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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 June 2018 (14.06.2018)

WIPO | PCT

(10) International Publication Number
WO 2018/104305 A1

(51) International Patent Classification:

C07C 311/46 (2006.01)	***C07D 213/75*** (2006.01)
A61K 31/18 (2006.01)	***C07D 275/06*** (2006.01)
A61P 29/00 (2006.01)	***C07D 295/13*** (2006.01)
C07D 205/04 (2006.01)	***C07D 295/192*** (2006.01)
C07D 207/06 (2006.01)	***C07D 307/14*** (2006.01)
C07D 207/10 (2006.01)	***C07D 307/77*** (2006.01)
C07D 207/12 (2006.01)	***C07D 309/04*** (2006.01)
C07D 209/94 (2006.01)	***C07D 405/12*** (2006.01)
C07D 209/96 (2006.01)	***C07D 491/10*** (2006.01)
C07D 211/38 (2006.01)	

(21) International Application Number:
PCT/EP2017/081530

(22) International Filing Date:
05 December 2017 (05.12.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
16203201.5 09 December 2016 (09.12.2016) EP

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

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

Declarations under Rule 4.17:

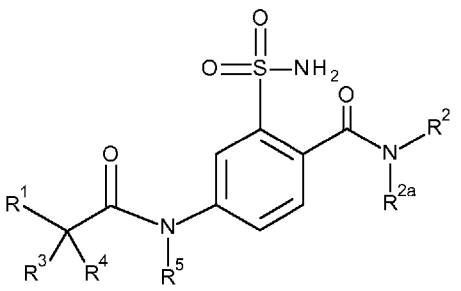
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

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

(54) Title: FIELD OF APPLICATION OF THE INVENTION

(I)



(57) Abstract: Substituted aromatic sulfonamides of formula (I) which are antagonists or negative allosteric modulators of P2X4, pharmaceutical compositions and combinations comprising said compounds and the use of said compounds for manufacturing a pharmaceutical composition for the treatment or prophylaxis of a disease.

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SULFAMOYLBENZAMIDES

FIELD OF APPLICATION OF THE INVENTION

The invention relates to substituted aromatic sulfonamides of formula (I) as described and defined herein, 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. The present invention, as described and defined herein, relates to pharmaceutical compositions and combinations comprising an active ingredient which is an antagonist or a negative allosteric modulator of P2X4. The use of such compounds for manufacturing a pharmaceutical composition for the treatment or prophylaxis of a disease, in particular in mammals, such as but not limited to diseases associated with pain, or for the treatment or prophylaxis of pain or neuronal damage and inflammation in the brain or spinal cord or arthritis or spondylitis syndromes (acute and chronic), inflammatory-induced pain, neuropathic pain, pelvic pain, cancer-associated pain, endometriosis-associated pain as well as endometriosis as such, cancer as such, multiple sclerosis as such, spinal cord or ischemic brain injury as such, as a sole agent or in combination with other active ingredients.

BACKGROUND OF THE INVENTION

Chronic inflammatory pain such as in, but not limited to, conditions of endometriosis and adenomyosis, arises as a consequence of inflammatory responses mounted by the immune system following tissue damage or local cell death and generally persists long after the initial injury has healed. Since a large percentage of patients with inflammatory diseases do not respond adequately to currently available anti-inflammatory treatments or analgesic drugs or suffer from intolerable side effects, investigation of alternative treatments for inflammatory conditions / disorders is warranted.

Adenosine triphosphate ATP is widely recognized as an important neurotransmitter implicated in various physiological and pathophysiological roles by acting through different subtypes of purinergic receptors (Burnstock 1993, Drug Dev Res 28:196-206; Burnstock 2011, Prog Neurobiol 95:229-274). To date, seven members of the P2X family have been cloned, comprising P2X1-7 (Burnstock 2013, Front Cell Neurosci 7:227). The P2X4 receptor is a ligand-gated ion channel that is expressed on a variety of cell types largely known to be involved in inflammatory/ immune processes specifically including monocytes, macrophages, mast cells and microglia cells (Wang et al., 2004, BMC

Immunol 5:16; Brone et al., 2007 Immunol Lett 113:83-89). Activation of P2X4 by extracellular ATP is known, amongst other things, to lead to release of pro-inflammatory cytokines and prostaglandins (PGE2) (Bo et al., 2003 Cell Tissue Res 313:159-165; Ulmann et al., 2010, EMBO Journal 29:2290-2300; de Ribero Vaccari et al., 2012, J Neurosci 32:3058-3066). Numerous lines of evidence in the literature using animal models implicate P2X4 receptor in nociception and pain. Mice lacking the P2X4 receptor do not develop pain hypersensitivity in response to numerous inflammatory challenges such as complete Freunds Adjuvant, carrageenan or formalin (Ulmann et al., 2010, EMBO Journal 29:2290-2300). In addition, mice lacking the P2X4 receptor do not develop mechanical allodynia after peripheral nerve injury, indicating an important role of P2X4 also in neuropathic pain conditions (Tsuda et al., 2009, Mol Pain 5:28; Ulmann et al., 2008, J Neurocsci 28:11263-11268).

Besides the prominent role of P2X4 in acute and chronic pain-related diseases (Trang and Salter, 2012, Purinergic Signalling 8:621-628; Burnstock , 2013 Eur J Pharmacol 716:24-40), P2X4 is considered as a critically important mediator of inflammatory diseases such as, respiratory diseases (e.g. asthma, COPD), lung diseases including fibrosis, cancer and atherosclerosis (Burnstock et al., 2012 Pharmacol Rev. 64:834-868).

EP 2 597 088 A1 describes P2X4 receptor antagonists and in particular a diazepine derivative of formula (III) or a pharmacologically acceptable salt thereof. Said document further disclosed the use of P2X4 receptor antagonist diazepine derivatives represented by the formula (I), (II), (III), or its pharmacologically acceptable salt, which shows P2X4 receptor antagonism, being effective as an agent for prevention or treatment of nociceptive, inflammatory, and neuropathic pain. In more detail, EP 2 597 088 A1 describes P2X4 receptor antagonists being effective as a preventive or therapeutic agent for pain caused by various cancers, diabetic neuritis, viral diseases such as herpes, and osteoarthritis. The preventive or therapeutic agent according to EP 2 597 088 A1 can also be used in combination with other agents such as opioid analgesic (e.g., morphine, fentanyl), sodium channel inhibitor (e.g., novocaine, lidocaine), or NSAIDs (e.g., aspirin, ibuprofen). The P2X4 receptor antagonist used for pain caused by cancers can be also used in combination with a carcinostatic such as a chemotherapic. Further P2X4 receptor antagonists and their use are disclosed in WO2013105608, WO2015005467 and WO2015005468.

“Discovery and characterization of novel, potent and selective P2X4 receptor antagonists for the treatment of pain” was presented at the Society for Neuroscience Annual Meeting

2014 (Carrie A Bowen et al.; poster N. 241.1) Said poster describes the methods to identify novel, potent and selective small-molecule antagonists that inhibit P2X4 across species, and how to evaluate selected compounds in experimental models of neuropatic and inflammatory pain. In particular a method for human, rat, mouse P2X4R Flipr-based screening, a human P2X4R electrophysiology assay, a suitable mouse neuropathy model and a mouse inflammation model were described.

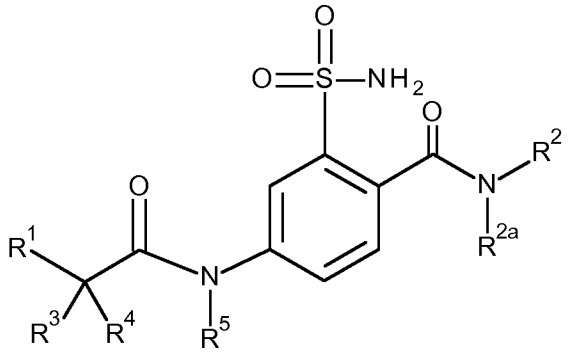
WO2015/088564 and WO2015/088565 provide P2X4 receptor modulating compounds, methods of their synthesis, pharmaceutical compositions comprising the compounds, and methods of their use. Said P2X4 receptor modulating compounds are useful for the treatment, prevention, and/or management of various disorders, including but not limited to, chronic pain, neuropathy, inflammatory diseases and central nervous system disorders.

There is no reference in the state of the art about substituted aromatic sulfonamides of general formula (I) as described and defined herein and to the use of said compounds for manufacturing a pharmaceutical composition for the treatment or prophylaxis of a disease, particularly to the use of substituted aromatic sulfonamides of general formula (I) for the treatment or prophylaxis of diseases associated with pain, or for the treatment or prophylaxis of pain syndromes (acute and chronic), inflammatory-induced pain, neuropathic pain, pelvic pain, cancer-associated pain, endometriosis-associated pain as well as endometriosis as such, cancer as such, and proliferative diseases as such like endometriosis, as a sole agent or in combination with other active ingredients.

Therefore, the inhibitors of P2X4 of the current invention represent valuable compounds that should complement therapeutic options either as single agents or in combination with other drugs.

DESCRIPTION OF THE INVENTION

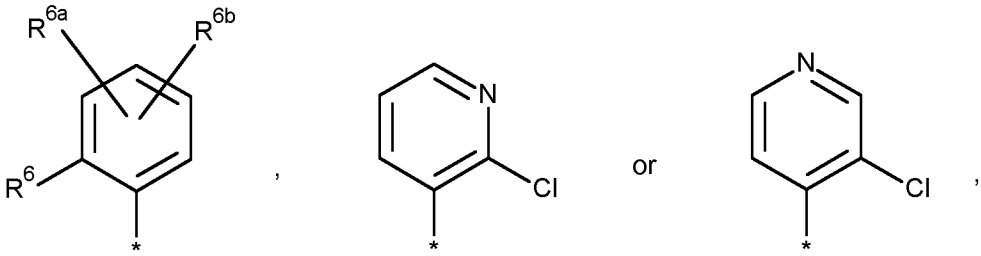
The present invention relates to a compound of formula (I)



(I)

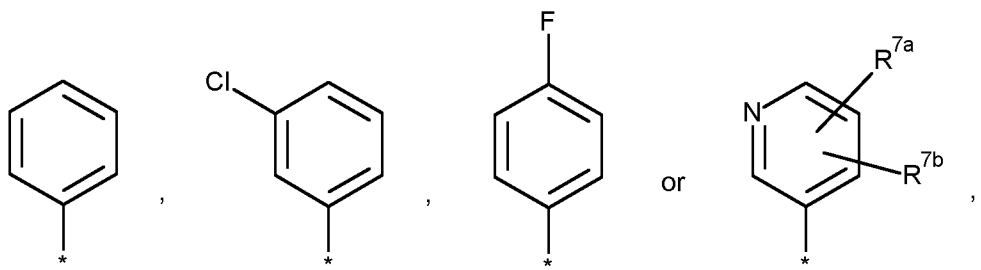
in which:

R^1 represents a group selected from:



wherein * indicates the point of attachment of said group with the rest of the molecule;

R^2 represents C_2-C_6-alkyl, C_1-C_6-haloalkyl, C_3-C_6-cycloalkyl, (C_3-C_6-cycloalkyl)-(C_1-C_3-alkyl)-, (C_5-C_6-heterocycloalkyl)-(C_1-C_3-alkyl)-
or a group selected from:



wherein * indicates the point of attachment of said group with the rest of the molecule and said C_2-C_6-alkyl groups are optionally substituted with C_1-C_4-alkoxy or $R^9R^{10}N$- and said C_3-C_6-cycloalkyl and C_5-C_6-heterocycloalkyl groups are optionally substituted with halogen or C_1-C_6-alkyl, and

R^{2a} represents hydrogen or methyl;

or

R^2 and R^{2a} together with the nitrogen atom to which they are attached form a 4- to 6-membered nitrogen containing heterocyclic ring, said ring optionally containing one additional heteroatom selected from O, S, NH, NR^a in which R^a represents a C_1-C_6-alkyl or C_1-C_6-haloalkyl group and being optionally substituted, one to three times, independently from each other, with halogen, C_1-C_4-alkyl, C_1-C_4-alkoxy or once annellated or spiro connected with C_3-C_6-cycloalkyl or C_4-C_6-heterocycloalkyl;

R^3 represents hydrogen or fluoro;

R^4 represents hydrogen, fluoro, methyl or OH;

R^5 represents hydrogen or C_1-C_3-alkyl;

R^6 represents hydrogen, halogen, cyano, nitro, OH, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy or F_3CS-;

R^{6a} and R^{6b} are the same or different and represent, independently from each other, respectively

R^{6a} hydrogen, halogen, hydroxy, nitro, cyano, C_1-C_4-alkyl, C_3-C_6-cycloalkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, HO-(C_2-C_4-alkoxy)-, (C_1-C_4-alkoxy)-(C_2-C_4-alkoxy)-, $R^9R^{10}N$-, R^8-C(O)-NH-, R^8-C(O)-, R^8-O-C(O)-, $R^9R^{10}N$-C(O)- or (C_1-C_4-alkyl)-SO_2-;

R^{6b} hydrogen, halogen, hydroxy, nitro, cyano, C_1-C_4-alkyl, C_3-C_6-cycloalkyl, C_1-C_4-haloalkyl, C_1-C_4-haloalkoxy, HO-(C_2-C_4-alkoxy)-, (C_1-C_4-alkoxy)-(C_2-C_4-alkoxy)-, $R^9R^{10}N$-, R^8-C(O)-NH-, R^8-C(O)-, R^8-O-C(O)-, $R^9R^{10}N$-C(O)- or (C_1-C_4-alkyl)-SO_2-; or

R^{6a} and R^{6b} adjacent to each other together represent a group selected from –O-CH_2-CH_2-, –O-CH_2-O- or –O-CH_2-CH_2-O-;

R^{7a} represents hydrogen, halogen, C_1-C_4-alkyl or C_1-C_4-haloalkyl;

R^{7b} represents hydrogen, halogen, C_1-C_4-alkyl or C_1-C_4-haloalkyl;

R^8 represents, independently from each respective occurence, C_1-C_6-alkyl, C_1-C_4-alkoxy-C_1-C_4-alkyl, C_3-C_6-cycloalkyl or C_1-C_4-haloalkyl;

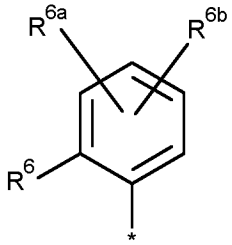
R^9 and R^{10} are the same or different and represent, independently from each other, hydrogen, C_1-C_4-alkyl, C_3-C_6-cycloalkyl, C_2-C_4-haloalkyl or $(CH_3)_2N$-C_1-C_4-alkyl or

together with the nitrogen atom to which they are attached form a 4- to 6-membered nitrogen containing heterocyclic ring, said ring optionally containing one additional heteroatom selected from O, S, NH, NR^a in which R^a represents a C_1-C_6-alkyl or C_2-C_6-haloalkyl group and being optionally substituted, one to three times, independently from each other, with halogen or C_1-C_4-alkyl;

or an N-oxide, a salt, a hydrate, a solvate, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

In a particular embodiment the invention refers to a compound of formula (I) in which

R^1 represents a group selected from:



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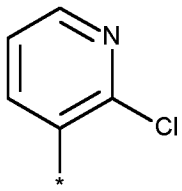

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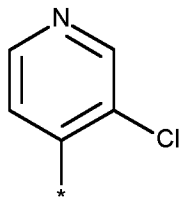
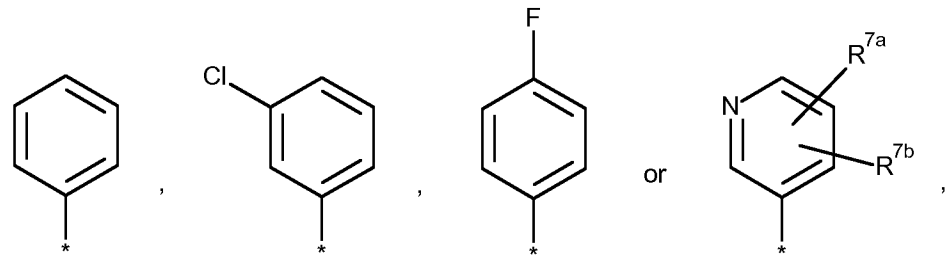


,

wherein * indicates the point of attachment of said group with the rest of the molecule;

R^2 represents C_2-C_6-alkyl, C_1-C_6-haloalkyl, C_3-C_6-cycloalkyl, (C_3-C_6-cycloalkyl)-(C_1-C_3-alkyl)-, (C_5-C_6-heterocycloalkyl)-(C_1-C_3-alkyl)- or a group selected from:



wherein * indicates the point of attachment of said group with the rest of the molecule and said C_2-C_6-alkyl groups are optionally substituted with C_1-C_4-alkoxy or $R^9R^{10}N$- and said C_3-C_6-cycloalkyl and C_5-C_6-heterocycloalkyl groups are optionally substituted with halogen or C_1-C_6-alkyl, and

R^{2a} represents hydrogen;

or

R^2 and R^{2a} together with the nitrogen atom to which they are attached form a 4- to 6-membered nitrogen containing heterocyclic ring, said ring optionally containing one additional heteroatom selected from O, S, NH, NR^a in which R^a represents a C_1-C_6-alkyl or C_1-C_6-haloalkyl group and being optionally substituted, one to three times, independently from each other, with halogen, C_1-C_4-alkyl, C_1-C_4-alkoxy or once annellated or spiro connected with C_3-C_6-cycloalkyl or C_4-C_6-heterocycloalkyl; and

R^3, R^4, R^5 represents hydrogen;

R^6 represents hydrogen, halogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy or C_1-C_4-haloalkoxy;

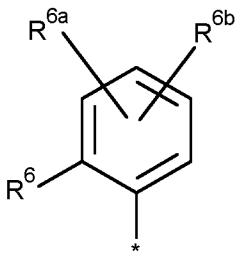
R^{6a} and R^{6b} are the same or different and represent, independently from each other, respectively hydrogen or halogen;

R^9 and R^{10} are the same or different and represent, independently from each other, C_1-C_4-alkyl or C_2-C_4-haloalkyl;

or an N-oxide, a salt, a hydrate, a solvate, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

In another embodiment the invention relates to a compound of formula (I), in which:

R^1 represents a group selected from:



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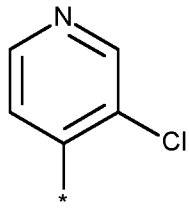
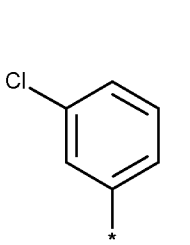


,

wherein * indicates the point of attachment of said group with the rest of the molecule;

R^2 represents C_2-C_6-alkyl, C_1-C_6-haloalkyl, C_3-C_6-cycloalkyl, (C_3-C_6-cycloalkyl)-(C_1-C_3-alkyl)-, (C_5-C_6-heterocycloalkyl)-methyl
or a group selected from:



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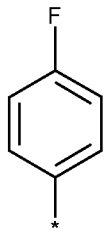

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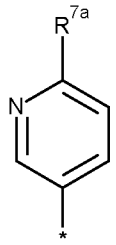

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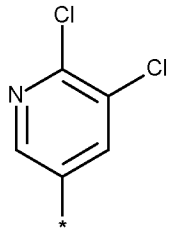


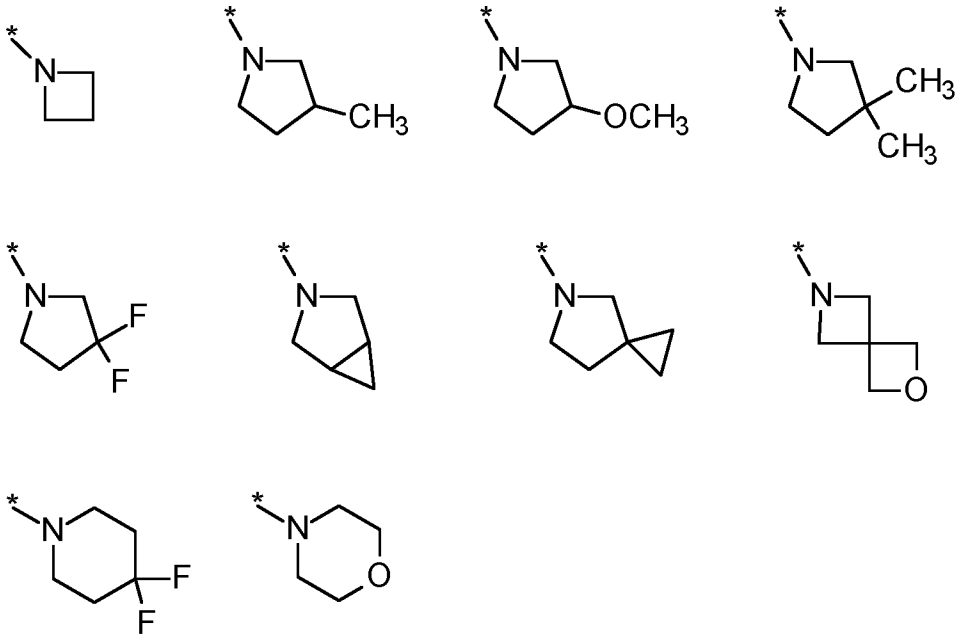
,

wherein * indicates the point of attachment of said group with the rest of the molecule and said C_2-C_6-alkyl groups are optionally substituted with C_1-C_4-alkoxy or $R^9R^{10}N$- and said C_3-C_6-cycloalkyl and C_5-C_6-heterocycloalkyl groups are optionally substituted with halogen or C_1-C_6-alkyl;

R^{2a} represents hydrogen

or

R^2 and R^{2a} together with the nitrogen atom to which they are attached form a nitrogen containing heterocyclic ring system selected from:



wherein * indicates the point of attachment of said group with the rest of the molecule;

R^3, R^4, R^5 represents hydrogen;

R^6 represents hydrogen, halogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy or C_1-C_4-haloalkoxy;

R^{6a} and R^{6b} are the same or different and represent, independently from each other, respectively

R^{6a} hydrogen or halogen;

R^{6b} hydrogen or halogen;

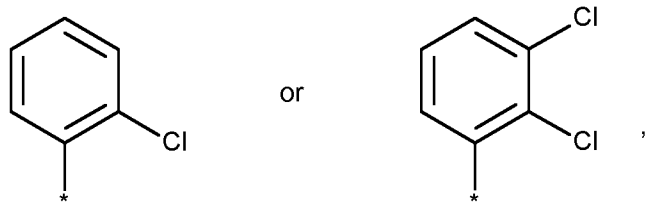
R^{7a} represents chloro or trifluoromethyl;

R^9 and R^{10} are the same or different and represent, independently from each other, C_1-C_4-alkyl or C_2-C_4-haloalkyl;

or an N-oxide, a salt, a hydrate, a solvate, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

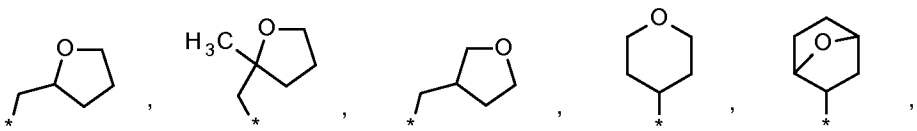
In a further embodiment the invention relates to a compound of formula (I), in which:

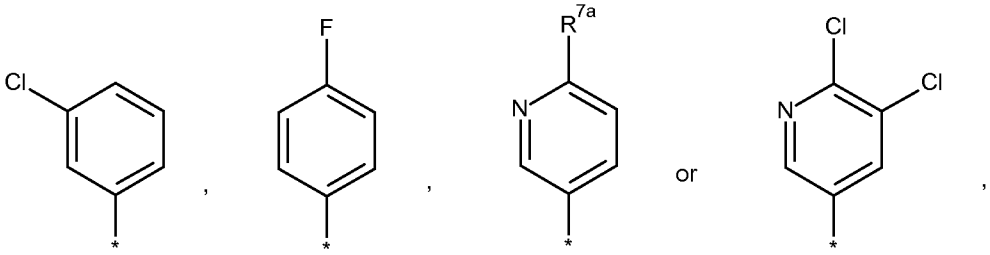
R^1 represents a group selected from:



wherein * indicates the point of attachment of said group with the rest of the molecule;

R^2 represents C_2-C_5-alkyl, C_2-C_4-haloalkyl, 3,3-difluorocyclobutyl, 1-methylcyclopentyl, (C_3-C_5-cycloalkyl)-(C_1-C_3-alkyl)- or a group selected from:

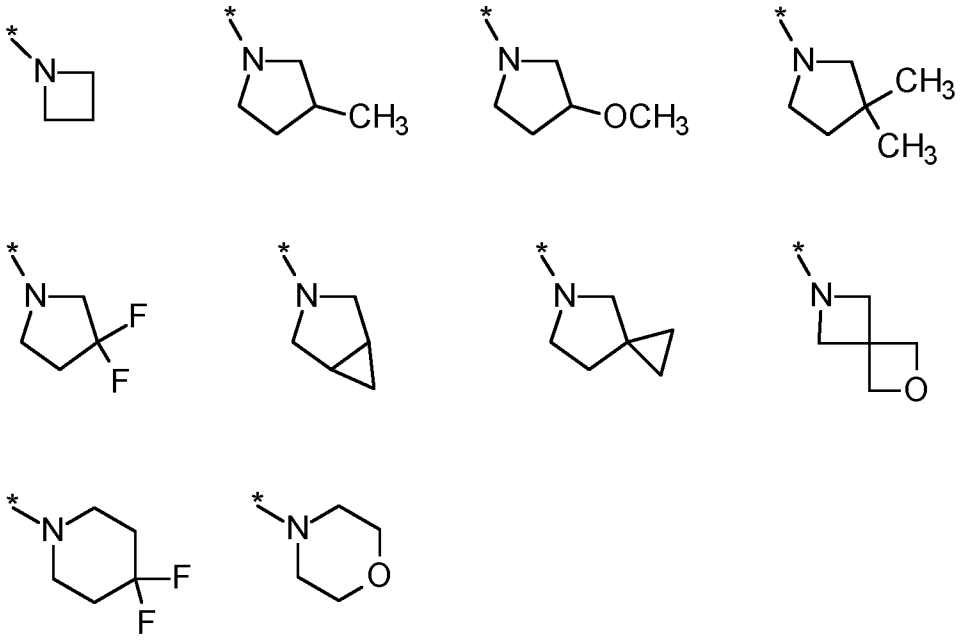




wherein * indicates the point of attachment of said group with the rest of the molecule and said C_2-C_5-alkyl groups are optionally substituted once with methoxy or $R^9R^{10}N$- and said C_3-C_5-cycloalkyl groups are optionally substituted once or twice with fluoro, chloro or methyl;

R^{2a} represents hydrogen or

R^2 and R^{2a} together with the nitrogen atom to which they are attached form a nitrogen containing heterocyclic ring system selected from:



wherein * indicates the point of attachment of said group with the rest of the molecule;

R^3, R^4, R^5 represents hydrogen;

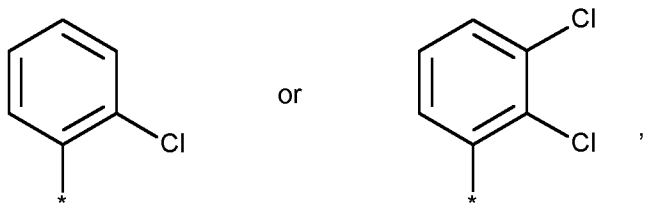
R^{7a} represents chloro or trifluoromethyl;

R^9 and R^{10} are the same or different and represent, independently from each other, methyl or C_2-haloalkyl;

or an N-oxide, a salt, a hydrate, a solvate, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

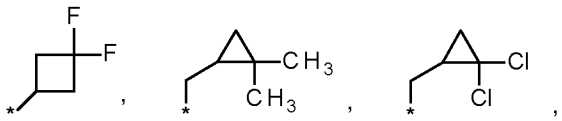
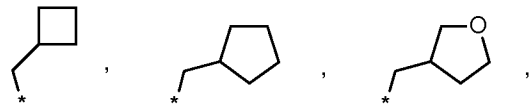
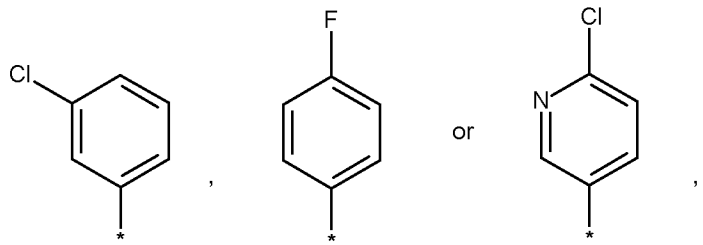
In particular the invention refers further to compounds of formula (I) as described supra, in which:

R^1 represents a group selected from:



wherein * indicates the point of attachment of said group with the rest of the molecule;

R^2 represents 2-methylbutyl, 2,2-difluoroethyl, 3,3,3-trifluoropropyl, 4,4,4-trifluorobutyl or a group selected from:

wherein * indicates the point of attachment of said group with the rest of the molecule;

R^{2a},R^3, R^4, R^5 represents hydrogen;

or an N-oxide, a salt, a hydrate, a solvate, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

One aspect of the invention are compounds of formula (I) as described in the examples, as characterized by their names in the title and their structures as well as the subcombinations of all residues specifically disclosed in the compounds of the examples.

In particular according to a further aspect of the present invention

R^6 represents hydrogen, halogen, cyano, nitro, OH, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy or F_3CS-; more in particualr

R^6 represents hydrogen, halogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy or C_1-C_4-haloalkoxy; more in particular chloro or fluoro.

Furthermore, R^{6a} and R^{6b} adjacent to each other together represent particularly a group selected from –O-CH_2-CH_2-, –O-CH_2-O- or –O-CH_2-CH_2-O-;

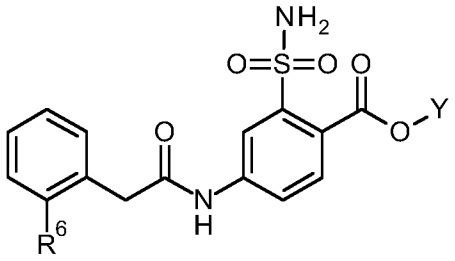
According to further particular embodiements of the present invention R^{6a} and R^{6b} are the same or different and represent, independently from each other, respectively hydrogen or halogen; more particularly hydrogen, chloro or fluoro.

The invention further refers to particular embodiment in which R^{7a} represents hydrogen, halogen, C_1-C_4-alkyl or C_1-C_4-haloalkyl, and more particularly chloro or trifluoromethyl;and R^{7b} represents hydrogen;

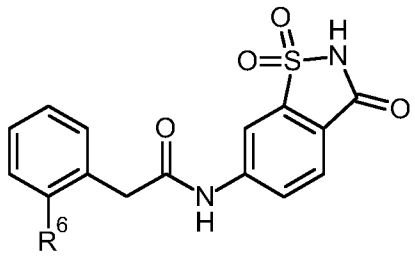
In particular the group R^8 represents, independently from each respective occurence, C_1-C_6-alkyl, C_1-C_4-alkoxy-C_1-C_4-alkyl, C_3-C_6-cycloalkyl or C_1-C_4-haloalkyl.

Furthermore the groups R^9 and R^{10} are in particular the same or different and represent, independently from each other, C_1-C_4-alkyl or C_2-C_4-haloalkyl.

Another aspect of the present invention are intermediates according to formulae **6a** and **8a**



6a



8a

wherein R^6 is as defined in the description and claims of this invention and Y represents C_1-C_3 alkyl.

Specific intermediates for the synthesis of compounds of formula (I) according to present invention are:

Methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate

2-(2-Chlorophenyl)-N-(1,1-dioxido-3-oxo-2,3-dihydro-1,2-benzothiazol-6-yl)acetamide

Another aspect of the invention relates to the use of any of the intermediates described herein for preparing a compound of formula (I) as defined herein or an N-oxide, a salt, a hydrate, a solvate, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

Preferred intermediates are the Intermediate Examples as disclosed below.

A further aspect of the invention are compounds of formula (I) which are present as their salts.

It is to be understood that the present invention relates to any sub-combination within any embodiment or aspect of the present invention of compounds of general formula (I) supra.

More particularly still, the present invention covers compounds of general formula (I) which are disclosed in the Example 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.

