, 2H), 7.39 (s, 1H), 8.06 (dd, 1H), 8.14 (d, 1H), 8.50 (d, 1H), 10.83 (s, 1H).

15

LC-MS (Method 4): $R_t = 1.23$ min; MS (ESIpos): $m/z = 376$ $[M+H]^+$.

Intermediate 18

N-(5-bromopyridin-2-yl)-3-[(chloroacetyl)amino]-4-(trifluoromethoxy)benzamide



20

A solution of the compound of intermediate 17 (2.00 g, 5.32 mmol) in toluene (70 mL) was treated with chloroacetyl chloride (0.64 mL, 7.98 mmol). The resulting mixture was stirred for 2 h at 100 °C

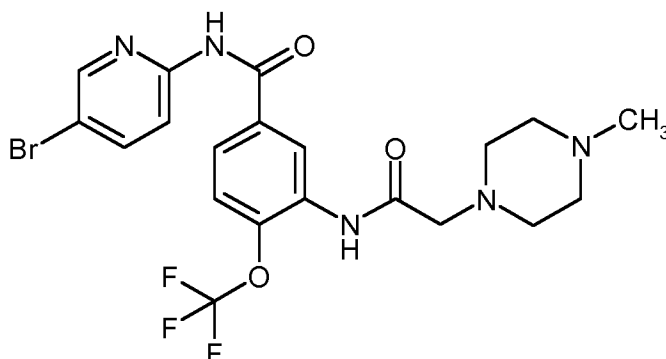
and concentrated after cooling to room temperature under reduced pressure to provide the title compound (2.41 g, 100%), which was used without further purification.

$^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ [ppm] = 4.39 (s, 2H), 7.57 (dd, 1H), 7.94 (dd, 1H), 8.09 (dd, 1H), 8.17 (d, 1H), 8.49 - 8.54 (m, 2H), 10.25 (s, 1H), 11.16 (s, 1H).

5 LC-MS (Method 4): R_t = 1.25 min; MS (ESIpos): m/z = 452 $[\text{M}+\text{H}]^+$.

Intermediate 19

N-(5-bromopyridin-2-yl)-3-[[4-methylpiperazin-1-yl]acetyl]amino}-4-(trifluoromethoxy)benzamide



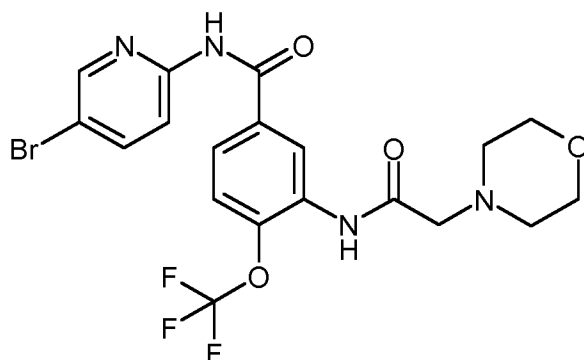
10 To a solution of the compound of intermediate 18 (1.20 g, 2.65 mmol) in DMF (20 mL) was added triethylamine (0.74 mL, 5.30 mmol), potassium iodide (88 mg, 0.53 mmol) and 1-methylpiperazine (0.59 mL, 5.30 mmol). The reaction mixture was stirred over night at room temperature. The mixture was concentrated. The remaining residue was dissolved in dichloromethane, washed with a 1M
15 aqueous solution of hydrogen chloride and a saturated aqueous solution of sodium bicarbonate, dried over sodium sulfate and concentrated to yield the title compound (1.29 g, 91%), which was used in the next step without further purification.

$^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ [ppm] = 2.19 (s, 3H), 2.30 - 2.46 (m, 4H), 2.54 - 2.64 (m, 4H), 3.20 (s, 2H), 7.58 (dd, 1H), 7.86 (dd, 1H), 8.08 (dd, 1H), 8.14 - 8.19 (m, 1H), 8.51 - 8.54 (m, 1H), 8.85 (d, 1H), 9.90 (s, 1H), 11.13 (s, 1H).

20 LC-MS (Method 4): R_t = 0.89 min; MS (ESIpos): m/z = 516 $[\text{M}+\text{H}]^+$.

Intermediate 20

N-(5-bromopyridin-2-yl)-3-[(morpholin-4-ylacetyl]amino]-4-(trifluoromethoxy)benzamide



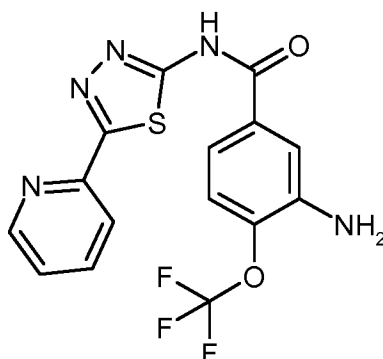
To a solution of the compound of intermediate 18 (1.20 g, 2.65 mmol) in DMF (20 mL) was added triethylamine (0.74 mL, 5.30 mmol), potassium iodide (88 mg, 0.53 mmol) and morpholine (0.46 mL, 5.30 mmol). The reaction mixture was stirred over night at room temperature. The mixture was concentrated. The remaining residue was triturated with a mixture of water (30 mL) and ethanol (20 mL) and stirred for 30 minutes. The precipitate was collected by filtration, washed with ethanol and dried to yield the title compound (960 mg, 72%).

$^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ [ppm] = 2.55 - 2.60 (m, 4H), 3.22 (s, 2H), 3.60 - 3.69 (m, 4H), 7.55 - 7.62 (m, 1H), 7.88 (dd, 1H), 8.08 (dd, 1H), 8.17 (d, 1H), 8.53 (d, 1H), 8.79 (d, 1H), 9.89 (s, 1H), 11.15 (s, 1H).

LC-MS (Method 4): R_t = 1.06 min; MS (ESIpos): m/z = 503 $[\text{M}+\text{H}]^+$.

Intermediate 21

3-amino-N-[5-(pyridin-2-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide



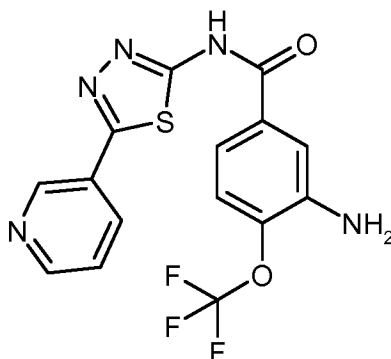
To a solution of 3-amino-4-(trifluoromethoxy)benzoic acid (known from WO2007/31791, 500 mg, 2.26 mmol) and 5-(pyridin-2-yl)-1,3,4-thiadiazol-2-amine (524 mg, 2.94 mmol, 1.3 equiv) in DMF (4.0 mL) was added (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, 2.35 g, 4.52 mmol, 2 equiv) and diisopropylethylamine (1.18 mL, 6.78 mmol, 3 equiv). The resulting mixture was stirred at room temperature over night, then triturated with water and ethanol and stirred for 15 minutes. The precipitate was collected by filtration and dried under reduced pressure at 50 °C. 830 mg (91% of theory) of the title compound were obtained.

$^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ [ppm] = 5.73 (s, 2H), 7.27 (dd, 1H), 7.37 (dd, 1H), 7.51 - 7.58 (m, 2H), 7.97 - 8.05 (m, 1H), 8.21 - 8.28 (m, 1H), 8.68 - 8.73 (m, 1H), 13.10 (s, 1H).

LC-MS (Method 4): $R_t = 1.12$ min; MS (ESIpos): $m/z = 382$ $[M+H]^+$.

Intermediate 22

3-amino-N-[5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide



5

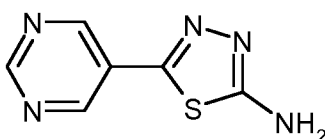
To a solution of 3-amino-4-(trifluoromethoxy)benzoic acid (known from WO2007/31791, 500 mg, 2.26 mmol) and 5-(pyridin-3-yl)-1,3,4-thiadiazol-2-amine (524 mg, 2.94 mmol, 1.3 equiv) in DMF (4.0 mL) was added (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, 2.35 g, 4.52 mmol, 2 equiv) and diisopropylethylamine (1.18 mL, 6.78 mmol, 3 equiv). The resulting mixture was stirred at room temperature over night, then triturated with water and ethanol and stirred for 15 minutes. The precipitate was collected by filtration, washed with ethanol and dried under reduced pressure at 50 °C. The remaining material was triturated with ethanol and stirred for 30 minutes. The precipitate was collected by filtration and dried under reduced pressure at 50 °C. 783 mg (84% of theory) of the title compound were obtained.

$^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ [ppm] = 5.74 (s, 2H), 7.28 (dd, 1H), 7.36 (dd, 1H), 7.52 (d, 1H), 7.59 (ddd, 1H), 8.37 (dt, 1H), 8.72 (dd, 1H), 9.16 (dd, 1H), 13.16 (s, 1H).

LC-MS (Method 4): $R_t = 1.02$ min; MS (ESIpos): $m/z = 382$ $[M+H]^+$.

Intermediate 23

5-(pyrimidin-5-yl)-1,3,4-thiadiazol-2-amine



2 g (16.12 mmol) of pyrimidine-5-carboxylic acid were added to 25 mL of trifluoromethanesulfonic acid on an ice bath. 1.45 g (15.91 mmol) of hydrazinecarbothioamide were added portionwise. At 10-15 °C 3.4 g (23.96 mmol) of phosphorous pentoxide were added portionwise. It was stirred for 7 h at rt. The reaction mixture was poured into ice/water and stirred for 45 min. The solution was made alkaline (pH >10) with a concentrated aqueous sodium hydroxide solution on an ice bath. It was stirred for 1 h at 0 °C. The precipitate was filtered off and dried under vacuum. The raw material was

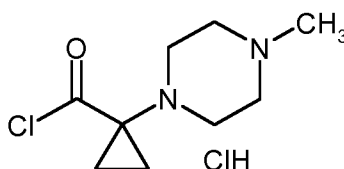
purified on silica gel (gradient hexane/ethylacetate). The fractions containing the desired product were combined and concentrated under vacuum. The residue was dissolved in water basified with diluted aqueous sodium hydroxide solution and stored for 24 h at 0 °C. The precipitated product was collected and dried under vacuum affording 423 mg (14%) of the title compound.

5 $^1\text{H-NMR}$ (400MHz, DMSO-d_6): δ [ppm]= 7.69 (s, 2H), 9.17 (s, 2H), 9.22 (s, 1H).

LC-MS (Method 4): R_t = 0.48 min; MS (ESIpos): m/z = 180 $[\text{M}+\text{H}]^+$.

Intermediate 24

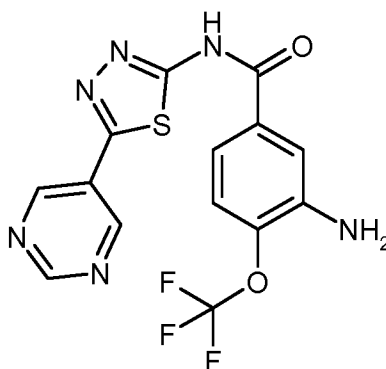
1-(4-methylpiperazin-1-yl)cyclopropanecarbonyl chloride hydrochloride (1:1)



100 mg (0.45 mmol) of 1-(4-methylpiperazin-1-yl)cyclopropanecarboxylic acid hydrochloride (1:1) (intermediate 3) were largely dissolved in 2 mL of anhydrous dichloromethane and 3.5 μL of anhydrous DMF. 0.453 mL (0.91 mmol) of oxalyl chloride were added and it was stirred for 4 h at rt. The volatiles were removed under vacuum and the residue was used without further purification.

Intermediate 25

3-amino-N-[5-(pyrimidin-5-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide



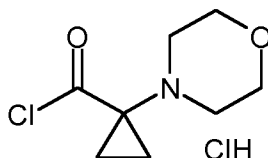
150 mg (0.68 mmol) of 3-amino-4-(trifluoromethoxy)benzoic acid which can be synthesized according to the method disclosed on page 213 of WO2008/75064A1, 134 mg (0.75 mmol) of 5-(pyrimidin-5-yl)-1,3,4-thiadiazol-2-amine (intermediate 23), 532 μL (3.05 mmol) of N-ethyl-N-isopropylpropan-2-amine, and 529 mg (1.02 mmol) of PYBOP in 4.5 mL of anhydrous DMF were stirred for 6 h at 50 °C. The volatiles were removed under vacuum and the residue was purified by HPLC (method 2). The residue was washed with water and dichloromethane. It was dried under vacuum at 50 °C yielding 215 mg (26%) of the title compound.

$^1\text{H-NMR}$ (400MHz, DMSO-d_6): δ [ppm]= 5.74 (s, 2H), 7.24 - 7.30 (m, 1H), 7.36 (dd, 1H), 7.52 (d, 1H), 9.31 (s, 1H), 9.37 (s, 2H), 13.24 (br. s, 1H).

LC-MS (Method 4): R_t = 1.00 min; MS (ESIpos): m/z = 383 $[\text{M}+\text{H}]^+$.

5 Intermediate 26

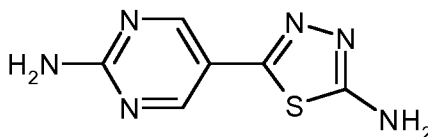
1-(morpholin-4-yl)cyclopropanecarbonyl chloride hydrochloride (1:1)



100 mg (0.48 mmol) of 1-(morpholin-4-yl)cyclopropanecarboxylic acid hydrochloride (1:1) (intermediate 5) were largely dissolved in 2 mL of anhydrous dichloromethane and 3.7 μL of anhydrous DMF. 0.482 mL (0.96 mmol) of oxalyl chloride were added and it was stirred for 4 h at rt. The volatiles were removed under vacuum and the residue was used without further purification.

Intermediate 27

5-(5-amino-1,3,4-thiadiazol-2-yl)pyrimidin-2-amine



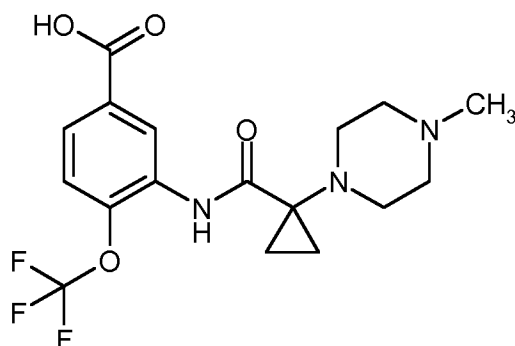
15 To 1.9 g of polyphosphoric acid were added 500 mg (3.59 mmol) of 2-aminopyrimidine-5-carboxylic acid portionwise. It was stirred for 5 min before 327.6 mg (3.59 mmol) of hydrazinecarbothioamide were added portionwise. It was stirred for 1 h at 140 °C. It was allowed to cool down and water was added. The pH was adjusted to 12 by adding 25 vol% aqueous ammonia solution. The precipitate was
20 filtered off and washed with water. It was dried under vacuum at 50 °C to yield 164 mg (23%) of the title compound, containing ca. 25 mol% of the starting material.

$^1\text{H-NMR}$ (300MHz, DMSO-d_6): δ [ppm]= 7.13 (s, 2H), 7.30 (s, 2H), 8.56 (s, 2H).

LC-MS (Method 3): R_t = 0.44 min; MS (ESIpos): m/z = 195 $[\text{M}+\text{H}]^+$.

25 Intermediate 28

3-({[1-(4-methylpiperazin-1-yl)cyclopropyl]carbonyl}amino)-4-(trifluoromethoxy)benzoic acid



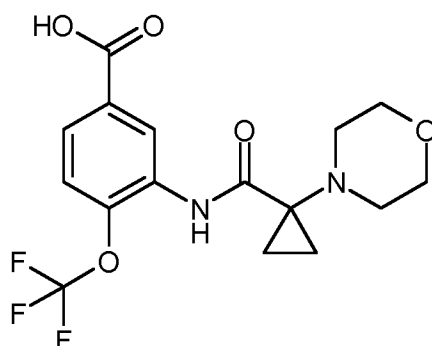
208 mg (0.94 mmol) of 3-amino-4-(trifluoromethoxy)benzoic acid which can be synthesized according to the method disclosed on page 213 of WO2008/75064A1 and 270 mg (1.13 mmol) of 1-(4-methylpiperazin-1-yl)cyclopropanecarbonyl chloride hydrochloride (1:1) (intermediate 24, prepared analogously) were stirred in 10 mL of anhydrous toluene under reflux for 3 h. The reaction mixture was allowed to cool down and concentrated under vacuum. The residue was purified by HPLC (method 2). The solid material was dried under vacuum at 50 °C to give 380 mg (44%) of the title compound.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 1.11 - 1.17 (m, 2H), 1.18 - 1.25 (m, 2H), 2.39 (s, 3H), 2.53 - 2.61 (m, 4H), 2.64 - 2.81 (m, 4H), 7.53 - 7.59 (m, 1H), 7.77 (dd, 1H), 8.12 (s, 1H), 8.83 (s, 1H), 10.33 (br. s, 1H).

LC-MS (Method 4): R_t = 0.69 min; MS (ESIpos): m/z = 388 [M+H]⁺.

Intermediate 29

3-((1-(morpholin-4-yl)cyclopropyl)carbonyl)amino)-4-(trifluoromethoxy)benzoic acid



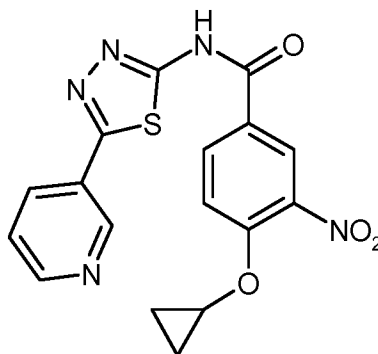
222 mg (1.00 mmol) of 3-amino-4-(trifluoromethoxy)benzoic acid which can be synthesized according to the method disclosed on page 213 of WO2008/75064A1 and 272 mg (1.20 mmol) of 1-(morpholin-4-yl)cyclopropanecarbonyl chloride hydrochloride (1:1) (intermediate 26, prepared analogously) were stirred in 10 mL of anhydrous toluene under reflux for 3 h. The reaction mixture was allowed to reach room temperature and was concentrated under vacuum. The residue was purified by HPLC (method 2). The solid material was dried under vacuum at 50 °C affording 226 mg (30%) of the title compound.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 1.12 - 1.18 (m, 2H), 1.25 - 1.30 (m, 2H), 2.43 - 2.48 (m, 4H), 3.65 - 3.73 (m, 4H), 7.55 - 7.61 (m, 1H), 7.77 (dd, 1H), 8.98 (d, 1H), 10.54 (s, 1H), 13.27 (br. s, 1H).

LC-MS (Method 4): $R_t = 1.12$ min; MS (ESIpos): $m/z = 375$ $[M+H]^+$.

Intermediate 30

4-(cyclopropyloxy)-3-nitro-N-[5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl]benzamide



5

100 mg (2.02 mmol) of 4-(cyclopropyloxy)-3-nitrobenzoic acid were dissolved in 5 mL of anhydrous DMF and 1.40 mL (8.07 mmol) of *N*-ethyl-*N*-isopropylpropan-2-amine were added. 431 mg (2.42 mmol) of 5-(pyridin-3-yl)-1,3,4-thiadiazol-2-amine and 2.04 g (0.31 mmol) of PYBOP were added. It was stirred over night at rt. The reaction mixture was poured into 100 mL of water. The precipitate was filtered off under suction, washed with water and dried under vacuum at 50 °C affording 790 mg (90%) of the title compound.

10

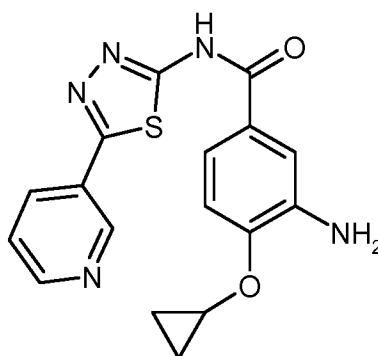
$^1\text{H-NMR}$ (400MHz, DMSO-d_6): δ [ppm] = 0.76 - 0.85 (m, 2H), 0.86 - 0.95 (m, 2H), 4.19 - 4.26 (m, 1H), 7.58 - 7.61 (m, 1H), 7.81 (d, 1H), 8.36 - 8.39 (m, 1H), 8.46 (dd, 1H), 8.68 - 8.76 (m, 2H), 9.16 (d, 1H), 13.43 (br. s, 1H).

15

LC-MS (Method 4): $R_t = 1.08$ min; MS (ESIpos): $m/z = 384$ $[M+H]^+$.

Intermediate 31

3-amino-4-(cyclopropyloxy)-N-[5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl]benzamide



20

100 mg (0.26 mmol) of 4-(cyclopropyloxy)-3-nitro-N-[5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl]benzamide (intermediate 30) were dissolved in 30 mL of DMF. 10 mL of methanol and 50 mg of 10% palladium on charcoal were added. It was hydrogenated for 30 min. 100 mg of 10% palladium on charcoal were

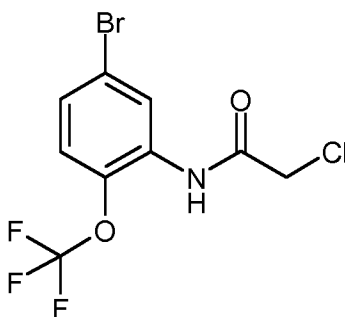
added and it was hydrogenated for 2 h. 100 mg of 10% palladium on charcoal and 5 mL of THF were added and it was hydrogenated for 1 h. The catalyst was filtered off and washed with 5 mL of THF, methanol and DMF respectively. The filtrate was concentrated under vacuum. 460 mg (1.20 mmol) of 4-(cyclopropyloxy)-3-nitro-N-[5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl]benzamide (intermediate 30) were dissolved in 100 mL of DMF. 30 mL of methanol and 200 mg of 10% palladium on charcoal were added. It was hydrogenated for 30 min. 200 mg of 10% palladium on charcoal were added and it was hydrogenated for 30 min. 400 mg of 10% palladium on charcoal were added and it was hydrogenated for 2.5 h. The catalyst was filtered off and washed with 10 mL of THF, methanol and DMF respectively. 200 mg of 10% palladium on charcoal was added to the filtrate and it was hydrogenated for 1.5 h. The last step was repeated and the catalyst was filtered off and washed with 20 mL of THF, methanol and DMF, respectively. The filtrate was concentrated to dryness under vacuum. The two batches were combined and 5 mL of methanol were added. It was stirred 30 min at 60 °C. The flask was allowed to reach rt and the the remaining solid was filtered off under suction and dried under vacuum at 50 °C yielding 217 mg (40%) of the title compound.

¹H-NMR (300MHz, DMSO-d₆): δ [ppm]= 0.65 - 0.88 (m, 4H), 3.89 - 3.99 (m, 1H), 4.96 (s, 2H), 7.19 (d, 1H), 7.34 - 7.39 (m, 1H), 7.50 (dd, 1H), 7.57 (dd, 1H), 8.32 - 8.38 (m, 1H), 8.67 - 8.72 (m, 1H), 9.12 - 9.16 (m, 1H), 12.91 (br. s, 1H).

LC-MS (Method 4): R_t = 0.94 min; MS (ESIpos): m/z = 354 [M+H]⁺.

Intermediate 32

N-[5-bromo-2-(trifluoromethoxy)phenyl]-2-chloroacetamide



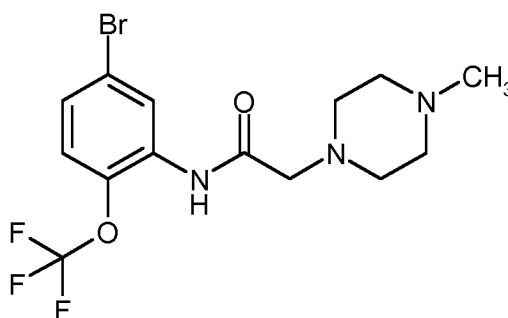
240 g (0.937 mol) of 5-bromo-2-(trifluoromethoxy)aniline were dissolved in 2400 mL of anh toluene. 112 mL (1.406 mol) of chloroacetyl chloride were added. It was stirred for 2 h at 100 °C. The reaction mixture was concentrated under vacuum. The residue was treated with 600 mL of cyclopentyl methyl ether and concentrated again. This procedure was performed twice yielding 324 g of the title compound.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 4.39 (s, 2H), 7.40 - 7.44 (m, 1H), 7.49 (dd, 1H), 8.20 (d, 1H), 10.23 (s, 1H).

LC-MS (Method 4): R_t = 1.27 min; MS (ESIpos): m/z = 332 [M+H]⁺.

Intermediate 33

N-[5-bromo-2-(trifluoromethoxy)phenyl]-2-(4-methylpiperazin-1-yl)acetamide



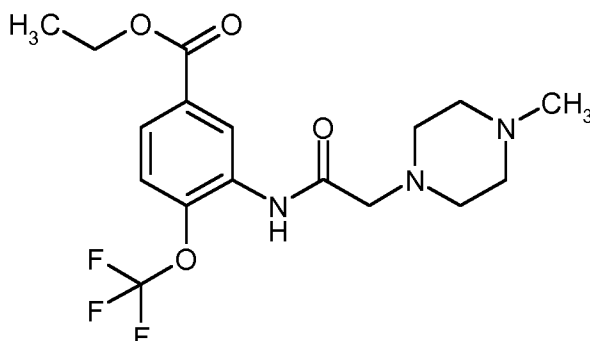
162 g (0.487 mol) of N-[5-bromo-2-(trifluoromethoxy)phenyl]-2-chloroacetamide (intermediate 32) were dissolved in 1620 mL of anhydrous DMF. 135.8 mL (0.974 mol) of N,N-diethylethanamine and 16.175 g (97.44 mmol) of potassium iodide were added. It was stirred overnight at room temperature. A second batch of the same size was prepared under analogous conditions. The two batches were combined. The reaction mixtures were concentrated and the residue was stirred with 3 L of water and 700 mL of ethanol for 1 h. The solid was filtered off with suction and dried at 50 °C under vacuum to afford 317 g (82%) of the title compound.

¹H-NMR (400 MHz, DMSO-d₆): δ [ppm] = 2.18 (s, 3H), 2.21 - 2.48 (m, 4H), 2.52 - 2.64 (m, 4H), 3.19 (s, 2H), 7.39 - 7.47 (m, 2H), 8.54 (d, 1H), 9.92 (s, 1H).

LC-MS (Method 1): R_t = 0.81 min; MS (ESIpos): m/z = 396 [M+H]⁺.

Intermediate 34

ethyl 3-[[[4-methylpiperazin-1-yl)acetyl]amino]-4-(trifluoromethoxy)benzoate



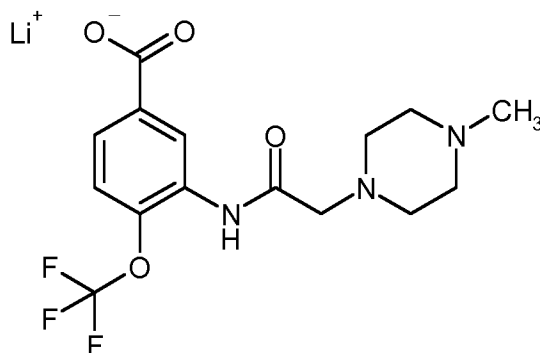
60 g (0.151 mol) of N-[5-bromo-2-(trifluoromethoxy)phenyl]-2-(4-methylpiperazin-1-yl)acetamide (intermediate 33) were dissolved in 600 mL of ethanol. 450 mg (0.76 mmol) of dichloropalladium - propane-1,3-diylbis(diphenylphosphine) (1:1) and 53 mL (0.380 mol) of N,N-diethylethanamine were added. The 2000 mL autoclave was charged with 12.5 bar of carbon monoxide and was stirred for 16 h at 100 °C. The reaction mixture was concentrated under vacuum and the residue was treated with dichloromethane. The insoluble material was filtered off and washed with dichloromethane. The filtrate was concentrated under vacuum and purified on silica gel (gradient dichloromethane/methanol) to yield 54 g (92%) of the title compound, which contained approximately 0.5 mole of N,N-diethylethanamine.

$^1\text{H-NMR}$ (400MHz, DMSO-d_6): δ [ppm]= 1.31 (t, 3H), 2.24 (s, 3H), 2.37-2.53 (m, 4H), 2.60 (br. s, 4H), 3.20 (s, 2H), 4.32 (q, 2H), 7.55 - 7.60 (m, 1H), 7.78 (dd, 1H), 8.86 (d, 1H), 9.89 (s, 1H).

LC-MS (Method 4): R_t = 0.81 min; MS (ESIpos): m/z = 390 $[\text{M}+\text{H}]^+$.

5 Intermediate 35

lithium 3-[[[4-methylpiperazin-1-yl)acetyl]amino]-4-(trifluoromethoxy)benzoate



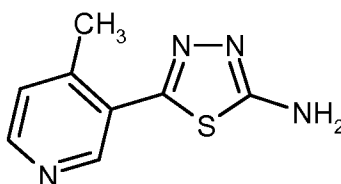
20 g (51.36 mmol) of ethyl 3-[[[4-methylpiperazin-1-yl)acetyl]amino]-4-(trifluoromethoxy)benzoate (intermediate 34) were dissolved in 50 mL of dioxane and 2 mL of water. 3.233 g (77.05 mmol) of lithium hydroxide monohydrate were added and it was stirred for 24 h at rt. The precipitate was filtered off and washed with dioxane to yield 17.0 g (90%) of the title compound, which was used without further treatment.

$^1\text{H-NMR}$ (300MHz, DMSO-d_6): δ [ppm]= 2.15 (s, 3H), 2.36 (br. s, 4H), 2.54 (br. s, 4H), 3.13 (s, 2H), 7.28 (dd, 1H), 7.67 (dd, 1H), 8.70 (s, 1H), 9.70 (br. s, 1H).

15 LC-MS (Method 1): R_t = 0.61 min; MS (ESIpos): m/z = 362 $[\text{M}+2\text{H-Li}]^+$. (JEJE 1382-5)

Intermediate 36

5-(4-methylpyridin-3-yl)-1,3,4-thiadiazol-2-amine



20 5.00 g (36.5 mmol) of 4-methylnicotinic acid were added to 18.9 g of polyphosphoric acid. 3.32 g (36.5 mmol) of hydrazinecarbothioamide were added portionwise. It was stirred for 1 h at 140 °C. After cooling down to 90 °C, water (70 mL) was added dropwise. After cooling to 0 °C, aqueous ammonium hydroxide solution (25%, 35 mL) was added till a pH value of 12 was achieved. The precipitate was collected by filtration, washed with water and dried under reduced pressure at 50 °C

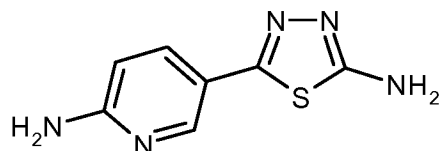
25 affording 1.75 g (25% of theory) of the title compound.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 2.51 (s, 3H), 7.39 (d, 1H), 7.47 (s, 2H), 8.46 (d, 1H), 8.68 (s, 1H).

LC-MS (Method 3): R_t = 0.58 min; MS (ESIpos): m/z = 193 [M+H]⁺.

5 Intermediate 37

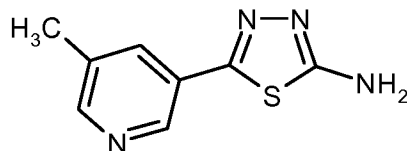
5-(5-amino-1,3,4-thiadiazol-2-yl)pyridin-2-amine



1.00 g (7.24 mmol) of 6-aminonicotinic acid was added to 3.74 g of polyphosphoric acid. 0.66 g (7.24 mmol) of hydrazinecarbothioamide was added portionwise. It was stirred for 1 h at 140 °C. After cooling down to 70 °C, water (6 mL) was added dropwise. After cooling to 0 °C, aqueous ammonium hydroxide solution (25%, 5 mL) was added till a pH value of 12 was achieved. The precipitate was collected by filtration, washed with water and dried under reduced pressure at 50 °C affording 730 mg of raw material which was used without further purification.

15 Intermediate 38

5-(5-methylpyridin-3-yl)-1,3,4-thiadiazol-2-amine



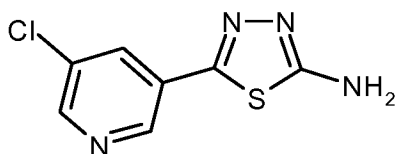
0.50 g (3.65 mmol) of 5-methylnicotinic acid was added to 1.89 g of polyphosphoric acid. 0.33 g (3.65 mmol) of hydrazinecarbothioamide was added portionwise. It was stirred for 1 h at 140 °C. After cooling down to 70 °C, water (6 mL) was added dropwise. After cooling to 0 °C, aqueous ammonium hydroxide solution (25%, 4 mL) was added till a pH value of 12 was achieved. The precipitate was collected by filtration, washed with water and dried under reduced pressure at 50 °C affording 500 mg (71% of theory) of the title compound.

¹H-NMR (300MHz, DMSO-d₆): δ [ppm]= 2.35 (s, 3H), 7.53 (s, 2H), 7.95 (s, 1H), 8.45 (d, 1H), 8.74 (d, 1H).

LC-MS (Method 4): R_t = 0.50 min; MS (ESIpos): m/z = 193 [M+H]⁺.

Intermediate 39

5-(5-chloropyridin-3-yl)-1,3,4-thiadiazol-2-amine



0.50 g (3.17 mmol) of 5-chloronicotinic acid was added to 1.65 g of polyphosphoric acid. 0.29 g (3.17 mmol) of hydrazinecarbothioamide was added portionwise. It was stirred for 1 h at 140 °C. After cooling down to 70 °C, water (6 mL) was added dropwise. After cooling to 0 °C, aqueous ammonium hydroxide solution (25%, 4 mL) was added till a pH value of 12 was achieved. The precipitate was collected by filtration, washed with water and dried under reduced pressure at 50 °C affording 460 mg (68% of theory) of the title compound.

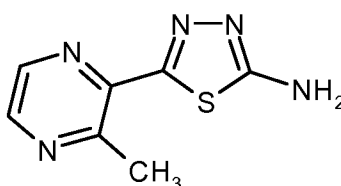
¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 7.64 (s, 2H), 8.26 (t, 1H), 8.67 (d, 1H), 8.91 (d, 1H).

LC-MS (Method 4): R_t = 0.69 min; MS (ESIpos): m/z = 213 [M+H]⁺.

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Intermediate 40

5-(3-methylpyrazin-2-yl)-1,3,4-thiadiazol-2-amine



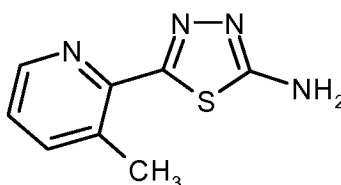
1.00 g (7.24 mmol) of 3-methylpyrazine-2-carboxylic acid was added to 3.75 g of polyphosphoric acid. 0.66 g (7.24 mmol) of hydrazinecarbothioamide was added portionwise. It was stirred for 1 h at 140 °C. After cooling down to 100 °C, water (12 mL) was added dropwise. After cooling to 0 °C, aqueous ammonium hydroxide solution (25%, 8 mL) was added till a pH value of 12 was achieved. The precipitate was collected by filtration, washed with water and dried under reduced pressure at 50 °C affording 388 mg (27% of theory) of the title compound.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 2.88 (s, 3H), 7.64 (s, 2H), 8.50 - 8.54 (m, 2H).

LC-MS (Method 4): R_t = 0.58 min; MS (ESIpos): m/z = 194 [M+H]⁺.

Intermediate 41

5-(3-methylpyridin-2-yl)-1,3,4-thiadiazol-2-amine



25

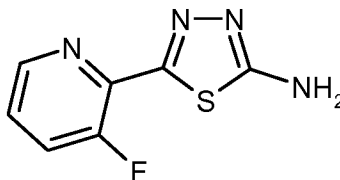
1.00 g (7.29 mmol) of 3-methylpyridine-2-carboxylic acid was added to 3.77 g of polyphosphoric acid. 0.80 g (8.75 mmol) of hydrazinecarbothioamide was added portionwise. It was stirred for 1 h at 140 °C. After cooling down to 70 °C, water (20 mL) was added dropwise. After cooling to 0 °C, aqueous ammonium hydroxide solution (25%, 25 mL) was added till a pH value of 12 was achieved. The precipitate was collected by filtration, washed with water and dried under reduced pressure at 50 °C affording 885 mg (62% of theory) of the title compound.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 2.65 (s, 3H), 7.31 (dd, 1H), 7.42 (s, 2H), 7.74 - 7.79 (m, 1H), 8.44 (dd, 1H).

LC-MS (Method 4): R_t = 0.68 min; MS (ESIpos): m/z = 193 [M+H]⁺.

Intermediate 42

5-(3-fluoropyridin-2-yl)-1,3,4-thiadiazol-2-amine



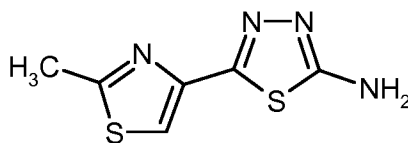
1.00 g (7.09 mmol) of 3-fluoropyridine-2-carboxylic acid was added to 3.67 g of polyphosphoric acid. 0.65 g (7.09 mmol) of hydrazinecarbothioamide was added portionwise. It was stirred for 1 h at 140 °C. After cooling down to 70 °C, water (24 mL) was added dropwise. After cooling to 0 °C, aqueous ammonium hydroxide solution (25%, 25 mL) was added till a pH value of 12 was achieved. The precipitate was collected by filtration, washed with water and dried under reduced pressure at 50 °C affording 694 mg (47% of theory) of the title compound.

¹H-NMR (300MHz, DMSO-d₆): δ [ppm]= 7.47 - 7.56 (m, 1H), 7.62 (s, 2H), 7.89 (ddd, 1H), 8.47 (dt, 1H).

LC-MS (Method 3): R_t = 0.62 min; MS (ESIpos): m/z = 197 [M+H]⁺.

Intermediate 43

5-(2-methyl-1,3-thiazol-4-yl)-1,3,4-thiadiazol-2-amine



1.00 g (6.99 mmol) of 2-methyl-1,3-thiazole-4-carboxylic acid was added to 3.62 g of polyphosphoric acid. 0.64 g (6.99 mmol) of hydrazinecarbothioamide was added portionwise. It was stirred for 1 h at 140 °C. After cooling down to 70 °C, water (10 mL) was added dropwise. After cooling to 0 °C, aqueous ammonium hydroxide solution (25%, 8 mL) was added till a pH value of 12 was achieved.

The precipitate was collected by filtration, washed with water and dried under reduced pressure at 50 °C affording 821 mg (59% of theory) of the title compound.

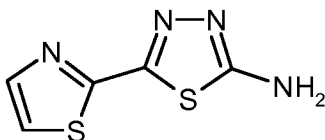
¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 2.69 (s, 3H), 7.33 (s, 2H), 7.96 (s, 1H).

LC-MS (Method 4): R_t = 0.65 min; MS (ESIpos): m/z = 199 [M+H]⁺.

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Intermediate 44

5-(1,3-thiazol-2-yl)-1,3,4-thiadiazol-2-amine



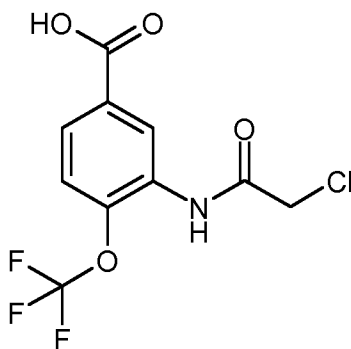
1.00 g (7.74 mmol) of 1,3-thiazole-2-carboxylic acid was added to 4.01 g of polyphosphoric acid. 0.71 g (7.74 mmol) of hydrazinecarbothioamide was added portionwise. It was stirred for 1 h at 140 °C. After cooling down to 70 °C, water (10 mL) was added dropwise. After cooling to 0 °C, aqueous ammonium hydroxide solution (25%, 8 mL) was added till a pH value of 12 was achieved. The precipitate was collected by filtration, washed with water and dried under reduced pressure at 50 °C affording 700 mg (49% of theory) of the title compound.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 7.71 (s, 2H), 7.83 (d, 1H), 7.93 (d, 1H).

LC-MS (Method 4): R_t = 0.60 min; MS (ESIpos): m/z = 185 [M+H]⁺.

Intermediate 45

3-[(chloroacetyl)amino]-4-(trifluoromethoxy)benzoic acid



20

To a solution of 3-amino-4-(trifluoromethoxy)benzoic acid (10.0 g, 45.2 mmol, known from WO2008/75064A1) and pyridine (4.02 mL, 49.7 mmol, 1.1 equiv) in CH₂Cl₂ (200 mL) at 0 °C was added chloroacetyl chloride (3.78 mL, 47.5 mmol, 1.05 equiv) dropwise. The resulting mixture was allowed to warm to room temperature and was stirred at that temperature for 3 h. The reaction mixture was treated with water and the phases were separated. The aqueous phase was extracted with a CH₂Cl₂ / isopropanol mixture (4:1). The combined organic phases were washed with brine,

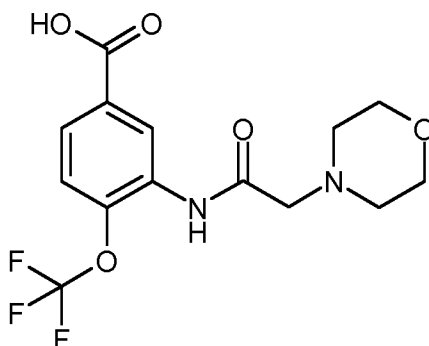
25

dried and concentrated under reduced pressure to give 13.5 g of raw material which was used without further purification.

LC-MS (Method 4): $R_t = 0.95$ min; MS (ESIpos): $m/z = 298$ $[M+H]^+$.

