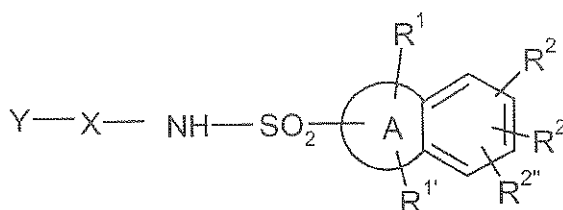


SULFONAMIDE DERIVATIVES AS CHYMASE INHIBITORS

The invention is concerned with novel sulfonamide derivatives of formula (I),



(I)

5 wherein

A is phenyl ring, or

heteroaryl ring, which is a monocyclic aromatic ring of 5 or 6 ring atoms, containing one or two ring heteroatoms selected from N, O and S, the remaining ring atoms being C, or

10 heterocyclyl ring, which is non-aromatic mono-cyclic ring of 5 or 6 ring atoms, containing one or two ring heteroatoms selected from N and S(O)_n (where n is an integer from 0 to 2), the remaining ring atoms being C, one of the ring carbon atom of the heterocyclyl ring being optionally replaced with a carbonyl group;

15 R¹ and R^{1'} are independently hydrogen, halogen, nitro, cyano, amino, C₁₋₆ alkyl, heteroalkyl, C₃₋₇ cycloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, hydroxy, C₁₋₆ alkoxy, -NR'R'', -(C₀₋₆ alkylene)-NR'R'', in which R' and R'' are independently selected from the group consisting of hydrogen, C₁₋₆ alkyl, heteroalkyl, formyl, C₁₋₆ alkylcarbonyl, optionally substituted C₃₋₇ cycloalkylcarbonyl, optionally substituted arylcarbonyl, optionally substituted heteroarylcarbonyl, optionally substituted heterocyclylcarbonyl, C₁₋₆ alkylsulfonyl, optionally substituted C₃₋₇

20

cycloalkylsulfonyl, optionally substituted arylsulfonyl, optionally substituted heteroarylsulfonyl and optionally substituted heterocyclysulfonyl, or

-(C₀₋₆ alkylene)-OR', in which R' is hydrogen, C₁₋₆ alkyl, heteroalkyl, formyl or C₁₋₆ alkylcarbonyl,

5 or R^{1'} does not exist, where only R¹ can exist;

R², R^{2'} and R^{2''} are independently hydrogen, halogen, cyano, nitro, amino, mono- or di-C₁₋₆ alkyl substituted amino, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, heteroalkyl, hydroxy or C₁₋₆ alkoxy;

10 X is phenylene optionally substituted by one, two or three substituents independently selected from the group consisting of halogen, cyano, nitro, amino, mono- or di- C₁₋₆ alkyl substituted amino, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, heteroalkyl, hydroxy, C₁₋₆ alkoxy, halo C₁₋₆ alkyl, halo C₁₋₆ alkoxy, heteroalkyloxy, C₁₋₆ alkylsulfonyl, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylthio, C₁₋₆ alkylsulfonyl-C₁₋₆ alkyl, C₁₋₆ alkylsulfinyl-C₁₋₆ alkyl, C₁₋₆ alkylthio C₁₋₆ alkyl, 15 acyl, formyl, C₁₋₆ alkoxy carbonyl, halo C₁₋₆ alkoxy carbonyl, heteroalkyloxycarbonyl and heteroalkylcarbonyl;

20 Y is optionally substituted heteroaryl, in which heteroaryl means a monocyclic aromatic radical of 6 ring atoms, containing one or two ring heteroatoms selected from N(O)_n (where n is 0 or 1), O, and S, the remaining ring atoms being C, or

optionally substituted heterocyclyl, in which heterocyclyl means a non-aromatic mono-cyclic radical of six ring atoms, containing one or two ring atoms are heteroatoms selected from N, O, or S(O)_n (where n is an integer from 0 to 2), the remaining ring atoms being C;

25 and prodrugs and pharmaceutically acceptable salts thereof.

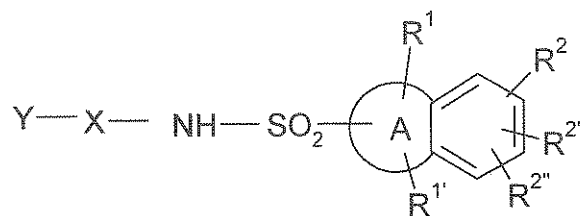
Further, the invention is concerned with a process and an intermediate for the manufacture of the above compounds, pharmaceutical preparations which contain such compounds, the use of these compounds for the production of pharmaceutical preparations as well as a process for the manufacture of the intermediate.

30 The compounds of formula (I) inhibit Chymase. Chymase is a serine proteinase with an expression pattern strictly limited to a sub-population of mast cells (M_{CT} mast cell).

- Chymase is activated only upon mast cell activation and degranulation which restricts the enzyme activity to M_{CT} positive tissues. Chymase is specifically cleaving a number of pathologically relevant substrates (Raymond, W. W., S. W. Ruggles, et al.; JBC 2003 278(36): 34517-34524) whereby it can activate Angiotensin II, Endothelin, TGF β , IL1, SCF, collagenase and degrade proteins like Thrombin, FN, APO A1,2. This pattern renders chymase an attractive target for allergic, inflammatory and fibrotic diseases. Indeed a number of successful animal studies with chymase inhibitors have demonstrated efficacy in atopic animals, vascular injury and atherosclerosis (Doggrell SA, Wanstall JC Can J Physiol Pharmacol. 2005 Feb;83(2):123-30; Lindstedt KA, Kovanen PT. Curr Opin Lipidol. 2004 Oct;15(5):567-73; Reed CE, Kita H. J Allergy Clin Immunol. 2004 Nov;114(5):997-1008; Takai S, et al. Eur J Pharmacol. 2004 Oct 6;501(1-3):1-8; Takai S, et al, Trends Pharmacol Sci. 2004 Oct;25(10):518-22; Takai S, Miyazaki M. Curr Vasc Pharmacol. 2003 Jun;1(2):217-24).
- Thus inhibition of chymase appears a useful modality in Allergy, Asthma, peripheral arterial occlusive disease, critical limb ischemia, vulnerable atherosclerotic plaque patients, unstable angina, congestive heart failure, left ventricular hypertrophy, ischemia reperfusion injury, cardiomyopathy, restenosis, rheumatoid arthritis, diabetic nephropathy, irritable Bowel Disease, Crohn's disease, wound healing (burns/ulcers in Diabetes/CLI).

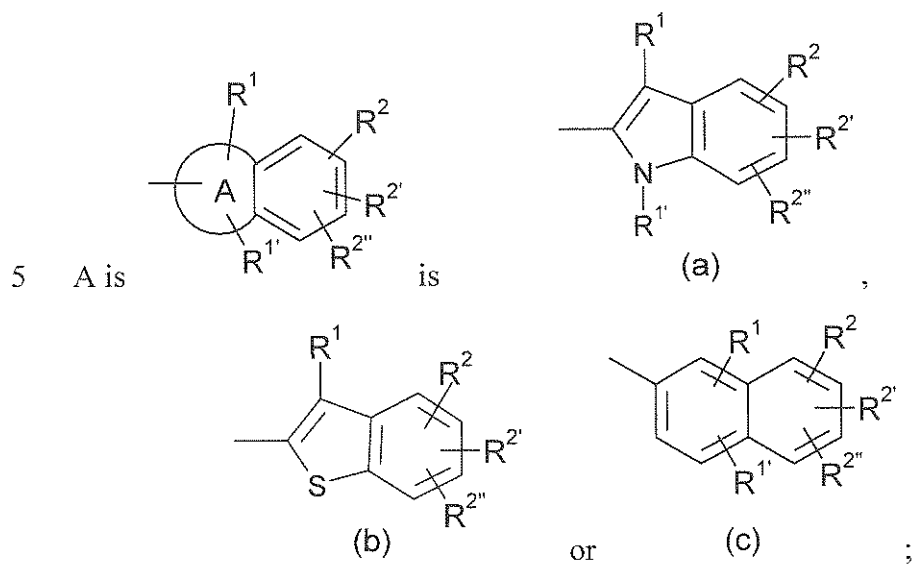
The present invention provides the novel compounds of formula (I) which are chymase inhibitors.

In a first aspect, there is provided compounds of formula (I)



(I)

wherein



R¹ and R^{1'} are independently hydrogen or C₁₋₆ alkyl,

or R^{1'} does not exist, where only R¹ can exist;

R², R^{2'} and R^{2''} are independently hydrogen or halogen;

5 X is phenylene optionally substituted by one, two or three substituents independently selected from the group consisting of halogen, cyano, nitro, amino, mono- or di- C₁₋₆ alkyl substituted amino, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, heteroalkyl, hydroxy, C₁₋₆ alkoxy, halo C₁₋₆ alkyl, halo C₁₋₆ alkoxy, heteroalkyloxy, C₁₋₆ alkylsulfonyl, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylthio, C₁₋₆ alkylsulfonyl-C₁₋₆ alkyl, C₁₋₆ alkylsulfinyl-C₁₋₆ alkyl, C₁₋₆ alkylthio C₁₋₆ alkyl, acyl, formyl, C₁₋₆ alkoxycarbonyl, halo C₁₋₆ alkoxycarbonyl, heteroalkyloxycarbonyl and heteroalkylcarbonyl;

15 Y is at the para position of the phenylene group as X, with respect to to -NH-SO₂- group and is optionally substituted heteroaryl, in which heteroaryl means a monocyclic aromatic radical of 6 ring atoms, containing one or two ring heteroatoms selected from N(O)_n (where n is 0 or 1), O, and S, the remaining ring atoms being C, or optionally substituted heterocyclyl, in which heterocyclyl means a non-aromatic mono-cyclic radical of six ring atoms, containing one or two ring atoms are heteroatoms selected from N, O, or S(O)_n (where n is an integer from 0 to 2), the remaining ring atoms being C;

20 and prodrugs and pharmaceutically acceptable salts thereof;

wherein, unless otherwise defined,

the term "heteroalkyl" means C₁₋₆ alkyl substituted by one or more substituents selected independently from the group consisting of nitro, hydroxy, halogen, cyano, C₁₋₆ alkoxy, formyl, C₁₋₆ alkylcarbonyl, carboxyl, C₁₋₆ alkylthio, C₁₋₆ alkyl sulfinyl, C₁₋₆ alkyl sulfonyl, amino and mono- or di-C₁₋₆ alkyl amino.

the term "aryl" means phenyl or naphthyl;

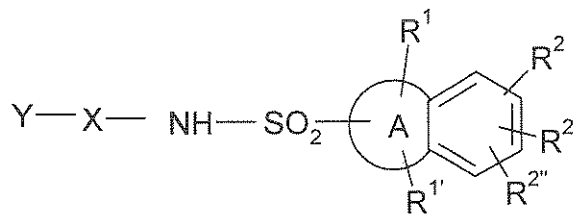
the term “heteroaryl” means a monocyclic or bicyclic radical of 5 to 12 ring atoms having at least one aromatic ring containing one, two, or three ring heteroatoms selected from N, O, and S, the remaining ring atoms being C, with the understanding that the attachment point of the heteroaryl radical will be on an aromatic ring;

the term “heterocyclyl” means a non-aromatic mono- or bi-cyclic radical of three to eight ring atoms in which one or two ring atoms are heteroatoms selected from N, O, or S(O)_n (where n is an integer from 0 to 2), the remaining ring atoms being C;

the term “optionally substituted aryl”, “optionally substituted heteroaryl”, “optionally substituted heterocyclyl” and “optionally substituted C₃₋₇ cycloalkyl” means, respectively aryl, heteroaryl, heterocyclyl and C₃₋₇ cycloalkyl optionally substituted by one or more substituents independently selected from the group consisting of halogen, nitro, cyano, amino, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, hydroxy, C₁₋₆ alkoxy, heteroalkyloxy, mono- or di- C₁₋₆ alkyl substituted amino, acyl, formyl, heteroalkylcarbonyl, C₁₋₆ alkoxy carbonyl, heteroalkyloxycarbonyl and heteroalkyl.

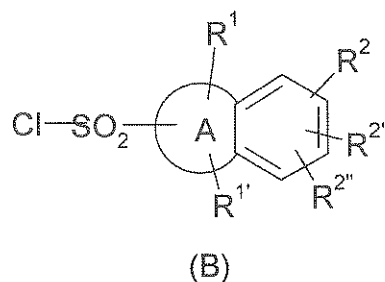
In a second aspect, there is provided 5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-pyridin-4-yl-2-trifluoromethyl-phenyl)-amide.

In a third aspect, there is provided a process for manufacturing compounds of formula (1),

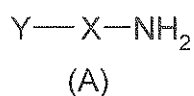


(1)

comprising a step of reacting compounds of formula (B)



with compounds of formula (A)



wherein A, R¹, R^{1'}, R², R^{2'}, R^{2''}, X and Y are as defined in the first aspect.

- 5 In a fourth aspect, there is provided pharmaceutical compositions comprising a compound as defined above and a pharmaceutically acceptable excipient.