Another embodiment of the invention are compounds according to the claims as disclosed in the Claims section wherein the definitions are limited according to the preferred or more preferred definitions as disclosed below or specifically disclosed residues of the exemplified compounds and subcombinations thereof.

Definitions

Constituents which are optionally substituted as stated herein, may be substituted, unless otherwise noted, one or more times, independently from one another at any possible position. When any variable occurs more than one time in any constituent, each definition is independent. For example, when R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, X and/or Y occur more than one time in any compound of formula (I) each definition of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, X and Y is independent.

Should a constituent be composed of more than one part, e.g. C_1-C_4-alkoxy-C_1-C_4-alkyl-, the position of a possible substituent can be at any of these parts at any suitable position. A hyphen at the beginning of the constituent marks the point of attachment to the rest of the molecule. Should a ring be substituted the substitutent could be at any suitable position of the ring, also on a ring nitrogen atom if suitable.

Furthermore, a constituent composed of more than one part and comprising several chemical residues, e.g. C_1-C_4-alkoxy-C_1-C_4-alkyl or phenyl-C_1-C_4-alkyl, should be read

from left to right with the point of attachment to the rest of the molecule on the last part (in the example mentioned previously on the C_1-C_4-alkyl residue)

The term “comprising” when used in the specification includes “consisting of”.

If it is referred to “as mentioned above” or “mentioned above” within the description it is referred to any of the disclosures made within the specification in any of the preceding pages.

“suitable” within the sense of the invention means chemically possible to be made by methods within the knowledge of a skilled person.

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

The term “halogen”, “halogen atom”, “halo-” or “Hal-” is to be understood as meaning a fluorine, chlorine, bromine or iodine atom, preferably a fluorine (fluoro) or chlorine (chloro) atom.

The term “C_1-C_4-alkyl” is to be understood as preferably meaning a linear or branched, saturated, monovalent hydrocarbon group having 1, 2, 3 or 4 carbon atoms, *e.g.* a methyl, ethyl, propyl, butyl, iso-propyl, iso-butyl, sec-butyl, tert-butyl group, 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 “C_1-C_4-haloalkyl” is to be understood as preferably meaning a linear or branched, saturated, monovalent hydrocarbon group in which the term “C_1-C_4-alkyl” is defined *supra*, and in which one or more hydrogen atoms is replaced by a halogen atom, in identically or differently, *i.e.* one halogen atom being independent from another. Particularly, said halogen atom is F. Said C_1-C_4-haloalkyl group is, for example, -CF_3, -CHF_2, -CH_2F, -CF_2CF_3, or-CH_2CF_3.

The term “C_1-C_4-alkoxy” is to be understood as preferably meaning a linear or branched, saturated, monovalent, hydrocarbon group of formula –O-alkyl, in which the term “alkyl” is defined *supra*, *e.g.* a methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, tert-butoxy or sec-butoxy group, or an isomer thereof.

The term "C_1-C_4-haloalkoxy" is to be understood as preferably meaning a linear or branched, saturated, monovalent C_1-C_4-alkoxy group, as defined *supra*, in which one or more of the hydrogen atoms is replaced, in identically or differently, by a halogen atom. Particularly, said halogen atom is F. Said C_1-C_4-haloalkoxy group is, for example, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, $-OCF_2CF_3$, or $-OCH_2CF_3$.

The term "C_1-C_4-hydroxyalkyl" is to be understood as meaning a linear or branched, saturated, monovalent hydrocarbon group in which the term "C_1-C_4-alkyl" is defined *supra*, and in which one or more hydrogen atoms is replaced by a hydroxy group, *e.g.* a hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1,2-dihydroxyethyl, 3-hydroxypropyl, 2-hydroxypropyl, 2,3-dihydroxypropyl, 1,3-dihydroxypropan-2-yl, 3-hydroxy-2-methyl-propyl, 2-hydroxy-2-methyl-propyl, 1-hydroxy-2-methyl-propyl group.

The term "C_1-C_4-alkoxy-C_1-C_4-alkyl" is to be understood as preferably meaning a linear or branched, saturated, monovalent alkyl group, as defined *supra*, in which one or more of the hydrogen atoms is replaced, in identically or differently, by a C_1-C_4-alkoxy group, as defined *supra*, *e.g.* methoxyalkyl, ethoxyalkyl, propyloxyalkyl, iso-propoxyalkyl, butoxyalkyl, iso-butoxyalkyl, tert-butoxyalkyl or sec-butoxyalkyl group, in which the term "C_1-C_4-alkyl" is defined *supra*, or an isomer thereof.

The term "C_3-C_6-cycloalkyl" is to be understood as meaning a saturated, monovalent, mono-, or bicyclic hydrocarbon ring which contains 3, 4, 5 or 6 carbon atoms ("C_3-C_6-cycloalkyl"). Said C_3-C_6-cycloalkyl group is for example, a monocyclic hydrocarbon ring, *e.g.* a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, or a bicyclic hydrocarbon ring.

The term "4- to 6-membered heterocycloalkyl" or "4- to 6-membered heterocyclic ring", is to be understood as meaning a saturated, monovalent, mono- or bicyclic hydrocarbon ring which contains 3, 4 or 5 carbon atoms, and one or more heteroatom-containing groups selected from C(=O), O, S, S(=O), $S(=O)_2$, NH, NR^a, in which R^a represents a C_1-C_6-alkyl- or C_1-C_6-haloalkyl- group ; 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, the nitrogen atom.

Particularly, said heterocycloalkyl can contain 4 or 5 carbon atoms, and one or more of the above-mentioned heteroatom-containing groups (a "5- 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, for example. Optionally, said heterocycloalkyl can be benzo fused.

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, 6, 9 or 10 ring atoms, and which contains at least one heteroatom which may be identical or different, said heteroatom being such as oxygen, nitrogen or sulfur. In addition said ring system can be benzocondensed. Particularly, heteroaryl is selected from thienyl, furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, thia-4H-pyrazolyl, and benzo derivatives thereof, such as, for example, benzofuranyl, benzothienyl, benzoxazolyl, benzisoxazolyl, benzimidazolyl, benzotriazolyl, indazolyl, indolyl, isoindolyl; or pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, and benzo derivatives thereof, such as, for example, quinolinyl, quinazolinyl, isoquinolinyl; or azocinyl, indolizinyl, purinyl, and benzo derivatives thereof; or cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthpyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, xanthenyl or oxepinyl.

In general, and unless otherwise mentioned, the heteroarylic radical 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 pyridyl group.

As mentioned *supra*, said nitrogen atom-containing ring can be partially unsaturated, *i.e.* it can contain one or more double bonds, such as, without being limited thereto, a 2,5-dihydro-1H-pyrrolyl, 4H-[1,3,4]thiadiazinyl, 4,5-dihydrooxazolyl, or 4H-[1,4]thiazinyl ring, for example, or, it may be benzo-fused, such as, without being limited thereto, a dihydroisoquinolinyl ring, for example.

The term “C_1-C_4”, as used throughout this text, *e.g.* in the context of the definition of “C_1-C_4-alkyl”, “C_1-C_4-haloalkyl”, “C_1-C_4-alkoxy”, or “C_1-C_4-haloalkoxy” is to be understood as meaning an alkyl group having a finite number of carbon atoms of 1 to 4, *i.e.* 1, 2, 3 or 4

carbon atoms. It is to be understood further that said term "C_1-C_4" is to be interpreted as any sub-range comprised therein, *e.g.* C_1-C_4, C_2-C_4, C_3-C_4, C_1-C_2, C_1-C_3, particularly C_1-C_2, C_1-C_3, C_1-C_4, in the case of "C_1-C_6-haloalkyl" or "C_1-C_4-haloalkoxy" even more particularly C_1-C_2.

Further, as used herein, the term "C_3-C_6", as used throughout this text, *e.g.* in the context of the definition of "C_3-C_6-cycloalkyl", is to be understood as meaning a cycloalkyl group having a finite number of carbon atoms of 3 to 6, *i.e.* 3, 4, 5 or 6 carbon atoms. It is to be understood further that said term "C_3-C_6" 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_6; particularly C_3-C_6.

The $R^9R^{10}N$-C(O)- group include, for example, -C(O)NH_2, -C(O)N(H)CH_3, -C(O)$N(CH_3)_2$, -C(O)N(H)CH_2CH_3, -C(O)N(CH_3)CH_2CH_3 or -C(O)$N(CH_2CH_3)_2$.

The $R^9R^{10}N$- group includes, for example, -NH_2, -N(H)CH_3, -$N(CH_3)_2$, -N(H)CH_2CH_3 and -N(CH_3)CH_2CH_3. In the case of $R^9R^{10}N$-, when R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4- to 6-membered nitrogen containing heterocyclic ring, said ring optionally containing one additional heteroatom selected from O, NH, NR^a in which R^a represents a C_1-C_6-alkyl- or C_1-C_6-haloalkyl- group, particularly a CH_3, or S and being optionally substituted, one to three times, independently from each other, with halogen or C_1-C_4-alkyl, particularly a CH_3.

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 optional substitution with the specified groups, radicals or moieties.

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", *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, particularly one, two, three or four, more particularly one, two or three, even more particularly one or two".

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.

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.

By "stable compound' or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The compounds of this invention may contain one or more asymmetric centre, depending upon the location and nature of the various substituents desired. Asymmetric carbon atoms may be present in the (R) or (S) configuration, resulting in racemic mixtures in the case of a single asymmetric centre, and diastereomeric mixtures in the case of multiple asymmetric centres. 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 (including enantiomers and diastereomers), 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.

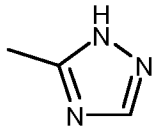
The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example, by the formation of diastereoisomeric salts using an optically active acid or base or formation of covalent diastereomers. Examples of appropriate acids are tartaric, diacetyltartaric, 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 Daicel, *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).

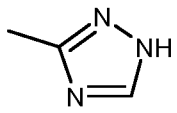
The present invention includes all possible stereoisomers of the compounds of the present invention as single stereoisomers, or as any mixture of said stereoisomers, *e.g.* R- or S- isomers, or E- or Z-isomers, in any ratio. Isolation of a single stereoisomer, *e.g.* a single enantiomer or a single diastereomer, of a compound of the present invention may

be achieved by any suitable state of the art method, such as chromatography, especially chiral chromatography, for example.

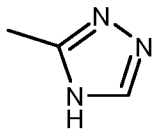
Further, the compounds of the present invention may exist as tautomers. For example, any compound of the present invention which contains a pyrazole moiety as a heteroaryl group for example can exist as a 1H tautomer, or a 2H tautomer, or even a mixture in any amount of the two tautomers, or a triazole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



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 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.

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.

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 CF3COOH", "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.

The salts include water-insoluble and, particularly, water-soluble salts.

Furthermore, derivatives of the compounds of formula (I) and the salts thereof which are converted into a compound of formula (I) or a salt thereof in a biological system (bioprecursors or pro-drugs) are covered by the invention. Said biological system is e.g. a mammalian organism, particularly a human subject. The bioprecursor is, for example, converted into the compound of formula (I) or a salt thereof by metabolic processes.

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 the context of the properties of the compounds of the present invention the term "pharmacokinetic profile" means one single parameter or a combination thereof including permeability, bioavailability, exposure, and pharmacodynamic parameters such as duration, or magnitude of pharmacological effect, as measured in a suitable experiment. Compounds with improved pharmacokinetic profiles can, for example, be used in lower doses to achieve the same effect, may achieve a longer duration of action, or a may achieve a combination of both effects.

It has now been found, and this constitutes the basis of the present invention, that said compounds of the present invention have surprising and advantageous properties.

In particular, compounds according to the present invention have surprisingly been found to effectively be active as an antagonist or a negative allosteric modulator of P2X4.
An allosteric modulator is a substance which indirectly influences (modulates) the effects of an agonist or inverse agonist at a target protein, for example a receptor. Allosteric modulators bind to a site distinct from that of the orthosteric agonist binding site. Usually they induce a conformational change within the protein structure. A negative modulator (NAM) reduces the effects of the orthosteric ligand, but is inactive in the absence of the orthosteric ligand.

Commercial utility and medical indications

As mentioned supra, the compounds of the present invention have surprisingly been found to effectively be active as an antagonist or a negative allosteric modulator of P2X4.

A compound according to the invention is used for the manufacture of a medicament.

A further aspect of the invention is the use of the compounds according to formula (I), (Ia) or (Ib) for the treatment or prophylaxis of a disease
Furthermore, the invention relates to a compound of general formula (I) (Ia) or (Ib), or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer 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.

The invention further relates to a method for using the compounds of general formula (I) (Ia) or (Ib) or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt

of said N-oxide, tautomer or stereoisomer to treat mammalian and human disorders and diseases, which include but are not limited to:

- genitourinary, gastrointestinal, respiratory, proliferative and pain-related diseases, conditions and disorders;
- gynecological diseases including primary and secondary dysmenorrhea, dyspareunia, vulvudynia, endometriosis and adenomyosis; endometriosis-associated pain; endometriosis-associated symptoms, wherein said symptoms are in particular abdominal pain, dysmenorrhea, dyspareunia, dysuria, dyschezia or pelvic hypersensitivity;
- urinary tract disease states including those associated with bladder outlet obstruction; urinary incontinence conditions such as reduced bladder capacity, increased frequency of micturition, urge incontinence, stress incontinence, or bladder hyperreactivity; benign prostatic hypertrophy; prostatic hyperplasia; prostatitis; detrusor hyperreflexia; overactive urinary bladder and symptoms related to overactive urinary bladder wherein said symptoms are in particular increased urinary frequency, nocturia, urinary urgency or urge incontinence; pelvic hypersensitivity; urethritis; prostatitis; prostatodynia; cystitis, in particular interstitial cystitis; idiopathic bladder hypersensitivity; kidney disease as hyperprostaglandin E syndrome, classic Bartter syndrome;
- cancer, cancer-related pain and cancer cachexia;
- epilepsy, partial and generalized seizures;
- respiratory disorders including asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, interstitial pulmonary fibrosis, bronchospasm, chronic chough, refractory chronic cough, ideopahtic chronic cough;
- gastrointestinal disorders including irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), biliary colic and other biliary disorders, renal colic, diarrhea-dominant IBS; gastroesophageal reflux, gastrointestinal distension, Crohn's disease and the like;
- fatty liver disorders, in particular NASH (Non-Alcoholic Steato-Hepatitis); fibrotic diseases including lung fibrosis, heart fibrosis, kidney fibrosis and fibrosis of other organs; metabolic syndrome including, for example, insulin resistance, hypertension, refractory hypertension, dyslipoproteinaemia and obesity, diabetes mellitus, in particular Diabetes type II, myocardial infarction; atherosclerosis; lipid disorders;

- neurodegenerative disorders such as Alzheimer's disease, Multiple Sclerosis, Parkinson's disease, brain ischemia, traumatic brain injury, spinal cord injury;
- pruritus.
- heart disorders including ischemia reperfusion injury, cardiac ischemia,

The present invention further relates to a method for using using the compounds of general formula (I) (Ia) or (Ib) or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer particularly a pharmaceutically acceptable salt thereof, or a mixture of same, to treat pain-associated mammalian disorders and diseases, which include but not limited to

- pain-associated diseases or disorders selected from the group consisting of hyperalgesia, allodynia, functional bowel disorders (such as irritable bowel syndrome), gout, arthritis (such as osteoarthritis, rheumatoid arthritis and ankylosing spondylitis), burning mouth syndrome, burns, migraine or cluster headaches, nerve injury, traumatic nerve injury, post-traumatic injuries (including fractures and sport injuries), neuritis, neuralgias, poisoning, ischemic injury, interstitial cystitis, cancer, trigeminal neuralgia, small fiber neuropathy, diabetic neuropathy, chronic arthritis and related neuralgias, HIV and HIV treatment-induced neuropathy, pruritus; impaired wound healing and disease of the skeleton like degeneration of the joints.

Furthermore, the present invention relates to a method for using using the compounds of general formula (I) (Ia) or (Ib) or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer particularly a pharmaceutically acceptable salt thereof, or a mixture of same, to treat mammalian and human disorders and diseases, which are associated with pain or pain syndromes that are in particular:

- pain syndromes (including hyperalgesia, allodynia, acute and chronic inflammatory and neuropathic pain), preferably inflammatory pain, low back pain, surgical pain, visceral pain, dental pain, periodontitis, premenstrual pain, endometriosis-associated pain, pain associated with fibrotic diseases, central pain, pain due to burning mouth syndrome, pain due to burns, pain due to migraine, cluster headaches, pain due to nerve injury, pain due to neuritis, neuralgias, pain due to poisoning, pain due to ischemic injury, pain due to interstitial cystitis, cancer pain, pain due to viral, parasitic or bacterial infections, pain due to traumatic nerve-injury, pain due to post-traumatic injuries (including fractures and sport injuries), pain due to trigeminal neuralgia, pain associated with small fiber neuropathy, pain associated

with diabetic neuropathy, postherpetic neuralgia, chronic lower back pain, neck pain phantom limb pain, pelvic pain syndrome, chronic pelvic pain, neuroma pain, complex regional pain syndrome, fibromyalgia, myofascial disorders, pain associated with gastrointestinal distension, chronic arthritic pain and related neuralgias, and pain associated with cancer, Morphine-resistant pain, pain associated with chemotherapy, HIV and HIV treatment-induced neuropathy; and pain associated with diseases or disorders selected from the group consisting of abdominal pain such as functional bowel disorders, irritable bowel syndrome, inflammatory bowl disease and selected from the group of arthritis (such as osteoarthritis, rheumatoid arthritis and ankylosing spondylitis).

Compounds of the invention are thus expected to be useful in the treatment of inflammation. The term "inflammation" is also understood to include any inflammatory disease, disorder or condition per se, any condition that has an inflammatory component associated with it, and/or any condition characterized by inflammation as a symptom, including, inter alia, acute, chronic, ulcerative, fibrotic, allergic and auto-immune disaeses, infection by pathogens, immune reactions due to hypersensitivity, entering foreign bodies, physical injury, necrosis, endometriosis and other forms of inflammation known to those skilled in the art. The term thus also includes, for the purposes of this invention, inflammatory pain, pain generally and/or fever. The compounds of the present invention may also be useful in the treatment, viral infections (e.g. influenza, common cold, herpes zoster, hepatitis C and HIV), bacterial infections, fungal infections, surgical or dental procedures, malignancies (e.g. melanoma, breast cancer, colon cancer, lung cancer and prostate cancer), arthritis, osteoarthritis, juvenile arthritis, rheumatoid arthritis, juvenile onset rheumatoid arthritis, rheumatic fever, ankylosing spondylitis, Hodgkin's disease, systemic lupus erythematosus, vasculitis, pancreatitis, nephritis, bursitis, conjunctivitis, iritis, scleritis, uveitis, wound healing, dermatitis, eczema, stroke, diabetes mellitus, autoimmune diseases, allergic disorders, rhinitis, ulcers, mild to moderately active ulcerative colitis, familial adenomatous polyposis, coronary heart disease, sarcoidosis and any other disease with an inflammatory component.

Compounds of the invention are also expected to be useful in the treatment of conditions associated or causing bone loss in a subject. Conditions that may be mentioned in this regard include osteoporosis, osteoarthritis, Paget's disease and/or periodontal diseases.

Based on the P2X4 antagonising activity the compounds according to the invention are useful for the relief of pain, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common

cold, lowere back and neck pain, dysmenorrhea, headache, migraine (acute and prophylactic treatment), toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, juvenile rheumatoid arthritis, degenerative joint diseases (osteoarthritis), acute gout and ankylosing spondylitis, acute, subacute and chronic musculoskeletal pain syndromes such as bursitis, burns, injuries, and pain following surgical (post-operative pain) and dental procedures as well as the preemptive treatment of surgical pain. The pain may be mild pain, moderate pain, severe pain, musculoskeletal pain, complex regional pain syndrome, neuropathic pain, back pain such as acute visceral pain, neuropathies, acute trauma, chemotherapy—induced mononeuropathy pain states, polyneuropathy pain states (such as diabetic peripheral neuropathy and/ or chemotherapy induced neuropathy), autonomic neuropathy pain states, pheriphaeral nervous system (PNS) lesion or central nervous system (CNS) lesion or disease related pain states, polyradiculopathies of cervical, lumbar or sciatica type, cauda equina syndrome, piriformis syndrome, paraplegia, quadriplegia, pain states related to various Polyneuritis conditions underlying various infections, chemical injuries, radiation exposure, underlying disease or deficiency conditions (such as beriberi, vitamin deficiencies, hypothyroidism, porphyria, cancer, HIV, autoimmune disease such as multiple sclerosis and spinal-cord injury, fibromyalgia, nerve injury, ischaemia, neurodegeneration, stroke, post stroke pain, inflammatory disorders, oesophagitis, gastroeosophagal reflux disorder (GERD), irritable bowel syndrome, inflammatory bowel disease, overactive bladder, pelvic hypersensitivity, urinary incontinence, cystitis, stomach, duodenal ulcer, muscle pain, pain due to colicky and referred pain. Compounds of thepresent invention may also be useful for the treatment or prevention of hemophilic arthropathy and Parkinson's disease.

The invention relates also to a method for using the compounds of general formula (I) (Ia) or (Ib) or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer particularly a pharmaceutically acceptable salt thereof, or a mixture of same, to treat conditions treatable by inhibition of prostanoid-induced smooth muscle contraction by preventing the synthesis of contractile prostanoids and hence may be of relevance to use in treatment of dysmenorrhea premature labor and asthma.

The present invention relates to a method for the compounds of general formula (I) (Ia) or (Ib) or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer particularly a pharmaceutically acceptable salt thereof, or a mixture of same, to treat cancer and hyperproliferative disorders. Hyperproliferative

discorders include, but are not limited to, for example: 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 cancers include, but are not limited to, invasive ductal carcinoma, invasive lobular carcinoma, and 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, and 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.

A preferred embodiment of the present invention relates to a method for using the compounds of general formula (I) (Ia) or (Ib) or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer particularly a pharmaceutically acceptable salt thereof, or a mixture of same, to treat a gynaecological disease, preferably dysmenorrhea, dyspareunia, vulvodynia or endometriosis, endometriosis-associated pain, or other endometriosis-associated symptoms, wherein said symptoms are in particular acute and chronic abdominal pain, dysmenorrhea, dyspareunia, dysuria, or dyschezia.

Another preferred embodiment of the present invention relates to a method for using the compounds of the present invention and compositions thereof, to treat a urinary tract disease, in particular overactive bladder or cystitis, preferably interstitial cystitis.

Another preferred embodiment of the present invention relates to a method for using the compounds of the present invention and compositions thereof, to treat a respiratory disorder, preferably cough, in particular chronic cough.

Another preferred embodiment of the present invention relates to a method for using the compounds of the present invention and compositions thereof, to treat a neurodegenerative disorders, preferably ischemic brain injury, spinal cord injury and Multiple Sclerosis.

Another preferred embodiment of the present invention relates to a method for using of general formula (I) (Ia) or (Ib) or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer particularly a pharmaceutically acceptable salt thereof, or a mixture of same, to treat arthritis, in particular rheumatoid arthritis and ankylosing spondylitis (Burnstock et al., 2012 Pharmacol Rev. 64:834-868).

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 gynaecological disease or a disease associated with undesired proliferation like endometriosis or cancer.

Preferably, the diseases treated with said method are gynaecological disorders, more preferably dysmenorrhea, dyspareunia or endometriosis, endometriosis-associated pain, or other endometriosis-associated symptoms, wherein said symptoms are in particular acute and chonic abdominal pain, dysmenorrhea, dyspareunia, dysuria, or dyschezia.

Further diseases, which can be treated with said method, are osteoarthritis, diabetic neuropathy, burning mouth syndrome, gastroesophageal reflux, migraine disorders, chronic cough, asthma, pruritus, irritable bowel disease, overactive urinary bladder, prostatic hyperplasia, interstitial cystitis.

Preferably, the method of treating the diseases mentioned above is not limited to the treatment of said disease but also includes the treatment of pain related to or associated with said diseases.

The compounds of the present invention can be used in particular in therapy and prevention, i.e. prophylaxis, of genitourinary, gastrointestinal, respiratory or pain-related disease, condition or disorder.

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 or auxiliary and a pharmaceutically effective amount of a compound, or salt thereof, of the present invention.

Another aspect of the invention is a pharmaceutical composition comprising a pharmaceutically effective amount of a compound of formula (I) and a pharmaceutically acceptable auxiliary for the treatment of a disease mentioned supra, especially for the treatment of haematological tumours, solid tumours and/or metastases thereof.

A pharmaceutically acceptable carrier or auxiliary is preferably a carrier that is 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. Carriers and auxiliaries are all kinds of additives assisting to the composition to be suitable for administration.

A pharmaceutically effective amount of compound is preferably that amount which produces a result or exerts the intended influence on the particular condition being treated.

The compounds of the present invention can be administered with pharmaceutically-acceptable carriers or auxiliaries 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, subcutaneously, intra uterine 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 auxiliaries, 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, methycellulose, 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.

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 administration, 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 charcoa)l ;

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 i.v. 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 i.v. infusion over about 60 minutes.

Lyophilised powder for i.v. 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.

Dose and administration

Based upon standard laboratory techniques known to evaluate compounds useful for the treatment of disorders and/ or disease, which are influenced by P2X4, 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. 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. A preferred oral unit dosage for a administration of the compounds of the present invention includes but is not limited to 0.1 mg/kg to about 10 mg/kg body weight one to three times a day to once a week. 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.

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 the present 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.

Those combined pharmaceutical agents can be other agents having antiproliferative, antinociceptive and/or antiinflammatory effects such as for example for the treatment of haematological tumours, solid tumours and/or metastases thereof and/or agents for the treatment of different pain syndromes and/or undesired side effects.The present invention relates also to such combinations.

Other anti-hyper-proliferative agents suitable for use with the composition of the invention include but are not limited to those compounds acknowledged to be used in the treatment of neoplastic diseases in Goodman and Gilman's The Pharmacological Basis of Therapeutics (Ninth Edition), editor Molinoff *et al.*, publ. by McGraw-Hill, pages 1225-1287, (1996), which is hereby incorporated by reference, especially (chemotherapeutic) anti-cancer agents as defined supra.

For example, the compounds of the present invention can be combined with known hormonal therapeutic agents.

In particular, the compounds of the present invention can be administered in combination or as co-medication with hormonal contraceptives. Hormonal contraceptives can be administered via oral, subcutaneous, transdermal, intrauterine or intravaginal route, for example as Combined Oral Contraceptives (COCs) or Progestin-Only-Pills (POPs) or hormone-containing devices like implants, patches or intravaginal rings.

COCs include but are not limited to birth control pills or a birth control method that includes a combination of an estrogen (estradiol) and a progestogen (progestin). The

estrogenic part is in most of the COCs ethinyl estradiol. Some COCs contain estradiol or estradiol valerate.

Said COCs contain the progestins norethynodrel, norethindrone, norethindrone acetate, ethynodiol acetate, norgestrel, levonorgestrel, norgestimate, desogestrel, gestodene, drospirenone, dienogest, or nomegestrol acetate.

Birth control pills include for example but are not limited to Yasmin, Yaz, both containing ethinyl estradiol and drospirenone; Microgynon or Miranova containing levonorgestrel and ethinyl estradiol; Marvelon containing ethinyl estradiol and desogestrel; Valette containing ethinyl estradiol and dienogest; Belara and Enriqa containing ethinyl estradiol and chlormadinonacetate; Qlaira containing estradiol valerate and dienogest as active ingredients; and Zoely containing estradiol and normegestrol.

POPs are contraceptive pills that contain only synthetic progestogens (progestins) and do not contain estrogen. They are colloquially known as mini pills.

POPs include but are not limited to Cerazette containing desogestrel; Microlut containing levonorgestrel and Micronor containing norethindrone.

Other Progeston-Only forms are intrauterine devices (IUDs), for example Mirena containing levonorgestrel, or injectables, for example Depo-Provera containing medroxyprogesterone acetate, or implants, for example Implanon containing etonogestrel.

Other hormone-containing devices with contraceptive effect which are suitable for a combination with the compounds of the present invention are vaginal rings like Nuvaring containing ethinyl estradiol and etonogestrel, or transdermal systems like contraceptive patches, for example Ortho-Evra containing ethinyl estradiol and norelgestromin or Apleek (Lisvy) containing ethinyl estradiol and gestodene.

A preferred embodiment of the present invention is the administration of a compound of general formula (I) in combination with a COC or a POP or other Progestin-Only forms as well as vaginal rings or contraceptive patches as mentioned above.

Furthermore, the compounds of the present invention can be combined with therapeutic agents or active ingredients, that are already approved or that are still under development for the treatment and/ or prophylaxis of diseases which are related to or mediated by P2X4.

For the treatment and/ or prophylaxis of urinary tract diseases, the compounds of the present invention can be administered in combination or as co-medication with any substance that can be applied as therapeutic agent in the following indications:

Urinary tract disease states including those associated with bladder outlet obstruction; urinary incontinence conditions such as reduced bladder capacity, increased frequency of micturition, urge incontinence, stress incontinence, or bladder hyperreactivity; benign prostatic hypertrophy; prostatic hyperplasia; prostatitis; detrusor hyperreflexia; overactive urinary bladder and symptoms related to overactive urinary bladder wherein said symptoms are in particular increased urinary frequency, nocturia, urinary urgency or urge incontinence; pelvic hypersensitivity; urethritis; prostatitis; prostatodynia; cystitis, in particular interstitial cystitis; idiopathic bladder hypersensitivity; kidney disease as hyperprostaglandin E syndrome, classic Bartter syndrome

For the treatment and/ or prophylaxis of overactive bladder and symptoms related to overactive bladder, the compounds of the present invention can be administered in combination or as co-medication in addition to behavioral therapy like diet, lifestyle or bladder training with anticholinergics like oxybutynin, tolterodine, propiverine, solifenacin, darifenacin, trospium, fesoterdine; ß-3 agonists like mirabegron; neurotoxins like onabutolinumtoxin A; or antidepressants like imipramine, duloxetine.

For the treatment and/ or prophylaxis of interstitial cystitis, the compounds of the present invention can be administered in combination or as co-medication in addition to behavioral therapy like diet, lifestyle or bladder training with pentosans like elmiron; antidepressants like amitriptyline, imipramine; or antihistamines like loratadine.

For the treatment and/ or prophylaxis of gynaecological diseases, the compounds of the present invention can be administered in combination or as co-medication with any substance that can be applied as therapeutic agent in the following indications:

dysmenorrhea, including primary and secondary; dyspareunia; endometriosis; endometriosis-associated pain; endometriosis-associated symptoms, wherein said symptoms are in particular acute and chronic abdominal pain, dysmenorrhea, dyspareunia, dysuria, or dyschezia.

For the treatment and/ or prophylaxis of dysmenorrhea, including primary and secondary; dyspareunia; endometriosis and endometriosis-associated pain, the compounds of the present invention can be administered in in combination with ovulation inhibiting

treatment, in particular COCs as mentioned above or contraceptive patches like Ortho-Evra or Apleek (Lisvy); or with progestogenes like dienogest (Visanne); or with GnRH analogous, in particular GnRH agonists and antagonists, for example leuprorelin, nafarelin, goserelin, cetrorelix, abarelix, ganirelix, degarelix; or with androgens: danazol.

For the treatment and/ or prophylaxis of diseases, which are associated with pain, or pain syndromes, the compounds of the present invention can be administered in combination or as co-medication with any substance that can be applied as therapeutic agent in the following indications:

pain-associated diseases or disorders like hyperalgesia, allodynia, functional bowel disorders (such as irritable bowel syndrome) and arthritis (such as osteoarthritis, rheumatoid arthritis and ankylosing spondylitis), burning mouth syndrome, burns, migraine or cluster headache, nerve injury, traumatic nerve injury, post-traumatic injuries (including fractures and sport injuries), neuritis, neuralgia, poisoning, ischemic injury, interstitial cystitis, viral, trigeminal neuralgia, small fiber neuropathy, diabetic neuropathy, chronic arthritis and related neuralgias, HIV and HIV treatment-induced neuropathy.

The compounds of the present invention can be combined with other pharmacological agents and compounds that are intended to treat inflammatory diseases, inflammatory pain or general pain conditions.

