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(71) Applicant: **BAYER PHARMA AKTIENGESELLSCHAFT** [DE/DE]; Müllerstr. 178, 13353 Berlin (DE).

(72) Inventors: **THEDE, Kai**; Stargarder Str. 62, 10437 Berlin (DE). **BENDER, Eckhard**; Gudrunstr. 9, Wohnung 9, 40764 Langenfeld (DE). **SCOTT, William**; 210 Saddle Hill Drive, Guilford, Connecticut 06437 (US). **RICHTER, Anja**; Schützenstr. 18, 12105 Berlin (DE). **ZORN, Ludwig**; Osianderweg 45a, 13509 Berlin (DE). **LIU, Ningshu**; Ringstr. 89a, 12203 Berlin (DE). **MÖNNING, Ursula**; Eichendamm 5, 15569 Woltersdorf (DE). **SIEGEL, Franziska**; Pappelallee 58, 10437 Berlin (DE). **GOLZ, Stefan**; Sperlingstr. 17, 45472 Mülheim an der Ruhr (DE). **HÄGEBARTH, Andrea**; An den Eldenaer Höfen 13, 10247 Berlin (DE). **LIENAU, Philip**; Jahnstr. 13, 10967 Berlin (DE). **PUEHLER, Florian**; 28 Croton St., Wellesley, Massachusetts 02481 (US). **BASTING, Daniel**; Düsseldorfer Str. 127, 51063 Köln (DE). **SCHNEIDER, Dirk**; Bodelschwinghweg 39, 42115 Wuppertal (DE). **MÖWES, Manfred**; Maßmannstr. 9, 12163 Berlin (DE).

(74) Agent: **BIP PATENTS**; c/o Bayer Intellectual Property GmbH, Alfred-Nobel-Str. 10, 40789 Monheim am Rhein (DE).

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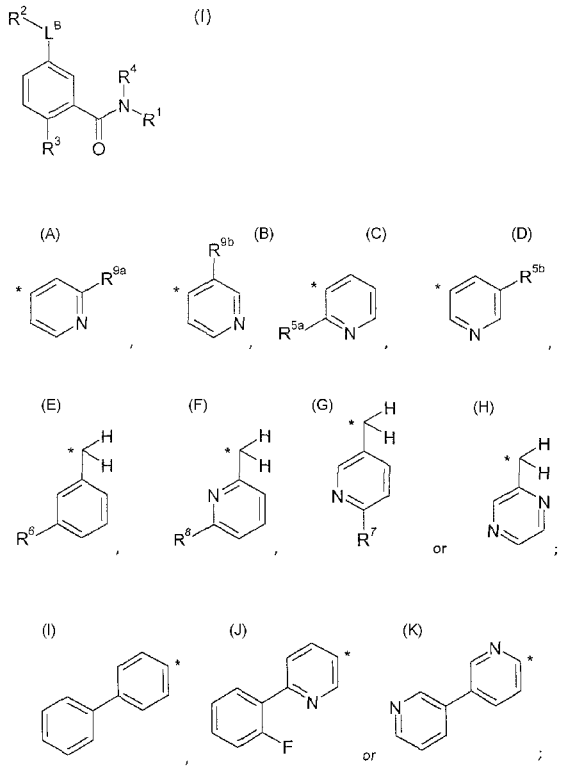
(54) Title: 3-CARBAMOYLPHENYL-4-CARBOXAMIDE AND ISOPHTALAMIDE DERIVATIVES AS INHIBITORS OF THE WNT SIGNALLING PATHWAY



(57) Abstract: 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 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, in which: R^1 represents a group selected from: C_1-C_3-alkoxy-C_2-C_5-alkyl-, (A), (B), (C), (D), (E), (F), (G) or (H); wherein * indicates the point of attachment to the rest of the molecule; R^2 represents a group selected from: (I), (J) or (K); wherein * indicates the point of attachment to the rest of the molecule.

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3-CARBAMOYLPHENYL-4-CARBOXAMIDE AND ISOPHTALAMIDE DERIVATIVES AS INHIBITORS OF THE WNT SIGNALLING PATHWAY

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 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.

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 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, 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.

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-3β), Axin-1 or -2 and Casein Kinase 1α. 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 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 impairement 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 (Blankesteijn, 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 initmal 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-Chaqmaqchi, 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 ß-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

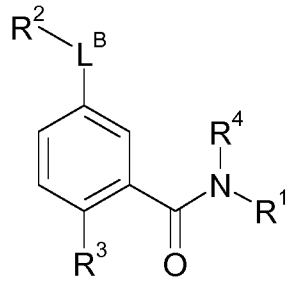
of formula (I) as described and defined herein. The same is true for the related publication WO 2004/006906 (A2) which discloses a method for treating a patient having a cancer or other neoplasm by administering to the patient a niclosamide.

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

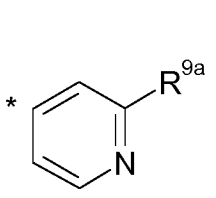
The present invention relates to compounds of general formula (I):



(I)

in which :

R^1 represents a group selected from:
C_1-C_3-alkoxy-C_2-C_5-alkyl-,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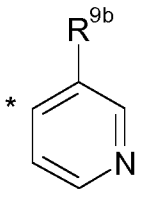
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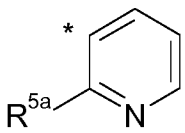
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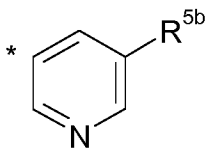
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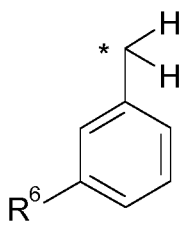
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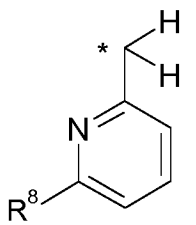
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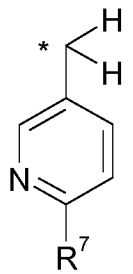
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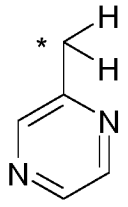
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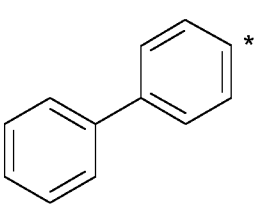
wherein * indicates the point of attachment to the rest of the molecule;

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^2 represents a group selected from: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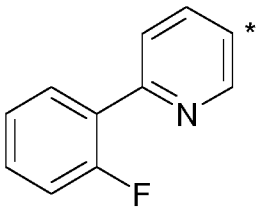
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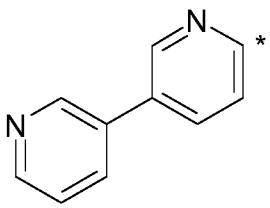

;

wherein * indicates the point of attachment to the rest of the molecule;

R^3 represents a group selected from: $-CH_3$, $-O-CH_3$, $-O-CF_3$;

R^4 represents a hydrogen atom or methyl group;

R^{5a} represents a hydrogen atom or methyl group;

R^{5b} represents a hydrogen atom or methyl group;

R^6 represents a hydrogen atom;

R^7 represents a hydrogen atom or a group selected from:
$-NH_2$ or $-N(H)-C(=O)-OC(CH_3)_3$;

R^8 represents a hydrogen atom, $-NH_2$ or methyl group;

R^{9a} represents a hydrogen atom or a halogen atom or a group selected from:
methyl, ethyl or methoxy;

R^{9b} represents a hydrogen atom or a halogen atom or a group selected from:
methyl, ethyl or methoxy;

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

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 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*.

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 iodine atom.

The term "C_1-C_6-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-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 ("C_1-C_4-alkyl"), *e.g.* a methyl, ethyl, propyl, butyl, iso-propyl, iso-butyl, sec-butyl, tert-butyl group, more particularly 1, 2 or 3 carbon atoms ("C_1-C_3-alkyl"), *e.g.* a methyl, ethyl, *n*-propyl- or *iso*-propyl group.

The term "halo-C_1-C_6-alkyl" is to be understood as preferably meaning a linear or branched, saturated, monovalent hydrocarbon group in which the term "C_1-C_6-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-C_1-C_6-alkyl group is, for example, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CF_2CF_3$, or $-CH_2CF_3$.

The term "C_1-C_6-alkoxy" is to be understood as preferably meaning a linear or branched, saturated, monovalent group of formula –O-(C_1-C_6-alkyl), in which the term "C_1-C_6-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-C_1-C_6-alkoxy" is to be understood as preferably meaning a linear or branched, saturated, monovalent C_1-C_6-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-C_1-C_6-alkoxy group is, for example, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, $-OCF_2CF_3$, or $-OCH_2CF_3$.

The term "C_1-C_6-alkoxy-C_1-C_6-alkyl" is to be understood as preferably meaning a linear or branched, saturated, monovalent C_1-C_6-alkyl group, as defined *supra*, in which one or more of the hydrogen atoms is replaced, identically or differently, by a C_1-C_6-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-C_1-C_6-alkoxy-C_1-C_6-alkyl" is to be understood as preferably meaning a linear or branched, saturated, monovalent C_1-C_6-alkoxy-C_1-C_6-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-C_1-C_6-alkoxy-C_1-C_6-alkyl group is, for example, $-CH_2CH_2OCF_3$, $-CH_2CH_2OCHF_2$, $-CH_2CH_2OCH_2F$, $-CH_2CH_2OCF_2CF_3$, or $-CH_2CH_2OCH_2CF_3$.

The term "C_1-C_6-alkoxy-C_2-C_6-alkoxy" is to be understood as preferably meaning a saturated, monovalent C_2-C_6-alkoxy group, as defined *supra*, in which one of the hydrogen atoms is replaced by a C_1-C_6-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 "C_2-C_6-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 ("C_2-C_3-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 "C_2-C_6-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 ("C_2-C_3-alkynyl"). Said C_2-C_6-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 "C_3-C_7-cycloalkyl" is to be understood as meaning a saturated, monovalent, monocyclic hydrocarbon ring which contains 3, 4, 5, 6 or 7 carbon atoms. Said C_3-C_7-cycloalkyl group is for example a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl ring. Particularly, said ring contains 3, 4, 5 or 6 carbon atoms ("C_3-C_6-cycloalkyl").

The term "C_4-C_8-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 ("C_4-C_6-cycloalkenyl"). Said C_4-C_8-cycloalkenyl group is for example a cyclobutenyl, cyclopentenyl, or cyclohexenyl group.

The term "C_3-C_6-cycloalkoxy" is to be understood as meaning a saturated, monovalent, monocyclic group of formula -O-(C_3-C_6-cycloalkyl), in which the term "C_3-C_6-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 azetidinyl, 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 "C_6-C_{14}-aryl" group), particularly a ring having 6 carbon atoms (a "C_6-aryl" group), *e.g.* a phenyl group; or a ring having 9 carbon atoms (a "C_9-aryl" group), *e.g.* an indanyl or indenyl group, or a ring having 10 carbon atoms (a "C_{10}-aryl" group), *e.g.* a tetralinyl, dihydronaphthyl, or naphthyl group, or a biphenyl group (a "C_{12}-aryl" group), or a ring having 13 carbon atoms, (a "C_{13}-aryl" group), *e.g.* a fluorenyl group, or a ring having 14 carbon atoms, (a "C_{14}-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-4H-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, indolizinyl, 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 heteroarylic 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 "C_1-C_6", as used throughout this text, *e.g.* in the context of the definition of "C_1-C_6-alkyl", "C_1-C_6-haloalkyl", "C_1-C_6-alkoxy", or "C_1-C_6-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 "C_1-C_6" is to be interpreted as any sub-range comprised therein, *e.g.* C_1-C_6, C_2-C_5, C_3-C_4, C_1-C_2, C_1-C_3, C_1-C_4, C_1-C_5, C_1-C_6; particularly C_1-C_2, C_1-C_3, C_1-C_4, C_1-C_5, C_1-C_6; more particularly C_1-C_4; in the case of "C_1-C_6-haloalkyl" or "C_1-C_6-haloalkoxy" even more particularly C_1-C_2.

Similarly, as used herein, the term "C_2-C_6", as used throughout this text, *e.g.* in the context of the definitions of "C_2-C_6-alkenyl" and "C_2-C_6-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 "C_2-C_6" is to be interpreted as any sub-range comprised therein, *e.g.* C_2-C_6, C_3-C_5, C_3-C_4, C_2-C_3, C_2-C_4, C_2-C_5; particularly C_2-C_3.

Further, as used herein, the term "C_3-C_7", as used throughout this text, *e.g.* in the context of the definition of "C_3-C_7-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 "C_3-C_7" is to be interpreted as any sub-range comprised therein, *e.g.* C_3-C_6, C_4-C_5, C_3-C_5, C_3-C_4, C_4-C_6, C_5-C_7; particularly C_3-C_6.

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.

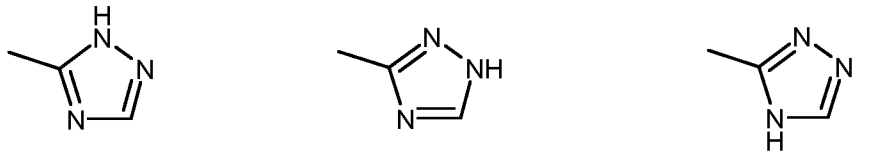
In order to limit different types of isomers from each other reference is made to IUPAC Rules Section E (Pure Appl Chem 45, 11-30, 1976).

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 ^{2}H (deuterium), ^{3}H (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, ^{125}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 ^{3}H 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 1*H* tautomer, or a 2*H* tautomer, or even a mixture in any amount of the two tautomers, or a triazole moiety for example can exist as a 1*H* tautomer, a 2*H* tautomer, or a 4*H* tautomer, or even a mixture in any amount of said 1*H*, 2*H* and 4*H* 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.

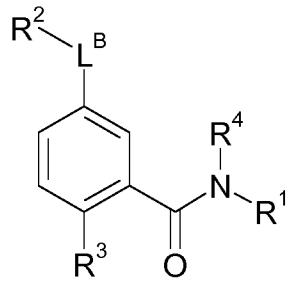
Further, the compounds of the present invention can exist in free form, *e.g.* as a free base, or as a free acid, or as a zwitterion, or can exist in the form of a salt. Said salt may be any salt, either an

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.

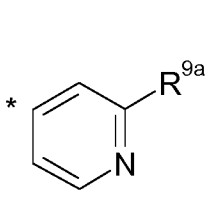
In accordance with a first aspect, the present invention covers compounds of general formula (I):



(I)

in which :

R^1 represents a group selected from:
C_1-C_3-alkoxy-C_2-C_5-alkyl-,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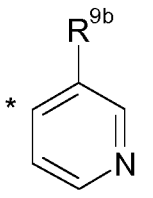
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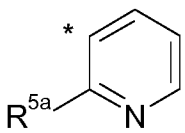
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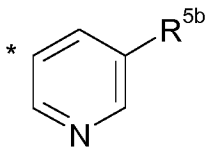
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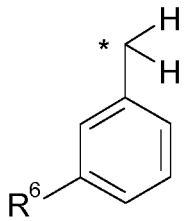
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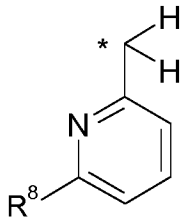
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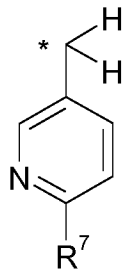
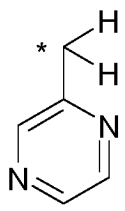
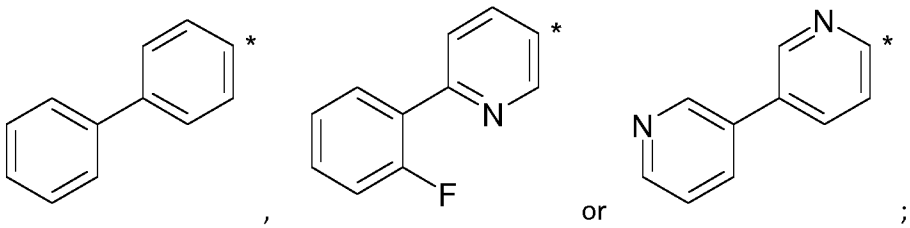

or

;

wherein * indicates the point of attachment to the rest of the molecule;

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^2 represents a group selected from:



wherein * indicates the point of attachment to the rest of the molecule;

R^3 represents a group selected from: $-CH_3$, $-O-CH_3$, $-O-CF_3$;

R^4 represents a hydrogen atom or methyl group;

R^{5a} represents a hydrogen atom or methyl group;

R^{5b} represents a hydrogen atom or methyl group;

R^6 represents a hydrogen atom;

R^7 represents a hydrogen atom or a group selected from:
$-NH_2$, $-N(H)-C(=O)-OC(CH_3)_3$;

R^8 represents a hydrogen atom, $-NH_2$ or methyl group;

R^{9a} represents a hydrogen atom or a halogen atom or a group selected from:
methyl, ethyl, methoxy;

R^{9b} represents a hydrogen atom or a halogen atom or a group selected from:
methyl, ethyl, methoxy;

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

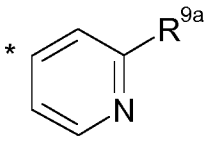
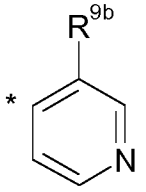
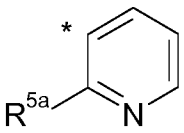
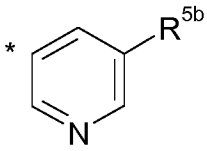
In a preferred embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^1 represents a C_1-C_3-alkoxy-C_2-C_5-alkyl- group.

In another preferred embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^1 represents a $-CH_2-CH_2-O-(C_1-C_3\text{-alkyl})$ or $-CH_2-CH_2-CH_2-O-(C_1-C_3\text{-alkyl})$ group.

In another preferred embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^1 represents a group selected from: $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-CH_2-O-CH_2-CH_3$, and $-CH_2-CH_2-CH_2-O-C(H)(CH_3)_2$.

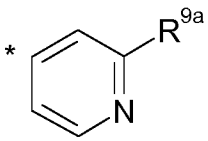
In another preferred embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^1 represents a group selected from: $-CH_2-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-CH_2-O-CH_2-CH_3$, and $-CH_2-CH_2-CH_2-O-C(H)(CH_3)_2$.

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

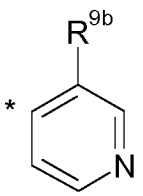

,

,

,

;

wherein * indicates the point of attachment to the rest of the molecule.

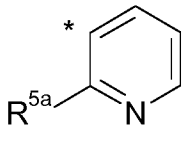
In another preferred embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^1 represents


; wherein * indicates the point of attachment to the rest of the molecule.

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

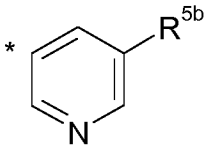

; wherein * indicates the point of attachment to the rest of the molecule.

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



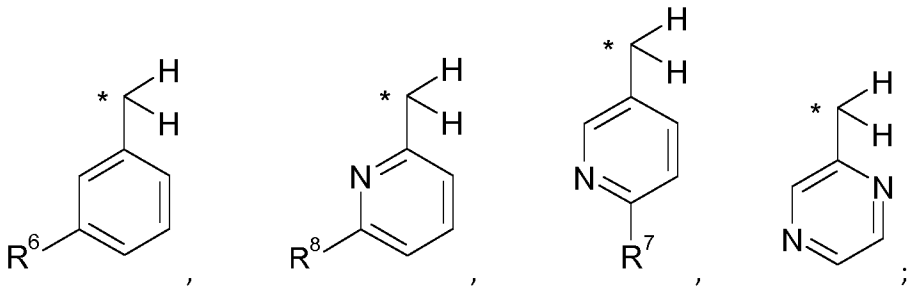
; wherein * indicates the point of attachment to the rest of the molecule.

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



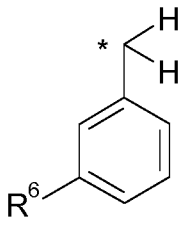
; wherein * indicates the point of attachment to the rest of the molecule.

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



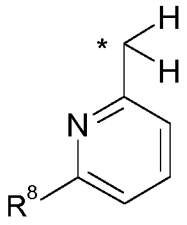
wherein * indicates the point of attachment to the rest of the molecule.

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



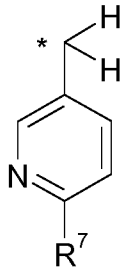
; wherein * indicates the point of attachment to the rest of the molecule.

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



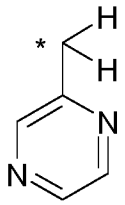
; wherein * indicates the point of attachment to the rest of the molecule.

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



; wherein * indicates the point of attachment to the rest of the molecule.

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

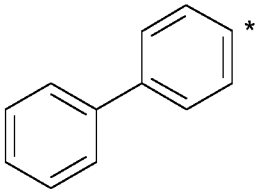


; wherein * indicates the point of attachment to the rest of the molecule.

In another 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.

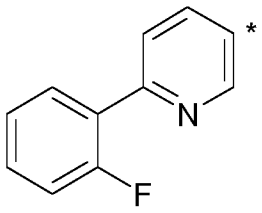
In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which L^B represents *C(=O)-N(H)**; wherein * indicates the point of attachment to R^2, and ** indicates the point of attachment to the phenyl group.

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



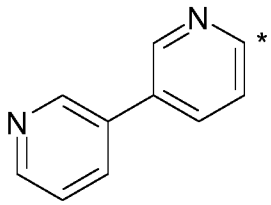
; wherein * indicates the point of attachment to the rest of the molecule.

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 the rest of the molecule.

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 the rest of the molecule.

In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^3 represents $-CH_3$.

In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^3 represents $-O-CH_3$.

In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^3 represents $-O-CF_3$.

In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^4 represents a hydrogen atom.

In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^4 represents a methyl group.

In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^{5a} represents a hydrogen atom.

In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^{5a} represents a methyl group.

In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^{5b} represents a hydrogen atom.

In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^{5b} represents a methyl group.

In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^{7} represents a hydrogen atom.

In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^{7} represents $-NH_2$ or $-N(H)-C(=O)-OC(CH_3)_3$.

In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^{8} represents a hydrogen atom.

In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^{8} represents a $-NH_2$ group.

In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^{8} represents a methyl group.

In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^{9a} represents a hydrogen atom.

In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^{9a} represents a halogen atom, preferably a fluorine atom or a chlorine atom.

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

supra, in which R^{9a} represents a methyl or ethyl group.

In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^{9a} represents a methoxy group.

In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^{9b} represents a hydrogen atom.

In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^{9b} represents a halogen atom, preferably a fluorine atom or a chlorine atom.

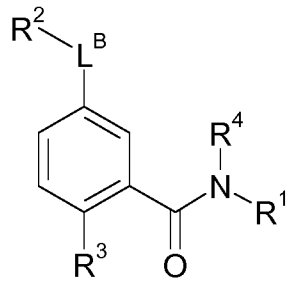
In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^{9b} represents a methyl group.

In another embodiment, the present invention relates to compounds of the general formula (I), *supra*, in which R^{9b} represents a methoxy group.

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

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

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



(I)

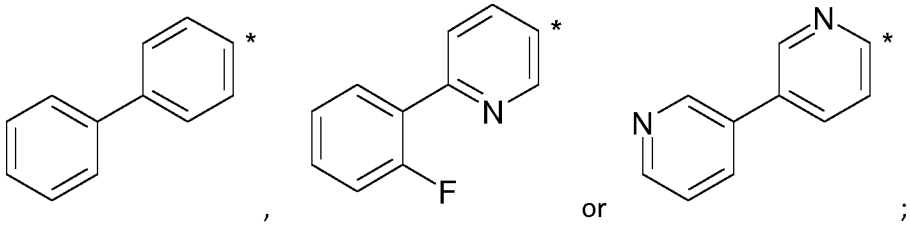
in which :

R^1 represents a group selected from: $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-CH_2-O-CH_2-CH_3$, and $-CH_2-CH_2-CH_2-O-C(H)(CH_3)_2$;

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^2 represents a group selected from:



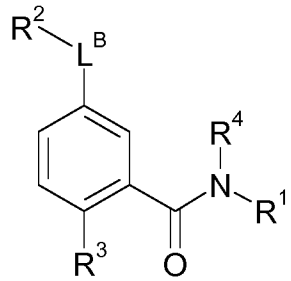
wherein * indicates the point of attachment to the rest of the molecule;

R^3 represents a group selected from: $-CH_3$, $-O-CH_3$, $-O-CF_3$;

R^4 represents a hydrogen atom;

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

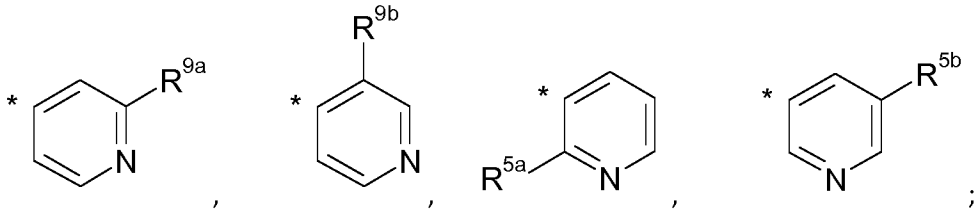
In another preferred embodiment, the present invention relates to compounds of general formula (I):



(I)

in which :

R^1 represents a group selected from:

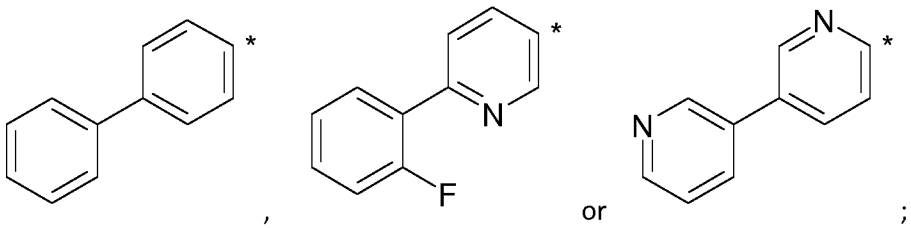


wherein * indicates the point of attachment to the rest of the molecule;

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^2 represents a group selected from:



wherein * indicates the point of attachment to the rest of the molecule;

R^3 represents a group selected from: $-CH_3$, $-O-CH_3$, $-O-CF_3$;

R^4 represents a hydrogen atom;

R^{5a} represents a hydrogen atom or methyl group;

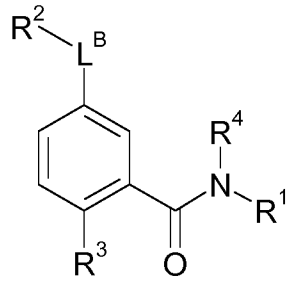
R^{5b} represents a hydrogen atom or methyl group;

R^{9a} represents a hydrogen atom or a halogen atom or a group selected from: methyl, ethyl or methoxy;

R^{9b} represents a hydrogen atom or a halogen atom or a group selected from: methyl, ethyl or methoxy;

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

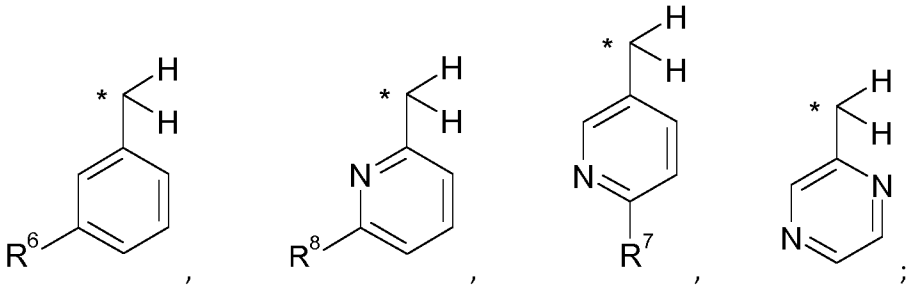
In another preferred embodiment, the present invention relates to compounds of general formula (I):



(I)

in which :

R^1 represents a group selected from:

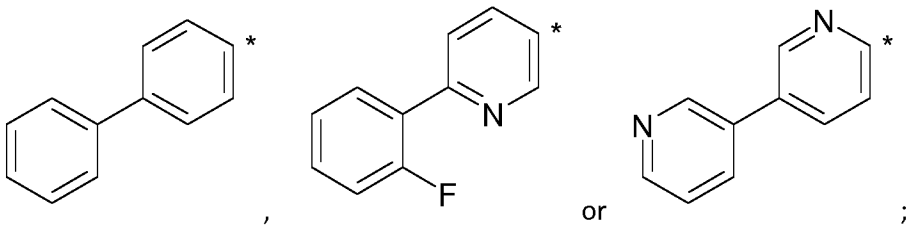


wherein * indicates the point of attachment to the rest of the molecule;

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^2 represents a group selected from:



wherein * indicates the point of attachment to the rest of the molecule;

R^3 represents a group selected from: $-CH_3$, $-O-CH_3$, $-O-CF_3$;

R^4 represents a hydrogen atom;

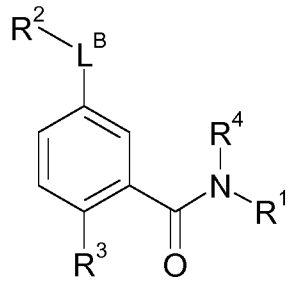
R^6 represents a hydrogen atom;

R^7 represents a hydrogen atom or a group selected from:
$-NH_2$ or $-N(H)-C(=O)-OC(CH_3)_3$;

R^8 represents a hydrogen atom, $-NH_2$ or methyl group;

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

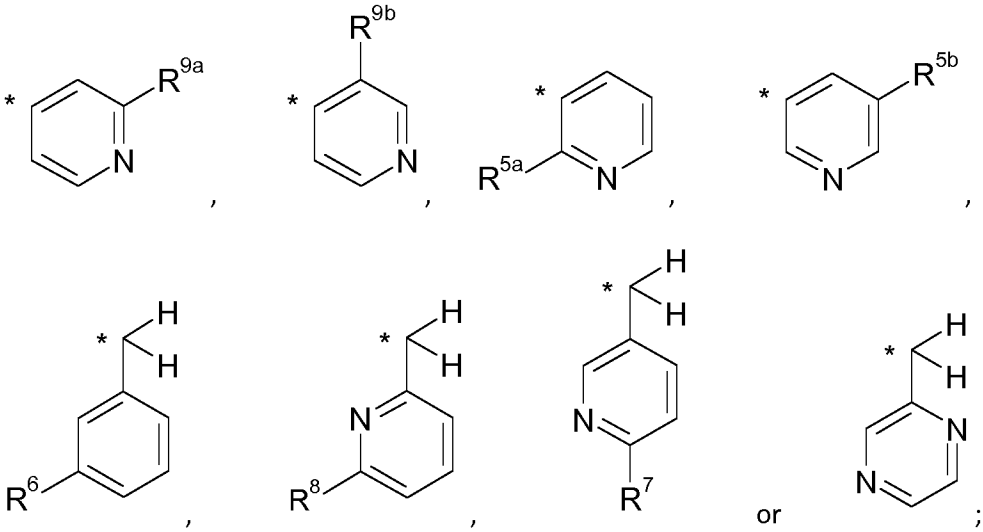
In another preferred embodiment, the present invention relates to compounds of general formula (I):



(I)

in which :

R^1 represents a group selected from:

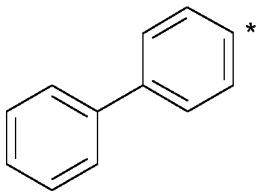


wherein * indicates the point of attachment to the rest of the molecule;

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^2 represents



;

wherein * indicates the point of attachment to the rest of the molecule;

R^3 represents a group selected from: $-CH_3$, $-O-CH_3$, $-O-CF_3$;

R^4 represents a hydrogen atom;

R^{5a} represents a hydrogen atom or methyl group;

R^{5b} represents a hydrogen atom or methyl group;

R^6 represents a hydrogen atom;

R^7 represents a hydrogen atom or a group selected from:
$-NH_2$, $-N(H)-C(=O)-OC(CH_3)_3$;

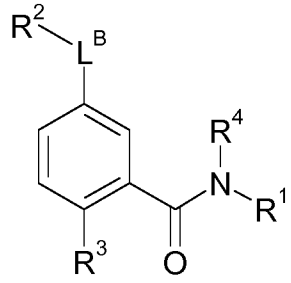
R^8 represents a hydrogen atom, $-NH_2$ or methyl group;

R^{9a} represents a hydrogen atom or a halogen atom or a group selected from:
methyl, ethyl, methoxy;

R^{9b} represents a hydrogen atom or a halogen atom or a group selected from:
methyl, ethyl, methoxy;

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

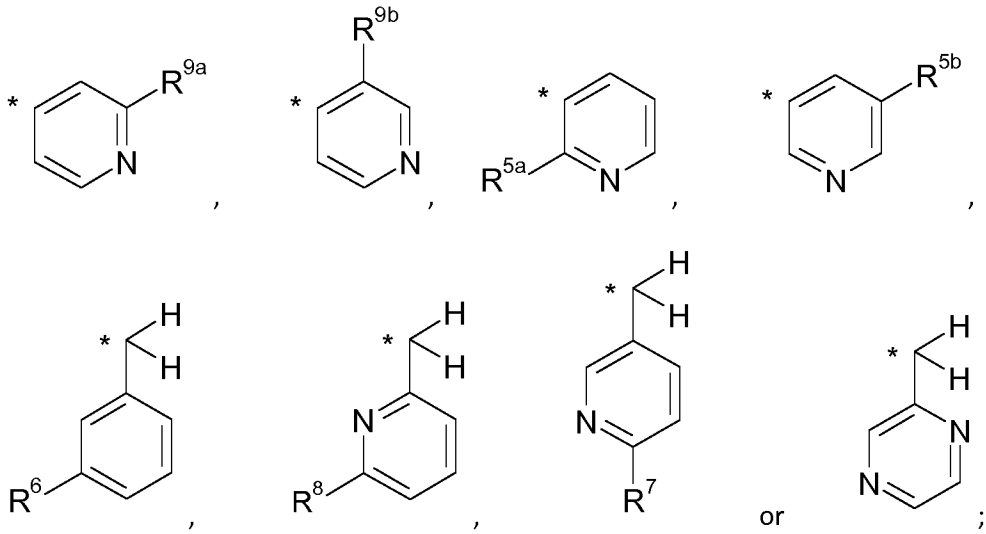
In another preferred embodiment, the present invention relates to compounds of general formula (I):