In a fifth aspect, there is provided the compounds as defined above for use as therapeutic active substances.

- 10 In a sixth aspect, there is provided the compounds as defined above for use as therapeutic active substances for the treatment and/or prophylaxis of atherotrombosis or asthma.

In a seventh aspect, there is provided the use of compounds as defined above for the preparation of medicaments for the therapeutic and/or prophylactic treatment of diseases which are associated with chymase.

Unless otherwise indicated, the following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

The term “halogen” or “halo” means fluorine, chlorine, bromine and iodine, with fluorine, chlorine and fluorine being preferred.

The term “C₁₋₆ alkyl”, alone or in combination with other groups, means a branched or straight-chain monovalent alkyl radical, having one to six carbon atoms. This term is further exemplified by such radicals as methyl, ethyl, n-propyl, isopropyl, n-butyl, s-butyl, t-butyl. C₁₋₄ alkyl is more preferred.

The term “halo C₁₋₆ alkyl”, alone or in combination with other groups, means C₁₋₆ alkyl in which one or more hydrogen has been replaced with same or different halogen, such as

$-\text{CH}_2\text{Cl}$, $-\text{CH}_2\text{CF}_3$, trifluoromethyl. As halogen, chlorine, fluorine or bromine is preferred, and chlorine or fluorine is more preferred.

The term "halo C_{1-6} alkoxy", alone or in combination with other groups, means C_{1-6} alkoxy in which one or more hydrogen has been replaced with same or different halogen.

- 5 As halogen, chlorine, fluorine or bromine is preferred, and chlorine or fluorine is more preferred.

The term "acyl", alone or in combination with other groups, means $-\text{CO}-\text{C}_{1-6}$ alkyl.

- The term "heteroalkyl" means C_{1-6} alkyl substituted by one or more substituents selected independently from the group consisting of nitro, hydroxy, halogen, cyano, C_{1-6} alkoxy, formyl, C_{1-6} alkylcarbonyl, carboxyl, C_{1-6} alkylthio, C_{1-6} alkyl sulfinyl, C_{1-6} alkyl sulfonyl, amino and mono- or di- C_{1-6} alkyl substituted amino. This term is further exemplified by such radicals as 2-hydroxyethyl, perfluoromethyl.
- 10

- The term " C_{3-7} cycloalkyl", alone or in combination with other groups, means a saturated monovalent cyclic hydrocarbon radical of three to seven ring carbons, e.g., cyclopropyl, cyclobutyl, cyclohexyl.
- 15

The term " C_{1-6} alkoxy", alone or in combination with other groups, means the group $\text{R}'-\text{O}-$, wherein R' is a C_{1-6} alkyl.

- The term " C_{2-6} alkenyl", alone or in combination with other groups, means a straight-chain or branched hydrocarbon residue comprising an olefinic bond, having two to six carbon atoms, such as e.g. ethenyl, 2-propenyl.
- 20

The term " C_{2-6} -alkynyl", alone or in combination with other groups, means a straight-chain or branched hydrocarbon residue comprising a tripple bond, having two to six carbon atoms, such as e.g. ethynyl, 2-propynyl.

- The term " C_{0-6} alkylene" means a bond or a straight chain or branched divalent saturated aliphatic hydrocarbon group of 1 to 6 carbon atoms. C_0 alkylene means a bond.
- 25

The term "aryl", alone or in combination with other groups, means a phenyl or a naphthyl group, preferably a phenyl group.

The term "heterocyclyl", alone or combination with other groups, means non-aromatic mono- or bi-cyclic radicals of three to eight ring atoms in which one or two ring atoms

are heteroatoms selected from N, O, or S(O)_n (where n is an integer from 0 to 2), the remaining ring atoms being C.

The term "heteroaryl" means a monocyclic or bicyclic radical of 5 to 12 ring atoms having at least one aromatic ring containing one, two, or three ring heteroatoms selected from N,
5 O, and S, the remaining ring atoms being C. Preferably, the attachment point of the heteroaryl radical will be on an aromatic ring.

The term "optionally substituted aryl", "optionally substituted heteroaryl", "optionally substituted heterocyclyl" and "optionally substituted C₃₋₇ cycloalkyl" means, respectively
10 aryl, heteroaryl, heterocyclyl and C₃₋₇ cycloalkyl optionally substituted by one or more substituents independently selected from the group consisting of halogen, nitro, cyano, amino, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, hydroxy, C₁₋₆ alkoxy, heteroalkyloxy, mono- or di- C₁₋₆ alkyl substituted amino, acyl, formyl, heteroalkylcarbonyl, C₁₋₆ alkoxy carbonyl, heteroalkyloxycarbonyl and heteroalkyl.

Preferred radicals for the chemical groups whose definitions are given above are those
15 specifically exemplified in Examples.

Compounds of formula (I) can form pharmaceutically acceptable acid addition salts. Examples of such pharmaceutically acceptable salts are salts of compounds of formula (I) with physiologically compatible mineral acids, such as hydrochloric acid, sulphuric acid, sulphurous acid or phosphoric acid; or with organic acids, such as methanesulphonic
20 acid, p-toluenesulphonic acid, acetic acid, lactic acid, trifluoroacetic acid, citric acid, fumaric acid, maleic acid, tartaric acid, succinic acid or salicylic acid. The term "pharmaceutically acceptable salts" refers to such salts. Compounds of formula (I) in which a COOH group is present can further form salts with bases. Examples of such salts are alkaline, earth-alkaline and ammonium salts such as e.g. Na-, K-, Ca- and
25 Trimethylammoniumsalt. The term "pharmaceutically acceptable salts" also refers to such salts. Acid addition salts as described above are preferred.

"Optional" or "optionally" means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "aryl group
30 optionally substituted with an alkyl group" means that the alkyl may but need not be present, and the description includes situations where the aryl group is substituted with an alkyl group and situations where the aryl group is not substituted with the alkyl group.

"Pharmaceutically acceptable excipient" means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipient that is acceptable for veterinary use as well as human pharmaceutical use. A "pharmaceutically acceptable excipient" as used in the specification and claims includes both one and more than one such excipient.

Compounds that have the same molecular Formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers." Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers". When a compound has an asymmetric center, for example, if a carbon atom is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn, Ingold and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture".

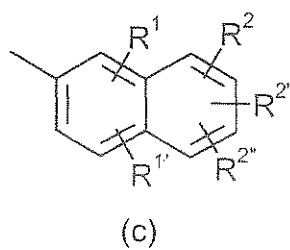
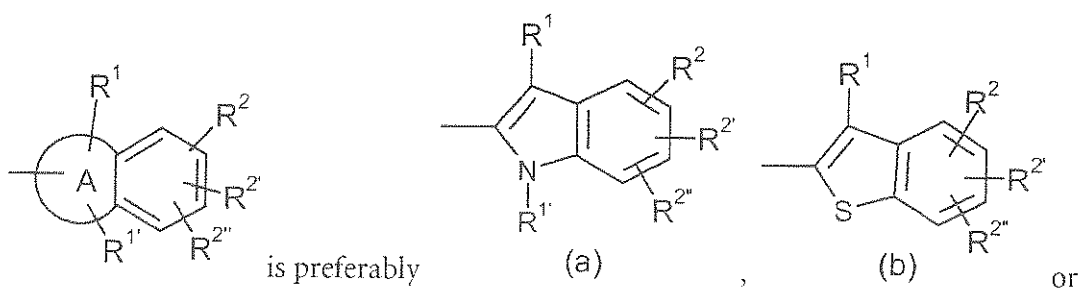
The compounds of formula (I) can possess one or more asymmetric centers. Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof, as well as individual epimers and mixture thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art.

While the broadest definition of A, R¹ to R², X and Y is described before, certain racicals are preferred.

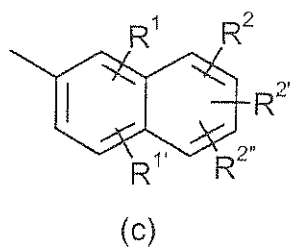
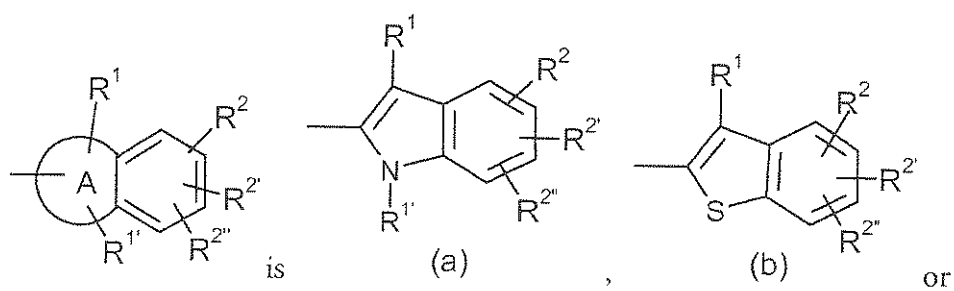
i) In the compound of formula (I), A is preferably phenyl ring or heteroaryl ring. Heteroaryl ring as A is preferably five membered ring.

ii) In the compound of formula (I),

- 7 -



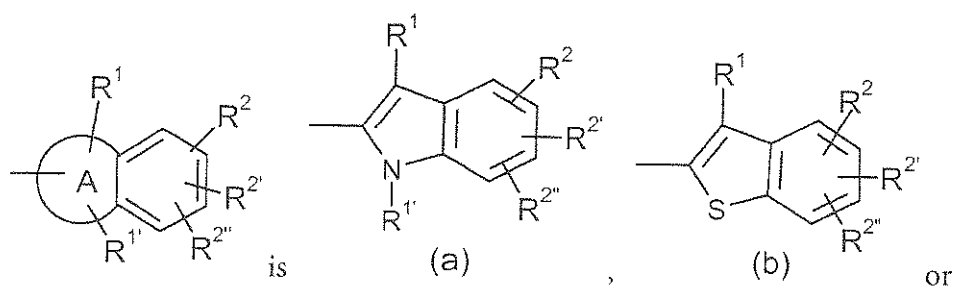
more preferably

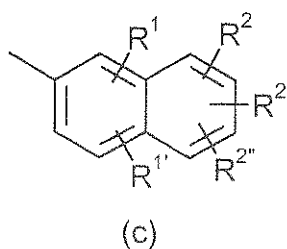


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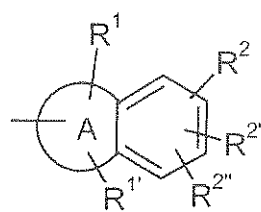
in which R^1 and $R^{1'}$ are independently hydrogen or C_{1-6} alkyl,

further more preferably

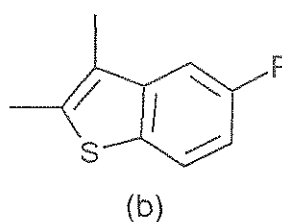




in which R^2 , $R^{2'}$ and $R^{2''}$ are independently hydrogen or halogen.



is especially



- iii) In the compound of formula (I), Y is preferably at the para position of the phenylene group as X, with respect to $-NH-SO_2-$ group.
- iv) In the compound of formula (I), X is preferably phenylene optionally substituted by one, two or three substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} alkoxy, halo C_{1-6} alkyl, halo C_{1-6} alkoxy, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl- C_{1-6} alkyl, C_{1-6} alkylsulfinyl- C_{1-6} alkyl, C_{1-6} alkylthio C_{1-6} alkyl and C_{1-6} alkoxycarbonyl, more preferably X is phenylene substituted by halo C_{1-6} alkyl or C_{1-6} alkylsulfonyl at the ortho position with respect to $-NH-SO_2-$ group, further more preferably X is phenylene substituted by trifluoromethyl or methylsulfonyl at the ortho position with respect to $-NH-SO_2-$ group.
- v) In the compound of formula (I), Y is preferably optionally substituted heteroaryl, in which heteroaryl means a monocyclic aromatic radical of 6 ring atoms, containing one or two ring nitrogen atoms, the remaining ring atoms being C, or optionally substituted heterocyclyl, in which heterocyclyl means a non-aromatic mono-cyclic radical of six ring atoms, containing one or two ring nitrogen atoms, the remaining ring atoms being C.
- More preferably, Y is pyridyl, pyrimidinyl or piperidyl, optionally substituted by one or two substituents independently selected from the group consisting of halogen, C_{1-6} alkoxy and C_{1-6} alkoxycarbonyl.