In addition to well-known medicaments which are already approved and on the market, the compounds of the present invention can be administered in combination with inhibitors of the P2X purinoceptor family (e,g, P2X3 and P2X7), with inhibitors of IRAK4, with inhibitors of PTGES and with antagonists of the prostanoid EP4 receptor.

In particular, the compounds of the present invention can be administered in combination with pharmacological endometriosis agents, intended to treat inflammatory diseases, inflammatory pain or general pain conditions and/or interfering with endometriotic proliferation and endometriosis associated symptoms, namely with inhibitors of Aldo-keto-reductase1C3 (AKR1C3) and with functional blocking antibodies of the prolactin receptor.

The compounds of the present invention can be combined with other pharmacological agents and compounds that are intended for the treatment, prevention or management of cancer.

In particular, the compounds of the present invention can be administered in combination with 131I-chTNT, abarelix, abiraterone, aclarubicin, ado-trastuzumab emtansine, afatinib,

aflibercept, aldesleukin, alemtuzumab, Alendronic acid, alitretinoin, altretamine, amifostine, aminoglutethimide, Hexyl aminolevulinate,amrubicin, amsacrine, anastrozole, ancestim, anethole dithiolethione, angiotensin II, antithrombin III, aprepitant, arcitumomab, arglabin, arsenic trioxide, asparaginase, axitinib, azacitidine, basiliximab, belotecan, bendamustine, belinostat, bevacizumab, bexarotene, bicalutamide, bisantrene, bleomycin, bortezomib, buserelin, bosutinib, brentuximab vedotin, busulfan, cabazitaxel, cabozantinib, calcium folinate, calcium levofolinate, capecitabine, capromab, carboplatin, carfilzomib, carmofur, carmustine, catumaxomab, celecoxib, celmoleukin, ceritinib, cetuximab, chlorambucil, chlormadinone, chlormethine, cidofovir, cinacalcet, cisplatin, cladribine, clodronic acid, clofarabine, copanlisib , crisantaspase, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, darbepoetin alfa, dabrafenib, dasatinib, daunorubicin, decitabine, degarelix, denileukin diftitox, denosumab, depreotide, deslorelin, dexrazoxane, dibrospidium chloride, dianhydrogalactitol, diclofenac, docetaxel, dolasetron, doxifluridine, doxorubicin, doxorubicin + estrone, dronabinol, eculizumab, edrecolomab, elliptinium acetate, eltrombopag, endostatin, enocitabine, enzalutamide, epirubicin, epitiostanol, epoetin alfa, epoetin beta, epoetin zeta, eptaplatin, eribulin, erlotinib, esomeprazole, estradiol, estramustine, etoposide, everolimus, exemestane, fadrozole, fentanyl, filgrastim, fluoxymesterone, floxuridine, fludarabine, fluorouracil, flutamide, folinic acid, formestane, fosaprepitant, fotemustine, fulvestrant, gadobutrol, gadoteridol, gadoteric acid meglumine, gadoversetamide, gadoxetic acid, gallium nitrate, ganirelix, gefitinib, gemcitabine, gemtuzumab, Glucarpidase, glutoxim, GM-CSF, goserelin, granisetron, granulocyte colony stimulating factor, histamine dihydrochloride, histrelin, hydroxycarbamide, I-125 seeds, lansoprazole, ibandronic acid, ibritumomab tiuxetan, ibrutinib, idarubicin, ifosfamide, imatinib, imiquimod, improsulfan, indisetron, incadronic acid, ingenol mebutate, interferon alfa, interferon beta, interferon gamma, iobitridol, iobenguane (123I), iomeprol, ipilimumab, irinotecan, Itraconazole, ixabepilone, lanreotide, lapatinib, lasocholine, lenalidomide, lenograstim, lentinan, letrozole, leuprorelin, levamisole, levonorgestrel, levothyroxine sodium, lisuride, lobaplatin, lomustine, lonidamine, masoprocol, medroxyprogesterone, megestrol, melarsoprol, melphalan, mepitiostane, mercaptopurine, mesna, methadone, methotrexate, methoxsalen, methylaminolevulinate, methylprednisolone, methyltestosterone, metirosine, mifamurtide, miltefosine, miriplatin, mitobronitol, mitoguazone, mitolactol, mitomycin, mitotane, mitoxantrone, mogamulizumab, molgramostim, mopidamol, morphine hydrochloride, morphine sulfate, nabilone, nabiximols, nafarelin, naloxone + pentazocine, naltrexone, nartograstim, nedaplatin, nelarabine, neridronic acid, nivolumabpentetreotide, nilotinib, nilutamide, nimorazole, nimotuzumab, nimustine, nitracrine, nivolumab,

obinutuzumab, octreotide, ofatumumab, omacetaxine mepesuccinate, omeprazole, ondansetron, oprelvekin, orgotein, orilotimod, oxaliplatin, oxycodone, oxymetholone, ozogamicine, p53 gene therapy, paclitaxel, palifermin, palladium-103 seed, palonosetron, pamidronic acid, panitumumab, pantoprazole, pazopanib, pegaspargase, PEG-epoetin beta (methoxy PEG-epoetin beta), pembrolizumab, pegfilgrastim, peginterferon alfa-2b, pemetrexed, pentazocine, pentostatin, peplomycin, Perflubutane, perfosfamide, Pertuzumab, picibanil, pilocarpine, pirarubicin, pixantrone, plerixafor, plicamycin, poliglusam, polyestradiol phosphate, polyvinylpyrrolidone + sodium hyaluronate, polysaccharide-K, pomalidomide, ponatinib, porfimer sodium, pralatrexate, prednimustine, prednisone, procarbazine, procodazole, propranolol, quinagolide, rabeprazole, racotumomab, radium-223 chloride, radotinib, raloxifene, raltitrexed, ramosetron, ramucirumab, ranimustine, rasburicase, razoxane, refametinib , regorafenib, risedronic acid, rhenium-186 etidronate, rituximab, romidepsin, romiplostim, romurtide, roniciclib , samarium (153Sm) lexidronam, sargramostim, satumomab, secretin, sipuleucel-T, sizofiran, sobuzoxane, sodium glycididazole, sorafenib, stanozolol, streptozocin, sunitinib, talaporfin, tamibarotene, tamoxifen, tapentadol, tasonermin, teceleukin, technetium (99mTc) nofetumomab merpentan, 99mTc-HYNIC-[Tyr3]-octreotide, tegafur, tegafur + gimeracil + oteracil, temoporfin, temozolomide, temsirolimus, teniposide, testosterone, tetrofosmin, thalidomide, thiotepa, thymalfasin, thyrotropin alfa, tioguanine, tocilizumab, topotecan, toremifene, tositumomab, trabectedin, tramadol, trastuzumab, trastuzumab emtansine, treosulfan, tretinoin, trifluridine + tipiracil, trilostane, triptorelin, trametinib, trofosfamide, thrombopoietin, tryptophan, ubenimex, valatinib , valrubicin, vandetanib, vapreotide, vemurafenib, vinblastine, vincristine, vindesine, vinflunine, vinorelbine, vismodegib, vorinostat, vorozole, yttrium-90 glass microspheres, zinostatin, zinostatin stimalamer, zoledronic acid, zorubicin.

Furthermore, the compounds of the present invention can be combined with active ingredients, which are well known for the treatment of cancer-related pain and chronic pain. Such combinations include, but are not limited to step II opiods like codeine phosphate, dextropropoxyphene, dihydro-codeine,Tramadol), step III opiods like morphine, fentanyl, buprenorphine, oxymorphone, oxycodone and hydromorphone; and other medications used for the treatment of cancer pain like steroids as Dexamethasone and methylprednisolone; bisphosphonates like Etidronate, Clodronate, Alendronate, Risedronate, and Zoledronate; tricyclic antidepressants like Amitriptyline, Clomipramine, Desipramine, Imipramine and Doxepin; class I antiarrhythmics like mexiletine and lidocaine; anticonvulsants like carbamazepine, Gabapentin, oxcarbazepine, phenytoin,

pregabalin, topiramate, alprazolam, diazepam, flurazepam, pentobarbital and phenobarbital.

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.

As will be appreciated by persons skilled in the art, the invention is not limited to the particular embodiments described herein, but covers all modifications of said embodiments that are within the spirit and scope of the invention as defined by the appended claims.

The following examples illustrate the invention in greater detail, without restricting it. Further compounds according to the invention, of which the preparation is not explicitly described, can be prepared in an analogous way.

The compounds, which are mentioned in the examples and the salts thereof represent preferred embodiments of the invention as well as a claim covering all subcombinations of the residues of the compound of formula (I) as disclosed by the specific examples.

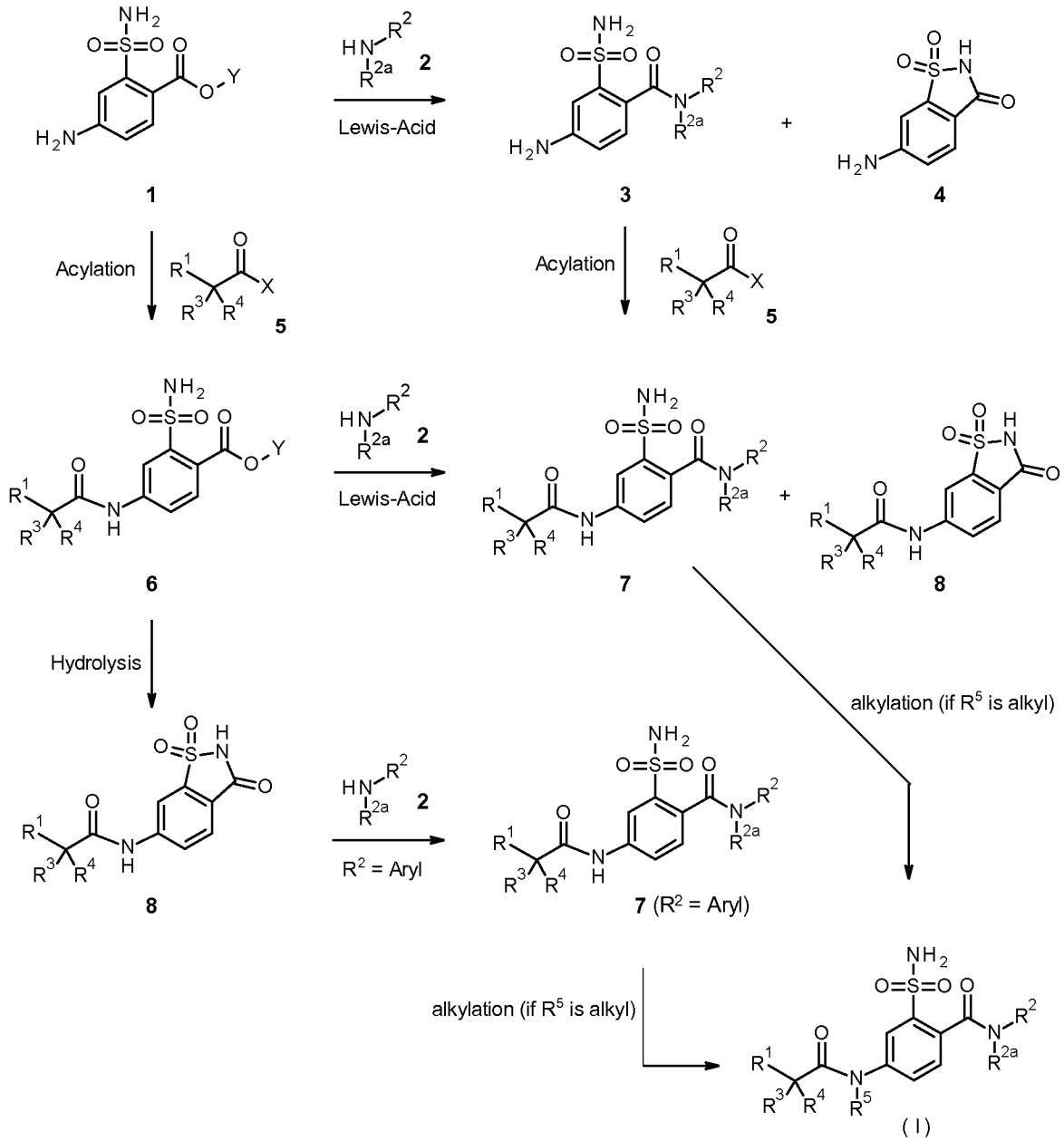
The term “according to” within the experimental section is used in the sense that the procedure referred to is to be used “analogously to”.

SYNTHESIS OF COMPOUNDS

The following schemes and general procedures illustrate general synthetic routes to the compounds of general formula (I) of the invention and are not intended to be limiting. It is obvious to the person skilled in the art that the order of transformations as exemplified in Scheme 1 can be modified in various ways. The order of transformations exemplified in Scheme 1 is therefore not intended to be limiting. In addition, interconversion of substituents, for example of residues R^1, R^2, R^{2a}, R^3, R^4, R^5, R^6, R^{6a}, R^{6b}, R^{7a}, R^{7b}, R^8, R^9, or R^{10} can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, halogenation, metallation, substitution or other reactions known to the person skilled in the art. These transformations include

those which introduce a functionality which allows for further interconversion of substituents. Appropriate protecting groups and their introduction and cleavage are well-known to the person skilled in the art.

All reagents used for the preparation of the compounds of the invention are commercially available, known in the literature or can be prepared as described.



Scheme 1: General procedures for the preparation of compounds of general formula (I), wherein R^1, R^2, R^{2a}, R^3, R^4 and R^5 are as defined in the description and claims of this invention; X represents hydroxy, chloro or fluoro; Y represents C_1-C_3 alkyl.

Compounds of general formula **(I)** can by synthesized as depicted in Scheme 1.

As hydrolysis of ester **1** to the corresponding carboxylic acid will result in immediate formation of bicyclic side product **4**, direct transformation of ester **1** into the corresponding carboxamide **3** is necessary. The person skilled in the art can perform this reaction in presence of a suitable Lewis acid (e.g. bis(trimethylaluminum)-1,4-diazabicyclo[2.2.2]octane (DABAL-Me_3)) and in a suitable solvent (e.g. THF). This reaction can be performed at room temperature or under slight cooling. Subsequent acylation to the corresponding bisamides **7** can be achieved for example by reaction with acyl chlorides or by standard peptide bond formation using all known procedures, such as reaction of the corresponding carboxylic acid in the presence of a coupling reagent e.g. HATU.

Alternatively, ester **1** can be first acylated to the corresponding amides **6**, for example by reaction with acyl chlorides or by standard peptide bond formation using all known procedures, such as reaction of the corresponding carboxylic acid in the presence of a coupling reagent e.g. HATU. As hydrolysis of the ester moiety of **6** to the corresponding carboxylic acid will again result in immediate formation of the corresponding bicyclic side product **8**, direct transformation of ester **6** or alternatively of compound **8** into the corresponding carboxamide **7** is necessary.

In case of aliphatic amines **2**, the person skilled in the art can perform this reaction in presence of a suitable Lewis acid (e.g. bis(trimethylaluminum)-1,4-diazabicyclo[2.2.2]octane (DABAL-Me_3)) and in a suitable solvent (e.g. THF). This reaction can be performed at room temperature or under slight cooling.

In case of aromatic amines **2**, the person skilled in the art can perform this reaction also in absence of a Lewis acid by stirring compound **8** and amine **2** (preferably using a large excess) at elevated temperature (preferable 100-200°C) in a high boiling solvent (e.g. toluene, xylene) for several hours.

Substituent R^5 (if C_1-C_3-alkyl), in particular methyl, can be introduced by alkylation in presence of a base.

The compounds according to the invention are isolated and purified in a manner known per se, e.g. by distilling off the solvent *in vacuo* and recrystallizing the residue obtained from a suitable solvent or subjecting it to one of the customary purification methods, such as chromatography on a suitable support material. Furthermore, reverse phase preparative HPLC of compounds of the present invention which possess a sufficiently basic or acidic functionality, may result in the formation of a salt, such as, in the case of a compound of the present invention which is sufficiently basic, a trifluoroacetate or formate salt for example, or, in the case of a compound of the present invention which is

sufficiently acidic, an ammonium salt for example. Salts of this type can either be transformed into its free base or free acid form, respectively, by various methods known to the person skilled in the art, or be used as salts in subsequent biological assays. Additionally, the drying process during the isolation of compounds of the present invention may not fully remove traces of cosolvents, especially such as formic acid or trifluoroacetic acid, to give solvates or inclusion complexes. The person skilled in the art will recognise which solvates or inclusion complexes are acceptable to be used in subsequent biological assays. It is to be understood that the specific form (e.g. salt, free base, solvate, inclusion complex) of a compound of the present invention as isolated as described herein is not necessarily the only form in which said compound can be applied to a biological assay in order to quantify the specific biological activity.

Salts of the compounds of formula (I) according to the invention can be obtained by dissolving the free compound in a suitable solvent (for example a ketone such as acetone, methylethylketone or methylisobutylketone, an ether such as diethyl ether, tetrahydrofuran or dioxane, a chlorinated hydrocarbon such as methylene chloride or chloroform, or a low molecular weight aliphatic alcohol such as methanol, ethanol or isopropanol) which contains the desired acid or base, or to which the desired acid or base is then added. The acid or base can be employed in salt preparation, depending on whether a mono- or polybasic acid or base is concerned and depending on which salt is desired, in an equimolar quantitative ratio or one differing therefrom. The salts are obtained by filtering, reprecipitating, precipitating with a non-solvent for the salt or by evaporating the solvent. Salts obtained can be converted into the free compounds which, in turn, can be converted into salts. In this manner, pharmaceutically unacceptable salts, which can be obtained, for example, as process products in the manufacturing on an industrial scale, can be converted into pharmaceutically acceptable salts by processes known to the person skilled in the art. Especially preferred are hydrochlorides and the process used in the example section.

Pure diastereomers and pure enantiomers of the compounds and salts according to the invention can be obtained e.g. by asymmetric synthesis, by using chiral starting compounds in synthesis and by splitting up enantiomeric and diasteriomeric mixtures obtained in synthesis.

Enantiomeric and diastereomeric mixtures can be split up into the pure enantiomers and pure diastereomers by methods known to a person skilled in the art. Preferably, diastereomeric mixtures are separated by crystallization, in particular fractional crystallization, or chromatography. Enantiomeric mixtures can be separated e.g. by forming diastereomers with a chiral auxilliary agent, resolving the diastereomers obtained

and removing the chiral auxilliary agent. As chiral auxilliary agents, for example, chiral acids can be used to separate enantiomeric bases such as e.g. mandelic acid and chiral bases can be used to separate enantiomeric acids by formation of diastereomeric salts. Furthermore, diastereomeric derivatives such as diastereomeric esters can be formed from enantiomeric mixtures of alcohols or enantiomeric mixtures of acids, respectively, using chiral acids or chiral alcohols, respectively, as chiral auxilliary agents. Additionally, diastereomeric complexes or diastereomeric clathrates may be used for separating enantiomeric mixtures. Alternatively, enantiomeric mixtures can be split up using chiral separating columns in chromatography. Another suitable method for the isolation of enantiomers is the enzymatic separation.

One preferred aspect of the invention is the process for the preparation of the compounds of general formula (I) (Ia) or (Ib) or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer according to the examples, as well as the intermediates used for their preparation.

Optionally, compounds of the formula (I) can be converted into their salts, or, optionally, salts of the compounds of the formula (I) can be converted into the free compounds. Corresponding processes are customary for the skilled person.

EXPERIMENTAL PART

Abbreviations

The following table lists the abbreviations used in this paragraph and in the Intermediate Examples and Examples section as far as they are not explained within the text body.

Abbreviation	Meaning
AcOH	acetic acid (ethanoic acid)
aq.	aqueous
boc	t-butoxycarbonyl
br	broad
CI	chemical ionisation
d	doublet
DAD	diode array detector
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DCM	dichloromethane
dd	double-doublet
DIPEA	diisopropylethylamine

DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
ELSD	Evaporative Light Scattering Detector
EtOAc	ethyl acetate
EtOH	ethanol
eq.	equivalent
ESI	electrospray (ES) ionisation
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
HPLC	high performance liquid chromatography
LC-MS	liquid chromatography mass spectrometry
m	multiplet
MeCN	acetonitrile
MeOH	methanol
MS	mass spectrometry
MTBE	methyl tert-butylether
NMR	nuclear magnetic resonance spectroscopy : chemical shifts (δ) are given in ppm. The chemical shifts were corrected by setting the DMSO signal to 2.50 ppm unless otherwise stated.
PDA	Photo Diode Array
PoraPak™;	a HPLC column obtainable from Waters
q	quartet
r.t. or rt	room temperature
Rt	retention time (as measured either with HPLC or UPLC) in minutes
s	singlet
SM	starting material
SQD	Single-Quadrupol-Detector
t	triplet
td	dublett of a triplet
dt	triplett of a dublet
TEA	triethylamine
THF	tetrahydrofuran
UPLC	ultra performance liquid chromatography

Other abbreviations have their meanings customary per se to the skilled person.

The various aspects of the invention described in this application are illustrated by the following examples which are not meant to limit the invention in any way.

Specific Experimental Descriptions

NMR peak forms in the following specific experimental descriptions are stated as they appear in the spectra, possible higher order effects have not been considered. Reactions employing microwave irradiation may be run with a Biotage Initator® microwave oven optionally equipped with a robotic unit. The reported reaction times employing microwave heating are intended to be understood as fixed reaction times after reaching the indicated reaction temperature. The compounds and intermediates produced according to the methods of the invention may require purification. Purification of organic compounds is well known to the person skilled in the art and there may be several ways of purifying the same compound. In some cases, no purification may be necessary. In some cases, the compounds may be purified by crystallization. In some cases, impurities may be stirred out using a suitable solvent. In some cases, the compounds may be purified by chromatography, particularly flash column chromatography, using for example prepacked silica gel cartridges, *e.g.* from Separtis such as Isolute® Flash silica gel or Isolute® Flash NH_2 silica gel in combination with a Isolera® autopurifier (Biotage) and eluents such as gradients of e.g. hexane/ethyl acetate or DCM/methanol. In some cases, the compounds may be purified by preparative HPLC using for example a Waters autopurifier equipped with a diode array detector and/or on-line electrospray ionization mass spectrometer in combination with a suitable prepacked reverse phase column and eluents such as gradients of water and acetonitrile which may contain additives such as trifluoroacetic acid, formic acid or aqueous ammonia. In some cases, purification methods as described above can provide those compounds of the present invention which possess a sufficiently basic or acidic functionality in the form of a salt, such as, in the case of a compound of the present invention which is sufficiently basic, a trifluoroacetate or formate salt for example, or, in the case of a compound of the present invention which is sufficiently acidic, an ammonium salt for example. A salt of this type can either be transformed into its free base or free acid form, respectively, by various methods known to the person skilled in the art, or be used as salts in subsequent biological assays. It is to be understood that the specific form (*e.g.* salt, free base etc) of a compound of the present invention as isolated as described herein is not necessarily the only form in which said compound can be applied to a biological assay in order to quantify the specific biological activity.

The percentage yields reported in the following examples are based on the starting component that was used in the lowest molar amount. Most reaction conditions were not optimized for yield. Air and moisture sensitive liquids and solutions were transferred via syringe or cannula, and introduced into reaction vessels through rubber septa. Commercial grade reagents and solvents were used without further purification. The term "concentrated in vacuo" refers to use of a Buchi rotary evaporator at a minimum pressure of approximately 15 mm of Hg. All temperatures are reported uncorrected in degrees Celsius (°C).

In order that this invention may be better understood, the following examples are set forth. These examples are for the purpose of illustration only, and are not to be construed as limiting the scope of the invention in any manner. All publications mentioned herein are incorporated by reference in their entirety.

Analytical LC-MS and UPLC-MS conditions

LC-MS and UPLC-MS data given in the subsequent specific experimental descriptions refer (unless otherwise noted) to the following conditions:

Method A

Instrument: Waters Acquity UPLC-MS SingleQuad; Column: Acquity UPLC BEH C18 1.7 µm, 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; flow 0.8 ml/min; temperature: 60 °C; DAD scan: 210-400 nm.

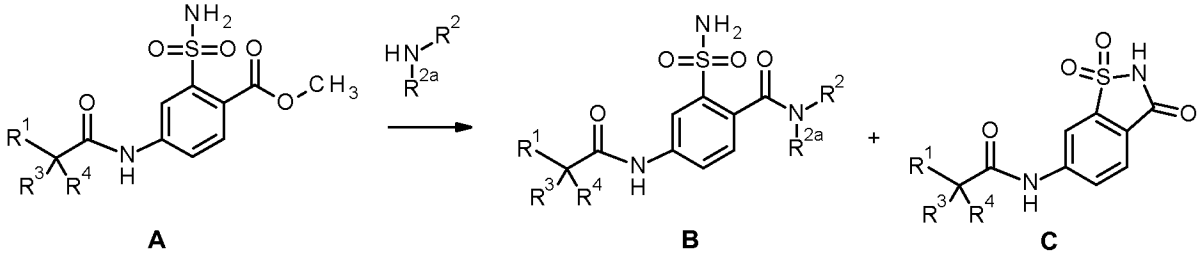
Method B

Instrument: Waters Acquity UPLC-MS SingleQuad; Column: Acquity UPLC BEH C18 1.7 µm, 50x2.1mm; eluent A: water + 0.2 vol % aqueous ammonia (32%), eluent B: acetonitrile; gradient: 0-1.6 min 1-99% B, 1.6-2.0 min 99% B; flow 0.8 ml/min; temperature: 60 °C; DAD scan: 210-400 nm.

Flash column chromatography conditions

"Purification by (flash) column chromatography" as stated in the subsequent specific experimental descriptions refers to the use of a Biotage Isolera purification system. For technical specifications see "Biotage product catalogue" on www.biotage.com.

General Experimental Procedures



General Procedure GP1.1

Ester **A** (0.52 mmol, 1.0 eq) and the corresponding amine (0.78 mmol, 1.5eq) were dissolved under nitrogen atmosphere in tetrahydrofuran (4 mL) and bis(trimethylaluminum)-1,4-diazabicyclo[2.2.2]octane (DABAL-Me_3) (1.57 mmol, 3.0 eq) was added slowly and portionwise. Then, it was stirred overnight at room temperature. The reaction mixture was quenched under ice-cooling with aqueous ammonium chloride solution and extracted twice with ethyl acetate. The combined organic phases were washed with brine and dried over sodium sulfate prior to being concentrated in vacuo. The crude was purified as indicated in the examples.

Bicycle **C** was also obtained to a major amount.

General Procedure GP1.2

Ester **A** (0.52 mmol, 1.0 eq) and the corresponding amine (0.78 mmol, 1.5eq) were dissolved under nitrogen atmosphere in tetrahydrofuran (4 mL) and bis(trimethylaluminum)-1,4-diazabicyclo[2.2.2]octane (DABAL-Me_3) (1.57 mmol, 3.0 eq) was slowly and added portionwise. Afterwards it was irradiated for 30 min at 130°C in the microwave. The reaction mixture was quenched with 1M-HCl and extracted with ethyl acetate. The organic phase was washed with brine and dried over sodium sulfate prior to being concentrated in vacuo. The crude was purified as indicated in the examples.

Bicycle **C** was also obtained to a major amount.

General Procedure GP1.3

Ester **A** (0.52 mmol, 1.0 eq) and the corresponding amine (0.78 mmol, 1.5eq) were dissolved under nitrogen atmosphere in tetrahydrofuran (4 mL) and bis(trimethylaluminum)-1,4-diazabicyclo[2.2.2]octane (DABAL-Me_3) (1.57 mmol, 3.0 eq)

was added slowly and portionwise. Then, it was stirred overnight at room temperature. The reaction mixture was quenched with 1M-HCl and extracted with ethyl acetate. The organic phase was washed with brine and dried over sodium sulfate prior to being concentrated in vacuo. The crude was purified as indicated in the examples.

Bicycle **C** was also obtained to a major amount.

General Procedure GP1.4

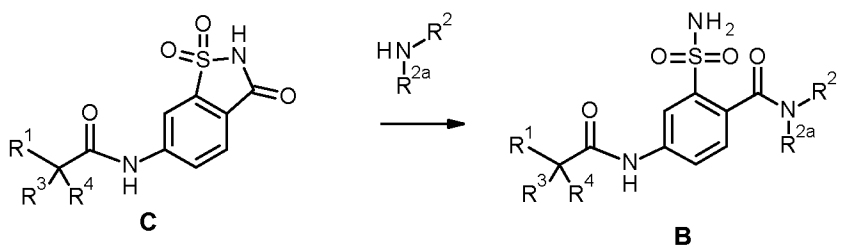
Ester **A** (0.52 mmol, 1.0 eq), the corresponding amine hydrochloride (0.78 mmol, 1.5 eq) and *N*,*N*-diisopropylethylamine (1.57 mmol, 3.0 eq) were dissolved under nitrogen atmosphere in tetrahydrofuran (4 mL) and bis(trimethylaluminum)-1,4-diazabicyclo[2.2.2]octane (DABAL-Me_3) (1.57 mmol, 3.0 eq) was added slowly and portionwise. Then, it was stirred overnight at room temperature. The reaction mixture was quenched with 1M-HCl and extracted with ethyl acetate. The organic phase was washed with brine and dried over sodium sulfate prior to being concentrated in vacuo. The crude was purified as indicated in the examples.

Bicycle **C** was also obtained to a major amount.

General Procedure GP1.5

Ester **A** (0.52 mmol, 1.0 eq) and the corresponding amine hydrochloride (0.78 mmol, 1.5eq) were dissolved under nitrogen atmosphere in tetrahydrofuran (4 mL) and bis(trimethylaluminum)-1,4-diazabicyclo[2.2.2]octane (DABAL-Me_3) (2.62 mmol, 5.0 eq) was added slowly and portionwise. Then, it was stirred overnight at room temperature. The reaction mixture was quenched under ice-cooling with aqueous ammonium chloride solution and extracted twice with ethyl acetate. The combined organic phases were washed with brine and dried over sodium sulfate prior to being concentrated in vacuo. The crude was purified as indicated in the examples.

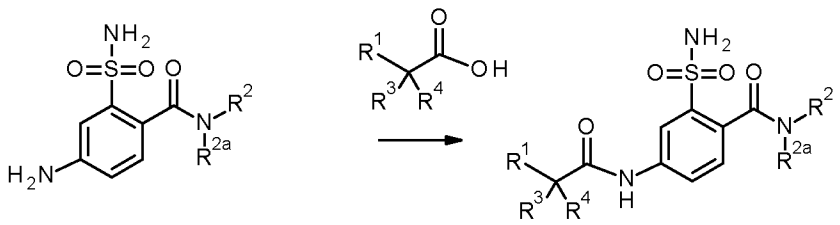
Bicycle **C** was also obtained to a major amount.



C **B**

General Procedure GP2

Bicycle **C** (0.29 mmol, 1.0 eq) and the corresponding amine (large excess) were dissolved in xylene (3 mL) and were stirred at 150-160°C for several hours as indicated in the examples. After cooling to room temperature the reaction mixture was diluted with *n*-hexane (100 mL) and the formed precipitate was isolated by filtration followed by purification as indicated in the examples.



D **B**

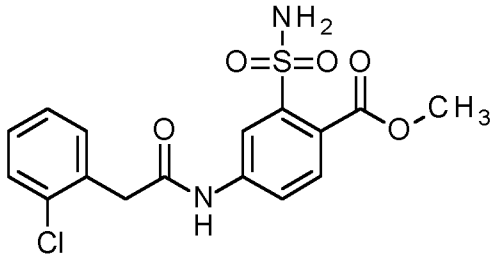
General procedure GP3.1

Crude substituted aniline **E** (1.29 mmol) was dissolved in dimethylformamide (10 mL in case of 1.29 mmol scale) followed by the addition of the corresponding acid (amount as indicated in examples), *N*,*N*-diisopropylethylamine (2.7 eq based on acid) and HATU (1.0 eq based on acid). The reaction mixture was either stirred overnight at room temperature or heated at 50°C until TLC showed consumption of starting material. After cooling to room temperature the reaction mixture was concentrated in vacuo. Ethyl acetate and water were added, the organic phase was dried and concentrated in vacuo, followed by purification as indicated in the examples.