5 **Intermediate 46**

3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzoic acid

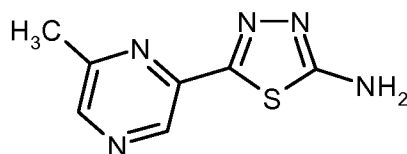


To a solution of the compound of intermediate 45 (13.5 g, 45.2 mmol) in DMF (200 mL) was added morpholine (7.9 mL, 90.5 mmol, 2.0 equiv), triethylamine (12.6 mL, 90.5 mmol, 2.0 equiv) and potassium iodide (1.50 g, 9.05 mmol, 0.2 equiv). The reaction mixture was stirred at room temperature for 2 days. The resulting mixture was concentrated, the remaining material was treated with water and extracted with a CH_2Cl_2 / isopropanol solution (4:1). The combined organic phases were washed with saturated brine, dried (Na_2SO_4 anhydrous), and concentrated under reduced pressure to give 15.9 g (91% of theory) of the title compound.

LC-MS (Method 4): $R_t = 0.74$ min; MS (ESIpos): $m/z = 349$ $[M+H]^+$.

Intermediate 47

5-(6-methylpyrazin-2-yl)-1,3,4-thiadiazol-2-amine



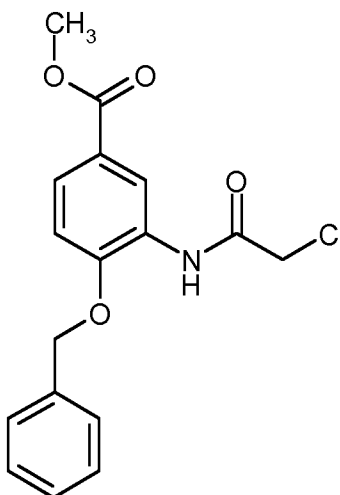
0.50 g (3.62 mmol) of 6-methylpyrazine-2-carboxylic acid was added to 1.88 g of polyphosphoric acid. 0.33 g (3.62 mmol) of hydrazinecarbothioamide was added portionwise. It was stirred for 1 h at 140 °C. After cooling down to 100 °C, water (6 mL) was added dropwise. After cooling to 0 °C, aqueous ammonium hydroxide solution (25%, 4 mL) was added till a pH value of 12 was achieved. The precipitate was collected by filtration, washed with water and dried under reduced pressure at 50 °C affording 476 mg (68% of theory) of the title compound.

$^1\text{H-NMR}$ (400MHz, DMSO-d_6): δ [ppm] = 2.53 (s, 3H), 7.68 (s, 2H), 8.54 (s, 1H), 9.05 (s, 1H).

LC-MS (Method 1): $R_t = 0.61$ min; MS (ESIpos): $m/z = 194$ $[M+H]^+$.

Intermediate 48

methyl 4-(benzyloxy)-3-[(chloroacetyl)amino]benzoate



5

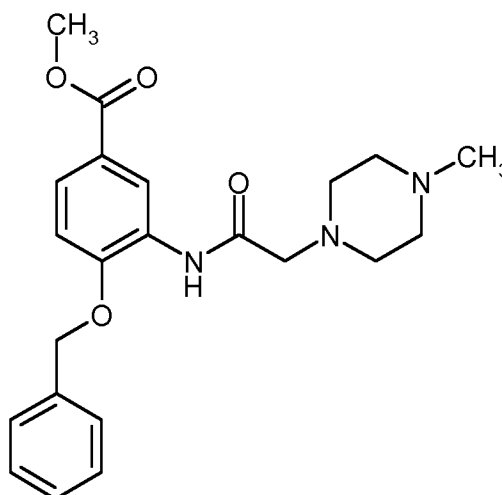
A solution of methyl 3-amino-4-(benzyloxy)benzoate (5.00 g, 19.4 mmol) in toluene (100 mL) was treated with chloroacetyl chloride (2.32 mL, 29.2 mmol). The resulting mixture was stirred for 2 h at 100 °C and concentrated after cooling to room temperature under reduced pressure to provide the title compound (6.49 g, 100%), which was used without further purification.

- 10 $^1\text{H-NMR}$ (400MHz, DMSO-d_6): δ [ppm]= 3.81 (s, 3H), 4.41 (s, 2H), 5.33 (s, 2H), 7.22 - 7.28 (m, 1H), 7.30 - 7.36 (m, 1H), 7.37 - 7.43 (m, 2H), 7.47 - 7.55 (m, 2H), 7.73 (dd, 1H), 8.52 - 8.59 (m, 1H), 9.63 (s, 1H).

LC-MS (Method 1): $R_t = 1.26$ min; MS (ESIpos): $m/z = 334$ $[M+H]^+$.

Intermediate 49

- 15 methyl 4-(benzyloxy)-3-[[4-methylpiperazin-1-yl]acetyl]amino}benzoate



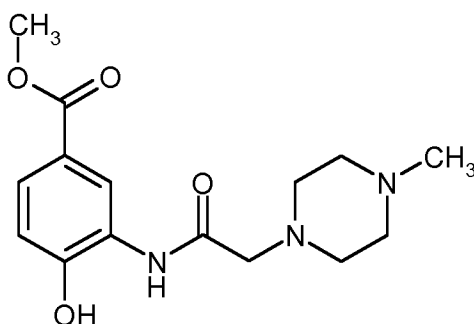
To a solution of the compound of intermediate 48 (2.56 g, 7.67 mmol) in DMF (27 mL) was added triethylamine (1.60 mL, 11.5 mmol), potassium iodide (197 mg, 1.19 mmol) and 1-methylpiperazine (1.28 mL, 11.5 mmol). The reaction mixture was stirred over night at room temperature. The mixture was concentrated. The remaining residue was triturated with water and ethanol and stirred for 30 minutes. The precipitate was collected by filtration, washed with ethanol and dried under reduced pressure to give 1.00 g (33% of theory) of the title compound. The filtrate was extracted with dichloromethane, the combined organic phases were washed with 1N aqueous hydrogen chloride solution and saturated aqueous sodium bicarbonate solution, dried and concentrated to give additional 1.40 g (46% of theory) of the title compound.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 1.95 - 2.20 (m, 4H), 2.01 (s, 3H), 2.34 - 2.48 (m, 4H), 3.09 (s, 2H), 3.83 (s, 3H), 5.24 (s, 2H), 7.34 (d, 1H), 7.38 - 7.49 (m, 3H), 7.52 - 7.57 (m, 2H), 7.73 (dd, 1H), 8.95 (d, 1H), 9.67 (s, 1H).

LC-MS (Method 4): R_t = 0.87 min; MS (ESIpos): m/z = 398 [M+H]⁺.

15 **Intermediate 50**

methyl 4-hydroxy-3-[[[4-methylpiperazin-1-yl)acetyl]amino]benzoate



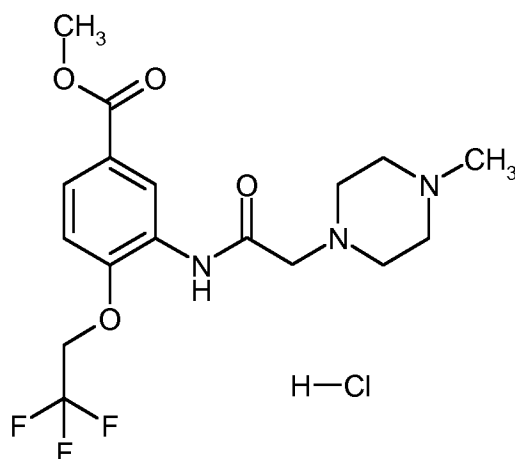
2.40 mg (6.04 mmol) of the compound of intermediate 49 were dissolved in 150 mL of a mixture of THF and methanol (3:2). 964 mg of 10% palladium on charcoal were added. It was hydrogenated for 1.75 h. The catalyst was filtered off and washed with THF and methanol. After concentration 1.70 g (92% of theory) of the title compound were obtained.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 2.21 (s, 3H), 2.35 - 2.48 (m, 4H), 2.53 - 2.63 (m, 4H), 3.14 (s, 2H), 3.79 (s, 3H), 6.95 (d, 1H), 7.58 (dd, 1H), 8.79 (d, 1H), 9.68 (s, 1H), 11.06 (s, 1H).

LC-MS (Method 4): R_t = 0.58 min; MS (ESIpos): m/z = 308 [M+H]⁺.

25 **Intermediate 51**

methyl 3-[[[4-methylpiperazin-1-yl)acetyl]amino]-4-(2,2,2-trifluoroethoxy)benzoate hydrochloride (1:1)



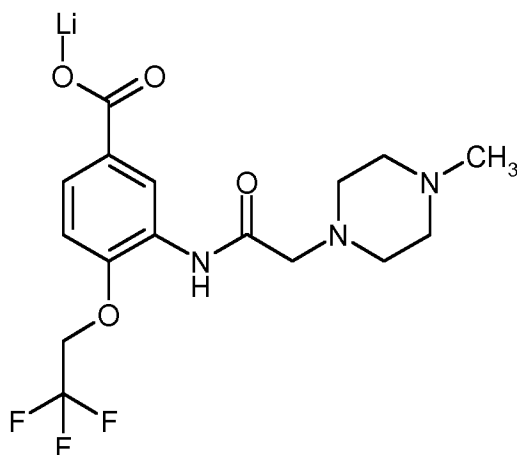
1.70 g (5.53 mol) of the compound of intermediate 50 were dissolved in 30 mL of acetonitrile. 2.45 g (17.7 mol) of potassium carbonate and 0.83 mL (5.81 mmol) of 2,2,2-trifluoroethyl trifluoromethanesulfonate were added. It was stirred for 4 h at 40 °C. The reaction mixture was filtered and treated with 1N aqueous hydrogen chloride solution, water and dichloromethane. The phases were separated, the aqueous phase was extracted with dichloromethane and the combined organic phases were washed with brine, dried and concentrated. 1.43 g (58% of theory) of the title compound were obtained.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 2.60 - 2.77 (m, 2H), 2.77 (s, 3H), 2.83 - 3.12 (m, 4H), 3.37 - 3.55 (m, 2H), 3.84 (s, 3H), 5.02 (q, 2H), 7.33 (d, 1H), 7.76 (dd, 1H), 8.78 (d, 1H), 9.59 (s, 1H), 10.08 (s, 1H).

LC-MS (Method 4): R_t = 0.71 min; MS (ESIpos): m/z = 390 [M+H-HCl]⁺.

Intermediate 52

lithium 3-[[4-methylpiperazin-1-yl)acetyl]amino]-4-(2,2,2-trifluoroethoxy)benzoate



1.40 g (3.29 mmol) of the compound of intermediate 51 were provided in 7 mL of dioxane. 236 mg (9.86 mmol) of lithium hydroxide and 0.12 mL of water were added and it was stirred at room temperature over night. 236 mg (9.86 mmol) of lithium hydroxide and 0.12 mL of water were added and it was stirred at room temperature over night. 236 mg (9.86 mmol) of lithium hydroxide and 0.12

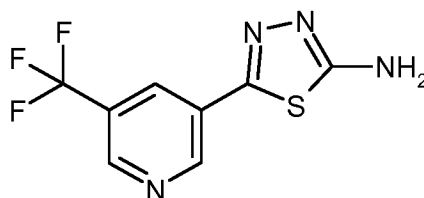
mL of water were added and it was stirred at room temperature over night. The reaction mixture was filtered and concentrated to give 1.25 g of raw material which was used without further purification.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 2.17 (s, 3H), 2.23 - 2.44 (m, 4H), 2.45 - 2.60 (m, 4H), 3.07 (s, 2H), 4.81 (s, 2H), 6.99 (s, 1H), 7.56 (s, 1H), 8.78 (s, 1H), 9.58 (s, 1H).

LC-MS (Method 3): R_t = 0.57 min; MS (ESIpos): m/z = 376 [M-Li+2H]⁺.

Intermediate 53

5-[5-(trifluoromethyl)pyridin-3-yl]-1,3,4-thiadiazol-2-amine



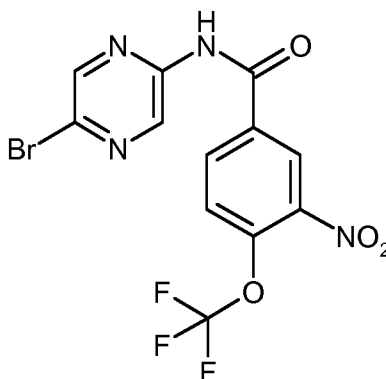
1.00 g (5.23 mmol) of 5-(trifluoromethyl)nicotinic acid was added to 2.71 g of polyphosphoric acid. 0.48 g (5.23 mmol) of hydrazinecarbothioamide was added portionwise. It was stirred for 1 h at 140 °C. After cooling down to 70 °C, water (12 mL) was added dropwise. After cooling to 0 °C, aqueous ammonium hydroxide solution (25%, 8 mL) was added till a pH value of 12 was achieved. The precipitate was collected by filtration, washed with water and dried under reduced pressure at 50 °C affording 882 mg (68% of theory) of the title compound.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 7.69 (s, 2H), 8.46 (s, 1H), 9.01 (d, 1H), 9.23 (d, 1H).

LC-MS (Method 4): R_t = 0.79 min; MS (ESIpos): m/z = 247 [M+H]⁺.

Intermediate 54

N-(5-bromopyrazin-2-yl)-3-nitro-4-(trifluoromethoxy)benzamide



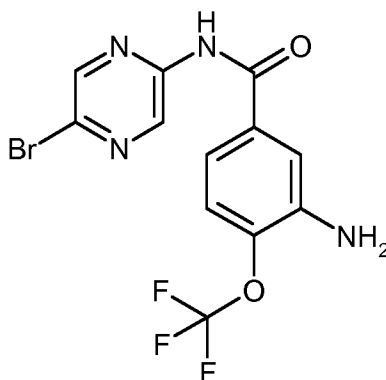
3.00 g (11.95 mmol) of 3-nitro-4-(trifluoromethoxy)benzoic acid and 2.50 g (14.34 mmol) of 5-bromopyrazin-2-amine were dissolved in 50 mL of anhydrous DMF. 12.49 mL (71.68 mmol) of N-ethyl-N-isopropylpropan-2-amine and 10.46 mL (17.92 mmol) of 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (50% in DMF) were added. It was stirred for 2 days at rt. 2.0 mL (3.43 mmol) of 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (50% in DMF) and 2.0 mL (11.48 mmol) of N-ethyl-N-isopropylpropan-2-amine were added and it was stirred overnight at rt. 2.0 mL (3.43 mmol) of 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (50% in DMF) and 2.0 mL (11.48 mmol) of N-ethyl-N-isopropylpropan-2-amine were added and it was stirred over the weekend at rt. The volatiles were removed under vacuum. Water was added and it was extracted three times with dichloromethane. The combined organic phases were washed twice with water, dried over magnesium sulfate and concentrated to dryness. The residue was triturated with ethanol, filtered off under suction and dried at 50 °C under reduced pressure affording 2.35 g (48%) of the title compound.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm] = 7.89 - 7.93 (m, 1H), 8.45 (dd, 1H), 8.72 (d, 1H), 8.81 (d, 1H), 9.23 (d, 1H), 11.72 (s, 1H).

LC-MS (Method 3): R_t = 1.12 min; MS (ESIpos): m/z = 407 [M+H]⁺.

Intermediate 55

3-amino-N-(5-bromopyrazin-2-yl)-4-(trifluoromethoxy)benzamide



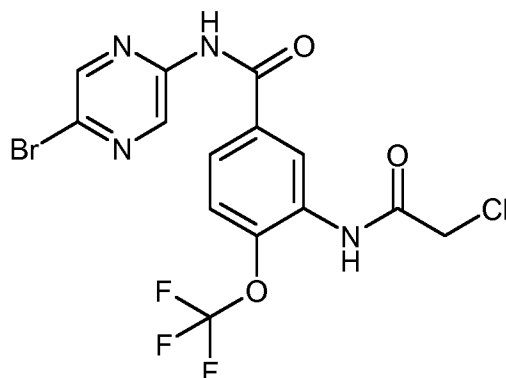
To 350 mg (0.86 mmol) of N-(5-bromopyrazin-2-yl)-3-nitro-4-(trifluoromethoxy)benzamide (intermediate 54) in 7.0 mL of anhydrous THF were added 8.56 mL (10.07 mmol) of titanium(III)chloride (15% in 10% of hydrochloric acid) at 0 °C. It was stirred overnight at rt. Solid sodium hydrogen carbonate was added until the pH was basic. Then solid sodium chloride was added. 80 mL of a mixture of ethyl acetate/THF (1 : 1) were added and it was stirred 2 h at rt. The solid material was filtered off, the organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate and concentrated. The residue was dried at 50 °C under reduced pressure to yield 300 mg (92%) of the title compound.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm] = 5.69 (s, 2H), 7.20 - 7.27 (m, 2H), 7.42 (s, 1H), 8.67 - 8.70 (m, 1H), 9.20 - 9.24 (m, 1H), 11.20 (s, 1H).

LC-MS (Method 4): R_t = 1.17 min; MS (ESIpos): m/z = 377 [M+H]⁺.

Intermediate 56

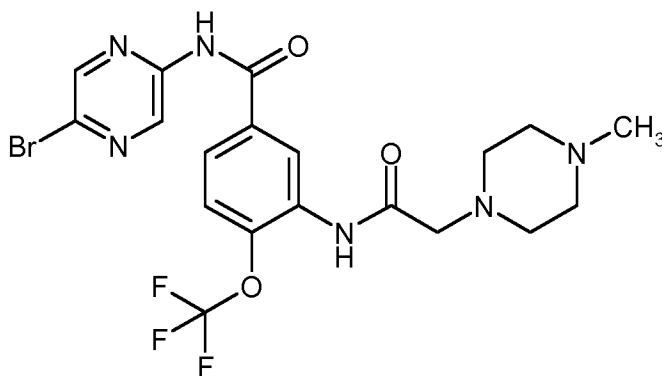
N-(5-bromopyrazin-2-yl)-3-[(chloroacetyl)amino]-4-(trifluoromethoxy)benzamide



- 5 50 mg (0.13 mmol) of 3-amino-N-(5-bromopyrazin-2-yl)-4-(trifluoromethoxy)benzamide (intermediate 55) and 21.6 μ L (0.27 mmol) of chloroacetyl chloride in 3.0 mL of anhydrous toluene were stirred for 2 h at 100 °C. The reaction mixture was allowed to reach rt. To the reaction mixture was added toluene and it was concentrated under vacuum. The residue was used without further purification in the next step.
- 10 LC-MS (Method 4): R_t = 1.16 min; MS (ESIpos): m/z = 453 $[M+H]^+$.

Intermediate 57

N-(5-bromopyrazin-2-yl)-3-[[4-methylpiperazin-1-yl]acetyl]amino-4-(trifluoromethoxy)benzamide



- 15 To 60.1 mg (0.13 mmol) of N-(5-bromopyrazin-2-yl)-3-[(chloroacetyl)amino]-4-(trifluoromethoxy)benzamide (intermediate 56) dissolved in 1.5 mL of anhydrous DMF were added 22.1 μ L (0.20 mmol) of 1-methylpiperazine and 27.7 μ L (0.20 mmol) of N,N-diethylethanamine. It was stirred overnight at rt and concentrated under vacuum. The residue was dissolved in ethyl acetate. The organic phase was washed three times with water, dried over magnesium sulfate and concentrated
- 20 to give 35 mg (51%) of the title compound. Saturated aqueous sodium carbonate solution was added to the combined aqueous layers. This aqueous layer was extracted three times with ethyl acetate.

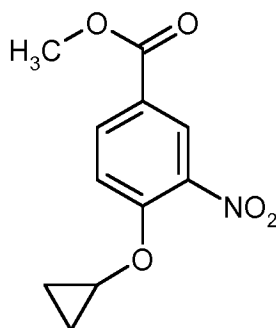
The combined organic layers were washed twice with water, dried over magnesium sulfate and concentrated affording 23 mg (33%) of the title compound, as a second crop.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm] = 2.18 (s, 3H), 2.28 - 2.48 (m, 4H), 2.53 - 2.66 (m, 4H), 3.21 (s, 2H), 7.60 - 7.64 (m, 1H), 7.89 (dd, 1H), 8.71 (d, 1H), 8.91 (d, 1H), 9.25 (d, 1H), 9.94 (s, 1H), 11.49 (s, 1H).

LC-MS (Method 4): R_t = 0.82 min; MS (ESIpos): m/z = 517 [M+H]⁺.

Intermediate 58

methyl 4-(cyclopropyloxy)-3-nitrobenzoate



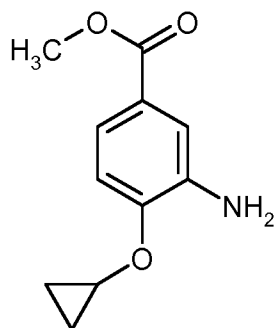
10.00 g (44.81 mmol) of 4-(cyclopropyloxy)-3-nitrobenzoic acid and 880 μL (16.18 mmol) of sulfuric acid (98%) in 27 mL of methanol were stirred for 24 h under reflux. 100 μL (1.84 mmol) of sulfuric acid (98%) were added and it was stirred for 3 h under reflux. The reaction mixture was allowed to cool down. 40 mL of methanol was added and it was concentrated on a rotavap at 60 °C to ca. 20 mL. The reaction mixture was allowed to reach rt under stirring. The solid material was filtered off under suction and washed with ice cold methanol. It was dried under vacuum to obtain 7.6 g (72% of theory) of the title compound. The filtrate was concentrated and treated with 10 mL of methanol at 60 °C. It was cooled down, filtered off and dried to obtain a second crop of 945 mg (9% of theory) of the title compound.

¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 0.756 (1.14), 0.764 (1.42), 0.769 (3.09), 0.776 (6.71), 0.780 (5.59), 0.783 (4.44), 0.787 (3.44), 0.795 (1.98), 0.830 (0.51), 0.835 (0.61), 0.839 (0.51), 0.849 (0.47), 0.875 (1.79), 0.890 (5.44), 0.896 (3.44), 0.901 (2.87), 0.905 (4.28), 0.908 (4.06), 0.911 (4.20), 0.924 (1.06), 0.926 (1.01), 3.319 (16.00), 4.175 (0.97), 4.182 (2.03), 4.190 (2.91), 4.198 (4.08), 4.205 (2.84), 4.213 (2.03), 4.220 (0.92), 7.744 (8.03), 7.766 (8.80), 8.224 (4.98), 8.229 (5.46), 8.245 (4.37), 8.251 (5.13), 8.370 (8.59), 8.376 (7.87).

LC-MS (Method 4): R_t = 1.16 min; MS (ESIpos): m/z = 238 [M+H]⁺.

Intermediate 59

methyl 3-amino-4-(cyclopropyloxy)benzoate



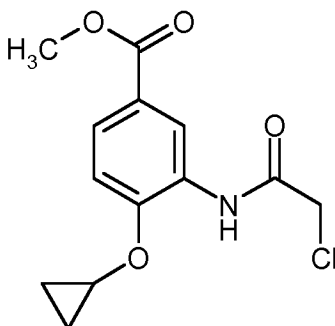
760 mg (3.20 mmol) of methyl 4-(cyclopropyloxy)-3-nitrobenzoate (intermediate 58) in 120 mL of methanol/THF 1:1 and 397 mg of palladium on calcium carbonate (10%) were hydrogenated under an atmosphere of hydrogen for ca. 16 h. It was filtered off through celite, washed with methanol and concentrated to afford 630 mg (95% of theory) of the title compound.

¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 0.666 (1.83), 0.672 (2.13), 0.679 (4.68), 0.685 (9.55), 0.688 (9.38), 0.692 (7.37), 0.696 (6.70), 0.704 (3.68), 0.733 (1.17), 0.738 (1.16), 0.746 (1.17), 0.748 (1.21), 0.773 (2.88), 0.783 (4.19), 0.787 (7.58), 0.802 (6.94), 0.806 (6.85), 0.807 (7.00), 0.822 (2.32), 0.842 (0.42), 1.354 (0.49), 2.522 (4.27), 2.668 (0.41), 3.322 (13.87), 3.739 (2.23), 3.813 (0.59), 3.870 (1.48), 3.877 (3.08), 3.884 (4.44), 3.892 (6.34), 3.899 (4.73), 3.907 (3.41), 3.914 (1.74), 3.948 (0.52), 4.907 (13.14), 7.132 (8.23), 7.152 (14.47), 7.200 (9.16), 7.205 (11.66), 7.221 (4.50), 7.226 (7.43), 7.234 (0.96), 7.252 (16.00), 7.257 (13.57).

LC-MS (Method 3): R_t = 1.03 min; MS (ESIpos): m/z = 208 [M+H]⁺.

15 Intermediate 60

methyl 3-[(chloroacetyl)amino]-4-(cyclopropyloxy)benzoate



2.5 mL (31.4 mmol) of chloroacetyl chloride were added to 3.26 g (15.73 mmol) of methyl 3-amino-4-(cyclopropyloxy)benzoate (intermediate 59) in 50 mL of anhydrous toluene. It was stirred for 2 h at 100 °C. It was concentrated and the residue was stirred with methanol. The solid material was filtered off under suction and dried at 45 °C under vacuum to obtain 2.93 g (66% of theory) of the title compound.

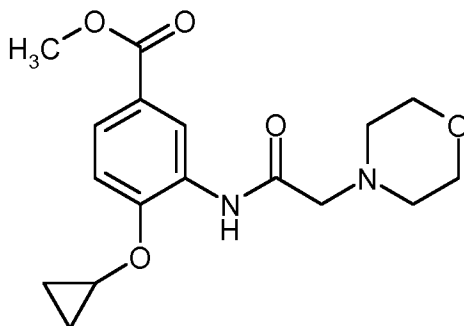
¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 0.763 (0.67), 0.772 (1.74), 0.778 (2.02), 0.786 (1.50), 0.794 (0.74), 0.844 (0.67), 0.853 (1.04), 0.858 (1.86), 0.868 (1.29), 0.872 (1.47), 0.875 (1.35), 0.877 (1.24), 2.523 (0.57), 3.825 (16.00), 4.026 (0.62), 4.034 (0.92), 4.041 (1.23), 4.049 (0.91), 4.056 (0.64), 4.384

(8.25), 7.440 (2.58), 7.462 (2.82), 7.772 (1.64), 7.777 (1.63), 7.793 (1.43), 7.798 (1.42), 8.586 (1.62), 8.592 (1.52), 9.466 (1.58).

LC-MS (Method 3): $R_t = 1.15$ min; MS (ESI^{neg}): $m/z = 282$ $[M-H]^-$.

5 Intermediate 61

methyl 4-(cyclopropyloxy)-3-[(morpholin-4-ylacetyl)amino]benzoate



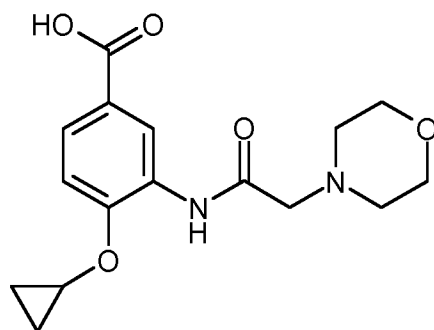
4.89 g (17.24 mmol) of methyl 3-[(chloroacetyl)amino]-4-(cyclopropyloxy)benzoate (intermediate 60) were suspended in 95 mL of anhydrous DMF. 4.5 mL (25.9 mmol) of N-ethyl-N-isopropylpropan-2-amine, 3.77 mL (43.1 mmol) of morpholine and 443 mg (2.67 mmol) of potassium iodide were added. It was stirred at rt overnight. It was concentrated on the rotavap. Methanol was added and it was concentrated again. This step was repeated. The residue was dried obtaining 5.63 g (98% of theory) of the title compound.

¹H-NMR (400 MHz, DMSO-*d*₆) δ [ppm]: 0.744 (0.48), 0.751 (0.61), 0.757 (1.56), 0.764 (2.63), 0.770 (1.77), 0.775 (1.22), 0.783 (0.70), 0.889 (0.61), 0.904 (2.10), 0.909 (1.56), 0.918 (1.67), 0.924 (1.76), 0.939 (0.41), 2.528 (2.83), 2.539 (3.94), 2.551 (2.88), 3.143 (8.83), 3.638 (3.02), 3.650 (4.14), 3.661 (2.92), 3.823 (16.00), 4.082 (0.65), 4.090 (0.96), 4.097 (1.29), 4.104 (0.94), 4.112 (0.66), 7.428 (2.69), 7.450 (3.03), 7.726 (1.74), 7.732 (1.77), 7.748 (1.50), 7.754 (1.51), 8.831 (2.62), 8.837 (2.61), 9.699 (2.01).

LC-MS (Method 3): $R_t = 1.13$ min; MS (ESI^{pos}): $m/z = 335$ $[M+H]^+$.

Intermediate 62

4-(cyclopropyloxy)-3-[(morpholin-4-ylacetyl)amino]benzoic acid



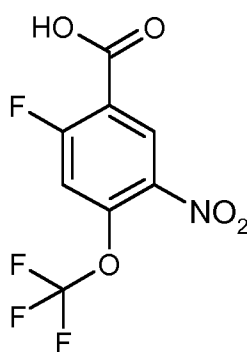
2.00 g (5.98 mmol) of methyl 4-(cyclopropyloxy)-3-[(morpholin-4-ylacetyl)amino]benzoate (intermediate 61) were dissolved in 20 mL of THF. 10 mL of methanol and 9 mL (18 mmol) of aqueous sodium hydroxide solution (2M) were added. It was stirred at rt over night. The volatiles were removed under vacuum and 20 mL of water were added. 9 mL of aqueous hydrochloric acid (2M) were added to adjust the pH to 3. The precipitate was filtered off under suction, washed twice with water and dried under vacuum at 45 °C obtaining 1.58 g (82% of theory) of the title compound.

¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 0.738 (0.87), 0.745 (1.13), 0.751 (2.67), 0.757 (4.53), 0.764 (3.18), 0.769 (2.10), 0.776 (1.27), 0.884 (1.07), 0.898 (3.68), 0.904 (2.77), 0.910 (2.15), 0.913 (2.94), 0.918 (3.13), 0.933 (0.73), 2.527 (4.90), 2.539 (6.85), 2.551 (5.08), 2.669 (0.41), 3.138 (16.00), 3.640 (5.23), 3.652 (7.23), 3.662 (5.26), 4.058 (0.58), 4.066 (1.17), 4.073 (1.70), 4.081 (2.28), 4.088 (1.65), 4.096 (1.18), 4.103 (0.56), 7.396 (4.81), 7.418 (5.37), 7.697 (3.44), 7.702 (3.20), 7.718 (2.84), 7.723 (2.94), 8.805 (5.10), 8.810 (4.88), 9.677 (3.82).

LC-MS (Method 4): R_t = 0.67 min; MS (ESIpos): m/z = 321 [M+H]⁺.

Intermediate 63

2-fluoro-5-nitro-4-(trifluoromethoxy)benzoic acid



To nitric acid (100%, 8.00 mL) at 0 °C was added fuming sulfuric acid (20% sulfur trioxide, 36 mL) dropwise. 2-Fluoro-4-(trifluoromethoxy)benzoic acid (8.00 g, 35.7 mmol) was added at room temperature and it was stirred over night. The reaction mixture was added into ice water dropwise and stirred for additional 10 minutes. The resulting precipitate was filtered off, washed with water and dried under reduced pressure to give the title compound (8.86 g, 92% of theory).

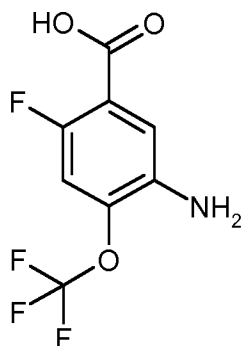
¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 1.907 (0.60), 2.322 (0.83), 2.327 (1.07), 2.332 (0.79), 2.523 (2.91), 2.665 (0.83), 2.669 (1.15), 2.674 (0.79), 7.934 (7.31), 7.937 (7.61), 7.959 (7.55), 7.963 (7.34), 8.612 (16.00), 8.631 (15.61).

LC-MS (Method 4): R_t = 0.99 min; MS (ESIpos): m/z = 270 [M+H]⁺.

5

Intermediate 64

5-amino-2-fluoro-4-(trifluoromethoxy)benzoic acid



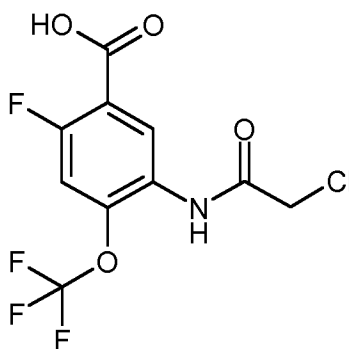
3.00 g (11.2 mmol) of the compound of intermediate 63 were dissolved in 90 mL of a mixture of THF and ethanol (1:2). 0.6 g of 10% palladium on charcoal (50% water) were added. It was hydrogenated for 2.5 h. The catalyst was filtered off and washed with THF and ethanol. After concentration 2.64 g (99% of theory) of the title compound were obtained.

¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 1.235 (0.60), 1.242 (0.81), 1.355 (1.02), 1.908 (1.41), 2.317 (0.60), 2.322 (1.32), 2.327 (1.83), 2.331 (1.29), 2.336 (0.57), 2.523 (5.63), 2.660 (0.63), 2.664 (1.29), 2.669 (1.77), 2.674 (1.26), 2.679 (0.57), 5.474 (15.31), 7.150 (6.92), 7.154 (7.25), 7.177 (7.07), 7.180 (7.16), 7.305 (16.00), 7.324 (16.00).

LC-MS (Method 4): R_t = 0.88 min; MS (ESIpos): m/z = 240 [M+H]⁺.

Intermediate 65

5-[(chloroacetyl)amino]-2-fluoro-4-(trifluoromethoxy)benzoic acid



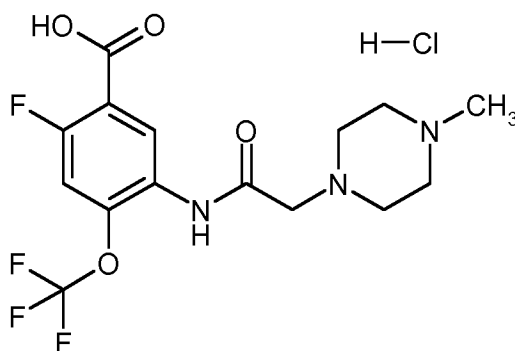
To a solution of the compound of intermediate 64 (2.69 g, 11.2 mmol) and pyridine (1.00 mL, 12.4 mmol, 1.1 equiv) in DCM (50 mL) at 0 °C was added chloroacetyl chloride (0.94 mL, 11.8 mmol, 1.05 equiv) dropwise. The resulting mixture was allowed to warm to room temperature and was stirred at that temperature over night. The resulting mixture was treated with water and the phases were separated. The aqueous phase was extracted with a DCM / isopropanol mixture. The combined organic phases were washed with brine, dried (Na₂SO₄ anh), and concentrated under reduced pressure to give the title compound (3.55 g, 100% of theory). This material was used in subsequent reactions without further purification.

¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 1.029 (0.73), 1.044 (0.74), 1.355 (0.44), 2.523 (1.54), 4.263 (3.15), 4.353 (16.00), 7.547 (1.91), 7.551 (2.06), 7.574 (1.99), 7.577 (1.97), 8.348 (3.09), 8.367 (3.14), 10.189 (3.56).

LC-MS (Method 4): R_t = 0.91 min; MS (ESIpos): m/z = 316 [M+H]⁺.

Intermediate 66

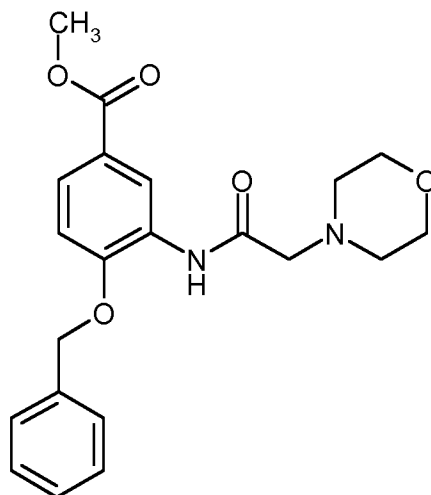
2-fluoro-5-[[[4-methylpiperazin-1-yl)acetyl]amino]-4-(trifluoromethoxy)benzoic acid hydrochloride (1:1)



To a solution of intermediate 65 (1.00 g, 3.17 mmol) in DMF (30 mL) was added triethylamine (0.66 mL, 4.75 mmol), potassium iodide (78.9 mg, 0.48 mmol) and 1-methylpiperazine (0.53 mL, 4.75 mmol). The reaction mixture was stirred over night at room temperature. The mixture was concentrated. The remaining residue was triturated with water, and a 1M aqueous solution of hydrogen chloride was added until a pH of 4 was achieved. The mixture was saturated with sodium chloride and extracted three times with a mixture of DCM/isopropanol 4:1. The combined organic phases were dried over sodium sulfate and concentrated to yield the desired crude material (487 mg, 37%). A 1M aqueous solution of hydrogen chloride was added to the aqueous phase until a pH of 7 was achieved. The mixture was extracted three times with a mixture of DCM/isopropanol 4:1. The combined organic phases were dried over sodium sulfate and concentrated to yield the desired crude material (171 mg, 13%). The two batches of the crude material were combined (632 mg, 48% of theory) and used in the next step without further purification.

Intermediate 67

methyl 4-(benzyloxy)-3-[(morpholin-4-ylacetyl)amino]benzoate



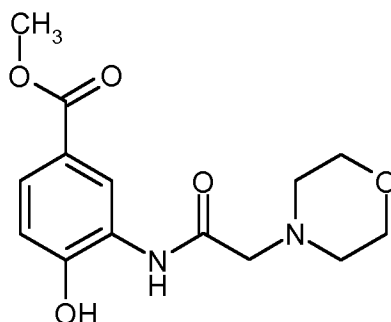
To a solution of the compound of intermediate 48 (6.49 g, 19.4 mmol) in DMF (70 mL) was added triethylamine (4.1 mL, 29.2 mmol), potassium iodide (500 mg, 3.01 mmol) and morpholine (2.5 mL, 29.2 mmol). The reaction mixture was stirred over night at room temperature. The mixture was concentrated. The remaining residue was triturated with water and ethanol and stirred for 30 minutes. The precipitate was collected by filtration, washed with ethanol and dried under reduced pressure to give 7.00 g (94% of theory) of the title compound.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]: 2.396 (2.44), 2.408 (3.91), 2.420 (2.71), 2.523 (0.77), 3.094 (9.28), 3.242 (2.06), 3.255 (3.07), 3.266 (2.16), 3.828 (16.00), 5.245 (7.05), 7.329 (2.37), 7.351 (2.65), 7.412 (0.97), 7.420 (0.53), 7.424 (1.13), 7.429 (2.35), 7.433 (3.39), 7.451 (3.10), 7.462 (0.53), 7.466 (0.95), 7.473 (0.75), 7.548 (2.49), 7.551 (2.75), 7.567 (2.00), 7.572 (1.72), 7.721 (1.66), 7.727 (1.72), 7.743 (1.47), 7.748 (1.54), 8.920 (2.78), 8.926 (2.86), 9.741 (1.97).

LC-MS (Method 4): $R_t = 1.02$ min; MS (ESIpos): $m/z = 385$ $[M+H]^+$.

Intermediate 68

methyl 4-hydroxy-3-[(morpholin-4-ylacetyl)amino]benzoate



7.00 g (18.2 mmol) of the compound of intermediate 67 were dissolved in 400 mL of a mixture of THF and methanol (3:2). 2.91 g of 10% palladium on charcoal were added. It was hydrogenated for 1.5 h. The catalyst was filtered off and washed with THF and methanol. After concentration 5.16 g (96% of theory) of the title compound were obtained.

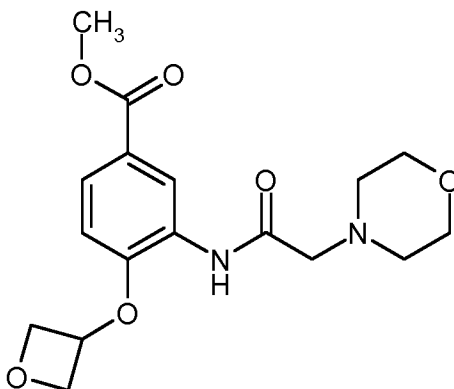
$^1\text{H-NMR}$ (400MHz, DMSO-d_6): δ [ppm]: 2.523 (0.68), 2.532 (2.48), 2.544 (3.48), 2.556 (2.67), 3.157 (8.73), 3.635 (3.00), 3.646 (3.94), 3.657 (2.94), 3.792 (16.00), 6.941 (2.87), 6.963 (3.08), 7.568 (1.81), 7.573 (1.75), 7.588 (1.58), 7.594 (1.68), 8.775 (2.63), 8.780 (2.67), 9.679 (1.72).

LC-MS (Method 1): $R_t = 0.54$ min; MS (ESIpos): $m/z = 295$ $[\text{M}+\text{H}]^+$.