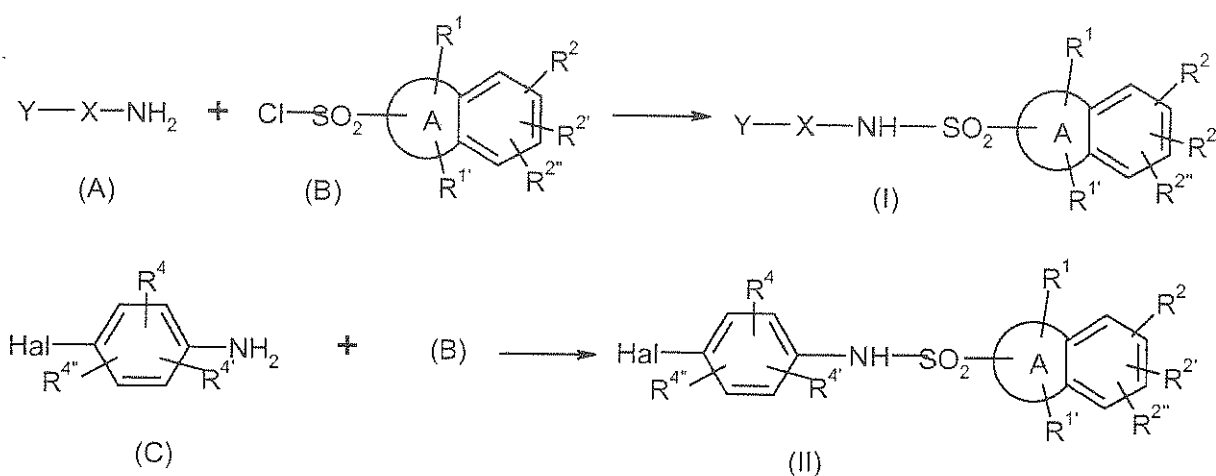
vi) A preferred compound of the invention is a compound of formula (I), which is

5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-pyridin-4-yl-2-trifluoromethyl-phenyl)-amide.

The compounds of the present invention can be prepared, for example, by the general
5 synthetic procedures described below.

General Synthetic Procedures

Scheme 1



In scheme 1, A, R^1 to $R^{2''}$, X, Y and Hal are as defined before. R^4 , $R^{4'}$ and $R^{4''}$ are
10 independently hydrogen, halogen, cyano, nitro, amino, mono- or di- C_{1-6} alkyl
substituted amino, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, heteroalkyl, hydroxy, C_{1-6} alkoxy,
halo C_{1-6} alkyl, halo C_{1-6} alkoxy, heteroalkyloxy, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6}
alkylthio, C_{1-6} alkylsulfonyl- C_{1-6} alkyl, C_{1-6} alkylsulfinyl- C_{1-6} alkyl, C_{1-6} alkylthio C_{1-6}
alkyl, acyl, formyl, C_{1-6} alkoxycarbonyl, halo C_{1-6} alkoxycarbonyl, heteroalkyloxycarbonyl
15 or heteroalkylcarbonyl.

The compounds of formula (I) and (II) are advantageously prepared by reacting sulfonyl
chloride (B) with amine (A) or with an aniline (C) in the presence of a base. The base is
preferably sodium hydride or an amine base selected from the group consisting of
pyridine, picoline, triethylamine, diethylamine, diisopropylethylamine and 4-N-
20 dimethylaminopyridine. The most preferred amines are pyridine and *N,N*-
dimethylaminopyridine (DMAP). The solvents of choice are aprotic solvents with
preferred ones selected from acetonitrile, dioxane, methylene chloride, tetrahydrofuran,
toluene, dimethoxyethane, *N,N*-dimethylacetamide, dimethylsulfoxide,

dimethylformamide and combinations thereof. The preferred temperature is in the range of 0°C to 100 °C.

Using compound (II) as an intermediate, compounds of formula (I) can be obtained by C-C bond forming reactions such as the Suzuki reaction, where the halide is reacted with
5 a suitably substituted boronic acid derivative in the presence of a base and a palladium catalyst.

The sulfonyl chlorides (B) are either commercially available or can be synthesized by state-of-the-art methods from naphthalene or bicyclic heteroaromatic compounds or derivatives thereof. In particular, the sulfonyl chloride group can be introduced starting
10 from an aryl lithium salt reacting with sulfur dioxide followed by oxidation/ chlorination with for example sulfuryl chloride or *N*-chlorosuccinimide. Alternatively, an activated aromatic position can be reacted with chlorosulfonic acid or a sulfur trioxide complex such as SO₃·DMF or SO₃·pyridine followed by chlorination with e.g. thionyl chloride.

Aniline compounds (A) are either commercially available or can be synthesized by state-
15 of-the-art methods. One option is to employ halogenated compound (C) in a C-C bond forming reactions such as the Suzuki reaction, where the halide is reacted with a suitably substituted boronic acid derivative in the presence of a base and a palladium catalyst. Halogenated aniline derivatives (C) are either commercially available or can be synthesized by state-of-the-art methods.

20

As described above, the compounds of formula (I) are active compounds and inhibit chymase. These compounds consequently prevent the activation of Angiotensin II, Endothelin, TGFb, III, SCF, collagenase and degradation of proteins like Thrombin, FN, APO A1,2. They therefore can be used for the treatment and/or prevention of allergic,
25 inflammatory and/or fibrotic diseases, such as allergy, asthma, peripheral arterial occlusive disease, critical limb ischemia, vulnerable atherosclerotic plaque patients, unstable angina, congestive heart failure, left ventricular hypertrophy, ischemia reperfusion injury, stroke, cardiomyopathy, restenosis, rheumatoid arthritis, diabetic nephropathy, irritable Bowel Disease, Crohns' disease, atherothrombosis and/or
30 burns/ulcers in Diabetes/CLI.

Prevention and/or treatment of allergic, inflammatory or fibrotic diseases, particularly atherothrombosis or asthma, is the preferred indication.

The invention therefore also relates to pharmaceutical compositions comprising a compound as defined above and a pharmaceutically acceptable excipient.

The invention likewise embraces compounds as described above for use as therapeutically active substances, especially as therapeutically active substances for the treatment and/or prophylaxis of allergic, inflammatory and/or fibrotic diseases, particularly as therapeutically active substances for the treatment and/or prophylaxis of allergy, asthma, peripheral arterial occlusive disease, critical limb ischemia, vulnerable atherosclerotic plaque patients, unstable angina, congestive heart failure, left ventricular hypertrophy, ischemia reperfusion injury, stroke, cardiomyopathy, restenosis, rheumatoid arthritis, diabetic nephropathy, irritable Bowel Disease, Crohns' disease, atherothrombosis and/or burns/ulcers in Diabetes/CLI.

The invention also relates to the use of compounds as described above for the preparation of medicaments for the therapeutic and/or prophylactic treatment of allergic, inflammatory and/or fibrotic diseases, particularly for the therapeutic and/or prophylactic treatment of allergy, asthma, peripheral arterial occlusive disease, critical limb ischemia, vulnerable atherosclerotic plaque patients, unstable angina, congestive heart failure, left ventricular hypertrophy, ischemia reperfusion injury, stroke, cardiomyopathy, restenosis, rheumatoid arthritis, diabetic nephropathy, irritable Bowel Disease, Crohns' disease, atherothrombosis and/or burns/ulcers in Diabetes/CLI. Such medicaments comprise a compound as described above.

The invention also relates to the process and the intermediates for manufacturing the compounds of formula (I) as well as the process for manufacturing the intermediates.

The inhibition of chymase by the compounds of the present invention can be demonstrated by the peptide substrate assay as described hereinafter.

For the chymase a substrate was chosen containing the 4 amino acid peptide AAPF as a standard substrate for chymotrypsin like compounds (succinyl-Ala-Ala-Pro-Phe-[7-amino-4-methylcoumarin]; Lockhart BE, et al., "Recombinant human mast-cell chymase: an improved procedure for expression in *Pichia pastoris* and purification of the highly active enzyme." *Biotechnol Appl Biochem.* published as immediate publication 26 May 2004 as manuscript BA20040074)). The peptide was synthesized with a purity of 95% from Bachem, Bubendorf, Switzerland). Chymase purified from human skin mast cells was obtained from Calbiochem (Merck Biosciences, San Diego, California, USA). The assay buffer was 0.15 M NaCl, 0.05M, Tris HCl , 0.05% CHAPS (3-[(3-

- Cholamidopropyl)-dimethylammonio]-1-propane sulphonate), 0.1mg/ml Heparin (Heparin sodium, Sigma, porcine intestinal mucosa), 0.02mM AAPF-substrate, 1nM Chymase at pH 7.4. The assay was performed in 96-well plates (Packard Optiplate), with a 0.05ml volume at room temperature. Chymase activity was indicated by the initial rate of increase in fluorescence at 340/440nm (excitation / emission) from free 7-amino-4-methylcoumarin released from the substrate. Inhibition of the activity by inhibitory compounds was read after 30 min pre-incubation with the chymase at room temperature in assay buffer without AAPF-substrate. The assay was then started by addition of the indicated concentration of AAPF-substrate.
- 10 The IC₅₀ values of the active compounds of the present invention preferably amount to about 1000 to 1 nM, especially about 30 to 1 nM.

Example	IC ₅₀ (nM)
Example 2	35
Example 16	106
Example 21	3

- The compounds of formula (I) and/or their pharmaceutically acceptable salts can be used as medicaments, e.g. in the form of pharmaceutical preparations for enteral, parenteral or topical administration. They can be administered, for example, perorally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions or suspensions or infusion solutions, or topically, e.g. in the form of ointments, creams or oils. Oral administration is preferred.
- 20 The production of the pharmaceutical preparations can be effected in a manner which will be familiar to any person skilled in the art by bringing the described compounds of formula I and/or their pharmaceutically acceptable salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.
- 25

Suitable carrier materials are not only inorganic carrier materials, but also organic carrier materials. Thus, for example, lactose, corn starch or derivatives thereof, talc, stearic acid

or its salts can be used as carrier materials for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carrier materials for soft gelatine capsules are, for example, vegetable oils, waxes, fats and semi-solid and liquid polyols (depending on the nature of the active ingredient no carriers might, however, be required in the case of soft gelatine capsules). Suitable carrier materials for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar. Suitable carrier materials for injection solutions are, for example, water, alcohols, polyols, glycerol and vegetable oils. Suitable carrier materials for suppositories are, for example, natural or hardened oils, waxes, fats and semi-liquid or liquid polyols. Suitable carrier materials for topical preparations are glycerides, semi-synthetic and synthetic glycerides, hydrogenated oils, liquid waxes, liquid paraffins, liquid fatty alcohols, sterols, polyethylene glycols and cellulose derivatives.

Usual stabilizers, preservatives, wetting and emulsifying agents, consistency-improving agents, flavour-improving agents, salts for varying the osmotic pressure, buffer substances, solubilizers, colorants and masking agents and antioxidants come into consideration as pharmaceutical adjuvants.

The dosage of the compounds of formula (I) can vary within wide limits depending on the disease to be controlled, the age and the individual condition of the patient and the mode of administration, and will, of course, be fitted to the individual requirements in each particular case. For adult patients a daily dosage of about 1 to 1000 mg, especially about 1 to 300 mg, comes into consideration. Depending on severity of the disease and the precise pharmacokinetic profile the compound could be administered with one or several daily dosage units, e.g. in 1 to 3 dosage units.

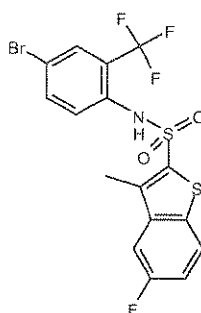
The pharmaceutical preparations conveniently contain about 1-500 mg, preferably 1-100 mg, of a compound of formula (I).

Examples

The following Examples serve to illustrate the present invention in more detail. They are, however, not intended to limit its scope in any manner.