Synthesis of Intermediates

Intermediate 1

Methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate



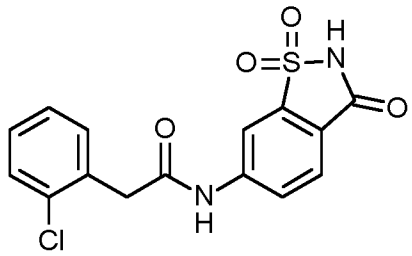
A solution of methyl 4-amino-2-sulfamoylbenzoate [CAS 2297-06-05] (5.00 g, 21.7 mmol) in tetrahydrofuran (109 mL) was treated under ice cooling with triethylamine (6.59 g, 65.2 mmol) and (2-chlorophenyl)acetyl chloride (4.52 g, 23.9 mmol). After stirring for two hours under ice cooling it was led to warm to room temperature overnight. The reaction mixture was concentrated in vacuo, and to the residue ethyl acetate and water were added, followed by stirring at room temperature for 30 hours. The resulting precipitate was filtered off, washed with water and ethyl acetate and dried to give the title compound (3.13 g, 8.18 mmol, 36% yield, 95% purity).

LC-MS (Method A): Rt = 0.99 min; MS (ESIneg): m/z = 381 $(M-H)^-$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 3.84 (s, 3H), 3.90 (s, 2H), 7.24 (s, 2H), 7.30 - 7.35 (m, 2H), 7.42 - 7.49 (m, 2H), 7.74 (d, 1H), 7.91 (dd, 1H), 8.31 (d, 1H), 10.82 (s, 1H).

Intermediate 2

2-(2-Chlorophenyl)-*N*-(1,1-dioxido-3-oxo-2,3-dihydro-1,2-benzothiazol-6-yl)acetamide



A solution of methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (4.30 g, 11.2 mmol) in methanol (200 mL) was treated at room temperature with aqueous 2M-NaOH solution (56.2 mL). After stirring overnight it was concentrated in vacuo. Water and ethyl acetate were added to the residue, it was acidified with diluted aqueous HCl-solution, the

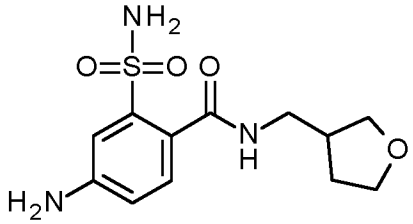
organic phase was removed and washed three times with water. Drying over sodium sulfate and concentration in vacuo led to the crude title compound (3.20 g, 9.12 mmol, 81% yield, 80% purity) that was used without further purification in the next step.

LC-MS (Method B): Rt = 0.54 min; MS (ESIpos): m/z = 351 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 3.95 (s, 2H), 7.31 - 7.37 (m, 2H), 7.43 - 7.50 (m, 2H), 7.88 (dd, 1H), 7.96 (d, 1H), 8.36 (d, 1H), 11.06 (s, 1H).

Intermediate 3

4-Amino-2-sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)benzamide



Methyl 4-amino-2-sulfamoylbenzoate [CAS 2297-06-05] (2.00 g, 8.69 mmol) and 1-(tetrahydrofuran-3-yl)methanamine (1.24 g, 12.2 mmol) were dissolved under nitrogen atmosphere in tetrahydrofuran (180 mL) and bis(trimethylaluminum)-1,4-diazabicyclo[2.2.2]octane (DABAL-Me_3) (6.68 g, 26.1 mmol) was added slowly and portionwise. Then, it was stirred overnight at room temperature. The reaction mixture was quenched under ice-cooling with aqueous ammonium chloride solution until pH 7 was reached. It was extracted several times with ethyl acetate. The organic phase was washed with brine solution and dried over sodium sulfate. The filtrate was concentrated in vacuo to give the crude title compound (400 mg) that was used in the next step without further purification.

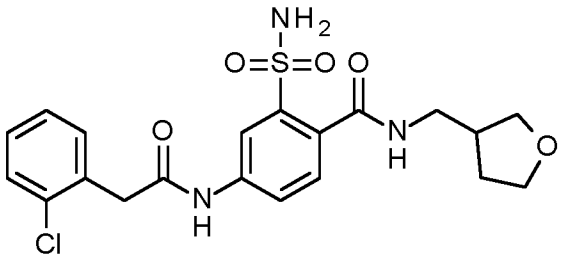
LC-MS (Method A): Rt = 0.47 min; MS (ESIpos): m/z = 300 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 1.55 - 1.64 (m, 1H), 1.88 - 2.04 (m, 2H), 3.14 - 3.20 (m, 1H), 3.43 - 3.47 (m, 1H), 3.57 - 3.75 (m, 3H), one probably proton under solvent/water, 5.97 (s, 2H), 6.67 (dd, 1H), 7.15 (d, 1H), 7.18 (s, 2H), 7.23 (d, 1H), 8.55 (t, 1H).

Synthesis of Examples

Example 1

4-{[(2-Chlorophenyl)acetyl]amino}-2-sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)benzamide



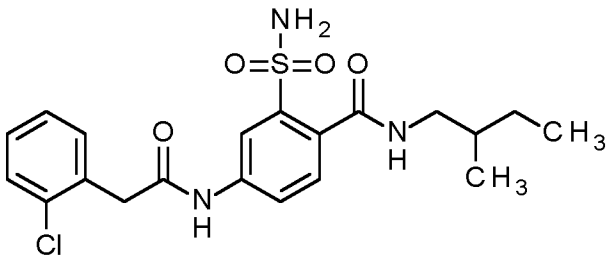
According to general procedure GP1.2 methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (300 mg, 0.78 mmol) and 1-(tetrahydrofuran-3-yl)methanamine (119 mg, 1.17 mmol) were converted in presence of DABAL-Me_3 (502 mg, 1.96 mmol) to the title compound which was purified at the end by preparative HPLC (Chromatorex C-18 10µm, 125x30mm, acetonitrile/water + 0.1% formic acid) (65 mg, 0.144 mmol, 18 % yield, 98 % purity).

LC-MS (Method A): Rt = 0.90 min; MS (ESIpos): m/z = 452 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 1.56 - 1.66 (m, 1H), 1.91 - 2.01 (m, 1H), 2.42 - 2.50 (m, 1H), 3.15 - 3.28 (m, 2H), 3.47 (dd, 1H), 3.58 - 3-65 (m, 1H), 3.67 - 3.77 (m, 2H), 3.89 (s, 2H), 7.19 (s, 2H), 7.29 - 7.36 (m, 2H), 7.42 - 7.49 (m, 2H), 7.53 (d, 1H), 7.91 (dd, 1H), 8.21 (d, 1H), 8.82 (t, 1H), 10.73 (s, 1H).

Example 2

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-(2-methylbutyl)-2-sulfamoylbenzamide



According to general procedure GP1.1 methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (200 mg, 0.52 mmol) and 2-methylbutan-1-amine (68.3 mg, 0.78 mmol) were converted in presence of DABAL-Me_3 (402 mg, 1.57 mmol) to the title compound which was purified at the end by preparative HPLC (Waters XBrigde C18 5µ

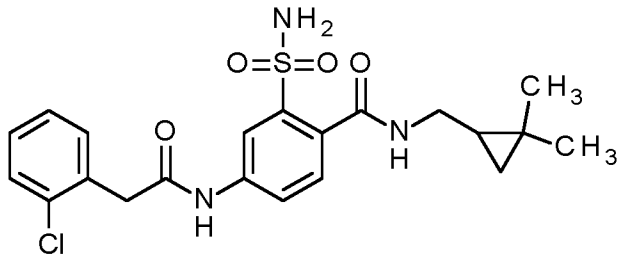
100x30mm, acetonitrile/water + 0.2% aqueous ammonia (32%)) (24 mg, 0.0548 mmol, 11 % yield, 98 % purity).

LC-MS (Method B): Rt = 1.08 min; MS (ESIpos): m/z = 438 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 0.86 - 0.91 (m, 6H), 1.07 - 1.20 (m, 1H), 1.38 - 1.50 (m, 1H), 1.58 - 1.69 (m, 1H), 3.00 - 3.08 (m, 1H), 3.11 - 3.20 (m, 1H), 3.89 (s, 2H), 7.20 (s, 2H), 7.29 - 7.36 (m, 2H), 7.41 - 7.49 (m, 2H), 7.52 (d, 1H), 7.91 (dd, 1H), 8.21 (d, 1H), 8.71 (t, 1H), 10.72 (s, 1H).

Example 3

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-[(2,2-dimethylcyclopropyl)methyl]-2-sulfamoylbenzamide



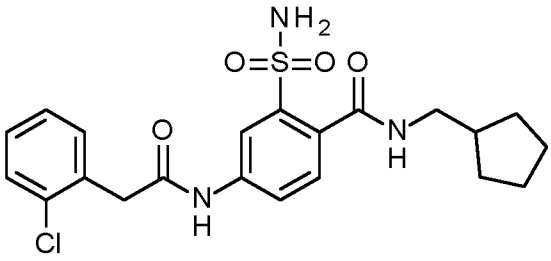
According to general procedure GP1.5 methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (200 mg, 0.52 mmol) and 1-(2,2-dimethylcyclopropyl)methanamine hydrochloride (106 mg, 0.78 mmol) were converted in presence of DABAL-Me_3 (670 mg, 2.61 mmol) to the title compound which was purified at the end by preparative HPLC (Waters XBrigde C18 5µ 100x30mm, acetonitrile/water + 0.2% aqueous ammonia (32%)) (11 mg, 0.0244 mmol, 5 % yield, 98 % purity).

LC-MS (Method B): Rt = 1.11 min; MS (ESIpos): m/z = 450 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 0.14 (t, 1H), 0.43 (dd, 1H), 0.80 - 0.89 (m, 1H), 1.04 (s, 3H), 1.10 (s, 3H), 3.12 - 3.22 (m, 1H), 3.24 - 3.33 (m, 1H), 3.89 (s, 2H), 7.22 (s, 2H), 7.29 - 7.36 (m, 2H), 7.42 - 7.48 (m, 2H), 7.52 (d, 1H), 7.92 (dd, 1H), 8.22 (d, 1H), 8.78 (t, 1H), 10.72 (s, 1H).

Example 4

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-(cyclopentylmethyl)-2-sulfamoylbenzamide



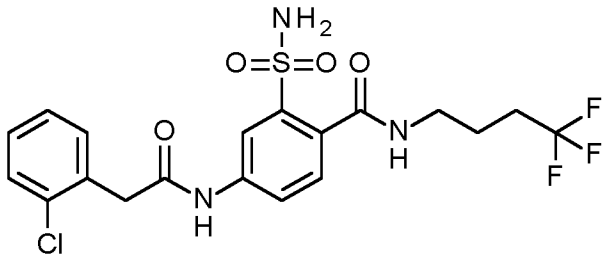
According to general procedure GP1.5 methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (200 mg, 0.52 mmol) and 1-cyclopentylmethanamine hydrochloride (106 mg, 0.78 mmol) were converted in presence of DABAL-Me_3 (670 mg, 2.61 mmol) to the title compound which was purified at the end by preparative HPLC (Waters XBrigde C18 5µ 100x30mm, acetonitrile/water + 0.2% aqueous ammonia (32%)) (13 mg, 0.0289 mmol, 6 % yield, 98 % purity).

LC-MS (Method B): Rt = 1.10 min; MS (ESIpos): m/z = 450 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 1.20 - 1.31 (m, 2H), 1.44 - 1.64 (m, 4H), 1.66 - 1.76 (m, 2H), 2.07 - 2.19 (m, 1H), 3.16 (dd, 2H), 3.89 (s, 2H), 7.21 (s, 2H), 7.29 - 7.37 (m, 2H), 7.41 - 7.48 (m, 2H), 7.52 (d, 1H), 7.91 (dd, 1H), 8.21 (d, 1H), 8.75 (t, 1H), 10.72 (s, 1H).

Example 5

4-{[(2-Chlorophenyl)acetyl]amino}-2-sulfamoyl-*N*-(4,4,4-trifluorobutyl)benzamide



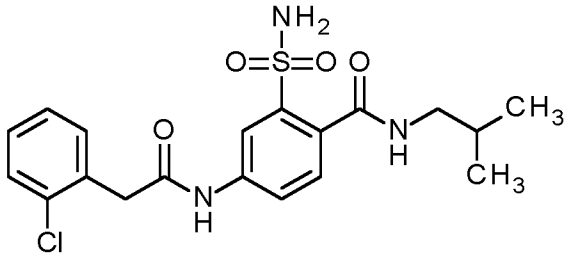
According to general procedure GP1.1 methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (250 mg, 0.65 mmol) and 4,4,4-trifluorobutan-1-amine (125 mg, 0.98 mmol) were converted in presence of DABAL-Me_3 (502 mg, 1.96 mmol) to the title compound which was purified at the end by preparative HPLC (Chromatorex C-18 10µm, 125x30mm, acetonitrile/water + 0.1% aqueous ammonia (32%)) (36 mg, 0.0753 mmol, 12 % yield, 98 % purity).

LC-MS (Method B): Rt = 1.05 min; MS (ESIpos): m/z = 478 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 1.68 - 1.78 (m, 2H), 2.28 - 2.42 (m, 2H), 3.28 - 3.35 (m, 2H), 3.89 (s, 2H), 7.18 (s, 2H), 7.29 - 7.37 (m, 2H), 7.42 - 7.48 (m, 2H), 7.55 (d, 1H), 7.92 (dd, 1H), 8.21 (d, 1H), 8.78 (t, 1H), 10.73 (s, 1H).

Example 6

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-isobutyl-2-sulfamoylbenzamide



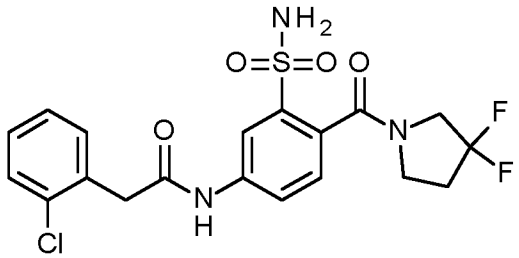
According to general procedure GP1.3 methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (250 mg, 0.65 mmol) and 2-methylpropan-1-amine (71.6 mg, 0.98 mmol) were converted in presence of DABAL-Me_3 (502 mg, 1.96 mmol) to the title compound which was purified at the end by preparative HPLC (Chromatorex C-18 10µm, 125x30mm, acetonitrile/water + 0.1% aqueous ammonia (32%)) (23 mg, 0.0543 mmol, 10 % yield, 98 % purity).

LC-MS (Method B): Rt = 1.02 min; MS (ESIpos): m/z = 424 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 0.91 (d, 6H), 1.78 - 1.90 (m, 1H), 3.04 (t, 2H), 3.88 (s, 2H), 7.20 (s, 2H), 7.29 - 7.36 (m, 2H), 7.41 - 7.49 (m, 2H), 7.53 (d, 1H), 7.91 (dd, 1H), 8.22 (d, 1H), 8.73 (t, 1H), 10.72 (s, 1H).

Example 7

2-(2-Chlorophenyl)-*N*-{4-[(3,3-difluoropyrrolidin-1-yl)carbonyl]-3-sulfamoylphenyl}acetamide



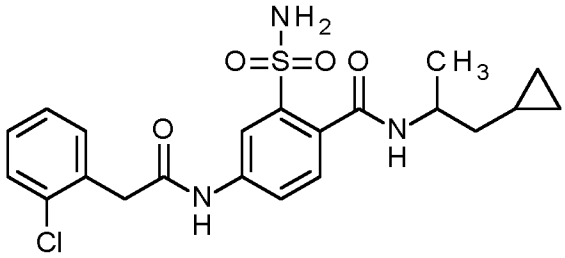
According to general procedure GP1.4 methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (250 mg, 0.65 mmol), 3,3-difluoropyrrolidine hydrochloride (141 mg, 0.98 mmol) and *N*,*N*-diisopropylethylamine (203 mg, 1.57 mmol) were converted in presence of DABAL-Me_3 (502 mg, 2.74 mmol) to the title compound which was purified at the end by preparative HPLC (Chromatorex C-18 10µm, 125x30mm, acetonitrile/water + 0.1% formic acid) (20 mg, 0.0437 mmol, 7 % yield, 98 % purity).

LC-MS (Method A): Rt = 1.03 min; MS (ESIpos): m/z = 458 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 2.35 - 2.48 (m, 2H), 3.40 (t, 1H), 3.61 (t, 1H), 3.70 (t, 1H), 3.84 - 3.93 (m, 3H), 7.07 - 7.11 (m, 2H), 7.29 - 7.37 (m, 2H), 7.42 - 7.50 (s, 3H), 7.88 (dd, 1H), 8.25 (dd, 1H), 10.72 (d, 1H).

Example 8

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-(1-cyclopropylpropan-2-yl)-2-sulfamoylbenzamide



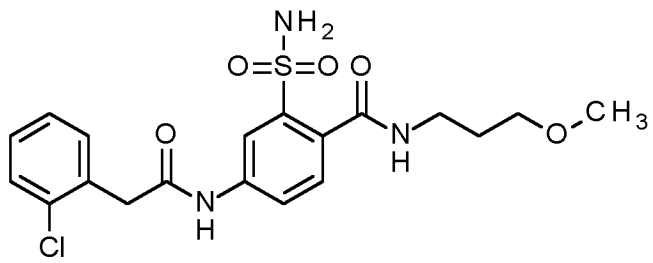
According to general procedure GP1.4 methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (200 mg, 0.52 mmol), 1-cyclopropylpropan-2-amine hydrochloride (106 mg, 0.78 mmol) and *N*,*N*-diisopropylethylamine (203 mg, 1.57 mmol) were converted in presence of DABAL-Me_3 (203 mg, 0.78 mmol) to the title compound which was purified at the end by preparative HPLC (Chromatorex C-18 10µm, 125x30mm, acetonitrile/water + 0.1% formic acid) (8 mg, 0.0178 mmol, 3 % yield, 95 % purity).

LC-MS (Method A): Rt = 1.13 min; MS (ESIpos): m/z = 450 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 0.01 - 0.13 (m, 2H), 0.36 - 0.48 (m, 2H), 0.71 - 0.82 (m, 1H), 1.16 (d, 3H), 1.22 - 1.31 (m, 1H), 1.46 - 1.55 (m, 1H), 3.89 (s, 2H), 3.96 - 4.06 (m, 1H), 7.21 (s, 2H), 7.28 - 7.37 (m, 2H), 7.41 - 7.52 (m, 3H), 7.90 (dd, 1H), 8.21 (d, 1H), 8.57 (d, 1H), 10.72 (s, 1H).

Example 9

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-(3-methoxypropyl)-2-sulfamoylbenzamide



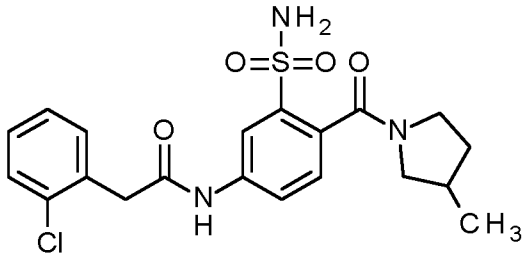
According to general procedure GP1.1 methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (200 mg, 0.52 mmol) and 3-methoxypropan-1-amine (70 mg, 0.78 mmol) were converted in presence of DABAL-Me_3 (402 mg, 1,57 mmol) to the title compound which was purified at the end by preparative HPLC (Waters XBrigde C18 5µ 100x30mm, acetonitrile/water + 0.2% aqueous ammonia (32%)) (30 mg, 0.0682 mmol, 13 % yield, 98 % purity).

LC-MS (Method B): Rt = 0.84 min; MS (ESIpos): m/z = 440 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 1.74 (p, 2H), 3.22 - 3.30 (m, 5H), 3.39 (t, 2H), 3.89 (s, 2H), 7.21 (s, 2H), 7.30 - 7.35 (m, 2H), 7.42 - 7.48 (m, 2H), 7.53 (d, 1H), 7.91 (dd, 1H), 8.20 (d, 1H), 8.71 (t, 1H), 10.72 (s, 1H).

Example 10

2-(2-Chlorophenyl)-*N*-{4-[(3-methylpyrrolidin-1-yl)carbonyl]-3-sulfamoylphenyl}acetamide



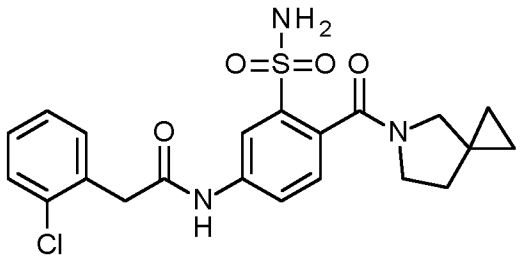
According to general procedure GP1.3 methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (200 mg, 0.52 mmol) and 3-methylpyrrolidine hydrochloride (95.3 mg, 0.78 mmol) were converted in presence of DABAL-Me_3 (402 mg, 1,57 mmol) the title compound which was purified at the end by preparative HPLC (Chromatorex C-18 10µm, 125x30mm, acetonitrile/water + 0.1% formic acid) (20.5 mg, 0.0470 mmol, 9 % yield, 98 % purity).

LC-MS (Method A): Rt = 1.06 min; MS (ESIpos): m/z = 436 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 0.93 (d, 1.5H), 1.05 (d, 1.5H), 1.40 - 1.55 (m, 1H), 1.89 - 2.07 (m, 1H), 2.12 - 2.31 (m, 1H), 2.76 (t, 0.5H), 2.99 (dd, 0.5H), 3.14 - 3.45 (m, 2H), 3.54 - 3.68 (m, 1H), 3.88 (s, 2H), 7.00 (s, 2H), 7.30 - 7.35 (m, 2H), 7.42 - 7.50 (m, 3H), 7.85 - 7.89 (m, 1H), 8.22 (d, 1H), 10.70 (s, 1H).

Example 11

***N*-[4-(5-Azaspiro[2.4]hept-5-ylcarbonyl)-3-sulfamoylphenyl]-2-(2-chlorophenyl)acetamide**



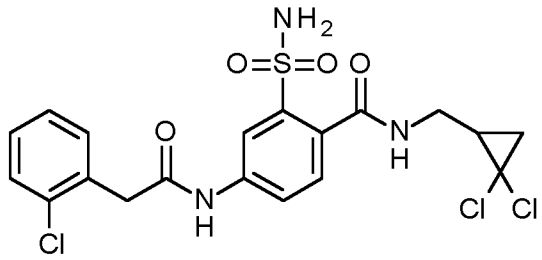
According to general procedure GP1.3 methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (200 mg, 0.52 mmol) and 5-azaspiro[2.4]heptane hydrochloride (105 mg, 0.78 mmol) were converted in presence of DABAL-Me_3 (402 mg, 1.57 mmol) to the title compound which was purified at the end by preparative HPLC (Chromatorex C-18 10µm, 125x30mm, acetonitrile/water + 0.1% formic acid) (25.2 mg, 0.0563 mmol, 11 % yield, 97 % purity).

LC-MS (Method A): Rt = 1.08 min; MS (ESIpos): m/z = 448 $(M+H)^+$

^{1}H-NMR (500MHz, DMSO-d_6) δ [ppm]: 0.45 - 0.53 (m, 2H), 0.55 - 0.65 (m, 2H), 1.69 - 1.83 (m, 2H), 3.00 - 3.09 (m, 1H), 3.25 - 3.31 (m, 1H), 3.33 - 3.40 (m, 1H), 3.60 (t, 1H), 3.86 (s, 1H), 3.87 (s, 1H), 6.99 (s, 2H), 7.27 - 7.35 (m, 2H), 7.40 - 7.51 (m, 3H), 7.82 - 7.88 (m, 1H), 8.18 (d, 0.5H), 8.22 (d, 0.5H), 10.67 (s, 0.5H), 10.69 (s, 0.5H).

Example 12

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-[(2,2-dichlorocyclopropyl)methyl]-2-sulfamoylbenzamide



According to general procedure GP1.2 methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (250 mg, 0.65 mmol) and 1-(2,2-dichlorocyclopropyl)methanamine (137 mg, 0.98 mmol) were converted in presence of DABAL-Me_3 (251 mg, 0.98 mmol) to the title compound which was purified at the end by preparative HPLC (Chromatorex C-18

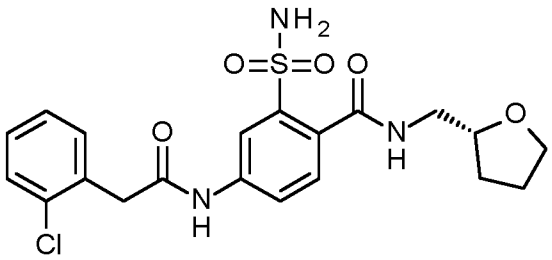
10µm, 125x30mm, acetonitrile/water + 0.1% formic acid) (89 mg, 0.181 mmol, 28 % yield, 98 % purity).

LC-MS (Method A): Rt = 1.10 min; MS (ESIpos): m/z = 490 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 1.45 (t, 1H), 1.77 (dd, 1H), 1.97 - 2.06 (m, 1H), 3.36 - 3.49 (m, 2H), 3.89 (s, 2H), 7.18 (s, 2H), 7.30 - 7.37 (m, 2H), 7.42 - 7.49 (m, 2H), 7.55 (d, 1H), 7.92 (dd, 1H), 8.23 (d, 1H), 9.06 (t, 1H), 10.74 (s, 1H).

Example 13

4-{[(2-Chlorophenyl)acetyl]amino}-2-sulfamoyl-*N*-[(2*R*)-tetrahydrofuran-2-ylmethyl]benzamide



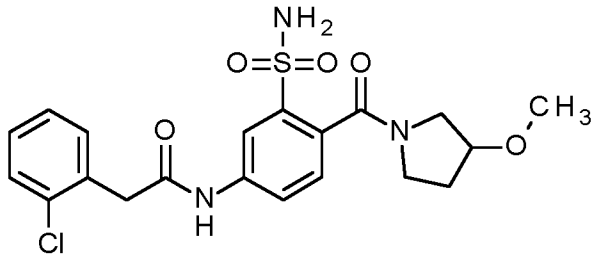
According to general procedure GP1.3 methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (200 mg, 0.52 mmol) and 1-[(2*R*)-tetrahydrofuran-2-yl]methanamine (79.3 mg, 0.78 mmol) were converted in presence of DABAL-Me_3 (402 mg, 1.57 mmol) to the title compound which was purified at the end by preparative HPLC (Chromatorex C-18 10µm, 125x30mm, acetonitrile/water + 0.1% aqueous ammonia (32%)) (9.2 mg, 0.0204 mmol, 4 % yield, 98 % purity).

LC-MS (Method B): Rt = 0.87 min; MS (ESIpos): m/z = 452 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 1.57 - 1.69 (m, 1H), 1.74 - 2.02 (m, 3H), 3.22 - 3.35 (m, 2H), 3.59 - 3.67 (m, 1H), 3.74 - 3.82 (m, 1H), 3.89 (s, 2H), 3.92 - 4.00 (m, 1H), 7.20 (s, 2H), 7.29 - 7.37 (m, 2H), 7.42 - 7.47 (m, 2H), 7.51 (d, 1H), 7.90 (dd, 1H), 8.21 (d, 1H), 8.79 (t, 1H), 10.73 (s, 1H).

Example 14

2-(2-Chlorophenyl)-*N*-{4-[(3-methoxypyrrolidin-1-yl)carbonyl]-3-sulfamoylphenyl}acetamide



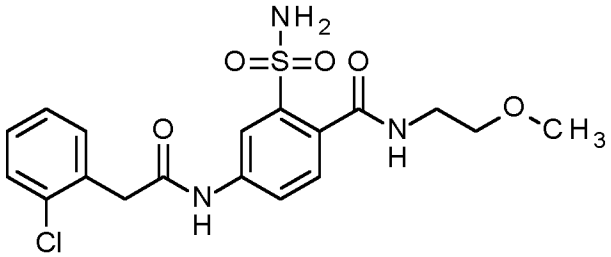
According to general procedure GP1.3 methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (200 mg, 0.52 mmol) and 3-methoxypyrrolidine hydrochloride (108 mg, 0.78 mmol) were converted in presence of DABAL-Me_3 (402 mg, 1.57 mmol) to the title compound which was purified at the end by preparative HPLC (Chromatorex C-18 10µm, 125x30mm, acetonitrile/water + 0.1% formic acid) (17.1 mg, 0.0378 mmol, 7 % yield, 96 % purity).

LC-MS (Method A): Rt = 0.94 min; MS (ESIpos): m/z = 452 $(M+H)^+$

^{1}H-NMR (500MHz, DMSO-d_6) δ [ppm]: 1.80 - 2.02 (m, 2H), 3.12 - 3.33 (m, 2H), 3.15 (s, 1.5H), 3.25 (s, 1.5H), 3.38 - 3.47 (m, 1H), 3.54 - 3.62 (m, 1H), 3.87 (s, 2H), 3.89 - 3.93 (m, 0.5H), 4.00 - 4.04 (m, 0.5H), 6.99 (s, 1H), 7.00 (s, 1H), 7.28 - 7.34 (m, 2H), 7.41 - 7.47 (m, 3H), 7.84 - 7.88 (m, 1H), 8.21 (d, 1H), 10.68 (s, 0.5H), 10.69 (s, 0.5H).

Example 15

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-(2-methoxyethyl)-2-sulfamoylbenzamide



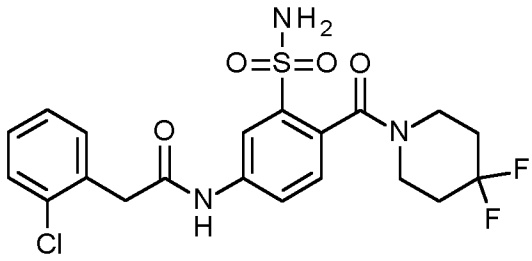
According to general procedure GP1.3 methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (200 mg, 0.52 mmol) and 2-methoxyethylamine (58.9 mg, 0.78 mmol) were converted in presence of DABAL-Me_3 (402 mg, 1.57 mmol) to the title compound which was purified at the end by preparative HPLC (Chromatorex C-18 10µm, 125x30mm, acetonitrile/water + 0.1% formic acid) (30 mg, 0.0704 mmol, 14 % yield, 98 % purity).

LC-MS (Method B): Rt = 0.82 min; MS (ESIpos): m/z = 426 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 3.28 (s, 3H), 3.35 - 3.41 (m, 2H), 3.43 - 3.48 (m, 2H), 3.89 (s, 2H), 7.19 (s, 2H), 7.29 - 7.37 (m, 2H), 7.41 - 7.48 (m, 2H), 7.50 (d, 1H), 7.90 (dd, 1H), 8.21 (d, 1H), 8.78 (t, 1H), 10.73 (s, 1H).

Example 16

2-(2-Chlorophenyl)-*N*-{4-[(4,4-difluoropiperidin-1-yl)carbonyl]-3-sulfamoylphenyl}acetamide



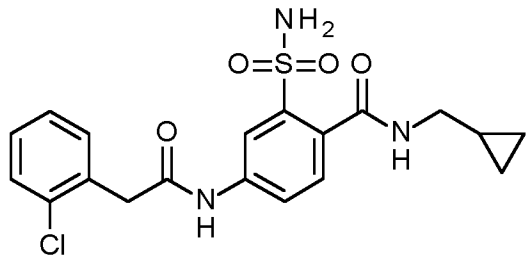
According to general procedure GP1.3 methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (200 mg, 0.52 mmol) and 4,4-difluoropiperidine (94.9 mg, 0.78 mmol) were converted in presence of DABAL-Me_3 (402 mg, 1.57 mmol) to the title compound which was purified at the end by preparative HPLC (Chromatorex C-18 10µm, 125x30mm, acetonitrile/water + 0.1% formic acid) (7 mg, 0.0148 mmol, 3 % yield, 96 % purity).

LC-MS (Method A): Rt = 1.08 min; MS (ESIpos): m/z = 472 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 1.90 - 2.17 (m, 4H), 3.21 - 3.33 (m, 2H), 3.45 - 3.56 (m, 1H), 3.89 (s, 2H), 3.91 - 4.00 (m, 1H), 7.04 (s, 2H), 7.27 – 7.37 (m, 2H), 7.42 - 7.49 (m, 3H), 7.85 - 7.90 (m, 1H), 8.26 (s, 1H), 10.70 - 10.75 (m, 1H).