(I)

in which :

R^1 represents a group selected from:

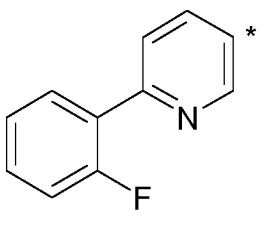


wherein * indicates the point of attachment to the rest of the molecule;

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^2 represents



;

wherein * indicates the point of attachment to the rest of the molecule;

R^3 represents a group selected from: $-CH_3$, $-O-CH_3$, $-O-CF_3$;

R^4 represents a hydrogen atom;

R^{5a} represents a hydrogen atom or methyl group;

R^{5b} represents a hydrogen atom or methyl group;

R^6 represents a hydrogen atom;

R^7 represents a hydrogen atom or a group selected from:
$-NH_2$, $-N(H)-C(=O)-OC(CH_3)_3$;

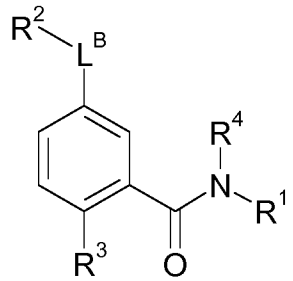
R^8 represents a hydrogen atom, $-NH_2$ or methyl group;

R^{9a} represents a hydrogen atom or a halogen atom or a group selected from:
methyl, ethyl, methoxy;

R^{9b} represents a hydrogen atom or a halogen atom or a group selected from:
methyl, ethyl, methoxy;

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

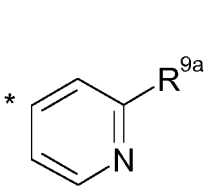
In another preferred embodiment, the present invention relates to compounds of general formula (I):



(I)

in which :

R^1 represents a group selected from: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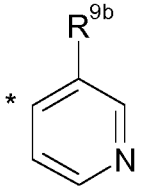
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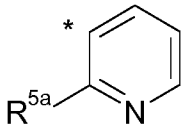
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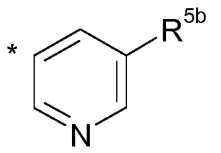
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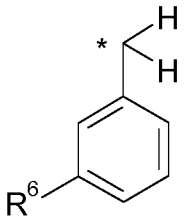
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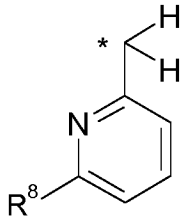
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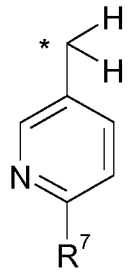
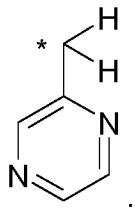
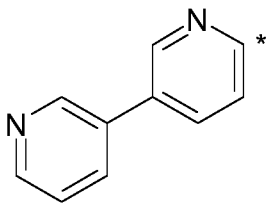

or

;

wherein * indicates the point of attachment to the rest of the molecule;

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^2 represents


;

wherein * indicates the point of attachment to the rest of the molecule;

R^3 represents a group selected from: $-CH_3$, $-O-CH_3$, $-O-CF_3$;

R^4 represents a hydrogen atom;

R^{5a} represents a hydrogen atom or methyl group;

R^{5b} represents a hydrogen atom or methyl group;

R^6 represents a hydrogen atom;

R^7 represents a hydrogen atom or a group selected from:

$-NH_2$, $-N(H)-C(=O)-OC(CH_3)_3$;

R^8 represents a hydrogen atom, $-NH_2$ or methyl group;

R^{9a} represents a hydrogen atom or a halogen atom or a group selected from: methyl, ethyl, methoxy;

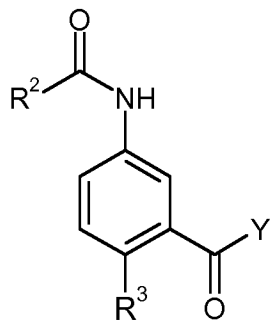
R^{9b} represents a hydrogen atom or a halogen atom or a group selected from: methyl, ethyl, methoxy;

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

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

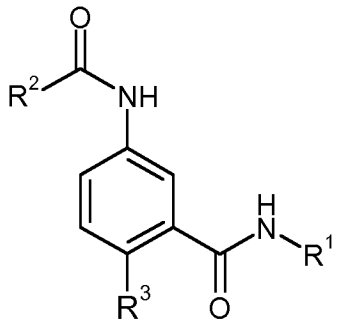
In accordance with another aspect, the present invention covers methods of preparing compounds of the present invention, said methods comprising the steps as described in the Experimental Section herein.

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 (A3) or (A4):

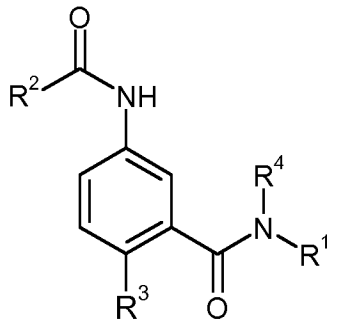


(A3): Y = OH
(A4): Y = Cl

in which R^2 and R^3 are as defined for general formula (I), *supra*;
to react with a compound of general formula H_2N-R^1 or HNR^1R^4, wherein R^1 and R^4 are as defined for the compounds of general formula (I), *supra*;
thereby giving, upon optional deprotection, a compound of general formula (Ia) or (Ic):



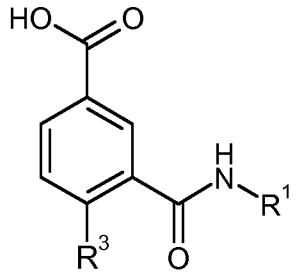
(Ia)



(Ic)

in which R^1, R^2, R^3 and R^4 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 (B5):

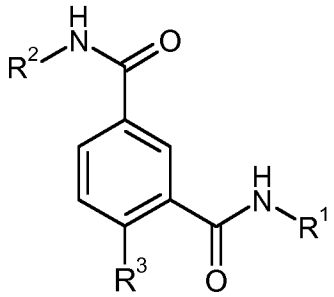


(B5)

in which R^1 and R^3 are as defined for general formula (I), *supra*;

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

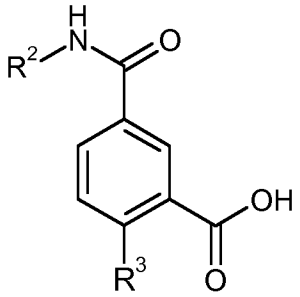
thereby giving, upon optional deprotection, a compound of general formula (Ib):



(Ib)

in which R^1, R^2 and R^3 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 (C4):

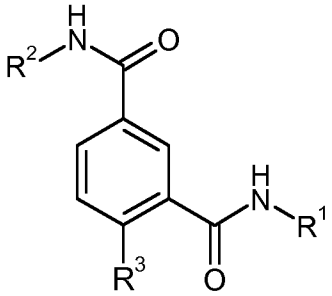


(C4)

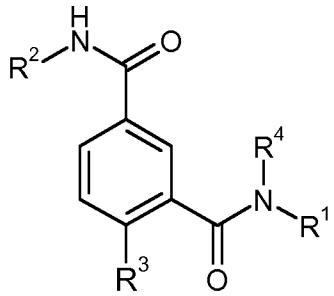
in which R^2 and R^3 are as defined for general formula (I), *supra*;

to react with a compound of general formula $H_2N\text{-}R^1$ or HNR^1R^4, wherein R^1 and R^4 are as defined for the compounds of general formula (I), *supra*;

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



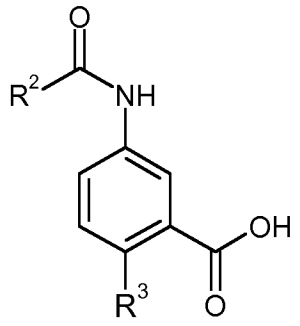
(Ib)



(Id)

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

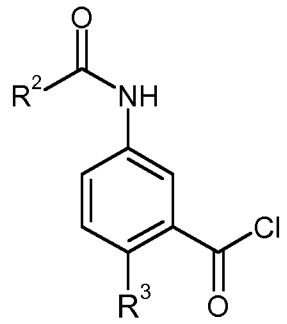
In accordance with a further aspect, the present invention covers intermediate compounds which are useful in the preparation of compounds of the present invention of general formula (I), particularly in the method described herein. In particular, the present invention covers intermediate compounds of general formula (A3):



(A3)

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

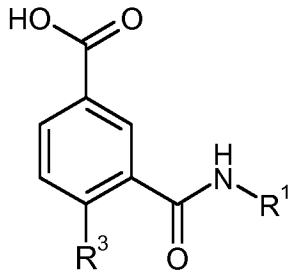
The present invention also covers intermediate compounds of general formula (A4):



(A4)

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

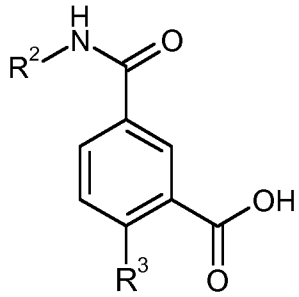
The present invention also covers intermediate compounds of general formula (B5):



(B5)

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

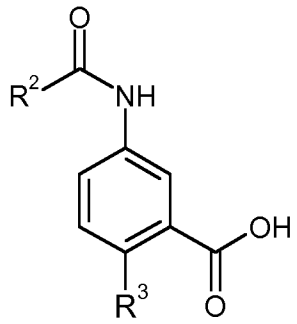
The present invention also covers intermediate compounds of general formula (C4):



(C4)

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

In accordance with yet another aspect, the present invention covers the use of the intermediate compounds of general formula (A3) :

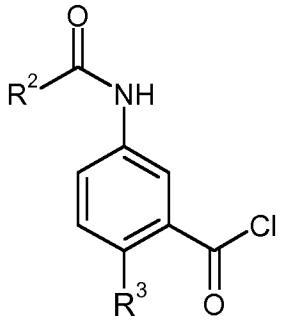


(A3)

in which R^2 and R^3 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 (A4) :

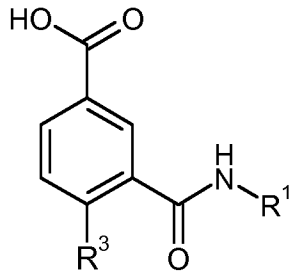


(A4)

in which R^2 and R^3 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 (B5) :

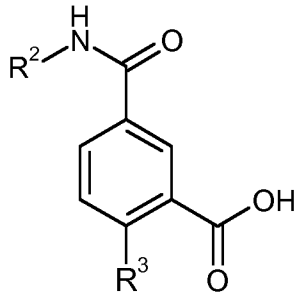


(B5)

in which R^1 and R^3 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 (C4) :



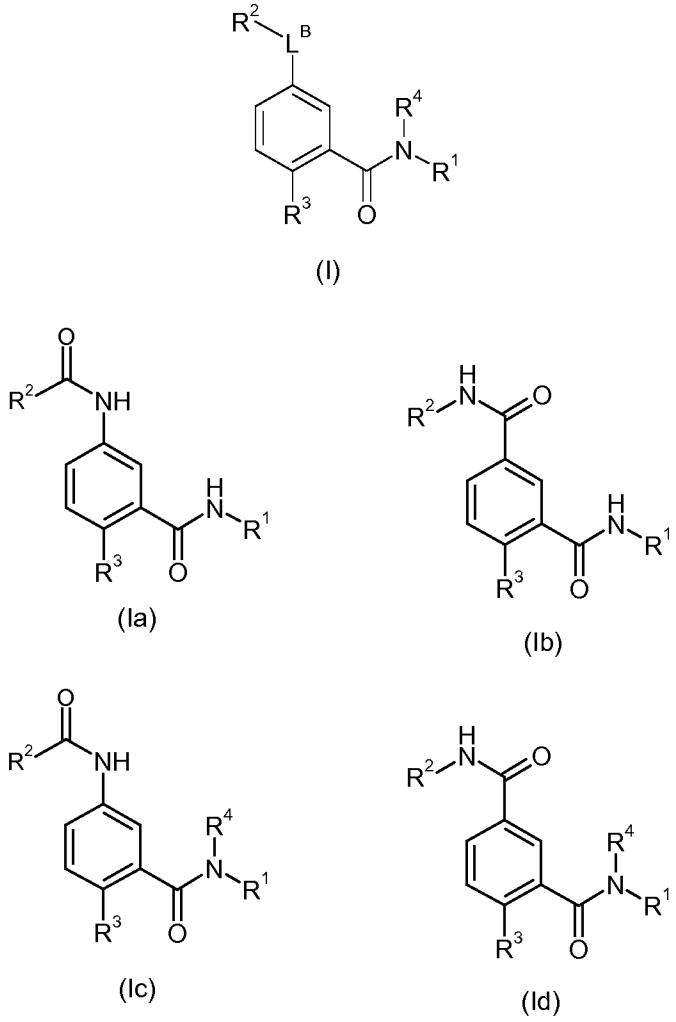
(C4)

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

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

GENERAL SYNTHESIS OF THE COMPOUNDS OF THE INVENTION

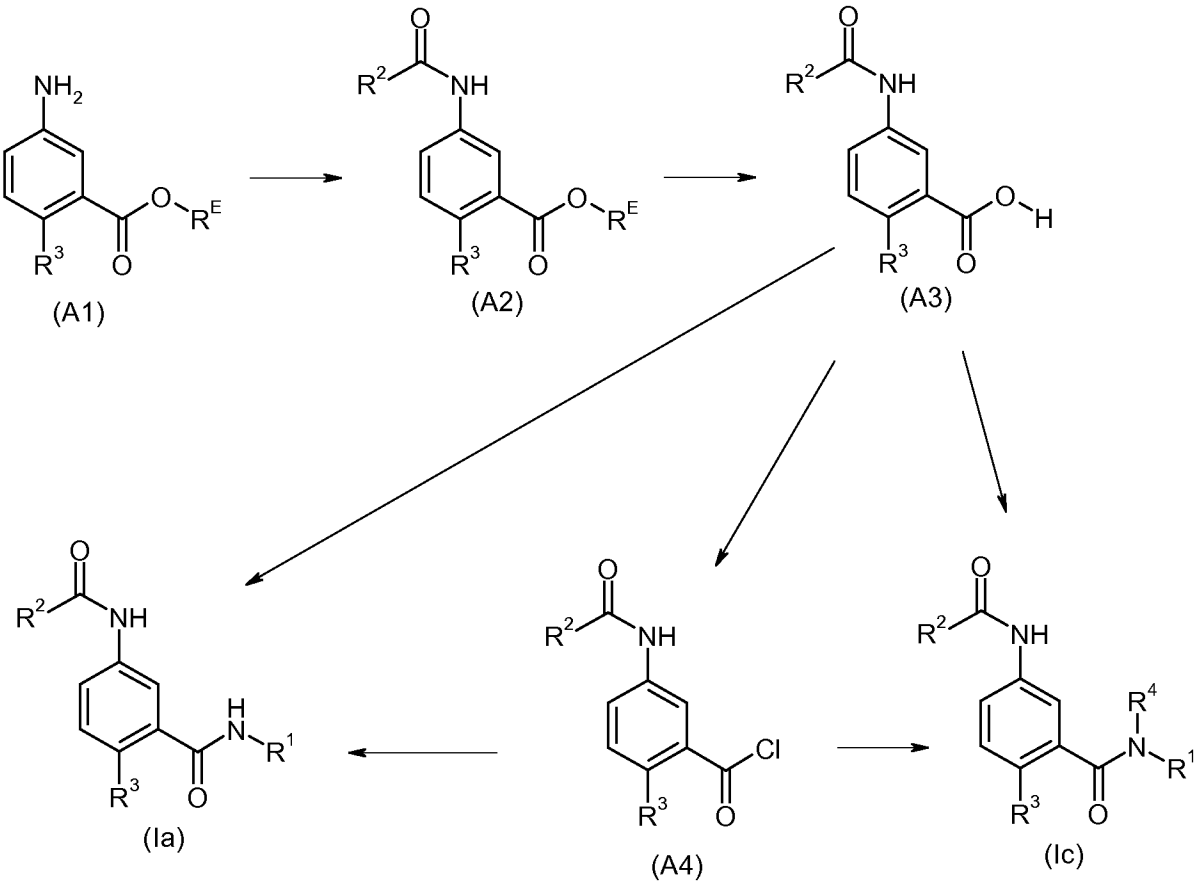
The following paragraphs outline a variety of synthetic approaches suitable to prepare compounds of formulae (Ia), (Ib), (Ic) and (Id), in which R^1, R^2, R^3 and R^4 are as defined for the compounds of general formula (I), *supra*. Formulae (Ia) and (Ib), in which R^4 represents hydrogen, both constitute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

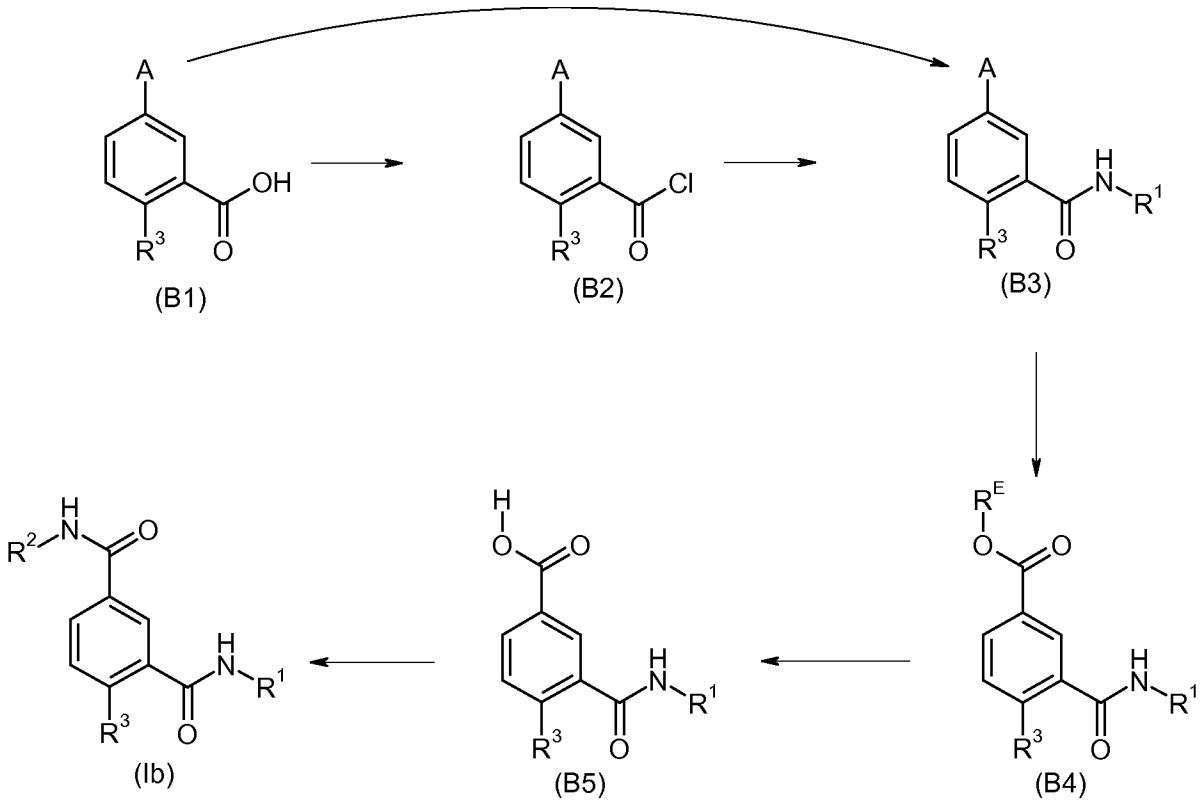
possible that two or more successive steps may be performed without work-up being performed between said steps, *e.g.* in a "one-pot" reaction, as it is well-known to a person skilled in the art.



Scheme X2: Preparation of compounds of the formulae (Ia) and (Ic) from *meta*-aminobenzoic acid ester derivatives of formula (A1)

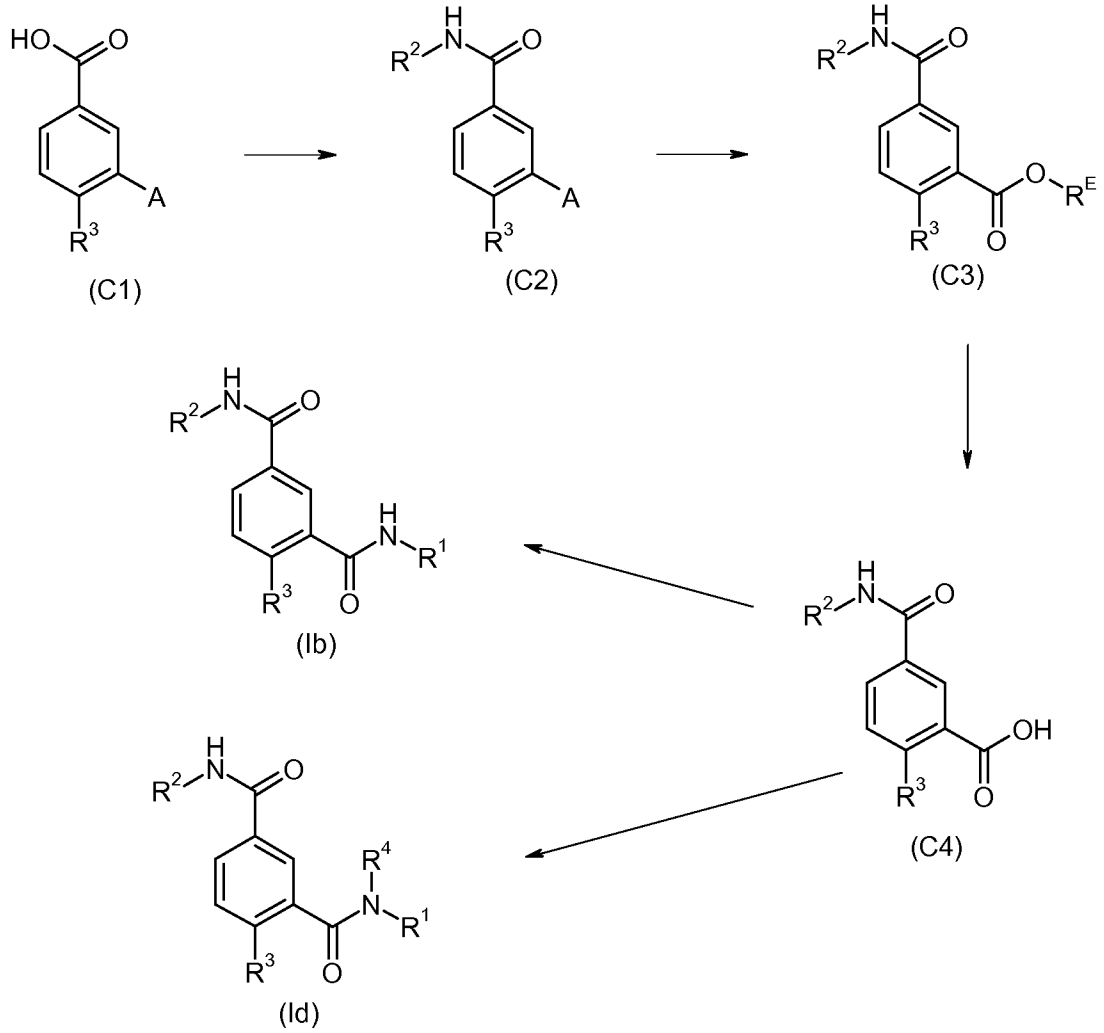
Scheme X2 outlines the preparation of compounds of formulae (Ia) and (Ic), in which R^1, R^2, R^3 and R^4 are as defined for the compounds of general formula (I), *supra*, starting from *meta*-aminobenzoic acid derivatives (A1), in which R^3 is as defined for the compounds of general formula (I), and in which R^E stands for a C_1-C_6-alkyl group, preferably methyl or ethyl. Aminobenzoic acid ester derivatives of formula (A1) are well known to a person skilled in the art, and are often commercially available. Said aminobenzoic acid esters of formula (A1) can be converted into amides of formula (A2). This can be accomplished directly by reacting a compound of formula (A1) with a carboxylic acid HO_2C-R^2, wherein R^2 is 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, HO_2C-R^2 can be converted into the corresponding benzoyl chloride Cl-(O=)C-R^2, in which R^2 is as defined for the compounds of general formula (I), by treatment

with a suitable chlorinating agent, such as oxalyl chloride. The carboxylic acid chlorides Cl-(O=)C-R^2 are commercially available in some instances. Then, said carboxylic acid chlorides are reacted with compounds of the formula (A1) in standard amide coupling reaction, which is known to persons skilled in the art of organic synthesis. The ester group present in compounds of formula (A2) can be saponified by reaction with e.g. lithium hydroxide to yield the lithium salt or after acidification, for example with hydrochloric acid, to yield the carboxylic acid of formula (A3). Said carboxylic acid of formula (A3) or the corresponding lithium salt is then converted into compounds of formula (Ia) or (Ic). This can be accomplished directly by reacting a compound of formula (A3) with an amino compound of formula H_2N-R^1 or HNR^1R^4, wherein R^1 and R^4 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 compound of formula (A3) can be converted into the corresponding benzoyl chloride of formula (A4), by treatment with a suitable chlorinating agent, such as oxalyl chloride. The carboxylic acid chloride of formula (A4) is then reacted in a standard amide coupling reaction with an amino compound of formula H_2N-R^1 or HNR^1R^4, wherein R^1 and R^4 are as defined for the compounds of general formula (I), to give the amides of general formula (Ia) or (Ic).



Scheme X3: Preparation of compounds of formula (Ib) from *meta*-bromobenzoic acid derivatives of formula (B1)

Scheme X3 outlines the preparation of compounds of formulae (Ib) in which R^1, R^2 and R^3 are as defined for the compounds of general formula (I), *supra*, starting from benzoic acid derivatives (B1), in which R^3 is as defined for the compounds of general formula (I), and A stands for chloro, bromo, iodo, trifluoromethylsulfonyloxy or nonafluorobutylsulfonyloxy. The benzoic acid derivatives of the formula (B1) are well known to a person skilled in the art, and are often commercially available. Said *meta*-substitutetd benzoic acid derivatives of the formula (B1) can be converted into amides of formula (B3), in which R^1 and R^3 are as defined for the compounds of general formula (I). This can be accomplished directly by reacting a compound of formula (B1) with an amino derivative of formula H_2N-R^1, wherein R^1 is 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 meta-substituted benzoic acid derivative (B1) can be converted into the corresponding benzoyl chloride (B2), by treatment with a suitable chlorinating agent, such as oxalyl chloride. The carboxylic acid chloride (B2) is then reacted in a standard amide coupling reaction with an amino derivative of formula H_2N-R^1, wherein R^1 is as defined for the compounds of general formula (I). The compound (B3) is then converted into the benzoic acid ester derivative (B4), wherein R^E stands for a C_1-C_6-alkyl group, preferably methyl or ethyl. This can be accomplished directly by reacting a compound of formula (B3) with carbonmonoxide and an alcohol R^E-OH, wherein R^E stands for a C_1-C_6-alkyl group, preferably methyl or ethyl, under palladium catalysis, for example trans-dichlorobis(triphenylphosphin)palladium(II), in the presence of a cosolvent, e.g. THF, and a tertiary aliphatic amine, e.g. triethylamine, at elevated temperatures, e.g. 100 °C, and pressure, e.g. 10 bar and higher. The ester group present in compounds of formula (B4) can be saponified by reaction with e.g. lithium hydroxide to yield the lithium salt or after acidification, for example with hydrochloric acid, to yield the carboxylic acid of formula (B5). Said carboxylic acid of formula (B5) or the corresponding lithium salt is then converted into compounds of formula (Ib). This can be accomplished directly by reacting a compound of formula (B5) with an amino compound of formula H_2N-R^2, wherein R^2 is 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.



Scheme X4: Preparation of compounds of formulae (Ib) and (Id) from *meta*-bromobenzoic acid derivatives of formula (C1)

Scheme X4 outlines the preparation of compounds of formulae (Ib) and (Id), in which R^1, R^2, R^3 and R^4 are as defined for the compounds of general formula (I), *supra*, starting from benzoic acid derivatives (C1), in which R^3 is as defined for the compounds of general formula (I), and A stands for chloro, bromo, iodo, trifluoromethylsulfonyloxy or nonafluorobutylsulfonyloxy. The benzoic acid derivatives of formula (C1) are well known to a person skilled in the art, and are often commercially available. Said *meta*-substituted benzoic acid derivatives of formula (C1) can be converted into amides of formula (C2), in which R^2 is as defined for the compounds of general formula (I). This can be accomplished directly by reacting a compound of formula (C1) with an amino derivative of formula H_2N-R^2, wherein R^2 is 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 meta-substituted

benzoic acid derivative (C1) can be converted into the corresponding benzoyl chloride, by treatment with a suitable chlorinating agent, such as oxalyl chloride. The carboxylic acid chloride is then reacted with an amino derivative of the formula H_2N-R^2, wherein R^2 is as defined for the compounds of general formula (I) affording the amide (C2). The compound (C2) is then converted into the benzoic acid ester derivative (C3), wherein R^E stands for a C_1-C_6-alkyl group, preferably methyl or ethyl. This can be accomplished directly by reacting a compound of the formula (C2) with carbonmonoxide and an alcohol R^E-OH, wherein R^E stand for a C_1-C_6-alkyl group, preferably methyl or ethyl, under palladium catalysis, for example trans-dichlorobis(triphenylphosphin)palladium(II), in the presence of an cosolvent, e.g. THF, and a tertiary aliphatic amine, e.g. triethylamine, at elevated temperatures, e.g. 100 °C, and pressure, e.g. 10 bar and higher. The ester group present in compounds of formula (C3) can be saponified by reaction with e.g. lithium hydroxide to yield the lithium salt or after acidification, for example with hydrochloric acid, to yield the carboxylic acid of formula (C4). Said carboxylic acid of formula (C4) or the corresponding lithium salt is then converted into compounds of formulae (Ib) or (Id). This can be accomplished directly by reacting a compound of formula (C4) with an amino compound of formula H_2N-R^1 or HNR^1R^4, wherein R^1 and R^4 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.

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.

Unless specified otherwise, suffixes to chemical names or structural formulae such as "hydrochloride", "trifluoroacetate", "sodium salt", or "x HCl", "x CF_3COOH", "x Na^+", for example, are to be understood as not a stoichiometric specification, but solely as a salt form.

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

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	*N*,*N*-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
ONf	nonafluorobutylsulfonyloxy
OTf	trifluoromethylsulfonyloxy
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: 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 XBrigde C18 5µ 100x30mm; water + 0.1% vol. formic acid (99%) / acetonitrile gradient; temperature: room temperature; injection: 2500 µL; 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 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 XBrigde C18 5µ 100x30mm; water + 0.2% vol. ammonia (32%) / acetonitrile gradient; temperature: room temperature; injection: 2500 µL; DAD scan: 210-400 nm.

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: Kinetex C18 from Phenomenex, 50 x 2.1 mm, 2.6 µm particle, 60 °C; solvent: A: water + 0.05% formic acid; B: acetonitrile + 0.05% formic acid; injection: 0.5 µL; 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.

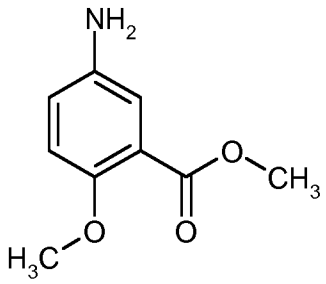
The ^{1}H-NMR data of selected examples are listed in the form of ^{1}H-NMR peaklists. For each signal peak the δ value in ppm is given, followed by the signal intensity, reported in round brackets. The δ value-signal intensity pairs from different peaks are separated by commas. Therefore, a peaklist is described by the general form: δ_1 (intensity$_1$), δ_2 (intensity$_2$), ... , δ_i (intensity$_i$), ... , δ_n (intensity$_n$).

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 ^{1}H-NMR peaklist is similar to a classical ^{1}H-NMR readout, and thus usually contains all the peaks listed in a classical NMR interpretation. Moreover, similar to classical ^{1}H-NMR printouts, 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 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 ^{1}H-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%.