5 Example 1

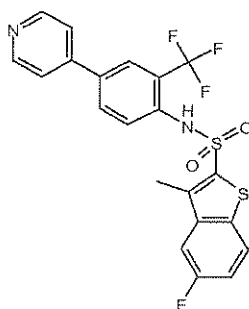
5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-bromo-2-trifluoromethyl-phenyl)-amide



- 10 To an ice cooled solution of 4-bromo-2-(trifluoromethyl)benzenamine (CAS 445-02-3, 18 g) in pyridine (25 ml) was added 5-fluoro-3-methylbenzo[b]thiophene-2-sulphonyl chloride (CAS:404964-34-7, 2.0 g). The reaction mixture was stirred at rt for 72h, concentrated under vacuum, and the residue was chromatographed over silica gel using heptane/chloroform as eluent to obtain 5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-bromo-2-trifluoromethyl-phenyl)-amide (2.35 g) as a colourless solid. MS (ISN): 465.9, 468.0 (M-H)⁻

Example 2

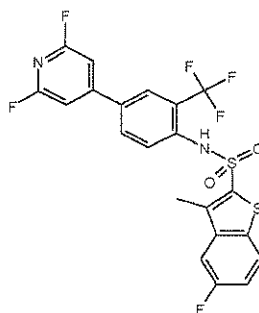
5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-pyridin-4-yl-2-trifluoromethyl-phenyl)-amide



A suspension of 5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-bromo-2-trifluoromethyl-phenyl)-amide (0.5 g) and 4-pyridineboronic acid (0.197 g) in 1,2-dimethoxyethane (6 ml), ethanol (2 ml) and 2 M aqueous sodium carbonate solution (4.0 ml) was degassed 3-4 times to remove oxygen, then
5 tetrakis(triphenylphosphine)palladium (0.065 g) was added. The reaction mixture was stirred at 80 °C for 3h, quenched with ice/water, and extracted with ethyl acetate. The organic layers were washed, dried and concentrated. The residue was chromatographed over silica gel using heptane/ethyl acetate as eluent to obtain the title compound (0.35 g)
10 as a yellowish solid. MS (ISP): 467.3 (M+H)⁺

Example 3

5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid [4-(2,6-difluoro-pyridin-4-yl)-2-trifluoromethyl-phenyl]-amide

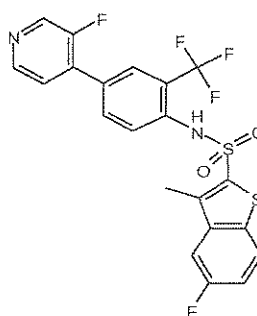


15 This compound was prepared in analogy to Example 2 starting from 5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-bromo-2-trifluoromethyl-phenyl)-amide (0.12 g) and 2,6-difluoropyridine-4-boronic acid (0.063 g) in 1,2-dimethoxyethane (1.5 ml), ethanol (0.32 ml) and 2 M aqueous sodium carbonate solution (1.0 ml) with tetrakis(triphenylphosphine)palladium (0.055 g) to obtain the title compound (0.055 g)
20 as a brownish solid. MS (ISP): 520.2 (M+ NH4)⁺

Example 4

5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid [4-(3-fluoro-pyridin-4-yl)-2-trifluoromethyl-phenyl]-amide

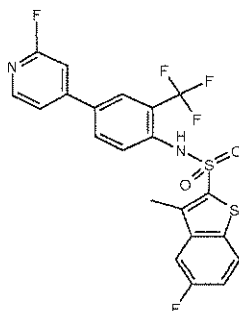
- 16 -



This compound was prepared in analogy to Example 2 starting from 5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-bromo-2-trifluoromethyl-phenyl)-amide (0.12 g) and 3-fluoropyridine-4-boronic acid hydrate (0.061 g) in 1,2-dimethoxyethane (1.5 ml), ethanol (0.32 ml) and 2 M aqueous sodium carbonate solution (1.0 ml) with tetrakis(triphenylphosphine)palladium (0.050 g) to obtain the title compound (0.025 g) as a yellowish foam. MS (ISP): 485.3 (M+ H)⁺

Example 5

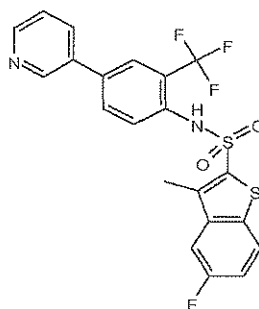
5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid [4-(2-fluoro-pyridin-4-yl)-2-trifluoromethyl-phenyl]-amide



This compound was prepared in analogy to Example 2 starting from 5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-bromo-2-trifluoromethyl-phenyl)-amide (0.12 g) and 2-fluoropyridine-4-boronic acid (0.072 g) in 1,2-dimethoxyethane (1.5 ml), ethanol (0.32 ml) and 2 M aqueous sodium carbonate solution (1.0 ml) with tetrakis(triphenylphosphine)palladium (0.065 g) to obtain the title compound (0.085 g) as a colourless foam. MS (ISN): 483.4 (M-H)⁻

Example 6

5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-pyridin-3-yl-2-trifluoromethyl-phenyl)-amide

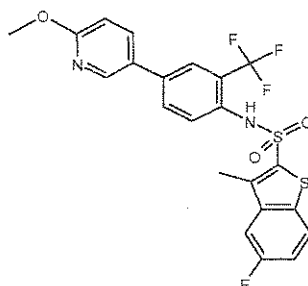


5

This compound was prepared in analogy to Example 2 starting from 5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-bromo-2-trifluoromethyl-phenyl)-amide (0.10 g) and 3-pyridineboronic acid (0.052 g) in 1,2-dimethoxyethane (1.5 ml), ethanol (0.32 ml) and 2 M aqueous sodium carbonate solution (0.8 ml) with
10 tetrakis(triphenylphosphine)palladium (0.050 g) to obtain the title compound (0.086 g) as a colourless solid. MS (ISP): 467.0 (M+H)⁺

Example 7

5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid [4-(6-methoxy-pyridin-3-yl)-2-trifluoromethyl-phenyl]-amide



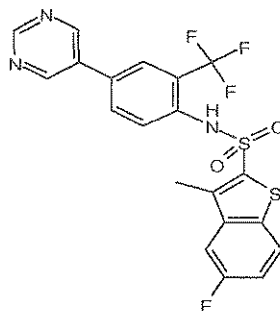
15

This compound was prepared in analogy to Example 2 starting from 5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-bromo-2-trifluoromethyl-phenyl)-amide (0.10 g) and 2-methoxy-5-pyridineboronic acid (0.065 g) in 1,2-dimethoxyethane (1.5 ml), ethanol (0.32 ml) and 2 M aqueous sodium carbonate solution (0.8 ml) with

tetrakis(triphenylphosphine)palladium (0.012 g) to obtain the title compound (0.081 g) as a colourless solid. MS (ISP): 497.3 (M+H)⁺

Example 8

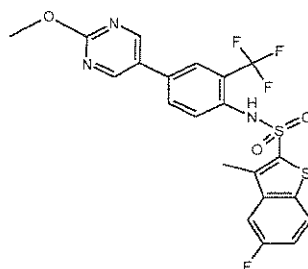
5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-pyrimidin-5-yl-2-trifluoromethyl-phenyl)-amide



This compound was prepared in analogy to Example 2 starting from 5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-bromo-2-trifluoromethyl-phenyl)-amide (0.10 g) and pyrimidine-5-boronic acid (0.053 g) in 1,2-dimethoxyethane (1.5 ml), ethanol (0.32 ml) and 2 M aqueous sodium carbonate solution (0.8 ml) with tetrakis(triphenylphosphine)palladium (0.012 g) to obtain the title compound (0.045 g) as a colourless solid. MS (ISN): 466.1 (M-H)⁻

Example 9

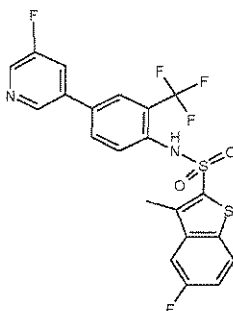
5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid [4-(2-methoxy-pyrimidin-5-yl)-2-trifluoromethyl-phenyl]-amide



This compound was prepared in analogy to Example 2 starting from 5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-bromo-2-trifluoromethyl-phenyl)-amide (0.10 g) and 2-methoxy-5-pyrimidineboronic acid (0.066 g) in 1,2-dimethoxyethane (1.5 ml), ethanol (0.32 ml) and 2 M aqueous sodium carbonate solution (1.0 ml) with
5 tetrakis(triphenylphosphine)palladium (0.012 g) to obtain the title compound (0.064 g) as a colourless solid. MS (ISP): 498.4 (M+H)⁺

Example 10

5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid [4-(5-fluoro-pyridin-3-yl)-2-trifluoromethyl-phenyl]-amide



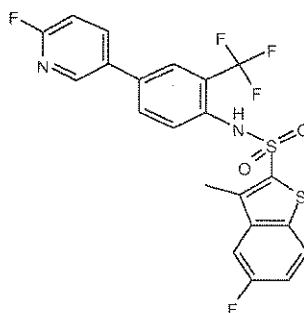
10

This compound was prepared in analogy to Example 2 starting from 5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-bromo-2-trifluoromethyl-phenyl)-amide (0.12 g) and 5-fluoropyridine-3-boronic acid (0.072 g) in 1,2-dimethoxyethane (1.5 ml), ethanol
15 (0.32 ml) and 2 M aqueous sodium carbonate solution (1.0 ml) with tetrakis(triphenylphosphine)palladium (0.015 g) to obtain the title compound (0.065 g) as a colourless solid. MS (ISP): 485.3 (M+H)⁺

Example 11

5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid [4-(6-fluoro-pyridin-3-yl)-2-trifluoromethyl-phenyl]-amide
20

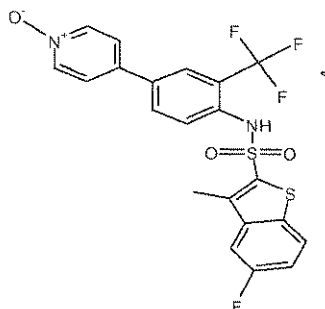
- 20 -



This compound was prepared in analogy to Example 2 starting from 5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-bromo-2-trifluoromethyl-phenyl)-amide (0.12 g) and 2-fluoropyridine-5-boronic acid (0.072 g) in 1,2-dimethoxyethane (1.5 ml), ethanol (0.32 ml) and 2 M aqueous sodium carbonate solution (1.0 ml) with tetrakis(triphenylphosphine)palladium (0.015 g) to obtain the title compound (0.070 g) as a colourless solid. MS (ISP): 485.3 (M+H)⁺

Example 12

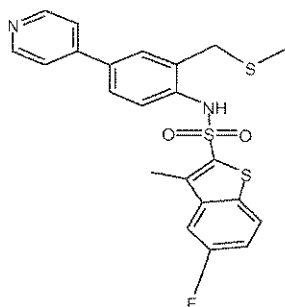
5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid [4-(1-oxy-pyridin-4-yl)-2-trifluoromethyl-phenyl]-amide



To a solution of 5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-pyridin-4-yl)-2-trifluoromethyl-phenyl)-amide (cf. Example 2, 0.27 g) in chloroform (5.0 ml) was added m-chloroperbenzoic acid 85 % (0.195 g). The reaction mixture was stirred at rt for 4h and washed with bicarbonate solution. The organic phase was dried over magnesium sulphate and concentrated. The residue was chromatographed on a silica gel column (10 g) using dichloromethane /methanol as eluent to obtain the title compound (0.065 g) as yellow foam. MS (ISP): 483.4 (M+H)⁺

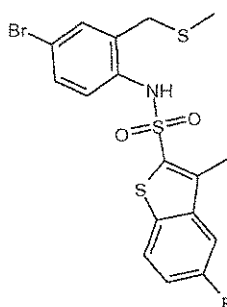
Example 13

5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-methylsulfanylmethyl-4-pyridin-4-yl-phenyl)-amide.



5

a) 5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-bromo-2-methylsulfanylmethyl-phenyl)-amide



10

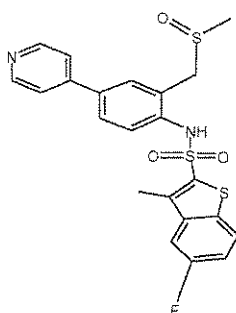
This compound was prepared in analogy to Example 1 starting from 4-bromo-2-methylsulfanylmethyl-phenylamine (Allen, David George; Eldred, Colin David; Judkins, Brian David; Mitchell, William Leonard, WO 9749699, 4.6 g) and 5-fluoro-3-methylbenzo[b]thiophene-2-sulphonyl chloride (1.06 g) to obtain the desired compound
 15 (1.3 g) as a brownish solid. MS (ISN): 458.1, 460.0 (M-H)⁺

b) 5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-methylsulfanylmethyl-4-pyridin-4-yl-phenyl)-amide.

This compound was prepared in analogy to Example 2 starting from 5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-bromo-2-methylsulfanylmethyl-phenyl)-amide (0.23 g) and 4-pyridineboronic acid (0.092 g) in 1,2-dimethoxyethane (10 ml), ethanol (2 ml) and 2 M aqueous sodium carbonate solution (2 ml) with
 5 tetrakis(triphenylphosphine)palladium (0.058 g) to obtain the title compound (0.153 g) as a brownish foam (0.153 g). MS (ISN): 457.2 (M-H)⁺

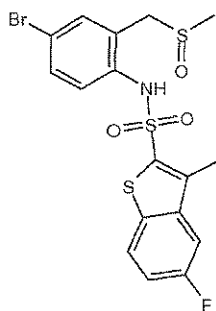
Example 14

5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-methanesulfinylmethyl-4-pyridin-4-yl-phenyl)-amide



10

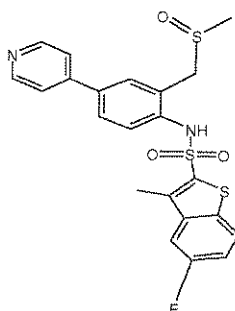
a) 5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-bromo-2-methanesulfinylmethyl-phenyl)-amide.