Example 17

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-(cyclopropylmethyl)-2-sulfamoylbenzamide



Bis(trimethylaluminum)-1,4-diazabicyclo[2.2.2]octane (DABAL-Me_3) (151 mg, 0.58 mmol) and 1-cyclopropylmethanamine (41.8 mg, 0.58 mmol) were dissolved in tetrahydrofuran (3 mL) and stirred under nitrogen atmosphere for one hour at 40°C. Afterwards methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (150 mg, 0.39 mmol) was added and the reaction mixture was irradiated in the microwave for 15min at 130°C.

As the reaction was incomplete bis(trimethylaluminum)-1,4-diazabicyclo[2.2.2]octane (DABAL-Me_3) (151 mg, 0.58 mmol) and 1-cyclopropylmethanamine (41.8 mg, 0.58 mmol)

were dissolved again in tetrahydrofuran (3 mL) and stirred under nitrogen atmosphere for one hour at 40°C. The reaction mixture from the first microwave irradiation was added and the reaction mixture was irradiated again in the microwave for 15min at 130°C.

The reaction mixture was quenched dropwise with 2N-HCl and extracted with ethyl acetate. The combined organic phases were washed with brine and dried over a Whatman filter prior to being concentrated in vacuo.

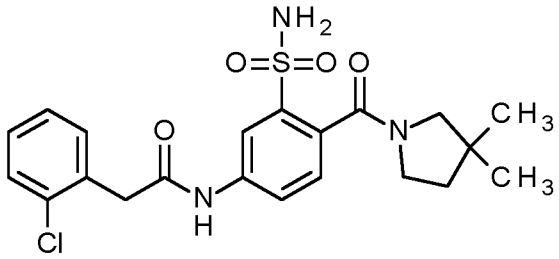
Purification by preparative HPLC (Chromatorex C-18 10µm, 125x30mm, acetonitrile/water + 0.1% formic acid) led to the title compound (4.4 mg, 0.0104 mmol, 3 % yield, 95 % purity).

LC-MS (Method A): Rt = 1.02 min; MS (ESIpos): m/z = 422 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 0.20 - 0.26 (m, 2H), 0.38 - 0.45 (m, 2H), 0.93 - 1.05 (m, 1H), 3.12 (t, 2H), 3.87 (s, 2H), 7.18 (s, 2H), 7.27 - 7.35 (m, 2H), 7.38 - 7.47 (m, 2H), 7.51 (d, 1H), 7.89 (dd, 1H), 8.20 (d, 1H), 8.76 (t, 1H), 10.71 (s, 1H).

Example 18

2-(2-Chlorophenyl)-*N*-{4-[(3,3-dimethylpyrrolidin-1-yl)carbonyl]-3-sulfamoylphenyl}acetamide



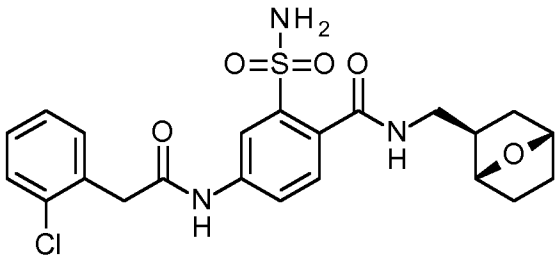
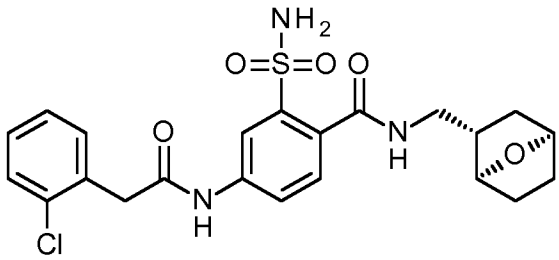
According to general procedure GP1.1 methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (200 mg, 0.52 mmol) and 3,3-dimethylpyrrolidine (77.7 mg, 0.78 mmol) were converted in presence of DABAL-Me_3 (402 mg, 1.57 mmol) to the title compound which was purified at the end by preparative HPLC (Waters XBrigde C18 5µ 100x30mm, acetonitrile/water + 0.2% aqueous ammonia (32%)) (17 mg, 0.0378 mmol, 7 % yield, 98 % purity).

LC-MS (Method B): Rt = 1.13 min; MS (ESIpos): m/z = 450 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 0.98 (s, 3.5H), 1.09 (s, 2.5H), 1.60 - 1.73 (m, 2H), 2.88 - 2.98 (m, 1H), 3.20 - 3.28 (m, 2H), 3.50 - 3.56 (m, 1H), 3.88 (s, 2H), 6.99 (s, 2H), 7.29 - 7.37 (m, 2H), 7.42 - 7.52 (m, 3H), 7.87 (dd, 1H), 8.20 - 8.23 (m, 1H), 10.71 (s, 1H).

Example 19

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-[(1*R*,2*R*,4*S*)-7-oxabicyclo[2.2.1]hept-2-ylmethyl]-2-sulfamoylbenzamide and 4-{[(2-Chlorophenyl)acetyl]amino}-*N*-[(1*S*,2*S*,4*R*)-7-oxabicyclo[2.2.1]hept-2-ylmethyl]-2-sulfamoylbenzamide


and


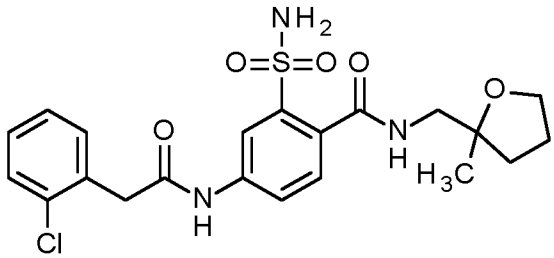
According to general procedure GP1.1 methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (200 mg, 0.52 mmol) and rel-1-[(1*R*,4*S*)-7-oxabicyclo[2.2.1]hept-2-yl]methanamine (99.7 mg, 0.78 mmol) were converted in presence of DABAL-Me_3 (402 mg, 1.57 mmol) to the title compound which was purified at the end by preparative HPLC (Waters XBrigde C18 5µ 100x30mm, acetonitrile/water + 0.2% aqueous ammonia (32%)) (18 mg, 0.0377 mmol, 7 % yield, 98 % purity).

LC-MS (Method B): Rt = 0.90 min; MS (ESIpos): m/z = 478 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 0.96 - 1.03 (m, 1H), 1.36 - 1.50 (m, 2H), 1.52 - 1.62 (m, 1H), 1.77 - 1.90 (m, 2H), 2.23 - 2.33 (m, 1H), 3.17 - 3.27 (m, 1H), 3.30 - 3.37 (m, 1H), 3.89 (s, 2H), 4.41 - 4.49 (m, 2H), 7.18 (s, 2H), 7.29 - 7.36 (m, 2H), 7.42 - 7.49 (m, 2H), 7.51 (s, 1H), 7.91 (dd, 1H), 8.21 (d, 1H), 8.76 (t, 1H), 10.72 (s, 1H).

Example 20

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-[(2-methyltetrahydrofuran-2-yl)methyl]-2-sulfamoylbenzamide



According to general procedure GP1.1 methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (200 mg, 0.52 mmol) and 1-(2-methyltetrahydrofuran-2-yl)methanamine (90.3 mg, 0.78 mmol) were converted in presence of DABAL-Me_3 (402

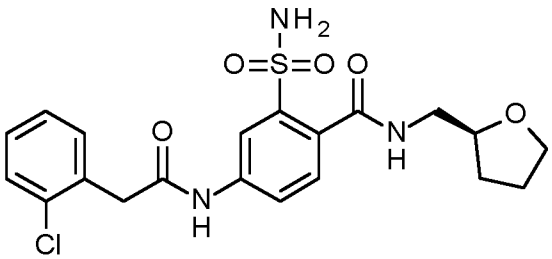
mg, 1.57 mmol) to the title compound which was purified at the end by preparative HPLC (Waters XBrigde C18 5µ 100x30mm, acetonitrile/water + 0.2% aqueous ammonia (32%)) (23 mg, 0.0494 mmol, 9 % yield, 98 % purity).

LC-MS (Method B): Rt = 0.91 min; MS (ESIpos): m/z = 466 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 1.18 (s, 3H), 1.52 - 1.60 (m, 1H), 1.83 - 2.00 (m, 3H), 3.22 - 3.33 (m, 2H), 3.70 - 3.79 (m, 2H), 3.89 (s, 2H), 7.20 (s, 2H), 7.30 - 7.36 (m, 2H), 7.42 - 7.48 (m, 2H), 7.52 (d, 1H), 7.90 (dd, 1H), 8.22 (d, 1H), 8.71 (t, 1H), 10.72 (s, 1H).

Example 21

4-{[(2-Chlorophenyl)acetyl]amino}-2-sulfamoyl-*N*-[(2*S*)-tetrahydrofuran-2-ylmethyl]benzamide



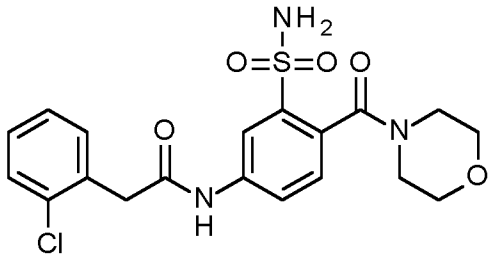
According to general procedure GP1.3 methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (200 mg, 0.52 mmol) and 1-[(2*S*)-tetrahydrofuran-2-yl]methanamine (79.3 mg, 0.78 mmol) were converted in presence of DABAL-Me_3 (402 mg, 1.57 mmol) to the title compound which was purified at the end by preparative HPLC (Chromatorex C-18 10µm, 125x30mm, acetonitrile/water + 0.1% aqueous ammonia (32%)) (6.2 mg, 0.0137 mmol, 3 % yield, 98 % purity).

LC-MS (Method B): Rt = 0.87 min; MS (ESIpos): m/z = 452 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 1.58 - 1.68 (m, 1H), 1.74 - 1.98 (m, 3H), 3.22 - 3.34 (m, 2H), 3.60 - 3.67 (m, 1H), 3.74 - 3.82 (m, 1H), 3.89 (s, 2H), 3.92 - 4.00 (m, 1H), 7.20 (s, 2H), 7.30 - 7.36 (m, 2H), 7.42 - 7.48 (m, 2H), 7.51 (d, 1H), 7.90 (dd, 1H), 8.21 (d, 1H), 8.73 (t, 1H), 10.73 (s, 1H).

Example 22

2-(2-Chlorophenyl)-*N*-[4-(morpholin-4-ylcarbonyl)-3-sulfamoylphenyl]acetamide



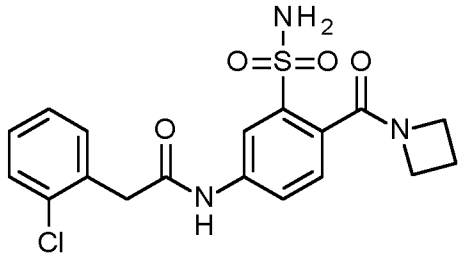
According to general procedure GP1.3 methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (200 mg, 0.52 mmol) and morpholine (68.3 mg, 0.78 mmol) were converted in presence of DABAL-Me_3 (402 mg, 1.57 mmol) to the title compound which was purified at the end by preparative HPLC (Chromatorex C-18 10µm, 125x30mm, acetonitrile/water + 0.1% aqueous ammonia (32%)) followed by another preparative HPLC (Chromatorex C-18 10µm, 125x30mm, acetonitrile/water + 0.1% aqueous ammonia (32%)) (18 mg, 0.0411 mmol, 8 % yield, 97 % purity).

LC-MS (Method A): Rt = 0.90 min; MS (ESIpos): m/z = 438 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 3.07 - 3.15 (m, 1H), 3.19 - 3.27 (m, 1H), 3.47 - 3.74 (m, 6H), 3.89 (s, 2H), 7.01 (s, 2H), 7.29 - 7.36 (m, 2H), 7.40 (d, 1H), 7.42 - 7.49 (m, 2H), 7.87 (dd, 1H), 8.25 (d, 1H), 10.72 (s, 1H).

Example 23

***N*-[4-(Azetidin-1-ylcarbonyl)-3-sulfamoylphenyl]-2-(2-chlorophenyl)acetamide**



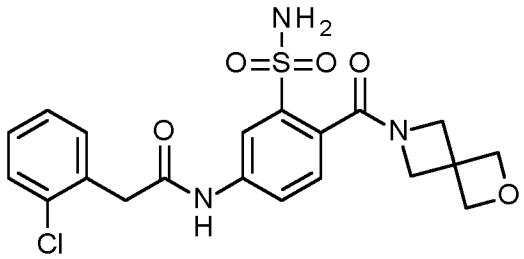
According to general procedure GP1.4 methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (200 mg, 0.52 mmol), azetidine hydrochloride (73.3 mg, 0.78 mmol) and *N*,*N*-diisopropylethylamine (203 mg, 1.57 mmol) were converted in presence of DABAL-Me_3 (402 mg, 1.57 mmol) to the title compound which was purified at the end by preparative HPLC (Chromatorex C-18 10µm, 125x30mm, acetonitrile/water + 0.1% aqueous ammonia (32%)) (56 mg, 0.137 mmol, 26 % yield, 97 % purity).

LC-MS (Method A): Rt = 0.93 min; MS (ESIpos): m/z = 408 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 2.18 - 2.28 (p, 2H), 3.88 (s, 2H), 3.91 (t, 2H), 4.03 (t, 2H), 7.10 (s, 2H), 7.29 - 7.36 (m, 2H), 7.41 - 7.51 (m, 3H), 7.87 (dd, 1H), 8.23 (d, 1H), 10.72 (s, 1H).

Example 24

2-(2-Chlorophenyl)-*N*-[4-(2-oxa-6-azaspiro[3.3]hept-6-ylcarbonyl)-3-sulfamoylphenyl]acetamide



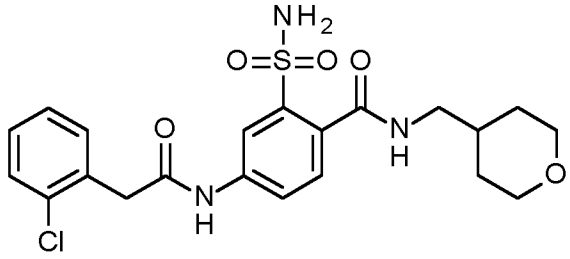
According to general procedure GP1.3 methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (200 mg, 0.52 mmol) and 2-oxa-6-azaspiro[3.3]heptane (77.7 mg, 0.78 mmol) were converted in presence of DABAL-Me_3 (402 mg, 1.57 mmol) to the title compound which was purified at the end by preparative HPLC (Chromatorex C-18 10µm, 125x30mm, acetonitrile/water + 0.1% aqueous ammonia (32%)) (3 mg, 0.00667 mmol, 1 % yield, 95 % purity).

LC-MS (Method B): Rt = 0.81 min; MS (ESIpos): m/z = 450 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 3.89 (s, 2H), 4.07 (s, 2H), 4.21 (s, 2H), 4.62 - 4.71 (m, 4H), 7.07 (s, 2H), 7.30 - 7.36 (m, 2H), 7.45 (s, 3H), 7.87 (dd, 1H), 8.23 (d, 1H), 10.73 (s, 1H).

Example 25

4-{[(2-Chlorophenyl)acetyl]amino}-2-sulfamoyl-*N*-(tetrahydro-2*H*-pyran-4-ylmethyl)benzamide



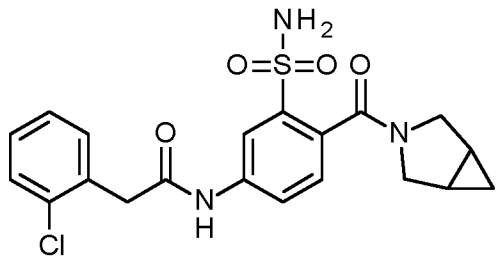
1,4-Diazabicyclo[2.2.2]octane (117 mg, 1.04 mmol) and 1-(tetrahydro-2*H*-pyran-4-yl)methanamine (90.3 mg, 0.78 mmol) were dissolved under nitrogen atmosphere in tetrahydrofuran (20 mL) and stirred for 30 min. Afterwards methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (200 mg, 0.52 mmol) and bis(trimethylaluminum)-1,4-diazabicyclo[2.2.2]octane (DABAL-Me_3) (402 mg, 1.57 mmol) were added. The reaction mixture was irradiated for 30 min at 130°C in the microwave followed by quenching with 1N-HCl and extraction with ethyl acetate. The organic phase was washed with brine and dried over a Whatmanfilter prior to being concentrated in vacuo. Purification by preparative HPLC (Waters XBrigde C18 5µ 100x30mm, acetonitrile/water + 0.1% formic acid) followed by another preparative HPLC (Waters XBrigde C18 5µ 100x30mm, acetonitrile/water + 0.2% aqueous ammonia (32%)) led to the title compound (12.7 mg, 0.0273 mmol, 5 % yield, 95 % purity).

LC-MS (Method B): Rt = 0.88 min; MS (ESIpos): m/z = 466 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 1.13 - 1.26 (m, 2H), 1.60 - 1.69 (m, 2H), 1.73 - 1.86 (m, 1H), 3.12 (t, 2H), 3.27 (td, 2H), 3.82 - 3.90 (m, 2H), 3.89 (s, 2H), 7.20 (s, 2H), 7.30 - 7.36 (m, 2H), 7.41 - 7.49 (m, 2H), 7.54 (d, 1H), 7.90 (dd, 1H), 8.22 (d, 1H), 8.76 (t, 1H), 10.72 (s, 1H).

Example 26

***N*-{4-[(1R,5S)-3-Azabicyclo[3.1.0]hex-3-ylcarbonyl]-3-sulfamoylphenyl}-2-(2-chlorophenyl)acetamide**



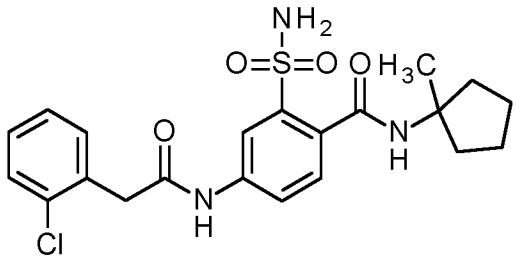
According to general procedure GP1.3 methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (200 mg, 0.52 mmol) and 3-azabicyclo[3.1.0]hexane (93.7 mg, 0.78 mmol) were converted in presence of DABAL-Me_3 (402 mg, 1.57 mmol) to the title compound which was purified at the end by preparative HPLC (Chromatorex C-18 10µm, 125x30mm, acetonitrile/water + 0.1% formic acid) (1.5 mg, 0.00346 mmol, 1 % yield, 96 % purity).

LC-MS (Method A): Rt = 1.03 min; MS (ESIpos): m/z = 434 $(M+H)^+$

^{1}H-NMR (600MHz, DMSO-d_6) δ [ppm]: 0.29 - 0.34 (m, 1H), 0.59 - 0.65 (m, 1H), 1.47 - 1.53 (m, 1H), 1.56 - 1.62 (m, 1H), 3.04 - 3.12 (m, 1H), 3.36 - 3.42 (m, 1H), 3.44 - 3.53 (m, 1H), 3.87 – 3.92 (m, 3H), 6.97 (s, 2H), 7.31 - 7.37 (m, 2H), 7.42 - 7.49 (m, 3H), 7.87 (dd, 1H), 8.22 (d, 1H), 10.69 (s, 1H).

Example 27

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-(1-methylcyclopentyl)-2-sulfamoylbenzamide



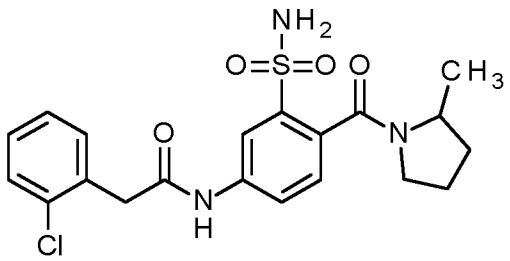
According to general procedure GP1.3 methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (100 mg, 0.26 mmol) and 1-methylcyclopentanamine (38.8 mg, 0.39 mmol) were converted in presence of DABAL-Me_3 (201 mg, 0.78 mmol) to the title compound which was purified at the end by preparative HPLC (Chromatorex C-18 10µm, 125x30mm, acetonitrile/water + 0.1% formic acid) (1.3 mg, 0.00289 mmol, 1 % yield, 97 % purity).

LC-MS (Method A): Rt = 1.14 min; MS (ESIpos): m/z = 450 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 1.42 (s, 3H), 1.47 - 1.76 (m, 6H), 2.10 - 2.20 (m, 2H), 3.88 (s, 2H), 7.13 (s, 2H), 7.29 - 7.36 (m, 2H), 7.40 - 7.49 (m, 3H), 7.87 (dd, 1H), 8.18 (d, 1H), 8.35 (s, 1H), 10.69 (s, 1H).

Example 28

2-(2-Chlorophenyl)-*N*-{4-[(2-methylpyrrolidin-1-yl)carbonyl]-3-sulfamoylphenyl}acetamide



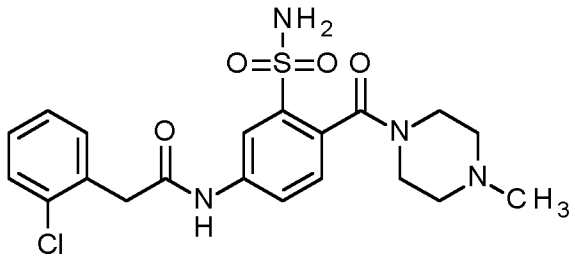
According to general procedure GP1.3 methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (200 mg, 0.52 mmol) and 2-methylpyrrolidine (66.7 mg, 0.78 mmol) were converted in presence of DABAL-Me_3 (402 mg, 1.57 mmol) to the title compound which was purified at the end by preparative HPLC (Chromatorex C-18 10µm, 125x30mm, acetonitrile/water + 0.1% formic acid) (2.2 mg, 0.00509 mmol, 1 % yield, 98 % purity).

LC-MS (Method A): Rt = 1.05 min; MS (ESIpos): m/z = 436 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 1.24 (d, 3H), 1.51 - 2.10 (m, 4H), 3.05 - 3.60 (m, 2H), 3.86 - 4.18 (m, 3H), 6.95 - 7.02 (m, 2H), 7.29 – 7.36 (m, 2H), 7.41 - 7.49 (m, 3H), 7.85 - 7.91 (m, 1H), 8.18 - 8.25 (m, 1H), 10.68 - 10.74 (m, 1H).

Example 29

2-(2-Chlorophenyl)-*N*-{4-[(4-methylpiperazin-1-yl)carbonyl]-3-sulfamoylphenyl}acetamide



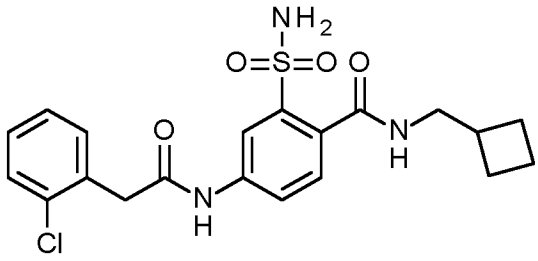
According to general procedure GP1.3 methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (2.20 g, 5.74 mmol) and 1-methylpiperazine (862 mg, 8.62 mmol) were converted in presence of DABAL-Me_3 (4.42 g, 17.2 mmol) to the title compound which was purified at the end by preparative HPLC (Chromatorex C-18 10µm, 125x30mm, acetonitrile/water + 0.1% aqueous ammonia (32%)) (49 mg, 0.109 mmol, 2 % yield, 99 % purity).

LC-MS (Method B): Rt = 0.83 min; MS (ESIpos): m/z = 451 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 2.18 (s, 3H), 2.22 - 2.29 (m, 2H), 2.33 - 2.40 (m, 2H), 3.06 - 3.26 (m, 2H), 3.51 - 3.70 (m, 2H), 3.88 (s, 2H), 6.98 (s, 2H), 7.29 - 7.35 (m, 2H), 7.37 (d, 1H), 7.42 - 7.49 (m, 2H), 7.86 (dd, 1H), 8.23 (d, 1H), 10.71 (s, 1H).

Example 30

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-(cyclobutylmethyl)-2-sulfamoylbenzamide



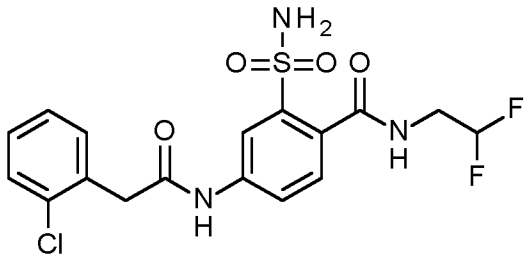
According to general procedure GP1.1 methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (77 mg, 0.20 mmol) and 1-cyclobutylmethanamine hydrochloride (36.7 mg, 0.30 mmol) were converted in presence of DABAL-Me_3 (155 mg, 0.60 mmol) to the title compound which was purified at the end by preparative HPLC (Chromatorex C-18 10µm, 125x30mm, acetonitrile/water + 0.1% aqueous ammonia (32%)) (13 mg, 0.0298 mmol, 15 % yield, 97 % purity).

LC-MS (Method B): Rt = 1.03 min; MS (ESIpos): m/z = 436 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 1.68 - 1.88 (m, 4H), 1.95 - 2.05 (m, 2H), one signal under DMSO peak, 3.26 (t, 2H), 3.88 (s, 2H), 7.21 (s, 2H), 7.30 - 7.36 (m, 2H), 7.42 - 7.52 (m, 3H), 7.90 (dd, 1H), 8.21 (d, 1H), 8.71 (t, 1H), 10.72 (s, 1H).

Example 31

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-(2,2-difluoroethyl)-2-sulfamoylbenzamide



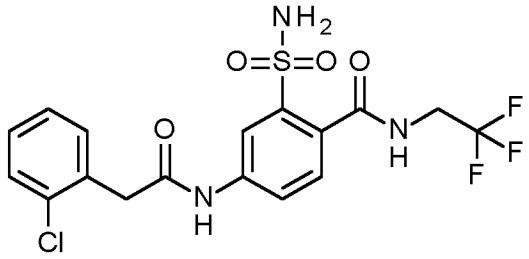
According to general procedure GP1.3 methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (150 mg, 0.39 mmol) and 2,2-difluoroethanamine (47.6 mg, 0.59 mmol) were converted in presence of DABAL-Me_3 (301 mg, 1.18 mmol) to the title compound which was purified at the end by preparative HPLC (Waters XBrigde C18 5µ 100x30mm, acetonitrile/water + 0.1% formic acid) (12 mg, 0.0278 mmol, 7 % yield, 95 % purity).

LC-MS (Method A): Rt = 0.94 min;MS (ESIpos): m/z = 432 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 3.59 - 3.72 (m, 2H), 3.89 (s, 2H), 6.09 (tt, 1H), 7.14 (s, 2H), 7.29 - 7.37 (m, 2H), 7.42 - 7.49 (m, 2H), 7.53 (d, 1H), 7.92 (dd, 1H), 8.24 (d, 1H), 9.12 (t, 1H), 10.75 (s, 1H).

Example 32

4-{[(2-Chlorophenyl)acetyl]amino}-2-sulfamoyl-*N*-(2,2,2-trifluoroethyl)benzamide



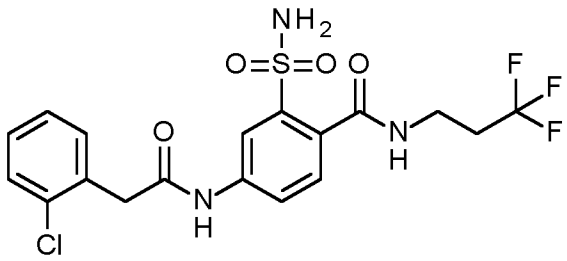
According to general procedure GP1.3 methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (150 mg, 0.39 mmol) and 2,2,2-trifluoroethanamine (58.2 mg, 0.59 mmol) were converted in presence of DABAL-Me_3 (301 mg, 1.18 mmol) to the title compound which was purified at the end by preparative HPLC (Waters XBrigde C18 5µ 100x30mm, acetonitrile/water + 0.1% formic acid) (4 mg, 0.00889 mmol, 2 % yield, 97 % purity).

LC-MS (Method A): Rt = 1.00 min; MS (ESIpos): m/z = 450 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 3.90 (s, 2H), 4.03 - 4.13 (m, 2H), 7.12 (s, 2H), 7.29 - 7.37 (m, 2H), 7.41 - 7.49 (m, 2H), 7.53 (d, 1H), 7.93 (dd, 1H), 8.26 (d, 1H), 9.37 (t, 1H), 10.77 (s, 1H).

Example 33

4-{[(2-Chlorophenyl)acetyl]amino}-2-sulfamoyl-*N*-(3,3,3-trifluoropropyl)benzamide



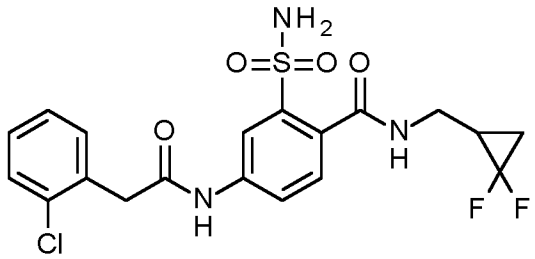
According to general procedure GP1.3 methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (200 mg, 0.52 mmol) and 3,3,3-trifluoropropan-1-amine (88.6 mg, 0.78 mmol) were converted in presence of DABAL-Me_3 (402 mg, 1.57 mmol) to the title compound which was purified at the end by preparative HPLC (Waters XBrigde C18 5µ 100x30mm, acetonitrile/water + 0.2% aqueous ammonia (32%)) (36 mg, 0.0776 mmol, 15 % yield, 97 % purity).

LC-MS (Method B): Rt = 0.96 min; MS (ESIpos): m/z = 464 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 2.50 - 2.60 (m, 2H, overlapped partly by solvent peak), 3.45 (q, 2H), 3.89 (s, 2H), 7.18 (s, 2H), 7.29 - 7.36 (m, 2H), 7.42 - 7.48 (m, 2H), 7.50 (d, 1H), 7.92 (dd, 1H), 8.22 (d, 1H), 8.92 (t, 1H), 10.74 (s, 1H).

Example 34

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-[(2,2-difluorocyclopropyl)methyl]-2-sulfamoylbenzamide



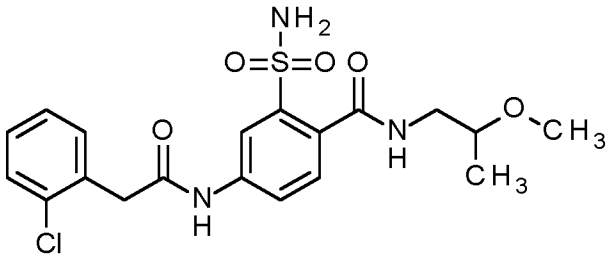
According to general procedure GP1.5 methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (200 mg, 0.52 mmol) and 1-(2,2-difluorocyclopropyl)methanamine hydrochloride (113 mg, 0.78 mmol) were converted in presence of DABAL-Me_3 (670 mg, 2.61 mmol) to the title compound which was purified at the end by preparative HPLC (Chromatorex C-18 10µm, 125x30mm, acetonitrile/water + 0.1% formic acid) (1.3 mg, 0.00284 mmol, 1 % yield, 96 % purity).

LC-MS (Method A): Rt = 1.01 min; MS (ESIpos): m/z = 458 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 1.28 - 1.38 (m, 1H), 1.53 - 1.66 (m, 1H), 1.90 - 2.04 (m, 1H), CH_2 probably below water signal, 3.89 (s, 2H), 7.18 (s, 2H), 7.30 - 7.36 (m, 2H), 7.42 - 7.49 (m, 2H), 7.53 (d, 1H), 7.92 (dd, 1H), 8.23 (d, 1H), 8.99 (t, 1H), 10.74 (s, 1H).