Intermediates

Intermediate 1

methyl 5-amino-2-methoxybenzoate



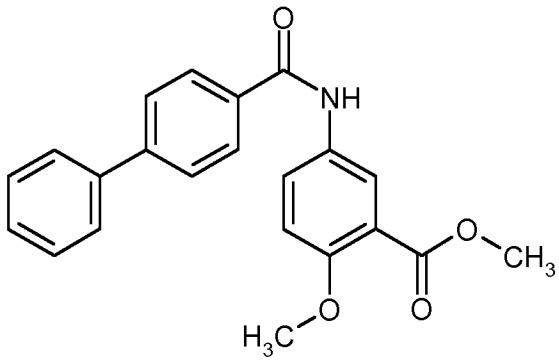
10.0 g (59.8 mmol, 1.0 equiv.) of 5-amino-2-methoxybenzoic acid were provided in 200 mL of methanol. 9.6 mL (179 mmol, 3.0 equiv.) of sulfuric acid were added dropwise and the reaction mixture was stirred at the reflux temperature over night. After cooling to room temperature and concentration, the remaining material was treated with ethyl acetate and neutralized by addition of a saturated, aqueous solution of sodium bicarbonate. The organic phase was separated, washed with water, dried over sodium sulfate, filtered and concentrated. 9.54 g (88% of theory) of the title compound were obtained and used without further purification.

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 3.309 (13.62), 3.740 (16.00), 4.856 (2.61), 6.715 (1.14), 6.722 (1.20), 6.737 (1.50), 6.744 (1.74), 6.839 (2.69), 6.861 (1.88), 6.885 (2.67), 6.892 (2.49).

LC-MS (Method 1): R_t = 0.47 min; MS (ESIpos): m/z = 182 $[M+H]^+$.

Intermediate 2

methyl 5-[(biphenyl-4-ylcarbonyl)amino]-2-methoxybenzoate

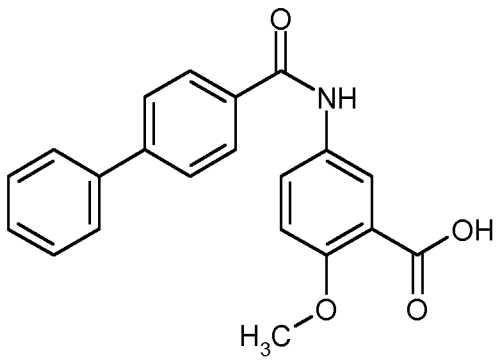


9.54 g (52.7 mmol, 1.0 equiv.) of the compound of intermediate 1 and 25.5 g (184 mmol, 3.5 equiv.) of potassium carbonate were provided in 250 mL of acetonitrile at 0 °C and 11.4 g (52.7 mmol, 1.0 equiv.) of biphenyl-4-carbonyl chloride and 200 mL of acetonitrile were added. The reaction mixture was stirred at room temperature over night, was then poured into ice water and stirred for 15 minutes. The solid material was filtered off, washed with water and dried. 18.0 g (94% of theory) of the title compound were obtained and used without further purification.

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 2.523 (0.90), 3.811 (16.00), 3.823 (14.70), 7.165 (2.14), 7.187 (2.30), 7.408 (0.58), 7.420 (0.49), 7.426 (1.75), 7.444 (1.34), 7.447 (0.80), 7.494 (2.18), 7.514 (3.46), 7.531 (1.56), 7.754 (3.29), 7.759 (1.62), 7.772 (2.90), 7.776 (2.06), 7.827 (3.56), 7.832 (1.38), 7.843 (1.46), 7.848 (4.17), 7.945 (1.34), 7.952 (1.42), 7.968 (1.23), 7.975 (1.34), 8.060 (4.15), 8.066 (1.48), 8.076 (1.40), 8.081 (3.41), 8.144 (2.80), 8.151 (2.65), 10.313 (2.74).

LC-MS (Method 4): R_t = 1.24 min; MS (ESIpos): m/z = 362 $[M+H]^+$.

Intermediate 3 5-[(biphenyl-4-ylcarbonyl)amino]-2-methoxybenzoic acid



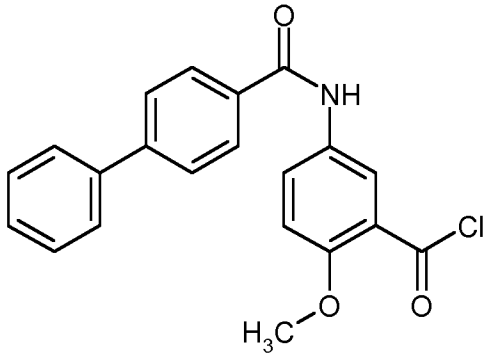
18.0 g (49.7 mmol, 1.0 equiv.) of the compound of intermediate 2 were provided in 100 mL of dioxane, a solution of 2.38 g (99.3 mmol, 2.0 equiv.) of lithium hydroxide in 60 mL of water was added at room temperature and the mixture was stirred for 19 h at room temperature. Water and a 2N aqueous hydrogen chloride solution were then added until an acidic pH of 1.5 - 2 was achieved. After stirring for 15 minutes, the precipitate was filtered off, washed with water and dried. 17.0 g (99% of theory) of the title compound were obtained and used without further purification.

^{1}H-NMR (300 MHz, DMSO-d_6) δ [ppm]: 3.566 (0.99), 3.820 (16.00), 7.127 (2.45), 7.157 (2.64), 7.398 (0.59), 7.403 (0.41), 7.415 (0.49), 7.423 (2.00), 7.430 (0.69), 7.442 (1.01), 7.447 (1.68), 7.452 (0.99), 7.488 (2.60), 7.508 (2.03), 7.513 (3.94), 7.530 (0.76), 7.537 (1.71), 7.541 (1.16), 7.739 (0.57), 7.748 (3.30), 7.751 (3.83), 7.756 (2.02), 7.767 (1.10), 7.775 (3.33), 7.780 (2.44), 7.820 (3.92), 7.827 (1.60), 7.842 (1.79), 7.849 (4.89), 7.923 (1.56), 7.932 (1.65), 7.953 (1.37), 7.962 (1.54), 8.057 (4.89), 8.064 (1.76), 8.079 (1.65), 8.086 (3.89), 8.111 (3.40), 8.120 (3.08), 10.281 (3.21), 12.640 (0.41).

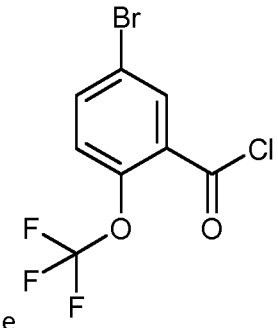
LC-MS (Method 4): R_t = 1.19 min; MS (ESIpos): m/z = 348 $[M+H]^+$.

Intermediate 4

5-[(biphenyl-4-ylcarbonyl)amino]-2-methoxybenzoyl chloride



2.00 g (5.76 mmol, 1.0 equiv.) of the compound of intermediate 3 were stirred in 133 mL of dichloromethane at room temperature. 0.04 mL (0.58 mmol, 0.1 equiv.) of DMF and 2.0 mL (23.0 mmol, 4.0 equiv.) of oxalyl chloride were added and the mixture was stirred for additional 2 h at 55 °C after the gas formation had stopped. 2.0 mL (23.0 mmol, 4.0 equiv.) of oxalyl chloride were added and the mixture was stirred for additional 4 h at 55 °C after the gas formation had stopped. After concentration, 2.34 g of raw material were obtained, which were used without further purification.

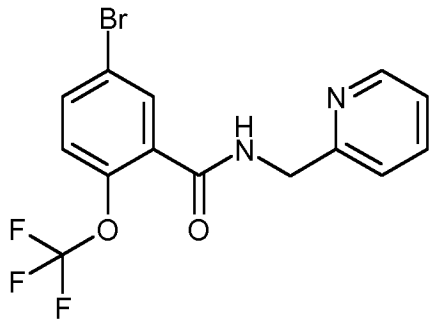


Intermediate 5 5-bromo-2-(trifluoromethoxy)benzoyl chloride

20.0 g (70.2 mmol, 1.0 equiv.) of 5-bromo-2-(trifluoromethoxy)benzoic acid were stirred in 300 mL of dichloromethane at room temperature. 0.27 mL (3.51 mmol, 0.1 equiv.) of DMF and 12.2 mL (140 mmol, 2.0 equiv.) 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, 19.9 g of raw material were obtained, which were used without further purification.

Intermediate 6

5-bromo-N-(pyridin-2-ylmethyl)-2-(trifluoromethoxy)benzamide



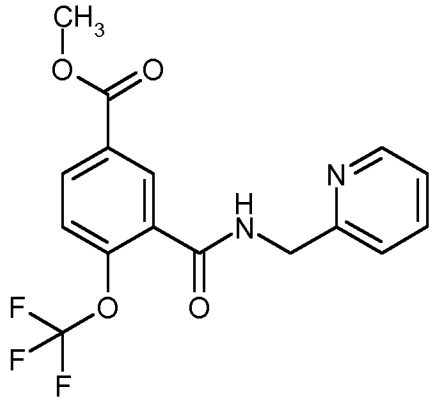
7.08 g (65.4 mmol, 1.0 equiv.) of 1-(pyridin-2-yl)methanamine were provided in 800 mL of tetrahydrofuran. 13.7 mL (98.2 mmol, 1.5 equiv.) of triethylamine and 19.9 g (65.4 mmol, 1.0 equiv.) of the compound of intermediate 5 were added at room temperature and it was stirred over night. The reaction mixture was poured into 800 mL of water and extracted with ethyl acetate. The combined organic phases were washed with a saturated, aqueous ammonium chloride solution and a saturated, aqueous sodium bicarbonate solution, were dried over sodium sulfate, filtered and concentrated under reduced pressure. The remaining material was dissolved in ethyl acetate, washed with a 1M aqueous sodium hydroxide solution, was dried over sodium sulfate, filtered and concentrated under reduced pressure. Purification by MPLC (Biotage Isolera; silica gel; hexane / EtOAc gradient) yielded 6.54 g (25% of theory) of the title compound.

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 2.322 (0.42), 2.327 (0.59), 2.331 (0.44), 2.523 (2.15), 2.664 (0.44), 2.669 (0.63), 2.674 (0.44), 3.321 (0.48), 4.523 (14.63), 4.537 (14.97), 7.266 (2.89), 7.269 (3.38), 7.279 (3.38), 7.281 (3.69), 7.285 (3.69), 7.288 (3.66), 7.297 (3.37), 7.300 (3.46), 7.365 (6.31), 7.384 (7.00), 7.398 (0.43), 7.420 (1.83), 7.425 (4.83), 7.429 (4.70), 7.446 (5.34), 7.450 (5.27), 7.758 (3.66), 7.763 (3.69), 7.778 (6.40), 7.782 (6.53), 7.791 (6.98), 7.797 (11.75), 7.802 (3.56), 7.812 (4.84), 7.819 (8.64), 7.833 (16.00), 7.839 (10.35), 7.886 (0.92), 7.980 (0.47), 8.003 (0.45), 8.509 (3.72), 8.512 (4.61), 8.516 (4.15), 8.521 (4.20), 8.524 (4.75), 8.528 (3.57), 9.146 (1.98), 9.161 (3.82), 9.176 (2.03), 9.877 (1.44).

LC-MS (Method 1): R_t = 1.02 min; MS (ESIpos): m/z = 375 $[M+H]^+$.

Intermediate 7

methyl 3-[(pyridin-2-ylmethyl)carbamoyl]-4-(trifluoromethoxy)benzoate



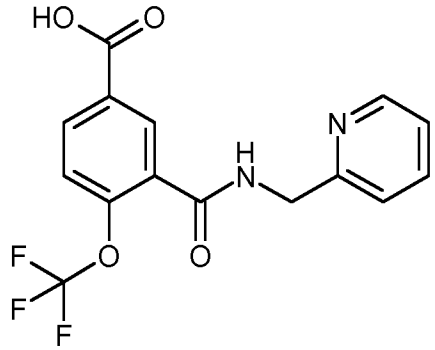
3.00 g (8.00 mmol, 1.0 equiv.) of the compound of intermediate 6, 1.15 g (1.60 mmol, 0.2 equiv.) of trans-dichlorobis(triphenylphosphin)palladium(II) and 2.8 mL (20.0 mmol, 2.5 equiv.) of triethylamine were dissolved in a mixture of 152 mL of methanol and 15.2 mL of DMSO. The solution was purged with carbon monoxide three times and was stirred in an autoclave in a carbon monoxide atmosphere (14 bar) at 100 °C over night. Ethyl acetate and water were added, the phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine, dried and concentrated. Another 3.00 g (8.00 mmol, 1.0 equiv.) of the compound of intermediate 6, 1.15 g (1.60 mmol, 0.2 equiv.) of trans-dichlorobis(triphenylphosphin)palladium(II) and 2.8 mL (20.0 mmol, 2.5 equiv.) of triethylamine were dissolved in a mixture of 152 mL of

methanol and 15.2 mL of DMSO. The solution was purged with carbon monoxide three times and was stirred in an autoclave in a carbon monoxide atmosphere (12 bar) at 100 °C over night. Ethyl acetate and water were added, the phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine, dried and concentrated. After purification by HPLC, 5.00 g (44% of theory) of the title compound were obtained.

1H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 2.326 (0.42), 2.523 (1.48), 2.539 (0.45), 2.669 (0.41), 3.342 (1.13), 4.553 (9.05), 4.568 (9.12), 7.278 (1.95), 7.280 (2.05), 7.290 (2.07), 7.292 (2.28), 7.297 (2.35), 7.299 (2.25), 7.309 (2.25), 7.311 (2.25), 7.367 (3.97), 7.386 (4.38), 7.599 (0.79), 7.604 (2.46), 7.608 (2.77), 7.623 (1.47), 7.627 (3.03), 7.632 (2.81), 7.636 (1.00), 7.774 (2.36), 7.778 (2.48), 7.793 (3.96), 7.797 (4.04), 7.812 (1.98), 7.817 (2.06), 8.132 (0.94), 8.144 (3.87), 8.150 (7.16), 8.162 (7.45), 8.167 (16.00), 8.174 (1.69), 8.521 (2.44), 8.525 (3.04), 8.528 (2.70), 8.533 (2.51), 8.536 (3.00), 8.540 (2.34), 9.190 (1.34), 9.205 (2.63), 9.220 (1.38).

LC-MS (Method 4): R_t = 0.91 min; MS (ESIpos): m/z = 355 $[M+H]^+$.

Intermediate 8 3-[(pyridin-2-ylmethyl)carbamoyl]-4-(trifluoromethoxy)benzoic acid



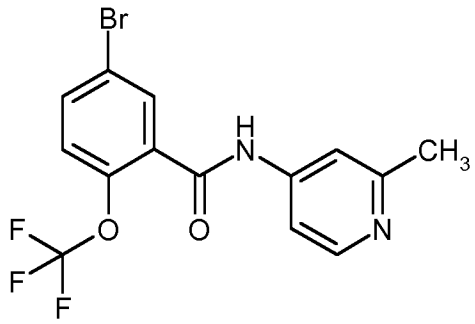
5.00 g (14.1 mmol, 1.0 equiv.) of the compound of intermediate 7 were provided in 70 mL of dioxane, a solution of 676 mg (28.2 mmol, 2.0 equiv.) of lithium hydroxide in 20 mL of water was added at room temperature and the mixture was stirred at room temperature over night. After concentration, water and a 1N aqueous hydrogen chloride solution were then added until an acidic pH of 5 was achieved. The precipitate was filtered off and dried. 4.56 g (95% of theory) of the title compound were obtained and used without further purification.

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 2.523 (0.44), 3.316 (1.16), 4.549 (7.88), 4.564 (7.84), 7.271 (1.81), 7.274 (1.92), 7.283 (1.98), 7.286 (2.27), 7.290 (2.21), 7.293 (2.09), 7.302 (2.02), 7.304 (2.06), 7.362 (3.65), 7.382 (3.97), 7.570 (2.23), 7.574 (2.49), 7.579 (1.34), 7.588 (1.52), 7.593 (2.66), 7.597 (2.16), 7.769 (2.03), 7.774 (2.10), 7.789 (3.55), 7.793 (3.49), 7.808 (1.79), 7.813 (1.75), 8.120 (3.04), 8.126 (5.09), 8.140 (6.55), 8.144 (16.00), 8.518 (2.40), 8.522 (3.00), 8.524 (2.57), 8.529 (2.45), 8.533 (2.82), 8.536 (2.34), 9.172 (1.45), 9.187 (2.85), 9.202 (1.39).

LC-MS (Method 1): R_t = 0.73 min; MS (ESIpos): m/z = 341 $[M+H]^+$.

Intermediate 9

5-bromo-N-(2-methylpyridin-4-yl)-2-(trifluoromethoxy)benzamide

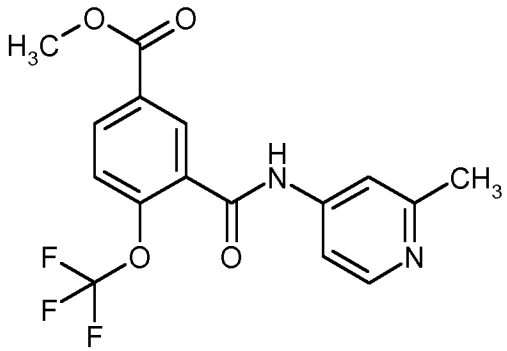


1.65 g (15.2 mmol, 1.1 equiv.) of 2-methylpyridin-4-amine were provided in 200 mL of tetrahydrofuran. 2.9 mL (20.8 mmol, 1.5 equiv.) of triethylamine and 4.20 g (13.8 mmol, 1.0 equiv.) of the compound of intermediate 5 were added at room temperature and it was stirred over night. The reaction mixture was poured into 250 mL of water and extracted with ethyl acetate. The combined organic phases were washed with a saturated, aqueous ammonium chloride solution and a saturated, aqueous sodium bicarbonate solution, were dried over sodium sulfate, filtered and concentrated under reduced pressure. 4.41 g (85% of theory) of the title compound were obtained and used without further purification.

^{1}H-NMR (300 MHz, DMSO-d_6) δ [ppm]: 2.444 (16.00), 7.415 (1.42), 7.423 (1.56), 7.434 (1.52), 7.441 (1.55), 7.483 (0.71), 7.488 (1.57), 7.493 (1.56), 7.498 (0.69), 7.513 (0.93), 7.518 (1.95), 7.522 (1.94), 7.537 (2.97), 7.544 (2.62), 7.856 (2.21), 7.865 (2.57), 7.886 (1.88), 7.894 (2.22), 7.968 (4.25), 7.976 (3.61), 8.343 (2.93), 8.361 (2.77), 10.852 (2.10).

LC-MS (Method 1): R_t = 0.87 min; MS (ESIpos): m/z = 375 $[M+H]^+$.

Intermediate 10methyl 3-[(2-methylpyridin-4-yl)carbamoyl]-4-(trifluoromethoxy)benzoate

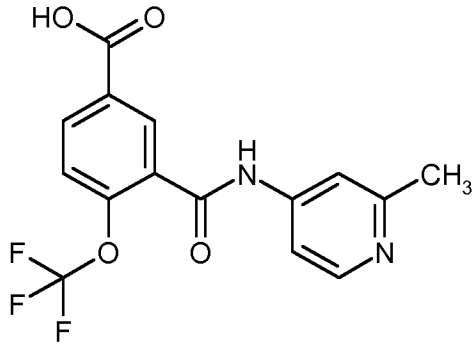


4.40 g (11.7 mmol, 1.0 equiv.) of the compound of intermediate 9, 1.68 g (2.35 mmol, 0.2 equiv.) of trans-dichlorobis(triphenylphosphin)palladium(II) and 4.1 mL (29.3 mmol, 2.5 equiv.) of triethylamine were dissolved in a mixture of 176 mL of methanol and 17.5 mL of DMSO. The solution was purged with carbon monoxide three times and was stirred in an autoclave in a carbon monoxide atmosphere (10 bar) at room temperature for 30 minutes. After applying a vacuum, the solution was purged with carbon monoxide and was stirred in an autoclave in a carbon monoxide atmosphere (12 bar) at 100 °C over night. Ethyl acetate and water were added, the phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine, dried and concentrated. 3.26 g of raw material of the title compound were obtained and used without further purification.

LC-MS (Method 4): R_t = 0.75 min; MS (ESIpos): m/z = 355 $[M+H]^+$.

Intermediate 11

3-[(2-methylpyridin-4-yl)carbamoyl]-4-(trifluoromethoxy)benzoic acid



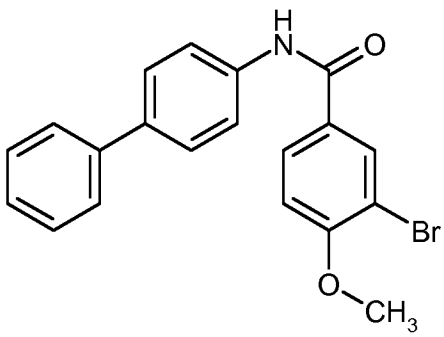
2.76 g (7.79 mmol, 1.0 equiv.) of the compound of intermediate 10 were provided in 33 mL of dioxane, a solution of 933 mg (39.0 mmol, 5.0 equiv.) of lithium hydroxide in 19 mL of water was added at room temperature and the mixture was stirred at room temperature over night. After concentration, water and a 1N aqueous hydrogen chloride solution were then added until a pH of 6 was achieved. The precipitate was filtered off and dried. 1.90 g (72% of theory) of the title compound were obtained and used without further purification.

^{1}H-NMR (300 MHz, DMSO-d_6) δ [ppm]: 2.437 (1.38), 2.449 (16.00), 3.946 (0.53), 7.436 (1.31), 7.444 (1.48), 7.455 (1.45), 7.462 (1.59), 7.539 (0.49), 7.543 (0.78), 7.548 (0.86), 7.566 (4.04), 7.572 (3.31), 7.588 (1.61), 7.600 (0.68), 7.605 (0.76), 7.612 (1.13), 7.623 (1.26), 7.627 (1.65), 7.636 (0.97), 7.643 (1.71), 7.649 (2.07), 7.655 (1.19), 7.661 (0.73), 7.668 (0.91), 7.674 (1.70), 7.679 (1.59), 7.684 (0.68), 8.181 (1.45), 8.189 (3.06), 8.200 (4.10), 8.207 (4.92), 8.212 (3.62), 8.220 (1.17), 8.350 (2.99), 8.369 (2.88), 10.922 (3.16).

LC-MS (Method 1): R_t = 0.71 min; MS (ESIpos): m/z = 341 $[M+H]^+$.

Intermediate 12

N-(biphenyl-4-yl)-3-bromo-4-methoxybenzamide



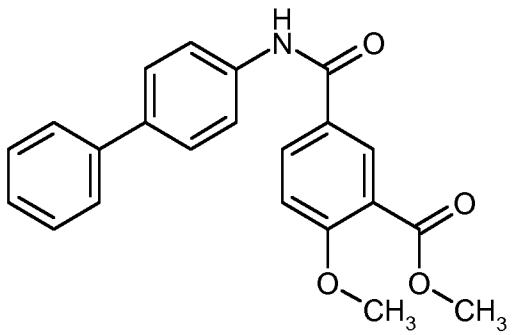
Under an atmosphere of argon 2.00 g (8.66 mmol) of 3-bromo-4-methoxybenzoic acid and 1.76 g (10.39 mmol) of biphenyl-4-amine were dissolved in 30.0 mL of anh DMF. 6.03 mL (34.62 mmol) of N-ethyl-N-isopropylpropan-2-amine and 5.41 g (10.39 mmol) of PYBOP were added. It was stirred over night at rt. It was concentrated on a rotavap. Water and methanol were added. The solid was filtered off under suction and the residue was washed with water and methanol. The remaining solid was dried under vacuum at 45 °C yielding 3.1 g (94% of theory) of the title compound.

^{1}H-NMR (300 MHz, DMSO-d_6) δ [ppm]: 3.948 (16.00), 7.254 (2.51), 7.284 (2.71), 7.307 (0.44), 7.312 (0.69), 7.316 (0.51), 7.329 (0.61), 7.336 (1.94), 7.343 (0.79), 7.356 (0.98), 7.361 (1.47), 7.365 (0.91), 7.429 (2.38), 7.435 (1.32), 7.451 (2.25), 7.456 (3.91), 7.473 (0.85), 7.479 (1.85), 7.658 (7.19), 7.666 (3.87), 7.689 (7.13), 7.849 (0.94), 7.857 (4.89), 7.864 (1.91), 7.879 (1.53), 7.886 (3.65), 7.896 (0.64), 8.022 (1.61), 8.029 (1.74), 8.051 (1.47), 8.058 (1.59), 8.253 (3.41), 8.261 (3.27), 10.268 (3.05).

LC-MS (Method 4): R_t = 1.39 min; MS (ESIpos): m/z = 383 $[M+H]^+$.

Intermediate 13

methyl 5-(biphenyl-4-ylcarbamoyl)-2-methoxybenzoate



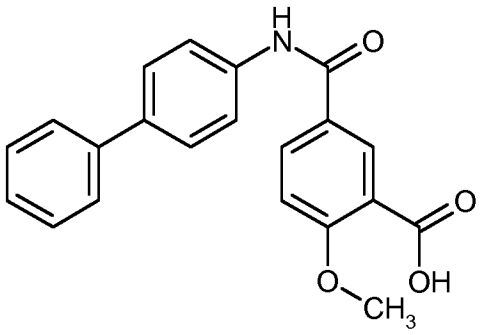
8.00 g (20.93 mmol) of N-(biphenyl-4-yl)-3-bromo-4-methoxybenzamide (intermediate 12) were dissolved in 360 mL of methanol and 36 mL of THF. 2.94 g (4.19 mmol) of dichloro[bis(triphenylphosphoranyl)]palladium and 7.29 mL (52.32 mmol) of N,N-diethylethanamine were added. The rection mixture was purged three times with carbonmonoxide. The vessel was filled with carbonmonoxide (12.2 bar) and stirred for 30 minutes at 20 °C. The carbonmonoxide was discharged and the vessel was evacuated (0.06 bar). The vessel was filled with carbonmonoxide (12.9 bar) and heated up to 100 °C. It was stirred for 27.5 h at 100 °C. The reaction mixture was concentrated on the rotavap and ethyl acetate and water were added. The layers were separated and the aqueous phase was extracted four times with ethyl acetate. The combined organic phases were washed with concentrated aqueous sodium chloride solution. It was dried over magnesium sulfate and concentrated. The residue was treated with diisopropyl ether and filtered off under suction. The solid material was dried under vacuum at 45 °C affording 5.1 g (63% of theory) of the title compound. Remaining product in the aqueous phase was filtered off under suction and the solid material was washed with water. The solid was dried under vacuum at 45 °C to give 2.8 g (36% of theory) of the title compound.

^{1}H-NMR (300 MHz, DMSO-d_6) δ [ppm]: 3.844 (16.00), 3.924 (14.08), 3.949 (0.43), 7.302 (2.32), 7.313 (0.93), 7.332 (3.05), 7.338 (2.36), 7.357 (0.87), 7.362 (1.36), 7.366 (0.81), 7.431 (2.21), 7.437 (1.20), 7.452 (2.16), 7.457 (3.58), 7.481 (1.71), 7.660 (6.57), 7.667 (3.66), 7.689 (6.79), 7.859 (4.53), 7.866 (1.67), 7.881 (1.50), 7.888 (3.30), 8.182 (1.43), 8.191 (1.56), 8.211 (1.27), 8.220 (1.42), 8.313 (3.14), 8.321 (2.76), 10.331 (2.79).

LC-MS (Method 4): R_t = 1.27 min; MS (ESIpos): m/z = 362 $[M+H]^+$.

Intermediate 14

5-(biphenyl-4-ylcarbamoyl)-2-methoxybenzoic acid



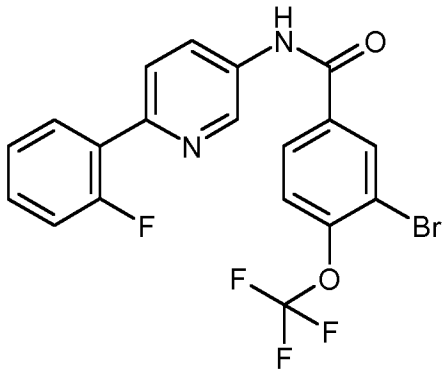
556.6 mg (23.24 mmol) of lithium hydroxide were added to 2.80 g (7.75 mmol) of methyl 5-(biphenyl-4-ylcarbamoyl)-2-methoxybenzoate (intermediate 13) in 62.8 mL of THF and 15.1 mL of methanol. It was stirred for 30 h at 40 °C. It was cooled down and concentrated on a rotavap. Water was added to the residue and the pH was adjusted with 1M HCl to pH 5. It was stirred 0.5 h and the solid material was filtered off under suction, dried under vacuum at 45 °C providing 2.6 g (99.6% of theory) of the title compound.

^{1}H-NMR (300 MHz, DMSO-d_6) δ [ppm]: 3.912 (16.00), 3.947 (0.53), 7.266 (2.68), 7.296 (2.89), 7.313 (0.97), 7.336 (2.38), 7.360 (1.79), 7.430 (2.84), 7.457 (4.63), 7.480 (2.32), 7.659 (7.66), 7.687 (9.19), 7.865 (5.52), 7.895 (4.24), 8.144 (1.67), 8.153 (1.86), 8.174 (1.59), 8.182 (1.76), 8.317 (3.54), 8.325 (3.44), 10.337 (3.83).

LC-MS (Method 4): R_t = 1.15 min; MS (ESIpos): m/z = 348 $[M+H]^+$.

Intermediate 15

3-bromo-N-[6-(2-fluorophenyl)pyridin-3-yl]-4-(trifluoromethoxy)benzamide



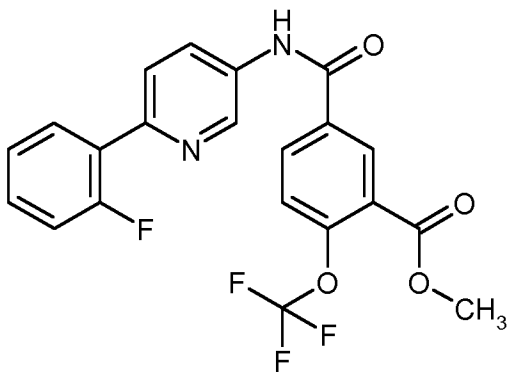
To 2.52 g (8.86 mmol) of 3-bromo-4-(trifluoromethoxy)benzoic acid and 2.00 g (10.63 mmol) of 6-(2-fluorophenyl)pyridin-3-amine (known from WO2014/147021) in 30.0 mL of anh DMF were added 6.17 mL (35.42 mmol) of N-ethyl-N-isopropylpropan-2-amine and 5.53 g (10.63 mmol) of PYBOP under argon. It was stirred at rt over night. The reaction mixture was concentrated on a rotavap. A mixture of water and methanol (1:1) was added and the solid material was filtered off by suction. The product was washed with water and methanol and dried under vacuum at 45 °C to yield 3.18 g (79% of theory) of the title compound.

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 1.231 (0.62), 1.729 (0.52), 2.326 (1.45), 2.669 (1.50), 3.008 (0.48), 7.310 (4.86), 7.317 (5.27), 7.321 (5.27), 7.330 (8.06), 7.338 (15.64), 7.357 (12.83), 7.408 (0.41), 7.447 (2.69), 7.452 (2.98), 7.459 (3.48), 7.465 (5.32), 7.471 (4.34), 7.481 (4.63), 7.486 (4.08), 7.490 (2.46), 7.498 (1.88), 7.503 (1.76), 7.737 (6.84), 7.741 (6.92), 7.759 (7.92), 7.762 (7.51), 7.832 (6.72), 7.836 (7.13), 7.838 (6.84), 7.853 (7.70), 7.859 (7.18), 7.942 (4.03), 7.947 (4.15), 7.962 (7.77), 7.966 (7.20), 7.982 (4.22), 7.987 (3.36), 8.103 (8.61), 8.108 (8.68), 8.124 (7.56), 8.130 (7.61), 8.285 (7.82), 8.292 (8.01), 8.307 (7.08), 8.313 (7.25), 8.433 (16.00), 8.439 (15.36), 9.051 (13.21), 9.057 (13.23), 10.751 (15.00).

LC-MS (Method 4): R_t = 1.44 min; MS (ESIpos): m/z = 455 $[M+H]^+$.

Intermediate 16

methyl 5-{[6-(2-fluorophenyl)pyridin-3-yl]carbamoyl}-2-(trifluoromethoxy)benzoate



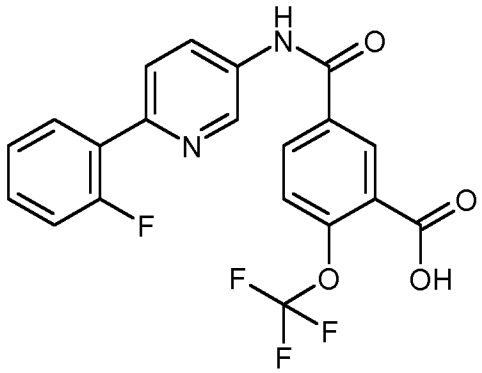
3.18 g (6.99 mmol) of 3-bromo-N-[6-(2-fluorophenyl)pyridin-3-yl]-4-(trifluoromethoxy)benzamide (intermediate 15) were dissolved in 220 mL of a mixture of methanol/THF (10:1). 1.14 g (1.40 mmol)

of 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex and 2.43 mL (17.46 mmol) of N,N-diethylethanamine were added. The reaction mixture was purged three times with carbonmonoxide. The vessel was filled with carbonmonoxide up to 11.8 bar and stirred for 30 minutes at 20 °C. The carbonmonoxide was released and it was evacuated at 0.06 bar. Then the vessel was charged with carbonmonoxide (13.4 bar) and stirred for 24 h at 100 °C. The carbonmonoxide was discharged and the mixture was concentrated on a rotavap. Water and ethyl acetate were added, the layers were separated and the aqueous layer was extracted four times with ethylacetate. The combined organic phases were washed with concentrated aqueous sodium chloride solution, dried over magnesium sulfate and concentrated. 10 mL of ethanol was added to the residue and it was stirred. It was filtered off by suction affording 2.02 g (70% of theory) of the title compound.