5

Intermediate 69

methyl 3-[(morpholin-4-ylacetyl)amino]-4-(oxetan-3-yloxy)benzoate



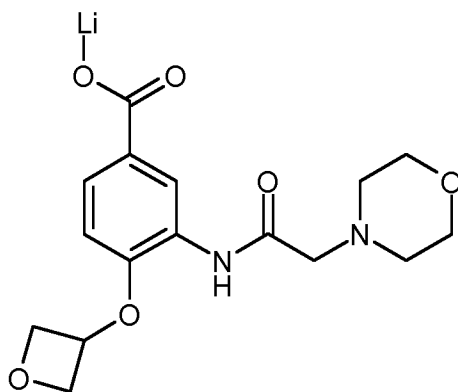
5.16 g (17.5 mmol) of the compound of intermediate 68 and 6.86 g (21.0 mmol) of cesium carbonate were provided in 60 mL of DMF. A solution of 4.80 g (21.0 mmol) of oxetan-3-yl-4-methylbenzenesulfonate in 40 mL of DMF was added and it was stirred for 116 h at 50 °C. The reaction mixture was concentrated. The remaining material was triturated with water and ethanol and stirred for 30 minutes. The precipitate was collected by filtration, washed with ethanol and dried under reduced pressure. The remaining material was triturated with ethanol under reflux. The precipitate was collected by filtration at room temperature, washed with ethanol and dried under reduced pressure to give 2.30 g (37% of theory) of the title compound.

$^1\text{H-NMR}$ (400MHz, DMSO-d_6): δ [ppm]: 2.523 (0.88), 2.566 (3.27), 2.577 (4.64), 2.589 (3.42), 3.193 (9.40), 3.661 (3.68), 3.673 (5.05), 3.685 (3.62), 3.821 (16.00), 4.612 (1.97), 4.624 (2.26), 4.629 (2.28), 4.632 (2.32), 4.643 (2.27), 5.000 (2.07), 5.017 (3.36), 5.020 (2.49), 5.035 (2.08), 5.473 (0.91), 5.488 (1.50), 5.500 (0.87), 5.503 (0.84), 6.830 (2.63), 6.851 (2.77), 7.638 (1.70), 7.644 (1.66), 7.659 (1.60), 7.664 (1.65), 8.902 (2.83), 8.907 (2.88), 9.850 (2.27).

LC-MS (Method 4): $R_t = 0.64$ min; MS (ESIpos): $m/z = 351$ $[\text{M}+\text{H}]^+$.

Intermediate 70

lithium 3-[(morpholin-4-ylacetyl)amino]-4-(oxetan-3-yloxy)benzoate



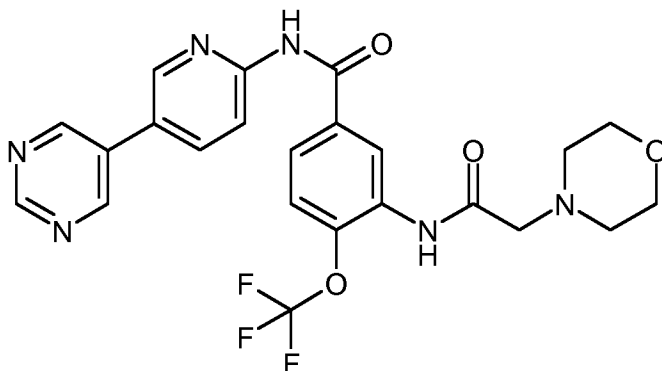
1.00 g (2.85 mmol) of the compound of intermediate 69 was provided in 11 mL of dioxane. 820 mg (34.3 mmol) of lithium hydroxide and 0.7 mL of water were added and it was stirred at room temperature for 6 h. 205 mg (8.56 mmol) of lithium hydroxide and 0.23 mL of water were added and it was stirred at room temperature over night. 410 mg (17.1 mmol) of lithium hydroxide and 0.46 mL of water were added and it was stirred at room temperature for 5 h. 410 mg (17.1 mmol) of lithium hydroxide and 0.46 mL of water were added and it was stirred at room temperature for 5 h. The reaction mixture was filtered and concentrated to give 980 mg of crude material which was used without further purification.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]: 2.322 (0.55), 2.326 (0.77), 2.331 (0.55), 2.523 (2.21), 2.554 (4.81), 2.566 (6.74), 2.577 (5.22), 2.634 (0.55), 2.664 (0.53), 2.669 (0.77), 2.673 (0.55), 3.145 (16.00), 3.294 (0.44), 3.555 (0.41), 3.566 (10.22), 3.662 (5.66), 3.674 (7.57), 3.685 (5.61), 4.582 (3.45), 4.594 (3.76), 4.596 (3.51), 4.599 (3.81), 4.601 (3.90), 4.613 (3.84), 4.966 (3.56), 4.983 (5.78), 5.001 (3.45), 5.334 (0.58), 5.346 (1.55), 5.349 (1.55), 5.361 (2.51), 5.373 (1.38), 5.376 (1.44), 5.388 (0.50), 5.751 (1.08), 6.538 (4.28), 6.559 (4.42), 7.504 (2.18), 7.510 (2.51), 7.526 (2.16), 7.531 (2.35), 8.696 (3.73), 8.701 (4.23), 9.641 (3.73).

Examples:

Example 1

3-[(morpholin-4-ylacetyl)amino]-N-[5-(pyrimidin-5-yl)pyridin-2-yl]-4-(trifluoromethoxy)benzamide



To a solution of the compound of intermediate 2 (190 mg, 0.55 mmol) and 5-(pyrimidin-5-yl)pyridin-2-amine (188 mg, 1.09 mmol, 2 equiv) in DMF (2.4 mL) was added (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, 568 mg, 1.09 mmol, 2 equiv) and

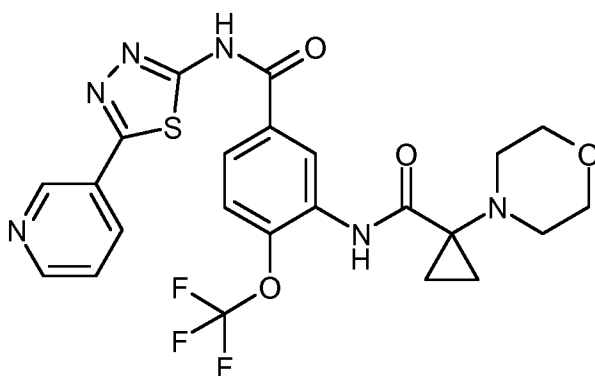
diisopropylethylamine (0.48 mL, 2.73 mmol, 5 equiv). The resulting mixture was stirred at room temperature for 3 days, then triturated with water and stirred for 15 minutes. The precipitate was collected by filtration and dried under reduced pressure at 50 °C. The remaining material was triturated with ethanol and stirred for 30 minutes. The precipitate was collected by filtration and dried under reduced pressure at 50 °C. 19 mg (7% of theory) of the title compound were obtained.

¹H-NMR (400 MHz, DMSO-d₆): δ [ppm] = 2.56 - 2.63 (m, 4H), 3.23 (s, 2H), 3.62 - 3.70 (m, 4H), 7.60 (dd, 1H), 7.92 (dd, 1H), 8.30 - 8.37 (m, 2H), 8.83 (d, 1H), 8.89 (dd, 1H), 9.22 (s, 1H), 9.24 (s, 2H), 9.90 (s, 1H), 11.18 (s, 1H).

LC-MS (Method 4): R_t = 0.84 min; MS (ESIpos): m/z = 503 [M+H]⁺.

Example 2

3-({[1-(morpholin-4-yl)cyclopropyl]carbonyl}amino)-N-[5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide



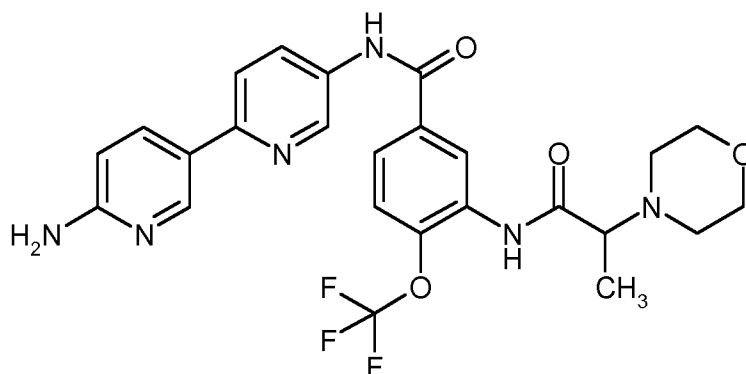
To a microwave vial was added the compound of intermediate 7 (95 mg, 0.17 mmol), pyridin-3-ylboronic acid (31.7 mg, 0.26 mmol, 1.5 equiv), cesium carbonate (112 mg, 0.34 mmol, 2 equiv) and a DMF / water mixture (2:1, 3 mL). The resulting suspension was purged with argon, treated with dichloro[bis(triphenylphosphoranyl)]palladium (Pd(PPh₃)₂Cl₂, 6.0 mg, 0.01 mmol, 5 mol%) and sealed. The resulting mixture was heated with a microwave apparatus at 100 °C for 0.5 h, was then cooled to room temperature. Dichloro[bis(triphenylphosphoranyl)]palladium (Pd(PPh₃)₂Cl₂, 6.0 mg, 0.01 mmol, 5 mol%) was added, the resulting mixture was heated with a microwave apparatus at 100 °C for 0.5 h, and was then cooled to room temperature. The reaction mixture was diluted with ethyl acetate. The phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with water and brine, dried over sodium sulfate and concentrated. Purification by HPLC (method 2) yielded 12.9 mg (14% of theory) of the title compound.

¹H-NMR (300 MHz, DMSO-d₆): δ [ppm] = 1.13 - 1.21 (m, 2H), 1.25 - 1.33 (m, 2H), 2.42 - 2.50 (m, 4H), 3.65 - 3.75 (m, 4H), 7.54 - 7.63 (m, 1H), 7.64 - 7.72 (m, 1H), 8.00 (dd, 1H), 8.37 (d, 1H), 8.72 (d, 1H), 9.09 (d, 1H), 9.14 - 9.21 (m, 1H), 10.57 (s, 1H), 13.52 (s, 1H).

LC-MS (Method 4): R_t = 1.20 min; MS (ESIpos): m/z = 535 [M+H]⁺.

Example 3

N-(6'-amino-2,3'-bipyridin-5-yl)-3-{{2-(morpholin-4-yl)propanoyl}amino}-4-(trifluoromethoxy)benzamide



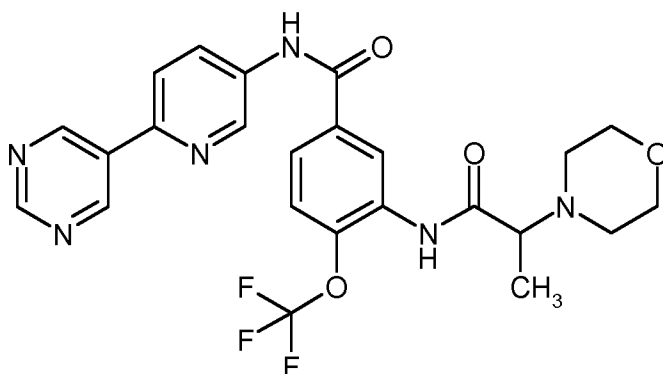
- 5 A solution of the compound of intermediate 13 (52.4 mg, 83 μ mol) in DCM (2.0 mL) was treated with trifluoroacetic acid (128 μ L, 1.66 mmol) and stirred at room temperature over night. The reaction mixture was diluted with saturated NaHCO_3 -solution and extracted with DCM three times. The combined organic layers were dried over a silicon filter and concentrated under reduced pressure. The crude material was suspended in ethanol and stirred for several minutes at 40 $^\circ\text{C}$. The resulting
10 fine precipitate was collected by filtration and dried to provide the title compound (22.2 mg, 49%).

$^1\text{H-NMR}$ (300 MHz, DMSO-d_6): δ [ppm] = 1.23 (d, 3H), 2.54 - 2.60 (m, 4H), 3.35 - 3.45 (m, 1H), 3.65 - 3.68 (m, 4H), 6.20 (s, 2H), 6.48 - 6.56 (m, 1H), 7.59 - 7.68 (m, 1H), 7.79 - 7.89 (m, 2H), 8.00 - 8.09 (m, 1H), 8.14 - 8.21 (m, 1H), 8.60 - 8.66 (m, 1H), 8.73 (d, 1H), 8.86 - 8.92 (m, 1H), 10.54 - 10.65 (m, 1H), 9.98 - 10.07 (m, 1H).

- 15 LC-MS (Method 1): R_t = 0.76 min; MS (ESI $^-$): m/z = 529 $[\text{M-H}]^-$.

Example 4

3-{{2-(morpholin-4-yl)propanoyl}amino}-N-[6-(pyrimidin-5-yl)pyridin-3-yl]-4-(trifluoromethoxy)benzamide



20

Argon was bubbled through a suspension of the compound of intermediate 12 (150 mg, 317 μ mol), pyrimidin-5-ylboronic acid (60.0 mg, 476 μ mol) and potassium carbonate (87.7 mg, 634 μ mol) in 1,2-

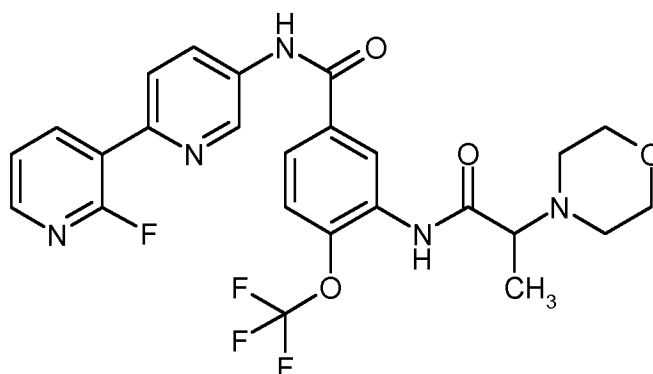
diethoxyethane (2.47 mL) and water (429 μ L) for several minutes. Afterwards 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride (116 mg, 159 μ mol) was added to the mixture, the tube was sealed and the reaction mixture was stirred over night at 90 °C. After cooling to room temperature, the mixture was filtered over a pad of Celite. The filtrate was concentrated in vacuum and the residue was purified by preparative HPLC (method 5) and preparative TLC to provide the title compound 4 (55.2 mg, 34%).

$^1\text{H-NMR}$ (300 MHz, DMSO-d_6): δ [ppm] = 1.23 (d, 3H), 2.52 - 2.62 (m, 4H), 3.40 (q, 1H), 3.65 - 3.68 (m, 4H), 7.60 - 7.68 (m, 1H), 7.79 - 7.88 (m, 1H), 8.19 (d, 1H), 8.33 - 8.42 (m, 1H), 8.75 (d, 1H), 9.08 (d, 1H), 9.23 (s, 1H), 9.44 (s, 2H), 10.06 (s, 1H), 10.80 (s, 1H).

LC-MS (Method 1): R_t = 0.89 min; MS (ESIpos): m/z = 517 $[\text{M}+\text{H}]^+$.

Example 5

N-(2'-fluoro-2,3'-bipyridin-5-yl)-3-[[2-(morpholin-4-yl)propanoyl]amino]-4-(trifluoromethoxy)benzamide



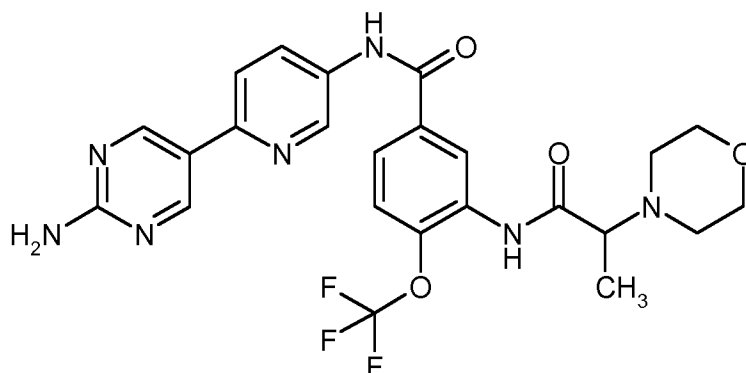
The title compound was prepared in a manner analogous to that described in example 4 starting from 150 mg (317 μ mol) of the compound of intermediate 12 and 67.1 mg (476 μ mol) of (2-fluoropyridin-3-yl)boronic acid. 28.5 mg (20%) of the desired compound 5 were obtained.

$^1\text{H-NMR}$ (300 MHz, DMSO-d_6): δ [ppm] = 1.24 (d, 3H), 2.54 - 2.63 (m, 4H), 3.36 - 3.46 (m, 1H), 3.65 - 3.68 (t, 4H), 7.52 (t, 1H), 7.66 (d, 1H), 7.81 - 8.00 (m, 2H), 8.24 - 8.39 (m, 2H), 8.46 - 8.57 (m, 1H), 8.75 (d, 1H), 9.10 (d, 1H), 10.06 (s, 1H), 10.79 (s, 1H).

LC-MS (Method 4): R_t = 0.98 min; MS (ESIpos): m/z = 534 $[\text{M}+\text{H}]^+$.

Example 6

N-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-3-[[2-(morpholin-4-yl)propanoyl]amino]-4-(trifluoromethoxy)benzamide



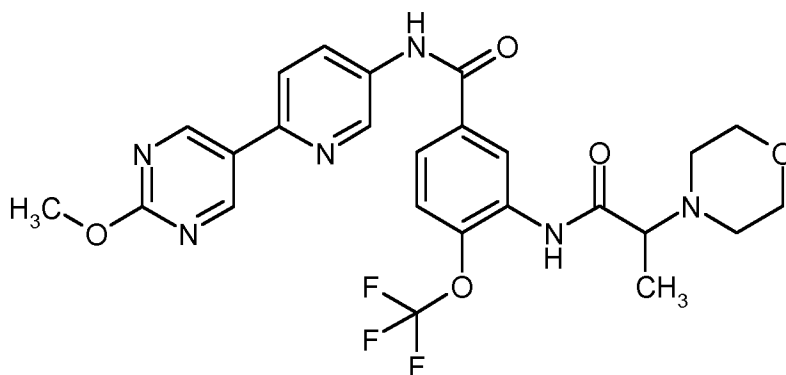
The title compound was prepared in a manner analogous to that described in example 4 starting from 150 mg (317 μ mol) of the compound of intermediate 12 and 66.1 mg (476 μ mol) of ((2-aminopyrimidin-5-yl)boronic acid. 77.6 mg (46%) of the desired compound 6 were obtained.

- 5 $^1\text{H-NMR}$ (300 MHz, DMSO-d_6): δ [ppm] = 1.22 (d, 3H), 2.53 - 2.63 (m, 4H), 3.41 (q, 1H), 3.65 - 3.68 (m, 4H), 6.94 (s, 2H), 7.64 (d, 1H), 7.79 - 7.95 (m, 2H), 8.22 (dd, 1H), 8.73 (d, 1H), 8.87 - 8.96 (m, 3H), 10.05 (s, 1H), 10.65 (s, 1H).

LC-MS (Method 4): R_t = 0.82 min; MS (ESIpos): m/z = 532 $[\text{M}+\text{H}]^+$.

10 **Example 7**

N-[6-(2-methoxypyrimidin-5-yl)pyridin-3-yl]-3-[[2-(morpholin-4-yl)propanoyl]amino]-4-(trifluoromethoxy)benzamide



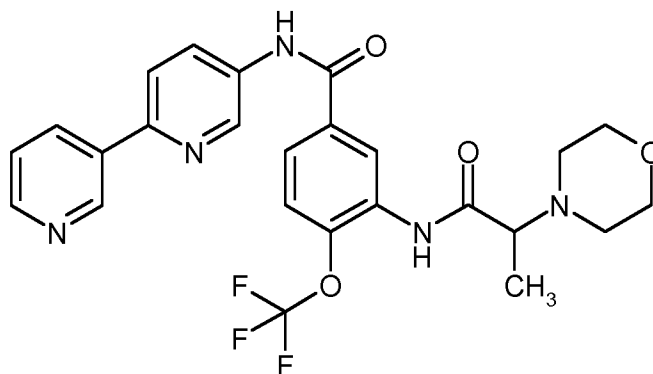
- 15 The title compound was prepared in a manner analogous to that described in example 4 starting from 150 mg (317 μ mol) of the compound of intermediate 12 and 75.5 mg (476 μ mol) of (2-methoxypyrimidin-5-yl)boronic acid. Purification by preparative HPLC (method 5) and subsequent preparative TLC yielded 19.8 mg (11%) of the desired compound 7.

- 20 $^1\text{H-NMR}$ (300 MHz, DMSO-d_6): δ [ppm] = 1.23 (d, 3H), 2.54 - 2.61 (m, 4H), 3.41 (q, 1H), 3.65 - 3.68 (m, 4H), 3.99 (s, 3H), 7.60 - 7.69 (m, 1H + toluene), 7.80 - 7.89 (m, 1H), 8.03 - 8.10 (m, 1H), 8.17 - 8.34 (m, 1H), 8.71 - 8.76 (m, 1H), 9.00 - 9.05 (m, 1H), 9.23 (s, 2H), 10.01 - 10.06 (m, 1H), 10.66 - 10.79 (m, 1H).

LC-MS (Method 4): R_t = 0.95 min; MS (ESI neg): m/z = 545 $[\text{M}-\text{H}]^-$.

Example 8

N-(2,3'-bipyridin-5-yl)-3-[[2-(morpholin-4-yl)propanoyl]amino]-4-(trifluoromethoxy)benzamide



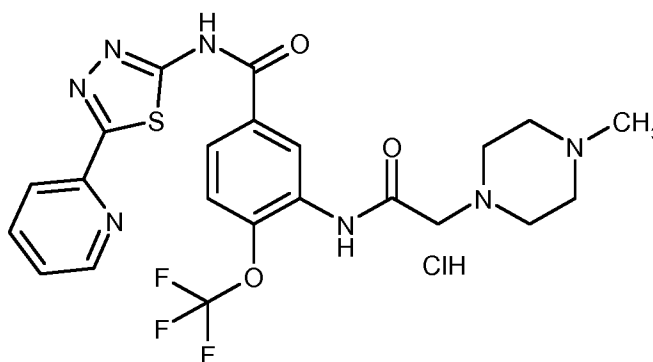
Argon was bubbled through a suspension of the compound of intermediate 12 (250 mg, 529 μ mol),
 5 pyridin-3-ylboronic acid (97.5 mg, 793 μ mol) and potassium carbonate (219 mg, 1.59 mmol) in 1,2-dimethoxyethane (4.1 mL) and water (410 μ L) for several minutes. Afterwards 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride-DCM-complex (45.6 mg, 53 μ mol) was added to the mixture, the tube was sealed and the reaction mixture was stirred over night at 95 °C. After cooling to room temperature, the mixture was filtrated over a pad of celite. The filtrate was
 10 concentrated under reduced pressure. The residue was purified by preparative HPLC to provide the title compound 8 (50 mg, 18%).

$^1\text{H-NMR}$ (300 MHz, DMSO- d_6): δ [ppm] = 1.23 (d, 3H), 2.53 - 2.63 (m, 4H), 3.41 (q, 1H), 3.65 - 3.68 (m, 4H), 7.52 (dd, 1H), 7.67 (d, 1H), 7.86 (dd, 1H), 8.10 (d, 1H), 8.33 (dd, 1H), 8.40 - 8.44 (m, 1H), 8.61 (dd, 1H), 8.75 (d, 1H), 9.05 (d, 1H), 9.26 (d, 1H), 10.06 (s, 1H), 10.75 (s, 1H).

15 LC-MS (Method 4): R_t = 1.13 min; MS (ESIpos): m/z = 516 $[\text{M}+\text{H}]^+$.

Example 9

3-[[[4-methylpiperazin-1-yl]acetyl]amino]-N-[5-(pyridin-2-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide hydrochloride



20

A solution of the compound of intermediate 14 (200 mg, 554 μ mol), 5-(pyridin-2-yl)-1,3,4-thiadiazol-2-amine (125 mg, 704 μ mol), (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, 392 mg, 754 μ mol) and diisopropylethylamine (263 μ L, 1.51 mmol) in DMF (2.17 mL) was

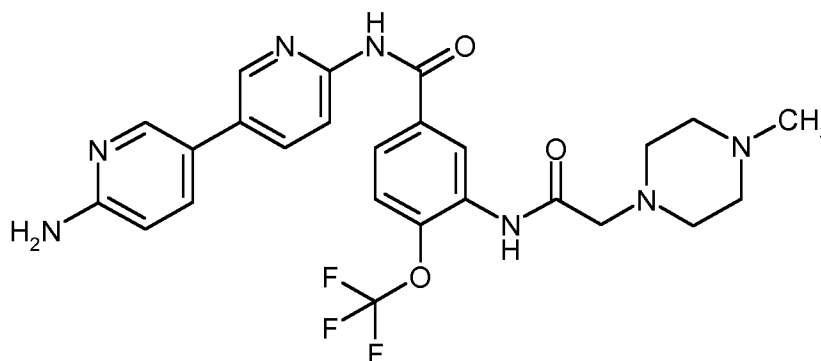
stirred for 36 h at room temperature. The mixture was filtered and purified by preparative HPLC (eluent: acetonitrile/water + 0.1% NH₃). The obtained material was dissolved in DMSO, poured into water and stirred over night. The resulting precipitate was collected by filtration to provide the desired compound 9 (35.0 mg, 12%).

- 5 ¹H-NMR (300 MHz, DMSO-d₆): δ [ppm] = 2.55 - 3.30 (m, 8H), 2.76 (s, 3H), 3.39 (s, 2H), 7.54 - 7.58 (m, 1H), 7.62 - 7.70 (m, 1H), 7.94 - 8.12 (m, 2H), 8.25 (d, 1H), 8.65 - 8.77 (m, 2H), 9.85 (s, 1H).

LC-MS (Method 4): R_t = 0.83 min; MS (ESI^{neg}): m/z = 520 [M-HCl-H]⁻.

Example 10

- 10 N-(6'-amino-3,3'-bipyridin-6-yl)-3-[[4-methylpiperazin-1-yl]acetyl]amino-4-(trifluoromethoxy)benzamide



- 15 To a microwave vial was added the compound of intermediate 19 (150 mg, 0.29 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (115 mg, 0.52 mmol, 1.8 equiv), cesium carbonate (189 mg, 0.58 mmol, 2 equiv) and a DMF / water mixture (2:1, 4.5 mL). The resulting suspension was purged with argon, treated with dichloro[bis(triphenylphosphoranyl)]palladium (Pd(PPh₃)₂Cl₂, 10.2 mg, 0.02 mmol, 5 mol%) and sealed. The resulting mixture was heated with a microwave apparatus at 100 °C for 0.5 h, was then cooled to room temperature. The reaction mixture was diluted with water and ethyl acetate. The precipitate was collected by filtration and dried. 120 mg (78% of theory) of the title compound were obtained.
- 20

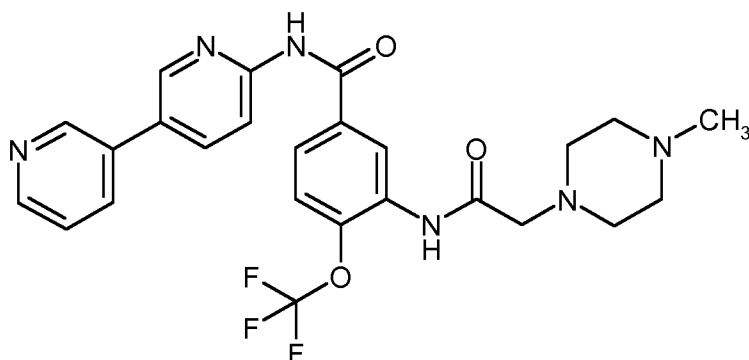
¹H-NMR (400 MHz, DMSO-d₆): δ [ppm] = 2.18 (s, 3H), 2.30 - 2.47 (m, 4H), 2.54 - 2.65 (m, 4H), 3.21 (s, 2H), 6.12 (s, 2H), 6.55 (d, 1H), 7.58 (dd, 1H), 7.77 (dd, 1H), 7.89 (dd, 1H), 8.05 (dd, 1H), 8.20 (d, 1H), 8.31 (d, 1H), 8.62 (d, 1H), 8.88 (d, 1H), 9.91 (s, 1H), 10.98 (s, 1H).

LC-MS (Method 4): R_t = 0.62 min; MS (ESI^{pos}): m/z = 530 [M+H]⁺.

25

Example 11

N-(3,3'-bipyridin-6-yl)-3-[[4-methylpiperazin-1-yl]acetyl]amino-4-(trifluoromethoxy)benzamide



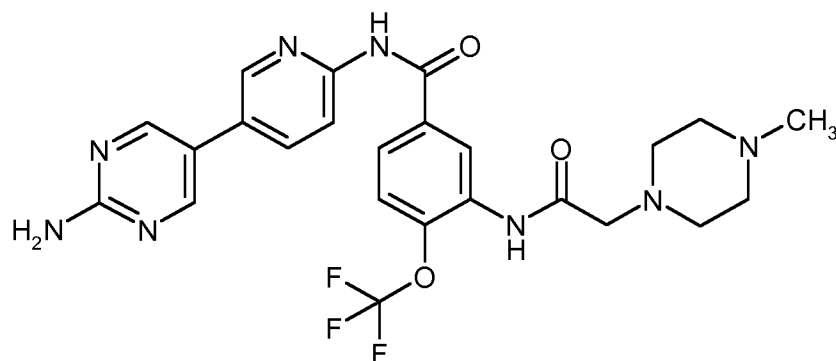
To a microwave vial was added the compound of intermediate 19 (150 mg, 0.29 mmol), pyridin-3-ylboronic acid (64.0 mg, 0.52 mmol, 1.8 equiv), cesium carbonate (189 mg, 0.58 mmol, 2 equiv) and a DMF / water mixture (2:1, 4.5 mL). The resulting suspension was purged with argon, treated with dichloro[bis(triphenylphosphoranyl)]palladium (Pd(PPh₃)₂Cl₂, 10.2 mg, 0.02 mmol, 5 mol%) and sealed. The resulting mixture was heated with a microwave apparatus at 100 °C for 0.5 h, was then cooled to room temperature. The reaction mixture was diluted with water and ethyl acetate. The phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with water, dried over sodium sulfate and concentrated. The remaining material was triturated with ethanol, collected by filtration and dried to give 32.8 mg (22% of theory) of the title compound.

¹H-NMR (400 MHz, DMSO-d₆): δ [ppm] = 2.18 (s, 3H), 2.27 - 2.48 (m, 4H), 2.55 - 2.65 (m, 4H), 3.21 (s, 2H), 7.52 (ddd, 1H), 7.60 (dd, 1H), 7.90 (dd, 1H), 8.15 - 8.20 (m, 1H), 8.24 - 8.33 (m, 2H), 8.61 (dd, 1H), 8.80 (dd, 1H), 8.90 (d, 1H), 8.99 (dd, 1H), 9.92 (s, 1H), 11.14 (s, 1H).

LC-MS (Method 4): R_t = 0.69 min; MS (ESIpos): m/z = 515 [M+H]⁺.

Example 12

N-[5-(2-aminopyrimidin-5-yl)pyridin-2-yl]-3-[[4-(4-methylpiperazin-1-yl)acetyl]amino]-4-(trifluoromethoxy)benzamide



To a microwave vial was added the compound of intermediate 19 (150 mg, 0.29 mmol), (2-aminopyrimidin-5-yl)boronic acid (73.0 mg, 0.52 mmol, 1.8 equiv), cesium carbonate (189 mg, 0.58 mmol, 2 equiv) and a DMF / water mixture (2:1, 4.5 mL). The resulting suspension was purged with argon, treated with dichloro[bis(triphenylphosphoranyl)]palladium (Pd(PPh₃)₂Cl₂, 10.2 mg, 0.02

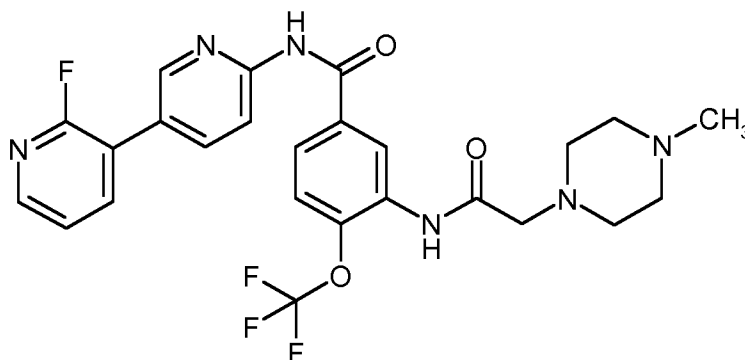
mmol, 5 mol%) and sealed. The resulting mixture was heated with a microwave apparatus at 100 °C for 0.5 h, was then cooled to room temperature. The reaction mixture was diluted with water and ethyl acetate. The precipitate was collected by filtration and dried. 105 mg (65% of theory) of the title compound were obtained.

- 5 ¹H-NMR (300 MHz, DMSO-d₆): δ [ppm] = 2.18 (s, 3H), 2.29 - 2.45 (m, 4H), 2.55 - 2.63 (m, 4H), 3.21 (s, 2H), 6.86 (s, 2H), 7.59 (d, 1H), 7.89 (dd, 1H), 8.09 - 8.16 (m, 1H), 8.23 (d, 1H), 8.65 (s, 2H), 8.68 (d, 1H), 8.89 (d, 1H), 9.92 (s, 1H), 11.05 (s, 1H).

LC-MS (Method 4): R_t = 0.70 min; MS (ESIpos): m/z = 531 [M+H]⁺.

10 **Example 13**

N-(2'-fluoro-3,3'-bipyridin-6-yl)-3-[[4-methylpiperazin-1-yl]acetyl]amino-4-(trifluoromethoxy)benzamide



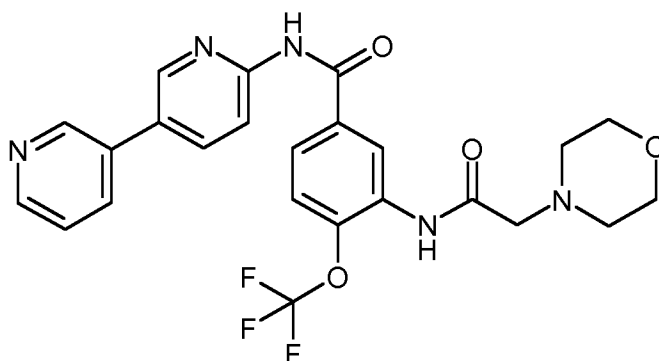
- To a microwave vial was added the compound of intermediate 19 (150 mg, 0.29 mmol), 2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (117 mg, 0.52 mmol, 1.8 equiv), cesium carbonate (189 mg, 0.58 mmol, 2 equiv) and a DMF / water mixture (2:1, 4.5 mL). The resulting suspension was purged with argon, treated with dichloro[bis(triphenylphosphoranyl)]palladium (Pd(PPh₃)₂Cl₂, 10.2 mg, 0.02 mmol, 5 mol%) and sealed. The resulting mixture was heated with a microwave apparatus at 100 °C for 0.5 h, was then cooled to room temperature. The reaction mixture was diluted with water and ethyl acetate. The phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with water, dried over sodium sulfate and concentrated. The remaining material was triturated with ethanol, collected by filtration and dried to give 39 mg (25% of theory) of the title compound.

- 25 ¹H-NMR (400 MHz, DMSO-d₆): δ [ppm] = 2.18 (s, 3H), 2.29 - 2.46 (m, 4H), 2.54 - 2.65 (m, 4H), 3.21 (s, 2H), 7.48 - 7.55 (m, 1H), 7.59 (dd, 1H), 7.90 (dd, 1H), 8.11 - 8.18 (m, 1H), 8.21 - 8.35 (m, 3H), 8.66 (s, 1H), 8.90 (d, 1H), 9.92 (s, 1H), 11.16 (s, 1H).

LC-MS (Method 4): R_t = 0.87 min; MS (ESIpos): m/z = 533 [M+H]⁺.

Example 14

N-(3,3'-bipyridin-6-yl)-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide



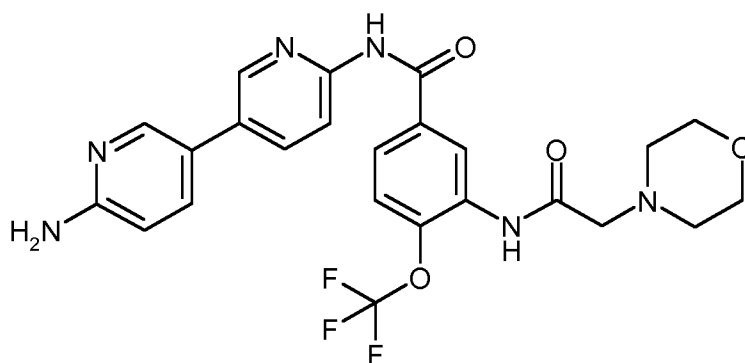
To a microwave vial was added the compound of intermediate 20 (150 mg, 0.30 mmol), pyridin-3-ylboronic acid (66 mg, 0.54 mmol, 1.8 equiv), cesium carbonate (194 mg, 0.60 mmol, 2 equiv) and a DMF / water mixture (2:1, 4.5 mL). The resulting suspension was purged with argon, treated with dichloro[bis(triphenylphosphoranyl)]palladium (Pd(PPh₃)₂Cl₂, 10.5 mg, 0.02 mmol, 5 mol%) and sealed. The resulting mixture was heated with a microwave apparatus at 100 °C for 0.5 h, was then cooled to room temperature. The reaction mixture was diluted with water and ethyl acetate. The phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with water, dried over sodium sulfate and concentrated. The remaining material was triturated with ethanol, collected by filtration and dried to give 33 mg (21% of theory) of the title compound.

¹H-NMR (400 MHz, DMSO-d₆): δ [ppm] = 2.56 - 2.61 (m, 4H), 3.23 (s, 2H), 3.61 - 3.69 (m, 4H), 7.50 - 7.55 (m, 1H), 7.59 (dd, 1H), 7.92 (dd, 1H), 8.14 - 8.21 (m, 1H), 8.24 - 8.33 (m, 2H), 8.61 (dd, 1H), 8.80 (dd, 1H), 8.83 (d, 1H), 8.98 (d, 1H), 9.90 (s, 1H), 11.13 (s, 1H).

LC-MS (Method 4): R_t = 0.79 min; MS (ESIpos): m/z = 502 [M+H]⁺.

Example 15

N-(6'-amino-3,3'-bipyridin-6-yl)-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide



To a microwave vial was added the compound of intermediate 20 (150 mg, 0.30 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (118 mg, 0.54 mmol, 1.8 equiv), cesium carbonate (194 mg, 0.60 mmol, 2 equiv) and a DMF / water mixture (2:1, 4.5 mL). The resulting

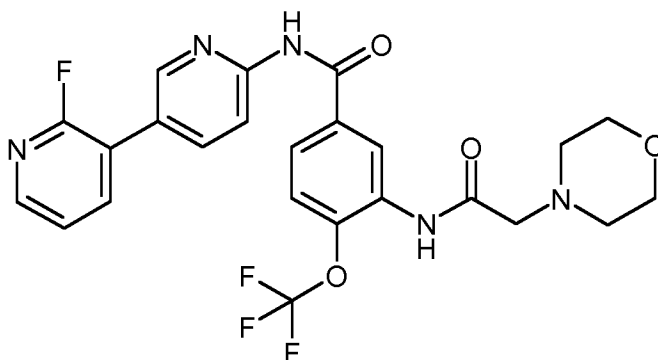
suspension was purged with argon, treated with dichloro[bis(triphenylphosphoranyl)]palladium ($\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, 10.5 mg, 0.02 mmol, 5 mol%) and sealed. The resulting mixture was heated with a microwave apparatus at 100 °C for 0.5 h, was then cooled to room temperature. The reaction mixture was diluted with water and ethyl acetate. The precipitate was collected by filtration and dried. 123 mg (79% of theory) of the title compound were obtained.

^1H -NMR (400 MHz, DMSO-d_6): δ [ppm] = 2.55 - 2.61 (m, 4H), 3.23 (s, 2H), 3.62 - 3.68 (m, 4H), 6.14 (s, 2H), 6.55 (d, 1H), 7.58 (dd, 1H), 7.77 (dd, 1H), 7.88 - 7.93 (m, 1H), 8.03 - 8.09 (m, 1H), 8.20 (d, 1H), 8.31 (d, 1H), 8.61 - 8.65 (m, 1H), 8.81 (d, 1H), 9.90 (s, 1H), 11.00 (s, 1H).

LC-MS (Method 4): R_t = 0.73 min; MS (ESIpos): m/z = 517 $[\text{M}+\text{H}]^+$.

Example 16

N-(2'-fluoro-3,3'-bipyridin-6-yl)-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide



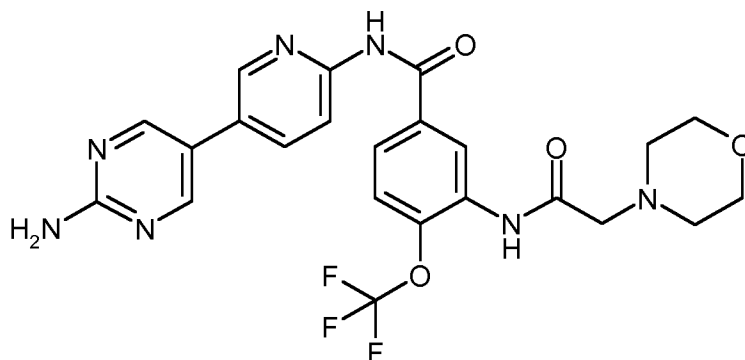
To a microwave vial was added the compound of intermediate 20 (150 mg, 0.30 mmol), 2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (120 mg, 0.54 mmol, 1.8 equiv), cesium carbonate (194 mg, 0.60 mmol, 2 equiv) and a DMF / water mixture (2:1, 4.5 mL). The resulting suspension was purged with argon, treated with dichloro[bis(triphenylphosphoranyl)]palladium ($\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, 10.5 mg, 0.02 mmol, 5 mol%) and sealed. The resulting mixture was heated with a microwave apparatus at 100 °C for 0.5 h, was then cooled to room temperature. The reaction mixture was diluted with water and ethyl acetate. The precipitate was filtered off and the filtrate was extracted with ethyl acetate. The combined organic phases were washed with water, dried over sodium sulfate and concentrated. The residue was purified by preparative HPLC (method 5) to give 52 mg (30% of theory) of the title compound.