Example 35

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-(2-methoxypropyl)-2-sulfamoylbenzamide



According to general procedure GP1.3 methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (200 mg, 0.52 mmol) and 2-methoxypropan-1-amine (69.9 mg, 0.78

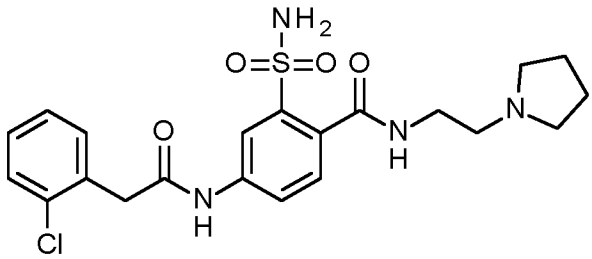
mmol) were converted in presence of DABAL-Me_3 (402 mg, 1.57 mmol) to the title compound which was purified at the end by preparative HPLC (Waters XBrigde C18 5µ 100x30mm, acetonitrile/water + 0.2% aqueous ammonia (32%)) (7 mg, 0.0159 mmol, 3 % yield, 97 % purity).

LC-MS (Method B): Rt = 0.86 min; MS (ESIpos): m/z = 440 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 1.11 (d, 3H), 3.21 - 3.27 (m, 2H), 3.27 (s, 3H), 3.45 - 3.51 (m, 1H), 3.89 (s, 2H), 7.19 (s, 2H), 7.30 - 7.36 (m, 2H), 7.42 - 7.48 (m, 2H), 7.52 (d, 1H), 7.90 (dd, 1H), 8.22 (d, 1H), 8.76 (t, 1H), 10.72 (s, 1H).

Example 36

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-[2-(pyrrolidin-1-yl)ethyl]-2-sulfamoylbenzamide



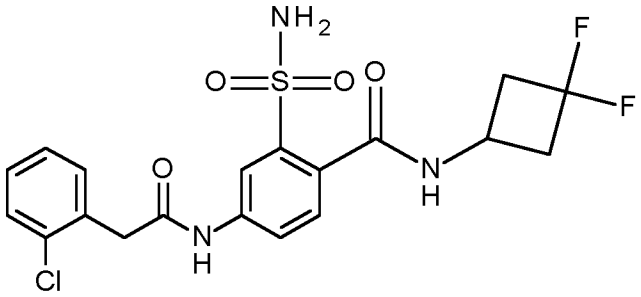
According to general procedure GP1.5 methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (150 mg, 0.39 mmol) and 2-(pyrrolidin-1-yl)ethanamine (67.1 mg, 0.59 mmol) were converted in presence of DABAL-Me_3 (502 mg, 1.96 mmol) to the title compound which was purified at the end by preparative HPLC (Waters XBrigde C18 5µ 100x30mm, acetonitrile/water + 0.1% formic acid) (2 mg, 0.00430 mmol, 1 % yield, 95 % purity).

LC-MS (Method A): Rt = 0.74 min; MS (ESIpos): m/z = 465 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 1.67 - 1.74 (m, 4H), 2.53 - 2.60 (m, 4H), 2.60 - 2.66 (m, 2H), CH_2 probably below water or solvent peak, 3.88 (s, 2H), 7.30 - 7.36 (m, 2H), 7.42 - 7.48 (m, 2H), 7.49 (s, 1H), 7.65 (s, 2H), 7.88 (dd, 1H), 8.21 (d, 1H), 8.48 (t, 1H), 10.69 (s, 1H).

Example 37

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-(3,3-difluorocyclobutyl)-2-sulfamoylbenzamide



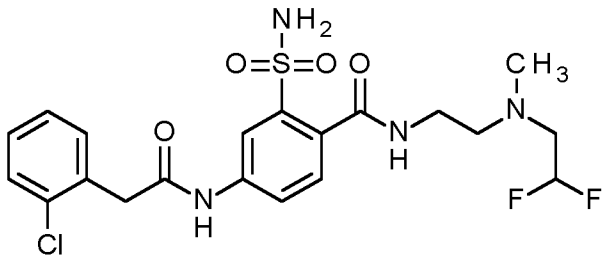
According to general procedure GP1.5 methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (150 mg, 0.39 mmol) and 3,3-difluorocyclobutanamine hydrochloride (84.4 mg, 0.59 mmol) were converted in presence of DABAL-Me_3 (502 mg, 1.96 mmol) to the title compound which was purified at the end by preparative HPLC (Waters XBrigde C18 5µ 100x30mm, acetonitrile/water + 0.1% formic acid) (2 mg, 0.00430 mmol, 1 % yield, 95 % purity).

LC-MS (Method A): Rt = 1.01 min; MS (ESIpos): m/z = 458 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 2.64 - 2.78 (m, 2H), 2.90 - 3.04 (m, 2H), 3.89 (s, 2H), 4.12 - 4.22 (m, 1H), 7.15 (s, 2H), 7.29 - 7.37 (m, 2H), 7.42 – 7.48 (m, 2H), 7.58 (d, 1H), 7.92 (dd, 1H), 8.22 (d, 1H), 9.14 (d, 1H), 10.74 (s, 1H).

Example 38

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-{2-[(2,2-difluoroethyl)(methyl)amino]ethyl}-2-sulfamoylbenzamide



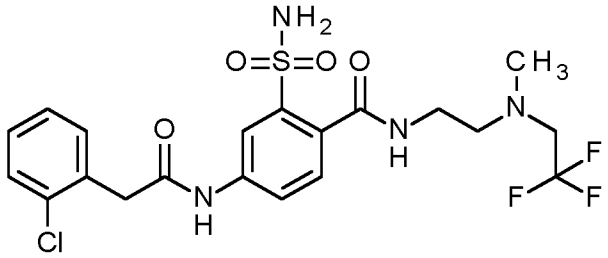
According to general procedure GP1.3 methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (150 mg, 0.39 mmol) and *N*-(2,2-difluoroethyl)-*N*-methylethane-1,2-diamine (81.2 mg, 0.59 mmol) were converted in presence of DABAL-Me_3 (301 mg, 1.18 mmol) to the title compound which was purified at the end purified by preparative HPLC (Chromatorex C-18 10µm, 125x30mm, acetonitrile/water + 0.1% aqueous ammonia (32%)) (3 mg, 0.00614 mmol, 1 % yield, 97 % purity).

LC-MS (Method B): Rt = 0.98 min; MS (ESIpos): m/z = 489 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 2.34 (s, 3H), 2.64 (t, 2H), 2.81 (td, 2H), two proton signals overlapped by water signal, 3.89 (s, 2H), 6.09 (tt, 1H), 7.25 (s, 2H), 7.29 - 7.37 (m, 2H), 7.42 - 7.48 (m, 2H), 7.51 (d, 1H), 7.91 (dd, 1H), 8.21 (d, 1H), 8.63 (t, 1H), 10.72 (s, 1H).

Example 39

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-{2-[methyl(2,2,2-trifluoroethyl)amino]ethyl}-2-sulfamoylbenzamide



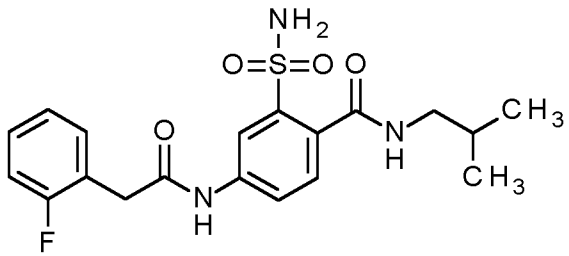
According to general procedure GP1.3 methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate (150 mg, 0.39 mmol) and *N*-methyl-*N*-(2,2,2-trifluoroethyl)ethane-1,2-diamine (91.8 mg, 0.59 mmol) were converted in presence of DABAL-Me_3 (301 mg, 1.18 mmol) to the title compound which was purified at the end purified by preparative HPLC (Waters XBrigde C18 5µ 100x30mm, acetonitrile/water + 0.1% formic acid) (22.9 mg, 0.0452 mmol, 12 % yield, 99 % purity).

LC-MS (Method A): Rt = 1.07 min; MS (ESIpos): m/z = 507 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 2.42 (s, 3H), 2.74 (t, 2H), 3.20 - 3.32 (m, 4H), 3.88 (s, 2H), 7.21 (s, 2H), 7.29 - 7.36 (m, 2H), 7.41 - 7.48 (m, 2H), 7.50 (d, 1H), 7.90 (dd, 1H), 8.20 (d, 1H), 8.66 (t, 1H), 10.72 (s, 1H).

Example 40

4-{[(2-Fluorophenyl)acetyl]amino}-*N*-isobutyl-2-sulfamoylbenzamide



Methyl 4-amino-2-sulfamoylbenzoate (2.00 g, 8.69 mmol) and 2-methylpropan-1-amine (953 mg, 13.0 mmol) were dissolved under nitrogen atmosphere in tetrahydrofuran (120

mL) and bis(trimethylaluminum)-1,4-diazabicyclo[2.2.2]octane (DABAL-Me3) (6.68 g, 26.1 mmol) was added slowly and portionwise. Then, it was stirred overnight at room temperature. The reaction mixture was quenched under ice-cooling with aqueous ammonium chloride solution until pH 7 was reached. It was extracted several times with ethyl acetate. The organic phase was washed with brine solution and dried over sodium sulfate. The filtrate was concentrated in vacuo and redissolved in DMF (8 mL).

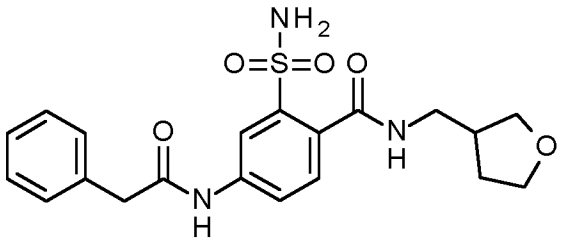
(2-Fluorophenyl)acetic acid (107 mg, 0.691 mmol), 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (T3P, 586 mg, 0.921 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (179 mg, 1.38 mmol) were added and it was stirred at 60°C for 2h, followed by stirring at room temperature overnight. Then, 0.1 M sodium bicarbonate solution (40 mL) was added, followed by stirring for 30 min. The reaction mixture was extracted three times with ethyl acetate. The combined organic phases were washed with brine solution, dried and concentrated in vacuo. Purification by preparative HPLC (Waters XBrigde C18 5µ 100x30mm, acetonitrile/water + 0.1% formic acid) led to the title compound (10.2 mg, 0.0250 mmol, 0.3% yield over two steps, 97% purity).

LC-MS (Method A): Rt = 0.99 min; MS (ESIpos): m/z = 408 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 0.90 (d, 6H), 1.78 - 1.88 (m, 1H), 3.04 (t, 2H), 3.78 (s, 2H), 7.15 - 7.22 (m, 4H), 7.30 - 7.37 (m, 1H), 7.39 (td, 1H), 7.52 (d, 1H), 7.90 (dd, 1H), 8.20 (d, 1H), 8.73 (t, 1H), 10.70 (s, 1H).

Example 41

4-[(Phenylacetyl)amino]-2-sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)benzamide



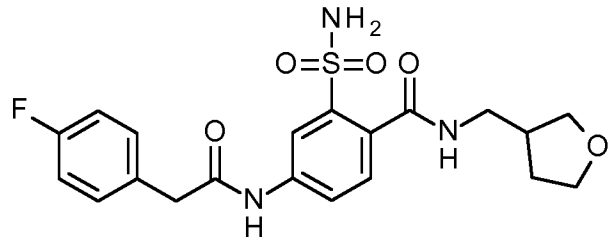
Conversion of crude 4-amino-2-sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)benzamide (60.0 mg, 0.20 mmol) and phenylacetic acid (40.9 mg, 0.30 mmol) according to general procedure GP3.1 followed by preparative HPLC (Waters XBrigde C18 5µ 100x30mm, acetonitrile/water + 0.2% aqueous ammonia (32%)) led to the title compound (9.0 mg, 0.0216 mmol, 11 % yield, 97 % purity).

LC-MS (Method B): Rt = 0.73 min; MS (ESIpos): m/z = 418 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 1.56 - 1.65 (m, 1H), 1.90 - 2.00 (m, 1H), 2.40 - 2.48 (m, 1H), 3.15 - 3.27 (m, 2H), 3.46 (dd, 1H), 3.57 - 3.77 (m, 5H), 7.17 (s, 2H), 7.23 - 7.30 (m, 1H), 7.33 (d, 4H), 7.51 (d, 1H), 7.91 (dd, 1H), 8.20 (d, 1H), 8.81 (t, 1H), 10.65 (s, 1H).

Example 42

4-{[(4-Fluorophenyl)acetyl]amino}-2-sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)benzamide



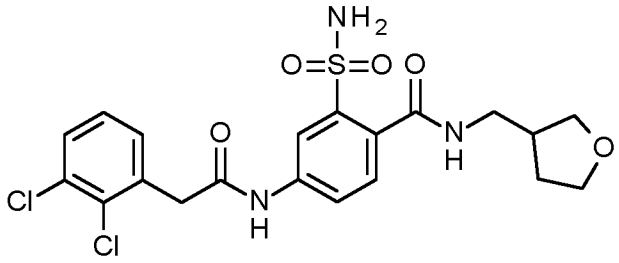
Crude 4-amino-2-sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)benzamide (60 mg, 0.200 mmol), (4-fluorophenyl)acetic acid (46.3 mg, 0.301 mmol), 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (T3P, 586 mg, 0.921 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (179 mg, 1.38 mmol) were dissolved in dimethylformamide (8 mL) and the reaction mixture was stirred at 60°C for 2h, followed by stirring at room temperature overnight. Then, 0.1 M sodium bicarbonate solution (40 mL) was added, followed by stirring for 30 min. The reaction mixture was extracted three times with ethyl acetate. The combined organic phases were washed with brine solution, dried and concentrated in vacuo. Purification by preparative HPLC (Waters XBrigde C18 5µ 100x30mm, acetonitrile/water + 0.1% formic acid) led to the title compound (10.8 mg, 0.0248 mmol, 12% yield, 97% purity).

LC-MS (Method A): Rt = 0.85 min; MS (ESIpos): m/z = 436 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 1.55 - 1.66 (m, 1H), 1.90 - 2.01 (m, 1H), 2.40 - 2.48 (m, 1H), 3.15 - 3.27 (m, 2H), 3.46 (dd, 1H), 3.57 - 3.65 (m, 1H), 3.65 - 3.77 (m, 4H), 7.12 - 7.20 (m, 4H), 7.33 - 7.39 (m, 2H), 7.51 (d, 1H), 7.90 (dd, 1H), 8.19 (d, 1H), 8.81 (t, 1H), 10.64 (s, 1H).

Example 43

4-{[(2,3-Dichlorophenyl)acetyl]amino}-2-sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)benzamide



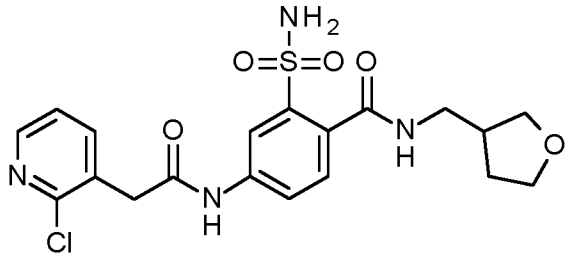
Crude 4-amino-2-sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)benzamide (60 mg, 0.200 mmol), (2,3-dichlorophenyl)acetic acid (61.6 mg, 0.301 mmol), 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (T3P, 586 mg, 0.921 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (179 mg, 1.38 mmol) were dissolved in dimethylformamide (4 mL) and the reaction mixture was stirred at 60°C for 2h, followed by stirring at room temperature overnight. Then, 0.1 M sodium bicarbonate solution (40 mL) was added, followed by stirring for 30 min. The reaction mixture was extracted three times with ethyl acetate. The combined organic phases were washed with brine solution, dried and concentrated in vacuo. Purification by preparative HPLC (Waters XBrigde C18 5µ 100x30mm, acetonitrile/water + 0.2% aqueous ammonia (32%)) led to the title compound (5.5 mg, 0.0113 mmol, 6% yield, 90% purity).

LC-MS (Method B): Rt = 0.91 min; MS (ESIpos): m/z = 486 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 1.55 - 1.65 (m, 1H), 1.90 - 2.01 (m, 1H), 2.40 - 2.48 (m, 1H), 3.17 - 3.25 (m, 2H), 3.47 (dd, 1H), 3.56 - 3.77 (m, 3H), 3.96 (s, 2H), 7.16 (s, 2H), 7.37 (d, 1H), 7.43 (dd, 1H), 7.52 (d, 1H), 7.58 (dd, 1H), 7.89 (dd, 1H), 8.19 (d, 1H), 8.86 (s, 1H), 10.76 (s, 1H).

Example 44

4-{[(2-Chloropyridin-3-yl)acetyl]amino}-2-sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)benzamide



Crude 4-amino-2-sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)benzamide (60 mg, 0.200 mmol), (2-chloropyridin-3-yl)acetic acid (51.6 mg, 0.301 mmol), 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (T3P, 586 mg, 0.921 mmol) and *N*-ethyl-*N*-

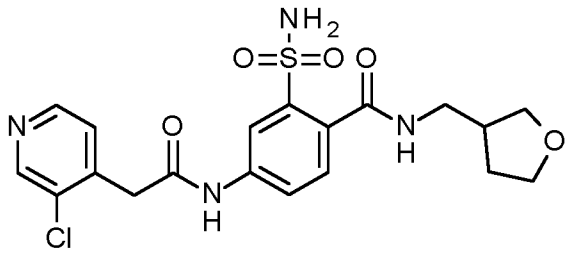
isopropylpropan-2-amine (179 mg, 1.38 mmol) were dissolved in dimethylformamide (4 mL) and the reaction mixture was stirred at 60°C for 2h, followed by stirring at room temperature overnight. Then, 0.1 M sodium bicarbonate solution (40 mL) was added, followed by stirring for 30 min. The reaction mixture was extracted three times with ethyl acetate. The combined organic phases were washed with brine solution, dried and concentrated in vacuo. Purification by preparative HPLC (Waters XBrigde C18 5µ 100x30mm, acetonitrile/water + 0.2% aqueous ammonia (32%)) led to the title compound (10.5 mg, 0.0232 mmol, 12% yield, 98% purity).

LC-MS (Method B): Rt = 0.60 min; MS (ESIpos): m/z = 453 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 1.56 - 1.65 (m, 1H), 1.90 - 2.00 (m, 1H), 2.41 - 2.48 (m, 1H), 3.16 - 3.28 (m, 2H), 3.47 (dd, 1H), 3.58 - 3.65 (m, 1H), 3.67 - 3.77 (m, 2H), 3.92 (s, 2H), 7.19 (s, 2H), 7.44 (dd, 1H), 7.52 (d, 1H), 7.88 (d, 1H), 7.91 (dd, 1H), 8.20 (d, 1H), 8.34 (dd, 1H), 8.82 (t, 1H), 10.77 (s, 1H).

Example 45

4-{[(3-Chloropyridin-4-yl)acetyl]amino}-2-sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)benzamide



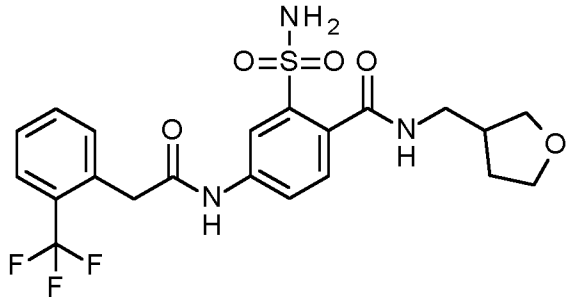
Crude 4-amino-2-sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)benzamide (60 mg, 0.200 mmol), (3-chloropyridin-4-yl)acetic acid (51.6 mg, 0.301 mmol), 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (T3P, 255 mg, 0.400 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (77.7 mg, 0.601 mmol) were dissolved in dimethylformamide (8 mL) and the reaction mixture was stirred at 60°C for 2h, followed by stirring at room temperature overnight. Then, 0.1 M sodium bicarbonate solution (40 mL) was added, followed by stirring for 30 min. The reaction mixture was extracted three times with ethyl acetate. The combined organic phases were washed with brine solution, dried and concentrated in vacuo. Purification by preparative HPLC (Waters XBrigde C18 5µ 100x30mm, acetonitrile/water + 0.1% formic acid) led to the title compound (15 mg, 0.0331 mmol, 17% yield, 97% purity).

LC-MS (Method A): Rt = 0.68 min; MS (ESIpos): m/z = 453 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 1.55 - 1.66 (m, 1H), 1.90 - 2.00 (m, 1H), 2.41 - 2-48 (m, 1H), 3.15 - 3.28 (m, 2H), 3.47 (dd, 1H), 3.58 - 3.65 (m, 1H), 3.66 - 3.77 (m, 2H), 3.95 (s, 2H), 7.19 (s, 2H), 7.50 (d, 1H), 7.53 (d, 1H), 7.89 (d, 1H), 8.19 (d, 1H), 8.50 (d, 1H), 8.62 (s, 1H), 8.82 (t, 1H), 10.81 (s, 1H).

Example 46

2-Sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)-4-({[2-(trifluoromethyl)phenyl]acetyl}amino)benzamide



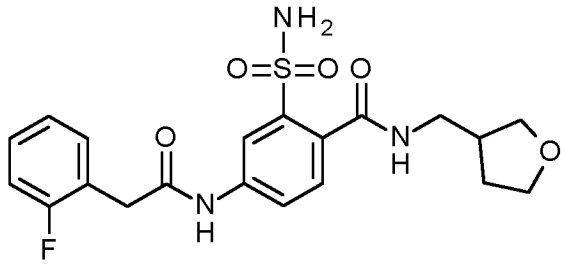
Conversion of crude 4-amino-2-sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)benzamide (60.0 mg, 0.20 mmol) and [2-(trifluoromethyl)phenyl]acetic acid (61.4 mg, 0.30 mmol) according to general procedure GP3.1 followed by preparative HPLC (Waters XBrigde C18 5µ 100x30mm, acetonitrile/water + 0.2% aqueous ammonia (32%)) led to the title compound (7.1 mg, 0.0146 mmol, 7 % yield, 97 % purity).

LC-MS (Method B): Rt = 0.87 min; MS (ESIpos): m/z = 486 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 1.55 - 1.65 (m, 1H), 1.90 - 2.00 (m, 1H), 2.40 - 2.48 (m, 1H), 3.15 - 3.27 (m, 2H), 3.47 (dd, 1H), 3.57 - 3.77 (m, 3H), 3.97 (s, 2H), 7.18 (s, 2H), 7.48 - 7.56 (m, 3H), 7.63 - 7.69 (m, 1H), 7.72 (d, 1H), 7.89 (dd, 1H), 8.19 (d, 1H), 8.81 (t, 1H), 10.70 (s, 1H).

Example 47

4-{[(2-Fluorophenyl)acetyl]amino}-2-sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)benzamide



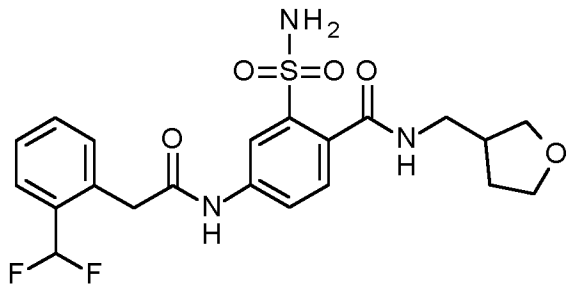
Conversion of crude 4-amino-2-sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)benzamide (60.0 mg, 0.20 mmol) and (2-fluorophenyl)acetic acid (46.3 mg, 0.30 mmol) according to general procedure GP3.1 followed by preparative HPLC (Waters XBridge C18 5µ 100x30mm, acetonitrile/water + 0.2% aqueous ammonia (32%)) led to the title compound (2.5 mg, 0.00574 mmol, 3 % yield, 98 % purity).

LC-MS (Method B): Rt = 0.75 min; MS (ESIpos): m/z = 436 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 1.55 - 1.65 (m, 1H), 1.90 - 2.01 (m, 1H), 2.40 - 2.48 (m, 1H), 3.14 - 3.27 (m, 2H), 3.47 (dd, 1H), 3.58 - 3.65 (m, 1H), 3.67 - 3.76 (m, 2H), 3.77 (s, 2H), 6.98 (s, 2H), 7.15 - 7.22 (m, 2H), 7.30 - 7.36 (m, 1H), 7.36 - 7.42 (m, 1H), 7.52 (d, 1H), 7.89 (dd, 1H), 8.18 (d, 1H), 9.06 (s, 1H), 10.69 (s, 1H).

Example 48

4-({[2-(Difluoromethyl)phenyl]acetyl}amino)-2-sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)benzamide



Conversion of crude 4-amino-2-sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)benzamide (60.0 mg, 0.20 mmol) and [2-(difluoromethyl)phenyl]acetic acid (56.0 mg, 0.30 mmol) according to general procedure GP3.1 followed by preparative HPLC (Waters XBridge C18 5µ 100x30mm, acetonitrile/water + 0.2% aqueous ammonia (32%)) led to the title compound (1.5 mg, 0.00320 mmol, 2 % yield, 99 % purity).

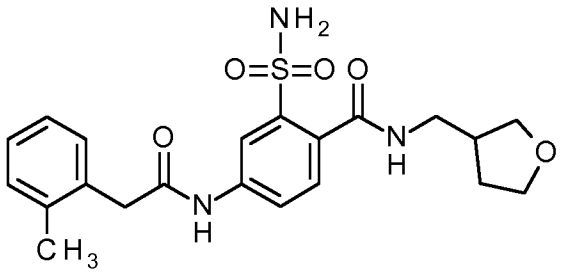
LC-MS (Method B): Rt = 0.83 min; MS (ESIpos): m/z = 468 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 1.56 - 1.65 (m, 1H), 1.90 - 2.00 (m, 1H), 2.41 - 2.49 (m, 1H), 3.15 - 3.27 (m, 2H), 3.47 (dd, 1H), 3.57 - 3.65 (m, 1H), 3.66 - 3.77 (m, 2H), 3.92

(s, 2H), 7.18 (s, 2H), 7.22 (t, 1H), 7.41 - 7.46 (m, 2H), 7.49 - 7.56 (m, 2H), 7.60 (d, 1H), 7.89 (dd, 1H), 8.19 (d, 1H), 8.82 (t, 1H), 10.69 (s, 1H).

Example 49

4-{[(2-Methylphenyl)acetyl]amino}-2-sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)benzamide



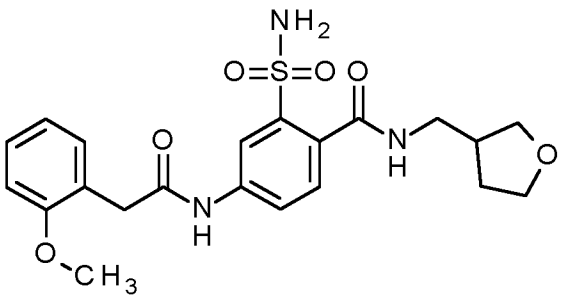
Conversion of crude 4-amino-2-sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)benzamide (60.0 mg, 0.20 mmol) and (2-methylphenyl)acetic acid (45.1 mg, 0.30 mmol) according to general procedure GP3.1 followed by preparative HPLC (Waters XBridge C18 5µ 100x30mm, acetonitrile/water + 0.2% aqueous ammonia (32%)) led to the title compound (16 mg, 0.0371 mmol, 19 % yield, 95 % purity).

LC-MS (Method B): Rt = 0.81 min; MS (ESIpos): m/z = 432 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 1.56 - 1.65 (m, 1H), 1.90 - 2.00 (m, 1H), 2.29 (s, 3H), 2.41 - 2.49 (m, 1H), 3.17 - 3.25 (m, 2H), 3.47 (dd, 1H), 3.58 - 3.77 (m, 5H), 7.13 - 7.26 (m, 6H), 7.51 (d, 1H), 7.92 (dd, 1H), 8.20 (d, 1H), 8.82 (t, 1H), 10.65 (s, 1H).

Example 50

4-{[(2-Methoxyphenyl)acetyl]amino}-2-sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)benzamide



Conversion of crude 4-amino-2-sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)benzamide (60.0 mg, 0.20 mmol) and (2-methoxyphenyl)acetic acid (50.0 mg, 0.30 mmol) according to general procedure GP3.1 followed by preparative HPLC (Waters XBridge C18 5µ

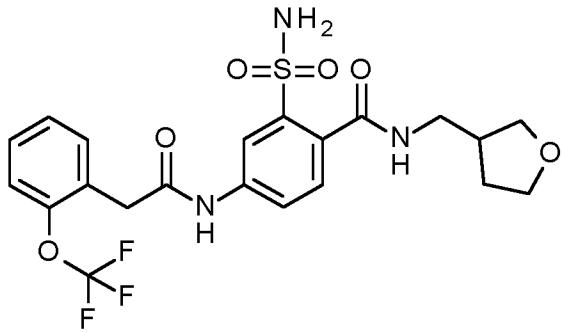
100x30mm, acetonitrile/water + 0.2% aqueous ammonia (32%)) led to the title compound (9 mg, 0.0201 mmol, 10 % yield, 90 % purity).

LC-MS (Method B): Rt = 0.77 min; MS (ESIpos): m/z = 448 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 1.56 - 1.65 (m, 1H), 1.89 - 2.00 (m, 1H), 2.40 - 2.46 (m, 1H), 3.18 - 3.25 (m, 2H), 3.47 (dd, 1H), 3.56 - 3.78 (m, 8H), 6.88 - 6.93 (m, 1H), 6.98 (d, 1H), 7.05 (s, 2H), 7.19 - 7.28 (m, 2H), 7.51 (d, 1H), 7.89 (dd, 1H), 8.20 (d, 1H), 8.98 (s, 1H), 10.54 (s, 1H).

Example 51

2-Sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)-4-({[2-(trifluoromethoxy)phenyl]acetyl}amino)benzamide



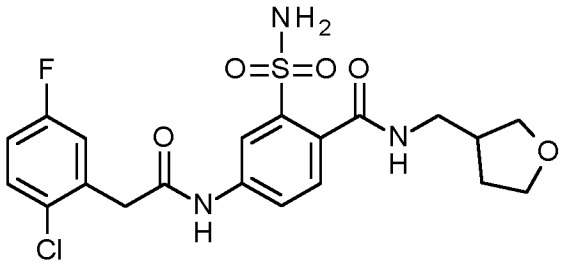
Conversion of crude 4-amino-2-sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)benzamide (60.0 mg, 0.20 mmol) and [2-(trifluoromethoxy)phenyl]acetic acid (66.2 mg, 0.30 mmol) according to general procedure GP3.1 followed by preparative HPLC (Waters XBridge C18 5µ 100x30mm, acetonitrile/water + 0.2% aqueous ammonia (32%)) led to the title compound (16 mg, 0.0319 mmol, 16 % yield, 90 % purity).

LC-MS (Method B): Rt = 0.92 min; MS (ESIpos): m/z = 502 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 1.56 - 1.65 (m, 1H), 1.90 - 2.00 (m, 1H), 2.41 - 2.47 (m, 1H), 3.15 - 3.27 (m, 2H), 3.47 (dd, 1H), 3.57 - 3.65 (m, 1H), 3.66 - 3.77 (m, 2H), 3.83 (s, 2H), 7.19 (s, 2H), 7.33 - 7.46 (m, 3H), 7.47 - 7.54 (m, 2H), 7.90 (dd, 1H), 8.18 (d, 1H), 8.82 (t, 1H), 10.71 (s, 1H).

Example 52

4-{[(2-Chloro-5-fluorophenyl)acetyl]amino}-2-sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)benzamide



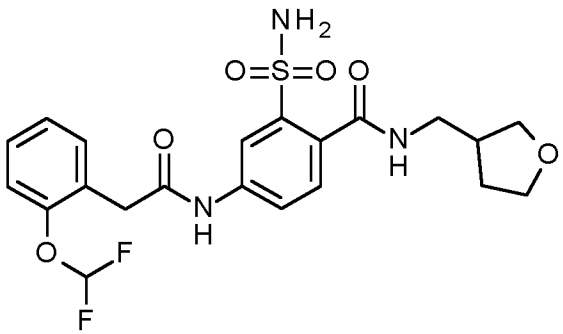
Conversion of crude 4-amino-2-sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)benzamide (60.0 mg, 0.20 mmol) and (2-chloro-5-fluorophenyl)acetic acid (56.7 mg, 0.30 mmol) according to general procedure GP3.1 followed by preparative HPLC (Waters XBridge C18 5µ 100x30mm, acetonitrile/water + 0.2% aqueous ammonia (32%)) led to the title compound (3 mg, 0.00638 mmol, 3 % yield, 97 % purity).