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 1.986 (0.57), 2.523 (0.80), 3.929 (16.00), 7.309 (0.56), 7.312 (0.66), 7.318 (0.71), 7.322 (0.72), 7.332 (1.01), 7.337 (1.87), 7.340 (2.21), 7.358 (1.93), 7.447 (0.44), 7.453 (0.48), 7.461 (0.51), 7.466 (0.72), 7.473 (0.58), 7.478 (0.48), 7.482 (0.62), 7.487 (0.68), 7.736 (1.01), 7.740 (1.03), 7.758 (1.12), 7.762 (1.00), 7.835 (0.85), 7.841 (0.91), 7.857 (1.04), 7.863 (0.93), 7.944 (0.62), 7.949 (0.61), 7.964 (1.08), 7.969 (0.97), 7.984 (0.57), 7.989 (0.47), 8.294 (1.34), 8.300 (1.38), 8.315 (1.17), 8.322 (1.25), 8.329 (1.48), 8.335 (1.55), 8.350 (1.25), 8.356 (1.43), 8.539 (2.62), 8.545 (2.50), 9.062 (1.84), 9.067 (1.90), 10.846 (2.21).

LC-MS (Method 4): R_t = 1.35 min; MS (ESIpos): m/z = 435 $[M+H]^+$.

Intermediate 17 5-{[6-(2-fluorophenyl)pyridin-3-yl]carbamoyl}-2-(trifluoromethoxy)benzoic acid



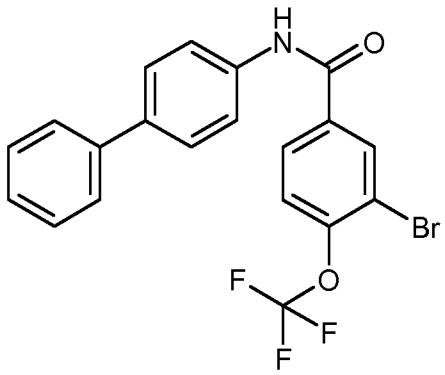
2.00 g (4.60 mmol) of methyl 5-{[6-(2-fluorophenyl)pyridin-3-yl]carbamoyl}-2-(trifluoromethoxy)benzoate (intermediate 16) were dissolved in 37.35 mL of THF and 9.0 mL of methanol. 330.8 mg (13.81 mmol) of lithium hydroxide were added and it was stirred for 30 h at 40 °C. The reaction mixture was cooled to rt and concentrated on a rotavap. Water was added to the residue and the pH was adjusted to 5 by the addition of potassium hydrogensulfate. It was stirred for half an hour. It was filtered off by suction, washed with water and dried under vacuum at 45 °C to give 1.57 g of the title compound which contained some impurities. A sample of 50 mg was purified by HPLC (method 2) to give 20.5 mg of the purified compound.

^{1}H-NMR (300 MHz, DMSO-d_6) δ [ppm]: 1.165 (5.12), 1.229 (1.15), 1.267 (0.80), 1.410 (0.65), 1.906 (0.85), 2.270 (2.76), 2.276 (2.21), 2.726 (2.96), 3.251 (2.96), 3.921 (12.94), 4.210 (1.20), 4.494 (1.30), 6.577 (0.65), 7.150 (0.65), 7.261 (1.15), 7.305 (6.52), 7.310 (6.87), 7.315 (6.27), 7.335 (16.00), 7.340 (13.44), 7.364 (11.08), 7.438 (3.96), 7.445 (4.16), 7.455 (5.32), 7.463 (7.02), 7.472 (5.87), 7.484 (5.92), 7.490 (5.37), 7.513 (4.31), 7.554 (3.21), 7.580 (2.56), 7.609 (2.16), 7.678 (4.82), 7.706 (4.76), 7.803 (1.66), 7.831 (7.77), 7.834 (7.77), 7.857 (7.67), 7.863 (6.77), 7.936 (5.07), 7.943 (4.46), 7.962 (9.23), 7.968 (7.87), 7.989 (5.07), 8.174 (1.40), 8.205 (1.55), 8.266 (4.92), 8.297 (11.94), 8.306 (8.73), 8.326 (7.32), 8.335 (6.57), 8.354 (3.56), 8.362 (3.06), 8.421 (1.00), 8.531 (10.63), 8.539 (9.83), 9.063 (13.99), 9.072 (13.64), 10.574 (2.91), 10.839 (13.69).

LC-MS (Method 4): R_t = 1.16 min; MS (ESIpos): m/z = 421 $[M+H]^+$.

Intermediate 18

N-(biphenyl-4-yl)-3-bromo-4-(trifluoromethoxy)benzamide



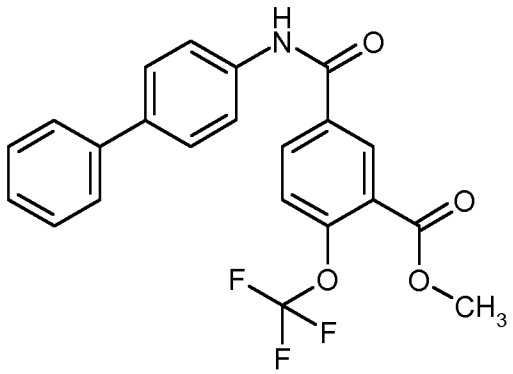
Under argon 2.00 g (7.02 mmol) of 3-bromo-4-(trifluoromethoxy)benzoic acid, 1.42 g (8.42 mmol) of biphenyl-4-amine, 4.89 mL (28.07 mmol) of N-ethyl-N-isopropylpropan-2-amine and 4.38 g (8.42 mmol) of PYBOP were stirred in 24.0 mL of anh N,N-Dimethylformamid at rt over night. Three such batches were combined and concentrated on a rotavap. A mixture of water/methanol 1:1 was added. The solid material was filtered off by suction, washed with water and methanol to obtain 9.0 g (98% of theory) of the title compound.

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 2.326 (0.43), 2.522 (1.55), 2.669 (0.43), 3.290 (0.50), 3.301 (1.18), 7.327 (1.77), 7.330 (1.09), 7.340 (1.37), 7.345 (4.78), 7.360 (1.96), 7.363 (3.32), 7.441 (5.62), 7.461 (9.20), 7.474 (1.83), 7.479 (4.75), 7.666 (7.77), 7.669 (8.73), 7.686 (16.00), 7.690 (8.85), 7.702 (3.76), 7.707 (13.36), 7.714 (4.94), 7.732 (3.76), 7.736 (3.60), 7.846 (1.55), 7.852 (11.81), 7.858 (3.48), 7.868 (2.98), 7.874 (9.04), 7.881 (1.24), 8.078 (4.47), 8.083 (4.57), 8.099 (3.88), 8.105 (4.04), 8.401 (8.36), 8.406 (8.26), 10.510 (6.96).

LC-MS (Method 3): R_t = 1.53 min; MS (ESIpos): m/z = 436 $[M+H]^+$.

Intermediate 19

methyl 5-(biphenyl-4-ylcarbamoyl)-2-(trifluoromethoxy)benzoate



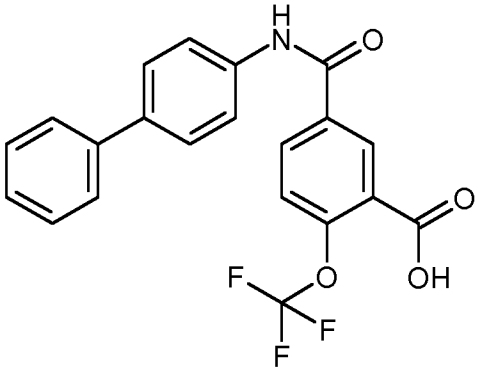
9.00 g (20.63 mmol) of N-(biphenyl-4-yl)-3-bromo-4-(trifluoromethoxy)benzamide (intermediate 18) were dissolved in 396 mL of methanol and THF (10:1). 2.90 g (4.13 mmol) of dichloro[bis(triphenylphosphoranyl)]palladium and 7.19 mL (51.58 mmol) of N,N-diethylethanamine were added. The reaction mixture was purged three times with carbonmonoxide. The vessel was filled with carbonmonoxide up to 11.6 bar and stirred for 30 minutes at 20 °C. The carbonmonoxide was released and it was evacuated at 0.06 bar. Then the vessel was charged with carbonmonoxide (13.2 bar) and stirred for 22 h at 100 °C. 1.30 g (1.85 mmol) of dichloro[bis(triphenylphosphoranyl)]palladium were added to the reaction mixture. It was purged three times with carbonmonoxide. The vessel was filled with carbonmonoxide up to 11.5 bar. It was stirred for 30 minutes at 20 °C. The carbonmonoxide was realeased and it was evacuated at 0.06 bar. The autoclave was charged with carbonmonoxide up to 13.5 bar and stirred for 22 h at 100 °C. The carbonmonoxide was discharged and the reaction mixture was concentrated on a rotavap. Water and ethyl acetate were added, the layers were separated and the aqueous layer was extracted three times with ethyl acetate. The combined organic phases were washed with concentrated aqueous sodium chloride solution, dried over magnesium sulfate and concentrated. 30 mL of ethanol were added to the residue and it was stirred for some time. It was filtered off by suction to give 7.39 g (91% of theory) of the title compound.

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 2.523 (0.62), 3.924 (16.00), 7.329 (0.61), 7.342 (0.43), 7.347 (1.58), 7.362 (0.64), 7.365 (1.14), 7.443 (1.89), 7.447 (0.75), 7.463 (3.06), 7.477 (0.70), 7.482 (1.60), 7.670 (2.61), 7.672 (2.94), 7.690 (5.60), 7.694 (2.50), 7.706 (1.72), 7.711 (4.90), 7.718 (0.90), 7.731 (1.22), 7.735 (1.11), 7.855 (0.52), 7.861 (3.98), 7.867 (1.12), 7.877 (1.00), 7.883 (3.03), 8.302 (1.47), 8.308 (1.55), 8.324 (1.32), 8.329 (1.45), 8.504 (2.76), 8.511 (2.60), 10.604 (2.29).

LC-MS (Method 4): R_t = 1.42 min; MS (ESIpos): m/z = 416 $[M+H]^+$.

Intermediate 20

5-(biphenyl-4-ylcarbamoyl)-2-(trifluoromethoxy)benzoic acid



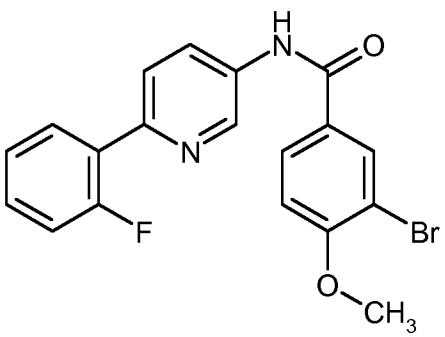
4.10 g (9.86 mmol) of methyl 5-(biphenyl-4-ylcarbamoyl)-2-(trifluoromethoxy)benzoate (intermediate 19) were dissolved in 80 mL of THF and 20 mL of methanol. 708.6 mg (29.59 mmol) of lithium hydroxide were added. It was heated up to 40 °C and stirred. After 1 h 40 mL of methanol were added to dissolve the precipitate. Then the reaction was stirred at 40 °C over the weekend. The reaction was allowed to reach rt. Water was added and the pH was adjusted to 5 with 2M HCl. It was stirred for 30 minutes and the solid material was filtered off by suction, dried under vacuum at 45 °C to obtain 3.54 g of the title compound containing some impurities. A sample of 50 mg was purified by HPLC (method 4) yielding 35.2 mg of the title compound.

^{1}H-NMR (300 MHz, DMSO-d_6) δ [ppm]: 1.735 (0.60), 1.745 (0.73), 1.757 (1.61), 1.779 (0.62), 1.907 (0.44), 2.270 (1.03), 2.525 (6.23), 2.726 (1.03), 2.732 (0.77), 3.576 (0.62), 3.599 (1.45), 3.621 (0.58), 3.842 (1.26), 3.912 (5.14), 3.922 (1.53), 7.268 (0.87), 7.297 (0.98), 7.320 (1.79), 7.337 (2.26), 7.344 (5.30), 7.351 (1.93), 7.364 (2.72), 7.369 (3.98), 7.373 (2.45), 7.436 (6.62), 7.457 (6.43), 7.462 (10.48), 7.480 (2.72), 7.486 (5.15), 7.659 (7.89), 7.666 (11.70), 7.669 (11.75), 7.683 (16.00), 7.686 (14.58), 7.693 (13.12), 7.698 (8.30), 7.712 (13.12), 7.863 (14.21), 7.870 (4.66), 7.885 (4.25), 7.892 (10.40), 8.146 (0.54), 8.154 (0.57), 8.184 (0.73), 8.246 (3.98), 8.254 (4.24), 8.275 (3.59), 8.283 (3.86), 8.318 (1.30), 8.327 (1.19), 8.496 (7.92), 8.504 (7.43), 10.335 (1.08), 10.601 (8.17).

LC-MS (Method 4): R_t = 1.27 min; MS (ESIpos): m/z = 402 $[M+H]^+$.

Intermediate 21

3-bromo-N-[6-(2-fluorophenyl)pyridin-3-yl]-4-methoxybenzamide



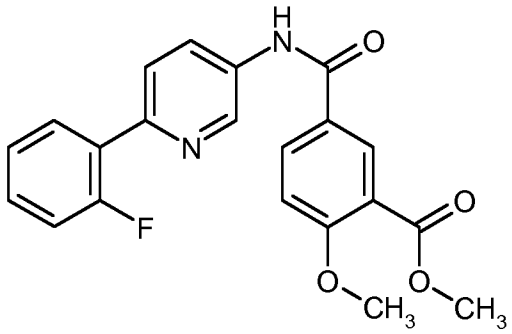
Under argon 2.05 g (8.86 mmol) of 3-bromo-4-methoxybenzoic acid and 2.00 g (10.63 mmol) of 6-(2-fluorophenyl)pyridin-3-amine (known from WO2014/147021) were dissolved in 30 mL of anh DMF. Then, 6.17 mL (35.42 mmol) of N-ethyl-N-isopropylpropan-2-amine and 5.53 g (10.63 mmol) of PYBOP were added. It was stirred at rt over night. The reaction mixture was concentrated on a rotavap. Water and methanol (1:1) were added to the residue. The solid material was filtered off by suction and washed with water and methanol. The solid material was dried under vacuum at 45 °C yielding 2.86 g (80% of theory) of the title compound.

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 3.957 (16.00), 7.283 (2.60), 7.304 (3.74), 7.312 (1.34), 7.315 (1.33), 7.325 (1.70), 7.333 (3.35), 7.353 (2.83), 7.439 (0.57), 7.444 (0.63), 7.452 (0.71), 7.458 (1.13), 7.464 (0.91), 7.473 (0.95), 7.478 (0.90), 7.483 (0.53), 7.490 (0.43), 7.808 (1.35), 7.812 (1.48), 7.814 (1.44), 7.829 (1.59), 7.835 (1.50), 7.940 (0.84), 7.946 (0.89), 7.960 (1.55), 7.965 (1.50), 7.980 (0.86), 7.985 (0.71), 8.047 (1.65), 8.052 (1.77), 8.068 (1.57), 8.074 (1.74), 8.278 (3.55), 8.284 (4.85), 8.291 (2.12), 8.306 (1.57), 8.312 (1.62), 9.057 (2.72), 9.064 (2.84), 10.505 (3.24).

LC-MS (Method 4): R_t = 1.27 min; MS (ESIpos): m/z = 401 $[M+H]^+$.

Intermediate 22

methyl 5-{[6-(2-fluorophenyl)pyridin-3-yl]carbamoyl}-2-methoxybenzoate



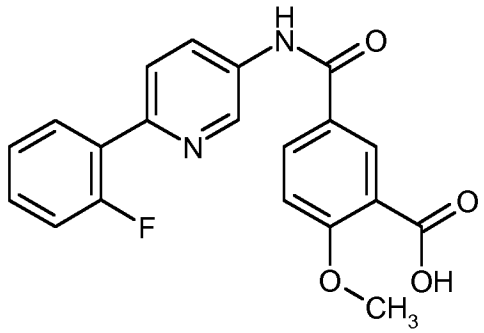
2.86 g (7.13 mmol) of 3-bromo-N-[6-(2-fluorophenyl)pyridin-3-yl]-4-methoxybenzamide (intermediate 21) were dissolved in 143 mL of a mixture of methanol / THF (10:1). 1.16 g (1.43 mmol) of 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex and 2.5 mL (17.93 mmol) of N,N-diethylethanamine were added. The reaction mixture was purged three times with carbonmonoxide. The autoclave was filled with carbonmonoxide up to 11.1 bar and stirred for 30 minutes at 20 °C. The carbonmonoxide was released and it was evacuated at 0.06 bar. Then the vessel was charged with carbonmonoxide (13.9 bar) and stirred for 24 h at 100 °C. The carbonmonoxide was discharged and the reaction mixture was concentrated on a rotavap. Ethyl acetate and water were added, the layers were separated and the aqueous layer was extracted three times with ethyl acetate. The combined organic phases were washed with concentrated aqueous sodium chloride solution, dried over magnesium sulfate and concentrated affording 2.3 g (85% of theory) of the title compound.

^{1}H-NMR (300 MHz, DMSO-d_6) δ [ppm]: 1.174 (0.74), 1.356 (0.47), 1.987 (1.35), 3.848 (16.00), 3.933 (14.42), 7.294 (0.80), 7.297 (0.91), 7.306 (0.99), 7.310 (1.11), 7.327 (3.69), 7.330 (3.86), 7.335 (3.18), 7.358 (4.49), 7.431 (0.67), 7.437 (0.78), 7.448 (0.83), 7.455 (1.18), 7.464 (0.99), 7.472 (0.86), 7.476 (1.04), 7.483 (0.99), 7.489 (0.67), 7.500 (0.61), 7.506 (0.61), 7.805 (1.22), 7.812 (1.32), 7.832 (1.35), 7.835 (1.43), 7.841 (1.40), 7.935 (0.83), 7.942 (0.84), 7.961 (1.50), 7.968 (1.35), 7.988 (0.79), 7.995 (0.64), 8.206 (1.43), 8.214 (1.59), 8.235 (1.30), 8.243 (1.51), 8.284 (1.54), 8.293 (1.64), 8.314 (1.39), 8.322 (1.48), 8.344 (3.14), 8.352 (2.93), 9.064 (2.54), 9.072 (2.58), 10.570 (2.96).

LC-MS (Method 4): R_t = 1.13 min; MS (ESIpos): m/z = 381 $[M+H]^+$.

Intermediate 23

5-{[6-(2-fluorophenyl)pyridin-3-yl]carbamoyl}-2-methoxybenzoic acid



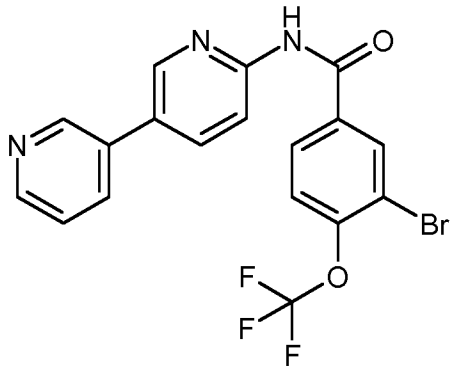
2.30 g (6.05 mmol) of methyl 5-{[6-(2-fluorophenyl)pyridin-3-yl]carbamoyl}-2-methoxybenzoate (intermediate 22) and 434.4 mg (18.14 mmol) of lithium hydroxide were stirred at 40 °C for 30 h in 49.0 mL of THF and 11.8 mL of methanol. The reaction mixture was allowed to cool down. It was concentrated on a rotavap and water was added. The pH was adjusted to pH 5 by adding potassium hydrogensulfate and it was stirred for 30 minutes. The solid was filtered off by suction and dried under vacuum at 45 °C to yield 2.1 g (95% of theory) of the title compound.

^{1}H-NMR (300 MHz, DMSO-d_6) δ [ppm]: 1.165 (0.57), 1.229 (1.26), 1.351 (1.87), 2.179 (0.40), 2.271 (0.88), 2.725 (0.89), 3.251 (1.09), 3.922 (16.00), 4.213 (1.07), 4.494 (1.07), 7.294 (3.75), 7.330 (6.47), 7.333 (6.22), 7.360 (3.99), 7.431 (1.46), 7.455 (2.65), 7.477 (2.83), 7.514 (2.44), 7.554 (2.33), 7.806 (2.51), 7.834 (2.72), 7.935 (1.61), 7.962 (2.75), 7.989 (1.53), 8.171 (2.07), 8.203 (2.01), 8.296 (2.48), 8.327 (2.48), 8.357 (4.10), 9.068 (4.28), 9.073 (4.24), 10.574 (4.33).

LC-MS (Method 4): R_t = 0.99 min; MS (ESIpos): m/z = 367 $[M+H]^+$.

Intermediate 24

N-(3,3'-bipyridin-6-yl)-3-bromo-4-(trifluoromethoxy)benzamide



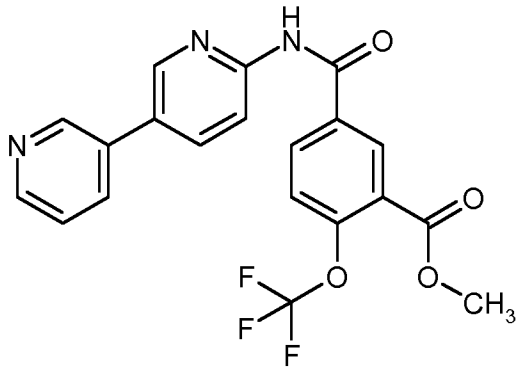
4.0 g (14.02 mmol) of 3-bromo-4-(trifluoromethoxy)benzoic acid were dissolved in 80 mL of anh DMF. 9.8 mL (56.26 mmol) of N-ethyl-N-isopropylpropan-2-amine, 2.4 mL (14.02 mmol) of 3,3'-bipyridin-6-amine and 10.9 g (20.95 mmol) of PYBOP were added. It was stirred at 50 °C over night. The reaction mixture was allowed to reach rt. 100 mL of water were added, and the precipitate was filtered off by suction and washed with water twice. 20 mL of methanol were added to the residue and it was stirred for 0.5 h at 60 °C. It was cooled down and filtered off. The solid was dried under vacuum at 50 °C affording 2.85 g (46% of theory) of the title compound.

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: -0.063 (0.67), 2.322 (1.41), 2.327 (1.82), 2.331 (1.34), 2.523 (11.09), 2.664 (1.34), 2.669 (1.88), 2.674 (1.41), 2.889 (0.40), 7.507 (5.24), 7.519 (5.78), 7.527 (5.98), 7.539 (5.78), 7.685 (6.05), 7.689 (6.12), 7.706 (6.59), 7.711 (6.45), 8.137 (7.87), 8.143 (8.27), 8.158 (8.07), 8.164 (11.43), 8.168 (8.07), 8.172 (5.78), 8.182 (4.57), 8.187 (6.25), 8.192 (4.57), 8.249 (3.43), 8.255 (3.43), 8.271 (11.23), 8.276 (12.17), 8.288 (16.00), 8.290 (15.93), 8.310 (4.50), 8.484 (14.66), 8.490 (14.99), 8.601 (8.07), 8.605 (7.87), 8.613 (8.40), 8.617 (7.93), 8.811 (10.42), 8.814 (11.03), 8.817 (11.70), 8.819 (10.08), 8.982 (10.82), 8.989 (11.16), 11.229 (9.61).

LC-MS (Method 3): R_t = 1.33 min; MS (ESIpos): m/z = 438 $[M+H]^+$.

Intermediate 25

methyl 5-(3,3'-bipyridin-6-ylcarbamoyl)-2-(trifluoromethoxy)benzoate



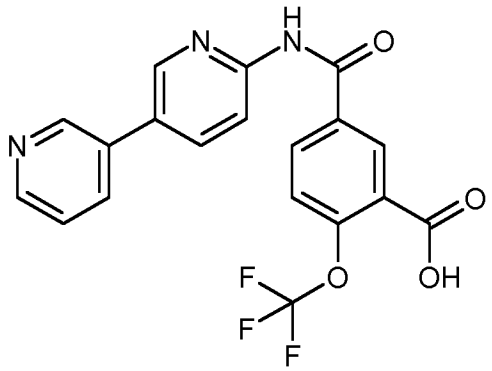
1.2 g (2.74 mmol) of N-(3,3'-bipyridin-6-yl)-3-bromo-4-(trifluoromethoxy)benzamide (intermediate 24) were dissolved in 55 mL of a mixture of methanol / THF (10:1). 450 mg (0.55 mmol) of 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex and 960 µL (6.85 mmol) of N,N-diethylethanamine were added. The reaction mixture was purged three times with carbonmonoxide. The autoclave was filled with carbonmonoxide up to 10.1 bar and stirred for 30 minutes at 20 °C. The carbonmonoxide was released and it was evacuated at 0.06 bar. Then the vessel was charged with carbonmonoxide (13.0 bar) and stirred for 24 h at 100 °C. The carbonmonoxide was discharged and the reaction mixture was concentrated on a rotavap. The residue was dissolved in 60 mL of ethanol at 60 °C. It was concentrated to ca. 30 mL and stirred 1 h on an ice bath. The solid material was filtered off and dried to give 630 mg (55% of theory) of the title compound.

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 2.523 (1.80), 3.162 (0.78), 3.175 (0.80), 3.920 (16.00), 7.509 (1.01), 7.521 (1.10), 7.529 (1.14), 7.541 (1.08), 7.678 (1.28), 7.681 (1.30), 7.699 (1.38), 7.703 (1.26), 8.164 (0.77), 8.169 (1.27), 8.175 (0.94), 8.184 (0.86), 8.189 (1.19), 8.194 (0.86), 8.256 (0.76), 8.262 (0.74), 8.277 (1.94), 8.283 (2.13), 8.302 (3.14), 8.324 (1.12), 8.364 (1.41), 8.370 (1.52), 8.385 (1.31), 8.392 (1.42), 8.578 (2.96), 8.584 (2.83), 8.603 (1.47), 8.607 (1.50), 8.615 (1.53), 8.619 (1.46), 8.814 (2.17), 8.816 (2.26), 8.821 (2.25), 8.985 (2.11), 8.987 (2.13), 8.992 (2.17), 11.319 (2.53).

LC-MS (Method 4): R_t = 1.11 min; MS (ESIpos): m/z = 418 $[M+H]^+$.

Intermediate 26

5-(3,3'-bipyridin-6-ylcarbamoyl)-2-(trifluoromethoxy)benzoic acid



11 mL of THF, 2.7 mL of methanol and 95 mg (3.95 mmol) of lithium hydroxide were added to 550 mg (1.32 mmol) of methyl 5-(3,3'-bipyridin-6-ylcarbamoyl)-2-(trifluoromethoxy)benzoate (intermediate 25). It was stirred 5 h at 40 °C and at rt over night. The reaction mixture was concentrated on a rotavap. Water was added and the pH was adjusted to 3 with potassium hydrogen sulfate. The solid material was filtered off by suction and washed with water. Dichloromethane was added to the residue and the dichloromethane was evacuated on a rotavap. This procedure was performed five times yielding 480 mg (91% of theory) of the title compound.

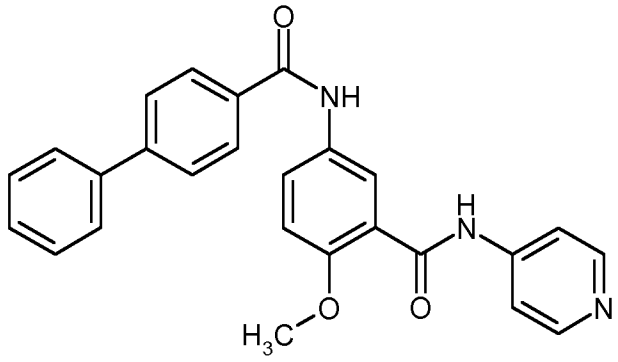
^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 1.167 (1.03), 1.230 (1.11), 1.907 (1.19), 2.317 (0.50), 2.322 (1.03), 2.327 (1.40), 2.331 (1.03), 2.336 (0.50), 2.523 (4.77), 2.660 (0.53), 2.664 (1.11), 2.669 (1.48), 2.674 (1.13), 2.678 (0.58), 2.729 (2.21), 2.888 (2.85), 3.506 (2.35), 3.835 (1.27), 3.891 (1.71), 3.900 (1.13), 3.914 (1.34), 3.940 (0.58), 7.507 (3.53), 7.519 (3.87), 7.526 (3.53), 7.528 (3.93), 7.539 (3.87), 7.582 (1.53), 7.585 (1.45), 7.603 (1.66), 7.606 (1.71), 7.616 (4.64), 7.620 (4.67), 7.637 (4.90), 7.641 (4.56), 7.951 (0.50), 8.063 (0.69), 8.162 (2.90), 8.167 (4.45), 8.172 (3.24), 8.182 (4.67), 8.188 (5.54), 8.192 (3.27), 8.204 (1.79), 8.210 (1.82), 8.242 (0.58), 8.249 (3.61), 8.255 (3.19), 8.270 (7.57), 8.276 (8.07), 8.301 (16.00), 8.307 (5.98), 8.322 (8.80), 8.329 (5.14), 8.406 (3.11), 8.413 (2.87), 8.536 (10.12), 8.542 (9.28), 8.600 (4.43), 8.605 (4.67), 8.612 (4.72), 8.617 (4.11), 8.807 (8.07), 8.809 (8.41), 8.814 (8.54), 8.982 (6.56), 8.984 (6.56), 8.989 (6.38), 11.283 (8.70).

LC-MS (Method 4): R_t = 0.87 min; MS (ESIpos): m/z = 404 $[M+H]^+$.

Examples:

Example 1

N-[4-methoxy-3-(pyridin-4-ylcarbamoyl)phenyl]biphenyl-4-carboxamide



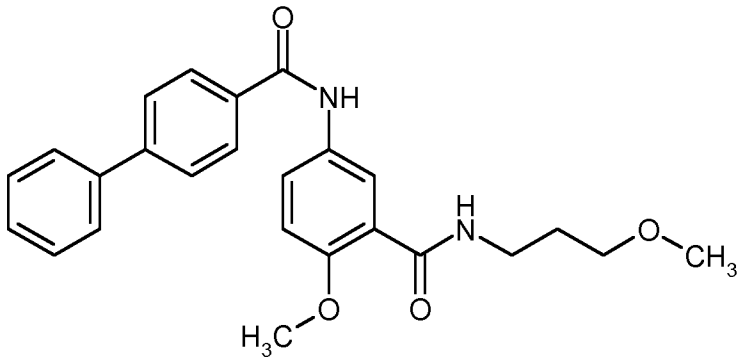
77.2 mg (0.82 mmol, 1.0 equiv.) of pyridin-4-amine were provided in 32 mL of tetrahydrofuran. 0.17 mL (1.23 mmol, 1.5 equiv.) of triethylamine and 300 mg (0.82 mmol, 1.0 equiv.) of the compound of intermediate 4 were added at room temperature and it was stirred over night. The reaction mixture was poured into 25 mL of water and extracted with dichloromethane. The combined organic phases were washed with a saturated, aqueous ammonium chloride solution and a saturated, aqueous sodium bicarbonate solution, were dried over sodium sulfate and concentrated under reduced pressure. Purification by HPLC (method 2) yielded 33.0 mg (9% of theory) of the title compound.

^{1}H-NMR (300 MHz, DMSO-d_6) δ [ppm]: 2.264 (0.42), 2.270 (0.56), 2.276 (0.41), 2.525 (3.54), 2.540 (2.19), 2.720 (0.44), 2.726 (0.55), 2.732 (0.43), 3.907 (16.00), 7.212 (2.64), 7.242 (2.83), 7.402 (0.69), 7.406 (0.50), 7.418 (0.57), 7.426 (2.28), 7.433 (0.83), 7.446 (1.27), 7.450 (2.01), 7.455 (1.20), 7.490 (2.96), 7.496 (1.36), 7.511 (2.20), 7.516 (4.36), 7.533 (0.84), 7.539 (1.91), 7.544 (1.28), 7.717 (4.07), 7.722 (2.94), 7.733 (3.11), 7.739 (4.36), 7.752 (3.61), 7.756 (4.31), 7.762 (2.23), 7.772 (1.29), 7.779 (3.72), 7.785 (2.63), 7.832 (4.33), 7.838 (1.62), 7.853 (1.84), 7.860 (5.40), 7.974 (1.56), 7.984 (1.86), 8.004 (1.35), 8.014 (1.79), 8.063 (5.08), 8.069 (6.74), 8.091 (1.81), 8.097 (4.26), 8.197 (0.60), 8.465 (4.85), 8.470 (3.11), 8.480 (3.08), 8.485 (4.43), 10.363 (3.57), 10.516 (3.31).

LC-MS (Method 4): R_t = 1.03 min; MS (ESIpos): m/z = 424 $[M+H]^+$.