^1H -NMR (400 MHz, DMSO-d_6): δ [ppm] = 2.56 - 2.62 (m, 4H), 3.23 (s, 2H), 3.62 - 3.69 (m, 4H), 7.52 (ddd, 1H), 7.58 - 7.62 (m, 1H), 7.92 (dd, 1H), 8.12 - 8.17 (m, 1H), 8.21 - 8.30 (m, 2H), 8.30 - 8.34 (m, 1H), 8.67 (s, 1H), 8.83 (d, 1H), 9.91 (s, 1H), 11.18 (s, 1H).

LC-MS (Method 4): R_t = 1.01 min; MS (ESIpos): m/z = 520 $[\text{M}+\text{H}]^+$.

Example 17

N-[5-(2-aminopyrimidin-5-yl)pyridin-2-yl]-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide



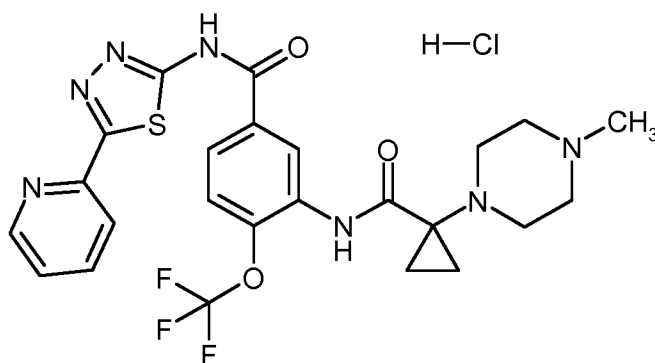
To a microwave vial was added the compound of intermediate 20 (150 mg, 0.30 mmol), (2-aminopyrimidin-5-yl)boronic acid (75.0 mg, 0.54 mmol, 1.8 equiv), cesium carbonate (194 mg, 0.60 mmol, 2 equiv) and a DMF / water mixture (2:1, 4.5 mL). The resulting suspension was purged with argon, treated with dichloro[bis(triphenylphosphoranyl)]palladium ($\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, 10.5 mg, 0.02 mmol, 5 mol%) and sealed. The resulting mixture was heated with a microwave apparatus at 100 °C for 0.5 h, was then cooled to room temperature. The reaction mixture was diluted with water and ethyl acetate. The precipitate was collected by filtration and dried. 116 mg (75% of theory) of the title compound were obtained.

$^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ [ppm] = 2.55 - 2.61 (m, 4H), 3.23 (s, 2H), 3.62 - 3.69 (m, 4H), 6.84 (s, 2H), 7.57 (dd, 1H), 7.91 (dd, 1H), 8.10 (dd, 1H), 8.21 (d, 1H), 8.64 (s, 2H), 8.66 - 8.69 (m, 1H), 8.82 (d, 1H), 9.90 (s, 1H), 11.04 (s, 1H).

LC-MS (Method 4): R_t = 0.80 min; MS (ESIpos): m/z = 518 $[\text{M}+\text{H}]^+$.

Example 18

3-([1-(4-methylpiperazin-1-yl)cyclopropyl]carbonyl)amino)-N-[5-(pyridin-2-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide hydrochloride



To a suspension of 174 mg (0.79 mmol) of the compound from intermediate 3 in 21 mL of dichloromethane were added 0.42 mL of 1-chloro-N,N,2-trimethylprop-1-en-1-amine (3.15 mmol, 4 equiv). The reaction mixture was stirred at room temperature for 2 h. The resulting mixture was

concentrated under reduced pressure, was then triturated with dichloromethane and was concentrated under reduced pressure. The remaining material was provided in 6 mL of dichloromethane and 0.19 mL of pyridine (2.36 mmol, 3 equiv) and 300 mg of the compound of intermediate 21 were added. The resulting suspension was stirred at room temperature over night.

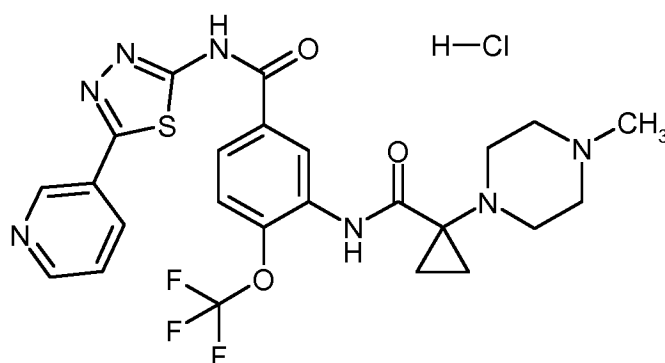
- 5 The resulting mixture was concentrated under reduced pressure, was then triturated with a mixture of 5 mL of water and 5 mL of ethanol, and the resulting mixture was stirred for 30 minutes. The remaining solids were removed by filtration, washed with ethanol, and were dried under reduced pressure to provide the title compound (280 mg, 60%).

¹H-NMR (400 MHz, DMSO-d₆): δ [ppm] = 1.17 - 1.26 (m, 4H), 2.63 - 2.75 (m, 2H), 2.78 (s, 3H), 2.88 - 2.99 (m, 2H), 3.02 - 3.16 (m, 2H), 3.42 - 3.53 (m, 2H), 7.56 (ddd, 1H), 7.66 (dd, 1H), 8.02 (td, 1H), 8.11 (dd, 1H), 8.25 (d, 1H), 8.64 - 8.75 (m, 2H), 10.02 (s, 1H), 10.18 (s, 1H), 13.35 (s, 1H).

LC-MS (Method 4): R_t = 0.88 min; MS (ESIpos): m/z = 548 [M-HCl+H]⁺.

Example 19

- 15 3-({[1-(4-methylpiperazin-1-yl)cyclopropyl]carbonyl}amino)-N-[5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide hydrochloride



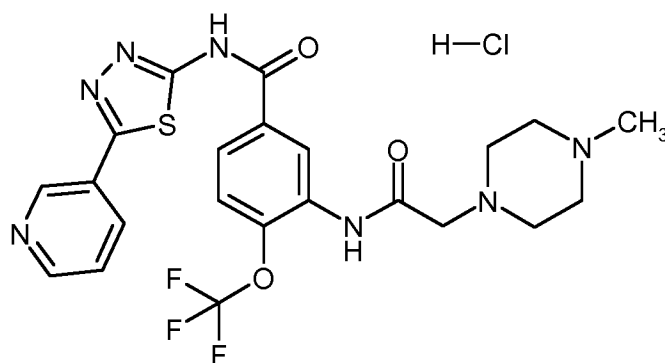
- To a suspension of 174 mg (0.79 mmol) of the compound from intermediate 3 in 21 mL of dichloromethane were added 0.42 mL of 1-chloro-N,N,2-trimethylprop-1-en-1-amine (3.15 mmol, 4 equiv). The reaction mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure, was then triturated with dichloromethane and was concentrated under reduced pressure. The remaining material was provided in 6 mL of dichloromethane and 0.19 mL of pyridine (2.36 mmol, 3 equiv) and 300 mg of the compound of intermediate 21 were added. The resulting suspension was stirred at room temperature over night.
- 25 The resulting mixture was concentrated under reduced pressure, was then triturated with a mixture of 5 mL of water and 5 mL of ethanol, and the resulting mixture was stirred for 30 minutes. The remaining solids were removed by filtration, washed with ethanol, and were dried under reduced pressure to provide the title compound (77.7 mg, 16%).

¹H-NMR (400 MHz, DMSO-d₆): δ [ppm] = 1.17 - 1.27 (m, 4H), 2.65 - 2.75 (m, 2H), 2.78 (s, 3H), 2.88 - 2.97 (m, 2H), 3.03 - 3.16 (m, 2H), 3.43 - 3.53 (m, 2H), 7.56 - 7.63 (m, 1H), 7.67 (dd, 1H), 8.10 (dd, 1H), 8.38 (dt, 1H), 8.67 (d, 1H), 8.73 (dd, 1H), 9.17 (d, 1H), 10.03 (s, 1H), 10.20 (s, 1H), 13.46 (s, 1H).

LC-MS (Method 4): $R_t = 0.79$ min; MS (ESIpos): $m/z = 548$ $[M-HCl+H]^+$.

Example 20

3-[[[4-methylpiperazin-1-yl]acetyl]amino]-N-[5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide hydrochloride



To a solution of the compound of intermediate 14 (300 mg, 0.64 mmol) and 5-(pyridin-3-yl)-1,3,4-thiadiazol-2-amine (229 mg, 1.28 mmol, 2 equiv) in DMF (4 mL) was added (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, 667 mg, 1.28 mmol, 2 equiv) and diisopropylethylamine (0.56 mL, 3.21 mmol, 5 equiv). The resulting mixture was stirred at room temperature over night, then triturated with ethanol and stirred at 60 °C. The precipitate was collected by filtration and dried under reduced pressure at 50 °C. The remaining material was triturated with ethanol and stirred for 30 minutes. The precipitate was collected by filtration and dried under reduced pressure at 50 °C. Purification by HPLC (column: chromatorex C18, 10 μ m, 125x30mm, mobile phase: acetonitrile/water) yielded 175 mg (49% of theory) of the title compound.

$^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ [ppm] = 2.72 - 2.99 (m, 4H), 2.76 (s, 3H), 2.99 - 3.26 (m, 4H), 3.39 (s, 2H), 7.60 (ddd, 1H), 7.66 (dd, 1H), 8.08 (dd, 1H), 8.35 - 8.40 (m, 1H), 8.71 - 8.76 (m, 2H), 9.15 - 9.19 (m, 1H), 9.85 (s, 1H), 11.57 (s, 1H).

LC-MS (Method 1): $R_t = 0.80$ min; MS (ESIpos): $m/z = 522$ $[M-HCl+H]^+$.

The following examples were prepared in analogy to the described methods, *supra*.

Table 1

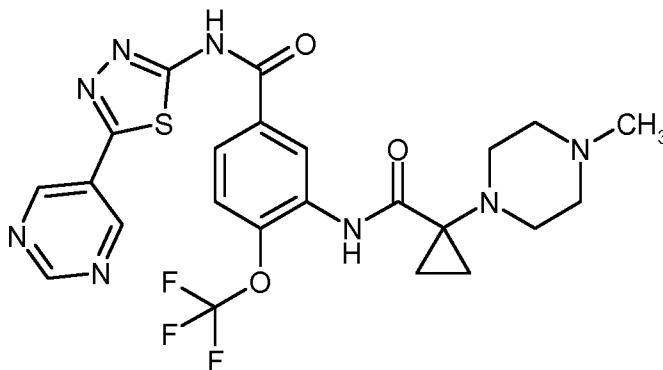
Example No	Structure	IUPAC Name	R_t [min] method

Example No	Structure	IUPAC Name	R _t [min] method
21		3-[[4-methylpiperazin-1-yl]acetyl]amino-N-[5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide	0.74 1
22		N-(2,4'-bipyridin-5-yl)-3-[[2-(morpholin-4-yl)propanoyl]amino]-4-(trifluoromethoxy)benzamide	1.14 3
23		N-(6'-fluoro-2,3'-bipyridin-5-yl)-3-[[2-(morpholin-4-yl)propanoyl]amino]-4-(trifluoromethoxy)benzamide	1.05 1
24		N-[4-methoxy-3-[(morpholin-4-ylacetyl]amino]phenyl]-6-(thiophen-2-yl)pyridine-3-carboxamide	1.10 3
25		N-[4-methoxy-3-[(morpholin-4-ylacetyl]amino]phenyl]-5-(pyridin-4-yl)thiophene-2-carboxamide	1.10 3

Example No	Structure	IUPAC Name	R _t [min] method
26		4-chloro-3-({[1-(4-methylpiperazin-1-yl)cyclopropyl]carbonyl}amino)-N-[5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl]benzamide	0.77 4
27		3-({[4-(4-methylpiperazin-1-yl)acetyl]amino}-N-[5-(2-methylpyridin-3-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide	0.69 3
28		N-[5-(2-methylpyridin-3-yl)-1,3,4-thiadiazol-2-yl]-3-({[4-(morpholin-4-yl)acetyl]amino}-4-(trifluoromethoxy)benzamide	0.69 3

Example 29

3-({[1-(4-methylpiperazin-1-yl)cyclopropyl]carbonyl}amino)-N-[5-(pyrimidin-5-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide



5

90 mg (0.24 mmol) of 3-amino-N-[5-(pyrimidin-5-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide (intermediate 25) and 84.4 mg (0.35 mmol) of 1-(4-methylpiperazin-1-yl)cyclopropanecarbonyl chloride hydrochloride (1:1) (intermediate 24) were stirred for 3 h under

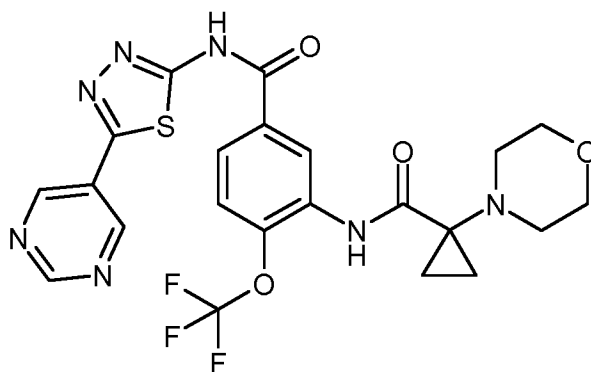
reflux in 7.5 mL of anhydrous toluene. The volatile was removed under vacuum and the residue was purified by HPLC (method 5) giving 60 mg (46%) of the title compound.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 1.15 - 1.21 (m, 2H), 1.22 - 1.28 (m, 2H), 2.34 (s, 3H), 2.54 - 2.77 (m, 8H), 7.61 - 7.66 (m, 1H), 8.02 (dd, 1H), 9.04 (d, 1H), 9.29 (s, 1H), 9.35 (s, 2H), 10.44 (s, 1H), 12.60 (br. s, 1H).

LC-MS (Method 3): R_t = 0.73 min; MS (ESIpos): m/z = 549 [M+H]⁺.

Example 30

3-({[1-(morpholin-4-yl)cyclopropyl]carbonyl}amino)-N-[5-(pyrimidin-5-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide



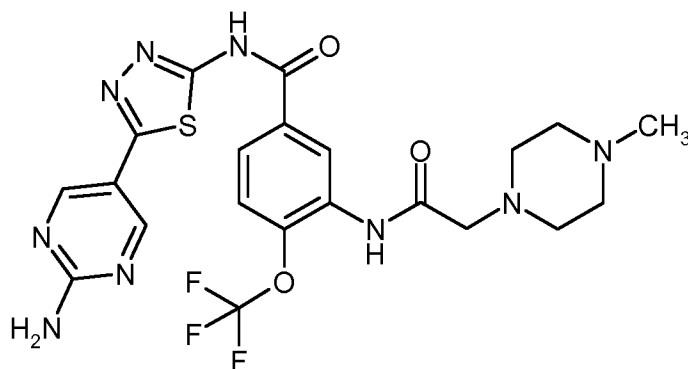
90 mg (0.24 mmol) of 3-amino-N-[5-(pyrimidin-5-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide (intermediate 25) and 79.8 mg (0.35 mmol) of 1-(morpholin-4-yl)cyclopropanecarbonyl chloride hydrochloride (1:1) (intermediate 26) were stirred for 3 h under reflux in 7.5 mL of anhydrous toluene. The volatile was removed under vacuum and the residue was purified by HPLC (method 5) giving 22 mg (17%) of the title compound.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 1.14 - 1.24 (m, 2H), 1.24 - 1.33 (m, 2H), 3.66 - 3.75 (m, 4H), 7.66 - 7.71 (m, 1H), 8.02 (dd, 1H), 9.10 (d, 1H), 9.33 (s, 1H), 9.39 (s, 2H), 10.59 (s, 1H), 13.50 (br. s, 1H).

LC-MS (Method 3): R_t = 0.72 min; MS (ESIpos): m/z = 536 [M+H]⁺.

Example 31

N-[5-(2-aminopyrimidin-5-yl)-1,3,4-thiadiazol-2-yl]-3-[[[4-methylpiperazin-1-yl]acetyl]amino]-4-(trifluoromethoxy)benzamide



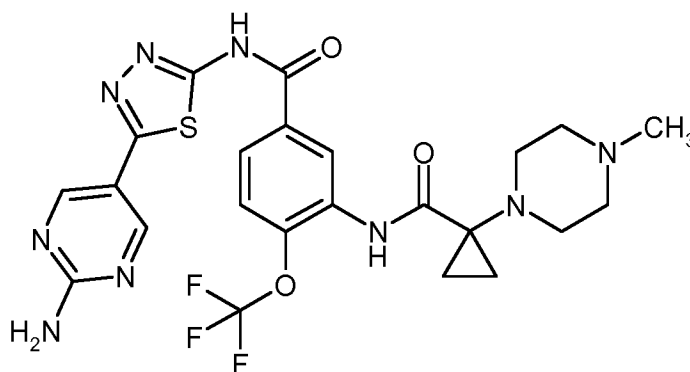
75 mg (0.20 mmol) of lithium 3-({[4-methylpiperazin-1-yl]acetyl]amino}-4-(trifluoromethoxy)benzoate (intermediate 35), 68.7 mg (0.27 mmol) of 5-(5-amino-1,3,4-thiadiazol-2-yl)pyrimidin-2-amine (intermediate 27), 142 μ L (0.82 mmol) of N-ethyl-N-isopropylpropan-2-amine and 159.4 mg (0.31 mmol) of PYBOP in 3 mL of anhydrous DMF were stirred for 5 h at rt. The volatiles were removed under vacuum and the residue was purified by HPLC (method 5) to yield 29 mg (26%) of the title compound.

$^1\text{H-NMR}$ (600MHz, DMSO-d_6): δ [ppm]= 2.25 (s, 3H), 2.32 - 2.76 (m, 8H), 3.24 (s, 2H), 7.27 (s, 2H), 7.60 - 7.64 (m, 1H), 8.00 (dd, 1H), 8.77 (s, 2H), 8.98 (d, 1H), 9.92 (s, 1H), 12.94 (br. s, 1H).

LC-MS (Method 3): R_t = 0.67 min; MS (ESIpos): m/z = 538 $[\text{M}+\text{H}]^+$.

Example 32

N-[5-(2-aminopyrimidin-5-yl)-1,3,4-thiadiazol-2-yl]-3-({[1-(4-methylpiperazin-1-yl)cyclopropyl]carbonyl]amino)-4-(trifluoromethoxy)benzamide



50 mg (0.13 mmol) of 3-({[1-(4-methylpiperazin-1-yl)cyclopropyl]carbonyl]amino)-4-(trifluoromethoxy)benzoic acid (intermediate 28), 43.5 mg (0.22 mmol) of 5-(5-amino-1,3,4-thiadiazol-2-yl)pyrimidin-2-amine (intermediate 27), 90 μ L (0.52 mmol) of N-ethyl-N-isopropylpropan-2-amine and 100.8 mg (0.19 mmol) of PYBOP in 3 mL of anhydrous DMF were stirred for 3 days at rt. The volatiles were removed under vacuum and the residue was purified by HPLC (method 5) to give 2 mg (3%) of the title compound.

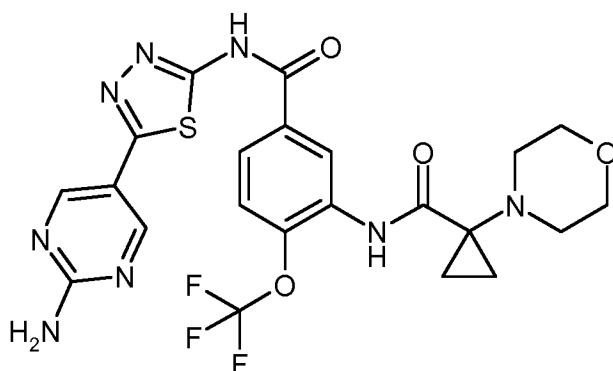
¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 1.13 - 1.19 (m, 2H), 1.23 - 1.28 (m, 2H), 2.21 (s, 3H), 2.37 - 2.81 (m, 8H), 7.23 (s, 2H), 7.59 - 7.64 (m, 1H), 7.97 (dd, 1H), 8.76 (s, 2H), 9.12 (d, 1H), 10.56 (s, 1H), 13.21 (br. s, 1H).

LC-MS (Method 3): R_t = 0.69 min; MS (ESIpos): m/z = 564 [M+H]⁺.

5

Example 33

N-[5-(2-aminopyrimidin-5-yl)-1,3,4-thiadiazol-2-yl]-3-({[1-(morpholin-4-yl)cyclopropyl]carbonyl}amino)-4-(trifluoromethoxy)benzamide



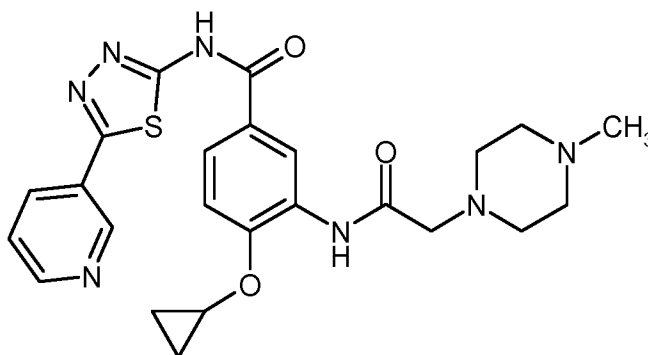
10 30 mg (0.08 mmol) of 3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzoic acid (intermediate 29), 27.0 mg (0.22 mmol) of 5-(5-amino-1,3,4-thiadiazol-2-yl)pyrimidin-2-amine (intermediate 27), 56 μL (0.32 mmol) of N-ethyl-N-isopropylpropan-2-amine and 62.6 (0.12 mmol) of PYBOP in 2 mL of anhydrous DMF were stirred for 3 days at rt. The volatiles were removed under vacuum and the residue was purified by HPLC (method 5) to yield 11 mg (25%) of the title compound.

15 ¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 1.14 - 1.20 (m, 2H), 1.27 - 1.33 (m, 2H), 2.52 - 2.82 (m, 4H), 3.66 - 3.75 (m, 4H), 7.29 (s, 2H), 7.63 - 7.69 (m, 1H), 7.99 (dd, 1H), 8.79 (s, 2H), 9.07 (d, 1H), 10.57 (s, 1H), 13.31 (br. s, 1H).

LC-MS (Method 3): R_t = 0.68 min; MS (ESIpos): m/z = 551 [M+H]⁺.

20 Example 34

4-(cyclopropyloxy)-3-[[[4-methylpiperazin-1-yl]acetyl]amino]-N-[5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl]benzamide



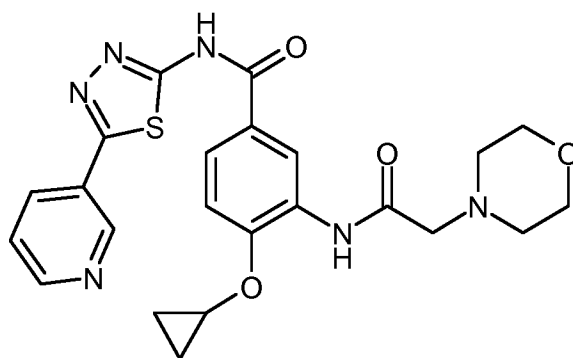
34 mg (0.22 mmol) of (4-methylpiperazin-1-yl)acetic acid and 38 mg (0.11 mmol) of 3-amino-4-(cyclopropyloxy)-N-[5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl]benzamide (intermediate 31) were suspended in 1 mL of anhydrous DMF. 112 mg (0.22 mmol) of PYBOP and 94 μ L (0.54 mmol) of N-ethyl-N-isopropylpropan-2-amine were added and stirred over night at 55 °C. The reaction mixture was concentrated under vacuum and purified by HPLC (method 5) with a 20 mg batch, which was synthesized analogously, to afford 23 mg (28%) of the title compound.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm] = 0.79 - 0.85 (m, 2H), 0.91 - 0.98 (m, 2H), 2.25 (s, 3H), 2.38 - 2.66 (m, 8H), 3.17 (s, 2H), 4.12 - 4.18 (m, 1H), 7.48 (d, 1H), 7.59 (dd, 1H), 8.01 (dd, 1H), 8.34 - 8.39 (m, 1H), 8.69 - 8.73 (m, 1H), 8.99 (d, 1H), 9.16 (d, 1H), 9.76 (s, 1H), 13.00 (br. s, 1H).

LC-MS (Method 3): R_t = 0.72 min; MS (ESIpos): m/z = 494 [M+H]⁺.

Example 35

4-(cyclopropyloxy)-3-[(morpholin-4-ylacetyl)amino]-N-[5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl]benzamide



80 mg (0.23 mmol) of 3-amino-4-(cyclopropyloxy)-N-[5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl]benzamide (intermediate 31) were suspended in 1 mL of anhydrous DMF. 315 μ L (1.81 mmol) of N-ethyl-N-isopropylpropan-2-amine, 52 mg (0.34 mmol) of morpholin-4-ylacetic acid and 264 μ L (0.45 mmol) of 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (50% in DMF) were added. It was stirred over night at rt. It was concentrated under vacuum and purified by HPLC (method 5) affording 46 mg (42%) of the title compound.

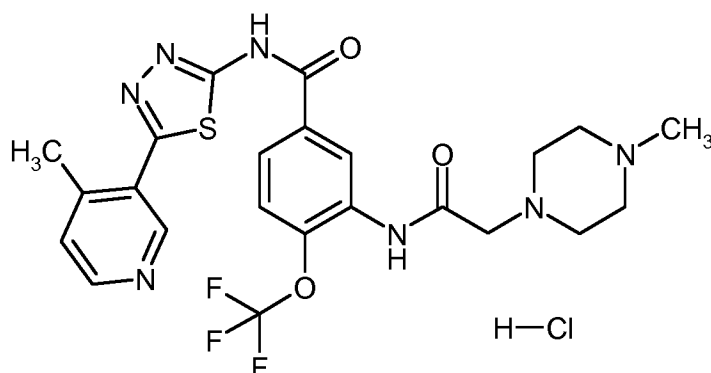
$^1\text{H-NMR}$ (400MHz, DMSO-d_6): δ [ppm]= 0.76 - 0.83 (m, 2H), 0.91 - 0.98 (m, 2H), 2.54 - 2.59 (m, 4H), 3.18 (s, 2H), 3.64 - 3.71 (m, 4H), 4.12 - 4.18 (m, 1H), 7.49 (d, 1H), 7.57 - 7.62 (m, 1H), 8.02 (dd, 1H), 8.35 - 8.39 (m, 1H), 8.72 (dd, 1H), 8.96 (d, 1H), 9.17 (d, 1H), 9.73 (s, 1H), 13.21 (br. s, 1H).

LC-MS (Method 3): R_t = 0.69 min; MS (ESIpos): m/z = 481 $[\text{M}+\text{H}]^+$.

5

Example 36

3-[[[4-methylpiperazin-1-yl)acetyl]amino]-N-[5-(4-methylpyridin-3-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide hydrochloride (1:1)



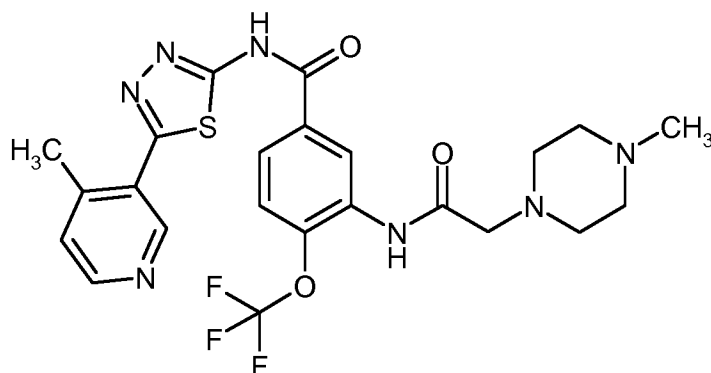
- 10 To a solution of the compound of intermediate 14 (167 mg, 0.36 mmol) and intermediate 36 (101 mg, 0.51 mmol, 1.4 equiv) in DMF (1.8 mL) was added (benzotriazol-1-yl)oxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, 825 mg, 1.59 mmol, 4.5 equiv) and diisopropylethylamine (0.34 mL, 1.96 mmol, 5.5 equiv). The resulting mixture was stirred at room temperature over night, then triturated with water and stirred for 15 minutes. The precipitate was
- 15 collected by filtration, dried under reduced pressure and purified by HPLC (column: chromatorex C18, mobile phase: acetonitrile/water + 0.1% formic acid). The remaining material was triturated with ethanol and stirred for 30 minutes. The precipitate was collected by filtration and dried under reduced pressure to give 31.6 mg (14% of theory) of the title compound.

20 $^1\text{H-NMR}$ (400MHz, DMSO-d_6): δ [ppm]= 2.57 (s, 3H), 2.72 (s, 3H), 2.73 - 3.21 (m, 8H), 3.37 (s, 2H), 7.48 (d, 1H), 7.66 (dd, 1H), 8.08 (dd, 1H), 8.57 (d, 1H), 8.76 (s, 1H), 8.85 (s, 1H), 9.87 (s, 1H).

LC-MS (Method 3): R_t = 0.73 min; MS (ESIpos): m/z = 536 $[\text{M}-\text{HCl}+\text{H}]^+$.

Example 37

25 3-[[[4-methylpiperazin-1-yl)acetyl]amino]-N-[5-(4-methylpyridin-3-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide



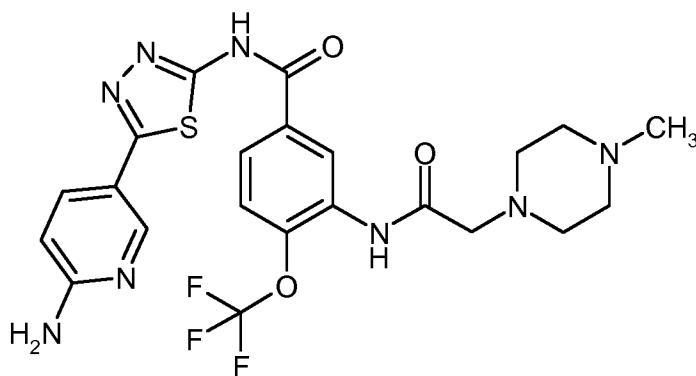
To a solution of the compound of intermediate 35 (300 mg, 0.82 mmol) and intermediate 36 (227 mg, 1.06 mmol, 1.3 equiv) in DMF (6 mL) was added (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, 1.70 g, 3.27 mmol, 4 equiv) and diisopropylethylamine (0.71 mL, 4.08 mmol, 5 equiv). The resulting mixture was stirred at room temperature over night, then triturated with water and stirred for 15 minutes. The precipitate was collected by filtration and dried under reduced pressure. The remaining material was triturated with ethanol and stirred for 30 minutes. The precipitate was collected by filtration, dried under reduced pressure and purified by HPLC (method 5) to give 166 mg (38% of theory) of the title compound.

$^1\text{H-NMR}$ (600MHz, DMSO-d_6): δ [ppm]= 2.31 (s, 3H), 2.57 (s, 3H), 2.60 - 2.73 (m, 4H), 3.26 (s, 2H), 7.46 (d, 1H), 7.64 (dd, 1H), 8.03 (dd, 1H), 8.55 (d, 1H), 8.84 (s, 1H), 8.96 (d, 1H), 9.92 (s, 1H), 12.75 (s, 1H).

LC-MS (Method 3): R_t = 0.72 min; MS (ESIpos): m/z = 536 $[\text{M}+\text{H}]^+$.

Example 38

N-[5-(6-aminopyridin-3-yl)-1,3,4-thiadiazol-2-yl]-3-[[4-methylpiperazin-1-yl)acetyl]amino]-4-(trifluoromethoxy)benzamide



To a solution of the compound of intermediate 35 (150 mg, 0.41 mmol) and intermediate 37 (171 mg, 0.53 mmol, 1.3 equiv) in DMF (3 mL) was added (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, 319 mg, 0.61 mmol, 1.5 equiv) and diisopropylethylamine (0.29 mL, 1.63 mmol, 4 equiv). The resulting mixture was stirred at room temperature over night, then concentrated and triturated with water (2 mL) and ethanol (1 mL) and stirred for 30 minutes. The precipitate was collected by filtration, washed with ethanol and dried under reduced pressure. The

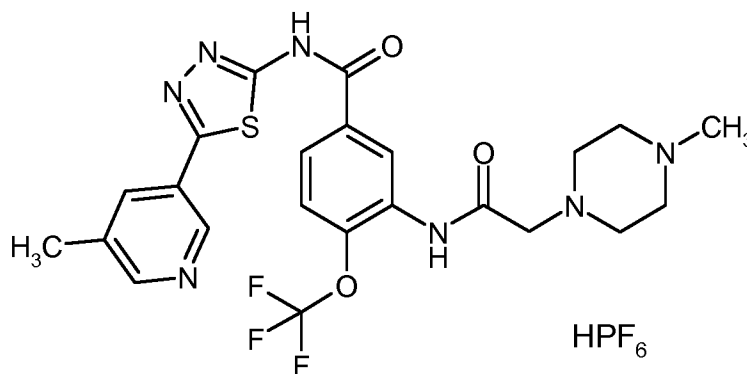
remaining material was purified by HPLC (column: chromatorex C18, mobile phase: acetonitrile/water + 0.1% ammonia). The remaining material was triturated with ethanol (2 mL) and stirred for 30 minutes. The precipitate was collected by filtration, washed with ethanol and dried under reduced pressure to give 38.6 mg (18% of theory) of the title compound.

- 5 $^1\text{H-NMR}$ (400MHz, DMSO-d_6): δ [ppm]= 2.22 (s, 3H), 2.36 - 2.48 (m, 4H), 2.55 - 2.65 (m, 4H), 3.22 (s, 2H), 6.51 - 6.60 (m, 3H), 7.62 (dd, 1H), 7.92 (dd, 1H), 7.99 (dd, 1H), 8.46 (d, 1H), 8.98 (d, 1H), 9.92 (s, 1H), 13.07 (s, 1H).

LC-MS (Method 3): R_t = 0.66 min; MS (ESIpos): m/z = 537 $[\text{M}+\text{H}]^+$.

10 **Example 39**

1-methyl-4-(2-([5-([5-(5-methylpyridin-3-yl)-1,3,4-thiadiazol-2-yl]carbamoyl)-2-(trifluoromethoxy)phenyl]amino)-2-oxoethyl)piperazin-1-ium hexafluorophosphate



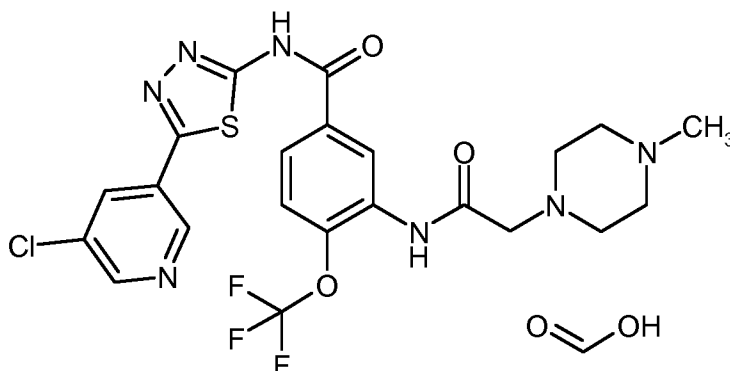
- To a solution of the compound of intermediate 35 (150 mg, 0.41 mmol) and intermediate 38 (102 mg, 0.53 mmol, 1.3 equiv) in DMF (3 mL) was added (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, 319 mg, 0.61 mmol, 1.5 equiv) and diisopropylethylamine (0.29 mL, 1.63 mmol, 4 equiv). The resulting mixture was stirred at room temperature over night. (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, 319 mg, 0.61 mmol, 1.5 equiv) and diisopropylethylamine (0.29 mL, 1.63 mmol, 4 equiv) were added and the resulting mixture was stirred at room temperature over night. The compound of intermediate 35 (150 mg, 0.41 mmol), (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, 319 mg, 0.61 mmol, 1.5 equiv) and diisopropylethylamine (0.29 mL, 1.63 mmol, 4 equiv) were added and the resulting mixture was stirred at room temperature over night, then concentrated and triturated with water (8 mL) and ethanol (3 mL) and stirred for 30 minutes. The precipitate was collected by filtration, washed with ethanol and dried under reduced pressure. The remaining material was purified by HPLC (method 2) to give 123 mg (55% of theory) of the title compound.

$^1\text{H-NMR}$ (400MHz, DMSO-d_6): δ [ppm]= 2.41 (s, 3H), 2.60 - 2.88 (m, 2H), 2.80 (s, 3H), 2.90 - 3.20 (m, 4H), 3.40 (s, 2H), 7.66 (dd, 1H), 8.08 (dd, 1H), 8.22 (s, 1H), 8.57 (s, 1H), 8.71 (d, 1H), 8.92 - 9.03 (m, 1H), 9.85 (s, 1H).

- 30 LC-MS (Method 4): R_t = 0.83 min; MS (ESIpos): m/z = 536 $[\text{M}-\text{HPF}_6+\text{H}]^+$.

Example 40

formic acid-N-[5-(5-chloropyridin-3-yl)-1,3,4-thiadiazol-2-yl]-3-[[4-methylpiperazin-1-yl]acetyl]amino}-4-(trifluoromethoxy)benzamide (1:1)



5

To a solution of the compound of intermediate 35 (150 mg, 0.41 mmol) and intermediate 39 (113 mg, 0.53 mmol, 1.3 equiv) in DMF (3 mL) was added (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, 319 mg, 0.61 mmol, 1.5 equiv) and diisopropylethylamine (0.29 mL, 1.63 mmol, 4 equiv). The resulting mixture was stirred at room temperature over night, then concentrated and triturated with water (8 mL) and ethanol (3 mL) and stirred for 30 minutes. The precipitate was collected by filtration, washed with ethanol and dried under reduced pressure. The remaining material was purified by HPLC (method 2) to give 75 mg (30% of theory) of the title compound.

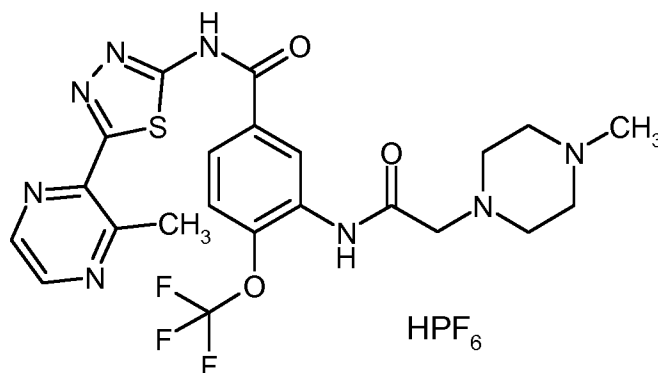
¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 2.55 (s, 3H), 2.70 - 2.81 (m, 4H), 2.82 - 2.97 (m, 4H), 7.63 (dd, 1H), 8.05 (dd, 1H), 8.13 (s, 1H), 8.49 (t, 1H), 8.77 (d, 1H), 8.84 (d, 1H), 9.11 (d, 1H), 9.88 (s, 1H), 11.60 - 12.94 (m, 2H).

15

LC-MS (Method 1): R_t = 0.85 min; MS (ESIpos): m/z = 556 [M-HCO₂H+H]⁺.

Example 41

20 1-methyl-4-(2-[[5-[[5-(3-methylpyrazin-2-yl)-1,3,4-thiadiazol-2-yl]carbonyl]-2-(trifluoromethoxy)phenyl]amino]-2-oxoethyl)piperazin-1-ium hexafluorophosphate



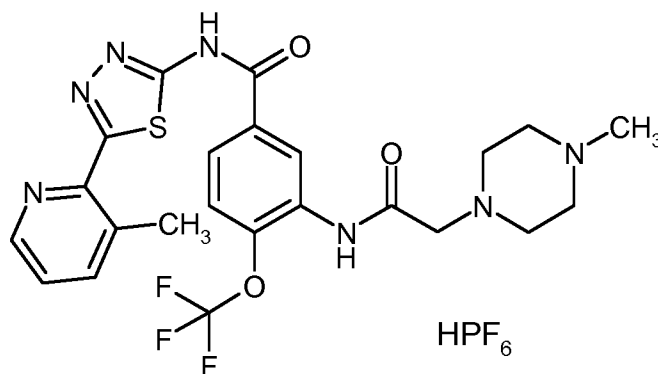
To a solution of the compound of intermediate 35 (150 mg, 0.41 mmol) and intermediate 40 (158 mg, 0.82 mmol, 2 equiv) in DMF (2 mL) was added (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, 425 mg, 0.82 mmol, 2 equiv) and diisopropylethylamine (0.36 mL, 2.04 mmol, 5 equiv). The resulting mixture was stirred at room temperature over night, then concentrated and triturated with water (5 mL) and ethanol (5 mL) and stirred for 30 minutes. The precipitate was collected by filtration and dried under reduced pressure. The remaining material was purified by HPLC (method 2) to give 12.3 mg (4% of theory) of the title compound.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 2.55 - 2.76 (m, 2H), 2.80 (s, 3H), 2.90 - 3.21 (m, 4H), 2.99 (s, 3H), 3.30 - 3.52 (m, 2H), 3.40 (s, 2H), 7.66 (dd, 1H), 8.10 (dd, 1H), 8.61 - 8.78 (m, 3H), 9.85 (s, 1H), 13.38 (s, 1H).

LC-MS (Method 1): R_t = 0.81 min; MS (ESIpos): m/z = 537 [M-HPF₆+H]⁺.