15

To a solution of 5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-bromo-2-methylsulfanylmethyl-phenyl)-amide (0.46 g) (cf. example 13a) in chloroform (25 ml) was added m-chloroperbenzoic acid 85 % (0.272 g). The reaction mixture was stirred at
 20 rt for 18h, concentrated, and the crude residue was chromatographed on silica gel using heptane/ethyl acetate as eluent to obtain the desired compound (0.31 g) as an off-white solid. MS (ISN): 473.9, 476.0 (M-H)⁺

b) 5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-bromo-2-methanesulfinylmethyl-phenyl)-amide



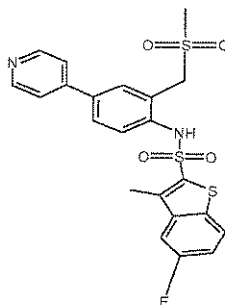
5

This compound was prepared in analogy to Example 2 starting from 5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-bromo-2-methanesulfinylmethyl-phenyl)-amide (0.238 g) and 4-pyridineboronic acid (0.092 g) in 1,2-dimethoxyethane (10 ml), ethanol (2 ml) and 2 M aqueous sodium carbonate solution (2 ml) with tetrakis(triphenylphosphine)palladium (0.058 g) to obtain the title compound (0.077 g) as a yellowish foam. MS (ISN): 473.3 (M-H)⁻

Example 15

5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-methanesulfonylmethyl-4-pyridin-4-yl-phenyl)-amide

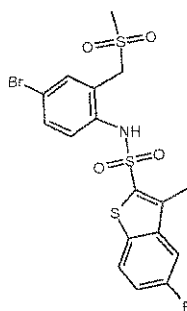
15



a) 5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-bromo-2-methanesulfonylmethyl-phenyl)-amide

20

- 24 -



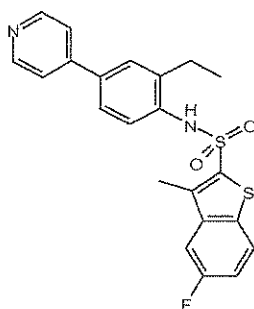
To a solution of 5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-bromo-2-methylsulfonylmethyl-phenyl)-amide (0.46 g) (cf. Example 13a) in chloroform (25 ml) was added 85 % m-chloroperbenzoic acid (0.272 g). The reaction mixture was stirred at
5 rt for 18h, concentrated, and the crude residue was chromatographed on silica gel using heptane/ethyl acetate as eluent to obtain the desired compound (0.138 g) as a brownish solid. MS (ISN): 490.0, 492.0 (M-H)⁻

b) 5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-methanesulfonylmethyl-4-pyridin-4-yl-phenyl)-amide
10

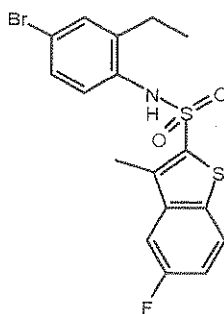
This compound was prepared in analogy to Example 2 starting from 5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-bromo-2-methanesulfonylmethyl-phenyl)-amide (0.123 g) and 4-pyridineboronic acid (0.0462 g) in 1,2-dimethoxyethane (5 ml), ethanol
15 (1 ml) and 2 M aqueous sodium carbonate solution (2 ml) with tetrakis(triphenylphosphine)palladium (0.035 g) to obtain the title compound (0.029 g) as a yellowish foam. MS (ISN): 489.1 (M-H)⁻

Example 16

5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-ethyl-4-pyridin-4-yl-phenyl)-amide.
20



a) 5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-bromo-2-ethyl-phenyl)-amide.



5 This compound was prepared in analogy to Example 1, starting from 4-bromo-2-ethylaniline (CAS:45762-41-2, 2.0 g) and 5-fluoro-3-methylbenzo[b]thiophene-2-sulphonyl chloride (0.265 g) in pyridine (2.0 ml) for 4h to obtain the desired compound (0.20 g) as a colourless solid. MS (ISP): 445.0, 447.0 (M+NH₄)⁺

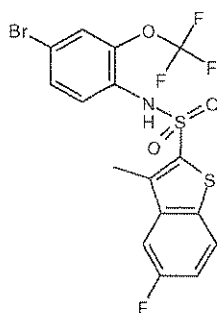
10 b) 5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-ethyl-4-pyridin-4-yl-phenyl)-amide.

This product was prepared in analogy to Example 2 starting from 5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-bromo-2-ethyl-phenyl)-amide (0.10 g) and 4-pyridineboronic acid (0.043 g) in 1,2-dimethoxyethane (1.5 ml), ethanol (0.25 ml) and 2
15 M aqueous sodium carbonate solution (0.9 ml) with tetrakis(triphenylphosphine)palladium (0.013 g) to obtain the title compound (0.025 g) as a yellowish foam. MS (ISP): 427.3 (M+H)⁺

Example 17

5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-bromo-2-trifluoromethoxy-phenyl)-amide.
20

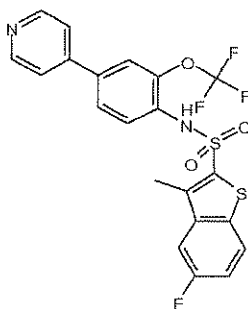
- 26 -



This compound was prepared in analogy to Example 1, starting from 4-bromo-2-(trifluoromethoxy)aniline (CAS: 175278-09-8, 2.82 g) and 5-fluoro-3-methylbenzo[b]thiophene-2-sulphonyl chloride (0.265 g) in pyridine (2.0 ml) for 18h to obtain the desired compound (0.12 g) as a colourless foam. MS (ISP): 501.0, 503.0 (M+NH₄)⁺

Example 18

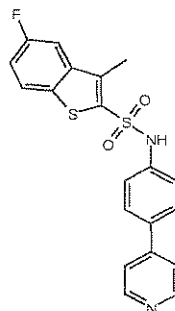
5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-pyridin-4-yl-2-trifluoromethoxy-phenyl)-amide



This compound was prepared in analogy to example 2 starting from 5-fluoro-3-methylbenzo[b]thiophene-2-sulfonic acid (4-bromo-2-trifluoromethoxy-phenyl)-amide (0.075 g) and 4-pyridineboronic acid (0.029 g) in 1,2-dimethoxyethane (1.5 ml), ethanol (0.25 ml) and 2 M aqueous sodium carbonate solution (0.6 ml) with tetrakis(triphenylphosphine)palladium (0.009 g) to obtain the title compound (0.055 g) as a colourless solid. MS (ISP): 483.0 (M+H)⁺

Example 19

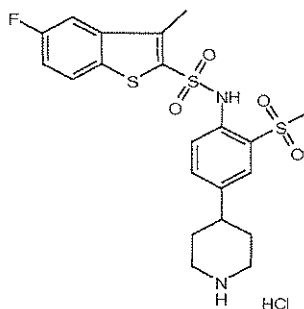
5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-pyridin-4-yl-phenyl)-amide



- 5 To a solution of (4-pyridine-4-yl)aniline (CAS: 13296-04-3, 0.290 g) in dichloromethane (12.0 ml) was added 5-fluoro-3-methylbenzo[b]thiophene-2-sulphonyl chloride (0.440 g) and DMAP (0.305 g). The reaction mixture was stirred at rt for 16 h, diluted with dichloromethane (12 ml) and chromatographed on silica gel using heptane/ ethyl acetate as eluent to obtain the title compound (0.205 g) as an off-white solid. MS (ISN): 397.1
- 10 (M-H)⁻

Example 20

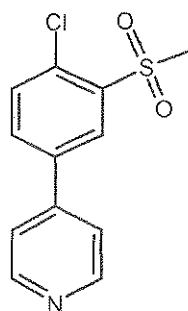
5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-methanesulfonyl-4-piperidin-4-yl-phenyl)-amide hydrochloride



15

- a) 4-(4-Chloro-3-methanesulfonyl-phenyl)-pyridine

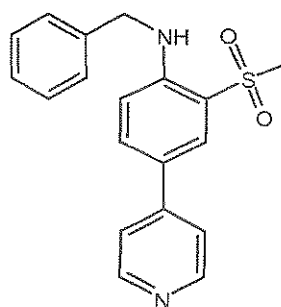
- 28 -



1-Bromo-4-chlorobenzene (12.25 g) was added portionwise to chlorosulfonic acid (56 g) at 5-10 °C. The resulting mixture was heated to 130 °C for 16h. After cooling, the mixture was added in a slow stream to well stirred ice/water (500 ml), and stirring was continued
5 for a further 30 minutes. The colourless precipitate was collected by filtration. The wet filter cake was taken up in dichloromethane, separated from the water, and the organic phase was dried and evaporated to dryness (14.1 g). The dried mixture of 2 isomers was dissolved in THF (20 ml) and added to a solution of sodium sulfite (15.3 g) in water (100 ml). The reaction was exothermic, and the pH went down. Ice and conc. NaOH were
10 added to keep the temperature at 20-30 °C and the pH at ca. 9. The reaction mixture was then stirred over night at rt and pH 9, acidified with conc. HCl to pH1, and cooled down. The precipitate was filtered off, washed with cold water and dried over P2O5 under high vacuum over night to obtain a colourless sulfinic acid derivative (10.5 g). This acid was dissolved in DMF (100 ml), methyl iodide (13 g) was added, followed by potassium
15 carbonate (14.0 g). The reaction mixture was stirred at rt overnight, and concentrated under high vacuum. To the residue was added water and extracted with tert-butylmethyl ether. The organics were washed, dried and concentrated. The residue was chromatographed over silica gel using cyclohexane/ethyl acetate as eluent to produce the methylsulfonyl derivative (9.1 g) which was still a mixture of 2 isomers. This mixture (9.0
20 g) was dissolved in dimethoxyethane (400 ml) and ethanol (90 ml) and displaced with 2M aqueous sodium carbonate solution (200 ml). The reaction mixture was degassed a few times, and tetrakis(triphenylphosphine)palladium (3.0 g) was added. The mixture was heated to 80 °C for 16h and concentrated to dryness. The residue was taken up in dichloromethane/water, extracted, dried and concentrated. The solid residue was taken
25 up in ether, filtered, washed and dried to obtain the desired compound (5.54 g) as off-white crystals. MS (EI): 267.1 (M)

b) Benzyl-(2-methanesulfonyl-4-pyridin-4-yl-phenyl)-amine

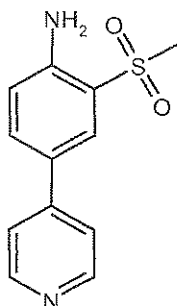
- 29 -



A suspension of 4-(4-chloro-3-methanesulfonyl-phenyl)-pyridin(5.5 g) in benzylamine (23 ml) was heated to 160 °C for 4h, concentrated under high vacuum. The residue was quenched with ice/water and extracted with ethyl acetate. The organic layers were
5 washed, dried and concentrated; the residue was chromatographed on silica gel with heptane/ethyl acetate. The compound containing fractions were evaporated, and the residue crystallized from methanol/ether to obtain the desired compound (5.75 g) as an off-white solid. MS (ISP): 339.1 (M+H)⁺

c) 2-Methanesulfonyl-4-pyridin-4-yl-phenylamine

10

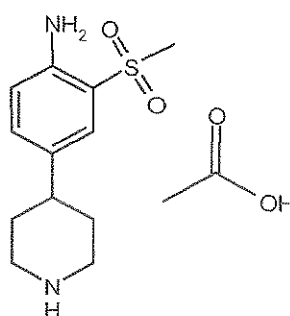


To a solution of benzyl-(2-methanesulfonyl-4-pyridin-4-yl-phenyl)-amine (2.0 g) in dioxane /methanol 1:1 (100 ml) was added 2N HCl (5 ml) and palladium black (1.0 g).

15 The reaction mixture was hydrogenated at 1.1 bar and rt for 18h. The catalyst was filtered off over a microfilter and washed with methanol. The filtrate was evaporated to dryness to obtain the desired compound (1.45 g) as a yellowish solid. MS (ISP): 249.1 (M+H)⁺

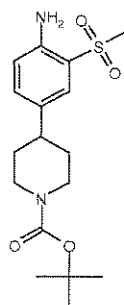
d) 2-Methanesulfonyl-4-piperidin-4-yl-phenylamine; compound with acetic acid

- 30 -



A suspension of 2-methanesulfonyl-4-pyridin-4-yl-phenylamine (0.70 g) and platinum oxide (0.70 g) in acetic acid (15 ml) was hydrogenated at 1.1 bar and 80 °C for 8h. The reaction mixture was cooled to rt, filtered over a microfilter, washed with acetic acid, and concentrated to dryness to obtain the title compound (0.89 g) as a light yellow amorphous powder. MS (ISP): 255.4 (M+H)⁺

e) 4-(4-Amino-3-methanesulfonyl-phenyl)-piperidine-1-carboxylic acid tert-butyl ester



10

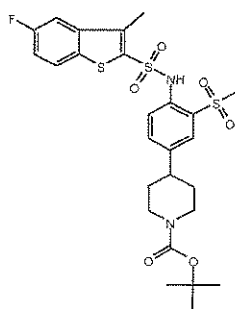
To a solution of 2-methanesulfonyl-4-piperidin-4-yl-phenylamine; compound with acetic acid (1.5 g) in dichloromethane (30 ml) was added di-tert-butylcarbonate (1.15 g) and saturated aqueous sodium carbonate solution (10 ml). The reaction mixture was stirred at rt for 3h and extracted with dichloromethane. The organic phases were dried and concentrated, and the residue was chromatographed on silica gel using heptane/ethyl acetate as eluent to obtain the desired compound (0.64 g) as an off-white solid. MS (ISP): 355.1 (M+H)⁺

15

f) 4-[4-(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonylamino)-3-methanesulfonyl-phenyl]-piperidine-1-carboxylic acid tert-butyl ester