Example 2

N-{4-methoxy-3-[(3-methoxypropyl)carbamoyl]phenyl}biphenyl-4-carboxamide



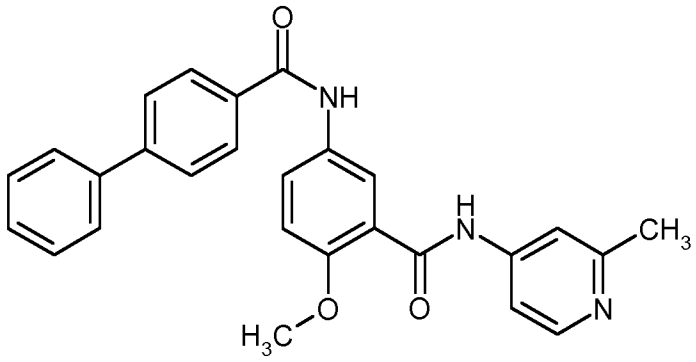
41.0 mg (0.46 mmol, 1.0 equiv.) of 3-methoxypropan-1-amine were provided in 24 mL of tetrahydrofuran. 0.10 mL (0.69 mmol, 1.5 equiv.) of triethylamine and 168.3 mg (0.46 mmol, 1.0 equiv.) of the compound of intermediate 4 were added at room temperature and it was stirred over night. The reaction mixture was poured into 25 mL of water and extracted with dichloromethane. The combined organic phases were washed with a saturated, aqueous ammonium chloride solution and a saturated, aqueous sodium bicarbonate solution, were dried over sodium sulfate and concentrated under reduced pressure. Purification by HPLC (method 2) yielded 75.4 mg (38% of theory) of the title compound.

^{1}H-NMR (300 MHz, DMSO-d_6) δ [ppm]: 1.716 (0.65), 1.737 (2.11), 1.759 (3.27), 1.781 (2.17), 1.803 (0.61), 2.525 (2.07), 2.540 (1.18), 3.221 (1.27), 3.234 (0.43), 3.315 (2.63), 3.330 (11.96), 3.339 (5.69), 3.357 (3.27), 3.380 (1.47), 3.389 (3.12), 3.410 (6.14), 3.430 (2.75), 3.823 (0.66), 3.890 (16.00), 5.759 (0.42), 7.134 (2.50), 7.164 (2.74), 7.399 (0.63), 7.404 (0.43), 7.415 (0.50), 7.423 (2.15), 7.431 (0.68), 7.443 (1.13), 7.448 (1.80), 7.452 (1.02), 7.489 (2.65), 7.494 (1.16), 7.509 (2.05), 7.514 (3.98), 7.531 (0.74), 7.538 (1.75), 7.542 (1.06), 7.749 (3.09), 7.753 (3.79), 7.759 (1.83), 7.770 (1.12), 7.777 (3.45), 7.782 (2.37), 7.819 (4.07), 7.826 (1.42), 7.841 (1.70), 7.848 (4.89), 7.855 (0.85), 7.949 (1.55), 7.959 (1.63), 7.979 (1.38), 7.988 (1.59), 8.067 (4.97), 8.073 (1.52), 8.089 (1.59), 8.095 (3.87), 8.140 (3.47), 8.149 (3.08), 8.266 (0.90), 8.285 (1.50), 8.303 (0.74), 10.312 (3.29).

LC-MS (Method 4): R_t = 1.16 min; MS (ESIpos): m/z = 419 $[M+H]^+$.

Example 3

N-{4-methoxy-3-[(2-methylpyridin-4-yl)carbamoyl]phenyl}biphenyl-4-carboxamide



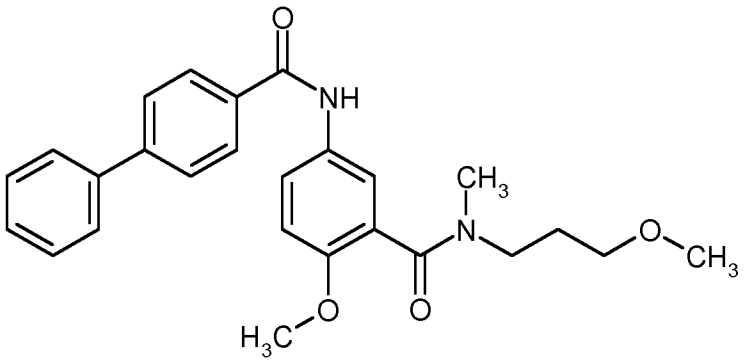
44.3 mg (0.41 mmol, 1.0 equiv.) of 2-methylpyridin-4-amine were provided in 16 mL of tetrahydrofuran. 0.09 mL (0.62 mmol, 1.5 equiv.) of triethylamine and 150 mg (0.41 mmol, 1.0 equiv.) of the compound of intermediate 4 were added at room temperature and it was stirred over night. The reaction mixture was poured into 25 mL of water and extracted with dichloromethane. The combined organic phases were washed with a saturated, aqueous ammonium chloride solution and a saturated, aqueous sodium bicarbonate solution, were dried over sodium sulfate and concentrated under reduced pressure. Purification by HPLC (method 2) yielded 24.0 mg (13% of theory) of the title compound.

^{1}H-NMR (300 MHz, DMSO-d_6) δ [ppm]: 2.270 (0.49), 2.413 (0.52), 2.444 (16.00), 2.525 (2.73), 2.540 (1.37), 2.726 (0.48), 3.325 (1.67), 3.909 (15.71), 7.208 (2.59), 7.239 (2.78), 7.402 (0.64), 7.418 (0.46), 7.426 (2.15), 7.434 (0.66), 7.446 (1.10), 7.450 (1.87), 7.455 (1.08), 7.490 (2.75), 7.496 (1.26), 7.511 (1.97), 7.516 (4.26), 7.528 (1.66), 7.534 (2.24), 7.540 (2.32), 7.544 (2.14), 7.547 (1.90), 7.553 (1.74), 7.594 (2.92), 7.601 (2.49), 7.752 (3.17), 7.756 (3.89), 7.762 (1.80), 7.772 (0.99), 7.779 (3.52), 7.784 (2.52), 7.831 (4.21), 7.838 (1.41), 7.853 (1.61), 7.860 (5.21), 7.970 (1.51), 7.979 (1.81), 8.000 (1.33), 8.009 (1.73), 8.061 (4.50), 8.069 (7.34), 8.090 (1.52), 8.097 (4.12), 8.143 (6.80), 8.326 (2.95), 8.344 (2.78), 10.361 (3.45), 10.422 (3.35).

LC-MS (Method 4): R_t = 1.07 min; MS (ESIpos): m/z = 438 $[M+H]^+$.

Example 4

N-{4-methoxy-3-[(3-methoxypropyl)(methyl)carbamoyl]phenyl}biphenyl-4-carboxamide



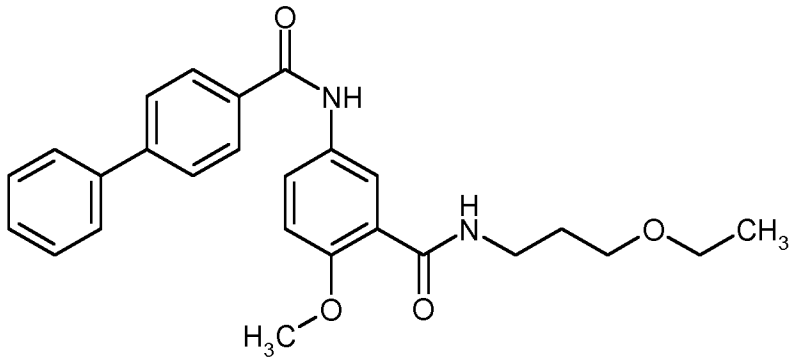
42.3 mg (0.41 mmol, 1.0 equiv.) of 3-methoxy-N-methylpropan-1-amine were provided in 15 mL of tetrahydrofuran. 0.09 mL (0.62 mmol, 1.5 equiv.) of triethylamine and 150 mg (0.41 mmol, 1.0 equiv.) of the compound of intermediate 4 were added at room temperature and it was stirred for 2 days. The reaction mixture was poured into 25 mL of water and extracted with dichloromethane. The combined organic phases were washed with a saturated, aqueous ammonium chloride solution and a saturated, aqueous sodium bicarbonate solution, were dried over sodium sulfate and concentrated under reduced pressure. Purification by HPLC (method 2) yielded 54.1 mg (30% of theory) of the title compound.

^{1}H-NMR (300 MHz, DMSO-d_6) δ [ppm]: 1.657 (0.71), 1.681 (0.98), 1.705 (0.76), 1.783 (1.08), 1.805 (1.67), 1.828 (1.13), 2.263 (0.41), 2.270 (0.60), 2.276 (0.45), 2.525 (3.30), 2.720 (0.47), 2.726 (0.64), 2.732 (0.46), 2.769 (10.43), 2.956 (8.83), 3.091 (12.96), 3.120 (0.79), 3.143 (1.10), 3.168 (1.27), 3.184 (1.41), 3.187 (1.40), 3.210 (0.75), 3.266 (16.00), 3.378 (1.39), 3.399 (2.82), 3.420 (1.34), 3.460 (0.66), 3.481 (0.97), 3.776 (8.68), 3.800 (10.40), 7.062 (1.39), 7.076 (1.71), 7.092 (1.59), 7.107 (1.76), 7.394 (0.48), 7.398 (0.76), 7.403 (0.49), 7.414 (0.63), 7.422 (2.44), 7.430 (0.86), 7.442 (1.34), 7.447 (2.17), 7.451 (1.34), 7.488 (3.21), 7.493 (1.66), 7.507 (2.37), 7.513 (4.81), 7.530 (0.93), 7.537 (2.04), 7.540 (1.40), 7.609 (2.06), 7.618 (3.66), 7.627 (1.96), 7.738 (0.94), 7.745 (4.04), 7.749 (5.20), 7.765 (1.61), 7.772 (4.17), 7.779 (3.85), 7.788 (2.00), 7.810 (1.78), 7.817 (5.56), 7.824 (2.08), 7.839 (2.19), 7.846 (5.90), 8.036 (3.45), 8.042 (4.09), 8.049 (1.49), 8.064 (3.11), 8.071 (2.89), 10.230 (2.95).

LC-MS (Method 3): R_t = 1.20 min; MS (ESIpos): m/z = 433 $[M+H]^+$.

Example 5

N-{3-[(3-ethoxypropyl)carbamoyl]-4-methoxyphenyl}biphenyl-4-carboxamide



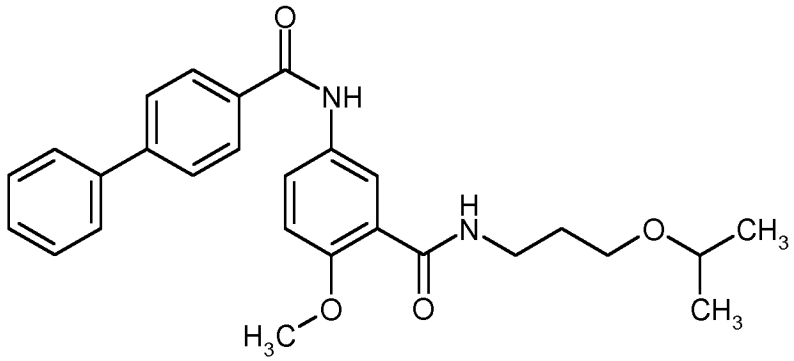
42.3 mg (0.41 mmol, 1.0 equiv.) of 3-ethoxypropan-1-amine were provided in 15 mL of tetrahydrofuran. 0.09 mL (0.62 mmol, 1.5 equiv.) of triethylamine and 150 mg (0.41 mmol, 1.0 equiv.) of the compound of intermediate 4 were added at room temperature and it was stirred for 2 days. The reaction mixture was poured into 25 mL of water and extracted with dichloromethane. The combined organic phases were washed with a saturated, aqueous ammonium chloride solution and a saturated, aqueous sodium bicarbonate solution, were dried over sodium sulfate and concentrated under reduced pressure. Purification by HPLC (method 2) yielded 51.6 mg (28% of theory) of the title compound.

^{1}H-NMR (300 MHz, DMSO-d_6) δ [ppm]: 1.099 (3.43), 1.123 (7.15), 1.146 (3.45), 1.736 (1.20), 1.758 (1.84), 1.779 (1.22), 3.302 (16.00), 3.319 (0.88), 3.341 (1.64), 3.361 (1.60), 3.383 (0.69), 3.400 (1.29), 3.423 (4.41), 3.442 (3.86), 3.447 (4.21), 3.462 (1.64), 3.470 (1.24), 7.130 (1.44), 7.160 (1.57), 7.423 (1.23), 7.430 (0.46), 7.443 (0.66), 7.447 (1.07), 7.452 (0.65), 7.488 (1.55), 7.493 (0.81), 7.508 (1.23), 7.513 (2.33), 7.531 (0.45), 7.537 (1.04), 7.542 (0.69), 7.748 (1.86), 7.751 (2.27), 7.757 (1.20), 7.768 (0.71), 7.775 (1.97), 7.780 (1.46), 7.816 (2.37), 7.823 (1.01), 7.838 (1.06), 7.845 (2.90), 7.852 (0.68), 7.942 (0.93), 7.951 (1.02), 7.972 (0.82), 7.981 (0.91), 8.066 (2.91), 8.073 (1.10), 8.088 (0.99), 8.094 (2.31), 8.131 (2.04), 8.140 (1.89), 8.206 (0.46), 8.225 (0.90), 8.245 (0.44), 10.291 (1.91).

LC-MS (Method 3): R_t = 1.26 min; MS (ESIpos): m/z = 433 $[M+H]^+$.

Example 6

N-{3-[(3-isopropoxypropyl)carbamoyl]-4-methoxyphenyl}biphenyl-4-carboxamide



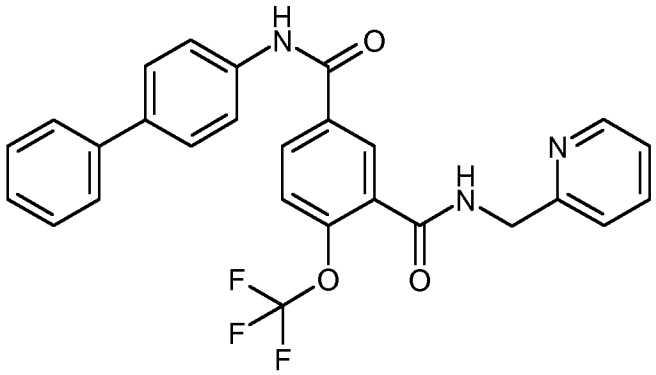
48.1 mg (0.41 mmol, 1.0 equiv.) of 3-(propan-2-yloxy)propan-1-amine were provided in 15 mL of tetrahydrofuran. 0.09 mL (0.62 mmol, 1.5 equiv.) of triethylamine and 150 mg (0.41 mmol, 1.0 equiv.) of the compound of intermediate 4 were added at room temperature and it was stirred for 2 days. The reaction mixture was poured into 25 mL of water and extracted with dichloromethane. The combined organic phases were washed with a saturated, aqueous ammonium chloride solution and a saturated, aqueous sodium bicarbonate solution, were dried over sodium sulfate and concentrated under reduced pressure. Purification by HPLC (method 2) yielded 51.6 mg (28% of theory) of the title compound.

^{1}H-NMR (300 MHz, DMSO-d_6) δ [ppm]: 1.084 (15.50), 1.104 (16.00), 1.709 (1.26), 1.731 (1.95), 1.753 (1.31), 2.270 (0.48), 2.726 (0.50), 3.337 (1.81), 3.356 (1.72), 3.379 (0.72), 3.413 (1.68), 3.434 (3.56), 3.455 (1.62), 3.495 (0.47), 3.515 (1.12), 3.535 (1.40), 3.556 (1.06), 3.576 (0.43), 3.887 (10.34), 7.129 (1.61), 7.160 (1.72), 7.399 (0.41), 7.423 (1.33), 7.431 (0.50), 7.443 (0.72), 7.447 (1.17), 7.452 (0.71), 7.488 (1.72), 7.493 (0.95), 7.508 (1.35), 7.514 (2.65), 7.532 (0.55), 7.537 (1.17), 7.542 (0.79), 7.748 (2.04), 7.751 (2.56), 7.757 (1.38), 7.768 (0.76), 7.775 (2.21), 7.780 (1.66), 7.816 (2.58), 7.823 (1.17), 7.838 (1.16), 7.845 (3.26), 7.940 (1.03), 7.949 (1.13), 7.969 (0.90), 7.978 (1.02), 8.066 (3.21), 8.073 (1.28), 8.088 (1.12), 8.094 (2.60), 8.125 (2.25), 8.135 (2.10), 8.171 (0.54), 8.190 (1.01), 8.209 (0.53), 10.290 (2.13).

LC-MS (Method 3): R_t = 1.31 min; MS (ESIpos): m/z = 447 $[M+H]^+$.

Example 7

N^1-(biphenyl-4-yl)-N^3-(pyridin-2-ylmethyl)-4-(trifluoromethoxy)isophthalamide



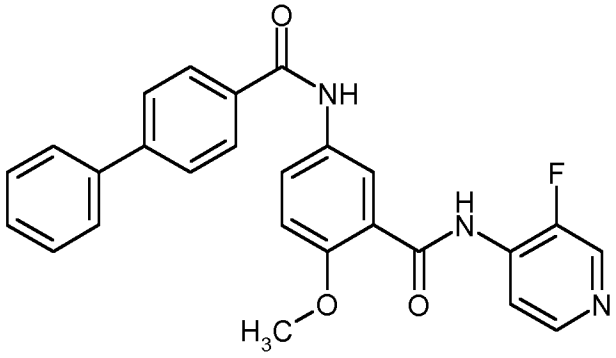
168 mg (0.99 mmol, 1.5 equiv.) of biphenyl-4-amine and 0.35 mL (1.99 mmol, 3.0 equiv.) of N,N-diisopropylethylamine were provided in 1 mL of DMF at room temperature. A solution of 230 mg (0.66 mmol, 1.0 equiv.) of the compound of intermediate 8 in 1 mL of DMF and 0.58 mL (0.99 mmol, 1.5 equiv.) of a 50% solution of 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (T3P) in DMF were added and the mixture was stirred at room temperature over night. After filtration, purification by HPLC (column: chromatorex C18, 10µm, 195x51mm, mobile phase: acetonitrile/water +0.1% formic acid gradient) yielded 151 mg (46% of theory) of the title compound.

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 1.174 (0.54), 1.988 (1.01), 2.322 (0.50), 2.327 (0.61), 2.332 (0.47), 2.523 (2.32), 2.664 (0.51), 2.669 (0.63), 2.674 (0.49), 4.580 (9.95), 4.596 (10.03), 7.281 (2.35), 7.284 (2.45), 7.293 (2.55), 7.297 (2.73), 7.299 (2.81), 7.303 (2.64), 7.312 (2.68), 7.315 (2.69), 7.328 (2.05), 7.331 (1.26), 7.346 (5.27), 7.362 (2.17), 7.365 (3.65), 7.368 (2.01), 7.402 (4.76), 7.422 (5.32), 7.443 (6.26), 7.463 (10.07), 7.476 (2.20), 7.481 (5.17), 7.629 (3.31), 7.633 (3.45), 7.646 (1.81), 7.651 (3.90), 7.655 (3.69), 7.669 (8.66), 7.671 (9.81), 7.688 (16.00), 7.693 (10.35), 7.704 (4.64), 7.710 (12.79), 7.716 (2.02), 7.781 (2.80), 7.786 (2.87), 7.800 (4.61), 7.805 (4.59), 7.820 (2.40), 7.824 (2.34), 7.868 (2.12), 7.874 (12.93), 7.880 (4.11), 7.891 (4.10), 7.896 (10.05), 7.903 (1.40), 8.171 (4.44), 8.177 (4.86), 8.193 (3.89), 8.198 (4.50), 8.250 (8.90), 8.256 (7.57), 8.528 (3.10), 8.534 (3.45), 8.540 (3.49), 8.547 (2.89), 9.190 (2.13), 9.205 (4.34), 9.220 (2.13), 10.549 (8.14).

LC-MS (Method 1): R_t = 1.24 min; MS (ESIpos): m/z = 492 $[M+H]^+$.

Example 8

N-{3-[(3-fluoropyridin-4-yl)carbamoyl]-4-methoxyphenyl}biphenyl-4-carboxamide



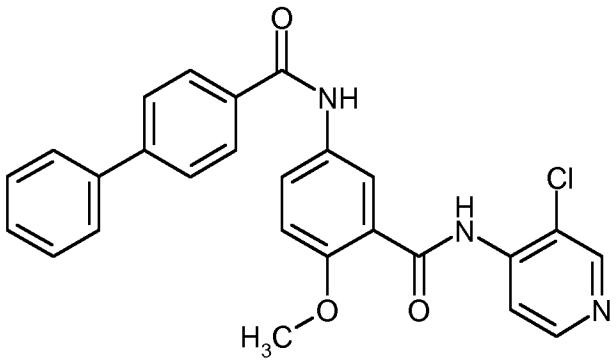
58.0 mg (0.52 mmol, 1.2 equiv.) of 3-fluoropyridin-4-amine and 0.23 mL (1.3 mmol, 3.0 equiv.) of N,N-diisopropylethylamine were provided in 1.8 mL of DMF at room temperature. 150 mg (0.43 mmol, 1.0 equiv.) of the compound of intermediate 3 and 0.30 mL (0.52 mmol, 1.2 equiv.) of a 50% solution of 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (T3P) in DMF were added and the mixture was stirred at room temperature over night. After filtration, purification by HPLC (method 2) yielded 30.0 mg (12% of theory) of the title compound.

^{1}H-NMR (300 MHz, DMSO-d_6) δ [ppm]: 1.905 (1.18), 2.258 (0.60), 2.263 (1.13), 2.270 (1.49), 2.276 (1.15), 2.720 (1.18), 2.726 (1.55), 2.732 (1.23), 3.169 (0.50), 3.801 (2.02), 4.046 (16.00), 5.750 (2.04), 7.319 (2.46), 7.349 (2.67), 7.405 (0.71), 7.429 (2.23), 7.437 (0.94), 7.449 (1.44), 7.453 (1.94), 7.457 (1.26), 7.494 (2.99), 7.514 (2.88), 7.520 (4.43), 7.537 (1.18), 7.543 (1.94), 7.547 (1.39), 7.757 (3.74), 7.761 (4.24), 7.766 (2.51), 7.784 (3.69), 7.789 (2.72), 7.817 (0.81), 7.836 (4.29), 7.857 (2.04), 7.864 (4.92), 8.056 (0.84), 8.088 (6.44), 8.098 (2.70), 8.116 (4.69), 8.128 (1.81), 8.365 (0.73), 8.383 (2.23), 8.403 (5.66), 8.415 (4.11), 8.424 (3.64), 8.606 (2.80), 8.614 (2.80), 10.422 (3.38), 10.627 (1.86), 10.633 (1.86), 10.637 (1.81).

LC-MS (Method 1): R_t = 1.26 min; MS (ESIpos): m/z = 442 $[M+H]^+$.

Example 9

N-{3-[(3-chloropyridin-4-yl)carbamoyl]-4-methoxyphenyl}biphenyl-4-carboxamide



To a solution of the compound of intermediate 3 (150 mg, 0.43 mmol, 1.0 equiv.) and 3-chloropyridin-4-amine (83.3 mg, 0.65 mmol, 1.5 equiv.) in DMF (10 mL) was added (1H-benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, 337 mg, 0.65 mmol, 1.5 equiv.) and diisopropylethylamine (0.30 mL, 1.73 mmol, 4.0 equiv.). The resulting mixture was stirred at

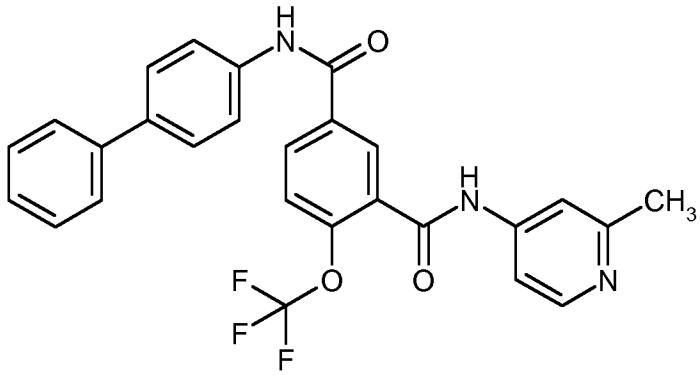
room temperature over night. 3-Chloropyridin-4-amine (55.5 mg, 0.43 mmol, 1.0 equiv.), (1H-benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, 225 mg, 0.43 mmol, 1.0 equiv.) and diisopropylethylamine (0.15 mL, 0.87 mmol, 2.0 equiv.) were added and the resulting mixture was stirred at room temperature over night. After concentration, purification by HPLC (Waters Autopurificationsystem, column: XBrigde C18 5µm 100x30 mm, solvent: water / acetonitrile + 0.2% ammonia (32%) gradient, rate: 50 mL/min, temperature: room temperature) yielded 21.0 mg (10% of theory) of the title compound.

^{1}H-NMR (300 MHz, DMSO-d_6) δ [ppm]: 1.107 (0.92), 1.224 (0.70), 1.646 (0.79), 2.074 (0.84), 2.084 (0.89), 2.525 (3.17), 2.540 (1.36), 4.131 (16.00), 7.360 (2.98), 7.379 (1.11), 7.391 (3.29), 7.405 (1.00), 7.421 (0.62), 7.429 (2.23), 7.437 (0.80), 7.448 (1.16), 7.453 (1.97), 7.458 (1.19), 7.494 (2.98), 7.514 (2.33), 7.519 (4.32), 7.536 (0.90), 7.543 (1.87), 7.547 (1.31), 7.759 (3.48), 7.762 (4.18), 7.767 (2.28), 7.779 (1.35), 7.786 (3.64), 7.791 (2.69), 7.838 (4.26), 7.845 (1.81), 7.860 (2.09), 7.867 (5.24), 8.092 (5.16), 8.099 (1.93), 8.113 (1.65), 8.120 (4.18), 8.137 (1.84), 8.146 (1.80), 8.167 (1.52), 8.176 (1.60), 8.492 (1.91), 8.510 (3.84), 8.539 (7.01), 8.548 (3.87), 8.559 (2.33), 8.679 (5.59), 10.466 (3.53), 10.958 (3.67).

LC-MS (Method 1): R_t = 1.33 min; MS (ESIpos): m/z = 458 $[M+H]^+$.

Example 10

N^1-(biphenyl-4-yl)-N^3-(2-methylpyridin-4-yl)-4-(trifluoromethoxy)isophthalamide



150 mg (0.44 mmol, 1.0 equiv.) of the compound of intermediate 11 and 384 µL (2.20 mmol, 5.0 equiv.) of N,N-diisopropylethylamine were provided in 4 mL of DMF at room temperature. 149 mg (0.88 mmol, 2.0 equiv.) of biphenyl-4-amine and 515 µL (0.88 mmol, 2.0 equiv.) of a 50% solution of 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (T3P) in DMF were added and the mixture was stirred at room temperature over night. After concentration, water was added and the mixture was extracted with dichloromethane. The combined organic phases were dried over sodium sulfate and concentrated. Purification by HPLC (method 2) yielded 22.0 mg (9% of theory) of the title compound.

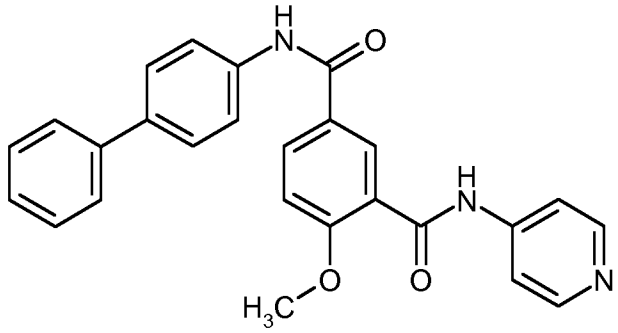
^{1}H-NMR (300 MHz, DMSO-d_6) δ [ppm]: 2.459 (16.00), 2.540 (1.90), 6.618 (0.96), 6.646 (1.04), 7.200 (0.43), 7.315 (0.47), 7.320 (0.82), 7.332 (1.67), 7.339 (1.14), 7.344 (2.41), 7.351 (1.03), 7.360 (1.94), 7.369 (1.90), 7.373 (1.11), 7.384 (0.58), 7.435 (2.77), 7.441 (1.30), 7.457 (2.40), 7.462 (4.57), 7.479 (2.35), 7.485 (2.83), 7.498 (1.73), 7.507 (1.02), 7.510 (0.96), 7.534 (0.74), 7.539 (0.58), 7.583 (2.86),

7.586 (2.95), 7.591 (2.74), 7.664 (3.75), 7.668 (4.38), 7.673 (2.23), 7.688 (5.94), 7.696 (3.86), 7.710 (3.26), 7.717 (6.60), 7.726 (1.19), 7.733 (1.12), 7.738 (1.88), 7.744 (1.67), 7.865 (0.77), 7.874 (5.66), 7.881 (1.65), 7.895 (1.46), 7.903 (4.06), 8.238 (1.84), 8.246 (2.03), 8.267 (1.62), 8.274 (1.94), 8.345 (3.73), 8.352 (3.31), 8.367 (2.99), 8.386 (2.75), 10.561 (3.43), 10.963 (3.53).

LC-MS (Method 4): R_t = 1.11 min; MS (ESIpos): m/z = 492 $[M+H]^+$.

Example 11

N^1-(biphenyl-4-yl)-4-methoxy-N^3-(pyridin-4-yl)isophthalamide



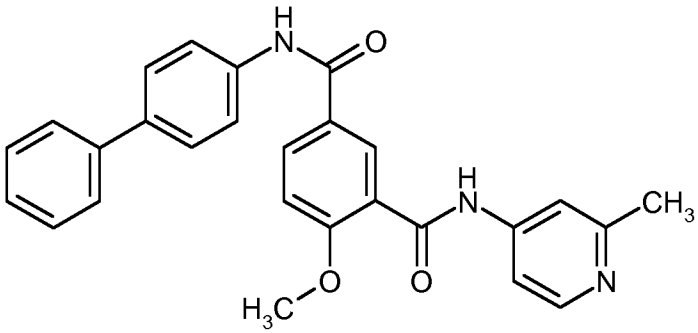
Under an atmosphere of argon 50.0 mg (0.14 mmol) of 5-(biphenyl-4-ylcarbamoyl)-2-methoxybenzoic acid (intermediate 14) were dissolved in 3.0 mL of anh DMF. 16.3 mg (0.17 mmol) of pyridin-4-amine, 0.03 mL (0.17 mmol) of N-ethyl-N-isopropylpropan-2-amine and 89.9 mg (0.17 mmol) of PYBOP were added and it was stirred over night at rt. It was concentrated on a rotavap and the residue was purified by HPLC (method 5) affording 29.7 mg (49% of theory) of the title compound.

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 2.326 (0.50), 2.523 (1.60), 2.539 (0.60), 2.669 (0.50), 3.896 (1.03), 3.969 (16.00), 7.316 (0.51), 7.319 (0.88), 7.338 (2.97), 7.341 (3.78), 7.353 (1.09), 7.356 (1.84), 7.363 (3.20), 7.436 (2.71), 7.456 (4.40), 7.470 (0.90), 7.475 (2.30), 7.666 (8.49), 7.683 (5.35), 7.687 (7.84), 7.694 (1.03), 7.718 (3.60), 7.722 (2.65), 7.730 (2.67), 7.734 (3.77), 7.875 (0.77), 7.882 (5.58), 7.887 (1.83), 7.898 (1.52), 7.903 (4.35), 7.910 (0.66), 7.913 (0.41), 8.180 (1.74), 8.186 (1.97), 8.202 (1.59), 8.208 (1.81), 8.280 (3.75), 8.286 (3.33), 8.478 (4.51), 8.482 (3.01), 8.490 (2.76), 8.494 (4.22), 10.321 (3.44), 10.602 (3.30).

LC-MS (Method 3): R_t = 1.22 min; MS (ESIpos): m/z = 424 $[M+H]^+$.

Example 12

N^1-(biphenyl-4-yl)-4-methoxy-N^3-(2-methylpyridin-4-yl)isophthalamide



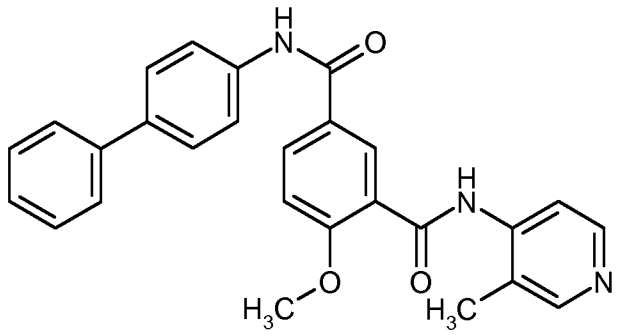
Under argon 50.0 mg (0.14 mmol) of 5-(biphenyl-4-ylcarbamoyl)-2-methoxybenzoic acid (intermediate 14) were dissolved in 3.0 mL of anh DMF. 18.7 mg (0.17 mmol) of 2-methylpyridin-4-amine, 0.03 mL (0.17 mmol) of N-ethyl-N-isopropylpropan-2-amine and 89.9 mg (0.17 mmol) of PYBOP were added and it was stirred over night at rt. 10 mg (0.09 mmol) of 2-methylpyridin-4-amine were added and it was stirred for 24 h at rt. It was concentrated on a rotavap and the residue was purified by HPLC (method 5) giving 15 mg (24% of theory) of the title compound.