Example 42

1-methyl-4-(2-([5-([5-(3-methylpyridin-2-yl)-1,3,4-thiadiazol-2-yl]carbamoyl)-2-(trifluoromethoxy)phenyl]amino)-2-oxoethyl)piperazin-1-ium hexafluorophosphate



To a solution of the compound of intermediate 35 (150 mg, 0.41 mmol) and intermediate 41 (104 mg, 0.53 mmol, 1.3 equiv) in DMF (2 mL) was added (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, 850 mg, 1.63 mmol, 4 equiv) and diisopropylethylamine (0.39 mL, 2.25 mmol, 5.5 equiv). The resulting mixture was stirred at room temperature over night, then triturated with water and stirred for 15 minutes. The precipitate was collected by filtration and dried under reduced pressure. The remaining material was triturated with ethanol and stirred for 30 minutes.

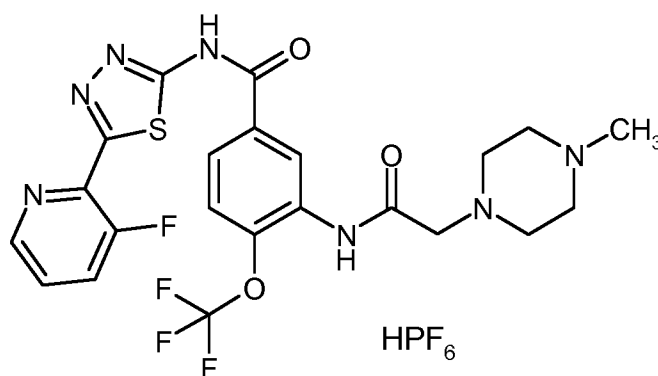
The precipitate was collected by filtration and dried under reduced pressure to give 108 mg (37% of theory) of the title compound.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 2.58 (s, 3H), 2.76 (s, 3H), 7.45 (dd, 1H), 7.65 (dd, 1H), 7.84 - 7.91 (m, 1H), 8.02 - 8.10 (m, 1H), 8.53 - 8.60 (m, 1H), 8.81 (s, 1H), 9.88 (s, 1H).

5 LC-MS (Method 3): R_t = 0.75 min; MS (ESIpos): m/z = 536 [M-HPF₆+H]⁺.

Example 43

4-(2-([5-([5-(3-fluoropyridin-2-yl)-1,3,4-thiadiazol-2-yl]carbamoyl)-2-(trifluoromethoxy)phenyl]amino)-2-oxoethyl)-1-methylpiperazin-1-ium hexafluorophosphate



10

To a solution of the compound of intermediate 35 (150 mg, 0.41 mmol) and intermediate 42 (110 mg, 0.53 mmol, 1.3 equiv) in DMF (2 mL) was added (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, 850 mg, 1.63 mmol, 4 equiv) and diisopropylethylamine (0.39 mL, 2.25 mmol, 5.5 equiv). The resulting mixture was stirred at room temperature over night, then triturated with water and stirred for 30 minutes. The precipitate was collected by filtration and dried under reduced pressure. The remaining material was purified by HPLC (method 2) to give 62.3 mg (21% of theory) of the title compound.

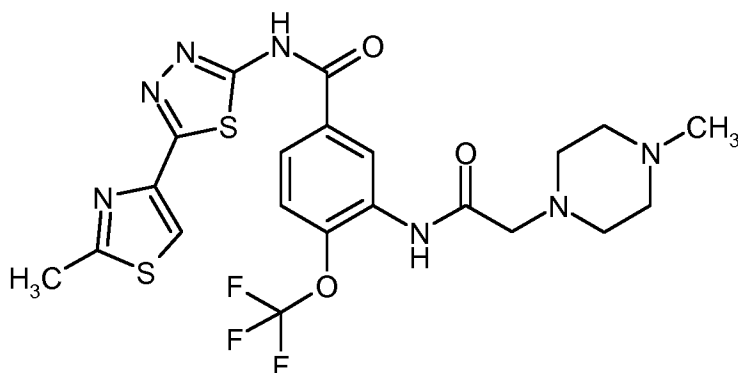
15

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 2.63 - 2.95 (m, 11H), 3.32 (s, 2H), 7.61 - 7.69 (m, 2H), 7.93 - 8.11 (m, 2H), 8.55 - 8.65 (m, 1H), 8.86 (d, 1H), 9.89 (s, 1H), 12.15 (s, 1H).

20 LC-MS (Method 3): R_t = 0.71 min; MS (ESIpos): m/z = 540 [M-HPF₆+H]⁺.

Example 44

3-([(4-methylpiperazin-1-yl)acetyl]amino)-N-[5-(2-methyl-1,3-thiazol-4-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide



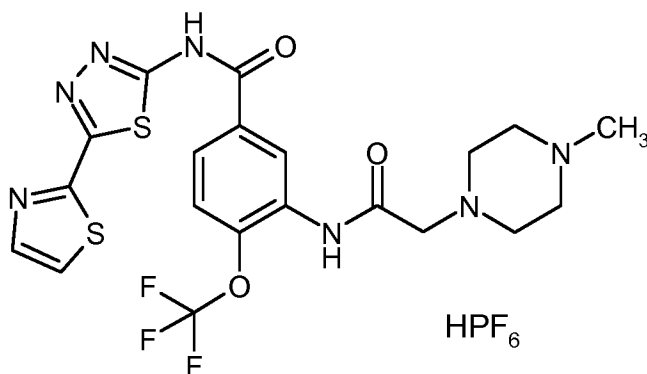
To a solution of the compound of intermediate 35 (150 mg, 0.41 mmol) and intermediate 43 (105 mg, 0.53 mmol, 1.3 equiv) in DMF (3 mL) was added (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, 425 mg, 0.82 mmol, 2 equiv) and diisopropylethylamine (0.29 mL, 1.63 mmol, 4 equiv). The resulting mixture was stirred at room temperature over night, then concentrated and triturated with water (8 mL) and ethanol (3 mL) and stirred for 30 minutes. The precipitate was collected by filtration, washed with ethanol and dried under reduced pressure. The remaining material was purified by HPLC (method 2 and 5) to give 10.3 mg (4% of theory) of the title compound.

$^1\text{H-NMR}$ (600MHz, DMSO-d_6): δ [ppm]= 2.23 (s, 3H), 2.38 - 2.54 (m, 4H), 2.55 - 2.68 (m, 4H), 2.75 (s, 3H), 3.23 (s, 2H), 7.61 (d, 1H), 8.01 (dd, 1H), 8.21 (s, 1H), 8.97 (d, 1H), 9.92 (s, 1H), 13.10 (s, 1H).

LC-MS (Method 3): R_t = 0.71 min; MS (ESIpos): m/z = 542 $[\text{M}+\text{H}]^+$.

Example 45

1-methyl-4-(2-oxo-2-[[5-[[5-(1,3-thiazol-2-yl)-1,3,4-thiadiazol-2-yl]carbonyl]-2-(trifluoromethoxy)phenyl]amino]ethyl)piperazin-1-ium hexafluorophosphate



To a solution of the compound of intermediate 35 (150 mg, 0.41 mmol) and intermediate 44 (98 mg, 0.53 mmol, 1.3 equiv) in DMF (3 mL) was added (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, 425 mg, 0.82 mmol, 2 equiv) and diisopropylethylamine (0.29 mL, 1.63 mmol, 4 equiv). The resulting mixture was stirred at room temperature over night, then concentrated and triturated with water (8 mL) and ethanol (3 mL) and stirred for 30 minutes. The precipitate was collected by filtration, washed with ethanol and dried under reduced pressure. The

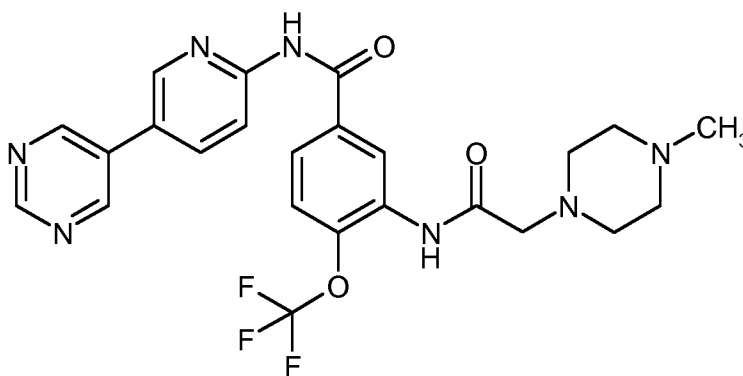
remaining material was triturated with ethanol (3 mL) and stirred under reflux. The precipitate was collected by filtration, washed with ethanol and dried under reduced pressure to give 76.3 mg (35% of theory) of the title compound.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 2.73 (s, 3H), 2.77 - 2.95 (m, 4H), 3.02 - 3.20 (m, 4H), 3.38 (s, 2H), 7.65 (dd, 1H), 8.00 (d, 1H), 8.06 - 8.11 (m, 2H), 8.75 (d, 1H), 9.85 (s, 1H).

LC-MS (Method 4): R_t = 0.87 min; MS (ESIpos): m/z = 528 [M-HPF₆+H]⁺.

Example 46

3-[[[4-methylpiperazin-1-yl)acetyl]amino]-N-[5-(pyrimidin-5-yl)pyridin-2-yl]-4-(trifluoromethoxy)benzamide



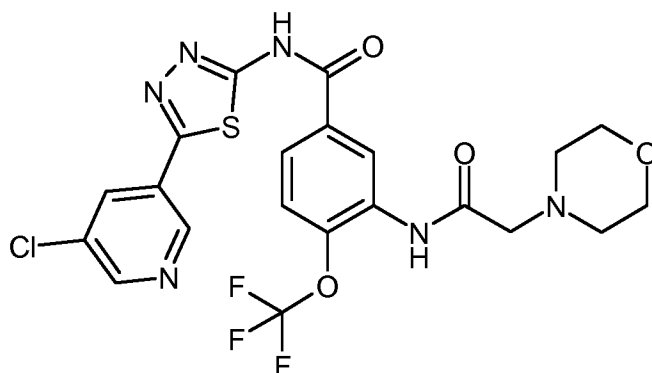
To a solution of the compound of intermediate 14 (150 mg, 0.32 mmol) and 5-(pyrimidin-5-yl)pyridin-2-amine (111 mg, 0.64 mmol, 2 equiv) in DMF (2 mL) was added (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, 334 mg, 0.64 mmol, 2 equiv) and diisopropylethylamine (0.28 mL, 1.60 mmol, 5 equiv). The resulting mixture was stirred at room temperature over night. (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, 334 mg, 0.64 mmol, 2 equiv) and diisopropylethylamine (0.28 mL, 1.60 mmol, 5 equiv) were added and the resulting mixture was stirred at room temperature for 3 days, then filtered, concentrated and purified by HPLC (method 5) to give 14.0 mg (8% of theory) of the title compound.

¹H-NMR (300MHz, DMSO-d₆): δ [ppm]= 2.18 (s, 3H), 2.29 - 2.49 (m, 4H), 2.54 - 2.65 (m, 4H), 3.21 (s, 2H), 7.60 (dd, 1H), 7.90 (dd, 1H), 8.29 - 8.38 (m, 2H), 8.86 - 8.93 (m, 2H), 9.20 - 9.28 (m, 3H), 9.93 (s, 1H), 11.21 (s, 1H).

LC-MS (Method 3): R_t = 1.06 min; MS (ESIpos): m/z = 516 [M+H]⁺.

Example 47

N-[5-(5-chloropyridin-3-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide



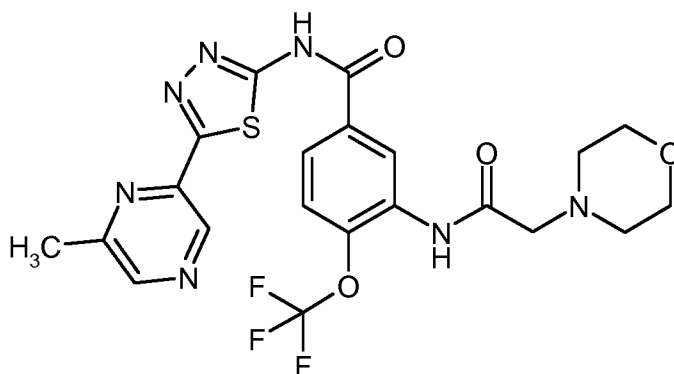
To a solution of the compound of intermediate 46 (150 mg, 0.39 mmol) and intermediate 39 (107 mg, 0.50 mmol, 1.3 equiv) in DMF (3 mL) was added (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, 303 mg, 0.58 mmol, 1.5 equiv) and diisopropylethylamine (0.27 mL, 1.55 mmol, 4 equiv). The resulting mixture was stirred at room temperature over night, then concentrated and the remaining material was triturated with water (8 mL) and ethanol (3 mL) and stirred for 30 minutes. The precipitate was collected by filtration, washed with ethanol and dried under reduced pressure. The remaining material was purified by HPLC (method 2) to give 12.5 mg (6% of theory) of the title compound.

$^1\text{H-NMR}$ (400MHz, DMSO-d_6): δ [ppm]= 2.56 - 2.63 (m, 4H), 3.24 (s, 2H), 3.62 - 3.69 (m, 4H), 7.61 (d, 1H), 8.03 (dd, 1H), 8.46 (s, 1H), 8.74 (d, 1H), 8.96 (d, 1H), 9.08 (s, 1H), 9.90 (s, 1H), 13.60 (s, 1H).

LC-MS (Method 4): R_t = 1.06 min; MS (ESIpos): m/z = 543 $[\text{M}+\text{H}]^+$.

Example 48

N-[5-(6-methylpyrazin-2-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide



To a solution of the compound of intermediate 46 (150 mg, 0.43 mmol) and intermediate 47 (166 mg, 0.86 mmol, 2 equiv) in DMF (2 mL) was added (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, 448 mg, 0.86 mmol, 2 equiv) and diisopropylethylamine (0.38 mL, 2.15 mmol, 5 equiv). The resulting mixture was stirred at room temperature over night, then concentrated and the remaining material was triturated with water (5 mL) and ethanol (5 mL) and stirred for 10 minutes. The precipitate was collected by filtration, washed with ethanol and dried

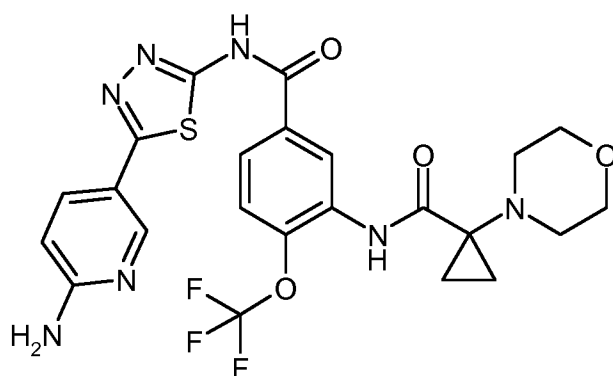
under reduced pressure. The remaining material was purified by HPLC (method 2) to give 21.0 mg (9% of theory) of the title compound.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 2.55 - 2.64 (m, 4H), 2.99 (s, 3H), 3.25 (s, 2H), 3.60 - 3.70 (m, 4H), 7.66 (dd, 1H), 8.04 (dd, 1H), 8.66 (s, 2H), 8.94 (d, 1H), 9.94 (s, 1H), 13.46 (s, 1H).

5 LC-MS (Method 4): R_t = 1.03 min; MS (ESIpos): m/z = 524 [M+H]⁺.

Example 49

N-[5-(6-aminopyridin-3-yl)-1,3,4-thiadiazol-2-yl]-3-({[1-(morpholin-4-yl)cyclopropyl]carbonyl}amino)-4-(trifluoromethoxy)benzamide



10

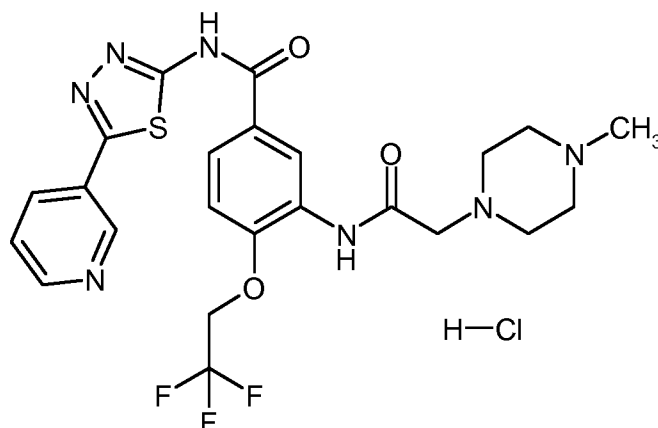
To a microwave vial was added the compound of intermediate 7 (95.0 mg, 0.18 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (78.0 mg, 0.35 mmol, 2 equiv), cesium carbonate (115 mg, 0.35 mmol, 2 equiv) and a DMF / water mixture (2:1, 4.5 mL). The resulting suspension was purged with argon, treated with dichloro[bis(triphenylphosphoranyl)]palladium
 15 (Pd(PPh₃)₂Cl₂, 6.2 mg, 0.09 mmol, 5 mol%) and sealed. The resulting mixture was heated with a microwave apparatus at 100 °C for 0.25 h, was then cooled to room temperature. The reaction mixture was filtered and purified by HPLC (column: chromatorex C18, mobile phase: acetonitrile/water + 0.1% ammonia). 38.0 mg (35% of theory) of the title compound were obtained.

20 ¹H-NMR (600MHz, DMSO-d₆): δ [ppm]= 1.15 - 1.18 (m, 2H), 1.23 - 1.26 (m, 2H), 2.45 - 2.48 (m, 4H), 3.67 - 3.72 (m, 4H), 6.23 (s, 2H), 6.50 (d, 1H), 7.42 (dd, 1H), 7.83 (dd, 1H), 7.94 (dd, 1H), 8.32 - 8.34 (m, 1H), 9.05 (d, 1H), 10.39 (s, 1H).

LC-MS (Method 3): R_t = 0.71 min; MS (ESIpos): m/z = 550 [M+H]⁺.

Example 50

25 3-{[(4-methylpiperazin-1-yl)acetyl]amino}-N-[5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl]-4-(2,2,2-trifluoroethoxy)benzamide hydrochloride (1:1)



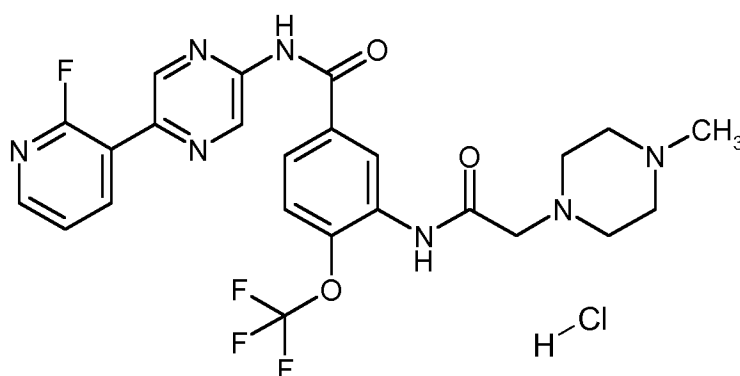
To a solution of the compound of intermediate 52 (150 mg, 0.22 mmol) and 5-(pyridin-3-yl)-1,3,4-thiadiazol-2-amine (51.0 mg, 0.28 mmol, 1.3 equiv) in DMF (3 mL) was added (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, 227 mg, 0.44 mmol, 2 equiv) and diisopropylethylamine (0.15 mL, 0.87 mmol, 4 equiv). The resulting mixture was stirred at room temperature for 2 days, then concentrated and triturated with water (8 mL) and ethanol (3 mL) and stirred for 30 minutes. The precipitate was collected by filtration, washed with ethanol and dried under reduced pressure. The remaining material was triturated with ethanol (4 mL) and stirred under reflux. After cooling to room temperature the precipitate was collected by filtration, washed with ethanol and dried under reduced pressure. The remaining material was triturated with ethanol (3 mL) and stirred under reflux. The precipitate was collected by filtration at 40 °C, washed with ethanol and dried under reduced pressure to give 42.6 mg (33% of theory) of the title compound.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 2.57 - 2.73 (m, 2H), 2.78 (s, 3H), 2.83 - 3.13 (m, 4H), 3.35 (s, 2H), 3.36 - 3.60 (m, 2H), 5.05 (q, 2H), 7.40 (d, 1H), 7.59 (ddd, 1H), 8.06 (dd, 1H), 8.37 (dt, 1H), 8.72 (dd, 1H), 8.90 (d, 1H), 9.17 (d, 1H), 9.55 (s, 1H), 9.62 (s, 1H), 13.2 (s, 1H).

LC-MS (Method 4): R_t = 0.77 min; MS (ESIpos): m/z = 536 [M-HCl+H]⁺.

Example 51

N-[5-(2-fluoropyridin-3-yl)pyrazin-2-yl]-3-[[4-methylpiperazin-1-yl]acetyl]amino-4-(trifluoromethoxy)benzamide hydrochloride (1:1)



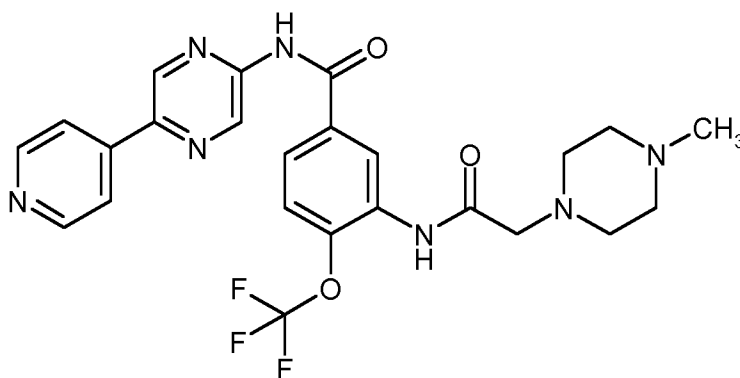
50 mg (0.10 mmol) of N-(5-bromopyrazin-2-yl)-3-[[4-methylpiperazin-1-yl]acetyl]amino-4-(trifluoromethoxy)benzamide (intermediate 57), 18.4 mg (0.13 mmol) of (2-fluoropyridin-3-yl)boronic acid, 19.4 mg (0.14 mmol) of potassium carbonate and 11.2 mg (9.67 μ mol) of tetrakis(triphenylphosphine)palladium(0) in 1.5 mL of anhydrous DMF were stirred for 2.5 h at 95 °C. 18 mg (0.13 mmol) of (2-fluoropyridin-3-yl)boronic acid and 10 mg (12.2 μ mol) of 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride-dichloromethane-complex were added and it was stirred for 8 h at 100 °C. 18 mg (0.13 mmol) of (2-fluoropyridin-3-yl)boronic acid and 19 mg (0.14 mmol) of potassium carbonate were added and it was stirred for 4 h at 100 °C. The reaction mixture was allowed to reach rt and concentrated under vacuum. The residue was purified by HPLC (method 5) and chiral HPLC (Chiralpak IC 5 μ m, 250 x 30 mm, acetonitrile/N-ethylethanamine 1000 : 1, 50 mL/min) giving 5 mg (9%) of the title compound.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm] = 2.57 - 3.19 (m, 11H), 3.38 (br. s, 2H), 7.56 - 7.66 (m, 2H), 8.01 (dd, 1H), 8.35 - 8.39 (m, 1H), 8.53 - 8.59 (m, 1H), 8.66 (br. s, 1H), 8.94 - 8.98 (m, 1H), 9.45 (br. s, 1H), 9.55 - 9.59 (m, 1H), 9.85 (s, 1H), 11.54 (s, 1H).

LC-MS (Method 4): R_t = 0.69 min; MS (ESIpos): m/z = 534 [M-HCl+H]⁺.

Example 52

3-[[4-methylpiperazin-1-yl]acetyl]amino-N-[5-(pyridin-4-yl)pyrazin-2-yl]-4-(trifluoromethoxy)benzamide



20

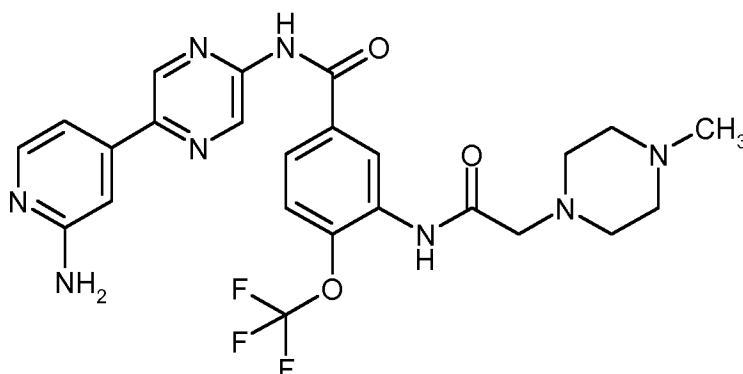
60 mg (0.12 mmol) of N-(5-bromopyrazin-2-yl)-3-[[4-methylpiperazin-1-yl]acetyl]amino-4-(trifluoromethoxy)benzamide (intermediate 57), 35.7 mg (0.17 mmol) of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine, 32.1 mg (0.23 mmol) of potassium carbonate and 4.74 mg (5.80 μ mol) of 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride-dichloromethane-complex in 0.1 mL of DMF, 0.4 mL of water and 0.55 mL of DME were stirred for 3 h at 95 °C. The reaction mixture was allowed to reach rt and concentrated. The residue was purified by HPLC (method 5) to yield 19.6 mg (31%) of the title compound.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm] = 2.19 (s, 3H), 2.31 - 2.47 (br. s, 4H), 2.54 - 2.65 (br. s, 4H), 3.22 (s, 2H), 7.62 - 7.66 (m, 1H), 7.93 (dd, 1H), 8.10 - 8.14 (m, 2H), 8.72 - 8.76 (m, 2H), 8.94 (d, 1H), 9.25 (d, 1H), 9.55 (d, 1H), 9.95 (s, 1H), 11.54 (s, 1H).

LC-MS (Method 3): R_t = 1.11 min; MS (ESIpos): m/z = 516 [M+H]⁺.

Example 53

N-[5-(2-aminopyridin-4-yl)pyrazin-2-yl]-3-[[4-methylpiperazin-1-yl]acetyl]amino}-4-(trifluoromethoxy)benzamide



5

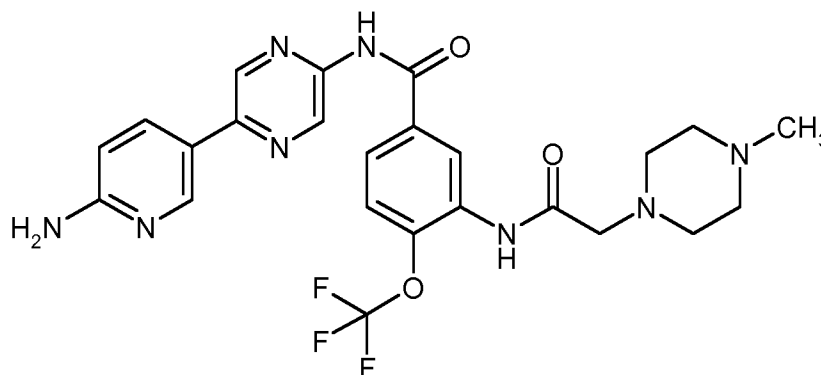
80 mg (0.15 mmol) of N-(5-bromopyrazin-2-yl)-3-[[4-methylpiperazin-1-yl]acetyl]amino}-4-(trifluoromethoxy)benzamide (intermediate 57), 51.1 mg (0.23 mmol) of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine, 42.8 mg (0.31 mmol) of potassium carbonate and 6.3 mg (7.71 μ mol) of 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride-dichloromethane-complex in 0.13 mL of DMF, 0.53 mL of water and 0.73 mL of DME were stirred for 5 h at 95 °C. 51 mg (0.23 mmol) of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine were added it was stirred for 2 h at 95 °C. The reaction mixture was allowed to reach rt and concentrated. The residue was purified by HPLC (method 5) to obtain 38 mg (46%) of the title compound.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm] = 2.19 (s, 3H), 2.40 (br. s, 4H), 2.60 (br. s, 4H), 3.22 (s, 2H), 6.10 (s, 2H), 7.17 - 7.21 (m, 2H), 7.61 - 7.65 (m, 1H), 7.93 (dd, 1H), 8.04 - 8.06 (m, 1H), 8.94 (d, 1H), 9.03 (d, 1H), 9.50 (d, 1H), 9.95 (s, 1H), 11.48 (s, 1H).

LC-MS (Method 3): R_t = 1.05 min; MS (ESIpos): m/z = 531 [M+H]⁺.

Example 54

N-[5-(6-aminopyridin-3-yl)pyrazin-2-yl]-3-[[4-methylpiperazin-1-yl]acetyl]amino}-4-(trifluoromethoxy)benzamide



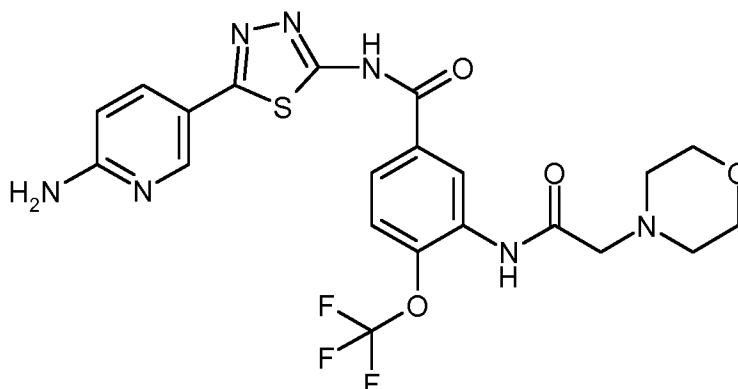
80 mg (0.15 mmol) of N-(5-bromopyrazin-2-yl)-3-[[4-(4-methylpiperazin-1-yl)acetyl]amino]-4-(trifluoromethoxy)benzamide (intermediate 57), 51.1 mg (0.23 mmol) of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine, 42.8 mg (0.31 mmol) of potassium carbonate and 6.3 mg (7.71 μ mol) of 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride-dichloromethane-complex in 0.13 mL of DMF, 0.53 mL of water and 0.73 mL of DME were stirred for 1 h at 95 °C. The reaction mixture was allowed to reach rt and concentrated. The residue was purified by HPLC (method 5) giving 41 mg (48%) of the title compound.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm] = 2.19 (s, 3H), 2.40 (br. s, 4H), 2.60 (br. s, 4H), 3.22 (s, 2H), 6.37 (s, 2H), 6.56 (d, 1H), 7.60 - 7.64 (m, 1H), 7.92 (dd, 1H), 8.11 (dd, 1H), 8.71 (d, 1H), 8.93 (dd, 2H), 9.36 (d, 1H), 9.94 (s, 1H), 11.27 (s, 1H).

LC-MS (Method 3): R_t = 1.05 min; MS (ESIpos): m/z = 531 [M+H]⁺.

Example 55

N-[5-(6-aminopyridin-3-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide



To a solution of the compound of intermediate 46 (150 mg, 0.39 mmol) and intermediate 37 (162 mg, 0.50 mmol, 1.3 equiv) in DMF (3 mL) was added (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, 303 mg, 0.58 mmol, 1.5 equiv) and diisopropylethylamine (0.27 mL, 1.55 mmol, 4 equiv). The resulting mixture was stirred at room temperature over night.

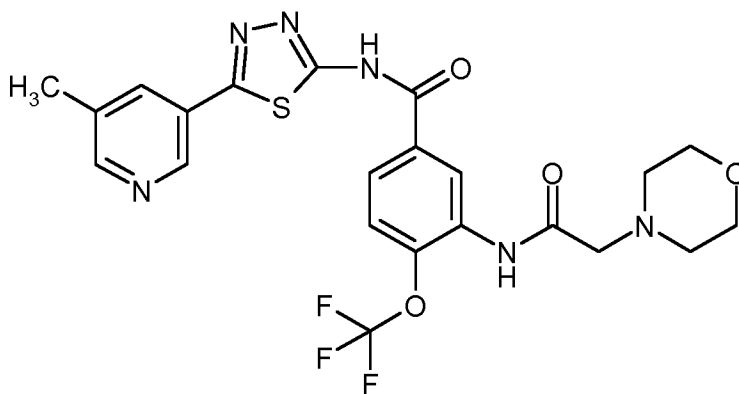
(Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, 303 mg, 0.58 mmol, 1.5 equiv) and diisopropylethylamine (0.27 mL, 1.55 mmol, 4 equiv) were added and the resulting mixture was stirred at room temperature for 6 hours, then concentrated and triturated with water (3 mL) and ethanol (2 mL) and stirred for 30 minutes. The precipitate was collected by filtration, washed with ethanol and dried under reduced pressure. The remaining material was purified by HPLC (column: chromatorex C18, mobile phase: acetonitrile/water + 0.1% ammonia). The remaining material was triturated with ethanol (2 mL). The precipitate was collected by filtration, washed with ethanol and dried under reduced pressure to give 26.7 mg (13% of theory) of the title compound.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 2.56 - 2.60 (m, 4H), 3.23 (s, 2H), 3.61 - 3.69 (m, 4H), 6.51 - 6.62 (m, 3H), 7.63 (dd, 1H), 7.92 (dd, 1H), 8.00 (dd, 1H), 8.47 (d, 1H), 8.93 (d, 1H), 9.92 (s, 1H), 13.32 (s, 1H).

LC-MS (Method 3): R_t = 0.64 min; MS (ESIpos): m/z = 524 [M+H]⁺.

Example 56

N-[5-(5-methylpyridin-3-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide



To a solution of the compound of intermediate 46 (150 mg, 0.39 mmol) and intermediate 38 (97.0 mg, 0.50 mmol, 1.3 equiv) in DMF (3 mL) was added (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, 303 mg, 0.58 mmol, 1.5 equiv) and diisopropylethylamine (0.27 mL, 1.55 mmol, 4 equiv). The resulting mixture was stirred at room temperature over night. (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, 303 mg, 0.58 mmol, 1.5 equiv) and diisopropylethylamine (0.27 mL, 1.55 mmol, 4 equiv) were added and the resulting mixture was stirred at room temperature for 2 days, then concentrated and triturated with water (8 mL) and ethanol (3 mL) and stirred for 30 minutes. The precipitate was collected by filtration, washed with ethanol and dried under reduced pressure. The remaining material was triturated with ethanol (3 mL) and stirred under reflux. After cooling to room temperature the precipitate was collected by filtration, washed with ethanol and dried under reduced pressure to give 125 mg (59% of theory) of the title compound.

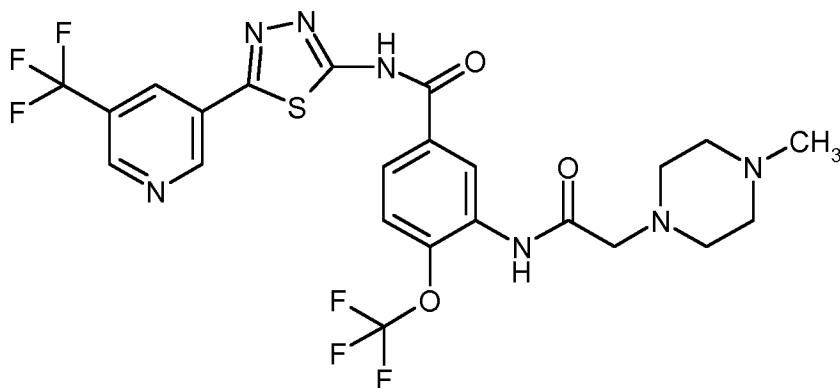
¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 2.41 (s, 3H), 2.56 - 2.61 (m, 4H), 3.24 (s, 2H), 3.63 - 3.69 (m, 4H), 7.59 - 7.69 (m, 1H), 8.03 (dd, 1H), 8.20 (s, 1H), 8.55 (s, 1H), 8.92 - 8.99 (m, 2H), 9.92 (s, 1H), 13.50 (s, 1H).

LC-MS (Method 4): R_t = 0.97 min; MS (ESIpos): m/z = 523 [M+H]⁺.

5

Example 57

3-[[[4-methylpiperazin-1-yl]acetyl]amino]-4-(trifluoromethoxy)-N-{5-[5-(trifluoromethyl)pyridin-3-yl]-1,3,4-thiadiazol-2-yl}benzamide



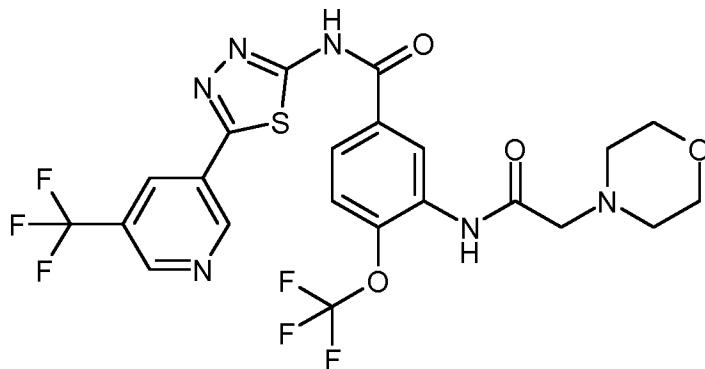
- 10 To a solution of the compound of intermediate 35 (229 mg, 0.63 mmol) and intermediate 53 (200 mg, 0.81 mmol, 1.3 equiv) in DMF (4 mL) was added (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, 650 mg, 1.25 mmol, 2 equiv) and diisopropylethylamine (0.44 mL, 2.50 mmol, 4 equiv). The resulting mixture was stirred at room temperature over night. (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, 650 mg, 1.25 mmol, 2 equiv) and
- 15 diisopropylethylamine (0.44 mL, 2.50 mmol, 4 equiv) were added and the resulting mixture was stirred at room temperature over night, then concentrated and triturated with water (11 mL) and ethanol (5 mL) and stirred for 30 minutes. The precipitate was collected by filtration, washed with ethanol and dried under reduced pressure. The remaining material was triturated with ethanol (3 mL) and stirred under reflux. After cooling to room temperature the precipitate was collected by
- 20 filtration, washed with ethanol and dried under reduced pressure. The remaining material was purified by HPLC (column: chromatorex C18, mobile phase: acetonitrile/water) to give 45.6 mg (12% of theory) of the title compound.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 2.38 (s, 3H), 2.55 - 2.80 (m, 8H), 3.27 (s, 2H), 7.58 (dd, 1H), 8.03 (dd, 1H), 8.64 (s, 1H), 8.93 (d, 1H), 9.04 - 9.09 (m, 1H), 9.39 (d, 1H), 9.87 (s, 1H).

- 25 LC-MS (Method 1): R_t = 0.93 min; MS (ESIpos): m/z = 590 [M+H]⁺.

Example 58

3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)-N-{5-[5-(trifluoromethyl)pyridin-3-yl]-1,3,4-thiadiazol-2-yl}benzamide



To a solution of the compound of intermediate 46 (150 mg, 0.43 mmol) and intermediate 53 (212 mg, 0.86 mmol, 2 equiv) in DMF (2 mL) was added (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, 448 mg, 0.86 mmol, 2 equiv) and diisopropylethylamine (0.38 mL, 2.15 mmol, 5 equiv). The resulting mixture was stirred at room temperature for 3 days, then triturated with water (10 mL) and ethanol (10 mL) and stirred for 10 minutes. The precipitate was collected by filtration, washed with ethanol and dried under reduced pressure. The remaining material was purified by HPLC (column: chromatorex C18, mobile phase: acetonitrile/water + 0.1% formic acid) to give 9.0 mg (4% of theory) of the title compound.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 2.56 - 2.63 (m, 4H), 3.25 (s, 2H), 3.62 - 3.69 (m, 4H), 7.67 (dd, 1H), 8.04 (dd, 1H), 8.73 (s, 1H), 8.96 (d, 1H), 9.13 (d, 1H), 9.47 (d, 1H), 9.95 (s, 1H), 13.56 (s, 1H).

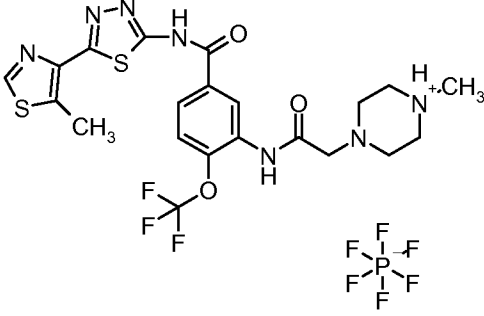
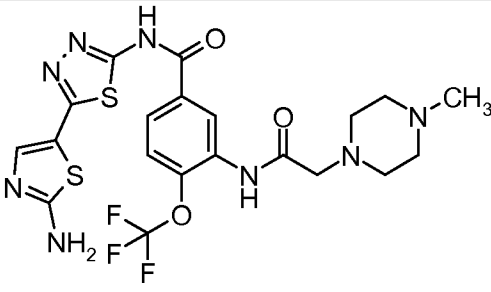
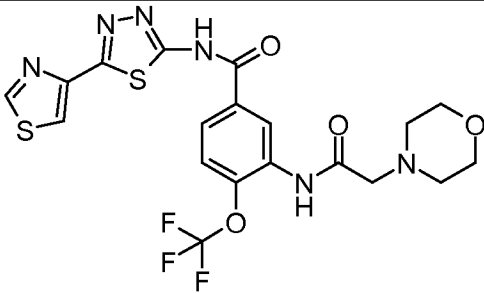
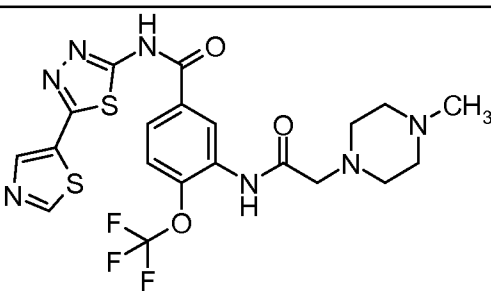
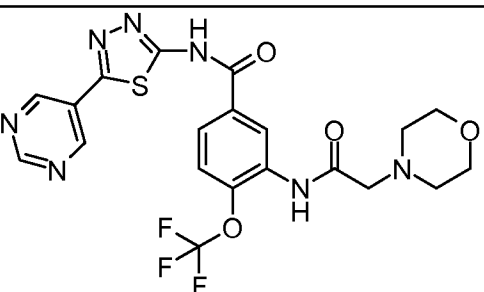
LC-MS (Method 4): R_t = 1.13 min; MS (ESIpos): m/z = 577 [M+H]⁺.