20

- 31 -



To an ice cooled suspension of sodium hydride (60-65 % in mineral oil, 0.030 g) in absolute DMSO (3 ml) was added 4-(4-amino-3-methanesulfonyl-phenyl)-piperidine-1-carboxylic acid tert-butyl ester (0.106 g). The mixture was stirred at 0-5 °C for 30 minutes, and a solution 5-fluoro-3-methylbenzo[b]thiophene-2-sulphonyl chloride (0.237 g) in absolute DMSO (1 ml) was added dropwise. The reaction mixture was stirred at rt for 5h, quenched with ice/water/1N HCl, and extracted with ethyl acetate. The organic phases were washed, dried and concentrated, and the residue was chromatographed over silica gel using heptane/ethyl acetate as eluent to obtain the desired compound (0.025 g) methylbenzo[b]thiophene-2-sulphonyl chloride (0.237 g) to obtain the desired compound (0.025 g) as a yellowish foam. MS (ISN): 581.3 (M-H)⁻ g)

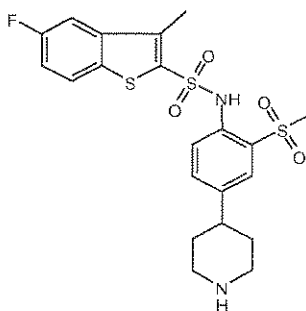
5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-methanesulfonyl-4-piperidin-4-yl-phenyl)-amide hydrochloride

A solution of 4-[4-(5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonylamino)-3-methanesulfonyl-phenyl]-piperidine-1-carboxylic acid tert-butyl ester (0.025 g) in ethyl acetate (1 ml) was treated with 2.5 N HCl/ethyl acetate (2 ml). The reaction mixture was stirred at rt for 2h. Ether (20 ml) was added, the precipitate was filtered off, washed with ether and dried under high vacuum over P₂O₅ to obtain the title compound (0.020 g) as a yellowish powder. MS (ISP): 483.3 (M+H)⁺

Example 21

5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-methanesulfonyl-4-piperidin-4-yl-phenyl)-amide

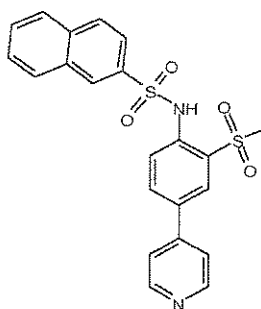
- 32 -



5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-methanesulfonyl-4-piperidin-4-yl-phenyl)-amide hydrochloride (cf. Example 20g, 6mg) was run through an HPLC-
 5 column with acetonitrile/water/formic acid to obtain the title compound (3mg) as an off-white foam. MS (ISP): 483.3 (M+H)⁺

Example 22

Naphthalene-2-sulfonic acid (2-methanesulfonyl-4-pyridin-4-yl-phenyl)-amide



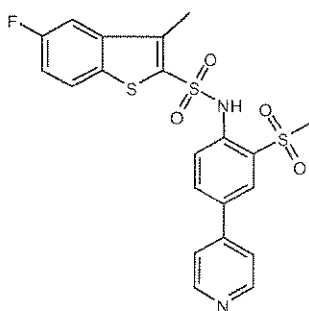
10

To a solution of 2-methanesulfonyl-4-pyridin-4-yl-phenylamine (cf. Example 20c, 0.046 g) in pyridine (0.5 ml) was added naphthalene-2-sulfochloride (0.051 g). The reaction mixture was stirred at 70 °C for 6h, diluted with dichloromethane and chromatographed on silica gel using dichloromethane/methanol/ammonia to obtain the title compound
 15 (0.025 g) as an off-white solid. MS (ISP): 439.1 (M+H)⁺

Example 23

5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-methanesulfonyl-4-pyridin-4-yl-phenyl)-amide

- 33 -

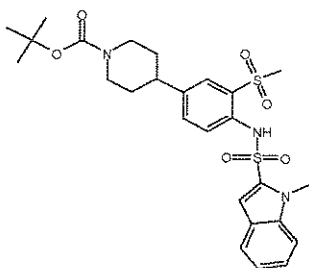


This compound was prepared in analogy to Example 20f starting from 2-methanesulfonyl-4-pyridin-4-yl-phenylamine (cf. Example 20c, 0.27 g) in

- 5 tetrahydrofuran (10 ml) and 5-fluoro-3-methylbenzo[b]thiophene-2-sulphonyl chloride (0.265 g) with sodium hydride (0.10 g) at rt for 18h to obtain the title compound (0.025g) as a yellow foam. MS (ISN): 475.0 (M-H)⁻

Example 24

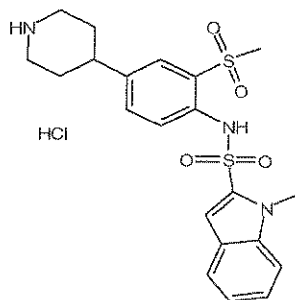
- 4-[3-Methanesulfonyl-4-(1-methyl-1H-indole-2-sulfonylamino)-phenyl]-piperidine-1-
10 carboxylic acid tert-butyl ester



- To a solution of 4-(4-amino-3-methanesulfonyl-phenyl)-piperidine-1-carboxylic acid tert-butyl ester (cf. Example 20e, 0.050 g) in dichloromethane (2.0 ml) was added 1-methyl-1H-indole-2-sulfonyl chloride (0.036 g; cf. Chan, Ming Fai; Wu, Chengde; Raju,
15 Bore Gowda; Kogan, Timothy; Kois, Adam; Verner, Erik Joel; Castillo, Rosario Silvestre; Yalamorri, Venkatachalapathi; Balaji, Vitukudi Narayanaiyengar, US 5962490) and DMAP (0.021 g). The reaction mixture was stirred at 80 °C for 18h, cooled and directly chromatographed on silica gel using heptane/ethyl acetate as eluent to obtain the title compound (0.048 g) as a yellowish foam. MS (ISN): 546.5 (M-H)⁺

Example 25

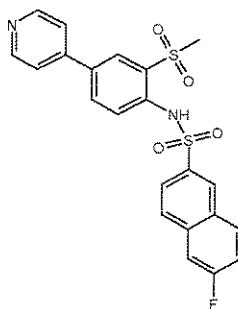
1-Methyl-1H-indole-2-sulfonic acid (2-methanesulfonyl-4-piperidin-4-yl-phenyl)-amide hydrochloride



- 5 A solution of 4-[3-methanesulfonyl-4-(1-methyl-1H-indole-2-sulfonylamino)-phenyl]-piperidine-1-carboxylic acid tert-butyl ester (0.038 g) was treated with 2.5 N HCl/ethyl acetate (2.5 ml). The reaction mixture was stirred at rt for 2h, then ether (20 ml) was added. The precipitate was collected, washed with ether and dried under high vacuum over P₂O₅ to produce the title compound (0.032 g) as an off-white powder. MS (ISN):
10 446.4 (M-H)⁻

Example 26

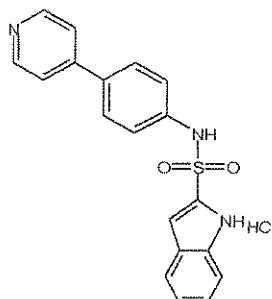
6-Fluoro-naphthalene-2-sulfonic acid (2-methanesulfonyl-4-pyridin-4-yl-phenyl)-amide



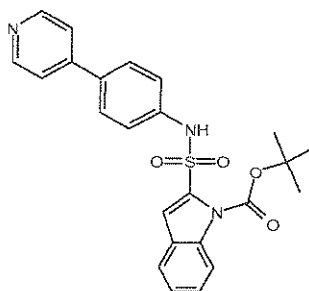
- To a solution of 2-methanesulfonyl-4-pyridin-4-yl-phenylamine (cf. Example 20c, 0.27 g) and 6-fluoro-naphthalene-2-sulfonyl chloride (0.148 g; cf. Brown, George Robert; Stokes, Elaine Sophie Elisabeth; Waterson, David; Wood, Robin. WO 9706802) in
15 dichloromethane (1.0 ml) was added DMAP (0.037 g). The reaction mixture was stirred at rt for 2h and directly chromatographed on silica gel using heptane/ethyl acetate as eluent to produce the title compound (0.098 g) as a colourless foam. MS (ISP): 457.3
20 (M+H)⁺

Example 27

1H-Indole-2-sulfonic acid (4-pyridin-4-yl-phenyl)-amide hydrochloride



a) 2-(4-Pyridin-4-yl-phenylsulfamoyl)-indole-1-carboxylic acid tert-butyl ester



5

To a solution of (4-pyridine-4-yl)aniline(CAS: 13296-04-3, 0.054 g) and 2-chlorosulfonyl-indole-1-carboxylic acid tert-butyl ester (0.120 g; cf. Shankar, Bandarpalle B.; Gilbert, Eric; Rizvi, Razia K.; Huang, Chunli; Kozlowski, Joseph A.; McCombie, Stuart; Shih, Neng-Yang. WO 2006002133) in 1,2-dichloroethane (5.0 ml) was added DMAP (0.047 g). The reaction mixture was stirred at 50 °C for 3h and chromatographed on silica gel using dichloromethane/ethyl acetate as eluent to obtain the desired compound (0.070 g) as a colourless powder. MS (ISP): 450.4 (M+H)⁺

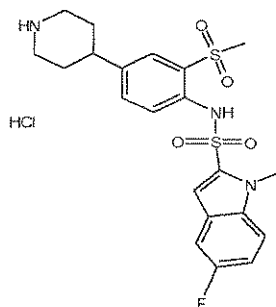
b) 1H-Indole-2-sulfonic acid (4-pyridin-4-yl-phenyl)-amide hydrochloride

To a solution of 2-(4-pyridin-4-yl-phenylsulfamoyl)-indole-1-carboxylic acid tert-butyl ester (0.030 g) in ethyl acetate (1.0 ml) was added 3.5N HCl/ethyl acetate (2.0 ml). The reaction mixture was stirred at 45 °C for 8h, then diluted with ether (40 ml). The precipitate was collected, washed with ether and dried under high vacuum over P₂O₅ to

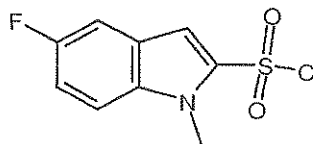
obtain the title compound (0.025 g) as a colourless amorphous powder. MS (ISP): 350.4 (M+H)⁺

Example 28

5-Fluoro-1-methyl-1H-indole-2-sulfonic acid (2-methanesulfonyl-4-piperidin-4-yl-phenyl)-amide hydrochloride

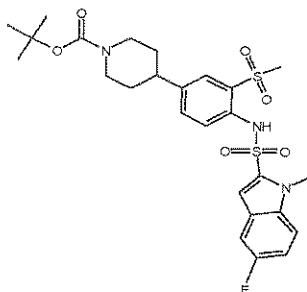


a) 5-Fluoro-1-methyl-1H-indole-2-sulfonyl chloride



- 10 To a solution of 1-methyl-5-fluoroindole(CAS: 116176-92-2, 1.98 g) in absolute ether (100 ml) was added dropwise at -78 °C tert-BuLi (1.7N in pentane, 12.4 ml). The reaction mixture was stirred at that temperature for 60 minutes, then sulfur dioxide was passed over the solvent surface until the exothermic reaction ceased. The mixture was further stirred for 30 minutes at rt and concentrated to dryness. The crude residue was
- 15 suspended in dichloromethane (100 ml) and NCS (2.94 g) was added. The reaction mixture was stirred at rt for 4h, quenched with ice/water, and extracted with dichloromethane. The organic phases were washed, dried and concentrated. The residue was chromatographed on silica gel using heptane/ethyl acetate as eluent to obtain the desired product (0.405 g) as a yellowish solid. MS (EI): 247.1 (M)

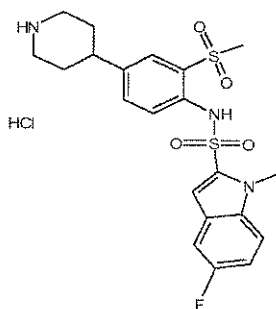
- b) 4-[4-(5-Fluoro-1-methyl-1H-indole-2-sulfonylamino)-3-methanesulfonyl-phenyl]piperidine-1-carboxylic acid tert-butyl ester



To a solution of 4-(4-amino-3-methanesulfonyl-phenyl)-piperidine-1-carboxylic acid
5 tert-butyl ester (cf. Example 24e, 0.048 g) in 1,2-dichloroethane (3.0 ml) was added 5-
fluoro-1-methyl-1H-indole-2-sulfonyl chloride (0.035 g) and DMAP (0.025 g). The
reaction mixture was stirred at 80 °C for 72h, diluted with dichloromethane (2 ml) and
chromatographed on silica gel using dichloromethane/ethyl acetate as eluent to obtain
the title compound (0.019 g) as an off-white foam. MS (ISN): 564.3 (M-H)⁺