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 1.729 (1.02), 1.737 (0.43), 1.746 (0.42), 2.322 (0.47), 2.327 (0.63), 2.331 (0.48), 2.448 (16.00), 2.523 (2.16), 2.664 (0.49), 2.669 (0.65), 2.674 (0.49), 3.001 (0.41), 3.008 (0.72), 3.018 (0.74), 3.843 (1.89), 3.849 (0.59), 3.923 (1.58), 3.968 (15.66), 7.316 (0.55), 7.320 (0.98), 7.336 (4.12), 7.357 (4.33), 7.437 (2.99), 7.441 (1.25), 7.456 (4.86), 7.475 (2.49), 7.530 (1.18), 7.535 (1.41), 7.544 (1.30), 7.549 (1.44), 7.591 (2.64), 7.596 (2.34), 7.665 (9.22), 7.683 (5.85), 7.687 (8.65), 7.862 (0.57), 7.875 (0.92), 7.881 (5.91), 7.887 (1.84), 7.898 (1.70), 7.903 (4.44), 7.910 (0.66), 8.175 (1.80), 8.182 (1.96), 8.198 (1.63), 8.203 (1.89), 8.273 (3.57), 8.278 (3.28), 8.338 (2.72), 8.353 (2.60), 10.321 (3.48), 10.334 (0.48), 10.501 (3.41).

LC-MS (Method 3): R_t = 1.25 min; MS (ESIpos): m/z = 438 $[M+H]^+$.

Example 13

N^1-(biphenyl-4-yl)-4-methoxy-N^3-(3-methylpyridin-4-yl)isophthalamide



50.0 mg (0.14 mmol) of 5-(biphenyl-4-ylcarbamoyl)-2-methoxybenzoic acid (intermediate 14) were dissolved in 3.0 mL of anh DMF under an atmosphere of argon. 18.9 mg (0.17 mmol) of 3-

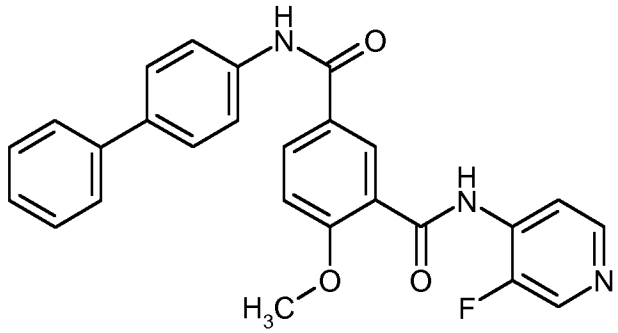
methylpyridin-4-amine, 0.03 mL (0.17 mmol) of N-ethyl-N-isopropylpropan-2-amine and 89.9 mg (0.17 mmol) of PYBOP were added and it was stirred over night at rt. It was concentrated on a rotavap and the residue was purified by HPLC (method 5) to yield 25.4 mg (40% of theory) of the title compound.

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 1.730 (0.66), 2.322 (0.60), 2.327 (0.84), 2.331 (0.70), 2.350 (16.00), 2.523 (2.64), 2.539 (1.30), 2.664 (0.57), 2.669 (0.76), 2.674 (0.56), 3.008 (0.46), 3.018 (0.46), 4.118 (14.78), 7.321 (0.65), 7.324 (1.03), 7.342 (2.78), 7.357 (1.17), 7.360 (1.89), 7.364 (1.05), 7.434 (3.23), 7.441 (3.56), 7.456 (5.11), 7.461 (5.71), 7.475 (1.27), 7.480 (2.79), 7.670 (5.15), 7.675 (8.64), 7.691 (6.15), 7.697 (7.47), 7.704 (1.26), 7.887 (1.02), 7.894 (6.39), 7.899 (2.19), 7.911 (1.93), 7.916 (5.16), 7.923 (0.75), 8.174 (1.40), 8.187 (1.56), 8.235 (2.00), 8.241 (2.10), 8.257 (1.95), 8.263 (1.93), 8.391 (2.80), 8.405 (2.50), 8.430 (4.84), 8.615 (3.67), 8.622 (3.65), 10.085 (3.75), 10.434 (4.04).

LC-MS (Method 3): R_t = 1.26 min; MS (ESIpos): m/z = 438 $[M+H]^+$.

Example 14

N^1-(biphenyl-4-yl)-N^3-(3-fluoropyridin-4-yl)-4-methoxyisophthalamide



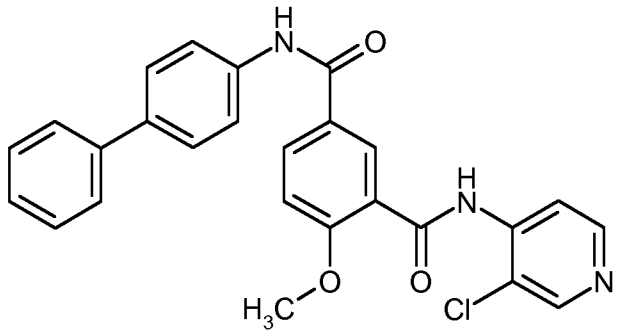
Under argon 50.0 mg (0.14 mmol) of 5-(biphenyl-4-ylcarbamoyl)-2-methoxybenzoic acid (intermediate 14) were dissolved in 3.0 mL of anh DMF. 19.4 mg (0.17 mmol) of 3-fluoropyridin-4-amine, 0.03 mL (0.17 mmol) of N-ethyl-N-isopropylpropan-2-amine and 89.9 mg (0.17 mmol) of PYBOP were added and it was stirred over night at rt. 10 mg (0.09 mmol) of 3-fluoropyridin-4-amine were added and it was stirred over night at rt. It was concentrated on a rotavap and the residue was purified by HPLC (method 5) to give 13.5 mg (21% of theory) of the title compound.

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 1.033 (0.40), 1.050 (0.40), 1.127 (0.40), 1.144 (0.40), 1.202 (0.54), 2.523 (1.07), 3.848 (0.83), 3.876 (1.31), 4.082 (16.00), 7.319 (0.56), 7.322 (0.86), 7.336 (0.90), 7.341 (2.29), 7.356 (1.03), 7.359 (1.58), 7.418 (2.73), 7.440 (5.25), 7.459 (4.42), 7.473 (1.18), 7.478 (2.28), 7.657 (0.83), 7.662 (1.44), 7.668 (4.49), 7.673 (7.31), 7.678 (2.88), 7.688 (5.11), 7.695 (6.17), 7.865 (0.68), 7.881 (0.95), 7.887 (5.83), 7.893 (1.86), 7.904 (1.63), 7.910 (4.26), 7.916 (0.65), 8.237 (1.76), 8.242 (1.79), 8.258 (1.59), 8.264 (1.71), 8.330 (0.95), 8.344 (1.67), 8.360 (1.36), 8.409 (3.63), 8.422 (2.53), 8.548 (3.52), 8.554 (3.41), 8.609 (3.20), 8.616 (3.25), 10.417 (3.42), 10.554 (1.99), 10.556 (2.00), 10.560 (1.93).

LC-MS (Method 3): R_t = 1.30 min; MS (ESIpos): m/z = 442 $[M+H]^+$.

Example 15

N^1-(biphenyl-4-yl)-N^3-(3-chloropyridin-4-yl)-4-methoxyisophthalamide



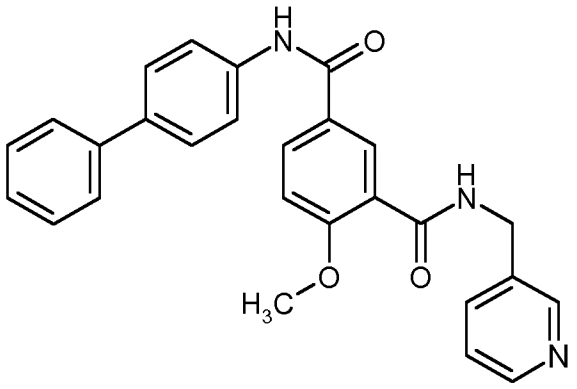
Under argon 100.0 mg (0.29 mmol) of 5-(biphenyl-4-ylcarbamoyl)-2-methoxybenzoic acid (intermediate 14) were dissolved in 6.0 mL of anh DMF. 44.4 mg (0.35 mmol) of 3-chloropyridin-4-amine, 0.06 mL (0.35 mmol) of N-ethyl-N-isopropylpropan-2-amine and 179.8 mg (0.35 mmol) of PYBOP were added and it was stirred over night at rt. It was concentrated on a rotavap and the residue was purified by HPLC (method 5) yielding 23 mg (17% of theory) of the title compound.

^{1}H-NMR (300 MHz, DMSO-d_6) δ [ppm]: 1.131 (0.48), 1.155 (1.00), 1.179 (0.52), 2.270 (0.47), 2.727 (0.50), 2.906 (0.43), 3.910 (1.39), 3.949 (0.75), 4.208 (16.00), 7.318 (0.80), 7.336 (1.06), 7.343 (2.30), 7.349 (0.91), 7.363 (1.25), 7.367 (1.73), 7.371 (1.03), 7.430 (1.09), 7.436 (2.82), 7.457 (2.90), 7.462 (4.57), 7.486 (4.66), 7.516 (2.78), 7.661 (2.13), 7.668 (4.85), 7.673 (7.49), 7.695 (5.40), 7.703 (6.72), 7.864 (0.71), 7.888 (5.62), 7.895 (2.39), 7.911 (1.73), 7.918 (4.03), 8.276 (1.69), 8.285 (1.83), 8.305 (1.76), 8.314 (1.82), 8.522 (10.34), 8.692 (4.86), 8.742 (3.56), 8.750 (3.55), 10.477 (3.48), 10.799 (3.68).

LC-MS (Method 3): R_t = 1.35 min; MS (ESIpos): m/z = 458 $[M+H]^+$.

Example 16

N^1-(biphenyl-4-yl)-4-methoxy-N^3-(pyridin-3-ylmethyl)isophthalamide



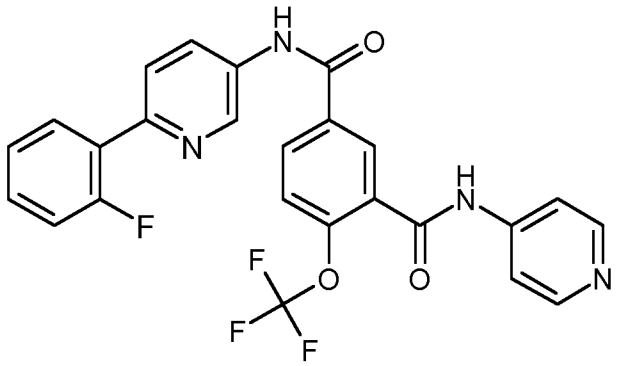
Under argon 100.0 mg (0.29 mmol) of 5-(biphenyl-4-ylcarbamoyl)-2-methoxybenzoic acid (intermediate 14) were dissolved in 6.0 mL of anh DMF. 37.4 mg (0.35 mmol) of 1-(pyridin-3-yl)methanamine, 0.06 mL (0.35 mmol) of N-ethyl-N-isopropylpropan-2-amine and 179.8 mg (0.35 mmol) of PYBOP were added and it was stirred over night at rt. It was concentrated on a rotavap and the residue was purified by HPLC (method 5) to afford 74.3 mg (59% of theory) of the title compound.

^{1}H-NMR (500 MHz, DMSO-d_6) δ [ppm]: 2.518 (0.66), 2.522 (0.46), 3.976 (16.00), 4.539 (3.42), 4.551 (3.40), 7.293 (2.64), 7.310 (2.78), 7.321 (0.84), 7.336 (2.08), 7.351 (1.42), 7.366 (1.06), 7.375 (1.13), 7.381 (1.17), 7.391 (1.19), 7.438 (2.33), 7.454 (3.75), 7.469 (2.05), 7.653 (0.52), 7.658 (4.76), 7.663 (4.25), 7.676 (5.83), 7.682 (2.71), 7.750 (0.73), 7.754 (1.28), 7.758 (0.90), 7.765 (0.75), 7.770 (1.20), 7.774 (0.81), 7.866 (0.55), 7.871 (5.14), 7.875 (1.44), 7.884 (1.26), 7.888 (4.14), 7.894 (0.44), 8.120 (1.80), 8.125 (1.84), 8.137 (1.55), 8.142 (1.62), 8.367 (3.34), 8.372 (3.47), 8.459 (1.56), 8.463 (1.47), 8.468 (1.61), 8.472 (1.46), 8.586 (2.00), 8.587 (2.11), 8.591 (2.09), 8.866 (0.71), 8.879 (1.46), 8.891 (0.71), 10.340 (3.08).

LC-MS (Method 3): R_t = 1.17 min; MS (ESIpos): m/z = 428 $[M+H]^+$.

Example 17

N^1-[6-(2-fluorophenyl)pyridin-3-yl]-N^3-(pyridin-4-yl)-4-(trifluoromethoxy)isophthalamide



Under argon 50.0 mg (0.12 mmol) of 5-{[6-(2-fluorophenyl)pyridin-3-yl]carbamoyl}-2-(trifluoromethoxy)benzoic acid (intermediate 17) and 13.4 mg (0.14 mmol) of pyridin-4-amine were dissolved in 3.0 mL of anh DMF. 62 µL (0.36 mmol) of N-ethyl-N-isopropylpropan-2-amine and 74.3

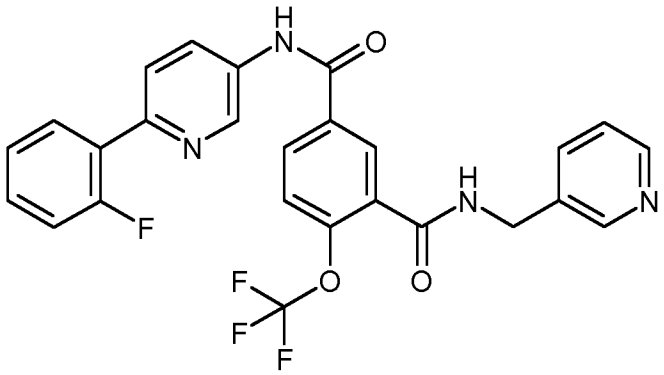
mg (0.14 mmol) of PYBOP were added. It was stirred at rt over night. The reaction mixture was concentrated on a rotavap and the residue was purified by HPLC (method 5) yielding 28.1 mg (48% of theory) of the title compound.

^{1}H-NMR (300 MHz, DMSO-d_6) δ [ppm]: 0.924 (0.46), 1.033 (1.04), 1.055 (1.07), 1.121 (0.54), 1.128 (1.04), 1.146 (1.07), 1.150 (1.11), 1.171 (0.43), 1.180 (0.61), 1.204 (1.25), 1.226 (0.89), 1.264 (0.43), 2.071 (6.00), 2.263 (1.50), 2.270 (2.00), 2.276 (1.50), 2.282 (0.82), 2.444 (1.36), 2.540 (3.43), 2.714 (0.79), 2.720 (1.50), 2.726 (2.04), 2.732 (1.54), 2.739 (0.75), 2.837 (1.14), 3.048 (1.18), 3.346 (1.11), 3.370 (0.61), 3.886 (3.11), 3.978 (0.50), 4.493 (0.43), 6.503 (0.57), 7.238 (0.79), 7.268 (0.93), 7.298 (4.43), 7.302 (5.18), 7.310 (5.54), 7.314 (5.46), 7.329 (9.79), 7.335 (14.39), 7.339 (14.07), 7.364 (13.07), 7.439 (3.54), 7.445 (3.93), 7.456 (4.50), 7.462 (6.21), 7.472 (4.79), 7.479 (4.46), 7.484 (5.29), 7.490 (4.64), 7.496 (2.89), 7.507 (2.46), 7.513 (2.39), 7.561 (0.93), 7.583 (0.71), 7.687 (11.18), 7.709 (11.71), 7.738 (7.64), 7.743 (7.50), 7.761 (4.32), 7.766 (7.89), 7.771 (7.21), 7.803 (0.79), 7.833 (7.00), 7.839 (7.21), 7.841 (6.89), 7.862 (8.32), 7.869 (7.57), 7.935 (4.64), 7.942 (4.54), 7.961 (8.50), 7.968 (7.57), 7.988 (4.68), 7.995 (3.61), 8.075 (0.46), 8.103 (0.68), 8.270 (8.07), 8.278 (8.75), 8.299 (8.93), 8.305 (16.00), 8.314 (10.14), 8.334 (7.43), 8.343 (7.57), 8.388 (14.96), 8.396 (13.21), 8.516 (9.89), 8.535 (9.25), 9.072 (13.82), 9.081 (13.86), 10.464 (0.75), 10.781 (10.64), 11.044 (11.68).

LC-MS (Method 4): R_t = 1.02 min; MS (ESIpos): m/z = 497 $[M+H]^+$.

Example 18

N^1-[6-(2-fluorophenyl)pyridin-3-yl]-N^3-(pyridin-3-ylmethyl)-4-(trifluoromethoxy)isophthalamide



Under argon 60.0 mg (0.14 mmol) of 5-{[6-(2-fluorophenyl)pyridin-3-yl]carbamoyl}-2-(trifluoromethoxy)benzoic acid (intermediate 17) and 18.5 mg (0.17 mmol) of 1-(pyridin-3-yl)methanamine were dissolved in 3.6 mL of anh DMF. 75 µL (0.43 mmol) of N-ethyl-N-isopropylpropan-2-amine and 89.1 mg (0.17 mmol) of PYBOP were added. It was stirred at rt over night. The reaction mixture was concentrated on a rotavap and the residue was purified by HPLC (method 5) yielding 36 mg (49% of theory) of the title compound.

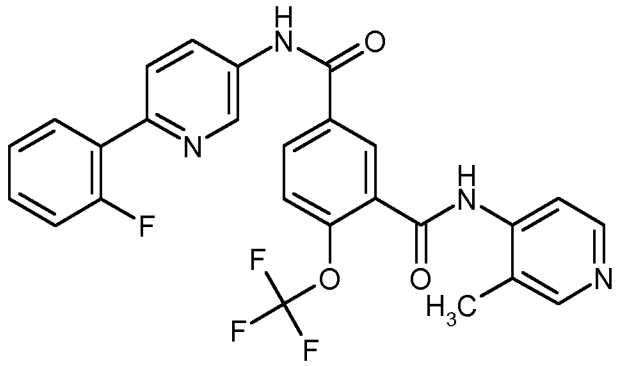
^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 2.317 (0.94), 2.322 (2.14), 2.327 (3.03), 2.331 (2.14), 2.336 (0.99), 2.523 (11.61), 2.539 (3.61), 2.659 (0.94), 2.664 (2.14), 2.669 (2.98), 2.674 (2.20), 2.679 (1.10), 4.215 (0.89), 4.220 (0.89), 4.493 (1.31), 4.498 (1.62), 4.512 (15.42), 4.527 (15.48), 7.308 (4.03), 7.310 (4.60), 7.318 (5.07), 7.321 (4.71), 7.331 (7.11), 7.338 (14.17), 7.339 (13.86), 7.358 (12.86), 7.374

(4.97), 7.386 (5.33), 7.387 (4.76), 7.392 (4.97), 7.394 (5.59), 7.405 (5.49), 7.447 (2.82), 7.451 (2.98), 7.459 (3.29), 7.465 (5.12), 7.471 (3.87), 7.478 (3.76), 7.481 (4.81), 7.485 (4.44), 7.490 (2.67), 7.499 (2.67), 7.503 (2.14), 7.528 (1.15), 7.550 (0.99), 7.576 (0.78), 7.646 (6.07), 7.651 (6.12), 7.668 (6.80), 7.672 (6.12), 7.747 (3.92), 7.752 (6.33), 7.757 (4.29), 7.767 (3.82), 7.772 (5.86), 7.777 (3.71), 7.830 (6.01), 7.836 (6.17), 7.851 (7.06), 7.857 (6.17), 7.942 (3.92), 7.947 (3.87), 7.962 (7.37), 7.966 (6.33), 7.982 (4.03), 7.987 (2.88), 8.188 (7.53), 8.194 (8.99), 8.210 (6.17), 8.215 (8.99), 8.235 (16.00), 8.242 (12.13), 8.296 (7.95), 8.302 (8.05), 8.317 (6.95), 8.324 (7.11), 8.482 (6.59), 8.487 (6.64), 8.494 (6.75), 8.499 (5.91), 8.590 (9.73), 8.592 (9.93), 8.596 (9.31), 9.065 (12.55), 9.071 (12.65), 9.190 (3.71), 9.206 (7.53), 9.220 (3.61), 10.773 (14.38).

LC-MS (Method 3): R_t = 1.14 min; MS (ESIpos): m/z = 511 $[M+H]^+$.

Example 19

N^1-[6-(2-fluorophenyl)pyridin-3-yl]-N^3-(3-methylpyridin-4-yl)-4-(trifluoromethoxy)isophthalamide



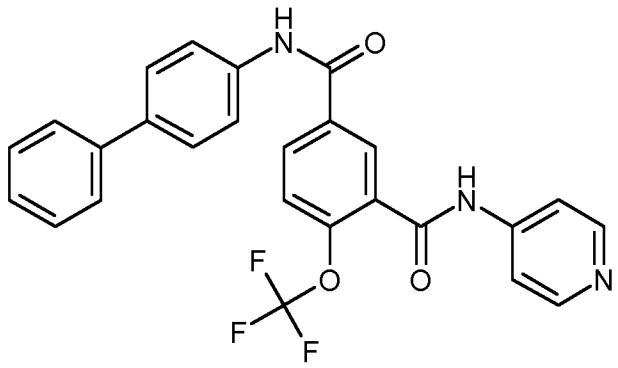
Under argon 60.0 mg (0.14 mmol) of 5-{[6-(2-fluorophenyl)pyridin-3-yl]carbamoyl}-2-(trifluoromethoxy)benzoic acid (intermediate 17) and 18.5 mg (0.17 mmol) of 3-methylpyridin-4-amine were dissolved in 3.6 mL of anh DMF. 75 µL (0.43 mmol) of N-ethyl-N-isopropylpropan-2-amine and 89.1 mg (0.17 mmol) of PYBOP were added. It was stirred at rt over night. The reaction mixture was concentrated on a rotavap and the residue was purified by HPLC (method 5) yielding impure material which was further purified by HPLC (Waters XBrigde C18 5µ 100x30mm; water + 0.1% vol. formic acid (99%) / methanol gradient; temperature: room temperature; injection: 3000 µL; DAD scan: 210-400 nm) giving 14.5 mg (20% of theory) of the title compound.

^{1}H-NMR (300 MHz, DMSO-d_6) δ [ppm]: 1.232 (1.34), 1.257 (1.17), 1.297 (0.72), 2.084 (1.67), 2.264 (0.84), 2.270 (1.17), 2.291 (16.00), 2.720 (0.61), 2.727 (0.78), 2.733 (0.56), 3.508 (0.56), 7.299 (1.00), 7.303 (1.11), 7.312 (1.28), 7.317 (1.28), 7.329 (2.06), 7.338 (3.51), 7.342 (3.34), 7.365 (3.34), 7.440 (0.78), 7.446 (0.84), 7.457 (0.95), 7.464 (1.39), 7.473 (1.06), 7.485 (1.17), 7.491 (1.00), 7.498 (0.56), 7.508 (0.45), 7.515 (0.45), 7.721 (1.95), 7.726 (2.12), 7.749 (2.95), 7.754 (3.01), 7.834 (1.62), 7.840 (1.84), 7.842 (1.62), 7.863 (2.01), 7.871 (1.73), 7.937 (1.11), 7.943 (1.06), 7.963 (2.01), 7.970 (1.73), 7.990 (1.06), 7.997 (0.84), 8.263 (1.95), 8.270 (2.06), 8.292 (1.73), 8.299 (2.01), 8.314 (2.23), 8.322 (2.17), 8.343 (1.84), 8.351 (1.90), 8.400 (5.35), 8.408 (5.02), 8.451 (2.79), 9.087 (3.40), 9.094 (3.34), 10.847 (0.67).

LC-MS (Method 3): R_t = 1.21 min; MS (ESIpos): m/z = 511 $[M+H]^+$.

Example 20

N^1-(biphenyl-4-yl)-N^3-(pyridin-4-yl)-4-(trifluoromethoxy)isophthalamide



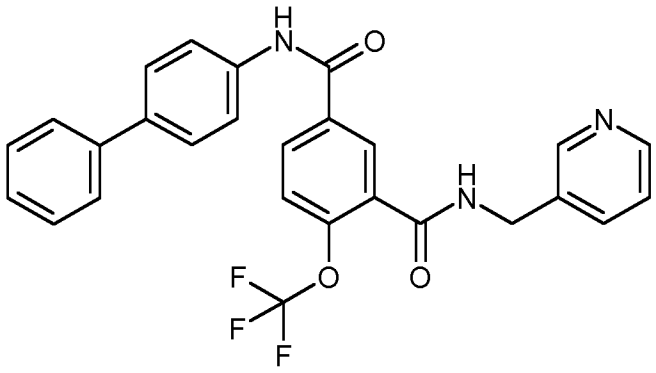
Under argon 50.0 mg (0.12 mmol) of 5-(biphenyl-4-ylcarbamoyl)-2-(trifluoromethoxy)benzoic acid (intermediate 20) and 14.1 mg (0.15 mmol) of pyridin-4-amine were dissolved in 3.0 mL of anh DMF. 65 µL (0.37 mmol) of N-ethyl-N-isopropylpropan-2-amine and 77.8 mg (0.15 mmol) of PYBOP were added. It was stirred at rt over night. The reaction mixture was concentrated on a rotavap and purified by HPLC (method 5) to afford 38.3 mg (64% of theory) of the title compound.

^{1}H-NMR (300 MHz, DMSO-d_6) δ [ppm]: 2.263 (0.44), 2.270 (0.61), 2.276 (0.47), 2.539 (1.05), 2.720 (0.45), 2.726 (0.63), 2.732 (0.47), 3.844 (1.01), 3.877 (0.53), 3.924 (0.85), 7.316 (0.77), 7.320 (1.33), 7.324 (0.90), 7.337 (1.20), 7.344 (3.85), 7.351 (1.43), 7.365 (1.84), 7.369 (2.95), 7.373 (1.73), 7.435 (4.71), 7.441 (2.36), 7.457 (4.26), 7.462 (7.68), 7.479 (1.58), 7.486 (3.64), 7.664 (6.97), 7.667 (8.04), 7.672 (4.92), 7.686 (16.00), 7.691 (14.67), 7.696 (9.02), 7.708 (11.03), 7.716 (13.24), 7.733 (1.77), 7.739 (3.17), 7.744 (2.94), 7.749 (1.28), 7.864 (1.87), 7.873 (9.72), 7.879 (3.40), 7.895 (2.78), 7.901 (7.10), 7.910 (1.19), 8.245 (3.15), 8.253 (3.61), 8.273 (2.72), 8.282 (3.28), 8.363 (6.02), 8.371 (5.47), 8.507 (7.00), 8.513 (5.05), 8.523 (4.80), 8.528 (6.63), 10.538 (5.52), 11.028 (5.29).

LC-MS (Method 4): R_t = 1.11 min; MS (ESIpos): m/z = 478 $[M+H]^+$.

Example 21

N^1-(biphenyl-4-yl)-N^3-(pyridin-3-ylmethyl)-4-(trifluoromethoxy)isophthalamide



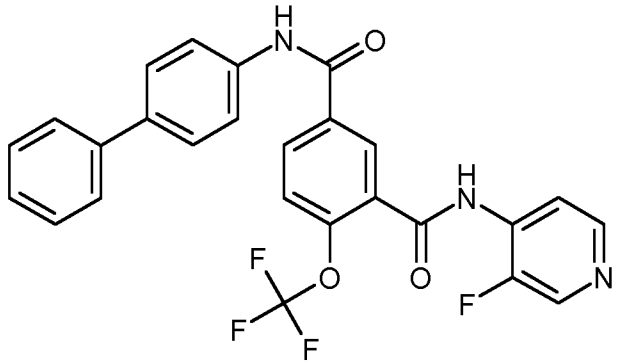
Under argon 60.0 mg (0.15 mmol) of 5-(biphenyl-4-ylcarbamoyl)-2-(trifluoromethoxy)benzoic acid (intermediate 20) and 19.4 mg (0.18 mmol) of 1-(pyridin-3-yl)methanamine were dissolved in 3.6 mL of anh DMF. 78 µL (0.45 mmol) of N-ethyl-N-isopropylpropan-2-amine and 93.4 mg (0.18 mmol) of PYBOP were added. It was stirred at rt over night. The reaction mixture was concentrated on a rotavap and purified by HPLC (method 5) to give 38 mg (52% of theory) of the title compound.

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 0.939 (0.44), 0.955 (0.44), 2.322 (0.77), 2.327 (1.04), 2.331 (0.78), 2.523 (3.54), 2.539 (1.40), 2.664 (0.78), 2.669 (1.06), 2.674 (0.80), 3.844 (0.80), 3.924 (0.69), 4.510 (10.41), 4.525 (10.48), 7.327 (2.44), 7.331 (1.46), 7.346 (6.10), 7.364 (4.48), 7.367 (2.79), 7.372 (3.52), 7.374 (3.52), 7.384 (3.57), 7.386 (3.30), 7.391 (3.77), 7.393 (3.77), 7.404 (3.79), 7.442 (7.27), 7.462 (11.43), 7.475 (2.51), 7.480 (6.03), 7.615 (1.46), 7.620 (3.85), 7.623 (3.94), 7.637 (1.88), 7.641 (4.36), 7.645 (4.05), 7.666 (9.80), 7.670 (11.41), 7.684 (16.00), 7.687 (14.23), 7.690 (10.28), 7.700 (5.03), 7.706 (14.78), 7.712 (2.24), 7.747 (2.51), 7.752 (4.15), 7.757 (2.61), 7.766 (2.35), 7.772 (3.74), 7.777 (2.28), 7.858 (2.08), 7.865 (15.00), 7.870 (4.76), 7.882 (4.46), 7.887 (11.70), 7.894 (1.60), 8.162 (4.85), 8.168 (6.03), 8.183 (3.90), 8.189 (6.09), 8.206 (10.90), 8.212 (8.04), 8.481 (4.46), 8.485 (4.70), 8.493 (4.68), 8.497 (4.43), 8.589 (6.34), 8.595 (6.41), 9.176 (2.39), 9.191 (4.97), 9.206 (2.41), 10.532 (9.33).

LC-MS (Method 3): R_t = 1.24 min; MS (ESIpos): m/z = 492 $[M+H]^+$.

Example 22

N^1-(biphenyl-4-yl)-N^3-(3-fluoropyridin-4-yl)-4-(trifluoromethoxy)isophthalamide



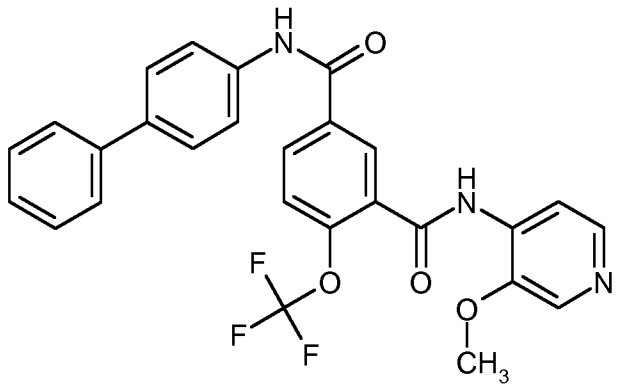
Under argon 60.0 mg (0.15 mmol) of 5-(biphenyl-4-ylcarbamoyl)-2-(trifluoromethoxy)benzoic acid (intermediate 20) and 20.1 mg (0.18 mmol) of 3-fluoropyridin-4-amine were dissolved in 3.6 mL of anh DMF. 78 µL (0.45 mmol) of N-ethyl-N-isopropylpropan-2-amine and 93.4 mg (0.18 mmol) of PYBOP were added. It was stirred at rt over night. The reaction mixture was concentrated on a rotavap and purified by HPLC (Waters XBrigde C18 5µ 100x30mm; water + 0.2% vol. ammonia (32%) / acetonitril gradient; temperature: room temperature; injection: 1000 µL; DAD scan: 210-400 nm) to afford 15 mg (20% of theory) of the title compound.

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 1.110 (2.20), 1.235 (1.48), 2.322 (1.68), 2.327 (2.36), 2.332 (1.80), 2.664 (1.84), 2.669 (2.40), 2.674 (1.84), 7.328 (1.60), 7.346 (4.28), 7.365 (3.04), 7.442 (4.96), 7.463 (8.48), 7.481 (4.36), 7.671 (8.84), 7.692 (16.00), 7.714 (12.00), 7.721 (5.20), 7.878 (9.92), 7.899 (7.96), 8.111 (2.00), 8.127 (3.28), 8.140 (2.20), 8.247 (3.28), 8.253 (3.60), 8.269 (3.12), 8.275 (3.40), 8.359 (6.76), 8.366 (6.24), 8.420 (5.76), 8.433 (5.32), 8.615 (5.92), 8.622 (5.92), 10.550 (7.08), 10.965 (6.08).

LC-MS (Method 3): R_t = 1.32 min; MS (ESIpos): m/z = 496 $[M+H]^+$.