LC-MS (Method B): Rt = 0.84 min; MS (ESIpos): m/z = 470 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 1.54 - 1.66 (m, 1H), 1.90 - 2.00 (m, 1H), 2.41 - 2.50 (m, 1H), 3.15 - 3.28 (m, 2H), 3.47 (dd, 1H), 3.57 - 3.65 (m, 1H), 3.66 - 3.77 (m, 2H), 3.90 (s, 2H), 7.07 - 7.24 (m, 3H), 7.36 (dd, 1H), 7.48 - 7.56 (m, 2H), 7.90 (dd, 1H), 8.20 (d, 1H), 8.84 (t, 1H), 10.74 (s, 1H).

Example 53

4-({[2-(Difluoromethoxy)phenyl]acetyl}amino)-2-sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)benzamide



Conversion of crude 4-amino-2-sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)benzamide (60.0 mg, 0.20 mmol) and [2-(difluoromethoxy)phenyl]acetic acid (60.8 mg, 0.30 mmol) according to general procedure GP3.1 followed by preparative HPLC (Waters XBridge C18 5µ 100x30mm, acetonitrile/water + 0.2% aqueous ammonia (32%)) led to the title compound (14 mg, 0.0290 mmol, 14 % yield, 97 % purity).

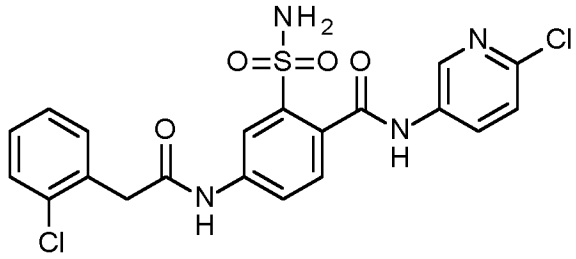
LC-MS (Method B): Rt = 0.84 min; MS (ESIpos): m/z = 484 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 1.56 - 1.65 (m, 1H), 1.90 - 2.00 (m, 1H), 2.40 - 2.48 (m, 1H), 3.16 - 3.27 (m, 2H), 3.47 (dd, 1H), 3.58 - 3.65 (m, 1H), 3.66 - 3.76 (m, 2H), 3.78

(s, 2H), 7.14 (t, 1H), 7.16 - 7.20 (m, 3H), 7.23 (td, 1H), 7.33 - 7.42 (m, 2H), 7.51 (d, 1H), 7.91 (dd, 1H), 8.19 (d, 1H), 8.82 (t, 1H), 10.67 (s, 1H).

Example 54

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-(6-chloropyridin-3-yl)-2-sulfamoylbenzamide



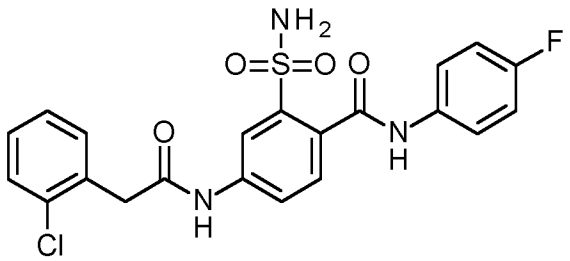
According to general procedure GP2 2-(2-chlorophenyl)-*N*-(1,1-dioxido-3-oxo-2,3-dihydro-1,2-benzothiazol-6-yl)acetamide (100 mg, 0.29 mmol) and 6-chloropyridin-3-amine (1.10 g, 8.55 mmol) were converted by stirring for 12h at 150°C in xylene (3 mL) to the title compound which was purified at the end by preparative HPLC (Waters XBrigde C18 5µ 100x30mm, acetonitrile/water + 0.1% formic acid) (11 mg, 0.0229 mmol, 8 % yield, 95 % purity).

LC-MS (Method A): Rt = 1.04 min; MS (ESIpos): m/z = 479 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 3.91 (s, 2H), 7.16 (s, 2H), 7.30 - 7.37 (m, 2H), 7.41 - 7.50 (m, 2H), 7.55 (d, 1H), 7.73 (d, 1H), 7.96 (dd, 1H), 8.17 (dd, 1H), 8.28 (d, 1H), 8.70 (d, 1H), 10.79 (s, 1H), 10.94 (s, 1H).

Example 55

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-(4-fluorophenyl)-2-sulfamoylbenzamide



According to general procedure GP2 2-(2-chlorophenyl)-*N*-(1,1-dioxido-3-oxo-2,3-dihydro-1,2-benzothiazol-6-yl)acetamide (100 mg, 0.29 mmol) and 4-fluoroaniline (633 mg, 5.70 mmol) were converted by stirring for 3h at 150°C in xylene (5 mL) to the title compound which was purified at the end by preparative HPLC (Chromatorex C-18 10µm,

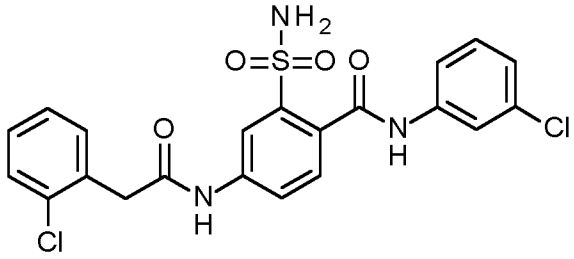
125x30mm, acetonitrile/water + 0.1% formic acid) (8 mg, 0.0173 mmol, 6 % yield, 97 % purity).

LC-MS (Method A): Rt = 1.14 min; MS (ESIpos): m/z = 462 $(M+H)^+$

^{1}H-NMR (500MHz, DMSO-d_6) δ [ppm]: 3.89 (s, 2H), 7.11 (s, 2H), 7.16 - 7.23 (m, 2H), 7.28 - 7.35 (m, 2H), 7.41 - 7.47 (m, 2H), 7.66 - 7.73 (m, 3H), 7.94 (dd, 1H), 8.26 (d, 1H), 10.63 (s, 1H), 10.74 (s, 1H).

Example 56

***N*-(3-Chlorophenyl)-4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzamide**



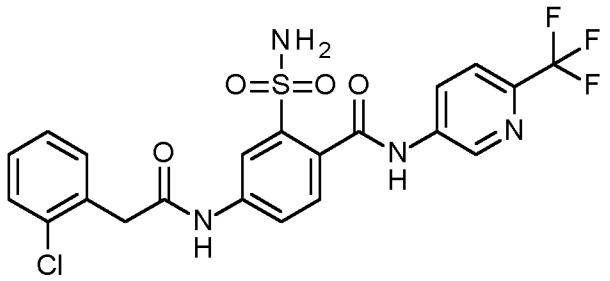
According to general procedure GP2 2-(2-chlorophenyl)-*N*-(1,1-dioxido-3-oxo-2,3-dihydro-1,2-benzothiazol-6-yl)acetamide (70.2 mg, 0.20 mmol) and 3-chloroaniline (603 mg, 4.72 mmol) were converted by stirring for 4h at 160°C in xylene (4.5 mL) to the title compound which was purified at the end by preparative HPLC (Chromatorex C-18 10µm, 125x30mm, acetonitrile/water + 0.1% formic acid) (10 mg, 0.0209 mmol, 10 % yield, 98 % purity).

LC-MS (Method A): Rt = 1.20 min; MS (ESIpos): m/z = 478 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 3.89 (s, 2H), 7.11 (s, 2H), 7.15 - 7.21 (m, 1H), 7.28 - 7.35 (m, 2H), 7.38 (t, 1H), 7.41 - 7.48 (m, 2H), 7.51 - 7.59 (m, 1H), 7.68 (d, 1H), 7.88 - 7.97 (m, 2H), 8.25 - 8.28 (m, 1H), 10.74 (s, 2H).

Example 57

4-{[(2-Chlorophenyl)acetyl]amino}-2-sulfamoyl-*N*-[6-(trifluoromethyl)pyridin-3-yl]benzamide



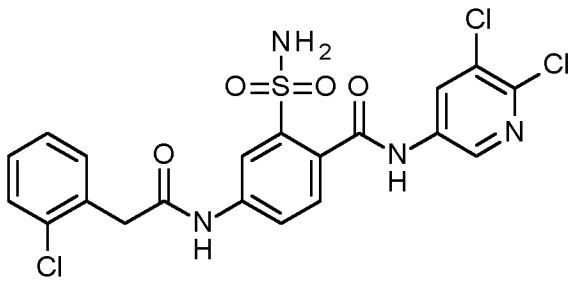
According to general procedure GP2 2-(2-chlorophenyl)-*N*-(1,1-dioxido-3-oxo-2,3-dihydro-1,2-benzothiazol-6-yl)acetamide (100 mg, 0.29 mmol) and 6-(trifluoromethyl)pyridin-3-amine (1.39 g, 8.55 mmol) were converted by stirring for 12h at 150°C in xylene (3 mL) to the title compound which was purified at the end by preparative HPLC (Waters XBrigde C18 5µ 100x30mm, acetonitrile/water + 0.1% formic acid) followed by another preparative HPLC (Waters XBrigde C18 5µ 100x30mm, acetonitrile/water + 0.2% aqueous ammonia (32%)) (7.6 mg, 0.0148 mmol, 5 % yield, 97 % purity).

LC-MS (Method B): Rt = 1.05 min; MS (ESIpos): m/z = 513 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 3.92 (s, 2H), 7.19 (s, 2H), 7.30 - 7.38 (m, 2H), 7.43 - 7.50 (m, 2H), 7.75 (d, 1H), 7.92 - 7.99 (m, 2H), 8.29 (d, 1H), 8.42 (dd, 1H), 8.98 (d, 1H), 10.81 (s, 1H), 11.17 (s, 1H).

Example 58

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-(5,6-dichloropyridin-3-yl)-2-sulfamoylbenzamide



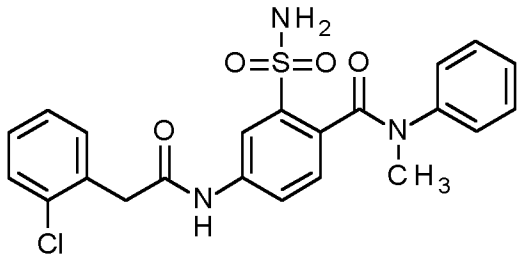
According to general procedure GP2 2-(2-chlorophenyl)-*N*-(1,1-dioxido-3-oxo-2,3-dihydro-1,2-benzothiazol-6-yl)acetamide (70 mg, 0.20 mmol) and 5,6-dichloropyridin-3-amine (65.1 mg, 0.40 mmol) were converted by stirring overnight at 150°C in xylene (2 mL) to the title compound which was purified at the end purified by preparative HPLC (Chromatorex C-18 10µm, 125x30mm, acetonitrile/water + 0.1% formic acid) (2 mg, 0.00389 mmol, 2 % yield, 95 % purity).

LC-MS (Method A): Rt = 1.14 min; MS (ESIpos): m/z = 513 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 3.91 (s, 2H), 7.01 - 7.39 (m, 4H), 7.41 - 7.52 (m, 2H), 7.73 (d, 1H), 7.96 (dd, 1H), 8.28 (d, 1H), 8.51 (d, 1H), 8.61 (d, 1H), 10.82 (s, 1H), 11.15 (s, 1H).

Example 59

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-methyl-*N*-phenyl-2-sulfamoylbenzamide



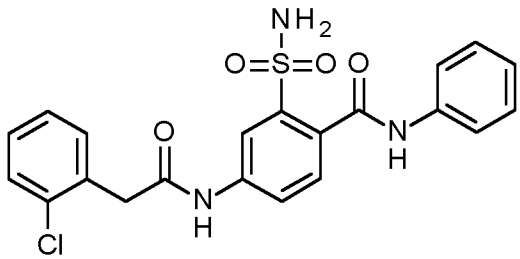
According to general procedure GP2 2-(2-chlorophenyl)-*N*-(1,1-dioxido-3-oxo-2,3-dihydro-1,2-benzothiazol-6-yl)acetamide (70.2 mg, 0.20 mmol) and *N*-methylaniline (450 mg, 4.20 mmol) were converted by stirring for 4h at 160°C in xylene (4.5 mL) to the title compound which was purified at the end by preparative HPLC (Chromatorex C-18 10µm, 125x30mm, acetonitrile/water + 0.1% formic acid) (15 mg, 0.0328 mmol, 16 % yield, 95 % purity).

LC-MS (Method A): Rt = 1.16 min; MS (ESIpos): m/z = 458 $(M+H)^+$

^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 3.38 (s, 3H), 3.80 (s, 2H), 7.00 - 7.07 (m, 3H), 7.12 (t, 1H), 7.20 - 7.50 (m, 9H), 8.14 (d, 1H), 10.52 (s, 1H).

Example 60

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-phenyl-2-sulfamoylbenzamide



According to general procedure GP2 2-(2-chlorophenyl)-*N*-(1,1-dioxido-3-oxo-2,3-dihydro-1,2-benzothiazol-6-yl)acetamide (77.2 mg, 0.22 mmol) and aniline (511 mg, 5.49 mmol) were converted by stirring for 4h at 160°C in xylene (4.5 mL) to the title compound

which was purified at the end by preparative HPLC (Chromatorex C-18 10µm, 125x30mm, acetonitrile/water + 0.1% formic acid) (20 mg, 0.0451 mmol, 20 % yield, 98 % purity).
LC-MS (Method A): Rt = 1.16 min
MS (ESIpos): m/z = 444 $(M+H)^+$
^{1}H-NMR (400MHz, DMSO-d_6) δ [ppm]: 3.89 (s, 2H), 7.05 - 7.15 (m, 3H), 7.28 - 7.38 (m, 4H), 7.41 - 7.48 (m, 2H), 7.65 - 7.72 (m, 3H), 7.94 (dd, 1H), 8.26 (d, 1H), 10.59 (s, 1H), 10.74 (s, 1H).

BIOLOGICAL ASSAYS

The following assays can be used to illustrate the commercial utility of the compounds according to the present invention.

Examples were tested in selected biological assays one or more times. When tested more than once, data are reported as either average (avg) values or as median values, wherein

- the average value, also referred to as the arithmetic mean value, represents the sum of the obtained values divided by the number of values obtained, and
- the median value represents the middle number of the group of obtained 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.

When no meaningful calculation of average values or median values is possible due to the existence of measurement values falling outside the detection range of the assay (indicated by < or > in the tables below) all individual measurement values are indicated.
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.

IN VITRO STUDIES

Human P2X4 HEK Cell FLIPR Assay

HEK293 cells stably expressing human P2X4 were plated in poly-D-lysine–coated 384-well plates at a seeding density of 30000 cells/well and incubated overnight. P2X4 function was assessed by measuring intracellular calcium changes using the calcium-chelating dye Fluo8-AM (Molecular Devices) on a fluorescent imaging plate reader (FLEX/FLIPR station; Molecular Devices). On the day of the assay, the medium was removed and the cells were incubated for 30 min at 37°C and 5% CO_2 in 30 µL of dye

buffer (Hank's balanced salt solution, 10 mM HEPES, 1.8 mM $CaCl_2$, 1 mM $MgCl_2$, 2 mM probenecid, 5mM D-glucose monohydrate, 5µM Fluo8-AM, pH=7.4). Compounds diluted in probenecid buffer (Hank's balanced salt solution, 10 mM HEPES, 1.8 mM $CaCl_2$, 1 mM $MgCl_2$, 2 mM probenecid, 5mM D-glucose monohydrate, pH=7.4) were added in a volume of 10 µL and allowed to incubate for 30 min at room temperature. The final assay DMSO concentration was 0.5%. The agonist, Bz-ATP (Tocris), was added in a volume of 10 µL at a concentration representing the EC_{80} value. The EC_{80} value of Bz-ATP was determined each assay day prior to compound profiling. The fluorescence was measured for an interval of 120 sec at 2 sec intervals. The excitation and emission wavelengths used to monitor fluorescence were 470-495 nm and 515-575 nm, respectively. The data was analyzed based on the increase in peak relative fluorescence units (RFU) compared to the basal fluorescence and the data was normalized to the agonist control. The compounds were tested in triplicates per plate and mean values were plotted in Excel XLFit to determine IC_{50} values, percentage of maximal inhibition and the Hill coefficients.

Example Number	Human P2X4 HEK Cells (FLIPR Assay) avg IC_{50} [nM]	Human P2X4 HEK Cells (FLIPR Assay) avg Efficacy [%]
1	23	90
2	37	80
3	52	84
4	54	77
5	41	72
6	138	79
7	114	93
8	121	88
9	121	74
10	124	83
11	154	96
12	82	71
13	212	90
14	262	87
15	278	86
16	281	92
17	312	80

18	325	77
19	411	88
20	398	76
21	431	85
22	570	106
23	543	92
24	606	60
25	715	85
26	856	93
27	1080	85
28	1211	104
29	4667	72
30	45	80
31	56	83
32	143	76
33	85	76
34	248	73
35	332	77
36	15323	59
37	70	76
38	568	78
39	943	73
40	746	78
41	369	88
42	290	85
43	42	94
44	2047	83
45	422	86
46	120	84
47	148	80
48	165	81
49	655	86
50	408	87

51	165	85
52	126	74
53	481	90
54	4	88
55	64	64
56	56	76
57	483	81
58	342	81
59	4432	71
60	3753	74

Human P2X4 HEK Cell Elektophysiology Assay

Electrophysiology Assay

Cell culture conditions: HEK-293 mito-Photina pcDNA3(neo-)/pPURO N/pcDNA3_P2RX4, clone 2a/4 (HEK-293 mito-Photina/hP2RX4) cells were cultured in EMEM Minimum Essential Medium Eagle with Earl's salts Balanced Salt Solution (BioWhittaker cat. BE12-125F) supplemented with 5 mL of 200 mM Ultraglutamine1 (BioWhittaker cat. BE17-605E/U1), 5 mL of 100X Penicillin/Streptomycin (BioWhittaker cat. DE17-602E; final concentration 1%), 4 mL of 50 mg/mL G418 (Sigma cat. G8168-100mL; final concentration 400 µg/mL), 10 µL of 10 mg/mL Puromicin (InvivoGen cat. ant-pr-1; final concentration 0,2 µg/mL) and 50 mL of Fetal Bovine Serum (Sigma cat. F7524; final concentration 10%).

Experimental protocol: HEK-293 cell lines are seeded 72 or 96 hours before experiment, at a concentration of 5 or 2.5 million cells, respectively onto a T225 flask. Just before the experiments cells are washed twice with D-PBS w/o Ca2+/Mg2+ (Euroclone cat. ECB4004L) and detached from the flask with trypsin-EDTA (Sigma, cat. T4174 diluted 1/10). Cells are then re-suspended in the suspension solution: 25 mL EX-CELL ACF CHO medium (Sigma, cat. C5467); 0.625 mL HEPES (BioWhittaker, cat. BE17-737E); 0.25 mL of 100x Penicillin/Streptomycin (BioWhittaker, cat. DE17-602E), 0.1 mL of Soybean Trypsin Inhibitor 10 mg/mL (Sigma, cat. T6522) and placed on the QPatch 16X.

Compound preparation and storage: Compound stock solutions (10 mM; 100% DMSO; stored at -20°C) were used. Fresh solutions from stock (1 or 3 mM, 100% DMSO) were prepared just before the experiments (0.1% final DMSO concentration).

DMSO solution was obtained from SIGMA (cat.# D-5879) and stored at room temperature.

Patch clamp analysis with QPatch16X (Figure 1): Standard whole-cell voltage clamp experiments are performed at room temperature using the multihole technology.

For the voltage clamp experiments on hP2X4, data are sampled at 2 KHz. After establishment of the seal and the passage in the whole cell configuration, the cells are held at -90 mV and the hP2X4 current is evoked by the agonist in the absence (vehicle period, i.e. 0.1% DMSO) or in the presence of the compound under investigation at increasing concentrations; see the application protocol in Figure 1.

Output: the maximum inward current induced by the agonist (ATP 5 microM).

The intracellular solution contained (mM) 135 CsF, 10 NaCl, 1 EGTA, 10 HEPES (pH 7.2 with CsOH) whereas the extracellular solution (mM) 145 NaCl, 4 KCl, 0.5 MgCl2, 1 CaCl2, 10 HEPES, 10 Glucose (pH 7.4 with NaOH).

For data collection, the Sophion software was used and the analysis was performed off-line using Excel and GraphPad Prism.

When possible, i.e. when the % of inhibition with the highest concentration tested was more than 50 %, the dose-response curves data were fitted with the following equation:

Y=100/(1+10^((LogIC50-X)*HillSlope))

[X is log of concentration; Y is normalized response (100% down to 0%, decreasing as X increases); LogIC_{50} same log units as X ; HillSlope is unitless slope factor or hill slope]

Example Number	Human P2X4 HEK Cells (PatchLiner Electrophysiology) avg IC_{50} [nM]	Number of Exp.
6	221	3
37	179	4

EX VIVO STUDIES

Human Monocyte P2X4 Assay

The principle of the assay is to measure calcium influx through endogenous P2X4 channels into primary human monocytes, following activation by 2',3'-O-(4-benzoyl-benzoyl)-ATP (Bz-ATP). Intracellular calcium concentration changes are measured with a FliprTM (Molecular Devices) device using a calcium sensitive dye (Fluo-8). In primary monocytes P2X4 is located at the lysosome membrane, therefore exocytosis has to be triggered to expose P2X4 at the cellular membrane.

Human peripheral blood mononuclear cells (PBMCs) from anticoagulated blood (blood cells, BC) are isolated via density gradient centrifugation. Whole blood is diluted 1:3 with PBS. Samples of 30 mL are layered carefully on top of 15 mL Biocoll (BIOCHROM) in 50 mL centrifuge tubes (Falcon). Tubes are centrifuged at 914 xg for 25 min at RT without brake. The PBMC layer is removed with a 10 mL pipette and transferred into tubes with ice-cold PBS in a total volume of 50 mL. Cells are washed twice by pelleting at 300 xg at 4°C, for 10 min and for 5 min respectively. PBMCs are re-suspended in 10 mL medium (X-vivo, Biozym Scientific) and counted in a Neubauer chamber.

Monocytes are isolated by negative selection using the Monocyte isolation kit II from Miltenyi (#130-091-153) according to the instructions. Isolation should be done fast and cells and solutions should be kept on ice at any time. PBMCs in batches of 10exp8 cells are pelleted (300 xg, 10 min) and re-suspended with 300 µL MACS buffer in a 50 mL Falcon tube. FcR Blocking reagent (100µl) and Biotin-Ab (100µl) are added, mixed and incubated on ice for 10 min. MACS buffer (300 µL) and anti-Biotin Micro-beads (100 µL) are added, mixed and incubated on ice for 15 min. Cells are washed by pelleting (300 xg for 10 min) and re-suspended in 500 µL MACS buffer. For each batch one separation column is placed in the MACS separator and rinsed with 3 mL MACS buffer. The cell suspension is added to the column, followed by 3 x 3 mL MACS buffer for washing, and the eluent containing the monocytes is collected. Cells were pelleted (300 xg for 10 min), re-suspended in X-vivo medium and counted. Monocytes are seeded into fibronectin-coated micro-plates (384-well, black, flat transparent bottom; Corning #3848) at a density of 30,000 cells/well in 50 µL, and cultivated over night (37°C, 5% CO_2).

Test substances are dissolved in 100% DMSO at a stock concentration of 10 mM and stored at -20°C in aliquots. Serial dilutions (2x) are prepared in DMSO and diluted 500x with assay buffer to generate the antagonist plate. In the Flipr measurement, 10 µL per well are transferred (4x dilution) and a final top concentrations of 5 µM and 0.05% DMSO are obtained in the assay. Agonist BzATP is stored at 10 mM in aliquots and diluted to an intermediate concentration of 15 µM to generate the agonist plate. In the Flipr measurement, 10 µL per well are transferred (5x dilution) so that a final assay concentration of 3 µM is obtained.

For the experiment, the medium of the cell plate is discarded manually and 70 µL/well loading buffer is added and incubated for 1h (37°C, 5% CO_2). Loading buffer contained HBSS (w/o calcium/magnesium), 10 mM Hepes pH 7.4, 5 µM Fluo-8 (AM) (Tebu-bio) and 50 mM methylamine (Sigma) to trigger exocytosis. Loading buffer is discarded manually and 30 µL/well low-calcium assay buffer (5 mM KCl, 145 mM NaCl, 0.5 mM $CaCl_2$, 13 mM

glucose, 10 mM Hepes pH 7.4) is added. The antagonist plate is transferred (10 µL/well) and after 15 min at RT the agonist plate (10 µL/well) is transferred.

Agonist addition is recorded for 240 seconds after a 10 second baseline. For analysis, a baseline correction is applied, and the maximum of the curve is extracted. Data are normalized towards 0% inhibition (signal at 3 µM BzATP) and 100% inhibition (absence of BzATP stimulation) and fitted with a four-parameter sigmoidal inhibition curve using Prism GraphPad to obtain IC_{50} values.

Human Whole Blood P2X4 Assay

In this assay, *ex vivo*, the blood of healthy female volunteers is first sensitized with lipopolysacharide (LPS) and then stimulated with ATP to trigger the release of Interleukin 1beta (IL-1β). In this system, the efficacy of P2X4 antagonists on the production of IL-1β in whole blood is tested. The cells are first treated with 100 ng/ml LPS for 2h and then stimulated with 3mM ATP and treated in triplicates with the test compounds at different concentrations. After 1h incubation, supernatant is taken and following centrifugation IL-1β in the supernatant is assayed using standard ELISA kits. The assay is performed with blood from different donors

***IN VIVO* STUDIES**

CFA Inflammation Model in Mice with Pain Behaviour Read Out

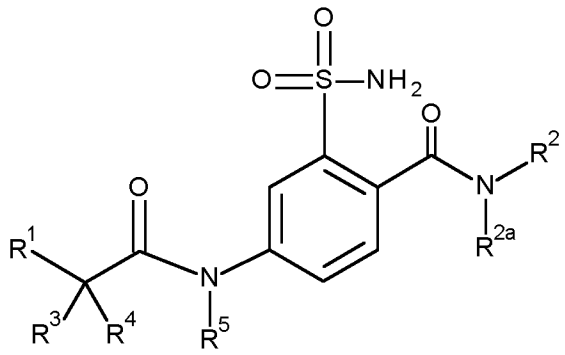
Wild type female C57BL/6 mice (Taconic) receive intraplantar injection of complete Freund´s adjuvant (CFA) (30 µL, 1 mg/mL, Sigma) into the left hind paw under isoflurane anesthesia. Animals are administered orally on day 2 post-CFA injection. Spontaneous pain-related behavior in freely moving animals is assessed using the automated dynamic weight bearing device (DWB, Bioseb, France) one hour after compound treatment according to published and validated protocols (Robinson et al., 2012; Tetreault et al., 2011; Gruen et al. 2014). For behavioral testing, the animal is placed inside a Plexiglas chamber in which the exerted pressure on the floor is measured. The animals are allowed to move freely within the apparatus for 5 min and subsequently pain behavior is recorded for a test period of another 5 min. The relative weight distribution is calculated by determining the ratio of the weight put on naïve (contralateral) vs. that put on the intraplantar CFA treated (ipsilateral) paws.

CFA-Induced Mechanical Hyperalgesia Model in Rat

Male Sprague Dawley rats are used. Mechanical hyperalgesia is induced by injecting 25 µL of Complete Freund's Adjuvant (CFA) into the plantar surface of the left hind paw. Mechanical hyperalgesia is measured using the Pressure Application Measurement apparatus (Ugo Basile, Gemonio, Italy). Briefly, a linearly increasing pressure is applied to an area of approximately 50 mm^2 of the plantar side of the hind paw, until a behavioural response (paw withdrawal) is observed or until the pressure reaches 1000 gf. The pressure at which the behavioural response occurres is recorded as the Paw Withdrawal Threshold (PWT). Both CFA-injected and contralateral PWTs are determined for each rat, in each treatment group and at each time point of the studies. Rats receive 3 oral doses of test compound at approximately 12 hours interval starting 1 hour prior to CFA injection. Mechanical hyperalgesia testing is performed 2 hours before CFA injection and 2 hours after the last dosing.