10

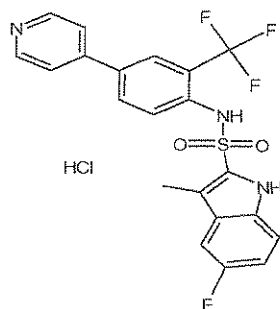
- c) 5-Fluoro-1-methyl-1H-indole-2-sulfonic acid (2-methanesulfonyl-4-piperidin-4-yl-phenyl)-amide hydrochloride



A solution of 4-[4-(5-fluoro-1-methyl-1H-indole-2-sulfonylamino)-3-methanesulfonyl-
15 phenyl]-piperidine-1-carboxylic acid tert-butyl ester (0.019 g) was treated with 2.5N
HCl/ethyl acetate (2.5 ml). The reaction mixture was stirred at rt for 3h, then ether (20
ml) was added. The precipitate was collected, washed with ether and dried under high
vacuum over P₂O₅ to produce the title compound (0.014 g) as an off-white amorphous
powder. MS (ISN): 464.0 (M-H)⁺

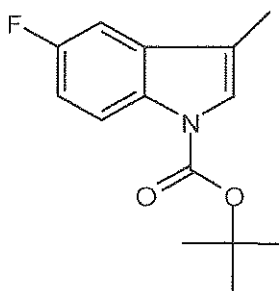
Example 29

5-Fluoro-3-methyl-1H-indole-2-sulfonic acid (4-pyridin-4-yl-2-trifluoromethyl-phenyl)-amide hydrochloride



5

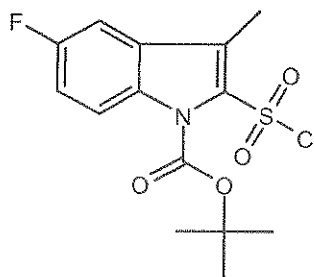
a) 5-Fluoro-3-methyl-indole-1-carboxylic acid tert-butyl ester



To a solution of 5-fluoro-3-methyl-indole (CAS: 392-13-2, 2.5 g) in THF (25 ml) were
10 added at 0-5 °C di-tert-butyl dicarbonate (4.02 g) and DMAP (0.205 g). The reaction
mixture was stirred at rt for 4h, concentrated, and the residue was chromatographed on
silica gel using heptane/ethyl acetate as eluent to obtain the desired compound (3.15 g) as
a colourless solid. MS (ISP): 250.1 (M+H)⁺

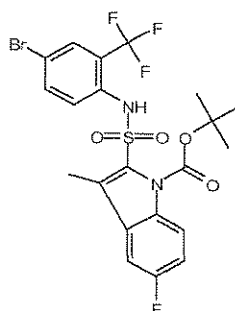
15 b) 2-Chlorosulfonyl-5-fluoro-3-methyl-indole-1-carboxylic acid tert-butyl ester

- 39 -



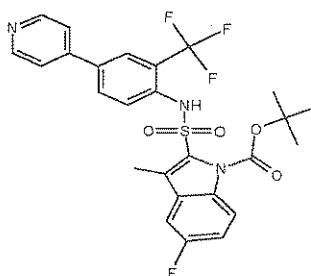
This compound was prepared in analogy to Example 28a starting from 5-fluoro-3-methyl-indole-1-carboxylic acid tert-butyl ester (1.0 g) in ether/THF 1:2 (15 ml), 1.7N tert-BuLi (2.85 ml), SO₂-gas and NCS (0.59 g) to obtain the title compound (0.80 g) as a
 5 colourless solid. MS (EI): 347.2, 247.1 (M and M-Boc)

c) 2-(4-Bromo-2-trifluoromethyl-phenylsulfamoyl)-5-fluoro-3-methyl-indole-1-carboxylic acid tert-butyl ester



10 This compound was prepared in analogy to Example 1 starting from 2-chlorosulfonyl-5-fluoro-3-methyl-indole-1-carboxylic acid tert-butyl ester (0.29 g) and 2-amino-5-bromobenzotrifluoride (2.0 g) in pyridine (5 ml) by stirring for 7 days at rt to obtain the title compound (0.095 g) as a colourless foam. MS (ISN): 551.4, 549.3 (M-H)⁻

15 d) 5-Fluoro-3-methyl-2-(4-pyridin-4-yl-2-trifluoromethyl-phenylsulfamoyl)-indole-1-carboxylic acid tert-butyl ester



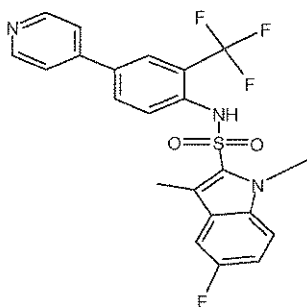
This compound was prepared in analogy to Example 2 starting from 2-(4-bromo-2-trifluoromethyl-phenylsulfamoyl)-5-fluoro-3-methyl-indole-1-carboxylic acid tert-butyl ester (0.108 g), 4-pyridineboronic acid (0.036 g) in 1,2-dimethoxyethane (5.0 ml),
 5 ethanol (0.4 ml) and 2 M aqueous sodium carbonate solution (0.8 ml) with tetrakis(triphenylphosphine)palladium (0.023 g) to obtain the desired compound (0.058 g) as a brownish foam. MS (ISN): 548.3 (M-H)⁻

e) 5-Fluoro-3-methyl-1H-indole-2-sulfonic acid (4-pyridin-4-yl-2-trifluoromethyl-phenyl)-amide hydrochloride
 10 phenyl)-amide hydrochloride

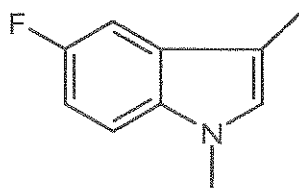
This compound was prepared in analogy to example 27b starting from 5-fluoro-3-methyl-2-(4-pyridin-4-yl-2-trifluoromethyl-phenylsulfamoyl)-indole-1-carboxylic acid tert-butyl ester (0.052 g), 2.5N HCl/ethyl acetate (10.0 ml) to obtain the title compound (0.041 g) as a brownish amorphous powder. MS (ISN): 448.4 (M-H)⁻

15 Example 30

5-Fluoro-1,3-dimethyl-1H-indole-2-sulfonic acid (4-pyridin-4-yl-2-trifluoromethyl-phenyl)-amide

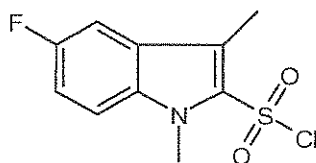


a) 5-Fluoro-1,3-dimethyl-1H-indole



To a solution of 5-fluoro-3-methyl-indole (CAS: 392-13-2, 2.5 g) in DMF (20 ml) was added potassium hydroxide (1.41 g). The suspension was stirred at rt for 1h and iodomethane (2.85 g) was added dropwise at 0-5 °C. The reaction mixture was stirred at
5 rt for 18h and concentrated under high vacuum. The residue was quenched with water and extracted with ethyl acetate. The organics were washed, dried and concentrated. The crude residue was chromatographed on silica gel using heptane/ ethyl acetate as eluent to obtain the desired compound (2.15 g) as a colourless liquid. MS (EI): 163.1 (M)

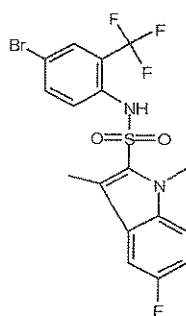
10 b) 5-Fluoro-1,3-dimethyl-1H-indole-2-sulfonyl chloride



This compound was prepared in analogy to Example 28a starting from 5-fluoro-1,3-dimethyl-1H-indole (1.0 g) in ether/THF 1:2 (15 ml), 1.7N tert-BuLi (4.33 ml), SO₂ gas and NCS (0.90 g) to obtain the title compound (0.27 g) as a yellowish solid. MS (ISN):
15 241.9 (M-F)

c) 5-Fluoro-1,3-dimethyl-1H-indole-2-sulfonic acid (4-bromo-2-trifluoromethyl-phenyl)-amide

- 42 -



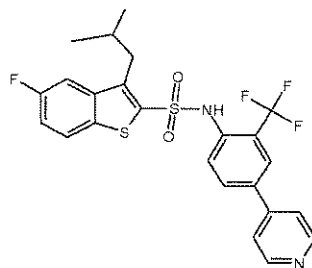
This compound was prepared in analogy to Example 1 starting from 5-fluoro-1,3-dimethyl-1H-indole-2-sulfonyl chloride (0.25 g) and 2-amino-5-bromobenzotrifluoride (2.3 g) in pyridine (5 ml) for 18h at 35 °C to obtain the title compound (0.293 g) as a yellow solid. MS (ISN): 551.4, 549.3 (M-H)⁻

d) 5-Fluoro-1,3-dimethyl-1H-indole-2-sulfonic acid (4-pyridin-4-yl-2-trifluoromethyl-phenyl)-amide

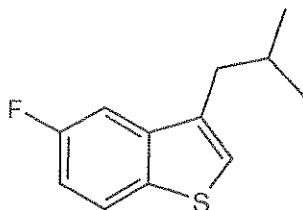
This product was prepared in analogy to Example 2 starting from 5-fluoro-1,3-dimethyl-1H-indole-2-sulfonic acid (4-bromo-2-trifluoromethyl-phenyl)-amide (0.100 g), 4-pyridineboronic acid (0.040 g) in 1,2-dimethoxyethane (5.0 ml), ethanol (1.0 ml) and 2 M aqueous sodium carbonate solution (1.0 ml) with tetrakis(triphenylphosphine)palladium (0.025 g) to obtain the title compound (0.058 g) as a brownish foam. MS (ISN): 462.4 (M-H)⁻

Example 31

5-Fluoro-3-isobutyl-benzo[b]thiophene-2-sulfonic acid (4-pyridin-4-yl-2-trifluoromethyl-phenyl)-amide.

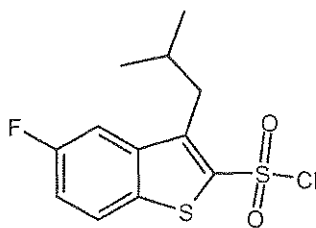


a) 5-Fluoro-3-isobutyl-benzo[b]thiophene



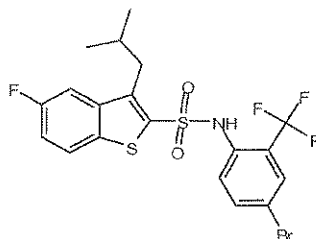
To a solution of 3-bromomethyl-5-fluorobenzo[b]thiophene (2.0 g; cf. Raga, Manuel; Palacin, Celia; Castello, Josep Maria; Ortiz, Jose A.; Cuberes, Maria Rosa; Moreno-Manas, Marcial, Eur. J. Med. Chem. (1986), 21(4), 329-32) in THF (30 ml) was added over 5
5 minutes isopropylmagnesium bromide (1.0 M, 16.6 ml). The reaction mixture was stirred at 50 °C for 5h, cooled, quenched with ice/water and ammonium chloride solution, and extracted with ethyl acetate. The organic phases were washed with water, dried and concentrated. The residue was chromatographed on silica gel using heptane/methylene chloride as eluent to obtain the title compound (1.35 g) as a yellowish
10 oil. MS (EI): 208.3 (M)

b) 5-Fluoro-3-isobutyl-benzo[b]thiophene-2-sulfonyl chloride



To a solution of 5-fluoro-3-isobutyl-benzo[b]thiophene 0.55 g) in chloroform (10 ml)
15 was added chlorosulfonic acid (1.54 g), and the resulting mixture was stirred at rt for 3h, quenched with ice/water, and extracted with methylene chloride. The organic phases were washed with water and aqueous sodium bicarbonate solution, dried and concentrated. The residue was chromatographed on silica gel using heptane/ethyl acetate as eluent to obtain the title compound (0.49 g) as a colourless oil. MS (EI): 306.8 (M)

c) 5-Fluoro-3-isobutyl-benzo[b]thiophene-2-sulfonic acid (4-bromo-2-trifluoromethyl-phenyl)-amide



This compound was prepared in analogy to Example 1 starting from 5-fluoro-3-isobutyl-benzo[b]thiophene-2-sulfonyl chloride (044 g), 2-amino-5-bromobenzotrifluoride (3.44 g) in pyridine (5 ml) for 18h at rt to obtain the desired compound (0.24 g) as a colourless solid. MS (ISN): 508.2, 510.3 (M-H)⁻

d) 5-Fluoro-3-isobutyl-benzo[b]thiophene-2-sulfonic acid (4-pyridin-4-yl-2-trifluoromethyl-phenyl)-amide

This compound was prepared in analogy to Example 2 starting from 5-fluoro-3-isobutyl-benzo[b]thiophene-2-sulfonic acid (4-bromo-2-trifluoromethyl-phenyl)-amide (0.10 g) and 4-pyridineboronic acid (0.036 g) in 1,2-dimethoxyethane (7 ml), ethanol (1 ml) and 2 molar sodium carbonate (2.0 ml) with tetrakis(triphenylphosphine)palladium (0.027 g) to obtain the title compound (0.47 g) as a yellowish solid. MS (ISN): 507.1 (M-H)⁻

Example A

Film coated tablets containing the following ingredients can be manufactured in a conventional manner:

<u>Ingredients</u>	Per tablet	
Kernel:		
Compound of formula (I)	10.0 mg	200.0 mg
Microcrystalline cellulose	23.5 mg	43.5 mg
Lactose hydrous	60.0 mg	70.0 mg
Povidone K30	12.5 mg	15.0 mg
Sodium starch glycolate	12.5 mg	17.0 mg

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Magnesium stearate	1.5 mg	4.5 mg
(Kernel Weight)	120.0 mg	350.0 mg
Film Coat:		
Hydroxypropyl methyl cellulose	3.5 mg	7.0 mg
Polyethylene glycol 6000	0.8 mg	1.6 mg
Talc	1.3 mg	2.6 mg
Iron oxide (yellow)	0.8 mg	1.6 mg
Titan dioxide	0.8 mg	1.6 mg

The active ingredient is sieved and mixed with microcrystalline cellulose and the mixture is granulated with a solution of polyvinylpyrrolidone in water. The granulate is mixed with sodium starch glycolate and magnesium stearate and compressed to yield kernels of

5 120 or 350 mg respectively. The kernels are lacquered with an aqueous solution / suspension of the above mentioned film coat.