The following examples were prepared in analogy to the described methods, *supra*.

Table 2

Example No	Structure	IUPAC Name	R _t [min] method
59		N-(5'-amino-2,2'-bipyrazin-5-yl)-3-[[4-methylpiperazin-1-yl]acetyl]amino-4-(trifluoromethoxy)benzamide	1.043

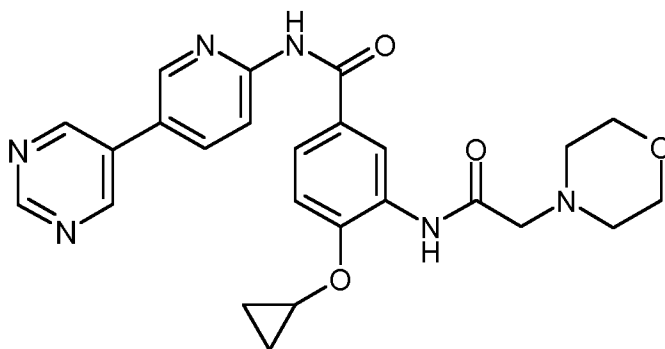
Example No	Structure	IUPAC Name	R _t [min] method
60		4-(cyclopropyloxy)-3-[[[(4-methylpiperazin-1-yl)acetyl]amino]-N-[5-(pyrazin-2-yl)-1,3,4-thiadiazol-2-yl]benzamide	0.81 4
61		3-[[[(4-methylpiperazin-1-yl)acetyl]amino]-N-[5-(4-methylpyridin-3-yl)-1,3,4-thiadiazol-2-yl]-4-(2,2,2-trifluoroethoxy)benzamide	0.70 3
62		3-[[[(4-methylpiperazin-1-yl)acetyl]amino]-N-[5-(4-methylpyridin-2-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide	0.73 3
63		3-[[[(4-methylpiperazin-1-yl)acetyl]amino]-N-[5-(4-methyl-1,3-thiazol-2-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide	0.96 4
64		3-[[[(4-methylpiperazin-1-yl)acetyl]amino]-N-[5-(1,3-thiazol-4-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide	0.68 3

Example No	Structure	IUPAC Name	R _t [min] method
65		1-methyl-4-(2-([5-([5-(5-methyl-1,3-thiazol-4-yl)-1,3,4-thiadiazol-2-yl]carbonyl)-2-(trifluoromethoxy)phenyl]amino)-2-oxoethyl)piperazin-1-ium hexafluorophosphate	0.84 1
66		N-[5-(2-amino-1,3-thiazol-5-yl)-1,3,4-thiadiazol-2-yl]-3-[[4-methylpiperazin-1-yl]acetyl]amino-4-(trifluoromethoxy)benzamide	0.66 3
67		3-[(morpholin-4-ylacetyl)amino]-N-[5-(1,3-thiazol-4-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide	0.67 3
68		3-[[4-methylpiperazin-1-yl]acetyl]amino-N-[5-(1,3-thiazol-5-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide	0.67 3
69		3-[(morpholin-4-ylacetyl)amino]-N-[5-(pyrimidin-5-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide	0.87 4

Example No	Structure	IUPAC Name	R _t [min] method
70		3-[[4-(4-methylpiperazin-1-yl)acetyl]amino]-4-(trifluoromethoxy)-N-{5-[4-(trifluoromethyl)pyridin-3-yl]-1,3,4-thiadiazol-2-yl}benzamide	0.79 3
71		N-[5-(4-methylpyridin-3-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide	0.67 3
72		4-(cyclopropyloxy)-3-[(morpholin-4-ylacetyl)amino]-N-[5-(pyrimidin-5-yl)-1,3,4-thiadiazol-2-yl]benzamide	0.64 3
73		4-(2-methoxyethoxy)-3-[[4-(4-methylpiperazin-1-yl)acetyl]amino]-N-[5-(4-methylpyridin-3-yl)-1,3,4-thiadiazol-2-yl]benzamide	0.60 3
74		4-(3-methoxypropoxy)-N-[5-(4-methylpyridin-3-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]benzamide	0.71 3

Example 75

4-(cyclopropyloxy)-3-[(morpholin-4-ylacetyl)amino]-N-[5-(pyrimidin-5-yl)pyridin-2-yl]benzamide



Step 1: 5 mL of thionyl chloride were added to 845 mg (2.64 mmol) of 4-(cyclopropyloxy)-3-[(morpholin-4-ylacetyl)amino]benzoic acid (intermediate 62) in 8.5 mL of anhydrous toluene. It was stirred for 1.5 h at 70 °C. The reaction mixture was concentrated to afford 950 mg of 4-(cyclopropyloxy)-3-[(morpholin-4-ylacetyl)amino]benzoyl chloride which was used without further purification in the next step.

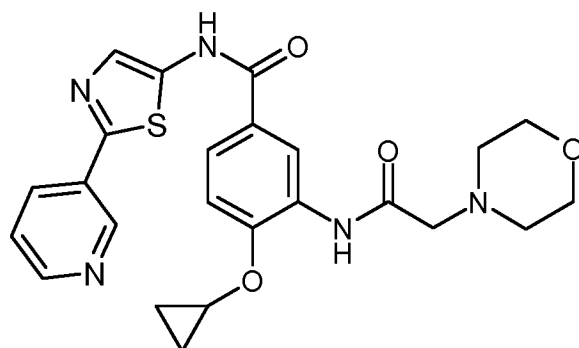
Step 2: 130 mg (0.38 mmol) of 4-(cyclopropyloxy)-3-[(morpholin-4-ylacetyl)amino]benzoyl chloride were suspended in 3.3 mL of anhydrous toluene. 1 mL of anhydrous pyridine and 86 mg (0.50 mmol) of 5-(pyrimidin-5-yl)pyridin-2-amine were added and it was stirred for 5 h at 100 °C and at rt overnight. The reaction mixture was concentrated and purified by HPLC (method 5) to yield 30 mg (16% of theory) of the title compound.

¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 0.756 (0.61), 0.762 (0.76), 0.769 (1.82), 0.775 (2.95), 0.781 (2.04), 0.786 (1.41), 0.794 (0.82), 0.907 (0.70), 0.922 (2.41), 0.927 (1.76), 0.936 (1.94), 0.940 (2.05), 0.942 (1.96), 0.956 (0.48), 2.323 (0.42), 2.327 (0.57), 2.523 (1.69), 2.545 (3.11), 2.557 (4.40), 2.568 (3.28), 2.665 (0.44), 2.669 (0.59), 2.674 (0.42), 3.164 (9.28), 3.657 (3.43), 3.669 (4.68), 3.680 (3.35), 4.105 (0.74), 4.113 (1.07), 4.120 (1.43), 4.127 (1.04), 4.135 (0.72), 7.417 (2.99), 7.439 (3.15), 7.894 (1.78), 7.899 (1.77), 7.915 (1.59), 7.921 (1.63), 8.325 (3.49), 8.330 (7.19), 8.333 (4.18), 8.351 (0.45), 8.848 (3.18), 8.854 (3.17), 8.862 (2.52), 8.867 (3.00), 8.871 (2.28), 9.211 (7.08), 9.236 (16.00), 9.691 (2.82), 10.890 (3.49).

LC-MS (Method 3): R_t = 1.01 min; MS (ESIpos): m/z = 475 [M+H]⁺.

Example 76

4-(cyclopropyloxy)-3-[(morpholin-4-ylacetyl)amino]-N-[2-(pyridin-3-yl)-1,3-thiazol-5-yl]benzamide



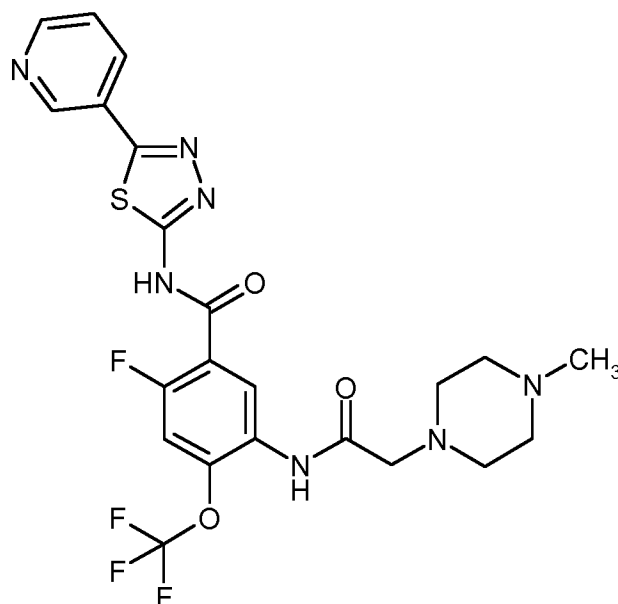
140 mg (0.39 mmol) of 4-(cyclopropyloxy)-3-[(morpholin-4-ylacetyl)amino]benzoic acid (intermediate 62) were suspended in 4 mL of anhydrous toluene. 118 mg (0.47 mmol) of 2-(pyridin-3-yl)-1,3-thiazol-5-amine dihydrochloride and 1 mL of anhydrous pyridine were added and it was stirred for 5 h at 100 °C and at rt over night. The reaction mixture was concentrated and purified by HPLC (method 5) affording 73 mg (39% of theory) of the title compound.

¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 0.763 (0.84), 0.770 (1.05), 0.776 (2.74), 0.782 (4.42), 0.789 (3.16), 0.793 (2.11), 0.801 (1.26), 0.910 (1.05), 0.925 (3.79), 0.930 (2.53), 0.939 (2.95), 0.943 (3.16), 0.945 (3.16), 0.960 (0.63), 1.232 (0.63), 1.907 (1.47), 2.069 (2.11), 2.317 (0.63), 2.322 (1.05), 2.327 (1.47), 2.332 (1.05), 2.336 (0.42), 2.523 (4.21), 2.547 (5.05), 2.559 (6.74), 2.571 (5.26), 2.660 (0.42), 2.665 (1.05), 2.669 (1.47), 2.674 (1.05), 2.679 (0.42), 3.131 (0.42), 3.171 (16.00), 3.264 (0.42), 3.275 (0.63), 3.290 (1.05), 3.297 (1.05), 3.366 (3.16), 3.382 (0.84), 3.657 (5.68), 3.669 (7.37), 3.679 (5.47), 4.107 (0.63), 4.114 (1.26), 4.122 (1.68), 4.130 (2.32), 4.137 (1.68), 4.145 (1.26), 4.152 (0.63), 7.494 (6.95), 7.507 (2.53), 7.509 (1.89), 7.516 (7.37), 7.528 (2.32), 7.821 (2.95), 7.827 (2.95), 7.843 (2.53), 7.848 (2.74), 7.867 (16.00), 8.063 (0.42), 8.235 (2.11), 8.239 (2.53), 8.244 (2.11), 8.254 (1.89), 8.260 (2.32), 8.264 (2.11), 8.598 (3.58), 8.602 (3.79), 8.610 (3.58), 8.614 (3.58), 8.845 (5.26), 8.850 (5.26), 9.088 (4.21), 9.090 (4.21), 9.094 (4.21), 9.096 (4.00), 9.717 (4.42), 11.859 (1.47).

LC-MS (Method 3): R_t = 0.96 min; MS (ESIpos): m/z = 480 [M+H]⁺.

Example 77

2-fluoro-5-[[[4-methylpiperazin-1-yl]acetyl]amino]-N-[5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide



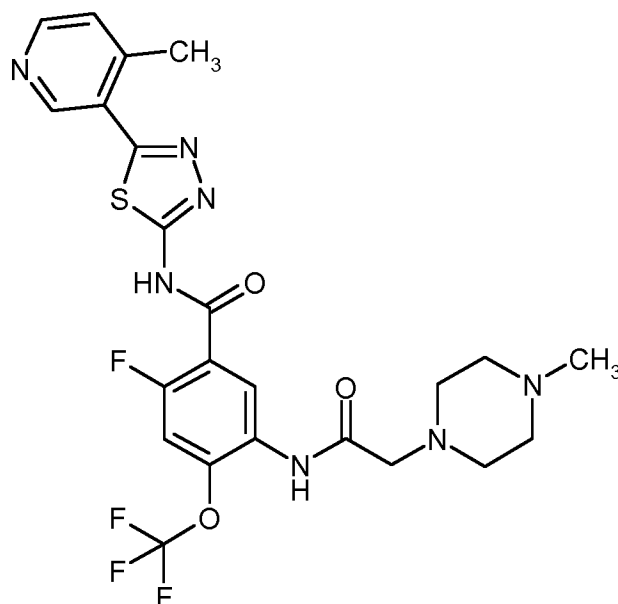
To a solution of the compound of intermediate 66 (150 mg, 0.36 mmol) and of 5-(pyridin-3-yl)-1,3,4-thiadiazol-2-amine (96.4 mg, 0.54 mmol, 1.5 equiv) in DMF (2 mL) was added (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, 376 mg, 0.72 mmol, 2 equiv) and diisopropylethylamine (0.31 mL, 1.80 mmol, 5 equiv). The resulting mixture was stirred at room temperature over night, then filtered, concentrated and purified by HPLC (method 5) to give 28.8 mg (14% of theory) of the title compound.

¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 1.235 (0.56), 1.251 (0.51), 1.907 (0.72), 2.322 (0.89), 2.326 (1.36), 2.340 (16.00), 2.523 (2.79), 2.539 (0.92), 2.645 (3.70), 2.664 (2.72), 2.669 (2.52), 2.674 (1.98), 3.240 (13.57), 7.545 (2.05), 7.557 (2.12), 7.559 (1.99), 7.565 (2.08), 7.577 (2.16), 7.625 (1.87), 7.629 (1.88), 7.651 (1.94), 7.654 (1.72), 8.313 (1.81), 8.317 (2.53), 8.323 (1.76), 8.332 (1.68), 8.337 (2.29), 8.343 (1.67), 8.553 (3.02), 8.571 (3.09), 8.669 (3.20), 8.673 (3.00), 8.681 (3.19), 8.685 (2.90), 9.124 (3.79), 9.130 (3.64), 9.842 (4.37).

LC-MS (Method 3): R_t = 0.71 min; MS (ESIpos): m/z = 540 [M+H]⁺.

Example 78

2-fluoro-5-[[[4-methylpiperazin-1-yl]acetyl]amino]-N-[5-(4-methylpyridin-3-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide



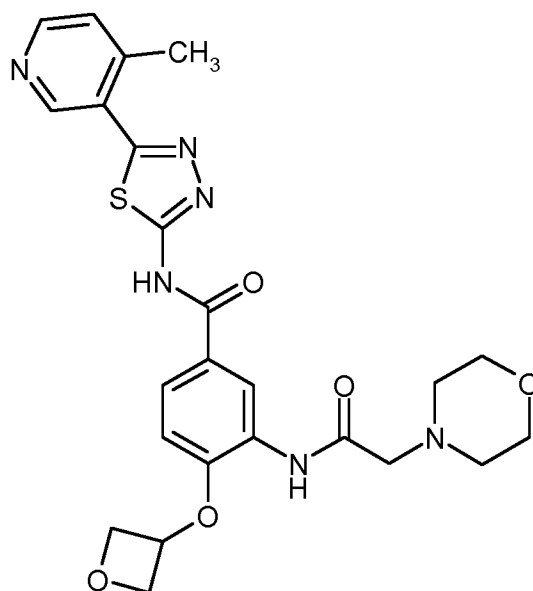
To a solution of the compound of intermediate 66 (150 mg, 0.36 mmol) and of intermediate 36 (104 mg, 0.54 mmol, 1.5 equiv) in DMF (2 mL) was added (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, 376 mg, 0.72 mmol, 2 equiv) and diisopropylethylamine (0.31 mL, 1.80 mmol, 5 equiv). The resulting mixture was stirred at room temperature over night, then filtered, concentrated and purified by HPLC (method 5) to give 13.5 mg (7% of theory) of the title compound.

¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 1.232 (0.74), 1.248 (0.73), 1.907 (0.59), 2.278 (0.92), 2.296 (9.99), 2.310 (0.96), 2.322 (0.56), 2.326 (0.68), 2.331 (0.49), 2.522 (2.48), 2.539 (1.32), 2.558 (16.00), 2.571 (2.02), 2.628 (2.14), 2.664 (0.97), 2.669 (1.04), 2.674 (0.82), 3.229 (8.84), 7.441 (2.07), 7.453 (2.12), 7.644 (1.13), 7.648 (1.14), 7.669 (1.13), 7.673 (1.07), 8.526 (2.60), 8.538 (2.64), 8.571 (1.96), 8.590 (2.01), 8.824 (4.19), 9.856 (2.66).

LC-MS (Method 3): R_t = 0.71 min; MS (ESIpos): m/z = 554 [M+H]⁺.

Example 79

N-[5-(4-methylpyridin-3-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]-4-(oxetan-3-yloxy)benzamide



To a mixture of the compound of intermediate 70 (150 mg, 0.44 mmol) and of intermediate 36 (137 mg, 0.57 mmol) in DMF (3 mL) was added (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, 456 mg, 0.88 mmol) and diisopropylethylamine (0.31 mL, 1.75 mmol).

- 5 The resulting mixture was stirred at room temperature over night, was concentrated under reduced pressure, was then triturated with ethanol and water and stirred for 30 minutes. The precipitate was collected by filtration, washed with ethanol and dried under reduced pressure. The remaining material was triturated with ethanol under reflux. The precipitate was collected by filtration at room temperature, washed with ethanol and dried under reduced pressure. The remaining material was
- 10 triturated with ethanol under reflux. The precipitate was collected by filtration at 40 °C, washed with ethanol and dried under reduced pressure to give 58.2 mg (23% of theory) of the title compound.

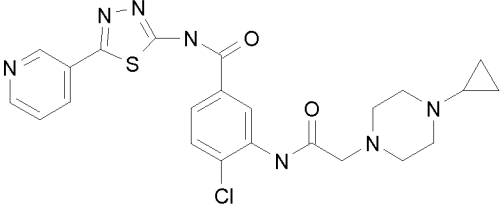
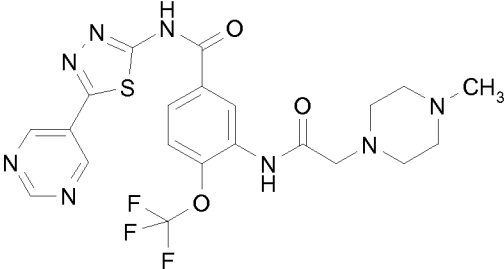
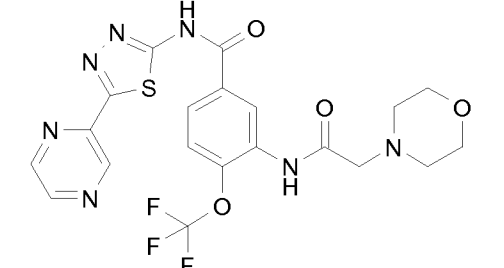
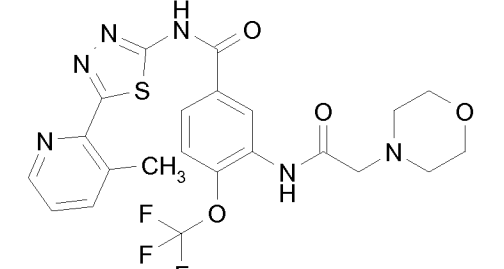
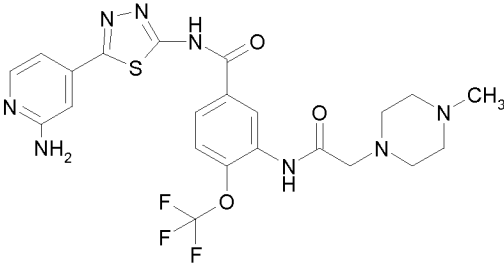
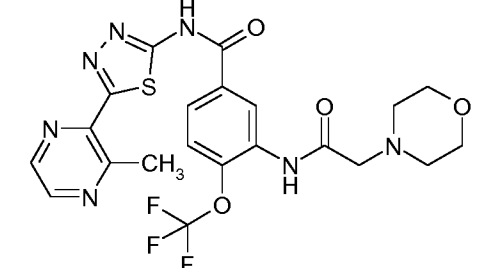
- ¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 1.908 (0.77), 2.322 (0.73), 2.327 (0.99), 2.332 (0.69), 2.523 (2.88), 2.564 (16.00), 2.577 (3.66), 2.585 (5.29), 2.597 (6.80), 2.609 (4.69), 2.665 (0.77), 2.669 (0.99), 2.674 (0.73), 3.206 (1.29), 3.224 (10.97), 3.679 (5.94), 3.691 (7.40), 3.702 (4.95), 4.634 (3.01), 4.646 (3.31), 4.648 (3.14), 4.653 (3.18), 4.665 (2.75), 5.016 (0.43), 5.033 (3.14), 5.051 (4.43), 5.068 (2.45), 5.507 (0.73), 5.519 (1.38), 5.522 (1.46), 5.534 (1.85), 5.548 (1.03), 6.877 (0.43), 6.899 (3.18), 6.921 (2.88), 7.461 (2.02), 7.473 (2.11), 7.924 (1.68), 7.930 (1.72), 7.946 (1.59), 7.951 (1.68), 8.553 (2.02), 8.566 (2.06), 8.846 (3.23), 8.980 (0.65), 9.020 (2.97), 9.026 (3.01), 9.849 (0.47), 9.878 (3.31).
- 15

LC-MS (Method 4): R_t = 0.67 min; MS (ESIpos): m/z = 511 [M+H]⁺.

20

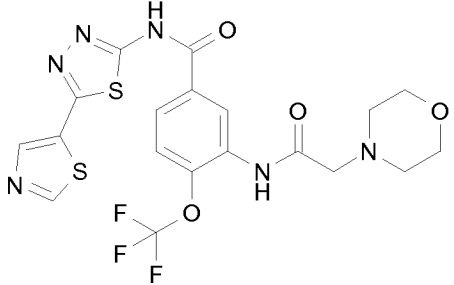
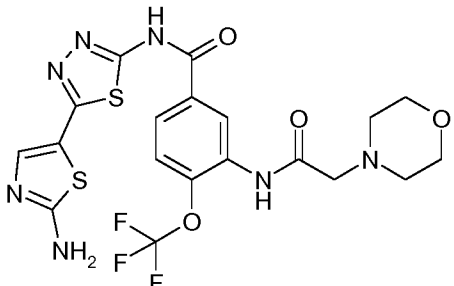
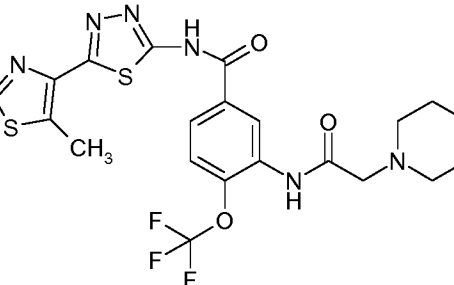
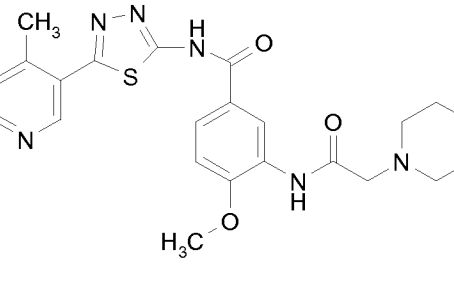
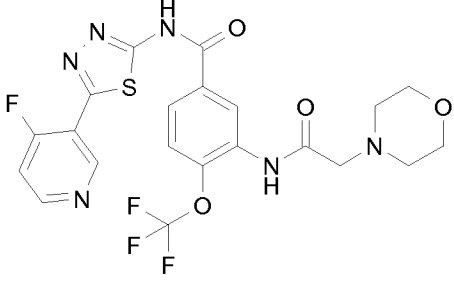
Examp le No	Structure	IUPAC Name	Rt [min] meth od

80		3-[(morpholin-4-ylacetyl)amino]-N-[5-(pyridin-2-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide	0.69 3
81		3-[(morpholin-4-ylacetyl)amino]-N-[5-(pyridin-4-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide	0.70 3
82		3-[(morpholin-4-ylacetyl)amino]-N-[5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide	0.68 3
83		3-[[4-methylpiperazin-1-yl]acetyl]amino-N-[5-(pyridin-4-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide	0.73 4
84		4-chloro-3-[[4-methylpiperazin-1-yl]acetyl]amino-N-[5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl]benzamide hydrochloride	0.66 3
85		4-chloro-3-([1-(4-cyclopropylpiperazin-1-yl)carbonyl]amino)-N-[5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl]benzamide	0.85 4

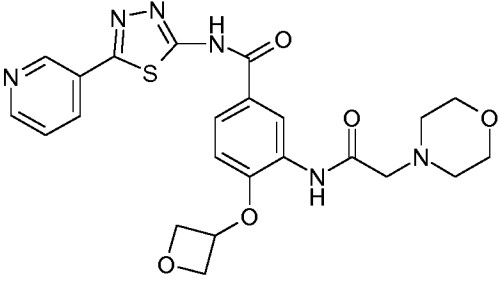
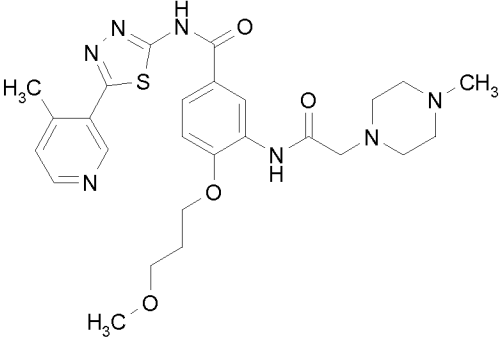
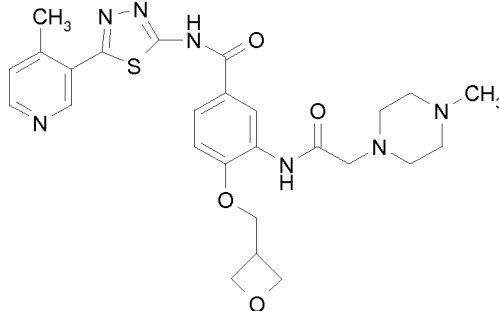
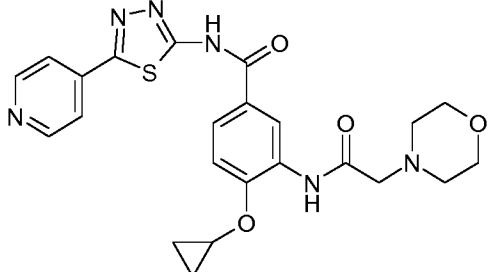
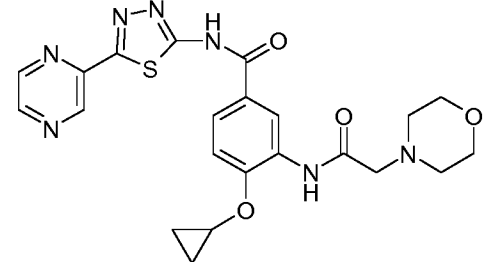
86		4-chloro-3-[[4-cyclopropylpiperazin-1-yl]acetyl]amino}-N-[5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl]benzamide	0.79 4
87		3-[[4-methylpiperazin-1-yl]acetyl]amino}-N-[5-(pyrimidin-5-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide	0.75 4
88		3-[(morpholin-4-yl)acetyl]amino]-N-[5-(pyrazin-2-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide	0.94 4
89		N-[5-(3-methylpyridin-2-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-yl)acetyl]amino]-4-(trifluoromethoxy)benzamide	0.72 3
90		N-[5-(2-aminopyridin-4-yl)-1,3,4-thiadiazol-2-yl]-3-[[4-methylpiperazin-1-yl]acetyl]amino]-4-(trifluoromethoxy)benzamide	0.69 3
91		N-[5-(3-methylpyrazin-2-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-yl)acetyl]amino]-4-(trifluoromethoxy)benzamide	0.98 4

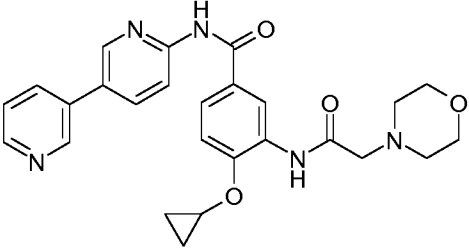
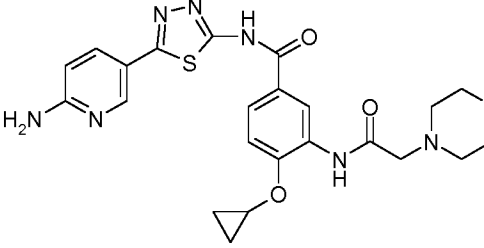
92		N-[5-(4-methyl-1,3-thiazol-2-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide	0.69 3
93		N-[5-(4-methylpyridin-2-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide	1.07 4
94		N-[5-(2-aminopyrimidin-5-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide	0.63 3
95		N-[5-(2-methyl-1,3-thiazol-4-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide	0.99 4
96		N-[5-(3-fluoropyridin-2-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide	0.69 3
97		3-[[4-methylpiperazin-1-yl]acetyl]amino-N-[5-(pyrazin-2-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide	0.76 4

98		N-[5-(2-aminopyridin-4-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide	0.66 3
99		3-[[4-methylpiperazin-1-yl]acetyl]amino-N-[5-(2-methyl-1,3-thiazol-5-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide	0.71 3
100		N-[5-(2-methyl-1,3-thiazol-5-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide	0.68 3
101		3-[(morpholin-4-ylacetyl)amino]-N-[5-(1,3-thiazol-2-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide	0.69 3
102		3-[[4-methylpiperazin-1-yl]acetyl]amino-N-[5-(6-methylpyrazin-2-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide	0.86 4

103		3-[(morpholin-4-ylacetyl)amino]-N-[5-(1,3-thiazol-5-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide	0.94 4
104		N-[5-(2-amino-1,3-thiazol-5-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide	0.75 3
105		N-[5-(5-methyl-1,3-thiazol-4-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide	1.01 4
106		4-methoxy-N-[5-(4-methylpyridin-3-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]benzamide	0.63 3
107		N-[5-(4-fluoropyridin-3-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide	0.70 3

108		N-[5-(4-methyl-1,3-thiazol-5-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide	0.98 4
109		N-[5-(4-fluoropyridin-3-yl)-1,3,4-thiadiazol-2-yl]-3-[[4-methylpiperazin-1-yl]acetyl]amino]-4-(trifluoromethoxy)benzamide	0.74 3
110		3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)-N-[5-(4-(trifluoromethyl)pyridin-3-yl)-1,3,4-thiadiazol-2-yl]benzamide	0.73 3
111		3-[[4-methylpiperazin-1-yl]acetyl]amino]-N-[5-(4-methyl-1,3-thiazol-5-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide	0.87 4
112		4-(cyclopropyloxy)-3-[[4-methylpiperazin-1-yl]acetyl]amino]-N-[5-(pyrimidin-5-yl)-1,3,4-thiadiazol-2-yl]benzamide	0.68 3

113		3-[(morpholin-4-ylacetyl)amino]-4-(oxetan-3-yloxy)-N-[5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl]benzamide	0.68 4
114		4-(3-methoxypropoxy)-3-[[4-(4-methylpiperazin-1-yl)acetyl]amino]-N-[5-(4-methylpyridin-3-yl)-1,3,4-thiadiazol-2-yl]benzamide	0.64 3
115		3-[[4-(4-methylpiperazin-1-yl)acetyl]amino]-N-[5-(4-methylpyridin-3-yl)-1,3,4-thiadiazol-2-yl]-4-(oxetan-3-ylmethoxy)benzamide	0.60 3
116		4-(cyclopropyloxy)-3-[(morpholin-4-ylacetyl)amino]-N-[5-(pyridin-4-yl)-1,3,4-thiadiazol-2-yl]benzamide	0.69 3
117		4-(cyclopropyloxy)-3-[(morpholin-4-ylacetyl)amino]-N-[5-(pyrazin-2-yl)-1,3,4-thiadiazol-2-yl]benzamide	0.86 4

118		N-(3,3'-bipyridin-6-yl)-4-(cyclopropyloxy)-3-[(morpholin-4-ylacetyl)amino]benzamide	1.07 3
119		N-[5-(6-aminopyridin-3-yl)-1,3,4-thiadiazol-2-yl]-4-(cyclopropyloxy)-3-[(morpholin-4-ylacetyl)amino]benzamide	0.62 3

Pharmaceutical compositions of the compounds of the invention

This invention also relates to pharmaceutical compositions containing one or more compounds of the present invention. These compositions can be utilised to achieve the desired pharmacological effect by administration to a patient in need thereof. A patient, for the purpose of this invention, is a mammal, including a human, in need of treatment for the particular condition or disease. Therefore, the present invention includes pharmaceutical compositions that are comprised of a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound, or salt thereof, of the present invention. A pharmaceutically acceptable carrier is preferably a carrier that is relatively non-toxic and innocuous to a patient at concentrations consistent with effective activity of the active ingredient so that any side effects ascribable to the carrier do not vitiate the beneficial effects of the active ingredient. A pharmaceutically effective amount of compound is preferably that amount which produces a result or exerts an influence on the particular condition being treated. The compounds of the present invention can be administered with pharmaceutically-acceptable carriers well known in the art using any effective conventional dosage unit forms, including immediate, slow and timed release preparations, orally, parenterally, topically, nasally, ophthalmically, optically, sublingually, rectally, vaginally, and the like.

For oral administration, the compounds can be formulated into solid or liquid preparations such as capsules, pills, tablets, troches, lozenges, melts, powders, solutions, suspensions, or emulsions, and may be prepared according to methods known to the art for the manufacture of pharmaceutical compositions. The solid unit dosage forms can be a capsule that can be of the ordinary hard- or

soft-shelled gelatine type containing, for example, surfactants, lubricants, and inert fillers such as lactose, sucrose, calcium phosphate, and corn starch.

In another embodiment, the compounds of this invention may be tableted with conventional tablet bases such as lactose, sucrose and cornstarch in combination with binders such as acacia, corn starch or gelatine, disintegrating agents intended to assist the break-up and dissolution of the tablet following administration such as potato starch, alginic acid, corn starch, and guar gum, gum tragacanth, acacia, lubricants intended to improve the flow of tablet granulation and to prevent the adhesion of tablet material to the surfaces of the tablet dies and punches, for example talc, stearic acid, or magnesium, calcium or zinc stearate, dyes, colouring agents, and flavouring agents such as peppermint, oil of wintergreen, or cherry flavouring, intended to enhance the aesthetic qualities of the tablets and make them more acceptable to the patient. Suitable excipients for use in oral liquid dosage forms include dicalcium phosphate and diluents such as water and alcohols, for example, ethanol, benzyl alcohol, and polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent or emulsifying agent. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance tablets, pills or capsules may be coated with shellac, sugar or both.

Dispersible powders and granules are suitable for the preparation of an aqueous suspension. They provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example those sweetening, flavouring and colouring agents described above, may also be present.

The pharmaceutical compositions of this invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil such as liquid paraffin or a mixture of vegetable oils. Suitable emulsifying agents may be (1) naturally occurring gums such as gum acacia and gum tragacanth, (2) naturally occurring phosphatides such as soy bean and lecithin, (3) esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan monooleate, (4) condensation products of said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil such as, for example, arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent such as, for example, beeswax, hard paraffin, or cetyl alcohol. The suspensions may also contain one or more preservatives, for example, ethyl or

n-propyl p-hydroxybenzoate ; one or more colouring agents ; one or more flavouring agents ; and one or more sweetening agents such as sucrose or saccharin.

Syrups and elixirs may be formulated with sweetening agents such as, for example, glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, and
5 preservative, such as methyl and propyl parabens and flavouring and colouring agents.

The compounds of this invention may also be administered parenterally, that is, subcutaneously, intravenously, intraocularly, intrasynovially, intramuscularly, or interperitoneally, as injectable dosages of the compound in preferably a physiologically acceptable diluent with a pharmaceutical carrier which can be a sterile liquid or mixture of liquids such as water, saline, aqueous dextrose and
10 related sugar solutions, an alcohol such as ethanol, isopropanol, or hexadecyl alcohol, glycols such as propylene glycol or polyethylene glycol, glycerol ketals such as 2,2-dimethyl-1,1-dioxolane-4-methanol, ethers such as poly(ethylene glycol) 400, an oil, a fatty acid, a fatty acid ester or, a fatty acid glyceride, or an acetylated fatty acid glyceride, with or without the addition of a pharmaceutically acceptable surfactant such as a soap or a detergent, suspending agent
15 such as pectin, carbomers, methylcellulose, hydroxypropylmethylcellulose, or carboxymethylcellulose, or emulsifying agent and other pharmaceutical adjuvants.

Illustrative of oils which can be used in the parenteral formulations of this invention are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, sesame oil, cottonseed oil, corn oil, olive oil, petrolatum and mineral oil. Suitable fatty acids include oleic acid,
20 stearic acid, isostearic acid and myristic acid. Suitable fatty acid esters are, for example, ethyl oleate and isopropyl myristate. Suitable soaps include fatty acid alkali metal, ammonium, and triethanolamine salts and suitable detergents include cationic detergents, for example dimethyl dialkyl ammonium halides, alkyl pyridinium halides, and alkylamine acetates ; anionic detergents, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and
25 sulfosuccinates ; non-ionic detergents, for example, fatty amine oxides, fatty acid alkanolamides, and poly(oxyethylene-oxypropylene)s or ethylene oxide or propylene oxide copolymers ; and amphoteric detergents, for example, alkyl-beta-aminopropionates, and 2-alkylimidazoline quarternary ammonium salts, as well as mixtures.

The parenteral compositions of this invention will typically contain from about 0.5% to about 25% by
30 weight of the active ingredient in solution. Preservatives and buffers may also be used advantageously. In order to minimise or eliminate irritation at the site of injection, such compositions may contain a non-ionic surfactant having a hydrophile-lipophile balance (HLB) preferably of from about 12 to about 17. The quantity of surfactant in such formulation preferably ranges from about

5% to about 15% by weight. The surfactant can be a single component having the above HLB or can be a mixture of two or more components having the desired HLB.

Illustrative of surfactants used in parenteral formulations are the class of polyethylene sorbitan fatty acid esters, for example, sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol.

The pharmaceutical compositions may be in the form of sterile injectable aqueous suspensions. Such suspensions may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents such as, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia ; dispersing or wetting agents which may be a naturally occurring phosphatide such as lecithin, a condensation product of an alkylene oxide with a fatty acid, for example, polyoxyethylene stearate, a condensation product of ethylene oxide with a long chain aliphatic alcohol, for example, heptadeca-ethyleneoxycetanol, a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol such as polyoxyethylene sorbitol monooleate, or a condensation product of an ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride, for example polyoxyethylene sorbitan monooleate.

The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent. Diluents and solvents that may be employed are, for example, water, Ringer's solution, isotonic sodium chloride solutions and isotonic glucose solutions. In addition, sterile fixed oils are conventionally employed as solvents or suspending media. For this purpose, any bland, fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can be used in the preparation of injectables.

A composition of the invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritation excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are, for example, cocoa butter and polyethylene glycol.

Another formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known

in the art (see, e.g., US Patent No. 5,023,252, issued June 11, 1991, incorporated herein by reference). Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Controlled release formulations for parenteral administration include liposomal, polymeric
5 microsphere and polymeric gel formulations that are known in the art.

It may be desirable or necessary to introduce the pharmaceutical composition to the patient via a mechanical delivery device. The construction and use of mechanical delivery devices for the delivery of pharmaceutical agents is well known in the art. Direct techniques for, for example, administering a drug directly to the brain usually involve placement of a drug delivery catheter into the patient's
10 ventricular system to bypass the blood-brain barrier. One such implantable delivery system, used for the transport of agents to specific anatomical regions of the body, is described in US Patent No. 5,011,472, issued April 30, 1991.

The compositions of the invention can also contain other conventional pharmaceutically acceptable compounding ingredients, generally referred to as carriers or diluents, as necessary or desired.
15 Conventional procedures for preparing such compositions in appropriate dosage forms can be utilized.

Such ingredients and procedures include those described in the following references, each of which is incorporated herein by reference: Powell, M.F. *et al.*, "Compendium of Excipients for Parenteral Formulations" PDA Journal of Pharmaceutical Science & Technology **1998**, 52(5), 238-311 ; Strickley, R.G. "Parenteral Formulations of Small Molecule Therapeutics Marketed in the United States
20 (1999)-Part-1" PDA Journal of Pharmaceutical Science & Technology **1999**, 53(6), 324-349 ; and Nema, S. *et al.*, "Excipients and Their Use in Injectable Products" PDA Journal of Pharmaceutical Science & Technology **1997**, 51(4), 166-171.