CLAIMS

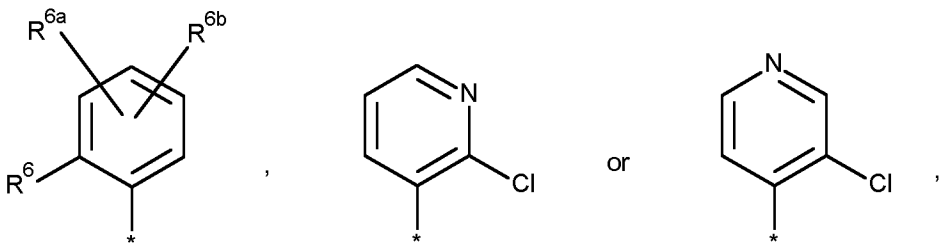
1. A compound of formula (I)



(I)

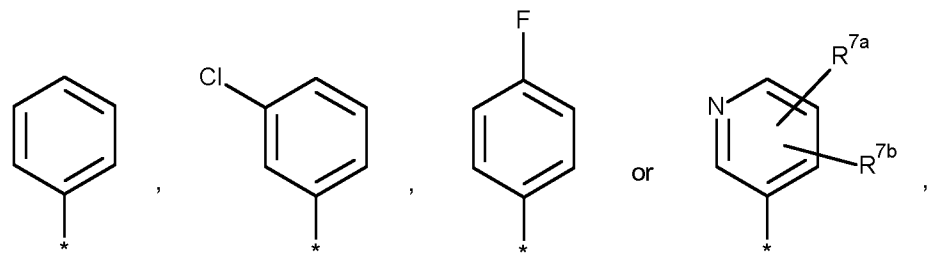
in which:

R^1 represents a group selected from:



wherein * indicates the point of attachment of said group with the rest of the molecule;

R^2 represents C_2-C_6-alkyl, C_1-C_6-haloalkyl, C_3-C_6-cycloalkyl, (C_3-C_6-cycloalkyl)-(C_1-C_3-alkyl)-, (C_5-C_6-heterocycloalkyl)-(C_1-C_3-alkyl)-
or a group selected from:



wherein * indicates the point of attachment of said group with the rest of the molecule and said C_2-C_6-alkyl groups are optionally substituted with C_1-C_4-alkoxy or $R^9R^{10}N$- and said C_3-C_6-cycloalkyl and C_5-C_6-heterocycloalkyl groups are optionally substituted with halogen or C_1-C_6-alkyl, and

R^{2a} represents hydrogen or methyl;

or

R^2 and R^{2a} together with the nitrogen atom to which they are attached form a 4- to 6-membered nitrogen containing heterocyclic ring, said ring optionally containing one additional heteroatom selected from O, S, NH, NR^a in which R^a represents a C_1-C_6-alkyl or C_1-C_6-haloalkyl group and being optionally substituted, one to three times, independently from each other, with halogen, C_1-C_4-alkyl, C_1-C_4-alkoxy or once annellated or spiro connected with C_3-C_6-cycloalkyl or C_4-C_6-heterocycloalkyl;

R^3 represents hydrogen or fluoro;

R^4 represents hydrogen, fluoro, methyl or OH;

R^5 represents hydrogen or C_1-C_3-alkyl;

R^6 represents hydrogen, halogen, cyano, nitro, OH, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy or F_3CS-;

R^{6a} and R^{6b} are the same or different and represent, independently from each other, respectively

R^{6a} hydrogen, halogen, hydroxy, nitro, cyano, C_1-C_4-alkyl, C_3-C_6-cycloalkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, HO-(C_2-C_4-alkoxy)-, (C_1-C_4-alkoxy)-(C_2-C_4-alkoxy)-, $R^9R^{10}N$-, R^8-C(O)-NH-, R^8-C(O)-, R^8-O-C(O)-, $R^9R^{10}N$-C(O)- or (C_1-C_4-alkyl)-SO_2-;

R^{6b} hydrogen, halogen, hydroxy, nitro, cyano, C_1-C_4-alkyl, C_3-C_6-cycloalkyl, C_1-C_4-haloalkyl, C_1-C_4-haloalkoxy, HO-(C_2-C_4-alkoxy)-, (C_1-C_4-alkoxy)-(C_2-C_4-alkoxy)-, $R^9R^{10}N$-, R^8-C(O)-NH-, R^8-C(O)-, R^8-O-C(O)-, $R^9R^{10}N$-C(O)- or (C_1-C_4-alkyl)-SO_2-; or

R^{6a} and R^{6b} adjacent to each other together represent a group selected from –O-CH_2-CH_2-, –O-CH_2-O- or –O-CH_2-CH_2-O-;

R^{7a} represents hydrogen, halogen, C_1-C_4-alkyl or C_1-C_4-haloalkyl;

R^{7b} represents hydrogen, halogen, C_1-C_4-alkyl or C_1-C_4-haloalkyl;

R^8 represents, independently from each respective occurence, C_1-C_6-alkyl, C_1-C_4-alkoxy-C_1-C_4-alkyl, C_3-C_6-cycloalkyl or C_1-C_4-haloalkyl;

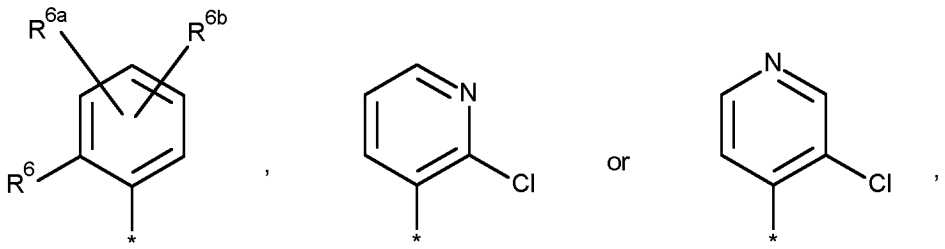
R^9 and R^{10} are the same or different and represent, independently from each other, hydrogen, C_1-C_4-alkyl, C_3-C_6-cycloalkyl, C_2-C_4-haloalkyl or $(CH_3)_2N$-C_1-C_4-alkyl or

together with the nitrogen atom to which they are attached form a 4- to 6-membered nitrogen containing heterocyclic ring, said ring optionally containing one additional heteroatom selected from O, S, NH, NR^a in which R^a represents a C_1-C_6-alkyl or C_2-C_6-haloalkyl group and being optionally substituted, one to three times, independently from each other, with halogen or C_1-C_4-alkyl;

or an N-oxide, a salt, a hydrate, a solvate, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

2. A compound of formula (I) according to claim 1, characterised in that

R^1 represents a group selected from:



wherein * indicates the point of attachment of said group with the rest of the molecule;

R^2 and R^{2a} together with the nitrogen atom to which they are attached form a 4- to 6-membered nitrogen containing heterocyclic ring, said ring optionally containing one additional heteroatom selected from O, S, NH, NR^a in which R^a represents a C_1-C_6-alkyl or C_1-C_6-haloalkyl group and being optionally substituted, one to three times, independently from each other, with halogen, C_1-C_4-alkyl, C_1-C_4-alkoxy or once annellated or spiro connected with C_3-C_6-cycloalkyl or C_4-C_6-heterocycloalkyl;

R^3, R^4, R^5 represents hydrogen;

R^6 represents hydrogen, halogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy or C_1-C_4-haloalkoxy;

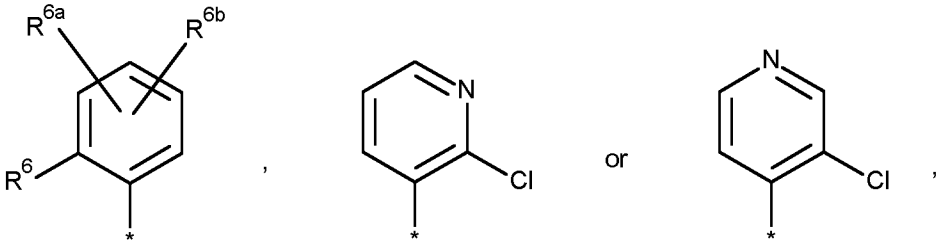
R^{6a} and R^{6b} are the same or different and represent, independently from each other, respectively hydrogen or halogen;

R^9 and R^{10} are the same or different and represent, independently from each other, C_1-C_4-alkyl or C_2-C_4-haloalkyl;

or an N-oxide, a salt, a hydrate, a solvate, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

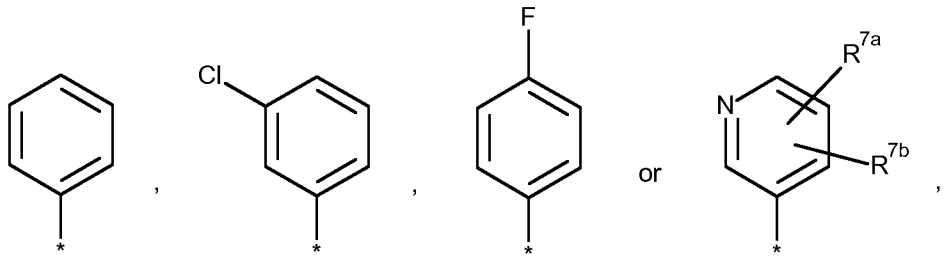
3. A compound of formula (I) according to claim 1, characterised in that

R^1 represents a group selected from:



wherein * indicates the point of attachment of said group with the rest of the molecule;

R^2 represents C_2-C_6-alkyl, C_1-C_6-haloalkyl, C_3-C_6-cycloalkyl, (C_3-C_6-cycloalkyl)-(C_1-C_3-alkyl)-, (C_5-C_6-heterocycloalkyl)-(C_1-C_3-alkyl)-
or a group selected from:



wherein * indicates the point of attachment of said group with the rest of the molecule and said C_2-C_6-alkyl groups are optionally substituted with C_1-C_4-alkoxy or $R^9R^{10}N$- and said C_3-C_6-cycloalkyl and C_5-C_6-heterocycloalkyl groups are optionally substituted with halogen or C_1-C_6-alkyl, and

R^{2a} represents hydrogen ,

R^3, R^4, R^5 represents hydrogen;

R^6 represents hydrogen, halogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy or C_1-C_4-haloalkoxy;

R^{6a} and R^{6b} are the same or different and represent, independently from each other, respectively hydrogen or halogen;

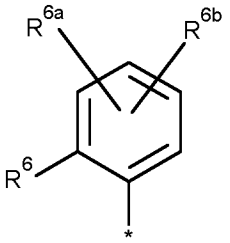
R^{7a} represents chloro or trifluoromethyl;

R^9 and R^{10} are the same or different and represent, independently from each other, C_1-C_4-alkyl or C_2-C_4-haloalkyl;

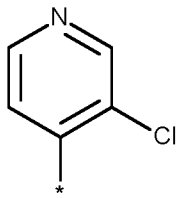
or an N-oxide, a salt, a hydrate, a solvate, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

4. A compound of formula (I) according to claim 1 or 2, characterized in that

R^1 represents a group selected from:



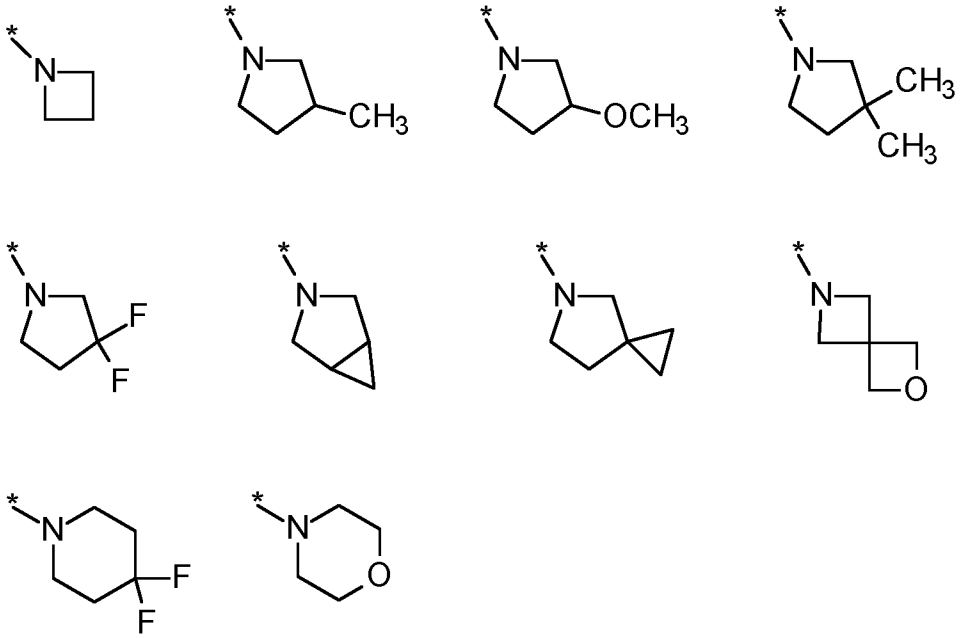
or



,

wherein * indicates the point of attachment of said group with the rest of the molecule;

R^2 and R^{2a} together with the nitrogen atom to which they are attached form a nitrogen containing heterocyclic ring system selected from:



wherein * indicates the point of attachment of said ring with the rest of the molecule;

R^3, R^4, R^5 represents hydrogen;

R^6 represents hydrogen, halogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy or C_1-C_4-haloalkoxy;

R^{6a} and R^{6b} are the same or different and represent, independently from each other, respectively

R^{6a} hydrogen or halogen;

R^{6b} hydrogen or halogen;

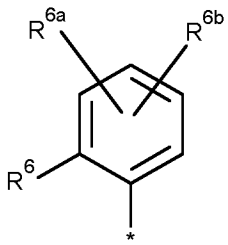
R^{7a} represents chloro or trifluoromethyl;

R^{9} and R^{10} are the same or different and represent, independently from each other, C_1-C_4-alkyl or C_2-C_4-haloalkyl;

or an N-oxide, a salt, a hydrate, a solvate, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

5. A compound of formula (I) according to claim 1 or 2, characterized in that

R^{1} represents a group selected from:



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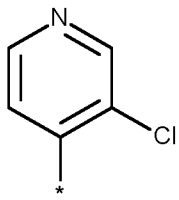
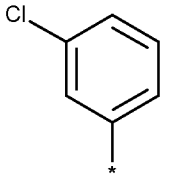


,

wherein * indicates the point of attachment of said group with the rest of the molecule;

R^{2} represents C_2-C_6-alkyl, C_1-C_6-haloalkyl, C_3-C_6-cycloalkyl, (C_3-C_6-cycloalkyl)-(C_1-C_3-alkyl)-, (C_5-C_6-heterocycloalkyl)-methyl

or a group selected from:



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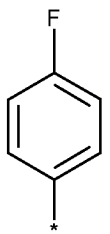

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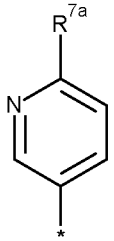
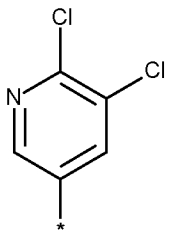


or



,

wherein * indicates the point of attachment of said group with the rest of the molecule and said C_2-C_6-alkyl groups are optionally substituted with C_1-C_4-alkoxy or $R^{9}R^{10}N$- and said C_3-C_6-cycloalkyl and C_5-C_6-heterocycloalkyl groups are optionally substituted with halogen or C_1-C_6-alkyl;

R^{2a} represents hydrogen

R^3, R^4, R^5 represents hydrogen;

R^6 represents hydrogen, halogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy or C_1-C_4-haloalkoxy;

R^{6a} and R^{6b} are the same or different and represent, independently from each other, respectively

R^{6a} hydrogen or halogen;

R^{6b} hydrogen or halogen;

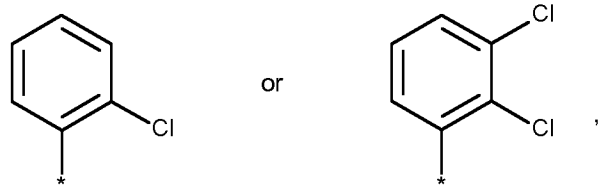
R^{7a} represents chloro or trifluoromethyl;

R^9 and R^{10} are the same or different and represent, independently from each other, C_1-C_4-alkyl or C_2-C_4-haloalkyl;

or an N-oxide, a salt, a hydrate, a solvate, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

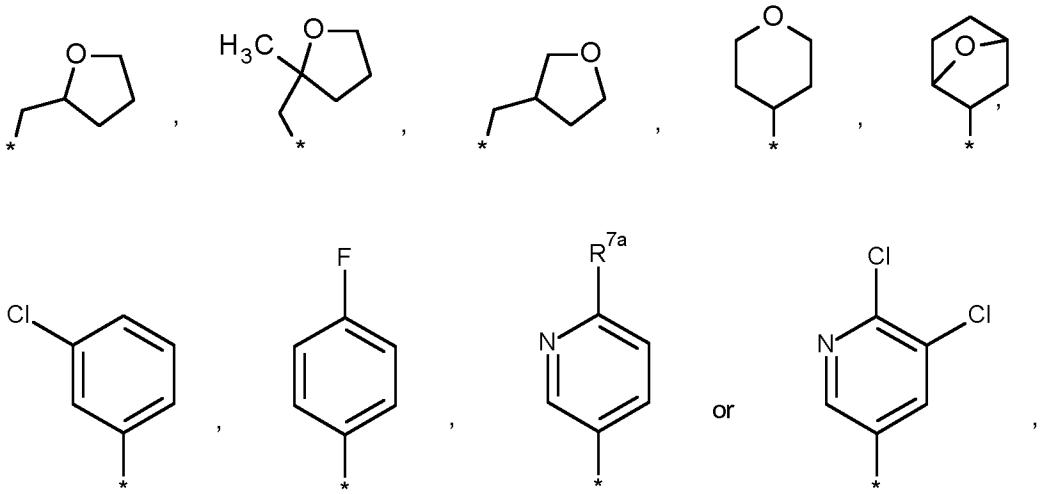
6. A compound of formula (I) according to claims 1 or 3, in which:

R^1 represents a group selected from:



wherein * indicates the point of attachment of said group with the rest of the molecule;

R^2 represents C_2-C_5-alkyl, C_2-C_4-haloalkyl, 3,3-difluorocyclobutyl, 1-methylcyclopentyl, (C_3-C_5-cycloalkyl)-(C_1-C_3-alkyl)- or a group selected from:



wherein * indicates the point of attachment of said group with the rest of the molecule and said C_2-C_5-alkyl groups are optionally substituted once with methoxy or $R^9R^{10}N$- and said C_3-C_5-cycloalkyl groups are optionally substituted once or twice with fluoro, chloro or methyl;

R^{2a} represents hydrogen ,

R^3, R^4, R^5 represents hydrogen;

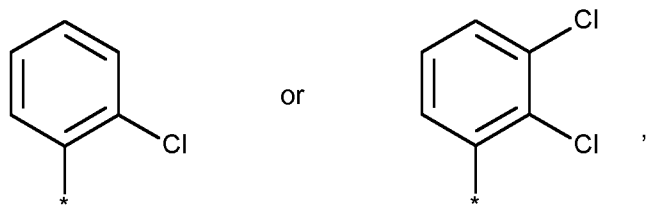
R^{7a} represents chloro or trifluoromethyl;

R^9 and R^{10} are the same or different and represent, independently from each other, methyl or C_2-haloalkyl;

or an N-oxide, a salt, a hydrate, a solvate, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

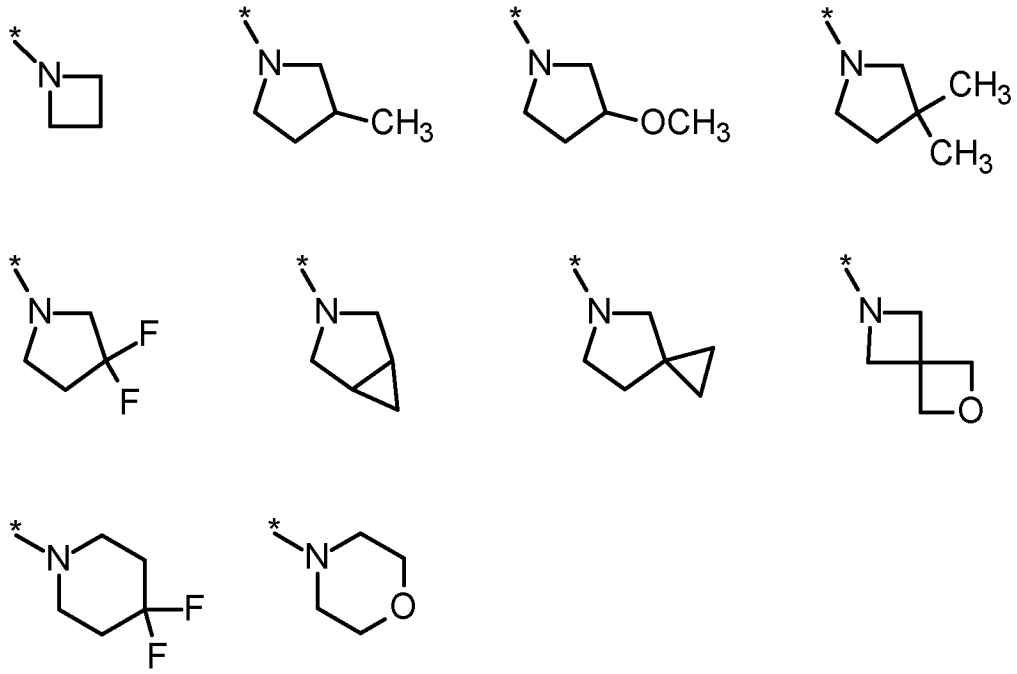
7. A compound of formula (I) according to claims 1 or 2, in which:

R^1 represents a group selected from:



wherein * indicates the point of attachment of said group with the rest of the molecule;

R^2 and R^{2a} together with the nitrogen atom to which they are attached form a nitrogen containing heterocyclic ring system selected from:



wherein * indicates the point of attachment of said ring with the rest of the molecule;

R^3, R^4, R^5 represents hydrogen;

or an N-oxide, a salt, a hydrate, a solvate, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

8. A compound according to claim 1 to 7 selected from the following list:

4-{[(2-Chlorophenyl)acetyl]amino}-2-sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)benzamide

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-(2-methylbutyl)-2-sulfamoylbenzamide

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-[(2,2-dimethylcyclopropyl)methyl]-2-sulfamoylbenzamide

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-(cyclopentylmethyl)-2-sulfamoylbenzamide

4-{[(2-Chlorophenyl)acetyl]amino}-2-sulfamoyl-*N*-(4,4,4-trifluorobutyl)benzamide

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-isobutyl-2-sulfamoylbenzamide

2-(2-Chlorophenyl)-*N*-{4-[(3,3-difluoropyrrolidin-1-yl)carbonyl]-3-sulfamoylphenyl}acetamide

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-(1-cyclopropylpropan-2-yl)-2-sulfamoylbenzamide

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-(3-methoxypropyl)-2-sulfamoylbenzamide

2-(2-Chlorophenyl)-*N*-{4-[(3-methylpyrrolidin-1-yl)carbonyl]-3-sulfamoylphenyl}acetamide

N-[4-(5-Azaspiro[2.4]hept-5-ylcarbonyl)-3-sulfamoylphenyl]-2-(2-chlorophenyl)acetamide

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-[(2,2-dichlorocyclopropyl)methyl]-2-sulfamoylbenzamide

4-{[(2-Chlorophenyl)acetyl]amino}-2-sulfamoyl-*N*-[(2*R*)-tetrahydrofuran-2-ylmethyl]benzamide

2-(2-Chlorophenyl)-*N*-{4-[(3-methoxypyrrolidin-1-yl)carbonyl]-3-sulfamoylphenyl}acetamide

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-(2-methoxyethyl)-2-sulfamoylbenzamide

2-(2-Chlorophenyl)-*N*-{4-[(4,4-difluoropiperidin-1-yl)carbonyl]-3-sulfamoylphenyl}acetamide

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-(cyclopropylmethyl)-2-sulfamoylbenzamide

2-(2-Chlorophenyl)-*N*-{4-[(3,3-dimethylpyrrolidin-1-yl)carbonyl]-3-sulfamoylphenyl}acetamide

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-[7-oxabicyclo[2.2.1]hept-2-ylmethyl]-2-sulfamoylbenzamide

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-[(1*R*,2*R*,4*S*)-7-oxabicyclo[2.2.1]hept-2-ylmethyl]-2-sulfamoylbenzamide

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-[(1*S*,2*S*,4*R*)-7-oxabicyclo[2.2.1]hept-2-ylmethyl]-2-sulfamoylbenzamide

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-[(2-methyltetrahydrofuran-2-yl)methyl]-2-sulfamoylbenzamide

4-{[(2-Chlorophenyl)acetyl]amino}-2-sulfamoyl-*N*-[(2S)-tetrahydrofuran-2-ylmethyl]benzamide

2-(2-Chlorophenyl)-*N*-[4-(morpholin-4-ylcarbonyl)-3-sulfamoylphenyl]acetamide

N-[4-(Azetidin-1-ylcarbonyl)-3-sulfamoylphenyl]-2-(2-chlorophenyl)acetamide

2-(2-Chlorophenyl)-*N*-[4-(2-oxa-6-azaspiro[3.3]hept-6-ylcarbonyl)-3-sulfamoylphenyl]acetamide

4-{[(2-Chlorophenyl)acetyl]amino}-2-sulfamoyl-*N*-(tetrahydro-2*H*-pyran-4-ylmethyl)benzamide

N-{4-[(1R,5S)-3-Azabicyclo[3.1.0]hex-3-ylcarbonyl]-3-sulfamoylphenyl}-2-(2-chlorophenyl)acetamide

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-(1-methylcyclopentyl)-2-sulfamoylbenzamide

2-(2-Chlorophenyl)-*N*-{4-[(2-methylpyrrolidin-1-yl)carbonyl]-3-sulfamoylphenyl}acetamide

2-(2-Chlorophenyl)-*N*-{4-[(4-methylpiperazin-1-yl)carbonyl]-3-sulfamoylphenyl}acetamide

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-(cyclobutylmethyl)-2-sulfamoylbenzamide

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-(2,2-difluoroethyl)-2-sulfamoylbenzamide

4-{[(2-Chlorophenyl)acetyl]amino}-2-sulfamoyl-*N*-(2,2,2-trifluoroethyl)benzamide

4-{[(2-Chlorophenyl)acetyl]amino}-2-sulfamoyl-*N*-(3,3,3-trifluoropropyl)benzamide

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-[(2,2-difluorocyclopropyl)methyl]-2-sulfamoylbenzamide

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-(2-methoxypropyl)-2-sulfamoylbenzamide

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-[2-(pyrrolidin-1-yl)ethyl]-2-sulfamoylbenzamide

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-(3,3-difluorocyclobutyl)-2-sulfamoylbenzamide

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-{2-[(2,2-difluoroethyl)(methyl)amino]ethyl}-2-sulfamoylbenzamide

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-{2-[methyl(2,2,2-trifluoroethyl)amino]ethyl}-2-sulfamoylbenzamide

4-{[(2-Fluorophenyl)acetyl]amino}-*N*-isobutyl-2-sulfamoylbenzamide

4-[(Phenylacetyl)amino]-2-sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)benzamide

4-{[(4-Fluorophenyl)acetyl]amino}-2-sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)benzamide

4-{[(2,3-Dichlorophenyl)acetyl]amino}-2-sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)benzamide

4-{[(2-Chloropyridin-3-yl)acetyl]amino}-2-sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)benzamide

4-{[(3-Chloropyridin-4-yl)acetyl]amino}-2-sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)benzamide

2-Sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)-4-({[2-(trifluoromethyl)phenyl]acetyl}amino)benzamide

4-{[(2-Fluorophenyl)acetyl]amino}-2-sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)benzamide

4-({[2-(Difluoromethyl)phenyl]acetyl}amino)-2-sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)benzamide

4-{[(2-Methylphenyl)acetyl]amino}-2-sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)benzamide

4-{[(2-Methoxyphenyl)acetyl]amino}-2-sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)benzamide

2-Sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)-4-({[2-(trifluoromethoxy)phenyl]acetyl}amino)benzamide

4-{[(2-Chloro-5-fluorophenyl)acetyl]amino}-2-sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)benzamide

4-({[2-(Difluoromethoxy)phenyl]acetyl}amino)-2-sulfamoyl-*N*-(tetrahydrofuran-3-ylmethyl)benzamide

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-(6-chloropyridin-3-yl)-2-sulfamoylbenzamide

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-(4-fluorophenyl)-2-sulfamoylbenzamide

N-(3-Chlorophenyl)-4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzamide

4-{[(2-Chlorophenyl)acetyl]amino}-2-sulfamoyl-*N*-[6-(trifluoromethyl)pyridin-3-yl]benzamide

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-(5,6-dichloropyridin-3-yl)-2-sulfamoylbenzamide

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-methyl-*N*-phenyl-2-sulfamoylbenzamide

4-{[(2-Chlorophenyl)acetyl]amino}-*N*-phenyl-2-sulfamoylbenzamide

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. 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.

11. 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.

12. Use according to claims 9 to 11, wherein said disease is a genitourinary, gastrointestinal, proliferative or pain-related disease, condition or disorder; cancer;

fibrotic diseases including lung fibrosis, heart fibrosis, kidney fibrosis and fibrosis of other organs; gynaecological diseases including dysmenorrhea, dyspareunia, endometriosis and adenomyosis; endometriosis-associated pain; endometriosis-associated symptoms, wherein said symptoms are in particular endometriosis-associated, dysmenorrhea, dyspareunia, dysuria, or dyschezia; pelvic hypersensitivity; urethritis; prostatitis; prostatodynia; cystitis; idiopathic bladder hypersensitivity; gastrointestinal disorders including irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), biliary colic and other biliary disorders, renal colic, diarrhea-dominant IBS, gastroesophageal reflux, gastrointestinal distension, Crohn's disease and the like; Parkinson's disease; Alzheimer's disease; myocardial infarction; atherosclerosis; lipid disorders; and pain-associated diseases selected from the group consisting of hyperalgesia, allodynia, functional bowel disorders (such as irritable bowel syndrome), arthritis (such as osteoarthritis and rheumatoid arthritis), burns, migraine or cluster headaches, nerve injury, neuritis, neuralgias, poisoning, ischemic injury, interstitial cystitis, cancer, traumatic nerve-injury, post-traumatic injuries (including fractures and sport injuries), trigeminal neuralgia, small fiber neuropathy, diabetic neuropathy, chronic arthritis and related neuralgias, HIV and HIV treatment-induced neuropathy, pruritus; impaired wound healing and disease of the skeleton like degeneration of the joints, ankylosing spondylitis.

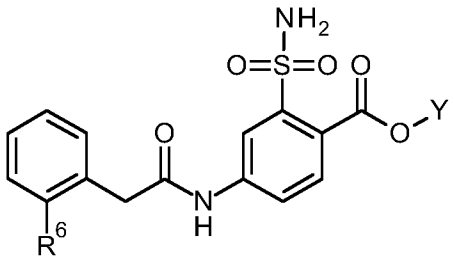
13. Use according to any one of claims 9 to 11, wherein said disease is a gynaecological disease, preferably dysmenorrhea, dyspareunia or endometriosis, adenomyosis, endometriosis-associated pain, or other endometriosis-associated symptoms, wherein said symptoms are in particular endometriosis-associated, dysmenorrhea, dyspareunia, dysuria, or dyschezia.

14. Use according to any one of claims 9 to 11, wherein said disease is associated with pain syndromes (including acute, chronic, inflammatory and neuropathic pain), preferably inflammatory pain, low back pain, surgical pain, visceral pain, dental pain, premenstrual pain, endometriosis-associated pain, pain associated with fibrotic diseases, central pain, pain due to burning mouth syndrome, pain due to burns, pain due to migraine, cluster headaches, pain due to nerve injury, pain due to neuritis, neuralgias, pain due to poisoning, pain due to ischemic injury, pain due to interstitial cystitis, cancer pain, pain due to viral, parasitic or bacterial infections, pain due to traumatic nerve-injury, pain due to post-traumatic injuries (including fractures and sport injuries), pain due to trigeminal neuralgia, pain associated with

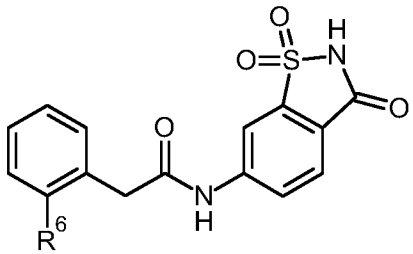
small fiber neuropathy, pain associated with diabetic neuropathy, chronic lower back pain, phantom limb pain, pelvic pain syndrome, chronic pelvic pain, neuroma pain, complex regional pain syndrome, pain associated with gastrointestinal distension, chronic arthritic pain and related neuralgias, and pain associated with cancer, pain associated with chemotherapy, HIV and HIV treatment-induced neuropathy; and pain associated with diseases or disorders selected from the group consisting of hyperalgesia, allodynia, functional bowel disorders (such as irritable bowel syndrome) and arthritis (such as osteoarthritis and rheumatoid arthritis).

15. A pharmaceutical composition comprising at least one compound according to any one of the claims 1 to 8, together with at least one pharmaceutically acceptable auxiliary.

16. An intermediate of formula **6a** or **8a**



6a



8a

wherein R^6 is as defined in the description and claims of this invention and Y represents C_1-C_3 alkyl.

17. An intermediate of the following formula:
Methyl 4-{[(2-chlorophenyl)acetyl]amino}-2-sulfamoylbenzoate
2-(2-Chlorophenyl)-N-(1,1-dioxido-3-oxo-2,3-dihydro-1,2-benzothiazol-6-yl)acetamide

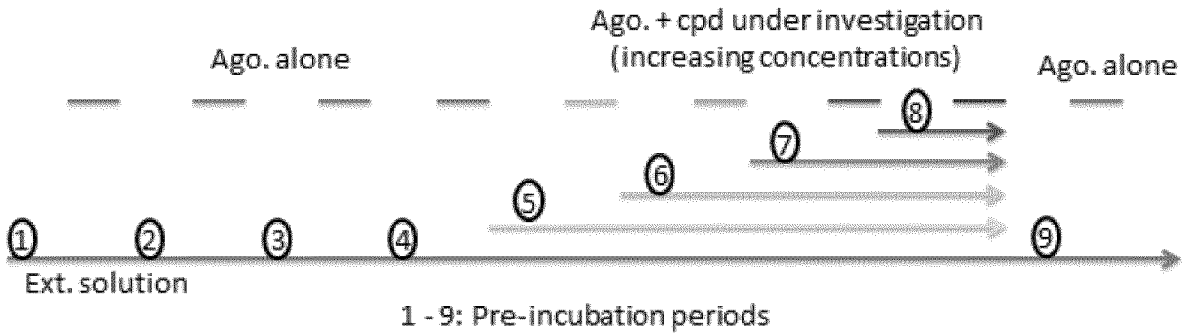

Ago. + cpd under investigation
(increasing concentrations)
Ago. alone
Ago. alone
1
2
3
4
5
6
7
8
9
Ext. solution
1 - 9: Pre-incubation periods

Fig. 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/081530

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C311/46 A61K31/18 A61P29/00 C07D205/04 C07D207/06
C07D207/10 C07D207/12 C07D209/94 C07D209/96 C07D211/38
C07D213/75 C07D275/06 C07D295/13 C07D295/192 C07D307/14

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)
C07C C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 2 597 088 A1 (NIPPON CHEMIPHAR) 29 May 2013 (2013-05-29) cited in the application claims 1, 21, 22	1-17
X	CN 104 529 933 A (UNIVVERSITY OF SHANDONG) 22 April 2015 (2015-04-22) paragraph [0081]; compound 1Q	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

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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"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
23 February 2018	05/03/2018

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	English, Russell

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2017/081530

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 2597088 A1	29-05-2013	CA 2807354 A1	19-01-2012
		CN 103080094 A	01-05-2013
		EP 2597088 A1	29-05-2013
		JP 5843770 B2	13-01-2016
		JP WO2012008478 A1	09-09-2013
		KR 20130041168 A	24-04-2013
		US 2013172550 A1	04-07-2013
		WO 2012008478 A1	19-01-2012
CN 104529933 A	22-04-2015	NONE	