Example B

Capsules containing the following ingredients can be manufactured in a conventional manner:

<u>Ingredients</u>	<u>Per capsule</u>
Compound of formula (I)	25.0 mg
Lactose	150.0 mg
Maize starch	20.0 mg
Talc	5.0 mg

10

The components are sieved and mixed and filled into capsules of size 2.

Example C

Injection solutions can have the following composition:

Compound of formula (I)	3.0 mg
-------------------------	--------

Polyethylene Glycol 400	150.0 mg
Acetic Acid	q.s. ad pH 5.0
Water for injection solutions	Ad 1.0 ml

The active ingredient is dissolved in a mixture of Polyethylene Glycol 400 and water for injection (part). The pH is adjusted to 5.0 by Acetic Acid. The volume is adjusted to 1.0 ml by addition of the residual amount of water. The solution is filtered, filled into vials
5 using an appropriate overage and sterilized.

Example D

Soft gelatin capsules containing the following ingredients can be manufactured in a conventional manner:

Capsule contents

Compound of formula (I)	5.0 mg
Yellow wax	8.0 mg
Hydrogenated Soya bean oil	8.0 mg
Partially hydrogenated plant oils	34.0 mg
Soya bean oil	110.0 mg
Weight of capsule contents	165.0 mg

Gelatin capsule

Gelatin	75.0 mg
Glycerol 85 %	32.0 mg
Karion 83	8.0 mg (dry matter)
Titan dioxide	0.4 mg
Iron oxide yellow	1.1 mg

The active ingredient is dissolved in a warm melting of the other ingredients and the mixture is filled into soft gelatin capsules of appropriate size. The filled soft gelatin capsules are treated according to the usual procedures.

5 Example E

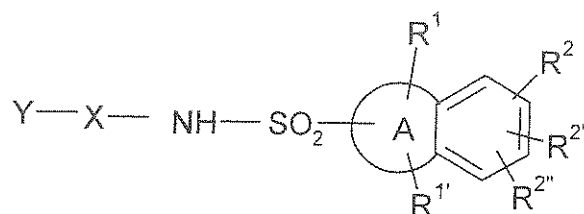
Sachets containing the following ingredients can be manufactured in a conventional manner:

Compound of formula (I)	50.0 mg
Lactose, fine powder	1015.0 mg
Microcrystalline cellulose (AVICEL PH 102)	1400.0 mg
Sodium carboxymethyl cellulose	14.0 mg
Polyvinylpyrrolidon K 30	10.0 mg
Magnesiumstearate	10.0 mg
Flavoring additives	1.0 mg

The active ingredient is mixed with lactose, microcrystalline cellulose and sodium
10 carboxymethyl cellulose and granulated with a mixture of polyvinylpyrrolidon in water.
The granulate is mixed with magnesiumstearate and the flavouring additives and filled
into sachets.

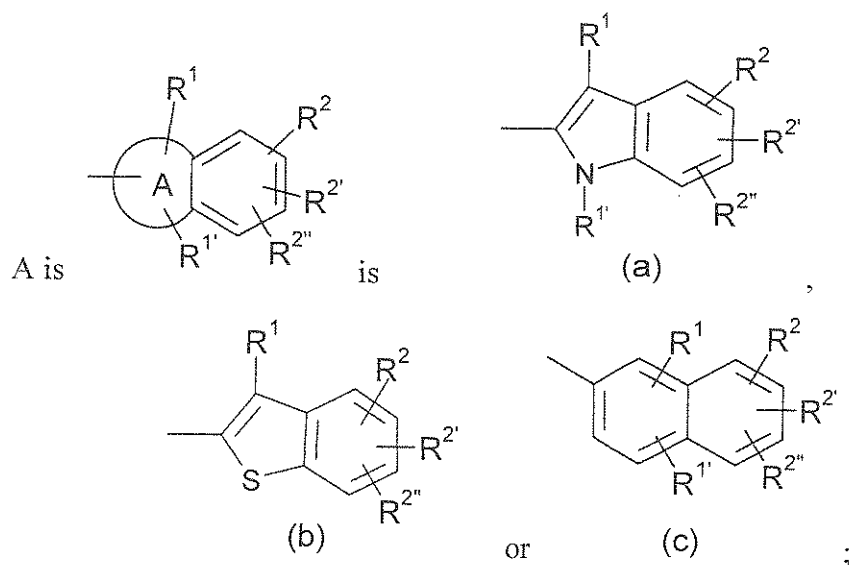
Claims:

1. Compounds of formula (I)



(I)

- 5 wherein



R^1 and $R^{1'}$ are independently hydrogen or C_{1-6} alkyl,

or $R^{1'}$ does not exist, where only R^1 can exist;

R^2 , $R^{2'}$ and $R^{2''}$ are independently hydrogen or halogen;

5 X is phenylene optionally substituted by one, two or three substituents independently selected from the group consisting of halogen, cyano, nitro, amino, mono- or di- C_{1-6} alkyl substituted amino, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, heteroalkyl, hydroxy, C_{1-6} alkoxy, halo C_{1-6} alkyl, halo C_{1-6} alkoxy, heteroalkyloxy, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl- C_{1-6} alkyl, C_{1-6} alkylsulfinyl- C_{1-6} alkyl, C_{1-6} alkylthio C_{1-6} alkyl, acyl, formyl, C_{1-6} alkoxycarbonyl, halo C_{1-6} alkoxycarbonyl, 10 heteroalkyloxycarbonyl and heteroalkylcarbonyl;

Y is at the para position of the phenylene group as X, with respect to to $-NH-SO_2-$ group and is optionally substituted heteroaryl, in which heteroaryl means a monocyclic aromatic radical of 6 ring atoms, containing one or two ring heteroatoms selected from $N(O)_n$ (where n is 0 or 1), O, and S, the 15 remaining ring atoms being C, or optionally substituted heterocyclyl, in which heterocyclyl means a non-aromatic mono-cyclic radical of six ring atoms, containing one or two ring atoms are heteroatoms selected from N, O, or $S(O)_n$ (where n is an integer from 0 to 2), the remaining ring atoms being C;

20 and prodrugs and pharmaceutically acceptable salts thereof;

wherein, unless otherwise defined,

the term "heteroalkyl" means C_{1-6} alkyl substituted by one or more substituents selected independently from the group consisting of nitro, hydroxy, halogen, cyano, C_{1-6} alkoxy, formyl, C_{1-6} alkylcarbonyl, carboxyl, C_{1-6} alkylthio, C_{1-6} alkyl 25 sulfinyl, C_{1-6} alkyl sulfonyl, amino and mono- or di- C_{1-6} alkyl amino.

the term "aryl" means phenyl or naphthyl;

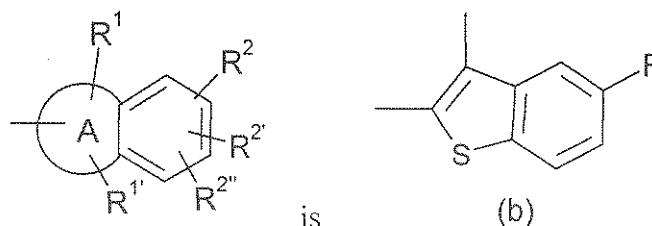
the term “heteroaryl” means a monocyclic or bicyclic radical of 5 to 12 ring atoms having at least one aromatic ring containing one, two, or three ring heteroatoms selected from N, O, and S, the remaining ring atoms being C, with the understanding that the attachment point of the heteroaryl radical will be on an aromatic ring;

the term “heterocyclyl” means a non-aromatic mono- or bi-cyclic radical of three to eight ring atoms in which one or two ring atoms are heteroatoms selected from N, O, or S(O)_n (where n is an integer from 0 to 2), the remaining ring atoms being C;

the term “optionally substituted aryl”, “optionally substituted heteroaryl”, “optionally substituted heterocyclyl” and “optionally substituted C₃₋₇ cycloalkyl” means, respectively aryl, heteroaryl, heterocyclyl and C₃₋₇ cycloalkyl optionally substituted by one or more substituents independently selected from the group consisting of halogen, nitro, cyano, amino, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, hydroxy, C₁₋₆ alkoxy, heteroalkyloxy, mono- or di- C₁₋₆ alkyl substituted amino, acyl, formyl, heteroalkylcarbonyl, C₁₋₆ alkoxycarbonyl, heteroalkyloxycarbonyl and heteroalkyl.

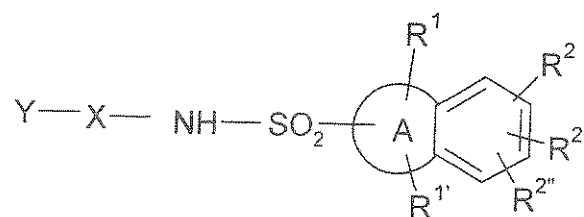
2. The compounds according to claim 1, wherein A is phenyl ring or heteroaryl ring.

3. The compounds according to any one of claims 1 to 2, wherein



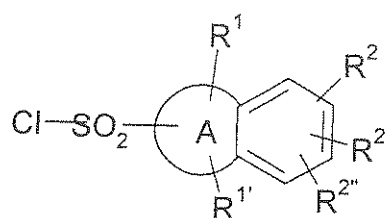
4. The compounds according to any one of claims 1 to 3, wherein X is phenylene optionally substituted by one, two or three substituents independently selected from the group consisting of halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo C₁₋₆ alkyl, halo C₁₋₆ alkoxy, C₁₋₆ alkylsulfonyl, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylthio, C₁₋₆ alkylsulfonyl-C₁₋₆ alkyl, C₁₋₆ alkylsulfinyl-C₁₋₆ alkyl, C₁₋₆ alkylthio C₁₋₆ alkyl and C₁₋₆ alkoxycarbonyl.
5. The compounds according to any one of claims 1 to 4, wherein X is phenylene substituted by halo C₁₋₆ alkyl or C₁₋₆ alkylsulfonyl at the ortho position with respect to -NH-SO₂- group.
6. The compounds according to any one of claims 1 to 4, wherein X is phenylene substituted by trifluoromethyl or methylsulfonyl at the ortho position with respect to -NH-SO₂- group.
7. The compounds according to any one of claims 1 to 6, wherein Y is optionally substituted heteroaryl, in which heteroaryl means a monocyclic aromatic radical of 6 ring atoms, containing one or two ring nitrogen atoms, the remaining ring atoms being C, or optionally substituted heterocyclyl, in which heterocyclyl means a non-aromatic mono-cyclic radical of six ring atoms, containing one or two ring nitrogen atoms, the remaining ring atoms being C.
8. The compounds according to any one of claims 1 to 7, wherein Y is pyridyl, pyrimidinyl or piperidyl, optionally substituted by one or two substituents independently selected from the group consisting of halogen, C₁₋₆ alkoxy and C₁₋₆ alkoxycarbonyl.
9. 5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-pyridin-4-yl-2-trifluoromethyl-phenyl)-amide.

10. A process for manufacturing compounds of formula (1),



(1)

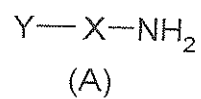
comprising a step of reacting compounds of formula (B)



(B)

5

with compounds of formula (A)



, wherein A, R^1 , $\text{R}^{1'}$, R^2 , $\text{R}^{2'}$, $\text{R}^{2''}$, X and Y are as defined in claim 1.

11. Pharmaceutical compositions comprising a compound according to any one of claims 1 to 9 and a pharmaceutically acceptable excipient.
- 5 12. The compounds according to any one of claims 1 to 9 for use as therapeutic active substances.
13. The compounds according to any one of claims 1 to 9 for use as therapeutic active substances for the treatment and/or prophylaxis of atherotrombosis or asthma.
- 10 14. Use of compounds according to any of claims 1 to 9 for the preparation of medicaments for the therapeutic and/or prophylactic treatment of diseases which are associated with chymase.
15. The use according to claim 14, wherein the disease is atherotrombosis or asthma.