Example 23

N^1-(biphenyl-4-yl)-N^3-(3-methoxypyridin-4-yl)-4-(trifluoromethoxy)isophthalamide



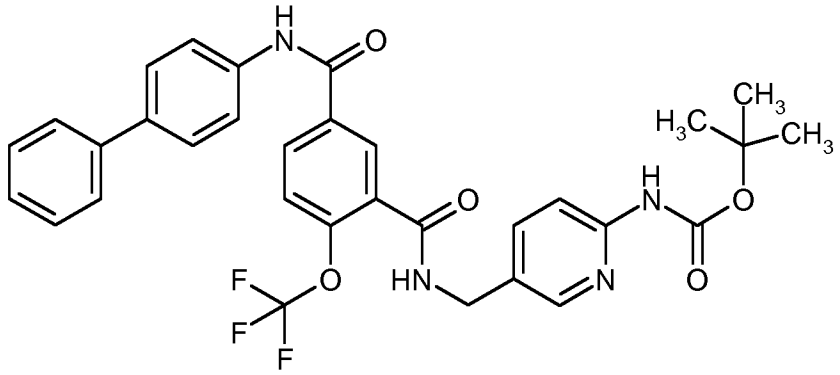
Under argon 60.0 mg (0.15 mmol) of 5-(biphenyl-4-ylcarbamoyl)-2-(trifluoromethoxy)benzoic acid (intermediate 20) and 22.3 mg (0.18 mmol) of 3-methoxypyridin-4-amine were dissolved in 3.6 mL of anh DMF. 78 µL (0.45 mmol) of N-ethyl-N-isopropylpropan-2-amine and 93.4 mg (0.18 mmol) of PYBOP were added. It was stirred at rt over night. The reaction mixture was concentrated on a rotavap and purified by HPLC (method 5) affording 28 mg (37% of theory) of the title compound.

^{1}H-NMR (500 MHz, DMSO-d_6) δ [ppm]: 2.518 (0.69), 2.522 (0.55), 3.952 (16.00), 7.332 (0.75), 7.346 (1.77), 7.361 (1.25), 7.446 (2.19), 7.462 (3.25), 7.477 (1.84), 7.672 (3.02), 7.673 (3.40), 7.688 (3.43), 7.693 (5.10), 7.697 (2.23), 7.711 (4.34), 7.716 (0.57), 7.883 (4.50), 7.896 (1.08), 7.900 (3.47), 8.146 (0.72), 8.157 (0.89), 8.221 (3.17), 8.232 (2.53), 8.236 (1.61), 8.241 (1.66), 8.253 (1.38), 8.258 (1.45), 8.376 (2.74), 8.381 (2.62), 8.411 (5.17), 10.170 (1.39), 10.559 (2.22).

LC-MS (Method 3): R_t = 1.36 min; MS (ESIpos): m/z = 508 $[M+H]^+$.

Example 24

tert-butyl [5-({[5-(biphenyl-4-ylcarbamoyl)-2-(trifluoromethoxy)benzoyl]amino}methyl)pyridin-2-yl]carbamate



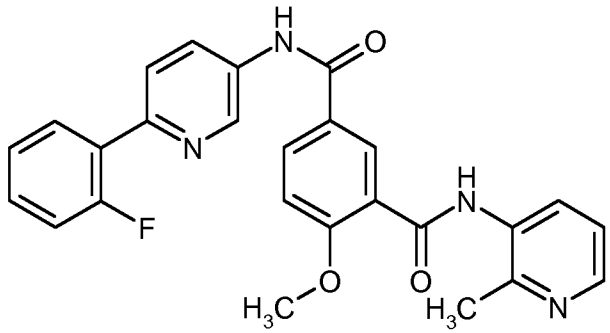
Under argon 100.0 mg (0.25 mmol) of 5-(biphenyl-4-ylcarbamoyl)-2-(trifluoromethoxy)benzoic acid (intermediate 20), 66.8 mg (0.30 mmol) of tert-butyl [5-(aminomethyl)pyridin-2-yl]carbamate, 52 µL (0.30 mmol) of N-ethyl-N-isopropylpropan-2-amine and 155.6 mg (0.30 mmol) of PYBOP were stirred in 5.2 mL of anh DMF. It was stirred for 1 h at rt. Water was added and the precipitate was filtered off by suction and washed three times with water. The solid material was dried under vacuum at 45 °C obtaining 140 mg of the title compound which contained some impurities. 40 mg were purified by HPLC (method 5) affording 19.5 mg (11% of theory) of the title compound.

^{1}H-NMR (300 MHz, DMSO-d_6) δ [ppm]: 1.469 (16.00), 2.270 (0.50), 2.525 (3.20), 2.540 (1.33), 2.726 (0.50), 4.424 (0.96), 4.443 (0.97), 7.344 (0.64), 7.368 (0.50), 7.435 (0.76), 7.457 (0.73), 7.461 (1.25), 7.486 (0.61), 7.607 (0.40), 7.612 (0.42), 7.635 (0.47), 7.640 (0.44), 7.662 (1.12), 7.666 (1.32), 7.677 (1.45), 7.684 (1.13), 7.690 (1.41), 7.694 (1.22), 7.707 (1.77), 7.714 (1.00), 7.722 (0.79), 7.751 (0.99), 7.755 (0.97), 7.780 (0.42), 7.783 (0.40), 7.861 (1.61), 7.869 (0.56), 7.884 (0.49), 7.891 (1.18), 8.148 (0.50), 8.156 (0.63), 8.184 (0.88), 8.191 (1.22), 8.198 (0.73), 8.232 (0.73), 8.239 (0.80), 8.242 (0.71), 9.119 (0.51), 9.714 (1.17), 10.533 (0.90).

LC-MS (Method 3): R_t = 1.43 min; MS (ESIpos): m/z = 607 $[M+H]^+$.

Example 25

N^1-[6-(2-fluorophenyl)pyridin-3-yl]-4-methoxy-N^3-(2-methylpyridin-3-yl)isophthalamide



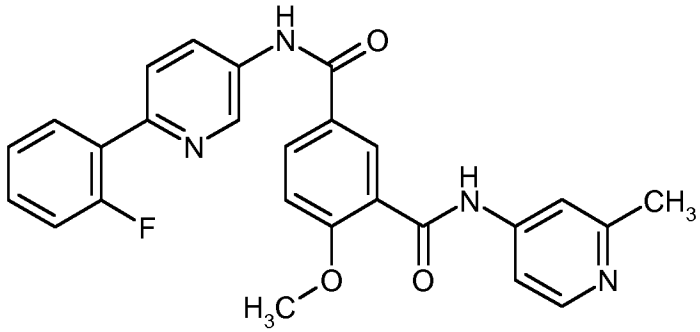
Under an atmosphere of argon, 50.0 mg (0.14 mmol) of 5-{[6-(2-fluorophenyl)pyridin-3-yl]carbamoyl}-2-methoxybenzoic acid (intermediate 23) and 17.7 mg (0.16 mmol) of 2-methylpyridin-3-amine were dissolved in 3.0 mL of anh DMF. 0.07 mL (0.41 mmol) of N-ethyl-N-isopropylpropan-2-amine and 85.2 mg (0.16 mmol) of PYBOP were added and it was stirred at rt over night. The reaction mixture was concentrated on a rotavap and the residue was purified py HPLC (method 5) affording 34 mg of impure material which was further purified by HPLC (Waters XBrigde C18 5µ 100x30mm; water + 0.1% vol. formic acid (99%) / acetonitril gradient; temperature: room temperature; injection: 1000 µL; DAD scan: 210-400 nm) to give 20.8 mg (33% of theory) of the title compound.

^{1}H-NMR (300 MHz, DMSO-d_6) δ [ppm]: 2.263 (0.47), 2.270 (0.61), 2.276 (0.45), 2.539 (2.84), 2.550 (16.00), 2.720 (0.45), 2.726 (0.61), 4.086 (12.26), 7.276 (1.15), 7.292 (1.34), 7.304 (2.32), 7.309 (1.68), 7.314 (1.62), 7.320 (1.67), 7.329 (2.10), 7.334 (2.90), 7.339 (2.96), 7.363 (2.18), 7.417 (2.12), 7.434 (0.99), 7.441 (1.41), 7.447 (2.64), 7.459 (1.43), 7.468 (0.99), 7.480 (0.98), 7.486 (0.87), 7.493 (0.48), 7.503 (0.40), 7.814 (1.38), 7.822 (1.45), 7.843 (1.68), 7.851 (1.44), 7.940 (0.93), 7.947 (0.85), 7.966 (1.67), 7.973 (1.48), 7.993 (0.91), 8.000 (0.73), 8.160 (1.97), 8.166 (1.78), 8.187 (1.54), 8.193 (1.55), 8.223 (1.38), 8.231 (1.48), 8.252 (1.34), 8.260 (1.40), 8.281 (1.77), 8.287 (1.81), 8.297 (1.84), 8.302 (1.70), 8.316 (1.87), 8.325 (1.83), 8.345 (1.51), 8.354 (1.55), 8.548 (2.77), 8.557 (2.77), 9.093 (2.87), 9.101 (2.87), 9.985 (3.41), 10.663 (3.14).

LC-MS (Method 3): R_t = 1.15 min; MS (ESIpos): m/z =457 $[M+H]^+$.

Example 26

N^1-[6-(2-fluorophenyl)pyridin-3-yl]-4-methoxy-N^3-(2-methylpyridin-4-yl)isophthalamide



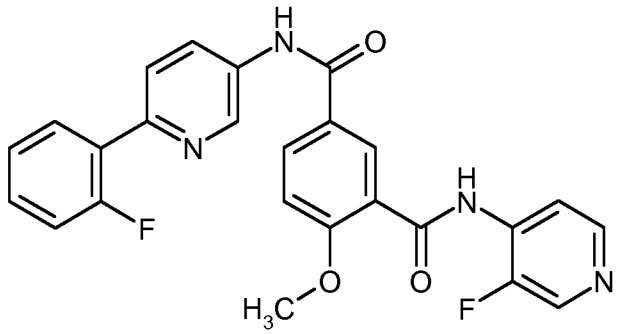
Under an atmosphere of argon, 60.0 mg (0.16 mmol) of 5-{[6-(2-fluorophenyl)pyridin-3-yl]carbamoyl}-2-methoxybenzoic acid (intermediate 23) and 21.3 mg (0.20 mmol) of 2-methylpyridin-4-amine were dissolved in 3.6 mL of anh DMF. 34 µL (0.20 mmol) of N-ethyl-N-isopropylpropan-2-amine and 102.3 mg (0.20 mmol) of PYBOP were added and it was stirred for 6 h at rt. 15 mg (0.14 mmol) of 2-methylpyridin-4-amine and 40 mg (0.08 mmol) of PYBOP were added and it was stirred at rt over the weekend. The reaction mixture was concentrated on a rotavap and the residue was purified py HPLC (method 5) to obtain 11.3 mg (15% of theory) of the title compound.

^{1}H-NMR (300 MHz, DMSO-d_6) δ [ppm]: 2.272 (1.42), 2.449 (16.00), 2.725 (1.29), 3.977 (10.54), 7.294 (1.33), 7.332 (3.68), 7.358 (4.74), 7.386 (2.50), 7.455 (1.91), 7.477 (1.95), 7.529 (2.67), 7.552 (2.92), 7.591 (3.83), 7.810 (1.84), 7.838 (2.07), 7.938 (1.12), 7.966 (1.84), 7.991 (1.06), 8.197 (1.71), 8.226 (1.74), 8.302 (4.42), 8.338 (3.79), 8.359 (2.41), 9.083 (2.94), 10.512 (3.07), 10.560 (3.17).

LC-MS (Method 3): R_t = 1.15 min; MS (ESIpos): m/z = 457 $[M+H]^+$.

Example 27

N^1-[6-(2-fluorophenyl)pyridin-3-yl]-N^3-(3-fluoropyridin-4-yl)-4-methoxyisophthalamide



Under an atmosphere of argon, 60.0 mg (0.16 mmol) of 5-{[6-(2-fluorophenyl)pyridin-3-yl]carbamoyl}-2-methoxybenzoic acid (intermediate 23) and 22.0 mg (0.20 mmol) of 3-fluoropyridin-4-amine were dissolved in 3.6 mL of anh DMF. 86 µL (0.49 mmol) of N-ethyl-N-isopropylpropan-2-amine and 102.3 mg (0.20 mmol) of PYBOP were added and it was stirred at rt over night. The reaction mixture was concentrated on a rotavap and the residue was purified py HPLC (Waters XBrigde C18 5µ 100x30mm; water + 0.2% vol. ammonia (32%) / acetonitril gradient; temperature: room temperature; injection: 1000 µL; DAD scan: 210-400 nm) to afford 10 mg (13% of theory) of the title compound.

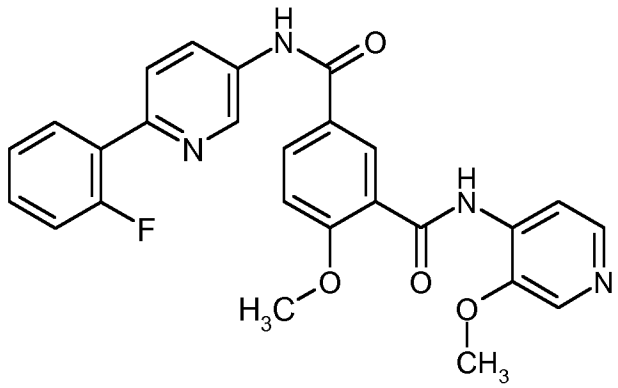
^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 1.235 (1.56), 1.259 (0.64), 2.317 (0.47), 2.322 (0.95), 2.327 (1.35), 2.331 (1.02), 2.336 (0.50), 2.523 (6.04), 2.659 (0.45), 2.664 (1.02), 2.669 (1.37), 2.674 (1.02), 2.679 (0.47), 4.089 (16.00), 7.306 (0.85), 7.309 (0.99), 7.316 (1.04), 7.320 (1.09), 7.329 (1.63), 7.338 (3.46), 7.357 (3.10), 7.442 (3.29), 7.455 (0.95), 7.465 (3.76), 7.477 (1.07), 7.481 (0.95), 7.486 (0.50), 7.494 (0.43), 7.499 (0.40), 7.818 (1.44), 7.824 (1.51), 7.840 (1.66), 7.846 (1.54), 7.935 (0.40), 7.948 (0.92), 7.953 (0.92), 7.967 (1.68), 7.972 (1.51), 7.988 (0.97), 7.992 (0.71), 8.258 (1.73), 8.265 (1.75), 8.280 (1.63), 8.286 (1.70), 8.315 (1.89), 8.322 (2.27), 8.337 (2.77), 8.344 (3.03), 8.356 (1.40), 8.411

(3.12), 8.425 (2.25), 8.573 (3.53), 8.579 (3.41), 8.612 (2.93), 8.619 (2.93), 8.717 (0.43), 9.089 (3.01), 9.095 (3.08), 10.559 (2.11), 10.562 (2.25), 10.565 (2.20), 10.656 (3.64).

LC-MS (Method 3): R_t = 1.21 min; MS (ESIpos): m/z = 461 $[M+H]^+$.

Example 28

N^1-[6-(2-fluorophenyl)pyridin-3-yl]-4-methoxy-N^3-(3-methoxypyridin-4-yl)isophthalamide



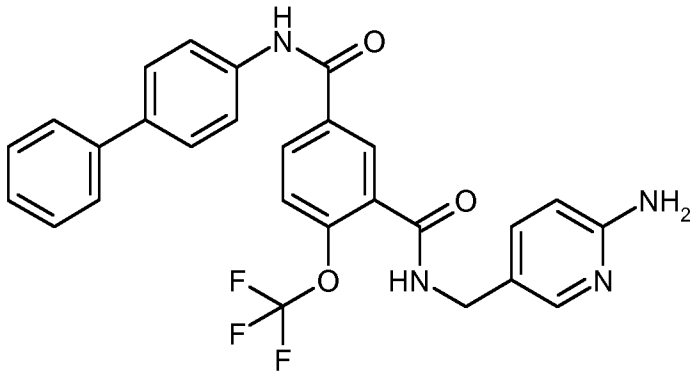
Under an atmosphere of argon, 60.0 mg (0.16 mmol) of 5-{[6-(2-fluorophenyl)pyridin-3-yl]carbamoyl}-2-methoxybenzoic acid (intermediate 23) and 24.4 mg (0.20 mmol) of 3-methoxypyridin-4-amine were dissolved in 3.94 mL of anh DMF. 86 µL (0.49 mmol) of N-ethyl-N-isopropylpropan-2-amine and 102.3 mg (0.20 mmol) of PYBOP were added and it was stirred at rt over night. The reaction mixture was concentrated on a rotavap and the residue was purified py HPLC (Waters XBrigde C18 5µ 100x30mm; water + 0.2% vol. ammonia (32%) / acetonitril gradient; temperature: room temperature; injection: 250 µL; DAD scan: 210-400 nm) affording 24.2 mg material which was impure and was purified further by HPLC (method 5) giving 2 mg (2% of theory) of the title compound.

^{1}H-NMR (300 MHz, DMSO-d_6) δ [ppm]: 2.270 (2.86), 2.725 (2.86), 3.884 (1.56), 4.085 (16.00), 4.196 (15.35), 7.297 (1.82), 7.336 (5.07), 7.365 (4.03), 7.437 (1.69), 7.460 (2.86), 7.488 (4.68), 7.518 (3.90), 7.820 (2.73), 7.848 (2.86), 7.943 (1.69), 7.970 (2.73), 7.996 (1.56), 8.216 (2.60), 8.236 (3.12), 8.273 (2.60), 8.310 (3.77), 8.346 (2.60), 8.392 (4.68), 8.407 (7.15), 8.783 (4.42), 9.093 (4.29), 10.709 (4.29), 10.758 (4.68).

LC-MS (Method 3): R_t = 1.19 min; MS (ESIpos): m/z = 473 $[M+H]^+$.

Example 29

N^3-[(6-aminopyridin-3-yl)methyl]-N^1-(biphenyl-4-yl)-4-(trifluoromethoxy)isophthalamide



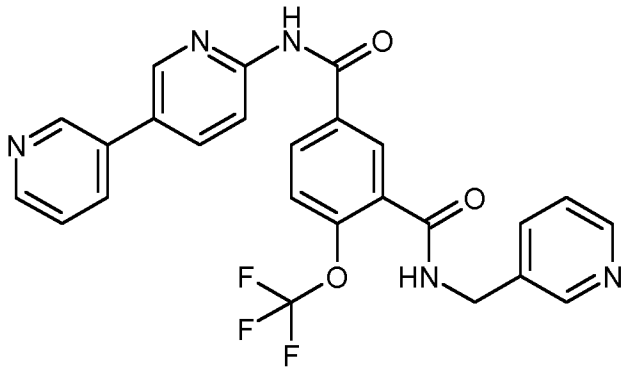
213 µL (2.77 mmol) of trifluoroacetic acid were added to 84.0 mg (0.14 mmol) of tert-butyl [5-({[5-(biphenyl-4-ylcarbamoyl)-2-(trifluoromethoxy)benzoyl]amino}methyl)pyridin-2-yl]carbamate (example 24) in 22 mL of dichloromethane. It was stirred at rt over night. A second batch with 10 mg (0.016 mmol) of tert-butyl [5-({[5-(biphenyl-4-ylcarbamoyl)-2-(trifluoromethoxy)benzoyl]amino}methyl)pyridin-2-yl]carbamate (example 24) in 0.9 mL of dichloromethane were treated with 25 µL (0.33 mmol) of trifluororacetic acid in the same way. The batches were combined and 20 mL of dichloromethane were added. It was neutralized with 1.5 mL of 2N NaOH. 10 mL of water were added and the layers were separated. The organic layer contained a precipitate and was concentrated. 2 mL of methanol were added and it was stirred for 15 minutes. The solid was filtered off by suction to yield 10 mg (14% of theory) of the title compound. The filtrate was purified by HPLC (method 5) to obtain 28 mg (40% of theory) of the title compound.

^{1}H-NMR (300 MHz, DMSO-d_6) δ [ppm]: 2.264 (0.55), 2.270 (0.66), 2.277 (0.54), 2.525 (4.17), 2.540 (1.90), 2.720 (0.54), 2.726 (0.73), 2.732 (0.54), 4.272 (7.57), 4.292 (7.64), 5.845 (12.84), 6.405 (5.26), 6.408 (5.35), 6.433 (5.62), 6.436 (5.97), 7.315 (0.94), 7.319 (1.63), 7.323 (0.95), 7.336 (1.65), 7.343 (8.50), 7.350 (5.14), 7.363 (2.40), 7.367 (4.91), 7.372 (5.34), 7.379 (3.81), 7.435 (5.72), 7.440 (2.51), 7.456 (4.77), 7.461 (9.25), 7.479 (1.86), 7.485 (4.46), 7.592 (2.49), 7.597 (2.89), 7.623 (3.21), 7.628 (2.71), 7.662 (7.57), 7.666 (9.35), 7.677 (10.28), 7.683 (5.74), 7.690 (8.51), 7.695 (6.52), 7.700 (5.02), 7.706 (12.72), 7.715 (2.08), 7.852 (1.76), 7.861 (12.55), 7.868 (3.72), 7.883 (3.82), 7.890 (14.37), 7.899 (6.77), 8.133 (3.22), 8.141 (5.53), 8.157 (6.81), 8.164 (16.00), 8.948 (1.85), 8.968 (4.06), 8.987 (1.82), 10.535 (6.46).

LC-MS (Method 3): R_t = 1.22 min; MS (ESIpos): m/z = 507 $[M+H]^+$.

Example 30

N^1-(3,3'-bipyridin-6-yl)-N^3-(pyridin-3-ylmethyl)-4-(trifluoromethoxy)isophthalamide



70 mg (0.17 mmol) of 5-(3,3'-bipyridin-6-ylcarbamoyl)-2-(trifluoromethoxy)benzoic acid (intermediate 26) were dissolved in 2 mL of anh DMF. 91 µL (0.52 mmol) of N-ethyl-N-isopropylpropan-2-amine, 22.5 mg (0.21 mmol) of 1-(pyridin-3-yl)methanamine, and 108 mg (0.21 mmol) of PYBOP were added and it was stirred at rt over night. The reaction mixture was poured into 30 mL of water. The solid material was filtered off by suction and washed with water three times. The solid was dried under vacuum at 50 °C to yield 42 mg (49% of theory) of the title compound.

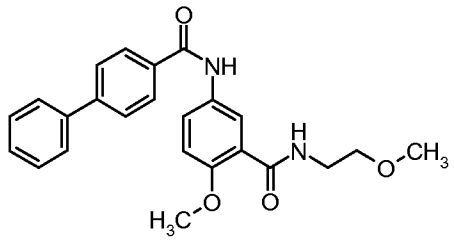
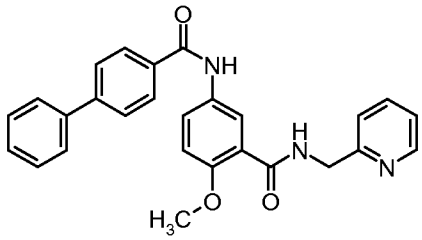
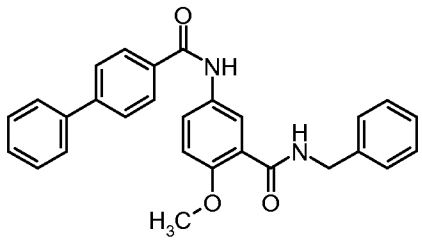
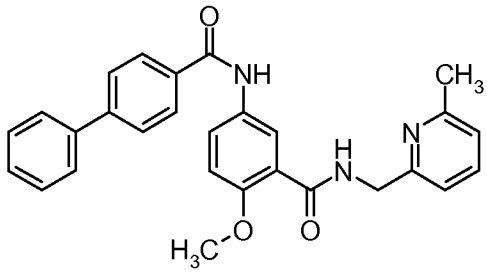
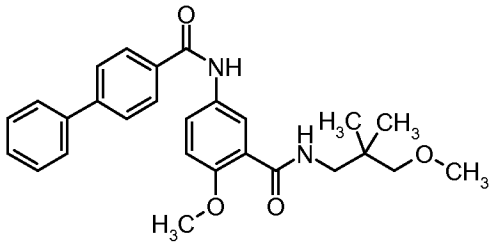
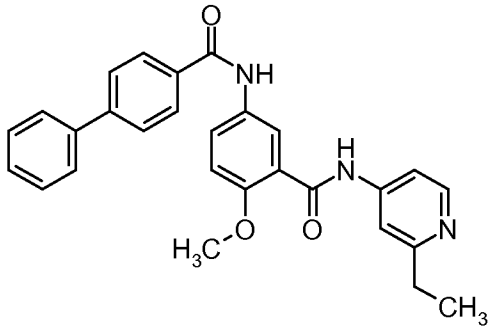
^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 1.232 (1.38), 1.894 (0.43), 2.317 (0.65), 2.322 (1.52), 2.326 (2.10), 2.331 (1.45), 2.336 (0.65), 2.522 (4.13), 2.659 (0.65), 2.664 (1.52), 2.668 (2.10), 2.673 (1.45), 2.678 (0.65), 2.729 (0.65), 2.888 (0.80), 3.281 (0.51), 3.288 (1.01), 3.355 (0.65), 3.362 (0.43), 3.369 (0.43), 3.506 (0.58), 3.971 (0.58), 4.514 (13.97), 4.529 (13.90), 7.376 (4.63), 7.388 (4.78), 7.389 (4.56), 7.395 (4.85), 7.396 (5.07), 7.407 (5.14), 7.509 (4.63), 7.521 (4.85), 7.523 (4.49), 7.528 (4.34), 7.530 (4.85), 7.542 (4.92), 7.597 (5.14), 7.600 (5.29), 7.614 (2.24), 7.618 (5.72), 7.622 (4.85), 7.750 (3.33), 7.755 (5.43), 7.761 (3.55), 7.770 (3.19), 7.775 (4.92), 7.780 (3.04), 8.065 (0.65), 8.165 (4.13), 8.169 (5.36), 8.175 (4.20), 8.184 (3.84), 8.190 (5.00), 8.194 (3.84), 8.218 (6.66), 8.225 (7.75), 8.240 (5.79), 8.246 (7.38), 8.255 (4.42), 8.262 (4.05), 8.276 (9.34), 8.283 (10.35), 8.292 (14.33), 8.297 (12.38), 8.306 (13.76), 8.308 (13.47), 8.327 (5.43), 8.483 (6.30), 8.488 (6.37), 8.495 (6.37), 8.500 (5.86), 8.596 (9.19), 8.601 (16.00), 8.605 (11.80), 8.613 (7.46), 8.617 (6.95), 8.812 (9.63), 8.814 (9.77), 8.818 (10.14), 8.820 (9.05), 8.984 (9.12), 8.991 (9.27), 9.142 (3.26), 9.157 (6.73), 9.172 (3.11), 11.215 (10.93).

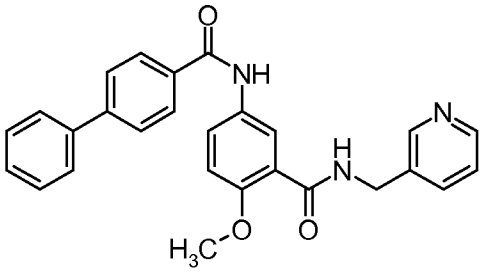
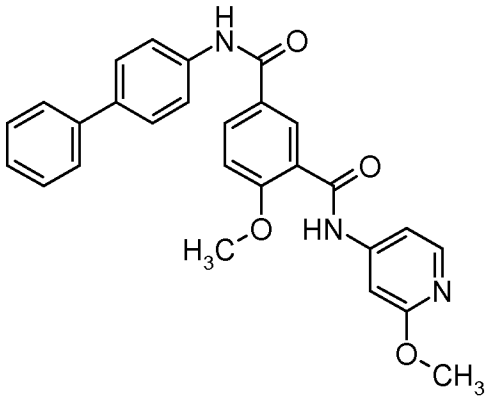
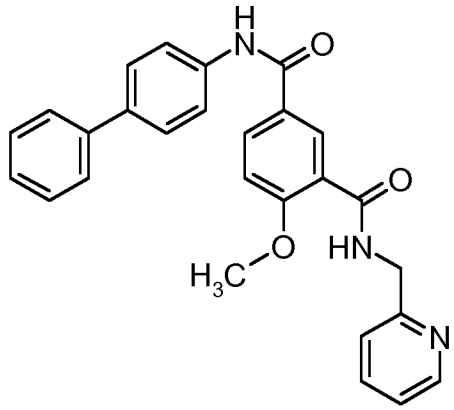
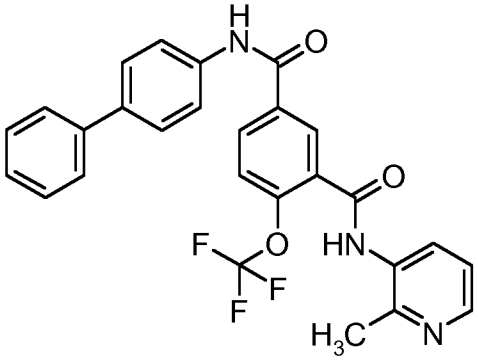
LC-MS (Method 3): R_t = 0.96 min; MS (ESIpos): m/z = 494 $[M+H]^+$.

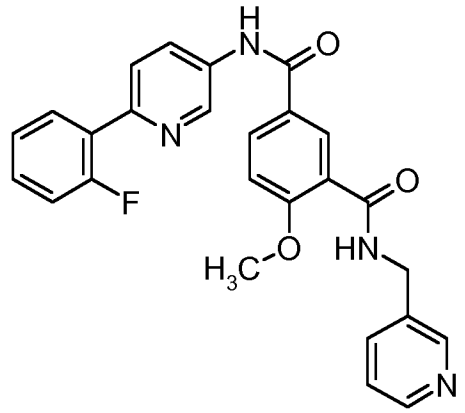
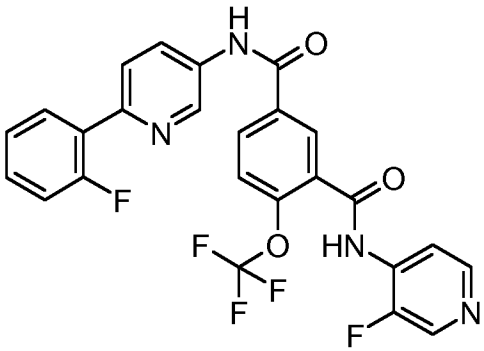
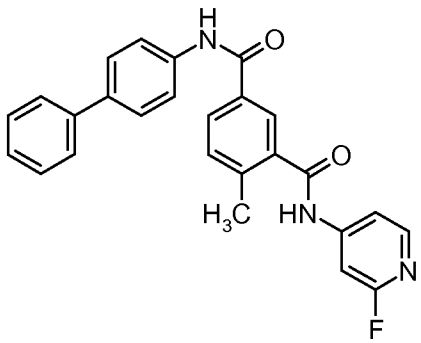
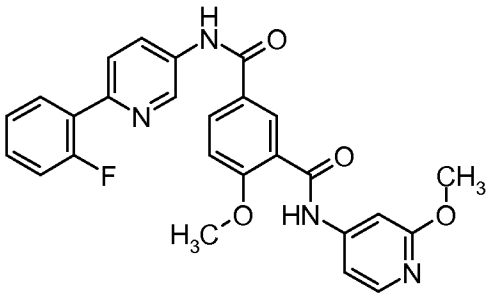
The following examples were prepared in analogy to the described methods, *supra*.