Commonly used pharmaceutical ingredients that can be used as appropriate to formulate the
25 composition for its intended route of administration include:

acidifying agents (examples include but are not limited to acetic acid, citric acid, fumaric acid, hydrochloric acid, nitric acid) ;

alkalinizing agents (examples include but are not limited to ammonia solution, ammonium carbonate, diethanolamine, monoethanolamine, potassium hydroxide, sodium borate, sodium
30 carbonate, sodium hydroxide, triethanolamine, triethylamine) ;

adsorbents (examples include but are not limited to powdered cellulose and activated charcoal) ;

aerosol propellants (examples include but are not limited to carbon dioxide, CCl_2F_2 , $\text{F}_2\text{ClC-CClF}_2$ and CClF_3)

air displacement agents (examples include but are not limited to nitrogen and argon) ;

5 **antifungal preservatives** (examples include but are not limited to benzoic acid, butylparaben, ethylparaben, methylparaben, propylparaben, sodium benzoate) ;

antimicrobial preservatives (examples include but are not limited to benzalkonium chloride, benzethonium chloride, benzyl alcohol, cetylpyridinium chloride, chlorobutanol, phenol, phenylethyl alcohol, phenylmercuric nitrate and thimerosal) ;

10 **antioxidants** (examples include but are not limited to ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorus acid, monothioglycerol, propyl gallate, sodium ascorbate, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metabisulfite) ;

binding materials (examples include but are not limited to block polymers, natural and synthetic rubber, polyacrylates, polyurethanes, silicones, polysiloxanes and styrene-butadiene copolymers) ;

15 **buffering agents** (examples include but are not limited to potassium metaphosphate, dipotassium phosphate, sodium acetate, sodium citrate anhydrous and sodium citrate dihydrate)

carrying agents (examples include but are not limited to acacia syrup, aromatic syrup, aromatic elixir, cherry syrup, cocoa syrup, orange syrup, syrup, corn oil, mineral oil, peanut oil, sesame oil, bacteriostatic sodium chloride injection and bacteriostatic water for injection)

chelating agents (examples include but are not limited to edetate disodium and edetic acid)

20 **colourants** (examples include but are not limited to FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8, caramel and ferric oxide red) ;

clarifying agents (examples include but are not limited to bentonite) ;

25 **emulsifying agents** (examples include but are not limited to acacia, cetomacrogol, cetyl alcohol, glyceryl monostearate, lecithin, sorbitan monooleate, polyoxyethylene 50 monostearate) ;

encapsulating agents (examples include but are not limited to gelatin and cellulose acetate phthalate)

flavourants (examples include but are not limited to anise oil, cinnamon oil, cocoa, menthol, orange oil, peppermint oil and vanillin) ;

humectants (examples include but are not limited to glycerol, propylene glycol and sorbitol) ;

levigating agents (examples include but are not limited to mineral oil and glycerin) ;

- 5 **oils** (examples include but are not limited to arachis oil, mineral oil, olive oil, peanut oil, sesame oil and vegetable oil) ;

ointment bases (examples include but are not limited to lanolin, hydrophilic ointment, polyethylene glycol ointment, petrolatum, hydrophilic petrolatum, white ointment, yellow ointment, and rose water ointment) ;

- 10 **penetration enhancers (transdermal delivery)** (examples include but are not limited to monohydroxy or polyhydroxy alcohols, mono-or polyvalent alcohols, saturated or unsaturated fatty alcohols, saturated or unsaturated fatty esters, saturated or unsaturated dicarboxylic acids, essential oils, phosphatidyl derivatives, cephalin, terpenes, amides, ethers, ketones and ureas)

plasticizers (examples include but are not limited to diethyl phthalate and glycerol) ;

- 15 **solvents** (examples include but are not limited to ethanol, corn oil, cottonseed oil, glycerol, isopropanol, mineral oil, oleic acid, peanut oil, purified water, water for injection, sterile water for injection and sterile water for irrigation) ;

stiffening agents (examples include but are not limited to cetyl alcohol, cetyl esters wax, microcrystalline wax, paraffin, stearyl alcohol, white wax and yellow wax) ;

- 20 **suppository bases** (examples include but are not limited to cocoa butter and polyethylene glycols (mixtures)) ;

surfactants (examples include but are not limited to benzalkonium chloride, nonoxynol 10, oxtoxynol 9, polysorbate 80, sodium lauryl sulfate and sorbitan mono-palmitate) ;

- 25 **suspending agents** (examples include but are not limited to agar, bentonite, carbomers, carboxymethylcellulose sodium, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, kaolin, methylcellulose, tragacanth and veegum) ;

sweetening agents (examples include but are not limited to aspartame, dextrose, glycerol, mannitol, propylene glycol, saccharin sodium, sorbitol and sucrose) ;

tablet anti-adherents (examples include but are not limited to magnesium stearate and talc) ;

tablet binders (examples include but are not limited to acacia, alginic acid, carboxymethylcellulose sodium, compressible sugar, ethylcellulose, gelatin, liquid glucose, methylcellulose, non-crosslinked polyvinyl pyrrolidone, and pregelatinized starch) ;

- 5 **tablet and capsule diluents** (examples include but are not limited to dibasic calcium phosphate, kaolin, lactose, mannitol, microcrystalline cellulose, powdered cellulose, precipitated calcium carbonate, sodium carbonate, sodium phosphate, sorbitol and starch) ;

- tablet coating agents** (examples include but are not limited to liquid glucose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, ethylcellulose, cellulose acetate phthalate and shellac) ;
- 10

tablet direct compression excipients (examples include but are not limited to dibasic calcium phosphate) ;

- tablet disintegrants** (examples include but are not limited to alginic acid, carboxymethylcellulose calcium, microcrystalline cellulose, polacrillin potassium, cross-linked polyvinylpyrrolidone, sodium alginate, sodium starch glycollate and starch) ;
- 15

tablet glidants (examples include but are not limited to colloidal silica, corn starch and talc) ;

tablet lubricants (examples include but are not limited to calcium stearate, magnesium stearate, mineral oil, stearic acid and zinc stearate) ;

tablet/capsule opaquants (examples include but are not limited to titanium dioxide) ;

- 20 **tablet polishing agents** (examples include but are not limited to carnuba wax and white wax) ;

thickening agents (examples include but are not limited to beeswax, cetyl alcohol and paraffin) ;

tonicity agents (examples include but are not limited to dextrose and sodium chloride) ;

- viscosity increasing agents** (examples include but are not limited to alginic acid, bentonite, carbomers, carboxymethylcellulose sodium, methylcellulose, polyvinyl pyrrolidone, sodium alginate and tragacanth) ; and
- 25

wetting agents (examples include but are not limited to heptadecaethylene oxycetanol, lecithins, sorbitol monooleate, polyoxyethylene sorbitol monooleate, and polyoxyethylene stearate).

Pharmaceutical compositions according to the present invention can be illustrated as follows:

Sterile IV Solution: A 5 mg/ml solution of the desired compound of this invention can be made using sterile, injectable water, and the pH is adjusted if necessary. The solution is diluted for administration to 1 – 2 mg/ml with sterile 5% dextrose and is administered as an IV infusion over about 60 minutes.

5 Lyophilised powder for IV administration: A sterile preparation can be prepared with (i) 100 - 1000 mg of the desired compound of this invention as a lyophilised powder, (ii) 32- 327 mg/ml sodium citrate, and (iii) 300 – 3000 mg Dextran 40. The formulation is reconstituted with sterile, injectable saline or dextrose 5% to a concentration of 10 to 20 mg/ml, which is further diluted with saline or dextrose 5% to 0.2 – 0.4 mg/ml, and is administered either IV bolus or by IV infusion over 15 – 60
10 minutes.

Intramuscular suspension: The following solution or suspension can be prepared, for intramuscular injection:

50 mg/ml of the desired, water-insoluble compound of this invention

5 mg/ml sodium carboxymethylcellulose

15 4 mg/ml TWEEN 80

9 mg/ml sodium chloride

9 mg/ml benzyl alcohol

Hard Shell Capsules: A large number of unit capsules are prepared by filling standard two-piece hard galantamine capsules each with 100 mg of powdered active ingredient, 150 mg of lactose, 50 mg of
20 cellulose and 6 mg of magnesium stearate.

Soft Gelatin Capsules: A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into molten gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules are washed and dried. The active ingredient can be dissolved in a mixture of polyethylene glycol,
25 glycerin and sorbitol to prepare a water miscible medicine mix.

Tablets: A large number of tablets are prepared by conventional procedures so that the dosage unit is 100 mg of active ingredient, 0.2 mg. of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg. of starch, and 98.8 mg of lactose. Appropriate aqueous and non-aqueous coatings may be applied to increase palatability, improve elegance and stability or

delay absorption.

Immediate Release Tablets/Capsules: These are solid oral dosage forms made by conventional and novel processes. These units are taken orally without water for immediate dissolution and delivery of the medication. The active ingredient is mixed in a liquid containing ingredient such as sugar, gelatin, pectin and sweeteners. These liquids are solidified into solid tablets or caplets by freeze drying and solid state extraction techniques. The drug compounds may be compressed with viscoelastic and thermoelastic sugars and polymers or effervescent components to produce porous matrices intended for immediate release, without the need of water.

10 Methods of Treatment

The compounds and compositions provided herein can be used as inhibitors of one or more members of the Wnt pathway, including one or more Wnt proteins, and thus can be used to treat a variety of disorders and diseases in which aberrant Wnt signaling is implicated, such as cancer and other diseases associated with abnormal angiogenesis, cellular proliferation, and cell cycling. Accordingly, the compounds and compositions provided herein can be used to treat cancer, to reduce or inhibit angiogenesis, to reduce or inhibit cellular proliferation and correct a genetic disorder due to mutations in Wnt signaling components. Non-limiting examples of diseases which can be treated with the compounds and compositions provided herein include a variety of cancers, diabetic retinopathy, neovascular glaucoma, rheumatoid arthritis, psoriasis, mycotic and viral infections, osteochondrodysplasia, Alzheimer's disease, osteoarthritis, polyposis coli, osteoporosis-pseudoglioma syndrome, familial exudative vitreoretinopathy, retinal angiogenesis, early coronary disease, tetra-amelia syndrome, Müllerian-duct regression and virilization, SERKAL syndrome, diabetes mellitus type 2, Fuhrmann syndrome, Al-Awadi/Raas-Rothschild/Schinzel phocomelia syndrome, odonto-onycho-dermal dysplasia, obesity, split-hand/foot malformation, caudal duplication syndrome, tooth agenesis, Wilms tumor, skeletal dysplasia, focal dermal hypoplasia, autosomal recessive anonychia, neural tube defects, alpha-thalassemia (ATRX) syndrome, fragile X syndrome, ICF syndrome, Angelman syndrome, Prader-Willi syndrome, Beckwith-Wiedemann Syndrome and Rett syndrome.

In accordance with another aspect therefore, the present invention covers a compound of general formula (I), or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, as described and defined herein, for use in the treatment or prophylaxis of a disease, as mentioned supra.

Another particular aspect of the present invention is therefore the use of a compound of general formula (I), described *supra*, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, for the prophylaxis or treatment of a disease.

5

Another particular aspect of the present invention is therefore the use of a compound of general formula (I) described *supra* for manufacturing a pharmaceutical composition for the treatment or prophylaxis of a disease.

- 10 The term "pharmaceutically acceptable salt" refers to a relatively non-toxic, inorganic or organic acid addition salt of a compound of the present invention. For example, see S. M. Berge, *et al.* "Pharmaceutical Salts," J. Pharm. Sci. **1977**, 66, 1-19.

- A suitable pharmaceutically acceptable salt of the compounds of the present invention may be, for example, an acid-addition salt of a compound of the present invention bearing a nitrogen atom, in a chain or in a ring, for example, which is sufficiently basic, such as an acid-addition salt with an inorganic acid, such as hydrochloric, hydrobromic, hydroiodic, sulfuric, bisulfuric, phosphoric, or nitric acid, for example, or with an organic acid, such as formic, acetic, acetoacetic, pyruvic, trifluoroacetic, propionic, butyric, hexanoic, heptanoic, undecanoic, lauric, benzoic, salicylic, 2-(4-hydroxybenzoyl)-benzoic, camphoric, cinnamic, cyclopentanepropionic, digluconic, 3-hydroxy-2-naphthoic, nicotinic, pamoic, pectinic, persulfuric, 3-phenylpropionic, picric, pivalic, 2-hydroxyethanesulfonate, itaconic, sulfamic, trifluoromethanesulfonic, dodecylsulfuric, ethansulfonic, benzenesulfonic, para-toluenesulfonic, methansulfonic, 2-naphthalenesulfonic, naphthalenedisulfonic, camphorsulfonic acid, citric, tartaric, stearic, lactic, oxalic, malonic, succinic, malic, adipic, alginic, maleic, fumaric, D-gluconic, mandelic, ascorbic, glucoheptanoic, glycerophosphoric, aspartic, sulfosalicylic, hemisulfuric, or thiocyanic acid, for example.

- Further, another suitably pharmaceutically acceptable salt of a compound of the present invention which is sufficiently acidic, is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically acceptable cation, for example a salt with N-methyl-glucamine, dimethyl-glucamine, ethyl-glucamine, lysine, dicyclohexylamine, 1,6-hexadiamine, ethanolamine, glucosamine, sarcosine, serinol, tris-hydroxy-methyl-aminomethane, aminopropandiol, sovak-base, 1-amino-2,3,4-butantriol. Additionally, basic nitrogen containing groups may be quaternised with such agents as lower alkyl

halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides ; dialkyl sulfates like dimethyl, diethyl, and dibutyl sulfate ; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others.

- 5 Those skilled in the art will further recognise that acid addition salts of the claimed compounds may be prepared by reaction of the compounds with the appropriate inorganic or organic acid via any of a number of known methods. Alternatively, alkali and alkaline earth metal salts of acidic compounds of the invention are prepared by reacting the compounds of the invention with the appropriate base via a variety of known methods.

10

Method of treating hyper-proliferative disorders

- The present invention relates to a method for using the compounds of the present invention and compositions thereof, to treat mammalian hyper-proliferative disorders. Compounds can be utilized to inhibit, block, reduce, decrease, etc., cell proliferation and/or cell division, and/or produce
- 15 apoptosis. This method comprises administering to a mammal in need thereof, including a human, an amount of a compound of this invention, or a pharmaceutically acceptable salt, isomer, polymorph, metabolite, hydrate, solvate or ester thereof ; etc. which is effective to treat the disorder. Hyper-proliferative disorders include but are not limited, e.g., psoriasis, keloids, and other hyperplasias affecting the skin, benign prostate hyperplasia (BPH), solid tumours, such as cancers of
- 20 the breast, respiratory tract, brain, reproductive organs, digestive tract, urinary tract, eye, liver, skin, head and neck, thyroid, parathyroid and their distant metastases. Those disorders also include lymphomas, sarcomas, and leukaemias.

Examples of breast cancer include, but are not limited to invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma in situ, and lobular carcinoma in situ.

- 25 Examples of cancers of the respiratory tract include, but are not limited to small-cell and non-small-cell lung carcinoma, as well as bronchial adenoma and pleuropulmonary blastoma.

Examples of brain cancers include, but are not limited to brain stem and hypophtalmic glioma, cerebellar and cerebral astrocytoma, medulloblastoma, ependymoma, as well as neuroectodermal and pineal tumour.

Tumours of the male reproductive organs include, but are not limited to prostate and testicular cancer. Tumours of the female reproductive organs include, but are not limited to endometrial, cervical, ovarian, vaginal, and vulvar cancer, as well as sarcoma of the uterus.

5 Tumours of the digestive tract include, but are not limited to anal, colon, colorectal, oesophageal, gallbladder, gastric, pancreatic, rectal, small-intestine, and salivary gland cancers.

Tumours of the urinary tract include, but are not limited to bladder, penile, kidney, renal pelvis, ureter, urethral and human papillary renal cancers.

Eye cancers include, but are not limited to intraocular melanoma and retinoblastoma.

10 Examples of liver cancers include, but are not limited to hepatocellular carcinoma (liver cell carcinomas with or without fibrolamellar variant), cholangiocarcinoma (intrahepatic bile duct carcinoma), and mixed hepatocellular cholangiocarcinoma.

Skin cancers include, but are not limited to squamous cell carcinoma, Kaposi's sarcoma, malignant melanoma, Merkel cell skin cancer, and non-melanoma skin cancer.

15 Head-and-neck cancers include, but are not limited to laryngeal, hypopharyngeal, nasopharyngeal, oropharyngeal cancer, lip and oral cavity cancer and squamous cell. Lymphomas include, but are not limited to AIDS-related lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, Burkitt lymphoma, Hodgkin's disease, and lymphoma of the central nervous system.

Sarcomas include, but are not limited to sarcoma of the soft tissue, osteosarcoma, malignant fibrous histiocytoma, lymphosarcoma, and rhabdomyosarcoma.

20 Leukemias include, but are not limited to acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and hairy cell leukemia.

These disorders have been well characterized in humans, but also exist with a similar etiology in other mammals, and can be treated by administering pharmaceutical compositions of the present invention.

25 The term "treating" or "treatment" as stated throughout this document is used conventionally, *e.g.*, the management or care of a subject for the purpose of combating, alleviating, reducing, relieving, improving the condition of, *etc.*, of a disease or disorder, such as a carcinoma.

Dose and administration

Based upon standard laboratory techniques known to evaluate compounds useful for the treatment of hyper-proliferative disorders and angiogenic disorders, by standard toxicity tests and by standard pharmacological assays for the determination of treatment of the conditions identified above in mammals, and by comparison of these results with the results of known medicaments that are used to treat these conditions, the effective dosage of the compounds of this invention can readily be determined for treatment of each desired indication. The amount of the active ingredient to be administered in the treatment of one of these conditions can vary widely according to such considerations as the particular compound and dosage unit employed, the mode of administration, the period of treatment, the age and sex of the patient treated, and the nature and extent of the condition treated.

The total amount of the active ingredient to be administered will generally range from about 0.001 mg/kg to about 200 mg/kg body weight per day, and preferably from about 0.01 mg/kg to about 20 mg/kg body weight per day. Clinically useful dosing schedules will range from one to three times a day dosing to once every four weeks dosing. In addition, "drug holidays" in which a patient is not dosed with a drug for a certain period of time, may be beneficial to the overall balance between pharmacological effect and tolerability. A unit dosage may contain from about 0.5 mg to about 1500 mg of active ingredient, and can be administered one or more times per day or less than once a day. The average daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous and parenteral injections, and use of infusion techniques will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily rectal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily vaginal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily topical dosage regimen will preferably be from 0.1 to 200 mg administered between one to four times daily. The transdermal concentration will preferably be that required to maintain a daily dose of from 0.01 to 200 mg/kg. The average daily inhalation dosage regimen will preferably be from 0.01 to 100 mg/kg of total body weight.

Of course the specific initial and continuing dosage regimen for each patient will vary according to the nature and severity of the condition as determined by the attending diagnostician, the activity of the specific compound employed, the age and general condition of the patient, time of administration, route of administration, rate of excretion of the drug, drug combinations, and the like. The desired mode of treatment and number of doses of a compound of the present invention or a pharmaceutically acceptable salt or ester or composition thereof can be ascertained by those skilled in the art using conventional treatment tests.

Preferably, the diseases of said method are haematological tumours, solid tumour and/or metastases thereof.

- 5 The compounds of the present invention can be used in particular in therapy and prevention, i.e. prophylaxis, of tumour growth and metastases, especially in solid tumours of all indications and stages with or without pre-treatment of the tumour growth.

10 Methods of testing for a particular pharmacological or pharmaceutical property are well known to persons skilled in the art.

The example testing experiments described herein serve to illustrate the present invention and the invention is not limited to the examples given.

15 **Combination therapies**

The term “combination” in the present invention is used as known to persons skilled in the art and may be present as a fixed combination, a non-fixed combination or kit-of-parts.

A “fixed combination” in the present invention is used as known to persons skilled in the art and is defined as a combination wherein the said first active ingredient and the said second active
20 ingredient are present together in one unit dosage or in a single entity. One example of a “fixed combination” is a pharmaceutical composition wherein the said first active ingredient and the said second active ingredient are present in admixture for simultaneous administration, such as in a formulation. Another example of a “fixed combination” is a pharmaceutical combination wherein the said first active ingredient and the said second active ingredient are present in one unit without
25 being in admixture.

A non-fixed combination or “kit-of-parts” in the present invention is used as known to persons skilled in the art and is defined as a combination wherein the said first active ingredient and the said second active ingredient are present in more than one unit. One example of a non-fixed combination or kit-of-parts is a combination wherein the said first active ingredient and the said second active
30 ingredient are present separately. The components of the non-fixed combination or kit-of-parts may be administered separately, sequentially, simultaneously, concurrently or chronologically staggered.

The compounds of this invention can be administered as the sole pharmaceutical agent or in combination with one or more other pharmaceutical agents where the combination causes no unacceptable adverse effects. The present invention relates also to such combinations. For example,

the compounds of this invention can be combined with known chemotherapeutic agents or anti-cancer agents, e.g. anti-hyper-proliferative or other indication agents, and the like, as well as with admixtures and combinations thereof. Other indication agents include, but are not limited to, anti-angiogenic agents, mitotic inhibitors, alkylating agents, anti-metabolites, DNA-intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzyme inhibitors, topoisomerase inhibitors, biological response modifiers, or anti-hormones.

The term “(chemotherapeutic) anti-cancer agents”, includes but is not limited to 131I-chTNT, abarelix, abiraterone, aclarubicin, aldesleukin, alemtuzumab, alitretinoin, altretamine, aminoglutethimide, amrubicin, amsacrine, anastrozole, arglabin, arsenic trioxide, asparaginase, azacitidine, basiliximab, BAY 80-6946, BAY 1000394, belotecan, bendamustine, bevacizumab, bexarotene, bicalutamide, bisantrene, bleomycin, bortezomib, buserelin, busulfan, cabazitaxel, calcium folinate, calcium levofolate, capecitabine, carboplatin, carmofur, carmustine, catumaxomab, celecoxib, celmoleukin, cetuximab, chlorambucil, chlormadinone, chlormethine, cisplatin, cladribine, clodronic acid, clofarabine, crisantaspase, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, darbepoetin alfa, dasatinib, daunorubicin, decitabine, degarelix, denileukin diftitox, denosumab, deslorelin, dibrospidium chloride, docetaxel, doxifluridine, doxorubicin, doxorubicin + estrone, eculizumab, edrecolomab, elliptinium acetate, eltrombopag, endostatin, enocitabine, epirubicin, epitiostanol, epoetin alfa, epoetin beta, eptaplatin, eribulin, erlotinib, estradiol, estramustine, etoposide, everolimus, exemestane, fadrozole, filgrastim, fludarabine, fluorouracil, flutamide, formestane, fotemustine, fulvestrant, gallium nitrate, ganirelix, gefitinib, gemcitabine, gemtuzumab, glutoxim, goserelin, histamine dihydrochloride, histrelin, hydroxycarbamide, I-125 seeds, ibandronic acid, ibritumomab tiuxetan, idarubicin, ifosfamide, imatinib, imiquimod, improsulfan, interferon alfa, interferon beta, interferon gamma, ipilimumab, irinotecan, ixabepilone, lanreotide, lapatinib, lenalidomide, lenograstim, lentinan, letrozole, leuporelin, levamisole, lisuride, lobaplatin, lomustine, lonidamine, masoprocol, medroxyprogesterone, megestrol, melphalan, mepitiothane, mercaptopurine, methotrexate, methoxsalen, Methyl aminolevulinate, methyltestosterone, mifamurtide, miltefosine, miriplatin, mitobronitol, mitoguazone, mitolactol, mitomycin, mitotane, mitoxantrone, nedaplatin, nelarabine, nilotinib, nilutamide, nimotuzumab, nimustine, nitracrine, ofatumumab, omeprazole, oprelvekin, oxaliplatin, p53 gene therapy, paclitaxel, palifermin, palladium-103 seed, pamidronic acid, panitumumab, pazopanib, pegaspargase, PEG-epoetin beta (methoxy PEG-epoetin beta), pegfilgrastim, peginterferon alfa-2b, pemetrexed, pentazocine, pentostatin, peplomycin, perfosfamide, picibanil, pirarubicin, plerixafor, plicamycin, poliglusam, polyestradiol phosphate, polysaccharide-K, porfimer sodium, pralatrexate, prednimustine, procarbazine, quinagolide, radium-223 chloride, raloxifene, raltitrexed, ranimustine, razoxane, refametinib, regorafenib, risedronic acid,

rituximab, romidepsin, romiplostim, sargramostim, sipuleucel-T, sizofiran, sobuzoxane, sodium glycididazole, sorafenib, streptozocin, sunitinib, talaporfin, tamibarotene, tamoxifen, tasonermin, teceleukin, tegafur, tegafur + gimeracil + oteracil, temoporfin, temozolomide, temsirolimus, teniposide, testosterone, tetrofosmin, thalidomide, thiotepa, thymalfasin, tioguanine, tocilizumab, 5 topotecan, toremifene, tositumomab, trabectedin, trastuzumab, treosulfan, tretinoin, trilostane, triptorelin, trofosfamide, tryptophan, ubenimex, valrubicin, vandetanib, vapreotide, vemurafenib, vinblastine, vincristine, vindesine, vinflunine, vinorelbine, vorinostat, vorozole, yttrium-90 glass microspheres, zinostatin, zinostatin stimalamer, zoledronic acid, zorubicin.

Generally, the use of cytotoxic and/or cytostatic agents in combination with a compound or 10 composition of the present invention will serve to:

- (1) yield better efficacy in reducing the growth of a tumor or even eliminate the tumor as compared to administration of either agent alone,
- (2) provide for the administration of lesser amounts of the administered chemotherapeutic agents,
- 15 (3) provide for a chemotherapeutic treatment that is well tolerated in the patient with fewer deleterious pharmacological complications than observed with single agent chemotherapies and certain other combined therapies,
- (4) provide for treating a broader spectrum of different cancer types in mammals, especially humans,
- 20 (5) provide for a higher response rate among treated patients,
- (6) provide for a longer survival time among treated patients compared to standard chemotherapy treatments,
- (7) provide a longer time for tumor progression, and/or
- (8) yield efficacy and tolerability results at least as good as those of the agents used alone, 25 compared to known instances where other cancer agent combinations produce antagonistic effects.

Biological assays

Examples were tested in selected biological assays one or more times. When tested more than once, data are reported as either average values or as median values, wherein

- the average value, also referred to as the arithmetic mean value, represents the sum of the values obtained divided by the number of times tested, and
- the median value represents the middle number of the group of values when ranked in ascending or descending order. If the number of values in the data set is odd, the median is the middle value. If the number of values in the data set is even, the median is the arithmetic mean of the two middle values.

Examples were synthesized one or more times. When synthesized more than once, data from biological assays represent average values or median values calculated utilizing data sets obtained from testing of one or more synthetic batch.

Measurement of the inhibitory activity of selected compounds on the Wnt signaling cascade

In order to discover and characterize small molecules which inhibit the constitutive active colorectal cancer cell (CRC) Wnt pathway, a cellular reporter assay was employed. The corresponding assay cell was generated by transfection of the colorectal cancer cell line HCT116 (ATCC, #CCL-247) with the Super TopFlash vector (Morin, Science 275, 1997, 1787-1790; Molenaar et al., Cell 86 (3), 1996, 391-399). The HCT116 cell line is cultivated at 37°C and 5% CO₂ in DMEM/F-12 (Life Technologies, #11320-074), supplemented with 2 mM glutamine, 20 mM HEPES, 1.4 mM pyruvate, 0.15% Na-bicarbonate and 10% foetal bovine serum (GIBCO, #10270), this cancer cell line is pathophysiological relevant since it carries a deletion of position S45 in the β -catenin gene, leading to constitutive active Wnt signaling. Stable transfectants were generated by cotransfection with pcDNA3 and selection of stable transfected cells with 1 mg/ml G418.

In a parallel approach, HCT116 cells were cotransfected with the FOP control vector and pcDNA3. The FOP vector is identical to the TOP construct, but it contains instead of functional TCF elements a randomized, non-functional sequence. For this transfection a stable transfected cell line was generated as well.

In preparation of the assay, the two cell lines were plated 24 hours before at 10000 cells per well of a 384 micro titre plate (MTP) in 30 μ L growth medium. Selective inhibitory activity for small molecules on the mutated Wnt pathway was determined after parallel incubation of both (TOP and FOP) HCT116 reporter cell lines with a compound dilution series from 50 μ M to 15 nM in steps of 3.16-fold dilutions in CAFTY buffer (130 mM NaCl, 5 mM KCl, 20 mM HEPES, 1 mM MgCl₂, 5 mM NaHCO₃, pH

7.4) containing 2 mM Ca^{2+} and 0.01% BSA. The compounds were thereby serially prediluted in 100% DMSO and thereafter in addition 50 fold into the CAFTY compound dilution buffer (described above). From this dilution 10 μL were added to the cells in 30 μL growth medium and incubated for 36 hours at 37°C and 5% CO_2 . Thereafter luciferase assay buffer (1:1 mixture of luciferase substrate buffer (20 mM Tricine, 2.67 mM MgSO_4 , 0.1 mM EDTA, 4 mM DTT, 270 μM Coenzyme A, 470 μM Luciferin, 530 μM ATP, pH adjusted to pH 7.8 with a sufficient volume of 5M NaOH) and Triton buffer (30 mL Triton X-100, 115 mL glycerol, 308 mg Dithiothreitol, 4.45 g $\text{Na}_2\text{HPO}_4 \cdot 2 \text{H}_2\text{O}$, 3.03 g TRIS HCl, ad 1l H_2O , pH 7.8) was added as equal volume to the compound solution on the cells to determine luciferase expression as a measure of Wnt signaling activity in a luminometer.

In order to determine the inhibitory activity of compounds for the WT Wnt signaling pathway, the Super TopFlash vector respectively FOP vector were cotransfected with pcDNA3 into HEK293 and stable transfected HEK293 cells were isolated by antibiotic selection. In preparation of compound testing, a dose response curve for the Wnt dependent luciferase expression was recorded by stimulating the assay cells with human recombinant Wnt-3a (R&D, #5036-WN-010) at different concentrations for 16 hours at 37°C and 5% CO_2 followed by subsequent luciferase measurement as described above to determine the Wnt-3a EC_{50} for the HEK293 TOP cell line on the day of testing. The recombinant human Wnt-3a was thereby used between 2500 and 5 ng/ml in two-fold dilution steps. To determine the inhibitory activity of compounds on the WT Wnt pathway they were prepared and diluted as described above for the constitutive active Wnt pathway and coincubated with the EC_{50} concentration of Wnt-3a for 16 hours at 37°C and 5% CO_2 on the HEK293 TOP respectively control HEK293 FOP cells. Measurement of luciferase expression was done as described for the constitutive active Wnt assay.

Table 2

Example No.	HCT116 TOPFlash IC50 [mol/L]	HCT116 FOPFlash IC50 [mol/L]
1	1.45E-7	$\geq 5.00\text{E-}5$
2	2.82E-7	$\geq 5.00\text{E-}5$
3	2.09E-8	$\geq 5.00\text{E-}5$
4	1.95E-8	$\geq 5.00\text{E-}5$
5	1.65E-8	$\geq 5.00\text{E-}5$
6	1.90E-8	$\geq 5.00\text{E-}5$
7	1.15E-7	$\geq 5.00\text{E-}5$
8	1.16E-8	$\geq 5.00\text{E-}5$
9	5.14E-7	2.25E-5
10	5.80E-8	$\geq 5.00\text{E-}5$
11	1.88E-8	$\geq 5.00\text{E-}5$
12	1.32E-7	$\geq 5.00\text{E-}5$
13	4.15E-8	$\geq 5.00\text{E-}5$
14	4,23E-8	$\geq 5,00\text{E-}5$
15	8,15E-8	$\geq 5,00\text{E-}5$
16	1,03E-7	$\geq 5,00\text{E-}5$
17	1,20E-7	$\geq 5,00\text{E-}5$
18	1.06E-7	1.03E-5
19	1.05E-7	$\geq 5.00\text{E-}5$
20	1.67E-7	4.00E-5
21	3.15E-7	$\geq 5.00\text{E-}5$
22	2.85E-7	$\geq 5.00\text{E-}5$

23	5.35E-8	$\geq 5.00E-5$
24	4.00E-6	$\geq 5.00E-5$
25	4.40E-6	$\geq 5.00E-5$
26	5.00E-7	$\geq 5.00E-5$
27	2.70E-6	$\geq 5.00E-5$
28	1.14E-6	$\geq 5.00E-5$
29	2.06E-7	$\geq 5.00E-5$
30	5.35E-7	$\geq 5.00E-5$
31	9.73E-7	$\geq 5.00E-5$
32	1.28E-7	$\geq 5.00E-5$
33	1.97E-7	$\geq 5.00E-5$
34	3.80E-7	1.40E-5
35	2.78E-7	$\geq 5.00E-5$
36	6.00E-8	$\geq 5.00E-5$
37	6.10E-7	$\geq 5.00E-5$
38	2.68E-7	$\geq 5.00E-5$
39	8.58E-8	$\geq 5.00E-5$
40	1.14E-7	$\geq 5.00E-5$
41	8.60E-7	$\geq 5.00E-5$
42	3.20E-7	3.85E-5
43	2.00E-6	3.20E-5
44	4.23E-7	$\geq 5.00E-5$
45	1.48E-6	4.50E-5
46	1.83E-8	$\geq 5.00E-5$

47	5.85E-7	$\geq 5.00E-5$
48	6.63E-7	$\geq 5.00E-5$
49	3.10E-7	$\geq 5.00E-5$
50	2.93E-7	2.05E-5
51	7.90E-8	$\geq 5.00E-5$
52	6.40E-8	$\geq 5.00E-5$
53	2.00E-6	$\geq 5.00E-5$
54	3.55E-8	$\geq 5.00E-5$
55	2.40E-7	$\geq 5.00E-5$
56	4.70E-7	$\geq 5.00E-5$
57	2.40E-7	$\geq 5.00E-5$
58	7.39E-6	2.73E-5
59	4.10E-6	$\geq 5.00E-5$
60	4.40E-6	$\geq 5.00E-5$
61	3.40E-7	$\geq 5.00E-5$
62	1.01E-6	8.55E-6
63	1.08E-6	4.35E-5
64	1.11E-6	4.60E-5
65	1.20E-6	$\geq 5.00E-5$
66	1.47E-6	$\geq 5.00E-5$
67	1.65E-6	$\geq 5.00E-5$
68	1.86E-6	$\geq 5.00E-5$
69	2.45E-6	$\geq 5.00E-5$
70	5.15E-6	$\geq 5.00E-5$

71	4.66E-6	$\geq 5.00E-5$
72	1.30E-6	$\geq 5.00E-5$
73	1.00E-6	$\geq 5.00E-5$
74	3.70E-6	$\geq 5.00E-5$
75	3.70E-8	$\geq 5.00E-5$
76	1.55E-7	$\geq 5.00E-5$
77	1.80E-7	$\geq 5.00E-5$
78	2.40E-7	$\geq 5.00E-5$
79	2.40E-7	$\geq 5.00E-5$
80	2.75E-5	$\geq 5.00E-5$
81	5.00E-5	$\geq 5.00E-5$
82	2.12E-5	$\geq 5.00E-5$
83	2.63E-5	$\geq 5.00E-5$
84	5.00E-5	$\geq 5.00E-5$
85	1.25E-5	$\geq 5.00E-5$
86	4.40E-5	$\geq 5.00E-5$
87	1.80E-5	$\geq 5.00E-5$
88	5.00E-5	$\geq 5.00E-5$
89	8.45E-7	$\geq 5.00E-5$
90	7.40E-6	3.10E-5
91	3.56E-5	$\geq 5.00E-5$
92	2.12E-5	$\geq 5.00E-5$
93	5.00E-5	$\geq 5.00E-5$
94	2.32E-5	$\geq 5.00E-5$

95	2.53E-5	$\geq 5.00E-5$
96	5.00E-5	$\geq 5.00E-5$
97	7.05E-6	$\geq 5.00E-5$
98	5.00E-5	$\geq 5.00E-5$
99	8.55E-6	$\geq 5.00E-5$
100	4.10E-5	$\geq 5.00E-5$
101	5.00E-5	$\geq 5.00E-5$
102	1.80E-7	$\geq 5.00E-5$
103	1.22E-5	$\geq 5.00E-5$
104	1.79E-5	$\geq 5.00E-5$
105	5.00E-5	$\geq 5.00E-5$
106	5.00E-5	$\geq 5.00E-5$
107	5.00E-5	$\geq 5.00E-5$
108	5.00E-5	$\geq 5.00E-5$
109	3.20E-5	$\geq 5.00E-5$
110	3.30E-5	$\geq 5.00E-5$
111	5.00E-5	$\geq 5.00E-5$
112	3.30E-7	$\geq 5.00E-5$
113	2.70E-5	$\geq 5.00E-5$
114	2.61E-5	$\geq 5.00E-5$
115	5.00E-5	$\geq 5.00E-5$
116	5.00E-5	$\geq 5.00E-5$
117	5.00E-5	$\geq 5.00E-5$
118	5.00E-5	$\geq 5.00E-5$

119	5.00E-5	$\geq 5.00E-5$
Ref.	1.38E-6	3.10E-6

“Ref.” in Table 2 means the compound niclosamide disclosed in prior art (compound 1-8 on page 36 of WO2011/035321A1).

5 Measurement of the inhibitory activity of selected compounds on the Wildtype Wnt signaling cascade

In order to discover and characterize small molecules which inhibit the wildtype Wnt pathway, a cellular reporter assay was employed. The corresponding assay cell was generated by transfection of the mammalian cell line HEK293 (ATCC, #CRL-1573) with the Super TopFlash vector (Morin, Science 275, 1997, 1787-1790; Molenaar et al., Cell 86 (3), 1996, 391-399). The HEK293 cell line is cultivated at 37°C and 5% CO₂ in DMEM (Life Technologies, #41965-039), supplemented with 2 mM glutamine, 20 mM HEPES, 1.4 mM pyruvate, 0.15% Na-bicarbonate and 10% foetal bovine serum (GIBCO, #10270). Stable transfectants were generated by selection with 300 µg/ml Hygromycin.

In a parallel approach, HEK293 cells were cotransfected with the FOP control vector and pcDNA3. The FOP vector is identical to the TOP construct, but it contains instead of functional TCF elements a randomized, non-functional sequence. For this transfection a stable transfected cell line was generated as well, based on selection with Geneticin (1 mg/ml).

In preparation of the assay, the two cell lines were plated 24 hours before beginning the test at 10000 cells per well in a 384 micro titre plate (MTP) in 30 µl growth medium. Before compound testing a dose response curve for the Wnt dependent luciferase expression was recorded by stimulating the assay cell line with human recombinant Wnt-3a (R&D, #5036-WN-010) at different concentrations for 16 hours at 37°C and 5% CO₂ followed by subsequent luciferase measurement, to determine the Wnt-3a EC₅₀ for the HEK293 TOP cell line on the day of testing. The recombinant human Wnt-3a was thereby applied between 2500 and 5 ng/ml in two-fold dilution steps.

Selective inhibitory activity for small molecules on the wildtype Wnt pathway was determined after parallel incubation of both (TOP and FOP) HEK293 reporter cell lines with a compound dilution series from 50 µM to 15 nM in steps of 3.16-fold dilutions in CAFTY buffer (130 mM NaCl, 5 mM KCl, 20 mM HEPES, 1 mM MgCl₂, 5 mM NaHCO₃, pH 7.4) containing 2 mM Ca²⁺ and 0.01% BSA.

The compounds were thereby serially prediluted in 100% DMSO and thereafter 50 fold into the CAFTY compound dilution buffer (described above). From this dilution 10 µl were added in combination with the EC₅₀ concentration of recombinant Wnt3a to the cells in 30 µl growth medium and incubated for 16 hours at 37°C and 5% CO₂. Thereafter luciferase assay buffer (1:1 mixture of

luciferase substrate buffer (20 mM Tricine, 2.67 mM MgSO₄, 0.1 mM EDTA, 4 mM DTT, 270 μM Coenzyme A, 470 μM Luciferin, 530 μM ATP, pH adjusted to pH 7.8 with a sufficient volume of 5M NaOH) and Triton buffer (30 ml Triton X-100, 115 ml glycerol, 308 mg Dithiothreitol, 4.45 g Na₂HPO₄ · 2 H₂O, 3.03 g TRIS HCl (CAS Number 1185-53-1), ad 1l H₂O, pH 7.8) was added in an equal volume to
5 determine luciferase expression as a measure of Wnt signaling activity in a luminometer. The Wnt inhibitory activity was determined as IC₅₀ of resulting dose response curves.

QPCR protocol

Real-time RT-PCR using a TaqMan fluorogenic detection system is a simple and sensitive assay for
10 quantitative analysis of gene transcription. The TaqMan fluorogenic detection system can monitor PCR in real time using a dual-labeled fluorogenic hybridization probe (TaqMan probe) and a polymerase with 5'-3' exonuclease activity.

Cells from different cancer cell lines (as HCT116, but not limited to) were grown at 500-1000
15 cells/well in 384 well cell culture plates. For cell lysis the cell medium was carefully removed. The cells were washed carefully once with 50 μL/well PBS. Then 9.75 μL/well cell lysis buffer (50 mM TRIS HCl pH 8.0, 40 mM NaCl, 1.5 mM MgCl₂, 0.5 % IGEPAL CA 630, 50mM Guanidium thiocyanate) and 0.25 μL RNaseOUT (40 U/μL, Invitrogen, 10777-019)) per well were added. The plate was incubated for 5 min at room temperature. Then 30 μL DNase/RNase-free water per well added and the lysates
20 were mixed. For the One-Step RT-PCR 2 μL lysate (each) was transferred to a 384 well PCR plate. The PCR reaction was composed by 5 μL 2x One Step RT qPCR MasterMix Plus, 0.05 μL Euroscript RT/RNase Inhibitor (50 U/μL, 20 U/μL) and 200 nM of the appropriate Primer/Hydrolysis Probe mix (primer sequences of forward, reverse and probe are given below for each analysed gene of interest or house keeping gene). 10 μL water were added per well. Seal the plate with an adhesive optical
25 film. The RT-PCR protocol was setup with 30 min 48°C, then 10 min 95°C followed by 50 cycles of 15 sec 95°C/1 min 60°C and a cooling step of 40°C for 30 sec using a Lightcycler LS440 from Roche. Relative expression was calculated using CP values from the gene of interest (e.g. AXIN2, but not limited to) and a house keeping gene (L32).