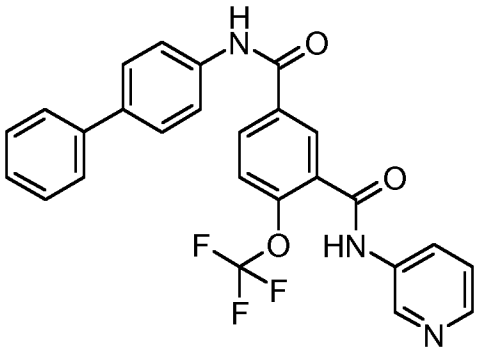
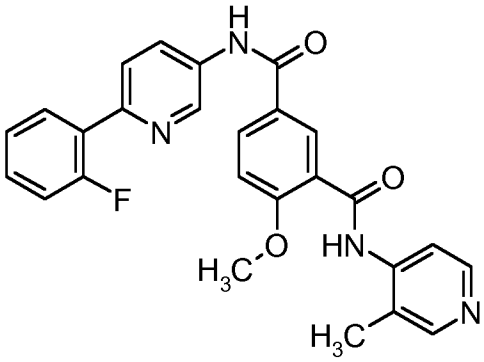
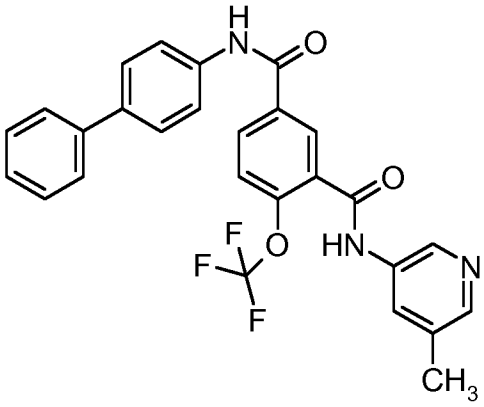
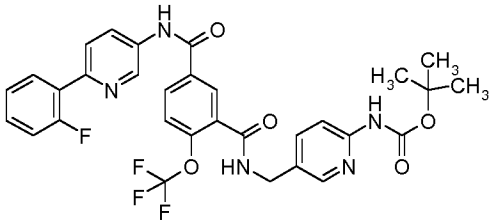
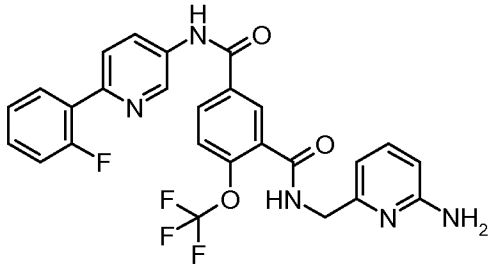
Table 1

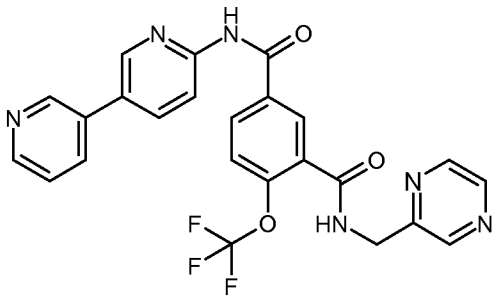
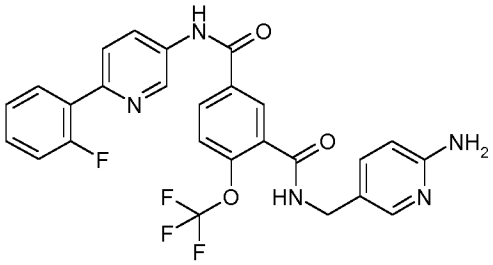
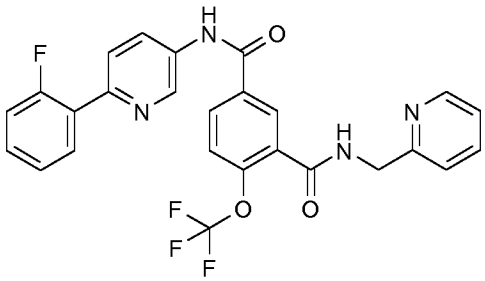
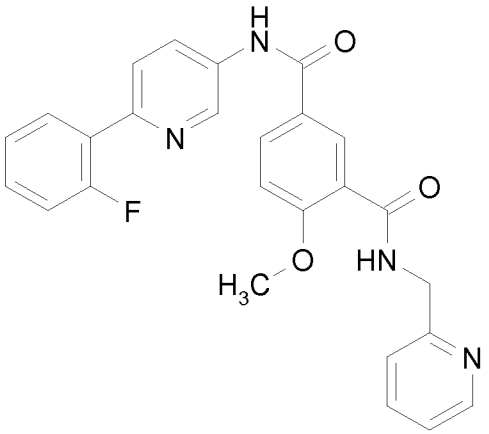
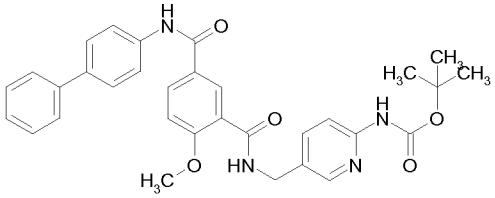
Example No	Structure	IUPAC Name	R_t [min] method

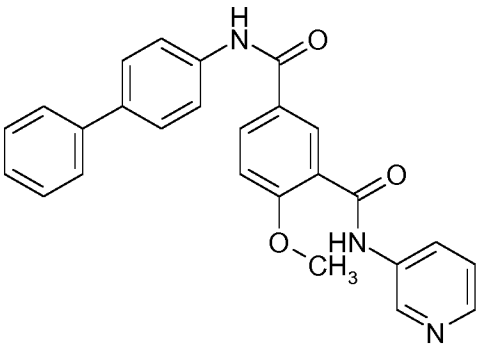
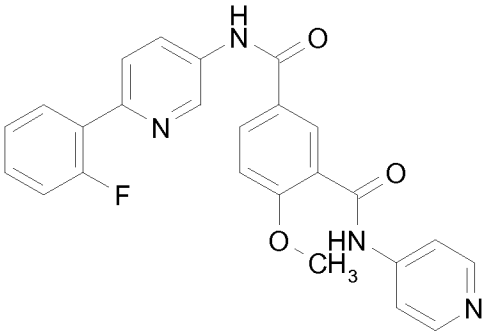
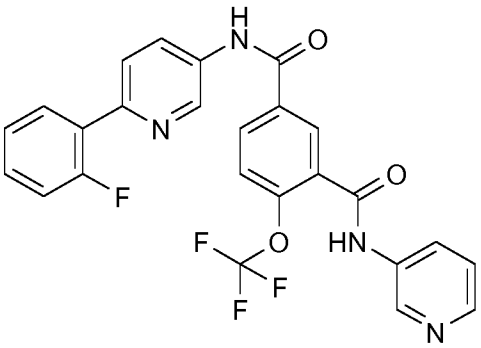
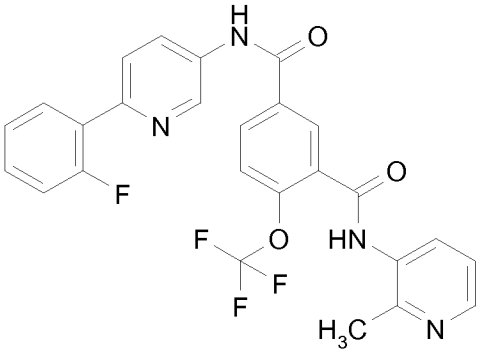
Example No	Structure	IUPAC Name	R_t [min] method
31		N-{4-methoxy-3-[(2-methoxyethyl)carbamoyl]phenyl}biphenyl-4-carboxamide	1.174
32		N-{4-methoxy-3-[(pyridin-2-ylmethyl)carbamoyl]phenyl}biphenyl-4-carboxamide	1.081
33		N-[3-(benzylcarbamoyl)-4-methoxyphenyl]biphenyl-4-carboxamide	1.334
34		N-(4-methoxy-3-{[(6-methylpyridin-2-yl)methyl]carbamoyl}phenyl)biphenyl-4-carboxamide	1.074
35		N-{4-methoxy-3-[(3-methoxy-2,2-dimethylpropyl)carbamoyl]phenyl}biphenyl-4-carboxamide	1.351
36		N-{3-[(2-ethylpyridin-4-yl)carbamoyl]-4-methoxyphenyl}biphenyl-4-carboxamide	1.303

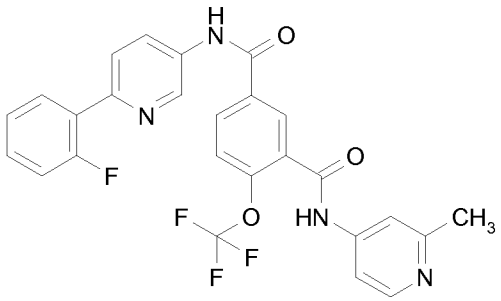
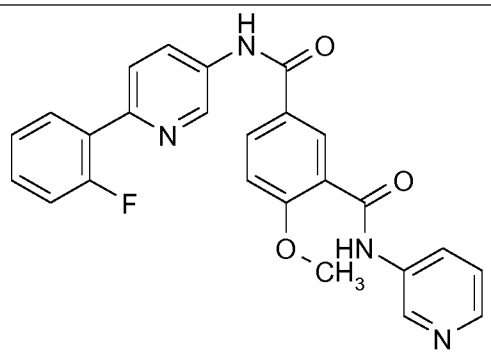
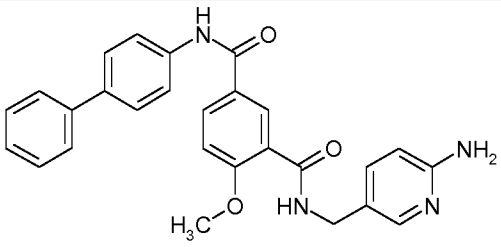
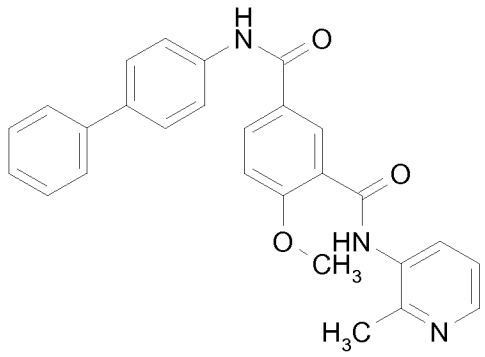
Example No	Structure	IUPAC Name	R_t [min] method
37		N-{4-methoxy-3-[(pyridin-3-ylmethyl)carbamoyl]phenyl} biphenyl-4-carboxamide	0.994
38		N^1-(biphenyl-4-yl)-4-methoxy-N^3-(2-methoxypyridin-4-yl)isophthalamide	1.283
39		N^1-(biphenyl-4-yl)-4-methoxy-N^3-(pyridin-2-ylmethyl)isophthalamide	1.213
40		N^1-(biphenyl-4-yl)-N^3-(2-methylpyridin-3-yl)-4-(trifluoromethoxy)isophthalamide	1.293

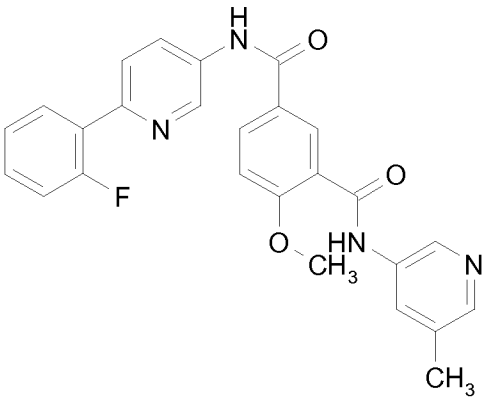
Example No	Structure	IUPAC Name	R_t [min] method
41		N^1-[6-(2-fluorophenyl)pyridin-3-yl]-4-methoxy-N^3-(pyridin-3-ylmethyl)isophthalamide	1.06 3
42		N^1-[6-(2-fluorophenyl)pyridin-3-yl]-N^3-(3-fluoropyridin-4-yl)-4-(trifluoromethoxy)isophthalamide	1.22 3
43		N^1-(biphenyl-4-yl)-N^3-(2-fluoropyridin-4-yl)-4-methylisophthalamide	1.30 3
44		N^1-[6-(2-fluorophenyl)pyridin-3-yl]-4-methoxy-N^3-(2-methoxypyridin-4-yl)isophthalamide	1.25 3

Example No	Structure	IUPAC Name	R_t [min] method
45		N^1-(biphenyl-4-yl)-N^3-(pyridin-3-yl)-4-(trifluoromethoxy)isophthalamide	1.273
46		N^1-[6-(2-fluorophenyl)pyridin-3-yl]-4-methoxy-N^3-(3-methylpyridin-4-yl)isophthalamide	1.163
47		N^1-(biphenyl-4-yl)-N^3-(5-methylpyridin-3-yl)-4-(trifluoromethoxy)isophthalamide	1.323
48		tert-butyl [5-({[5-{[6-(2-fluorophenyl)pyridin-3-yl]carbamoyl}-2-(trifluoromethoxy)benzoyl]amino}methyl)pyridin-2-yl]carbamate	1.353
49		N^3-[(6-aminopyridin-2-yl)methyl]-N^1-[6-(2-fluorophenyl)pyridin-3-yl]-4-(trifluoromethoxy)isophthalamide	1.173

Example No	Structure	IUPAC Name	R_t [min] method
50		N^1-(3,3'-bipyridin-6-yl)-N^3-(pyrazin-2-ylmethyl)-4-(trifluoromethoxy)isophthalamide	0.97 3
51		N^3-[(6-aminopyridin-3-yl)methyl]-N^1-[6-(2-fluorophenyl)pyridin-3-yl]-4-(trifluoromethoxy)isophthalamide	1.15 3
52		N^1-[6-(2-fluorophenyl)pyridin-3-yl]-N^3-(pyridin-2-ylmethyl)-4-(trifluoromethoxy)isophthalamide	1.20 3
53		N^1-[6-(2-fluorophenyl)pyridin-3-yl]-4-methoxy-N^3-(pyridin-2-ylmethyl)isophthalamide	1.11 3
54		tert-butyl [5-({[5-(biphenyl-4-ylcarbamoyl)-2-methoxybenzoyl]amino}methyl)pyridin-2-yl]carbamate	1.37 4

Example No	Structure	IUPAC Name	R_t [min] method
55		N^1-(biphenyl-4-yl)-4-methoxy-N^3-(pyridin-3-yl)isophthalamide	1.223
56		N^1-[6-(2-fluorophenyl)pyridin-3-yl]-4-methoxy-N^3-(pyridin-4-yl)isophthalamide	0.914
57		N^1-[6-(2-fluorophenyl)pyridin-3-yl]-N^3-(pyridin-3-yl)-4-(trifluoromethoxy)isophthalamide	1.183
58		N^1-[6-(2-fluorophenyl)pyridin-3-yl]-N^3-(2-methylpyridin-3-yl)-4-(trifluoromethoxy)isophthalamide	1.084

Example No	Structure	IUPAC Name	R_t [min] method
59		N^1-[6-(2-fluorophenyl)pyridin-3-yl]-N^3-(2-methylpyridin-4-yl)-4-(trifluoromethoxy)isophthalamide	1.223
60		N^1-[6-(2-fluorophenyl)pyridin-3-yl]-4-methoxy-N^3-(pyridin-3-yl)isophthalamide	1.113
61		N^3-[(6-aminopyridin-3-yl)methyl]-N^1-(biphenyl-4-yl)-4-methoxyisophthalamide	1.153
62		N^1-(biphenyl-4-yl)-4-methoxy-N^3-(2-methylpyridin-3-yl)isophthalamide	1.253

Example No	Structure	IUPAC Name	R_t [min] method
63		N^1-[6-(2-fluorophenyl)pyridin-3-yl]-4-methoxy-N^3-(5-methylpyridin-3-yl)isophthalamide	1.15 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 form 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 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 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

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, 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 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 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

form 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 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 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.

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 (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 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 carbonate, sodium hydroxide, triethanolamine, trolamine) ;

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, $F_2ClC\text{-}CClF_2$ and $CClF_3$)

air displacement agents (examples include but are not limited to nitrogen and argon) ;

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) ;

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) ;

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)

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) ;

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) ;

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) ;

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) ;

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) ;

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) ;

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) ;

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) ;

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) ;

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) ;

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

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.

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 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

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 galantine capsules each with 100 mg of powdered active ingredient, 150 mg of lactose, 50 mg of 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, 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.

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-Wiedemarm 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.

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.

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, naphthalinedisulfonic, 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 strearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others.

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.

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 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 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.

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.

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.

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.

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.

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.

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.

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.

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.

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 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 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 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, toposisomerase 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 levofolinate, 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, leuprorelin, levamisole, lisuride, lobaplatin, lomustine, lonidamine, masoprocol, medroxyprogesterone, megestrol, melphalan, mepitiostane, 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, 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 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,

(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,

(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, 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.

Some of the compounds of general formula (I) show low solubility in aqueous media and organic solvents. This can affect the possibility to assess the activity of such compounds with the described assays. Therefore, the high IC_{50} value of some compound might be a result of the low solubility.

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% CO_2 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 µL 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 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 $MgCl_2$, 5 mM $NaHCO_3$, 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 $Na_2HPO_4 \cdot 2\ H_2O$, 3.03 g TRIS HCl, ad 1l H_20, 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 EC50 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 IC_{50} [mol/L]	HCT116 FOPFlash IC_{50} [mol/L]
1	4.83 E-7	3.50 E-5
2	4.95 E-7	≥ 5.00 E-5
3	9.17 E-8	2.80 E-5
4	8.15 E-7	1.22 E-5
5	6.08 E-7	3.10 E-5
6	3.83 E-7	1.44 E-5
7	3.59 E-7	≥ 5.00 E-5
8	1.29 E-7	≥ 5.00 E-5
9	1.49 E-7	≥ 5.00 E-5
10	6.00 E-7	1.00 E-5
11	4.15 E-7	1.15 E-5
12	6.35 E-7	1.35 E-5
13	4.05 E-7	≥ 5.00 E-5
14	1.44 E-7	≥ 5.00 E-5
15	9.00 E-7	≥ 5.00 E-5
16	6.40 E-7	≥ 5.00 E-5
17	6.75 E-7	≥ 5.00 E-5
18	9.50 E-7	1.85 E-5
19	8.78 E-7	≥ 5.00 E-5
20	3.35 E-7	7.55 E-6
21	1.60 E-7	3.25 E-5
22	3.75 E-7	≥ 5.00 E-5
23	2.43 E-7	≥ 5.00 E-5
24	8.35 E-7	2.30 E-5
25	8.40 E-7	≥ 5.00 E-5
26	3.60 E-7	≥ 5.00 E-5
27	6.45 E-7	≥ 5.00 E-5
28	2.25 E-7	≥ 5.00 E-5
29	7.60 E-7	1.60 E-5
30	4.20 E-7	3.15 E-5
31	4.59 E-6	≥ 5.00 E-5
32	1.33 E-6	≥ 5.00 E-5
33	3.35 E-6	≥ 5.00 E-5
34	3.65 E-6	≥ 5.00 E-5
35	4.35 E-6	≥ 5.00 E-5
36	1.43 E-6	2.90 E-5
37	1.80 E-6	2.50 E-5
38	1.11 E-6	2.10 E-5
39	3.40 E-6	≥ 5.00 E-5

Example No	HCT116 TOPFlash IC_{50} [mol/L]	HCT116 FOPFlash IC_{50} [mol/L]
40	2.25 E-6	≥ 5.00 E-5
41	1.60 E-6	≥ 5.00 E-5
42	2.13 E-6	≥ 5.00 E-5
43	1.37 E-6	≥ 5.00 E-5
44	2.82 E-6	≥ 5.00 E-5
45	2.60 E-6	≥ 5.00 E-5
46	2.23 E-6	≥ 5.00 E-5
47	2.63 E-6	≥ 5.00 E-5
48	2.05 E-6	3.70 E-5
49	4.80 E-6	≥ 5.00 E-5
50	1.70 E-6	≥ 5.00 E-5
51	1.80 E-6	1.40 E-5
52	1.75 E-6	1.20 E-5
53	1.00 E-5	≥ 5.00 E-5
54	3.20 E-6	1.60 E-5
55	4.90 E-6	2.30 E-5
56	1.80 E-6	8.00 E-6
57	2.60 E-6	1.10 E-5
58	1.90 E-6	6.60 E-6
59	1.70 E-6	5.50 E-6
60	6.05 E-6	1.10 E-5
61	3.40 E-5	≥ 5.00 E-5
62	4.50 E-5	≥ 5.00 E-5
63	2.67 E-5	≥ 5.00 E-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% CO_2 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% CO_2 followed by subsequent luciferase measurement, 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 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 $MgCl_2$, 5 mM $NaHCO_3$, pH 7.4) containing 2 mM Ca^{2+} 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 EC_{50} concentration of recombinant Wnt3a to the cells in 30 µl growth medium and incubated for 16 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 $Na_2HPO_4 \cdot 2\ H_2O$, 3.03 g TRIS HCl (CAS Number 1185-53-1), ad 1l H_20, pH 7.8) was added in an equal volume to determine luciferase expression as a measure of Wnt signaling activity in a luminometer. The Wnt inhibitory activity was determined as IC_{50} of resulting dose response curves.

QPCR protocol

Real-time RT-PCR using a TaqMan fluorogenic detection system is a simple and sensitive assay for 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 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 $MgCl_2$, 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 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 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: TCTGTGGGGAAGAAATTCCATACCG)

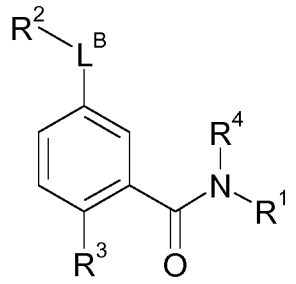
Sequence Listings

SEQ ID NO

1	AAGTTCATCCGGCACCAGTC
2	TGGCCCTTGAATCTTCTACGA
3	CCCAGAGGCATTGACAACAGGG
4	AGGCCAGTGAGTTGGTTGTC
5	AGCTCTGAGCCTTCAGCATC
6	TCTGTGGGGAAGAAATTCCATACCG

Claims

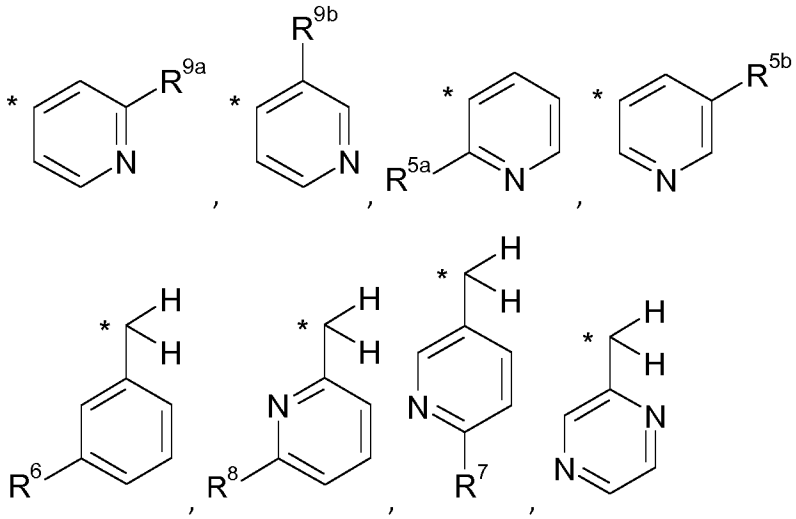
1. A compound of general formula (I) :



(I)

in which :

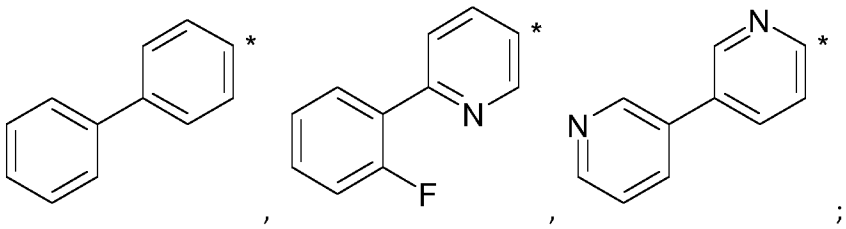
R^1 represents a group selected from:
C_1-C_3-alkoxy-C_2-C_5-alkyl-,



wherein * indicates the point of attachment to the rest of the molecule;

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^2 represents a group selected from:



wherein * indicates the point of attachment to the rest of the molecule;

R^3 represents a group selected from: $-CH_3$, $-O-CH_3$, $-O-CF_3$;

R^4 represents a hydrogen atom or methyl group;

R^{5a} represents a hydrogen atom or methyl group;

R^{5b} represents a hydrogen atom or methyl group;

R^6 represents a hydrogen atom;

R^7 represents a hydrogen atom or a group selected from:
$-NH_2$, $-N(H)-C(=O)-OC(CH_3)_3$;

R^8 represents a hydrogen atom, $-NH_2$ or methyl group;

R^{9a} represents a hydrogen atom or a halogen atom or a group selected from:
methyl, ethyl, methoxy;

R^{9b} represents a hydrogen atom or a halogen atom or a group selected from:
methyl, ethyl, methoxy;

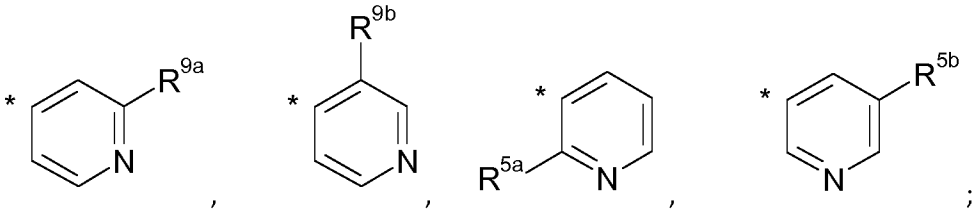
or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

2. A compound according to claim 1, wherein :

R^1 represents a group selected from: $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-CH_2-O-CH_2-CH_3$, and $-CH_2-CH_2-CH_2-O-C(H)(CH_3)_2$.

3. A compound according to claim 1, wherein :

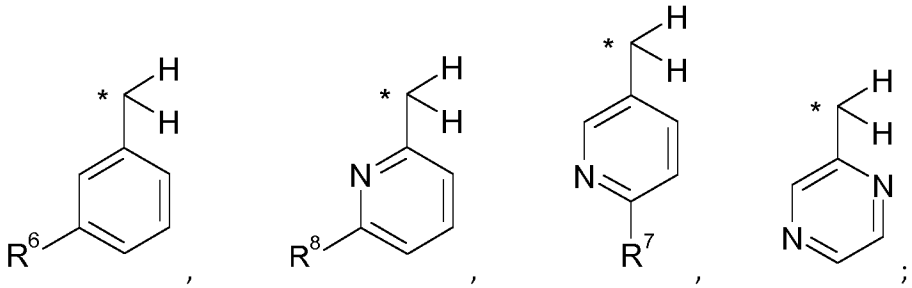
R^1 represents a group selected from:



wherein * indicates the point of attachment to the rest of the molecule.

4. A compound according to claim 1, wherein :

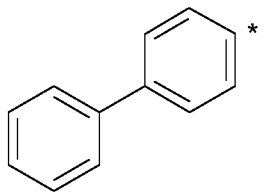
R^1 represents a group selected from:



wherein * indicates the point of attachment to the rest of the molecule.

5. A compound according to claim 1, 2, 3 or 4, wherein :

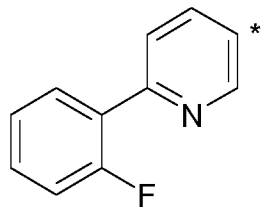
R^2 represents



; wherein * indicates the point of attachment to the rest of the molecule.

6. A compound according to claim 1, 2, 3, or 4, wherein :

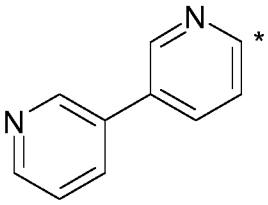
R^2 represents



; wherein * indicates the point of attachment to the rest of the molecule.

7. A compound according to claim 1, 2, 3 or 4, wherein :

R^2 represents



; wherein * indicates the point of attachment to the rest of the molecule.

8. A compound according to claim 1, which is selected from the group consisting of :

N-[4-methoxy-3-(pyridin-4-ylcarbamoyl)phenyl]biphenyl-4-carboxamide,

N-{4-methoxy-3-[(3-methoxypropyl)carbamoyl]phenyl}biphenyl-4-carboxamide,

N-{4-methoxy-3-[(2-methylpyridin-4-yl)carbamoyl]phenyl}biphenyl-4-carboxamide,

N-{4-methoxy-3-[(3-methoxypropyl)(methyl)carbamoyl]phenyl}biphenyl-4-carboxamide,

N-{3-[(3-ethoxypropyl)carbamoyl]-4-methoxyphenyl}biphenyl-4-carboxamide,

N-{3-[(3-isopropoxypropyl)carbamoyl]-4-methoxyphenyl}biphenyl-4-carboxamide,

N^1-(biphenyl-4-yl)-N^3-(pyridin-2-ylmethyl)-4-(trifluoromethoxy)isophthalamide,

N-{3-[(3-fluoropyridin-4-yl)carbamoyl]-4-methoxyphenyl}biphenyl-4-carboxamide,

N-{3-[(3-chloropyridin-4-yl)carbamoyl]-4-methoxyphenyl}biphenyl-4-carboxamide,

N^1-(biphenyl-4-yl)-N^3-(2-methylpyridin-4-yl)-4-(trifluoromethoxy)isophthalamide,

N^1-(biphenyl-4-yl)-4-methoxy-N^3-(pyridin-4-yl)isophthalamide,

N^1-(biphenyl-4-yl)-4-methoxy-N^3-(2-methylpyridin-4-yl)isophthalamide,

N^1-(biphenyl-4-yl)-4-methoxy-N^3-(3-methylpyridin-4-yl)isophthalamide,

N^1-(biphenyl-4-yl)-N^3-(3-fluoropyridin-4-yl)-4-methoxyisophthalamide,

N^1-(biphenyl-4-yl)-N^3-(3-chloropyridin-4-yl)-4-methoxyisophthalamide,

N^1-(biphenyl-4-yl)-4-methoxy-N^3-(pyridin-3-ylmethyl)isophthalamide,

N^1-[6-(2-fluorophenyl)pyridin-3-yl]-N^3-(pyridin-4-yl)-4-(trifluoromethoxy)isophthalamide,

N^1-[6-(2-fluorophenyl)pyridin-3-yl]-N^3-(pyridin-3-ylmethyl)-4-(trifluoromethoxy)isophthalamide,

N^1-[6-(2-fluorophenyl)pyridin-3-yl]-N^3-(3-methylpyridin-4-yl)-4-(trifluoromethoxy)isophthalamide,

N^1-(biphenyl-4-yl)-N^3-(pyridin-4-yl)-4-(trifluoromethoxy)isophthalamide,

N^1-(biphenyl-4-yl)-N^3-(pyridin-3-ylmethyl)-4-(trifluoromethoxy)isophthalamide,

N^1-(biphenyl-4-yl)-N^3-(3-fluoropyridin-4-yl)-4-(trifluoromethoxy)isophthalamide,

N^1-(biphenyl-4-yl)-N^3-(3-methoxypyridin-4-yl)-4-(trifluoromethoxy)isophthalamide,

tert-butyl [5-({[5-(biphenyl-4-ylcarbamoyl)-2-(trifluoromethoxy)benzoyl]amino}methyl)pyridin-2-yl]carbamate,

N^1-[6-(2-fluorophenyl)pyridin-3-yl]-4-methoxy-N^3-(2-methylpyridin-3-yl)isophthalamide,

N^1-[6-(2-fluorophenyl)pyridin-3-yl]-4-methoxy-N^3-(2-methylpyridin-4-yl)isophthalamide,

N^1-[6-(2-fluorophenyl)pyridin-3-yl]-N^3-(3-fluoropyridin-4-yl)-4-methoxyisophthalamide,

N^1-[6-(2-fluorophenyl)pyridin-3-yl]-4-methoxy-N^3-(3-methoxypyridin-4-yl)isophthalamide,

N^3-[(6-aminopyridin-3-yl)methyl]-N^1-(biphenyl-4-yl)-4-(trifluoromethoxy)isophthalamide,

N^1-(3,3'-bipyridin-6-yl)-N^3-(pyridin-3-ylmethyl)-4-(trifluoromethoxy)isophthalamide,

N-{4-methoxy-3-[(2-methoxyethyl)carbamoyl]phenyl}biphenyl-4-carboxamide,

N-{4-methoxy-3-[(pyridin-2-ylmethyl)carbamoyl]phenyl}biphenyl-4-carboxamide,

N-[3-(benzylcarbamoyl)-4-methoxyphenyl]biphenyl-4-carboxamide,

N-(4-methoxy-3-{[(6-methylpyridin-2-yl)methyl]carbamoyl}phenyl)biphenyl-4-carboxamide,

N-{4-methoxy-3-[(3-methoxy-2,2-dimethylpropyl)carbamoyl]phenyl}biphenyl-4-carboxamide,

N-{3-[(2-ethylpyridin-4-yl)carbamoyl]-4-methoxyphenyl}biphenyl-4-carboxamide,

N-{4-methoxy-3-[(pyridin-3-ylmethyl)carbamoyl]phenyl}biphenyl-4-carboxamide,

N^1-(biphenyl-4-yl)-4-methoxy-N^3-(2-methoxypyridin-4-yl)isophthalamide,

N^1-(biphenyl-4-yl)-4-methoxy-N^3-(pyridin-2-ylmethyl)isophthalamide,

N^1-(biphenyl-4-yl)-N^3-(2-methylpyridin-3-yl)-4-(trifluoromethoxy)isophthalamide,

N^1-[6-(2-fluorophenyl)pyridin-3-yl]-4-methoxy-N^3-(pyridin-3-ylmethyl)isophthalamide,

N^1-[6-(2-fluorophenyl)pyridin-3-yl]-N^3-(3-fluoropyridin-4-yl)-4-(trifluoromethoxy)isophthalamide,

N^1-(biphenyl-4-yl)-N^3-(2-fluoropyridin-4-yl)-4-methylisophthalamide,

N^1-[6-(2-fluorophenyl)pyridin-3-yl]-4-methoxy-N^3-(2-methoxypyridin-4-yl)isophthalamide,

N^1-(biphenyl-4-yl)-N^3-(pyridin-3-yl)-4-(trifluoromethoxy)isophthalamide

N^1-[6-(2-fluorophenyl)pyridin-3-yl]-4-methoxy-N^3-(3-methylpyridin-4-yl)isophthalamide

N^1-(biphenyl-4-yl)-N^3-(5-methylpyridin-3-yl)-4-(trifluoromethoxy)isophthalamide,

tert-butyl [5-({[5-{[6-(2-fluorophenyl)pyridin-3-yl]carbamoyl}-2-(trifluoromethoxy)benzoyl]amino}methyl)pyridin-2-yl]carbamate,

N^3-[(6-aminopyridin-2-yl)methyl]-N^1-[6-(2-fluorophenyl)pyridin-3-yl]-4-(trifluoromethoxy)isophthalamide, and

N^1-(3,3'-bipyridin-6-yl)-N^3-(pyrazin-2-ylmethyl)-4-(trifluoromethoxy)isophthalamide,

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

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.

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.

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.

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.

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.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/053211

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 C07D213/73 C07D213/75 C07D401/12 A61K31/435
A61P35/00 C07C15/04
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D C07C

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2014/147182 A2 (BAYER PHARMA AG [DE]) 25 September 2014 (2014-09-25) compounds 1, 2, 7, 8, 23, 27, 28, 32-66	1-16
A	CN 101 186 586 A (UNIV TIANJIN TECHNOLOGY [CN]) 28 May 2008 (2008-05-28) Formula I; table 1	1-16

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

☒ See patent family annex.

* Special categories of cited documents :

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

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"O" document referring to an oral disclosure, use, exhibition or other means

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

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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 May 2016	23/05/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bakboord, Joan

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2016/053211

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2014147182 A2	25-09-2014	CA 2907528 A1	25-09-2014
		EP 2976343 A2	27-01-2016
		US 2016052898 A1	25-02-2016
		WO 2014147182 A2	25-09-2014
CN 101186586 A	28-05-2008	NONE	