Used primers

L32 (forward primer: AAGTTCATCCGGCACCAGTC; reverse primer: TGGCCCTTGAATCTTCTACGA;
probe: CCCAGAGGCATTGACAACAGGG)

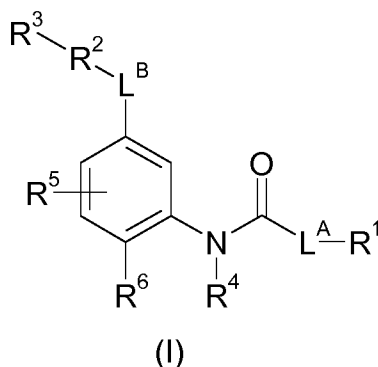
AXIN2 (forward primer: AGGCCAGTGAGTTGGTTGTC; reverse primer: AGCTCTGAGCCTTCAGCATC;
probe: TCTGTGGGGAAGAAATTCATACCG)

Sequence Listings

5	SEQ ID NO	
	1	AAGTTCATCCGGCACCAGTC
	2	TGGCCCTTGAATCTTCTACGA
	3	CCCAGAGGCATTGACAACAGGG
	4	AGGCCAGTGAGTTGGTTGTC
10	5	AGCTCTGAGCCTTCAGCATC
	6	TCTGTGGGGAAGAAATTCATACCG

Claims

1. A compound of general formula (I) :



5 in which :

L^A represents a methylene or ethylene group, said methylene or ethylene group being optionally substituted, one or more times, identically or differently, with a substituent selected from:

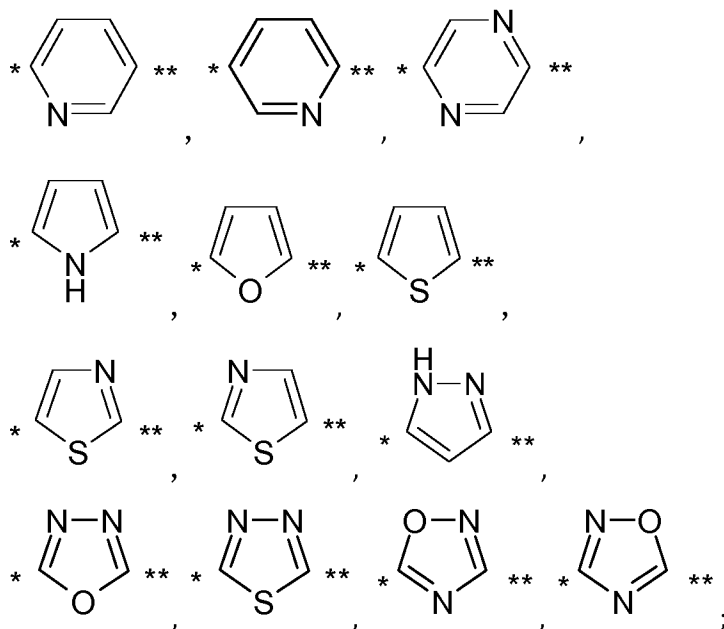
10 hydroxy-, cyano-, C_1 - C_3 -alkyl-, C_1 - C_3 -alkoxy-, halo- C_1 - C_3 -alkyl-, hydroxy- C_1 - C_3 -alkyl-, halo- C_1 - C_3 -alkoxy-, C_3 - C_7 -cycloalkyl-, 3- to 10-membered heterocycloalkyl-;
or, when two substituents are present at the same carbon atom, the two substituents, together with the carbon atom they are attached to, may form a C_3 - C_6 -cycloalkyl- or 3- to 6-membered heterocycloalkyl- ring; wherein said ring is optionally
15 substituted one or more times, identically or differently, with a substituent selected from: halo-, hydroxy-, cyano-, C_1 - C_3 -alkyl-, C_1 - C_3 -alkoxy-;

L^B represents $*N(H)-C(=O)**$ or $*C(=O)-N(H)**$;
wherein " * " indicates the point of attachment to R^2 , and " ** " indicates the point of
20 attachment to the phenyl group;

R^1 represents a group selected from:

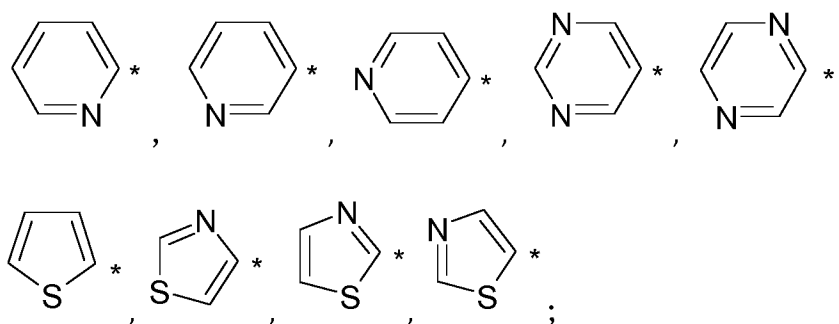
5- to 8-membered heterocycloalkyl-, 4- to 10-membered heterocycloalkenyl-, aryl-, heteroaryl-, and $-N(R^7)-(C_1-C_6-alkyl)$;
25 wherein said 5- to 8-membered heterocycloalkyl-, 4- to 10-membered heterocycloalkenyl-, aryl-, heteroaryl-, and $-N(R^7)-(C_1-C_6-alkyl)$ group is optionally substituted, one or more times, identically or differently, with a substituent selected from: halo-, hydroxy-, cyano-, C_1 - C_3 -alkyl-, C_1 - C_3 -alkoxy-, halo- C_1 - C_3 -alkyl-, hydroxy- C_1 - C_3 -alkyl-, halo- C_1 - C_3 -alkoxy-, C_3 - C_7 -cycloalkyl-;

R² represents a group selected from:



wherein " * " indicates the point of attachment to R³, and " ** " indicates the point of attachment to L^B; wherein said group is optionally substituted, one or more times, identically or differently, with a C₁-C₃-alkyl- group;

R³ represents a group selected from:



wherein " * " indicates the point of attachment to R²;

wherein said group is optionally substituted one time with a substituent selected from:

halo-, hydroxy-, -N(R⁹)(R¹⁰), -N(H)C(=O)R⁹, cyano-, nitro-, C₁-C₃-alkyl-, C₁-C₃-alkoxy-, halo-C₁-C₃-alkyl-, hydroxy-C₁-C₃-alkyl-, amino-C₁-C₃-alkyl-, halo-C₁-C₃-alkoxy-;

R⁴ represents a hydrogen atom or a C₁-C₃-alkyl- group;

R⁵ represents a hydrogen atom or a halogen atom or a group selected from:

cyano-, C₁-C₃-alkyl-, C₁-C₃-alkoxy-;

R⁶ represents a group selected from:

C₁-C₆-alkyl-, C₂-C₆-alkenyl-, C₂-C₆-alkynyl-,

C₁-C₆-alkoxy-, C₃-C₆-cycloalkoxy-, halo-, hydroxy-, cyano-, aryl-,

heteroaryl-, (3- to 10-membered heterocycloalkyl)-O-,

-N(R⁹)(R¹⁰), -C(=O)-O-C₁-C₄-alkyl-, -C(=O)-N(R⁹)(R¹⁰), R⁹-S-, R⁹-S(=O)-, R⁹-S(=O)₂-;

said C₁-C₆-alkyl-, C₂-C₆-alkenyl-, C₂-C₆-alkynyl-, aryl-, heteroaryl-, and C₁-C₆-alkoxy- group being optionally substituted, one or more times, identically or differently, with a substituent

selected from: halo-, cyano-, nitro-, hydroxy-, C₁-C₃-alkyl-, C₁-C₃-alkoxy-, halo-C₁-C₃-alkoxy-,

hydroxy-C₁-C₃-alkoxy-, C₁-C₃-alkoxy-C₂-C₃-alkoxy-,

C₃-C₇-cycloalkyl-, C₄-C₇-cycloalkenyl-,

3- to 10-membered heterocycloalkyl-, 4- to 10-membered heterocycloalkenyl-,

aryl-, heteroaryl-, -C(=O)R⁹, -C(=O)O-(C₁-C₄-alkyl), -OC(=O)-R⁹, -N(H)C(=O)R⁹, -N(R¹⁰)C(=O)R⁹,

-N(H)C(=O)NR¹⁰R⁹, -N(R¹¹)C(=O)NR¹⁰R⁹, -N(H)R⁹, -NR¹⁰R⁹,

-C(=O)N(H)R⁹, -C(=O)NR¹⁰R⁹, R⁹-S-, R⁹-S(=O)-, R⁹-S(=O)₂-,

-N(H)S(=O)R⁹, -N(R¹⁰)S(=O)R⁹, -S(=O)N(H)R⁹, -S(=O)NR¹⁰R⁹,

-N(H)S(=O)₂R⁹, -N(R⁹)S(=O)₂R¹⁰, -S(=O)₂N(H)R⁹, -S(=O)₂NR¹⁰R⁹,

-S(=O)(=NR¹⁰)R⁹, -N=S(=O)(R¹⁰)R⁹;

R⁷ represents a hydrogen atom or a C₁-C₃-alkyl- or C₁-C₃-alkoxy-C₁-C₃-alkyl- group;

R⁹, R¹⁰, R¹¹

represent, independently from each other, a hydrogen atom or a C₁-C₃-alkyl- or

C₁-C₃-alkoxy-C₁-C₃-alkyl- group;

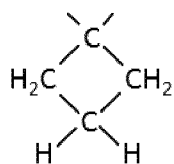
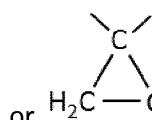
or

R⁹R¹⁰ together with the atom or the group of atoms they are attached to, form a 3- to 10-membered heterocycloalkyl- or 4- to 10-membered heterocycloalkenyl- group;

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

2. A compound according to claim 1, wherein :

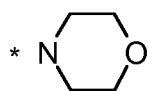
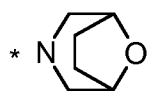
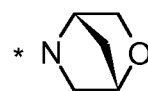
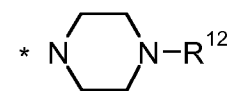
L^A represents -CH₂-, -CH(CH₃)-, -C(CH₃)₂-, -CH(C₂H₅)-,



or $\text{H}_2\text{C}-\text{CH}_2$; wherein the cyclobutyl- and the cyclopropyl- ring are optionally substituted one or more times, identically or differently, with a substituent selected from: halo-, hydroxy-, cyano-, $\text{C}_1\text{-C}_3\text{-alkyl}$ -, $\text{C}_1\text{-C}_3\text{-alkoxy}$ -.

3. A compound according to claim 1 or 2, wherein :

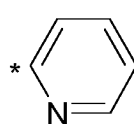
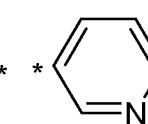
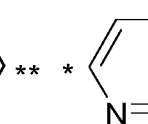
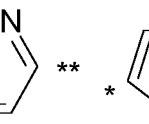
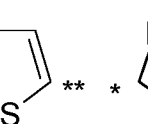
5 R^1 represents a group selected from:



, , , ; wherein * indicates the point of attachment to L^A ; and wherein R^{12} represents methyl, ethyl or cyclopropyl.

4. A compound according to claim 1, 2 or 3, wherein :

10 R^2 represents a group selected from:



, , , , ; wherein " * " indicates the point of attachment to R^3 , and " ** " indicates the point of attachment to L^B .

5. A compound according to claim 1, 2, 3 or 4, wherein :

15 R^4 represents a hydrogen atom, and

R^5 represents a hydrogen atom.

6. A compound according to claim 1, 2, 3, 4 or 5, wherein :

R^6 represents a group selected from:

20 $\text{C}_1\text{-C}_6\text{-alkyl}$ -, $\text{C}_1\text{-C}_6\text{-alkoxy}$ -, $\text{C}_3\text{-C}_6\text{-cycloalkoxy}$ -, halo-, hydroxy-, fluoro- $\text{C}_1\text{-C}_6\text{-alkyl}$ -, fluoro- $\text{C}_1\text{-C}_6\text{-alkoxy}$ -, phenyl-, 5- to 6-membered heteroaryl-, cyano-, $-\text{C}(=\text{O})-\text{O}-\text{C}_1\text{-C}_4\text{-alkyl}$ -, $-\text{C}(=\text{O})-\text{N}(\text{R}^9)(\text{R}^{10})$ -, $\text{R}^9\text{-S-}$ -, $\text{R}^9\text{-S}(=\text{O})\text{-}$ -, $\text{R}^9\text{-S}(=\text{O})_2\text{-}$;

said $\text{C}_1\text{-C}_6\text{-alkyl}$ - or $\text{C}_1\text{-C}_6\text{-alkoxy}$ - group being optionally substituted, one or more times, identically or differently, with a substituent selected from: $\text{C}_1\text{-C}_3\text{-alkyl}$ -, $\text{C}_1\text{-C}_3\text{-alkoxy}$ -, halo- $\text{C}_1\text{-C}_3\text{-alkoxy}$ -,

25 hydroxy- $\text{C}_1\text{-C}_3\text{-alkoxy}$ -, $\text{C}_1\text{-C}_3\text{-alkoxy-C}_2\text{-C}_3\text{-alkoxy}$ -, $\text{C}_3\text{-C}_7\text{-cycloalkyl}$ -,

3- to 10-membered heterocycloalkyl-, aryl-, heteroaryl-, $-\text{C}(=\text{O})\text{R}^9$ -,

$-\text{C}(=\text{O})\text{O}-(\text{C}_1\text{-C}_4\text{-alkyl})$ -, $-\text{OC}(=\text{O})-\text{R}^9$ -, $-\text{N}(\text{H})\text{C}(=\text{O})\text{R}^9$ -, $-\text{N}(\text{R}^{10})\text{C}(=\text{O})\text{R}^9$ -, $-\text{N}(\text{H})\text{C}(=\text{O})\text{NR}^{10}\text{R}^9$ -,

$-\text{N}(\text{R}^{11})\text{C}(=\text{O})\text{NR}^{10}\text{R}^9$ -, $-\text{N}(\text{H})\text{R}^9$ -, $-\text{NR}^{10}\text{R}^9$ -, $-\text{C}(=\text{O})\text{N}(\text{H})\text{R}^9$ -, $-\text{C}(=\text{O})\text{NR}^{10}\text{R}^9$.

7. A compound according to claim 1, 2, 3, 4, 5 or 6, wherein :

R⁶ represents a group selected from:

C₁-C₆-alkyl-, C₁-C₆-alkoxy-, C₃-C₆-cycloalkoxy-, halo-, hydroxy-, cyano-,

5 -C(=O)-O-C₁-C₄-alkyl, -C(=O)-N(R⁹)(R¹⁰), R⁹-S-, R⁹-S(=O)-, R⁹-S(=O)₂-;

said C₁-C₆-alkyl-, and C₁-C₆-alkoxy- group being optionally substituted, one or more times, identically or differently, with a substituent selected from:

halo-, C₁-C₃-alkoxy-, C₁-C₃-alkoxy-C₂-C₃-alkoxy-, C₃-C₇-cycloalkyl-.

10 8. A compound according to claim 1, which is selected from the group consisting of :

3-[(morpholin-4-ylacetyl)amino]-N-[5-(pyrimidin-5-yl)pyridin-2-yl]-4-(trifluoromethoxy)benzamide,

3-([1-(morpholin-4-yl)cyclopropyl]carbonyl)amino)-N-[5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide,

15 N-(6'-amino-2,3'-bipyridin-5-yl)-3-[[2-(morpholin-4-yl)propanoyl]amino]-4-(trifluoromethoxy)benzamide,

3-[[2-(morpholin-4-yl)propanoyl]amino]-N-[6-(pyrimidin-5-yl)pyridin-3-yl]-4-(trifluoromethoxy)benzamide,

N-(2'-fluoro-2,3'-bipyridin-5-yl)-3-[[2-(morpholin-4-yl)propanoyl]amino]-4-(trifluoromethoxy)benzamide,

20 N-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-3-[[2-(morpholin-4-yl)propanoyl]amino]-4-(trifluoromethoxy)benzamide,

N-[6-(2-methoxypyrimidin-5-yl)pyridin-3-yl]-3-[[2-(morpholin-4-yl)propanoyl]amino]-4-(trifluoromethoxy)benzamide,

N-(2,3'-bipyridin-5-yl)-3-[[2-(morpholin-4-yl)propanoyl]amino]-4-(trifluoromethoxy)benzamide,

25 3-[[4-methylpiperazin-1-yl]acetyl]amino)-N-[5-(pyridin-2-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide,

N-(6'-amino-3,3'-bipyridin-6-yl)-3-[[4-methylpiperazin-1-yl]acetyl]amino]-4-(trifluoromethoxy)benzamide,

N-(3,3'-bipyridin-6-yl)-3-[[4-methylpiperazin-1-yl]acetyl]amino]-4-(trifluoromethoxy)benzamide,

30 N-[5-(2-aminopyrimidin-5-yl)pyridin-2-yl]-3-[[4-methylpiperazin-1-yl]acetyl]amino]-4-(trifluoromethoxy)benzamide,

N-(2'-fluoro-3,3'-bipyridin-6-yl)-3-[[4-methylpiperazin-1-yl]acetyl]amino]-4-(trifluoromethoxy)benzamide,

- N-(3,3'-bipyridin-6-yl)-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide,
- N-(6'-amino-3,3'-bipyridin-6-yl)-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide,
- N-(2'-fluoro-3,3'-bipyridin-6-yl)-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide,
- 5 N-[5-(2-aminopyrimidin-5-yl)pyridin-2-yl]-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide,
- 3-([1-(4-methylpiperazin-1-yl)cyclopropyl]carbonyl)amino)-N-[5-(pyridin-2-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide,
- 3-([1-(4-methylpiperazin-1-yl)cyclopropyl]carbonyl)amino)-N-[5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide,
- 10 3-[(4-methylpiperazin-1-yl)acetyl]amino)-N-[5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide,
- 3-[(4-methylpiperazin-1-yl)acetyl]amino)-N-[5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide,
- N-(2,4'-bipyridin-5-yl)-3-{[2-(morpholin-4-yl)propanoyl]amino}-4-(trifluoromethoxy)benzamide,
- 15 N-(6'-fluoro-2,3'-bipyridin-5-yl)-3-{[2-(morpholin-4-yl)propanoyl]amino}-4-(trifluoromethoxy)benzamide,
- N-[4-methoxy-3-[(morpholin-4-ylacetyl)amino]phenyl]-6-(thiophen-2-yl)pyridine-3-carboxamide,
- N-[4-methoxy-3-[(morpholin-4-ylacetyl)amino]phenyl]-5-(pyridin-4-yl)thiophene-2-carboxamide,
- 4-chloro-3-([1-(4-methylpiperazin-1-yl)cyclopropyl]carbonyl)amino)-N-[5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl]benzamide,
- 20 3-[(4-methylpiperazin-1-yl)acetyl]amino)-N-[5-(2-methylpyridin-3-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide,
- N-[5-(2-methylpyridin-3-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide,
- 25 3-([1-(4-methylpiperazin-1-yl)cyclopropyl]carbonyl)amino)-N-[5-(pyrimidin-5-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide,
- 3-([1-(morpholin-4-yl)cyclopropyl]carbonyl)amino)-N-[5-(pyrimidin-5-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide,
- N-[5-(2-aminopyrimidin-5-yl)-1,3,4-thiadiazol-2-yl]-3-[(4-methylpiperazin-1-yl)acetyl]amino)-4-(trifluoromethoxy)benzamide,
- 30 N-[5-(2-aminopyrimidin-5-yl)-1,3,4-thiadiazol-2-yl]-3-([1-(4-methylpiperazin-1-yl)cyclopropyl]carbonyl)amino)-4-(trifluoromethoxy)benzamide,
- N-[5-(2-aminopyrimidin-5-yl)-1,3,4-thiadiazol-2-yl]-3-([1-(morpholin-4-yl)cyclopropyl]carbonyl)amino)-4-(trifluoromethoxy)benzamide,

4-(cyclopropyloxy)-3-[[4-methylpiperazin-1-yl]acetyl]amino}-N-[5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl]benzamide,

4-(cyclopropyloxy)-3-[(morpholin-4-ylacetyl)amino]-N-[5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl]benzamide,

5 3-[[4-methylpiperazin-1-yl]acetyl]amino}-N-[5-(4-methylpyridin-3-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide,

3-[[4-methylpiperazin-1-yl]acetyl]amino}-N-[5-(4-methylpyridin-3-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide,

10 N-[5-(6-aminopyridin-3-yl)-1,3,4-thiadiazol-2-yl]-3-[[4-methylpiperazin-1-yl]acetyl]amino}-4-(trifluoromethoxy)benzamide,

3-[[4-methylpiperazin-1-yl]acetyl]amino}-N-[5-(5-methylpyridin-3-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide,

N-[5-(5-chloropyridin-3-yl)-1,3,4-thiadiazol-2-yl]-3-[[4-methylpiperazin-1-yl]acetyl]amino}-4-(trifluoromethoxy)benzamide,

15 3-[[4-methylpiperazin-1-yl]acetyl]amino}-N-[5-(3-methylpyrazin-2-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide,

3-[[4-methylpiperazin-1-yl]acetyl]amino}-N-[5-(3-methylpyridin-2-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide,

20 N-[5-(3-fluoropyridin-2-yl)-1,3,4-thiadiazol-2-yl]-3-[[4-methylpiperazin-1-yl]acetyl]amino}-4-(trifluoromethoxy)benzamide,

3-[[4-methylpiperazin-1-yl]acetyl]amino}-N-[5-(2-methyl-1,3-thiazol-4-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide,

3-[[4-methylpiperazin-1-yl]acetyl]amino}-N-[5-(1,3-thiazol-2-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide,

25 3-[[4-methylpiperazin-1-yl]acetyl]amino}-N-[5-(pyrimidin-5-yl)pyridin-2-yl]-4-(trifluoromethoxy)benzamide,

N-[5-(5-chloropyridin-3-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide,

30 N-[5-(6-methylpyrazin-2-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide,

N-[5-(6-aminopyridin-3-yl)-1,3,4-thiadiazol-2-yl]-3-[[1-(morpholin-4-yl)cyclopropyl]carbonyl]amino}-4-(trifluoromethoxy)benzamide,

3-[[4-methylpiperazin-1-yl]acetyl]amino}-N-[5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl]-4-(2,2,2-trifluoroethoxy)benzamide,

- N-[5-(2-fluoropyridin-3-yl)pyrazin-2-yl]-3-[[4-methylpiperazin-1-yl]acetyl]amino]-4-(trifluoromethoxy)benzamide,
- 3-[[4-methylpiperazin-1-yl]acetyl]amino}-N-[5-(pyridin-4-yl)pyrazin-2-yl]-4-(trifluoromethoxy)benzamide,
- 5 N-[5-(2-aminopyridin-4-yl)pyrazin-2-yl]-3-[[4-methylpiperazin-1-yl]acetyl]amino]-4-(trifluoromethoxy)benzamide,
- N-[5-(6-aminopyridin-3-yl)pyrazin-2-yl]-3-[[4-methylpiperazin-1-yl]acetyl]amino]-4-(trifluoromethoxy)benzamide,
- N-[5-(6-aminopyridin-3-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]-4-
- 10 (trifluoromethoxy)benzamide,
- N-[5-(5-methylpyridin-3-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide,
- 3-[[4-methylpiperazin-1-yl]acetyl]amino}-4-(trifluoromethoxy)-N-{5-[5-(trifluoromethyl)pyridin-3-yl]-1,3,4-thiadiazol-2-yl}benzamide,
- 15 3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)-N-{5-[5-(trifluoromethyl)pyridin-3-yl]-1,3,4-thiadiazol-2-yl}benzamide,
- N-(5'-amino-2,2'-bipyrazin-5-yl)-3-[[4-methylpiperazin-1-yl]acetyl]amino]-4-(trifluoromethoxy)benzamide,
- 4-(cyclopropyloxy)-3-[[4-methylpiperazin-1-yl]acetyl]amino}-N-[5-(pyrazin-2-yl)-1,3,4-thiadiazol-2-
- 20 yl]benzamide,
- 3-[[4-methylpiperazin-1-yl]acetyl]amino}-N-[5-(4-methylpyridin-3-yl)-1,3,4-thiadiazol-2-yl]-4-(2,2,2-trifluoroethoxy)benzamide,
- 3-[[4-methylpiperazin-1-yl]acetyl]amino}-N-[5-(4-methylpyridin-2-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide,
- 25 3-[[4-methylpiperazin-1-yl]acetyl]amino}-N-[5-(4-methyl-1,3-thiazol-2-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide,
- 3-[[4-methylpiperazin-1-yl]acetyl]amino}-N-[5-(1,3-thiazol-4-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide,
- 3-[[4-methylpiperazin-1-yl]acetyl]amino}-N-[5-(5-methyl-1,3-thiazol-4-yl)-1,3,4-thiadiazol-2-yl]-4-
- 30 (trifluoromethoxy)benzamide,

- N-[5-(2-amino-1,3-thiazol-5-yl)-1,3,4-thiadiazol-2-yl]-3-[[4-methylpiperazin-1-yl]acetyl]amino]-4-(trifluoromethoxy)benzamide,
- 3-[(morpholin-4-ylacetyl)amino]-N-[5-(1,3-thiazol-4-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide,
- 5 3-[[4-methylpiperazin-1-yl]acetyl]amino]-N-[5-(1,3-thiazol-5-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide,
- 3-[(morpholin-4-ylacetyl)amino]-N-[5-(pyrimidin-5-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide,
- 3-[[4-methylpiperazin-1-yl]acetyl]amino]-4-(trifluoromethoxy)-N-[5-[4-(trifluoromethyl)pyridin-3-yl]-1,3,4-thiadiazol-2-yl]benzamide,
- 10 N-[5-(4-methylpyridin-3-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide,
- 4-(cyclopropyloxy)-3-[(morpholin-4-ylacetyl)amino]-N-[5-(pyrimidin-5-yl)-1,3,4-thiadiazol-2-yl]benzamide,
- 15 4-(2-methoxyethoxy)-3-[[4-methylpiperazin-1-yl]acetyl]amino]-N-[5-(4-methylpyridin-3-yl)-1,3,4-thiadiazol-2-yl]benzamide,
- 4-(3-methoxypropoxy)-N-[5-(4-methylpyridin-3-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]benzamide,
- 4-(cyclopropyloxy)-3-[(morpholin-4-ylacetyl)amino]-N-[5-(pyrimidin-5-yl)pyridin-2-yl]benzamide,
- 20 4-(cyclopropyloxy)-3-[(morpholin-4-ylacetyl)amino]-N-[2-(pyridin-3-yl)-1,3-thiazol-5-yl]benzamide,
- 2-fluoro-5-[[4-methylpiperazin-1-yl]acetyl]amino]-N-[5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide,
- 2-fluoro-5-[[4-methylpiperazin-1-yl]acetyl]amino]-N-[5-(4-methylpyridin-3-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide,
- 25 N-[5-(4-methylpyridin-3-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]-4-(oxetan-3-yl)benzamide,
- 3-[(morpholin-4-ylacetyl)amino]-N-[5-(pyridin-2-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide,
- 3-[(morpholin-4-ylacetyl)amino]-N-[5-(pyridin-4-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide,
- 30 3-[(morpholin-4-ylacetyl)amino]-N-[5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide,

- 3-[[[4-methylpiperazin-1-yl)acetyl]amino]-N-[5-(pyridin-4-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide,
- 4-chloro-3-[[[4-methylpiperazin-1-yl)acetyl]amino]-N-[5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl]benzamide hydrochloride,
- 5 4-chloro-3-([1-(4-cyclopropylpiperazin-1-yl)cyclopropyl]carbonyl)amino)-N-[5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl]benzamide,
- 4-chloro-3-[[[4-cyclopropylpiperazin-1-yl)acetyl]amino]-N-[5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl]benzamide,
- 10 3-[[[4-methylpiperazin-1-yl)acetyl]amino]-N-[5-(pyrimidin-5-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide,
- 3-[(morpholin-4-ylacetyl)amino]-N-[5-(pyrazin-2-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide
- N-[5-(3-methylpyridin-2-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide,
- 15 N-[5-(2-aminopyridin-4-yl)-1,3,4-thiadiazol-2-yl]-3-[[[4-methylpiperazin-1-yl)acetyl]amino]-4-(trifluoromethoxy)benzamide,
- N-[5-(3-methylpyrazin-2-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide,
- N-[5-(4-methyl-1,3-thiazol-2-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide,
- 20 N-[5-(4-methylpyridin-2-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide,
- N-[5-(2-aminopyrimidin-5-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide,
- 25 N-[5-(2-methyl-1,3-thiazol-4-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide,
- N-[5-(3-fluoropyridin-2-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide,
- 30 3-[[[4-methylpiperazin-1-yl)acetyl]amino]-N-[5-(pyrazin-2-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide,
- N-[5-(2-aminopyridin-4-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide,
- 3-[[[4-methylpiperazin-1-yl)acetyl]amino]-N-[5-(2-methyl-1,3-thiazol-5-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide,

- N-[5-(2-methyl-1,3-thiazol-5-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide,
- 3-[(morpholin-4-ylacetyl)amino]-N-[5-(1,3-thiazol-2-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide,
- 5 3-[[4-methylpiperazin-1-yl]acetyl]amino}-N-[5-(6-methylpyrazin-2-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide,
- 3-[(morpholin-4-ylacetyl)amino]-N-[5-(1,3-thiazol-5-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide
- 10 N-[5-(2-amino-1,3-thiazol-5-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide,
- N-[5-(5-methyl-1,3-thiazol-4-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide,
- 4-methoxy-N-[5-(4-methylpyridin-3-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]benzamide,
- 15 N-[5-(4-fluoropyridin-3-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide,
- N-[5-(4-methyl-1,3-thiazol-5-yl)-1,3,4-thiadiazol-2-yl]-3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)benzamide,
- N-[5-(4-fluoropyridin-3-yl)-1,3,4-thiadiazol-2-yl]-3-[[4-methylpiperazin-1-yl]acetyl]amino}-4-(trifluoromethoxy)benzamide,
- 20 3-[(morpholin-4-ylacetyl)amino]-4-(trifluoromethoxy)-N-{5-[4-(trifluoromethyl)pyridin-3-yl]-1,3,4-thiadiazol-2-yl}benzamide,
- 3-[[4-methylpiperazin-1-yl]acetyl]amino}-N-[5-(4-methyl-1,3-thiazol-5-yl)-1,3,4-thiadiazol-2-yl]-4-(trifluoromethoxy)benzamide,
- 25 4-(cyclopropyloxy)-3-[[4-methylpiperazin-1-yl]acetyl]amino}-N-[5-(pyrimidin-5-yl)-1,3,4-thiadiazol-2-yl]benzamide,
- 3-[(morpholin-4-ylacetyl)amino]-4-(oxetan-3-yloxy)-N-[5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl]benzamide,
- 4-(3-methoxypropoxy)-3-[[4-methylpiperazin-1-yl]acetyl]amino}-N-[5-(4-methylpyridin-3-yl)-1,3,4-thiadiazol-2-yl]benzamide,
- 30 3-[[4-methylpiperazin-1-yl]acetyl]amino}-N-[5-(4-methylpyridin-3-yl)-1,3,4-thiadiazol-2-yl]-4-(oxetan-3-ylmethoxy)benzamide,
- 4-(cyclopropyloxy)-3-[(morpholin-4-ylacetyl)amino]-N-[5-(pyridin-4-yl)-1,3,4-thiadiazol-2-yl]benzamide,

4-(cyclopropyloxy)-3-[(morpholin-4-ylacetyl)amino]-N-[5-(pyrazin-2-yl)-1,3,4-thiadiazol-2-yl]benzamide,

N-(3,3'-bipyridin-6-yl)-4-(cyclopropyloxy)-3-[(morpholin-4-ylacetyl)amino]benzamide, and

5 N-[5-(6-aminopyridin-3-yl)-1,3,4-thiadiazol-2-yl]-4-(cyclopropyloxy)-3-[(morpholin-4-ylacetyl)amino]benzamide,

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

10 **9.** A compound of general formula (I), or a stereoisomer, a tautomer, an N oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, according to any one of claims 1 to 8, for use in the treatment or prophylaxis of a disease.

10. A pharmaceutical composition comprising a compound of general formula (I), or a stereoisomer, a tautomer, an N oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, according to any one of claims 1 to 8, and a pharmaceutically acceptable diluent or carrier.

15 **11.** A pharmaceutical combination comprising :

- one or more first active ingredients selected from a compound of general formula (I) according to any of claims 1 to 8, and
- one or more second active ingredients selected from chemotherapeutic anti cancer agents.

20 **12.** Use of a compound of general formula (I), or a stereoisomer, a tautomer, an N oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, according to any one of claims 1 to 8, for the prophylaxis or treatment of a disease.

25 **13.** Use of a compound of general formula (I), or a stereoisomer, a tautomer, an N oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, according to any one of claims 1 to 8, for the preparation of a medicament for the prophylaxis or treatment of a disease.

14. Use according to claim 9, 12 or 13, wherein said disease is a disease in which aberrant Wnt signalling is implicated in a patient.

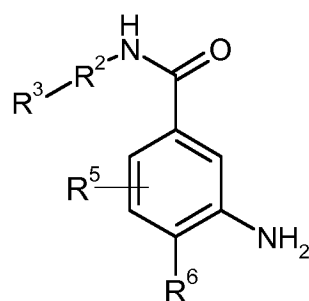
30 **15.** Use according to claim 9, 12, 13 or 14, wherein the disease is a genetic disease caused by mutations in Wnt signaling components, wherein the genetic disease is chosen from: polyposis coli, osteoporosispseudoglioma syndrome, familial exudative vitreoretinopathy, retinal angiogenesis, early coronary disease, tetra-amelia syndrome, Müllerian-duct regression and virilization, SERKAL

syndrome, diabetes mellitus type 2, Fuhrmann syndrome, Al-Awadi/Raas-Rothschild/Schinzel phocomelia syndrome, odonto-onycho-dermal dysplasia, obesity, splithand/foot malformation, caudal duplication syndrome, tooth agenesis, Wilms tumor, skeletal dysplasia, focal dermal hypoplasia, autosomal recessive anonychia, neural tube defects, alpha-thalassemia (ATRX) syndrome, fragile X syndrome, ICF syndrome, Angelman syndrome, Prader-Willi syndrome, Beckwith-Wiedemarm Syndrome and Rett syndrome.

16. Use according to claim 9, 12, 13 or 14, wherein the disease is a disease of uncontrolled cell growth, proliferation and/or survival, an inappropriate cellular immune response, or an inappropriate cellular inflammatory response, particularly in which the uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune response, or inappropriate cellular inflammatory response is mediated by the Wnt pathway, more particularly in which the disease of uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune response, or inappropriate cellular inflammatory response is a haematological tumour, a solid tumour and/or metastases thereof, e.g. leukaemias and myelodysplastic syndrome, malignant lymphomas, head and neck tumours including brain tumours and brain metastases, tumours of the thorax including non small cell and small cell lung tumours, gastrointestinal tumours, endocrine tumours, mammary and other gynaecological tumours, urological tumours including renal, bladder and prostate tumours, skin tumours, and sarcomas, and/or metastases thereof.

17. Use of

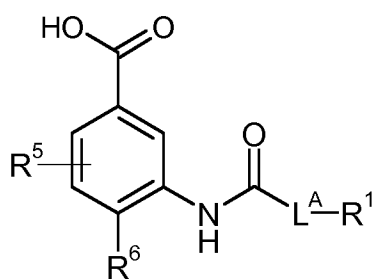
an intermediate compound of general formula (VI):



(VI)

in which R², R³, R⁵, and R⁶ are as defined for general formula (I) in any one of claims 1 to 8,
or

an intermediate compound of general formula (XI):



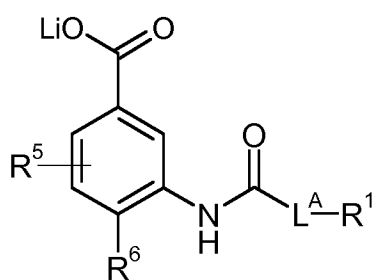
(XI)

in which L^A , R^1 , R^5 , and R^6 are as defined for the compounds of general formula (I) in any one of claims 1 to 8,

5

or

an intermediate compound of general formula (XIa):

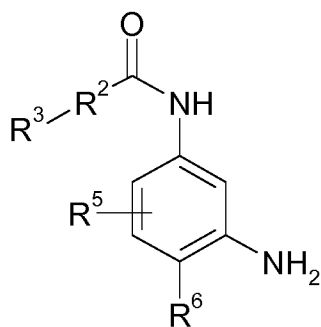


(XIa)

10 in which L^A , R^1 , R^5 , and R^6 are as defined for general formula (I) in any one of claims 1 to 8,

or

an intermediate compound of general formula (XVII):

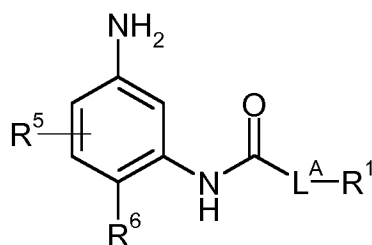


(XVII)

15 in which R^2 , R^3 , R^5 , and R^6 are as defined for general formula (I) in any one of claims 1 to 8,

or

an intermediate compound of general formula (XXII):

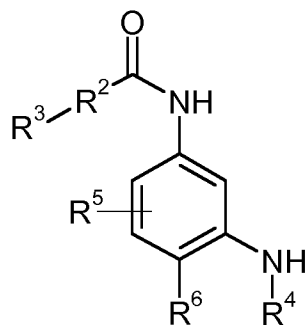


(XXII)

5 in which L^A , R^1 , R^5 and R^6 are as defined for general formula (I) in any one of claims 1 to 8,

or

an intermediate compound of general formula (XXIV):

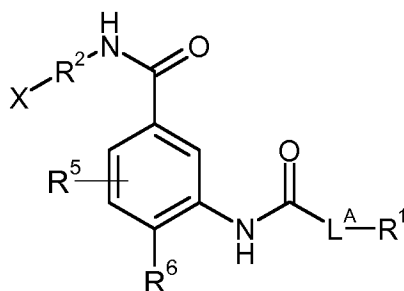


(XXIV)

10 in which R^2 , R^3 , R^4 , R^5 and R^6 are as defined for general formula (I) in any one of claims 1 to 8,

or

an intermediate compound of general formula (XXV):



(XXV)

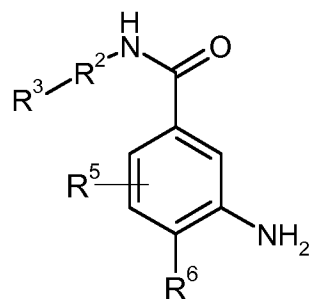
15 in which L^A , R^1 , R^2 , R^5 and R^6 are as defined for general formula (I) in any one of claims 1 to 8,

and X represents a group enabling palladium catalysed coupling reactions, such as chloro, bromo, iodo, trifluoromethylsulfonyloxy, nonafluorobutylsulfonyloxy or a boronic acid or an ester thereof,

for the preparation of a compound of general formula (I) according to any one of claims 1 to 8.

5

18. An intermediate compound of general formula (VI):



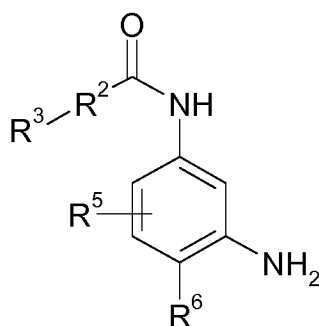
(VI)

in which R^2 , R^3 , R^5 , and R^6 are as defined for general formula (I) in any one of claims 1 to 8,

10

or

an intermediate compound of general formula (XVII):

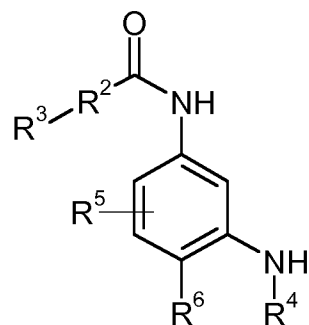


(XVII)

15 in which R^2 , R^3 , R^5 , and R^6 are as defined for general formula (I) in any one of claims 1 to 8,

or

an intermediate compound of general formula (XXIV):

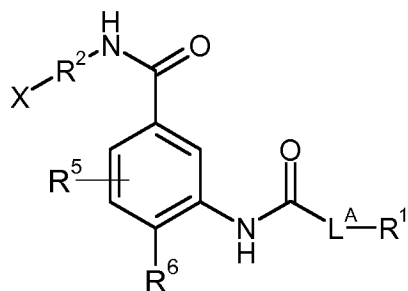


(XXIV)

in which R^2 , R^3 , R^4 , R^5 and R^6 are as defined for general formula (I) in any one of claims 1 to 8,

5 or

an intermediate compound of general formula (XXV):



(XXV)

in which L^A , R^1 , R^2 , R^5 and R^6 are as defined for general formula (I) in any one of claims 1 to 8,

10 and X represents a group enabling palladium catalysed coupling reactions, such as chloro, bromo, iodo, trifluoromethylsulfonyloxy, nonafluorobutylsulfonyloxy or a boronic acid or an ester thereof.